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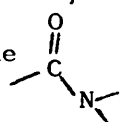
SECTION 1.

THE ATISANE - ACONANE INTERCONVERSION.

SUMMARY

The first section of this thesis is concerned with a biogenetic-type approach to the synthesis of the aconitine-lycoctonine group of diterpene alkaloids. The synthetic precursor, atisine, was transformed in an eleven step sequence into a keto-tosylate. This material underwent a novel, stereospecific pyrolytic rearrangement to give a key intermediate in the proposed atisane-aconane biogenesis, whose constitution and stereochemistry were confirmed by anx-ray crystallographic analysis, conducted on a heavy atom derivative.

Our efforts to convert this intermediate into the desired aconitine-lycoctonine skeleton, a task which had already been accomplished in principle by other workers, met with limited success.

N.M.R. studies on some acetamides, obtained in the foregoing synthesis, revealed an interesting example of restricted rotation around the  bond. Variable temperature work enabled a crude barrier to rotation to be extracted.

The second section of the thesis, also in the realm of diterpenes, concerns the synthesis of the cassane skeleton, in a biogenetically-patterned fashion, from isopimaric acid. The route from isopimaric acid to an important intermediate enone is described. Despite numerous attempts,we could not induce the Wagner-Meerwein rearrangement in this enone,which would have resulted in the desired cassane skeleton.

CHAPTER 1.

INTRODUCTION.

For almost a century, the diterpene alkaloids[1] of the Garrya, Aconitum and Delphinium species have provided a formidable challenge to the ingenuity of the organic chemist. The early stimulus undoubtedly resulted from the pharmacological properties of the plants containing these substances and extracts of Aconitum, for example, have been used to relieve a wide variety of ailments. Unfortunately, the extremely toxic nature of some of the Delphinium alkaloids, their lethal dose for man being in the order of a milligram, has seriously limited their applications in modern medicine. Further stimulus arose when it rapidly became evident that these alkaloids were structurally very complex and were a potential source of fascinating mechanistic and degradative problems.

One of the early difficulties in the study of the diterpene alkaloids, which was common to many other branches of natural product chemistry, was in the aquisition of pure materials for chemical degradation. The closely related alkaloids frequently formed mixtures which were not easily separable by the techniques available at that time and for this reason much of the early work is now of historical rather than

chemical interest. In fact, some of these results were so confusing and contradictory that they seriously impeded, rather than aided, later work. Structure elucidation was further hampered by the plethora of products, which resulted from the application of classical degradation techniques to molecules which were heavily substituted with oxygen functionality. Until the early 1950's, success was limited to the recognition of the relative disposition of various oxygen substituents, mainly due to oxidation and pyrolysis experiments. Unfortunately, these experiments were less clear cut as regards defining the carbon skeleton and as far as the more complex alkaloids were concerned, dehydrogenation was also of little value and at one stage positively misleading.

The real breakthroughs in the chemistry of these alkaloids came in the mid 1950's, with the development and widespread use of new and very powerful physical tools. These compounds, in particular, proved to be excellent substrates for X-ray crystallography because of the relatively easy introduction of a heavy atom and the key to the interpretation of the wealth of chemical information accumulated throughout the years was found in the brilliant X-ray work of Przybylska, which established the structure[2] and later the absolute configuration[3] of des(oxymethylene)-lycoctonine(1). The X-ray method was also instrumental in elucidating the structure

of the simpler alkaloid, veatchine(2)[4,5] via the azaphenanthrene dehydrogenation product(3). Using the lycoctonine skeleton as a basis, the structure of delpheline[6] was deduced and by a combination of X-ray and chemical correlation methods the structures of a great variety of other diterpene alkaloids rapidly emerged.

The diterpene alkaloids may be divided into two broad catagories; those with a C_{20} skeleton and those with a C_{19} skeleton. The C_{20} compounds are relatively simple, non-toxic amino alcohols and they may be distinguished chemically from the C_{19} type in that they revert to phenanthrene on selenium or palladium dehydrogenation. These compounds are not extensively oxygenated, containing usually two or three hydroxyls and occasionally an acetate or benzoate ester and, in contrast to the C_{19} variety, their structures were, in the main, assigned from chemical studies. Furthermore, the C_{20} alkaloids all have counterparts in the non-basic tetracyclic diterpenoids, from which they may be formally derived by interposition of a nitrogen residue, typically an ethylamine or β-amino-ethanol function, between C(19) and C(20). In fact, the main subgroups, of which there are two, within the C_{20} classification are based on the non-nitrogenous skeletons.

Atisine(4) is the parent compound of the first subgroup, whose members have been isolated from both Aconitum and Delphinium species. Their biogenetic precursor may be

(-) atisirene, in which rings C and D constitute a bicyclo-[2,2,2]octane system. Although isolated by Broughton[7] in 1877, the structure of atisine(4) was only conclusively established in 1954 by Wiesner,[4,8] following the excellent groundwork of Jacobs[9] and his collaborators. In recent years, some Aconitum species indigenous to Japan and India have yielded several interesting alkaloids based on an atisine skeleton, but possessing an additional ring fusion between C(14) and C(20). Hetisine(5), whose heptacyclic nature was discerned by X-ray crystallography[10] and the recently isolated spiradine-D(6)[11] exemplify these compounds. The majority of the hetisine-type alkaloids also contain a N-C(6) bond.

The garrya C_{20} subgroup, isolated from Garrya species and typified by veatchine(7), are formally derived from the (-)-kaurene skeleton, with the characteristic bicyclo [3,2,1]-octane residue. Wiesner noted the very close chemical similarity between veatchine and atisine, as elucidated by Jacobs, and proposed the structure (7) for veatchine. This postulate has since been rigorously proved. In parallel with the atisines, there is a group of modified garrya diterpene alkaloids, of which lucidusculine, whose structure (8) was determined by X-rays,[12] is representative. These compounds form a link between the garrya and atisine bases in that, although they were isolated from aconitum species, they

possess kauranoid skeletons. There is a small group of four such alkaloids, all containing an N-ethyl group, three oxygen substituents sited as in lucidusculine and certainly the most striking feature, a bond between C(7) and C(20).

The second main catagory of diterpene alkaloids, the C_{19} bases or aconitines, are composed of highly toxic ester bases, isolated from both Aconitum and Delphinium species. On mild hydrolysis, these alkaloids are readily cleaved into a relatively non-toxic, C_{19} amino part, which is characteristically heavily substituted with hydroxyl and methoxyl functions, and one or more simple carboxylic acids such as acetic, benzoic or veratric acids. In complexity, the aconitines range from the extensively oxygenated lycoctonine (9) and aconine(10) to the lactonic derivative heterophylline (11), one of the most recent examples to come to light. The elucidation of the structures of these compounds are excellent examples of the use of the powerful physical tools, X-ray crystallography and high resolution mass spectroscopy. The diterpenoid nature of the alkaloids is emphasised by the structural presentation, (9) for example. The seven and five membered rings are denoted B and C respectively and a very significant feature is the fusion between C(7) and C(20). This type of skeleton is not found among the non-nitrogenous tetracyclic diterpenoids. Historically, the C_{19} alkamine residues fell into two distinct classes; those resembling

lycoctonine in possessing a C(7) hydroxyl group and those resembling aconitine which lacks this feature.

Biogenetically, the C_{20} diterpene alkaloids were easily accommodated within the general scheme (1) expounded for the tetracyclic diterpenes.[13] Thus these compounds may be derived from geranyl-geraniol(12) or geranyl-linaloöl(13) via the bicyclic alcohol(14) and Wenkert's ion(16). Nitrogen insertion is considered to be a secondary transformation. However, it is clear that the C_{19} alkaloids cannot be formed by direct collapse of Wenkert's ion(16). In 1956, almost immediately after Przybylska and Marion reported the results of their X-ray investigation on des-(oxymethylene)-lycoctonine,[14] two groups of workers, Valenta and Wiesner and Cookson and Trevett,[15] independently proposed a simple biogenetic relationship between the aconitine-lycoctonine(C_{19}) and the atisine diterpene alkaloids. This resulted from the realisation that the published structure (21) could be rewritten in the now accepted form (1). Their ideas are embodied in the structural sequence (22)→(23)→(24). The precursor (22), which could be easily derived from atisine (4), might lose the carbon atom C(17) in a biological fashion which has ample precedent.[16,17] A Wagner-Meerwein rearrangement triggered by a suitable leaving group at C(15),(22)→(23), could, in principle, convert the B/C-6/6 ring system of atisine into the desired B/C-7/5 system of the aconitines.

Finally, the ring closure step forming the bond between C(7) and C(20), (23)→(24), may proceed by a normal Mannich reaction, using the enolate anion generated at C(7). The precise order in which these steps would occur was not stipulated.

The chemical feasibility of the cyclisation reaction, (23)→(24), has since been demonstrated *in vitro* by Wiesner and Büchi[18] in 1959 and later by Edwards[19] in 1965 and resulted from a re-interpretation of the mechanism of the pyrolysis reaction which generates the well-known series of "pyro" compounds[1a] in the aconitine type alkaloids. This pyrolysis reaction, which was undergone by any of the aconitines containing a C(8) acetate group, was formerly thought to involve, despite the very mild conditions employed, the usual six-membered transition state (25)→(26). However, Büchi's group discovered that pyrolysis of aconitine-N-oxide (27) at 190° did not produce the expected "pyro" ketone(28), but instead yielded a compound whose properties were in accord with the nitrone structure (29), (R=Bz). This product could be rationalised by a concerted fragmentation (30) and an examination of a molecular model of aconitine showed that the stringent stereoelectronic requirements[20,21] were met as N-C(20)-C(7)-C(8)-OAc are coplanar. Mild acid treatment (perchloric acid in methanol at r.t.) of the nitrone (29) (R=H) effected a facile cyclisation reaction, regenerating

the aconitine skeleton in the form of the crystalline perchlorate (31). Edwards also came to the same mechanistic conclusions about the mild pyrolytic loss of acetic acid from the aconitines. His ideas are embodied in the reaction sequence (32)→(33)→(34) as applied to bikhaconitine (32) i.e., a rapid reversible equilibrium (32)⇌(33) with a slower reaction of acetate with the C(15) hydrogen to give the observed olefinic product (34). These postulates were amply borne out by the reductive trapping of the intermediate (33) to give (35), which, on re-oxidation with mercuric acetate spontaneously cyclised to the known alkaloid bikhaconine (36).

In the light of these experiments, the original biogenetic relationship between the lycoctonine-aconitine and atisine alkaloids was modified in detail, as shown in the scheme (37)→(38)→(39). The first step embodies a Wagner-Meerwein rearrangement leading, by elimination of a proton, to the "pyro" intermediate (38), from which the lycoctonine-aconitine skeleton (39) may be obtained by formation of a bond joining C(7) and C(20) <u>via</u> a Prins reaction.

A brief survey of the known C_{19} diterpene alkaloids shows that the foregoing principles are in accord with the invariable existence of oxygen substituents at C(8) and C(14). Thus the C(8) oxygen (see structure (40)) has its biogenetic origin in either the Wagner-Meerwein or the Prins reaction, whilst

the C(14) oxygen marks the scar of C(17) in the atisine precursor. However, there are two other oxygens which may be of some biogenetic significance. Every known lycoctonine-aconitine alkaloid contains a C(1) oxygen substituent, (hydroxyl or methoxyl) and, in addition, all except the further modified lactonic type e.g. heterophylline (11), bear a methoxyl group at C(16). These observations, together with the co-occurence of the following compounds in the Aconitum species and a mechanistically plausible pathway for their interconversion (41)→(42)→(43), which makes use of the existing oxygen functions in the precursor, led Overton[22] to make the very attractive suggestion that the biogenetic precursors of the lycoctonine-aconitine alkaloids are the modified garryas e.g. lucidusculine (8). An outstanding feature of this postulate is that the C(7)-C(20) bond already exists in the precursor (41). The first step envisaged, (41)→(42), involves a Wagner-Meerwein rearrangement, some of the driving force for which may be found in the release of the strain inherent in the bicyclo[2,2,1] heptane system composed of ring B and C(20). Loss of C(17) may also occur at an early stage. Finally, a second Wagner-Meerwein type acyl migration, with loss of a suitable derivative of the C(12) oxygen, (42)→(43), would give rise to the required lycoctonine-aconitine skeleton.

Although there is much speculation as to the biogenesis

of the diterpene alkaloids, there is very little *in vivo* experimental evidence available to substantiate it. Some attempts have been made to establish the mevalonate origin of these compounds *via* radioisotope labelling techniques. In the first of these in 1963, Herbert and Kirby,[23] using detached leaves of *Delphinium elatum*, failed to incorporate d.l. [2-^{14}C]-mevalonic acid into delpheline(44). However, they were able to demonstrate that l-[methyl-^{14}C] methionine was incorporated and, by degradation, that it appeared mainly in the methoxyls. Their explanation for the lack of mevalonate incorporation, i.e., that it was being used in the biosynthesis of the non-basic plant terpenoids before it reached the site of alkaloid synthesis, was questioned by Benn and May.[24] These workers suspected that the site of biosynthesis was in the plant roots and accordingly, using whole plants, managed to obtain very poor incorporation of [1-^{14}C] and [2-^{14}C] acetate and [2-^{14}C] mevalonate into lycoctonine and browniine. More convincing results were obtained by Waller[25] and his coworkers, who succeeded in 1967 in incorporating [2-^{14}C] glycine and [2-^{14}C] mevalonate into the C_{19} alkaloid delcosine. From the extent of glycine incorporation, it was concluded that the intact molecule was fused into the preformed oxygenated diterpene skeleton and gave rise to the N-ethyl side chain. By establishing the terpenoid character of these alkaloids, the foregoing

experiments lend some support to the proposed biogenetic schemes. However, a great deal more work is necessary before the intimate details of the biosynthesis of the diterpene alkaloids are revealed.

There has been a great upsurge of interest in the synthetic approaches to the diterpene alkaloids in recent years and, in order to put the following work into perspective, reference will be made to a few of the more significant advances. The main synthetic effort has been directed towards the C_{20} alkaloids i.e., atisine and garrya types, undoubtedly due to the relative simplicity of their structures. Pelletier,[26] for example, has, in the synthesis of atisine, elaborated rings C and D starting from the amide ester (45), which was a key intermediate in the correlation of the atisine and garrya alkaloids. Another intermediate in this synthesis, the enone (46), was obtained in a 23 step process starting from the compound (47) in the first complete stereospecific synthesis of racemic atisine reported by Nagata et. al.[27,28] Initially, this work was concerned with the construction of the heterocyclic ring (48) via hydrocyanation of the enone (47) and rings C and D were subsequently produced by base closure of the keto-mesylate (49) to the ketone (50), whose further transformation by standard means afforded atisine (4). A variation of this route provided a neat synthesis of the Garrya alkaloids.[29] This involved hydroboration of the olefin(51)

to the alcohol (52), the brosylate of which rearranged very smoothly in base to a ketone (53) of the garrya skeleton. Two other C_{20} diterpene alkaloid syntheses of note are those of Masamune[30] starting from the aromatic compound (54) and Wiesner et. al.[31], starting from 5-methoxy-2-tetralone. The most recent work has tended to deal with improving the the approaches to important intermediates. Matsumoto et. al.[32] and Turner[33] have concentrated on the formation of the heterocyclic ring by employing reductive cyclisation techniques on compounds of the type (55), whilst, at the other extreme, Zalkow et. al.[34] have been experimenting with the formation of rings C and D via a Diels-Alder reaction on podocarpic acid precursors. Very few people indeed have ventured towards the more difficult C_{19} alkaloid synthesis. Perhaps the most adventurous work in this direction is that of Wiesner, who has described approaches to the alkaloids with a bridge in ring B i.e., the lucidusculine and aconitine types, which are entirely different from the rather steroid-like approaches to the simpler bases. Thus Wiesner has converted (56) into the ketal-lactam (57)[35] and from methoxytetralone has obtained (58),[36] which is very closely related to aromatisation products of aconitine and delphine e.g. (59).

The work discussed in the following section concerns a novel synthetic approach to the aconitine-lycoctonine alkaloids, which is modelled on the modified biogenetic

scheme (37)→(38)→(39). Using a suitably modified atisine (4) precursor, we planned to synthesise the C_{19} base skeleton by a Wagner-Meerwein rearrangement to a B/C-7/5 system such as (38), followed by formatiom of the C(7)-C(20) bond by a Prins reaction. These experiments have a two-fold objective. Firstly, they provide a very elegant synthetic route to the aconitine-lycoctonine alkaloids and secondly, they should demonstrate the chemical feasibility of the proposed biogenesis and, in doing so, make it seem a little more plausible. The detailed approaches to this synthesis and their results are discussed in the subsequent section.

DISCUSSION

In parallel with the foregoing biogenetic postulates, our synthetic approach to the aconane skeleton was divided into two very distinct stages. The first objective was the conversion of the atisane B/C-6/6 ring system (60) into a B/C-7/5 system of the type (61), and from there the aconane skeleton (62), which was the final objective, could be obtained by the formation of a bond between carbon atoms (7) and (20). The proposed route to the attainment of the first of these goals is shown in condensed form in the structures (4)→(64)→(65) and the short term aim was the conversion of atisine (4) into the key intermediate (64).

The starting material for the synthesis, atisine (4), could be obtained in varying yields from the ground roots of Aconitum Heterophyllum, a species indigenous to the Himalayas. Since its isolation almost a century ago, this compound has been the subject of extensive chemical investigation[1] and its structure and stereochemistry are now well established. [One point which was not rigorously proved was the configuration of the hydroxyl at C15. It has been assigned the β-configuration on rather tenuous grounds.[1b] Initially, we assumed this to be correct and our assumption was vindicated by the work discussed later]. Three main points needed attention in order to convert

atisine to the key intermediate (64) viz., the oxazolidine ring system, the epimerisation of the hydroxyl at C15 and the oxidative cleavage of the exomethylene group.

Brief perusal of the literature revealed that the oxazolidine ring in this particular compound was more labile than normal and underwent reaction with a great variety of common reagents. This high degree of reactivity can be correlated with the tendancy of the system to exist in the open imminium form (66) and the reasons proposed for this will be discussed later. Indeed the unstable nature of the oxazolidine is emphasised by the observation that atisine (4) can be smoothly converted to isoatisine (67) by refluxing in methanol for a very short period. Hence it was very apparent that first priority in the synthesis should be given to the conversion of the oxazolidine system into a more stable functionality. Again recourse to the literature revealed that Edwards[37] and Pelletier[38] had elaborated a very elegant method of converting atisine to the amide alcohol (68). This compound was ideal for our purposes because, firstly, the nitrogen was tied up in a form which was unlikely to interfere in the reactions necessary to rearrange rings B and C and secondly, the acetamide, in principle, should be easily reduced at a later stage giving rise to the N-ethyl group which is a common feature in aconitine alkaloids. Reaction of atisinium hydrochloride

with acetic anhydride and acetic acid at reflux for a short time afforded almost quantitatively the crystalline diacetate (69). Treatment of this diacetate with concentrated aqueous potassium hydroxide at 0°, followed by immediate extraction into chloroform, provided the carbinolamine (70), which was smoothly converted, on heating, to the azomethine acetate (71), ν(C=N) 1648cm.$^{-1}$ (In the ensuing discussion i.r. data refer to carbon tetrachloride solutions unless otherwise stated). During the heating process, acetaldehyde was evolved and the mechanism of the reaction was viewed by Edwards as a concerted cyclic fragmentation (72). Sodium borohydride reduction of the azomethine acetate (71), followed by acetylation with acetic anhydride and pyridine and selective hydrolysis with methanolic sodium hydroxide, afforded the amide alcohol (68) *via*, the intermediacy of the amine acetate (73) and the amide acetate (74). The overall yield for this series of reactions based on atisine was in the order of 70%.

With the nitrogen satisfactorily protected, attention was focussed on the functional requirements of rings C and D, such that the skeletal rearrangement (60)→(61) might take place. In general what is required is that the bond between carbon atoms (8) and (9) in (60) should migrate to a new position between carbon atoms (9) and (14) thus giving (61). Now, rings C and D constitute a bicyclo[2,2,2]-octane

system and consequently, the process envisaged was simply an extension of the celebrated bicyclo[2,2,2]-octane → bicyclo-[3,2,1]octane interconversion (75) → (76).[39] This reaction has been widely studied in a variety of bicyclo[2,2,2]octane derivatives in connection with the classical-non-classical carbonium ion controversy. In our system (60), the driving force for the rearrangement would be provided by a build-up of positive charge on C(14), caused by the departure of a suitable derivative, e.g., a p-toluene sulphonate ester, of the C(14) hydroxyl function. If the rearrangement is considered to be a concerted process, then the configuration of the departing function is of the utmost importance. The stereoelectronic requirements of the transition state for a concerted rearrangement demand that the C(14)-O bond be trans and antiparallel to the migrating bond. Thus, in the case in question, two possible rearrangements may occur depending on the configuration of the C(14) oxygen function. The transition states and expected products from each are shown in the diagrams (77) → (79) and (80) → (82). At this time, any effect that the exomethylene will have on the course of these reactions is being neglected. From the foregoing comments, it is clear that epimerisation of the natural C(15) hydroxyl configuration is necessary to attain the α- configuration, which leads to the desired skeleton (82).

In pursuit of this transformation, oxidation of the amide alcohol (68) with activated manganese dioxide[40] in chloroform provided only a very low yield of the required amide enone (83), even after prolonged reaction times. However, both the Sarett oxidation,[41] using chromium trioxide in pyridine, and the Snatzke oxidation,[42] using chromium trioxide in dry dimethyl formamide with a catalytic amount of concentrated sulphuric acid, afforded satisfactory yields of crystalline amide enone (83). The anomalously high enone carbonyl frequency,[43] 1712cm^{-1}, in this compound may be due in part to twisting of the chromophore.

Treatment of the amide enone (83) with sodium borohydride in methanol gave equal amounts of the required epi-amide alcohol (84) and the original amide alcohol (68), together with some material which did not contain an exomethylene and and whose n.m.r. spectrum was consistent with a mixture of saturated alcohols (85). The allylic alcohols (68) and (84) were easily separable by preparative t.l.c., but unfortunately the synthetic utility of the reaction was diminished by the extent to which the fully saturated alcohols (85) appeared in large scale preparations.

At this point, some preliminary investigations aimed at effecting rearrangements of the types (78)→(79) and (81)→(82) were undertaken. Both the allylic alcohols (68) and (84), in anhydrous pyridine, were treated with brosyl chloride

at 0°, in an attempt to prepare the corresponding brosylates (86) and (87). Unfortunately, even very careful work-up produced only complex mixtures of products. Many other workers have experienced similar difficulties in the attempted preparation of allylic sulphonate esters.[44] Undoubtedly, as soon as the allylic brosylate was formed, it collapsed to a very stable ion pair of the type (88) and the complexity of the product distribution is easily explained by the variety of capture processes open to this ion in the work-up It was also evident that this participation by the olefinic bond would result in complete loss of stereospecificity and either of the epimeric alcohols should provide the same product distribution. Therefore, these experiments were abandoned in favour of the more rational approaches described later.

In the light of the above observations, it was considered desirable to modify the exomethylene group before proceeding any further. Now C(17) is the carbon atom which, as has been pointed out in the introduction, was assumed to be lost in the biosynthesis of aconitines from atisine (4). Furthermore, in every known aconitine, (see introduction for some examples) the position where this carbon atom would have occurred i.e. attached to C(14) in (82), is marked by an oxygen function. Ozonisation of the amide alcohol (68) failed to produce the desired ketol (89), but instead produced a

compound whose i.r. ν(OH) (broad band) 3400-2500cm^{-1} and ν(C=O) 1720cm^{-1} and analytical t.l.c. properties were consistent with those of a carboxylic acid. An explanation for this result was found in the participation of the hydroxyl group in the decomposition of the intermediate ozonide [see (90)]. This problem of overoxidation was overcome by using the corresponding allylic acetates (74) and (91). These were easily and efficiently prepared by reaction of the amide alcohols (68) and (84) with acetic anhydride in anhydrous pyridine at r.t. in the usual manner. Treatment of the allylic acetate (74) in dry ether, containing a little pyridine, with osmium tetroxide, afforded a mixture of osmates, which were easily cleaved to the epimeric diols (92) with hydrogen sulphide gas. This diol mixture underwent a facile oxidation with sodium metaperiodate to the crystalline keto-acetate (93) $C_{23}H_{33}NO_4$, m.p. 199-200°, $[\alpha]_D$-123° (c=1.30). The i.r. spectrum of this keto-acetate exhibited carbonyl stretching frequencies at 1758 and 1743cm^{-1} due to the acetate and ketone respectively and the unusual values may be attributed to mutual electrostatic interactions.[46] The epimeric keto-acetate (94), $C_{23}H_{33}NO_4$, m.p. 219-222°, $[\alpha]_D$+23° (c=1.22) was prepared by ozonisation of the allylic acetate (91). This compound, as expected, displayed very similar spectral properties to (93), including the carbonyl bands at 1755 and 1740cm^{-1}. Both of these oxidations worked

reasonably well, but were replaced in later work by the more efficient and convenient procedure of Pappo et al.[47] Thus, by this method, the allylic acetate (74) in aqueous dioxan was converted cleanly, in one step, to the keto-acetate (93) by sodium metaperiodate and a catalytic amount of osmium tetroxide.

Very mild hydrolysis with methanolic sodium carbonate at r.t. converted the keto-acetates (93) and (94) into the ketols (89), $C_{21}H_{31}NO_3$, m.p. 213-218°, $[\alpha]_D$-93° (c=1.07) and (95), m.p. 210-216°, $[\alpha]_D$+7° (c=0.87), respectively, in acceptable yields. Under more vigorous hydrolytic conditions, a mixture of all four possible isomeric ketols was obtained from either keto-acetate.

Finally our short term aim, namely the preparation of the key intermediate, the keto-toxylate (64), was achieved by reaction of the ketol (95) with p-toluene sulphonyl chloride in pyridine. The structure of this compound was supported in the i.r. by the very high ketonic ν(C=O)[46] at 1747cm^{-1} and the characteristic sulphonate ester bands at 1373, 1188 and 1176cm^{-1}. Furthermore, the n.m.r. spectrum was fully consistent with the proposed structure. By the same method, the isomeric keto-tosylate (96) $C_{28}H_{37}NSO_5$, m.p. 197-198°, $[\alpha]_D$-112° (c=1.10) and the keto-brosylate (97) were prepared from the ketol (89).

Before discussing the rearrangements undergone by the

above keto-tosylates, some work will be described, whose aim was to find a more efficient method of epimerising the hydroxyl group at C(15). A very elegant procedure for inverting such a functionality, reported by Chang et al.,[48] is illustrated in the series of part structures (98)→(102). The key step in the sequence is an S_N2 type displacement of tosylate anion by dimethyl formamide to give the iminium salt (100), which is hydrolysed to the formate (101) in the work up. The formate is readily hydrolysed to the inverted alcohol on passage through an alumina column. However, various attempts to apply this reaction to the keto-tosylate (96) all resulted in complex mixtures of products.

Every other hydroxyl inversion method took advantage of the symmetry of the bicyclo[222] octane system. An examination of a molecular model, or part structure (103), reveals that a hydroxyl group at C(14) would experience the same degree of steric interference in either configuration. Therefore, if some means of setting up an equilibrium between the epimers could be achieved, then a 50% yield of the required alcohol would result. On heating the ketol (89) in chloroform containing a little p-toluene sulphonic acid only non-polar material, which was not further characterised, arose. Reaction with ethylene glycol under acid catalysis readily converted the ketol (89) into the ketal alcohol (104), $C_{23}H_{35}NO_4$, m.p. 182-183°, $[\alpha]_D$ -39° (c=1.30) as could be seen from a four

proton singlet at 6.02τ in the n.m.r. spectrum due to OCH_2CH_2O. This compound afforded the opportunity to employ oxidation-reduction methods to convert the C(15) β-hydroxyl into its epimer. However, the desired thermodynamic equilibrium proportions of the ketal alcohols (104) and (105) did not materialise when the ketal alcohol (104) was subjected to heating with either sodium and fluorenone or aluminium isopropoxide and acetone. Thus, deketalisation of the products from the foregoing reactions with perchloric acid in tetrahydrofuran[49], or by the acetone-p-toluene sulphonic acid exchange procedure[50], afforded mainly the ketol (89) and no evidence of the desired ketol (95) was apparent.

The success that we were seeking appeared when the oxidation and reduction procedures were separated. Oxidation of the ketal alcohol (104) with chromium trioxide in pyridine according to Sarett[41], afforded in high yield the crystalline ketal ketone (106) $C_{23}H_{33}NO_4$, m.p. 211-211.5°, $[\alpha]_D$ +6° (c=0.76), ν(C=O) 1736cm^{-1}. A mixture of the ketal alcohols (104) and (105) were obtained by standard sodium borohydride reduction of this ketone. Chromatographic separation of the ketal alcohol mixture proved to be very difficult and consequently was postponed until after the deketalisation step. Several methods were investigated for removing the ketal protecting group. On small scale, the acetone-p-toluene sulphonic acid procedure used previously looked promising. Unfortunately,

when the reaction was scaled up complications arose and the major products had spectral properties which were consistent with the dimeric compounds (107), or some other form of disguised ketol, i.e. the i.r. spectrum displayed hydroxyl absorption at 3595 and 3420cm^{-1} and no carbonyl absorption, whilst the n.m.r. spectrum indicated that the O-CH_2CH_2O grouping was absent. These spectroscopic conclusions were substantiated by the discovery that the ketols (89) and (95) could be obtained by treatment of the dimers with dilute mineral acid.

Exposure of a solution of the ketal alcohol mixture in chloroform to dilute hydrochloric acid at r.t. also effected the desired deketalisation. Furthermore, brief heating of the ketal alcohol mixture in 75% aqueous acetic acid caused smooth removal of ethylene glycol to give an almost quantitative mixture of the desired ketols (89) and (95) and this proved to be the method of choice. The epimeric ketols were easily separable by preparative t.l.c. and high overall yields of the desired ketol (95) could be obtained by recycling the ketol of natural configuration (89) through the ketalisation, oxidation, reduction and deketalisation procedure. At this point it seems opportune to summarise the most efficient route discovered for converting atisine (4) into the required ketol (95). From atisine (4) the allylic acetate (74) was prepared *via* (69), (70), (71) and (73) as described

before. This compound was smoothly transformed into the keto-acetate (93) by the osmium tetroxide-sodium metaperiodate procedure of Pappo et al.[47] From here, ketalisation with p-toluene sulphonic acid and ethylene glycol in benzene provided the ketal-acetate, ν (C=O)1741cm^{-1} (108), which was readily hydrolysed to the ketal alcohol (104) by sodium carbonate in aqueous methanol at r.t. In an equally effective and sometimes more convenient preparation, the ketal alcohol (104) could be obtained from the ketal-acetate (108) by brief heating in a mixture of aqueous potassium hydroxide and methanol. Finally, the ketol (95) was obtained from the ketal-alcohol (104) by oxidation to (106), sodium borohydride reduction, deketalisation and chromatographic separation.

Now that a satisfactory route to the keto-tosylate (64) had been developed, we could return to the consideration of its rearrangement. In parallel with the foregoing discussion, it was anticipated that the keto-tosylate (64) would rearrange on acetolysis to give a mixture of the keto-olefins (65), perhaps through the intermediacy of the acetate (109) or by direct collapse of an intermediate carbonium ion of the type (110); whereas, the keto-tosylate (96) having the oxygen function at C(15) in the natural β-configuration was expected under similar conditions to afford the keto-olefin (111).

Careful consideration was extended to the effect on this rearrangement of the ketone group at C(16). As explained

previously, it was desirable to have some sort of oxygen function at this position as it would, on rearrangment, give rise to the C(14) oxygen function which always occurs in the aconitines. If the oxygen function was a carbonyl group, then, in the keto-tosylate (64), position C(16) is satisfactorily blocked and therefore, excluding the possibility of a Favorski reaction using the proton at C(12), the only courses of reaction open to the molecule are nucleophilic displacement or rearrangement in the desired sense. In short, the carbonyl would make the rearrangement sought more probable by limiting the number of alternative reaction pathways. In addition, the carbonyl group, by destabilising the build-up of positive charge at C(15), might be expected to induce a concerted, and therefore stereospecific, rearrangement. This is in direct contrast to the participation by the exomethylene group observed in a previous reaction. Furthermore, the carbonyl would be expected to facilitate the recognition of the required product in the reaction mixture. Thus extrapolation from the parent bicyclo[3,2,1] oct-2-ene-8-one system[51] suggested that the carbonyl stretching frequency in the desired product should be in the region of 1760cm.$^{-1}$

On the other hand, the presence of a carbonyl group in this position will undoubtedly retard the rearrangement by inhibiting the rate-determining C-OTs bond cleavage. A similar situation was explored by Gassman and Marshall,[52]

who demonstrated that the keto-tosylate (112) reacted many times slower than its saturated analogue (113). It was also realised that an α-carbonyl group would increase the susceptibility of the adjacent C(15) to nucleophilic attack.[53] However, to be forewarned is to be forearmed, and these two latter difficulties could, in principle, easily be surmounted by adopting the correct reaction conditions.

Unfortunately, contrary to our expectations, acetolysis of either keto-tosylate in buffered acetic acid at 150° gave rise to the same oily product. This was established by comparison of the i.r., g.l.c. and mass spectra. The product, which was obtained almost quantitatively in both cases, exhibited, in addition to the amide band at 1647cm^{-1}, a carbonyl band at 1760cm^{-1} typical of a bicyclo[3,2,1]-octen-8-one system. The presence of the olefinic bond was established by reaction with osmium tetroxide and its tetrasubstituted nature by the absence of vinyl proton absorption in the n.m.r. The mass spectrum indicated a molecular weight of 327 and displayed a prominent ion at 299 (p-28), which is in accord with the proposed bicyclic ketone part-structure. Thus one would expect that facile loss of carbon monoxide from the strained ketone system <u>via</u> a stabilised allylic radical [illustrated (114)→(116)] would be a very favourable process in the mass spectrometer. On the basis of this evidence, the product was assigned the keto-olefin structure (111).

This unexpected result, namely the almost complete conversion of the keto-tosylate (64) into the keto-olefin (111), was not influenced by changes in the solvolytic conditions. Further support for the suggested structure (111) of the keto-olefin comes from the following experimental observations. The keto-olefin (111) reacted very slowly with osmium tetroxide at r.t. This could be understood by examination of a molecular model, which revealed that reaction of osmium tetroxide on the more sterically favoured β-face of the double bond would give rise to a very strained ring system indeed, whereas approach on the α-face would meet with serious interference. The reaction afforded a very small amount of a compound whose t.l.c. behaviour was consistent with a diol and a major product containing a carbonyl (1722cm^{-1}) and a hydroxyl (3600cm^{-1} and a broad band at 3340cm^{-1}). The major product was not further characterised, but was evidently derived from the diol.[54]

The proposed relationship between the olefinic bond and the carbonyl was also supported by the amorphous hydroxyl-olefin (117), obtained on sodium borohydride reduction of the keto-olefin (111). It had been established that sodium borohydride reduction of the parent bicyclo-[3,2,1] oct-2-ene-8-one system afforded almost excusively, the isomer with the hydroxyl <u>syn</u> to the double bond.[55] In agreement with

this, the high dilution i.r. spectrum of the hydroxy-olefin (117) had a hydroxyl absorption band at 3573cm^{-1}, indicating the presence of an intramolecular hydrogen bond between the hydroxyl group and the π-electrons of the double bond.

To establish beyond doubt the existence of a bicyclo-[3,2,1]oct-2-en-8-one system in the rearrangement product, we turned to a reaction reported by Buchanan et. al.[56] These workers observed that, on heating bicyclic compounds of this type in methanol containing concentrated sulphuric acid, addition of methanol to the carbonyl group was followed by a very smooth fragmentation reaction (118)→(119)→(120). However, in our more complex example the major product from prolonged reaction of the keto-olefin (111) with concentrated sulphuric acid in methanol was the dimethoxy-ketal (121) and this result was not changed when the reaction was repeated using aqueous sulphuric acid. The disappearance of the 1760cm^{-1} carbonyl absorption in the i.r. and the appearance of a six proton singlet at 6.78 τ ($-OCH_3$) in the n.m.r. spectrum suggested the dimethoxy-ketal structure and this was substantiated by the regeneration of the keto-olefin (111) on reaction with p-toluene sulphonic acid in acetone. A further attempt to induce the required fragmentation reaction by using a mixture of concentrated hydrochloric acid and glacial acetic acid also failed, the keto-olefin (111) being returned unchanged.

The following procedures served to further characterise the keto-olefin (111) system. The ketal-olefin (122) was obtained by treatment of the keto-olefin (111) with ethylene glycol in benzene, using p-toluene sulphonic acid as a catalyst. This compound was smoothly transformed, on heating with lithium aluminium hydride in tetrahydrofuran, to the ketal amine (123), whose i.r. spectrum lacked the carbonyl absorption at 1647cm^{-1} due to the amide, but exhibited very characteristic Bohlmann Bands[57] at 2745-2795cm^{-1} due to the tertiary amine function. A crystalline derivative was prepared by neutralisation of a solution of this ketal amine (123) in methanol with hydriodic acid. Dilution of the methanolic solution with ether furnished the hydriodide salt (124) (X=I) in the form of small rosettes m.p. 228-232°. This procedure required the utmost care as excess acid caused decomposition of the product *via* deketalisation. By similar means, the hydrobromide (124) (X=Br), m.p. 245° (sub) was obtained.

Having dealt with the evidence for the keto-olefin structure (111), some attention will now be given to the mechanism by which it was formed from both keto-tosylates (64) and (96). One way of explaining the formation of a common product would be to invoke the intervention of a common intermediate. In other words, an explanation could be that both keto-tosylates solvolyse *via* the intermediacy

of the classical carbonium ion (125) and not by a concerted pathway. However, this seemed intuitively unlikely, as the postulated carbonium ion would suffer severe destabilisation from the adjacent carbonyl group. Another explanation which was worthy of consideration was that initially, the solvolyses went as planned i.e. (96)→(111) and (64)→(65), but the products were interconvertible, reverting to the thermodynamically stable keto-olefin (111) under the reaction conditions. However, this was also discarded, as the only apparent mechanism for interconversion involved the intermediacy of the classical carbonium ion (125).

Having discounted these processes, we returned to a consideration of concerted mechanisms which were in accord with accepted stereoelectronic principles. Thus, it was assumed that the keto-tosylate (96) reacted by the concerted pathway discussed previously to give the keto-olefin (111) and that, for reasons discussed later, the rate of this reaction was very much faster than the corresponding (64)→(65) process. Also, it was necessary to suggest that some other process was taking place to invert the configuration of the tosylate function in (64) faster than it could solvolyse to the keto-olefins (65). One possibility might be that the keto-tosylate (64) was undergoing a fast nucleophilic displacement by acetate anion to give the keto-acetate (93), which was then solvolysing by a process similar to the one

envisaged for the keto-tosylate (96). This proposal is in line with the established retarding effect of an α-carbonyl group on an S_N1 reaction and its accelerating effect on an S_N2 process.[58] In order to test its feasibility, the keto-acetate (93), which had been prepared before, was subjected to the acetolysis conditions. On heating at 150° in anhydrous acetic acid containing fused sodium acetate and a little p-toluene sulphonic acid, for 48 hours, the keto-acetate (93) afforded only a very small amount (<10%) of the desired keto-olefin (111). Thus, the pathway from (64)→ (65) involving this keto-acetate as an intermediate could not be the major one. A mixture of the epimeric keto-acetates (93) and (94), in equal amounts by analytical t.l.c., constituted the greater proportion of material (>80%) isolated from the foregoing solvolysis. Hydrolysis of this mixture with sodium carbonate in aqueous methanol, afforded the corresponding ketols (89) and (95), which were readily separated and characterised.

The keto-tosylate rearrangement result may also be explained by a rapid epimerisation of the keto-tosylate (64) to the keto-tosylate (96), followed by solvolysis. If this mechanism is correct, one might be able to detect the postulated intermediate (96). With this aim in view, solvolysis of the keto-tosylate (64) in buffered acetic acid at reflux temperature (~118°) was monitored by with-

drawing aliquots of the reaction mixture after specific periods of time and subjecting them to analytical t.l.c. After 3½ hours had elapsed, the more mobile keto-tosylate (96) was present in the reaction mixture to the extent of 30% and very little reaction to the product keto-olefin had taken place. The keto-tosylate (96) was identified by the presence of bands which were characteristic of this compound (e.g., 968cm^{-1} and 1023cm^{-1}) in the fingerprint region of the i.r. spectrum of the mixture. Furthermore, it was shown that the concentration of the keto-olefin (111) increased with time at the expense of the keto-tosylates.

However, there remained two possible pathways for the epimerisation of (64) into (96). The first involved enolisation to the intermediate (126), which, in view of the symmetry of the bicyclo[2,2,2] octane system, would be expected to collapse with equal probability to either of the epimeric tosylates. Secondly, it is possible to imagine that the keto-tosylate (64) reacts by an S_N1 process to an intimate ion pair[59] (127), which may collapse by inversion to give (96). In the hope of distinguishing between these, the solvolysis of the keto-tosylate (64) was repeated in acetic anhydride and deuterium oxide. If the enolisation mechanism is functioning, then the C(15) proton should be replaced by deuterium to give (128), which should subsequently

rearrange to give the deuterated keto-olefin (129). Unfortunately, when the keto-olefin was isolated from the reaction, it was shown by mass spectroscopy to consist of a mixture of D_0, D_1, D_2 and D_3 species. N.m.r. spectroscopy revealed that some of the deuterium had been incorporated into the acetamido group. The mass spectrum of the deuterated mixture was not amenable to interpretation and thus, the extent to which the deuterium had been incorporated into the desired C(15) position could not be determined. In summary, the formation of the keto-olefin (111) from the keto-tosylate (64) is explained by prior inversion to the keto-tosylate (96), probably via an enol intermediate (126).

However, the question of why the keto-tosylate (96) reacts more readily than the keto-tosylate (64) remains to be answered. Some insight into this may be acquired from the study of a molecular model. The most striking feature in the model, from the steric interaction point of view, and the one which probably causes most distortion to the molecular framework, is the very severe non-bonded interaction between hydrogens attached to C(14) and C(20) [see (130)]. This interaction is similar to that between two methyl groups in a 1,3 diaxial situation in cyclohexane, but it may be a little more unfavourable due to the rigid geometry of the system. Herein may be found the major part of the explanation for the differing reactivities between the

epimeric keto-tosylates. Examination of the proposed transition state for the β-tosylate (78) reveals that, as the C(15)-O bond breaks, the C(8)-C(14) bond begins to interact with the build-up of positive charge at C(15). The result of this interaction is that C(14) moves away from C(20) and so greatly reduces the steric compression between the hydrogens in question. In contrast, relief of steric hindrance of this sort does not occur to the same extent in the reaction of the α-tosylate, whose transition state may be envisaged as in (81).

There are many instances in the chemistry of atisine and its congeners, where this steric interference was thought to provide the driving force for reaction. For example, a simple way in which the C(14)-C(20) hydrogen interaction can be relieved is by the conversion of the C(20) carbon from tetrahedral to trigonal status. Thus it could be anticipated that, whenever possible, C(20) would prefer to be trigonal. This reasoning has been substantiated by the demonstration that refluxing isoatisine diacetate chloride (131) in acetic anhydride results in complete conversion to the atisine salt (132).[60] In a similar fashion, the azomethine (133) was smoothly isomerised, almost quantitatively, on heating in diglyme, into (134).[61] Perhaps the most striking example of the influence of this interaction is to be found in the chemistry of ajaconine. Edwards and Dvornik[62]

showed that the carbinolamine (135), derived from ajaconine, was transformed by methanolic alkali into a mixture of the iso compound (136) and a hydroxy lactam (137). This unusual product results from an intramolecular Cannizzaro-type reaction involving a transannular hydride transfer from C(20) to C(7) [see (138)] and the driving force for the reaction must, to a large extent, be due to the relief of the C(20)-C(14) hydrogen non-bonded interaction. It is interesting to note that in hetisine (5), which co-occurs with atisine in Aconitum heterophyllum, this interaction has been eliminated by bond formation.

Soon after our observations were made, Pelletier and Ichihara[63] described some work, also modelled on the proposed atisane-aconane biogenesis, which provided similar results. They reported that treatment of either of the epimeric alcohols (139) or (140) with phosphorus tribromide afforded a single product, to which the rearranged structure (142) was assigned. Furthermore, this compound was also obtained on solvolysis of the tosylate (141). An analogous rearrangement to the hydroxy-olefin (143) occurred on reacting the epoxide mixture (144) with sulphuric acid. These transformations could be satisfactorily rationalised by invoking the intermediacy of the classical carbonium ion (145), which would collapse with migration of the α-bridge, as a result of the C(20)-C(14) hydrogen

interaction discussed above.

At this point, it was apparent that under normal solvolysis conditions, the desired keto-olefins (65) would not be generated from the keto-tosylate (64). If this rearrangement were to be effected, conditions would have to be devised, wherein the inversion of the C(15) oxygen function is inhibited. Also, it was still desirable from a concertedness viewpoint to retain the C(16) carbonyl function. At the time when we were considering these points, some work appeared in the literature which arrested our attention. Kwart and Hoster[64] observed that a Wagner-Meerwein rearrangement took place on pyrolysis of 2-methyl-2-phenylpropyl acetate (146) to give mainly the unconjugated olefin (147). A further literature survey uncovered several more examples of this phenomenon. One of the first recorded examples of rearrangement during acetate pyrolysis, although this was not realised till some time later,[65] was that of patchouli acetate[66] (148). On heating to 300°, this compound was efficiently transformed, with evolution of acetic acid, to a mixture of the olefins, α-patchoulene (149, endocyclic) and γ-patchoulene (149, exocyclic). This unusual rearrangement undoubtedly occurs in these systems because of the impossibility of the normal 1,2 acetate elimination. Thus, in (146) there are no hydrogens on the carbon adjacent to the one bearing the acetate group and in (148), 1,2

elimination would lead to an anti-Bredt olefin.

In analogy with these, it was realised that our keto-esters contained the necessary features to allow them to undergo this type of pyrolytic rearrangement. Furthermore, it was anticipated that the keto-tosylate (64) might undergo this process more easily than the corresponding acetate (94), due to the weaker nature of the C(15)-O bond in the former compound. Now, if the rearrangement reaction in the keto-tosylate (64) is considered to be unimolecular and synchronous, then, when the C(15)-O bond is breaking, an O-H bond can only be formed with one of the two protons shown in (150). Also as there was no reason to suppose that the usual stereoelectronic requirements would not hold, then the bond which is <u>trans</u> and antiparallel to both the C-H and C-O bonds being ruptured i.e., C(8)-C(9) in (150), should migrate. Thus, at first sight, the products expected from pyrolysis of the keto-tosylate (64) would be the keto olefin (152) when H_A was removed and the keto-olefin (154) when H_B was removed. In like fashion, pyrolysis of the β-tosylate (96) was expected to afford the tetrasubstituted keto-olefin (111) and perhaps a small amount of the trisubstituted keto-olefin (155).

Some initial evaluation of the pyrolysis of the keto-tosylates (64) and (96) was done by effecting the reaction on a g.l.c column. This procedure was very convenient, as

reaction and product analysis were accomplished in one step. Thus a solution of the keto-tosylates (64) and (96) in chloroform was injected on to a 5% SE30 stationary phase at 225° and the resultant g.l.c traces are shown in figures (1) and (2), respectively. The most important result obtainable from these traces was that, in contrast to solvolysis, pyrolysis of the epimeric tosylates gave rise to different products. The main product derived from the β-epimer (96) was the expected keto-olefin (111) (retention time 1.86 relative to hexacosane). The ∝-epimer (64) provided four products, of which two, of retention times 2.18 and 2.06 relative to hexacosane, displayed g.l.c. properties, which were expected of either of the desired compounds (152) or (154). The appearance of a substantial amount of the keto-olefin (111) in this mixture seemed to indicate that the g.l.c. packing was taking some part in the reaction. However, this procedure served well in indicating that compounds of the desired retention times i.e., 2.18 and 2.06 were being formed and the following experiments were designed to maximise the yields of these materials and characterise them.

Extrapolation of the keto-tosylate (64) pyrolysis to g.c.m.s. provided mass spectra which were unsatisfactory and served only to establish that the molecular weight of all four products was 327. i.e., (corresponding to a loss

of p-toluene sulphonic acid). No reaction took place on heating the finely divided keto-tosylate (64) in an evacuated sealed tube at temperatures up to 180°. Unfortunately at higher temperatures a dark, chloroform insoluble, resin was formed, whose i.r. spectrum indicated that the acetamide (1646cm^{-1}) had disappeared. A little more success was achieved when the keto-tosylate (64) was adsorbed on to a discarded g.l.c packing and heated *in vacuo* at 300°. Under these conditions approximately 10% of the desired material (retention time 2.18) was observed by g.l.c. However, again the major product (50%; r.r.t.0.63) did not contain an acetamido group and the keto-olefin (111) formed the remaining 40% of product. In an effort to reduce the time during which the products had to endure the high temperatures involved, the reaction was repeated in a sublimation tube. Thus the tube containing the finely divided keto-tosylate (64), *in vacuo*, was plunged into the heating block set at 300°. In a very short time, the products of pyrolysis had distilled out and were subjected to analysis by t.l.c, g.l.c and i.r. This revealed that 50% of the keto-tosylate had not reacted, and more encouragingly, that the reacted material contained the desired product (r.r.t 2.18 and 2.06) and the keto-olefin (111)(r.r.t 1.86) in the proportions of (33%) and (49%), respectively, by g.l.c.

As these solid phase pyrolyses did not produce the

required material in yields which were acceptable, recourse was made to solution pyrolysis. Prolonged reflux of a solution of the keto-tosylate (64) in collidine did not induce any reaction. Unfortunately, at higher temperatures (300°), this solution provided a very complex mixture of products.

By far the best results were obtained by gas-phase pyrolysis (thermolysis) (diagram of set-up in experimental), in which the products experienced a very short time indeed in the hot zone. Thus pyrolysis of the keto-tosylate (64) in a gas phase, flow system at a temperature of approximately 500° and pressure of 0.5mm. furnished material (r.r.t. 2.12), which was later shown to be the keto-olefin (154), [perhaps containing a little of the isomeric (152)] in a yield of 77% as estimated by g.l.c. [The effective yield is probably even greater than the g.l.c.-estimated yield because the small amount of keto-olefin (111) (10%) recorded is almost certainly derived from unchanged tosylate, which reacted on g.l.c. Separation of the products from unreacted keto-tosylate by preparative t.l.c was very difficult and was complicated by the instability of the keto-olefin (154).]

