

**SYNTHETIC STUDIES IN NATURAL
PRODUCT CHEMISTRY.**

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Thesis submitted
by
ROBERT McCRINDLE
for the degree of
Doctor of Philosophy
of the
University of Glasgow.

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SUMMARY of the Thesis submitted by ROBERT McCRINDLE for the degree of Doctor of Philosophy of the University of Glasgow.

Synthetic Studies in Natural
Product Chemistry.

I. A stereospecific total synthesis of D-(-)-shikimic acid:-

The evidence which led to assignment of the structure and absolute stereochemistry of shikimic acid is reviewed.

The role of shikimic acid in biosynthesis is discussed, including its transformation into aromatic amino-acids, lignin and alkaloids, as is its formation from carbohydrates.

A synthetic approach to shikimic acid via the dehydro-acid corresponding to XXII was unsuccessful. The Diels-Alder adduct (XXXI) of trans-trans-1,4-diacetoxybutadiene and acrylic acid provided the starting point for a successful synthesis. Hydroxylation with osmium tetroxide, isopropylation and elimination of acetic acid led to (+)-shikimic acid which was resolved via the quinine methoxy-salt of the corresponding triacetate.

II. The catalytic hydrogenation of cyclic anhydrides:-

Catalytic hydrogenation of the adduct (XXIV) prepared in Part (I) led, in addition to the expected saturated anhydride (XXIX), to the lactol (XXXV), the lactone (XXXVIII) and the acid (XXXIX). A series of anhydrides, chosen to throw light on the influence of structure on the course of hydrogenation,

were subjected to catalytic reduction. The three possible products were not obtained in all cases. An attempt is made to rationalise the observed products in terms of the structures of the initial adducts and postulated intermediates.

III. Approaches to the total synthesis of diterpenoids:-

Published diterpene synthesis are briefly reviewed.

Two projected routes to dl-ambreinolide, which is capable of further transformation into the naturally occurring bicyclic diterpenes such as manool, sclareol, cativic acid, and labdanolic acid, are outlined.

The first route, based on the condensation of 2-methylcyclopentane-1,3-dione with ethyl vinyl ketone, failed when elaboration of the bicyclic enone (CXVI) was attempted.

A second approach envisaged the simultaneous formation of rings (A) and (B) by condensation of the vinyl ketone (CXLVI) with the cyclopentanedione. The preparation of this vinyl ketone is recorded.

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**SECTION I.- A Stereospecific Total Synthesis
of D-(-)-Shikimic Acid.**

I. The Constitution and Stereochemistry of Shikimic Acid.

Eykman (1), in 1885, extracted from the leaves and fruits of a Japanese plant, *Illicium religiosum* (Japanese "Shikimi-no-ki"), eugenol, safrole, protocatechuic acid and a white crystalline compound m.p. 180° , which was readily soluble in water and dilute alcohol but nearly insoluble in organic solvents. This new compound was found to be acidic and to be laevorotatory. The compound was named shikimic acid and gave an elemental analysis corresponding to the molecular formula $C_7H_{10}O_5$. Other sources of the new acid were sought (2) with little success, apart from the fruits of other members of the species of the *Illicium* genus. At the same time it was shown that distillation of the acid gave phenol, carbon dioxide and small quantities of protocatechuic acid. The similarity of shikimic acid to another natural product quinic acid (3) was indicated - the anhydride of the latter being isomeric with the former.

An attempt (4) was made to assign a structure to shikimic acid (1) in 1891 by Eykman. The oily esters of acetic, propionic and butyric acid were prepared and they were shown to be triesters by titration. The carboxylic acid, with its pronounced monobasic character, had thus three hydroxyl groups and all five of the oxygen atoms in the molecular formula were then accounted for. The presence of an olefinic bond was demonstrated by reduction of the acid to a dihydro-acid with sodium amalgam in a solution containing mineral acid. This dihydro-acid gave benzoic acid on prolonged boiling with concentrated acid and it had already been shown (2) that shikimic acid itself yielded protocatechuic acid on heating. It was thus established as a trihydroxy tetrahydrobenzoic acid.

Although later workers (5) studied shikimic acid it was forty years

before there was any further light thrown on its structure. About 1935, Fischer and Dangschat carried out a series of investigations which allowed the assignment of the constitution and stereochemistry to the entire molecule. The relative positions of the reactive groups were determined (6) by reactions analogous to those employed in the degradation of quinic acid (3b) which had been assigned the structure of a 1,3,4,5-tetrahydrohexahydrobenzoic acid (II). The methyl ester (III) was prepared with methanol/HCL or diazomethane and hydrogenated catalytically to the dihydro-ester (IV). This latter compound reacted with two mols. of periodic acid to give a dialdehyde (identified as methyl tricarballylate-1,5-dialdehyde (V) by formation of the bis-p-nitrophenylhydrazene). Bromine oxidation of the dialdehyde yielded the corresponding diacid which was converted to tricarballylic acid (VI) by saponification. It was then proposed that shikimic acid is an anhydroquinic acid since each of the aldehyde groups in the dialdehyde have an adjacent methylene group and hence the three hydroxyl groups occupy positions 3, 4, 5 of the cyclohexene carboxylic acid. This then left two possible positions for the olefinic bond namely 1,2 or 1,6. At the same time it was found that an acetone derivative could be formed readily, thus suggesting the presence of two cis vicinal hydroxyl groups.

Further work (7) by the same authors supported the above assignment of structure. Methyl shikimate (III) itself was carefully oxidised first by slow addition of periodic acid solution at room temperature and then with perpropionic acid to the expected unsaturated aconitic acid (VII).

The stereochemistry of dihydroshikimic acid was soon established (8). Like shikimic acid itself, the dihydro-acid was converted smoothly into an isopropylidene derivate. Furthermore, the dihydro-acid is converted by heat into a σ -lactone (VIII). It was then possible to assign to

dihydroshikimic acid a probable stereochemistry (IX). In shikimic acid the hydroxyl groups were expected to have the same stereochemistry and thus the only problem left was how to determine the position of the olefinic bond (the carboxyl group in shikimic acid must lie in the plane of the ring because of the presence of the olefinic bond in the 1, 2 or 1, 6 position).

Methyl isopropylidene-shikimate (X) was acetylated and hydroxylated with potassium permanganate (9). The product (XI) was saponified and oxidised with alkaline periodate to 2-keto-4, 5, 6-trihydroxy-5, 6-isopropylidene-7-aldehydeheptane-1-carboxylic acid (XII), which was analysed as the dinitrophenylhydrazone. The aldehyde-acid on treatment with hypobromite gave isopropylidene-trihydroxyadipic hemilactone (XIII). The methyl ester of the latter compound reacted with methyl magnesium iodide to give an acetonised pentahydric alcohol (XIV) which was indifferent to lead tetracetate and thus contained no neighbouring free hydroxyl groups. The methylene group in this pentahydric alcohol was thus shown to be in the β -position to the acetonised pair of hydroxyl groups and consequently the olefinic bond in shikimic acid links carbon atom 1 to carbon atom 6. At the same time Fischer and Dangschat showed that the above aldehyde-acid (XII), on oxidation with bromine, gave isopropyl-trihydroxyadipic acid hemialdehyde lactone (XV), which, on catalytic hydrogenation and acid treatment, gave a known compound, glucodesonic acid lactone (XVI). The formation of this last compound confirmed that the olefinic bond was in the 1,6 position and also that the hydroxyl groups at 3, 4, 5 have the same absolute configuration in shikimic acid as in D-glucose.

Further confirmation of the structures of shikimic and quinic acids came from their interconversions. In 1938 Fischer and Dangschat (10)

converted quinic acid to shikimic acid. When 3-acetyl-4, 5-methylenequinic amide (XVII) was heated with p-toluenesulphonyl chloride in pyridine 3-acetyl-4, 5-methyleneshikimic nitrile (XVIII) was formed.

In 1953 Grewe (11) accomplished the reverse interconversion. Shikimic acid dibromide (XIX) was converted to bromoquinic acid lactone (XX) on heating with silver carbonate. Hydrogenolysis of the bromo-substituent in this lactone afforded quinic acid lactone (XXI).

The final proof of the constitution and stereochemistry of the two naturally occurring acids came in 1954 with Grewe's synthesis of quinic acid (12), which is summarised diagrammatically on p. 8a.

II. The Role of Shikimic Acid in the Biosynthesis of Natural Products.

For a long time amino-acids were regarded as the building units in the biosynthesis of the alkaloids (13) but no definite evidence had been forthcoming as to the origin of the aromatic rings present in certain of these amino-acids until the discovery (14) in 1950 that shikimic acid is an intermediate in their formation. Biosynthesis of the carbon skeleton of these aromatic amino-acids is confined to the lower organisms, plant material being the main ultimate source of these acids for animals. This biosynthetic pathway has been elucidated by work with micro-organisms by use of two main techniques. Davis and his school have studied the requirements and excretion products of mutants of micro-organisms and several workers have used isotope techniques based on the introduction of labeled precursors into the biosynthetic pathway.

Davis used an ingenious method (15) for the production and isolation of mutants of micro-organisms from parent wild-type strains. He isolated mutants, deficient in the ability to produce essential substances, by a method based on the discovery that dilute penicillin will not kill dormant bacteria. These 'blocked' mutants can be used to determine the steps in a metabolic sequence. If compound X is necessary for the growth of an organism and this compound is produced by the sequence ---

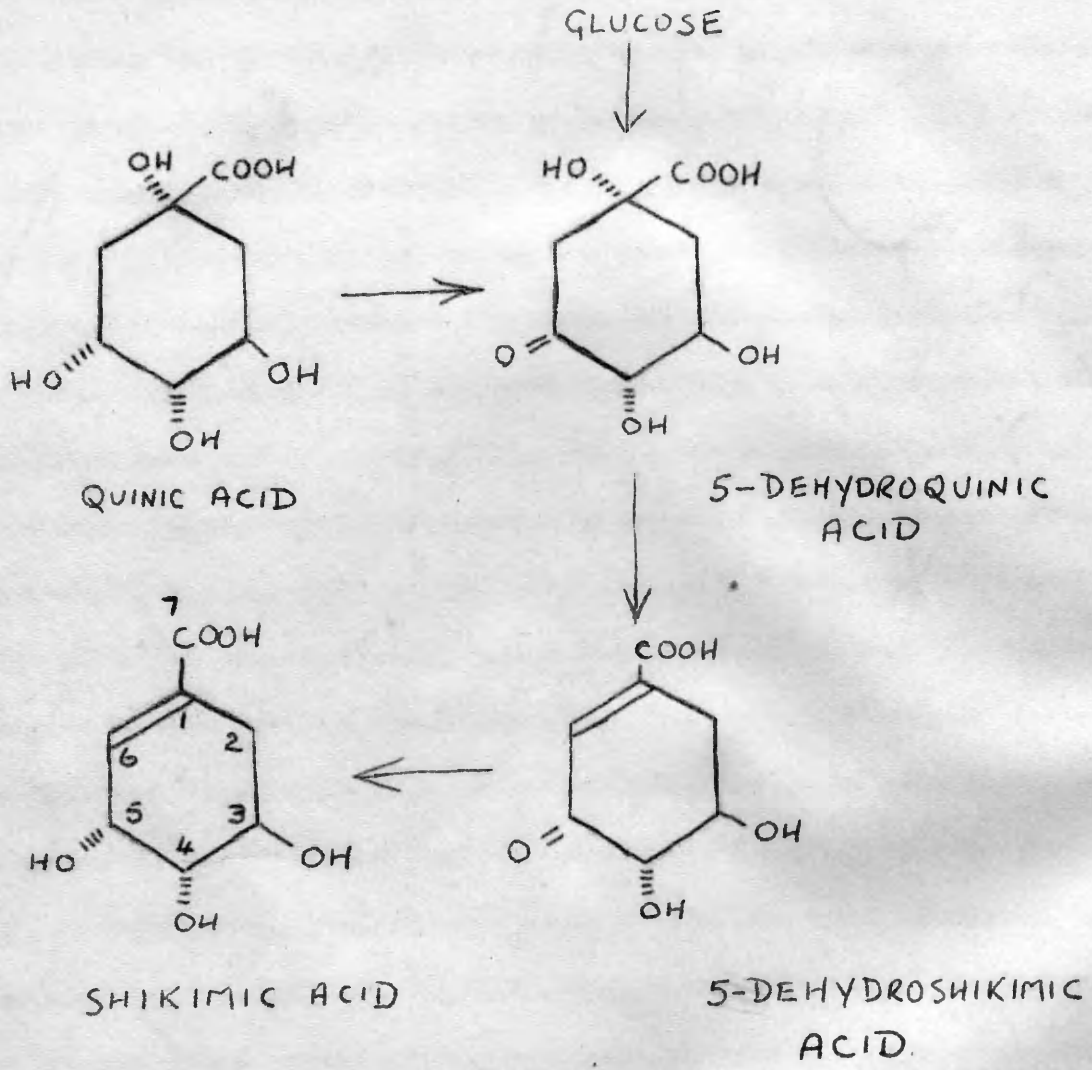


then for a mutant blocked in the conversion of B to C, growth will not take place unless C, D, or a subsequent compound in the metabolic path is supplied to the organism. Furthermore, compound B may accumulate in

the culture medium if A is supplied. The method is complicated owing to the existence of alternative pathways, incomplete blockage, and the lack of growth-factor activity displayed by some of the precursors.

The biosynthesis of the aromatic amino-acids.- Several mutants of *Escherichia coli* (15), and one of *Neurospora* (16), were isolated, that required at least four aromatic compounds for growth. These were tyrosine, phenylalanine, tryptophan, and p-aminobenzoic acid. Subsequently it was shown that a fifth aromatic compound, p-hydroxybenzoic acid (17), and even a sixth factor, as yet unidentified, are required by most of the bacterial strains. The common aromatic structure of the five compounds led to an empirical search for a possible common precursor that could replace them. After testing a large number of substances, it was found that shikimic acid, at that time a relatively obscure natural product, could relieve the growth inhibition (14, 17). Using other bacterial strains, blocked in a later reaction in the same sequence, shikimic acid was isolated from the culture filtrates (18). Furthermore, it was shown that in a growing *E. coli* culture, forming tyrosine freely from glucose, added labeled shikimic acid was the source of a substantial amount of the tyrosine formed.

Identification (19) of the immediate precursor of shikimic acid soon followed. Using the technique of syntrophism (the ability of one mutant to produce a substance necessary for the growth of another mutant), it was found that mutants blocked immediately before shikimic acid accumulated a precursor that was a growth factor for strains with still earlier blocks. Using the microbiological response to follow the course of purification, the precursor was isolated (19) and identified



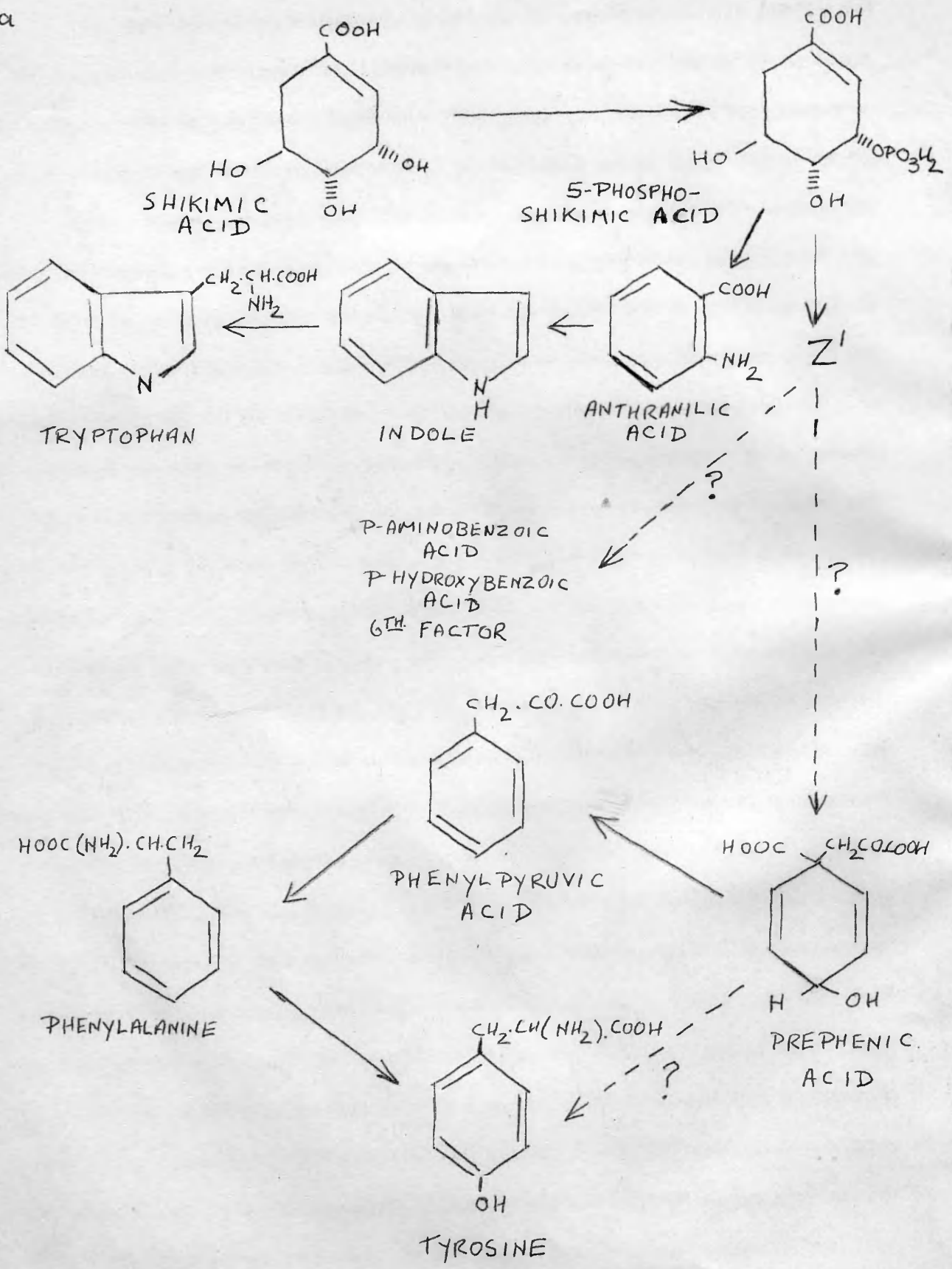
as 5-dehydroshikimic acid, a substance labile to heat and alkali.

The recognition of the penultimate precursor was a much slower process because of its lack of growth-factor activity for mutants blocked before it. Only after a secondary mutation was carried out on the organisms, and a large number of cells had been screened, was a rare secondary derivative obtained that responded well (20) to the new compound. This secondary mutant was then used for bioassay during purification of the compound which proved on isolation to be 5-dehydroquinic acid (21).

Quinic acid, a closely related compound with a wide distribution in the plant kingdom, had been suggested as a possible intermediate in aromatic biosynthesis, because of its growth-activity for a Neurospora mutant (22) and for certain Aerobacter secondary mutants (20). However, E.coli mutants that responded to 5-dehydroquinic acid neither responded to quinic acid nor accumulated it. For these reasons it was decided that quinic acid is not an intermediate in the biosynthetic path but rather is introduced into the path by an adventitious enzyme present in Aerobacter (20). Further support for this view arose from the discovery that this enzyme, quinic dehydrogenase, is present in extracts of wild-type Aerobacter but absent from those of several other organisms that can synthesis their aromatic amino acids. In contrast, these organisms, including mutants of E.coli, all yielded 5-dehydroquinase (23) and 5-dehydroshikimic reductase (24), the enzymes responsible for the inter-conversion of 5-dehydroquinic acid, 5-dehydroshikimic acid, and shikimic acid. If quinic acid were an equally obligatory intermediate, quinic dehydrogenase would be expected to have a similarly wide distribution.

The general direction of the biosynthetic pathway had now been

12a



proved but the elucidation of the steps immediately before and immediately after the portion of the path discussed above has presented many problems. Davis isolated (25) two derivatives of shikimic acid from mutants blocked in steps immediately before the amino acids. Both compounds give shikimic acid on treatment with mineral acid. One compound has been identified as 5-phosphoshikimic acid. The other compound, named Z_1 by Davis, is much more acid labile than 5-phosphoshikimic acid and may be a cyclic acetal of shikimic acid with pyruvic acid (26). Some mutants accumulate large amounts of Z_1 together with traces of shikimic acid and phosphoshikimic acid, while others accumulate the latter two compounds and no Z_1 (25). It was then accepted that Z_1 arises at a later stage in the biosynthetic chain than the other two compounds. It seems possible that both these compounds are members of the biosynthetic pathway and not side reaction products even although they are completely devoid of nutritional activity. Enzymatic work, similar to that used for quinic acid, should clear up this problem. Meanwhile, Davis had shown that E.coli mutants that require phenylalanine or phenylpyruvic acid for growth accumulate a non-aromatic compound. This compound, prephenic acid, which was isolated and its structure determined by Weiss and Gilvarg (27), has the unusual property of giving rise, in the presence of acid, to an active growth factor for the mutant that accumulated it (28). Indeed, unless precautions are taken to keep the culture medium alkaline, these mutants first accumulate prephenic acid and then the concentration of prephenic acid decreases while that of the active growth factor increases. This growth factor was identified as phenylalanine itself (28,29) and it was shown to be formed via

phenylpyruvic acid (28). Thus prephenic acid and phenylpyruvic acid follow Z_1 in the biosynthetic pathway and are the immediate precursors of phenylalanine in *E.coli*. The above workers postulated the condensation of a shikimate and a pyruvate unit in the biosynthesis of prephenic acid while it had been shown experimentally that this last compound affords phenylpyruvic acid readily (28) by dehydration and decarboxylation.

