STUDIES IN CYCLOHEPTENES

THESIS

presented to the University of Glasgow

for the degree of Ph.D.

by

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I should like to express my gratitude to Professor R.A. Raphael, F.R.S., for the opportunity to carry out this research and to Dr. G.L. Buchanan for the untiring encouragement and assistance which he has given me during the last three years.

I also with to thank Mrs. F. Lawrie and Miss A.M. Robertson for recording the high-resolution infra-red absorption spectra, Mr. J.M.L. Cameron, B.Sc., and his staff for micro analysis, Mr. J. Gall and Mr. J. Lennon for recording proton magnetic resonance spectra and Dr. W. McCrae for the low temperature spectra.

The work described in this thesis was performed during the tenure of a Maintenance Award from the United States Air Force European Office of Aerospace Research and to this body I should like to express my gratitude.

SUMMARY.

Part I.

Chapter 1 describes a synthesis of the colchicine skeleton, namely, desmethoxydesacetamido-8,9,10,11,12-hexahydrocolchicine.. This was accomplished by utilising the bridge-cleavage reaction of a bicyclo-(3,2,1)-octan-8-one to the cycloheptene carboxylic acid. The acid produced was elaborated, via its methyl ketone to an O-acetate which on reduction, yielded the above alcohol.

In chapter 2 this cleavage reaction was employed in an unambiguous and selective synthesis of β-carboxy-tropolone.

Part II.

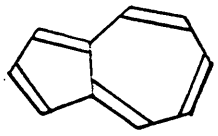
The acid catalysed bridge-fission of 1-carbethoxy-bicyclo-(3,2,1)-oct-3-ene-8-one was found to yield, after esterification, 1,1-dicarbethoxycyclohept-3-ene and 1,1-dicarbethoxycyclohept-4-ene in the ratio of 4 : 1. The predominance of the former was rationalised as a stereochemical effect and this led to an investigation of the conformation of cycloheptene. It was shown by n.m.r., that, in benzocyclohepten-3,7-diol, the seven-membered ring is in the chair conformation.

CONTENTS.

PART I

Chapter 1.

A synthetic approach to colchicine



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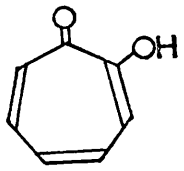

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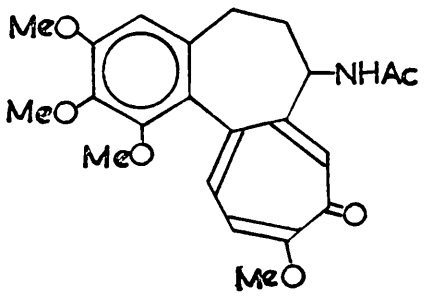

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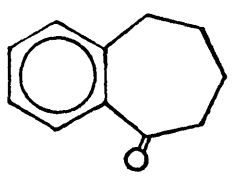
INTRODUCTION

In recent years seven-membered ring compounds have acquired an increased importance as the starting materials in the synthesis of azulenes[1] (1) and compounds which contain the cycloheptatrienolone (or tropolone) system[2] (2) such as the alkaloid colchicine (3), this being one of the many naturally occurring compounds which contain the cycloheptanoid ring. A study of the literature on the synthetic approaches to the alkaloid alone, (see references 32-37), illustrates the difficulties encountered in synthesising substituted seven-membered rings.

Most methods for the preparation of alicyclic compounds inevitably involve a reaction leading to ring closure, and, it has long been recognised that two factors contribute to the ease with which this may be effected viz., strain factor and the distance factor. Of these the latter is believed to be the more important, except in the case of medium rings (7-12 membered) where conformational strain is the dominant factor.

There are several condensation reactions, however, which yield cycloheptane rings, (albeit, in low yields), and these include the reactions of Ruzicka, Ziegler, Dieckmann, Prelog etc.,[3] many of which incorporate a



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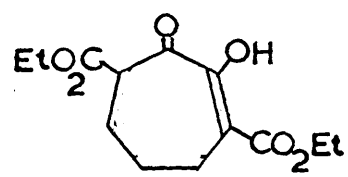

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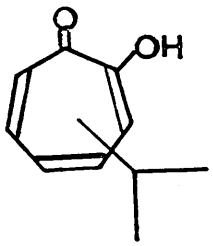
high dilution technique. Besides these intramolecular ring closures, which involve diesters, there are a number of others using diacids, dinitriles, diketenes (Blomquist) and dihalo compounds. But all of these suffer from the fact that the yield of the cycloheptane ring is, at best, only fair (≯50%). An exception to this is the intramolecular cyclisation of phenyl substituted acids or acid chlorides which result in a good yield of benzosuberones[4] (4). Besides the intramolecular ring closures the seven-membered ring can be prepared by intermolecular condensation of diesters e.g., in the synthesis of 3,7-dicarbethoxycycloheptan-1,2-dione (5) by reaction of pimelic and oxalic acid esters.[5]

An alternative method of preparation of seven-membered ring compounds is ring expansion of the corresponding cyclohexane. This route has been particularly applicable in the preparation of unsaturated rings such as tropones and tropolones. Indeed, using this type of reaction Doering[6] in 1951 completed the first synthesis of tropone by ring expansion of anisole with diazomethane.

Generally the synthesis of tropolones and tropones can be grouped into three main classes.



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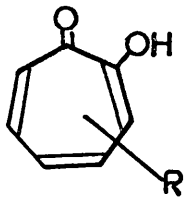

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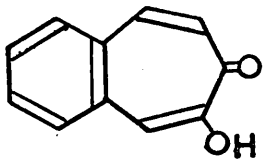
R= Me, Et, Bu^t



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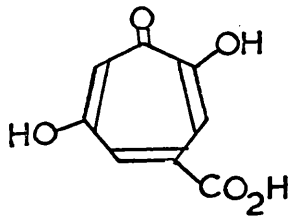
(a) synthesis starting from preformed seven-membered rings

(b) condensation reactions leading to a tropolone ring

(c) ring expansion of unsaturated cyclohexanes.

In the first group comes the method of Cook[7] and others[8] who started from cycloheptandione which was brominated then dehydrohalogenated to yield tropolone. As a general synthetic application, however, this proc edure was limited by the inaccessibility of the appropriately substituted dione. Nevertheless, this has been successfully applied to the synthesis of the thujiplicins[7,8] (6) and methyl-,[9,10] ethyl-,[11] and tert.-butyl tropolones[12] (7). The substituted cycloheptanones used as starting materials in these syntheses having been prepared by cyclisation of substituted suberic acids[12] or ring enlargement of substituted cyclohexanones.[7]

In the second group, i.e., condensation reactions, the proc edure has been used in the synthesis of 4,5-benzotropolones (8) or its derivatives. This is done by the condensation of phthalaldehyde and substituted acetones, such as bromo-,[13] hydroxy-,[14] methoxy-,[15] or phenoxyacetone.[16] This method is however of very limited value,



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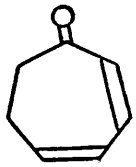

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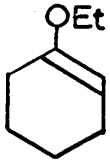

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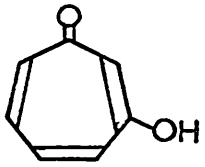

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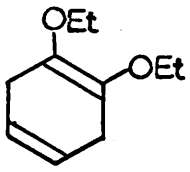

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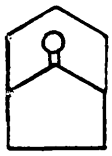
Of the ring expansion methods those using diazomethane are best known and, indeed, this constitutes one of the most efficient methods of making cycloheptanone itself. Bartels-Keith[17] further extended this method by reacting such diazo-alkyls as diazoacetic ester with certain aromatic compounds and on using veratrole this yielded the well-known mould metabolite stipitatic acid[17] (9). Besides using diazo compounds in the ring expansion of aromatic compounds Dobson[18] has applied carbene addition reactions to prepare cycloheptadienones (10) from ethoxy-cyclohexene (11) and this method was further extended by Birch[19] to prepare, the hitherto inaccessible, 3-hydroxy-tropone (12) from 1,2-dimethoxycyclohexa-1,4-diene (13). This type of ring expansion from cyclohexenes to cyclo-heptenes has also been accomplished by Chapman[20] and van Tamelin[21] by base rearrangement of dihydrobenzyltosylates. The resulting cycloheptadienones prepared by these methods can then be readily converted to both tropones[22] and tropolones.[23]

Almost all the aforementioned methods suffer from the handicap of poor yields and/or non-selectivity in the tropolone produced. This latter fault is best exemplified by considering the synthesis of a β-substituted tropolone (cf. 42). The normal method of preparation would be ring



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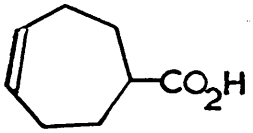

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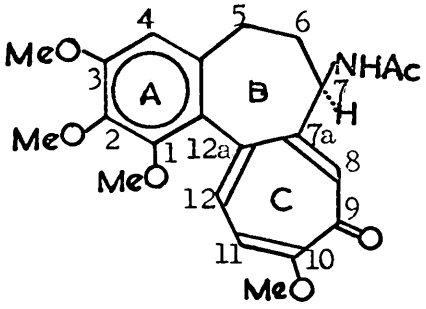

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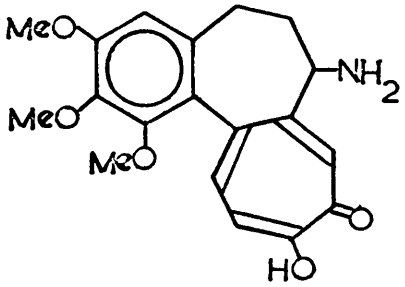
expansion of the 3-substituted cyclohexanone with diazomethane. This in itself would produce two cycloheptanones substituted at both the 3 and 4 positions which on oxidation would produce two diones. Conversion of these would then yield both β and γ-substituted tropolones. Thus a more selective method of production of the seven-membered ring is required which would also go in higher yields. Such a method has come to hand in recent years in this department[24] and elsewhere.[25,26] This route involves the bridge-cleavage of a bicyclo-(3,2,1)-octan-8-one (14) by acid to yield the cycloheptene carboxylic acid (15). Thus by constructing suitable bicyclic precursors this reaction could be used to synthesize both tropolones and naturally occurring cycloheptanoid compounds such as azulenes and the alkaloid colchicine.

The structure of colchicine, the chief alkaloid of Colchicum autumnale L., has been established as (3). The absolute configuration of the acetamido group in ring B was determined by Corrodi,[27] the tropolonoid structure of ring C having been initially postulated by Dewar[28] and later confirmed, using X-ray diffraction methods, by Pepinsky.[29]



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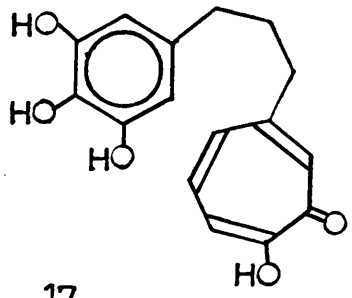

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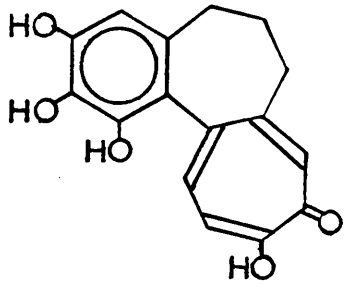

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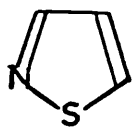
As has been said, the difficulties presented by the alkaloid as a synthetic problem can be seen by the number of failures reported since 1950 but, finally, a total synthesis was achieved simultaneously by the independent groups of Eschenmoser[30] and van Tamelin[31] in 1959. Almost all the reported syntheses can be classified as of two kinds; the one which preforms rings A and B followed by formation of ring C and the other which involves the prior forming of rings A and C then cyclisation of the B ring.

In the first category falls the routes of Eschenmoser, van Tamelin and Martel[32] while the second includes those of Nakamura[33] and his school, and the biogenetically based synthesis of Scott and his co-workers.[34] This final and most recently published work is notable for its brevity, where the total number of steps in the sequence to desacetamido colchiceine[35] (16) is only five. The critical cyclisation step in this route is the unique oxidative coupling of the bicyclic pyrogallol (17) to yield the tricyclic structure (18) which could be obtained by demethylation of (16). Although Scott's route was very concise, unlike the earlier routes which were all both lengthy and laborious, its shortcomings lie in the low yields in the critical cyclisation step and the practical difficulties which such a reaction entails.



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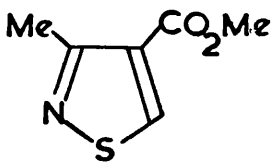

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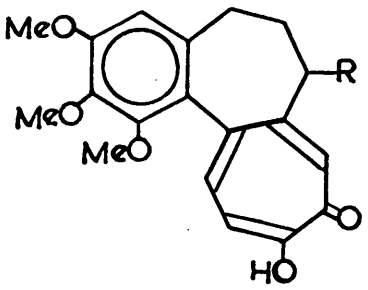

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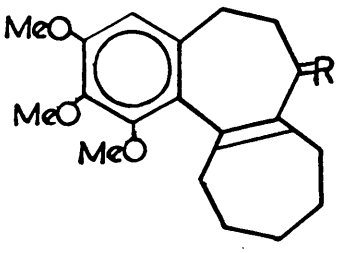
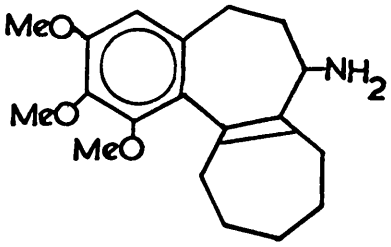
a. R = Br.

b. R = NH_2.



22 R = O

23 R = NOH



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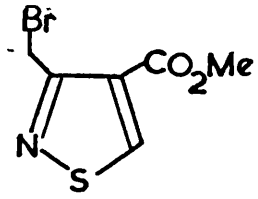

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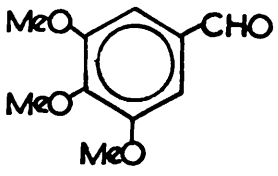

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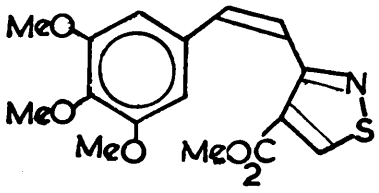

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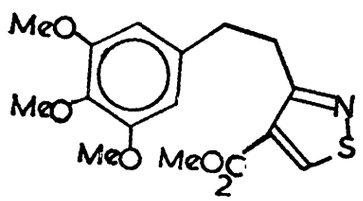
The exception to the above categorised approaches was the total synthesis of racemic colchiceine (16) by Woodward.[36] One of the most remarkable facets of this route was the unusual choice of starting material which was the chemical unit of the isothiazole (19). The heterocyclic employed was 3-methyl-4-carbomethoxy isothiazole (20) and onto the three ring carbon atoms the rest of the colchicine skeleton was built. The isothiazole unit was used as it incorporates a relatively unreactive nitrogen with particularly low basicity due to the adjacent sulphur atom At the same time the position of this sulphur is such that its elimination at the end of the synthesis, so opening of the heterocyclic ring, affords a free amine which can readily be acetylated.

This is a unique method of insertion of the amine group, the more frequently used method being allylic bromination to yield the 7-bromo compound (21a) followed by amination to (21b). The Japanese workers also employed a different method by first forming the tricyclic ketone (22) which was converted via its oxime (23) to the amine (24) prior to tropolonisation of the cycloheptene ring C.

The 3-bromo derivative of the isothiazole (25) was condensed with 3,4,5-trimethoxy benzaldehyde (26) by a Wittig reaction to yield the styryl intermediate (27)



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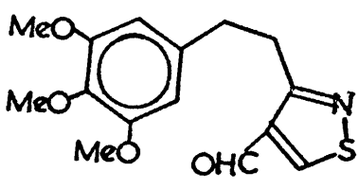

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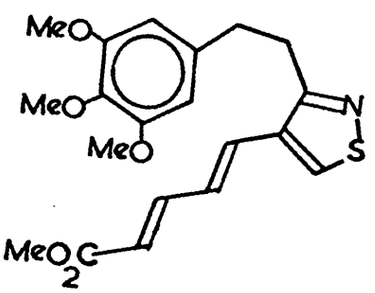

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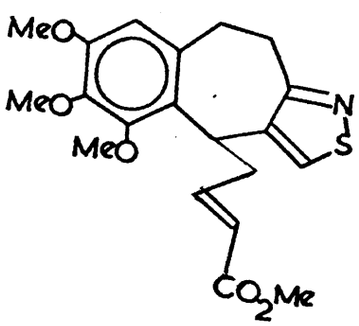

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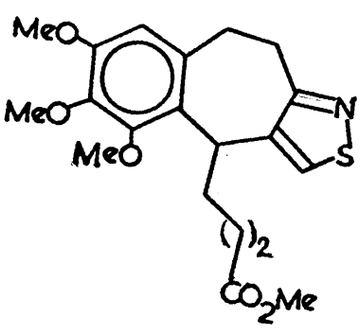

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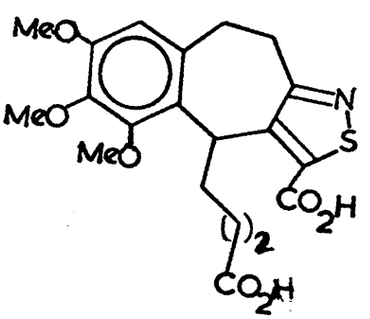

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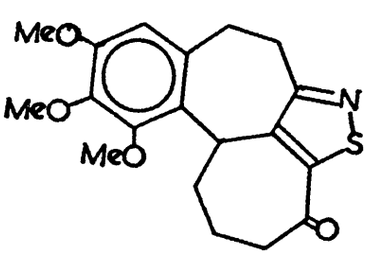

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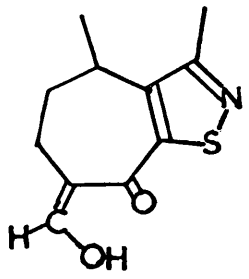
which was reduced using diimide to the saturated compound (28). Although ring B could have been readily generated at this juncture this was not done as it was intended to utilize the carbomethoxy group for further transformations leading to ring C.

The dicyclic ester was converted to the aldehyde (29) using formaldehyde and then underwent a Wittig condensation with γ-bromocrotonic ester to yield the unsaturated compound (30) with the side chain attached directly to the isothiazole ring at C_4. This side chain was intended to be incorporated as part of the ring C skeleton. The tricyclic compound (31) was obtained by acid catalysed cyclisation of (30) and the remaining double bond of the side chain was removed by diimide reduction to yield (32).

The next part of the synthesis required conversion of the acid C_5 proton on the isothiazole ring to a carboxy group. This was done by generation of the corresponding anion, using phenyllithium or even better o-lithiumbiphenyl, and carbonylation with carbon dioxide to give the diacid (33). Base-catalysed cyclisation of the corresponding dimethyl ester gave a tetracyclic keto-ester which after hydrolysis and decarboxylation afforded the ketone (34) containing all the carbon-carbon bonds present in colchicine.



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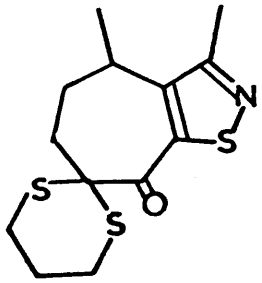

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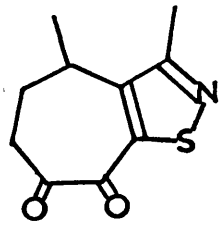

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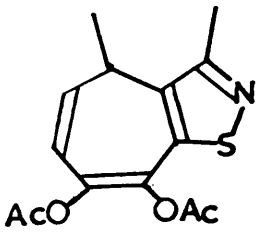

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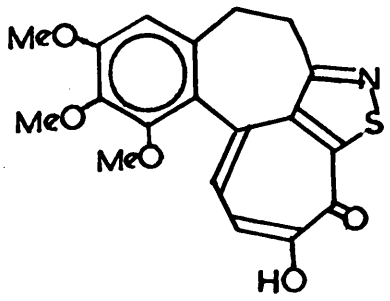

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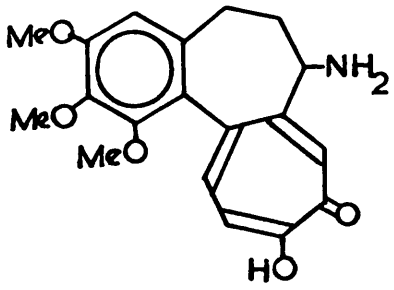

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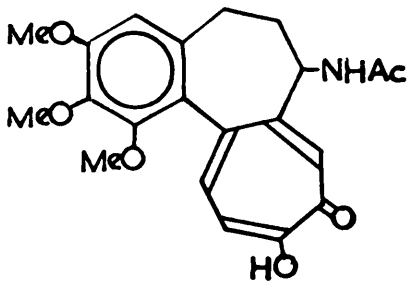

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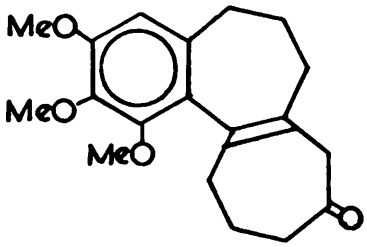

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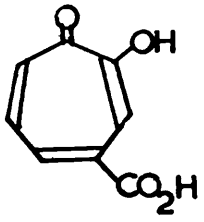

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It was now required to insert an oxygen on the methylene adjacent to the ketonic function. Formylation of the ketone gave the α-formyl ketone (35) which after reaction with trimethylene-p-toluenethiolsulfonate gave the 1,3-dithiane (36) which could be hydrolysed in the presence of mercuric acetate to the corresponding α-diketone (37). The transformation of the α-diketone to the tropolone was accomplished via the dienolate (38) which, in the presence of base and oxygen, was converted to the tetracyclic tropolone (39).

The incipient amino group was now released by desulphurisation with Raney nickel to yield the racemic desacetyl compound (16) which on acetylation gave synthetic d,l-colchiceine (40).

In spite of its novelty and elegance the Woodward synthesis, like the others, involves the inelegant stepwise construction of the seven-membered ring system. One of the objectives of the work described in this thesis was the use of bicyclo-(3,2,1)-octanones as intermediates in a more elegant synthesis of the colchicine skeleton (41). The second objective was to use similar intermediates in a new and unambiguous synthesis of substituted tropolones (e.g., 42).

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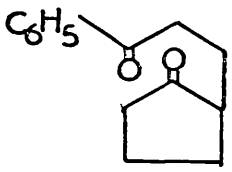
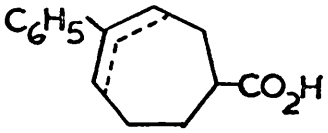
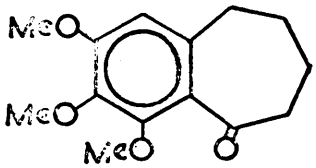

C6H5
O
O

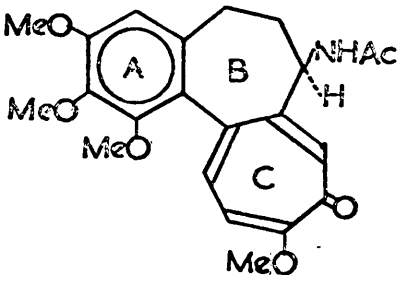
1


C6H5
CO2H

2


MeO
MeO
MeO
O

4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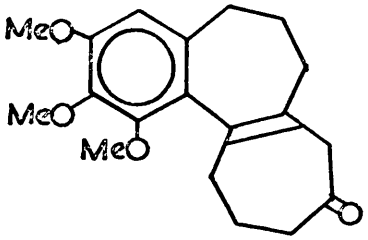
MeO
MeO
A
B
C
NHAc
H
O
O
MeO

3


MeO
MeO
MeO
O

5

Discussion.

Recent work in this department[1] has shown that acid treatment of a benzoylethylcyclopentanone (1) yielded, in one step, the phenylcycloheptene carboxylic acid (2). It was considered possible that this synthesis could be used to construct the ring system of the tropolone alkaloid, colchicine (3). This seemed an interesting objective and indeed, in his recent biogenetic synthesis of colchicine[2] Scott said "the challenge to the synthetic organic chemist offered by the alkaloid was not only worthy but perhaps unique".

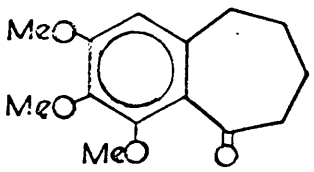
The difficulty in designing a flexible and succinct synthesis for this system falls into two parts;

(a) the formation of the 6-7-7 ring system,

(b) the transformation of ring C to the tropolone ring.

Using this new method it was thought that the first difficulty could be easily short-circuited if the proper precursor was chosen. Thus, for this reason 3,4,5-trimethoxybenzosuberone (4) was chosen as by using this rings A and B of the colchicine system are already constructed.