The reaction was repeated on a preparative scale and it proved possible by careful t.l.c., on ammoniacal silver nitrate coated chromatoplates, to isolate material consisting mainly of the keto-olefin (154). This structure was supported by i.r. (1760cm^{-1} due to the carbonyl in the bicyclo [3,2,1]-

octene system), n.m.r (τ=4.80, multiplet due to the vinyl proton) and mass spectroscopy (molecular weight 327). G.l.c. analysis indicated that there were two minor contaminants present, of which one might have been the isomer (152). However, the authenticity of this is open to question as these impurities may have been derived from the very unstable keto-olefin (154). The spectral data were also consistent with the structure (155), but this possibility was eliminated as treatment of the keto-olefin, isolated by preparative t.l.c. from the pyrolysis, with gaseous hydrogen chloride in chloroform, failed to produce any of the tetrasubstituted isomer (111).

It was felt that the unstable nature of the keto-olefin (154) arose from the bicyclo [3,2,1] octenone system and thus some experiments were directed to forming a derivative, which was both stable and easily separable from the rest of the pyrolysate. Sodium borohydride reduction, (expected to afford the epimer with the hydroxyl <u>syn</u> to the olefin[51]), of the crude pyrolysate provided a mixture of compounds, which was not readily amenable to separation and, furthermore, acetylation of this mixture did not improve matters. The derivative of choice proved to be the oily ethylene ketal (156), which was prepared by treatment of the crude pyrolysate with dry ethylene glycol in benzene, using p-toluene sulphonic acid as a catalyst. This compound exhibited the desired stability and could be conveniently separated from the pyrolysate by a combination

of t.l.c over untreated and ammoniacal silver nitrate "Kieselgel". The physical data were in accord with the proposed structure, the most significant features being the loss of the 1760cm^{-1} carbonyl absorption, a four proton singlet ($-OC\underline{H}_2C\underline{H}_2O$) at τ=6.02, a one proton multiplet (vinyl hydrogen) at τ=4.75 and molecular weight 371 by mass spectoscopy. The fraction of the crude pyrolysate, which had been reduced with sodium borohydride was easily reconverted into the carbonyl form by Sarett oxidation.

For clarity the result of subsequent work namely, that the keto-olefin (154) was formed almost exclusively in the gas-phase pyrolysis of (64), has been used in the foregoing discussion. Now, the chronological order of events will be restored. At this point in the synthesis, it was not clear whether a mixture of the isomeric keto-olefins (152) and (154) had been formed in the pyrolysis. Furthermore, if there was a mixture, to what extent had it been modified by ketalisation? Some work was undertaken to resolve these problems, as a knowledge of the position of the double bond was important for the formation of a C(7)-C(20) bond later in the synthesis. Partial deketalisation of the ketalised product (156 and/or 157) afforded a keto-olefin (152 and/or 153), which remained homogeneous after extensive g.l.c. investigation.

Having failed to effect any separation with the olefins, recourse was made to examination of derivatives of the

olefins. Treatment of the ketal-olefin (156 and/or 157) with lithium aluminium hydride in tetrahydrofuran, afforded in high yield the corresponding amino-ketal (158 and/or 159), (no 1646cm^{-1} absorption due to acetamide; Bohlmann bands 2755-2800cm^{-1}; τ=9.00, three proton triplet, J_{AX}=7Hz, $C\underline{H}_3C\underline{H}_2$; τ=4.79, one proton multiplet, vinyl hydrogen; molecular weight 357 by m.s.), which was also homogeneous on t.l.c and g.l.c. Attempted hydroboration of this amino-ketal to the amino-alcohol (160 and/or 161) failed and only material whose i.r. spectrum indicated that it was non-hydroxylic was obtained. The steric situation of the olefinic bond (in both isomers) is such that cis - addition can only occur from the β-face, and therefore, the usual complication of cis α and cis β derivatives could be neglected. The ketal-olefin (156 and/or 157) underwent osmylation with osmium tetroxide in ether, containing a little pyridine, to the diol (162 and/or 163), (hydroxyl absorption at 3533 and 3468cm^{-1}), which could not be resolved into more than one spot by t.l.c. An examination of the molecular models of the keto-diols (164) and (165) revealed that there was a possibility of hydrogen-bonding between the secondary hydroxyl in (164) and the carbonyl, whereas this was impossible in (165). Consequently, it was anticipated that high dilution i.r. studies on the product from deketalisation of the diol (162 and/or 163) might shed some light on the isomeric composition. Unfortunately, this

avenue could not be explored, as deketalisation provided only material containing carbonyl absorption at 1730cm^{-1}, which was probably derived from further reaction of the keto-diol (164 and/or 165). Subsequently, it was discovered that attempts to prepare the parent system (167) had also failed, probably due to a facile retroaldol reaction.[67] Finally, oxidation of the diol (162 and/or 163) with sodium meta-periodate in aqueous dioxan resulted in a complex mixture of products, from which no conclusions on the possibility of isomeric olefins could be formed. These investigations provided no evidence for the formation of a mixture of olefins, either in the pyrolysis or ketalisation reactions. Thus we were led to believe that pyrolysis gave rise to essentially a single keto-olefin, which was formulated as (154) on the basis of mechanistic and stereochemical argue- discussed later.

Before moving on to the second stage, namely the C(7)-C(20)bond formation stage, of our synthesis, it was thought advisable to obtain some concrete evidence on the keto-olefin structure (154). The complexity of the system and, more importantly, the amount of the material available, left us little choice but to resort to X-ray crystallography. Furthermore, the abundance of functionality in the molecule suggested that the preparation of a suitable crystalline derivative would not be too difficult. As luck would have

it, the first derivative, the p-iodobenzoate (168)[ν(OH), 3485cm^{-1} and ν(C=O) benzoate 1714cm^{-1}] which was readily prepared by treatment of the diol (162) with p-iodobenzoyl chloride in anhydrous pyridine, turned out to be amorphous. Various attempts to crystallise the octahedral osmate complexes (169) (R=pyridine and R=β-picoline), obtainable by reaction of the ketal olefin (156) with osmium tetroxide in the presence of the appropriate base,[68] failed to produce material of the desired crystalline form. Finally, careful neutralisation of the amino-ketal (158) with dilute hydriodic and hydrobromic acids afforded the beautifully crystalline salts (170a) and (b), respectively. Slow recrystallisation of the hydriodide (170a) from methanol - ether gave small rods, m.p. 240-243.5° and these were used in the X-ray analysis (described later), which confirmed the structure and stereochemistry (154) assigned to the keto-olefin, mainly from spectroscopic information and mechanistic arguements.

Gas phase pyrolysis of the β-epimer (96) provided, in high yield, the expected keto-olefin (111), whose identity with material obtained in the solvolyses was established by g.l.c., t.l.c and spectroscopic comparison. It was further anticipated that the keto-acetates (93) and (94), prepared by acetylation of the respective ketols (89) and (95), would react on pyrolysis in a similar fashion to the keto-tosylates. However, when subjected to the keto-tosylate pyrolysis

conditions (500° and 0.5mm) the keto-acetates did not react, and this may reflect the stronger nature of the C(15)-OAc bond.

We shall now return to a consideration of the mechanism of this unusual pyrolytic rearrangement. In 1961, Bunton et. al.[69] suggested that a seven membered cyclic transition state (171), in which breaking of a C-H bond is synchronous with the migration of C-C bond electrons and separation of the leaving group, would account for the formation of camphene (172) of high optical purity, from the pyrolysis of isobornyl methyl xanthate. These workers stressed the analogy between solvolysis and pyrolysis reactions of this very special system, but did not establish whether their proposed seven membered transition state was charge-separated, homolytic or carbene in nature. Some time later, Kwart and Hoster[64] considered two mechanisms in order to explain the pyrolytic rearrangement of 2-methyl-2-phenylpropyl acetate (146). These were, firstly, a two step sequence *via* the ion-pair (173) and, secondly, a completely concerted process (174). The former mechanism was rejected on the grounds that a predominance of the more stable conjugated isomer (175) should result from the collapse of the ion-pair (173). However, an excess of the unconjugated isomer (147) was observed and they explained the presence of the conjugated isomer (175) by subsequent thermal isomerisation of (147). They concluded that their results were best

rationalised by the seven membered concerted mechanism (174) and favoured a process in which each of the bonds was broken homolytically.

The mechanism which we envisaged to explain our pyrolytic rearrangements, is somewhere between the ion-pair and concerted homolytic processes of Kwart and Hoster and is analogous to that proposed by Depuy and King,[70] and later by Smith et. al.,[71] to account for the effects of substituents on the reaction rate in the normal 1,2 elimination acetate pyrolysis reaction. The elimination of p-toluene-sulphonic acid takes place via an essentially synchronous mechanism, with some charge separation resulting in the formation of a partial carbonium ion at C(15). The transition state for the β-keto-tosylate (96) is shown in (176). The suggestion is that heterolytic C(15)-O bond cleavage is of primary importance and thus the strength of this bond determines the ease of reaction. The charge build-up at C(15) is stabilised by interaction with the C(8)-C(14) bond (in 176) and the C(9)-H and the C(8)-C(14) bonds are ruptured as the C(15)-O bond undergoes heterolysis. Thus, the proposed mechanism is similar to a carbonium ion reaction and should display similar substituent effects. The synchronous mechanism is in accord with the stereospecific nature of the reaction and the arrangement of atoms, i.e. the C-O and C-H bonds are parallel and antiperiplanar to the migrating C-C bond, shown in (176) has been observed in the few known cases,

namely patchouli acetate and isobornyl xanthate, and is probably optimal.

A similar seven membered transition state may be formed with C(7)-H_B (176), leading to the trisubstituted olefin (155). In the proposed concerted transition state the strength of the breaking C-H bond should influence the rate of the reaction, although to a smaller extent than the C-O bond strength. The tertiary C(9)-H bond would be expected to be weaker than the secondary C(7)-H bond and this would explain why the olefin (155) was not observed in the pyrolysis. Alternatively, (155) may have been formed, but subsequently isomerised to (111) under the reaction conditions.

By extrapolation, the transition states for the pyrolysis of the α-keto-tosylate (64), may be drawn as (177) and (178), leading to the keto-olefins (152) and (154) respectively. Herein may be found the reason for the observation of only one of the possible keto-olefins, (154), in the pyrolysis reaction. Careful examination of the transition state (177) reveals that it leads, in a concerted fashion, not to the stable cycloheptene ring B containing a <u>cis</u> double bond, but to a cycloheptene containing a <u>trans</u> double bond. The highly strained nature of the <u>trans</u>-olefin means that the process leading to it will be of a very high energy relative to the process leading to the other isomer (154) and thus only the formation of the latter is to be expected from the keto-

tosylate (64). The stereoelectronic requirements of the concerted process leading to the cis olefin (152) may be satisfied, [as shown in (179)], when ring B adopts a boat conformation. However, for well established reasons, this boat conformer will be of a substantially higher energy than the corresponding chair conformer, and therefore, again, the transition state will be destabilised relative to (178).

The stereospecific nature of the foregoing pyrolysis reactions establishes beyond doubt, that the configuration of the C(15) hydroxyl group in atisine (4) is β. As has been previously pointed out, the stereochemical assignment of this hydroxyl was made difficult by the inherent symmetry of the bicyclo[2,2,2] octane system. Pelletier[72] and Whalley[73] favoured the β-orientation in atisine, because this compound was less strongly adsorbed on alumina than its C(15) epimer. They assumed that the epimer containing the hydroxyl and acetamido functions on the same side of the molecule would be more strongly retained by alumina. This arguement is tenuous because of conflicting views on the nature of the adsorption process. A further tentative assignment, also β, was made by Edwards,[74] on the basis that the compound (180) derived from ajaconine, [same C(15) hydroxyl configuration as atisine] failed to form a benzylidene ketal. Unfortunately, the C(15) epimeric compound was not prepared for comparison.

The synthesis of the ring B/C-7/5 system, as in compound (156),

marked the completion of our first synthetic goal. Now our attention was devoted to the second, and final, stage, which was the conversion of our key intermediate (156) into an aconane-type skeleton, by formation of a bond between C(7) and C(20). As has been explained in the introduction, this part of the synthesis has received attention from previous workers, who demonstrated its feasibility in a system of a similar nature to ours. At this point, it may be opportune to briefly restate the substance of this earlier work and to describe some later observations, which, when considered together, will illustrate the chemical reactivity of the of the C(7)-C(20) bond.

The early work by Büchi[75] and subsequently Edwards, centred around an unusually mild acetate pyrolysis reaction, which was characteristic of aconitines containing a C(8) acetate group. For example, on heating to approximately 200°, neoline (181) was smoothly transformed into pyroneoline (182) by by elimination of acetic acid. This reaction, which afforded a number of "pyro" compounds, was originally regarded as a straightforward 1,2 cis elimination, despite the strained nature of the resultant double bond. In an attempt to explain the facile nature of the pyrolysis, the fore-named workers invoked a two-step mechanism, shown in the part structures (183)→(184)→(185). Both groups of workers verified their postulates by isolating an "open" C(7)-C(20) bond ruptured,

intermediate of the type (186). They further demonstrated that this compound, on reoxidation spontaneously cyclised to the "pyro" derivative (185) *via* the intermediacy of (184). Furthermore, Edwards considered that this type of mechanism could also account for the ready replacement of the C(8) acetoxy-group by a methoxy group, when bikhaconitine (32), for example, is heated in methanol at 130°.

A distinguishing feature has been noted in the ultra-violet spectra of these "pyro" compounds,[76] *viz*., they all display an absorption maximum at approximately 235-245nm., which disappears on acidification. Wiesner *et. al*.,[76] proposed that this band originated in a chromophore, which consisted of the nitrogen lone pair, the C(7)-C(20) sigma bond and the π-electron pair of the C(8)-C(15) double bond and arose on electronic excitation of the normal system (185) to the charge transfer complex (187). (Part structures are used for ease of illustration). Some time later Cookson *et. al*.[77] expressed the same thoughts in a paper entitled "σ-coupled π-electron systems" and documented some further examples. Very recently, Wiesner *et. al*.,[78] provided some convincing experimental support for their postulates in the form of a photoreduction product (188). They reasoned that if the excited state of desmethoxy pyrodelphonine (189) resembled (187), then it should be amenable to reductive trapping. In the event, it was found that (188) could be obtained in high yield by irradiating

(189) in the presence of sodium borohydride. A molecular orbital interpretation of Wiesner's excited state is shown in part structure (190) and illustrates the steric situation in which the π-system of the imino [C(20)-N] group interacts with the allylic anion system C(8)-C(9)-C(15). The foregoing work clearly demonstrates the special chemical nature of the C(7)-C(20) bond and, furthermore, shows that it may easily be formed from a precursor such as (186).

In parallel with this work and the previously discussed biogenetic postulates, the plan for the final stages in our synthesis are outlined in structures (191)→(194). Fundamentally, to accomplish our aims two operations were necessary; (a) conversion of the C(20)-N bond to the required oxidation level and (b) isomerisation of the C(8)-C(15) double bond to the C(7)-C(8) position. That the oxidation step should precede the isomerisation became apparent from a consideration of the relative stabilities of the olefin isomers (191) and (195) (R = Ac). It has been demonstrated experimentally that (191) was thermodynamically very much more stable than (195). Thus, the tosylate pyrolysis reaction produced (191) almost exclusively and vigorous acid treatment, viz. in the ketalisation step, failed to isomerise it into (195) in detectable amount. The reasons for the greater thermodynamic stability of (191) have been discussed fully in the X-ray section of this thesis. One of the major factors in the destabilisation of

(195) is the non-bonded interaction of the C(7)-C(8) double bond with the syn hydrogen attached to C(20). Therefore, it could be anticipated that, if this interaction could be removed by oxidation of the C(20)-N bond to an imino function, then the olefin isomerisation would be facilitated. Our initial task thus became the conversion of (191) (R = Ac) to a compound of the type (196), whose further transformation to the required aconitine skeleton (193) would be assured, providing an equilibrium between (196) and (192) could be established. Because of the spontaneity of the closure reaction (192) ⟶ (193), the equilibrium between (196) and (192) need only produce the tiniest amount of (192) to catalyse the reaction (196)→(193).

Our approach to the oxidation of the C(20)-N bond took two main forms. Thus, either one could oxidise an intermediate of the secondary amine form (191) (R = H), which presented two sites of attack to the oxidant with the probable production of two imino isomers, C(20)-N and C(19)-N, or one could use the more easily obtainable tertiary amine (191) (R = Et), which could conceivably result in three imino isomers. The secondary amine route appeared to offer least complication in the oxidation step and this was borne out by some model experiments. [Extensive use was made of model compounds at this stage to conserve valuable material]. Treatment of the secondary amine acetate (73), whose preparation was described

previously, with Sarett reagent, afforded in high yield the imine (71), which was identical with material prepared by the route described at the beginning of the synthesis. This imine underwent facile methylation on reaction with methyl iodide in acetone at r.t., to produce the crystalline methiodide (197). No difficulties in the extrapolation of these mild procedures to the secondary amine (191)(R = H) were foreseen and the use of ethyl iodide should provide, after separation of the imino isomers, some (196).

Unfortunately, this route to the aconitines *via* the secondary amine (191) (R = H) was blocked by difficulties encountered in the hydrolysis step (191) (R = Ac)→(191) (R = H). Although a variety of hydrolysis methods were attempted no success was achieved. For example, even prolonged treatment of the acetamide (74) [model for (191;R = Ac)] with strong base under forcing conditions, *viz*. potassium hydroxide/hydrazine hydrate in ethylene glycol, produced a mixture of compounds, containing only a very little secondary amine. When subjected to the more sophisticated Meerwein hydrolysis procedure,[80] using triethyloxonium fluoroborate in methylene chloride followed by stirring in dilute acid, only deketalisation of the acetamide (191) (R = Ac) resulted. We did not discover whether our lack of success in this method was attributable to failure to form the intermediate imino-ether (198) or to the hydrolysis of this intermediate returning the acetamide.

Perhaps significantly, the hydrolysis step was carried out under different pH conditions without affecting the result. Brown[81] reported success in converting tertiary amides to aldehydes and secondary amines, by partial reduction with complex aluminium hydrides. Several attempts to cleave the model amide (68) to the corresponding secondary amine (199), using either lithium di- or triethoxy aluminium hydride, conveniently prepared by the action of dry ethanol or ethyl acetate on lithium aluminium hydride, failed and resulted in either no reduction, or complete reduction to the ethyl amine.

Concurrently, attempts were being made to synthesise the iminium salt (196), by direct oxidation of the tertiary amine (191; R = Et). Treatment of the latter compound with mercuric acetate in anhydrous acetic acid (necessary to avoid deketalisation) at 50°, provided two products, in addition to a little starting amine. The major component, (86% by g.l.c), was shown to be identical with the acetamide (191; R = Ac) by m.s., i.r., t.l.c. and g.l.c. and a scheme for its derivation by over-oxidation of the tertiary amine (191; R = Et) is illustrated in the structures (200)→(204). Due to shortage of material and separation difficulties, the study of the minor component was confined to g.c.m.s. Unfortunately, the mass spectrum of this compound did not correspond in molecular weight to either of the desired possibilities, (193; R = Et; MW = 355) or (194; R = Et; MW = 415), the highest peak being

of m/e 357. A little further information about this material was derived from the N-bromosuccinimide oxidation discussed below and this will be contributed in the appropriate section.

In some pilot scale mercuric acetate oxidations, the supposedly initially formed "acetate salts" (205) were extracted and heated in dimethyl sulphoxide[82], in an effort to induce equilibration between the various double bond isomers and push the reaction towards the thermodynamically stable C(7)-C(20) bonded compound (193; R = Et). However, the product distribution was not appreciably affected by this, or indeed any other slight changes in the reaction conditions. The main conclusion drawn from the reaction was that, as feared, oxidation occurred preferentially at the side chain methylene, instead of at the desired C(20) methylene.

In a second, small scale, attempt to synthesise the iminium salt (196), a solution of the tertiary amine (191;R = Et), in benzene, was reacted for a short period at r.t. with N-bromosuccinimide. Again, the three main products, as detected by g.l.c., seemed invariant to minor changes in the reaction and work-up conditions. Despite the small quantity of material, a fair amount of information was gleaned from the g.l.c., g.c.m.s. and i.r. properties of the mixture. The major component, (59%; R.R.T. = 3.75), had molecular weight 371 and contained a carbonyl band at 1643cm.$^{-1}$ Also, this compound was shown, by comparative g.l.c., to be different from the acetamide (191;

R = Ac) and it was slowly reduced by lithium aluminium hydride to the starting tertiary amine (191; R = Et). Either of the lactams, (206) or (207), seemed best suited to the above data. Unfortunately, the unstable nature of the second component of the mixture (7% R.R.T. = 2.63) precluded its identification.

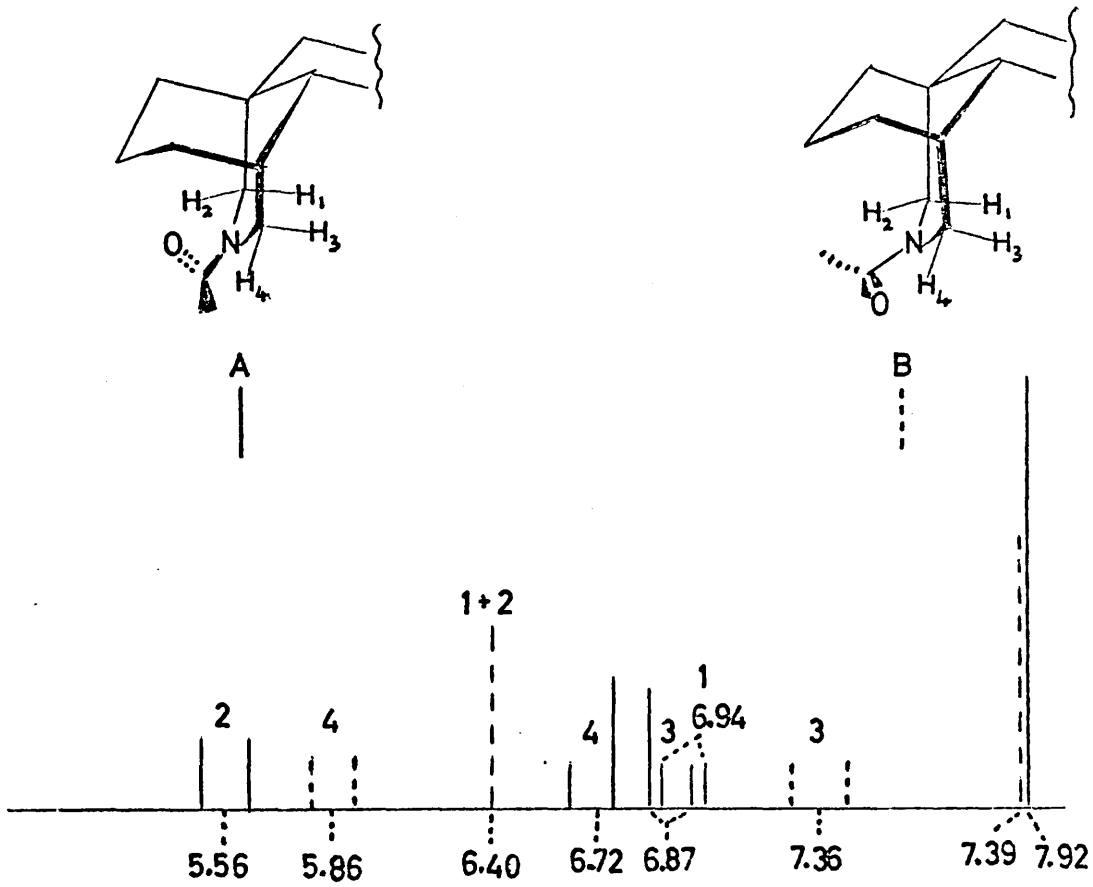
From the aconane synthesis point of view, the third product (29%; R.R.T. = 2.06) proved to be the most interesting one. This material was almost identical by g.l.c. and m.s. to the minor product from the mercuric acetate oxidation and reverted readily to the starting tertiary amine (191; R = Et), on lithium aluminium hydride reduction. Now, we had previously shown, by high resolution mass spectroscopy, that the fragmentation pattern of the compounds (191; R = Et and R = Ac) and (206) or (207), was dominated in the more easily interpretable, higher m/e regions by an anomalous ketal cleavage, illustrated in (208)→(210). Interestingly, this ketal breakdown pattern was not evident in the mass spectrum of the third oxidation product. The result of the action of lithium aluminium hydride on this latter component suggests that the ketal group is intact and thus, it appears that the mercuric acetate or N-bromosuccinimide has converted the amine part of the molecule into a functionality, which directs the fragmentation of the molecule on electron impact. From a consideration of the mechanisms of the oxidation reactions and a knowledge of mechanistic mass spectroscopy, it would seem likely that the

compound in question has the carbinolamine structure, (211) or (212). This means, in effect, that, in the mass spectrum of the carbinolamine, the peak at highest m/e i.e., 357 is not the molecular ion. Only by an assumption of this nature can all of the evidence be reconciled.

Limitations of time and, perhaps more critically material, halted the synthesis at this stage. There were indications that N-bromosuccinimide was oxidising the tertiary amine (191; R = Et) in the desired C(20) position, albeit to a small extent. It was realised that, under the very mild conditions of the reaction, isomerisation of the C(8)-C(15) double bond to the C(8)-C(9) position was improbable and, in consequence so was the formation of the C(7)-C(20) bond during the reaction. However, should the carbinolamine (211) have been formed, then it may be predicted, that it would be readily converted into the aconane compound (193; R = Et), by heating in the presence of a double bond isomerisation catalyst.

In retrospect, the best synthetic approach to the C(7)-C(20) bond formation was indisputably <u>via</u> the intermediacy of the secondary amine (191; R = H) and this compound might have been easily obtained had more consideration been extended to the choice of amine protecting group in the early stages of the synthesis.

FIGURE (5).



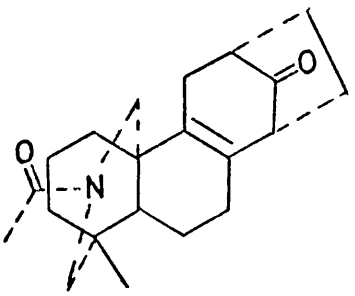
RESTRICTED ROTATION ABOUT THE C-N BOND IN AMIDES.

Nuclear magnetic resonance studies have revealed a very interesting case of restricted rotation around the $-\overset{O}{\overset{\|}{C}}-\overset{}{N}<$ bond in the acetamide (68) and in each of its synthetic congeners, including the rearranged acetamides (111) and (154). This effect is apparent in the room temperature n.m.r. spectra of these compounds, all of which display a complexity of peaks in the τ = 5-7 region and, sometimes, a doublet for the $CH_3\overset{O}{\overset{\|}{C}}-\overset{}{N}<$ protons.

Hindered rotation in amides has been widely studied[83] and the barrier to internal rotation has generally been ascribed to partial double bond character in the $\overset{O}{\overset{\|}{C}}-N<$ bond. This gives rise to two conformers, for example (A) and (B) in figure (5), and the recorded spectrum contains a superposition of resonances from both conformers. The regions of interest in the room temperature spectrum of the acetamide (68), viz., the peaks due to $-CH_2NCH_2-$ and $CH_3\overset{O}{\overset{\|}{C}}N$, are reproduced in figure (5). Double irradiation and integration enabled us to disentangle the resonances belonging to the conformers (A) and (B), (continuous and dotted lines), although which peaks belonged to which conformer could not be decided on the basis of this spectrum alone.

Protons which are near the oxygen atom e.g., H_1 and H_2 in (A), are strongly perturbed by the magnetic anisotropy

FIGURE (6).



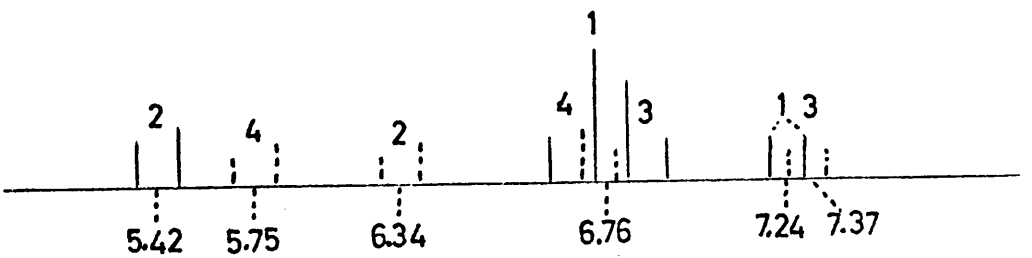
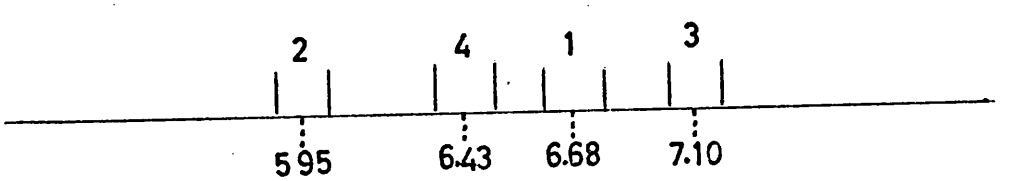


FIGURE (7).



of the amide function, whilst the chemical shifts of protons furthest from the oxygen atom e.g. H_3 and H_4 in (A), are not affected to any great extent. Furthermore, of the protons H_1 and H_2 in (A), the one in the plane of the amide group, H_2, will be strongly deshielded,[84] whilst the axial proton, H_1, will be shielded to a small degree. Thus, each conformer may be expected to contain an AX system for the protons nearest the oxygen atom and an AB, or perhaps an A_2, system for the protons furthest away from the oxygen atom. Indeed, consideration of figure (5) reveals an AX system (5.56 and 6.94τ) and an AB system (6.72 and 6.87τ) for the conformer which occurs in largest amount (65%), whereas the other conformer (35%) gives rise to an AX system (5.86 and 7.36τ) and an A_2 system (6.40τ). The coupling constant J_{AX} or J_{AB} is 14Hz. This spectrum also contained separate resonances (7.89 and 7.92τ) for the $CH_3C(=O)N$ protons in each conformer.

The problem of deciding which conformer belonged to which set of peaks in figure (5), was solved by comparison with the spectrum of the rearranged acetamide (111), figure (6). In this compound, only the chemical shifts of the protons H_1 and H_2 [figure (5)] should be appreciably influenced by the C(8)-C(9) double bond. Proton H_1, in particular, falls in the shielding zone of this olefinic bond[85] and is thus easily assigned by its large upfield shift in the spectrum of (111) i.e. 6.40→6.76τ and 6.94→7.24τ. This information coupled

with double irradiation experiments and a knowledge of the magnetic anisotropy of the amide function discussed before, enabled us to assign the spectrum in dotted lines [figure (5)] to conformer B and also each resonance to a particular proton.

Some variable temperature studies were pursued in order to estimate the magnitude of the barrier to rotation. On raising the temperature of a tetrachloroethane solution of the acetamide (68), the resonances for the $-CH_2NCH_2-$ protons began to broaden and finally collapsed completely at 115°. On further heating, a new series of peaks began to appear in the τ = 5-7 region of the spectrum. At 160°, full construction of the new spectrum had been achieved and it was noticably much less complex than the original [see figure (7)]. At this temperature, interconversion of the conformers (A) and (B) is so fast, that the spectrometer can only record an average chemical shift for each of the relevant protons. This averaged spectrum, [figure (7)], consists of the two expected AX systems and the proton assignments were checked by double irradiation. Furthermore, at temperatures above 100°, a singlet was observed for the $CH_3C(=O)N$ protons.

As far as determining the barrier to rotation around the $O=C-N$ bond was concerned, the intermediate temperatures were of importance. At 80°, the resonances for the $CH_3C(=O)N$ protons in the separate conformers just coalesced and using this temperature and the room temperature separation of the peaks, (4Hz),

a very crude barrier of 19Kcals.was derived.[86] It is emphasised that this calculation is of a very approximate nature. However, the result obtained is in excellent agreement with the very accurate value, 18.2K.cals, derived for dimethylacetamide.[87]

More than a year after the completion of this work, Pelletier[88] also reported restricted rotation in the acetamide (68). However, he made no attempt to interpret the $-CH_2NCH_2-$ region of the spectrum and thereby, overlooked the existence of this phenomenon in the rearranged compound (111).

GENERAL EXPERIMENTAL

All melting points (m.p.) were determined on a Kofler hot-stage apparatus and are uncorrected.

Ultra-violet (u.v.) spectra were measured using a Unicam S.P. 800 spectrophotometer.

Routine infra-red (i.r.) spectra were recorded, in carbon tetrachloride solution, on a Perkin-Elmer 237 spectrophotometer and high resolution spectra were obtained using a Unicam S.P. 100 double-beam spectrophotometer, equipped with an S.P.130 sodium chloride prism-grating double monochromator operated under vacuum, or a Perkin-Elmer 225 instrument.

Proton magnetic resonance (n.m.r.) spectra were measured in deuterochloroform solution on a Perkin-Elmer R.10, a Varian T.60, or a Varian H.A.100 spectrometer, with tetramethyl silane as an internal reference. The Varian 100M.Hz. instrument was used in those cases in which spin decoupling or temperature variation was employed.

Mass spectra (m.s.) were routinely determined on G.E.C.-A.E.I. M.S.9 or M.S.12 spectrometers, whilst mixtures were normally examined by means of an L.K.B.9000 gas-liquid chromatograph-mass spectrometer (g.c.m.s.).

Chloroform solutions were used for optical rotation measurements, which were determined on a Hilger-Watts photoelectric polarimeter.

"Woelm" alumina, deactivated to the appropriate Brockmann grade, was used for column chromatography. Thin (0.25mm.) and thick (0.50mm.) layer chromatoplates were prepared from Merck "Kieselgel G" and detection was achieved by means of ceric ammonium sulphate, iodine or water.

Analytical gas-liquid chromatography (g.l.c.) was performed on a Pye-Argon or a Perkin-Elmer F.11 chromatograph.

Where necessary, solvents were purified and dried in the recommended manner and reagents were either distilled or recrystallised.

Light petroleum refers to the fraction of b.p.60-80°.

All organic extracts were dried over anhydrous sodium sulphate.

Only the major i.r. and n.m.r. absorptions or peaks of diagnostic value are reported in the experimental section.

EXPERIMENTAL

ATISINE (4).

Methanol extraction of the finely ground root of Aconitum Heterophyllum according to Edwards[89], afforded atisine (4), as a light brown oil. Colourless needles m.p. 310-311°, $[\alpha]_D$ = +24° (c = 0.86 in H_2O); lit. $[\alpha]_D$ = +28° (c = 1.6 in H_2O), were obtained on recrystallisation of the hydrochloride from methanol-ether.

ATISINIUM CHLORIDE DIACETATE (69).

A suspension of atisinium chloride (3g; 0.0079moles) in acetic anhydride (12mls) and acetic acid (2mls) was refluxed for 30mins. The solution was cooled, evaporated in.vacuo. to a small volume and repeatedly azeotroped with methanol-benzene, until free from acetic acid. The resultant pinkish diacetate (3.3g; 90%) afforded pure atisinium chloride diacetate (69) as needles, m.p. 240-243° (lit. value, 243.5-245°), on recrystallisation from methanol-acetone.

AZOMETHINE ACETATE (71).

Ice-cold aqueous potassium hydroxide solution (14ml of 40%) was added to a vigorously agitated, ice-cold, emulsion of chloroform (10ml), atisinium diacetate hydrochloride (69) (3g; 0.0065moles) and water (8ml) and the agitation was

continued for 2mins. The layers were separated and the aqueous layer was thoroughly extracted with chloroform. The combined chloroform extracts were refluxed for 45mins., during which a strong odour of acetaldehyde was apparent, and then the solvent was removed *in.vacuo*. The dark residue was redissolved in chloroform, washed with 4N sodium carbonate solution, water and dried. Evaporation of the chloroform *in. vacuo*. yielded the crude azomethine acetate (71), (2·1g;74%), as a semi-crystalline mass, which was subjected to sodium borohydride reduction without further purification.

AMINE ACETATE (73).

Sodium borohydride (2·5g) was added to a solution of the azomethine acetate (71) (2.8g; 0.0082moles) in methanol (50mls), with cooling, and the resultant solution was allowed to stand at r.t. for 5hrs. The methanolic solution was reduced to low bulk *in.vacuo*. and then partitioned between water and chloroform. The organic layer was washed and dried as usual and evaporation *in.vacuo*. afforded the crude amine acetate (73) (2.3g), as a yellowish crystalline mass. Repeated crystallisation of a sample from ether yielded pure material, as prisms, m.p. 167-168°. (lit. 168-169°).

AMIDE ACETATE (74).

A solution of the amine acetate (73) (2.5g; 0.0073moles) in dry pyridine (15ml) and acetic anhydride (15mls) was allowed to stand at r.t. for 20hrs. The solution was diluted with methanol-benzene and repeatedly evaporated in.vacuo. until free from acetic anhydride and pyridine. The oily residue (2.8g) was recrystallised from acetone-light petroleum (40:60) and gave the amide acetate (74) as needles, m.p. 152-154°. (lit. flat blades from ether, m.p. 169.5-170.5°)
i.r. 3082, 1739, 1645, 1239, 1044, 1031cm^{-1}.
τ = 9.13 (s,3H), 7.92 (one half doublet), 7.87 (s,3H + other half doublet), 5.10 (d,1H, J_{AX} = 4Hz), 4.95 (d,2H, J_{AB} = 8Hz), 5-7 (-CH_2NCH_2- hindered rotation).

AMIDE ALCOHOL (68).

A solution of the amide acetate (74) (3g; 0.0078moles) in methanol (25mls) was treated with a solution of aqueous sodium hydroxide (3ml of 50%) and water (3mls) and boiled under reflux for 45mins. The solvent was removed in. vacuo. and the residue partitioned between dilute sulphuric acid and chloroform. The combined chloroform extracts were washed with water, brine and dried. Evaporation of the solvent in. vacuo. gave the crude amide alcohol (68), (2.1g; 78%), which recrystallised from chloroform-acetone as fine needles, m.p. 224-226°. (lit. 229-230.5°).

i.r. 3617, 3072, 1644, 1047cm.$^{-1}$

τ = 9.14 (s,3H), 7.91 (d,3H), 7.66 (b.s,1H), 4.95(d,2H), 6.43 (s,1H) and 5-7 ($-CH_2NCH_2-$ hindered rotation). Hydroxylic proton at 8.18τ by D_2O exchange.

AMIDE ENONE (83).

(a) MANGANESE DIOXIDE OXIDATION :- Activated manganese dioxide (3g) was added to a solution of the amide alcohol (68) (0.5g; 1.46m.moles) in chloroform (50mls) and the mixture was refluxed for 6hrs. An oil (3g) was obtained by filtration and evaporation in. vacuo. Analytical t.l.c. in an ethyl acetate-light petroleum (3 : 2) solvent system, revealed that the more polar amide enone (83) had formed to the extent of approximately 10%. This was confirmed by infra-red.

(b) SHATZKE OXIDATION :- A solution of the amide alcohol (68) (0.215g; 0.63m.moles) and chromium trioxide (70mgs) in dimethyl formamide (5mls) and concentrated sulphuric acid (2 drops), was set aside at r.t. for 60hrs. The solution was quenched in water and extracted with chloroform. The combined chloroform extracts were thoroughly washed with water, then brine and dried. Removal of the solvent in. vacuo. and preparative t.l.c. of the resultant oil in an ethyl acetate-light petroleum (4 : 1) solvent system, afforded the amide enone (83) (130mgs; 60%), which crystallised in colourless

prisms, m.p. 140-145°, from acetone. (lit. 143-150°, 160-164°, double melting point dependent on heating rate).

i.r. 1712, 1645, 1280, 1045, 944cm.$^{-1}$

τ = 9.12 (s,3H), 7.90 (d,3H), 7.24 (m,1H), 4.54 (AB system $\Delta\nu_{AB}$ 72Hz; J_{AB} = 2Hz, 2H), 5-7 (-C$\underline{H}_2$NC$\underline{H}_2$- hindered rotation).

(c) SARETT OXIDATION :- A solution of the amide alcohol (68) (2g; 0.0058moles) in dry pyridine (30ml) was added, with stirring, to a suspension of the complex, prepared from chromium trioxide (3g) and dry pyridine (30ml), at r.t. After 20hrs methanol (20ml) was added and stirring was continued for 30mins. Evaporation in. vacuo., thorough extraction of the residue with hot acetone and evaporation of the combined extracts yielded a brown resin (1.52g), from which the amide enone (83) (1.20g; 60%) was recovered by preparative t.l.c. as before.

ACETYLATION OF THE AMIDE ALCOHOL (68).

A solution of the amide alcohol (68) (50mgs; 0.146m.moles) in dry pyridine (1ml) and acetic anhydride (1ml) was set aside at r.t. for 48hr. The usual azeotropic work-up provided a crystalline material (55mg), which was identical in all respects to an authentic sample of the amide acetate (74).

SODIUM BOROHYDRIDE REDUCTION OF THE AMIDE ENONE (83).

Sodium borohydride (250mg) was added to a solution of the amide enone (83) (194mg; 0.571m.moles) in methanol (10ml) with cooling. After 6hrs. at r.t., the solvent was removed *in. vacuo*. and chloroform extraction, as before, afforded a resin (180mg), which was shown to consist of three components by analytical t.l.c. in an ethyl acetate/light petroleum (4 : 1) solvent system. Preparative t.l.c. in this solvent gave the least polar material as an oil (15mg), which was shown to be consistent with a mixture of the saturated amide alcohols (85).

i.r. 3612, 1645cm^{-1} no ν(=C-H).

A sample of this material was acetylated and afforded the following n.m.r. data.

τ = 9.14(s), 9.09(s), 7.92(d), 5.46(s), 5.37(s).

The material of intermediate polarity (32mg; 42%) was identical to the amide alcohol (68).

The most polar material was the amide alcohol (84) (75mg; 38%), which recrystallised as colourless prisms, m.p. 178-179°, from acetone. (lit. value 176-177°.)

i.r. 3619, 3074, 1646, 1044cm^{-1}.

τ = 9.14 (s,3H), 7.92 (d,3H), 7.67 (m,1H), 6.40 (s,1H), 4.95 (d,2H), 5-7 ($-CH_2NCH_2-$ hindered rotation)

REACTION OF p-BROMOBENZENESULPHONYL CHLORIDE ON THE AMIDE ALCOHOL (68).

P-bromobenzene sulphonyl chloride (300mg) was added to a solution of the amide alcohol (68) (100mg; 0.292m.moles) in anhydrous pyridine (5ml) at 0°. After 2hrs at r.t. and 24hrs in the fridge, the mixture was poured on to cracked ice (10g) and concentrated hydrochloric acid (1ml) and extracted thoroughly with chloroform. The combined chloroform extracts were washed with 10% sodium bicarbonate solution, water, brine and dried. Evaporation of the solvent *in. vacuo*. gave a red oil (164mg), which was shown to be a complex mixture by analytical t.l.c. in ethyl acetate.

A similarly complex mixture was obtained when the amide alcohol (84) was subjected to the above reaction conditions.

AMIDE ACETATE (91).

The amide alcohol (84) (30mg; 0.088m.moles) was treated at r.t. with dry pyridine (1ml) and acetic anhydride (1ml) for 48hrs. Work-up in the usual manner gave the amorphous amide acetate (91) (31mg), which did not crystallise from the usual solvents.

i.r. 3088, 3070, 3036, 1739, 1644, 1236, 1027cm^{-1}

τ = 9.14 (s,3H), 7.92 (d,6H), 7.64 (m,1H), 5.13 (s,1H), 4.95 (d,2H), 5-7 (-$C\underline{H}_2NC\underline{H}_2$- hindered rotation).

OZONOLYSIS OF THE AMIDE ALCOHOL (68).

A solution of the amide alcohol (68) (500mg; 1.458m.moles) in ethyl acetate (50ml) was treated with ozonised oxygen at -60° for 3hrs. Acetic acid (20ml) and zinc granules (0.5g) were added to the blue solution, which was then agitated overnight. After filtration, the solution was taken to dryness *in. vacuo.*, with benzene as an azeotrope in the final stages. The residue was dissolved in ethyl acetate, washed thoroughly with water and dried. Removal of the solvent *in. vacuo.* afforded a white solid (470mg), whose mobility in analytical t.l.c., using an ethyl acetate - light petroleum (4 : 1) solvent system, suggested a carboxylic acid.
i.r. 3400 - 2500 (broad), 1720, 1645cm^{-1}.

OSMYLATION OF THE AMIDE ACETATE (74).

Osmium tetroxide (30mg) was dissolved in a solution of the amide acetate (74) (30mg; 0.078m.moles) in dry ether (15ml) and pyridine (0.5ml) and set aside in the dark at r.t. After 2days, the ether was removed and the dark crystalline residue was dissolved in benzene. Treatment of this solution with hydrogen sulphide gas for 10mins., filtration through a celite pad and evaporation of the solvent *in. vacuo.* yielded a brown gum (32mg), which was shown to consist of two very polar compounds by analytical t.l.c. in chloroform-methanol (95:5). Together with i.r. information, this suggested a mixture of

the epimeric diols (92), which were subjected to sodium periodate without separation.

i.r. 3450 (broad) 1734, 1646, 1233, 1044, 1031cm.$^{-1}$

SODIUM METAPERIODATE ON THE DIOLS (92).

The crude diol mixture (92) (30mg; 0.071m.moles) in methanol (10ml) was mixed with sodium metaperiodate (100mg) in water (10ml) and the solution was set aside at r.t. for 2days. The solution was reduced to low bulk in. vacuo. and partitioned between ethyl acetate and water. The organic phase was washed with water, brine and dried. Removal of the solvent in. vacuo. gave a colourless oil, from which the keto-acetate (93) (24mg; 87%), was extracted by preparative t.l.c. in a chloroform-methanol (95 : 5) solvent system. Recrystallisation from acetone-light petroleum (40 : 60) afforded needles, m.p. 199-200°, $[\alpha]_D$ - 123° (c = 1.30 in chloroform).

i.r. 1758, 1743, 1647, 1226, 1063, 1045cm.$^{-1}$

τ = 9.09 (s,3H), 7.88 (q,3H), 7.80 (s,3H), 5.15 (s,1H) 5-7 ($-CH_2NCH_2-$ hindered rotation).

[Found : C,71.45; H,8.67; N,3.60%; $C_{23}H_{33}NO_4$ requires C,71.29; H,8.58; N,3.61%].

OZONOLYSIS OF THE AMIDE ACETATE (91).

Ozonised oxygen was passed through a solution of the amide acetate (91) (30mg; 0.078m.moles) in ethyl acetate (20ml) at -60° for 3hrs. The mixture was worked up reductively with acetic acid and zinc as before, to yield an oil, which was shown to consist of two components by analytical t.l.c. in chloroform-methanol (95 : 5). Preparative t.l.c. in the above solvent system afforded the more mobile keto-acetate (94) (15mg; 53%), which crystallised from acetone-light petroleum (40 : 60) as prisms, m.p. 219-222°, $[\alpha]_D$ = +23° (c = 1.22 in chloroform).

i.r. 1755, 1740, 1646, 1226, 1048cm^{-1}

τ = 9.11(s,3H), 7.88(d,3H), 7.86(s,3H) 5.16(s,1H) 5-7 ($-C\underline{H}_2NC\underline{H}_2-$ hindered rotation)

[Found : C,71.39; H,8.67; N,3.87%; $C_{23}H_{33}NO_4$

[Found : C,71.39; H,8.67; N,3.87%; $C_{23}H_{33}NO_4$

requires C,71.29; H,8.58; N,3.61%].

The more polar product had an i.r. spectrum very similar to the above, except the 1646cm^{-1} peak was very much less intense. This product seems to be derived by further oxidation of the amide function of the keto-acetate (94).

HYDROLYSIS OF THE KETO-ACETATE (93).

A solution of the keto-acetate (93) (50mg; 0.129m.moles) in methanol (5ml) and water(0.5ml) was saturated with solid sodium carbonate and stirred at r.t. for 24hrs. The solution was reduced to low bulk in. vacuo. and partitioned between

water and chloroform. The organic layer was washed with water, brine and dried. Evaporation of the solvent in. vacuo. afforded an oil (40mg), from which the ketol (89) (20mg; 45%) was extracted by preparative t.l.c. in a methanol-chloroform (2 : 98) solvent system. Recrystallisation from acetone, with a trace of chloroform, afforded prisms, m.p. 213-218°, (dependant on heating rate), $[\alpha]_D$ = -93°, (c = 1.07 in chloroform).
i.r. 3520, 1730, 1645, 1284, 1271, 1215, 1105, 1084, 1041cm^{-1}.
τ = 9.13(s,3H), 7.93(d,3H), 6.56(s,1H), 5-7 ($-CH_2NCH_2-$ hindered rotation).
[Found : C,73.07; H,8.96; N,3.98% $C_{21}H_{31}NO_3$
requires C,73.00; H,9.05; N,4.05%].

HYDROLYSIS OF THE KETO-ACETATE (94).

The keto-acetate (94) was subjected to the sodium carbonate hydrolysis procedure described in the preceding experiment. Work-up and preparative t.l.c. afforded the ketol (95), which crystallised in prisms, m.p. 210-216°, (dependant on heating rate), $[\alpha]_D$ +7°, (c = 0.87 in chloroform), from acetone containing a trace of chloroform.
i.r. 3535, 1730, 1645, 1279, 1268, 1196, 1101, 1053cm^{-1}.
τ = 9.11(s,3H), 7.88(d,3H), 7.55(mlH), 6.61(s,1H) 5-7 ($-CH_2NCH_2-$ hindered rotation).
[Found : C,72.89; H,9.06; N,4.08% $C_{21}H_{31}NO_3$
requires C,73.00; H,9.05; N,4.05%].

KETOTOSYLATE (96).

A solution of the ketol (89) (200mg; 0.580m.moles) and recrystallised p-toluene sulphonyl chloride (300mg) in anhydrous pyridine (10ml), was set aside in the fridge for 4 days. The solution was worked-up in a manner similar to the p-bromosulphonylation reaction described previously and afforded the crude ketotosylate (96) (330mg), as a red oil. Preparative t.l.c. using a methanol-chloroform (2 : 98) solvent, gave the pure ketotosylate (96) (250mg; 86%), which recrystallised in needles, m.p. 197-198°, from acetone-ether. $[\alpha]_D$ -112° (c = 1.10 in chloroform).

i.r. 1747, 1645, 1373, 1188, 1176, 1030, 985, 860cm.$^{-1}$

τ = 9.12(s,3H), 7.91(b.s.,3H), 7.56(s,3H), 5.61(s,1H), 2.34 (A_2B_2 quartet, 4H, J_{AB} = 8Hz), 5-7 ($-CH_2NCH_2-$ hindered rotation).

[Found : C,67.29; H,7.45; N,2.71. $C_{28}H_{37}NSO_5$ requires C,67.31; H,7.47; N,2.80%].

KETOBROSYLATE (97).

The ketol (89) (10mg; 0.029m.moles) was reacted with p-bromosulphonyl chloride (50mg) in dry pyridine (2ml) as above. Work-up and separation by chromatoplate, afforded the pure amorphous ketobrosylate (97) (9mg).

i.r. 1746, 1646, 1377, 1190, 1180, 1031, 924, 862cm.$^{-1}$

ATTEMPTED EPIMERISATION OF THE KETOL (89).