The final stages in the biosynthesis of tyrosine in any organism have not been completely clarified. Some micro-organisms (e.g. *Vibrio* (30) and *Pseudomonas* (31)) may resemble the higher organisms in being able to convert phenylalanine directly to tyrosine. In contrast, other micro-organisms (e.g. *Aerobacter aerogenes* (31), *Lactobacillus arabinosus* (32) and *Neurospora crassa* (33)) form tyrosine by a route not involving phenylalanine but no immediate precursors in this route appear to have been reported. However, Sprinson has shown, by isotopic studies with *E.coli*, that even although tyrosine is not formed from phenylalanine, the method of introduction of the tyrosine side chain is very similar to that postulated above for the introduction of the phenylalanine side chain. He (34) grew *E.coli* on a mixture of unlabeled glucose and labeled shikimic acid and subsequently isolated and degraded the tyrosine. The carboxyl of the shikimate unit had been eliminated and as carbon atoms 2 and 6 of the tyrosine ring corresponded to carbon atoms 2 and 6 of the shikimate unit, the side chain of tyrosine must have entered the position vacated by the shikimate carboxyl.

Recently, experiments (35, 36) with mutants of *E.coli*, requiring tryptophan for growth, have revealed the final stages in the biogenesis of this amino acid. By means of nutritional, metabolite accumulation and

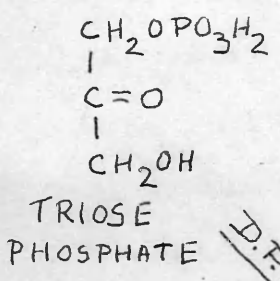
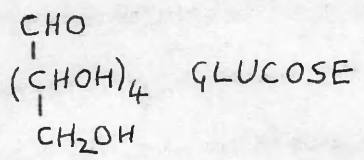
enzymatic studies, Yanofsky (35, 36) has shown that tryptophan is synthesised by the following sequence from anthranilic acid -

1. Anthranilic acid + 5-phosphoribosyl pyrophosphate $\rightarrow \rightarrow$ indole-3-glycerol phosphate.
2. Indole-3-glycerol phosphate \rightarrow indole + triose phosphate.
3. Indole + L-serine \rightarrow L-tryptophan.

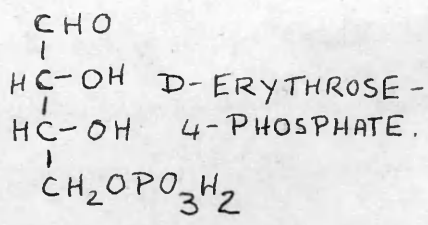
Srinivasan has now shown (37) that the first member in the above sequence, anthranilic acid, is biosynthesised from shikimic acid-5-phosphate and L-glutamine. He observed that shikimic acid itself, or the 'common precursor' Z_1 , could not replace the acid phosphate and that of all the amino donors which were tested, L-glutamine proved the most effective.

The biosynthetic pathways to the other three essential factors, p-aminobenzoic acid, p-hydroxybenzoic acid and the 'sixth factor' from shikimic acid do not appear to have been studied with any success. However, techniques which have been successful in proving the stages in the biosynthesis of 5-dehydroquinic acid from carbohydrates may meet with a similar success in the stages immediately after shikimic acid.

The biosynthesis of shikimic acid from carbohydrates.- Gilvarg and Bloch (38,39) grew the yeast *Saccharomyces cerevesiae* on a mixture of either labeled acetate and unlabeled glucose or unlabeled acetate and labeled glucose. In the presence of glucose they found no incorporation of labeled acetate into tyrosine or phenylalanine although there was extensive labeling of glutamic acid, aspartic acid, leucine and lysine. Glucose is therefore the aromatic precursor in yeasts. Sprinson and Shigeura obtained (40) a similar result by replacing the yeast by an *E.coli* mutant. However, advancement in the knowledge of the steps in the

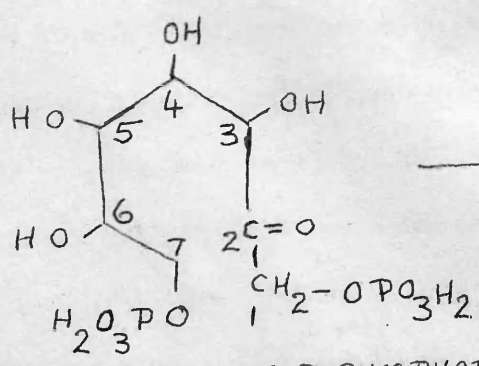
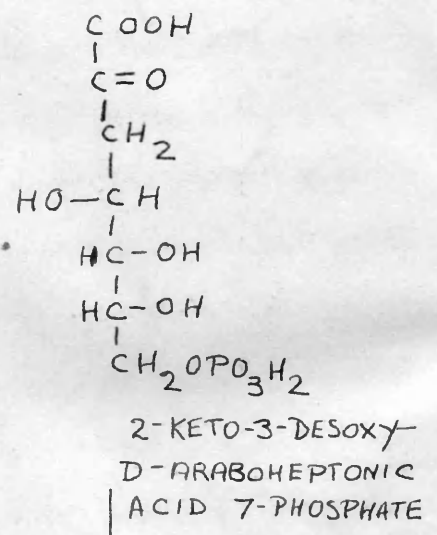
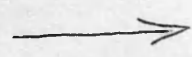
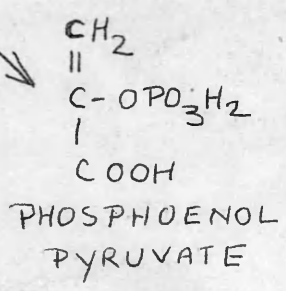


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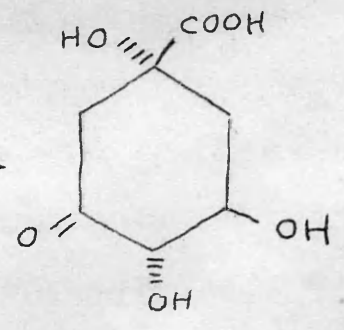


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SEDHEPTULOSE-1,7-DIPHOSPHATE



5-DEHYDROQUINIC ACID

biosynthesis of 5-dehydroquinic acid was delayed until the development of a new technique. Kalan and Srinivasan decided that, for detailed analysis of the pathway, it might be more fruitful to use a preparation that would carry out these early stages unhampered by the permeability barrier of the cell wall. Such a preparation became available through the finding that sonic extracts (i.e. the supernatant solution obtained by centrifugation of mutant cells which have been disrupted, by means of sonic oscillations, in a phosphate buffer) of a mutant blocked after 5-dehydroshikimic acid can form (41) this compound from various phosphorylated carbohydrates (e.g. glucose-6-phosphate, glucose-1-phosphate, fructose-6-phosphate, fructose-1, 6-diphosphate and ribose-5-phosphate). It was then considered that, since shikimic acid has a seven-carbon atom skeleton, a seven-carbon open chain compound might be an intermediate. Sedoheptulose-7-phosphate was tested and found to be incorporated (41).

It had been shown earlier, by experiments using variously labeled glucose and intact mutant cells, that shikimic acid was formed via a tetrose and a triose (42). Furthermore, two teams of workers (43,44) had obtained a heptose from a triose and a tetrose. Condensation of triose phosphate with tetrose phosphate occurred under the influence of aldolase to give sedoheptulose-1, 7-diphosphate. This last compound then seemed a likely intermediate in the biosynthetic pathway and it was found to be converted to shikimic acid more efficiently (45) than the monophosphate. The question then arose as to whether or not the formation of shikimic acid involved cyclisation of the complete heptose chain. Earlier work (42) had indicated that carbon atoms 3, 4, 5, 6 of shikimic acid arise from tetrose phosphate and the other three carbon atoms from triose phosphate. With bacterial extracts similar results are obtained (45), carbon atoms 1 to 3,

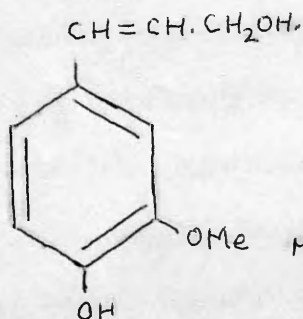
and 4 to 7 of sedoheptulose-1, 7-diphosphate giving rise to carbon atoms 7, 1, 2 and 3 to 6 of shikimic acid respectively. This, however, gives no indication of whether or not the intact chain is cyclised. That the chain does not cyclise without fracture was deduced as follows. In the only known reaction forming sedoheptulose-1, 7-diphosphate i.e. the condensation of triose phosphate with tetrose phosphate, carbon atoms 1,2,3 of the diphosphate are derived from carbon atoms 1,6;2,5;3,4 of glucose (44). Cyclisation of the intact chain of the diphosphate would then yield a shikimic acid molecule with the sequence, carbon atoms 1,5;2,5;3,4 of glucose in positions C,7;C,1;C,2, respectively. However, the reverse sequence was found (42) by the use of specifically labeled glucose and intact mutant cells. It therefore appears that, in these experiments, carbon atoms 1,2,3 of the diphosphate were detached and inverted before they were incorporated into the shikimate precursor. This interpretation has been supported by further work with these bacterial extracts. This work (46,47) showed that, for the formation of shikimic acid, the disphosphate cleaves to D-erythrose-4-phosphate and triose phosphate. The triose phosphate is then converted to phosphoenolpyruvate under the influence of diphosphopyridine nucleotide. Recombination of the two fragments gives 2-keto-3-desoxy-D-araboheptonic acid 7-phosphate which then cyclises to 5-dehydroquinic acid. The enzyme under whose influence the recombination takes place has been purified (48) and named 2-keto-3-desoxy-D-araboheptonic acid 7-phosphate synthetase. Only phosphoenolpyruvate and D-erythrose-4-phosphate were activated by the enzyme. Despite the excellent utilisation of sedoheptulose-1, 7-diphosphate in *E.coli*, it does not appear to be an obligatory intermediate because of the ease of

formation (42) of the triose and the tetrose phosphate from glucose by pathways not involving this diphosphate.

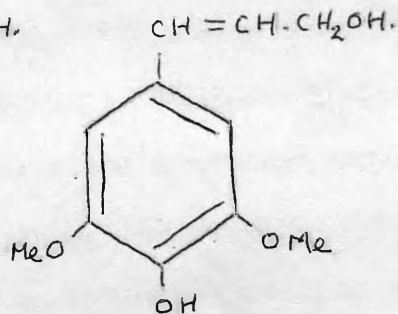
The synthetic path of the aromatic ring in amino-acid metabolism has thus been clearly defined for E.coli and a similar path seems (49) to exist in Neurospora. Shikimic acid may also be an intermediate in the formation of other natural products containing aromatic rings (at one time shikimic acid was regarded as a relatively rare compound but now its presence has been detected in at least forty-nine species of the higher plants (50)). The shikimate-prephenate pathway has been proposed for the biosynthesis of the tannins (51,52,53,54) and flavonoid plant constituents (51,55). Furthermore, Wenkert has shown that the shikimate-prephenate pathway can be utilised in the interpretation (52) of the absolute configuration of the yohimbe, the strychnos, and the cinchona alkaloids and that all alkaloids are derivable (53), at least formally, from formaldehyde, acetate, pyruvate, erthyrose, shikimate and prephenate units by routes which are analogous in every detail to well known enzymic reactions.

The biosynthesis of lignin.- These are postulated biosynthetic pathways but it has been proved experimentally that prephenate is responsible for the C₆-C₃ units of lignin. Early work on the chemistry of lignin led to theories that it is a polymer of some unit with a phenylpropane skeleton (56). Freudenberg adduced further evidence in support of this concept by his discovery (57) that coniferyl alcohol undergoes polymerisation to a lignin-like substance in the presence of oxidising enzymes from Arancaria. The structural similarity of coniferyl alcohol and phenylpyruvic acid then suggested the possibility of the existence of a similar biosynthetic

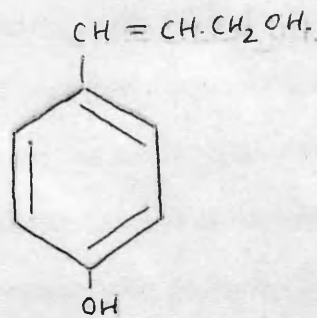
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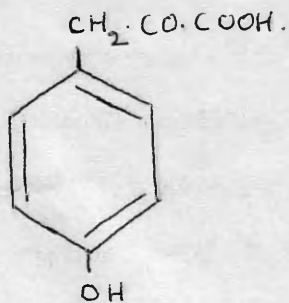
CONIFERYL ALCOHOL



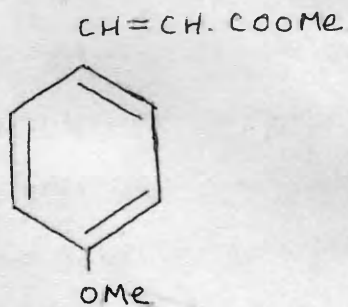
SINAPYL ALCOHOL



p-HYDROXYCINNAMYL ALCOHOL



p-HYDROXYPHENYL PYRUVIC
ACID



METHYL p-METHOXY-
CINNAMATE

pathway in higher plants to the route for amino-acid metabolism found for *E.coli*. Brown and Neish showed (58) that labeled shikimic acid and labeled phenylalanine (chosen because of its close structural and metabolic relationship to phenylpyruvic acid) act as direct precursors of about the same efficiency for the C_6-C_3 polymer lignin. Meanwhile, Eberhardt and Schubert had taken up researches which have shown that shikimate must be regarded as a direct precursor of the aromatic rings of lignin.

During the course of investigations (59) of the metabolism of *Lentinus lepideus* (Lelep), a mould producing the so called 'brown rot' in wood, phospho-shikimic acid and a number of keto-acids, including pyruvic acid and *p*-hydroxyphenylpyruvic, were detected in the culture medium. It had been shown earlier (60) that Lelep can be grown on media containing glucose, xylose, etc. as sole carbon sources and that, after several weeks of incubation, methyl *p*-methoxycinnamate appeared as a crystalline deposit in the culture medium. Eberhardt then proposed (59) that the results obtained from the study of the metabolism of Lelep suggested a relationship between the biogenesis of the above aromatic ester and the biogenesis of tyrosine in *E.coli*. Furthermore, since this aromatic ester is structurally related to Freudenberg's proposed (61) building stones for lignin (coniferyl alcohol, sinapyl alcohol and *p*-hydroxycinnamyl alcohol), he proposed a shikimate biosynthetic pathway for these alcohols as well. That this proposal was essentially correct was shown (62) by the incorporation of labeled shikimic into a living sugar cane plant (cf.ref.58). The lignin isolated was radioactive and the vanillin obtained by oxidative degradation of the lignin showed a distribution of C^{14} atoms comparable to the distribution of C^{14} atoms in the originally incorporated shikimic acid.

Later, carboxyl-labeled p-hydroxyphenylpyruvic acid was shown to be (63) a direct precursor for lignin and in this case oxidation of the lignin to vanillin (non-radioactive) and alkaline degradation to oxalic acid (radioactive) indicated the utilisation of the hydroxy-acid as a unit in the course of its conversion to lignin. It then seemed likely that lignin was formed from shikimate via the prephenate pathway. Finally, Schubert showed (64) that *Lelepl* incorporates labeled glucose into methyl p-methoxycinnamate and the labeling of the carbon skeleton of the products allows a similar biosynthetic pathway (via shikimic acid) to the pathway found in *E.coli*.

III. A Stereospecific Total Synthesis of D-(-)-Shikimic Acid.

The biological importance of shikimic acid led us to attempt a synthesis which would make possible the construction of a specifically labeled molecule. It was hoped at the same time to confirm the constitution and stereochemistry of shikimic acid which had been revealed by Fischer and Dangschat's degradative work (6,9).

In the first approach, the dehydroshikimic acid corresponding to (XXII) was envisaged as an intermediary stage although by analogy with the isomeric, naturally occurring dehydroshikimic acid (19)(XXIII), difficulties were expected due to its potential ease of aromatisation. This ease of aromatisation is not surprising since, when the carbonyl of (XXIII) is in the enolic form, the compound is a trihydroxydihydrobenzoic acid which would be expected to dehydrate very readily to a dihydroxybenzoic acid. Hydroxylation by osmium tetroxide of the known adduct (65)(XXIV) of 2-acetoxymethoxyfuran and maleic anhydride afforded the diol (XXV), whose probable stereochemistry is assigned on the basis of precedents (66). The adduct is assumed to be the endo-isomer and the osmium tetroxide should attack the less hindered face of the molecule i.e. the side away from the acetoxy group. Attempts at cis-hydroxylation using Woodward's procedure (67) or hydrogen peroxide in tert-butanol with osmium tetroxide as a catalyst (68) were unsuccessful. In the latter case dark oils were produced while, in the former case, the only crystalline solid isolated was maleic acid formed, presumably, by decomposition of the adduct (XXIV). Treatment of the diol (XXV) with acetone in the presence of anhydrous copper sulphate, or anhydrous hydrochloric acid, converted it smoothly into the crystalline isopropylidene derivative (XXVI). The next projected step was hydrolysis

of the anhydride (XXVI) to the dicarboxylic acid (XXVII), to be followed by selective decarboxylation and subsequent β -elimination of the tosyloxy-ester (XXVIII) to the dehydroshikimic acid derivative (XXII). Stereo-selective reduction of this ketone (XXII) would then give the acetone derivative of shikimic acid (I; R=R''=H, R'+R' = $>CMe_2$). In practice we were unable to define conditions for the base-induced cleavage of the hemiketal acetate (69)(XXVI) which did not also result in aromatisation, except by using excess sodium methoxide in dry methanol for deacetylation of the dimethyl ester of the anhydride (XXVI). The ultraviolet spectrum of the product from this reaction is consonant with that expected for the product of β -elimination of the hydroxyl group from the diester of the acid (XXVII). However, this unsaturated dimethyl ester requires saponification to allow mono-decarboxylation and such treatment yields aromatic products. It was thought that this difficulty might be circumvented by using the disodium salt, instead of the diester, for deacetylation but conditions necessary for reaction were found to lead to aromatic products. Attempts were then made to bring about acetolysis using Brederick's (76) technique i.e. treatment of a suspension or a solution of the acetoxy-compound in methanol with a large excess of ethereal diazomethane. A solution of the dimethyl ester, corresponding to the anhydride (XXVI), in methanol, when treated with excess ethereal diazomethane, afforded a new compound which did not contain the expected hydroxyl and carboxyl groups but which was, in fact, a dimethyl ester isomeric with starting material. A similar isomerisation has been reported by Bergmann and Sprinzak (77), the methylation of (-)-1-bromo-2-methyl-succinic acid with ethereal diazomethane yielding the corresponding

(\pm)-dimethyl ester. A suspension of the disodium salt corresponding to the anhydride (XXVI) in methanol-dimethylformamide did not react with excess ethereal diazomethane. The desired ring-opening was, in fact, accomplished in the course of model experiments with the related dihydro-adduct (XXIX). This anhydride, when heated with 10 mols. of aqueous potash (conditions which rapidly aromatised the isopropylidene derivative (XXVI)), yielded the keto-acid (XXX). The infrared spectrum of the product obtained by heating the toluene-*p*-sulphonate of the methyl ester of this keto-acid in either collidine or pyridine indicated the presence of unsaturation but attempts at purification of the product failed. However, when the toluene-*p*-sulphonyloxy-ester was heated in pyridine in the presence of 2,4-dinitrophenylhydrazine the 2,4-dinitrophenylhydrazone of the product of β -elimination (XXXa) of the keto-acid (XXX) was isolated.

The successful route to shikimic acid employed as starting material the Diels-Alder adduct (XXXI) of trans-trans-1,4-diacetoxybutadiene (70) and acrylic acid. The stereochemistry of this adduct may be predicted with certainty on the basis of the Alder rules (71) which state that 1, 4-substituted trans-trans-dienes react with acrylic acid to yield adducts in which the two diene substituents and the carboxyl group are on the same side of the newly formed cyclohexene ring (for a close stereochemical analogy see a synthesis of alleinositol (72)). The cis-diol (XXXII; R-H) was prepared from the unsaturated anhydride (XXXI) by treatment with osmium tetroxide and was assigned the stereochemistry shown, on the assumption of hydroxylation at the less hindered face of the molecule. With diazomethane the diol (XXXII; R-H) gave the crystalline methyl ester which was converted into its isopropylidene derivative (XXXIII; R-Me).