The problem of conversion to the fully tropolone ring C was to be overcome by first synthesising a known degradation product of colchicine viz., desmethoxydesacetamido-8,10,11,12-tetrahydrocolchicine (5) and, using



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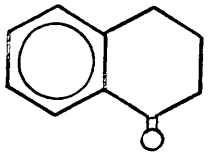

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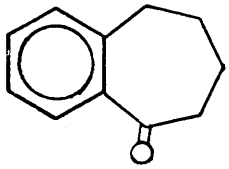

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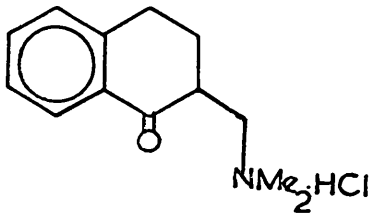

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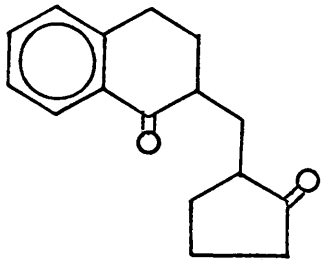

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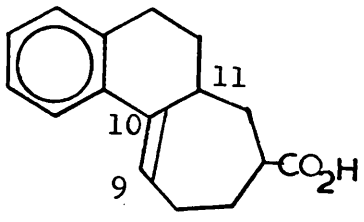

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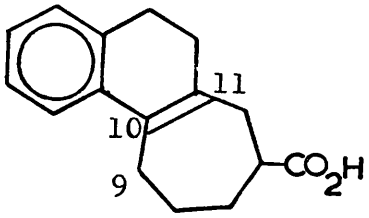

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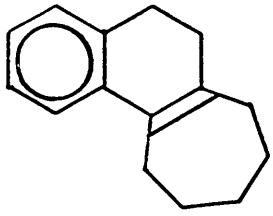
this as a relay, to complete the synthesis by converting the cycloheptenone ring to a tropolone by known methods.

Due to the comparative inaccessibility of 3,4,5-trimethoxybenzosuberone (4) the proposed synthetic route was to be simultaneously investigated using two other alicyclic aromatic ketones, viz., α-tetralone (6) and 2,3-benzosuberone (7).

α-Tetralone was converted by means of dimethylamine hydrochloride and p-formaldehyde to its known Mannich base,[3] β-dimethylaminomethyl-α-tetralone hydrochloride (8). The free base underwent a Michael condensation with cyclopentanone to produce the 1,5-diketone β-(2'-cyclopentanonylmethyl)-α-tetralone (9) in 59% yield and the latter underwent the ring expansion reaction in the presence of glacial acetic acid - concentrated hydrochloric acid (3:1 v/v) yielding acidic as well as neutral components.

The crystalline acid, $C_{16}H_{18}O_2$, was anticipated to be 1,2-benzobicyclo-(5,4,0)-undec-9,(10)-ene-6-carboxylic acid (10), but, this was found not to be the case as the n.m.r., spectra showed no olefinic protons. Thus the double bond was $\Delta^{10,11}$ (11) and not $\Delta^{9,10}$ (10). This can readily be rationalised on the basis of a simple double-bond migration from the trisubstituted to the more stable tetrasubstituted position. The tetrasubstituted nature



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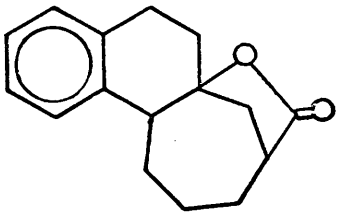

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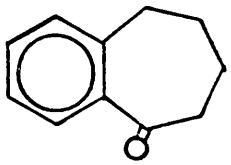

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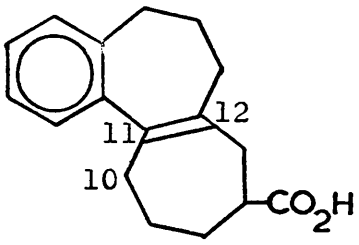
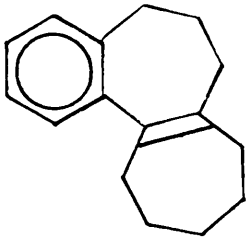


15b



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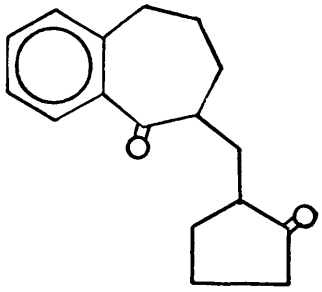

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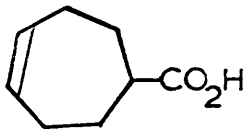
of the double-bond was further shown by the ultra-violet spectra which showed the styrene system consistent with the literature values quoted[4] for the parent hydrocarbon (13), viz., $\lambda_{max.}^{EtOH}$ 268 mμ (log ε, 3·8) as compared with the found values of $\lambda_{max.}^{EtOH}$ 268 mμ (log ε, 3·76).

The neutral material consisted of starting diketone and a slightly less polar compound which was successfully isolated, by preparative t.l.c., as a crystalline solid. This compound was given the lactonic structure (14) on the basis of its infra-red spectrum ($\nu_{CO}^{CHCl_3}$ 1762 cm.$^{-1}$) and by analogy with results of previous ring expansion reactions.

The occurrence of this lactone is an undesirable side reaction, as it cuts the yield of acid down to 40%, but no successful method of elimination could be determined.

By an exactly similar route 2,3-benzosuberone (7) was converted to 1,2-benzobicyclo-(5,5,0)-dodec-11(12)-ene-7-carboxylic acid (15b). The double bond position was once again determined by n.m.r., and the styrene system was correlated with the known hydrocarbon[5] (16).

On the occasion of this ring expansion no lactonisation was seen to occur, the only neutral compound being starting diketone (17). The fact that no lactonisation occurred can only be due to a conformational effect of



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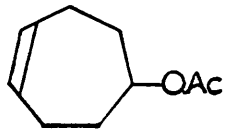

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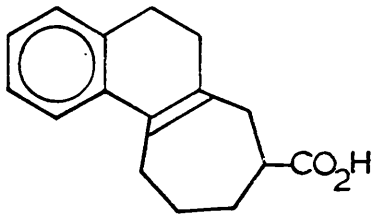

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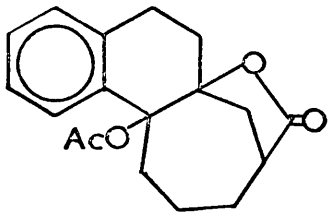
the fused seven membered rings. From a consideration of models it can be seen that ring B is in a pseudo-boat conformation while ring C can adopt any conformation desired but due to the fixed conformation of ring B the carboxylic group cannot approach the double bond and so lactonisation is prohibited. Thus the difficulty of preventing lactone formation and thereby loss of acid has resolved itself.

It can now be seen that this sequence could readily be applied to the synthesis of the colchicine skeleton. Indeed, the carboxyl group could be utilised as an incipient oxygen function if a sufficiently selective method of degradation could be designed without involving the use of nucleophilic reagents. Thus reactions of the Hündsdieker type are not possible as the halogen atom would rapidly attack the remaining aromatic position.

In 1962, Cope[6] published an elegant procedure whereby he converted 4-cyclohepten-1-carboxylic acid (18) to 4-cyclohepten-1-yl-acetate(19) by means of a lead tetra-acetate oxidation. When this reaction was applied to 1,2-benzobicyclo-(5,4,0)-10(11)-ene-6-carboxylic (11) acid a crystalline material was obtained. Recrystallisation from petrol yielded a compound, $C_{18}H_{20}O_4$, which showed two carbonyl bands in the infra-red at 1784 $cm.^{-1}$ and 1750 $cm.^{-1}$



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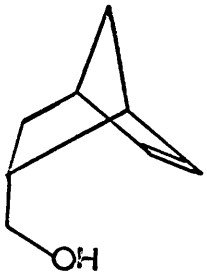

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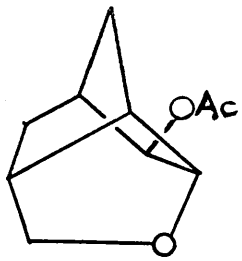

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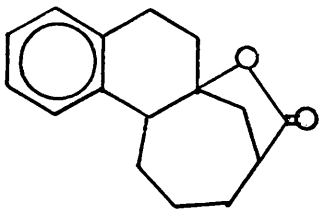

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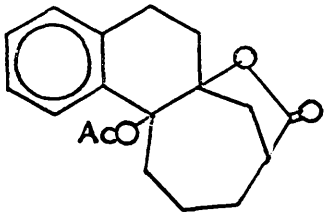
indicating a γ-lactone and an acetate. This conclusion was further corroborated by the occurrence of a singlet in the n.m.r. spectra at 8·05 τ (3 protons) and a multiplet at 6·3 τ (1 proton). The latter signal was assigned to the -C<u>H</u>-CO-O- system while the former is typical of an acetate group. Thus the acetoxy-lactone structure (20) was assigned the results being later correlated to the findings of Moriarty and Kapida. These workers reported that lead tetraacetate oxidation of 2α-hydroxymethylbicyclo-(2,2,1)-hept-5-ene (21) resulted in the formation of the acetoxy-oxide, 6-oxatricyclo-(3,2,1,$1^{3,8}$)-nonan-4β-ol-acetate (22) the results being rationalised by application of a mechanistic pathway which could readily be extrapolated to incorporate the above results.[9]

As further proof for the allocated structure the acetoxy-lactone (20) was hydrogenolysed in glacial acetic acid in the presence of 5% Pd/C at a pressure of 4 atmospheres to yield the known lactone (14).

As the tricyclic acid, derived from 2,3-benzosuberone, did not undergo lactonisation during its formation, it was decided to apply the lead tetraacetate reaction to this system in the expectation that ease of lactonisation was the driving force for the above failure. Unfortunately



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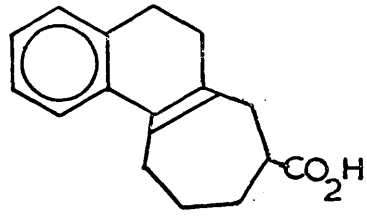

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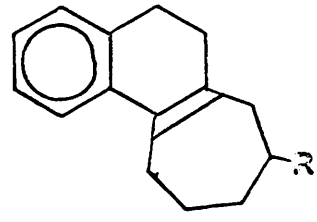
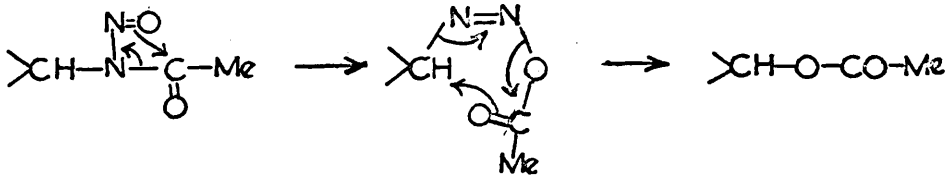


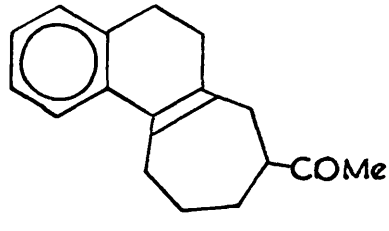
23. R = NH_2

24. R = OH



25

26



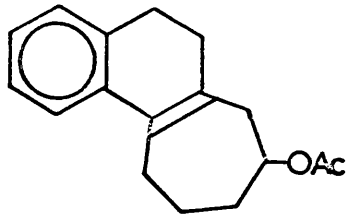
27

the same type of acetoxy-lactone (20) was recovered and so the promising procedure had to be abandoned in favour of more classical routes.

The tricyclic acid (11) was converted via the Curtius reaction[8] to 6-amino-1,2-benzobicyclo-(5,4,0)-undec-10(11)-ene (23) which was intended to undergo a deamination reaction to yield the alcohol (24).

The conversion was attempted using nitrous acid[9] under a variety of conditions but all resulted in a complex mixture and so were unsuccessful. This is not unexpected as the procedure involves the generation of a carbonium ion in a system which has a high likelihood of rearranging. Thus a method was required which did not involve the generation of this reactive intermediate. Such a method was known whereby the N-acetate was first formed, converted to the N-nitrosamide and this species underwent an intramolecular rearrangement to the acetate [(25) → (26)].[10] Application of this procedure to the compound in hand failed to produce any more satisfactory results than the nitrous acid rearrangements, and so this route via the amine was not further investigated.

The tricyclic acid was converted into its methyl-ketone (27) using methyl lithium.[7] Some difficulty was experienced in this preparation but eventually a yield of



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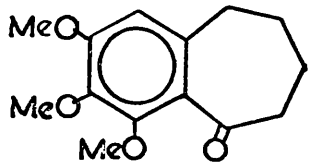

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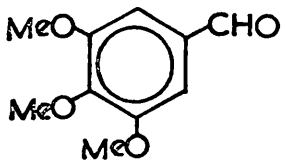


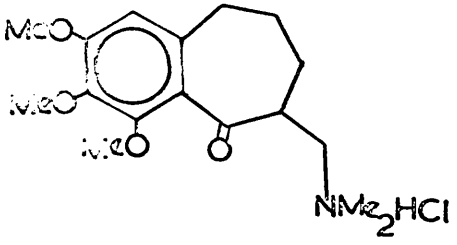
29

78% was achieved by using a molar ratio of 1:5:10 of acid : methyl iodide : lithium.

The methyl ketone underwent a Baeyer-Villiger oxidation to yield the acetate (28), this reaction having been carried out using as oxidising agent peracetic, perbenzoic and trifluroperacetic acids but optimum results were obtained by using m-chloroperbenzoic after the method of Meinwald.[11]

At this point study of the model compound was abandoned as the goal had been achieved i.e., the conversion of the carboxylic group to an oxygen function.

As has been said the progenitor for the colchicine skeleton was to be 3,4,5-trimethoxybenzsuberone (4) and this was not too readily accessible. There are two methods of preparation of this compound but both suffer from certain shortcomings. The first method which was employed was that of Koo[12] and it suffers from the fact that it is a lengthy and laborious procedure (8 stages), the second method was that of Loewenthal[13] and though much shorter, it required as starting material 3,4,5-trimethoxybenzaldehyde (29) which was generated by a Rosenmund reaction on 3,4,5-trimethoxybenzoic acid,[14] the maximum yield of this reaction being less than 30%. Fortunately the aldehyde was commercially available, and by application of both



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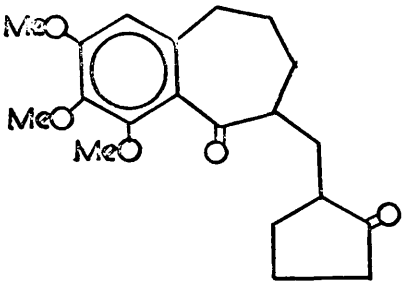
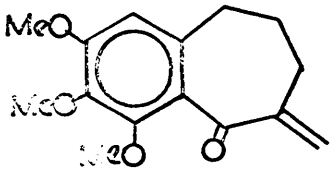


31



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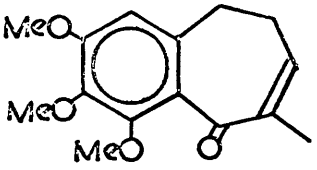
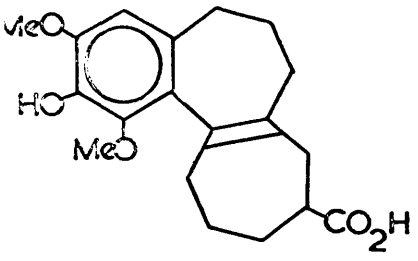


33

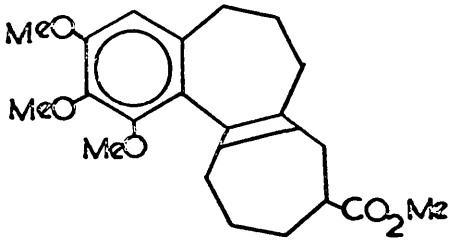
these methods a supply of the ketone was obtained.

The Mannich base, 4-dimethylaminomethyl-3',4',5'-trimethoxy 1,2-benzocycloheptene-3-one hydrochloride (30) was prepared by the usual method in 95% yield as pale yellow crystals m.p., 159-162°C. The free base was generated using 4N sodium hydroxide and underwent condensation with cyclopentanone to yield the 1,5-diketone (31). Purification of this compound was first attempted by means of distillation but this yielded two compounds which showed no 1750 $cm.^{-1}$ band in the infra-red but did exhibit double-bond absorption ($\nu_{C=C}^{nujol}$ 1650 $cm.^{-1}$) and yielded deep-red dinitrophenyl hydrazides. On this basis the α,β unsaturated ketone structures (32), (33), were assigned and were rationalised as being due to the occurrence of a retro-Michael reaction. Consequently the diketone was purified prior to ring expansion by column chromatography on silica eluting with benzene.

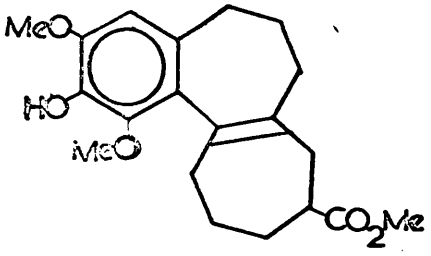
Treatment of the diketone (31) with glacial acetic acid / concentrated hydrochloric acid yielded mainly acidic material and a low recovery of neutral material, the latter consisting solely of starting diketone ($\nu_{C=O}^{film}$ 1742 $cm.^{-1}$ and 1686 $cm.^{-1}$).


MeO
HO
MeO
CO2H

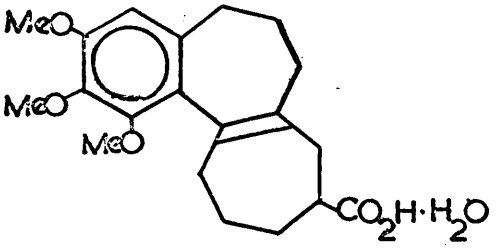
34


MeO
MeO
MeO
CO2Me

35


MeO
HO
MeO
CO2Me

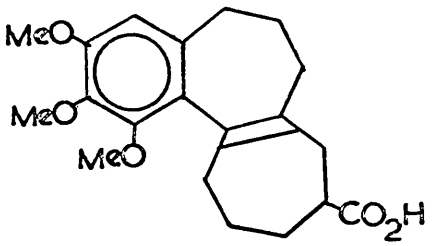
36


MeO
MeO
MeO
CO2H·H2O

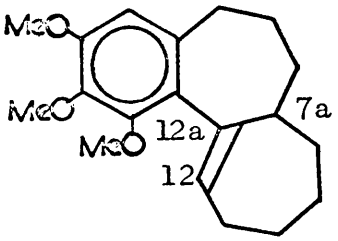
37

The acidic material was found to be unstable to air and gave a positive ferric chloride test. Thus one or more of the methoxyls had undergone hydrolysis to a phenolic group and the n.m.r., spectra showed that the product was a dimethoxyphenolic acid as a singlet at 6·2 τ (6 protons) indicated that hydrolysis had only occurred once. It is well known that in substituted aromatic systems containing three adjacent methoxy groups, the central group is readily hydrolysed due to steric congestion.[15] On this basis the structure allocated was the 2,5-dimethoxy-3-hydroxy acid (34).

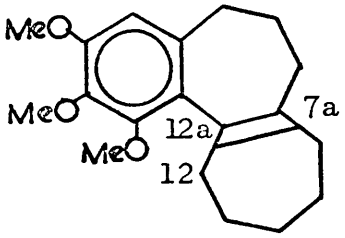
Conversion to the trimethoxy ester (35) was carried out by means of dimethyl sulphate in 4N sodium hydroxide[16] after attempts using diazomethane yielded only the unstable phenolic ester (36). The fully methylated compound was hydrolysed by refluxing with methanolic potassium hydroxide to yield a gummy solid, $C_{20}H_{28}O_6$, which would not crystallise. This was shown by analysis to be the monohydrated acid (37) and this conclusion was checked by methylation with diazomethane to yield the methyl ester, $C_{21}H_{28}O_5$ (35). The infra-red spectrum of the latter showed no hydroxyl signal but had a methyl ester at 1730 $cm.^{-1}$ while the n.m.r., spectrum showed singlets at 6·2 τ (9 protons, 3 methoxyls) and 6·35 τ (3 protons, methyl ester)


MeO
MeO
MeO
CO2H

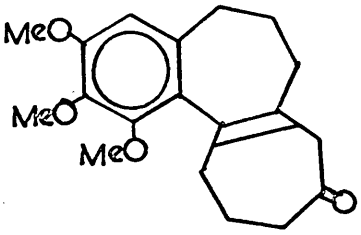
38


MeO
MeO
MeO
12a
12
7a

40


MeO
MeO
MeO
12a
12
7a

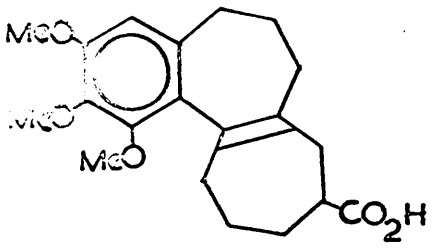
39


MeO
MeO
MeO

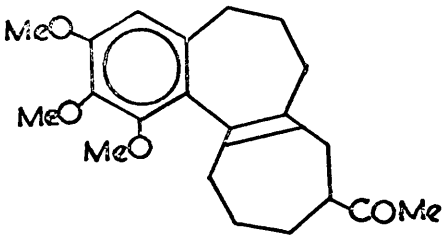
5

The acid (38), showed characteristic absorption at 3550-2840 cm.$^{-1}$ (acidic hydroxyl) and the presence of both monomeric ($\nu_{CO}^{CCl_4}$ 1744 cm.$^{-1}$) and dimeric ($\nu_{CO}^{CCl_4}$ 1711 cm.$^{-1}$) forms, this being verified by characteristic behaviour on dilution.

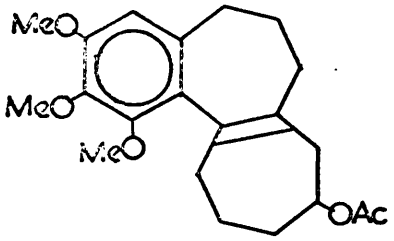
The structure proposed was further justified by correlation of its ultra-violet spectrum [$\lambda_{max.}^{EtOH}$ 258 mμ (log ε, 3·74) and $\lambda_{min.}^{EtOH}$ 245 mμ (log ε, 3·64)] with that of desmethoxydesoxydesacetamido-8,9,10,11,12-heptahydrocolchicine[17] (39) which is $\lambda_{max.}^{EtOH}$ 256 mμ (log ε, 4·1), $\lambda_{min.}^{EtOH}$ 243 mμ (log ε, 3·95). This reference compound was obtained by Rapaport[17] by degradation of colchicine although its structure was not fully fixed, the position of the double bond being in question. The position of double bond was either Δ^{7a-12a} (39) or Δ^{12-12a} (40) [19] but the former was the more favoured position by a number of workers.[18] In the synthetic material the position of the double bond was shown unequivocally by n.m.r., to be Δ^{7a-12a} and this fact was later to have disastrous effects on the proposed synthesis. By the same degradation technique Rapaport produced the tricyclic ketone desmethoxydesacetomido-8,10,11,12-tetrahydrocolchicine (5), and this was intended to be utilised as a relay for the eventual total synthesis of colchicine.


MeO
MeO
MeO
CO_2H

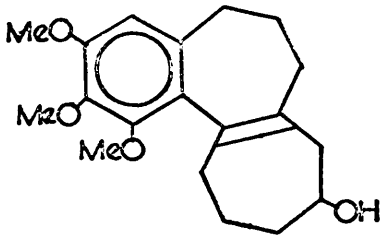
38


MeO
MeO
MeO
COMe

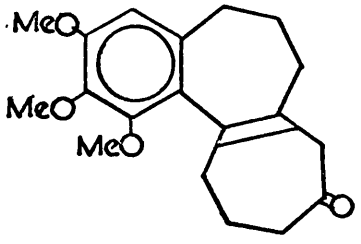
41


MeO
MeO
MeO
OAc

42


MeO
MeO
MeO
OH

43


MeO
MeO
MeO
O

5

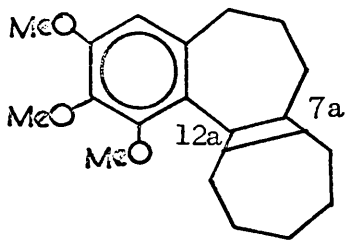
The conversion of the tricyclic carboxylic acid (38) to the methyl ketone (41) was eventually accomplished in optimum yield of 80% by using the molar ratio lithium : methyl iodide : acid of 50:30:1; any deviation from this resulting in much lower yields of ketone.

The methyl ketone underwent smooth conversion to the acetate (42) by means of the Baeyer-Villiger oxidation using m-chloroperbenzoic acid at room temperature for four days.