The ketol (89) (5mg; 0.015m.moles) and p-toluene sulphonic acid (2mg) were dissolved in chloroform (10ml) and the resultant solution was refluxed under nitrogen for 4hrs. Analytical t.l.c. in methanol-chloroform (2 : 98) of the reaction mixture, revealed two products, which were less polar than the starting ketol (89). The reaction was abandoned at this stage.

REACTION OF THE KETO-TOSYLATE (96) WITH DIMETHYLFORMAMIDE.

A sealed glass ampule containing a solution of the keto-tosylate (96) (30mg; 0.060m.moles) in dimethylformamide (1.2g), was suspended over refluxing ethanol (~78°) for 24hrs. The reaction mixture was thrown into water and chloroform extracted. The combined organic fractions were thoroughly washed with water, then brine and dried. In order to hydrolyse any formates present, the solution was passed through an alumina (Grade III, neutral) column and evaporated to dryness *in. vacuo*. Analytical t.l.c. in a methanol-chloroform (2 : 98) solvent system, revealed a complex mixture of at least six compounds, including minor amounts of the ketols (89) and (95), together with some starting keto-tosylate (96) (~30%). Variation of temperature and time of reaction did not produce a reasonable yield of the desired ketol (95).

KETAL ALCOHOL (104).

Dry ethylene glycol (0.5ml) and p-toluene sulphonic acid (8mg) was added to a solution of the ketol (89) (30mg; 0.087m. moles) in sodium dried benzene (15ml) and refluxed for 18hrs. During this time water separation was achieved by means of a Dean-Stark apparatus, containing silica-gel. The solution was evaporated to low bulk in. vacuo. and partitioned between sodium bicarbonate solution and ethyl acetate. The combined ethyl acetate extracts were washed thoroughly with water, then brine and dried. Removal of the solvent in. vacuo. yielded a whitish oil (40gm), from which the desired ketal alcohol (104) (27mg; 80%) was obtained by preparative t.l.c. in chloroform-methanol (98 : 2). Recrystallisation from acetone afforded prisms, m.p. 182-183°, $[\alpha]_D$-39° (c = 1.50 in chloroform).
i.r. 3520, 1743, 1172, 1168, 1111 1083, 1040cm.$^{-1}$
τ = 9.16,(s,3H), 7.90(d,3H), 6.97(s,1H), 6.93(b.s.1H, hydroxylic proton by D_2O exchange), 6.02(s,4H), 5-7 ($-C\underline{H}_2NC\underline{H}_2-$ hindered rotation).
[Found : C,71.05; H,9.05; N,3.43% $C_{23}H_{35}NO_4$
requires C,70.92; H,9.06; N,3.60%].

ATTEMPTED EQUILIBRATION OF THE KETAL ALCOHOLS (104) AND (105).
(a) ALUMINIUM ISOPROPOXIDE :- A sealed tube was prepared containing a mixture of the ketal alcohol (104) (8mg; 0.021m.moles), aluminium isopropoxide (5mg; 0.03m.moles), acetone (1.5μl) and

isopropanol (0.3ml). After 4 days at 100°, the contents of the tube were quenched with dilute hydrochloric acid and extracted with chloroform. The combined chloroform extracts were washed with sodium bicarbonate solution, water, brine and dried. Evaporation of the solvent in. vacuo. provided material, which was identical in all respects to the starting ketal alcohol (104).

(b) Na/FLUORENONE :- A solution of the ketal alcohol (104) (10mg; 0.026m.moles), sodium metal (5mg) and fluorenone (10mg) in dry toluene (2ml) was sealed in a glass ampule and immersed in an oil bath at 100°. After 90hrs., the contents of the tube were thrown into water and ethyl acetate extracted. Evaporation of the solvent in. vacuo. afforded an oily residue, which was deketalised by p-toluene sulphonic acid in acetone (described before). Analytical t.l.c. of the product in methanol-chloroform (2 : 98), revealed a single compound, which was shown to be identical to the ketol (89).

DEKETALISATION OF THE KETAL ALCOHOL (104).

(a) PERCHLORIC ACID :- A solution of the ketal alcohol (104) (5mg; 0.013m.moles) and 3N perchloric acid (3 drops) in tetrahydrofuran (1ml) was set aside at r.t. for 20hrs. Work-up was achieved by neutralisation with sodium bicarbonate solution and chloroform extraction as usual. Analytical t.l.c.

in chloroform-methanol (95 : 5) revealed that very little of the desired ketol (89) had been formed. In the main, a mixture of very polar material and starting ketal alcohol (104) was present.

(b) p-TOLUENE SULPHONIC ACID/ACETONE :- p-toluene sulphonic acid (2mg) was dissolved in a solution of the ketal alcohol (104) (5mg; 0.013m.moles) in acetone (1ml). After 18hrs. at r.t., the solution was partitioned between chloroform and sodium bicarbonate solution. The organic phase was washed with water, brine and dried. Evaporation of the solvent in. vacuo. afforded an oil (4mg), which crystallised in prisms, m.p.210-215°, from acetone/chloroform. This material was shown to be identical in all respects to the ketol (89).

KETAL KETONE (106).

The ketal alcohol (104) (200mg; 0.513m.moles) in dry pyridine (2ml) was added with stirring to the pyridine-chromium trioxide complex, prepared from chromium trioxide (300mg) and pyridine (3ml), and stirring was continued for 48hrs at r.t. The Sarett work-up, as described previously, afforded a brown oil, from which the pure ketal ketone (106) (150mg; 75%) was extracted by preparative t.l.c. in methanol-chloroform (2 : 98). Recrystallisation from acetone gave rods, m.p. 211-211.5°, $[\alpha]_D$ +6° (c = 0.76 in chloroform).

i.r. 1736, 1646, 1181, 1171, 1040, 1027, 1018 $cm.^{-1}$

τ = 9.16(s,3H), 7.94(d,3H), 5.89(centre of A_2B_2 system, 4H), 5-7 ($-CH_2NCH_2-$ hindered rotation).

[Found : C,71.10; H,8.60; N,3.56%. $C_{23}H_{33}NO_4$ requires C,71.29; H,8.58; N,3.61%.]

SODIUM BOROHYDRIDE REDUCTION OF THE KETAL KETONE (106).

A solution of the ketal ketone (106) (65mg; 0.168m.moles) in methanol (5ml) was treated with sodium borohydride (300mg), with cooling, in the usual way. After 4hrs. at r.t., work-up afforded a colourless oil (68mg), which, when analysed by t.l.c. in methanol-chloroform (2 : 98), revealed two equally intense, slightly overlapping spots. These were assumed to be the epimeric ketal alcohols (104) and (105) (the less polar compound was identified by t.l.c. comparison with an authentic sample) and because of the difficulty of separation were subjected, as a mixture, to deketalisation.

DEKETALISATION OF THE KETAL ALCOHOL MIXTURE (104) AND (105).

(a) p-TOLUENE SULPHONIC ACID-ACETONE :- The ketal alcohol mixture (65mg; 0.167m.moles) was dissolved in acetone (10ml) and p-toluene sulphonic acid (10mg) was added. After 60hrs. at r.t., the reaction mixture was worked-up to yield a colourless oil (60mg), which contained four compounds by analytical t.l.c. in methanol-chloroform (2 : 98). Preparative t.l.c. afforded the ketol (89) (5mg) and the ketol (95) (5mg),

together with two more polar compounds (20mg each). The n.m.r. and i.r. spectra of these more polar compounds were very similar and suggested that they were some disguised forms of the ketols (89) and (95). A dimer structure (107) would probably fit the spectral data.

i.r. 3595, 3420(broad), 1646cm^{-1} and seven fairly intense peaks in the 1000 - 1200cm^{-1} region.

τ = 9.13(s,3H), 7.89(d,3H), 6.55(s,1H), 5-7 ($-CH_2NCH_2-$ hindered rotation).

p-Toluene-sulphonic acid-acetone treatment at reflux produced the same distribution of products as above.

(b) <u>50% AQUEOUS ACETIC ACID</u> :- The mixture of ketal alcohols (104) and (105) (1g; 2.571m.moles) was dissolved in 75% aqueous acetic acid (30ml) and refluxed for 30mins. The solution was cooled, neutralised with sodium carbonate solution and ethyl acetate extracted, washing with water, brine and drying. Evaporation of the solvent <u>in. vacuo.</u> gave a yellow oil (950mg) which, when subjected to preparative t.l.c. in a methanol-chloroform (5 : 95) solvent system, yielded the ketol (89) (0.320mg; 36%) and the ketol (95) (280mg; 32%).

The two polar compounds from (a) were subjected to conditions (b) and were found to revert quantitatively to a mixture of the known ketols (89) and (95).

(c) HYDROCHLORIC ACID :- The mixture of ketal alcohols (104) and (105) (10mg; 0.026m.moles) was dissolved in chloroform (1ml) and dilute aqueous hydrochloric acid (5drops) was added. Homogeneity was obtained by adding methanol and the solution was set aside at r.t. for 18hrs. Work-up was achieved by neutralisation and ethyl acetate extraction as in (b). Analytical t.l.c. of the product revealed a mixture consisting mainly (>80%) of the ketols (89) and (95), together with a very small amount of more polar material.

OSMIUM TETROXIDE-PERIODATE CLEAVAGE OF THE AMIDE ACETATE (74).

The amide acetate (74) (50mg; 0.130m.moles) and osmium tetroxide (5mg) in aqueous dioxan (5ml) was stirred at r.t. for 5mins., during which the solution turned dark brown. Sodium metaperiodate (50mg) was added and stirring was continued for 18hrs. The white precipitate was filtered off and the colourless solution was partitioned between ethyl acetate and water. The combined ethyl acetate extracts were washed thoroughly with water, then brine and dried. A colourless oil (35mg), which later solidified, was obtained on removal of the solvent *in. vacuo*. This material was homogeneous on t.l.c. in methanol-chloroform (2 : 98) and proved to be identical in all respects to the keto-acetate (93).

KETAL ACETATE (108).

This compound was prepared quantitatively from the keto-acetate (93) by the ethylene glycol/p-toluene sulphonic acid/ benzene procedure previously described. The oily ketal acetate (108) defied all attempts at recrystallisation.

i.r. 1741, 1645, 1241, 1179, 1114, 1044, 1031cm.$^{-1}$

τ = 9.15(s,3H), 7.90(d,3H), 7.85(s,3H), 6.13(m,4H), 5.70(s,1H), 5-7 ($-CH_2NCH_2-$ hindered rotation).

HYDROLYSIS OF THE KETAL ACETATE (108).

(a) The ketal acetate (108) (4.31g; 0.010moles) was dissolved in methanol (250ml) and a solution of sodium carbonate (4g) in water (50ml) was added. After 3 days at r.t., the usual work-up provided a brown oil (3.30g; 85%), which later crystallised into a feathery mass. This was shown to be the ketal alcohol (104).

(b) A solution of the ketal-acetate (108) (170mg; 0.395m.moles) in methanol (20ml) and 25% aqueous potassium hydroxide (2ml) was refluxed under nitrogen for 30 mins. The cooled solution was evaporated to low bulk *in. vacuo.*, carefully neutralised with dilute hydrochloric acid and partitioned between chloroform and water. The organic phase was washed with water, brine and dried. Preparative t.l.c. in methanol-chloroform (2 : 98) of the brown gum obtained on removal of the solvent *in. vacuo.*,

afforded material (130mg), which was identical in all respects to the ketal alcohol (104).

ACETOLYSIS OF THE KETO-TOSYLATE (96).

(a) ACETIC ACID-SODIUM ACETATE AT 55° :- The keto-tosylate (96) (20mg; 0.040m.moles) was dissolved in anhydrous acetic acid (2.5ml), which contained fused sodium acetate (8mg), and the sealed tube containing the solution was immersed in an oil bath at 55°. After 48hrs., the contents of the tube were neutralised with sodium bicarbonate solution and extracted thoroughly with ethyl acetate. The combined organic extracts were washed with water, brine and dried. Removal of the ethyl acetate in. vacuo. afforded material which was identical in all respects to the starting keto-tosylate (96).

(b) ACETIC ACID-SODIUM ACETATE AT 150° :- The above reaction was repeated at 150° for 48hrs. and work-up as before yielded an oil (14mg), which was shown to contain one major product, slightly more mobile than the keto-tosylate (96), by analytical t.l.c. in a methanol-chloroform (2 : 98) solvent system. Preparative t.l.c. afforded the rearranged keto-olefin (111) (11mg; 83%) as an oil, which failed to crystallise from the usual solvents.

i.r. 1760, 1647, 1270, 1196, 1149, 1033cm.$^{-1}$

G.l.c. retention time of the keto-olefin (111) on a 5% SE 30 stationary phase at 225° was 1.87, relative to n-hexacosane. Molecular weight was 327 by mass spectroscopy.

(c) ACETIC ACID-UREA AT 150° :- Substitution of urea for fused sodium acetate gave exactly the same result as (b).

KETO-TOSYLATE (64).

The ketol (95) (180mg; 0.360m.moles) and freshly re-crystallised p-toluene sulphonyl chloride (300mg) were dissolved in the minimum volume of anhydrous pyridine (2ml) and set aside at 0°. After 4 days, a red oil (300mg) was obtained by the work-up procedure previously described. Preparative t.l.c. in methanol-chloroform (2 : 98), furnished the pure ketotosylate (64) (177mg; 68%) as a poorly crystalline solid. Despite several attempts, satisfactory crystalline material was not obtained.

i.r. 1746, 1646, 1373, 1190, 1179, 1023, 991, 963, 920, 873cm^{-1}.

τ = 9.10(s,3H), 7.89(s,3H), 7.53(s,3H), 5.58(s,1H), 2.31 (q, A_2B_2 system, 4H, J_{AB} = 8Hz), 5-7 ($-\underline{CH_2}N\underline{CH_2}-$ hindered rotation).

SOLVOLYSIS OF THE KETO-TOSYLATE (64).

(a) ACETIC ACID/SODIUM ACETATE :- A solution of the keto-tosylate (64) (90mg; 0.180m.moles) in anhydrous acetic acid (4ml) and fused sodium acetate (40mg) was heated at 150° in a sealed tube for 48hrs. The usual work-up afforded a yellow oil (65mg), which was essentially a single spot, slightly less polar than the starting keto-tosylate on analytical t.l.c. in a methanol-chloroform (2 : 98) solvent system. This oil was shown to be identical in all respects (t.l.c., g.l.c., m.s., i.r., n.m.r.) to the keto-olefin (111).

(b) ACETIC ACID/UREA/SODIUM PERCHLORATE :- A solution of the keto-tosylate (64) (50mg; 0.100m.moles), urea (15mg) and sodium perchlorate (28mg) in anhydrous acetic acid (1ml) was treated at 150° for 48hrs, as above. Again, on work-up the reaction product was found to be almost exclusively the keto-olefin(111).

(c) TRIFLUOROACETIC ACID/TRIFLUOROACETIC ANHYDRIDE/UREA :- A solution of the keto-tosylate (64) (10mg, 0.020m.moles) and urea (10mg) in trifluoroacetic acid (1ml), containing trifluoro-acetic anhydride (2 drops), was refluxed (~72°) for 48hrs. The solution was taken to dryness *in. vacuo.*, the final stages being accomplished by azeotroping with carbon tetrachloride. The residue was taken up in ethyl acetate and washed with

sodium bicarbonate solution, water, brine and dried. Evaporation of the solvent *in. vacuo.* afforded only unreacted keto-tosylate (64).

SOLVOLYSIS OF THE KETO-ACETATE (93).

A solution of the keto-acetate (93) (10mg; 0.026m.moles), fused sodium acetate (10mg) and p-toluene sulphonic acid (5mg) in anhydrous acetic acid(2ml), was heated at 150° for 48hrs as before. On work-up and analytical t.l.c. in methanol-chloroform (2 : 98), four compounds were detected. The two more polar compounds, in major amount (>80%), were shown to be the keto-acetates (93) and (94) in equal proportions, by comparative t.l.c. with authentic specimens and by i.r. The i.r. spectrum of the crude product contained the following bands, i.r. 1755, 1741(shoulder), 1646, 1226, 1059, 1047cm^{-1}.

One of the two minor (<10%) products, the more mobile one, was shown to be identical to the keto-olefin (111). The other one was not identified.

A sample (5mg) of the crude reaction product was dissolved in methanol (3ml), a few drops of water added and the resultant solution was saturated with solid sodium carbonate. After 18 hours at r.t. the reaction was worked up in the usual manner to give an oil, which was shown by i.r. (i.r. 3535, 1729, 1646, 1052, 1043cm^{-1}) and analytical t.l.c. in methanol-chloroform (2 : 98), to consist of mainly the

ketols (89) and (95). These ketols were readily separated by prep. t.l.c. and characterised.

ACETOLYSIS OF THE KETO-TOSYLATE (64) AT REFLUX TEMPERATURE.

A solution of the keto-tosylate (64) (6mg; 0.012m.moles) and fused sodium acetate (30mg) in anhydrous acetic acid (3ml) was heated at reflux (~118°). After specific periods of time, samples (2ml) were removed by pipette and worked up with ethyl acetate and sodium bicarbonate solution as before.

(a) 30 mins :- Analytical t.l.c. showed starting keto-tosylate (64), as did the i.r. spectrum.

i.r. 1745, 1644, 1372, 1188, 1178cm^{-1}.

(b) 3.5hrs :- Analytical t.l.c. showed two spots, which on comparison with authentic samples, proved to be the starting keto-tosylate (64) (70%) and the more mobile keto-tosylate (96) (30%). The i.r. spectrum contained peaks similar to (a). However, the fingerprint region suggested that some of the keto-tosylate (96) was present (e.g. 968cm^{-1} and 1023cm^{-1}).

(c) 25hrs :- Analytical t.l.c. showed three spots. The major (>50%) most mobile compound proved to be the keto-olefin (111) and the other two, the keto-tosylates (64) and (96) in equal proportions, by comparative t.l.c.

i.r. 1759, 1646, 1371, 1189, 1178, 1032cm^{-1}.

The tosylate bands (1371, 1189, 1178cm^{-1}) in the i.r. spectrum were very much reduced in intensity.

ACETOLYSIS OF THE KETO-TOSYLATE (64) IN D_2O/ACETIC ANHYDRIDE.

The keto-tosylate (64) (10mg; 0.020m.moles) in acetic anhydride (3ml), fused sodium acetate (30mg) and deuterium oxide (0.5ml), was heated at reflux for 48hrs. The keto-olefin (111) was extracted as usual and analysed for deuterium by m. s. and n.m.r. M.s. revealed the deuteriated species D_1 (39%), D_2 (27%) and D_3 (11%). The remainder of the material (23%) did not contain deuterium. Deuterium was shown to have been incorporated in the acetamide methyl by integration of the appropriate region in the n.m.r. spectrum.

PYROLYSIS OF THE KETO-TOSYLATE (64).

(a). COMPARISON OF THE KETO-TOSYLATES (64) AND (96) ON G.L.C.:- Each of the keto-tosylates in chloroform solution was injected normally into a g.l.c. column, the stationary phase being 5% SE 30, at 225°. The resultant traces are shown in figures (1) and (2), with the retention times of each component, relative to the n-alkane hexacosane, shown above each peak.

Approximate ratios of components are

5 : 6 : 7 = 61 : 17 : 22%

and 1 : 2+3 : 4 = 19 : 37 : 44%

(peaks 2 and 3 are not well resolved).

Cross injection indicated that peak (1) corresponds to peak (5), (2) corresponds to (6) and (4) corresponds to (7). Cross injection also indicated that peak (5)(or 1) was the keto-olefin (111).

FIGURE (1).

KETO-TOSYLATE (96).

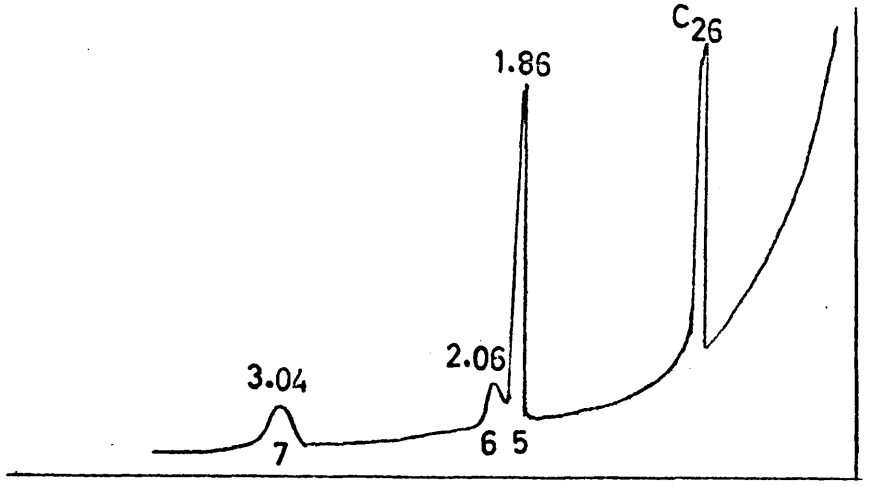
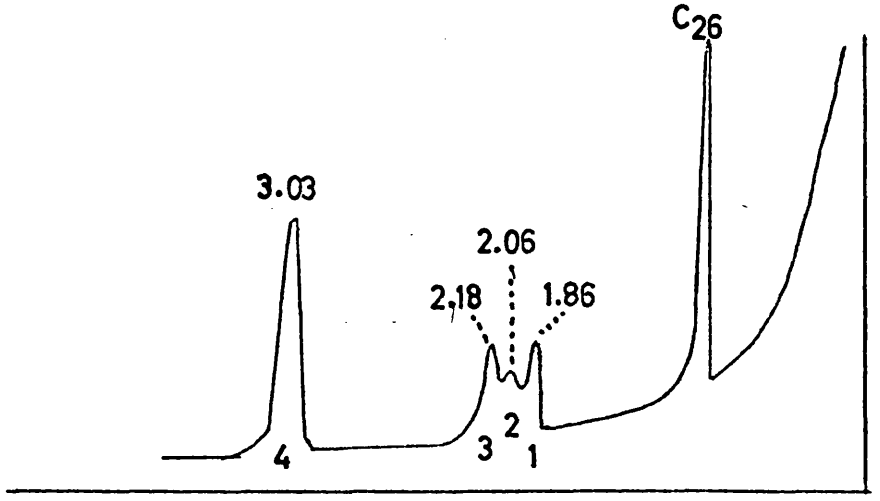


FIGURE (2).

KETO-TOSYLATE (64).



(b) The finely divided, solid keto-tosylate (64) (10mg; 0.020 m.moles) was pyrolysed at 180°, for 30mins, in a sealed tube. On cooling, the oil extracted from the tube was found to be pure starting material.

The keto-tosylate (10mg) was returned to the sealed carius tube and heated at 300° for 1hr. A dark insoluble resin was obtained, whose i.r. spectrum lacked the 1646cm^{-1} amide band.

(c) The solid keto-tosylate (64) (10mg; 0.020m.moles) was placed in a sublimation tube, which was then evacuated. The tube was inserted in a heating block at 300° and the products rapidly condensed on the cold zone of the tube. The oil was taken up in ethyl acetate, which was washed with sodium bicarbonate solution, water, brine and dried. Analytical t.l.c. in methanol-chloroform (2 : 98) of the material obtained on removal of the solvent <u>in. vacuo.</u>, revealed some starting keto-tosylate (64), which was not well resolved from the major keto-olefin spot. There was also one more polar spot in minor yield.

i.r. 1760, 1745(shoulder), 1735(shoulder), and 1373, 1190, 1178cm^{-1} tosylate bands very much reduced in intensity.

G.l.c. on 5% SE 30 at 225°, showed the same peaks as in the pyrolytic g.l.c. of the keto-tosylate (64). However, the proportion of each was different. 1 : 2 + 3 : 4 = 49 : 33 : 18%

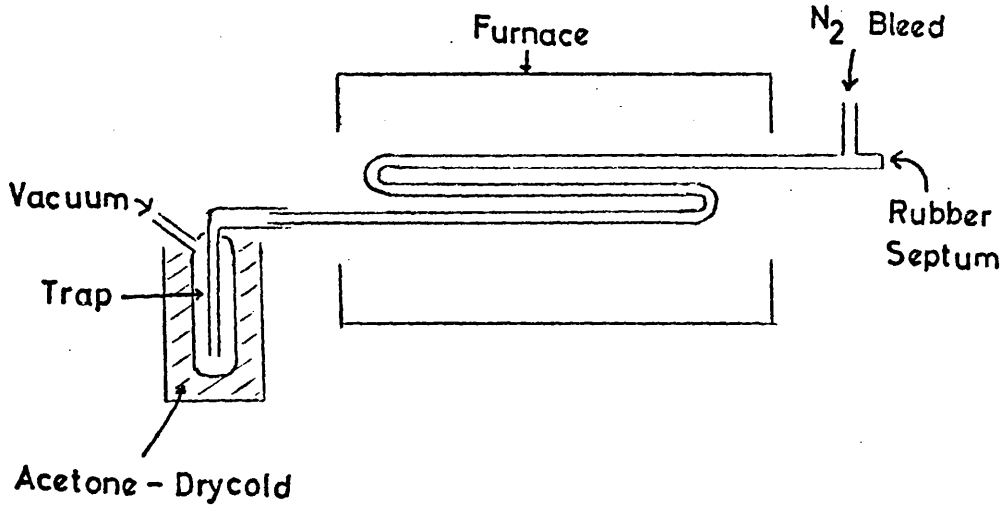
Thus, the keto-olefin (111) constituted almost 50% of the product.

(d) A solution of the keto-tosylate (64) (10mg; 0.020m.moles) in redistilled collidine (2ml) was heated at reflux for 18hrs. Ethyl acetate was added and the resultant solution was washed with dilute hydrochloric acid, water, brine and dried. Evaporation of the ethyl acetate in. vacuo. afforded an oil (9mg), whose i.r. spectrum was identical to that of the starting keto-tosylate (64).

At higher temperatures (up to 300°) in a sealed tube, a complex mixture of products was obtained.

(e) A solution of the keto-tosylate (64) (15mg; 0.030m.moles) in chloroform (5ml) was thoroughly mixed with a sample of 1% SE 30 g.l.c. packing (125mg) and the solvent was removed in. vacuo. The resultant dispersion was heated in a sealed tube for 15min at 300°. Ethyl acetate extraction afforded an oil (11mg) whose i.r. spectrum had bands at 1760, 1646, 1260 and 1080-1010(broad)cm^{-1}. The main product seemed to be rearranged keto-olefin (1760cm^{-1}), with the reduced intensity 1646cm^{-1} band indicating loss of amide. No keto-tosylate was present. G.l.c. showed three peaks with retention times 0.63(50%), 1.85(40%) and 2.18(10%), relative to the n-alkane hexacosane (C_{26}), on 5% SE 30 at 225°. The first peak corresponds to the loss of the acetamide (1646) in the i.r. spectrum.

FIGURE (3).


Furnace
N_2 Bleed
Vacuum
Trap
Rubber
Septum
Acetone - Drycold

(f). A pyrolysis tube was set up [see figure (3)] with a vacuum pump at one end and a nitrogen bleed at the other. The trap was cooled with acetone-drycold, the hot zone of the tube was adjusted to approximately 400° and the vacuum to 0.5mm. A slight positive pressure was maintained throughout by use of the nitrogen bleed. A solution of the keto-tosylate (64) (10mg; 0.020m.moles) in carbon tetrachloride (100μl) was introduced into the hot zone via a rubber septum on the end of the pyrolysis tube. The products condensed almost immediately on the cold part of the tube and the cooled collection vessel and were collected by extracting with chloroform. The combined chloroform extracts were washed with sodium bicarbonate solution, water, brine and dried. Removal of the solvent in. vacuo. gave an oil.

i.r. 1760, 1746, 1646, 1370, 1268, 1190, 1178cm^{-1}.

The tosylate peaks (1370, 1190, 1178cm^{-1}) were reduced to about 50% of their original intensities.

Analytical t.l.c. in methanol-chloroform (2 : 98) revealed the presence of some unchanged keto-tosylate (64) and some keto-olefin of about the same polarity, together with two minor, more polar spots.

G.l.c. on a 5% SE 30 phase at 225°, showed the same pattern of peaks as in the g.l.c. pyrolysis of the keto-tosylate (64), but in different proportions.

1 : 2 + 3 : 4 = 10 : 77 : 13%.

In subsequent runs, the temperature of the hot zone of the pyrolysis tube varied from 400-600° and acetone was substituted for carbon tetrachloride, because of solubility problems when large amounts of the keto-tosylate were pyrolysed.

In a typical preparative-scale run, the keto-tosylate (64) (470mg; 0.940m.moles) in acetone (2ml) was injected into the hot zone (~600°) of the tube. The products (400mg) were collected as before and shown to contain some returned keto-tosylate (~50%) by i.r.(bands at 1370, 1190, 1178 cm^{-1}). This material, after being recycled twice, yielded the crude oily reaction product (250mg), containing no keto-tosylate.

i.r. 1759, 1743, 1646, 1270, 1235, 1214, 1189, 1047cm^{-1}.

Analytical t.l.c. in ethyl acetate revealed one main, very diffuse spot of similar polarity to the starting keto-tosylate and a lot of streaking due to decomposition. Preparative t.l.c., using ammoniacal silver nitrate coated chromatoplates and repeated elution with ethyl acetate, afforded the oily keto-olefin mixture (65) (105mg).

i.r. 1760, 1648, 1270, 1188, 1036cm^{-1}.

τ = 9.08(s), 9.12(s), 7.92(b.s,3H), 4.80(b.m,1H),
5-7 ($-CH_2NCH_2-$ hindered rotation).

Molecular weight by mass spectroscopy was 327.

G.l.c. :- 5% SE 30 at 225° revealed two peaks with retention times 2.17(95%) and 1.85(5%) relative to the n-alkane hexacosane whereas, 1% QF 1 at 225° revealed three peaks with retention

times 6.64(66%), 6.11(17%) and 5.53(17%) relative to the C_{34} n-alkane. None of these peaks corresponded to the keto-olefin (111). The keto-olefin mixture (65) was very unstable and decomposition may have affected the above data.

ATTEMPTED ISOMERISATION OF THE KETO-OLEFIN MIXTURE (65).

A solution of the keto-olefin mixture (65) (2mg) in chloroform (1ml), was saturated with gaseous hydrogen chloride and set aside at r.t. for 20hrs. Evaporation of the solvent *in. vacuo.* provided material, which was identical to starting material on g.l.c., using a 5% SE 30 stationary phase at 225°.

KETO-ACETATES (93) AND (94).

The ketol (89) (200mg; 0.580m.moles) and the ketol (95) (200mg; 0.580m.moles) were each treated with acetic anhydride (2ml) and anhydrous pyridine (2ml) at r.t. in the usual way. Work-up after 48hrs, provided almost quantitative yields of the keto-acetate (93) and the keto-acetate (94) respectively.

ATTEMPTED PYROLYSIS OF THE KETO-ACETATE (94).

The keto-acetate (94) (20mg; 0.052m.moles) in carbon tetrachloride was pyrolysed at 600° in the flow set up described before (f). The material, which was recovered from the trap (15mg), proved to be identical to the starting keto-acetate by i.r., t.l.c. and g.l.c. (retention time was 3.39

relative to the n-alkane hexacosane, on 5% SE 30 at 225°).

PYROLYSIS OF THE KETO-TOSYLATE (96).

A solution of the keto-tosylate (96) (20mg; 0.040m.moles) in carbon tetrachloride (1ml), was injected into the pyrolysis tube [set up as in (f)], which had previously been stabilised at 500°. The oil (15mg) obtained from the trap consisted mainly of the keto-olefin (111) and starting keto-tosylate, by analytical t.l.c. in methanol-chloroform (2 : 98).
i.r. 1759, 1745(shoulder), 1646, 1373, 1270, 1191, 1180, 1033cm^{-1}.
The tosylate bands (1373, 1191 and 1180cm^{-1}) were weak (~50%) in comparison to those of the starting material.
G.l.c. on 1% SE 30 at 225°, gave a trace which was almost identical to figure (1) and the major product was the keto-olefin (111).

SODIUM BOROHYDRIDE REDUCTION OF THE CRUDE PRODUCT FROM THE GAS PHASE PYROLYSIS OF THE KETO-TOSYLATE (64).

A solution of the crude pyrolysis product (10mg) in methanol (1ml) was treated with sodium borohydride (10mg) at r.t. in the usual manner. Work-up after 18hrs. and evaporation of the solvent in. vacuo., furnished a brownish oil (9mg), which consisted of one unresolved streak on a normal chromatoplate and at least five spots, including the keto-tosylate (64), on an ammoniacal silver nitrate treated chromatoplate eluted several times with ethyl acetate.

i.r. 3620, 3570, 1645, 1268, 1248, 1189, 1178, 1101, 1089, 1054, 1035cm^{-1}.

Acetylation of the mixture with acetic anhydride (0.5ml) and pyridine (0.5ml) at r.t. afforded a mixture of acetates (i.r. 1738, 1646, 1237cm^{-1}), which were inseparable by analytical t.l.c.

KETAL OLEFIN (156).

The crude product (40mg) from the gas phase pyrolysis of the keto-tosylate (64), p-toluene sulphonic acid (20mg) and redistilled ethylene glycol (1ml) in sodium dried benzene (20ml), was refluxed for 18hrs, with water being removed by a Dean-Stark set-up as before. The reaction mixture was thrown into dilute sodium hydroxide solution and the usual ethyl acetate work-up yielded a brown oil (35mg), from which the major component i.e., the impure ketal olefin (156) (14mg), was removed by preparative t.l.c. over "Kieselgel G", using ethyl acetate as the eluting solvent. Further t.l.c. on ammoniacal silver nitrate treated "Kieselgel G", afforded the pure ketal olefin (156) (9mg) as an oil, which did not crystallise from the usual solvents.

i.r. 1646, 1353, 1269, 1121, 1041cm^{-1}.

τ = 9.08(s,3H), 7.93(d,3H), 6.02(s,4H), 4.75(m,1H) 5.8-7.5 (-CH_2NCH_2- hindered rotation). Molecular weight by mass spectroscopy was 371. Retention time was 1.79 relative to the

n-alkane octacosane (5.96 relative to C_{24}) on a 1% SE 30 stationary phase at 225°.

THE HYDROXY-OLEFIN (117).

Sodium borohydride (20mg) was added with cooling and swirling to a solution of the keto-olefin (111) (10mg; 0.031m.moles) in methanol (2ml). Work-up and evaporation of the solvent *in vacuo*., gave an oil (10mg), from which the amorphous hydroxy-olefin (117) (6mg) was extracted by preparative t.l.c. in chloroform - methanol (98 : 2).

i.r. 3573, 1646, 1268, 1100, 1089, 1037cm^{-1}.

This material was homogeneous on both g.l.c. and t.l.c.

DEKETALISATION OF THE KETAL OLEFIN(156).

A solution of the ketal olefin (156) (2mg) in acetone (2ml) was treated with p-toluene sulphonic acid at r.t. for 18hrs. The usual work-up furnished a product (i.r. 1760, 1646cm^{-1}), which was shown by g.l.c., on a 1% QF1 stationary phase at 225°, to be a mixture of two compounds, the keto-olefin (154) (80%) (retention time 6.64 relative to the C_{34} n-alkane) and the starting ketal olefin (156) (20%).

KETAL AMINE (158).

A solution of the ketal olefin (156) (50mg; 0.135m.moles), in dry tetrahydrofuran (5ml), was added dropwise to a stirred suspension of lithium aluminium hydride (60mg), in dry tetrahydrofuran (10ml), at r.t. The resultant solution, containing a fine grey suspension, was refluxed for 4hrs and then stirred overnight at r.t. Water was added dropwise with continued stirring until, when agitation had been stopped, a white granular precipitate was obtained. The precipitate was filtered off and the tetrahydrofuran solution taken to dryness in. vacuo. Preparative t.l.c. of the residue in a diethylamine-cyclohexane (1 : 9) solvent system, afforded the pure ketal amine (158) (35mg; 73%), as an oil.

i.r. 2755-2800, 1450, 1350, 1327, 1169, 1120, 1099, 1057, 1044cm^{-1}.

τ = 9.19(s,3H), 9.00(t,3H, J_{AX}=7Hz), 6.06(s,4H), 4.79(m,1H).

Molecular weight by mass spectroscopy was 357.

Retention time was 1.65, relative to the C_{24} n-alkane, on a 1% SE 30 phase at 200° and 1.73 at 225°.

ATTEMPTED HYDROBORATION OF THE KETAL AMINE (158).

Redistilled boron-trifluoride etherate (30mg) was added to a stirred mixture of the ketal amine (158) (5mg; 0.014m.moles), sodium borohydride (5mg) and dry diglyme (5ml), in an atmosphere of dry, oxygen free, nitrogen and the clear solution was allowed to stir at r.t. After 2hrs, water (2 drops), and

3N sodium hydroxide solution (0.5ml) were added, followed by dropwise addition of 30% hydrogen peroxide solution (0.5ml). The heterogeneous mixture was extracted with ethyl acetate and the combined extracts were washed thoroughly with water, then brine and dried. Evaporation of the solvent afforded an oily material (i.r. 1729, 1280, 1121, 1070cm^{-1}), which was not further characterised.

ATTEMPTED HYDROLYSIS OF THE KETAL AMIDE (156) VIA TRIETHYL-OXONIUM TETRAFLUOROBORATE.

The Meerwein reagent, triethyloxonium fluoroborate, was prepared under an atmosphere of dry nitrogen, as in Organic Synthesis,[90] using epichlorohydrin (0.224ml; 2.86m.moles) and boron trifluoride etherate (0.48ml; 3.81m.moles) in dry ether (0.5ml). All reagents were carefully purified and dried in the recommended manner. After stirring for two hours, the resultant oily triethyloxonium tetrafluoroborate was washed free of excess reagents with ether and dissolved in dry methylene chloride (0.5ml). The ketal amide (156) (4mg; 0.011 m.moles) in dry methylene chloride (0.5ml) was added by syringe through a rubber septum and the yellow solution was stirred at r.t. After 1½hrs., the solvent was blown off with dry nitrogen, and the residue was dissolved in tetrahydrofuran (1ml) containing 0.01N hydrochloric acid (5 drops). After an additional 30mins at r.t. the solution was partitioned between

dilute sodium hydroxide solution and ethyl acetate and the organic phase was washed with water, brine and dried. Removal of the solvent in. vacuo. afforded an oil (40mg), from which the keto-amide (75) (3mg) was extracted by preparative t.l.c. in ethyl acetate. The remainder of the material was a high boiling oil generated from the reagents.

Despite several more attempts with varying pH conditions in the hydrolysis step (e.g. aqueous sodium carbonate or dioxan-10% aqueous acetic acid), no amide hydrolysis was observed.

HYDROLYSIS OF THE AMIDE ACETATE (74) UNDER FORCING CONDITIONS.

A solution of the amide acetate (74) (15mg; 0.039m.moles), potassium hydroxide (80mg) and hydrazine hydrate (2 drops of 100%) in dry ethylene glycol (3ml), was refluxed under nitrogen for 18hrs. The solution was extracted with ethyl acetate, which was washed thoroughly with water, then brine and dried. An oil (10mg) was obtained on evaporation of the solvent in. vacuo., (i.r. 2620, 1746, 1645, 1225, 1040cm^{-1}), which proved to be a mixture of the starting amide acetate (74), the amide alcohol (68) and a little amine, by comparative t.l.c. in chloroform-methanol (98.2). The amine fraction (4mg) was separated by extraction with dilute hydrochloric acid and shown to consist mainly of two compounds, by analytical t.l.c. in diethylamine-light petroleum (1 : 9).

THE KETAL DIOL (162).

A solution of the ketal olefin (156) (9mg; 0.022m.moles) and osmium tetroxide (50mg) in dry ether (5ml) containing anhydrous pyridine (0.25ml), was set aside in the dark at r.t. for 5 days. The usual hydrogen sulphide work-up afforded the ketal diol (162) (8mg, 81%) as a gum, which appeared to be homogeneous on analytical t.l.c.
i.r. 3533, 3448, 1730(weak), 1645, 1270, 1230(broad), 1104, 1067cm.$^{-1}$ Seven peaks in region 1153-1038cm.$^{-1}$ The hydroxyl frequencies did not change on dilution.

ATTEMPTED DEKETALISATION OF THE KETAL DIOL (162).

The ketal diol (162) (4mg; 0.008m.moles) in acetone (2ml) was treated with p-toluene sulphonic acid (10mg) at r.t. as before. After 18hrs, the usual work-up afforded an oil (3mg)
i.r. 1760, 1730(broad), 1646, 1269(broad), 1121, 1073, 1051cm.$^{-1}$

THE p-IODOBENZOATE (168).

A solution of the ketal diol (162) (5mg; 0.012m.moles) and freshly recrystallised p-iodobenzoyl chloride (25mg) in anhydrous pyridine (1ml), was set aside at r.t overnight. The solution was thrown into water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed thoroughly with water, then sodium bicarbonate solution, water, brine and dried The pure, amorphous p-iodobenzoate (168) (3mg) was obtained

on evaporation of the solvent *in. vacuo.* and preparative t.l.c. of the residue (10mg) in chloroform-methanol(98 : 2). Crystallisation could not be induced from any of the usual solvents.

i.r. 3485, 1714, 1271, 1178, 1119, 1103cm.$^{-1}$

THE KETAL AMINE SALTS (170) (a) and (b).

A solution of the ketal amine (158) (5mg; 0.014m.moles) in methanol (few drops) was carefully neutralised with a very dilute methanolic solution of hydriodic acid [concentrated aqueous hydriodic acid (2 drops) in methanol (2ml)]. The solution was then made faintly acidic, diluted with ether and the crystalline hydriodide salt (170a) rapidly filtered off. The salt was crystallised rapidly several times from methanol-ether to remove all traces of excess acid and finally afforded small single rods, m.p. 240-243.5°, on slow recrystallisation.

A similar procedure with dilute hydrobromic acid produced a crystalline hydrobromide (170b), which gave fine needles, m.p. 250° (sublimed) from methanol-ether.

OSMATES OF THE KETAL AMIDE (156).

(1) PYRIDINE :- The ketal amide (156) (10mg; 0.027m.moles) and osmium tetroxide (8mg) were dissolved in dry tetrahydrofuran (1ml) containing anhydrous pyridine (2 drops)

and set aside at r.t. in the dark. After 18hrs, a whitish amorphous-looking osmate (169; R = Py) had formed. Several abortive attempts were made to crystallise this material from the usual solvents.

(2) β-PICOLINE :- A similar procedure to the above was employed using freshly distilled β-picoline as the base. A red crystalline osmate formed after several hours. However, this osmate (169; R = Pic) always crystallised in small clusters, which were not suitable for the purpose intended. Variation of the crystallising solvent did not seem to affect the crystalline form.

COMPLEX HYDRIDE REDUCTION OF THE AMIDE ALCOHOL (68).

(1) LITHIUM DIETHOXY ALUMINIUM HYDRIDE :- A solution of lithium diethoxy aluminium hydride in dry ether (5ml), prepared from lithium aluminium hydride (130mg; 3.43m.moles) and dry ethanol (0.4ml; 6.86m.moles), was added to a stirred solution of the amide alcohol (68) (15mg; 0.044m.moles), in dry ether (2ml) at 0°C in a nitrogen atmosphere. The resultant suspension was stirred for 1hr. and the excess hydride was carefully decomposed with water, giving the usual granular solid. Filtration and the normal lithium aluminium hydride work-up afforded the oily tertiary amine alcohol (12mg), which proved to be homogeneous by t.l.c.

i.r. 3630, 2770, 1172, 1105, 1047cm.$^{-1}$

τ = 9.24(s,3H), 8.96(t,3H,J_{AX} = 6Hz), 4.94(m,2H), 6.40(s,1H).

(2) LITHIUM TRIETHOXY ALUMINIUM HYDRIDE :- A solution of the amide alcohol (68) (15mg; 0.044m.moles) in dry tetrahydrofuran (1ml) was added, under the above conditions, to a solution of lithium triethoxy aluminium hydride in dry tetrahydrofuran (3ml), prepared from ethyl acetate (40.6mg; 0.473 m.moles) and lithium aluminium hydride (12mg; 0.316m.moles). After 1hr at 0°, work-up, as above, afforded an oil (14mg), which was shown to consist of mainly starting material (>90%) and a little amine by i.r. and t.l.c.

SODIUM METAPERIODATE ON THE DIOL (162).

A solution of sodium metaperiodate (20mg) in water (2ml) was mixed with a solution of the diol (162) (12mg; 0.030m.moles) in dioxan (2ml) at r.t. After 18hrs, the solution was partitioned between water and ethyl acetate. The ethyl acetate layer was washed thoroughly with water, then brine and dried. Evaporation of the solvent in. vacuo. afforded an oil (10mg), which was homogeneous on analytical t.l.c. in methanol-chloroform (5 : 95) and identical in polarity to the starting diol. However, the i.r. spectrum indicated that some aldehyde (i.r. 2710, 1727cm^{-1}) was present, in addition to starting material.

Longer reaction times yielded a complex mixture of at least

five products, as revealed by analytical t.l.c. The i.r. of the crude product established that deketalisation (i.r. 1760cm^{-1}) was occurring and that the amide band (i.r. 1646) was very much reduced in intensity.

SARETT OXIDATION OF THE AMINE ACETATE (73).

A solution of the amine acetate (73) (20mg; 0.058m.moles), in anhydrous pyridine (1ml), was added at r.t. with stirring to the chromium trioxide-pyridine complex, prepared from chromium trioxide (50mg) and anhydrous pyridine (o.5ml). After 18hrs., the usual acetone work-up provided a gum (17mg), from which the imino-acetate (71) (12mg; 60%) was extracted by preparative t.l.c. in a diethylamine-light petroleum (1 : 9) solvent system. Recrystallisation from light petroleum gave needles, m.p. 142-145° (lit value 144-148°)

i.r. 3075, 1740, 1648, 1231, 1039, 1018, 903cm.$^{-1}$

A sample of the imino-acetate (5mg) was dissolved in acetone (few drops) and methyl iodide (1ml) was added. After a few hours at r.t., small rosettes of the methiodide were evident.

ATTEMPTED ACID CATALYSED REARRANGEMENT OF THE KETO-OLEFIN (111).

(1) SULPHURIC ACID - METHANOL :- A solution of the keto-olefin (111) (10mg; 0.031m.moles) in methanol (4ml), concentrated sulphuric acid (0.4ml) and water (0.2ml), was refluxed under nitrogen. After 48hrs., the solution was reduced to low bulk

in. vacuo., neutralised with aqueous sodium carbonate and extracted with ethyl acetate. Evaporation of the dried organic layer afforded an oil (9mg), which was shown to consist of one major product of similar polarity to the starting keto-olefin, by analytical t.l.c. in methanol-chloroform (2 : 98). This material was separated out by preparative t.l.c. and proved to be the oily dimethoxy-ketal (121) (5mg).

i.r. 1646, 1269, 1204, 1120, 1111, 1062cm.$^{-1}$

τ = 9.13(s,3H), 7.94(b.s.,3H), 6.78(s,6H).

On treatment with p-toluene-sulphonic acid in acetone at r.t. for 18hrs., the dimethoxy-ketal afforded a quantitative yield of the keto-olefin (111).

(2) HYDROCHLORIC ACID - ACETIC ACID :- A solution of the keto-olefin (111) (10mg; 0.031m.moles) in concentrated hydrochloric acid (1ml) and glacial acetic acid (3ml), was heated at reflux, under nitrogen, for 24hrs. Ethyl acetate work-up as above yielded only the starting keto-olefin (111).

AMIDE KETAL (122).

The keto-olefin (111) (20mg; 0.061m.moles), p-toluene sulphonic acid (10mg) and dry ethylene glycol (0.5ml) in sodium dried benzene (10ml), was refluxed for 18hrs., with water separation as usual. Ethyl acetate work-up furnished the oily amide ketal (122) (20mg; 88%), which proved to be

homogeneous on t.l.c. in methanol-chloroform (2 : 98) and which was reduced without further purification.

KETAL AMINE (123).

The amide ketal (122) (20mg; 0.054m.moles) in dry tetrahydrofuran was subjected to the lithium aluminium hydride (50mg) reduction described before. Work-up and preparative t.l.c. in diethylamine-light petroleum (1 : 9), provided the oily ketal amine (123) (14mg; 73%).

i.r. 2745-2795, 1200, 1150, 1108, 1087, 1047cm^{-1}.

Neutralisation of the ketal amine (123) in methanol with dilute hydriodic acid furnished a hydriodide (124; X = I), which recrystallised in small rosettes, m.p. 228-232°, from methanol-ether. By similar means, a hydrobromide, m.p. 245° (sublimes) was prepared.

MERCURIC ACETATE OXIDATION OF THE KETAL AMINE (191; R = Et).

A solution of the ketal amine (191; R = Et) (20mg; 0.056 m.moles) and mercuric acetate (70mg; approx. 4 molar excess) in anhydrous acetic acid (4ml), was heated at 50° for 18hrs. The solution was cooled, filtered free from mercurous acetate, and saturated with hydrogen sulphide. After a further filtration through a "celite" pad the solvent was removed *in. vacuo.* at low temperature, using benzene as an azeotrope. In a variety of experiments the following two main work-up procedures were used.

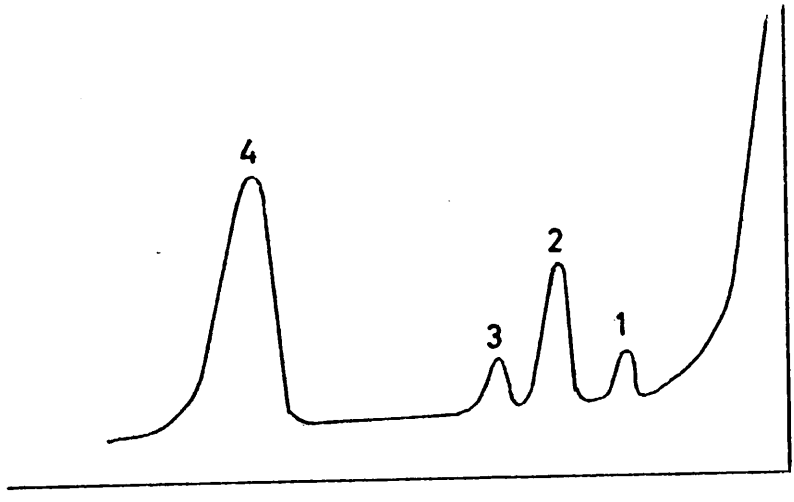
(a). The residue was taken up in ethyl acetate and washed with sodium hydroxide solution, water and brine. An oil (17mg) was obtained on removal of the solvent *in. vacuo*.

(b). The residue was taken up in dimethylsulphoxide (or diglyme) (1ml) and heated at reflux under nitrogen. After 30mins, the solution was cooled, and diluted with ethyl acetate. The ethyl acetate solution was washed with aqueous sodium hydroxide, water several times and brine. An oil (16mg) was obtained on removal of the solvent *in. vacuo*.
The product, i.r. 1646, 1270, 1111, 1047, 1020cm^{-1}, was identical from both work-ups and analytical t.l.c. in diethylamine-light petroleum (1 : 9) revealed the presence of one major and one minor component together with a little starting ketal amine (191; R = Et).