Base-promoted elimination of acetic acid could now be expected to occur in the desired manner, consequent upon activation provided by the methoxycarbonyl group (73). Additionally, of the two chair conformations, (XXXIIIa and b), which the ester can adopt, the former preferred on the basis of non-bonded interactions, also affords the opportunity for trans-diaxial elimination(74). Although the desired elimination could be effected partially by the conventional procedure (i.e. treatment with an aqueous or alcoholic solution of a strong base), protracted experimentation established that it could be made to occur in 80% yield by heating the diacetate (XXXIII; R-Me) with powdered magnesium oxide at 290°. When heated alone at 450°, this compound was recovered in practically quantitative yield. At temperatures above 500° the compound was aromatised. The racemate of the unsaturated monoacetate (I; R-Me, R' + R' = >CMe₂, R''=Ac) obtained in this way crystallised when seeded with the (-)-form; the ultraviolet and infrared film spectra of the two compounds were identical. Hydrolysis of the (±)-form afforded (±)-shikimic acid, m.p. 191-192°, whose ultra-violet and infrared (KCl disc) spectra were virtually identical with those of the natural acid. Resolution of this (±)-acid was attempted. Salts of natural shikimic acid with a number of alkaloids were prepared, and the most promising for effecting resolution seemed to be the salt with (+)-quinidine, which crystallised beautifully from methanol. However, on dissolving (±)-shikimic acid and (+)-quinidine in a minimum of warm methanol, shikimic acid crystallised from the solution instead. The salt of (±)-shikimic acid with a quaternary base, (-)-quinine methohydroxide, was next prepared in order to exclude the possibility of shikimic acid crystallising in preference to the salt. However, crystallisation of this salt from

various mixed solvents did not effect a resolution and it was suggested that this failure was a result of the solubility characteristics of the salt being completely governed by the three hydroxyl groups in shikimic acid. The triacetate (I, R=H, R'-R''=Ac) was then prepared and resolved via its quinine methoxyhydroxy-salt whence the salt of (-)-tri-O-acetylshikimic acid, identical (m.p., mixed m.p., $[\alpha]_D$, ultraviolet and infrared spectra) with material prepared from natural shikimic acid, was obtained. Hydrolysis afforded D-(-)-shikimic acid, identified by the same criteria with the naturally occurring material.

EXPERIMENTAL.

(Formulae flowsheets for this section are on Pages 47-51).

M.p.s were taken on the Kofler block; $[\alpha]_D$ are in MeOH.

Ultraviolet absorption spectra were determined for EtOH solutions with the Unicam S.P. 500 spectrophotometer, infrared spectra with the Perkin-Elmer 13 (by Dr. G. Eglinton and his colleagues) and the Infracord Spectrophotometer. Microanalyses were carried out by Mr. J.M.L. Cameron and his associates. Chromatographic alumina was prepared and standardised by Brockmann's method (75). Light petroleum refers to the fraction of b.p. 60-80° unless otherwise stated.

2,5-Diacetoxy-2,5-dihydrofuran was prepared by the method of Clausen-Kaas and Elming (65).

2-Acetoxyfuran.- The above dihydrofuran was pyrolysed in the presence of β -naphthalene sulphonic acid by a method based on that of Cava (65). It was found that increasing the proportion of solvent, dibutyl phthalate, limited the amount of black polymeric material formed and that the optimum temperature for pyrolysis was 125-140°.

The dihydrofuran (10g.) and β -naphthalenesulphonic acid (200mg.) were dissolved in dibutyl phthalate (35 ml.) and heated under vacuum (2mm.) on an oil bath. Pyrolysis commenced at about 100° (bath temperature) and on raising the bath temperature to 125° this pyrolysis became vigorous as evidenced by the brisk distillation of a straw-coloured liquid which was collected in a receiver, cooled to -80°. This liquid was redistilled at 2mm. up a six inch Vigreux column and the fraction of b.p. 30-38° was collected (5.5 g.).

3-Acetoxy-3,6-epoxycyclohex-4-ene-1,2-dicarboxylic

Anhydride (XXIV)(65).- When maleic anhydride (6 g.), in a minimum of dry ether, was added to 2-acetoxifuran (5.5 g.), the ether refluxed spontaneously and the adduct (XXIV) started to separate. The large colourless prisms (8 g.), m.p. 138-140°, after crystallisation from cold ethyl acetate-light petroleum had m.p. 146° (Clausen-Kaas and Elming (65) found m.p. 132-133°).

3-Acetoxy-3,6-epoxy-4,5-dihydrocyclohexane-1,2-dicarboxylic

Anhydride (XXV).- This adduct (XXIV)(950 mg.) in dry redistilled dioxan (20 ml.) was added to osmium tetroxide (1 g.) in dry ether (10 ml.) and kept at room temperature in the dark for 20 hrs. A greenish flocculent precipitate settled out of solution during this time. Excess of hydrogen sulphide was passed into the suspension, the osmium sulphide was filtered off after 4 hrs. and extracted with warm ethyl acetate (3 x 10 ml.). The filtrate and washings were combined and passed through a thin celite pad to remove traces of the black sulphide which had passed through the filter. Removal of solvent afforded the anhydride (XXV) as a wax (1.08 g.) which was pure enough for use in the next stage. This wax was crystallised, with difficulty, from dioxan-benzene as colourless needles m.p. 132-135° with the expected infrared spectrum i.e. absorption maxima at 3480, 3350 (hydroxyl); 1865, 1780 (anhydride) and 1720 cm.⁻¹(acetate). The compound, however, did not analyse well presumably because of solvation in the crystal but when the compound was crystallised from warm water a hydrate of the corresponding diacid was obtained, m.p. 142° (Found: C, 40.7; H, 4.35. C₁₀H₁₂O₉·H₂O requires C, 40.8; H, 4.8%).

Attempts to prepare this diol (XXV) by other techniques.-

(a) Silver acetate (7.35 g.) and powdered iodine (5.08 g.)⁽⁶⁷⁾ were added to the adduct (XXIV)(4.48 g.) in dry "AnalaR" acetic acid (130 ml.). The mixture was shaken vigorously for 45 min. and then water (0.75 ml.) in acetic acid (10 ml.) was added and the resultant mixture refluxed for 75 min. After addition of sodium chloride (30 g.), the cooled mixture was shaken for 30 mins. and the insoluble salts were collected. The filtrate, on evaporation, left an oil (2.3 g.) which gradually deposited a crystalline solid (1.2 g.) m.p. 150-151°. This compound was acidic and it reacted with an ethereal solution of diazomethane to give a compound containing nitrogen. The acid was shown to be identical (m.p., mixed m.p. and infrared spectra) with a specimen of authentic maleic acid and the nitrogenous compound was identified as the product of diazomethane addition to dimethyl maleate. The analytical specimen of this addition product (hexagonal plates from ethyl acetate-light petroleum) had m.p. 97-98° (Found: C, 45.3; H, 5.05; N, 15.2. $C_7H_{10}N_2O_4$ requires C, 45.15; H, 5.4; N, 15.05%). The infrared spectrum (nujol mull) of this ester had sharp maxima at 3330(NH), 1740 (ester), 1700 ($\alpha\beta$ -unsaturated ester) and 1540 cm^{-1} (C=N) thus indicating rearrangement of the first-formed adduct (XXXIVa) to 3,4-dimethoxy-carbonyl-4, 5-dihydropyrazole (XXXIVb).

(b) The adduct (XXIV)(3.2 g.) was dissolved in a solution (8.5 ml.) of hydrogen peroxide (6%) in tert-butanol (68). This solution was cooled to 0° and osmium tetroxide (10 mg.) in pure tert-butanol (2 ml.) was added. The brown mixture, after being kept in the refrigerator for 3 days, was poured into excess dilute ferrous sulphate solution and

allowed to stand at room temperature for 2 hrs. The solution was saturated with sodium chloride and constantly extracted with ethyl acetate for 12 hrs. Removal of solvent afforded a dark intractable oil which was methylated with diazomethane solution and then chromatographed on silica gel but no fraction could be made to crystallise.

3-Acetoxy-3, 6-epoxy-4, 5-isopropylidenedioxycyclohexane-1,2-dicarboxylic anhydride.- The above diol (XXV)(1.08 g.) dissolved in dry "AnalaR" acetone (40 ml.) was shaken with anhydrous copper sulphate (8 g.) for 80 hrs. The copper sulphate was filtered off and washed with dry acetone. The residue, from evaporation of the solvent from the combined washings and filtrate, was kept at $100^{\circ}/15$ mm. for 5 mins. to remove mesityl oxide formed by self-condensation of the acetone. The white product, when washed with cold benzene, left an insoluble fraction (350 mg.)(unchanged diol). Rapid filtration of the benzene extract through silica (20 g.) furnished on removal of solvent the isopropylidene derivative (XXVI)(755 mg.), needles (from benzene-light petroleum), m.p. $227-228^{\circ}$ (Found: C, 52.1; H, 4.55. $C_{13}H_{14}O_8$ requires C, 52.35; H, 4.75%) with an infrared spectrum showing no hydroxyl absorption ($3300-3500$ $cm.^{-1}$ region).

This isopropylidene derivative (XXVI) was also prepared by dissolving anhydrous hydrochloric acid gas in the acetone instead of adding solid anhydrous copper sulphate. However, yields of the acetone were in general poorer because of the high proportion of the benzene-insoluble fraction which contained large amounts of acidic material (infrared evidence). (This acidic material probably arose from hydration of the anhydride by water released on formation of the acetone derivative.)

This acetonide (XXVI), when dissolved in methanol and treated with an ethereal solution of diazomethane, gave the corresponding dimethyl ester in quantitative yield on removal of the solvents. This ester formed needles (from ethyl acetate-light petroleum) and was sublimed for analysis at 0.1 mm.; m.p. 206-207° (Found: C, 52.25; H, 5.55. $C_{15}H_{20}O_9$ requires C, 52.3; H, 5.85%).

Attempted Cleavage of the Hemiketal Acetate (XXVI) and its Derivatives.-

(a) The anhydride (10 mg.) in dry "AnalaB" pyridine (2 ml.) was kept at (i) 20° for 16 hrs., (ii) 100° for 2 hrs., and (iii) reflux for 5 hrs. Removal of solvent in each case afforded a quantitative recovery of starting material.

(b) The anhydride (45 mg.) was kept with triethylamine (2 ml.) and methanol (3 ml.) at 20° for 3 days. Removal of solvent and treatment with ethereal diazomethane afforded the dimethyl ester corresponding to starting material (identified by m.p. mixed m.p. and infrared spectrum).

(c) The dimethyl ester (prepared from 300 mg. of anhydride) was dissolved in methanol (5 ml.) and treated with a very large excess of ethereal diazomethane for 6 days at 20° in an attempt to bring about acetolysis (see Bredereck et al.(76)). Removal of solvents afforded an oil (345 mg.) which gradually deposited a mixture of colourless needles and cubes. The oil was washed away with light petroleum containing a few drops of ethyl acetate and the residue allowed to crystallise slowly from light petroleum, containing a little ethyl acetate, as colourless cubes. These cubes on recrystallising quickly from the same solvent afforded colourless needles, m.p. 127-128° (180 mg.). This compound did not show the infrared absorption expected for the product of acetolysis

i.e. absorption in the 3300-3500 cm.^{-1} region (hydroxyl) and analysis showed it to be an isomeric dimethyl ester (Found: C, 52.45; H, 5.6; OAc, 17.25; OMe, 12.85. $\text{C}_{15}\text{H}_{20}\text{O}_9$ requires C, 52.3; H, 5.85; OAc, 18.0; OMe, 12.5%). The infrared spectra of the two compounds were similar in the fingerprint region but differed markedly in the carbonyl region, the three ester groups in the first isomer giving (both in nujol mull and solution in carbon tetrachloride) one sharp peak at 1750 cm.^{-1} , while in the second isomer there were two sharp peaks at 1738 and 1760 cm.^{-1} (for both the above states). (For an analogy to this isomerisation see Bergmann and Sprinzak (77).)

(d) The anhydride (50 mg.) was dissolved in the minimum of hot water and treated with sodium methoxide (2 mol.) in methanol. The solvents were removed and the residue dried thoroughly by heating at 140°/mm. for 90 mins. This disodium salt was stirred in 1:1 methanol-dimethyl formamide (in which it was slightly soluble) with an excess of ethereal diazomethane for three days. An aqueous solution of the residue, obtained by removal of the solvents, was exactly neutralised with dilute aqueous hydrochloric acid, saturated with sodium chloride and constantly extracted with ethyl acetate for 12 hrs. The solid remaining on evaporation of ethyl acetate from the extract was dissolved in methanol and on treatment with an ethereal solution of diazomethane afforded the dimethyl ester (m.p., mixed m.p., and infrared spectrum) corresponding to starting material i.e. the first dimethyl ester.

(e) This dimethyl ester (60 mg.) was dissolved in dry methanol (20 ml.) containing sodium methoxide (4 mol.) and kept at 20° for 16 hrs. Exact neutralisation with 0.02 N-hydrochloric acid, saturation with sodium

chloride, and constant extraction with ethyl acetate afforded an oil (55 mg.) which contained a small amount of acidic material (inferred from the infrared spectrum). The oil was treated for a short time with diazomethane and then heated for 30 mins. with 2,4-dinitrophenylhydrazine (50 mg.) in pyridine (5 ml.) (78) in an attempt to prepare derivatives of any ketones formed by opening of the hemiketal bridge. The pyridine was removed at 0.1 mm., the residue dissolved in chloroform and placed on a bentonite-kieselguhr (4:1) column (2.5 g.). Elution with chloroform afforded a pale yellow oil (32 mg.). The infrared absorption maximum at 1740, with a shoulder at 1720 cm.^{-1} (diester and cyclohexanone respectively) and the ultraviolet spectrum (λ_{max} 214 μ ; ϵ 8000) of this oil did not disallow the assignment of structure (XXVIIa) to the compound. The oil was recovered unchanged from treatment with hydroxylamine hydrochloride and sodium acetate in hot aqueous methanol in an attempt to form an oxime. (The inability of this compound to form either an oxime or a phenylhydrazone was possibly owing to blocking by the methoxycarbonyl groups.) Later fractions from the chromatogram, eluted by chloroform-ethyl acetate, seemed to consist mainly of 2,4-dinitrophenylhydrazine, identified by its characteristic ultraviolet spectrum.

(f) The dried disodium salt (prepared as in (d) above from 95 mg. of anhydride), suspended in dry methanol (30 ml.), was refluxed with sodium methoxide (2 mol.) in methanol for 4 hrs. Enough water was added to the cooled mixture to take the salts into solution. Neutralisation with 0.02N-hydrochloric acid, evaporation of solvents at 15 mm., and extraction of the residue with ethyl acetate afforded a gum (63 mg.)

which had almost continuous absorption in the ultraviolet region between 220 and 290 m μ and an intense band near 1600 cm.⁻¹ in the infrared spectrum (aromatic-type absorption).

When a suspension of the sodium salt was stirred with the same proportion of sodium methoxide in methanol as above for 7 days at 20°, the product, isolated as above, had almost identical spectral properties.

Methylation of the products with diazomethane and chromatography over activated alumina (grade 5) afforded, in both cases, only fractions exhibiting marked aromatic absorption in the infrared region.

(g) The first dimethyl ester (98 mg.) in acetone (50 ml.) was treated with 0.02 N-hydrogen chloride in acetone (0.5 ml.) for 16 hrs. at 20°. Neutralisation with 0.01 N-sodium hydroxide, removal of solvents, and extraction with ethyl acetate gave back starting material quantitatively.

(h) The anhydride (90 mg.) was treated at 20° with sodium hydroxide (36 mg.; 3 mol.) in absolute ethanol (30 ml.). After 12 hrs. the solution was neutralised with dilute hydrochloric acid and the solvents removed under vacuum. Ethyl acetate extracted a gum from the residue which gave a blue-green colour with ferric chloride and in the ultraviolet showed λ_{max} 218, 260 and 295 m μ (compare protocatechuic acid).

(i) The diol (XXV) (85 mg.), dissolved in a 2% solution of potassium hydroxide in ethanol (5 ml.), was kept at 50° for 45 min. Removal of solvent, dissolution of the residue in saturated aqueous ammonium sulphate, and continuous extraction with ethyl acetate afforded an oil (33 mg.) with an aromatic-type ultraviolet spectrum λ_{max} 255-260 (ϵ 5000) and 290-292 m μ (ϵ 2200).

3-Acetoxy-3, 6-epoxycyclohexane-1, 2-dicarboxylic Anhydride (XXIX).-

The adduct (XXIV)(2.0g.) in "AnalaR" ethyl acetate (50 ml.) was shaken with Adams catalyst (50 mg.) in an atmosphere of hydrogen until one mol. had been absorbed (10 mins.). The catalyst was filtered off and the residue from evaporation of the solvent, on crystallisation from ethyl acetate-light petroleum, afforded the saturated anhydride (XXIX)(1.86 g.), as needles, m.p. 165-166° (Found: C, 52.8; H, 4.7. $C_{10}H_{10}O_6$ requires C, 53.1; H, 4.45%).

2-Hydroxy-5-oxocyclohexanecarboxylic Acid (XXX).- This saturated anhydride (XXIX)(1.25 g., 0.0055 mole) in aqueous potassium hydroxide (2.8 g., 0.05 mole, in 10 ml.) was heated on the steam-bath for 1 hr. The cooled solution was acidified, saturated with sodium chloride and constantly extracted with ethyl acetate for 16 hrs. The yellow oily residue remaining on removal of solvent from the dried extract afforded, on trituration with chloroform, the monocarboxylic acid (XXX)(510 mg.) which crystallised from chloroform as colourless hexagonal plates m.p. 140-141° (Found: C, 53.3; H, 6.2. $C_7H_{10}O_4$ requires C, 53.15; H, 6.35%).

This crystalline acid (340 mg.) was dissolved in methanol (5 ml.) and treated with excess ethereal diazomethane solution. Evaporation of the solvents left a colourless oil (360 mg.) which could not be made to crystallise. This gum was placed on chromatographic silica (1.5 g.) in benzene. Benzene-5% ether eluted material which still failed to crystallise but which exhibited infrared absorption (film) at 3400 (hydroxyl), 1730 (ester), and 1720 cm^{-1} (cyclohexanone) and which was therefore accepted as the methyl ester of the acid (XXX).

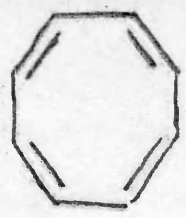
This ester (330 mg.) and recrystallised toluene-p-sulphonyl chloride (600 mg.) were dissolved in a minimum of dry "AnalaR" pyridine and allowed to stand at room temperature for two days. The white crystalline mass, which had separated, was filtered off and found to consist of a mixture of needles and prisms. The mixture was washed, first with ethyl acetate to remove pyridine and traces of reagent, and then with water which dissolved the needles (pyridine hydrochloride), leaving the large prisms of the toluene-p-sulphonate of the methyl ester. These crystals (460 mg.) when dried had m.p. 176-178° and were analytically pure (Found: C, 55.35; H, 5.5. $C_{15}H_{18}O_6S$ requires C, 55.2; H, 5.55%).

Attempts at Elimination of Toluene-p-sulphonic Acid from this

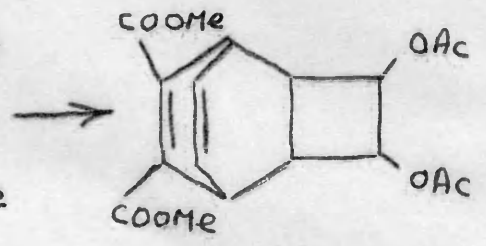
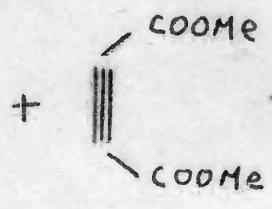
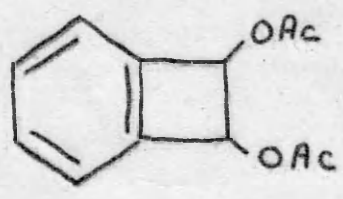
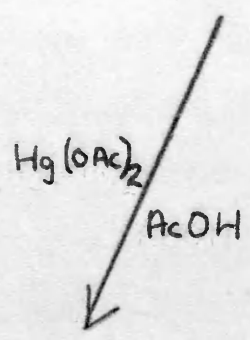
Methyl Ester.-

(a) The tosyloxy-ester (40 mg.) in collidine (1 ml.) was heated at 90° in a sealed tube for 6 hrs. On allowing the solution to cool, nicely crystalline starting material (10 mg.) separated (identified by m.p., mixed m.p., and infrared spectrum).

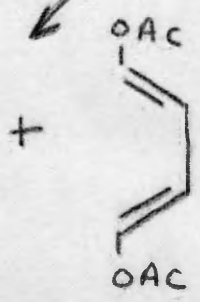
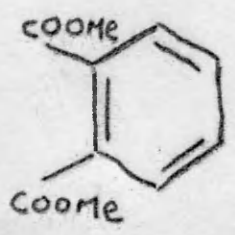
(b) The toluene-p-sulphonate (60 mg.) in collidine (1 ml.) was kept at 150° in a sealed tube for 3 hrs. The base was distilled out at 0.2 mm. and traces remaining were removed by azeotropic distillation with benzene (4 x 10 ml.). From the infrared spectrum of the resulting yellow oil (strong peaks at 1710, 1640, and a weaker peak at 1600 cm^{-1}) it was deduced that toluene-p-sulphonic acid had been eliminated from the starting material which exhibits infrared absorption maxima at 1740 (methyl ester), 1710 (cyclohexanone), and 1600 cm^{-1} (aromatic ring). However, chromatography of this oil (or its product of methylation with ethereal diazomethane) over activated alumina or chromatographic silica gave no crystallisable fraction or indeed any fraction which did not



CYCLO-OCTATETRAENE



PYROLYSIS



TRANS-TRANS-1,4-DIACETOXYBUTADIENE

contain large amounts of a toluene-*p*-sulphonate or other aromatic compound (identified by absorption in the infrared spectrum at 1600 cm.^{-1}).