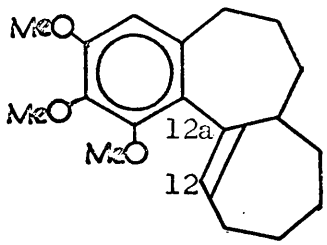
It should be noted that after each reaction the product was isolated by column chromatography on silica and purified by distillation while its structure was monitored by the usual spectroscopic methods viz., n.m.r., infra-red and ultra-violet.

The acetate was reduced by lithium aluminium hydride to yield the crystalline alcohol (43), desmethoxydes-acetamido-8,9,10,11,12-hexahydrocolchicine, m.p., 151-3°C which analysed for $C_{19}H_{20}O_4$ and showed all the required spectroscopic details of the proposed structure.

Prior to oxidation to the required ketone (5) Professor Rapaport was approached for an authentic sample of desmethoxydesacetamido-8,10,11,12-tetrahydrocolchicine (5). He reported that more recent n.m.r., studies of this compound had shown that the double bond was not in



39



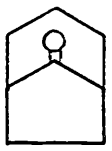
40

the tetrasubstituted position, 7a-12a (39), but rather in the trisubstituted position, 12-12a (40). Thus due to the lack of available materials at this juncture and the inherent difficulties in migration of the double bond this promising synthesis was discontinued.

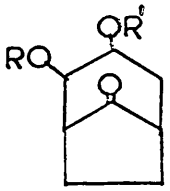
PART I

Chapter 2.

Synthesis of β-carboxytropolone



44



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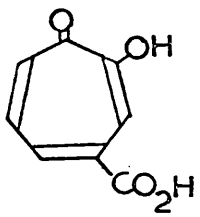
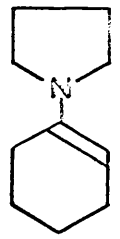


46

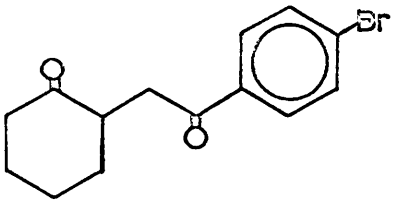
Other workers in this laboratory have shown that bridged bicyclic molecules of type (44) can be used to synthesise cycloheptane derivatives by bridge-fission reactions.[1] One important class of seven-membered ring compounds are tropolones whose synthesis often employs a cycloheptan-1,2-dione as precursor. However, this route suffers from one disadvantage - the difficulty in synthesising a particularly substituted 1,2-dione (see introduction p. 4). It seemed possible to solve this problem by preparing a suitably oxygenated bicyclo-(3,2,1)-octan-8-one(45) and breaking the bridge. This is the objective of the work described in this section.

Cyclisation of a cyclopentanone substituted with a three carbon chain has been the most frequently used approach to the bicyclo-(3,2,1)-octan-8-one (44) system and for this reason ring closure of a cyclohexanone with a two carbon side chain was investigated. The formation of the more highly strained five membered ring system was also expected to facilitate bridge-fission.

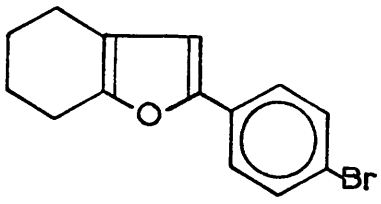
By formation of a suitably substituted bicyclo-(3,2,1)-octan-8-one and application of the bridge-cleavage reaction yielding a seven membered ring a synthesis of substituted tropolone, as β-carboxytropolone (46), could be undertaken.



47



48



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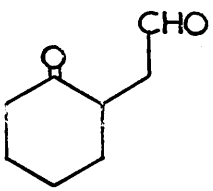

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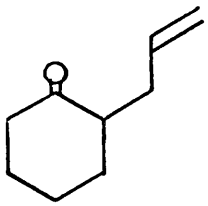
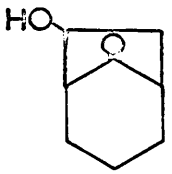


51

The pyrrolidine enamine of cyclohexanone (47) was condensed with p-bromophenacylbromide to yield the diketone, 2-p-bromophenacylcyclohexanone[20] (48) as colourless needles (m.p., 85-6°C). Cyclisation of the 1,4-diketone under acidic conditions (HCl/HAc) produced only one compound (89% yield), $C_{14}H_{13}OBr$ (P = 276/8 m/e). This compound showed no carbonyl absorption in the infra-red but did exhibit a trisubstituted C-C double bond at 1633 $cm.^{-1}$ (C = C stretching vibration) and at 915 $cm.^{-1}$ (out of plane deformation) which was verified by the occurrence of a singlet at 3·25 τ (1 proton) in the n.m.r., spectrum. On the basis of this and the ultra-violet spectrum the furan structure (49) was deduced. This was not unexpected as 1,4-diketones are known to cyclise to form furanoid compounds under acidic conditions.

Attention was now turned to the preparation of 2-cyclohexanoneacetaldehyde (50) as a possible precursor to the bicyclic system. 2-Allylcyclohexanone[21] (51) underwent oxidative cleavage of the terminal double bond by ozonisation after attempts involving the von Rudolff[22] and the Lemieux[23] oxidations had failed to give yields greater than 20%. The keto-aldehyde was obtained, after distillation, as a colourless oil which rapidly decomposed on standing to a deep red gum. The t.l.c., of this



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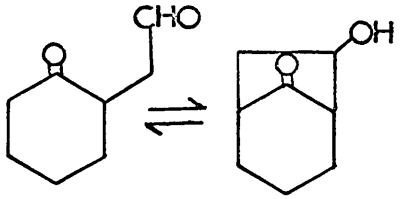

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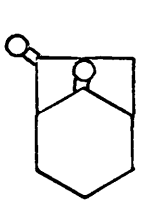
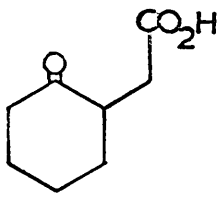
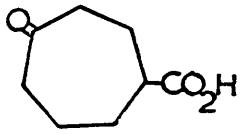


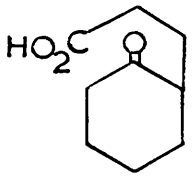




53 54 55

gum showed it to contain the keto-aldehyde which could readily be separated by fractional distillation (b.p., 80-82°C/0·5 mm.,) and at least three other compounds which were not further investigated.

Cyclisation of the keto-aldehyde under acidic conditions (dilute hydrochloric acid/dioxan, conc., sulphuric acid, 20% sulphuric acid/dioxan, BF_3 etherate/acetate), or mildly basic conditions (Et_3N / pyridine) were ineffectual, but an 80% yield of 6-hydroxybicyclo-(3,2,1)-octan-8-one (52) was obtained by shaking with 8% KOH under nitrogen, overnight. Although the ketol structure (52) was allocated all attempts to isolate the pure isomeric alcohols from starting keto-aldehyde failed. It became progressively obvious that an equilibrium existed between the bicyclic alcohols and the open chain aldehyde (50) $\rightleftharpoons$ (52) where the equilibrium clearly lay in favour of the unstrained aldehyde. This was further shown when attempted formation of bicyclo-(3,2,1)-octan-2,8-dione (53) by Jones oxidation yielded 2-cyclohexanone acetic acid (54) formed by oxidation of the aldehyde instead of the bicyclic dione or the compound obtained by ring expansion, viz., cycloheptanone-4-carboxylic acid (55) which had been previously prepared by Grob.[25]



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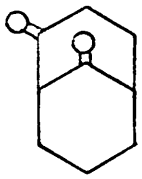

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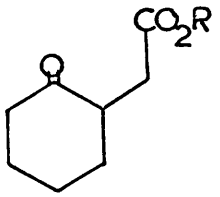
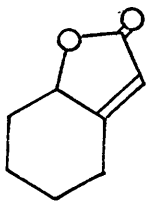


58 R = Et

54 R = H



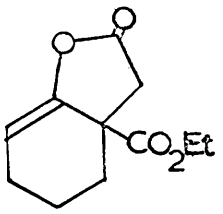
59

Attempts were also made to "trap" the bicyclic alcohols as derivatives (acetates, tosylates, benzoates, α-naphthyl-isocyanates) and so force the equilibrium in the direction of the closed compound but these were unsuccessful.

The appearance of this difficulty at the outset indicated that the pursuance of this route was going to be unfruitful and so other methods of obtaining the bicyclic skeleton were sought.

In synthetical studies related to gibberelins and certain alkaloids which contain the bicyclo-(3,2,1)-octan-8-one system it was found that the action of acid on substituted 2-cyclohexanone acetic acid generated the bicyclo system.[26] Indeed it has been reported,[27] that, distillation of β-2-oxocyclohexylpropionic acid (56) out of tetralin resulted in formation of bicyclo-(3,3,1)-nonane-4,9-dione (57), but when applied to the generation of the (3,2,1)-analog it yielded only a black intractable tar.

Ethylcyclohexanone-2-acetate (58) and its acid (54) when refluxed with BF_3 etherate resulted in a 73% yield of a low melting solid which was shown to be the αβ-unsaturated-γ-lactone (59) which has been previously prepared by Linstead.[28] No bicyclic material was isolated.



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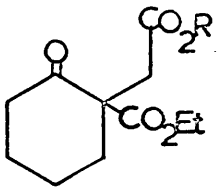
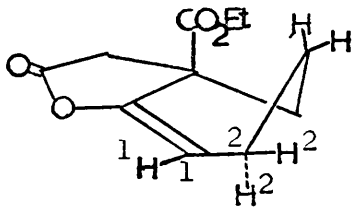


61 a. R = Et.

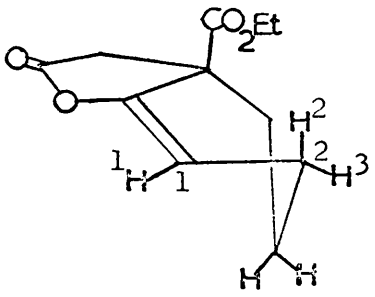
b. R = H



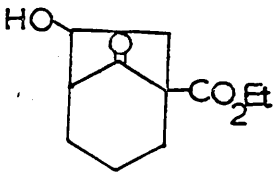
62a

While difficulty was being experienced in obtaining the ketol by the above routes, investigation of an alternative procedure which required the enol-lactone (60) was instigated.

Ethyl-1-carbethoxycyclohexanone-2-acetate[29] (61a) or carbethoxycyclohexanone-2-acetic acid[30] (61b) when refluxed with BF_3 etherate or pyrolysed with fused sodium acetate resulted in good yield of a sweet smelling liquid, $C_{11}H_{14}O_4$, which was assigned the enol-lactone structure (60). The infra-red spectra showed carbonyl absorption at 1822 $cm.^{-1}$ (enol-lactone) and 1735 $cm.^{-1}$ (ester) and a trisubstituted double bond at 1704 $cm.^{-1}$ (C = C stretching vibration). The high absorption for both the carbonyl and the double bond can be explained on the basis of strain, caused by the double bond being exocyclic to the already strained lactone. The n.m.r. spectrum of the enol-lactone (cf. 60) showed typical ethyl ester pattern as a quartet at 5·8 τ and a triplet at 8·7 τ and signals at 4·6 τ (1 proton, J = 4 cps., triplet) and 7·8 τ (2 protons, C_2-H, multiplet). The conformation of the lactone may be deduced by application of the Karplus relationship[31] to the coupling between the proton (H^1) at C_1 and the adjacent pair of protons on C_2 (H^2 and H^3). The conclusion reached is that the conformation is that shown (62a)



62b



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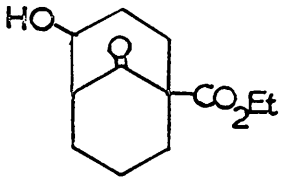

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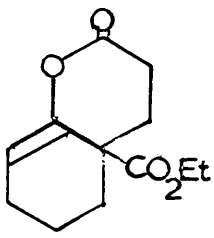


65

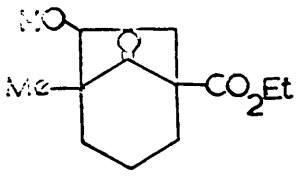
and not (62b) where the theoretical coupling constants are $J_{H_1-H_2}$ = 8 cps., and $J_{H_1-H_3}$ = 2 cps.

Conversion of the enol-lactone to 1-carbethoxy-6-hydroxybicyclo-(3,2,1)-octan-8-one (63) was attempted in two distinct ways.

The first method involved the Fujimoto reaction.[32] The enol-lactone was added to an ethereal solution of phenylmagnesiumbromide to yield an oil which t.l.c., showed to contain mainly unreacted enol-lactone and a variety of other more polar compounds. The infra-red of the oil showed none of the required hydroxyl absorption and so this route was not further investigated.

The second method involved the use of a reaction which has been investigated in this Department and applied successfully to the production, in high yield, of the bicyclo-(3,3,1)-nonan-9-one (64) system from enol lactones (65). This method involves the dropwise addition of the enol-lactone to a solution of lithium aluminium tertiary-butoxyhydride in dry tetrahydrofuran at -70°C under nitrogen.[33]

The enol-lactone (60) was treated as above to yield an oil whose infra-red showed weak hydroxyl absorption (ν_{OH}^{film} 3500 cm.$^{-1}$), t.l.c., indicating several components.



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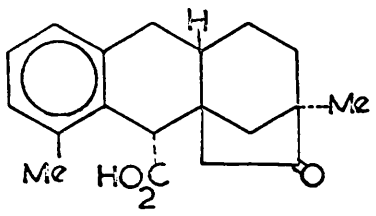

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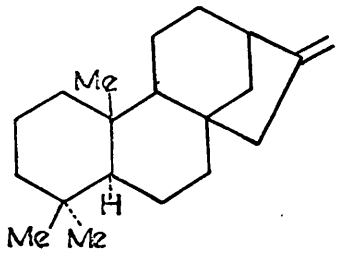

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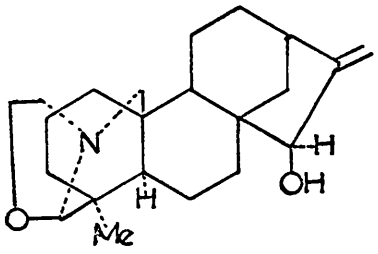

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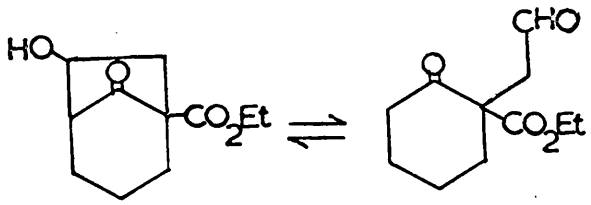


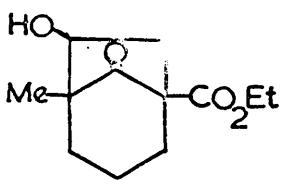
63 70

Repeated column chromatography on silica yielded initially lactone then a pale yellow camphoraceous oil. The infra-red spectrum of this oil showed absorption at 3600 $cm.^{-1}$ (hydroxyl) but it was also found to be very unstable rapidly decomposing to a dark brown gum whose t.l.c., indicated an inseparable mixture of unknown composition.

These results, coupled with earlier failures involving 2-cyclohexanone acetaldehyde, lead to the conviction, that, this route to the bicyclo-(3,2,1)-octan-8-one system incorporating closure of a two carbon side chain onto cyclohexanone was not feasible. All further attempts along this route were abandoned.

The instability of this system is rather surprising when it is realised that analogous compounds such as 1-carbethoxy-5-methylbicyclo-(3,2,1)-octan-6-ol-8-one[34] (66) exhibit normal stability as do intermediates involved in the synthesis of gibberelins[35] (67), kaurene[36] (68), and diterpenoid alkaloids of the Garrya group, e.g., garrine[37] (69).

A tentative explanation can be given by consideration of the proposed equilibrium between the closed and open-chain systems (63) $\rightleftharpoons$ (70). The ring closure reaction initially involves the generation of a carbanion at C_6 (70) and it is well known that the stability of these inter-



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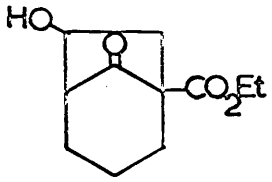

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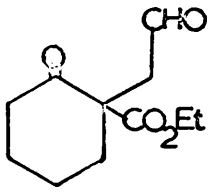

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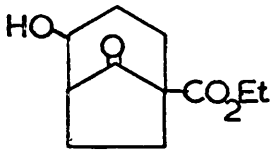

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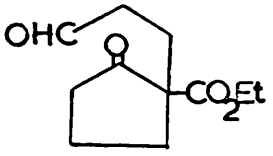
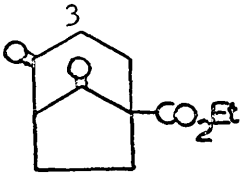


72

mediates increases from tertiary to primary. Thus the carbanion generated in the formation of the 5-methyl compound (66) is tertiary and so the equilibrium is biased towards the strained bicyclo system. In the case of the non-methylated compound (63), however, the inherent ring strain of the bicyclic product coupled with the increased stability of the secondary carbanion (70) favours the unstable aldehyde and so causes the retro-aldol reaction to predominate.

Having recognised the difficulty in preparing the 6-hydroxy compound (63) it now appeared wiser to alter the proposed tropolone synthesis to incorporate the known 4-hydroxyl compound (71).

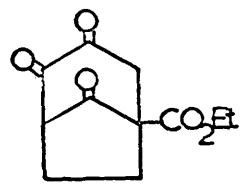
Carbethoxycyclopentanone was condensed with acrolein in the presence of triethylamine to yield, in one step, 1-carbethoxy-4-hydroxybicyclo-(3,2,1)-octan-8-one (71) as an epimeric mixture. A slight adaptation of the known method of preparation[38] was involved, in that, immediately after the dropwise addition of acrolein was completed, the ice bath was removed so allowing the reaction mixture to reach room temperature more rapidly. By employing this procedure the product isolated was totally ketols containing none of the keto-aldehyde (72) which could only otherwise be removed by column



73

Solvent	$\nu(cm^{-1})$	$\Delta\nu$	$\Delta\nu_{\frac{1}{2}}a$	ε
CH_3CN	1764 1719 (sh)	45	6·5 –	494 616
$CHCl_3$	1766 1722 (sh)	44	7·0 –	515 –
CCl_4	1766 1723	43	6·0 –	539 630
Hexane	1771 1727	44	6·5 –	334 349

Table 1.



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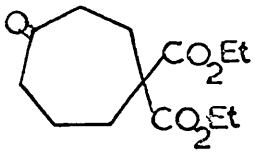
Treatment of the epimeric mixture of alcohols with standard Jones reagent yielded, after distillation, the dione (73) as a clear liquid. The infra-red spectrum of this in a variety of solvents (see table 1) showed the split carbonyl phenomena which has been observed in other cyclic 1,3,-diketones and is due, not to Fermi resonance, but to carbonyl dipole-dipole interaction.[39]

The dione was considered as a potential precursor to a tropolone as oxygen insertion at C_3 would, on bridge cleavage, result in a cycloheptane ring bearing two adjacent oxygenated centres. This compound could readily be converted into a cycloheptan-1,2-dione and thence to the required tropolone.

Initial attempts to prepare 1-carbethoxybicyclo-(3,2,1)-octan-3,4,8-trione (74) by selenium dioxide oxidation[40] of the dione (73) resulted in complex mixtures and so a less direct method was sought.

Bromination with bromine in acetic or chloroform resulted in the formation of acidic non-bicyclic compounds as did N-bromosuccinamide[41] whereas milder conditions such as cupric bromide,[42] pyridiumbromideperbromide[43] and phenyltrimethylammoniumtribromide[44] resulted in a good recovery of starting material. This resistance to halogenation can be accounted for by the fact that bromination



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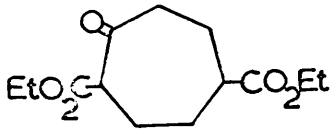

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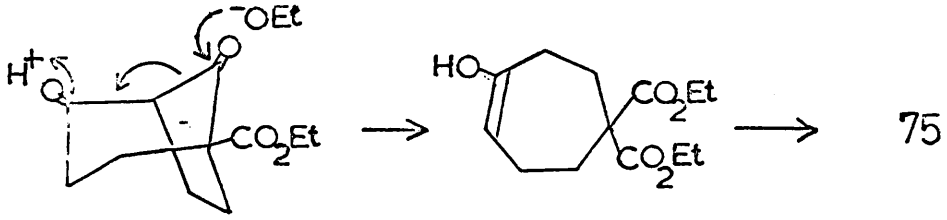
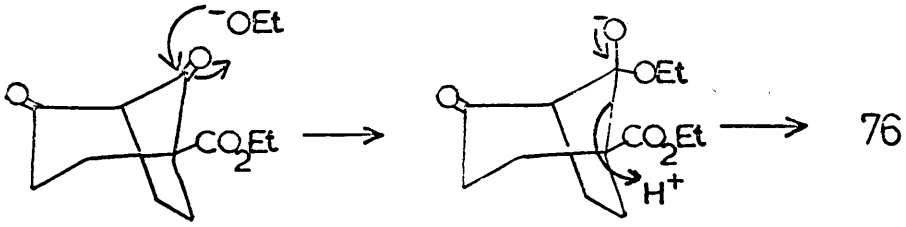


SCHEME 1

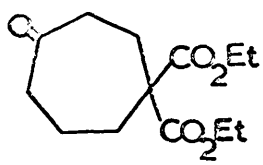


SCHEME 2

requires enolisation which would introduce strain into an already highly strained system.

The occurrence of acids, which obviously arise from bridge fission, under the mildly acidic conditions of bromination led to a study of the stability of the diketone. It was found to be unexpectedly reactive under both acidic and basic conditions; indeed, refluxing in aqueous dioxan was sufficient to induce ring expansion to a mixture of acids. These were separated, as their diethyl esters, by column chromatography on silica. They were found to be epimeric as both analysed for $C_{13}H_{20}O_5$ and had the same molecular weight as determined by mass spectrometry (P = 256 m/e). On the basis of previous work done in these laboratories[45] it was anticipated that these isomers would be 1,1-dicarbethoxycycloheptan-4-one (75) and 1,5-dicarbethoxycycloheptan-4-one (76) the former being formed by the simple bridge fission reaction, the latter having occurred by cleavage of the β-ketoester system as shown in schemes (1) and (2).

The most polar isomer showed carbonyl absorption in the infra-red at 1735 $cm.^{-1}$ (ester) and 1702 $cm.^{-1}$ (cycloheptanone) while the n.m.r., spectrum had the methylenes of the ethyl ester functions as a pair of overlapping quartets centred at 5·85 τ (4 protons). The



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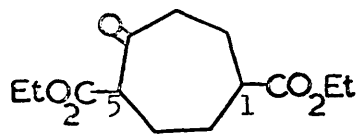

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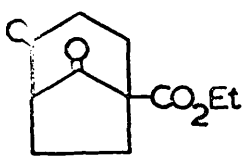

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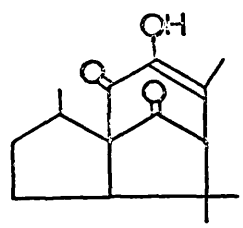


77

Reaction conditions	75	76
H_2O/dioxane, 100°/30 min.*	70	30
NaOEt/EtOH, 78°/30 min.	12·5	87·5
$6NH_2SO_4$/dioxane, 100°/30 min.*	95	5
4MNaOH/ether, 20°/5 min.*	75·5	24·5
$NaBH_4$/MeOH, 20°/12 hr.	66	34

* esterified with diazoethane before g.l.c.

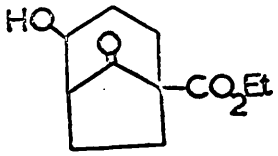
Table 2.

methyls appeared as a single triplet at 8·7 τ (6 protons). On the basis of this, and the fact that no significant ultra-violet absorption was observed, the gem-diester structure (75) was allocated.

The other isomer gave a positive ferric chloride test and a base shift in the ultra-violet from $\lambda_{max.}$ 222 mμ to $\lambda_{max.}$ 287 mμ. Thus, this is the β-keto-ester (76). This was further shown by the occurrence of the methylenes of the ester functions as a pair of quartets at 5·72 τ (2 protons) and 5·79 τ (2 protons) accompanied by the methyls as a pair of triplets at 8·74 τ (3 protons) and 8·78 τ (3 protons). Within the envelope of these quartets lay the C_5-H whose position was predicted by Shoolery's Rules[46] at 5·9 τ as was that of the C_1-H (7·3 τ , multiplet).

Under a number of conditions the varying proportions of each diester was analysed by g.l.c., on a 5% Q.F.1., column at 175°C and a 1% A.P.L., column at 150°C (see table 2).