G.l.c. on a 1% SE 30 stationary phase at 225°, showed that the two products were in the ratio of 86 : 14. The major component (retention times 5.96 and 1.79 relative to the C_{24} and C_{28} n-alkanes, respectively) was shown, by g.c.m.s, to have molecular weight 371 and was found to be identical in all respects (m.s., g.l.c., t.l.c., i.r.) to the ketal amide (191; R = Ac).

The minor component (retention time 2.10 relative to the C_{24} n-alkane) had molecular weight 357 by g.c.m.s.

FIGURE (4).

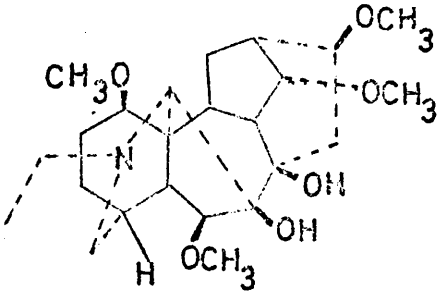


N-BROMOSUCCINIMIDE OXIDATION OF THE KETAL AMINE (191; R = Et).

A solution of the ketal amine (5mg; 0.014m.moles), in dry benzene (1ml), was mixed in a separating funnel with a solution of N-bromosuccinimide (5mg), in dry benzene (1ml). The resultant yellow solution was shaken for 2mins, diluted with benzene, washed with 10% aqueous sodium hydroxide (a quarter of the volume of the benzene solution), then twice with water and dried. The oil, resulting from the removal of the benzene *in vacuo*., was dissolved in methanol (2ml), containing a little chloroform, and a few drops of 10% aqueous potassium hydroxide were added. After stirring at r.t. for 12hrs, the solution was partitioned between water and chloroform. Evaporation of the dried chloroform extract afforded an oil (4mg), i.r. 1643, 1181, 1123, 1108(shoulder), 1050cm^{-1}., which was shown to consist of two major and several minor products by analytical t.l.c. in diethylamine-light petroleum (1 : 9) and methanol-chloroform (2 : 98) solvent systems. G.l.c., on a 1% SE 30 stationary phase at 225°, revealed three compounds, in addition to a little starting amine [peak (1)] (5%). (Figure 4). Component (2) (29%), retention time 2.06 relative to the C_{24} n-alkane, had molecular weight 357 by G.C.M.S. Component (3) (7%), retention time 2.63 relative to the C_{24}n-alkane, seemed to be unstable and a satisfactory molecular weight was not obtained. Component (4) (59%), retention times 3.75 and 1.13 relative to $C_{24}$and C_{28}n-alkanes, respectively had molecular

weight 371 by G.C.M.S.

A solution of the N-bromosuccinimide product (2mg), in dry tetrahydrofuran, was refluxed with lithium aluminium hydride for two hrs. and then stirred at r.t. overnight. The usual work-up provided material, whose g.l.c. trace contained only peaks (1) and (4) in approx. equal proportions i.e. peaks (2) and (3) had reverted to starting amine. Furthermore, the i.r. spectrum of the mixture still contained the 1643cm^{-1} carbonyl absorption, although reduced slightly in intensity.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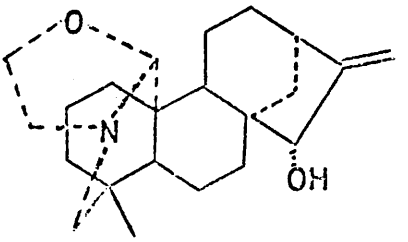
OCH3
N
OH
OH
H
OCH3

1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N
OH

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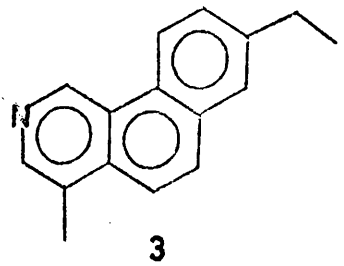
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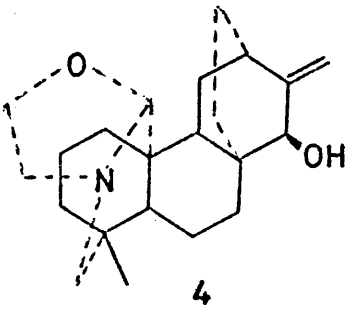
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N
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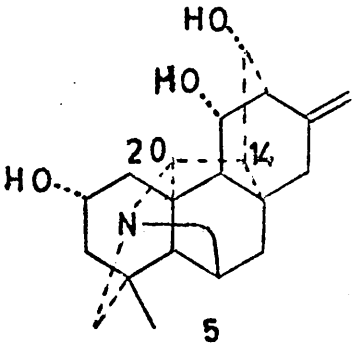
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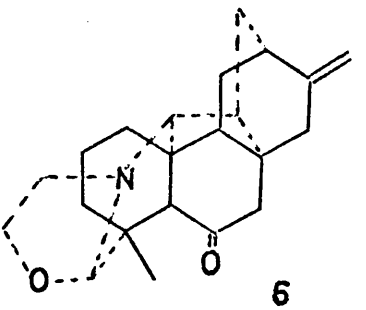
HO
20
14
HO
N

5


N
O
O

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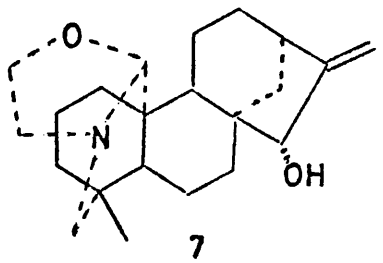
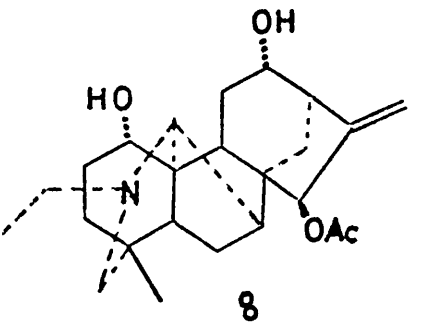
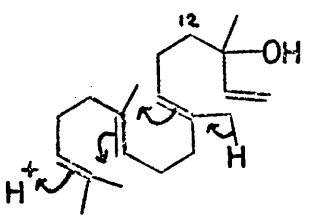

O
N
OH

7


OH
HO
N
OAc

8

SCHEME 1.



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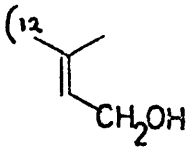

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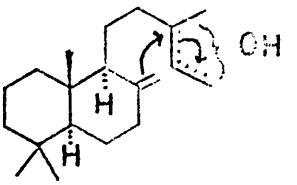

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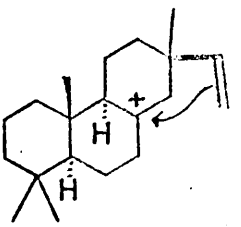

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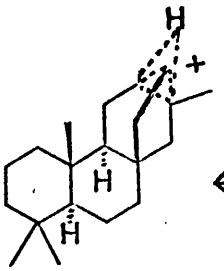

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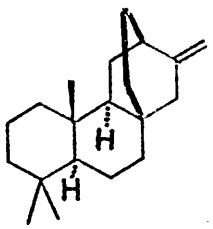

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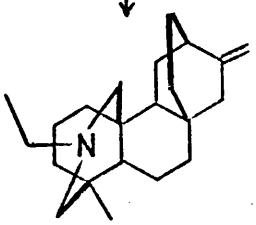

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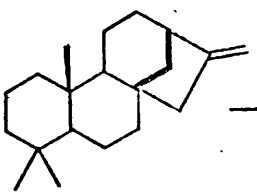

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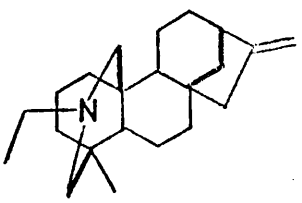

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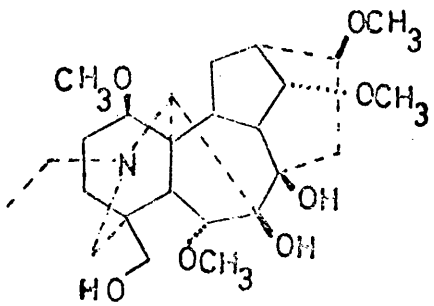

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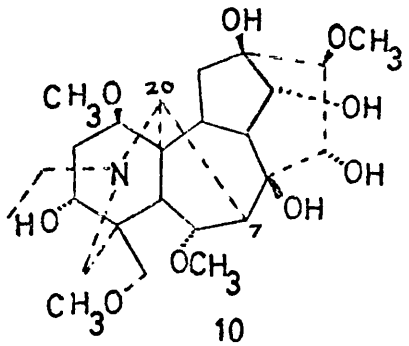

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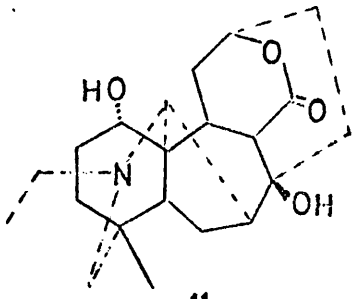

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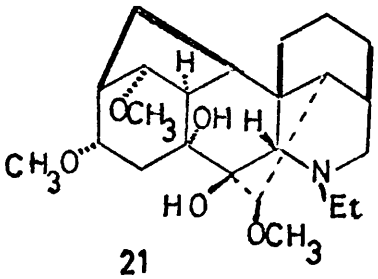

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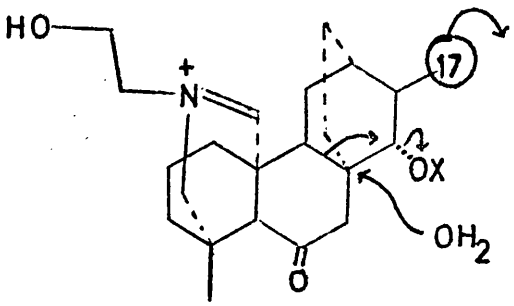

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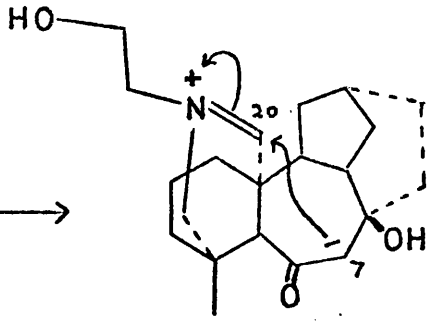

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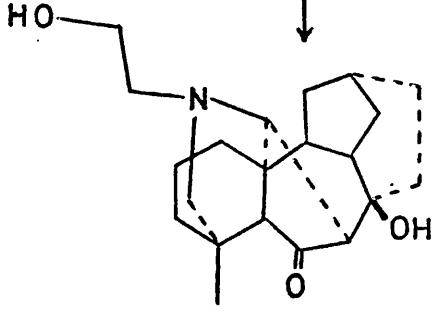

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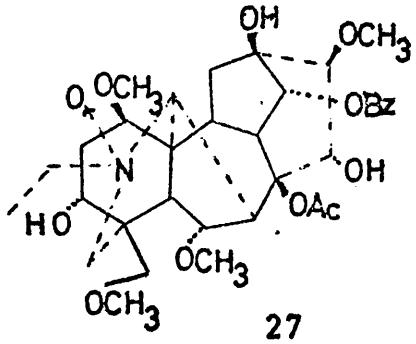

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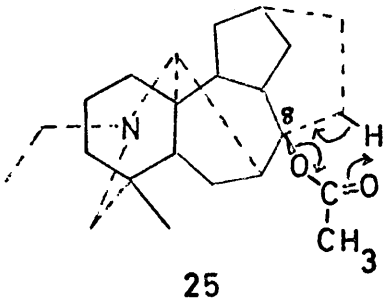

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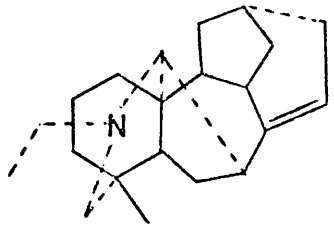

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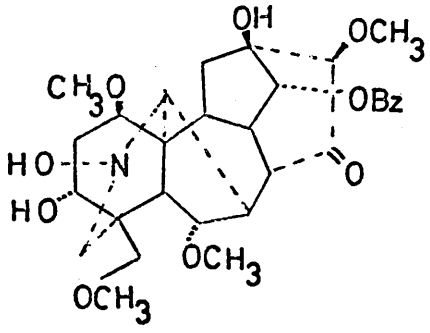

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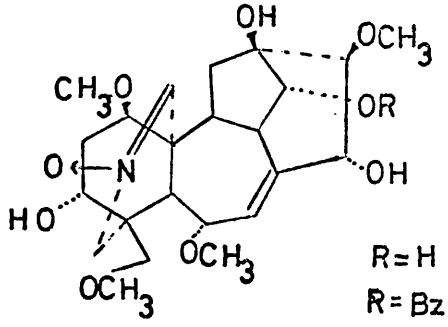

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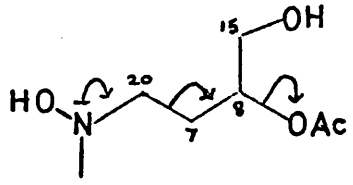

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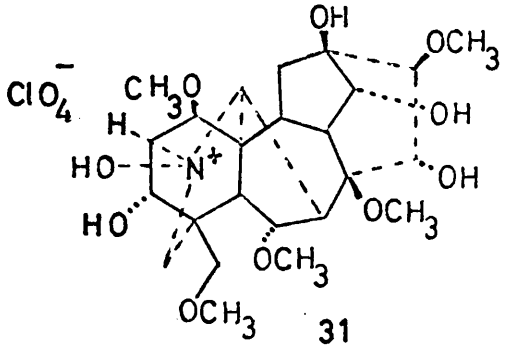

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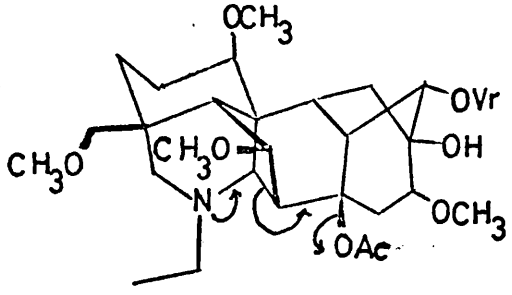

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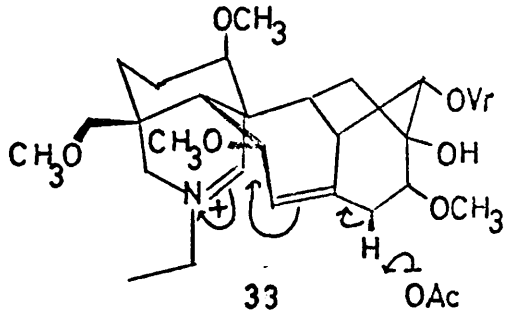

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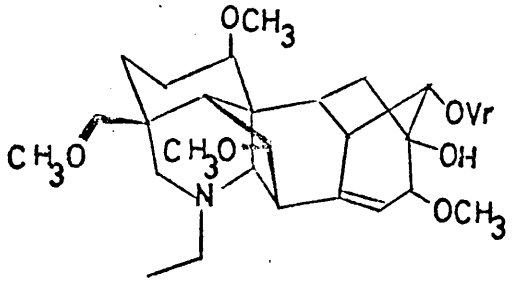

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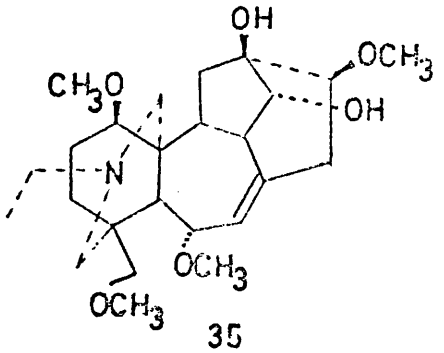

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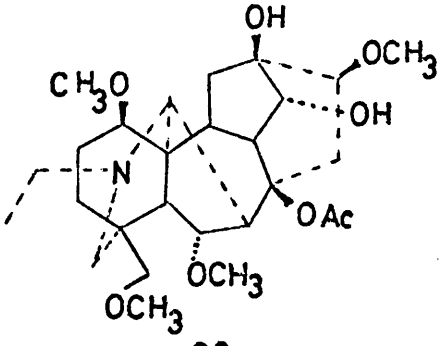

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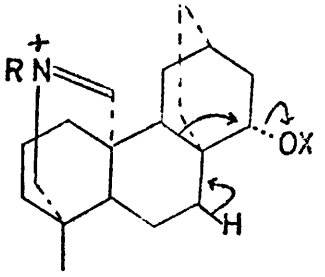

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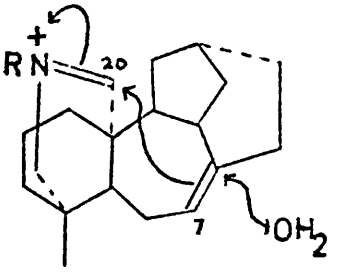

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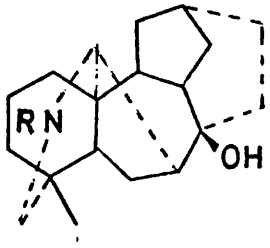

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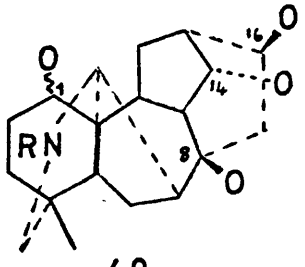

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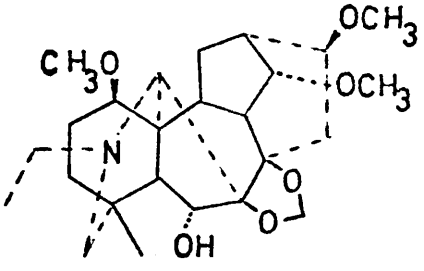

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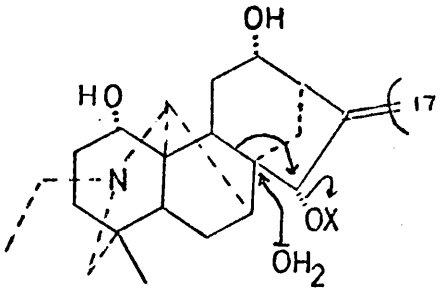

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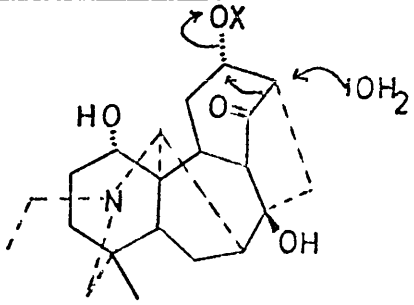

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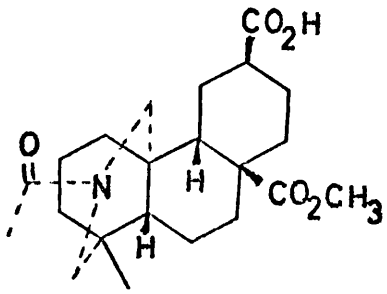

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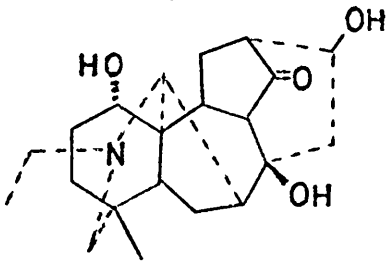

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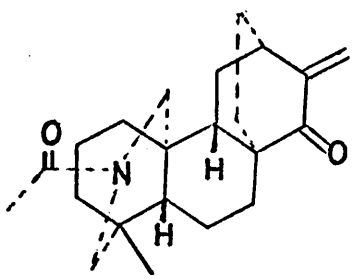

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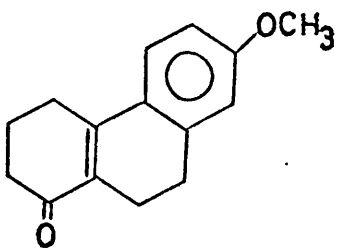

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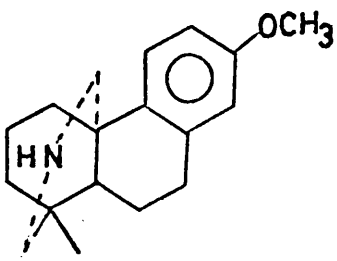

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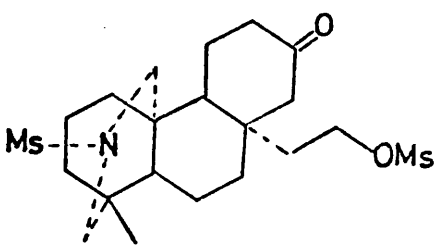

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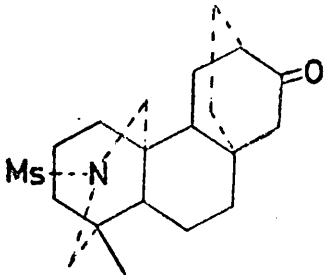

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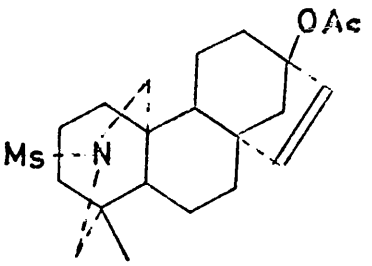

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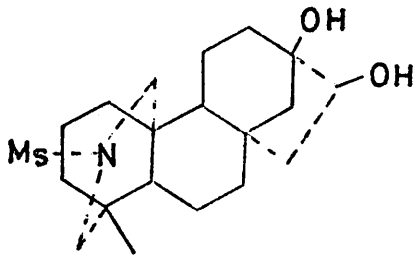

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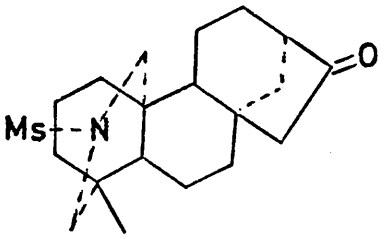

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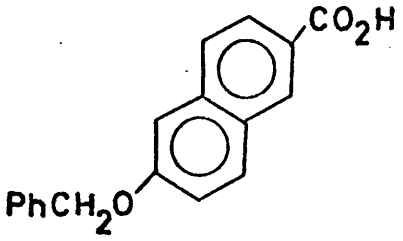

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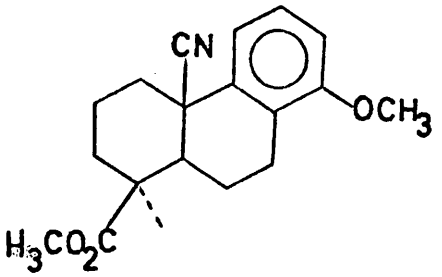

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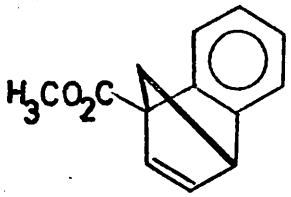

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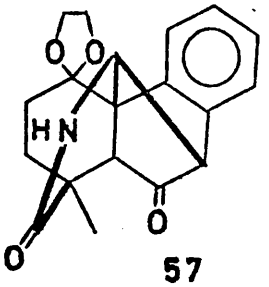

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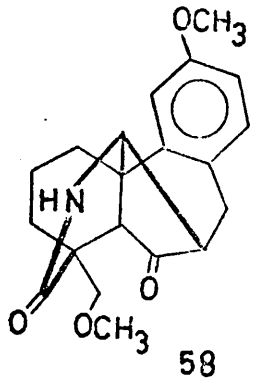

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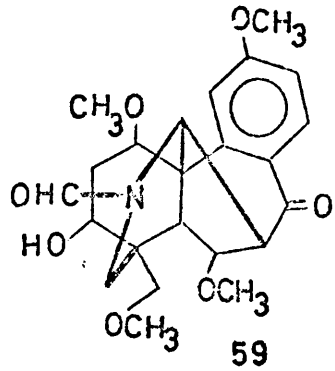

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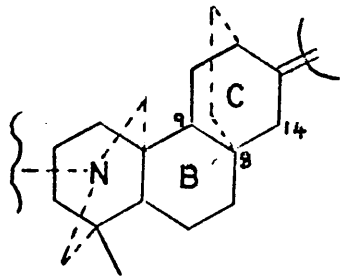

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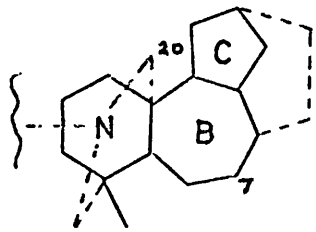

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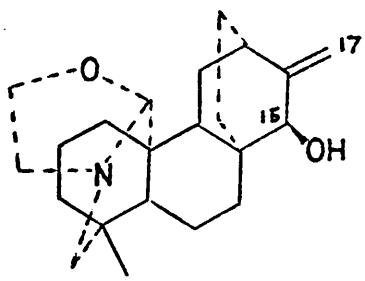

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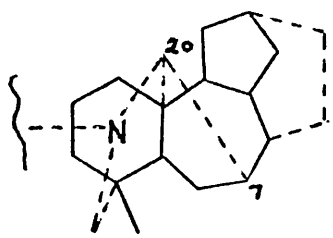

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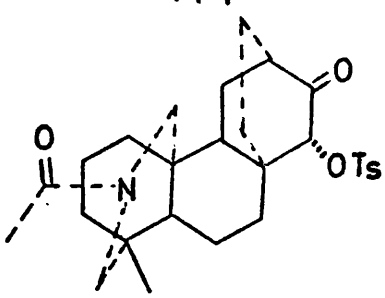

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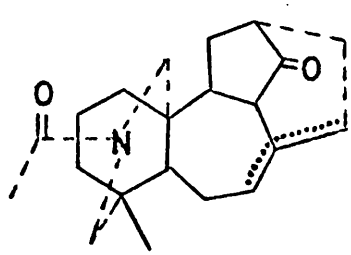

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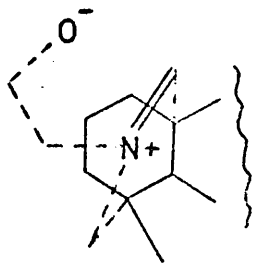

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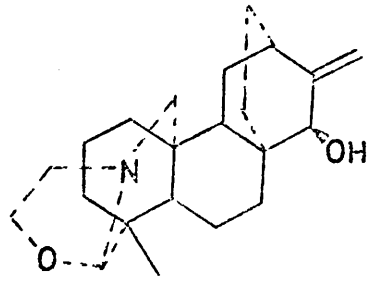

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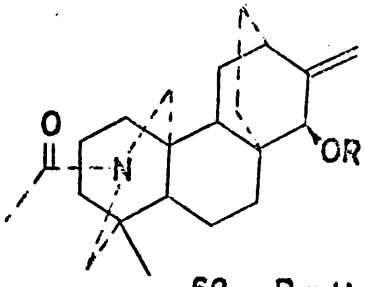
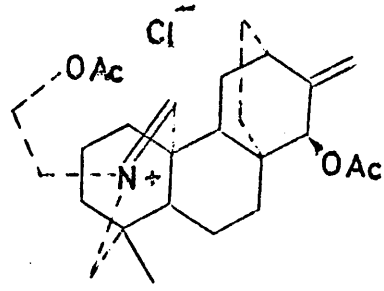


68 R = H
74 R = Ac



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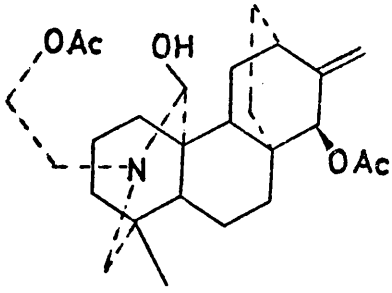

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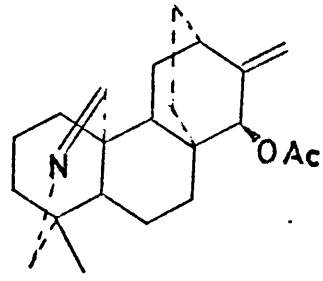

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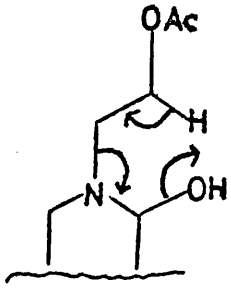

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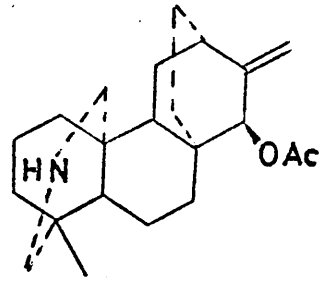

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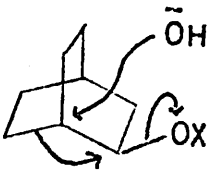

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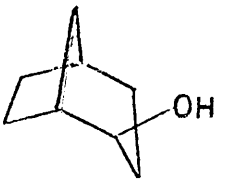

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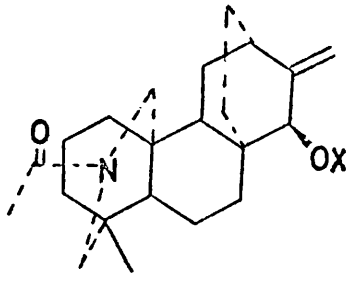

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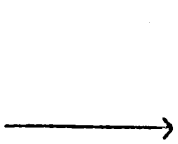

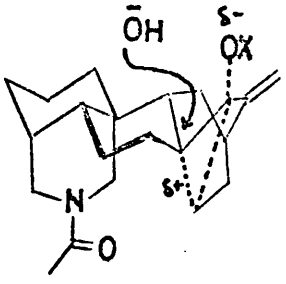

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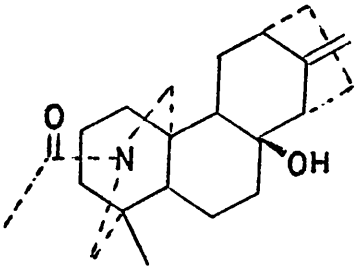

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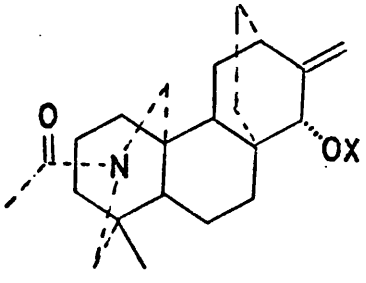

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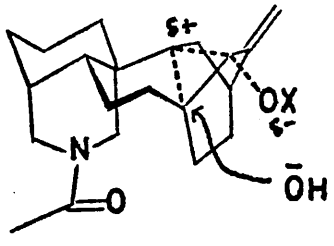

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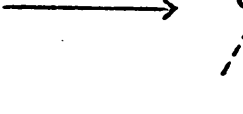

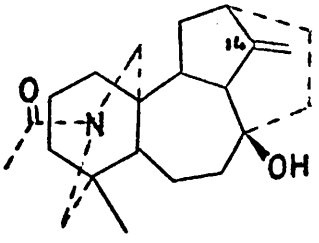

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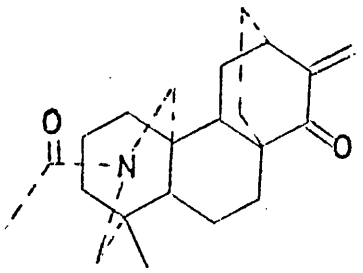

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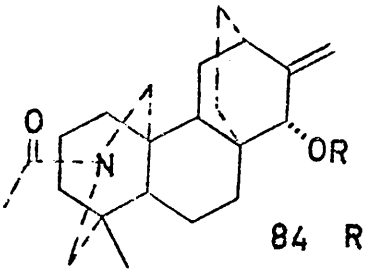
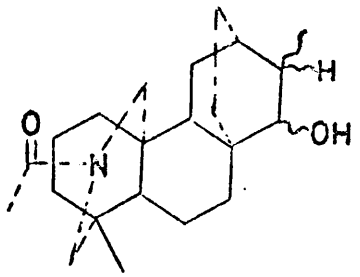


84 R = H

87 R = Bs

91 R = Ac



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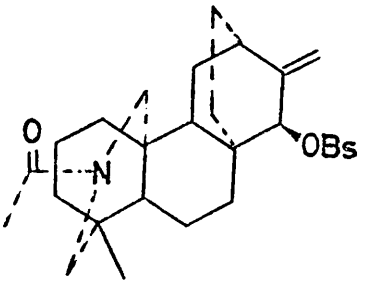

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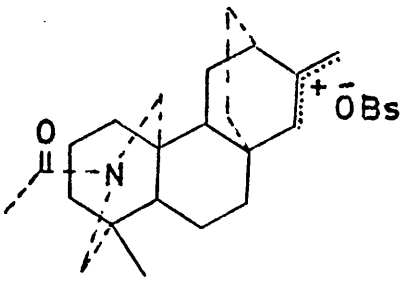

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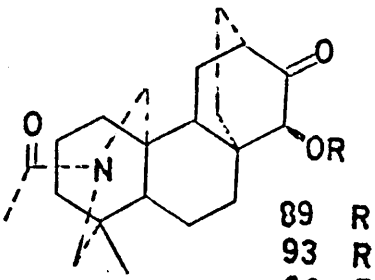
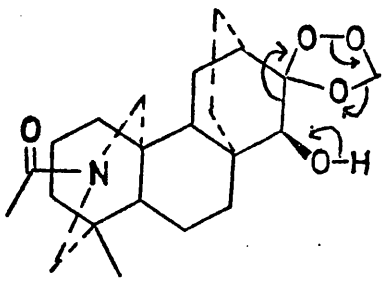


89 R = H

93 R = Ac

96 R = Ts

97 R = Bs



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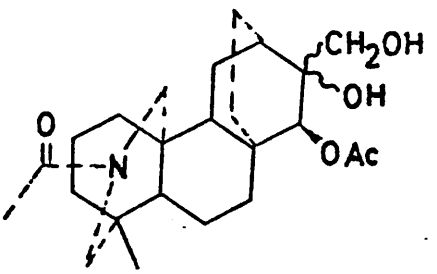

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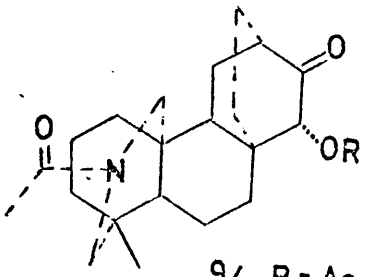
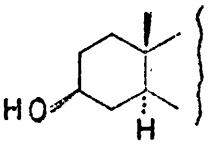


94 R = Ac
95 R = H



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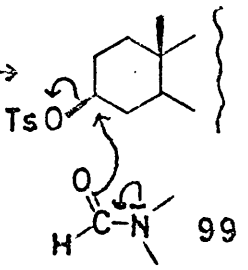

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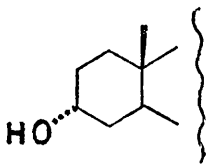

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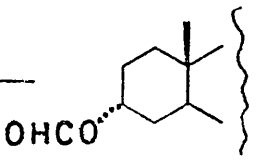

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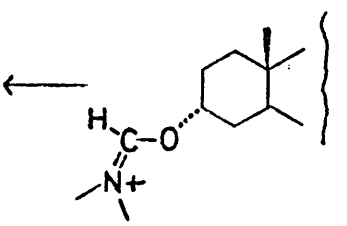

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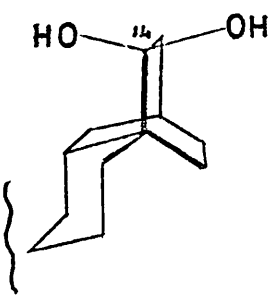

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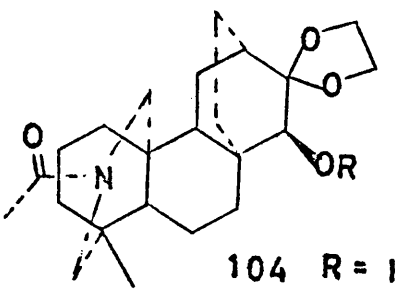
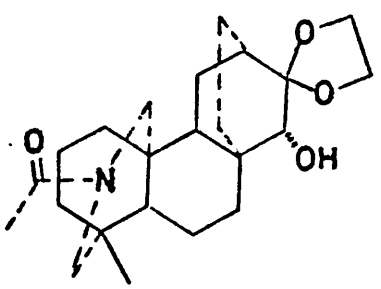


104 R = H
108 R = Ac



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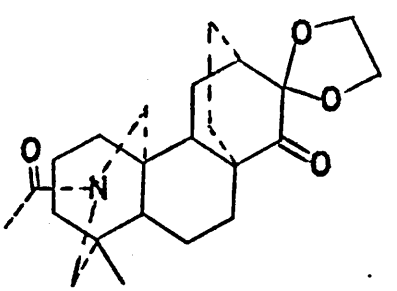

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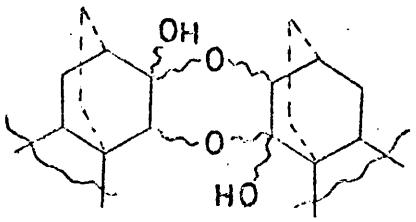

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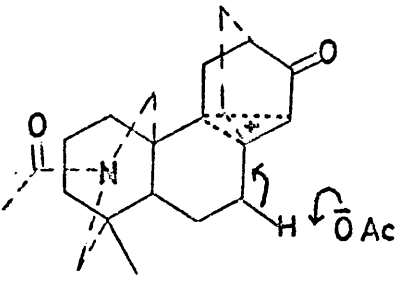

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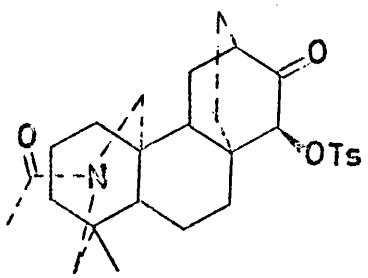

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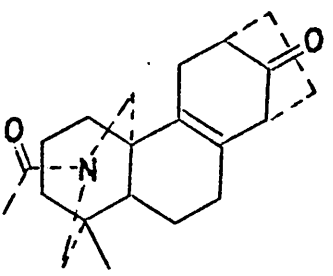

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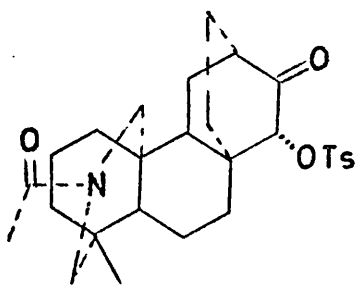

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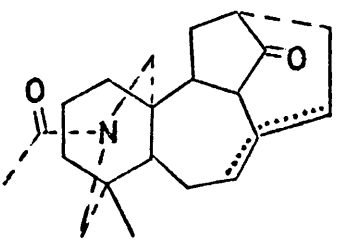

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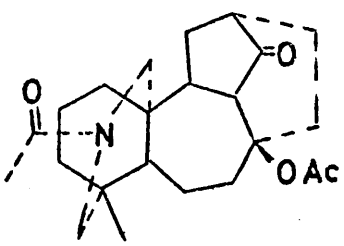

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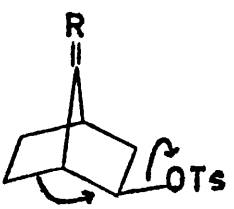
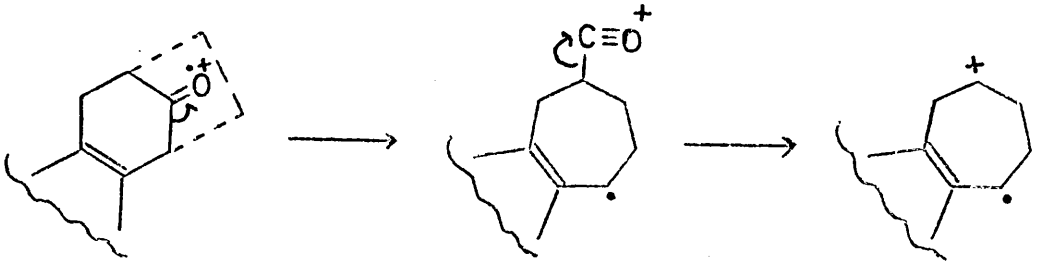
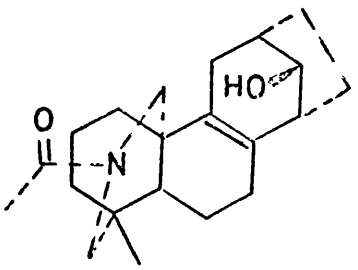


112 R = O
113 R = H_2



114 115 116



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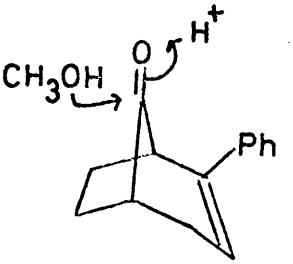

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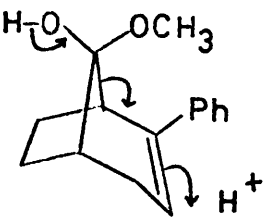

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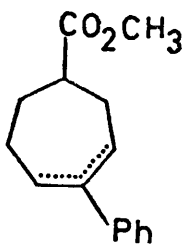

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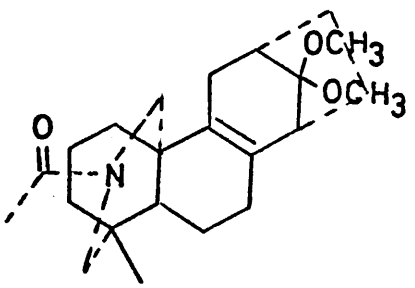

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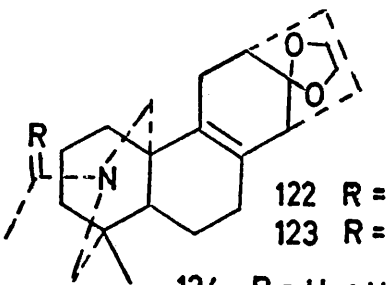
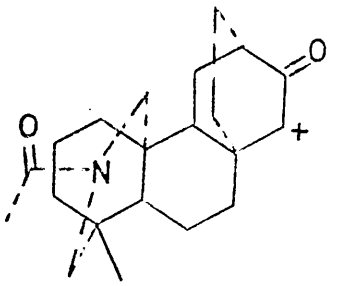


122 R = O
123 R = H_2
124 R = H_2; HX SALT



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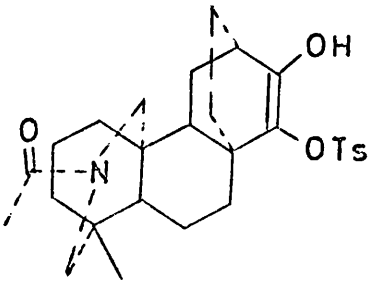

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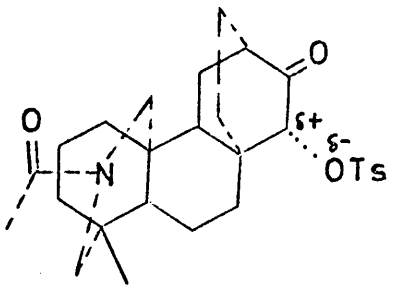

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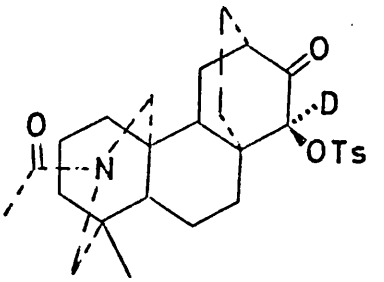

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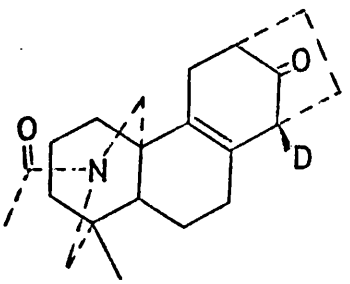

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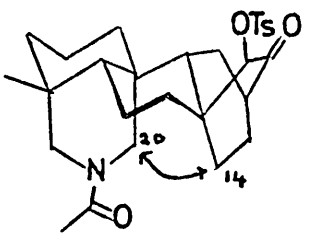
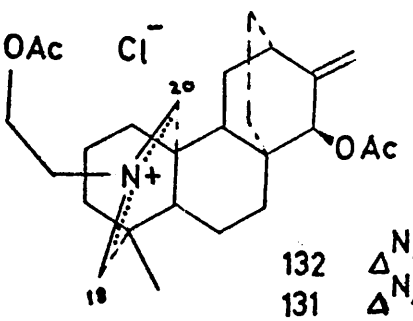
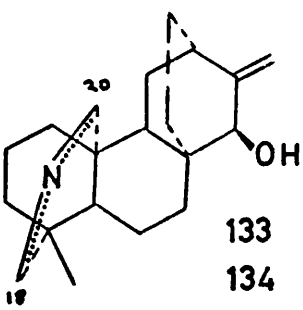


130



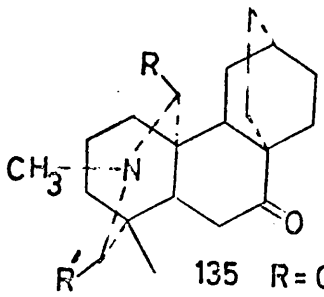
132 $\Delta^{N,20}$

131 $\Delta^{N,18}$

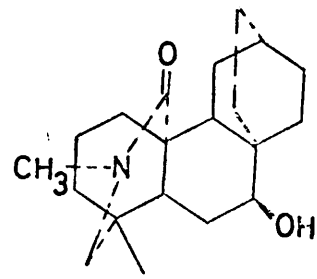


133 $\Delta^{N,18}$

134 $\Delta^{N,20}$



135 R = OH ; R′ = H
136 R = H ; R′ = OH



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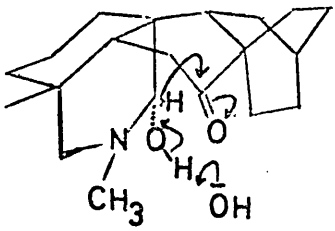

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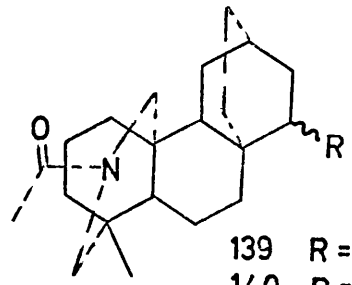
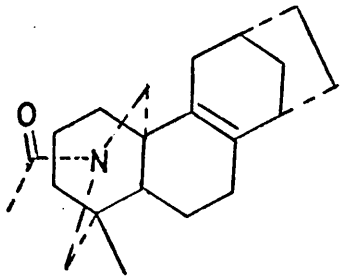
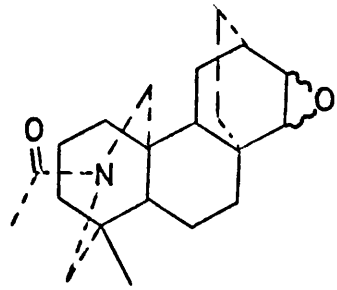


139 R = βOH
140 R = αOH
141 R = αOTs



142



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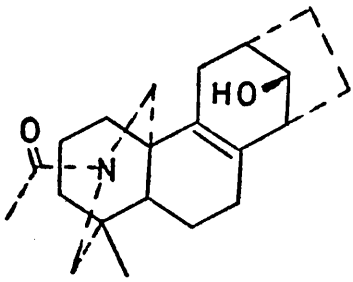

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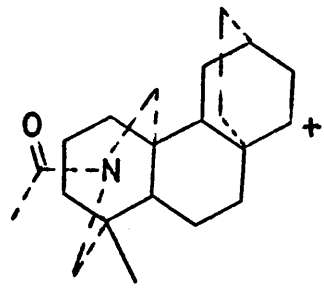

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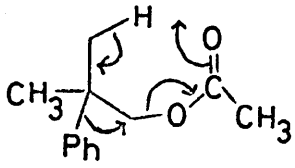

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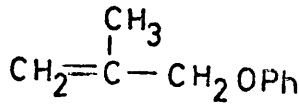

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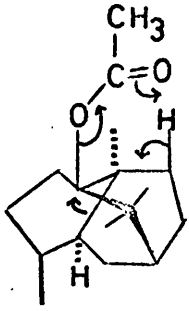

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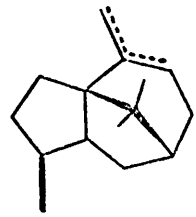

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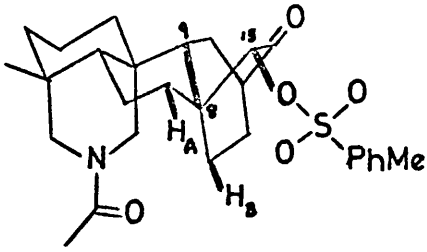

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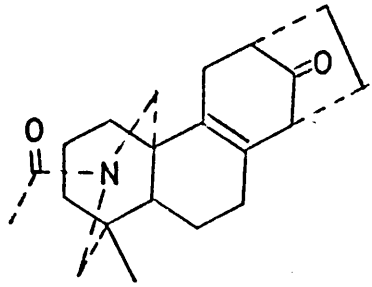

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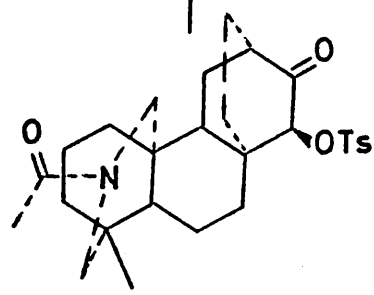

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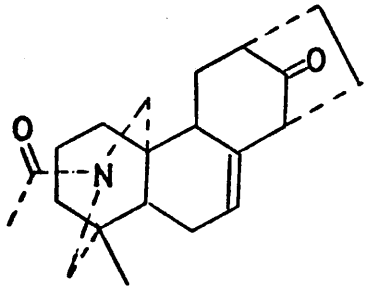

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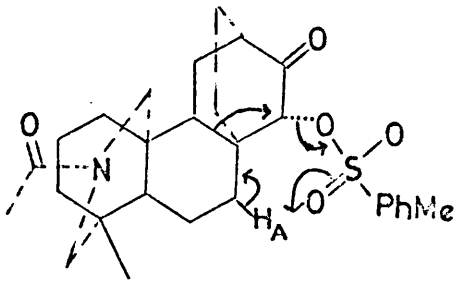

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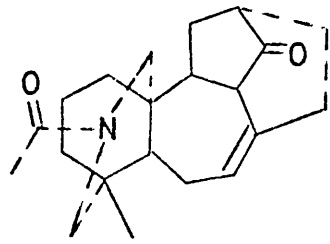