(c) A similar product (infrared spectrum) to that obtained in (b) above resulted on heating the toluene-*p*-sulphonate (20 mg.) in pyridine (1 ml.) at 100° for 90 mins. and removing the base.

(d) The toluene-*p*-sulphonyloxy-ester (160 mg.) and 2, 4-dinitrophenylhydrazine (100 mg.) were heated together in pyridine (3 ml.) on the steam-bath for 90 mins. The pyridine was removed at 0.05 mm. and the residue in chloroform (15 ml.) filtered through bentonite-kieselguhr (4:1). The dinitrophenyl-hydrazone obtained by evaporation of the solvent (40 mg.) furnished orange needles (from ethanol), m.p. $166-168^\circ$ λ_{max} 360 m μ (ϵ 18,800) (Found; C, 50.05; H, 4.1; N, 16.45. $\text{C}_{14}\text{H}_{14}\text{O}_6\text{N}_4$ requires C, 50.3; H, 4.2; N, 16.75%) and was thus the dinitrophenylhydrazone of the desired elimination product.

trans-trans-1, 4-Diacetoxybutadiene was prepared from cyclo-octatetraene by the reaction sequence, represented graphically on page 35 α of Heppe (70a) as modified by Cope and his co-workers (70b).

2, 5-Diacetoxycyclohex-3-ene-carboxylic Acid (XXI).— This diene (2.0 g.), acrylic acid (freshly distilled; 2.0 g.), and quinol (100 mg.) were mixed and kept at $85-90^\circ$ under nitrogen for 3 hrs. Excess of unpolymerised acrylic acid was removed at 0.5 mm. and the residue extracted with warm benzene (2 x 30 ml.), in which the acrylic acid polymer did not dissolve. The extract was evaporated to about 10ml. and a little light petroleum added, whereupon colourless crystals and a small amount of a pale-brown oil separated from the solution. This contaminating oil was

washed away with cold ether and left the crystalline adduct (XXXI) (1.55 g.). The ether washings afforded a further crop (230 mg.). The analytical specimen crystallised as leaflets from benzene-light petroleum and had m.p. 141-143° (Found: C, 54.6; H, 5.85. $C_{11}H_{14}O_6$ requires C, 54.55; H, 5.85%).

2,5-Diacetoxy-3,4-dihydroxycyclohexanecarboxylic Acid (XXXII).

- The adduct (XXXI) (1.0 g.) in dry ether (50 ml.) was added to osmium tetroxide (1.0 g.) in dry ether (10 ml.) and dry pyridine (6 ml.). The mixture was kept at 20° in the dark for 5 days during which time a dark-brown mass was gradually precipitated. The osmate suspension was saturated with hydrogen sulphide and allowed to stand for 2 hrs.; filtration and removal of solvent left a dark oil (160 mg.) which, on trituration with benzene, afforded crystalline diol (30 mg.) and an oil which deposited crystalline starting material (110 mg.). The hard residual cake of solid was readily broken up on addition of methanol (15 ml.) and the suspension was then again saturated with hydrogen sulphide. Working up in the usual way yielded the major amount of diol (XXXII;R=H) (690 mg.) as a dark gum. Sublimation at 200-210° (bath-temperature)/0.8 mm. then afforded the pure diol (310 mg.) in prisms, m.p. 225-226° (Found: C, 48.0; H, 5.8. $C_{11}H_{16}O_8$ requires C, 47.8; H, 5.85%).

Methyl 2,5-Diacetoxy-3,4-dihydroxycyclohexanecarboxylate

(XXXII;R=Me).- The acid (XXXII;R=H), dissolved in methanol, was treated with redistilled ethereal diazomethane. Removal of solvents afforded the methyl ester (XXXII;R=Me), in quantitative yield, as a colourless solid which, on crystallisation from benzene-light petroleum, formed plates m.p. 161-163°. The analytical specimen was prepared by sublimation

at 160°/0.8 mm. (Found: C, 49.75; H, 6.1. $C_{11}H_{16}O_8$ requires C, 49.65; H, 6.25%).

Methyl 2,5-diacetoxy-3,4-isopropylidenedioxycyclohexane-dicarboxylate (XXXIII;R=Me).— Dry hydrogen chloride gas was bubbled vigorously for 15 sec. through a solution of the methylester (XXXII;R=Me) (480 mg.) in dry acetone (50 ml.). The solution, after standing at room temperature for 16 hrs., was shaken with excess of solid sodium hydrogen carbonate for 10 mins. The solid was filtered off and the acetone evaporated. The oily residue (490 mg.) was dissolved in dry benzene and placed on a column of activated alumina (15 g.; grade V). Elution with benzene afforded the acetone derivative (XXXIII;R=Me) (280 mg.) and, by elution with ethyl acetate, unchanged diol (170 mg.). The product, when sublimed at 130°/0.1 mm. for analysis, formed prisms, m.p. 146–147° (Found: C, 54.65; H, 6.6. $C_{15}H_{22}O_8$ requires C, 54.55; H, 6.7%).

When the methyl ester (XXXII;R=Me) (480 mg.) in dry acetone (50 ml.) was shaken with anhydrous copper sulphate for 5 days and the solid and solvent removed the residue was found to be unchanged diol (480 mg.).

This isopropylidene derivative (XXXIII;R=Me) was more conveniently and profitably prepared from the adduct (XXXI) as follows:— The adduct (900 mg.) was kept with osmium tetroxide (1.0 g.) in dry ether (20 ml.) for 3 days. The osmate separated as a hard brown cake which was easily crushed after the addition of methanol (30 ml.). The resulting suspension was saturated with hydrogen sulphide and allowed to stand for 2 hrs. Removal of solid and solvent left the diol (1.1 g.) as a dark oil. This oil in methanol (20 ml.) was treated with an excess of an ethereal diazomethane solution. The residue from evaporation of the

solvents was dissolved in acetone (100 ml.) and dry hydrogen chloride gas passed into the solution for 15 secs. After 16 hrs. the solution was shaken with excess of solid sodium hydrogen carbonate for 10 mins. Removal of solid and solvent, and sublimation of the residue at 130-140°/0.8 mm. afforded the acetone derivative (XXXII; R=Me) (740 mg., 59%) with m.p. 145-147°.

Isopropylidene Derivative (I; R=Me, R'+R'=>CMe₂, R''=Ac) of (+)-Methyl Shikimate Acetate.- (a) The diacetate (XXXIII; R=Me) (100 mg.) was mixed with magnesium oxide (500 mg.) and kept at 290°/760 mm. for 2 mins. The volatile material was then distilled off at 10 mm., the distillate melted and allowed to run back into the magnesium oxide and the sequence repeated twice.

The colourless oil (65 mg.) so obtained crystallised when seeded with the ester (I; R=Me, R'+R'=>CMe₂, R''=Ac) prepared from naturally derived shikimic acid (m.p. 75-76°) and had m.p. 68-72° (mixed m.p. 66-70°). The ultraviolet spectrum (λ_{max} 211-212 m μ ; ϵ 9000) and infrared spectrum (film) were virtually identical with those of the natural material and proved the absence of aromatic products (Found: C, 58.1; H, 6.65. Calc. for C₁₃H₁₈O₆: C, 57.75; H, 6.7%).

(b) 10 mg. portions of the diacetate (XXXIII; R=Me) were passed through 4 ft. of pyrex tubing which was being heated in an electric furnace. The following conditions were tested:- (i) 150° at 0.1, 15, or 760 mm.; (ii) 300 and 450° at 0.1 or 760 mm. in nitrogen; (iii) 250° at 15 mm. (the pyrex tubing packed with "Staybrite" gauze). In each case the diacetate was recovered unchanged.

(c) The diacetate sublimed unchanged when intimately mixed with five times its weight of powdered soft glass and kept at $300^{\circ}/0.1$ mm. in nitrogen.

(d) Heating at $560^{\circ}/0.1$ mm. in nitrogen afforded a colourless oil which was judged by its infrared spectrum to be aromatic (appearance of strong absorption near 1600 cm.^{-1}).

(e) Heated at $290^{\circ}/15$ mm., mixed with five times its weight of magnesium oxide and suspended in silicone fluid, the diacetate (XXXIII; R-Me) afforded the desired product (20-30%) which could be separated from contaminating silicone fluid only with difficulty.

Base-induced Elimination of Acetic Acid from the Diacetate

(XXXII; R-Me).— The diacetate (50 mg.) was kept in dry methanol (10 ml.) containing dissolved sodium (40 mg.) at 20° for 3 days. Distilled water (3 ml.) was then added and after 6 hrs. the solution was passed through an ion-exchange column of Amberlite I.R.-120 (H). The resulting oil, which failed to crystallise, was treated with ethereal diazomethane solution. The residue, on removal of solvent, was acetylated with acetic anhydride/pyridine. The oily product (78 mg.) showed unsaturation in the ultraviolet (λ_{max} 210-214 m μ ; ϵ 3200-3300) and in the infrared (1650 cm.^{-1}). It was absorbed on activated alumina (3g.; grade V). Benzene eluted a fraction (22 mg.), with enhanced ultraviolet absorption (λ_{max} 210-214 m μ ; ϵ 5400), which was treated with 1:4 aqueous-methanolic 0.02N-potassium hydroxide for 16 hrs. Filtration through an acidic ion-exchange resin (Amberlite I.R.-120 (H); 10 g.) and evaporation of the solvents at 15 mm. afforded an oil (9 mg.) which on trituration with methanol formed crystalline (+)-shikimic acid identical (infrared spectrum) with material obtained as below.

(⁺)-Shikimic Acid.- The isopropylidenedioxy-ester (90 mg.) obtained as in (a) above was kept in 1:4 aqueous acetic acid (5 ml.) for 26 hrs., the solvents were removed at 0.1 mm., and the residue, dissolved in methanol (2 ml.) was treated with 1:4 aqueous-methanolic 0.02N-potassium hydroxide for 16 hrs. at 20°. The solution was then filtered through Amberlite I.R.-120 (H)(10 g.) and the solvents evaporated at 15 mm. The resulting oil (40 mg.) on trituration with methanol-ethyl acetate afforded colourless needles m.p. 191-192°; the mixed m.p. with natural (-)-shikimic acid of m.p. 190-191° was 188-191°. The synthetic material had $\lambda_{\text{max.}}$ 212 m μ (ϵ 8200), while (-)-shikimic acid has $\lambda_{\text{max.}}$ 213 m μ (ϵ 8900). The infrared spectrum (KCl disc or nujol mull) showed minor differences in the fingerprint region from that of (-)-shikimic acid and the hydroxyl absorption did not give rise to the sharply defined peaks found in the infrared spectrum of the natural acid at 3200, 3370 and 3450 cm.⁻¹, instead, there was one broad maximum at 3250 cm.⁻¹.

Attempted Resolution of (⁺)-Shikimic Acid.-

(a) (⁺)-Shikimic acid (20 mg.) and (+)-quinidine (14 mg.; 0.8 equiv.) were dissolved in the minimum of warm methanol. The solution was seeded with (+)-quinidine (-)-shikimate (m.p. 215-218°; $[\alpha]_D$ 133°; c 0.25) and allowed to stand at room temperature for 50 hrs. Crystals (3.7 mg.; m.p. 194-195°) separated which were not the salt (mixed m.p. 170-200°) but were shikimic acid infrared spectrum (KCl disc) virtually identical with that of (⁺)-shikimic acid resolved to the extent of about 20% ($[\alpha]_D$ -50°; c 0.25). $[\alpha]_D$ was not improved by further crystallisation.

(b) (-)-Quinine methochloride (1 g.) and silver oxide (1 g.) in distilled water (5 ml.) were stirred at 0° for 15 mins.(78). The mixture

was then shaken at room temperature for 3 hrs. and the solid collected. The solution was diluted to 10 ml. with distilled water and 1 ml. fractions standardised with 0.1N-sulphuric acid.

(-)-Shikimic acid (23 mg.) in water (1 ml.) was treated with the standard (-)-quinine methohydroxide solution (2 ml.; 1.01 mol.) and the water removed at 0.1 mm. The residue on crystallisation 3 times from methanol-ethyl acetate afforded tight balls of fine needles (38 mg.) m.p. 200-202°, $[\alpha]_D -211^\circ$ (c 0.37).

When (+)-shikimic acid (23 mg.) was treated similarly, tight balls of stouter needles (32 mg.) were obtained after three crystallisations, m.p. 205-206°, mixed m.p. 195-202°, and $[\alpha]_D -144^\circ$ (c. 0.68). Further crystallisation or change of solvent did not improve this.

Resolution of (+)-Tri-O-acetylshikimic Acid.- (+)-Shikimic Acid (36 mg.) was kept with acetic anhydride (1 ml.) and pyridine (1 ml.) for 16 hrs. Removal of solvent afforded an oil (86 mg.) whose infrared spectrum (film) was essentially identical with that of naturally derived material. To this oil (86 mg.) in aqueous methanol (5 ml.) was added one equivalent of (-)-quinine methohydroxide in water (see above). Removal of solvent left a colourless froth (164 mg.) which was dissolved in methanol (3-4 drops), ethyl acetate (5 ml.), and ether (3-4 ml.); an amorphous fraction (33 mg.) (A) separated. Addition of ether (3-4 ml.) to the filtrate gave crystals (38 mg.) (B), forming long plates, m.p. 189-191° $[\alpha]_D -189^\circ$ (c 0.35), from methanol-ethyl acetate; after two further crystallisations, these had m.p. 189-191°, $[\alpha]_D -200^\circ$ (Found: C, 62.45; H, 6.6; N, 4.65. $C_{34}H_{42}O_{10}N_2CH_3OH$ requires C, 62.75; H, 6.85; N, 4.2%); the m.p. was not depressed on admixture with naturally derived material. The latter,

after three crystallisations, had m.p. 190-192°, $[\alpha]_D -203^\circ$ (c 0.38).

The mother-liquors from (B) afforded a further quantity (36 mg.) of semi-crystalline solid (C) and a gum (48 mg.) (D). Fractions (A) and (D), after passage through Amberlite I.R.-120 (H), furnished essentially tri-O-acetylshikimic acid (infrared spectrum) of $[\alpha]_D$ respectively -60° and $+45^\circ$.

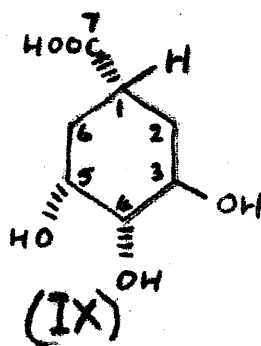
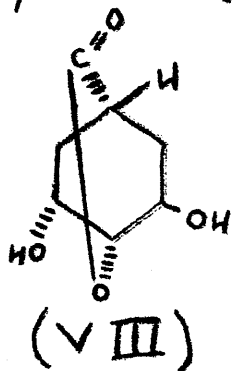
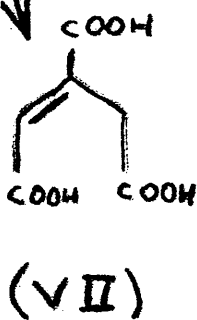
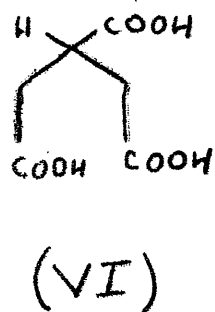
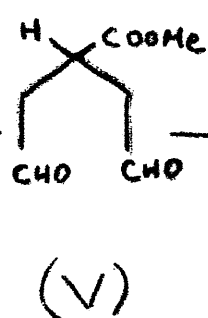
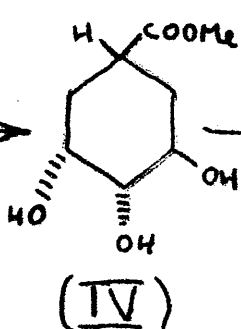
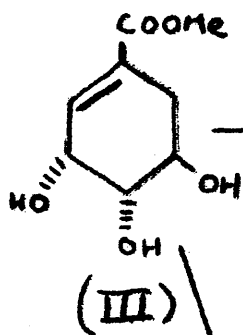
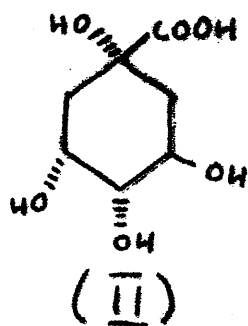
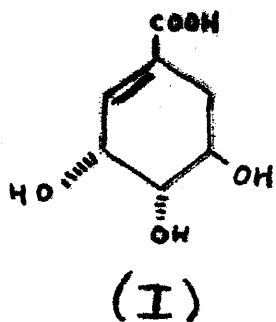
(-)-Shikimic Acid. The above salt (B) (40 mg., $[\alpha]_D -200^\circ$) was kept with potassium hydroxide (220 mg.) in 1:4 aqueous methanol (10 ml.) for 16 hrs. and the solution filtered through Amberlite I.R.-120(H). Removal of solvent from the filtrate and crystallisation from methanol-ethyl acetate furnished substantially pure (-)-shikimic acid (8 mg.), m.p. 190-191°, $[\alpha]_D -161^\circ$ (c 0.57). The mixed m.p. with natural shikimic acid (m.p. 190-191°, $[\alpha]_D -157$ (c 0.94)) was 190-191°. The infrared spectra (KCl discs) of the two substances were superposable.

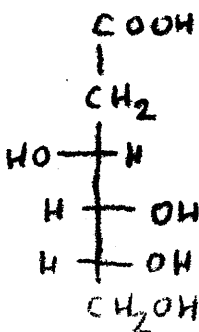
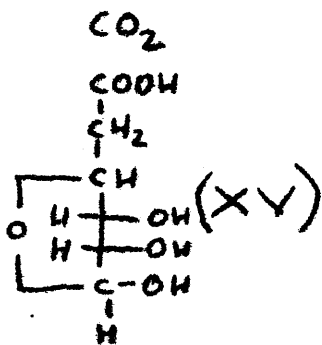
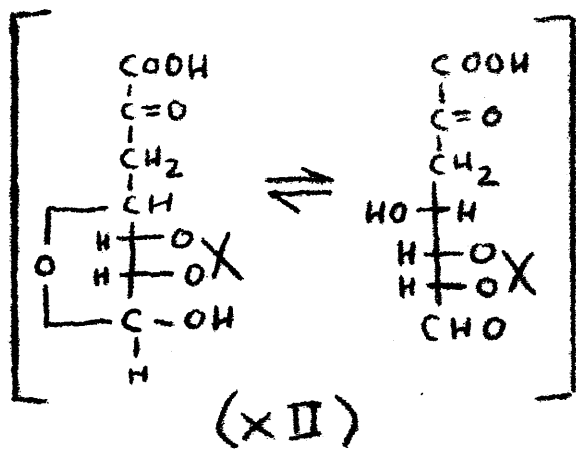
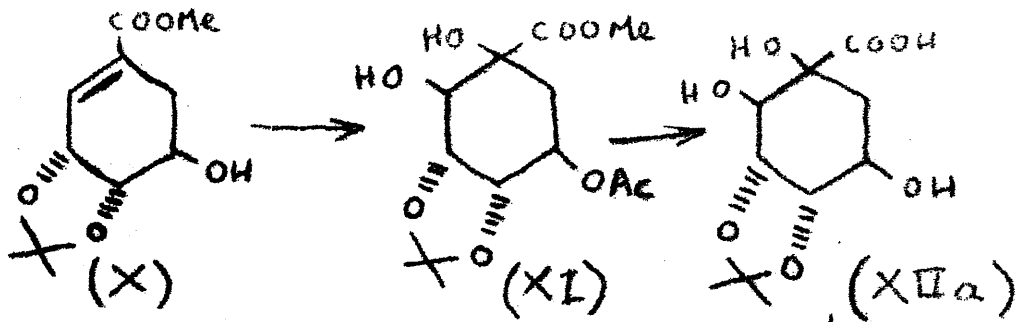
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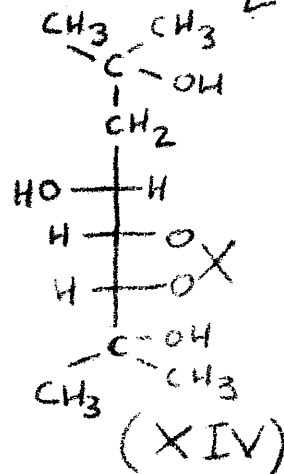
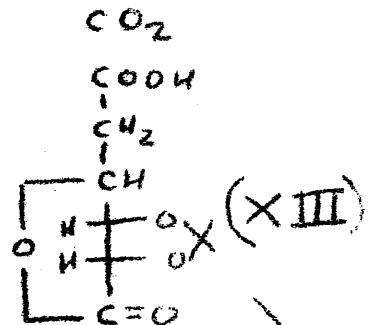
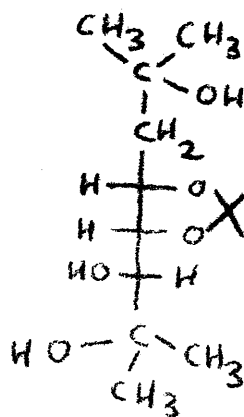
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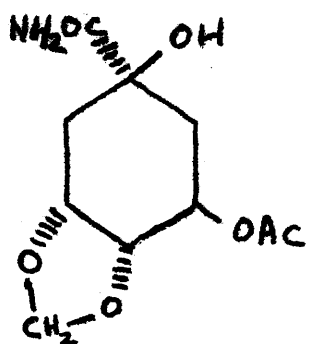