The instability of the dione can be explained by the increased ring strain caused by the conversion of the tetrahedral carbon at C_4 (cf. 73) to the trigonal carbonyl. This high lability appeared to be in contradiction to the stability of pipitzol[47] (77) which has a similar bicyclic



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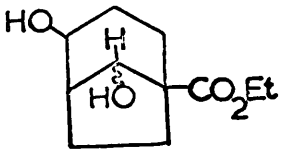

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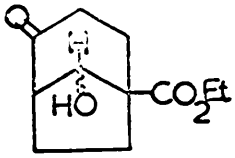

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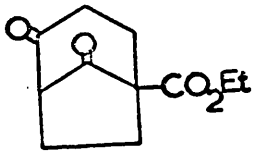


73

1,3-dione structure but as all attempts to introduce any other functionality into dione e.g., C_3 carbonyl or C = C at C_2-C_3 failed this anomaly could not be investigated.

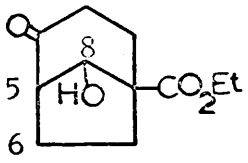
As has been said the driving force for the ring expansion lies in the strain caused by the carbonyls, hence, conversion of the bridge carbon from a trigonal to a tetrahedral shape would result in a more stable system which would be more likely to sustain manipulation.

Reduction of the ketols (71) with sodium borohydride yielded the diols (78) as a hygroscopic crystalline material which was shown by g.l.c., analysis to consist of 73·5% equatioral epimer with 26·5% axial.

Oxidation of the diols with excess Jones reagent resulted in 53% 1-carbethoxy-8-hydroxybicyclo-(3,2,1)-octan-3-one (79) and, unexpectedly, 47% 1-carbethoxybicyclo-(3,2,1)-octan-3,8-dione (73) as analysed by g.l.c., on an 10% A.P.L. column at 150°C.

The occurrence of the dione is in contradiction with Woodwards findings[48] that conversion of the C_8 carbon from tetrahedral to trigonal would be unfavourable enough not to take place under normal oxidation procedure.

By using only the required amount of oxidant a good yield (86%) of the ketone (80) could be obtained as a



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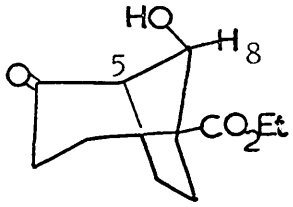

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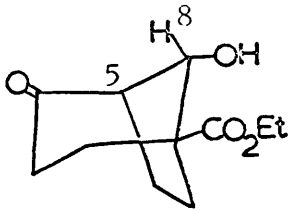
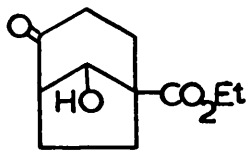


82

colourless liquid. The infra-red spectrum showed absorption at 3622 cm.$^{-1}$ (free hydroxy), 3582 cm.$^{-1}$ (bonded hydroxyl) and a broad carbonyl at 1723 cm.$^{-1}$ (hydrogen bonded ester and cyclohexanone). The n.m.r., spectra exhibited characteristic ester signals along with a doublet at 5·4 τ (1 proton, J = 6 cps.,) and a triplet at 7·2 τ (1 proton, C_5-H).

Borohydride reduction of the C_8 carbonyl (cf. 80) can result in the formation of both syn- and anti-epimers, (81) and (82). Examination of models shows that the C_5 proton couples with only one of the adjacent C_6 protons, (the other lies at 90° to the C_5-H bond), and so would be split to a doublet. In the case of the syn epimer further coupling between the C_5 and C_8 protons should be observed, the C_5 proton to a triplet and the C_8 proton to a doublet. In the anti-epimer (82), however, no further coupling would occur between C_5-H and C_8-H, because these are at 90° to each other, and so the C_5 proton would remain a doublet while the C_8 proton would appear as a singlet. Thus by consideration of this data it can be seen that only the syn-alcohol has been produced by hydride reduction. This is in agreement with Woodwards findings.



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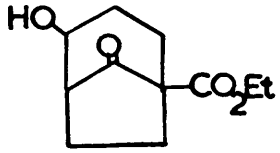
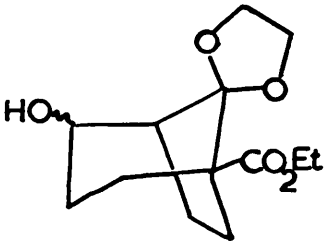


71



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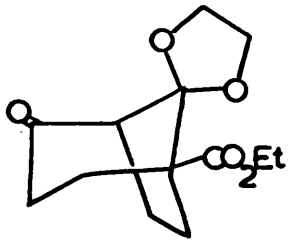
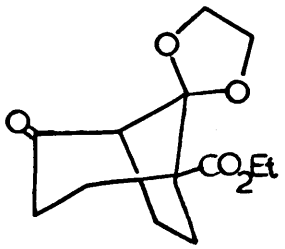


84

The keto-alcohol (80) was found to be hygroscopic and somewhat unstable hence another route was sought whereby the C_8 carbonyl could be protected with its eventual regeneration in mind and so ketalisation was carried out.

The keto-alcohol (71) was treated under reflux with p-toluene sulphonic acid - ethylene ketal, in a system incorporating a water separator,[49] to yield the ketal 1-carbethoxy-8-ethylenedioxybicyclo-(3,2,1)-octan-4-ol (83) as a colourless oil b.p., 142-4°C/0·03 mm., in 70% yield. The oil showed absorption at 3620-3523 $cm.^{-1}$ (hydroxyl) and 1725 $cm.^{-1}$ (ester) the absence of the 1750 $cm.^{-1}$ band indicating complete reaction of starting material.

As ketals are known to be cleaved by acid the oxidation to 1-carbethoxy-8-ethylenedioxybicyclo-(3,2,1)-octan-4-one (84) was carried out using chromium trioxide in pyridine.[50] This resulted in a 44% conversion to the ketone as determined by g.l.c., analysis on 1% P.E.G.A., at 150°C. At this time a second method came to hand which had been employed[51] in the oxidation of steroidal alcohols incorporating a ketal which remained uncleaved. This method involved chromium trioxide in dimethylformamide containing a trace of conc., sulphuric acid but resulted



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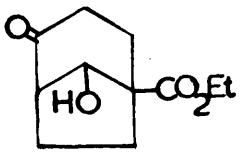

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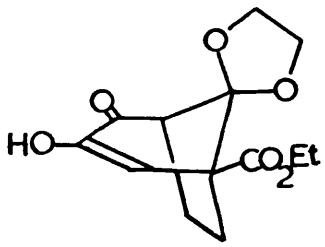


85

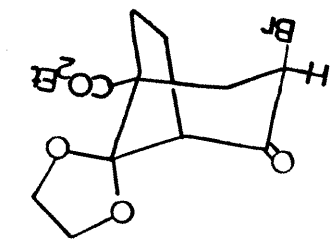
in only a 20% conversion to the required ketone. Surprisingly, the oxidation was eventually carried out in 97% yield by employing the normal Jones technique at 0°C to yield the ketone (84) as a colourless liquid. The infra-red showed no hydroxyl absorption but showed peaks at 1732 $cm.^{-1}$ (ester) and 1722 $cm.^{-1}$ (ketone). The n.m.r., spectrum further showed that functionality had been retained: a singlet at 5·95 τ (4 protons, ethylenedioxy), ester signals at 5·9 τ and 8·7 τ and a doublet at 7·5 τ (1 proton, C_5).

The unexpected stability of the ketal under acidic conditions can readily be attributed to the strain produced by formation of a trigonal carbon at C_8.

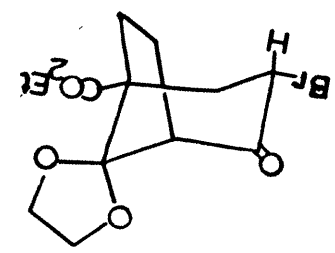
The stability of the ketal-ketone (84) made it a more favourable intermediate than the hydroxyl-ketone (80) and hence all further work was carried out on this system.

The problem which now arose was the insertion of an oxygenated group at C_3 prior to ring expansion. Direct methods such as selenium dioxide oxidation[40] and Barton's autoxidation[52] technique failed to produce the expected diosphenol (85). This compound was later formed by an unexpected but not unknown method.

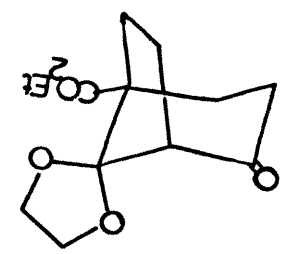
86a



86b

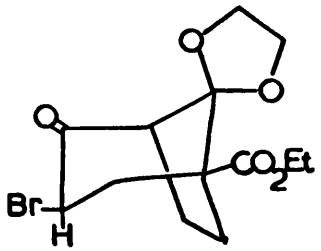


84

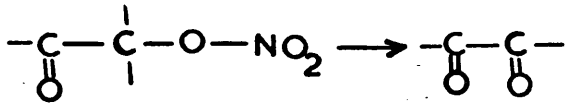


The ketone (84) underwent bromination with bromine- in glacial acetic acid to yield an oil which on trituration with ether yielded colourless crystals. Analysis agreed with $C_{13}H_{11}OBr$, indicating that only mono-bromination had occurred. The crude reaction mixture obtained from bromination was shown by t.l.c., to contain two bromocompounds, axial and equatorial isomers, (86a) and (86b), but repeated trituration with ether failed to yield a pure sample of the non-crystalline material. It was also found that neither distillation nor chromatography yielded a pure sample of the other isomer as the oil was found to decompose on application of either of these techniques. The n.m.r., spectra of the pure bromo-ketone showed signals at 5·2 τ (1 proton, quartet, $\nu^{\frac{1}{2}}$ = 20 cps.,), 5·95 τ (4 protons, ethylene dioxy) 7·1 τ (2 protons, doublet, C_2-H), a doublet at 7·5 τ (1 proton, C_5-H) and typical ethyl ester pattern as a quartet at 5·75 τ with a triplet at 8·7 τ.

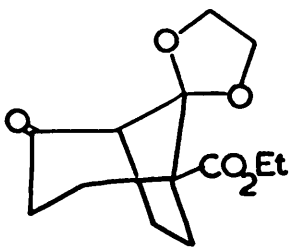
The configuration of the crystalline isomer was established by consideration of the breadth of the multiplet obtained for the C_3 proton in the n.m.r., spectra. It is known[53] that coupling between an axial proton and adjacent axial and equatorial protons results in a much wider band than an equatorial proton coupled

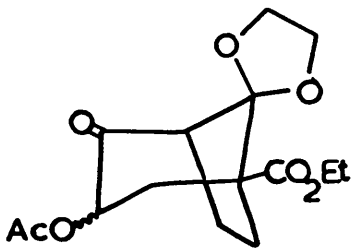


86b



87 88



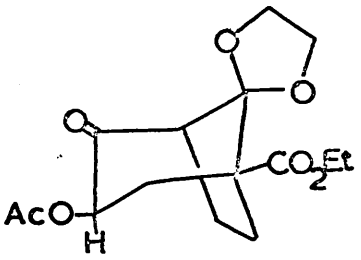


84 89

with adjacent axial and equatorial protons. In the case of the crystalline bromo compound the half-band width was found to be ca. 20 cps., and so the equatorial configuration (86b) was allocated.

It is well established, that, α-bromo-ketones can be converted to α-diketones by action of dimethylsulphoxide[54] or by first forming the nitrate ester (87) which readily undergoes rearrangement, in the presence of piperidine, to the diketone[56] (88). Nevertheless application of both these methods to either the crystalline equatorial bromo compound or the epimeric oil resulted in recovery of only starting material.

Treatment of 1-carbethoxy-8-ethylenedioxybicyclo-(3,2,1)-octan-4-one (84) with lead tetraacetate in glacial acetic acid, containing a trace of BF_3 etherate[56], produced an oil which on distillation crystallised as colourless plates analysing $C_{15}H_{20}O_7$ i.e., mono-acetoxy ketone (89). The infra-red spectrum showed carbonyl absorption at 1735 $cm.^{-1}$ (esters) and 1754 $cm.^{-1}$, this latter being due to a ketonic carbonyl bearing an adjacent equatorial acetate. In the n.m.r., spectra the ketone showed singlets at 5·95 τ (4 protons, ethylenedioxy), 7·9 τ (3 protons, acetate), a doublet at 7·3 τ (1 proton, C_5) and a quartet at 4·5 τ (1 proton,



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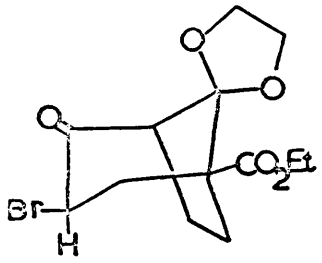
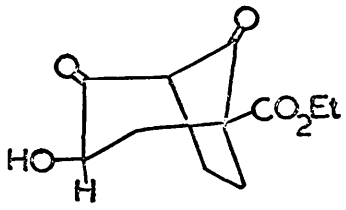


86b



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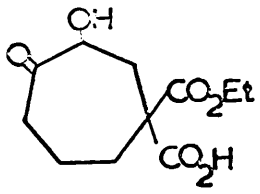
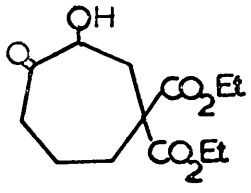


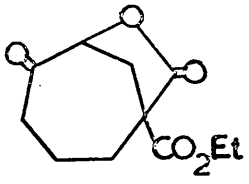
92a



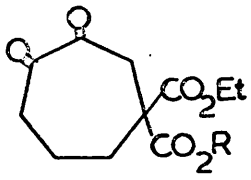
93

half band width ca. 15 cps.,). This latter signal corresponds to an axial proton and, hence, an equatorial acetate (90) by application of an identical argument to that invoked for the equatorial bromo compound (86b). This similarity in relationship of vincinal couplings in α-acetoxy and α-bromo ketones has been observed by Johnson and Williamson[57]. Thus by application of their ammended Karplus equation the individual coupling constants can be calculated and compared with those found by inspection. These results further proved the equatorial nature of the substituents, viz., $J_{a,a}^{theory}$ = 12 cps., $J_{a,e}^{theory}$ = 6 cps., i.e., $J_{a,a}^{theory} + J_{a,e}^{theory}$ = 18 cps., compared with the value found for the bromo-compound (86b) of $J_{a,a} + J_{a,e}$ = 20 cps., and for the acetoxy-ketone (90) $J_{a,a} + J_{a,e}$ = 15 cps.

Refluxing the acetoxy-ketone in dilute sulphuric acid/dioxan mixture resulted in hydrolysis of the acetate with cleavage of the ketal. This generated the unstable diketone (91) which underwent spontaneous ring expansion to 1-carbethoxy-1-carboxy-3-hydroxycycloheptan-4-one (92a). The acid was esterified with diazoethane to yield diester (93) as a pale oil which showed absorption at 3535 $cm.^{-1}$ (hydroxyl) and 1735 $cm.^{-1}$ (diester) and whose n.m.r., showed an absence of singlets at 5·95 τ and 7·9 τ

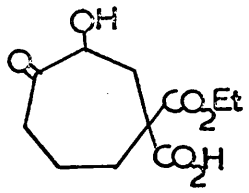


92b

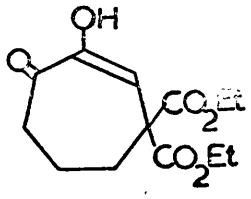


94 R=H

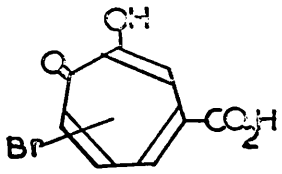
95 R=Et



92a



96

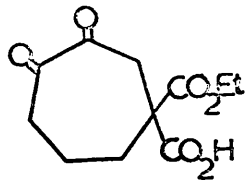


97

indicating complete reaction of starting material. Also present was a trace of the expected lactone (92b).

1-Carbethoxy-1-carboxycycloheptan-1,2-dione (94) was obtained as a clear liquid by treatment of pure hydroxy keto-acid (92a) with Jones reagent at 0°C. The infra-red of the diester (95) obtained by esterification showed no absorption in the hydroxyl region, indicating that oxidation had gone to completion; but showed carbonyl absorption at 1735 $cm.^{-1}$ (diester) and 1710 $cm.^{-1}$(dione). The ultra-violet spectra of both the acid (94) and the diester (95) showed a characteristic bathochromic shift from $\lambda_{max.}$ 237 mμ to $\lambda_{max.}$ 310 mμ on addition of base. Also present in the ultra-violet spectra was a shoulder at $\lambda_{max.}$ 265 mμ which indicated that some enolised ketone (96) was present.

Conversion of the dione (94) to the unstable bromotropolone[58] (97) was carried out by bromination using bromine in glacial acetic acid and dehydrobromination, accompanied by decarboxylation by warming on a steam bath for 30 minutes with 4N sodium hydroxide. This procedure yielded a dark oil which rapidly decomposed but whose ultra-violet spectra showed the essential tropolonoid characteristics and also gave positive results with a number of colour tests e.g., ferric



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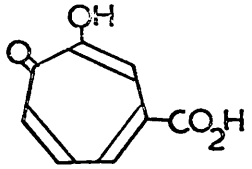

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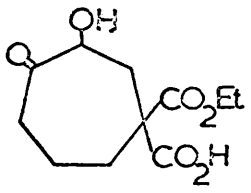
chloride, cupric acetate, and cupric sulphate.

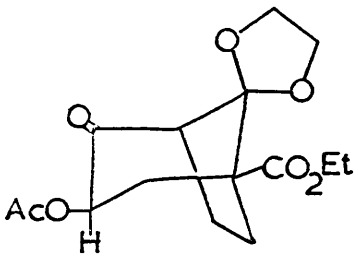
Hence, without further purification the crude material was debrominated in 4N sodium hydroxide by hydrogenation in the presence of 10% Pd/C.

The resultant brown solid sublimed as pale yellow crystals (m.p., 216-218°C) in overall 47% yield based on the diketone (94) and is the expected β-carboxytropolone (46) (m.p., 217°C).[59] It gave the expected green ferric chloride and cupric acetate tests and exhibited absorption in the infra-red at 3400-3100 $cm.^{-1}$ (acidic hydroxyl) 1670 $cm.^{-1}$ (acid carbonyl) and 1605 $cm.^{-1}$ (tropolone C = O) while the ultra-violet gave absorption at $\lambda_{max.}$ 244 mμ (log ε, 4·5); 324 mμ (log ε, 3·8); 370 mμ (log ε. 3·75) which compared well with the literature values.[59] The n.m.r., spectrum showed a complex signal pattern at 2·5 - 3 τ (4 protons) which corresponds to an aromatic type structure and the pattern can be correlated to the few β-substituted tropolones whose n.m.r., data is available.[60]

This work provides a new synthesis of a β-substituted tropolone by a route which does not, at the same time, produce other isomers, and it should be possible to adapt it to synthesise more complex molecules.



92a



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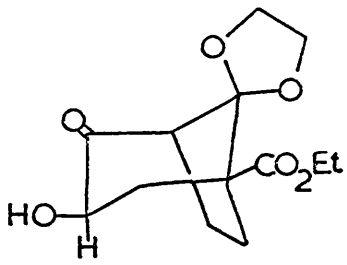

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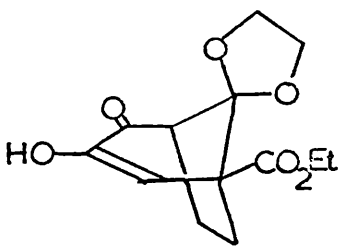
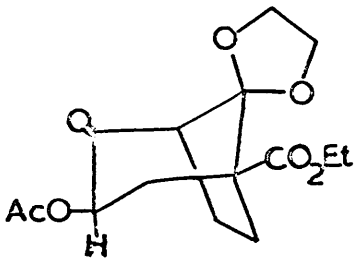


85

As a proposed alternative route to 1-carbethoxy-1-carboxycycloheptan-3-ol-4-one (92a) the acetoxy-ketone (89) was hydrolysed with mild KOH-ethanol by stirring at room temperature overnight. Removal of solvent yielded a base soluble oil which gave a positive ferric chloride test. Trituration of this oil with ether yielded a crystalline compound, $C_{13}H_{18}O_6$, whose molecular weight was determined by mass spectroscopy (P = 268 m/e). The infra-red showed peaks at 3554 $cm.^{-1}$ (weakly hydrogen-bonded hydroxyl) with a shoulder at 3450 $cm.^{-1}$ (bonded hydroxyl), 3022 $cm.^{-1}$ (C – H asymmetric stretching vibration), carbonyl absorption at 1735 $cm.^{-1}$ (ester), 1686 $cm.^{-1}$ (conjugated ketone) and a trisubstituted double bond at 1660 cm^{-1}.[61] The ultra-violet spectrum showed absorption at $\lambda_{max.}$ 266 mμ (ε, 8,285) with a shift on addition of base to $\lambda_{max.}$ 306 mμ. This showed conclusively that the compound obtained was not the simple acyloin (98) expected by hydrolysis, as such a structure would not have an ultra-violet spectra of this type. It is well known[62] that α-hydroxy ketones readily undergo air oxidation in the presence of base to yield diosphenols hence this structure (85) was allocated to the above product.



89

The n.m.r., spectra (100 m/c) showed singlets at 3·64 τ (1 olefinic proton), 3·8 τ (1 proton, broad hydroxyl), 6·1 τ (4 protons, ethylene dioxy) and a doublet at 7·06 τ (1 proton, C_5). When the n.m.r. was run in the presence of dimethylsulphoxide the hydroxyl at 3·8 τ shifted to lower field (1·64 τ) as a sharp singlet thus illustrating tertiary hydroxyl of the enolised diketone.[63]

This proposed entry into the potential cycloheptan-1,2-dione system was not pursued as the alternative route via the acetoxy ketone (89) had been successfully completed.

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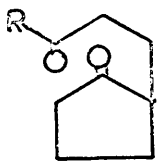
PART II

Conformation of a cycloheptene



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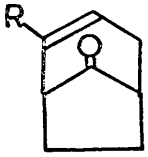

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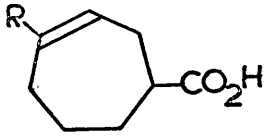

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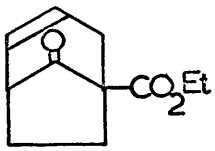

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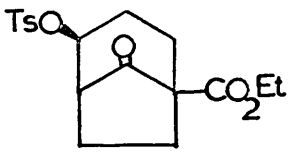
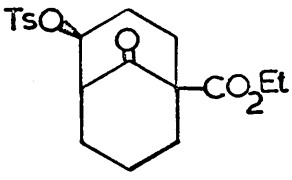


5a



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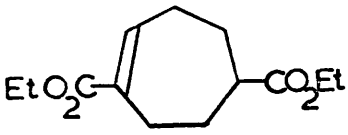


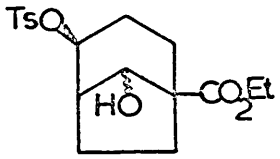
7

Introduction and Discussion.

Although several workers in this laboratory[1] have studied the conversion (1) → (2) → (3) in which R is aromatic or aliphatic, no attempt had been made to investigate the simple case where R = H. There are practical difficulties[2] in preparing (1, R = H), and for this reason it was decided to aim at a synthesis of (4), which could then be subjected to the acid-catalysed bridge-fission reaction.

Attempts have been made to prepare (4) by elimination of the axial tosylate group from (5) using ethoxide, but, this resulted, as in the bicyclo-(3,3,1)-nonan-9-one analogue(6),[3] in bridge cleavage to yield 1,5-dicarbethoxy cyclohept-1-ene[1] (7). The formation of the diester has been rationalised as cleavage of the β-keto-ester system followed by β-elimination of the tosyl group. If this is correct then removal of the β-keto-ester function should stabilise the system and so facilitate the expulsion of the tosyl group.

The axial tosylate (5a) was reduced by sodium boro-hydride to yield a pale oil which t.l.c., showed to contain two components. The major, and less polar, component, having the same rf value as the axial tosylate, was readily isolated by preparative t.l.c. The infra-red spectrum showed a bonded hydroxyl ($\nu_{OH}^{CCl_4}$ 3494 cm.$^{-1}$)



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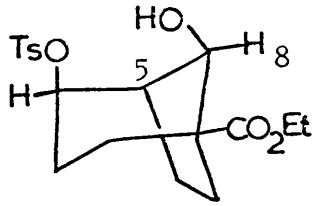

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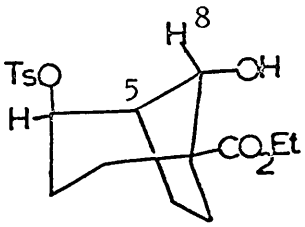
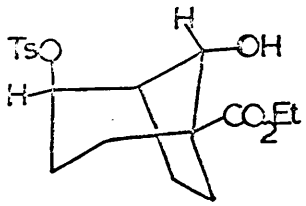


10

and a single carbonyl at 1743 $cm.^{-1}$ (carbethoxy). The absence of the 1750 $cm.^{-1}$ absorption indicating complete reaction of starting material. On this basis the hydroxy-tosylate structure (8) was given and although analytical confirmation was not obtained the correct molecular weight was obtained by mass spectroscopy (P = 351 m/e).