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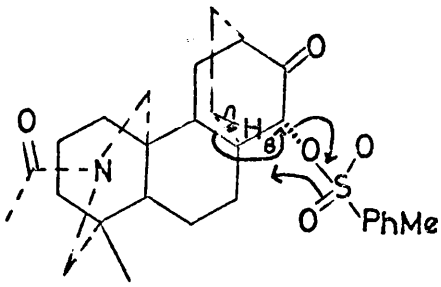

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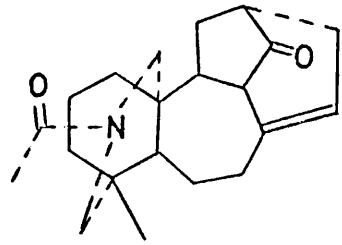

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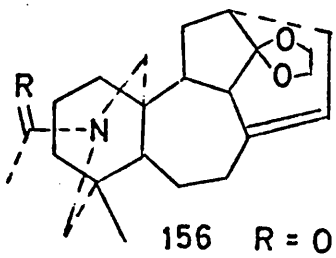
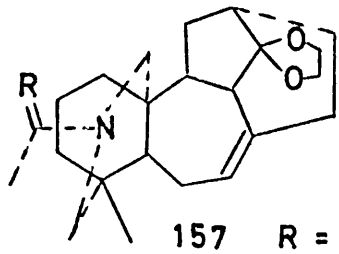
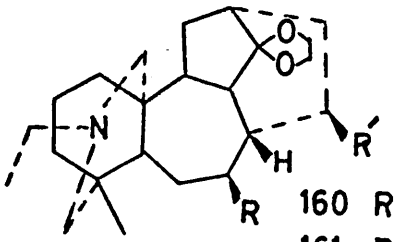


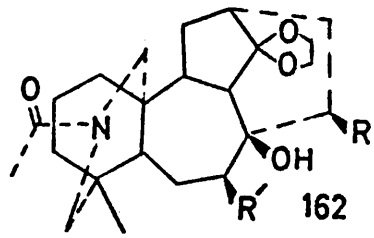
156 R = O
158 R = H_2



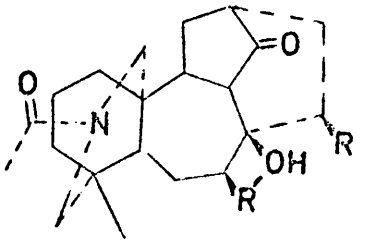
157 R = O
159 R = H_2



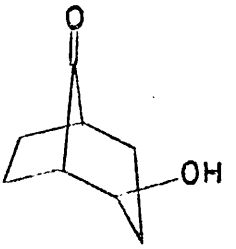
160 R = OH; R′ = H
161 R = H; R′ = OH



162 R = OH; R′ = H
163 R = H; R′ = OH



164 R = OH ; R' = H
165 R = H ; R' = OH



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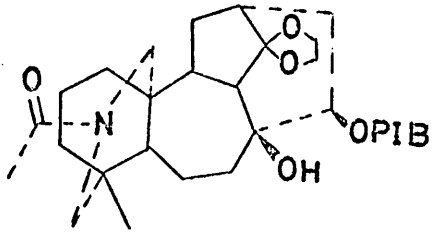

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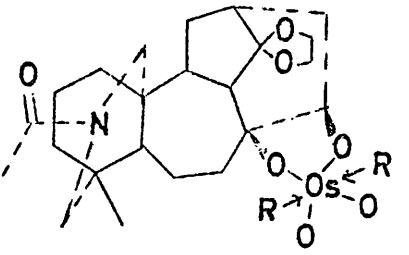

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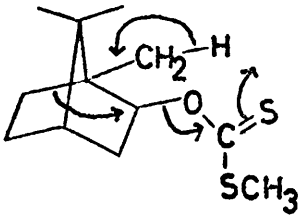

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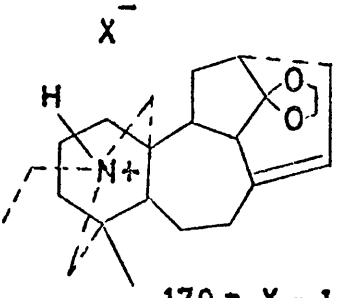
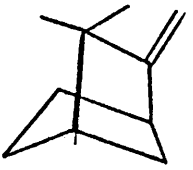


170 a X = I
b X = Br



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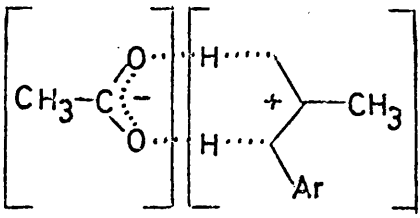

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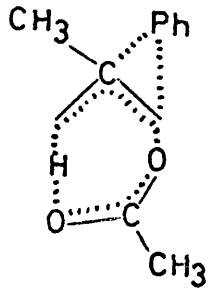

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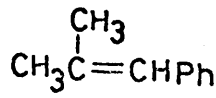

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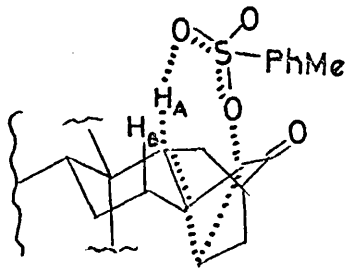

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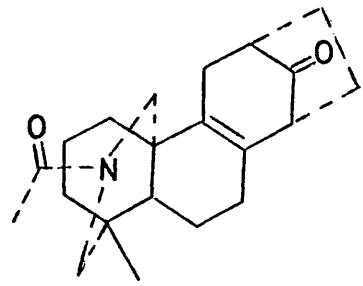

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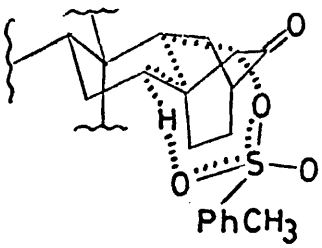

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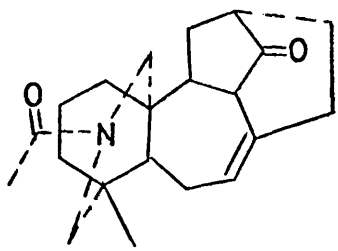

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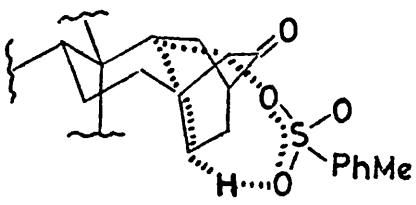

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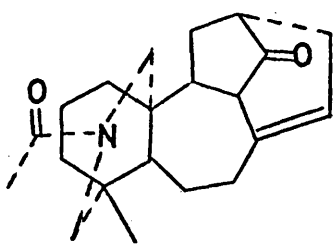

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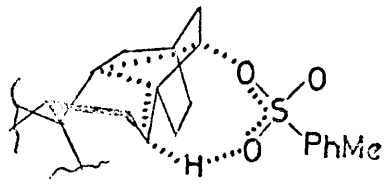

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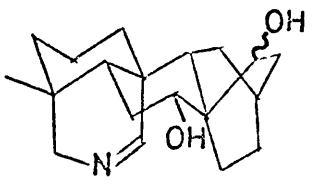

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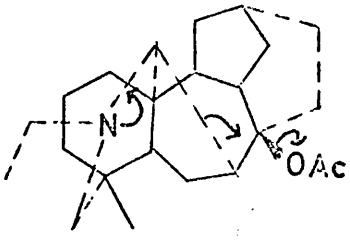

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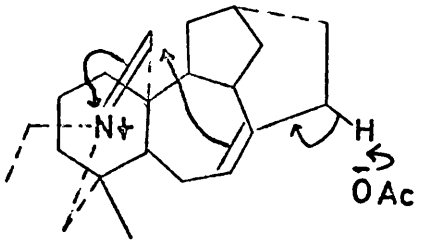

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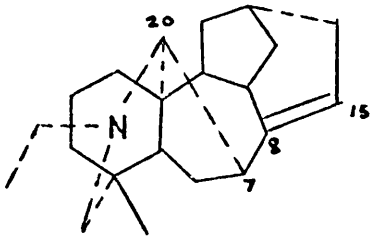

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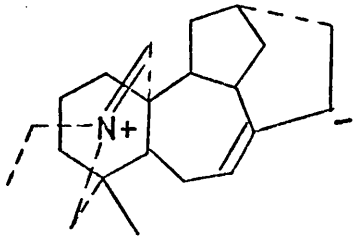

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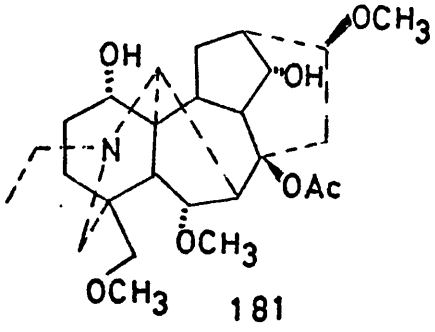

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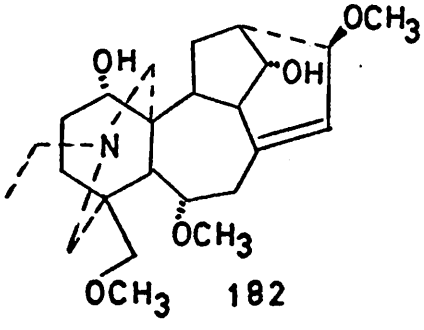

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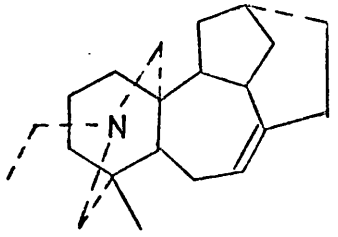

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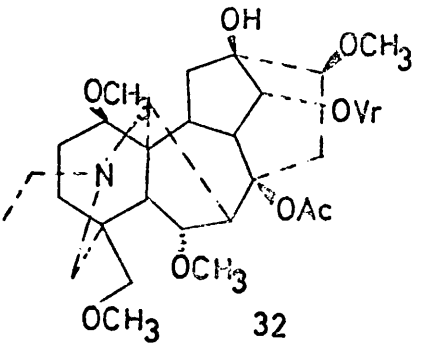

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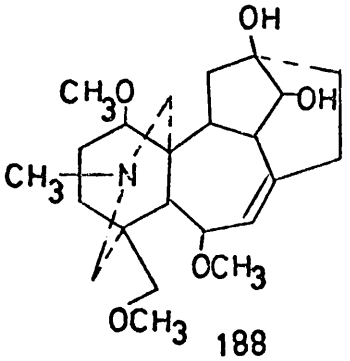

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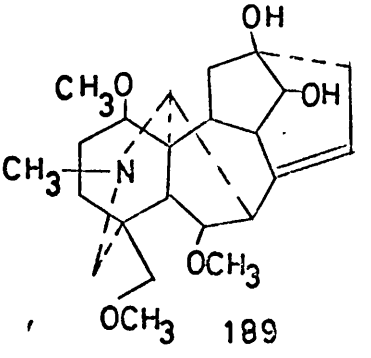

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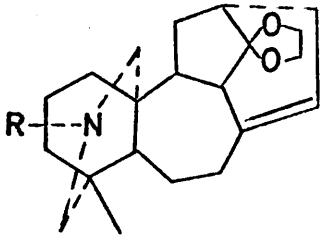

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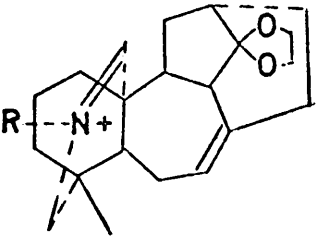

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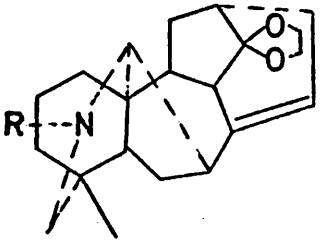

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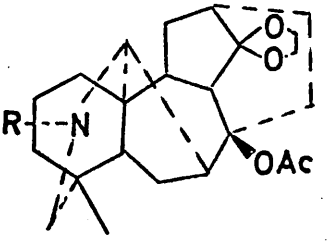

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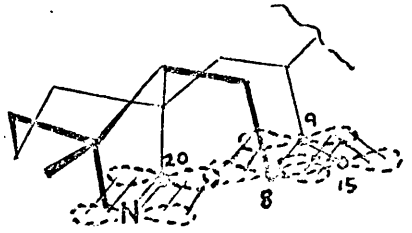

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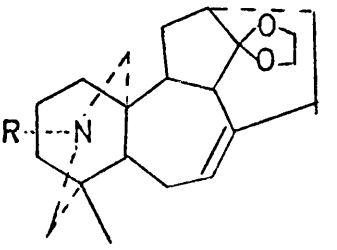

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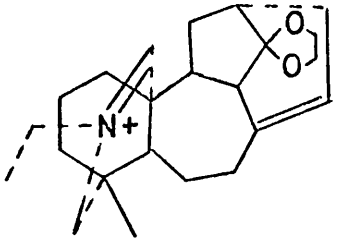

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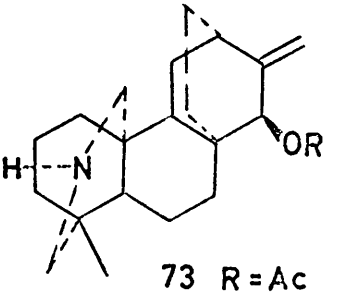
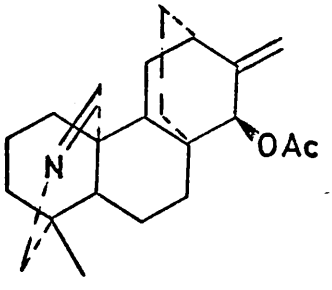


73 R = Ac

199 R = H



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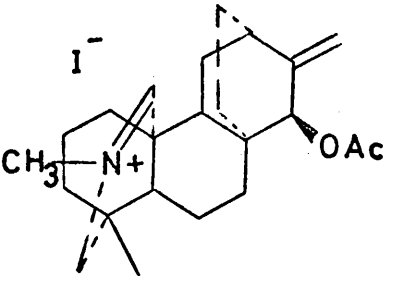

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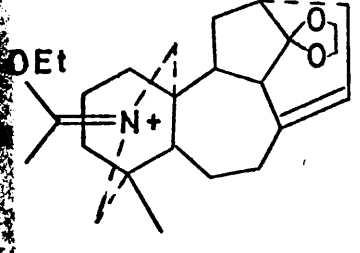

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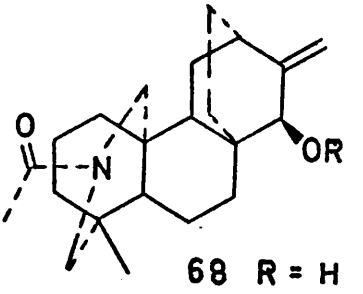
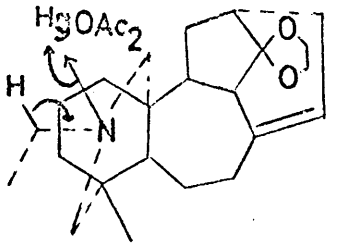


68 R = H

74 R = Ac



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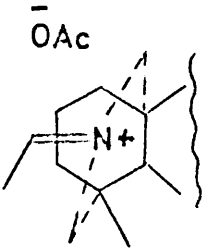

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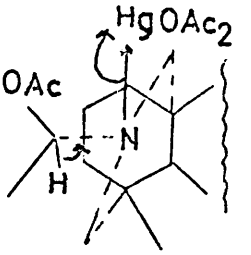

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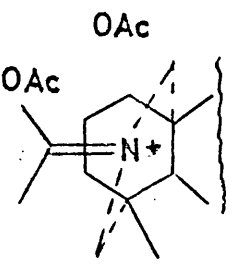
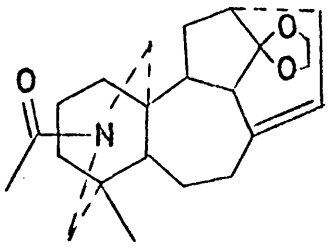


203

H_2O



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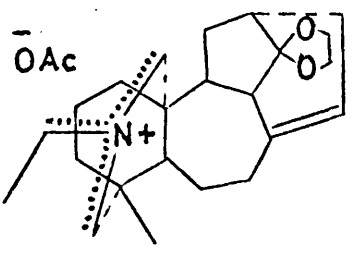
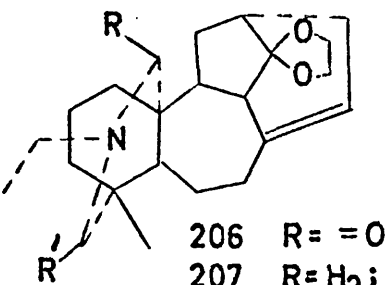
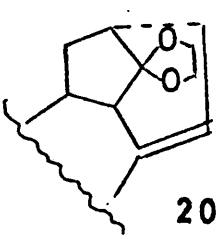


205



206 R = =O; R = H_2
207 R = H_2; R = =O
211 R = OH; R = H_2
212 R = H_2; R = OH



208

$\xrightarrow[31]{-CH_3O}$ [209] $\xrightarrow[28]{-CO}$ [210]

CHAPTER 2.

X-RAY ANALYSIS.

THE STRUCTURE OF THE KETO-OLEFIN FROM PYROLYSIS OF THE KETO-TOSYLATE (64).

The conversion of the keto-olefin (154) into the hydriodide salt of the amino-ketal (158) was described in a previous chapter and examination of a single crystal of this material by standard X-ray and chemical techniques afforded the following data.

CRYSTAL DATA.

$C_{23}H_{36}NO_2I$, M = 485, Monoclinic,

a = 11.20(3), b = 7.81(2), c = 12.92(3)Å,

β = 107.4(0.5)°, U = 1078Å^3, D_m = 1.46 (by flotation in aqueous potassium iodide), Z = 2,

D_c = 1.49, F(000) = 500, Linear absorption coefficient for Cu K_α X-rays (λ = 1.542Å),

μ = 120cm, Space Group $P2_1$ (C_2^2, N°4).

CRYSTALLOGRAPHIC MEASUREMENTS.

The unit cell parameters were obtained from oscillation and Weissenberg photographs taken with Ni-filtered Cu-K_α ($\lambda = 1.5418$Å) radiation and from precession photographs taken with Zr-filtered Mo-K_α ($\lambda = 0.7107$Å) radiation. The systematic absences in the X-ray spectra (o$\underline{k}$o absent if $\underline{k}$ is odd), together with the optical activity of the derivative, established the space group as $P2_1$.

Three-dimensional intensity data were obtained from equi-inclination Weissenberg films[91] of the $\underline{h}o$-6$\underline{l}$ reciprocal lattice nets, taken with Cu K_α radiation and a needle shaped crystal of small cross section (0.1mm^2), rotating about the needle ($\underline{b}$) axis. The intensities were measured by visual comparison with a calibrated wedge and corrected for the appropriate Lorentz and polarisation factors. No absorption corrections were applied. In all, 1260 independent reflexions were measured; no account was taken of unobserved reflexions during the analysis. In the early stages of the structure determination, the structure amplitudes were placed on an approximately absolute scale by making $k\Sigma|Fo| = \Sigma|Fc|$ for each layer.

STRUCTURE DETERMINATION.

The x and z co-ordinates of the iodide ion were obtained from the Harker section at V = 0.5 of the three - dimensional Patterson function. The Space group $P2_1$ is polar in the y - direction and the y-co-ordinate of the iodide ion was arbitrarily set at zero. The analysis then proceeded directly on the basis of the phase - determining heavy - atom method[92]. The first electron-density distribution, calculated with phase angles appropriate to the iodide ion and observed structure amplitudes, was inevitably slightly complicated by the presence of pseudo-mirror planes at y = 0, $\frac{1}{2}$, etc. Nevertheless, by careful selection of atomic sites, it proved possible to recognise the complete molecular structure, although not all of the atoms were included in the second round of structure factor calculations, because of some ambiguities in their precise y-co-ordinates. A further two rounds of electron density and structure factor calculations allowed precise co-ordinates for all the non-hydrogen atoms in the structure to be determined and lowered the discrepancy factor R to 0.23.

Table 1

Fractional Co-ordinates, Isotropic Thermal Parameters ($Å^2$) and e.s.d.'s.

	x/a	y/b	z/c	Uiso
I(1)	0.08246 (2)	-0.00132 (0)	0.16714 (2)	0.0840 (1)
N(1)	0.20646 (25)	0.59180 (45)	0.17987 (23)	0.0545 (7)
O(1)	0.75773 (32)	0.93085 (47)	0.33911 (27)	0.1066 (11)
O(2)	0.87705 (29)	0.71253 (48)	0.42873 (25)	0.0914 (9)
C(1)	0.38485 (40)	0.81811 (69)	0.11654 (35)	0.0761 (12)
C(2)	0.28378 (44)	0.78354 (77)	0.01180 (40)	0.0791 (14)
C(3)	0.29268 (44)	0.60174 (80)	-0.03220 (39)	0.0846 (14)
C(4)	0.31106 (34)	0.46676 (75)	0.05384 (30)	0.0748 (12)
C(5)	0.44049 (30)	0.49422 (125)	0.14282 (26)	0.0719 (9)
C(6)	0.47743 (48)	0.34156 (74)	0.21973 (41)	0.0828 (15)
C(7)	0.62177 (64)	0.30974 (98)	0.27638 (51)	0.1095 (20)
C(8)	0.66656 (33)	0.47690 (98)	0.35477 (30)	0.0777 (11)
C(9)	0.66373 (43)	0.63903 (68)	0.30438 (38)	0.0697 (13)
C(10)	0.54527 (41)	0.75683 (67)	0.28065 (34)	0.0736 (12)
C(11)	0.42534 (45)	0.69072 (71)	0.19922 (39)	0.0772 (13)
C(12)	0.54892 (49)	0.78718 (84)	0.39783 (43)	0.1028 (16)
C(13)	0.69018 (48)	0.79775 (79)	0.46882 (42)	0.0941 (15)
C(14)	0.74777 (41)	0.78016 (70)	0.38975 (36)	0.0790 (13)
C(15)	0.68556 (41)	0.46064 (81)	0.46060 (37)	0.0920 (15)

Table 1 cont'd.

C(16)	0.70916 (53)	0.63520 (91)	0.53243 (48)	0.1148 (19)
C(18)	0.21150 (33)	0.45027 (56)	0.10701 (30)	0.0681 (11)
C(19)	0.29770 (51)	0.29008 (89)	-0.01169 (45)	0.0872 (16)
C(20)	0.32799 (34)	0.64879 (58)	0.26120 (30)	0.0627 (10)
C(21)	0.11873 (33)	0.54532 (56)	0.25960 (29)	0.0699 (11)
C(22)	-0.01718 (36)	0.50000 (107)	0.18305 (31)	0.0866 (13)
C(23)	0.87885 (44)	1.01509 (130)	0.37894 (37)	0.1056 (15)
C(24)	0.95922 (64)	0.85966 (109)	0.43248 (53)	0.1403 (23)

Table 2

Interatomic distances (Å) and angles °.

(a) Bonded distances

C(1) - C(2)	1.51	C(10)- C(12)	1.52
C(1) - C(11)	1.43	C(11)- C(20)	1.57
C(2) - C(3)	1.54	C(12)- C(13)	1.58
C(3) - C(4)	1.50	C(13)- C(14)	1.39
C(4) - C(5)	1.57	C(13)- C(16)	1.49
C(4) - C(18)	1.48	C(14)- O(1)	1.37
C(4) - C(19)	1.60	C(14)- O(2)	1.48
C(5) - C(6)	1.53	C(15)- C(16)	1.63
C(5) - C(11)	1.73	C(18)- N(1)	1.46
C(6) - C(7)	1.58	C(20)- N(1)	1.52
C(7) - C(8)	1.64	C(21)- N(1)	1.66
C(8) - C(9)	1.42	C(21)- C(22)	1.59
C(8) - C(15)	1.33	C(23)- O(1)	1.46
C(9) - C(10)	1.57	C(23)- C(24)	1.55
C(9) - C(14)	1.64	C(24)- O(2)	1.46
C(10)- C(11)	1.53		

(b) Bonded angles.

C(2)	C(1)	C(11)	122
C(1)	C(2)	C(3)	112
C(2)	C(3)	C(4)	113
C(3)	C(4)	C(5)	110
C(3)	C(4)	C(18)	117
C(3)	C(4)	C(19)	104
C(5)	C(4)	C(18)	109
C(5)	C(4)	C(19)	115
C(18)	C(4)	C(19)	102
C(4)	C(5)	C(6)	112
C(4)	C(5)	C(11)	104
C(6)	C(5)	C(11)	117
C(5)	C(6)	C(7)	118
C(6)	C(7)	C(8)	104
C(7)	C(8)	C(9)	118
C(7)	C(8)	C(15)	119
C(9)	C(8)	C(15)	122
C(8)	C(9)	C(10)	121
C(8)	C(9)	C(14)	111
C(10)	C(9)	C(14)	91
C(9)	C(10)	C(11)	117
C(9)	C(10)	C(12)	97
C(11)	C(10)	C(12)	120
C(5)	C(11)	C(10)	114
C(1)	C(11)	C(5)	111
C(1)	C(11)	C(10)	107
C(1)	C(11)	C(20)	114
C(5)	C(11)	C(20)	102
C(10)	C(11)	C(20)	109
C(10)	C(12)	C(13)	108
C(12)	C(13)	C(14)	100
C(12)	C(13)	C(16)	103
C(14)	C(13)	C(16)	108
C(9)	C(14)	C(13)	105
C(9)	C(14)	O(1)	112
C(9)	C(14)	O(2)	107
C(13)	C(14)	O(2)	114
C(13)	C(14)	O(1)	113
O(1)	C(14)	O(2)	105
C(8)	C(15)	C(16)	117
C(13)	C(16)	C(15)	115
C(4)	C(18)	N(1)	114
C(11)	C(20)	N(1)	109
C(22)	C(21)	N(1)	107
C(18)	N(1)	C(20)	118
C(18)	N(1)	C(21)	112
C(20)	N(1)	C(21)	102
O(1)	C(23)	C(24)	99
O(2)	C(24)	C(23)	109
C(14)	O(1)	C(23)	115
C(14)	O(2)	C(24)	106

(c) Some non-bonded intramolecular distances.

C(1)	...C(4)	2.91	C(8)	...C(12)	2.89
C(1)	...N	2.96	C(8)	...C(13)	2.88
C(1)	...C(12)	3.56	C(8)	...C(20)	3.86
C(1)	...C(9)	3.61	C(9)	...C(13)	2.40
C(1)	...C(18)	3.45	C(9)	...C(16)	2.84
C(2)	...C(18)	3.09	C(9)	...C(20)	3.63
C(2)	...C(20)	3.28	C(9)	...C(23)	3.74
C(2)	...N	2.97	C(9)	...C(24)	3.66
C(2)	...C(5)	3.05	C(10)	...O(1)	2.65
C(3)	...N	3.17	C(10)	...C(15)	3.32
C(3)	...C(11)	3.00	C(10)	...C(16)	3.36
C(3)	...C(20)	3.71	C(11)	...C(18)	3.00
C(4)	...C(20)	3.00	C(11)	...C(14)	3.78
C(5)	...N	2.90	C(11)	...C(13)	3.93
C(5)	...C(8)	3.13	C(12)	...C(20)	2.79
C(5)	...C(9)	2.96	C(12)	...C(15)	2.96
C(6)	...C(20)	3.06	C(12)	...O(1)	2.89
C(6)	...N	3.52	C(13)	...C(23)	3.19
C(6)	...C(18)	3.02	C(13)	...C(24)	3.22
C(6)	...C(9)	3.10	C(14)	...C(15)	2.82
C(6)	...C(10)	3.37	C(15)	...O(2)	3.03
C(6)	...C(19)	3.09	C(16)	...O(2)	2.68
C(6)	...C(15)	3.41	C(16)	...O(1)	3.56
C(7)	...C(10)	3.60	C(16)	...C(24)	3.84
C(7)	...C(11)	3.66	C(18)	...C(22)	3.03
C(8)	...O(2)	2.92	C(18)	...I	3.98
C(8)	...C(11)	3.30	C(20)	...C(22)	3.87

(d) Interatomic distances

$I \ldots N^{I}$	3.45
$I \ldots C(21)^{I}$	3.72
$O(1) \ldots C(7)^{II}$	3.32
$C(2) \ldots C(22)^{III}$	3.69
$C(7) \ldots C(23)^{I}$	3.61

The superscripts refer to the following equivalent positions:-

I: $\underline{x}, -1+\underline{y}, \underline{z},$

II: $\underline{x}, 1+\underline{y}, -\underline{z},$

III: $-\underline{x}, 1/2+\underline{y}, -\underline{z}.$

TABLE (3)

H	K	L	Fo	Fc
0	0	2	46.6	50.8
0	0	3	67.2	78.5
0	0	4	25.9	27.0
0	0	5	49.9	51.1
0	0	6	59.6	57.9
0	0	7	38.0	36.1
0	0	8	20.1	12.8
0	0	9	28.7	30.3
0	0	10	10.2	11.3
0	0	11	13.2	14.8
0	0	12	11.0	10.6
0	0	13	5.9	1.4
0	0	14	5.8	5.2
1	0	1	17.9	8.1
1	0	2	121.1	146.6
1	0	3	47.6	57.0
1	0	4	5.4	5.6
1	0	5	57.9	61.8
1	0	6	49.5	43.2
1	0	7	5.0	6.0
1	0	8	36.2	37.1
1	0	9	27.2	22.9
1	0	11	17.2	16.9
1	0	12	13.2	12.7
1	0	14	4.8	5.5
1	0	15	3.5	3.0
1	0	-2	112.5	114.7
1	0	-3	108.3	114.8
1	0	-4	84.9	89.4
1	0	-5	18.4	18.8
1	0	-6	42.4	42.8
1	0	-7	30.4	35.5
1	0	-8	5.8	8.3
1	0	-9	20.2	20.2
1	0	-10	27.9	24.2
1	0	-12	18.6	19.6
1	0	-13	10.5	9.7
1	0	-15	7.8	8.0
2	0	1	65.5	55.1
2	0	2	107.7	109.3
2	0	3	46.6	43.4
2	0	4	4.8	6.0
2	0	5	51.6	60.2
2	0	6	16.3	15.8
2	0	7	19.0	21.8
2	[illegible]	[illegible]	[illegible]	33.3
2	0	9	17.7	14.9
2	0	10	13.5	16.1
2	0	11	10.0	10.7
2	0	12	6.7	3.4
2	0	13	5.9	4.2
2	0	14	4.3	4.1
2	0	0	10.9	3.9
2	0	-1	99.8	94.8
2	0	-2	37.7	24.2
2	0	-3	112.4	112.6
2	0	-4	62.9	59.6
2	0	-5	17.0	25.4
2	0	-6	5.6	4.2
2	0	-7	52.9	57.9
2	0	-8	14.8	15.9
2	0	-9	16.6	18.2
2	0	-10	27.0	30.9
2	0	-11	11.8	11.4
2	0	-12	8.5	9.6
2	0	-13	11.9	14.4
2	0	-14	8.9	8.0
2	0	-15	3.3	2.8
2	0	-16	4.5	5.3
3	0	1	72.6	68.6
3	0	2	49.7	47.0
3	0	3	19.3	21.0
3	0	4	59.4	59.7
3	0	5	35.8	42.7
3	0	6	7.8	3.9
3	0	7	24.8	27.5
3	0	8	18.4	19.0
3	0	9	7.7	4.0
3	0	10	7.8	8.1
3	0	11	14.1	11.5
3	0	13	4.8	6.0
3	0	14	6.6	4.2
3	0	0	46.2	36.1
3	0	-1	79.9	76.7
3	0	-2	117.3	118.5
3	0	-3	5.7	5.9
3	0	-4	20.4	23.5
3	0	-5	69.5	83.2
3	0	-6	25.1	21.5
3	0	-7	35.6	47.5
3	0	-8	23.5	24.3
3	0	-9	7.4	8.7
3	0	-10	20.2	24.3
3	0	-11	12.2	14.1
3	0	-12	6.4	3.8
3	0	-13	10.7	10.2
3	0	-14	7.0	6.1
4	0	1	36.7	35.6
4	0	2	10.3	9.9
4	0	3	31.9	34.6
4	0	4	30.6	32.5
4	0	5	22.6	21.4
4	0	6	5.6	7.5
4	0	7	23.2	24.6
4	0	8	21.5	16.9

H	K	L	Fo	Fc
8	0	-7	26.8	25.6
8	0	-8	7.7	9.0
8	0	-9	11.0	12.1
8	0	-10	12.8	19.1
8	0	-11	5.5	6.3
8	0	-12	5.2	5.4
8	0	-13	8.9	11.3
9	0	1	21.3	19.3
9	0	2	10.1	9.5
9	0	3	6.4	1.3
9	0	4	14.0	13.6
9	0	5	13.1	11.8
9	0	7	6.7	6.9
9	0	8	10.4	5.2
9	0	0	12.6	9.1
9	0	-1	49.3	32.1
9	0	-2	30.7	27.0
9	0	-4	22.0	18.6
9	0	-5	22.2	22.1
9	0	-6	8.3	4.6
9	0	-7	18.2	17.5
9	0	-8	17.5	19.1
9	0	-10	11.4	12.7
9	0	-11	6.8	11.5
9	0	-13	4.5	8.1
10	0	0	8.5	10.2
10	0	1	22.4	17.7
10	0	2	7.7	6.7
10	0	4	8.6	8.6
10	0	5	8.4	4.4
10	0	7	9.3	5.4
10	0	-1	6.4	3.9
10	0	-2	7.8	8.8
10	0	-3	22.6	17.1
10	0	-4	22.8	17.1
10	0	-5	22.8	21.4
10	0	-6	11.1	8.2
10	0	-7	15.0	11.7
10	0	-8	11.0	11.4
10	0	-10	5.2	4.5
10	0	-11	7.0	9.8
10	0	-14	5.6	8.3
11	0	1	11.5	8.1
11	0	3	6.5	6.6
11	0	4	12.0	7.4
11	0	6	4.2	4.3
11	0	0	4.3	6.8
11	0	-2	14.3	12.0
11	0	-3	11.3	10.8
11	0	-4	5.5	2.3
11	0	-5	12.2	9.7
11	0	-6	12.9	11.7
11	0	-8	11.3	11.2
11	0	-9	8.7	9.3
11	0	-11	5.7	6.7
12	0	1	5.6	2.9
12	0	3	6.5	4.4
12	0	4	3.7	2.1
12	0	0	5.3	5.4
12	0	-2	11.4	7.5
12	0	-3	8.7	8.2
12	0	-4	5.0	5.6
12	0	-5	4.1	4.3
12	0	-6	9.9	8.7
12	0	-8	5.4	5.2
12	0	-9	4.4	5.7
13	0	0	5.4	4.8
13	0	-1	3.9	4.6
13	0	-3	5.4	6.7
0	1	2	42.5	46.9
0	1	3	33.1	29.6
0	1	4	56.2	60.8
0	1	5	53.5	58.8
0	1	6	6.7	10.2
0	1	7	36.6	36.2
0	1	8	30.8	29.1
0	1	9	6.3	7.0
0	1	10	13.4	17.2
0	1	11	10.7	12.9
0	1	13	7.5	9.9
0	1	14	5.0	7.5
1	1	1	95.2	86.8
1	1	2	45.4	50.7
1	1	3	41.1	39.7
1	1	4	54.7	60.7
1	1	5	32.7	38.2
1	1	6	24.6	27.8
1	1	7	40.9	45.3
1	1	8	14.0	14.1
1	1	9	8.7	6.6
1	1	10	17.5	18.6
1	1	11	7.6	7.6
1	1	13	8.2	9.3
1	1	14	4.6	5.3
1	1	-1	11.3	98.9
1	1	-2	77.3	70.6
1	1	-3	55.9	57.4
1	1	-4	44.6	52.6
1	1	-5	56.1	60.6
1	1	-6	26.2	28.2
1	1	-7	20.7	22.4
1	1	-8	32.3	39.9
1	1	-9	11.1	12.4
1	1	-10	11.5	12.6
1	1	-11	18.2	22.6

H	K	L	Fo	Fc
6	1	6	8.1	6.5
6	1	7	13.5	15.9
6	1	8	7.5	8.4
6	1	10	5.2	6.2
6	1	11	3.7	4.2
6	1	0	21.8	18.1
6	1	-1	72.8	61.1
6	1	-2	29.6	25.6
6	1	-3	10.2	7.9
6	1	-4	32.1	33.6
6	1	-5	32.0	36.9
6	1	-6	8.7	6.8
6	1	-7	32.4	35.6
6	1	-8	23.1	27.7
6	1	-9	6.6	8.2
6	1	-10	16.4	22.6
6	1	-11	12.0	18.7
6	1	-13	6.5	9.2
6	1	-14	5.3	6.7
7	1	1	42.1	39.3
7	1	2	23.8	20.5
7	1	3	18.6	17.8
7	1	4	22.1	22.5
7	1	5	12.7	10.6
7	1	7	15.4	14.5
7	1	8	8.1	5.9
7	1	10	6.1	5.9
7	1	11	5.6	3.9
7	1	0	19.2	16.5
7	1	-1	13.3	10.0
7	1	-2	44.7	37.0
7	1	-3	26.4	22.4
7	1	-4	30.4	24.9
7	1	-5	33.5	36.0
7	1	-6	12.4	11.9
7	1	-7	12.6	12.9
7	1	-8	25.3	27.6
7	1	-9	9.1	12.0
7	1	-10	8.7	9.8
7	1	-11	12.0	15.4
7	1	-12	5.2	6.8
8	1	0	20.3	19.9
8	1	1	17.6	15.6
8	1	3	20.5	18.7
8	1	4	15.8	15.5
8	1	6	8.9	10.6
7	1	7	9.6	14.5
8	1	9	6.4	5.4
8	1	10	7.1	4.7
8	1	-1	9.8	5.6
8	1	-2	25.1	22.8
8	1	-3	14.7	14.9
8	1	-4	6.9	4.0
8	1	-5	20.1	19.1
8	1	-6	23.0	23.8
8	1	-7	7.3	2.0
8	1	-8	16.3	21.8
8	1	-9	11.9	13.9
8	1	-11	6.1	10.0
8	1	-12	5.0	7.5
9	1	0	22.4	19.6
9	1	1	14.1	12.0
9	1	3	10.7	13.5
9	1	4	9.1	6.8
9	1	6	7.6	6.7
9	1	7	5.9	4.2
9	1	-1	9.1	6.0
9	1	-2	21.2	17.7
9	1	-3	23.7	22.8
9	1	-4	10.4	10.8
9	1	-5	13.1	15.0
9	1	-6	21.5	23.3
9	1	-7	6.1	7.6
9	1	-8	6.9	8.4
9	1	-9	12.7	15.3
9	1	-12	4.8	7.5
10	1	0	20.7	16.3
10	1	1	7.5	3.7
10	1	2	10.4	10.8
10	1	3	10.1	10.1
10	1	5	5.1	6.5
10	1	6	5.9	5.1
10	1	-1	12.4	14.3
10	1	-2	11.2	6.6
10	1	-3	16.1	16.4
10	1	-4	12.8	14.7
10	1	-6	10.7	11.4
10	1	-7	12.7	14.3
10	1	-9	6.7	10.3
10	1	-10	5.0	8.2
11	1	0	8.8	7.8
11	1	2	9.4	8.8
11	1	3	4.4	3.0
11	1	5	4.8	4.6
11	1	-1	13.7	13.9
11	1	-2	6.0	5.6
11	1	-3	8.0	5.5
11	1	-4	10.5	11.7
11	1	-6	6.7	6.5
11	1	-7	7.8	10.6
11	1	-10	5.9	8.8
12	1	1	5.4	6.3
12	1	2	6.6	6.8
12	1	-1	7.0	7.0
12	1	-2	8.2	9.0

H	K	L	Fo	Fc
4	2	-4	37.4	36.0
4	2	-5	53.4	49.7
4	2	-6	17.1	15.9
4	2	-7	27.0	27.7
4	2	-8	15.8	23.3
4	2	-9	8.9	14.8
4	2	-10	8.4	10.6
4	2	-11	13.0	18.2
4	2	-12	6.1	8.0
4	2	-14	4.5	7.5
5	2	0	43.4	36.7
5	2	1	44.4	41.2
5	2	2	11.9	7.9
5	2	3	27.3	26.7
5	2	4	27.4	29.8
5	2	5	13.7	11.3
5	2	6	14.4	16.5
5	2	7	8.0	12.8
5	2	9	9.4	10.6
5	2	10	10.7	10.4
5	2	-1	13.8	10.0
5	2	-2	52.3	51.0
5	2	-3	53.1	47.7
5	2	-5	45.7	42.1
5	2	-6	29.4	32.2
5	2	-7	5.7	5.4
5	2	-8	24.5	31.0
5	2	-9	21.7	30.8
5	2	-11	9.2	13.0
5	2	-12	6.1	9.9
6	2	0	41.3	36.1
6	2	1	16.6	15.8
6	2	2	17.8	19.4
6	2	3	31.6	33.4
6	2	4	9.9	13.1
6	2	5	5.1	6.8
6	2	6	18.3	20.8
6	2	7	9.7	8.7
6	2	8	5.9	7.3
6	2	9	6.8	10.2
6	2	10	4.9	3.9
6	2	-1	32.6	26.0
6	2	-2	34.1	29.1
6	2	-3	47.0	41.7
6	2	-4	21.1	18.2
6	2	-5	21.4	16.9
6	2	-6	29.9	33.9
6	2	-7	19.8	22.2
6	2	-8	9.0	10.1
6	2	-9	15.9	22.1
6	2	-10	6.8	10.1
6	2	-12	7.3	13.6
7	2	0	38.8	33.2
7	2	2	20.0	17.3
7	2	3	19.7	17.2
7	2	4	6.7	5.4
7	2	5	11.9	14.7
7	2	6	10.1	13.6
7	2	8	6.2	7.6
7	2	9	5.5	5.0
7	2	-1	33.7	30.0
7	2	-3	35.5	31.7
7	2	-4	38.5	34.9
7	2	-5	6.0	9.1
7	2	-6	31.5	30.7
7	2	-7	20.2	21.6
7	2	-9	9.1	14.9
7	2	-10	6.1	12.0
7	2	-12	7.2	13.4
8	2	0	15.9	15.3
8	2	1	13.9	11.9
8	2	2	19.3	21.6
8	2	3	13.0	11.5
8	2	5	10.5	13.0
8	2	6	5.8	6.5
8	2	8	8.3	8.1
8	2	-1	37.9	31.7
8	2	-2	30.6	22.3
8	2	-3	20.7	18.2
8	2	-4	39.0	34.0
8	2	-5	15.5	12.5
8	2	-6	9.7	10.4
8	2	-7	20.0	24.1
8	2	-8	9.6	10.4
8	2	-9	9.2	11.2
8	2	-10	11.8	17.4
9	2	0	8.1	6.1
9	2	1	20.5	18.1
9	2	2	15.9	16.3
9	2	4	9.8	11.0
9	2	5	9.3	9.6
9	2	7	5.6	6.2
9	2	8	4.5	5.1
9	2	-1	13.5	15.4
9	2	-2	31.2	22.2
9	2	-4	18.0	17.6
9	2	-5	21.3	20.0
9	2	-7	16.8	18.7
9	2	-8	9.2	8.5
9	2	-10	5.1	9.8
9	2	-11	5.7	9.7
10	2	0	9.6	7.4
10	2	1	13.1	13.7
10	2	3	5.6	5.7
10	2	4	7.5	8.1

H	K	L	Fo	Fc
4	3	-2	10.4	12.1
4	3	-3	49.8	43.4
4	3	-4	52.4	51.4
4	3	-5	6.2	4.8
4	3	-6	31.0	35.1
4	3	-7	32.3	32.9
4	3	-8	10.9	14.4
4	3	-9	14.1	23.1
4	3	-10	14.6	25.4
4	3	-12	8.3	11.7
4	3	-13	5.5	6.9
5	3	0	33.9	32.7
5	3	1	33.9	26.8
5	3	2	39.8	43.0
5	3	3	15.4	17.3
5	3	4	17.6	16.6
5	3	5	24.2	32.6
5	3	6	7.3	8.4
5	3	7	8.5	6.4
5	3	8	11.2	15.2
5	3	-1	58.5	43.5
5	3	-2	25.8	21.8
5	3	-3	24.5	23.4
5	3	-4	49.8	45.0
5	3	-5	20.1	19.8
5	3	-6	10.6	10.4
5	3	-7	20.1	23.8
5	3	-8	7.9	8.9
5	3	-9	13.1	20.2
5	3	-10	8.5	10.8
6	3	0	11.7	8.7
6	3	1	28.8	27.9
6	3	2	22.4	23.4
6	3	4	17.4	20.6
6	3	5	16.3	21.3
6	3	7	12.7	14.7
6	3	8	7.0	8.3
6	3	-1	31.9	28.3
6	3	-2	43.5	34.2
6	3	-3	10.3	3.3
6	3	-4	36.4	35.0
6	3	-5	26.6	22.8
6	3	-6	11.3	11.6
6	3	-7	26.3	33.6
6	3	-8	12.9	13.4
6	3	-10	13.5	18.0
6	3	-11	7.3	12.1
7	3	0	7.7	2.4
7	3	1	31.5	34.0
7	3	2	14.1	15.4
7	3	3	12.5	11.1
7	3	4	14.7	19.6
7	3	5	7.4	6.0
7	3	6	7.2	7.2
7	3	7	8.9	12.1
7	3	-1	16.1	15.5
7	3	-2	39.2	28.3
7	3	-3	14.6	11.2
7	3	-4	14.8	13.6
7	3	-5	20.9	22.9
7	3	-6	16.9	17.2
7	3	-7	15.9	18.1
7	3	-8	22.6	26.4
7	3	-9	10.4	11.8
8	3	0	22.3	19.3
8	3	1	14.6	16.8
8	3	3	14.8	16.9
8	3	4	8.5	11.4
8	3	6	6.7	7.6
8	3	-2	28.9	25.0
8	3	-3	15.7	13.0
8	3	-4	9.1	5.7
8	3	-5	21.4	22.7
8	3	-6	14.5	16.8
8	3	-8	8.5	12.4
8	3	-9	7.4	9.6
9	3	0	16.5	16.8
9	3	1	6.0	7.2
9	3	2	7.3	5.8
9	3	3	9.2	12.0
9	3	6	6.7	7.6
9	3	-1	7.4	6.8
9	3	-2	12.8	10.8
9	3	-3	19.5	17.9
9	3	-4	7.4	6.8
9	3	-5	12.8	10.5
9	3	-6	16.5	17.3
9	3	-7	8.5	7.9
9	3	-8	6.0	6.9
9	3	-9	9.3	13.3
10	3	0	8.3	10.1
10	3	-1	9.4	11.9
10	3	-3	9.5	11.7
10	3	-4	14.7	15.1
10	3	-6	9.4	11.7
10	3	-7	8.3	8.6
10	3	-9	5.6	10.2
10	3	-10	5.3	7.2
11	3	0	6.5	6.1
11	3	-1	6.7	7.4
11	3	-4	8.0	11.1
0	4	1	16.5	26.9
0	4	2	11.1	21.9
0	4	3	35.2	41.7
0	4	4	25.5	27.3

H	K	L	Fo	Fc
7	4	-1	29.5	20.3
7	4	-2	8.5	2.7
7	4	-3	29.3	25.7
7	4	-4	25.6	21.2
7	4	-6	16.1	17.3
7	4	-7	11.6	12.7
8	4	0	7.4	9.0
8	4	1	9.1	6.4
8	4	2	12.9	15.0
8	4	3	7.4	7.4
8	4	-1	22.0	19.3
8	4	-2	16.4	10.5
8	4	-3	8.9	11.0
8	4	-4	20.1	20.2
8	4	-5	18.0	12.0
8	4	-6	9.1	9.4
8	4	-7	14.9	14.4
8	4	-8	9.1	7.4
9	4	0	7.4	4.5
9	4	1	8.9	10.6
9	4	2	8.8	11.4
9	4	-1	14.8	14.5
9	4	-2	12.9	11.9
9	4	-4	7.4	9.3
9	4	-5	14.9	12.1
9	4	-7	7.3	11.6
9	4	-8	8.8	10.7
0	5	1	13.2	30.3
0	5	2	22.7	28.8
0	5	3	9.2	8.4
0	5	4	24.3	27.1
0	5	5	21.4	28.1
0	5	7	13.4	15.0
0	5	8	10.6	16.0
1	5	0	21.7	23.1
1	5	1	34.4	45.5
1	5	2	15.8	21.3
1	5	3	18.1	18.8
1	5	4	24.2	28.9
1	5	5	13.4	12.3
1	5	6	15.4	18.1
1	5	7	17.9	21.4
1	5	-1	16.0	22.9
1	5	-2	32.5	41.2
1	5	-3	13.2	13.3
1	5	-4	16.6	17.4
1	5	-5	26.8	32.8
1	5	-6	11.3	12.4
1	5	-7	12.2	10.0
1	5	-8	16.6	19.0
2	5	0	35.0	36.5
2	5	1	25.9	26.6
2	5	2	10.0	6.3
2	5	3	27.9	31.1
2	5	4	15.7	15.1
2	5	5	9.5	5.1
2	5	6	17.6	17.2
2	5	7	11.9	13.9
2	5	-1	7.4	5.9
2	5	-2	25.6	27.6
2	5	-3	37.3	39.1
2	5	-4	7.6	8.5
2	5	-5	28.2	25.5
2	5	-6	21.1	23.6
2	5	-8	14.8	21.7
2	5	-9	10.8	15.9
3	5	0	34.3	28.7
3	5	1	15.9	9.9
3	5	2	17.1	11.7
3	5	3	24.0	28.5
3	5	4	9.4	13.5
3	5	5	11.2	9.0
3	5	6	9.1	12.0
3	5	-1	20.6	19.6
3	5	-2	17.2	15.6
3	5	-3	38.6	33.3
3	5	-4	18.4	14.8
3	5	-5	11.5	10.6
3	5	-6	21.5	24.0
3	5	-7	13.2	13.3
3	5	-9	10.8	14.7
4	5	0	30.9	30.1
4	5	1	6.1	3.9
4	5	2	27.1	25.9
4	5	3	16.6	19.2
4	5	5	15.8	20.0
4	5	6	10.8	12.9
4	5	-1	37.1	28.0
4	5	-2	7.0	2.3
4	5	-3	29.2	22.7
4	5	-4	26.0	23.8
4	5	-6	20.0	21.1
4	5	-7	14.4	19.1
4	5	-9	9.3	11.1
4	5	-10	7.6	8.7
5	5	1	14.3	9.4
5	5	2	20.4	18.6
5	5	4	11.8	10.3
5	5	5	12.0	15.6
5	5	0	10.3	9.6
5	5	-1	34.7	27.5
5	5	-2	20.6	14.1
5	5	-3	15.8	15.2
5	5	-4	25.2	22.1
5	5	-5	16.1	13.2

TABLE (3) CONT.