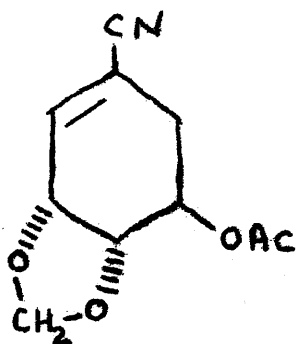
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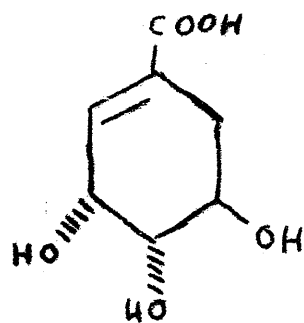
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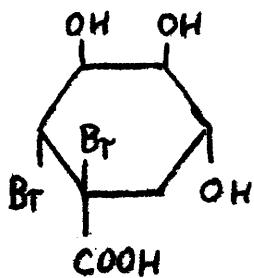
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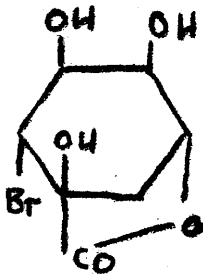
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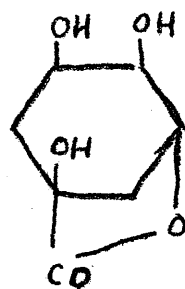
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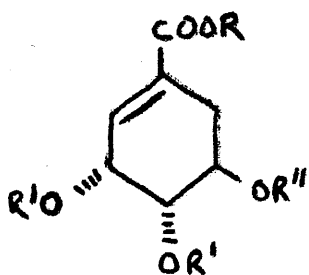
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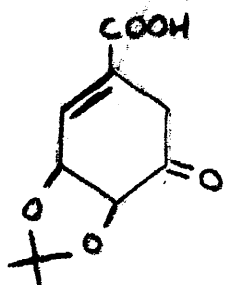
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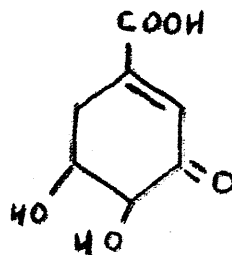
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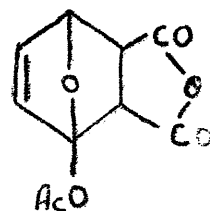
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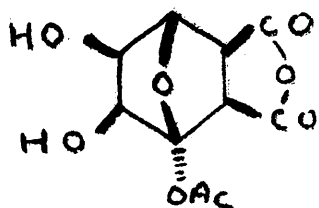
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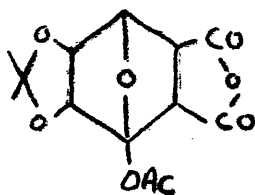
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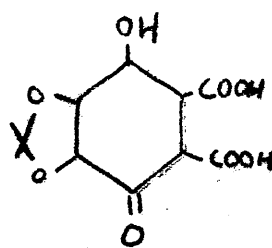
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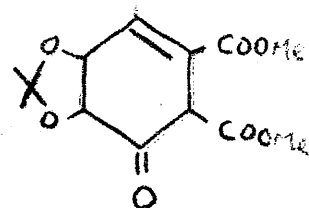
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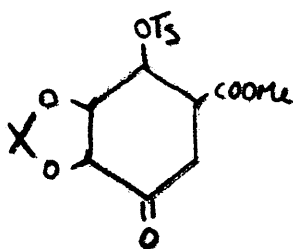
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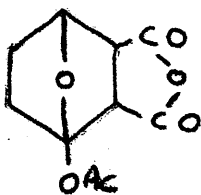
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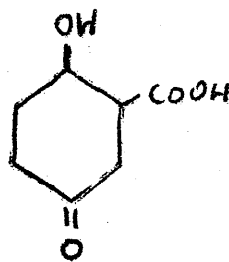
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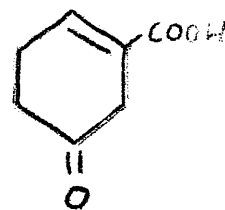
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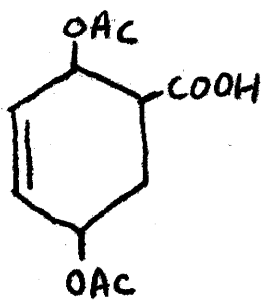


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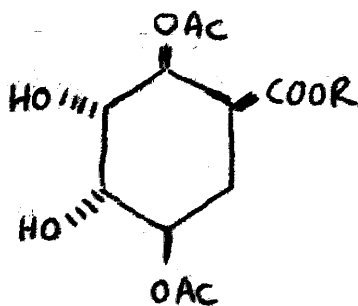


(XXXa)

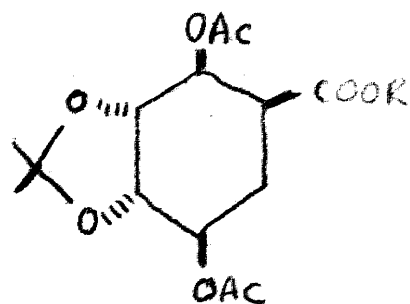




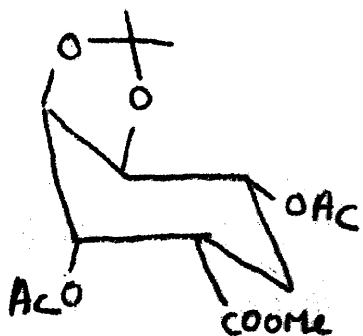
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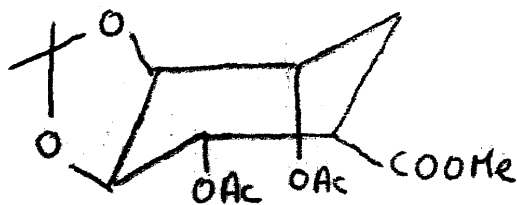
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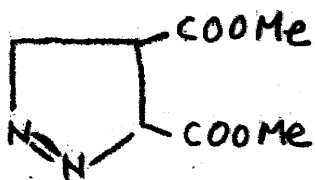
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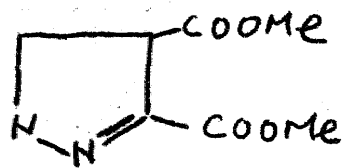
(XXXIIIa)



(XXXIIIb)



(XXXIVa)



(XXXIVb)

**SECTION II.— The Catalytic Hydrogenation of
Cyclic Anhydrides.**

The Catalytic Hydrogenation of Cyclic Anhydrides.

In the course of the catalytic hydrogenation of the acetoxyfuran-maleic anhydride adduct (XXIV) to the dihydro-adduct (XXIX) in ethyl acetate with platinum oxide as catalyst, it was found that the uptake of hydrogen did not stop at one mol. Indeed, complete hydrogenation in the presence of 50% of Adams catalyst entailed the uptake of two mols. The product of this complete hydrogenation was a crystalline solid which analysed for a tetrahydro-derivative of the adduct (XXIV). This new compound was shown to have the structure of the lactol (XXXV) (the cyclic form (79) of the semi-aldehyde corresponding to the anhydride (XXIX)) as follows:-

The infrared spectrum did not exhibit the characteristic doublet in the carbonyl region displayed by compounds containing the anhydride grouping. Further evidence for the loss of the anhydride group came from the observation that, whereas when the dihydro-adduct (XXIX) was refluxed in ethanol, the monomethyl ester (XXXVI) was formed, while similar treatment of this tetrahydro-adduct, afforded unchanged starting material. It was also shown that the compound was readily oxidised with chromic acid, one oxygen equivalent being used up in the formation of the anhydride (XXIX), identified as the corresponding dimethyl ester. Justification for writing the compound as existing entirely in the closed form (XXXV) depended upon the infrared spectrum (80) (both in the solid state and in solution), there being no peaks in the carbonyl region nor near 3000 cm.^{-1} which could be assigned to carboxylic absorption, while there was a strong peak in the hydroxyl region and a peak at 1770 cm.^{-1} (in solution) due to the lactol carbonyl. Proof for the position of the hydroxyl group in the lactol (XXXV) is cited later.

The preparation of the corresponding lactones by catalytic hydrogenation of succinic and glutaric anhydrides is well known (81), although drastic conditions (high temperature and pressure) have usually been used; however, the formation of lactols has not been previously reported, in spite of the fact that a very large number of adducts formed by union of a diene with maleic anhydride have been hydrogenated to the corresponding dihydro-adduct by this technique (81b). This gap in the literature and the possibility of defining a less tedious route to semi-aldehydes than the one via a semi-ester which is in use at present (82), prompted us to undertake further investigations concerning the catalytic hydrogenation of anhydrides.

The mother-liquors from crystallisation of the lactol (XXXV) were examined for any other products of hydrogenation and, by chromatography, a small amount (2%) of the lactone (XXXVIII) was isolated, its structure being assigned on the basis of infrared absorption and analytical evidence. The hydrogenation was then conducted in acetic acid in an attempt to produce a greater proportion of this lactone. The rate, and amount, of hydrogen uptake were greater in this case between 3 and 4 mols. of hydrogen being consumed and, as well as a small amount of the lactol, large amounts of both the lactone (about 45%) and a new compound (about 40%) were formed. The infrared spectrum and analysis of this last compound made it seem likely that it was an acid of structure (XXXIX). That it was this acid and not the acid with the carboxyl and methyl groups interchanged was shown by cleavage of the hemiketal acetate in a manner analogous to that used in the conversion of the saturated anhydride (XXIX) to the keto-acid (XXX). The product of alkaline hydrolysis was the decarboxylated keto-

alcohol (identified as the 2,4-dinitrophenylhydrazene (XL)). Thus the carboxyl must have been in the β -position to the ketone in the product and therefore in the β -position to the acetoxy group in the starting material. Further support for this structure (XXXIX) arose from the discovery that the acid on pyrolysis afforded the γ -lactone (XLI) (infrared absorption).

The relative positions of the methylene and carbonyl groups in the lactone ring of (XXXVIII) could not be deduced from the structure of the acid (XXXIX) since the interconversion of these compounds was not accomplished. However, treatment of the lactone with alkali gave a ketone which formed the 2,4-dinitrophenylhydrazene (XLII), thus proving that the same anhydride carbonyl group had undergone reduction in the formation of both the acid and the lactone. It had already been shown that the lactol could be converted by catalytic hydrogenation to the lactone, hence the structure (XXXV) which had been tentatively assigned to the lactol was correct. Subsequently a small amount of the acid (XXXIX) was isolated during this conversion of the lactol to lactone, thus finally verifying that the same carbonyl group had been reduced in the production of all three compounds.

Hydrogenations of the exo-cis furan-maleic anhydride adduct (83) (XLIII) were carried out in order to establish the role (if any) of the acetoxy group. In ethyl acetate solution, the lactol (XLV) was produced but in this case a much greater amount of lactone (XLVI) was formed concurrently (yields up to 100% depending on how long the hydrogenation was allowed to proceed). In acetic acid both the lactone and the acid (XLVII) were again produced but the acid was present in smaller amount

(about 30%).

The acetoxy group thus plays some role but whether the effect is an electronic one ((a) within the molecule itself, e.g. stabilisation of the lactol by hydrogen-bonding between the hydroxyl of the lactol and the acetoxy group or (b) in affecting the extent or position of binding of the molecule to the catalyst surface) or a simple physical bulk effect ((c) by hindering approach of hydrogen from the catalyst or (d) an effect similar to (b) above but resulting from a physical block rather than an electronic attraction) is not clear (at present).

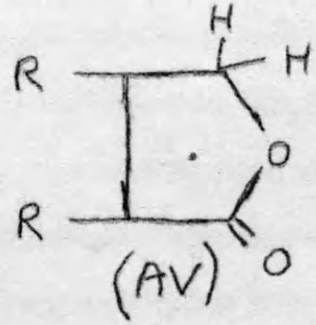
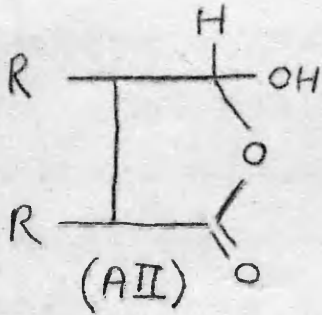
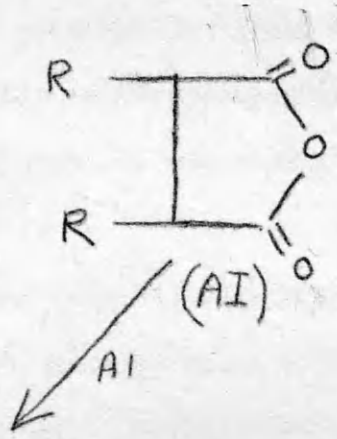
A compound with a carbon rather than an oxygen bridge was next subjected to hydrogenation. The adduct (84)(XLVIII) of cyclopentadiene and maleic anhydride was prepared and hydrogenated in ethyl acetate and here again, as was found for the furan adduct, the lactol (XLIX) could be isolated if the hydrogenation was not allowed to go to completion. Hydrogenation to completion in this case afforded a large amount of the hydroxy-acid (L) as well as the lactone (LI). The hydroxy-acid was converted into the lactone by refluxing it in benzene.

The effect of a substituent near to the site of hydrogen attack was next tested, the adduct (84)(LII) of cyclopentadiene and citraconic anhydride being used. The hydrogenation of this compound in ethyl acetate tended to stop more readily at the lactol (LIII) stage, the rate of hydrogen uptake falling nearly to zero when the product ratio of lactol (LIII) to the lactone (LIV) was about 5:1. The structures (LIIIa) and (LIVa) were proposed for the two compounds on assumption of hydrogenation of the carbonyl group less hindered by the methyl substituent.

The methyl and acetoxy groups in the adducts (LII) and (XXIV)

57a.

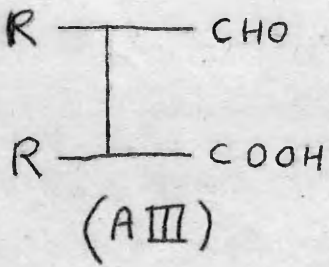
A



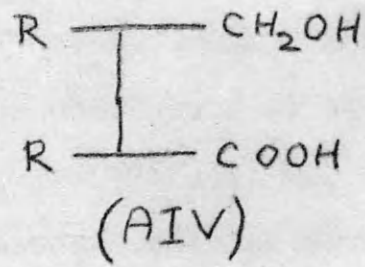
A5

A2

A4



A3



(although not in strictly equivalent positions) both exert a retarding effect on the hydrogenation of lactol to lactone, the effect being more marked in the case of the acetoxy-furan adduct (XXIV). It must be assumed that a combination of steric and electronic factors are at play in both cases.

The four compounds so far investigated were 1,4-bridged cyclohexanes. The hydrogenation of a compound with the simple cyclohexane skeleton, hexahydrophthalic anhydride (LVI), was next examined. In ethyl acetate, the lactone (LVII) was formed along with the corresponding hydroxy-acid, while hydrogenation in acetic acid afforded additionally a third compound, the acid (LIX). Estimation of yields was difficult in this latter case, complete separation by chromatography being impossible because of the ease with which the lactone opened and closed. No lactol could be detected in the products either spectroscopically (infrared) or by preparation of a 2,4-dinitrophenylhydrazone.

The simplest five-membered cyclic anhydride, succinic anhydride (LXI), when hydrogenated in ethyl acetate, yielded a mixture of the hydroxy-acid (LXII) corresponding to butyrolactone (LXIII) and a small amount of butyric acid (LXIV), but again no lactol was detected.

In the formation of a lactone (AV) or hydroxy-acid (AIV) from an anhydride (AI), the only readily conceivable routes proceed via the lactol (AII) (see the reaction sequence A on page 57 α). It is assumed in step (A4) that certain of the hydroxy-acids will dehydrate spontaneously to the corresponding lactone.

We have found that the hydrogenation of an anhydride to the corresponding lactol, lactone or methyl acid requires relatively drastic

conditions (10-50% of Adams catalyst) when compared with those necessary for reduction of aldehydes and ketones ($\frac{1}{2}$ % Adams catalyst)(81c). Thus if there is any aldehydo-acid in the equilibrium (A2), this pathway (A2,A3,A4) to the lactone will have some importance and the lactol formed slowly in step (A1) will then be consumed quickly in step (A3). On this basis the lactol (AII) will appear in substantial amounts only where the equilibrium (A2) is entirely in its favour, so that the facile pathway (A3,A4) to the lactone does not play an important part.

Results obtained from the hydrogenation of the cyclopentadiene adducts support this proposal. Thus, if it is assumed that the lactol (LIII) is stabilised by the angular methyl group with respect to the corresponding aldehydo-acid (steric compression within the aldehydo-acid molecule being partially released on ring closure; see the stability of fully substituted succinic anhydrides (87)), then the lactol should appear as a major product accompanied by minor amounts of lactone; any hydroxy-acid would, by the same token, be expected to lactonise. In the case of the unsubstituted adduct (XLVIII), sufficient aldehydo-acid exists in equilibrium to provide a ready pathway for the conversion of lactol (XLIX) to lactone (LI). The major product should therefore consist of lactone and hydroxy-acid, lactol appearing only in minor amounts. The experimental findings are entirely consonant with such an interpretation.

Of the six compounds investigated, lactols were isolated from anhydrides of bridged cyclohexane rings and here indeed a special lactol stability would be expected. The cyclohexane ring will be held in the boat conformation by the 1,4 bridge and the significant bonds from this unit, for either an exo or endo-cis-anhydride, are coplanar and at angles

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which, from molecular models, are seen to be ideal for formation of a strainless planar lactol ring.

The apparent need for this special rigid system led us to study the hydrogenation of cis-cyclobutane-1,2-dicarboxylic anhydride (LXV)(85). No complete separation of the products was effected but it was evident that the hydrogenation had afforded mainly the acid (LXVI) along with the diacid (LXVIII) presumably formed by hydration of the starting material with water generated by reduction of the platinum oxide catalyst. However, no lactol could be detected (inability to form a 2,4-dinitrophenylhydrazone) and from study of models it became obvious that although cis bonds from adjacent carbon atoms of a cyclobutane ring lie in one plane, the angles are distorted away from the ideal value for the lactol ring.

A glutaric anhydride would not be expected (from models) to give a stable lactol and when dl-camphoric anhydride (LXIX) was hydrogenated, a mixture of acids was obtained which could be partially separated by crystallisation to give the new dl-hydroxy-acid (LXXI) a compound convertible to dl- β -campholide (LXXIII). When the hydrogenation was repeated with optically active camphoric anhydride and the mixture obtained separated, the other product was identified as the hydroxy-acid (LXX) corresponding to α -campholide (LXXII). The hydrogenation was therefore not completely stereospecific although the α -isomer predominated in the product ($\beta : \alpha = 2:1$) as might be expected.

In all the above cases, formation of the lactol or lactone is perhaps unexpected; what is even more surprising is that the former can be isolated and also that the third product, the methyl acid, is formed at all. The isolation of the lactol has been explained by invoking the need for a

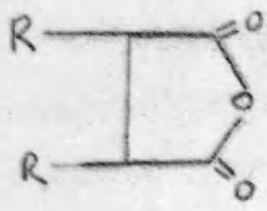
system which can clamp the lactol ring in a planar yet strainless conformation; however, it is much more difficult to put forward a rational explanation for the production of the methyl acid.

Formation of hexahydro-*o*-toluic acid (LIX) has previously been reported (86), from hydrogenation of phthalic anhydride, and it could be postulated that if reduction of the anhydride occurred before reduction of the aromatic ring, then the resulting lactone could undergo benzylic hydrogenolysis to give *o*-toluic acid which could then react further to give the acid (LIX). However, benzylic, allylic or vinylic activation appears unnecessary since we have shown that the methyl acid (LIX) can be obtained by hydrogenation of the saturated anhydride (LVI).