The n.m.r., spectrum substantiated the allocated structure in having tosyl signals at 2·3 τ (4 protons, A_2B_2 aromatic) and a singlet at 7·59 τ (3 protons, $-Ar-CH_3$) along with signals at 5·4 τ (1 proton, ill-defined quartet; C_4 proton), 5·57 τ (1 proton, doublet, C_8 proton) and 8·15 τ (1 proton, multiplet, C_5 proton).

An examination of models of both epimeric alcohols showed that with the syn-epimer (9) coupling of the bridgehead proton at C_5 with the C_8 proton would be expected to produce a doublet for the latter, whereas in the anti-epimer (10) in which the C_5-H bond is at 90° to the C_8-H bond and so no splitting would result and the C_8 proton would appear as a singlet. On this basis it can be seen that the major component obtained from hydride reduction was syn-8-hydroxy-1-carbethoxy-4-tosyl-bicyclo-(3,2,1)-octan (9).



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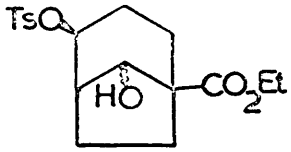

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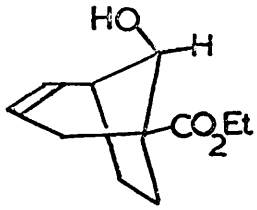
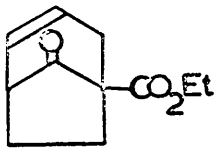


11

The minor, polar compound was not purified but can be assumed to be the anti-epimer (10).

The formation of the syn-alcohol explains the anomolous rf value as the hydroxy group can hydrogen bond to the oxygen of the axial tosyl group and so greatly diminishes the polarity of the system .

The tosylate (8) was refluxed with sodium ethoxide in ethanol for times up to 2 hours but only starting material was recovered and so more forcing conditions were necessary. After refluxing for two hours with sodium tertiary butoxide in tertiary butanol a cloudy oil was isolated which was shown by t.l.c., and i.r., to be acidic, the latter also showing no tosyl signals at 1294, 1268, 1272 $cm.^{-1}$. Esterification with diazo-ethane gave a pale yellow oil which distilled as a clear liquid $C_{11}H_{16}O_3$ and this was given the olefinic structure (11). The infra-red spectrum showed absorption at 3625 $cm.^{-1}$ and 3570 $cm.^{-1}$ (hydroxyl), cis carbon-carbon double bond at 3025 $cm.^{-1}$ (asymmetric stretching frequency) and 680 $cm.^{-1}$ (out-of-plane vibration). The n.m.r., showed a multiplet at 4·2 τ for the two olefinic protons and a signal for the allylics as a multiplet at 7·9 τ (3 protons).



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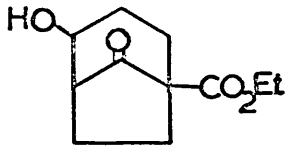

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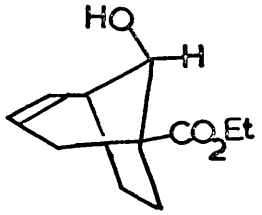
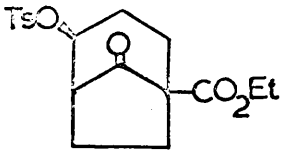


11

Attempts were also made to prepare the unsaturated ketone (4) by simple dehydration of the hydroxy-ketone (12). These attempts failed when such reagents as thionyl chloride,[4] phosphorus oxychloride[5] and phosphorous tribromide,[6] all in pyridine, were used. Concentrated sulphuric acid also failed as did pyrolysis of the ketols with oxalic[7] or boric[8] acids. However, treatment of the epimeric ketols with polyphosphoric acid[9] resulted in a dark oil from which a clear liquid, $C_{11}H_{14}O_3$, could be distilled b.p., 70-75°C/0·06 mm. The infra-red spectrum, which was transparent in the hydroxyl region thus signifying complete dehydration having occurred, showed normal ester carbonyl absorption ($\nu_{CO}^{CCl_4}$ 1735 cm.$^{-1}$) with higher carbonyl absorption at 1763 cm.$^{-1}$. This latter signal is characteristic of an unsaturated bicyclo-(3,2,1)-octan-8-one[1] and on this basis the 1-carbethoxybicyclo-(3,2,1)-oct-3-ene-8-one structure (4) was assigned. The n.m.r., spectrum of the olefin had a complex pattern at 4·3 τ (2 protons, ethylenic) and 6·8 τ (1 proton, C_5-H) while the allylic protons appeared as a doublet at 7·88 τ (2 protons).

Reduction of the olefin (4) with sodium borohydride yielded a liquid which was shown to be syn- -hydroxy-1-carbethoxybicyclo (3,2,1)-oct-3-ene (11) by comparison with an authentic sample.



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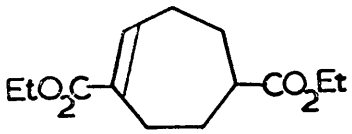

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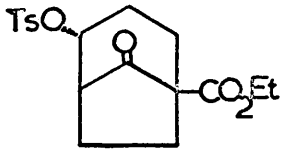
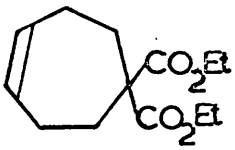


5b



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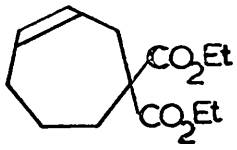
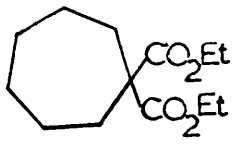


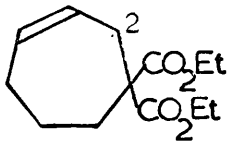
14

As has been shown,[1] in the presence of base the axial tosylate (5a) underwent bridge cleavage to yield 1,5-dicarbethoxycyclohept-1-ene (7) while the equatorial epimer (5b) gave 1,1-dicarbethoxycyclohept-4-ene (13). It was anticipated that the latter compound could also be formed by bridge fission of the olefin. However, refluxing with glacial acetic-concentrated hydrochloric acid yielded, after esterification with diazoethane, three compounds two of which were identified by g.l.c., retention times as (7) and (13). The third, and major component, was present in ratio of 4:1 as compared with the gem-diester (13) and was separated by column chromatography on silica as a clear liquid. This analysed as $C_{13}H_{20}O_4$ the result being corroborated by determination of its molecular weight by mass spectrometry (P = 240 m/e). The infra-red spectrum was not particularly instructive exhibiting only signals for ester carbonyl ($\nu_{CO}^{CCl_4}$ 1729 cm.$^{-1}$) a cis double bond ($\nu_{C=C}^{CS_2}$ 685 cm.$^{-1}$) while the ultra-violet spectrum further correlated the disubstituted nature of the double bond by showing no conjugated carbonyl was present [$\lambda_{max.}^{EtOH}$ 208 mμ (ε, 160)].

The cycloheptene structure (14) was given on the basis of the n.m.r., spectra obtained which showed a typical gem diethyl ester pattern as a pair of over-



15a



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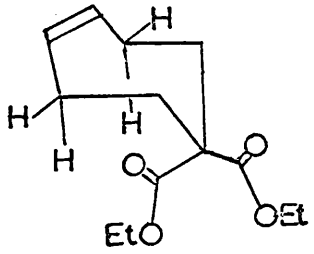
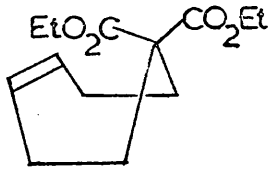


16

lapping quartets centred at 5·8 τ (4 protons) and a triplet at 7·8 τ (6 protons) while olefinic protons appeared as a multiplet at 4·0 τ (2 protons). Also present in the n.m.r., spectrum was an undefined multiplet at 6·8 τ (1 proton) which has been allocated the equatorial allylic proton at C_2. Examination of models shows that of the pair of allylic protons at C_2 one, the equatorial, lies within the deshielding zone of the ester functions and the double bond and so is moved downfield with reference to the axial proton on C_2.

The ring structure was shown unequivocally when an authentic sample of 1,1-dicarbethoxycyclohept-4-ene was reduced in the presence of 5% Pd/c to yield 1,1-dicarbethoxycycloheptane (15a) and the identical compound was obtained when the proposed 1,1-dicarbethoxycyclohept-3-ene (14) was similarly reacted.

The migration of the double bond from the expected C_4 position to C_3 can be explained on the basis of unfavourable steric interaction. Examination of models shows, if the chair conformation (16) is assumed to predominate, that the ester function at C_1 experiences 1,3-interaction with the axial allylic protons. This congestion can be removed by double bond migration and this could occur readily under the acidic reaction conditions.



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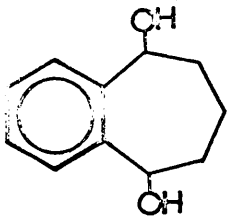

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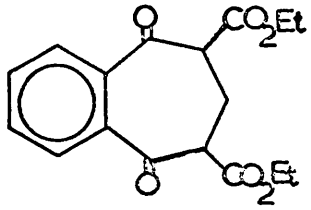

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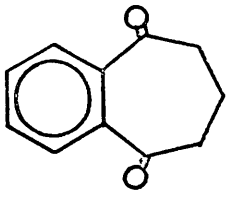

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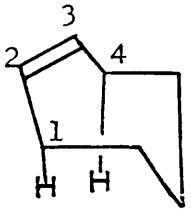
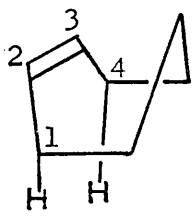
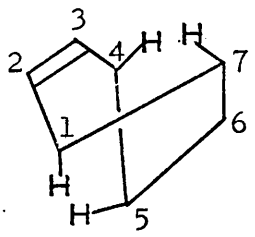


21a



21b



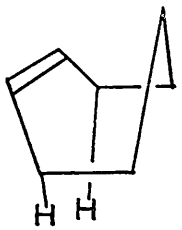
21c

Models also illustrate that the assumption of a preferred chair conformation is not unreasonable as in the boat conformation (17) the ester function approaches the double bond to such an extent as to be prohibitive.

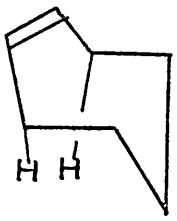
The occurrence of this interesting stereochemical aspect led to a decision to investigate the conformation of the cycloheptene ring and for this purpose the readily available benzocycloheptene-3,7-diol (18) was chosen.

The synthesis of the diol was initially carried out using the procedure of Barltrop, Johnson and Meakins[10] but the yields were very poor and so the method had to be adapted.[11] By isolating and purifying the intermediate β-keto-ester (19) prior to decarbethoxylation a much improved yield of the dione (20) was obtained. The dione was then reduced in presence of Adams catalyst to yield the crystalline cis diol (18).

The conformation of cycloheptene resembles that of cyclohexane in that it can be depicted in the chair (21a), boat (21b), or twist(skew)-boat (21c) conformations. Although there has been a considerable amount of study of the cyclohexane system,[12] incorporating both theoretical calculations[13] and practical observations relatively little is known of the preferred conformation of cycloheptane. The reason for this contrast in knowledge of six- and



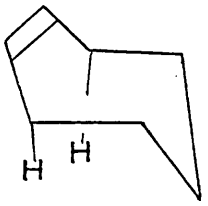
21b



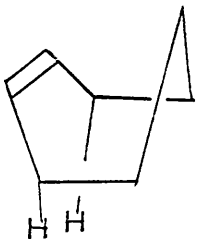
21a

seven-membered rings is that while simple cyclohexane derivatives exist as the above mixture of conformers which are separated by large energy barriers the corresponding cycloheptanes exist, in general, as a mixture of a large number of conformers which are only separated by a small energy barrier. Some detailed calculations have been carried out on the geometry of cycloheptane,[14] some more approximate ones on cycloheptene[15] and cycloheptanone.[16] There is also a variety of evidence available regarding the flexibility[17] of the system and of the conformational interconversion process[18] involved in ring inversion.

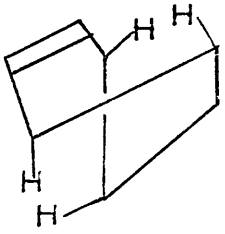
There has been no report of a study of the flexible cycloheptane system, other than the calculations of Hendrickson,[13] whereas in the more rigid cycloheptene system the published results, concerning its conformation, have been both confused and somewhat contradictory. Although both the boat (21b) and chair (21a) have objectionable (*ca.* 2 Å) H_1-H_4 interactions the vector analysis treatment of Pauncz and Ginsberg[14b] indicated that the boat would be the more stable by 0·67 Kcal/mole. Allinger,[19] however, noted that these workers had only considered H-H interactions whereas his van der Waals interaction calculations indicated a repulsion energy between the double bond and the near proton at the "prow"



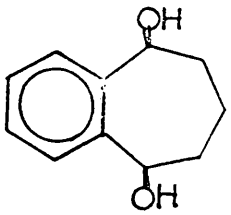
21a



21b



21c



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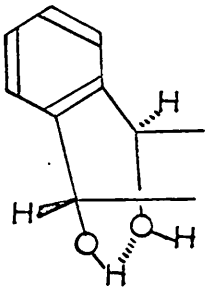


22

of the boat to be in the order of 4·6 Kcal/mole. The magnitude of this value thus suggested that the boat was the less stable of the conformers. From these dipole moment studies Allinger concluded that an equilibrium existed (21a) $\rightleftharpoons$ (21b) with a 92% predominance of the former, but, in these calculations no consideration was taken of the twist-boat (21c) conformation.

In a low temperature n.m.r., study of a series of benzo derivatives Friebolin,[20] considering only conformers (21a) and (21c), found that the seven-membered ring of benzocycloheptene was, at least, 95% in the chair form; also that the activation energy of ring inversion was 13·0 ± 1·5 Kcal/mole i.e., inversion of (21a) $\rightleftharpoons$ (21c).

Thus it seemed that a study of a benzocycloheptene was required which took into consideration all three conformations. This was undertaken using the cis diol (18) which was particularly suitable for study as the substituents do not, of themselves, forbid any of the above conformations,

In carbon tetrachloride solution the diol showed strong intra-molecular hydrogen bonding (ν_{OH} 3600, 3508 $cm.^{-1}$ the ratios remained unchanged on dilution) and must therefore be represented as (22) with axial hydroxyl groups. In dimethylsulphoxide the infra-red

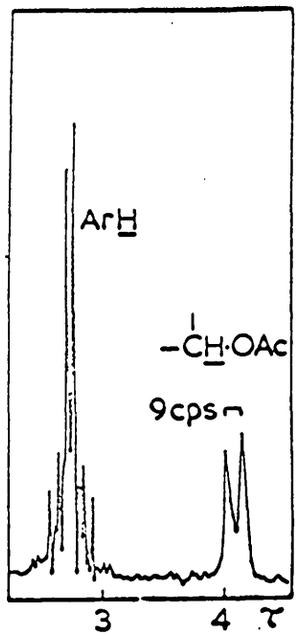


Fig. 2, diacetate

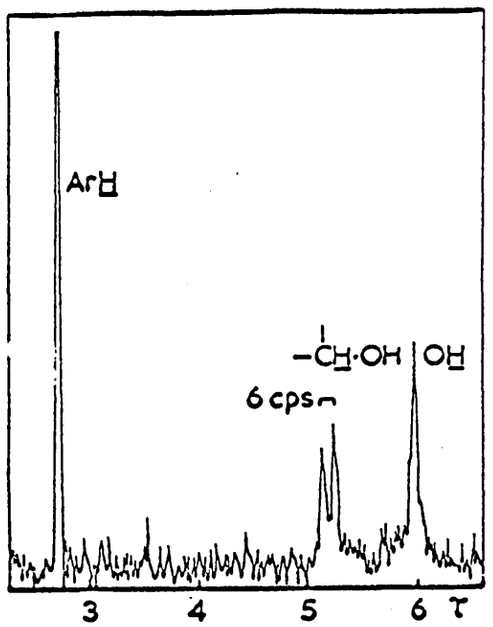


Fig. 1, diol in $CDCl_3$

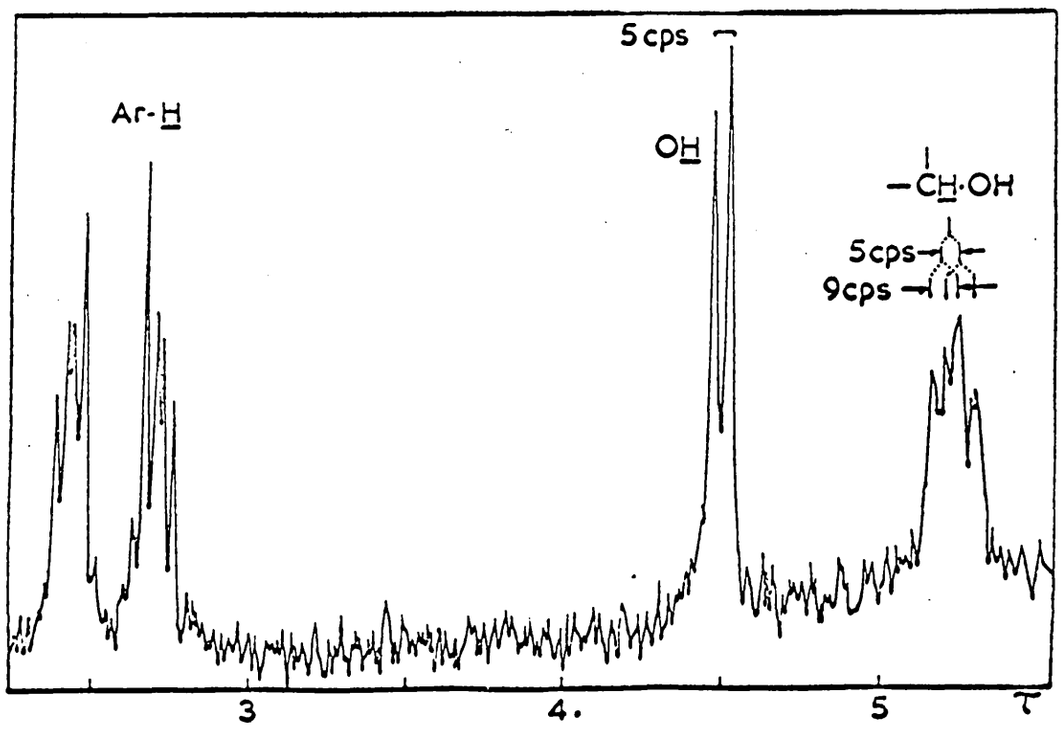
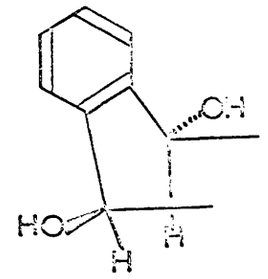


Fig. 3, diol in D.M.S.O.



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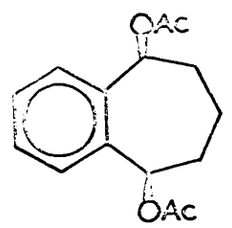

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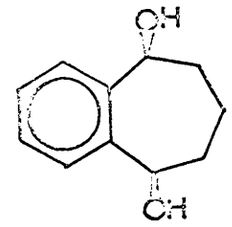
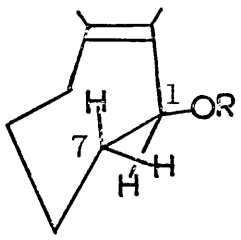


18

spectrum shows a single broad hydroxyl band (ν_{OH} 3330 cm.$^{-1}$) due to hydrogen bonding with the solvent, and here the hydroxyl groups, which have no reason to remain axial, are probably equatorial (23). These assignments can be corroborated from the n.m.r., spectrum of the diol (see Figs. 1 and 2).

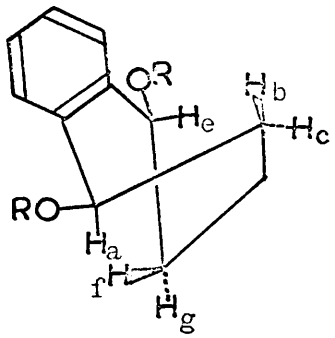
In deuterochloroform solution, the aromatic protons of the diol appear as a clean singlet (2·7 τ) but in dimethylsulphoxide the same protons show up as an A_2B_2 system centred at 2·6 τ, due to the influence of the equatorial oxygen atoms on the two adjacent aromatic protons. The possibility that this might be a solvent effect was considered, but was excluded by observing that the aromatic signal of tetralin appeared as a clean singlet in either solvent. That it is an effect of structure rather than of solvent is also demonstrated by Fig. 3 in which the diacetate (24) is seen to give the same A_2B_2 pattern in deuterochloroform solution. It can therefore be inferred that in the diacetate (24) and in a dimethylsulphoxide solution of the diol (18) the oxygen substituents are equatorial.

An examination of molecular models reveals that in cycloheptene, an equatorial C_1-H will be at approximately 90° to one of the adjacent C-H bonds in either the boat or



25

chair conformation. It is therefore not surprising that in Fig. 1., the 5·2 τ signal is only a doublet (J = 6 cps.,). However, this is not true of an axial C_1-H. Such a bond subtends an angle of 90° with one of the adjacent C_7-H bonds only if the ring is in the chair conformation (25). In the boat conformation neither of these angles is 90° (they are in fact 15° and 150°) and so multiple coupling should be observed. Thus the appearance of the 4·05 τ signal as a doublet (J = 9 cps.,) in Fig. 3, excludes the boat conformation but is fully consistent with the chair conformation (25) in which the dihedral angles are 90° and 155°. By application of the Karplus relationship[21] the calculated coupling constants are of the order obtained by inspection. In Fig. 2, however, the occurrence of the 6·3 τ signal as a quartet is due to further coupling of C_1-H with the hydroxyl proton, this being known to occur when dimethylsulphoxide is used as a solvent.[22] By inspection J_{H_1-OH} is 5 cps., thus on application of the simple multiplicity rules $J_{H_1-H_7}$ is 9 cps., and this further indicates that the ring is in the chair and not the boat conformation.



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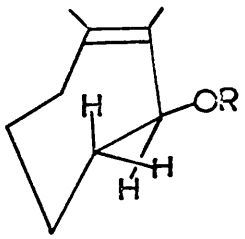

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The twist-boat conformation (26) presents a slightly more complicated picture, for here one of the benzylic C-H bonds will be pseudo-equatorial and the other pseudo-axial; but it appears from models that each will show significant coupling with only one of the adjacent protons (Angles H_aH_b and $H_eH_g = 90°$: $H_aH_c = 150°$: $H_eH_f = 30°$). Pseudorotation produces the mirror image structure involving identical angles. These conformations as such, are incompatible with the observed spectra, for the two benzylic protons would have different chemical shifts and the aromatic protons signal would not be symmetrical. However, rapid interconversion could conceivably make the benzylic protons appear equivalent, and account for the simplicity of the NMR signal. In an attempt to overcome this objection, the spectrum of the diacetate (24) has been recorded on a 100 mc., instrument at -30°, -60° and -85°. No change of any sort was observed. There is therefore no evidence for the "slowing down" of this interconversion, and the most rational deduction is that the cycloheptene ring is in the chair conformation (25).

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EXPERIMENTAL

General

Melting points were recorded on a Kofler microscope hot stage and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on Perkin Elmer 137 and Unicam S.P. 200 spectrophotometers. Solution spectra were determined on a Unicam S.P. 100 double-beam spectrophotometer equipped with an S.P. 130 sodium chloride prism grating double beam monochromator operated under vacuum conditions. Ultra-violet absorption spectra were determined on a Unicam S.P. 800 spectrophotometer in ethanolic solution.

Nuclear magnetic resonance spectra were recorded on a Perkin Elmer R.S. 10 (60 megacycle) in deuterated chloroform with tetramethylsilane as internal reference.

Thin layer chromatography (t.l.c.,) and preparative thin layer chromatography (prep. t.l.c.,) employed kieselgel G silica using 30% ethylacetate in petrol as the solvent system unless otherwise stated.

Petrol refers to that fraction of petroleum ether, b.p., 60 - 80°.

β-Dimethylamino-α-tetralone hydrochloride (8)

The α-tetralone (25 g.,) was refluxed for 17 hours with paraformaldehyde (6·75 g.,) and dimethylamine hydrochloride (15·25 g.,) in anhydrous ethanol after the addition of a few drops of concentrated hydrochloric acid. The resultant solution was reduced in volume and on cooling yielded a pale cream solid which was recrystallised from acetone-ethanol (4:1) as colourless plates (25 g.,) m.p., 156-9°. The mother liquors further yielded 1·75g., thus giving a total yield of 26·75 g., 66·5%.