4	0	9	7.2	9.4
4	0	10	17.5	16.2
4	0	11	11.3	6.3
4	0	13	6.1	4.6
4	0	0	28.0	24.5
4	0	-1	28.1	28.0
4	0	-2	71.0	66.3
4	0	-3	17.5	18.2
4	0	-4	14.3	8.4
4	0	-5	26.6	32.1
4	0	-6	6.8	2.1
4	0	-7	4.2	0.5
4	0	-8	37.9	43.7
4	0	-9	14.8	19.8
4	0	-10	11.8	15.1
4	0	-11	21.2	23.9
4	0	-12	11.1	8.8
4	0	-13	6.9	9.0
4	0	-14	5.7	6.9
5	0	1	33.7	33.7
5	0	2	40.1	23.8
5	0	3	21.5	21.2
5	0	4	25.3	22.7
5	0	6	15.6	19.1
5	0	7	29.2	24.2
5	0	9	10.9	12.9
5	0	10	15.8	10.9
5	0	12	4.9	3.9
5	0	0	86.5	74.3
5	0	-1	23.9	16.0
5	0	-2	38.3	34.9
5	0	-3	25.7	27.0
5	0	-4	53.2	40.3
5	0	-5	59.7	56.8
5	0	-6	36.8	37.5
5	0	-7	11.8	3.3
5	0	-8	15.1	22.5
5	0	-9	17.5	23.9
5	0	-10	6.9	7.8
5	0	-11	10.1	14.7
5	0	-12	11.5	13.4
5	0	-13	6.2	3.9
5	0	-14	6.9	8.8
5	0	-15	5.4	6.5
6	0	1	29.8	25.3
6	0	2	22.7	19.9
6	0	3	24.5	23.9
6	0	4	35.3	25.6
6	0	5	12.5	13.4
6	0	6	18.9	21.0
6	0	7	11.5	8.8
6	0	9	14.7	11.3
6	0	10	3.8	2.5
6	0	11	3.2	4.3
6	0	0	44.6	44.3
6	0	-1	22.7	23.5
6	0	-2	23.9	22.5
6	0	-3	69.7	68.4
6	0	-4	28.2	31.3
6	0	-5	35.8	33.5
6	0	-6	39.1	41.9
6	0	-7	18.5	21.3
6	0	-8	12.8	14.7
6	0	-9	16.2	21.1
6	0	-10	6.3	7.4
6	0	-12	7.1	13.3
6	0	-14	3.9	5.0
6	0	-15	4.1	4.3
7	0	0	28.5	24.1
7	0	1	8.8	1.1
7	0	2	37.2	36.9
7	0	3	25.9	24.4
7	0	4	10.7	5.5
7	0	5	9.5	12.5
7	0	6	19.5	17.3
7	0	8	7.3	8.3
7	0	9	9.7	6.3
7	0	-1	33.4	31.6
7	0	-2	20.8	14.5
7	0	-3	42.0	38.2
7	0	-4	43.0	41.4
7	0	-5	6.6	6.8
7	0	-6	18.0	20.0
7	0	-7	20.4	24.3
7	0	-8	6.7	5.2
7	0	-9	13.9	18.3
7	0	-10	11.0	16.6
7	0	-11	4.5	5.3
7	0	-12	9.9	14.5
7	0	-13	5.9	6.7
7	0	-15	4.9	6.5
8	0	2	32.1	26.9
8	0	3	17.3	11.9
8	0	4	16.6	14.7
8	0	5	12.3	12.8
8	0	6	12.0	7.6
8	0	8	12.4	9.5
8	0	9	8.7	3.9
8	0	0	28.7	20.0
8	0	-1	42.8	36.5
8	0	-2	31.4	29.7
8	0	-3	28.7	23.1
8	0	-4	29.9	30.4
8	0	-5	11.3	12.4
8	0	-6	26.6	23.0
1	1	-12	8.1	8.7
1	1	-14	5.2	6.7
2	1	1	113.6	94.0
2	1	2	8.3	9.6
2	1	3	58.6	61.9
2	1	4	39.3	45.0
2	1	5	12.1	13.5
2	1	6	28.5	35.6
2	1	7	24.1	28.1
2	1	9	23.8	24.8
2	1	10	16.6	18.5
2	1	12	9.1	10.7
2	1	13	6.2	6.9
2	1	0	62.2	52.6
2	1	-1	49.2	29.0
2	1	-2	74.2	68.6
2	1	-3	95.1	87.8
2	1	-4	15.9	6.1
2	1	-5	52.2	57.5
2	1	-6	46.0	58.2
2	1	-7	7.2	8.0
2	1	-8	30.7	40.6
2	1	-9	23.2	27.7
2	1	-11	11.9	12.9
2	1	-12	8.2	11.3
3	1	1	55.1	43.2
3	1	2	15.2	15.3
3	1	3	52.1	55.2
3	1	4	44.8	42.0
3	1	5	20.2	23.8
3	1	6	31.1	38.8
3	1	7	14.1	12.8
3	1	8	13.2	16.1
3	1	9	18.4	18.9
3	1	11	7.3	7.2
3	1	12	9.4	9.3
3	1	0	99.6	85.8
3	1	-1	79.1	62.1
3	1	-2	77.6	68.4
3	1	-3	78.8	67.1
3	1	-4	36.2	30.0
3	1	-5	23.0	26.3
3	1	-6	58.5	70.2
3	1	-7	21.6	19.3
3	1	-8	25.4	27.8
3	1	-9	25.1	30.0
3	1	-10	11.3	14.4
3	1	-11	9.2	10.0
3	1	-12	10.7	16.0
3	1	-14	5.4	7.1
3	1	-15	5.2	7.8
4	1	0	98.4	82.3
4	1	1	3.8	3.3
4	1	2	96.6	82.7
4	1	3	66.2	61.6
4	1	4	7.4	3.4
4	1	5	34.1	38.8
4	1	6	28.4	32.1
4	1	7	4.1	2.7
4	1	8	16.4	19.5
4	1	9	10.7	9.7
4	1	10	4.3	4.4
4	1	11	9.3	8.4
4	1	12	6.0	6.6
4	1	-1	55.4	46.8
4	1	-2	7.8	12.3
4	1	-3	75.3	73.5
4	1	-4	84.1	84.1
4	1	-5	12.3	10.0
4	1	-6	59.2	63.7
4	1	-7	30.5	35.4
4	1	-9	22.1	28.0
4	1	-10	13.2	19.3
4	1	-11	6.9	8.2
4	1	-12	9.8	12.8
4	1	-13	7.3	11.6
4	1	-15	4.7	6.9
5	1	0	21.4	18.1
5	1	1	23.3	22.9
5	1	2	60.3	57.9
5	1	3	27.2	26.5
5	1	4	31.6	33.5
5	1	5	33.7	38.7
5	1	6	14.6	12.5
5	1	7	12.2	13.0
5	1	8	18.3	18.0
5	1	9	7.4	7.4
5	1	11	5.1	6.6
5	1	-1	79.9	67.7
5	1	-2	47.6	42.9
5	1	-3	35.1	30.6
5	1	-4	55.8	52.9
5	1	-5	34.6	31.4
5	1	-6	18.1	21.6
5	1	-7	36.9	43.8
5	1	-8	16.1	19.1
5	1	-9	17.1	24.4
5	1	-10	18.7	24.3
5	1	-12	10.7	10.0
5	1	-13	8.9	13.6
6	1	1	45.5	43.6
6	1	1	35.0	43.6
6	1	3	10.4	8.9
6	1	4	20.7	24.2
6	1	5	22.7	23.3
12	1	-4	9.6	10.0
12	1	-5	8.3	9.0
12	1	-7	6.0	8.8
12	1	-8	5.2	7.8
12	1	-10	3.9	6.1
13	1	-2	5.0	6.3
13	1	-5	5.7	7.4
13	1	-6	4.0	4.3
0	2	1	36.1	52.4
0	2	2	52.5	55.5
0	2	3	70.6	81.7
0	2	4	58.8	64.2
0	2	5	17.4	20.4
0	2	6	49.9	59.5
0	2	8	18.7	20.5
0	2	9	24.2	29.6
0	2	10	15.0	17.7
0	2	11	6.1	8.8
0	2	12	8.9	12.6
1	2	0	96.8	108.0
1	2	1	21.7	20.1
1	2	2	105.2	106.4
1	2	3	57.3	63.4
1	2	4	25.7	19.4
1	2	5	32.7	37.9
1	2	6	35.5	42.2
1	2	8	24.7	32.5
1	2	9	15.2	21.9
1	2	10	8.6	9.3
1	2	11	12.2	15.0
1	2	12	8.2	9.2
1	2	-1	86.4	87.6
1	2	-2	48.1	38.3
1	2	-3	61.7	58.0
1	2	-4	45.5	53.3
1	2	-5	19.5	18.6
1	2	-6	35.6	36.0
1	2	-7	26.0	30.8
1	2	-9	24.6	31.5
1	2	-10	12.3	15.7
1	2	-12	6.8	10.0
1	2	-13	4.9	8.0
2	2	0	41.2	33.5
2	2	1	37.8	31.8
2	2	2	66.4	57.0
2	2	3	38.8	37.9
2	2	4	43.5	46.8
2	2	5	44.2	51.5
2	2	6	20.0	27.7
2	2	7	8.4	12.2
2	2	8	12.1	18.0
2	2	9	9.5	11.9
2	2	10	6.1	7.9
2	2	11	10.4	14.4
2	2	-1	104.3	97.2
2	2	-2	68.0	58.1
2	2	-3	45.3	40.7
2	2	-4	61.4	68.5
2	2	-5	17.5	16.9
2	2	-6	31.0	31.3
2	2	-7	36.4	51.8
2	2	-8	13.8	16.9
2	2	-9	13.3	18.8
2	2	-10	14.5	18.6
2	2	-11	6.1	10.2
2	2	-12	9.1	14.0
2	2	-13	10.0	13.5
3	2	0	6.6	2.6
3	2	1	81.6	74.6
3	2	2	43.0	41.9
3	2	3	16.8	14.1
3	2	4	31.0	35.5
3	2	5	31.6	39.5
3	2	6	5.8	8.2
3	2	7	24.7	30.4
3	2	8	27.1	29.7
3	2	10	6.8	10.4
3	2	11	9.6	11.6
3	2	-1	74.5	57.4
3	2	-2	56.5	41.5
3	2	-3	15.3	10.5
3	2	-4	55.9	55.2
3	2	-5	35.4	35.5
3	2	-6	9.9	14.2
3	2	-7	27.5	31.1
3	2	-8	20.8	26.4
3	2	-10	14.5	23.1
3	2	-11	[illegible]	22.0
3	2	-13	5.0	8.0
3	2	-14	5.2	7.9
4	2	0	37.9	30.1
4	2	1	49.2	46.5
4	2	2	33.9	32.7
4	2	3	16.8	18.7
4	2	4	34.2	35.3
4	2	5	12.4	9.3
4	2	6	18.4	21.9
4	2	7	22.0	25.3
4	2	8	10.5	13.3
4	2	9	11.8	11.5
4	2	10	10.2	10.6
4	2	13	4.2	5.6
4	2	-1	27.9	23.4
4	2	-2	74.0	59.0
4	2	-3	16.7	12.6
10	2	7	4.5	4.9
10	2	-1	9.2	8.9
10	2	-2	16.8	14.3
10	2	-3	6.9	5.8
10	2	-4	9.7	9.7
10	2	-5	18.4	18.1
10	2	-7	8.6	8.8
10	2	-8	10.4	13.3
10	2	-10	5.6	8.6
10	2	-11	4.5	8.4
11	2	0	6.9	6.9
11	2	1	6.7	7.0
11	2	3	6.8	7.1
11	2	4	4.8	6.0
11	2	-2	10.2	12.0
11	2	-3	14.5	13.1
11	2	-5	12.5	12.5
11	2	-6	9.2	9.3
11	2	-8	8.4	10.0
11	2	-9	4.6	6.6
12	2	0	6.8	7.2
12	2	3	3.5	3.9
12	2	-3	6.5	7.1
12	2	-6	5.9	7.7
13	2	0	3.5	4.2
13	2	-3	4.3	5.7
13	2	-6	4.8	6.0
0	3	1	38.7	56.5
0	3	2	32.5	47.7
0	3	3	47.9	43.4
0	3	4	50.9	44.3
0	3	5	39.5	42.4
0	3	6	6.4	6.7
0	3	7	25.1	26.5
0	3	8	20.0	24.3
0	3	9	9.2	8.3
0	3	10	12.8	15.8
0	3	11	8.5	13.3
1	3	0	24.8	29.0
1	3	1	40.7	48.9
1	3	2	25.8	23.6
1	3	3	13.3	12.7
1	3	4	37.0	43.9
1	3	5	25.7	23.3
1	3	6	19.9	16.1
1	3	7	22.1	25.8
1	3	8	11.9	14.4
1	3	9	7.2	8.8
1	3	10	11.3	17.5
1	3	-1	30.9	43.4
1	3	-2	62.8	58.6
1	3	-3	65.0	63.5
1	3	-4	30.1	30.6
1	3	-5	66.6	68.3
1	3	-6	28.2	24.9
1	3	-7	20.8	22.5
1	3	-8	25.3	33.0
1	3	-9	12.1	13.8
1	3	-11	12.8	16.7
2	3	0	54.5	43.9
2	3	1	65.3	66.7
2	3	2	5.2	5.5
2	3	3	42.2	41.8
2	3	4	34.1	43.4
2	3	5	10.3	11.4
2	3	6	33.2	39.6
2	3	7	25.8	29.7
2	3	8	8.2	8.6
2	3	9	14.7	13.5
2	3	10	8.5	10.0
2	3	-1	23.1	25.1
2	3	-2	62.9	55.4
2	3	-3	78.2	67.9
2	3	-4	8.0	4.1
2	3	-5	16.9	23.1
2	3	-6	29.0	35.8
2	3	-8	20.2	23.0
2	3	-9	19.7	24.7
3	3	1	25.3	27.1
3	3	2	28.0	26.3
3	3	3	53.0	61.3
3	3	5	18.9	19.2
3	3	6	20.4	26.3
3	3	8	8.4	9.0
3	3	9	10.5	14.7
3	3	0	59.5	53.6
3	3	-1	45.9	35.4
3	3	-2	42.0	30.4
3	3	-3	44.5	37.5
3	3	-4	36.8	34.5
3	3	-5	34.0	32.3
3	3	-6	44.0	55.9
3	3	-7	18.4	23.5
3	3	-8	20.3	29.1
3	3	-9	15.6	20.3
3	3	-11	7.4	10.3
3	3	-12	6.4	13.0
4	3	0	55.1	46.8
4	3	1	11.1	7.3
4	3	2	27.5	25.6
4	3	3	34.1	44.1
4	3	5	17.3	19.4
4	3	6	15.5	22.5
4	3	8	11.3	15.3
4	3	-1	[illegible]	49.0
0	4	5	23.8	25.1
0	4	6	30.0	33.7
0	4	7	13.9	15.0
0	4	8	8.6	9.6
0	4	9	15.6	18.9
1	4	0	39.6	48.7
1	4	1	9.4	5.4
1	4	2	51.1	52.6
1	4	3	32.6	38.3
1	4	4	8.8	10.7
1	4	5	28.3	31.9
1	4	6	21.7	22.1
1	4	7	10.7	5.9
1	4	8	17.6	21.2
1	4	9	9.1	14.7
1	4	-1	30.4	36.6
1	4	-2	14.1	10.7
1	4	-3	38.7	43.7
1	4	-4	17.6	25.0
1	4	-5	12.9	7.5
1	4	-6	24.5	28.6
1	4	-7	18.7	24.8
1	4	-9	13.6	17.2
2	4	0	29.4	33.8
2	4	1	28.8	25.1
2	4	2	48.5	54.3
2	4	3	20.7	25.2
2	4	4	20.2	17.0
2	4	5	25.7	31.6
2	4	6	14.7	20.1
2	4	8	13.7	17.8
2	4	9	10.5	13.3
2	4	-1	50.8	49.4
2	4	-2	14.3	13.1
2	4	-3	36.3	37.4
2	4	-4	46.0	39.6
2	4	-5	18.3	18.3
2	4	-6	17.5	14.9
2	4	-7	24.3	26.8
2	4	-9	10.2	13.1
2	4	-10	13.9	18.3
3	4	0	7.6	8.6
3	4	1	36.5	30.5
3	4	2	32.2	36.6
3	4	4	28.5	32.5
3	4	5	24.7	32.7
3	4	6	8.5	7.7
3	4	7	19.9	24.3
3	4	8	10.5	13.9
3	4	-1	54.5	47.2
3	4	-2	55.7	43.1
3	4	-3	15.0	7.9
3	4	-4	43.4	42.4
3	4	-5	27.4	26.3
3	4	-6	8.4	6.2
3	4	-7	13.7	20.7
3	4	-8	10.9	17.0
3	4	-10	11.8	16.5
4	4	0	27.9	22.9
4	4	1	34.3	31.5
4	4	2	21.6	21.7
4	4	3	19.8	17.7
4	4	4	22.6	24.9
4	4	5	8.5	12.2
4	4	6	10.2	10.7
4	4	7	12.9	18.0
4	4	8	7.4	8.7
4	4	-1	31.9	30.1
4	4	-2	41.4	38.8
4	4	-3	24.6	18.7
4	4	-4	17.7	12.1
4	4	-5	32.6	35.6
4	4	-6	8.8	7.8
4	4	-7	18.7	20.3
4	4	-8	22.2	29.1
5	4	0	36.3	32.4
5	4	1	25.8	27.5
5	4	3	16.4	17.1
5	4	4	20.4	24.6
5	4	6	12.9	14.4
5	4	7	9.1	10.9
5	4	-1	11.5	6.6
5	4	-2	32.0	25.3
5	4	-3	37.9	34.9
5	4	-5	32.4	32.0
5	4	-6	26.6	23.6
5	4	-8	14.3	15.8
5	4	-9	13.8	17.7
6	4	0	33.8	30.4
6	4	1	15.0	12.9
6	4	2	23.5	22.0
6	4	3	17.5	[illegible]
6	4	5	10.5	9.5
6	4	-1	18.6	15.0
6	4	-2	12.7	9.2
6	4	-3	34.6	30.5
6	4	-4	17.0	7.7
6	4	-5	10.5	9.4
6	4	-6	26.2	27.9
6	4	-7	16.7	17.2
6	4	-9	10.5	15.9
7	4	0	12.2	14.0
7	4	2	15.5	13.0
7	4	3	10.5	10.0
7	4	0	5.0	8.5
5	5	-6	11.3	13.9
5	5	-7	15.7	16.7
6	5	1	16.3	18.4
6	5	2	17.4	20.0
6	5	4	9.3	10.8
6	5	5	7.6	10.6
6	5	-1	26.7	19.3
6	5	-2	24.2	12.9
6	5	-4	24.6	20.8
6	5	-5	21.1	17.8
6	5	-7	10.7	12.9
6	5	-8	9.3	12.6
7	5	0	16.0	10.0
7	5	1	20.8	17.8
7	5	2	10.8	10.7
7	5	4	10.5	11.9
7	5	-1	11.8	13.2
7	5	-2	25.7	23.0
7	5	-3	14.9	8.8
7	5	-4	14.9	15.1
7	5	-5	18.5	14.1
7	5	-6	10.7	5.9
7	5	-7	9.3	8.8
7	5	-8	10.7	13.5
8	5	0	12.0	10.5
8	5	1	7.6	10.6
8	5	3	8.9	11.1
8	5	4	6.9	8.8
8	5	-2	15.3	12.3
8	5	-3	14.3	12.1
8	5	-5	12.1	12.1
8	5	-6	12.0	13.4
8	5	-8	7.4	10.5
9	5	0	9.0	10.5
9	5	-2	7.5	7.0
9	5	-3	13.0	11.6
9	5	-4	7.5	5.5
9	5	-5	7.4	8.1
9	5	-6	10.4	10.8
.0	5	-1	9.6	8.0
0	6	1	6.1	11.0
0	6	2	13.0	15.8
0	6	3	19.5	27.3
0	6	4	8.5	12.0
0	6	5	10.9	10.4
0	6	6	13.1	15.2
1	6	0	13.8	20.8
1	6	2	15.3	21.1
1	6	3	13.8	[illegible]
1	6	5	13.9	15.8
1	6	6	8.5	17.0
1	6	-1	15.1	21.6
1	6	-2	4.9	7.8
1	6	-3	14.4	20.1
1	6	-4	15.2	18.1
1	6	-6	12.9	15.0
1	6	-7	10.6	12.9
2	6	1	9.1	5.9
2	6	2	19.4	21.0
2	6	3	11.3	14.5
2	6	5	17.7	20.3
2	6	6	8.7	9.6
2	6	0	21.4	21.2
2	6	-1	22.9	25.7
2	6	-2	10.4	10.0
2	6	-3	15.8	14.7
2	6	-4	20.1	22.7
2	6	-6	10.0	12.6
2	6	-7	10.5	16.9
3	6	0	12.1	9.0
3	6	1	26.0	22.3
3	6	2	26.9	25.4
3	6	4	15.6	18.1
3	6	5	10.6	11.3
3	6	-1	24.0	22.1
3	6	-2	25.7	22.2
3	6	-4	23.0	20.5
3	6	-5	19.1	20.4
3	6	-7	12.2	15.1
4	6	0	22.9	13.5
4	6	1	17.2	20.4
4	6	4	13.8	16.5
4	6	-1	8.9	8.7
4	6	-2	25.3	22.3
4	6	-3	10.6	7.3
4	6	-4	9.5	9.2
4	6	-5	17.3	15.5
4	6	-6	8.5	8.4
5	6	0	19.2	17.1
5	6	1	18.7	14.3
5	6	3	12.4	13.8
5	6	4	8.8	9.6
5	6	-2	19.7	17.3
5	6	-3	19.9	14.7
5	6	-4	8.3	3.7
5	6	-5	15.9	16.2
5	6	-6	12.3	13.3
6	6	0	13.7	13.0
6	6	3	12.5	11.0
6	6	-1	19.2	10.6
6	6	-3	23.6	19.1
6	6	-4	13.7	11.7
6	6	-5	8.8	8.8
6	6	-6	10.8	12.9
7	6	-1	12.5	[illegible]

FIGURE (8)

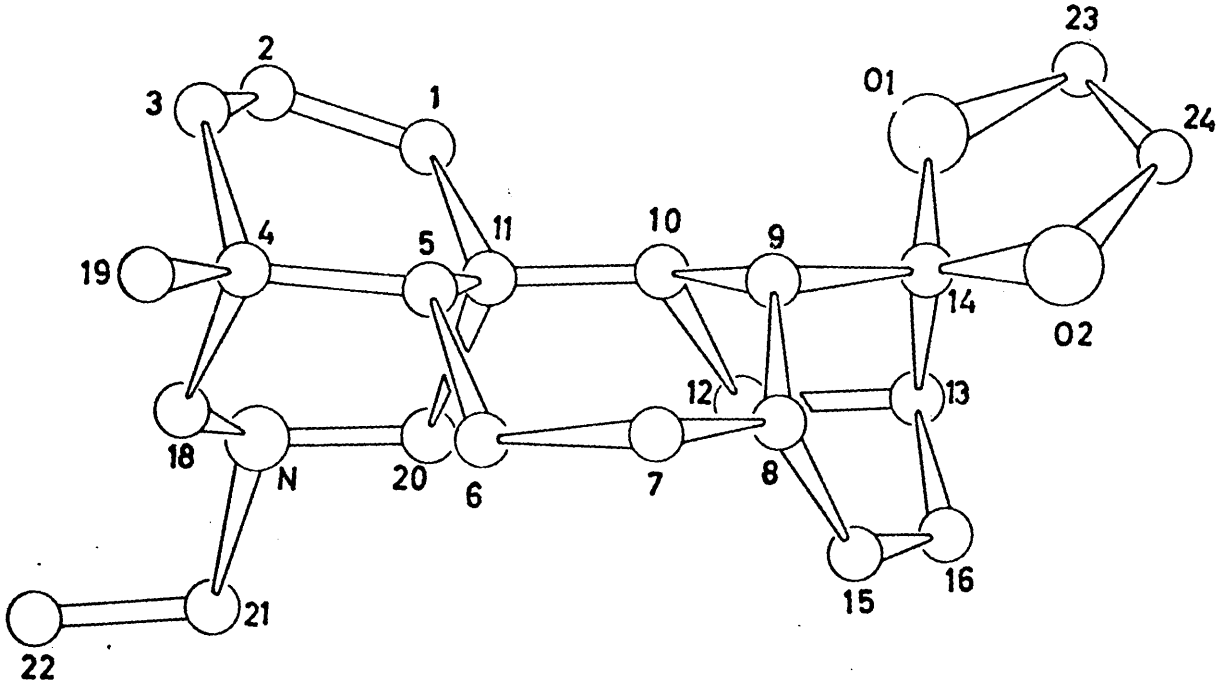


FIGURE (9)

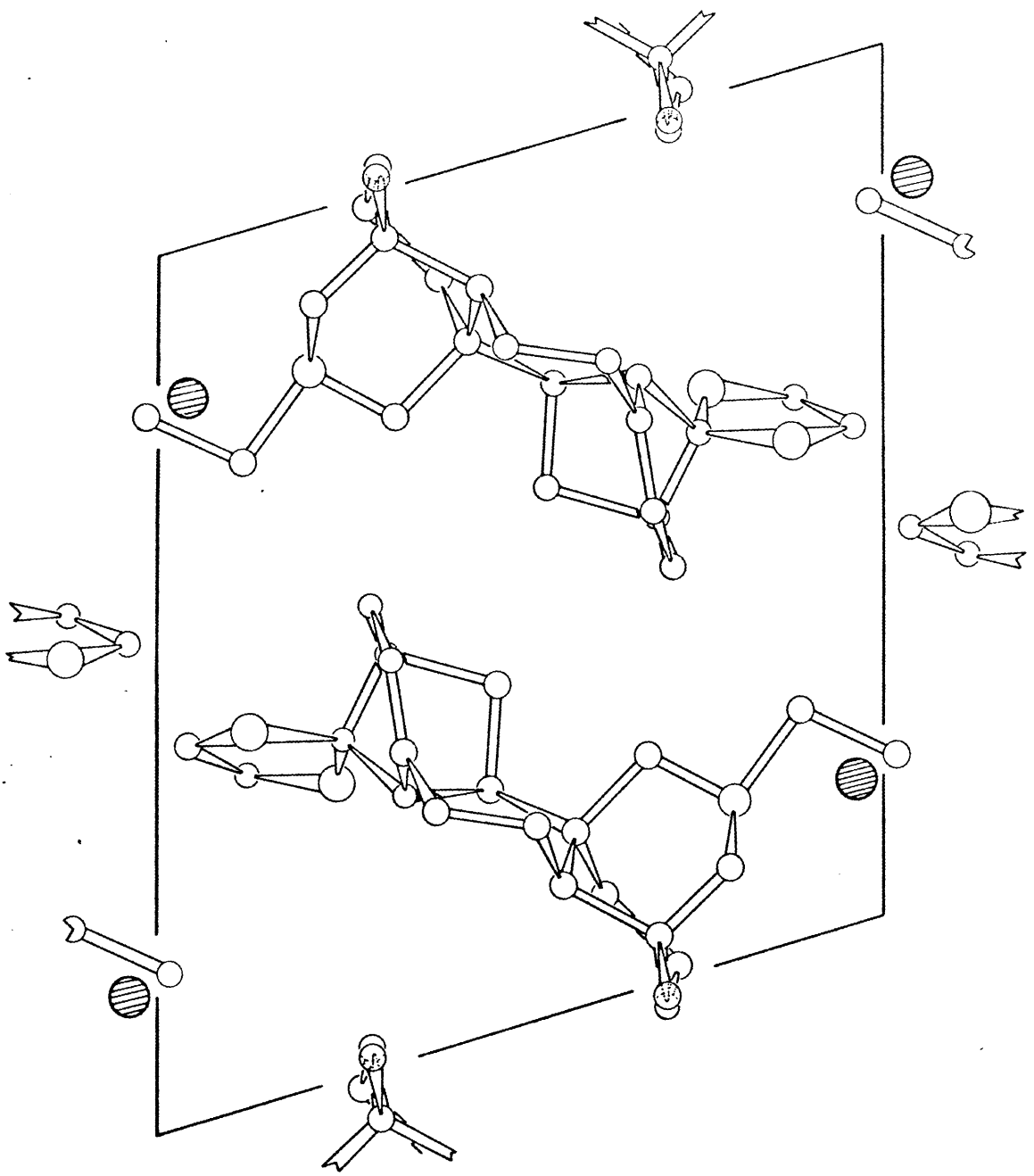
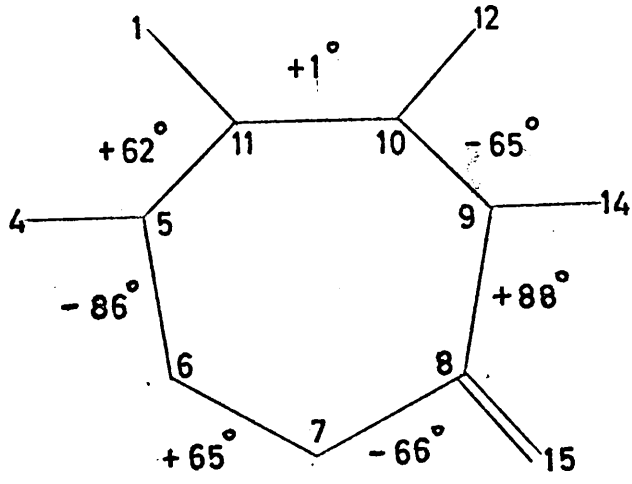


FIGURE (10).



DIHEDRAL ANGLES.

LEAST SQUARES REFINEMENT.

Our treatment of the refinement stage of the analysis was governed to a large extent by the fact that, at this point, we had already achieved our objectives, namely, the determination of the molecular structure and the position of the double bond at C(8). Accordingly, extensive least-squares refinement was considered to be neither worthwhile nor justifiable and only six cycles of calculations were computed to establish the reliability of the structure beyond doubt. Initially, with unit weights applied to the reflexions, four cycles of refinement adjusted the positional, isotropic thermal and layer scale factors and lowered R to 0.16. A weighting scheme of the form,

$$\sqrt{w} = \left\{\left[1-\exp(-50\sin^2\theta/\lambda)^2\right]/\left[1+0.001/Fo/+0.0001/Fo/^2\right]\right\}^{\frac{1}{2}}$$

was applied in the last two cycles, by which time the isotropic refinement had converged with R = 0.14. Because the space group $P2_1$ is polar, the iodide ion y-co-ordinate was not allowed to refine. For computational convenience, no allowance was made for the imaginary part of the anomalous dispersion correction for iodine, so that there may be some small errors in the y-co-ordinates.[93]

The final atomic co-ordinates and isotropic thermal parameters are listed in table (1), along with their estimated standard deviations. All intra-and inter-molecular distances < 4Å were calculated; bond lengths and angles, some non-bonded

intramolecular distances and the shorter intermolecular contacts are listed in table(2). Table(3) contains a compilation of the observed structure amplitudes and final values of the calculated structure factors. A view of the $C_{23}H_{36}NO_2^+$ ion, which also illustrates our numbering scheme, is in Figure (8) and the contents of the unit cell when viewed along the b-axis is in figure (9).

DISCUSSION.

The results of this analysis are in complete agreement with the deductions based on chemical and mechanistic considerations. The absolute configuration of the hydriodide (170a) was not determined and the assignment illustrated in Figure (8) was derived from the known absolute stereochemistry[1b] of the precursor, atisine (4). The accuracy of the analysis is not high (due in part to slow crystal decomposition during irradiation) and it is felt that the observed variation in $Csp^3 - Csp^3$ bond lengths more truly reflects this than do the estimated standard deviations.

The conformation adopted by the derivative is shown in Figures (8) and (9). Some very interesting conformational properties are revealed in the azabicyclo-[3,3,1] nonane system, which is composed of atoms C(1).....C(5), C(11), C(13), C(20) and N. Considerable deformation from an ideal twin-chair conformation is apparent. The severe non-bonded

interaction between C(2)H and N(H) [for numbering scheme see figure(8)] causes very marked flattening, which is conveniently described in terms of the dihedral angle between the planes of C(1), C(2), C(3) and C(18), N, C(20). In an undeformed ideal model this angle would be 0°, whereas in our example it is a spectacular 31°. Furthermore, these planes both make an angle of 16° with the C(4), C(5), C(11) plane. An essentially similar result has been reported for bicyclo[3,3,1] nonane[94] and tricyclo [5,3,1,1,^{2}6]dodecane systems,[95] which have been examined by X-ray methods. However, there is a very important difference between our system and those previously examined. In the latter molecules, there is no evidence of twisting in the carbocyclic framework (which had originally been seriously considered as a mechanism for the relief of the predictably severe non-bonded interactions), but in the present case the azabicyclo-[3,3,1] nonane moiety is twisted and the transannular distances C(3)...C(20) and C(1)...C(18), which would have been identical in the absence of twisting, are 3.71 and 3.45Å respectively. It is felt that the twisting may be a consequence of the strain induced by the eclipsed situation around the C(10) - C(11) bond.

The seven membered ring, C(5).....C(11) adopts a regular chair conformation, as revealed by the torsional angles around the ring [Figure(10)]. The general trend of the angles in the ring is to exceed the tetrahedral value, the mean

value being 116°. Similar increases in valency angles have been observed in several other seven membered rings, such as in isoclovene hydrochloride[96] (116.5°), bromogeigerin acetate[97] (116°), isophotosantonic lactone[98] (115°) and taxadiene tetraol[99] (115.7°).

Atoms C(8), C(9), C(10), C(12).....C(16) constitute a bicyclo [3,2,1] octene system, which shows evidence of being under considerable strain. This is particularly apparent in the cyclopentane ring portion, whose twisting is seen in the distances of atoms C(10)(1.36Å) and C(12)(0.96Å) from the plane of C(9), C(14), C(13). The atoms C(7), C(8), C(9), C(15) and C(16) at the double bond are essentially coplanar, the root mean-square deviation of these atoms from the best plane through them being 0.04Å.

Finally, in the ethylene ketal ring, the atom C(14) is 0.33Å from the best plane through the remaining atoms O(1), C(23), C(24), O(2). This corresponds to an envelope conformation, the ring being folded through 157° about the line intersecting atoms O(1) and O(2).

MOLECULAR PACKING.

All the intermolecular distances (shown in table 2) are close to, or greater than, the normal Van der Waals distances, with the exception of O(1).....C(7). This distance, 3.32Å, may indicate an example of a C-H...O hydrogen bond. Several

values, ranging from 3.21 to 3.34Å have been reported for authentic C-H...O hydrogen bonds in a number of crystal structures. The only other short intermolecular contact of note is between the iodide ion and the positively charged nitrogen atom.

CONFORMATIONAL ANALYSES OF THE OLEFINIC KETALS(156) AND (157).

Mechanistic considerations suggested that the keto-olefin (154), with the double bond in the 8(15) position, would be formed exclusively in a concerted pyrolytic rearrangement of the keto-tosylate (64). However, it was deemed possible that the 7(8) isomer, which was the important one from the point of view of C(7)-C(20) bond formation, might result from the 8(15) compound, either by thermal equilibration during pyrolysis, or by acid-catalysed isomerisation in the subsequent ketalisation procedure. Our failure to detect the 7(8) olefin under the forementioned conditions points to a thermodynamic preference for the 8(15) double bond and this is rationalised in terms of the following conformational analyses of the olefinic ketals (156) and (157).

In the subsequent discussion angle strain, which is of relatively minor importance, is neglected and attention focussed on the more important non-bonded and torsional interactions.

The olefinic ketal (156) was shown, by X-ray crystallography,

FIGURE 10

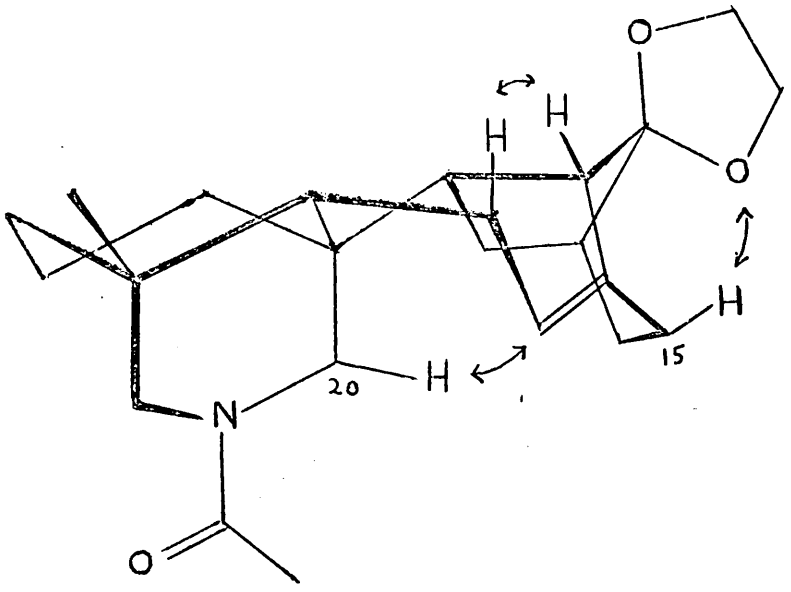
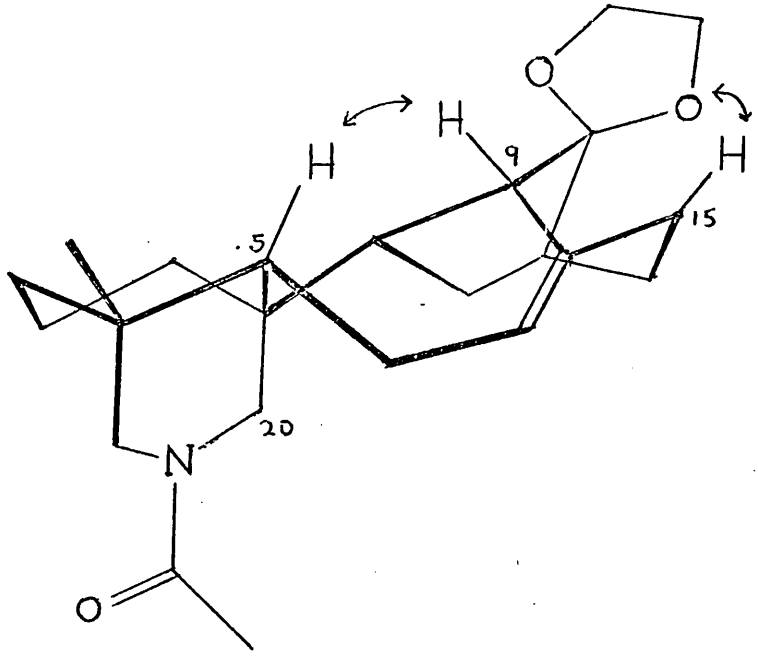


FIGURE 11



to adopt a conformation (figures 8 and 9) in which the seven-membered ring B was a stable chair. An examination of a molecular model led us to believe that this conformer would be the lowest energy one even in the absence of crystal forces. However, there are two conformational possibilities for the 7(8) olefinic ketal (157). In the first, the seven membered ring B adopts a regular boat geometry (figure 11) and in the second, (obtainable from the first, using Fieser Models, by rotation about the C(5)-C(6) bond), ring B adopts a conformation mid-way between a chair and a boat, (denoted half-chair) (figure 12), in which C(5), C(6), C(7), C(8) and C(9) are coplanar.

The major non-bonded interactions for each conformer, derived from Fieser Models, are tabulated below. For comparative purposes, those interactions which appear in all three conformers have been neglected.

8(15) OLEFINIC KETAL (156) :- (1) C(20)H's...C(12)H.

7(8) OLEFINIC KETAL (157) :-

	Boat Conformer		Half-Chair Conformer
(1)	C(20)H...C = C	(1)	C(20)H's...C(12)H
(2)	C(15)H...O	(2)	C(5)H.....C(9)H
(3)	C(6)H...C(9)H	(3)	C(15)H...O

From the foregoing data, it is apparent that there is only one destabilising interaction of note in the 8(15) isomer (156). This arises from the eclipsed situation of substituents attached to the C(10) - C(11) bond and results in substantial steric compression between the C(20) hydrogens and one of those attached to C(12).

The half chair conformer of the 7(8) isomer (157) also contains this interaction, but in the boat conformer it is replaced by an extremely severe interaction between a C(20) hydrogen and the π-electron system of the 7(8) double bond. A second important source of strain in both conformers of the 7(8) isomer (157) is a consequence of the tetrahedral carbon atom at C(15). The six membered ring composed of atoms C(8), C(9), C(14), C(13), C(16) and C(15) is constrained in a flattened boat conformation, in which there is a bowsprit-type interaction between one of the oxygens of the ethylene ketal and a C(15) hydrogen. Thirdly, both conformers of the olefinic ketal (157) are prone to destabilising transannular hydrogen interactions i.e. C(6)H...C(9)H in the boat and C(5)H..C(9)H in the half chair, in the seven membered ring B.

These non-bonded interactions, together with the additional torsional strain associated with the 7(8) conformers, must be sufficient to swing the equilibrium between the olefinic ketals (156) and (157) almost entirely in favour of the 8(15) form (156).

The order of the synthetic operations necessary to convert the 8(15) olefinic ketal (156) into the compound (193; R = Et), containing the C(7)-C(20) bond, follows from these conformational considerations. Thus, it was decided that the oxidation of (191; R = Et) into the iminium compound (192; R = Et) should precede the equilibration of the olefinic bond from the 8(15) to the 7(8) position. The importance of this is that one of the major destabilising forces, viz., the C(20) hydrogen..... C(7)═ C(8) repulsion, in (157) is removed in the iminium compound (192; R = Et) and therefore, it seemed probable that the 7(8) double bond isomer would exist in greater amount in the equilibrium (192; R = Et)⇌(196), than it did in the equilibrium (156)⇌(157).

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SECTION 2.

THE ISOPIMARANE - CASSANE INTERCONVERSION.

INTRODUCTION.

The alkaloids[1] from the Erythrophleum species constitute the main body of compounds, which contain the cassane skeleton (1), one of the main diterpenoid structural types. For many years, it has been realised that these compounds, although extremely toxic, possess a number of potentially very useful pharmacological properties. For example, they display remarkable cardiac activity of the Digitalis type and this property, together with their possible applications as local anaesthetics and opthalmic drugs, has stimulated much research in recent years.[2,3] Clarke et. al., in particular, have been very active in synthesising analogues of these compounds with configurational and functional group variations and evaluating the effects of these on the biological activity.

Cassaine (2), the most extensively investigated[4] of the group, erythrophleguine (3)[5] and coumingine (4)[6] provide typical examples of the alkaloid structures and illustrate the general pattern of functionality observed. In effect, these compounds are composed of a series of oxygenated C_{20} $\alpha\beta$-unsaturated carboxylic acids, which have been esterified by β-, mono or di,-N-methyl ethanolamine. In addition to an occasional axial carboxylic acid or methyl ester at C(4), oxygen functions appear most consistently at C(7), in the form of a hydroxyl or ketone, and at C(3), as a hydroxyl or

an ester of the β-hydroxyisovaleryl type. A few compounds of the cassane type have been isolated from non-Erythrophleum sources. These are characterised by a furan moiety and exemplified by vouacapenic acid (5)[7]. A feature of the more recent members of this series e.g., ε-caesalpin (6)[8] is the extensive nuclear oxygenation.

The vast majority of the early chemical investigations were performed on cassaic acid (7), the hydrolysis product of cassaine (2), and the constitution and stereochemistry embodied in structure (7) are now well established. The gross structural features of this compound were deduced from standard classical procedures. Skilful use of selenium dehydrogenation, coupled with the replacement of oxygen substituents by methyl markers via the Grignard reaction, enabled the carbon skeleton and sites of oxygenation to be established by characterisation of the derived polyalkylphenanthrenes. These conclusions about the basic skeleton were verified by the transformation of vouacapenic acid (5), whose structure was elucidated independently, to cassanic acid (8), a derivative of cassaic acid. Furthermore, the existence of an αβ-unsaturated carboxylic acid in cassaic acid was recognised from U.V. spectral data and confirmed by mild oxidation.

The trans nature of the A/B ring fusion and the absolute configuration of the cassanes were established by oxidation of methyl tetrahydrovinhaticoate, the C(4) epimer of methyl

tetrahydrovouacapenate, to the tricarboxylic acid (9) of known absolute configuration. Later work, which was of a mainly synthetic nature, provided evidence for the remaining stereochemical assignments. Thus, oxidation of the C(3) hydroxyl and subsequent reduction, under conditions known to provide the thermodynamically stable alcohol, (the equatorial one in a trans fused A/B system), returned material of the natural configuration. The configuration assigned to the C(9) hydrogen resulted from the synthesis of the key intermediate (10) under basic conditions, which ensured the more stable trans-anti backbone arrangement. This material was then converted into a degradation product of cassaic acid in a manner such that no further epimerisation at C(9) could occur. Furthermore, the B/C ring junction represents the thermodynamically stable situation, since no epimerisation was noted on any of the numerous occasions in which cassane derivatives with a C(7) carbonyl function were involved in reactions, which could equilibrate the configuration at C(8). Thus the C(8) hydrogen should be β as it is well established that the trans-anti-trans system is thermodynamically favoured over the trans-anti-syn arrangement. The two remaining stereochemical points in cassaic acid, namely the configurations at C(14) and C(16), will be discussed later.

At this point, some discussion on the proposed biogenesis of the cassane skeleton is in order. This structure is formally

derived from geranyl geraniol (11) in a manner which is entirely in accord with the Biogenetic Isoprene Rule.[9] The intermediate labdane (12) is envisaged as cyclising to a tricyclic skeleton of the pimarane type (13), which can further rearrange to the desired cassane (14). The exact nature of the postulated intermediate (13) e.g., whether there is an oxygen function at C(16) or whether there is an 8(14) double bond, is not clear. This is also true of the detailed mechanism of the Wagner-Meerwein rearrangement (13)→(14).

From a compilation of the known cassanes, it was determined that an oxygen function occurs at C(7) in all except the further modified furanoid types. This feature may be of significance with respect to the biogenesis of these compounds. This line of thought led to the proposal that the cassane precursor might be an enone e.g., (15) and a mechanistically plausible suggestion for the Wagner-Meerwein step in the biosynthesis is depicted in the sequence (15)→(16)→(17). The mechanism would also give rise to the observed B/C *trans* fusion and the C(16) carbonyl, which is an invariant feature of the cassanes, might assist in the transition state of the reaction by rendering the C(15) protons acidic. Very recently, an enone (18),[10] of a similar constitution to the above has been isolated from *Aralia cordata*.

The work described in the following section was designed to test the *in. vitro.* feasibility of this proposal and, in

turn, would constitute a novel approach to the synthesis of cassane analogues. At the period when these ideas were conceived, the stereochemistry at C(16) in the cassanes was unknown and, more importantly, that at C(14) was ambiguous. Mathieson et. al.[11] favoured the β-equatorial configuration for the C(14) methyl, based on the isolation of the ketone (19) from ozonolysis of 7-desoxycassamic acid, obtained from cassamic acid (20) by a Clemmensen reduction, whilst the opposite configuration was supported by Turner et. al.[12], also in the light of ozonolysis together with some synthetic studies. Consequently, there was some doubt as to whether the starting material for our synthesis should be of the pimarane type, with a C(13) α-methyl, or the isopimarane type, with a C(14) β-methyl. An examination of molecular models revealed that either an α-methyl or a β-methyl at C(13) would satisfy the stereoelectronic requirements in the transition state of the rearrangement. This results from the observation that ring C can exist in either of the two distinct, energetically favourable, half-chair conformations, depending on the pseudo-equatorial preference of the larger $-CH_2CHO$ group attached to C(13). Thus diagram (21) shows the most favourable conformation when the methyl at C(13) is β and (22) when the methyl at C(13) is α. As there seemed little to choose between the two possibilities, the experiment became one of convenience and isopimaric acid (23), which contains a C(13) β methyl, was

chosen as the starting material because of its ready availability.

As luck would have it, very soon after our synthetic work was underway, evidence, derived almost entirely from synthesis, began to accumulate in favour of a C(14) α-methyl in the cassanes. Mori and Matsui[13] synthesised the ketone (24) en route to racemic desoxocassamic acid, which, from its mode of formation, and stability to base must contain a C(14) β-methyl group. They then demonstrated that this material was epimeric to that obtained from natural sources and concluded that the natural configuration for the C(14) methyl was α.

Very soon after this, Turner et. al.[14] and Clarke et. al.[15] published work, which clarified the configurational interrelationships between the oxygen function at C(7), the C(14) methyl group and the carboxyl group at C(17) and established beyond doubt, that the stereochemistry of cassaic acid is as depicted in (7). The key to the elucidation of the configuration at C(14) by Turner et. al., was in the observation that the acetate (25) of methyl cassaiate provided, on ozonisation, the unstable acetoxy diketone (26), which underwent a ready isomerisation to (27) in base. The assignments in (26) and (27) derive from the assumption that the more thermodynamically stable isomer should be the one in which the C(14) methyl group is equatorial i.e. (27). This was duly verified by the investigation of the epimeric ketals (28) and (29). Either

ketal, on treatment with p-toluene sulphonic acid in benzene, produced an equilibrium mixture of the two in nearly equal proportions. The equilibrium is presumably established through the intermediacy of the enol ether (30). Thus the configuration, which is strongly favoured in the diketone (27) is destabilised in the corresponding ketal derivative (29). An equatorial, but not an axial group at C(14) would be destabilised by the adjacent ethylene ketal ring. The soundness of these arguements was further supported by optical rotation and n.m.r. measurements on various cassane derivatives. This investigation culminated in the total synthesis of cassaic acid. Shortly afterwards, Clarke et. al. confirmed that the natural configuration of the C(14) methyl was α and also derived the configuration at C(16), which was the only stereochemical feature not conclusively assigned. This was done by the synthesis and examination of three of the four possible configurational arrangements at C(16) and C(14), shown in part structure form (31)→(33). Not surprisingly the isomer (34), with the carboxyl cis. to the equatorial methyl, could not be obtained. In the synthesis, particular attention was paid to the possibility of epimerisation at C(14) in the elaboration of the acetylidene side chain from the corresponding ketone. That no epimerisation occurred was ensured by using the ketone (35), in which the C(14) α-methyl was configurationally locked by the equatorial C(7) hydroxyl function. In other words, if

the C(14) methyl epimerised to the β-equatorial position, it would encounter a severe interaction with the equatorial hydroxyl at C(7), of the 1,3 diaxial type in cyclohexanes. By comparing the n.m.r. spectrum of methyl cassaiate with those of the synthetic materials (31)→(33), the relative configurations shown in (25) were deduced. The features of special interest in these spectra, were the chemical shift of the C(14) hydrogen and the magnitude of the coupling constant between the C(8) and C(14) hydrogens. O.R.D. measurements and other spectral data were entirely in accord with the above assignments.