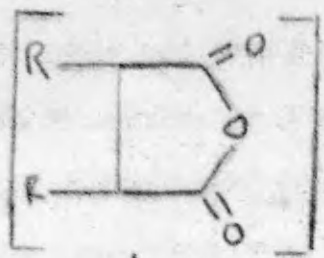
Speculation on possible mechanisms for this hydrogenolysis soon makes it seem probable that the sequence of reactions proposed above for formation of the lactone via the lactol is over-simplified. In attempting to propose a feasible mechanism for the series of hydrogenation steps a difficulty presents itself immediately in that an anhydride might be expected to be resistant to hydrogenation since neither esters nor acids react under similar circumstances (ethyl acetate and acetic acid were used as solvents in our experiments). Ketones and aldehydes do hydrogenate under these conditions, presumably because the carbenyl group can be suitably polarised to allow adsorption and reduction at the catalyst surface. In the case of an ester, the polarisability will be diminished by the alkoxyl group. However, in an anhydride, the oxygen atom which is tending to disallow polarisation is shared between two carbonyl groups. An anhydride might then be expected to show a susceptibility to catalytic hydrogenation, intermediate between that of an ester, lactone etc. and that of an aldehyde

61a

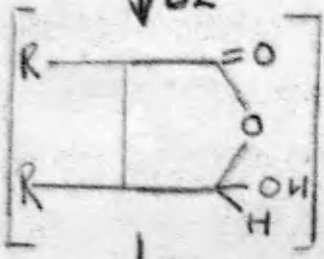
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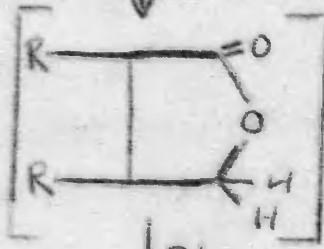
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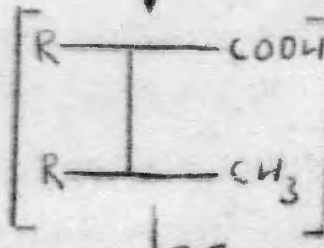
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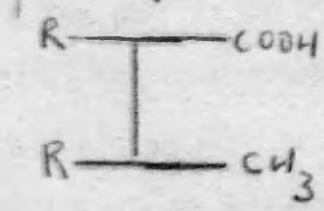
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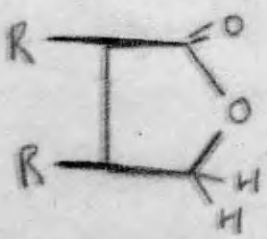
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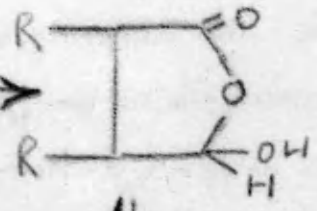
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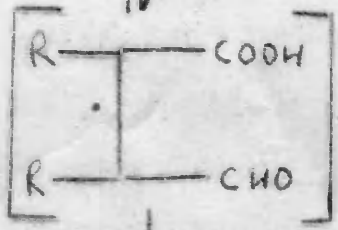
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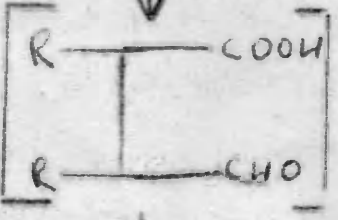
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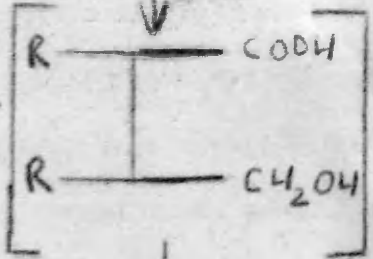
B8



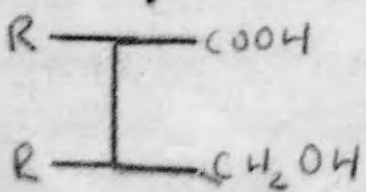
B9



B10

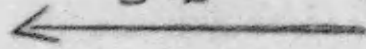


B11



B12

B13



or ketone and, as the work reported here has shown, this susceptibility is sufficient to allow hydrogenation to proceed in the presence of freshly prepared platinum. However, the lactone and lactol, if the latter exists in solution nearly entirely in this cyclic state, once disassociated from the catalyst should show as little tendency for further reduction as an ester. The further reduction of the lactol must then involve either hydrogenolysis of the hydroxyl group while the molecule is still attached to the catalyst, or recombination of the aldehydo-acid, formed by opening of the lactol ring, with catalyst followed by hydrogenation. The further reduction of the lactone is unlikely to proceed via the free hydroxy-acid since simple primary hydroxyls do not normally hydrogenolyse and therefore must take place before the lactone or the hydroxy-acid molecule can leave the catalyst's surface.

These points can be summarised as in the reaction sequence A, further elaborated in B (see page 6/a, an asterisk implies attachment to the catalyst). It involves a simple electrostatic union (B1) of the polarised anhydride carbonyl group with the catalyst's surface and subsequent addition of hydrogen (B2) across the double bond of this carbonyl group to give the lactol. Next, there could be either hydrogen addition across the C-OH bond (B3) to give the lactone directly or release of the lactol from the catalyst (B7), opening of the lactol ring (B8) and reduction of the carbonyl group of the resulting aldehydo-acid, after resorption on the catalyst (B9). Hydrogenolysis of either the $\text{CH}_2\text{-O}$ bond of the lactone ring (B4) or the $\text{CH}_2\text{-OH}$ bond of the primary alcohol (B13) will afford the methyl acid. The unusual hydrogenolyses in steps (B3), (B4), and (B13) can be explained by saying that these reactions are energetically more

favourable than normally, the molecule being more closely associated with the catalyst's surface because it has just undergone reduction there. Also, since a smaller proportion of methyl acid (to lactone) is formed on hydrogenation of the lactol rather than the anhydride, the steps (B3) and (B4) must have some importance when starting from the anhydride.

Although the mechanism of the formation of the methyl acids in our experiments has not been clarified, it seems likely that this new hydrogenolysis is linked with the long known benzylic, allylic, phenylic, and vinylic hydrogenolyses of hydroxy or alkoxy groups (89). No convincing explanation has been put forward for these hydrogenolyses although some progress has been made towards the solution of the problem (90). However, they may well be due to the fact that fission of the C-O bond by hydrogen can only take place when the molecule has become attached to the catalyst's surface at its unsaturated centre (with or without subsequent reduction of this centre) in an analogous manner to B above.

EXPERIMENTAL.

(Formulae flowsheets for this section are on Pages 81-84).

Catalytic Hydrogenation of the Adduct (XXIV) of Acetoxyfuran
and Maleic Anhydride.-

(i) To the Lactol (XXXV)

The adduct (XXIV) (1.5 g) in "AnalaR" ethyl acetate (40 ml.) was shaken with Adams catalyst (200 mg.) in an atmosphere of hydrogen. There was a more or less immediate uptake of 1 mol. of hydrogen (160 ml.) followed by a much slower uptake of a further 1.3 mol. (200 ml.) during 16 hrs. Removal of catalyst and solvent afforded a white solid which, on crystallisation twice from ethyl acetate, afforded the lactol (XXXV) (1.3 g.) as large colourless needles m.p. 206-207° (Found: C, 52.75; H, 5.0. $C_{10}H_{12}O_6$ requires C, 52.65; H, 5.3%). The infrared spectrum exhibited a sharp peak (nujol mull) at 3265 cm^{-1} (hydroxyl) and twin peaks in the carbonyl region (solution in chloroform) at 1770 (carbonyl of lactol) and 1750 cm^{-1} (acetate).

Evidence for the Structure of the Lactol (XXXV).-

The dihydro-adduct (XXIX) (50 mg) was heated for 30 mins. in the steam-bath in ethanol (5 ml.). Evaporation of solvent afforded the mono-ethyl ester (XXXVIa) or (XXXVIb) which formed needles from ethyl acetate m.p. 148° (Found: C, 52.9; H, 6.0. $C_{12}H_{16}O_7$ requires C, 52.95; H, 5.9%).

The tetrahydro-adduct was recovered unchanged after heating for 30 mins. in ethanol.

The tetra hydro-compound (22.8 mg.) was dissolved in a standard solution of chromic acid in acetic acid (10 ml. of 0.06 N solution; 3 oxygen equivalents) and kept at 20° for 16 hrs. Fractions (1 ml.) of

the solution were then taken and 6N-sulphuric acid (6 drops) and excess solid potassium iodide added. The iodine thus liberated was titrated with standard 0.002N-thiosulphate solution. These titrations demonstrated that 1 oxygen equivalent had been used. To the remainder of the solution excess methanol was added and, after 30 mins., the solvents were removed at 15 mm. Extraction of the residue with ethyl acetate afforded a white solid which was dissolved in methanol and treated with excess redistilled ethereal diazomethane. Removal of solvents afforded the dimethyl ester (XXXVII) (identical (m.p. and mixed m.p.) with a sample prepared from the anhydride (XXIX) by dissolution in methanol and treatment with ethereal diazomethane) which crystallised as colourless needles from ethyl acetate-light petroleum, m.p. 138° (Found: C, 52.85; H, 5.9. $C_{12}H_{16}O_7$ requires C, 52.95; H, 5.9%).

(ii) To the Lactone (XXXVIII).-

The hydrogenation of the anhydride (XXIV) (250 mg.) in "AnalaR" ethyl acetate (20 ml.) over Adams catalyst (50 mg.) was repeated as in (i) above. The product was a solid which had an infrared spectrum (nujol mull) nearly identical with that of pure lactol (XXXV). This solid was allowed to crystallise from ethyl acetate and afforded lactol (190 mg.) m.p. $205-207^{\circ}$. The residue obtained by evaporation of the mother-liquors from this crystallisation was chromatographed over silica (2g.), elution with benzene yielding the lactone (XXXVIII) (4 mg.) which crystallised from light petroleum as large colourless prisms m.p. $142-143^{\circ}$ (Found: C, 56.55; H, 5.5. $C_{10}H_{12}O_5$ requires C, 56.6; H, 5.7%). The infrared spectrum (nujol mull) of this compound exhibited no hydroxyl absorption ($3000-3500\text{ cm.}^{-1}$) but had one sharp peak at 1740 cm.^{-1} (superimposed

γ -lactone and acetate).

(iii) To the Methyl Acid (XXXIX).-

(A) The adduct (XXIV) (210 mg.) was hydrogenated in dry "AnalaR" acetic acid (30 ml.) in the presence of Adams catalyst (100 mg.). After 6 hrs. the uptake of hydrogen had practically ceased and the catalyst and solvent were removed. The residue (195 mg.) was placed on silica (8 g.) in benzene and afforded, by elution with

(a) benzene - 0.5% ether, the lactone (XXXVIII) (69 mg.) identified by m.p. and infrared spectrum

(b) benzene - 5% ether, the methyl acid (XXXIX) (60 mg.)

(c) ethyl acetate, a mixture (36 mg.) of lactol (XXXV) and the methyl acid. Separation of this mixture was effected by crystallisation from benzene, the lactol (28 mg.) being nearly insoluble in cold benzene, while the methyl acid (10 mg.) was very soluble.

(B) A hydrogenation similar to (A) above, using the anhydride (XXIX) (610 mg.), platinum oxide (300 mg.), and "AnalaR" acetic acid (80 ml.), was allowed to proceed for 24 hrs. The product was fractionated as in (A) above into the lactone (298 mg.) and the methyl acid (272 mg.) but in this case no lactol could be isolated.

The methyl acid (XXXIX), from (A) or (B), when sublimed at $120^{\circ}/0.1$ mm., afforded colourless needles m.p. $147-150^{\circ}$ (Found: C, 56.25; H, 6.35. $C_{10}H_{14}O_5$ requires C, 56.05; H, 6.6%), ν_{max} . (nujol mull) 2500-2700 (hydroxyl of carboxyl), 1740 (acetate), and 1695 cm.^{-1} (carboxyl).

Evidence for the Relative Positions of the Carboxyl and the Acetoxy Groups in the Methyl Acid.-

(a) Cleavage of the hemiketal with base.-

The methyl acid (330 mg.) was heated on the steam-bath for 1 hr.

in aqueous methanol (1:4)(15 ml.) containing sodium hydroxide (600 mg.). Carbon dioxide was evolved vigorously when the cooled solution was passed through a column of an acid resin (I.R.120(H)). The solvents were evaporated at 15 mm. to about 5 ml. and 2,4-dinitrophenylhydrazine (500 mg.) in 4N-hydrochloric acid (15 ml.) was added. The solution was heated on the steam-bath for 5 mins., cooled, and extracted with chloroform (2 x 20 ml.). The combined extracts were washed with water (20 ml.), dried, and filtered through bentonite-kieselguhr (4:1)(10g.). Evaporation of the solvent afforded an oil (94 mg.) which crystallised on trituration with chloroform. This solid afforded the 2:4-dinitrophenylhydrazone (XL)(28 mg.) as orange needles m.p. 169-173° on crystallisation from ethyl acetate-light petroleum (Found: C, 50.55; H, 5.4; N, 17.8. $C_{18}H_{16}O_5N_4$ requires C, 50.65; H, 5.25; N, 18.2%).

(b) Formation of the γ -lactone (XLI).-

The methyl acid (50 mg.) was heated at 200° for 5 mins. and the product sublimed at 80°/0.1 mm. The sublimate afforded the lactone (XLI) (28 mg.) as large colourless prisms from benzene-light petroleum m.p. 80-81°. The analytical specimen, obtained by resublimation at 80°/0.1 mm., had m.p. 83-84° (Found: C, 62.3; H, 6.4. $C_8H_{10}O_3$ requires C, 62.3; H, 6.55%), ν_{max} . 1760 (γ -lactone) and 1705 cm^{-1} (cyclohexanone).

Evidence for the Relative Positions of the Carboxyl and the Acetoxy Groups in the Lactone (XXXVIII).-

Cleavage of the hemiketal with base.

A suspension of the lactone (200 mg.) in a solution of sodium hydroxide (400 mg.) in water (5 ml.) was refluxed for 1 hr. The cooled solution was acidified with 5N-hydrochloric acid and then heated on the

steam-bath for 3 mins. with 2:4-dinitrophenylhydrazine (500 mg.) in 5N-hydrochloric acid. The solution on cooling was extracted with chloroform (2 x 20 ml.), the combined extracts being washed with water and dried. The residue (210 mg.), from evaporation of the solvent, was dissolved in hot benzene and placed on activated alumina (grade V). Benzene eluted unreacted 2,4-dinitrophenylhydrazine (50 mg.), and ethyl acetate-chloroform (1:10) eluted the 2,4-dinitrophenylhydrazone (XLII) (80 mg.) which, on crystallisation five times from ethyl acetate-light petroleum, formed yellow needles m.p. 158-160°. (Found: C, 48.35; H, 4.95; N, 17.2. $C_{15}H_{16}O_6N_4$ requires C, 48.15; H, 4.95; N, 17.3%).

Hydrogenation of the Lactol (XXXV).--

The lactol (120 mg.) was hydrogenated in "AnalaR" acetic acid (20 ml.) over platinum oxide (55 mg.). The product was isolated as before and unreacted lactol was removed by crystallisation from benzene. The mother-liquors were chromatographed over silica, benzene-0.5% ether eluting the lactone (XXXVIII) (54 mg.) and benzene-5% ether eluting the methyl acid (XXXIX) (26 mg.). These compounds were identified by their m.p.s and infrared spectra.

Attempted Hydrogenation of the Lactone (XXXVIII).--

The lactone (50 mg.) in "AnalaR" acetic acid (20 ml.) was shaken with Adams catalyst (50 mg.) in an atmosphere of hydrogen for 6 hrs. There was no significant hydrogen uptake.

Hydrogenation of the Adduct (XLIII) of Furan and Maleic Anhydride.--

(a) In ethyl acetate.

The adduct (83) (1g.) in "AnalaR" ethyl acetate (50 ml.) was shaken in hydrogen over platinum oxide catalyst (200 mg.). After 6 hrs. the

shaking was discontinued, the uptake of hydrogen being 2.2 mols. The residue, on removal of catalyst and solvent, was placed on silica (40 g.) in benzene. Elution with benzene yielded the lactone (XLVI) (210 mg.; 23%), which crystallised from ethyl acetate-light petroleum in long colourless needles m.p. 126-127° (Found: C, 62.35; H, 6.5. $C_8H_{10}O_3$ requires C, 62.3; H, 6.55%), ν_{max} . (nujol mull) 1745 cm^{-1} (δ -lactone).

Elution with chloroform yielded the lactol (XLV) (767 mg.; 75%) which, after crystallisation from ethyl acetate-light petroleum three times, afforded colourless cubes m.p. 180-181° (Found: C, 56.6; H, 6.0. $C_8H_{10}O_4$ requires C, 56.45; H, 5.9%). The infrared spectrum (nujol mull) exhibited peaks at 3220 (hydroxyl) and 1720 cm^{-1} . This latter peak, attributed to the carbonyl of the lactol, appeared at 1765 cm^{-1} when the spectrum of the compound was determined for a chloroform solution.

(b) In acetic acid.

The adduct (lg.) was hydrogenated as in (a) above but the reaction was stopped after the uptake of 1 mol.

The dihydro-adduct (83) (XLIV) m.p. 114-116°, thus formed, was dissolved in "AnalaR" acetic acid (40 ml.) and hydrogenated in the presence of Adams catalyst (450 mg.). After 20 hrs., during which time just over 2 mols. of hydrogen were absorbed, the uptake of gas stopped. The catalyst was collected and the acetic acid removed under reduced pressure, the residue being chromatographed over silica (40 g.). Elution with benzene-5% ether afforded successively the lactone (XLVI) (650 mg.; 70%), identified by its m.p. and infrared spectrum and then the methyl acid (XLVII) (270 mg.; 28%), which formed stout colourless rods (from ethyl acetate-light petroleum) m.p. 142-143° (Found: C, 61.35; H, 7.7. $C_8H_{12}O_3$ requires C, 61.5;

H, 7.75%), ν_{\max} . (nujol mull) 2700-3200 (hydroxyl of carboxyl) and 1690 cm.^{-1} (carboxyl).

Attempted Hydrogenation of the Lactone (XLVI).-

The lactone (200 mg.) in "AnalaR" acetic acid was shaken in hydrogen over platinum oxide catalyst (100 mg.) for 6 hrs. without appreciable absorption of the gas.

Hydrogenation of the adduct (XLVIII) of Cyclopentadiene and Maleic Anhydride.-

(a) To a mixture of the lactol, lactone and hydroxy-acid.

The adduct (84)(570 mg.) in "AnalaR" ethyl acetate (30 ml.) was hydrogenated in the presence of Adams catalyst (100 mg.). Gas absorption had stopped after 18 hrs. and the catalyst and solvent were then removed. The infrared spectrum (nujol mull) of the residue exhibited a broad hydroxyl peak at 3450 cm.^{-1} and carbonyl peaks at 1750 and 1700 cm.^{-1} , as well as diffuse absorption in the 2500-2800 cm.^{-1} region, suggestive of the presence of a carboxylic acid. Chromatography of the residue over silica (20g) afforded by elution with benzene, first, the known saturated anhydride (84)(140 mg.), corresponding to the adduct (XLVIII), and then the lactone (L)(145 mg.) which formed colourless prisms from light petroleum m.p. 148-149° (Found: C, 70.95; H, 7.85. $\text{C}_9\text{H}_{12}\text{O}_2$ requires C, 71.0; H, 7.95%), ν_{\max} . (nujol mull) 1760 cm.^{-1} (γ -lactone).

Chloroform eluted the lactol (XLIX)(135 mg.) which, on crystallisation from ethyl acetate-light petroleum, formed colourless plates m.p. 120-121° (Found: C, 64.0; H, 7.4. $\text{C}_9\text{H}_{12}\text{O}_3$ requires C, 64.25; H, 7.2%), ν_{\max} . (nujol mull) 3290 (hydroxyl) and 1740 cm.^{-1} (carbonyl of lactol).

Acetone eluted the hydroxy-acid (LI)(80 mg.) which had infrared

absorption maxima (nujol mull) at 3430 (hydroxyl), 2500-2800 (hydroxyl of carboxyl), and 1705 cm.^{-1} (carboxyl) and could be converted into the lactone (L) (identified by m.p., mixed m.p. and infrared spectrum) by heating in benzene for 1 hr. at 80°.

(b) To a mixture of the lactone and hydroxy-acid.

On repeating the above hydrogenation of the adduct (500 mg.) in the presence of a larger amount of catalyst (200 mg.), the product was identified as a mixture of the lactone (L) and the corresponding hydroxy-acid (LI) by study of the infrared spectrum and from the observation that the mixture, when heated in benzene at 80° for 1 hour, afforded a homogeneous specimen of the lactone (m.p. and infrared spectrum).

Hydrogenation of the Adduct (LII) of Cyclopentadiene and Citraconic Anhydride.-

The adduct (84) (500 mg.) in "AnalaR" ethyl acetate (30 ml.) was shaken in hydrogen over platinum oxide catalyst (150 mg.). The absorption of gas had stopped after 18 hrs. and the catalyst and solvent were removed. Chromatography of the residue over silica (20 g.) and elution with benzene yielded the lactone (LIV) (84 mg.) which, on repeated crystallisation from light petroleum (b.p. 40-60°), formed ill-defined crystals m.p. 129-131°. Rechromatography over silica and further crystallisation did not improve the appearance of the crystals m.p. 130-131° (Found: C, 71.95; H, 8.55. $\text{C}_{10}\text{H}_{14}\text{O}_2$ requires C, 72.25; H, 8.5%), ν_{max} . (nujol mull) 1765 cm.^{-1} (γ -lactone).

Elution of the column with chloroform afforded the lactol (LIII) (288 mg.), which formed colourless plates (from ethyl acetate-light petroleum) m.p. 182-183° (Found: C, 65.9; H, 7.65. $\text{C}_{10}\text{H}_{14}\text{O}_3$ requires

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C, 65.9; H, 7.75%), ν_{\max} . (nujol mull) 3270 (hydroxyl) and 1735 cm^{-1} (carbonyl of lactol).

Hydrogenation of the lactol (LIII).-

The lactol (100 mg.) was hydrogenated in ethyl acetate (20 ml.) over platinum oxide catalyst (100 mg.), the uptake of hydrogen stopping after the absorption of 0.5 mol. The residue from removal of catalyst and solvent was chromatographed as above on silica (4g.) and afforded unchanged lactol (48 mg.) and the lactone (LIV) (43 mg.), which again formed ill-defined crystals m.p. 129-131° (from light petroleum (b.p. 40-60°)).