β-(2'-Cyclopentanonylmethyl)-α-tetralone (9)

The Mannich base (8) (20 g.,) in cyclopentanone (24·2 g.,) was heated for 1 hr., at 80°, with continuous stirring, during which time dimethylamine was evolved. The resulting solution was cooled, neutralised with acetic acid and dissolved in ether. The ethereal solution was washed with brine, dried over magnesium sulphate and distilled in vacuo to remove solvent and unreacted cyclopentanone. The residue solidified on standing and crystallised from light petroleum (60-80°) in colourless needles, m.p., 56-58°. Yield 14 g., (59%). (Found, C, 79·62; H. 7·24. $C_{16}H_{18}O_2$ requires C, 79·31; H, 7·49%.) The infra-red spectrum shows carbonyl

absorption (CCl_4) at 1754 cm.$^{-1}$ (cyclopentanone) and 1703 cm.$^{-1}$ (α-tetralone).

1,2-Benzobicyclo-(5,4,0)-undec-10(11)-ene-6-carboxylic acid (10).

The diketone (9) (10 g.,) in glacial acetic acid (80 ml.,) and concentrated hydrochloric acid (25 ml.,) was boiled under reflux for 17 hr. Most of the solvent was removed in vacuo, and the residual oil was flooded with water and finally extracted with ether. The ether solution was extracted twice with aqueous sodium hydroxide, washed with brine, dried and evaporated, yielding a (neutral) gum, which showed ν_{CO}^{film} 1780, 1750 and 1680 cm.$^{-1}$, indicating the presence of a lactone and starting diketone. The alkaline extract was acidified and extracted with ether. This extract was washed with brine, dried over magnesium sulphate and evaporated. The (solid) residue crystallised from light petroleum in colourless needles, m.p., 113-115°. Yield 4 g., (40%). (Found, C, 79·09; H, 7·20. $C_{16}H_{18}O_2$ requires C, 79·31; H, 7·49%.) The infra-red showed absorption (CCl_4) at 3540-2830 cm.$^{-1}$ (acidic hydroxyl) and 1700 cm.$^{-1}$ (carbonyl). The n.m.r., spectra gave a multiplet at 2·65 τ (aromatic), triplet at 7·0 τ (benzylic) and an undefined splitting at 7·45 τ ()C<u>H</u>-CO_2H).

The ultra-violet spectrum showed absorption at $\lambda_{max.}^{EtOH}$ 268 (ε, 5,800) and 254 mμ (ε, 9,100). The lactone was separated from diketone by prep. t.l.c., and characterised as colourless crystalline needles m.p., 128-30°C (Found, C, 79·44; H, 7·52. $C_{16}H_{18}O_2$ requires C, 79·31; H, 7·49%.) The infra-red spectrum in chloroform showed absorption at 1762 $cm.^{-1}$ (γ-lactone) and 730-770 $cm.^{-1}$ (o-disubstituted aromatic).

β-Dimethylamino-benzosuberone hydrochloride (15)

Benzosuberone (5 g., 0·0312 mole) was refluxed with paraformaldehyde (2·28 g., 0·045 mole) and dimethylamine hydrochloride (3·24 g., 0·045 mole) in ethanol (75 ml.,) for 6 hrs., after addition of a few drops of concentrated hydrochloric acid. The ethanol was removed in vacuo yielding a brown gum which solidified on trituration with tetrahydrofuran and recrystallised from ethanol-tetrahydrofuran as yellow plates m.p., 138-139°C. Yield 5·1 g., 67·5%.

2-(2'-Cyclopentanonylmethyl)-benzsuberone (17)

The Mannich base (15) (5·2 g.,) and cyclopentanone (6·3 g.,) were reacted together as described above, and gave the crude diketone (6 g., 83·5%) which showed ν_{CO}^{film} 1680 and 1750 cm.$^{-1}$. It was used directly in the next step.

1,2-Benzobicyclo-(5,5,0)-dodec-11(12)-ene-7-carboxylic acid (15b)

The crude diketone (6 g.,) in glacial acetic acid (50 ml.,) and concentrated hydrochloric acid (15 ml.,) was boiled under reflux for 17 hours and worked up by the procedure described above. The neutral fraction showed no evidence of lactone by-product. The acidic component crystallised in cream coloured needles from light petroleum m.p., 156-160°. (Found, C, 78·98; H, 7·44; $C_{17}H_{20}O_2$ requires C, 79·60; H, 7·86%.) The infra-red spectrum (CCl_4) showed absorption at 3540-2830 cm.$^{-1}$ (acidic hydroxyl) and 1690 cm.$^{-1}$ (carbonyl). The n.m.r., spectrum gave the aromatic protons as a quartet at 2·9 τ and the α proton to the carboxylic function as a multiplet at 7·6 τ. The ultra-violet spectrum in ethanol had $\lambda_{max.}$ 268 mμ (log ε 3·709) and a molecular weight of 256 (required 256) was obtained by mass spectral measurements.

6-amino-1,2-benzobicyclo-(5,4,0)-undec-10(11)-ene (23)

The acid (10) (1 g., 0·0043 mole) was refluxed for two hours with a three mole excess of oxalyl chloride (1·77 g., 0·013 mole) in dry benzene (25 ml.,). On removal of solvent and excess oxalyl chloride under vacuum a brown solid was obtained which showed to be the acid chloride by infra-red absorption at 1796 $cm.^{-1}$. This was taken up in dry benzene and after the addition of an equimolar amount of activated sodium azide was refluxed for five hours, after which time 10 ml., of 4N sodium hydroxide was added and reflux continued for a further two hours. The benzene layer was then separated off, dried over magnesium sulphate and on evaporating to dryness gave a brown resinous solid which on addition of ether yielded a colourless crystalline material m.p., 243-247°C. On recrystallisation from ethyl-acetate-petrol colourless needles were obtained (600 mg.,) m.p. 245-247°C. The infra-red (CCl_4) showed absorption at 3445 $cm.^{-1}$ (amine).

Reaction of lead tetra-acetate on (10)

To a stirred solution of 1·452 g., (0·006 mole) of the acid and 6·486 g., (0·047 mole) of fused sodium acetate in 30 ml., of glacial acetic heated at 70±5°C was added 3·987 g., (0·01 mole) of freshly prepared lead tetra-acetate in three portions over ½ hour. Stirring continued for a further ½ hour at 70°C and the resulting greenish-yellow solution was cooled to room temperature, diluted with water and extracted with ether. The ethereal solution was dried over magnesium sulphate and reduced to dryness to yield a yellow oil (1·3 g.,), which solidified on standing. This solid (20) recrystallised from 60/80 pet., ether as colourless plates m.p., 136-138°C. (Found, C, 71·45; H, 6·08. $C_{18}H_{20}O_4$ requires C, 71·98; H, 6·71%.) The infra-red (CCl_4) showed absorption at 1784 cm.$^{-1}$ (γ-lactone), 1750 and 1228 cm.$^{-1}$ (acetate). The n.m.r., an undefined band at 6·3 τ (-C<u>H</u>-CO-) and a singlet at 8·05 (acetate). The ultra-violet spectrum showed weak absorption at $\lambda_{max.}$ 268 m; (ε, 420),

Hydrogenolysis of the Acetoxy-lactone (20)

The lactone (20) (242 mg.,) was dissolved in 50 ml., of glacial acetic acid and hydrogenolysed at 4 atms., and 40°C using 150 mg., of 5% Pd/C as catalyst for 11 hours. The catalyst was filtered off and the acetic acid removed under vacuum, to yield a brownish solid, which was taken up in ether. The ethereal solution was brine washed, dried over magnesium sulphate and on reducing to dryness produced a crystalline material which was shown to contain two compounds. These were separated by thick layer chromatography to yield pure lactone (100 mgs.,) and acetoxylactone (20) (125 mgs.,). The lactone was shown, spectroscopically, to be identical with the lactone (14) obtained as a by-product from the preparation of (10). ($\nu_{CO}^{CHCl_3}$ 1763 $cm.^{-1}$).

Methyl ketone (27)

Methyl lithium was prepared by the addition of methyl iodide (3·75 ml., 0·05 mole) to a stirred suspension of lithium (0·71 g., 0·10 mole) in dry ether (25 ml.,) under nitrogen, over a period of five minutes and the mixture refluxed with stirring for a further hour.

The resultant methyl lithium solution was added dropwise to a stirred solution of the acid (10) (2 gm.,

0·009 mole) in anhydrous ether (50 ml.,) under a nitrogen atmosphere. After refluxing for two hours the solution was carefully diluted with water, ether extracted, brine washed, dried over magnesium sulphate and the ether removed under vacuum to yield a pale yellow oil (1·45g.,) 78%. (Found, C, 84·55; H, 8·41. $C_{17}H_{20}O$ requires C, 84·96; H, 8·39%.) The infra-red showed methyl ketone absorption at 1707 $cm.^{-1}$ and the n.m.r., gave signals at 2·75 τ (aromatic) 7·3 τ (multiplet, 1H, -C<u>H</u>-$COCH_3$) and 7·85 τ (singlet, 3H, -$COCH_3$).

<u>4-Dimethylaminomethyl-3',4',5'-trimethoxy-1,2-benzocyclo-hepten-3-one hydrochloride (30)</u>

The trimethyoxybenzosuberone (4) (25 g., 0·1 mole) was refluxed 7 hours with para-formaldehyde (13·5 ., 0·15 mole) and dimethylamine hydrochloride (19·27 g., 0·24 mole) in anhydrous ethanol (250 ml.,) after the addition of a few drops of concentrated hydrochloric acid. The resultant solution was reduced in volume and cooled, to yield the crystalline hydrochloride (35 g.,). Which was subsequently recrystallised from an ethyl acetate-pet ether mixture, as colourless crystals m.p., 159-162° yield 33 g., (95%). The infra-red showed absorption at 2720-2470 $cm.^{-1}$ (amino hydrochloride) and 1690 $cm.^{-1}$

(carbonyl). The n.m.r., spectrum gave a singlet at 3·49 τ (aromatic), 6·15 (methoxyl) and a broad peak at 7·2 τ ($-N-Me_2$).

Base treatment yielded the unstable free base which was used without further purification.

4-(2-Oxocyclopentylmethyl)-3',4',5'-trimethoxy-1,2-benzocyclohepten-3-one (31)

The Mannich base (30) (33 g., 0·104 mole) in cyclopentanone (32 g., 0·382 mole) was refluxed for 75 mins., with continuous stirring, during which time dimethylamine was evolved. The resulting solution was cooled, neutralised with acetic acid and dissolved in ether. The ethereal solution was washed with brine (x4) and dried over anhydrous magnesium sulphate. On removal of solvent, the reaction product (60 g.,) was purified firstly by distillation (this resulted in the occurrence of a retro-Michael and so was abandoned) and finally by column chromatography which produced a yellowish oil which would not solidify. (Found, C, 69·21; H, 7·29. $C_{20}H_{26}O_5$ requires C, 69·34; H, 7·51%). The infra-red showed absorption at 1742 $cm.^{-1}$ (cyclopentonyl) and 1686 $cm.^{-1}$ (conjugated carbonyl). The n.m.r., showed the presence of one aromatic proton (singlet, 3·5 τ), three methoxyl

groups (singlet, 6·1 τ) and two protons α-carbonyl (multiplet, 7·25 τ).

Ring Expansion

The diketone (31) (15 g., 0·043 mole) in glacial acetic acid (150 ml.,) and concentrated hydrochloric acid (50 ml.,) was boiled under reflux for 18 hours. Most of the solvent was removed in vacuo, and the residual oil was flooded with water and finally extracted with ether. The ether solution was extracted with 4N NaOH (x6), washed with brine and dried over anhydrous magnesium sulphate. On removal of solvent a (neutral) gum was obtained which showed ν_{CO}^{film} 1686, 1742 cm.$^{-1}$ indicating the presence of starting material (no indication of lactonisation having occurred).

The alkaline extract was acidified and extracted with ether. This extract was washed with brine, dried over magnesium sulphate and evaporated to dryness to yield a brown gum which was unstable in the atmosphere turning very dark red and consequently satisfactory analytical data could not be obtained. The infra-red (liquid film) showed absorption at 3540-2800 cm.$^{-1}$ (acidic hydroxyl), 1744 and 1711 cm.$^{-1}$ (monomeric and dimeric acid). A positive phenol test was obtained with ethanolic ferric chloride i.e., a phenolic acid.

Methylation of phenolic acid (34)

The acid (34) (13·397 g., ca. 0·043 mole) was taken up in a solution of potassium hydroxide (20 g.,) in 50 ml., of water and to this was added dimethyl sulphate (30 g.,) after which the mixture was refluxed for one hour. On cooling, the mixture was made just alkaline and ether extracted, brine washed and dried over magnesium sulphate. Removal of solvent yielded a brown oil which distilled as a pale yellow liquid and gave a negative ferric chloride test. (Found, C, 70·89; H, 8·92. $C_{21}H_{28}O_5$ required C, 70·56; H, 8·07%.) The infra-red spectrum had no absorption above 2950 $cm.^{-1}$ (no acidic hydroxyl) but had methyl ester at 1730 and 1230 $cm.^{-1}$ which was verified by n.m.r., (singlet, 6·35 τ)

The alkaline extract was acidified and ether extracted; the ethereal extract was brine washed, dried over magnesium sulphate then evaporated to dryness. The gummy residue (5·5 g.,) was negative to ferric chloride and its infra-red (CCl_4) showed it was the required trimethoxy acid 3550-2840 $cm.^{-1}$ (acidic hydroxyl), 1744 $cm.^{-1}$ (monomeric) and 1711 $cm.^{-1}$ (dimenic). The n.m.r., also supported this conclusion and its ultra-violet spectrum showed characteristic absorption at $\lambda_{max.}$ 258 mμ (ε, 5,500) $\lambda_{min.}$ 245 mμ (ε, 4,365).

Desoxydesmethoxydesacetamido-8,9,10,11,12-hexahydocolchicine 9-carboxylic acid (38)

The methyl ester (11 g.,) was refluxed for 3 hours in a potassium hydroxide (10 g.,) - methanol (30 ml.,) solution. On cooling the mixture was basified with 4N NaOH and ether extracted. The ethereal solution was brine washed, dried and evaporated to yield a light brown oil (ca 1 g.,) which showed ν_{CO}^{film} 1690, 1745 and 1775 cm.$^{-1}$ indicating the presence of diketone and a lactone.

The alkaline extract was acidified and extracted with ether. The ethereal solution was brine washed and dried over magnesium sulphate. On removal of solvent a brown gum was obtained (9 g., 85%). (Found, C, 66·00; H, 8·03. $C_{21}H_{26}O_5.H_2O$ requires C, 65·92; H, 7·74%.) Spectroscopic data was identical with that obtained from the acid above.

9-Acetyldesoxydesmethoxydesacetamido-8,9,10,11,12-hexahydrocolchicene (41)

Methyl lithium was prepared by the addition of methyl iodide (10 ml., 0·13 mole) to a stirred suspension of lithium (1·5 g., 0·2 mole) in dry ether (50 ml.,) under nitrogen, over a period of five minutes and the mixture refluxed with stirring for a further hour.

The resultant methyl lithium solution was added dropwise to a stirred solution of the acid (38) (1·25 g., 0·004 mole) in anhydrous ether (50 ml.,) under nitrogen. After refluxing for two hours the solution was carefully diluted with water, ether extracted, brine washed over magnesium sulphate and evaporated under vacuum to a pale, yellow viscous oil, b.pt., 181-3° / 0·15 mm., (1·05 g., 80%). Found, C, 73·47; H, 8·31. $C_{21}H_{28}O_4$ requires C, 73·23; H, 8·19%.) The infra-red (CCl_4) showed the presence of the methyl ketone at 1707 $cm.^{-1}$. The n.m.r., showed three singlets 3·65 τ (aromatic) 6·27 τ (methoxyls) and 7·93 τ (methyl ketone).

Baeyer-Villiger reaction on (41)

A solution of the methyl ketone (41) (0·9 g., 0·004 mole) in chloroform (5 ml.,) was added to a stirred solution of m-chloroperbenzoic acid (2 g., 0·012 mole) in chloroform (15 ml.,). The mixture was left in the dark at room temperature for two days. At this time crystals of peracid came out of solution and these were filtered off and washed with chloroform. The chloroform solution was washed firstly with 10% bisulphite then with sodium carbonate solution. This resulted in an emulsion which was filtered through celite 535, then dried over magnesium

sulphate and on removal of solvent yielded the acetate (42) as a yellow oil (850 mg., 88%) t.l.c. in 30% ethyl acetate/petrol indicate mainly two compounds viz., acetate and the alcohol obtained by hydrolysis. The infra-red of the acetate (CCl_4) showed absorption at 1750 $cm.^{-1}$ (acetate carbonyl) and n.m.r., had a singlet at 8·05 τ (acetate methyl) and a multiplet at 2·8 τ (aromatic).

Desmethoxydesacetamido-8,9,10,11,12-hexahydrocolchicine-o-acetate (42)

A solution of the methyl ketone (41) (1·25 g., 0·0036 mole) in chloroform (7 ml.,) was added to a stirred solution of m-chloroperbenzoic acid (2·47 g., 0·0144 mole) in chloroform (20 ml.,). The mixture was then left in the dark at room temperature for four days which time crystals of peracid came out of solution. These were washed with chloroform and the combined chloroform solutions washed firstly with 10% bisulphite then with sodium carbonate solution. The resultant chloroform emulsion was filtered through celite 535 then dried over magnesium sulphate. Removal of solvent yielded a very pale yellow oil (750 mg., 82·5%) which t.l.c., again indicated to be a mixture of alcohol and acetate, this being used without further purification for the next stage. The acetate was shown by

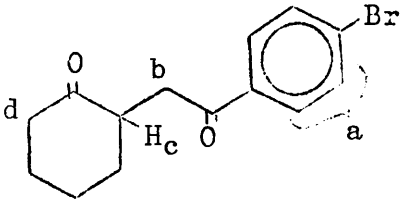
the presence of carbonyl absorption in the infra-red at 1740 $cm.^{-1}$ and a singlet in the n.m.r., at 8·05 τ.

Desmethoxydesacetamido-8,9,10,11,12-hoxahydrocolchicine (43)

To a stirred solution of the acetate (42) (0·750 g., 0·0002 mole) in ether (5 ml.,) was added, slowly, solid lithium aluminium hydride (0·344 g., 0·0008 mole) and the solution left overnight at room temperature. The excess hydride was destroyed with moist acetone and the solution was then diluted with 25 ml., of water. The solution was extracted with ether and the ethereal extract dried over magnesium sulphate. Removal of solvent yielded the alcohol (43) which was recrystallised from aqueous ethanol as colourless plates m.p., 151-153°C (0·430 g., 62%). Found, C, 71·64; H, 7·78. $C_{19}H_{20}O_4$ requires C, 71·67; H, 8·23%.) The infra-red (nujol) showed absorption at 3450 $cm.^{-1}$ (hydroxyl) but no carbonyl. The n.m.r., had a singlet at 3·65 τ (aromatic) and multiplets at 5·4 τ (>C<u>H</u>-OH) and 6·25 τ (methoxyl). The ultra-violet spectrum showed the characteristic absorption at $\lambda_{max.}$ 257 mμ (log ε 3·74) $\lambda_{min.}$ 254 (log ε, 3·64).

2-p-Bromophenacylcyclohexanone (48)

A solution of p-bromophenacyl bromide (118 g., 0·4 mole) in dry benzene was added over a period of 45 mins., to a stirred, boiling solution of the pyrolidine enamine of cyclohexanone (65·8 g., 0·4 mole) in 100 ml., anhydrous benzene. Stirring and heating was continued for a further 2 hours, water (100 ml.,) was then added and the mixture was then cooled and the benzene layer was washed (x3) with 6N HCl, (x3) with brine, dried and evaporated. The resulting diketone (48) crystallised from ethanol m.p., 85-6°. (Found, C, 56·75; H, 5·33; Br, 27·11. $C_{14}H_{15}O_2Br$ requires C, 56·8; H, 5·08; Br, 27·29%.) The infra-red spectrum (CCl_4) showed carbonyl absorption at 1707 $cm.^{-1}$ (hexanone) and 1691 $cm.^{-1}$ (acetophenone).



H_a 2·35 τ (4 protons, quartet)

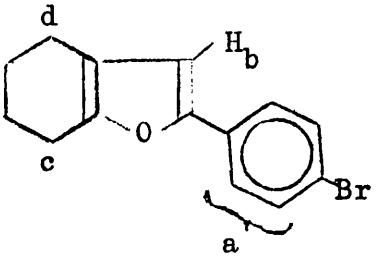
H_b 6·41 τ (2 protons, doublet, J = 6 cps)

H_c 7·0 τ (1 proton, multiplet)

H_d 7·5 τ (2 protons, multiplet).

Cyclisation of diketone (48)

The diketone (48) (3 g.,) was refluxed for 20 hours in a mixture of concentrated hydrochloric acid (10 ml.,) and glacial acetic acid (50 ml.,). Most of the solvent was removed in vacuo, and the residual oil flooded with water and finally extracted with ether. The ethereal extract was brine washed and dried over magnesium sulphate. Removal of solvent yielded the furan (49) which re-crystallised from ethanol as colourless needles, m.p., 123-125° (2·5 g., 89%). (Found, C, 60·49; H, 4·60; Br, 29·2. $C_{14}H_{13}BrO$ required C, 60·53; H, 4·68; Br, 28·85%.) The infra-red was transparent to carbonyl absorption but did show absorption at 1633 $cm.^{-1}$ (KCl disc, trisubstituted C = C) and in CS_2 solution at 915 $cm.^{-1}$ (-O-C = C-H) and a series of peaks from 826-797 $cm.^{-1}$ (1,4-disubstituted aromatic). The ultra-violet spectrum showed absorption at $\lambda_{max.}$ 205 mμ (ε, 2,140), 228 mμ (ε, 2,280) and 308 mμ (ε, 9,300) n.m.r.:-



H_a 2·6 τ (4 protons, singlet)

H_b 3·63 τ (1 proton, singlet)

H_c 7·45 τ (2 protons, multiplet)

H_d 8·15 τ (2 protons, multiplet).

Mass spectral determination of molecular weight gave a value of P = 276/8 m/e (required value 277).

2-Oxocyclohexylacetaldehyde (50)

(a) By ozonolysis

2-Allylcyclohexanone (51) (10 g.,) in AnalR ethyl acetate (250 ml.,) underwent ozonolysis at -80°C over a period of 3 hours. The blue coloured solution was allowed to warm up to room temperature and finely powdered zinc (10 g.,) and acetic acid (250 ml.,) were added. The mixture was stirred at room temperature for 15 hours after which time the zinc was removed by filtration. The organic layer was washed with sodium carbonate (x6), ferrous sulphate (x3) and finally brine . After drying removal of solvent yielded the aldehyde as a colourless oil, b.p., 80-82°/0·5 mm., (5·5 g., 58·5%). (Found, C, 68·10; H, 8·41. $C_8H_{12}O_2$ requires C, 68·55; H, 8·63%.)

(b) Lemieux-von Rudoloff oxidation

Potassium permanganate (1·9 g., 0·012 mole), anhydrous potassium carbonate (12·42 g., 0·09 mole) and sodium iodate (37·8 g., 0·272 mole) in 1 litre of water was mixed with a solution of allylcyclohexanone (5 g., 0·036 mole) in 250 ml., dioxan and 250 ml., benzene was stirred at room temperature for 5 hours. The solution was then extracted with ethylacetate (x3), washed with water (x2), brine (x2) and dried over magnesium sulphate. Removal of solvent yielded the aldehyde as a pale yellow oil (0·3 g., 20%).

(c) Von Rudoloff oxidation

Allylcyclohexanone (13·8 g., 0·1 mole) in ether (150 ml.,) and water (150 ml.,) was stirred at room temperature with osmium tetroxide (0·2 g.,). To this dark solution was added sodium metaperiodate (65 g., 0·3 mole) over a period of 40 minutes and the solution stirred at room temperature for two days.

The solid periodate was filtered off and into the straw coloured ethereal solution was passed gaseous hydrogen sulphide until no more osmium sulphide separated out. The black precipitate was separated off and the ethereal solution dried over magnesium sulphate. Removal of solvent yielded a dark yellow liquid which on

distillation yielded a colourless oil, b.p., 80-83°/0·5 mm., (5 g., 36%). (Found, C, 68·10; H, 8·41. $C_8H_{12}O_2$ requires C, 68·55; H, 8·63%.) The infra-red showed absorption at 2862 cm.$^{-1}$ (aldehyde) and 1713 cm.$^{-1}$ (cyclohexanone). The n.m.r., showed typical aldehyde signal at 0·12 τ (singlet) and also had signals at 6·3 τ (doublet, 2 protons) and 7·3 τ (multiplet, 1 proton). n_d^{25} 1·4728.