From the foregoing results, the most obvious biogenetic precursor for the cassanes was a pimarane of the type (36), with a C(13) α-methyl, which could rearrange to a cassane with an axial C(14) methyl, perhaps *via*. the proposed enone system. However, on closer examination of the problem, two more things became apparent. Firstly, in the cassanes, the C(14) methyl group occupies a site, which is susceptible to epimerisation, through enolisation of the αβ unsaturated carbonyl function. The second striking thing, which emerged mainly from the work of Turner *et. al.*,[14] is that, in systems such as (35), where a mechanism exists for epimerisation at C(14), the epimer composition at equilibrium is determined to a large extent by the configuration of the oxygen grouping at C(7). Thus on treatment with base, the ketone (37) was readily

isomerised into (35),[15] undoubtedly in order that the C(14) methyl group should escape the unfavourable interaction with the C(7) hydroxyl.

Consequently, it is just feasible that the cassanes may arise through an isopimarane [C(13) β-methyl] intermediate. By a Wagner-Meerwein rearrangement this could, in principle, be transformed into a C(14) β-methyl cassane, which could subsequently be epimerised to the natural configuration. For the epimerisation to yield the C(14) α-methyl the C(14) β-methyl would have to be destabilised by a suitable substituent at C(7). The type of scheme which may be envisaged, is illustrated in (38)→(41). The equatorial methyl at C(14) in the intermediate (39) would encounter interactions from both the C(7)OX substituent and the C(16) hydrogen, which, in the terminology of Johnson,[14] would be designated double A(1,3) strain. These unfavourable interactions could be eliminated by the C(14) methyl epimerising to the relatively strain free axial situation (40) via. enolisation of the αβ unsaturated aldehyde system.

In conclusion, although it turned out that we had not chosen the most obvious precursor for our chemical investigations, in the light of the foregoing arguements, it was possible that we might yet attain our goal, namely a cassane synthesis. The synthesis of the enone intermediate and its further transformations are described in the following section.

DISCUSSION.

Our overall plan for the synthesis of a compound of the cassane group (45), which was the result of some speculative thinking on the cassane biogenesis, is summarised in the structures (23)→(45). The essential feature of the synthesis is the Wagner-Meerwein rearrangement leading to the unsaturated ester (43), which could hopefully be subsequently converted into a cassane structure (45), by modification of the stereochemistry at C(14) along the lines indicated in the introduction. The initial phase of the work was concerned with the preparation of the key intermediate enone (42) from the readily available isopimaric acid (23). For practical reasons, it was decided that the carbonyl function at C(16) in (42), whose task it was to ensure the relative acidity of the C(15) protons and thereby facilitate the generation of a double bond between C(13) and C(15), should be a methyl ester rather than an aldehyde function.

The starting material for our synthesis was isopimaric acid, whose constitution and stereochemistry (23) have been established beyond question.[17] This compound was isolated by us from American Gum Rosin, according to the fractional crystallisation procedure of Baldwin *et. al.*,[18] and converted quantitatively into the corresponding crystalline methyl ester (46) [ν(C = O) 1731cm^{-1}; τ = 6.38, 3H singlet due to -OC$\underline{H}_3$]

with diazomethane in ether. Oxygenation of the side chain in (46) was accomplished by the selective hydroboration reaction developed by Brown.[19] Thus, reaction of methyl isopimarate (46) with a solution of diisoamylborane in diglyme, under strictly anhydrous conditions, followed by alkaline hydrogen peroxide oxidation,[20] afforded the known hydroxy-ester (47) [ν(O-H) 3637 cm^{-1}; τ = 6.30, 2H triplet due to CH_2-OH] in good yield.

Treatment of this material with osmium tetroxide in ether, containing a little pyridine at r.t. yielded, after reduction of the osmates with hydrogen sulphide, a mixture of the anticipated isomeric triol esters (48) and (49). Chromatographic separation of this mixture afforded a crystalline component, $C_{21}H_{36}O_5$, m.p. 166-168°, $[\alpha]_D$ = -2° (c = 0.86), in 51% yield and a brownish semi-crystalline component, whose characterisation was hindered by decomposition, in 5% yield. The low overall yield was caused by poor recovery of these very polar compounds in the separation stage. Taking into account the well established cis mode of addition during the osmylation process and the predisposition of the tricyclic diterpene system toward attack from the less hindered α-side, it was expected that the preponderantly formed triol ester would have the stereochemistry represented by (48). Support for this assignment was found in the n.m.r. spectrum of the crystalline isomer. The C(7) proton in this spectrum appeared at 6.65τ as a narrow triplet (J_{AX} = 3Hz), which is consistent with

the proton being equatorial (and therefore β) and coupled to two adjacent protons, one axial and one equatorial.

An examination of a molecular model of this triol ester (see structure 50) revealed that a stereochemical situation existed, that might allow us to convert this compound into a $\Delta^{8,14}$ olefin, without serious contamination from the more thermodynamically favoured $\Delta^{8,9}$ isomer. Thus, there is only one proton, namely the axial one attached to C(14), that could satisfy the stereoelectronic requirements for the transition state of a bimolecular elimination reaction involving the tertiary hydroxyl at C(8).[21] Consequently, some efforts were directed to effecting this concerted trans dehydration, leading to a $\Delta^{8,14}$ olefin, which, once formed, could be discouraged from isomerising into the $\Delta^{8,9}$ position, by incorporating the double bond into an enone system, through mild oxidation of the C(7) hydroxyl group.

The compound actually used in the dehydration was the hydroxy-diacetate (51), which afforded protection for the primary and secondary hydroxyl functions. This material, $C_{25}H_{40}O_7$, m.p. 110-111°, $[\alpha]_D = -28°$ (c = 1.02), was readily prepared from the triol ester (48), by the usual acetic anhydride-pyridine technique. In later stages of the work, it was found that vastly improved yields of the triol ester (48) could be obtained by acetylation of the crude triol ester mixture, prior to chromatographic separation. The less polar hydroxy-diacetate

(51) was more easily recovered from the "Kieselgel" and the triol ester (48) was smoothly regenerated by r.t. hydrolysis with potassium hydroxide in aqueous methanol.

Treatment of the hydroxy-diacetate (51) with phosphorus oxychloride in pyridine at r.t. and subsequent preparative t.l.c., enabled us to obtain an oily olefin diacetate (53%) (i.r. was devoid of hydroxyl absorption). Unfortunately, the n.m.r. spectrum of this material proved it to be a mixture of the olefin diacetates (52) and (53). Integration of this spectrum allowed us to determine which peaks belonged to which isomer and also, their relative abundances. Thus, the tetra-substituted olefin (52) (τ = 5.90, 2H triplet, J_{AX} = 7Hz, -C$\underline{H}_2$-OAc; τ = 5.05, 1H multiplet, C$\underline{H}$-OAc) was present to the extent of 65% and the desired trisubstituted olefin (53) (τ = 5.93, 2H triplet, J_{AX} = 7Hz, C$\underline{H}_2$-OAc; τ = 4.78, 1H multiplet C$\underline{H}$-OAc; τ = 4.40, 1H doublet, J_{AX} = 2Hz, $\rangle C = C\text{-}\underline{H}$) only to the extent of 35%. Further attempts to separate the isomers by t.l.c proved abortive and it was hoped that this could be accomplished after further chemical transformation.

Hydrolysis of the olefin diacetate mixture with potassium hydroxide in aqueous methanol at r.t., yielded a product, which exhibited two cleanly separated components, whose mobilities were entirely consistent with the required olefin-diols (54) and (55) on analytical t.l.c. Separation by preparative t.l.c. afforded an oil and a crystalline solid, m.p. 115-116.5°.

The spectral properties of the oil, of which the most notable were the hydroxyl absorption at 3620 and 3400cm^{-1} in the i.r. and the absence of vinyl proton absorption in the n.m.r., were in accord with the tetrasubstituted olefin structure (54). In contrast, the spectral properties of the crystalline compound were certainly far removed from those expected of the trisubstituted olefin-diol (55). The i.r. spectrum of this material was devoid of any hydroxylic absorption, although the n.m.r. spectrum indicated that the $-CH_2-CH_2-O-$ side chain was still intact by the presence of a two proton triplet (J_{AX} = 8Hz) at 6.15τ. Furthermore, the compound contained a trisubstituted double bond, whose presence was revealed by a one proton multiplet at 4.28τ and its molecular weight by mass spectroscopy was 332. It was also discovered that this crystalline material was very much less polar on analytical t.l.c. than the compound which we had hoped to isolate. This information, together with mechanistic considerations, suggested that the crystalline component possessed the tetrahydrofuran structure (56) and that it had been derived from the suspected olefin-diol (55) by a facile cyclisation reaction catalysed by the chromatographic "Kieselgel".

In an attempt to circumvent this rearrangement, the crude olefin-diol mixture, from the olefin-diacetate hydrolysis reaction, was oxidised, in fair yield, by activated manganese dioxide[22] in ether to a mixture of the enone alcohols (57)

and (58). (λ_{max} 250 nm; $\varepsilon \approx 8{,}000$). Again, this mixture proved to be inseparable by chromatography. However, the i.r. spectrum, which contained two enone carbonyl absorptions, i.e. 1668cm^{-1} (strong) and 1691cm^{-1} (very weak), was consistent with (57) being by far the major isomer. Thus, it has been established[23] that the carbonyl stretching bands of cisoid enones of the type (58), occur at higher frequencies, (approx. 1690cm^{-1}) than do the corresponding transoid systems (approx. 1670cm^{-1}) and also, that the olefin stretching band tends to be very much more intense in the cisoid case.

These transformations clearly indicated that the dehdration reaction had not gone according to plan, as the major product was the tetrasubstituted olefin. Now, the very mild but highly effective phosphorus oxychloride in pyridine method has been widely used in structural studies, in view of its reputed <u>trans</u> stereospecificity, which is the result of a supposed bimolecular reaction of the intermediate phosphate ester (59). An excellent example of the strict <u>trans</u> requirements is to be found in the steroids (60) and (62),[24] where the axial alcohol (60) eliminates to the endo olefin (61), whilst the equatorial alcohol (62) affords, almost exclusively, the exo olefin (63). However, there is reason to believe that sometimes the balance in this reaction is tipped in favour of an E_1 mechanism. Support for the unimolecular decomposition of the intermediate phosphate ester is derived from the occasional isolation of the thermodynamic

product in excess, in the dehydration of some equatorial tertiary cyclohexanols[25] and from cases of rearrangement,[26] which admittedly only occur in special structures.

A re-examination of the molecular model of the hydroxy-diacetate (51) revealed that, in the most obvious conformation (64), there is a large steric interference between the C(20) methyl group and the axial proton at C(14). Herein may lie the major part of the reason for the lack of stereospecificity in the phosphorus oxychloride dehydration of this compound. If the conformation shown (64) is accepted as the one which undergoes reaction, then it is apparent that the approach of the base, pyridine, towards the relevant C(14) proton would be seriously discouraged by the C(20) methyl group, and this might result in an increase in the involvement of the competing unimolecular ionisation mechanism, with the observed steric consequences. It is assumed that under the mildly basic reaction conditions, the possibility of equilibration between the olefin isomers (52) and (53) can be neglected. In search of another explanation, we considered that the large non-bonded interaction between the C(20) methyl and the axial C(11) and C(14) protons might destabilise the proposed conformer (64) to such an extent, that the alternative conformer (65) becomes important. In this conformer rings A and C are chairs, whilst ring B is a boat. However, although there is now free access to the C(14) protons, the stereoelectronic requirements for an E_2 reaction cannot be

satisfied in this conformation, as the tertiary C(8) hydroxyl has adopted an equatorial aspect with respect to ring C.

Further dehydration experiments directed towards the enone system (66) performed by McCreadie[27] on the model ketol system (67) also proved abortive. Elimination of water from the ketol (67) took place to only a very small extent on refluxing with phosphorus oxychloride in pyridine and the product was reported to consist of almost entirely transoid enone (68). Although the C(7) carbonyl group almost certainly slows down both the E_2 and E_1 processes, it might be expected to strongly favour the concerted bimolecular reaction giving rise to the cisoid enone (66). The fact that there is a preponderance of transoid product, reflects the high energy nature of the E_2 process, which is probably a result of the steric interactions previously discussed. McCreadie also found that dehydration of the ketol (67) with thionyl chloride in pyridine at r.t. produced mainly (68).

At this point, the dehydration route to the cisoid enone did not look very promising. However, it was decided to synthesise a ketol, analogous to (67), and make several more attempts to induce it to eliminate in the required direction. Oxidation of the triol ester (48) by the Snatzke method, using chromium trioxide in dry dimethyl formamide, containing a small amount of concentrated sulphuric acid, at r.t., resulted in a very complex mixture of products. In contrast, a very clean

product, $C_{21}H_{30}O_5$, m.p. 215-224°, $[\alpha]_D = -12°$ (c = 0.69), whose spectral properties were in accord with the keto-lactone formulation (69), was isolated from the reaction of the triol ester (48) with N-bromosuccinimide in aqueous dioxan at r.t. The i.r. spectrum of this compound was devoid of hydroxylic absorption and the carbonyl region, which consisted of a broad band between 1720 and 1735cm^{-1}, was not very informative. Careful integration of the carbonyl absorption, using the ketol (67) as a standard, enabled us to determine the existence of three carbonyl functions. The n.m.r. spectrum supported the existence of $C\underline{H}_2CO$- and $C\underline{H}_2CO_2$- functions by absorption, attributable to four protons, in the τ = 7.64-7.81 region. The keto-lactone structure was deduced from the above information and a knowledge of the molecular weight, 362, from mass spectroscopy. Consideration of the mechanism of the N-bromosuccinimide oxidation, leads us to suggest that the keto-lactone (69) arises <u>via</u> the intermediacy of the hemi-acetal (70).

The synthesis of this keto-lactone, although unexpected, was soon turned to advantage and provided the key to the synthesis of the required enone system (42). A conformational analysis of the keto-lactone system (69) showed that, in addition to the all chair conformer (71) which was similar to that of the hydroxy-diacetate (64) and which suffered from the same destabilising C(20) methyl-C(11);C(14) proton interaction, there existed another conformer(72) which was worthy of

consideration. This conformer, in which ring B adopts a half-chair geometry (not too limiting in view of the C(7) carbonyl) and ring C adopts a somewhat distorted boat conformation, does not suffer from any major non-bonded interactions, but is prone to the torsional strain associated with a boat cyclohexane. However, the importance of this conformation (72), in contrast to the other conformations (64) and (65) examined in the hydroxy-diacetate and the keto-lactone (71) cases, is that an E_2 elimination involving the lactone group and one of the C(14) protons is feasible, both from the stereoelectronic and the steric approach control points of view. Another feature worthy of note in this keto-lactone system, is that there is no possibility of the eliminated carboxylic acid recyclising to regenerate the δ lactone system (69). i.e., the product enone system (73) is not readily amenable to protonation in the β position.

In line with the foregoing discussion, it was found that the keto-lactone (69) was converted, almost quantitatively, into the anticipated cisoid enone (73) by reaction with a dilute methanolic solution of sodium methoxide at reflux temperature. That the methoxide ion did in fact rupture a C(14)-H bond in an E_2 process, was established by the isolation of the carboxylic acid. The alternative process which may be visualised, i.e., nucleophilic attack by the methoxide ion on the lactone carbonyl group to give the intermediate ketol

(74), which could subsequently dehydrate to give (42), is limited by the lack of a suitable E_2 pathway for dehydration, as in the hydroxy-diacetate (51) case.

The cisoid enone (73) was characterised as the corresponding methyl ester (42), $C_{22}H_{32}O_5$, m.p. 116-118°, $[\alpha]_D = +2°$ (c = 0.63), formed by methylation with diazomethane in the usual fashion. Support for the cisoid enone structure (42) came from the carbonyl absorption band at 1692cm^{-1}, coupled with a characteristically intense ν(C = C) band at 1618cm^{-1}, in the i.r. spectrum.[28] The vinyl proton appeared at 3.24τ as a doublet, J_{AX} = 2.5Hz, due to long range allylic coupling[29] with an axial C(9) proton and a six proton singlet at 6.38τ was in evidence for the methyl protons of the two methyl esters. Finally, the u.v. spectrum exhibited a maximum at 250 nm. (ε = 9,600).

Cleavage of the lactone system of the keto-lactone (69), also occurred on prolonged refluxing with concentrated sulphuric acid in dry methanol. However, in this case, the product was a chromatographically inseparable mixture of the transoid and cisoid enones (75) and (42). The intensities of the characteristic i.r. absorption bands of these enones, 1692cm^{-1} (cisoid) and 1668cm^{-1} (transoid), revealed that they existed in equal proportions. The reaction is envisaged as proceeding <u>via</u> the protonated intermediate (76), which collapses to the cisoid enone (42) by a concerted anti elimination. A two step mechanism involving a discreet carbonium ion would be disfavoured

by the C(7) cabonyl group. the presence of the thermodynamically favoured transoid enone (75) can be accounted for by subsequent acid-catalysed rearrangement of the kinetic product, as was demonstrated in later work.

Having established a satisfactory route to the cisoid enone system (42), attention was focussed on the more basic matter of inducing a Wagner-Meerwein rearrangement, which would result in the migration of the C(13) methyl group to the C(14) position i.e. (42)→(43). Some preliminary attempts to accomplish this centred round the generation of the allylic carbonium ion system (77), whose geometry resembled very closely, that of the transition state postulated for the intended enone rearrangement [see structure (20)], and which might conceivably collapse in the required manner to the $\alpha\beta$-unsaturated methyl ester (78).

Treatment of the enone (42) with sodium borohydride in ethanol at r.t. furnished an oil, which was homogeneous on t.l.c. and which was assigned the allylic alcohol structure (79). The main spectroscopic features of this compound were a hydroxyl band in the i.r. at 3610cm^{-1}, with a corresponding absorption for the carbinyl proton in the n.m.r., as a poorly resolved quartet centered at 6.06τ and a vinyl proton, as a broad singlet at 4.26τ. There is ample precedent[30] for the reduction yielding the equatorial alcohol and this stereo-

chemical assignment is further supported by the coupling shape of the carbinyl proton signal.

The allylic alcohol (79) was smoothly converted into the p-nitrobenzoate ester (80), by reaction with p-nitrobenzoyl chloride in anhydrous pyridine at r.t., as was evident from the absence of hydroxyl absorption and the presence of a multitude of characteristic nitro-benzoate bands in the i.r. spectrum and the presence of a four proton singlet at 1.72 τ in the n.m.r., attributable to the aromatic protons. Acetolysis of the p-nitrobenzoate (80) in buffered acetic acid at reflux temperature and subsequent chromatography, provided an oily product, whose t.l.c. mobility was consistent with an elimination product, perhaps of the expected $\alpha\beta$-unsaturated methyl ester (78) type. However, the u.v. spectrum quickly destroyed our hopes by exhibiting a triple maxima, 236, 242 and 250 nm. (ε = 10,000), which was characteristic of a hetero-annular diene chromophore,[31] and which, together with i.r. and n.m.r. data, suggested the formulation (81) for the solvolysis product. This result could be rationalised either by the probable intermediate allylic carbonium ion collapsing by elimination of a proton to the diene (82), which subsequently isomerised to the thermodynamically favoured diene (81), or by the double bond isomerising to the $\Delta^{8,9}$ position prior to solvolysis. A further attempt to induce the desired methyl migration, <u>via</u> the intermediacy of (77), by reacting the

allylic alcohol(79) with formic acid in chloroform, failed, the sole product from the reaction being the corresponding allylic formate(83). This compound underwent a facile hydrolysis reaction on an acid washed alumina column, to provide material whose i.r. spectrum and t.l.c. mobility were identical to those of the original allylic alcohol(79).

The ketal system(84) provided the focal point for a second attempt to synthesise the cassane product(43). This approach was divided into two distinct parts. The elegant approach to the Wagner-Meerwein rearrangement seemed to be in the ketal cleavage reaction(84)→(85), which could supposedly be induced by a Lewis acid, under non-nucleophilic conditions, in parallel with the work of Johnson[32]. However, it was also realised that, if an allylic ketal could be produced from the reaction of the enone (42) under normal acid catalysis conditions, then it would probably be the tetrasubstituted compound(86) and not the desired trisubstituted compound (84). Furthermore, it had been established that the mechanism of the ketalisation reaction, as applied to an enone, involves an initial protonation step(87), in which the olefinic bond could participate[33]. This was clearly demonstrated in the reaction of cholest-4-en-3-one with ethylene glycol under acid catalysis, which produced the olefin-ketal(88) in which olefin isomerisation had taken place[34]. Thus, it was thought worthwhile to subject the enone(42) to normal ketalising conditions, more in the hope of detecting some rearrangement

product, than producing the trisubstituted olefin ketal (84).

In the event, a solution of the enone (42), dry ethylene glycol and p-toluene sulphonic acid in sodium dried benzene was refluxed for 18hrs., during which the water produced was removed with silica gel. Unfortunately, no products of re-arrangements were detected in this reaction and, surprisingly, no C(7) ketal was isolated. The only compounds formed and separated by preparative t.l.c., were the monotosylate of ethylene glycol, the tetrasubstituted enone system (75)[ν(C=O) enone 1669cm^{-1}] and a compound, which contained the tetrasubstituted enone system by i.r., but had also incorporated ethylene glycol and p-toluene sulphonic acid. This latter compound was not fully characterised, but was tentatively assigned the structure (89) on the basis of its i.r. spectrum and the isolation of an analogous compound described later. Reaction of the enone (42) with concentrated sulphuric acid in dry methanol at reflux temperature proved to be no more successful and the i.r. spectrum of the product indicated that the only reaction taking place was the slow isomerisation of the trisubstituted enone (42) to the tetrasubstituted enone (75). A further attempt to induce an acid-catalysed methyl migration in the enone (42) using the Lewis acid, boron trifluoride etherate in refluxing benzene, proved abortive, the starting material being returned unchanged. This reaction has recently been used by Atkinson[35] to induce an intramolecular

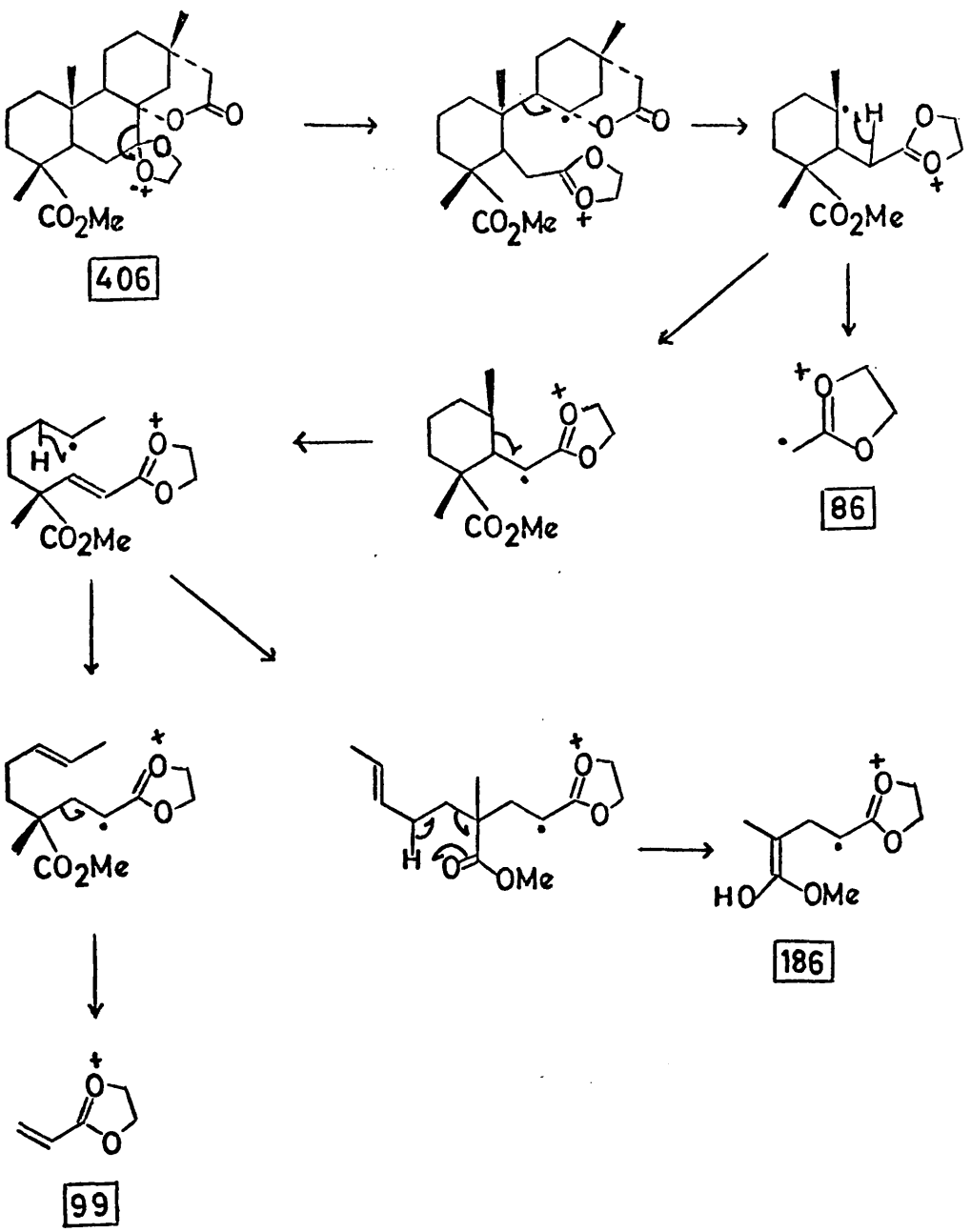
1,5 hydride shift in the acyclic enone system (90) to give the intermediate (91), which cyclised spontaneously to the methyl ketone (92).

Convinced that a facile acid-catalysed rearrangement of the enone (42) was unlikely, we turned our attention to the synthesis of the olefinic ketal (84), with a view to the cleavage reaction (84)→(85), referred to previously. An initial attempt to form this olefinic ketal by a mild trans-ketalisation, using the ketal of methyl ethyl ketone and boron trifluoride etherate, failed, the starting enone (42) being recovered unchanged.

In order to circumvent the isomerisation of the $\Delta^{8,14}$ olefin, it was decided to synthesise the ketal lactone (93) and then cleave the lactone ring by the methoxide elimination reaction discussed previously, to give the required olefinic ketal (84). Ketalisation of the keto-lactone (69), using the usual ethylene glycol-p-toluene sulphonic acid conditions, afforded the ketal lactone (93), m.p. 209-209.5°, in poor yield. Incorporation of the $-O-CH_2CH_2O-$ group was apparent from a four proton multiplet at 6.07τ in the n.m.r. spectrum. Furthermore, the i.r. spectrum was devoid of hydroxylic absorption and the compound failed to undergo reduction with sodium borohydride in methanol, in contrast to the very rapid reduction observed in the parent keto-lactone (69) system. These facts supported the ketal lactone formulation (93), which was made even more plausible

FIGURE (13).

The fragment ions at m/e 186, 99 and 86 were all very abundant and are considered to arrive as follows :-



by the presence of certain very predictable, fragment ions, all derived from the ketal function in its mass spectrum.[36] (see figure 13).

The major product from the ketalisation procedure was assigned the structure (94) contaminated by a tiny amount of the isomeric enone (89) and the various functionalities were all clearly defined in the i.r. or n.m.r. spectra. As anticipated, hydrolysis of this material with sodium hydroxide in aqueous methanol, followed by methylation with diazomethane, produced an almost quantitative yield of the cisoid enone (42). Several prolonged attempts to form the ethylene ketal of the tosylate enone (94) with ethylene glycol and p-toluene sulphonic acid failed and only a slow isomerisation to the transoid enone (89), which was easily followed by the increase in intensity of the 1670cm^{-1} absorption band, was evident. A regularly occurring by-product of these reactions was the mono-tosylate of ethylene glycol.

Reaction of the ketal-lactone (93) with sodium methoxide in methanol at reflux temperature yielded, instead of the expected unsaturated acid, a crystalline compound, whose properties could be accounted for by the hydroxy-ketal structure (95). Thus, the i.r. spectrum indicated the presence of a hydroxyl, 3545 and 3460cm^{-1}, and its tertiary nature was apparent from the absence of carbinyl proton absorption in the n.m.r. Furthermore, two three proton singlets at 6.34τ and 6.38τ established the presence

of the two methyl esters and a four proton multiplet at 6.03 τ the presence of the $-O-CH_2CH_2-O-$ grouping. The molecular weight from mass spectroscopy, 438, revealed the addition of one molecule of methanol to the ketal-lactone (93).

Recourse to a molecular model provided an explanation for the differing reactivities of the keto-lactone (69) and the ketal lactone (93) towards methoxide. In the foregoing discussion, it was concluded that there were two energetically similar conformations (71) and (72) possible in the keto-lactone (69) case and that only the latter satisfied the requirements of an E_2 elimination reaction. Now, when the carbonyl function is replaced by the ketal in conformation (72), the additional steric strain involved must be sufficient to completely disfavour this conformer, relative to the all chair one (96). In consequence, the E_2 elimination is completely inhibited and the methoxide ion follows the alternative course, namely nucleophilic attack on the lactone carbonyl group, giving rise to the observed hydroxy-ketal (95).

Some additional support for the assigned structure (95) comes from a consideration of the n.m.r. spectra of the ketal-lactone (93) and the hydroxy-ketal (95). The most stable conformation for both of these compounds is undoubtedly the all chair one i.e. (96) and thus, in the conversion of (93)$\rightarrow$(95), there should be a minimal change in geometry. This is, as anticpated, reflected in the constancy of the quaternary methyl

resonances in going from (93), 9.00, 8.94 and 8.85τ, to (95), 8.99, 8.92 and 8.83τ. Attempted transketalisation of the hydroxy-ketal (95) with acetone, using p-toluene sulphonic acid as a catalyst, resulted in the recyclisation of this compound to the ketal lactone (93).

In a final attempt to induce the desired rearrangement, we investigated the possibility of producing a carbonium ion at C(14) by an acid-catalysed cleavage of the epoxy-ketone (97). Steric considerations suggested that epoxidation of the enone (42) would result in a predominance of the required α-epoxide (97). Thus, in this isomer, if the C(14)-O bond did undergo heterolysis, then the well established stereoelectronic requirements in the transition state would be satisfied for methyl migration. There are literature precedents for αβ-epoxy-ketones cleaving in the required direction.[37] Unfortunately, however, in the case in question, (97), no clear cut prediction was possible on the direction of epoxide opening.

In the event, an acceptable yield of the oily α-epoxy-ketone (97) was isolated from the reaction of the enone (42) with 30% hydrogen peroxide in methanol, containing a quantity of dilute aqueous sodium hydroxide. This reaction was complicated by hydrolysis of the C(16) methyl ester and extreme caution was necessary in the work-up to prevent premature reaction of the epoxide function. An attempt to epoxidise the enone (42) without hydrolysing the methyl ester, using 30% hydrogen peroxide

and sodium bicarbonate,[38] was unsuccessful. Support for the epoxy-ketone structure (97) came from the mass spectral molecular weight of 392, which corresponded to addition of an oxygen atom to the enone (42), and the replacement of the enone carbonyl band by a 1720cm^{-1} carbonyl band, due to the unconjugated system. The C(14) proton appeared in the n.m.r. spectrum as a singlet at 6.60τ.

Several attempts were made to cause the epoxide function in (97) to react in the required manner. In the first, the epoxy-ketone (97) was returned unchanged from prolonged contact with grade $\underline{\text{III}}$ acidic alumina in benzene. Treatment of the epoxy-ketone (97) with boron trifluoride etherate in dry benzene at r.t. resulted in two products, which were easily separated by preparative t.l.c. The structure of the minor, more polar, component (98), was easily deduced from its i.r. spectrum i.e. the γ-lactone (1784cm^{-1}), the methyl ester (1730cm^{-1}) and the transoid enone (1676cm^{-1}) carbonyl bands were well resolved, and supported by mass spectrometric molecular weight determination.

However, the structure of the major component was not so obvious and its determination was hampered by the unstable nature of the compound. On the basis of the following evidence it was decided that this material was boron difluoride complexed β-dicarbonyl system (99). One of the main clues to the structure was found in the mass spectrum, whose highest peak was at m/e 420, 28 mass units higher than the starting epoxide. This peak

was discounted as the molecular ion, as there was a peak at m/e 409 (loss of 11amu.) and it could be satisfactorily rationalised in terms of loss of hydrogen fluoride (20amu) from the boron difluoride complex (440amu.). A u.v. absorption band at 312 nm. (ε = 8,900), provided the second main clue. This band could only be reconciled with some kind of enolised β-diketone system and it bears a relationship to the parent β-diketone (isolated later)(100) absorption, λ_{max} 297 nm. (ε = 8,800), similar to that found by Sagredos,[39] who studied β-diketones of the type (101) and their BF_3 complexes. The i.r. and n.m.r. spectra were entirely in accord with the formulation (99), a point of special significance in the i.r. being a strong band at 1350cm^{-1} attributable to a B-O stretching mode.

Initially, we were surprised that this complex did not decompose in the presence of mineral acid, but recourse to the literature[40] soon convinced us that this type of complex was a remarkably stable entity. Sodium borohydride in methanol reduced the complex in reasonable yield to the β-ketol (102). In this compound, the hydroxyl group was strongly hydrogen bonded to the carbonyl, as was apparent from the positions of the i.r. absorption bands, 3560cm^{-1} and 1698cm^{-1} respectively, and the loss of a two proton multiplet in the n.m.r. at approximately 7.5τ in going from the complex to the β-ketol, points to the structure (102) rather than the isomeric (103). The β-ketol (102) underwent quantitative acetylation with acetic

anhydride in pyridine to (104) and the result of breaking the intramolecular hydrogen bond was reflected in the return of the carbonyl frequency to its expected position, 1717cm.$^{-1}$

Slow cleavage of the epoxide function also occurred on refluxing a benzene solution of the epoxy ketone (97) containing a catalytic amount of hydriodic acid. The u.v. properties (λ_{max} 297 nm., ε = 8,800, changing to λ_{max} 316 nm., ε = 17,600 in base) of the sole product from the reaction indicated that it was the β-diketone (100). This assignment was borne out by i.r. and n.m.r. measurements. Further support for the structure of the boron difluoride complex (99) came from the correlation of one of the decomposition products of the complex with this β-diketone (100).

EXPERIMENTAL.

METHYL ISOPIMARATE (46).

Isopimaric acid (23), which was isolated from American Gum Rosin according to Baldwin et. al.[18], was methylated with diazomethane in ether in the usual manner. Recrystallisation of the residue from methanol afforded methyl isopimarate (46), as colourless needles, m.p. 62-62.5°.

i.r. 3084, 1731, 1639, 1249, 1009, 992, 914cm^{-1}.

τ = 9.13(s,3H), 9.08(s,3H), 8.73(s,3H), 6.38(s,3H), 4.71(d,1H, J_{AX}= 6Hz), 5.24-5.36 (ABC system).

HYDROXY-ESTER (47).

To a solution of diisoamylborane, prepared from sodium borohydride (0.151g;0.004moles), 2-methyl-2-butene (0.73g; 0.010moles), and boron trifluoride etherate (0.74g; 0.005moles) in dry diglyme (4ml), was added in a nitrogen atmosphere, at 0° with stirring, a solution of methyl isopimarate (46) (1.482g; 0.005moles) in dry diglyme (4ml), over a few minutes. The mixture was stirred for 60hrs. at room temperature and cooled to -10°. A few drops of water were added to destroy the excess diisoamyl borane and then cold 3N sodium hydroxide solution (2ml). This was followed by dropwise addition of hydrogen peroxide solution (2ml of 30%), at such a rate that the temperature did not exceed 50°. The mixture was extracted

with ether and the combined ether extracts were washed thoroughly with water, brine and dried. Evaporation of the solvent in. vacuo. furnished an oil, (1.832g), from which the hydroxy-ester (47), (1.110g; 71%), m.p. 90-91°, was obtained as colourless needles, by preparative t.l.c. in ethyl acetate-light petrol (1 : 3) and recrystallisation from light petroleum.

i.r. 3637, 1728, 1246, 1145, 1051cm^{-1}

τ = 9.19, 9.10, 8.73(alls,3H), 8.45(s,1H; OH by D_2O exchange), 6.38(s,3H), 6.30(t,2H; J_{AX} = 8Hz), 4.75(d,1H, J_{AX} = 5Hz).

Molecular weight from mass spectroscopy was 334.

OSMYLATION OF THE HYDROXY-ESTER (47).

The hydroxy-ester (47), (0.765g; 0.0023moles) in dry ether (15ml) was added to osmium tetroxide (0.7g; 0.0028moles) in a mixture of dry ether (10ml) and anhydrous pyridine (1ml). Dark brown crystals of the osmate complex formed after a few minutes. After five days at r.t., the ether was replaced by benzene and hydrogen sulphide was bubbled through the solution for 15minutes. The black, almost colloidal, precipitate of osmium sulphide was filtered off and the benzene evaporated in. vacuo., leaving the crude glycol mixture as a dark brown crystalline mass. Analytical t.l.c. in ethyl acetate-light petrol (7 : 3) revealed two products and a little starting material.

Preparative t.l.c., in the above solvent system, afforded the α-triol ester (48) (0.429g; 51%), which recrystallised from light petrol-chloroform, as fine white needles, m.p. 166-168°, $[\alpha]_D$ = -2°(c = 0.86)

i.r. 3637, 3496, 3427, 1726,1717(shoulder), 1256, 1245, 1168, 1079, 1039cm^{-1}.

τ = 9.10, 8.93, 8.81(all s,3H), 6.65(t,1H,J_{AX}= 3Hz), 6.34 (s,3H), 6.31(t,2H,J_{AX}= 8Hz), 6.18(b.s.,2or3H,OH by D_2O exchange). Molecular weight from mass spectroscopy was 368.

[Found : C,68.19; H,10.07%; $C_{21}H_{36}O_5$ requires C,68.44; H,9.85%].

The less polar β-triol ester (49) was isolated as a brownish semi-crystalline compound (0.040g; 5%). However, further purification and characterisation was hindered by rapid decomposition.

OXIDATION OF THE α-TRIOL ESTER (48).

(1). SNATZKE :- Chromium trioxide (11mg) was added, with swirling, to a solution of the α-triol ester (48), (10mg; 0.027m.moles) in dry dimethylformamide (1ml) and concentrated sulphuric acid (1 drop). The reaction mixture was allowed to stand at r.t. for 48hrs, after which it was poured into water, and ethyl acetate extracted. Evaporation of the solvent *in. vacuo.* afforded an oil, which was shown, by analytical t.l.c., using ethyl acetate-petrol (3 : 2) as the developing solvent, to

consist of seven compounds.

(2). N-BROMOSUCCINIMIDE :- A solution of the α-triol ester (48), (380mg; 1.03m.moles) in aqueous dioxan (10ml) was mixed with a solution of N-bromosuccinimide (2g; 11.23m.moles) in 90% aqueous dioxan (10ml) and set aside in the dark at r.t. for 48hrs. Water was added and the solution was extracted thoroughly with chloroform. The combined extracts were washed with water, brine and dried. On removal of the solvent *in. vacuo.* an oil was obtained, from which the keto-lactone (69) (0.273g; 73%), was separated by preparative t.l.c. in an ethyl acetate-light petroleum (7 : 3) solvent system. After several recrystallisations from ethyl acetate-light petrol (40 : 60) colourless prisms, m.p. 215-224°, $[\alpha]_D = -12°$ (c = 0.69) were procured. i.r. (KBr disc) 1720, 1735(shoulder), 1253, 1230, 1225(shoulder), 1198, 1091, 1031cm^{-1}. Carbonyl intensity measurements, using the ketol (67) as a standard, indicated three carbonyls.

τ = 8.98,(s,3H), 8.82(s,6H), 7.81(s,1H), 7.64(d,J = 1Hz) + 7.69(shoulder) (3H in all), 6.36(s,3H).

Molecular weight by mass spectroscopy was 362.

[Found : C,69.38; H,8.35%; $C_{21}H_{30}O_5$
requires C,69.58; H,8.34%].

ACETYLATION OF THE α-TRIOL-ESTER (48).

The α-triol-ester(48)(0.100g;0.27m.moles), was dissolved in anhydrous pyridine (2ml), acetic anhydride (2ml) added, and the solution left at r.t. for 20hrs. Evaporation of the solvent *in. vacuo.* and purification by preparative t.l.c. in ethyl acetate-light petrol (1 : 1) yielded the desired hydroxy diacetate (51), (0.091g; 75%), which crystallised from ether-light petrol (40 : 60) as fine white needles, m.p. 110-111°, $[\alpha]_D$ = -23° (c = 1.02).

i.r. 3592, 3552, 1744(v.b.), 1365, 1239(b), 1023cm^{-1}.

τ = 9.08, 8.96, 8.81, 7.97, 7.88, 6.36(all s,3H), 5.83(t,2H, J_{AX}= 8Hz), 5.32(t,1H, J_{AX}= 5Hz).

[Found : C,66.43; H,8.83%; $C_{25}H_{40}O_7$ requires C,66.34; H,8.91%].

PHOSPHORUS OXYCHLORIDE DEHYDRATION OF THE HYDROXY DIACETATE(51).

To a solution of the hydroxy diacetate (51) (50mg; 0.11 m.moles) in dry pyridine (2ml), was added dropwise,with swirling and cooling,freshly distilled phosphorus oxychloride (20 drops) and the mixture was set aside at r.t. overnight. The solvent was carefully azeotroped off with benzene at low temperature *in. vacuo.* and the residue was partitioned between water and ether. Drying and evaporation of the solvent *in. vacuo.* afforded an oil, from which the oily olefin diacetate mixture (52) and (53), (26mg; 53%), was extracted by preparative

t.l.c., using an ethyl acetate-light petrol (3 : 7) solvent system. This mixture could not be resolved by t.l.c.

i.r. 1730-40(broad band), 1230, 1030, 1365, 1675cm.$^{-1}$

τ = 9.10, 9.03, 8.82, 9.20, (all s) 7.98(s,6H), 6.38(s,3H), 5.90(t,J_{AX}= 7Hz), 5.93(t,J_{AX}= 7Hz), 5.05(m), 4.78(m), 4.40(d,J=2Hz)

The mixture was shown to consist of approximately 65% $\Delta^{8,9}$ by integration of the relevant n.m.r. peaks.

HYDROLYSIS OF THE OLEFIN DIACETATE MIXTURE (52) AND (53).

The olefin diacetate mixture (52) and (53)(100mg; 0.23m.moles) in ethanol (2ml) and 10% ethanolic potassium hydroxide solution (2ml) was left at r.t. for 24hrs. Water was added and the resultant solution was thoroughly extracted with ether. The combined extracts were washed with water, brine and dried. An oily residue (70mg), which consisted of two major compounds, as shown by analytical t.l.c., in ethyl acetate-light petroleum (7 : 3), was obtained by evaporation of the ether *in. vacuo*. These were separated by t.l.c., by developing the chromatoplate three times in the above solvent system. The least polar material was the oily $\Delta^{8,9}$ isomer (54) (36mg; 44%).

i.r. 3620, 3400(broad), 1728, 1230, 1175, 1150, 1118, 1062, 1045cm.$^{-1}$

τ = 9.10, 9.05, 8.81, (all s, 3H), 7.87 (b.s., OH by D_2O exchange), 6.35(s,3H), 6.92(t,2H, J_{AX}= 8Hz).

The most polar material, the $\Delta^{8,14}$ isomer (55) (14mg; 17%)

rearranged on elution from the Kieselgel, to the very non-polar tetrahydrofuran (56), which recrystallised in clusters of needles, m.p. 115-116.5°, from light petroleum (40 : 60).

i.r. 1730, 1232, 1189, 1179, 1142, 1115, 1044cm^{-1}.

τ = 9.18, 9.03, 8.75, 6.43, (all s, 3H), 6.15(t,2H, J_{AX}= 8Hz) 4.28(m,1H).

Molecular weight by mass spectroscopy was 332.

MANGANESE DIOXIDE OXIDATION OF THE OLEFIN-DIOL MIXTURE (54) AND (55).

The crude oily olefin diol mixture (54) and (55) (20mg) from the previous hydrolysis reaction was dissolved in ether (5ml), powdered manganese dioxide (500mg) was added and the resultant heterogeneous modification was stirred at r.t. After 18hrs, the manganese dioxide was filtered off and the ether evaporated *in. vacuo.* leaving an oil (15mg). Preparative t.l.c., in an ethyl acetate-light petroleum (1 : 1) solvent system, afforded an oil (7mg), which was shown to be mainly the $\Delta^{8,9,}$ enone (57), by i.r.

i.r. 3632, 1730, 1691(weak), 1668, 1162cm^{-1} and u.v. λ_{max}= 250nm. (ε = 8,000) (calc λ_{max}= 249 nm.).

HYDROLYSIS OF THE HYDROXY-DIACETATE (51).

The hydroxy-diacetate (51) was hydrolysed in 10% methanolic potassium hydroxide at r.t. as usual and yielded, almost quantitatively, a product, which was identical in all respects to the α-triol ester (48).

REACTION OF THE KETO-LACTONE (69) WITH METHANOL/SULPHURIC ACID.

A solution of the keto-lactone (69) (10mg; 0.028m.moles) in dry methanol (5ml) and concentrated sulphuric acid (0.5ml), was refluxed under nitrogen for 2 days. The solution was reduced to low bulk *in. vacuo.*, neutralised with aqueous sodium hydroxide solution and extracted with ethyl acetate. The combined ethyl extracts were washed with water, brine and dried. Removal of the solvent *in. vacuo.* afforded an oil (9mg), which was shown to contain one major component by analytical t.l.c. in ethyl acetate-light petroleum (7 : 3). This was separated by preparative t.l.c. and found to be a 1 : 1 mixture of the enones (75) and (42), which could not be resolved by t.l.c.

i.r. 1732, 1737(shoulder), 1692, 1668, 1226, 1152, 1111cm.$^{-1}$

λ_{max} 249 nm. (ε = 9,000).

REACTION OF THE KETO-LACTONE (69) WITH SODIUM METHOXIDE.

To a refluxing solution of the keto-lactone (69) (100mg; 0.276m.moles) in dry methanol (30ml) was added sodium metal (0.6g) in small pieces over five minutes. The solution was allowed to reflux for a further 30 mins under nitrogen and then reduced to low bulk *in. vacuo*. Dilute hydrochloric acid was added till pH 5 and the precipitate was quickly extracted into ether, which was washed with water and dried. Methylation of the ether layer and evaporation *in. vacuo*., gave a semi-crystalline material, which contained two products by analytical t.l.c. in ethyl acetate-light petroleum (3 : 7). The less polar, major product was separated by preparative t.l.c. in the above solvent system and proved to be the cisoid enone (42) (83mg; 80%), which crystallised as needles, m.p. 116-118°, $[\alpha]_D$ = +2°(c = 0.63), from ethyl acetate-light petroleum (40 : 60).

i.r. 1732, 1738(shoulder), 1692, 1618, 1228, 1182, 1151, 1120, 1078cm^{-1}. λ_{max}= 250 nm. (ε = 9,600)

τ = 9.14, 8.89, 8.76(all s, 3H), 7.72(s, 2H), 7.66(s, 2H) 6.38(s, 6H), 3.24(d,1H, J_{AX}= 2.5Hz).

[Found : C,69.93; H,8.55%; $C_{22}H_{32}O_5$ requires C,70.18; H,8.57%].

SODIUM BOROHYRIDE REDUCTION OF THE CISOID ENONE (42).

The cisoid enone (42) (20mg; 0.053m.moles) was dissolved in ethanol (1ml), sodium borohydride (5mg) added and the solution was set aside at r.t. for 30mins. The solution was partitioned between water and ethyl acetate and the latter layer was washed with water, brine and dried. The oily allylic alcohol (79) (18mg; 90%), which was homogeneous on analytical t.l.c., was obtained on removal on the solvent *in. vacuo*.

i.r. 3610, 1734, 1739(shoulder), 1234, 1178, 1150, 1121, 1082, 1010cm^{-1}.

τ = 9.19, 8.93, 8.80(all s,3H), 7.73(s,2H), 6.33, 6.36(s,3H), 6.06(q, poorly resolved, 1H), 4.26(b.s.,1H).

Molecular weight was 378 by mass spectroscopy.

THE p-NITROBENZOATE ESTER (80).

The allylic alcohol (79) (8mg; 0.021m.moles) and freshly recrystallised p-nitrobenzoyl chloride (25mg) were dissolved in the minimum volume of anhydrous pyridine and set aside at r.t. After 72hrs, the solution was thrown into aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed thoroughly with water, brine and dried. Evaporation of the solvent *in. vacuo*.and preparative t.l.c., in an ethyl acetate-light petroleum (1 : 1) solvent system, afforded the pure p-nitrobenzoate ester (80) (10mg; 91%).

i.r. 1730, 1737(shoulder), 1350, 1275, 1240, 1178, 1153, 1119, 1104, 1066, 1010, 874cm.$^{-1}$

τ = 9.10, 8.92, 8.77(s,3H), 7.82(s,2H), 6.50(s,3H), 6.33 (s,3H), 4.43(b.s.,1H), 1.72(b.s.,1H). 1H under the 6.50 and 6.33 peaks.

ACETOLYSIS OF THE p-NITROBENZOATE ESTER (80).

A solution of the p-nitrobenzoate ester (80) (10mg; 0.019 m.moles) and urea (15mg) in dry acetic acid was refluxed under nitrogen for 20hrs. After cooling, careful neutralisation with sodium bicarbonate and ethyl acetate extraction as usual yielded, on removal of the solvent in. vacuo., an oil (7mg) which was shown to contain one major component by analytical t.l.c. Preparative t.l.c. in ethyl acetate-light petroleum afforded this least polar component, as an oil (3mg), which proved to have the diene structure (81).

i.r. 3020(shoulder), 1732, 1739(shoulder), 1350, 1340, 1275, 1235, 1190, 1150, 1110, 1074cm.$^{-1}$

λ_{max} 236, 242, 250 nm. (triple maxima), (ε = 10,000).

τ = 8.92, 8.80, 8.75(s,3H), 7.73(s), 6.36, 6.33(both s,3H) ~ 4.60(m). The n.m.r. spectrum was very weak due to lack of material.

Mass spectral molecular weight was 360.

ATTEMPTED FORMIC ACID REARRANGEMENT OF THE ALLYLIC ALCOHOL(79).

Formic acid (99%; 0.2ml) was added to a stirred solution of the allylic alcohol (79) (5mg; 0.014m.moles) in chloroform (0.5ml) at 0°. The temperature of the solution was allowed to rise to r.t. and stirring was continued. After 72hrs., neutralisation was effected with sodium bicarbonate solution and ethyl acetate extraction and evaporation as before, furnished an oil (5mg). Analytical t.l.c. revealed a single product, in addition to some starting material, which was less polar than the starting alcohol and this was separated by preparative t.l.c. in ethyl acetate-petrol (1 : 1).

i.r. 1733, 1739(shoulder), 1236, 1177, 1152(shoulder), 1133, 1107, 1064cm.$^{-1}$

This compound was shown to be the simple allylic formate (83). Thus, hydrolysis on an acid washed alumina column returned material identical by t.l.c. and i.r. to the allylic alcohol(79).

ATTEMPTED KETALISATION OF THE ENONE (42).