Hydrogenation of cis-1,2,5,6-tetrahydrophthalic anhydride.-

The anhydride (525 mg.) in "AnalaR" ethyl acetate (40 ml.) was shaken over platinum oxide catalyst (200 mg.) in hydrogen. After 18 hrs. the uptake of gas had stopped and the catalyst and solvent were removed leaving an oil (530 mg.). The infrared spectrum of this oil exhibited strong continuous absorption between 2500 and 3500 cm^{-1} and a wide band between 1680 and 1780 cm^{-1} , with a maximum at 1700 cm^{-1} , indicating the presence of a large proportion of carboxylic material in the product. A small sample of the product was treated with Brady's reagent to test for the presence of lactol. No 2,4-dinitrophenylhydrazene derivative was isolated.

Attempts to separate the components of the hydrogenation product by chromatography on silica failed, although earlier fractions were enriched in material exhibiting infrared absorption at about 1760 cm^{-1} (γ -lactone?), while later fractions were judged from their infrared spectrum to be acid-enriched. The product obtained by heating a small amount of these later fractions in benzene on the steam-bath for 30 mins. showed a marked decrease in carboxylic (1700 and 2500-3200 cm^{-1}) and

hydroxylic ($3200-3500 \text{ cm.}^{-1}$) absorption, and a corresponding increase in absorption at 1760 cm.^{-1} (γ -lactone). The hydrogenation product was then assumed to consist mainly of a mixture of the lactone (LVII) and the corresponding hydroxy-acid, and this was confirmed as follows:-

(a) Oxidation to the diacid corresponding to the anhydride (LVI).-

The reduction product (150 mg.) was heated for 30 mins. on the steam-bath with saturated alkaline permanganate (2 oxygen equivalents). The cooled solution on acidification was extracted with ethyl acetate, this extract being then wash with water and dried. The solid (65 mg.) afforded by removal of the ethyl acetate, when crystallised from ethyl acetate-light petroleum, had m.p. $190-193^\circ$ and was identical (m.p., mixed m.p., and infrared spectrum) with an authentic sample (88) of cis-hexahydrophthalic acid m.p. 192° .

(b) Formation of the s-benzyl thiuronium salt.-

The reduction product (250 mg.), suspended in water (5 ml.) containing 1 drop of phenolphthalein-indicator solution, was heated on the steam-bath and ca. 1 N-sodium hydroxide solution added dropwise with shaking until a permanent pink colour resulted. The p H of the solution was then adjusted by the addition of 2 drops of 1N-hydrochloric acid solution. On treatment with s-benzyl thiuronium chloride (1g.) in warm water (5 ml.) a white crystalline precipitate (270 mg.) formed immediately. This s-benzyl thiuronium salt (LVIII) on crystallisation from ethyl acetate formed colourless prisms m.p. 166° (Found: C, 59.45; H, 7.6, N, 8.65. $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ requires C, 59.25; H, 7.45; N, 8.65%).

Hydrogenation of cis-Hexahydrophthalic Anhydride (LVI).-

The hexahydro-compound (88) was prepared from the tetrahydro-compound by hydrogenation in ethyl acetate in the presence of Adams

catalyst (1%).

This hexahydro-compound (310 mg.) in "AnalaR" acetic acid (30 ml.) was shaken in hydrogen over Adams catalyst (195 mg.). Removal of catalyst and solvent left an oil (300 mg.), which was judged from its infrared spectrum (film) to consist of lactonic (1760 cm.^{-1}) and acidic material (1700 and $2500\text{--}2800\text{ cm.}^{-1}$). Chromatography of the oil on silica gave no separation of the components of the mixture (infrared evidence).

The recovered material (280 mg.) was kept on "Woelm's" acid alumina (grade V) for 18 hrs. in an attempt to cyclise any hydroxy-acid in the mixture. Elution with light petroleum-5% benzene afforded a fraction (73 mg.) which was shown to be essentially the lactone (LVII), by formation of the *s*-benzyl thiourenium salt (LVIII) as in (b) above.

Elution with ethyl acetate afforded an oil (110 mg.) which exhibited carboxylic absorption in the infrared spectrum at 1700 and $2500\text{--}2800\text{ cm.}^{-1}$ as well as weak lactonic absorption at 1750 cm.^{-1} . This last fraction was shown to consist mainly of the methyl acid (LIX) by preparation of the *s*-benzyl thiourenium salt (LX) in nearly quantitative yield (by the method used for the preparation of the salt of the lactone (LVII) as described in (b) above). The salt crystallised from ethyl acetate as colourless prisms m.p. $168\text{--}170^{\circ}$ (Found: C, 62.15; H, 7.6; N, 8.6.

$\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$ requires C, 62.3; H, 7.85; N, 9.0%).

Hydrogenation of Succinic Anhydride (LXI).-

Succinic anhydride (2 g.) in "AnalaR" ethyl acetate (100 ml.) was hydrogenated in the presence of Adams catalyst (1g.). After 24 hrs. and an uptake of just over 2 mols. of hydrogen, the catalyst was collected and the solvent distilled out through a short upright Vigreux column to

prevent loss of product. The resulting oil (2g.), which showed marked hydroxylic (3200-3500 cm.^{-1}) and carboxylic (2500-2800 and 1700 cm.^{-1}) absorption in the infrared, was heated on the steam-bath for 3 hrs. during which time an aqueous layer was formed (cyclisation of the hydroxy-acid (LXII) to butyrolactone (LXIII)). Ether (20 ml.) was added to the cooled mixture followed by anhydrous magnesium sulphate. Removal of the solid and solvent left an oil (1.85 g.) from which a colourless liquid (240 mg.) distilled at 150-160°/760 mm. The infrared spectrum of this distillate could be superposed on the infrared spectrum of authentic n-butyric acid (b.p. 162°/760 mm.), while the infrared spectra of the residue (1.6 g.) and authentic butyrolactone were also identical.

Hydrogenation of cis-Cyclobutane - 1,2-dicarboxylic anhydride (LXV).--

The cis-anhydride (85)(1.24 g.) in "AnalaR" ethyl acetate (70 ml.) was shaken in hydrogen over platinum oxide (630 mg.) for 4 hrs. during which time nearly 3 mols. of the gas were absorbed. Removal of catalyst and solvent afforded an oil (1.15 g.), which exhibited marked carboxylic absorption near 1700 cm.^{-1} and between 2500-2800 cm.^{-1} in the infrared. The s-benzyl thiuronium salt (LXVII) of the methyl acid (LXVI) was prepared as above from a sample of this oil (200 mg.). The white crystalline precipitate, when recrystallised from ethyl acetate, formed colourless prisms m.p. 164-167° (Found: C, 59.7; H, 6.95; N, 10.3. $\text{C}_{14}\text{H}_{20}\text{O}_2\text{N}_2\text{S}$ requires C, 60.0; H, 7.2; N, 10.0%).

Attempts to demonstrate the presence of lactol in a sample of the reduction product by preparation of a 2,4-dinitrophenylhydrazone derivative with Brady's reagent failed as did the following attempts to isolate derivatives of any hydroxy-acid (or lactone) formed.

(i) The p-nitrobenzyl ester.-

The oily hydrogenation product (400 mg.) was carefully neutralised (phenolphthalein indicator) by dropwise addition of an aqueous sodium hydroxide (10%) solution. The resulting solution was acidified with 2 drops of 1 N-hydrochloric acid solution and then treated with p-nitrobenzyl bromide (800 mg.) in methanol (5 ml.). The solution was refluxed for 2 hrs. and the solvents removed at 15 mm. Dissolution of the residue in water (10 ml.) and ethyl acetate (20 ml.), extraction of the aqueous layer with ethyl acetate (2 x 20 ml.), and evaporation of the combined organic solutions, afforded an oil (850 mg.). This oil was chromatographed on activated alumina (grade III) and, on elution with light petroleum containing increasing amounts of benzene, the following fractions were obtained successively:-

(a) Unreacted crystalline p-nitrobenzyl bromide (380 mg.) (identified by m.p. and infrared spectrum).

(b) A mobile oil (180 mg.) which seemed to consist essentially of the p-nitrobenzyl ester of the methyl acid (LXVI) since it exhibited no hydroxyl (3000-3500) peak in the infrared but one peak in the carbonyl region at 1730 cm.^{-1} (ester).

(c) Crystalline p-nitrobenzyl alcohol (170 mg.) (identified by m.p. and infrared spectrum).

(ii) The anilide.-

Redistilled methyl chloroformate (400 mg.) in dry ether (10 ml.) was added to an ice-cold solution of the reduction product (420 mg.) and triethylamine (2 ml.) in dry ether (10 ml.). This mixture was kept in the refrigerator for 90 mins. during which time a white precipitate formed and then treated with aniline (400 mg.) in dry ether (10 ml.). The solution

was allowed to heat up to room temperature, diluted with ethyl acetate (50 ml.), and washed with saturated aqueous sodium bicarbonate (2 x 20 ml.) and water (2 x 20 ml.). The solvents were removed from the dried solution, affording an oil (620 mg.). This oil gradually deposited colourless needles (6 mg.) which were shown to be identical (m.p., mixed m.p., and infrared spectrum) with an authentic specimen of the dianilide of *cis*-cyclobutane-1,2-dicarboxylic acid (LXVIII). The residual oil was chromatographed over activated alumina (grade V) but no separation of the components of the mixture was effected.

Hydrogenation of (+)-Camphoric Anhydride.-

(+)-Camphoric anhydride (500 mg.) in "AnalaR" ethyl acetate (40 ml.) was shaken with Adams catalyst (150 mg.) in hydrogen. A very slow uptake of the gas took place, 0.75 mol. (16 ml.) being absorbed in three days. The catalyst and solvent were removed and the residue chromatographed over silica (20 g.), elution with benzene affording starting material (310 mg.).

Elution with chloroform afforded an oil (118 mg.) which absorbed in the infrared at 3300 (hydroxyl), 2500-2800 (hydroxyl of carboxyl) and 1700 cm.^{-1} (carboxyl). This oil, on crystallisation from ethyl acetate, afforded colourless prisms (22 mg.) of the hydroxy-acid (LXX) or (LXXI) m.p. 134-137° (Found: C, 64.7; H, 9.85. $\text{C}_{10}\text{H}_{18}\text{O}_3$ requires C, 64.5; H, 9.75%).

The oil obtained from the mother-liquors could not be made to crystallise.

The hydroxy-acid (LXX) or (LXXI) (14 mg.) was heated on the steam-bath for 1 hr. with 0.1 N-sulphuric acid solution. On cooling a solid lactone (8 mg.) separated, which had ν_{max} (in carbon disulphide) 1740 (δ -lactone) and 1040 cm.^{-1} . The infrared spectra of optically active

α - and β -campholide were then compared and found to be fairly similar, apart from the presence of this peak at 1040 cm.^{-1} found in the spectrum of authentic β -campholide (91) but absent from the spectrum of authentic α -campholide (92).

Hydrogenation of (-)-Camphoric Anhydride.-

The anhydride (2g.) was hydrogenated in "AnalaR" ethyl acetate (100 ml.) in the presence of Adams catalyst (1g.). After 18 hrs., during which time there was an uptake of 1.5 mol. of hydrogen, the catalyst and solvent were removed and the residue chromatographed over silica. Elution with benzene yielded starting material (800 mg.) and then elution with chloroform yielded an acidic (infrared absorption at 1700 and $2500\text{-}2800 \text{ cm.}^{-1}$) fraction (1.2 g.).

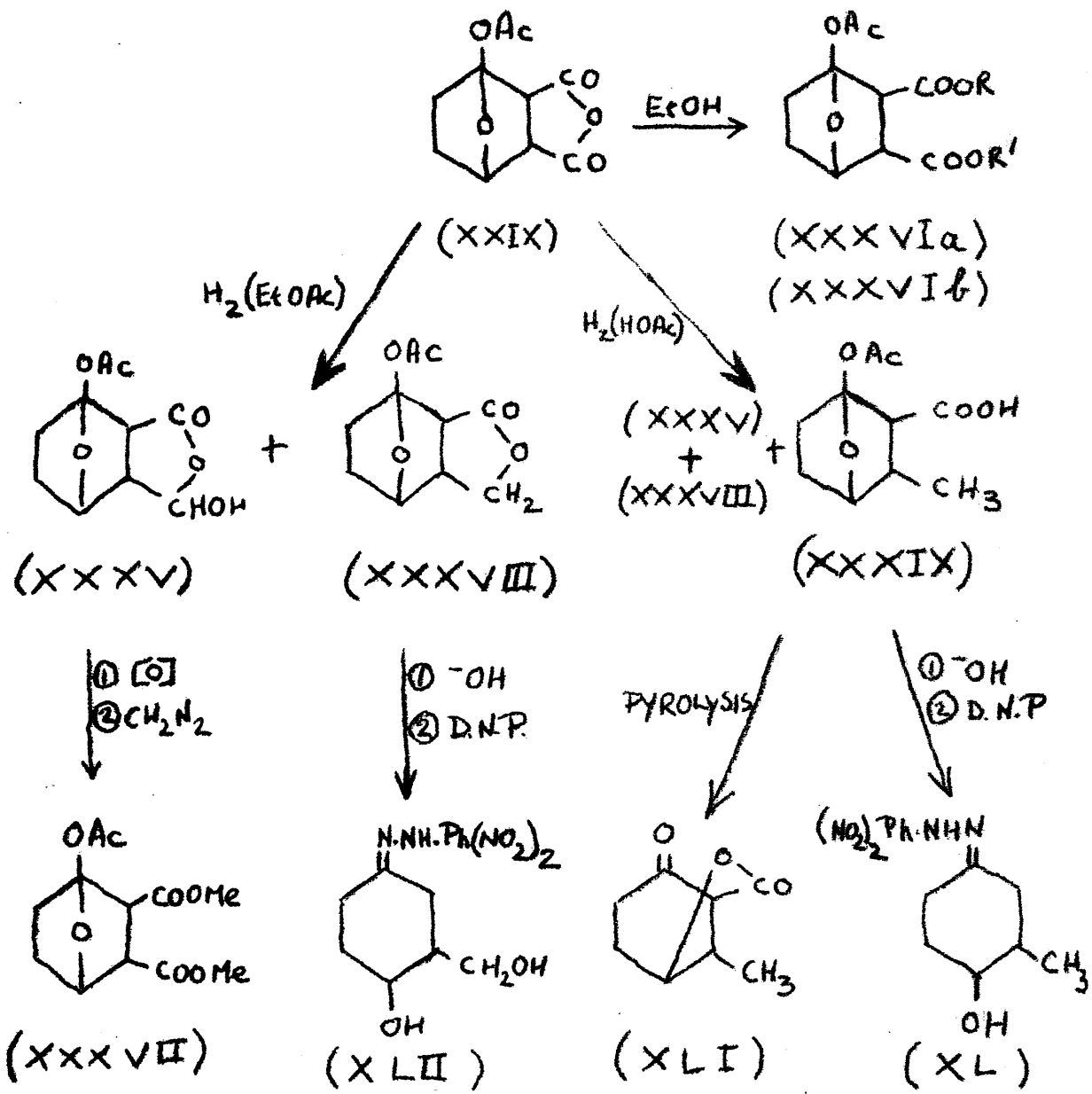
A portion (876 mg.) of this latter fraction on crystallisation from ethyl acetate-light petroleum afforded needles (412 mg.) of the known hydroxy-acid (LXX) m.p. $118\text{-}119^{\circ}$ (Salmon-Legagneur and Vene (93) found m.p. 119°). The needles were collected and converted by heating with 0.1 N-sulphuric acid for 1 hr. into α -campholide (LXXII) m.p. $206\text{-}210^{\circ}$, $[\alpha]_{\text{D}}^{22} -24^{\circ}$ (c 1.5), (the infrared spectra of this compound and of authentic α -campholide m.p. $210\text{-}212^{\circ}$, $[\alpha]_{\text{D}}^{18} -20^{\circ}$ (92), were identical).

The mother-liquors of the hydroxy-acid (LXX) were diluted with light petroleum, whereupon the known hydroxy-acid (LXXI) slowly crystallised as cubes (220 mg.) m.p. $113\text{-}115^{\circ}$. (Salmon-Legagneur and Vene (93) found m.p. $116\text{-}117^{\circ}$). These cubes on lactonisation (as above) afforded β -campholide (LXXIII) m.p. $215\text{-}219^{\circ}$, $[\alpha]_{\text{D}}^{22} + 29^{\circ}$ (c 0.9) (identified by comparison of the infrared spectrum with that of authentic β -campholide m.p. $218\text{-}220^{\circ}$, $[\alpha]_{\text{D}}^{18} + 35^{\circ}$ (c 8) (91)).

The oily residue (240 mg.) from the mother-liquors of the hydroxy-acid (LXXI) was lactonised (as above) and the product, an oil (180 mg.), chromatographed on activated alumina (grade III)(6 g.). Elution with light petroleum afforded successively α -campholide (65 mg.) m.p. 206-212° and then β -campholide (90 mg.) m.p. 212-217°.

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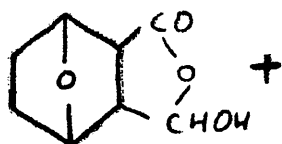


$(\text{XXXVIa}) \text{ (R=H; R'=Et)}$
 $(\text{XXXVIb}) \text{ (R=Et; R'=H)}$



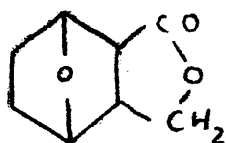
(XLIII)

(XLIV)



(XLV)

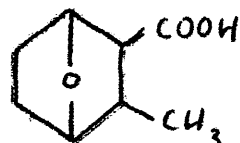
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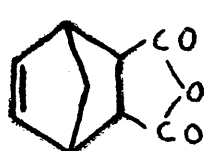
(XLVI)

$H_2(HOAc)$

(XLVI)

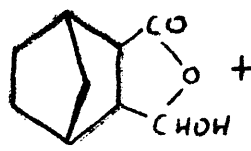


(XLVII)

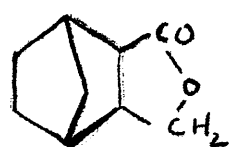


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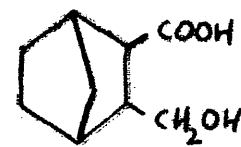
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EtOAc



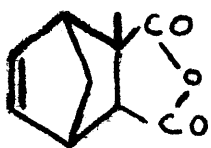
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(L)

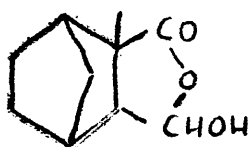


(LI)

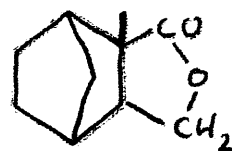


(LII)

H_2
EtOAc

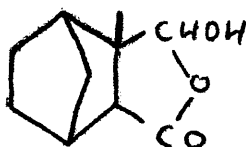


(LIII a)

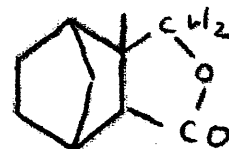


(LIV a)

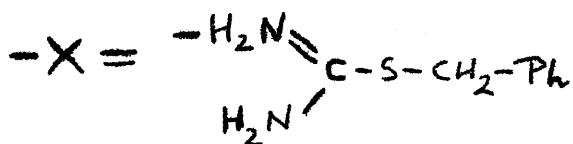
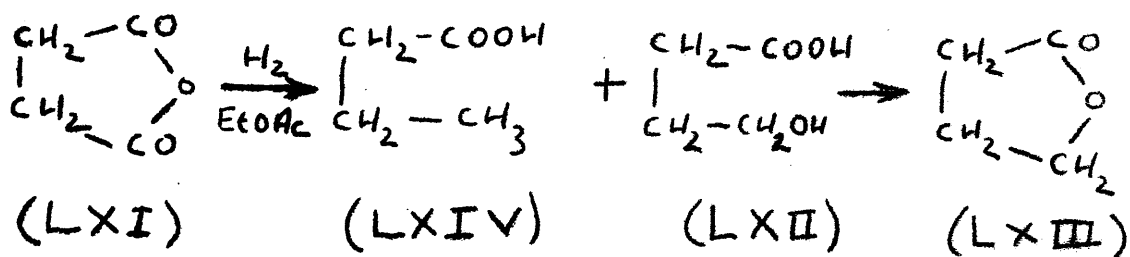
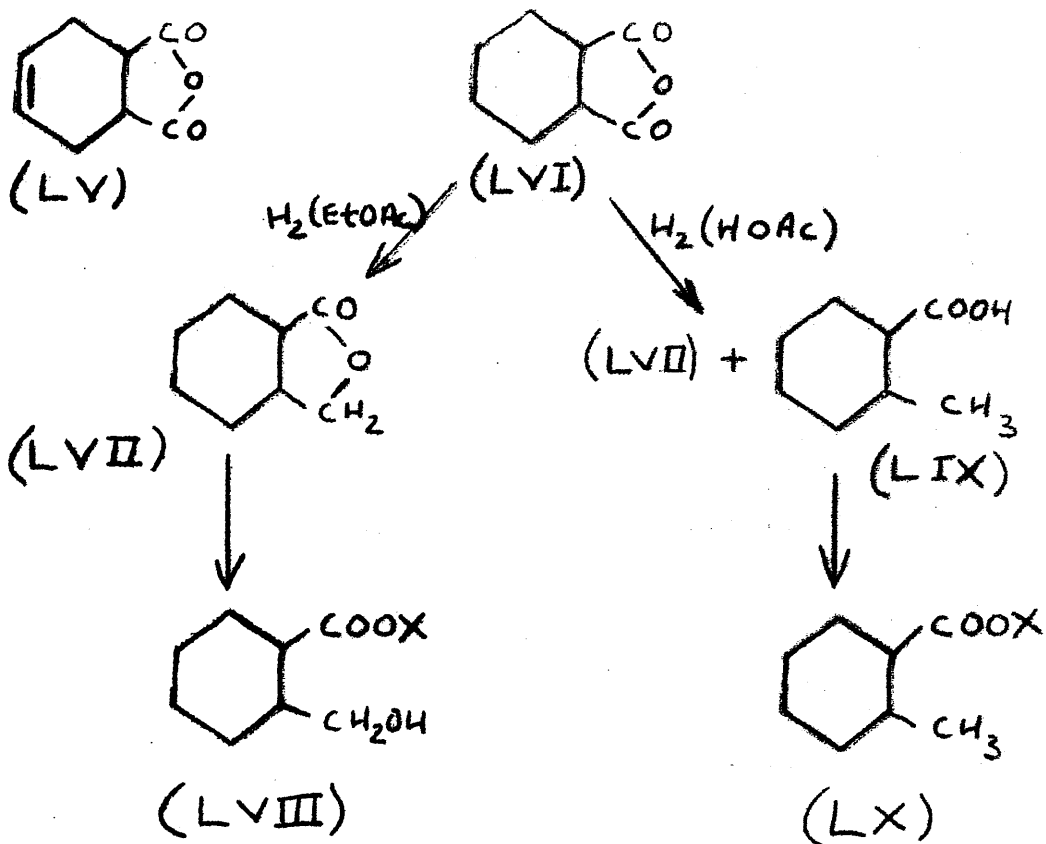
OR



(LIII b)



(LIV b)



**SECTION III.- Approaches to the Total Synthesis
of Diterpenoids.**

Synthetic work in the diterpene field (for a recent review of the chemistry of diterpenes see ref. (94)) has met with success mainly in the production of tricyclic diterpenes with one aromatic ring. The presence of this aromatic ring simplifies the problem of synthesis by reducing the number of asymmetric centres. Most of the approaches to these compounds fall into a few well-defined general routes, which are exemplified below.