Preparation of lactone (59)

(a) Cyclohexanone-2-acetic acid (54) or its ethyl ester (0·004 mole) in glacial acetic acid (10 ml.,) was heated under reflux with BF_3,$4Et_2O$ (2 ml.,) for 1 hour. The reaction mixture was cooled, added to water and ether extracted. The ethereal extract was washed with water, sodium carbonate, water dried ($MgSO_4$). Removal of solvent yielded the lactone, as a pale yellow oil which on distillation (b.p., 110-2°/1 mm.,) crystallised as colourless plates, m.p., 28-30°C. (Lit., value 29-31°).

(b) The acid (54) (5 g.,) was heated to 300°C for 1 hour and on cooling the resulting oil was distilled to yield colourless plates m.p., 29-31°C. The infra-red spectrum (film) showed absorption at 1644 cm.$^{-1}$ (trisubstituted C = C) and a broad band at 1740-1780 cm.$^{-1}$ which in CCl_4

solution was resolved into three peaks at 1733 $cm.^{-1}$(s), 1778, 1792 $cm.^{-1}$ (Fermi resonance or contamination by isomeric enol-lactone.)

The n.m.r., showed one ethylenic proton as a very fine triplet at 4·26 τ and a multiplet at 5·3 τ (1 proton -C<u>H</u>-O-).

<u>Ethyl cyclohexanone-2-acetate (58)</u>

The enamine (47) (20 g., 0·132 mole) in absolute methanol (200 ml.,) was stirred and treated, under reflux with ethylbromoacetate (32 g., 1·5 x 0·132 mole) added dropwise over 45 mins. Heating and stirring was continued for a further 2 hours after which time 100 ml., of water was added through the reflux column and the solution heated for 2 hours then 150 ml., of methanol was distilled off. The solution was then cooled, water (100 ml.,) added and extracted with ether. The ethereal extract was dried over magnesium sulphate and removal of solvent yielded a dark liquid which on distillation gave the required ester as a colourless liquid b.p., 80-85°/0·7 mm., (lit value 95-101°/1·5 mm.,).

Attempted formation of bicyclo-(3,2.1)-octan-2,8-dione (53).

(a) Cyclohexanone-2-acetic acid (2 g.,) was dissolved in redistilled tetralin and to this was added a catalytic amount of p-toluene sulphonic acid. The reaction mixture was slowly distilled in order to remove any water formed during the reaction. This resulted in a black intractable tar and the method was abandoned.

(b) The mixture of isomeric alcohols (52) (0·19 g.,) in acetone (5 ml.,) was oxidised using Jones reagent (0·18 ml.,) at 0°C. The green solution was diluted with water and ethylacetate extracted. After drying removal of solvent yielded an acidic compound which was shown to be cyclohexanone-2--acetic acid.

Attempted formation of 6-hydroxybicyclo-(3,2,1)-octan-8-one (52)

Cyclohexanoneacetaldehyde (5 g.,) was added to 100 ml., of 8% NaOH and the suspension was stirred at room temperature under nitrogen for 25 hours. The green solution was diluted with water and ether extracted. The ethereal extract was washed with 4N NaOH, brine and dried over magnesium sulphate. Removal of solvent yielded a camphoraceous yellow oil (3·213 g., 60%) which t.l.c., indicated to consist of two compounds, viz.,

isomeric alcohols which on distillation resulted in a mixture of at least six compounds.

Infra-red (film) showed absorption at 3350 $cm.^{-1}$ (hydroxyl) and 1700 $cm.^{-1}$ (cyclohexanone).

A number of other conditions were used in attempts to form this compound (page 27) but no method was devised whereby a stable sample or derivative was obtained.

Ethyl-1-carbethoxycyclohexanone-2-acetate (61a)

Carbethoxycyclohexanone (70 g., 0·354 mole) was added to a suspension of finely powdered sodium (9·7 g.,) in anhydrous benzene (400 cc.,) with stirring and refluxing. After 2 hours ethyl chloroacetate (51·5 g.,) was added to the reaction mixture and refluxing continued for a further 4 hours with stirring. After cooling the benzene solution was washed with water and dried over magnesium sulphate. Removal of solvent gave a pale yellow oil which on distillation yeilded the diester b.p., 130-133°/1 mm., n_d^{25} 1·4629 (lit., value 142-150°/5 mm., n_d^{25} 1·4620).

Carbethoxycyclohexanone-2-acetic acid (61b)

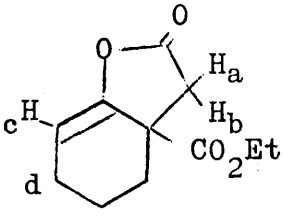
The diester (61a) (5 g., 0·02 mole) was stirred at room temperature overnight in ethanolic potassium hydroxide (0·8 g., in 100 ml.,). Ethanol was removed under vacuum and the resulting solid dissolved in water acidified and ether extracted. The ethereal extract was brine washed and dried over magnesium sulphate. Removal of solvent yielded a colourless oil (4·3 g., 81%). T.l.c., in a buffered solvent system viz., benzene-dioxan-acetic acid (90:25:4) indicated the presence of two compounds which when esterified yielded one methyl-ethyl ester (retention time 27-25 mins.,). Thus assumed to be an equilibrium mixture of lactol(61c) $\rightleftharpoons$ acid (61b). Infra-red showed absorption 3475-2800 $cm.^{-1}$ (acidic hydroxy), 1780 $cm.^{-1}$ (lactol), 1730 $cm.^{-1}$ (ester) and 1710 $cm.^{-1}$ (cyclohexanone)

Preparation of enol lactone (60)

(a) Carbethoxycyclohexanone-2-acetic acid or its ester (1 g.,) in glacial acetic acid (17 ml.,) and freshly distilled $BF_3.Et_2O$ (5 ml.,) was refluxed for $1\frac{1}{2}$ hours. The solution was then added to ice water and ether extracted. The ethereal extract was washed with water, sodium carbonate, water and brine. After drying ($MgSO_4$) removal of solvent yielded the sweet smelling lactone as

a low melting solid (30-35°C) (600 mg., 73%).

(b) The keto-acid (61b) (1 g.,) was refluxed with fused sodium acetate (100 mg.,) and acetic anhydride (17 ml.,) overnight. The solution was cooled and added to ice water then ether extracted. The ethereal extract was washed with water, sodium carbonate, water and dried over magnesium sulphate. Removal of solvent yielded the low melting lactone (31-35°C) (750 mg., 80%). (Found, C, 62·5; H, 6·79. $C_{11}H_{14}O_4$ requires C, 62·85; H, 6·71%.) The infra-red (CCl_4) showed absorption at 1822 cm.$^{-1}$ (γ-lactone), 1740 cm.$^{-1}$ (ester), 1704 cm.$^{-1}$ (C = C). The ultra violet spectrum showed absorption at $\lambda_{max.}$ 213 mμ (ε, 19,065).



H_d 7·8 τ (multiplet)

H_a 7·22 τ (singlet)

H_b 7·31 τ (singlet)

H_c 4·6 τ (triplet J = 4,3 cps)

Attempted formation of 1-Ethoxycarbonyl-6-hydroxybicyclo-(3,2,1)-octan-8-one (63)

(a) An ethereal solution of phenyl magnesium bromide [from magnesium (0·41 g.,) and bromobenzene (2·74 g.,) in anhydrous ether (25 ml.,)] was added dropwise with stirring to a solution of enol lactone (1·68 g.,) in 25 ml., anhydrous ether and the reaction mixture refluxed for 3 hours. After cooling and decomposition of solid complex with mineral acid (6N HCl) ether was added and organic layer washed with 4N NaOH, brine and dried over magnesium sulphate. Removal of solvent yielded a brown oil which t.l.c., indicated to be mainly starting material but contained traces of four other compounds; i.r., indicated no hydroxyl and so this approach was not further pursued.

(b) Lithium aluminium tertiarybutoxyhydride reduction

To the enol-lactone (1·4 g.,) at -70°C in dry tetrahydrofuran (10 ml.,) was added dropwise and under N_2 complex hydride (2·4 g.,) in dry tetrahydrofuran (20 ml.,) over a period of 1 hour with stirring. The temperature was then allowed to rise to room temperature and the stirred solution left for 12 hours. The solution was neutralised with 6N HCl and ether extracted. The ethereal extract was washed with brine, bicarbonate, brine and dried over magnesium sulphate. On evaporation

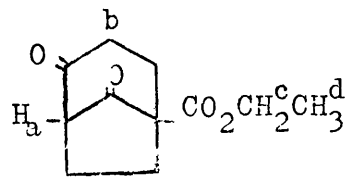
the ethereal solution turned pink and yielded a brown oil (947 mg.,). The infra-red showed weak hydroxyl absorption at 2750 $cm.^{-1}$ along with carbonyls at 1785, 1725 and 1710 $cm.^{-1}$. t.l.c., showed a complex mixture and chromatography on silica yielded a pale yellow oil which rapidly turned brown on standing. The instability of this material thus formed suggested that this approach unsuitable and so was abandoned.

1-Ethoxycarbonyl-4-hydroxybicyclo-(3,2,1)-octan-8-one (71)

Redistilled acrolein (50 ml.,) was added dropwise over a period of 20 minutes to a stirred solution of 2-carbethoxycyclopentanone (100 g.,) and triethylamine (7·5 ml.,) in anhydrous benzene (500 ml.,) at 0°C. After addition was complete the ice-bath was removed immediately and the mixture was stirred at room temperature for 57 hours, then neutralised with acetic acid, brine washed and dried over magnesium sulphate. Removal of volatiles yielded a brownish oil which on distillation yielded the required epimeric alcohols (71), b.p., 130°/ 0·2 mm., (see reference 38).

1-Ethoxycarbonyl-bicyclo(3,2,1)-octan-4,8-dione (73)

The epimeric alcohols (71) (10 g., 0·047 mole) were oxidised by standard Jones reagent at 0°C in acetone. The solution was poured into water (1 l.,) and thoroughly extracted with ethyl acetate. The extract was brine washed, dried over magnesium sulphate and evaporated to a brown oil which on distillation gave the colourless dione (73), b.p., 136°/0·25 mm., (8·98 g., 86·5%). (Found, C, 63·11; H, 6·82. $C_{11}H_{14}O_4$ required C, 62·85; H, 6·71%.) The infra-red showed carbonyl absorption at 1766 and 1723 cm.$^{-1}$ (see table 1)



H_a 6·65 τ (doublet, J = 6 cps.)

H_b 7·4 τ (2H, multiplet)

H_c 5·7 τ (quartet

H_d 8·65 τ (triplet)

g.l.c., retention time 24·5 minutes on 10% A.P.L., 150°C 54 ml./min., 150 V.

Reactions on dione (73) (see Table 2).

The products were analysed by g.l.c.

(a) H_2O/dioxan.

A solution of the diketone (500 mgs.,), water (5 ml.,) and dioxan (5 ml.,) was refluxed for 4 hours. The solution was then added to ice-water and ether extracted. The ethereal extract was washed with sodium carbonate, brine and dried over magnesium sulphate. Removal of solvent yielded a dark brown semi-solid (6 mgs.,).

The carbonate solution was acidified with 6N HCl and ether extracted. The ethereal extract was brine washed and dried over magnesium sulphate. Removal of solvent yielded a brown liquid (350 mgs.,) which was esterified with diazoethane without further purification. G.l.c., analysis showed it to be a mixture of (75) and (76).

(b) H_2SO_4/dioxan

The diketone (100 mgs.,) was refluxed in a mixture of dioxan (10 ml .,) and 6N H_2SO_4 (1 ml.,) for 30 minutes. The reaction mixture was poured into ice water and ether extracted. The ethereal extract was basified and the basic extract was then acidified, ether extracted and brine washed. The dried ethereal extract on removal of solvent yielded a colourless oil which was esterified with diazo-

ethane, and identified (g.l.c.,) as a mixture of (75) and (76).

(c) NaOEt/EtOH

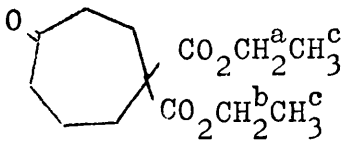
The diketone (500 mgs., 0·0024 mole) in ethanol (5 ml.,) was refluxed with a solution of sodium ethoxide (70 mgs., sodium and 10 ml., ethanol) for 30 minutes. The reaction mixture was added to ice and ether extracted. The ethereal extract was brine washed, dried and on removal of solvent yielded a colourless liquid (370 mgs.,), mixture of (75) and (76).

(d) 4N NaOH/Et_2O

The diketone (1 g.,) was shaken up with 4N NaOH (10 ml.,) and ether (100 ml.,) for 2 minutes at room temperature. The basic layer was extracted with ether after acidification, brine washed and dried. Removal of solvent yielded a brown oil part of which was esterified with diazoethane and the remainder with diazomethane. The ethyl ester was found to be a mixture of (75) and (76) by g.l.c., analysis. The methyl ester was a mixture of (75a) and (75b).

(e) Sodium borohydride/methanol

The diketone (500 mgs., 0·0025 mole) in methanol (10 ml.,) was stirred overnight at room temperature with sodium borohydride (25 mgs., 0·0006 mole). The solution was acidified with 6N HCl, diluted with water (50 ml.,) and thoroughly ether extracted. After drying, removal of solvent gave a colourless oil (470 mgs.,). T.l.c., indicated three components and these were separated by chromatography on Grade III alumina. The most polar compound was shown to be the keto-alcohol (80). The others were identified as (75) and (76). The diethyl ester (75) was identified as follows: Found, C, 60·59; H, 7·86. $C_{13}H_{20}O_5$ requires C, 60·92; H, 7·87%. The infra-red showed absorption at 1735 cm.$^{-1}$ (ester carbonyl), 1702 cm.$^{-1}$ (cycloheptanone) and 1225 cm.$^{-1}$ (C-O stretch)



H_a 5·82 τ (2H, quartet)

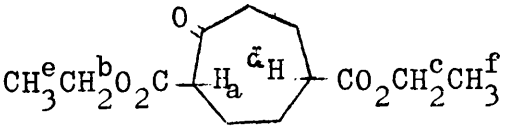
H_b 5·85 τ (2H, quartet)

H_c 8·75 τ (6H, triplet).

The ultra violet only indicated end-absorption at $\lambda_{max.}$ 212 mμ which was unaltered on the addition of 4N NaOH. Mass spectral determination gave the molecular weight i.e., 256.

G.l.c., retention time was 16·5 minutes on 5% Q.F.I., at 175° with a gas flow of 35 ml.,/min.

The diethyl ester (76) showed infra-red absorption at 1720 $cm.^{-1}$ (ester), 1705 $cm.^{-1}$ (cycloheptanone), 1680 $cm.^{-1}$ (β-keto-ester) and 1240 $cm.^{-1}$ (ester C-O stretch). Found, C, 60·87; H, 8·35. $C_{13}H_{20}O_5$ requires C, 60·92; H, 7·87%.)



H_a	5·9	τ (undefined, 1H)
H_b	5·8	τ (quartet, 2H)
H_c	5·85	τ (quartet, 2H)
H_d	7·2	τ (undefined, 1H)
H_e	8·75	τ (triplet, 3H)
H_f	8·8	τ (triplet, 3H)

The ultra-violet spectrum showed typical β-keto ester absorption at $\lambda_{max.}$ 222 mμ with a bathochromic shift on

addition of NaOH to $\lambda_{max.}$ 210 and 287 mμ.

The ester gave a green colouration with ferric chloride.

Attempted bromination of diketone (73)

(a) Bromine/chloroform (or acetic acid)

The diketone (1 g., 0·004 mole) in chloroform (or acetic acid) (5 ml.,) was cooled to 0°C and to this was added liquid bromine (1·3 ml.,). The dark brown colour did not fade and only starting material was recovered.

(b) N-Bromosuccinamide/CCl_4

The diketone (1 g., 0·004 mole) was dissolved in CCl_4 and to this was added N-bromosuccinamide (712 mg., 0·004 mole) and benzoylperoxide (0·1 g.,). The solution was refluxed and stirred overnight after which time the succinamide was filtered off and the solution washed with ferrous sulphate then dried over magnesium sulphate. Removal of solvent yielded a brown oil which t.l.c, indicated to contain starting material and four other compounds. Chromatography on silica gel yielded only complex acidic material i.e., decomposition of the unstable bicyclic skeleton having occurred.

(c) N-Bromosuccinamide/glacial acetic acid

The diketone (1 g., 0·004 mole) was dissolved in chloroform (15 ml.,) and to this was added N-bromosuccinamide (712 mg., 0·004 mole) and acetic acid (2 ml.,). The solution was refluxed for 4 hours then diluted with water. The aqueous solution was ether extracted, brine washed and dried. Removal of solvent yielded a dark brown oil which t.l.c., indicated to contain only acid material.

(d) Pyridinium bromide perbromide

To a solution of the diketone (500 mg., 0·0024 mole) in pyridine (5 ml.,) was added, dropwise, with stirring, pyridinium bromide perbromide (760 mg., 0·0024 mole) in pyridine (5 ml.,) over 15 minutes and the brown-red solution stirred at room temperature overnight. The solution was then added to ice water, washed with 4N HCl, ether extracted, washed with sodium bicarbonate solution, brine and dried over magnesium sulphate. Removal of solvent yielded a pale oil which t.l.c., and i.r., showed to contain only starting diketone.

(e) Cupric bromide

The solution of the diketone (100 mg., 0·0005 mole) and cupric bromide (288 mg., 0·001 mole) in ethanol (10 ml.,) was refluxed until a colour change of red → pale yellow was observed (ca. 5 hours). The solution was added to ice water and the resulting milky solution chloroform extracted. The chloroform extract was brine washed and dried over magnesium sulphate. Removal of solvent yielded a clear oil (47 mg.,). A positive Belstein test was obtained and t.l.c., indicated two overlapping spots which could not be separated. Indeed any attempts at separation e.g., chromatography or distillation resulted in either ring expansion or total destruction to yield tars.

(f) Phenyltrimethylammoniumtribromide

To the diketone (100 mg., 0·0005 mole) in dry tetrahydrofuran (3 ml.,) was added phenyltrimethyl-ammoniumtribromide (190 mg., 0·0005 mole) and the flask shaken for a few minutes until phenyltrimethylammonium-bromide comes out of solution. 5% Sodium carbonate was added to solution and ether extracted. The ethereal extract was brine washed, dried and removal of solvent yielded only the starting diketone.

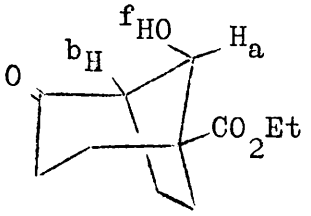
At this juncture all attempts to obtain a bromo-derivative were abandoned as supplementary evidence indicated that the diketone was too unstable even for the mildest reagents (see table 2)

1-Carbethoxy-bicyclo(3,2,1)-octan-4,8-diol(78)

To a stirred solution of keto-alcohol (71) (27 g., 0·12 mole) in ethanol (50 ml.,) was added sodium boro-hydride (7·56 g., 0·2 mole) and the solution left at room temperature overnight. This was then acidified using 6N HCl, diluted with water, and chloroform extracted. The chloroform extract was brine washed, dried and on removal of solvent yielded a colourless liquid b.p., 140°/0·5 min., (16·87 g., 73%) which on distillation crystallised to colourless plates m.p., 86-88°C., and recrystallised from CCl_4, but was too hygroscopic to analyse well. The infra-red showed absorption at 3628-3575 $cm.^{-1}$ (hydroxyl) 1732-1710 $cm.^{-1}$ (carbethoxy). The n.m.r., showed the C_8 hydroxyl to be totally syn (HC-OH, doublet 5·4 τ) while g.l.c., analysis gave two compounds of retention time 12·8 mins., (73·5%, equatorial isomer) and 8·6 mins., (26·5% axial) on 1% P.E.G.A., 150°, 40 ml.,/min.

1-Carbethoxy-8-hydroxybicyclo-(3,2,1)-octan-4-one (80)

The bicyclic diol (300 mgs.,) in acetone (10 ml.,) was oxidised at 0°C with standard Jones reagent. Methanol was added to destroy excess reagent and the green solution added to a large volume of water (250 ml.,) and ethyl acetate extracted. The ethyl acetate extract was brine washed, dried over magnesium sulphate and yielded a colourless oil b.p., 115-118°/0·05 mm., (257 mg., 86·5%). It picked up atmospheric moisture too rapidly to permit accurate analysis. The infra-red showed absorption 3623-3582 $cm.^{-1}$ (hydroxyl) 1730-1720 $cm.^{-1}$ (carbonyl of ester and ketone).



H_a 5·4 τ (1H, doublet)

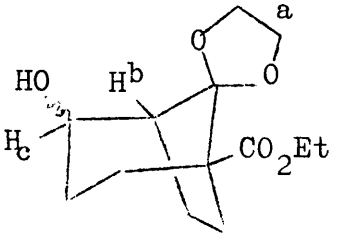
H_b 7·2 τ (1H, triplet)

H_c 6·8 τ (1H, broad singlet)

The ultra-violet showed absorption at $\lambda_{max.}$ 209 mμ and the compound had at retention time on g.l.c., of 40·25 mins., on 10% A.P.L.; 150° at 40 ml.,/min.

1-Carbethoxy-8-ethylenedioxy bicyclo-(3,2,1)-octan-4-ol (83)

The ketol (71), (20 g., 0·092 mole) was heated with ethylene glycol (58·48 g., 0·92 mole) and p-toluene sulphonic acid (17·92 g., 0·095 mole) at 80° for 2 hours, then added to an ice cold, stirred solution of potassium hydroxide (5·3 g., 0·28 mole) and stirring continued for 15 minutes. The solution was diluted to 750 ml., with water and chloroform extracted. The chloroform solution was brine washed and dried over magnesium sulphate. Removal of solvent yielded a brown oil which on distillation gave the ketal b.p., 142-4°/0·03 mm., (35 g., 70%). (Found, C, 60·47; H, 7·4. $C_{13}H_{20}O_5$ requires C, 60·92; H, 7·87%.) The infra-red showed hydroxyl absorption at 3620 and 3523 $cm.^{-1}$ and carbonyl at 1725 $cm.^{-1}$ (ester).



H_a 6·08 τ (4H, singlet)

H_b 8·0 τ (undefined 1H)

H_c 6·0 τ (undefined 1H)

g.l.c., retention times 22·4 mins., (80%, equatorial), 8·4 mins., (15%, axial) on 1% P.E.G.A., 150°C, 40 ml./min., 1500 V.

1-Carbethoxy-8-ethylenedioxybicyclo-(3,2,1)-octan-4-one (84)

(a) Sarett oxidation

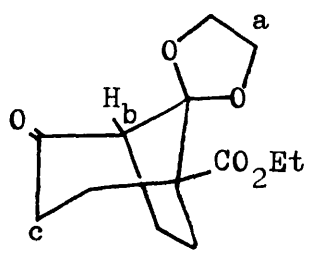
To the ketal (83) (500 mgs., 0·002 mole) in dry pyridine (2 ml.,) was added CrO_3 (200 mgs., 0·002 mole) in dry pyridine (5 ml.,) and the slurry left stirring at room temperature for 3 days. Methanol was added to destroy excess chromic and this was followed by ethyl acetate (10 ml.,) and water (5 ml.,). The salts were removed by filtration and the solution was extracted with ethyl acetate. The ethyl acetate extract was brine washed, dried and removal of solvent yielded a yellow oil which by g.l.c., on 1% P.E.G.A., at 150°C and 50 ml.,/min., showed only a 44·5% conversion to ketone (84).

(b) Snatzke oxidation

To the ketal (500 mgs., 0·002 mole) in D.M.F., (5 ml.,) was added CrO_3 (200 mgs., 0·002 mole). To this was added D.M.F., (10 ml.,) containing concentrated sulphuric acid (2 drops). The dark solution was stirred for five minutes then allowed to stand at room temperature for 3 days. Methanol was added and the solution diluted with water then extracted with ethyl acetate. The extract was brine washed, dried over magnesium sulphate and on removal of solvent yielded a pale brown oil. G.l.c., on 1% P.E.G.A., 150°C, 50 ml.,/min., indicated only 26% conversion to the required ketone (84).

(c) Jones oxidation

The ketal (4·9 g., 0·014 mole) in acetone (50 ml.,) was oxidised at 0°C, by standard Jones reagent. Methanol was added and the solution added to water (500 ml.,). The aqueous solution was extracted with ethyl acetate which was brine washed, and dried over magnesium sulphate. Evaporation yielded the ketone as a colourless liquid b.p., 132-3°/0·15 mm., (4·8 g., 97%). (Found, C, 61·22; H, 7·16. $C_{13}H_{18}O_5$ requires C, 61·41; H, 7·14%.) The infra-red was transparent to hydroxyl absorption but did show carbonyl at 1732 $cm.^{-1}$ (ester) and 1722 (shoulder) $cm.^{-1}$ (ketone). The ultra-violet showed end-absorption at $\lambda_{max.}$ 206 mμ.



H_a 6·0 τ (4H, singlet)

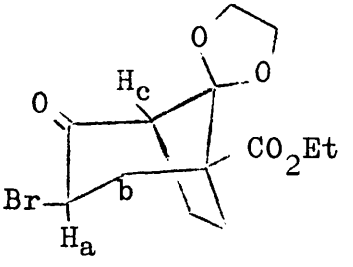
H_b 7·5 τ (1H, doublet, J = 5 cps.)