Freshly redistilled boron trifluoride etherate (4 drops) was added with swirling, to a solution of the enone (42) (20mg; 0.054m.moles) in the ketal of methyl ethyl ketone (0.5ml), at r.t. After 48hrs, the solution was taken to dryness *in. vacuo.* and the residue proved to be identical in all respects to the starting enone (42).

ATTEMPTED KETALISATION OF THE KETO-LACTONE (69).

A solution of the keto-lactone (69) (40mg; 0.11m.moles), p-toluene sulphonic acid (40mg) and dry ethylene glycol (1ml) in sodium dried benzene was refluxed for 18hrs., with continuous water separation by means of silica gel in a Dean-Stark apparatus. The solution was quenched in aqueous sodium bicarbonate and thoroughly extracted with ethyl acetate. The combined extracts were washed with water, brine and dried. Analytical t.l.c., in an ethyl acetate-light petroleum solvent system, of the oil (55mg), obtained by removal of the solvent in. vacuo., revealed two major products. Preparative t.l.c. afforded the faster running enone tosylate (94) (30mg; 0.054 m.moles), which was contaminated by a small amount of the isomeric $\Delta^{8,9}$ enone (89).

i.r. 1733, 1740(shoulder), 1692, 1670(v. small), 1619, 1380, 1225, 1191, 1181, 1153, 1123, 1100, 1025, 962, 910cm.$^{-1}$

τ = 9.15, 8.94, 9.79(all s,3H), 7.91(m), 7.72(s,4H), 7.55 (s,3H), 6.37(s,3H), 5.82(s,4H), 3.36(d,1H), 2.50(q,4H).

The more polar ketal lactone (93) was obtained as an oil (15mg), which was found to be contaminated by the monotosylate of ethylene glycol. Purification by prep t.l.c. and recrystallisation from ether-light petrol (40-60), gave small prisms, m.p. 209-209.5.°

i.r. 1731, 1740(shoulder), 1322, 1283, 1245, 1198, 1162, 1145, 1124, 1096, 1051, 1040, 1030, 1018, 950cm.$^{-1}$

τ = 9.00, 8.94, 8.85(all s,3H), 7.73(b.s.), 6.34(s,3H), 6.07 (m,4H). m.s. m/e = 86, 91, 186.

Molecular ion at m/e = 406.

CONVERSION OF THE ENONE TOSYLATE (94) TO THE ENONE (42).

A solution of the enone tosylate (94) (10mg; 0.018m.moles) and aqueous sodium hydroxide (0.5ml, 2%) in methanol (4.5ml), was refluxed under nitrogen for 30mins. Reduction to low bulk in. vacuo., acidification and ethyl acetate extraction in the usual manner, afforded a product (6mg), which, after methylation with diazomethane in ether, was shown to be identical in all respects to the enone (42).

ATTEMPTED KETALISATION OF THE ENONE TOSYLATE (94).

The enone tosylate (94) (20mg; 0.036m.moles) was subjected to the ethylene glycol/p-toluene sulphonic acid in benzene at reflux conditions. Work-up as before and preparative t.l.c. in ethyl acetate-light petroleum (3 : 2), yielded a 1 : 1 mixture of the enone tosylates (89) and (94) (9mg). The i.r. spectrum of this product and the enone tosylate (94) were identical, except for a very much more intense 1670cm^{-1} band in the former. A second compound (12mg) extracted from the preparative chromatoplate was the monotosylate of ethylene glycol.

REACTION OF THE KETAL LACTONE (93) WITH SODIUM METHOXIDE.

The ketal lactone (93) (12mg; 0.030m.moles) was reacted with sodium methoxide in methanol under conditions identical to those used on the keto-lactone (69). Work-up yielded the crystalline hydroxy-ketal (95) (10mg; 77%), which was shown to be almost pure by analytical t.l.c. in ethyl acetate-light petroleum (2 : 3).

i.r. 3545, 3460, 1731, 1739, 1230, 1200, 1155, 1096, 1054, 1042, 1034, 950cm^{-1}.

τ = 8.99, 8,92, 8.83(all s,3H), 7.30(s,3H, one of which was OH by D_2O exchange), 6.36, 6.33(both s,3H), 6.03(m,4H).

ATTEMPTED DEKETALISATION OF THE HYDROXY-KETAL (95).

A solution of the hydroxy-ketal (95) (5mg; 0.012m.moles) and p-toluene sulphonic acid (2mg) in acetone (1ml) was set aside at r.t. for 18hrs. Sodium bicarbonate solution was added and ethyl acetate extraction, washing with water and brine, afforded a crystalline material (4mg), which was shown to be identical to the ketal lactone (93).

SODIUM BOROHYDRIDE REDUCTION OF THE KETAL LACTONE (93).

Sodium borohydride (2mg) was added to a solution of the ketal lactone (93) (1mg) in methanol (0.5ml) and the reaction was monitored by analytical t.l.c. in an ethyl acetate-light petroleum (3 : 2) solvent system. After 24hrs. at r.t. the

ketal lactone was unchanged.

In contrast the keto-lactone (69) (1mg), under the above conditions, was reduced almost immediately at r.t. to the corresponding alcohol, as shown by analytical t.l.c.

ATTEMPTED KETALISATION OF THE ENONE (42).

(a). ETHYLENE GLYCOL :- The enone (42) (15mg; 0.040m.moles) was treated with ethylene glycol (10 drops) and p-toluene sulphonic acid (15mg) in dry benzene (10ml) at reflux as before. After 18hrs., the usual work-up afforded an oil (25mg), the three components of which were separated by preparative t.l.c. in ethyl acetate-light petroleum (2 : 3). Each compound was identified by its i.r. spectrum. The most polar was the oily mono-tosylate of ethylene glycol (9mg). That of intermediate polarity was the enone tosylate (89) (5mg) and the most mobile component was the $\Delta^{8,9}$ enone (75) (5mg).

(b). METHANOL/SULPHURIC ACID :- A solution of the enone (42) (15mg; 0.040m.moles) and concentrated sulphuric acid (3 drops) in dry methanol (5ml) was refluxed for 24hrs. under nitrogen. Dilute sodium hydroxide solution was added and ethyl acetate extraction, washing with water and brine as usual, yielded, on evaporation of the solvent in. vacuo., an oil (10mg). I.r., n.m.r. and analytical t.l.c. proved that the oil contained the starting enone(42), together with a small amount (~10%) of

the $\Delta^{8,9}$ isomer (75)

EPOXIDATION OF ENONE (42).

(a). 30% Hydrogen peroxide solution (20 drops) was added with stirring to an ice cold solution of the enone (42) (50mg; 0.133 m.moles) in methanol (9ml) and acetone (1ml). Water (0.5ml) was added and the solution was saturated with solid sodium bicarbonate. The temperature was allowed to rise to r.t and stirring was continued for 48hrs. Work-up was achieved by water dilution and ethyl acetate extraction. Analytical t.l.c. and i.r. on the reaction product revealed >90% starting material.

(b). 4N sodium hydroxide solution (1.5ml) was added to the enone (42) (300mg; 0.798m.moles) in methanol (20ml) and the solution was cooled to 0°. This temperature was maintained whilst 30% hydrogen peroxide solution (2.3ml) was added dropwise with stirring and then allowed to rise to 25°. After 48hrs., the solution was evaporated to low bulk at 25° in.vacuo. and carefully neutralised with N hydrochloric acid. The organic material was rapidly extracted into ether and immediately methylated with diazomethane. After elimination of the excess diazomethane, filtration through celite and evaporation of the ether in. vacuo. afforded an oil (300mg). Analytical t.l.c. in ethyl acetate-light petroleum (2 : 3) revealed one major product, slightly more polar than the starting enone, and

three minor products. Preparative t.l.c. in the above solvent system furnished the oily α-epoxy-ketone (97) (152mg; 49%).

i.r. 1730, 1721, 1230, 1194, 1150cm^{-1}.

τ = 8.90, 8.82 and 8.69(all s,3H), 7.59(m,4H), 6.60(s,1H) and 6.34(s,6H).

Molecular weight from mass spectroscopy was 392.

CLEAVAGE OF THE EPOXY-KETONE (97).

(a). ALUMINA :- A solution of the epoxy-ketone (97) (5mg) in sodium dried benzene (2ml) was agitated with grade III acidic alumina (500mg) at r.t. After 24hrs., filtration and removal of the solvent in. vacuo. afforded an oil, whose t.l.c. mobility and i.r. spectrum were identical to those of the starting material.

(b). BORON TRIFLUORIDE ETHERATE :- Redistilled boron trifluoride etherate (10 drops) was added with swirling to a solution of the epoxy-ketone (97) (30mg; 0.077m.moles) in dry benzene (5ml) at 0°. After the addition was complete, the temperature of the solution was allowed to rise to 25°. 24hrs. later, the reaction mixture was quenched with sodium bicarbonate solution and extracted with ethyl acetate as usual. Evaporation of the solvent in. vacuo. afforded an oil (26mg), which was shown by analytical t.l.c., in an ethyl acetate-light petroleum (2 : 3) solvent system, to contain two compounds

in addition to a little starting material. Preparative t.l.c. afforded the oily boron difluoride complex (99) (10mg).
i.r. 1730(broad), 1493, 1385, 1350, 1170(broad), 1046cm.$^{-1}$
τ = 9.15, 8.73, and 8.70(all s,3H), complexity of peaks centred at 7.55 (3H), 6.90(half of AB system, 1H, J_{AB}= 16Hz, other half contained in 7.55τ region), 6.29 and 6.27 (both s, 3H). The highest peak in the mass spectrum of (99) occurred at m/e = 420. i.e. molecular ion - HF(20).
λ_{max}= 312 nm.(ε = 8,900).
The boron difluoride complex was slightly unstable and one of the decomposition products was shown to be the β-diketone (100), by comparison with material prepared later.

The more polar component of the mixture (3mg) was assigned the γ-lactone structure (98).
i.r. 1785, 1730, 1676, 1163, 1112cm.$^{-1}$
Molecular weight by mass spectroscopy was 360.

(c). HYDROGEN IODIDE :- A solution of the epoxy-ketone (97) (30mg; 0.077m.moles) in benzene, containing concentrated hydriodic acid (1 drop), was heated under reflux for 60hrs. Evaporation of the solvent *in. vacuo.* and subsequent preparative t.l.c. in an ethyl acetate-light petroleum (2 : 3) solvent system, yielded the β-diketone (100) (10mg), as an oil.
i.r. 3430(v. broad), 1730, 1610(band disguised by carbon tetrachloride opaque region), 1215(broad), 1168, 1150, 1107cm.$^{-1}$

τ = 9.16, 8.80 and 8.75(all s,3H), 7.78(b.s.,2H), 7.70 and 7.02 (AB system; 2H; J_{AB}= 16Hz), 6.35 and 6.33 both (s,3H).
λ_{max}= 297 nm.(ε= 8,800), which changed to
λ_{max}= 316 nm.(ε= 17,600) in base.
The remainder of the material isolated was unchanged epoxy-ketone (97).

FURTHER CHARACTERISATION OF THE BORON DIFLUORIDE COMPLEX (99).

(a). ACID STABILITY :- A chloroform solution of the boron difluoride complex was shaken with dilute hydrochloric acid for several minutes. Separation and work-up of the organic phase in the usual manner afforded material identical by analytical t.l.c. and i.r. to the starting compound.

(b). SODIUM BOROHYDRIDE REDUCTION :- Sodium borohydride (50mg) was added with swirling to a solution of the boron difluoride complex (99) (15mg; 0.034m.moles), in methanol (3ml) and the resultant solution was set aside at 0° for 4hrs. Work-up, as described previously, provided an oil (12mg), which was shown to consist of one major and four minor components by analytical t.l.c. in ethyl acetate-light petroleum (2 : 3). The major component, the β-hydroxy-ketone (102) (6mg) was separated by preparative t.l.c.

i.r. 3560, 1736, 1698, 1200-1140(v. broad), 1104, 1079 and 1058cm.$^{-1}$

τ = 8.99, 8.80 and 8.78(all s,3H), 7.78 and 7.34(AB system; J_{AB}=16Hz,2H), 6.40(s,6H).

Molecular weight by mass spectroscopy was 394.

(c). KETO-ACETATE (23) :- The β-hydroxy-ketone (102) (2mg) was acetylated with acetic anhydride-pyridine as usual, to give the β-acetoxy-ketone (104) as an oil.

i.r. 1737, 1716, 1190, 1139, 1099, 1064 and 1022cm^{-1}.

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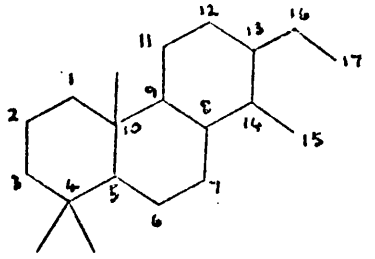

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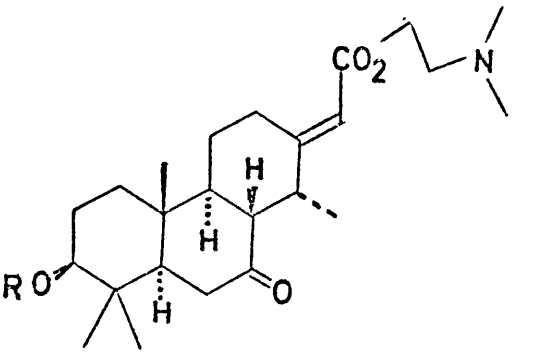

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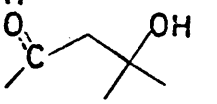
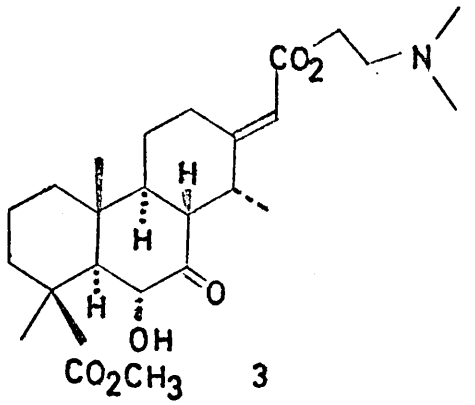
4 R = 



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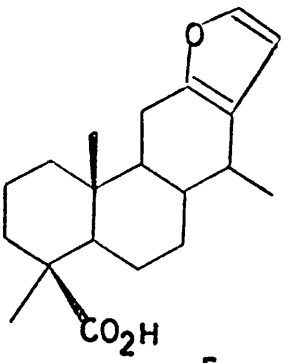

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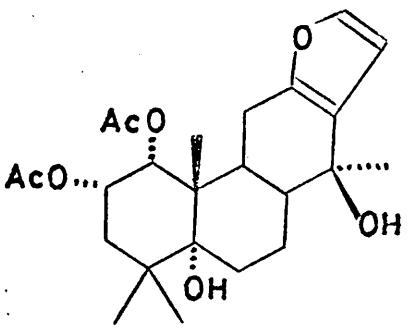

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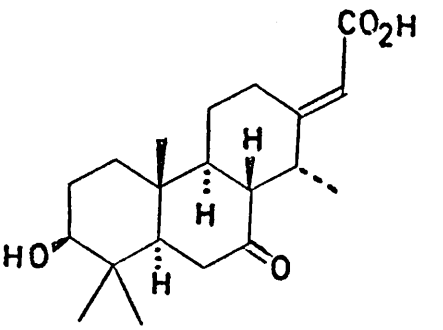

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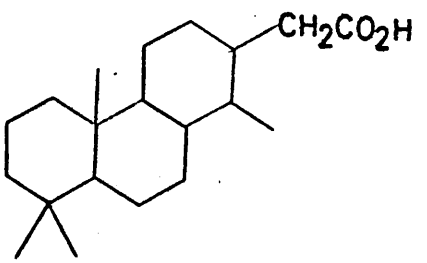

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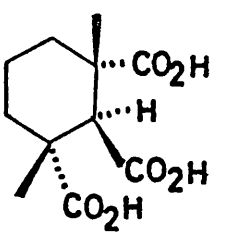

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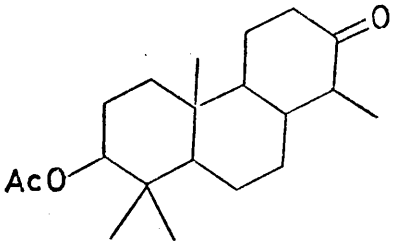

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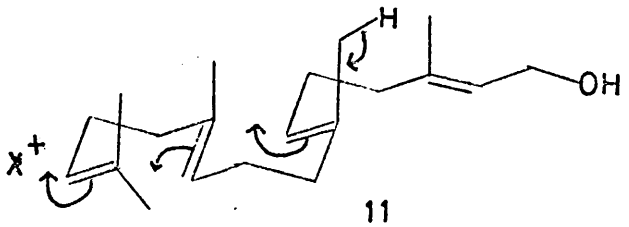

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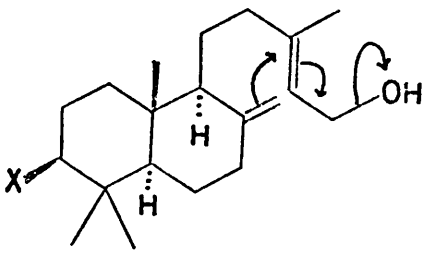

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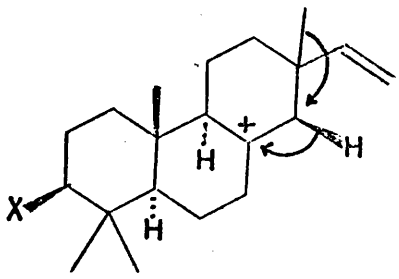

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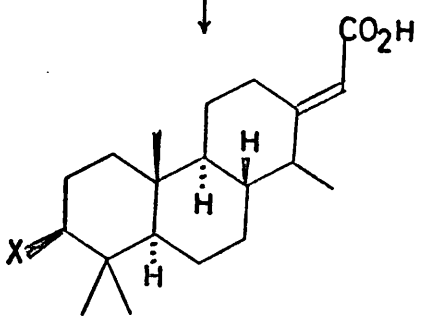

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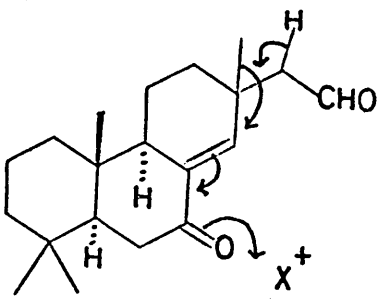

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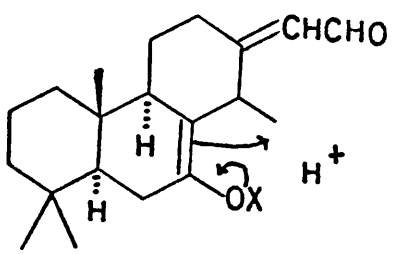

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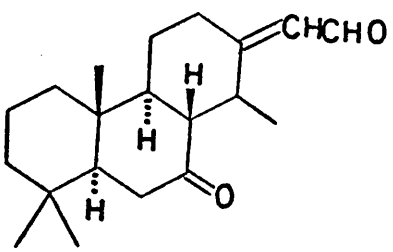

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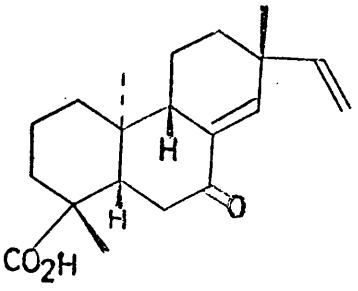

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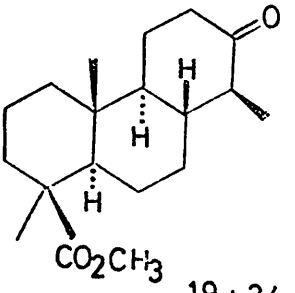

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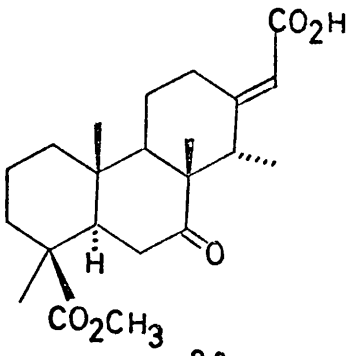

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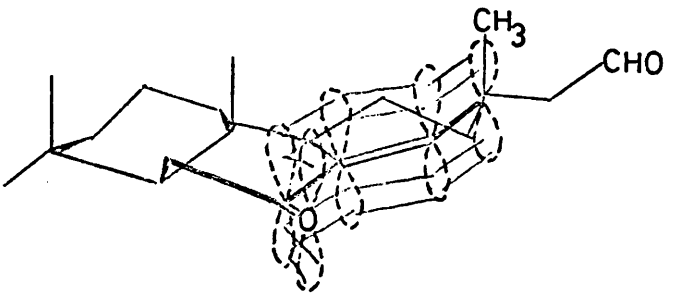

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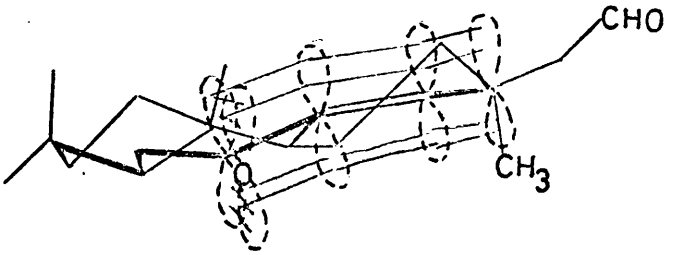

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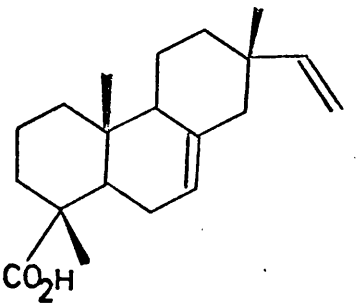

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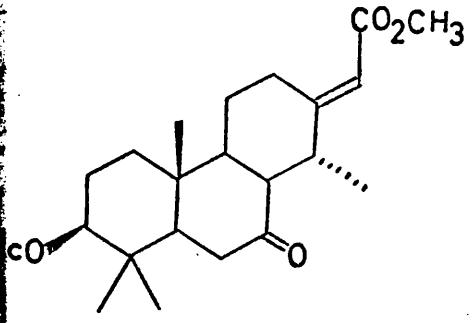

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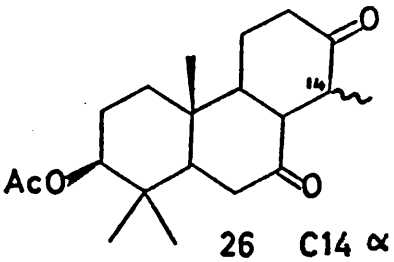

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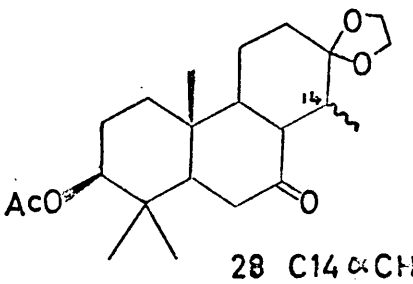
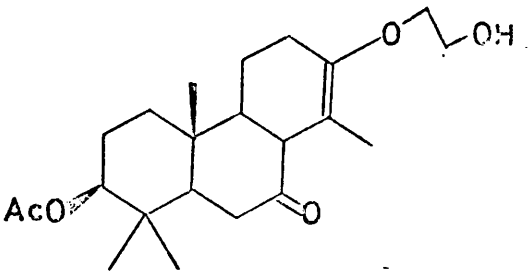


28 C14 α CH_3
29 C14 β CH_3



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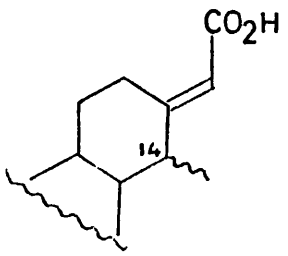
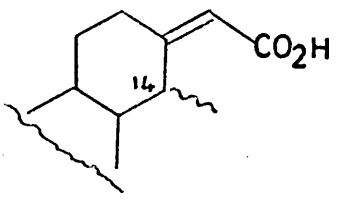
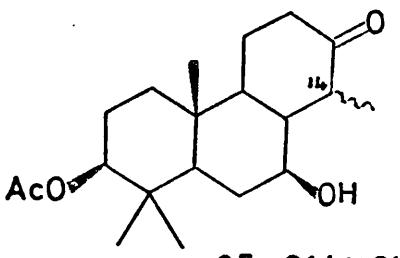


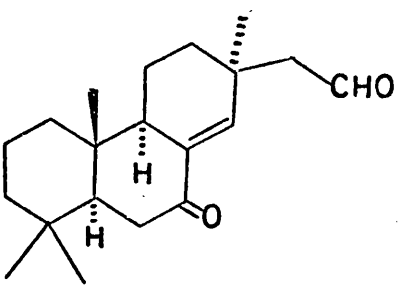
31 C14 α CH_3
33 C14 β CH_3



32 C14 α CH_3
34 C14 β CH_3



35 C14 α CH_3
37 C14 β CH_3



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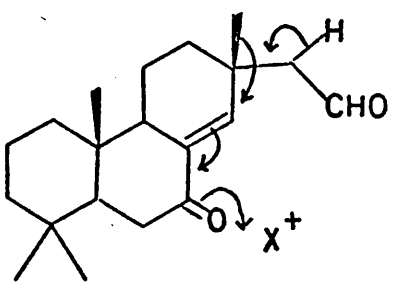

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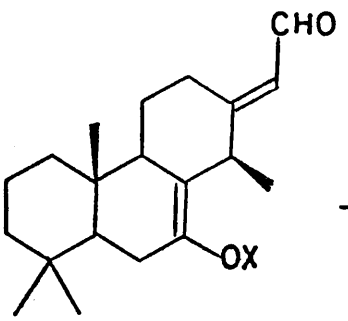

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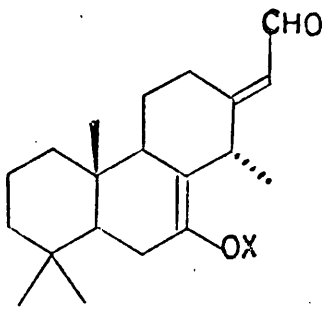

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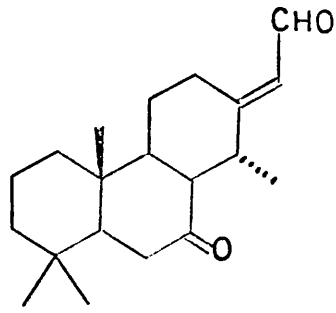

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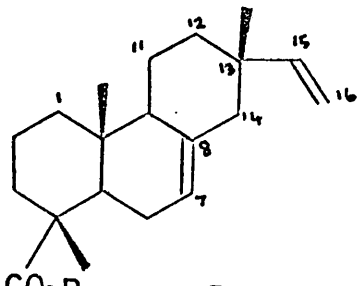
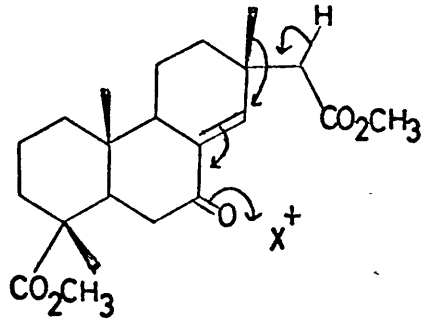


23 R = H
46 R = CH_3



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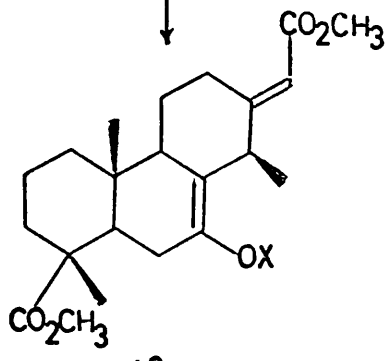

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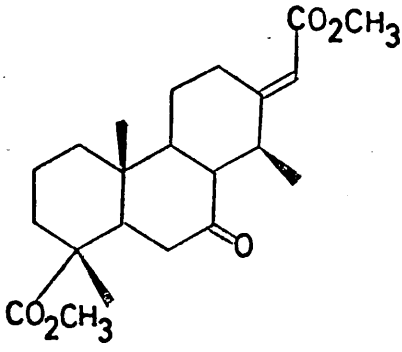

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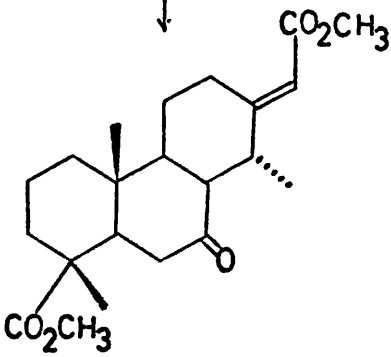

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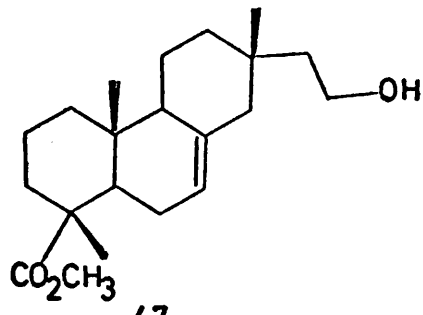

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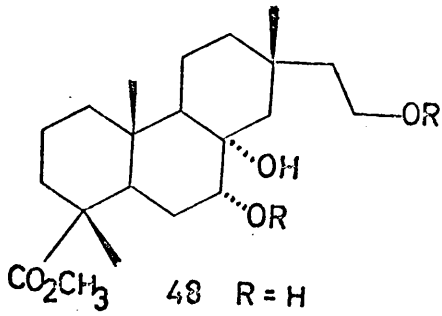
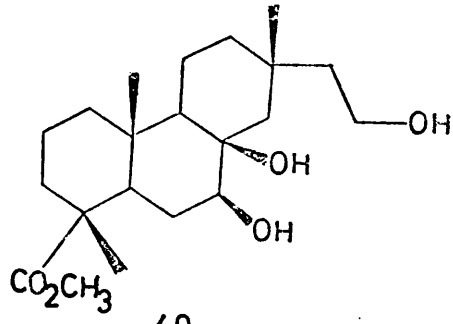


48 R = H
51 R = Ac



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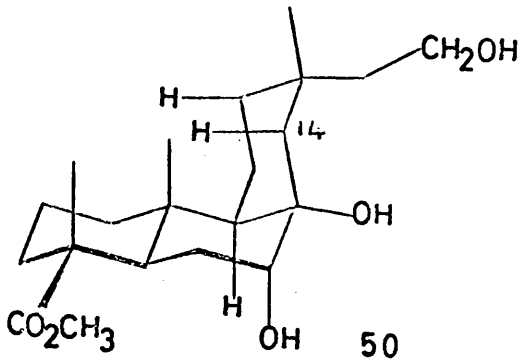

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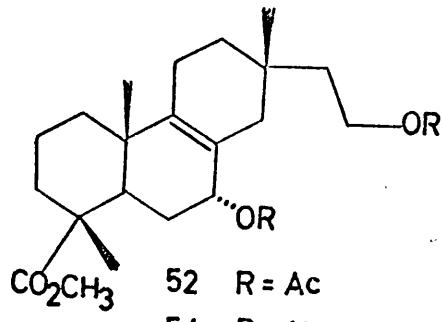
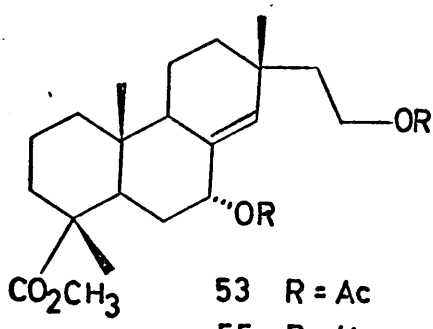
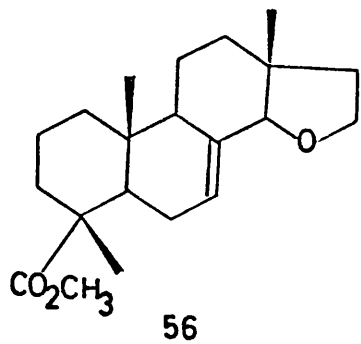


52 R = Ac
54 R = H



53 R = Ac
55 R = H



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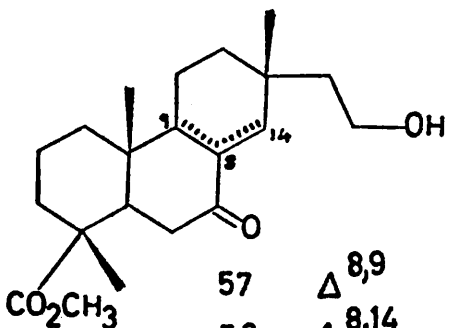
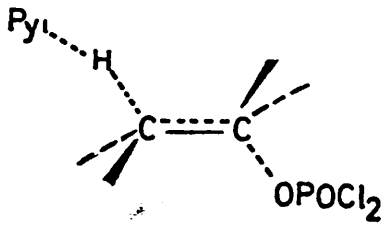


57 $\Delta^{8,9}$
58 $\Delta^{8,14}$



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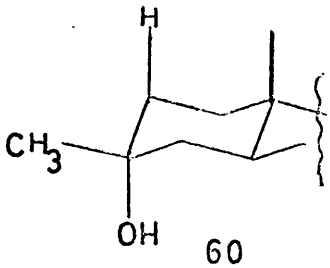

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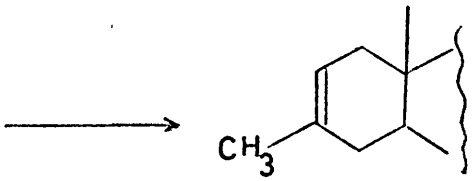

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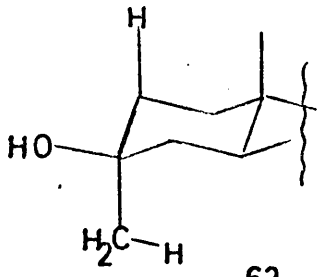

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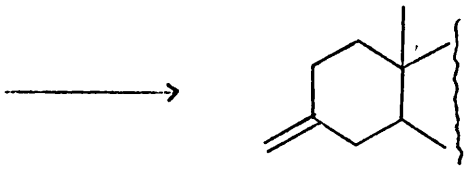

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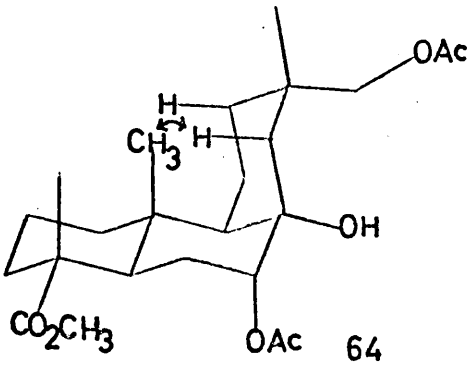

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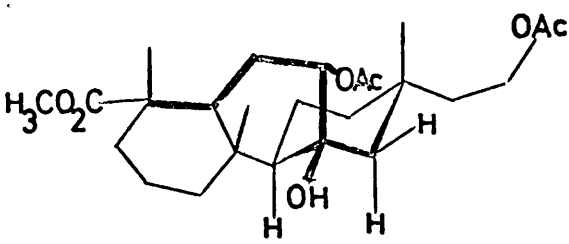

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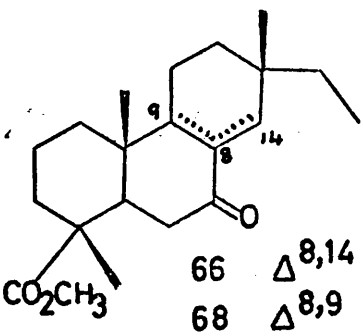
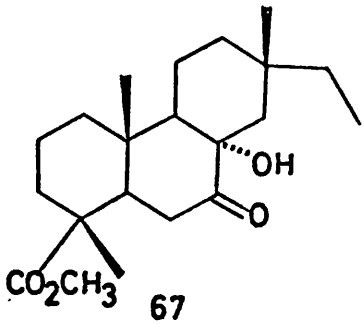


66 $\Delta^{8,14}$

68 $\Delta^{8,9}$



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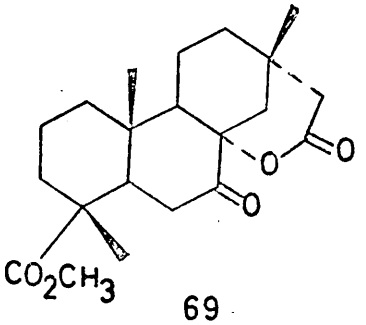

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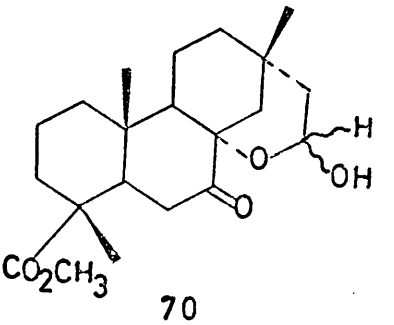

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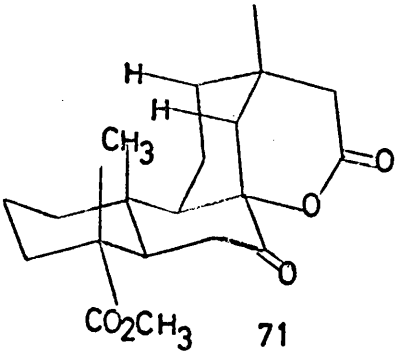

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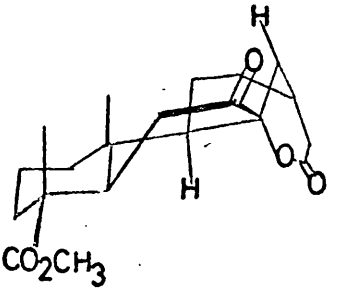

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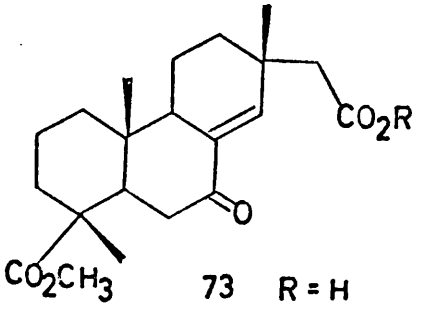
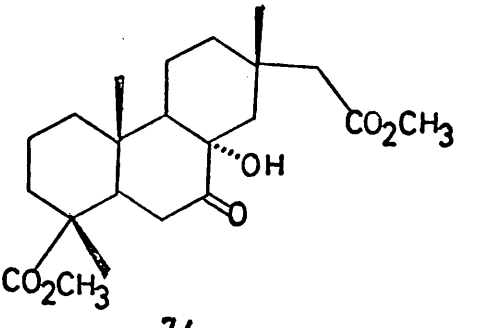


73 R = H

42 R = CH_3



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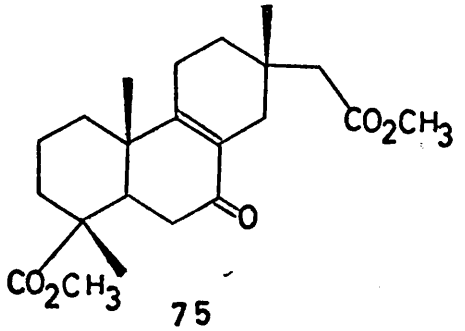

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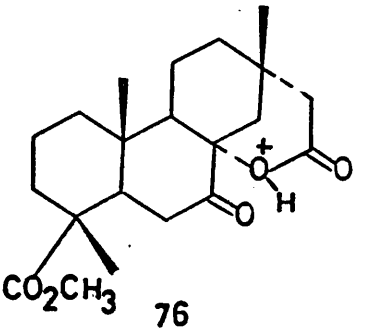

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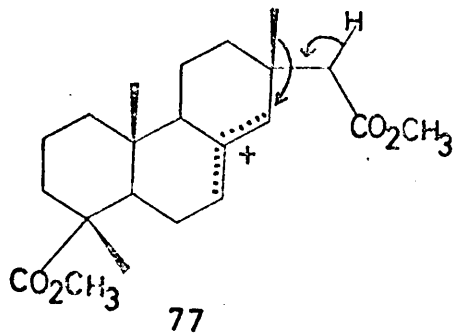

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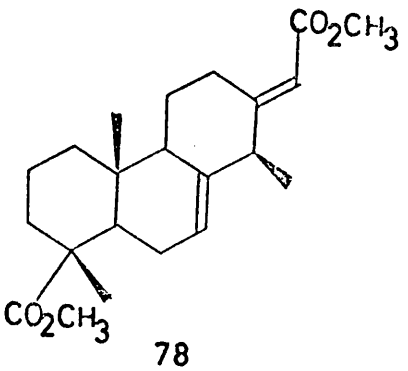

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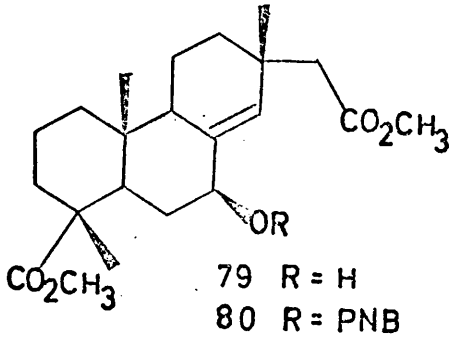
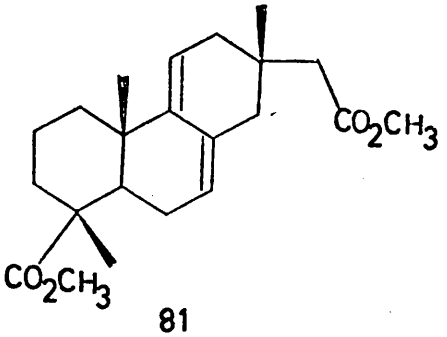
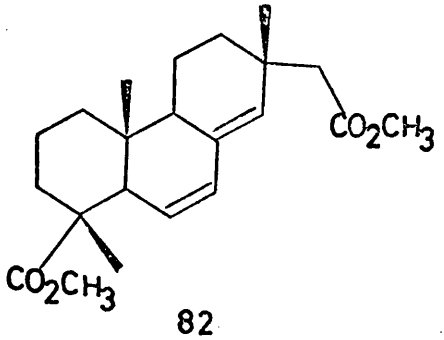


79 R = H
80 R = PNB
83 R = CHO



81



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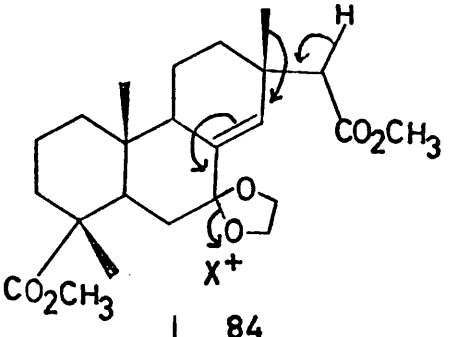

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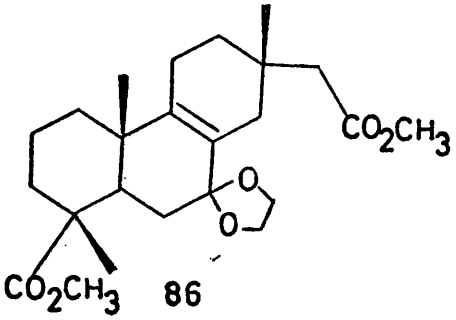

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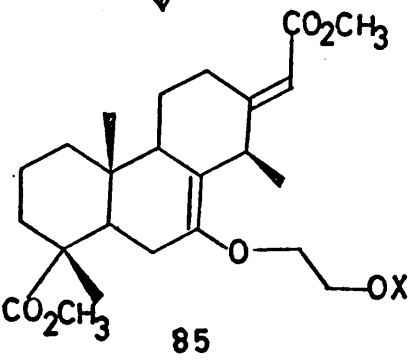

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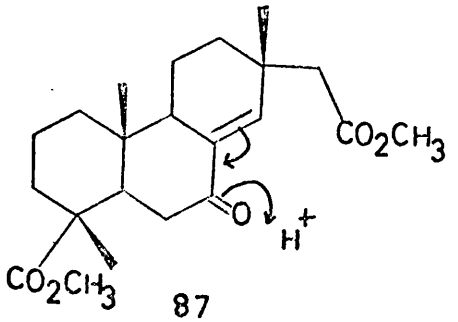

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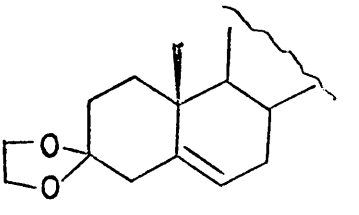

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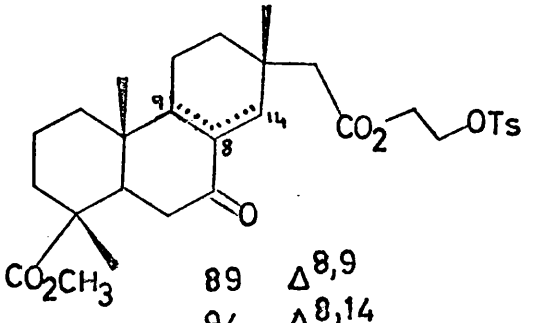
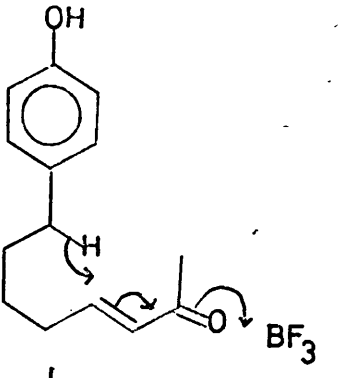


89 $\Delta^{8,9}$
94 $\Delta^{8,14}$



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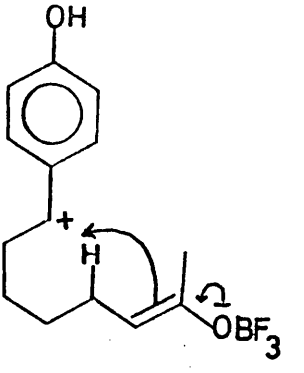

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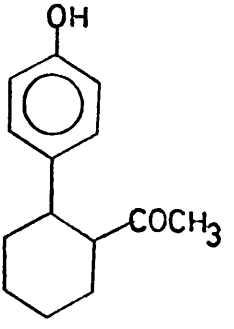

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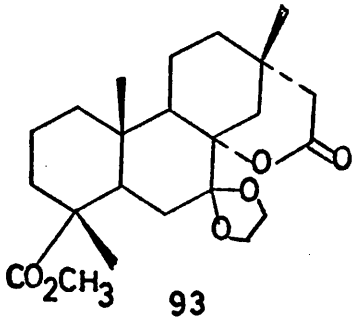

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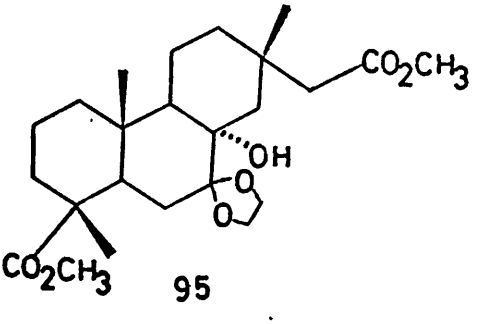

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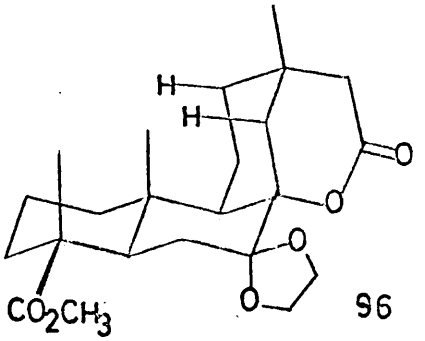

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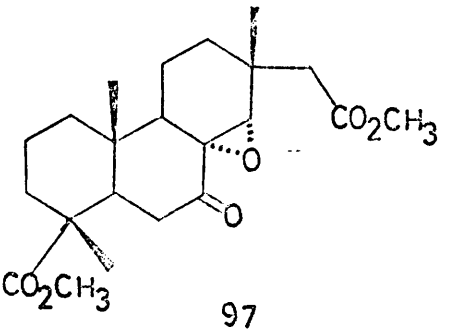

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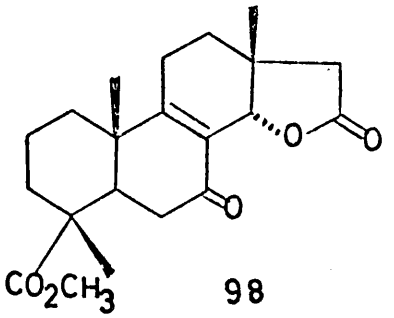

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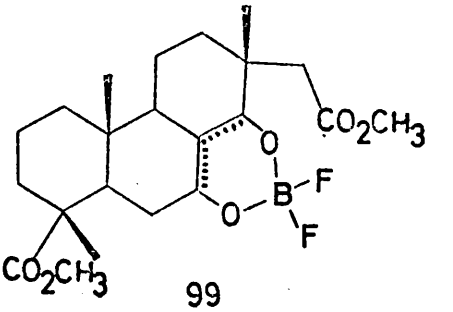

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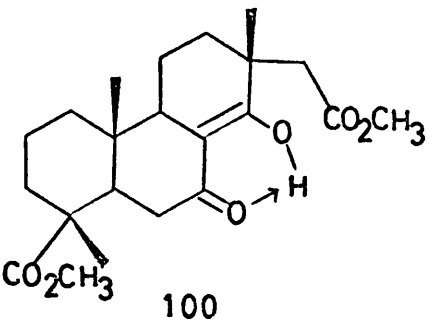

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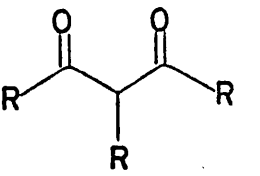
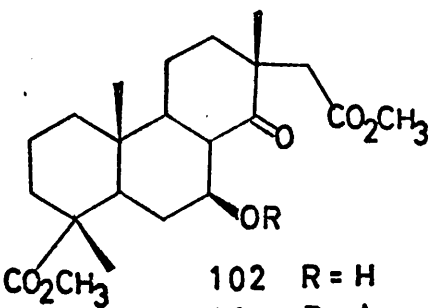


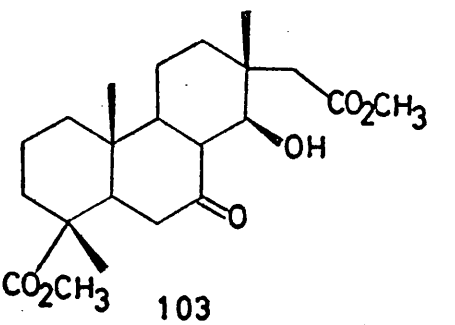
R = Alkyl

101



102 R = H

104 R = Ac



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