H_c 7·6 τ (2H, multiplet)

g.l.c., indicated at 91% conversion to the required ketone retention time 12·25 mins., with 9% of equatorial alcohol remaining (20 mins.,) on 1% P.E.G.A., 150°, 50 ml.,/min.

1-Carbethoxy-3-bromo-8-ethylenedioxybicyclo-(3,2,1)-octan-4-one (86a), (86b)

To a solution of the ketone (84) (4·8 g., 0·02 mole) in chloroform (25 ml.,) was added, dropwise, bromine (1·3 ml., 0·023 mole) until the brown colouration persisted. The mixture was washed with aqueous sodium bisulphite, brine and dried over magnesium sulphate. Removal of solvent yielded a brown oil (6·63 g.,) which by t.l.c., in 30% ethyl acetate/pet., ether and developed with $AgNO_3$/fluorescein, showed the present of two bromo compounds, one of which was isolated by addition of ether, m.p., 99-101°. (Found, C, 46·95; H, 5·39; Br, 21·05. $C_{13}H_{17}O_5Br$ requires C, 46·91; H, 5·10; Br, 21·05%.) The infra-red showed broad carbonyl absorption at 1730 $cm.^{-1}$ while ultra-violet had a $\lambda_{max.}$ 215 mμ



H_a 5·2 τ (1 proton, quartet, J_{sum} = 20 cps.)

H_b 7·1 τ (2 protons, doublet)

H_c 7·5 τ (1 proton, doublet)

The high J_{sum} value for the CH-Br signal along with the bathochromic shift in the infra-red and lack of shift in the ultra-violet indication that the Br is equatorial (86b).

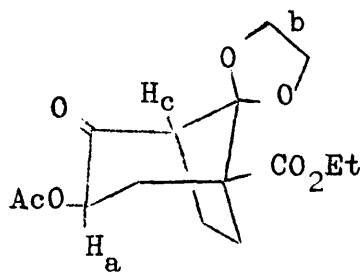
A pure sample of the axial isomer (86a) could not be obtained and so all future reactions were done on the mixture.

1-Carbethoxy-3-acetoxy-9-ethylenedioxy bicyclo-(3,2,1)-octan-4-one (89)

1-Carbethoxy-8-ethylenedioxy bicyclo-(3,2,1)-octan-4-one (4·8 g., 0·019 mole) in glacial acetic acid (50 ml.,) containing freshly distilled BF_3 etherate (4 ml.,) was refluxed with lead tetraacetate (8·86 g., 0·02 mole) under nitrogen until a negative starch iodide test was obtained (ca. 1 hour).

The light brown solution was poured onto ice water and ether extracted. The ethereal extract was brine washed and dried over magnesium sulphate. Removal of solvent yielded a pale brown oil which on distillation crystallised as colourless plates to give the acetate (89) m.p., 55-58° , b.p., 25° /0·07 mm. (Found, C, 58·15; H, 6·32. $C_{15}H_{20}O_7$ requires C, 57·69; H, 6·45%.) The infra-red spectrum showed absorption at 1754 $cm.^{-1}$ which

corresponds to a ketone bearing an α-acetoxy group in the equatorial conformation (90). Also present in the spectrum was a broad ester band at 1735 $cm.^{-1}$



H_a 4·5 τ (1 proton, quartet J_{sum} ca. 15 cps.)

H_b 5·95 τ (4 protons, singlet)

H_c 7·3 τ (1 proton, doublet)

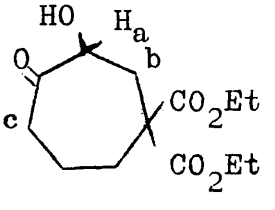
H_d 7·9 τ (3 protons, singlet)

The molecular weight was determined as 312 by mass spectroscopy (P = 312 m/e).

4,4-Dicarbethoxy-3-hydroxy-cycloheptan-4-one (93)

The acetoxy ketone (90) (11 g.,) was refluxed with dilute sulphuric acid (50 ml.,) and dioxan (100 ml.,) overnight. The solution was constant ether extracted for two days then the ethereal extract was dried over magnesium sulphate. Removal of solvent yielded a sweet smelling brown oil which was esterified with diazoethane

and distilled to yield the alcohol as a clear liquid b.p., 130°/1·0 mm., (6·6 g., 77%). Also present in very small (~5%) amounts was ethyl 5,8-dioxo-7-oxabicyclo(4,2,1)-nonane-1-carboxylate (92b) which could be removed by isolating the acid as its salt before esterification. The lactone was characterised spectroscopically but was not further investigated. (Found, C, 57·4; H, 7·78. $C_{13}H_{20}O_6$ requires C, 57·34; H, 8·87%.) The infra-red spectrum showed absorption at 3530 cm.$^{-1}$ (hydroxyl) and carbonyl absorption at 1735 cm.$^{-1}$ (ester) and 1720 cm.$^{-1}$ (cycloheptanone).



H_a 5·35 τ (1H, undefined)

H_b 6·7 τ (2H, quartet)

H_c 7·5 τ (2H, multiplet)

The ultra-violet spectrum showed no significant absorption.

1,1-Dicarbethoxycycloheptan-1,2-dione (95)

1,1-Dicarbethoxy-3-hydroxycycloheptan-4-one (93) (1 g.,) was oxidised in acetone at 0°C using 8N Jones reagent. The green solution was added to a large volume of water (500 cc.,) and ethyl acetate extracted. The extract was washed with water, brine and dried over magnesium sulphate and on removal of solvent yielded the dione as a pale yellow oil (b.p., 98-104°/0·65 mm., 958 mg., 95%). (Found, C, 57·85; H, 6·78. $C_{13}H_{18}O_6$ requires C, 57·74; H, 6·75%.) The infra-red spectrum showed no hydroxyl absorption but exhibited double carbonyl absorption at 1725 $cm.^{-1}$ (ester) and 1710 $cm.^{-1}$ (α-diketone). The ultra-violet spectrum exhibited absorption at $\lambda_{max.}^{EtOH}$ 237 mμ (log. ε 3·6), 265 mμ (log. ε 2·28) and had a bathochrome shift on addition of base to $\lambda_{max.}$ 310 mμ.

β-Carboxytropolone (46)

4-Carbethoxy-4-carboxycycloheptan-1,2-dione (94) (2 g., 0·0082 mole) in glacial acetic acid (8 ml.,) was stirred at room temperature and to this was added, dropwise, bromine (0·846 ml., 0·0164 mole) in acetic acid (10 ml.,). There was a copione evolution of HBr fumes and on completion of addition of bromine the pale yellow

solution was left aside at room temperature for 3 hours. The solution was warmed on a steam bath until evolution ceased by which time (ca. 1·5 hours) the solution has become dark in colour; 4H NaOH (10 ml.,) was added and the solution warmed for a further 30 minutes. The basic solution was cooled and hydrogenated in the presence of 10% Pd/C., until uptake of hydrogen had ceased. The catalyst was removed by filtration, the solution acidified with 6N HCl and constantly ether extracted for 2 days. The ethereal extract was brine washed and dried over magnesium sulphate. Removal of solvent <u>in vacuo</u> (temp., $\not>$40°C) yielded a pale brown solid which sublimed as pale yellow needles (150-160°/0·1 mm., 660 mg., m.p., 216-218°C lit value 217°C). The following tests were carried out:

ferric chloride - deep green colouration;

cupric acetate - green colouration;

copper sulphate - green colouration.

The ultra-violet spectrum compared well with the literature values, viz.,

$\lambda_{max.}$ 244 mμ	log ε 4·5	lit. $\lambda_{max.}$	244-6	log ε 4·49
$\lambda_{max.}$ 324 mμ	log ε 3·8	$\lambda_{max.}$	324-5	log ε 3·79
$\lambda_{max.}$ 370 mμ	log ε 3·75	$\lambda_{max.}$	367-9	log ε 3·77

The infra-red obtained was similar to that quoted in literature and the n.m.r., showed only a complex multiplet at 2·4-3 τ (4H) and a low field signal for carboxylic proton (0·1 τ).

1-Carbethoxy-8-ethylenedioxybicyclo-(3,2,1)-octan-3,4-dione (85).

(a) Selenium dioxide oxidation

1-Carbethoxy-8-ethylenedioxybicyclo-(3,2,1)-octan-4-one (84) (210 mg., 0·0008 mole) in either ethanol (10 ml.,) or acetic anhydride (10 ml.,), was refluxed overnight with freshly sublimed selenium dioxide (90 mg,, 0·0008 mole). Finely precipitated silver was added and the solution refluxed a further hour after which time the black precipitate was filtered off and the reddish filtrate added to water and ether extracted. The ethereal extract was brine washed, dried over magnesium sulphate and removal of solvent yielded a deep red oil which t.l.c., showed to be an inseparable mixture of compounds.

(b) Autoxidation

The ketone (200 mg., 0·0008 mole) was suspended in $Bu^{t}OH$ (10 ml.,) containing $Bu^{t}OK$ (1·28 g.,) and shaken under oxygen, in a standard hydrogenation apparatus for 1·5 hours.

The solution was then diluted with water (15 ml.,) and acidified with 6N HCl then extracted with chloroform. The chloroform extract was washed with bicarbonate, water and finally brine, then dried over magnegium sulphate. Removal of solvent yielded a dark oil which was shown to be a complex mixture with no constituent predominating.

(c) Nitrate ester rearrangement

In an attempt to make the nitrate ester (87) a solution of silver nitrate (200 mg., 0·0007 mole) in acetonitrile (2 ml.,) was added to 1-carbethoxy-3-bromo-8-ethylenedioxy-bicyclo-(3,2,1)-octan-4-one (100 mg., 0·0004 mole) in acetonitrile (5 ml.,) and left in the dark at room temperature for 3 days, after which time no perceptible change was seen on investigation of reaction mixture by t.l.c., or g.l.c.. Several attempts were made to prepare the nitrate ester but unfortunately none were successful.

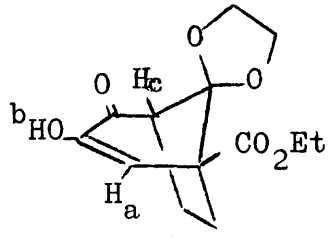
(d) Dimethylsulphoxide oxidation

The bromo-ketone (86) (100 mg., 0·0004 mole) was dissolved in dry redistilled dimethylsulphoxide (4 ml.,) and left at room temperature overnight. The solution was added to water and chloroform extracted. The chloroform extract was brine washed, dried and removal of solvent yielded a crystalline solid which was shown to be starting material.

(e) Base hydrolysis - oxidation

To a dilute solution of ethanolic potassium hydroxide (6 pellets KOH in 25 ml., ethanol) was added the acetoxy-ketone (1 g.,) and the solution stirred at room temperature overnight. The bulk of the ethanol was removed under vacuum and the resulting solid dissolved in water. The solution was then separated into acidic and neutral components the latter yielding only a trace of material (~10 mg.,) and so was not further investigated. The base soluble material recrystallised from ether as large plates (m.p., 96-7°C) and was shown to be the diosphenol of 1-carbethoxy-8-ethylenedioxybicyclo-(3,2,1)-octan-3,4-dione (85) (580 mg., 62·5%) having a positive ferric chloride test and characteristic u.v. (Found, C, 58·35; H, 6·17. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·01%.) The infra-red showed strong hydroxyl absorption at 3554 $cm.^{-1}$

and a shoulder at 3450 $cm.^{-1}$ (bonded and unbonded) there was also absorption at 3022 $cm.^{-1}$ (C = C overtone), 1737 (ester), 1686 (carbonyl) and 1660 $cm.^{-1}$(trisubstituted C = C). There was absorption in the ultra-violet at $\lambda_{max.}$ 266 mμ (ε, 8,285) which showed a shift on addition of base to $\lambda_{max.}$ 306 mμ (ε, 6,430).



H_a 3·64 τ (1H, singlet)

H_b 3·95 τ (1H, singlet in $CDCl_3$)

1·64 τ (1H, singlet in D.M.S.O.)

H_c 7·06 τ (1H, doublet)

The molecular weight was determined by mass spectroscopy as 268 (required 268).

1-Carbethoxybicyclo-(3,2,1)-octan-3-ene-8-one (4)

(a) Acetic or Propionic acid/H_2O on axial (5a) or equatorial (5b) tosylate

The tosylate (100 mg.,) in aqueous acetic acid (10:1, HAc: H_2O) was refluxed for times of 4-12 hours. On cooling the solution was washed with water (x3), carbonate then ether extracted. The ethereal extract was brine washed and dried over magnesium sulphate. Removal of solvent yielded a colourless solid which t.l.c., in acid solvent indicated to be one compound which on esterification with diazoethane yielded the starting tosylate. Thus hydrolysis of the carbethoxy group was occurring.

(b) $POCl_3$/pyridine on epimeric alcohols

The alcohols (100 mg.,) were dissolved in dry pyridine (5 ml.,) and to this was added phosphorous oxychloride (1 ml.,) in dry pyridine (2 ml.,) dropwise with stirring and left at room temperature overnight. The solution was poured onto ice water and ether extracted. The ethereal extract was washed with 6N HCl, brine and dried over magnesium sulphate. Removal of solvent yielded a yellow oil which was shown by t.l.c., to be starting material.

(c) $SOCl_2$/pyridine on epimeric alcohols

The alcohols (100 mg.,) in dry pyridine (5 ml.,) treated at 0°C with redistilled thionyl chloride (1 ml.,) and allowed to slowly reach room temperature over ½ hour. The pyridine was removed under vacuum to yield starting material.

(d) PCl_3/pyridine on epimeric alcohols

The alcohols (100 mgs.,) in dry pyridine (2 ml.,) were stirred at 0°C whilst PCl_3 (0·5 ml.,) in dry ether (2 ml.,) was added dropwise. Stirring was continued at room temperature for 3 hours. Then water added. The aqueous solution was ether extracted, washed with 6N HCl followed by bicarbonate. The ethereal solution yielded the chloride which was added to a solution of KOH (1 g.,) in ethanol (6 ml.,) and heated under reflux for 1 hour. This resulted in extensive charring and only a black tar was obtained.

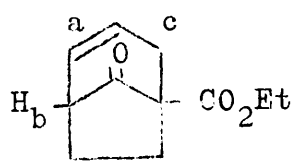
(e) Concentrated sulphuric acid

The alcohols (5 g.,) were stirred at 0°C and to this was added concentrated sulphuric acid (5 ml.,) and stirred at 0°C for 1 hour. The dark solution was added to ice water and ether extracted. The ethereal extract was brine washed and dried over magnesium sulphate then the

solvent was removed under vacuum to yield a dark brown oil which t.l.c., showed to be a complex mixture. Similar results were obtained on pyrolysis at 300°C with boric and oxalic acid.

(f) Polyphosphoric acid

The alcohols (2 gm.,) and polyphosphoric acid (40 gm.,) were stirred on a steam bath for 1 hour at ca. 85°C. then poured, with stirring into ice water and ether extracted. The ethereal extract was washed with water, bicarbonate and brine then dried over magnesium sulphate. Removal of solvent yielded a black oil which distilled as a clear liquid (4) b.p., 70-75°C/0·06 mm. (Found, C, 68·19; H, 7·94. $C_{11}H_{14}O_3$ requires C, 68·02; H, 7·27%.) Infra-red (CCl_4) showed no hydroxyl absorption but had peaks at 1763 $cm.^{-1}$ (bridge carbonyl) and 1735 $cm.^{-1}$ (ester) and in CS_2 showed a cis double bond at 680 $cm.^{-1}$.



H_a 4·3 τ (2H, complex multiplet)

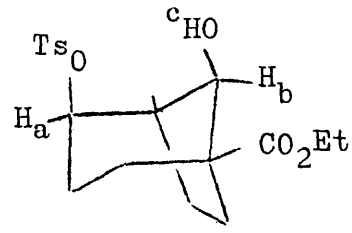
H_b 6·8 τ (1H, multiplet)

H_c 7·88 τ (2H, doublet).

The correct molecular weight of 194 was obtained by mass spectroscopic determination.

1-Ethoxycarbonyl-4-tosyloxybicyclo-(3,2,1)-octan-8-ol axial (8)

The axial isomer of 1-ethoxycarbonyl-4-tosyloxybicyclo-(3,2,1)-octan-8-one (1 g., 0·0028 mole) in dioxan (10 ml.,) was stirred at room temperature overnight with sodium borohydride (228 mg., 0·006 mole). The excess hydride was destroyed with 6N HCl and the acidic solution ether extracted. The ethereal extract was brine washed, dried and removal of solvent yielded a clear oil (850 mg.,) which t.l.c., indicated to contain two compounds in ratio of approximately 10:1. The most abundant being the least polar and consequently the syn-alcohol. The infra-red (CCl_4) of this compound showed intramolecular hydrogen bonding at 3594 $cm.^{-1}$ which did not alter on dilution and the infra-red also showed the presence of the ester and tosyl functions.



H_a 5·4 τ (multiplet)

H_b 5·57 τ (doublet)

H_c 7·05 τ (broad singlet)

H_d 8·15 τ (multiplet)

Attempts to eliminate the tosylate group were carried out on the isomeric mixture.

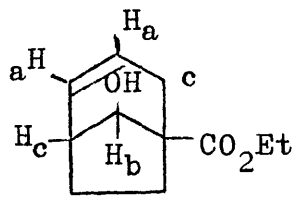
1-Carbethoxybicyclo-(3,2,1)-oct-2-en-8-ol (11)

(a) Sodium ethoxide

The axial tosylate (5) (100 mg., 0·0003 mole) in dry ethanol (2 ml.,) added dropwise to a solution of sodium ethoxide [from 50 mg., Na in 5 ml., ethanol] and stirred with reflux under nitrogen for 2 hours. The clear solution was poured onto ice water, neutralised with 6N HCl and ether extract. The ethereal extract was brine washed, dried and removal of solvent yielded a clear liquid which was identified as only starting material by t.l.c., and infra-red.

(b) Sodium tertiary butoxide

The axial tosylate (100 mg., 0·0003 mole) in dry tert., butanol (2 ml.,) was added dropwise to a solution sodium tert., butoxide [from 50 mg., sodium in 5 ml., of tert., butanol] and stirred with reflux under nitrogen for 2 hours during which time the solution became cloudy. The solution was poured onto ice water, neutralised with 6H HCl and ether extracted. The ethereal extract was brine washed, dried and removal of solvent yielded a cloudy oil which on esterification with diazoethane yielded a clear liquid (45 mg., b.p., 85°/0·05 mm.,). (Found, C, 66·74; H, 8·73. $C_{11}H_{16}O_3$ requires C, 67·32; H, 8·22%.) The infra-red spectrum showed absorption at 3625 cm.$^{-1}$ and 3570 cm.$^{-1}$ (hydroxyl), 3025 cm.$^{-1}$ (C = C asymmetric stretching vibration) 1725 cm.$^{-1}$ (ester) and a cis disubstituted C = C at 680 cm.$^{-1}$.



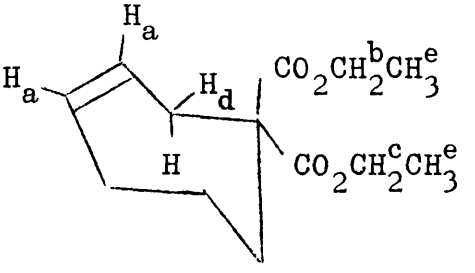
H_a 4·25 τ (2 protons, multiplet)

H_b 6·25 τ (1 proton, undefined)

H_c 7·95 τ (3 protons, undefined)

Action of HCl/HAc on 1-ethoxycarbonylbicyclo-(3,2,1)-oct-3-en-8-one (4)

The unsaturated bicycle (326 mg.,) in a mixture of glacial acetic acid (6 ml.,) and concentrated hydrochloric acid (2 ml.,) was refluxed overnight. The solution was poured onto ice water then ether extracted. The ethereal extract was washed with 6N NaOH and the basic solution was then acidified with 6N HCl and ether extracted. The ethereal solution was brine washed and dried. Removal of solvent yielded a brown solid which was esterified with diazoethane in ether and yielded a pale yellow liquid (138 mg., 39%) which g.l.c., analysis indicated to consist of 1,1-dicarbethoxycyclohept-3-ene (14) and 1,1-dicarbethoxycyclohept-4-ene (13) in ratio of 4:1 along with a trace of 1,5-dicarbethoxycyclohept-4-ene (7) the latter pairs of compounds being identified by comparison with authentic materials A sample of each was obtained by preparative t.l.c., and 1,1-dicarbethoxycyclohept-3-ene (14) identified. (Found, C, 64·80; H, 8·66. $C_{13}H_{20}O_4$ requires C, 64·98; H, 8·39%.) The infra-red showed carbonyl absorption at 1729 $cm.^{-1}$ and cis double bond (CS_2) at 685 $cm.^{-1}$. The ultra-violet spectrum gave end-absorption at $\lambda_{max.}$ 205 mμ (ε, 160).



H_a 4·0 τ (2H, multiplet)

H_b 5·83 τ (2H, quartet)

H_c 5·85 τ (2H, quartet)

H_d 6·85 τ (1H, undefined)

H_e 7·8 τ (6H, triplet)

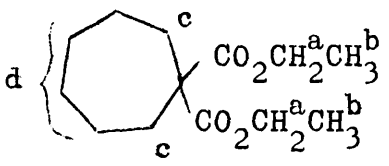
The molecular weight determined by mass spectroscopy.

Reduction of 1,1-dicarbethoxycyclohept-4-ene (13) and 1,5-dicarbethoxycyclohept-1-ene (7)

The unsaturated compound (1 g.,) in acetic acid (50 ml.,) was reduced under H_2 in presence of 5% Pd/C (100 mg.,) catalyst for 2 hours until uptake of hydrogen had ceased. The catalyst was filtered off and the acetic acid removed under vacuum to yield a brown oil (1 g.,) which t.l.c., showed to contain two spots and these were separated by preparative t.l.c., and shown to be the saturated esters viz., 1,1-dicarbethoxycycloheptane (15a) and 1,5-dicarbethoxycycloheptane (15b).

1,1-dicarbethoxycycloheptane (15a):-

(Found, C, 64·60; H, 9·34. $C_{13}H_{22}O_4$ requires, C, 64·44; H, 9·15%.) The infra-red showed only carbonyl absorption at 1729 $cm.^{-1}$ and no ultra-violet absorption was obtained.



The n.m.r., spectrum gave a pair of overlapping quartets centred at 5·8 τ and 5·83 τ ($4H_a$) and singlets at 7·9 τ ($4H_b$), 8·53 τ ($8H_d$) and triplet 8·75 τ ($6H_b$).

1,5-dicarbethoxycycloheptane (15b):-

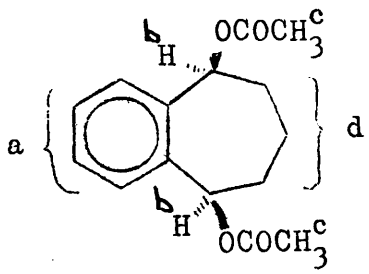
(Found, 64·55; H, 9·4. $C_{13}H_{20}O_4$ requires, C, 64·44; H, 9·15%.) The infra-red was transparent to carbon-carbon double bond absorption but showed ester carbonyl at 1732 $cm.^{-1}$. The n.m.r., showed a quartet at 5·85 τ (4H), a broad singlet at 7·6 τ (2H), multiplet at 8·2 τ (10H) and a triplet at 8·65 τ (6H).

Reduction of (14)

The unsaturated diester (14) in glacial acetic acid (50 ml.,) was reduced under hydrogen in the presence of 5% Pd/C catalyst for 2 hours until the uptake of hydrogen had ceased. Removal of solvent yielded a pale oil which distilled as a clear liquid (b.p., 80-85°/0·1 mm.,). This was shown to be identical, in every respect, with 1,1-dicarbethoxycycloheptane (15).

Benzocycloheptene-3,7-diol diacetate (24)

Benzocycloheptene-3,7-diol (18) (151 mg., 0·00084 mole) was dissolved in dry pyridine (3·5 ml.,) and to this was added analar acetic anhydride (1·5 ml., 0·002 mole) and the solution was left at room temperature in the dark for 3 days. After this time it was poured onto ice water and colourless crystals separated out. These were filtered off and recrystallised from aqueous ethanol as colourless plates (181 mg.,) m.p., 122-3°C. (Found, C, 68·66; H, 7·00. $C_{15}H_{18}O_4$ requires C, 68·69; H, 6·92%.) The infra-red spectrum was transparent in the hydroxyl region but showed strong carbonyl absorption at 1735 $cm.^{-1}$.



H_a 2·65 τ (4H, A_2B_2 spectrum)

H_b 4·00 τ (2H, doublet)

H_c 7·85 τ (6H, singlet)

H_d 8·10 τ (6H, singlet)