Methods of synthesis based on the generally accepted biogenetic route to terpenoid compounds (95) by acid-catalysed multiple cyclisations of aliphatic or ω -phenyl aliphatic precursors have led to complex mixtures probably because the in vitro processes were not fully concerted (95b; 96). However, some success has been achieved starting with either purely aliphatic or ω -phenyl aliphatic compounds. An example of the former case (for others see refs. (95c) and (96) and refs. therein cited) is the formation (97) of an abietatriene (LXXV) from farnisylidenemethyl isopropyl ketone (LXXIV); examples of the latter case are the syntheses of racemic 6-methoxypodocarpatriene (LXXVII) from (LXXVI;R-OMe) (98) and a podocarpa-5, 7,13-triene (99) of unspecified stereochemistry from (LXXVI;R-H) and (LXXVIII).

Phenethylcyclohexanols are more efficient starting materials. Racemic 0-methylpodocarpic ester (LXXX;R-Me) has resulted from cyclisation of the phenethylcyclohexanol (LXXIX) (100), while a later synthesis (101) of racemic podocarpic acid (LXXX;R-H) (for a recent synthesis of d-podocarpic acid see ref. (102)) differed in that the phenolic hydroxyl group was introduced after the cyclisation step. Ferruginol (LXXXI) has also been

synthesised by a closely analogous route via the intermediate (LXXVII), introduction of the isopropyl group being effected by acetylation, with subsequent modification of the resulting 7-acetoxy group (103). Barltrop in his synthesis of totarol (LXXXII) (104) also used this technique for construction of the molecular skeleton. The intermediate (LXXXIII) was reduced with lithium in ammonia to the $\alpha\beta$ -unsaturated cyclohexenone (LXXXIV) which was isopropylated and then dehydrogenated.

β -Tetralones have also been utilised as starting materials for diterpene syntheses. Dehydroabiatic acid (LXXXV) was prepared from the tetralone (LXXXVI) via (LXXXVII), the product of ring extension of the tetralone with ethyl vinyl ketone (105). Ferruginol (LXXXI) has been prepared by similar techniques (106).

Advances in the synthesis of non-aromatic diterpenes have recently been reported, especially of those containing the 4,4,9-trimethyl-trans-decalin system, such as the alcohols, manool (LXXXVIII)(107) and sclareol (LXXXIX)(107; 108) and the acids, cativic acid (XC)(109) and labdanolic acid (XCI)(110). Possible intermediates for the synthesis of diterpenes of this class have been prepared with the correct basic decalin skeleton and a carbonyl group to allow introduction of the side-chains e.g. (XCII) (111), (XCIII)(112), (XCIV)(113), (XCV;R=Ac)(114), (XCV;R=Bz)(115), and (XCVI)(116; 114a). Barltrop, however, has produced a more fruitful intermediate (LXXXIV)(104a) (used in the preparation of totarol (LXXXII) (104c)) which was recently converted into dl-ambreinolide (XCVII)(117), a degradation product of manool (118) and sclareol (119). (+)-Ambreinolide, obtained from natural sources, was subsequently used as a relay in the synthesis of sclareol and 13-episclareol (120b) as described below, and

thence to the corresponding labdanolic acids (120a). The previous conversion of sclareol to manool is recorded (108). The optically active lactone (XCVII) gave the lithium salt (XCVIII) which, when treated with methyl-lithium, afforded the hydroxy-ketone (XCIX). Acetylation followed by ethynylation gave a mixture of ethynylcarbinols (C) which were separated and reduced by lithium aluminium hydride to sclareol (LXXXIX) and 13-episclareol.

Barltrop has also prepared (121) (by an analogous route to that used for the production of (LXXXIV) (104a)) a possible intermediate (CII) for the synthesis of the non-aromatic resin acids, such as agathenedicarboxylic acid (CI).

An attempted synthesis of bicyclic diterpenes with the trans-decalin ring junction was proposed and ambreinolide (XCVII), in which side chains are already attached in a stereochemically correct manner, was considered a suitable intermediate. This intermediate was then to be converted into the diterpenes by routes similar to those by which Barltrop has now accomplished this conversion (120).

In the projected synthesis of ambreinolide the cyclopentane-dione (CVIII) which has been prepared from diethyl oxalate (CIII) and butan-2-one (CIV) (122; 123; 124) was envisaged as starting material. It was hoped that ring extension with ethyl vinyl ketone would give the ene-dione (CXVI), further ring extension, this time with methyl vinyl ketone, then yielding (CXX). Introduction of the gem-dimethyl groups by standard techniques (125) would afford the diene-dione (CXXI), stereoselective reduction of the olefinic bonds and removal of the cyclohexane carbonyl group then producing the ketone (CXXII). This ketone might then be oxidised to ambreinolide (this oxidative conversion has now been reported by Eschenmoser (96)).

The ring extension of the starting cyclopentane-dione (CVIII) was effected by conditions analogous to those used by Newman for condensation of similar compounds (126). Condensation of (CVIII) with the amino-ketone (CXI) in the presence of pyridine followed by an acidic work-up as advocated by Newman resulted in the formation of a mixture containing the hydroxy-dione (CXV), the ene-dione (CXVI), and the trione (CXIV). A neutral work-up proved more efficient, the hydroxy-dione was isolated in greater yield and, being a crystalline solid, could be readily purified. Little ene-dione was detected (spectroscopically) in this case but the trione was again

isolated and, by heating with diethylamine, provided a further amount of the hydroxy-dione. By heating in benzene with β -naphthalene sulphonic acid the hydroxy-dione was converted very efficiently into the ene-dione which, on condensation with methyl vinyl ketone in *t*-butanol in the presence of potassium *t*-butoxide, afforded an oil which probably consisted of the hydroxy-ene-dione (CXXIII), since dehydration with β -naphthalene sulphonic acid as catalyst afforded an oil exhibiting the infrared and ultraviolet absorption which would be expected for the dienone (CXXIV).

The cyclopentane carbonyl group was then protected by formation of the ethylene ketal (CXVII), this ketal forming preferentially possibly because of the blocking effect on the cyclohexene carbonyl group of the adjacent methyl group, the two groups being held in one plane by the olefinic bond. The monoketal (CXVII), however, could not be made to condense with methyl vinyl ketone. Ring extension as used by Woodward for formation of ring A in his steroid synthesis (127) was next attempted. It was hoped that condensation of the monoketal with acrylonitrile would yield the nitrile (CXXV) which could then be converted into the enol lactone (CXXVII) via the acid (CXXVI). The enol lactone by reaction with methyl magnesium bromide would then afford the monoketal (CXXVIII). Cyanoethylation did take place but the product was an intractable oil as was the acidic material obtained by basic hydrolysis of this oil. It seemed possible that reaction was taking place at both α -positions to the unprotected carbonyl group. The crystalline derivative (CXIX) was then prepared by the usual method (128) but this compound also yielded oily intractable cyano and carboxy-compounds as before. The possibility existed that some cyano-ethylation had taken place in the cyclopentane ring because of vinylogous

activation by the cyclohexene carbonyl group; this approach was therefore abandoned.

The next approach was undertaken with the intention of condensing the cyclopentane-dione (CVIII) with a vinylic ketone which would afford a product in which the side chain necessary for further ring extension was already present. Such a vinylic ketone is the compound (CXXIX) ($>C=X$ is a potential carbonyl group) which would yield the hydroxy-dione (CXXX) by condensation with the cyclopentane-dione. The product of conversion of the potential carbonyl group into a free carbonyl group would be expected to cyclise very readily to the intermediate (CXXXI) which, on dehydration, could be elaborated as before.

Condensation of ethyl acetoacetate (CXXXII) with methyl methacrylate (CXXXIII) in methanol containing sodium methoxide (cf. ref. 129) afforded the keto-diester (CXXXIV; R-Me or Et) (some trans-esterification probably taking place). The keto-diester, when refluxed in 5N-sulphuric acid, yielded a mixture of the keto-acid (CXXXV) and the corresponding ester (CXXXVI). The vinyl ketone (CXXIX; X=O) could not be prepared by condensation (130) of ethylene with the keto-carboxylic acid chloride (CXXXVIIIa), since this last compound spontaneously formed the enol lactone (CXXXVIII). Protection of the carbonyl group of the keto-acid with an acid stable group (to withstand the acidic conditions used in the condensation with ethylene) was proposed. The corresponding enol acetate failed to form (131). The ketal (CXXXIX) with 2-mercaptoethan-1-ol was prepared but formation of the corresponding acid chloride could not be effected. Protection by hydrogenation to the hydroxy-acid (CXXXVIIa) proved impracticable since dehydration to the corresponding lactone took place spontaneously.

The desired monoketal (CXLVI) was prepared as follows:- The keto-acid (CXXXV) was converted into the ketal-acid (CXLI) via the corresponding methyl esters (ketalisation of the free acid resulted in such concurrent esterification). This ketal acid, by treatment with methyl lithium (132), yielded the monoketal (CXLII) which afforded the amino-ketone (CXLV) by condensation with the diamine (CXLIV). The structure was assigned on the basis of the infrared and ultraviolet absorption of the amino-ketone itself and also of its distillation product (CXLVI).

The condensation of this amino-ketone with the cyclopentane-dione has now to be attempted.

(Formulae flowsheets for this section are on pages 112-119).

Ethyl 4-methyl-2,3,5-trioxocyclopentylglyoxylate. (CV).--

Dry redistilled butan-2-one (CIV) (36 g.) was condensed with pure ethyl oxalate (CIII) (160 g.) in the presence of sodium ethoxide in dry ethanol, as described by Diels (122). The product formed pale yellow needles (46 g.) m.p. 160° (from ethyl acetate), ν_{\max} . (nujol mull) 3250 (strong broad peak) (hydroxyl of enol), 1755 (strong sharp peak) (?), and 1650 cm.^{-1} (very strong broad peak) (?).

3-Methylcyclopentane-1,2,4-trione (CVI).--

The above glyoxylate (30 g.), when heated with 50% aqueous orthophosphoric acid, afforded the trione (122) which crystallised from aqueous solution as very pale yellow needles (14.8 g.) of the hydrate m.p. $116-119^{\circ}$, ν_{\max} . (nujol mull) 3450, 3300, 1740, 1680, and 1650 cm.^{-1} .

2-Methylcyclopentane-1,3-dione (CVIII).--

The monosemicarbazone (CVII) (3 g.) of the trione (CVI), when heated to 180° in ethylene glycol with potassium hydroxide (124), afforded the dione (925 mg.) as colourless plates (from methanol) m.p. $214-216^{\circ}$. The infrared spectrum (nujol mull) exhibited diffuse absorption at $2400-2700 \text{ cm.}^{-1}$ and a strong broad maximum at 1570 cm.^{-1} , the only peak in the carbonyl region being an exceedingly weak one at 1690 cm.^{-1} .

β -Chloroethyl Ethyl Ketone (CX).--

Propionyl chloride (CIX) (90 g.) underwent Friedel-Crafts condensation with ethylene, as described by Woodward (130b) and McMahon (130a), in chloroform in the presence of anhydrous aluminium chloride. We found, however, that reaction only proceeded when the ethylene gas was liberated directly below a vibro-mixer. The product was distilled through an upright

Vigreux column (10 in.) and the fraction b.p. 48°/14mm. (n_D^{24} 1.4335) (52 g.) was collected.

1-Diethylaminopentan-3-one (CXI).-

The above chloro-ketone (50 g.) reacted with diethylamine to give the hydrochloride of the desired amine (133). The amine was set free with sodium hydroxide and distilled through an upright Vigreux column (10 in.). The fraction b.p. 40-45°/1 mm. (n_D^{24} 1.4350) (22 g.) was collected.

Methyl Vinyl Ketone (CXII).-

Commercial methyl vinyl ketone (actually an aqueous solution) was shaken with anhydrous potassium carbonate and distilled at 120 mm. The early fractions of the distillate were collected separately (methyl vinyl ketone distils azeotropically with water), from the later main fraction of pure vinyl ketone b.p. 32-33°/120 mm.

1-Diethylaminobutan-3-one (CXIII).-

Methyl vinyl ketone (70 g.) was purified as above and treated with diethylamine (80.5 g.) in glacial acetic acid (126). The product was fractionally distilled through an upright Vigreux column (10 in.) and had b.p. 62°/6 mm. (n_D^{24} 1.4333) (48 g.).

Condensation of 1-Diethylaminopentan-3-one with 2-Methylcyclopentane-1,3-dione.-

The dione (CVIII) (2.8 g.), the amino-ketone (CXI) (4.7 g.), and dry "AnalaR" pyridine (2 ml.) were heated in refluxing benzene (sodium-dried; 35 ml.) for 18 hrs. (cf. ref. 126). The cooled solution was diluted to 50 ml. with benzene, washed with dilute aqueous hydrochloric acid (30 ml.) and a saturated solution of sodium chloride (2 x 25 ml.), and dried. Removal of the solvent yielded an oil (1.8 g.) which gradually deposited

large colourless cubes. The contaminating oil was washed away with cold ether and the residual solid (480 mg.), on crystallisation from ethyl acetate-light petroleum, afforded the hydroxy-dione (CXV) m.p. 150-151° (Found: C, 67.45; H, 8.3. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%), ν_{max} . (nujol mull) 3500 (hydroxyl) and 1725 cm^{-1} (superimposed cyclopentanone and cyclohexanone).

Evaporation of solvent from the ether washings afforded a red oil (1.3 g.) which was chromatographed over silica (50 g.). Benzene-10% ether eluted an oil (850 mg.) (fraction A) which exhibited absorption in the infrared (film) at 1740 (broad and intense) and 1670 cm^{-1} (sharp and less intense) ($\alpha\beta$ -unsaturated cyclohexenone) and in the ultraviolet λ_{max} 248 m μ (ϵ 3500). It was concluded that this oil contained about 30% of the ene-dione (CXVI) since this compound would be expected (from Woodward's rules (134)) to have λ_{max} 254 m μ (ϵ 10000). Elution of the column with ethyl acetate afforded a further quantity of the hydroxy-compound (CXV) (160 mg.) m.p. 148-151°.

The combined aqueous layers from the original extraction, after standing at room temperature for 22 hrs., were extracted with benzene (50 ml.). The organic layer was washed with saturated sodium chloride solution (2 x 20 ml.) and dried. Removal of the benzene afforded a red oil (950 mg.), which was placed on silica (30 g.), elution with benzene-10% ether yielding a colourless viscous oil (850 mg.) which had infrared absorption maxima (film) at 1670 ($\alpha\beta$ -unsaturated cyclohexenone) and 1750 cm^{-1} (cyclopentanone) and ultraviolet absorption λ_{max} 249 m μ (ϵ 11500) and therefore consisted essentially of the ene-dione (CXVI), which had b.p. 114°/0.6 mm. (Found: C, 74.05; H, 8.1. $C_{11}H_{14}O_2$ requires C, 74.15; H, 7.9%).

Elution of the column with ethyl acetate afforded the hydroxy-dione (CXV) (80 mg.) m.p. 148-150°.

Fraction A. - A portion (710 mg.) was heated with redistilled diethylamine (2 ml.) in refluxing benzene (25 ml.) for 18 hrs. Evaporation of solvents afforded an oil which exhibited a strong peak in the infrared (film) at 3400 cm.^{-1} (hydroxyl) as well as carbonyl absorption similar to that of starting material (at 1740 and 1670 cm.^{-1}). This oil and β -naphthalene sulphonic acid (50 mg.) were heated in refluxing benzene (25 ml.) for 2 hrs. The cooled solution was filtered through a short column of activated alumina (grade III), evaporation of the solvent then affording an oil (540 mg.), which was shown spectroscopically to contain a high proportion of the ene-dione (CXVI) (intensified 1670 cm.^{-1} peak in the infrared and ultraviolet absorption $\lambda_{\text{max}}^{249}$ (ϵ 7,000)).

The ene-dione (CXVI) was formed more efficiently as follows, via the hydroxy-dione (CXV).

The Hydroxy-dione (CXV).-

The dione (CVIII) (6.7 g.), the amino-ketone (CXI) (11.25 g.), and dry "AnalaR" pyridine (2 ml.) were heated in refluxing benzene (100 ml.) for three days. The solvents were removed at 1 mm. and the dark semi-crystalline residue quickly chromatographed over silica (300 g.), benzene-50% ether eluting an oil (8 g.), while elution with ether afforded the hydroxy-dione (4 g.) which, on crystallisation from ethyl acetate-light petroleum, had m.p. 150-151°.

The oil (8 g.) was heated in refluxing benzene (40 ml.) with redistilled diethylamine for 18 hrs. Removal of solvents and chromatography over silica as before afforded a further quantity of the alcohol (2.8 g.)

m.p. 150-151°, on crystallisation from ethyl acetate-light petroleum.

The Ene-dione (CXVI).-

A solution of the alcohol (CXV) (220 mg.) and β -naphthalene sulphonic acid (20 mg.) in benzene (25 ml.) was refluxed for 2 hrs. The cooled solution was filtered through a short column of activated alumina (grade III), removal of the solvent affording practically pure (infrared and ultraviolet spectra) ene-dione (198 mg.).

Attempted Condensations of the Ene-dione (CXVI) with Methyl Vinyl Ketone (or 1-Diethylaminobutan-3-one).-

(i) The ene-dione (470 mg.), the amino-ketone (CXIII) (455 mg.), and pyridine (0.2 ml.) were dissolved in benzene (10 ml.) and the solution heated under reflux for 18 hrs. The solvents were removed at 0.2 mm., and the residual oil (520 mg.) was judged to consist essentially of starting material (infrared (film) spectra of product and starting material superposable, and the product exhibited ultraviolet absorption $\lambda_{\text{max}} 249\text{m}\mu$ (ϵ 10,000)).

(ii) The product from (i) was treated with the amino-ketone (400 mg.) and triethylamine (0.2 ml.) in benzene as before. Starting material was again recovered.

(iii) *t*-Butanol (1 ml.) containing potassium (10 mg.) was added, with stirring and ice-cooling, to the ene-dione (444 mg.) and freshly distilled methyl vinyl ketone (210 mg.; 1.2 mol.) in dry *t*-butanol (10 ml.). After standing under nitrogen at room temperature for 18 hrs., the solution was acidified with glacial acetic acid. The solvents were taken off under vacuum (0.2 mm.), and the residue extracted with warm ethyl acetate (2 x 20ml.). Chromatography of the residual oil (640 mg.) over silica afforded by elution

with (a) benzene-20% ether, starting material (70 mg.) (ultraviolet and infrared spectra).

(b) benzene-50% ether, an oil (150 mg.) ν_{\max} . (film) 3400 (strong) (hydroxyl), 1740 (weak) (cyclopentanone), 1710 (strong) (cyclohexanone?), and 1670 cm.^{-1} (very strong) ($\alpha\beta$ -unsaturated cyclohexenone).

(c) ethyl acetate, an oil (295 mg.), ν_{\max} . (film) 3400 (very strong) (hydroxyl), 1740 (very weak) (cyclopentanone), 1710 (very strong) (cyclohexanone), and 1670 (film) (very strong) ($\alpha\beta$ -unsaturated cyclohexenone). The ultraviolet spectrum λ_{\max} 249mm (ϵ 10,000), showed the presence of the chromophore of starting material.

A portion (40 mg.) of this last fraction was refluxed in benzene with β -naphthalene sulphonic acid (25 mg.) for 1 hr. The cooled solution on filtration through a short activated alumina column (grade III) and evaporation of solvent yielded an oil (28 mg.) which exhibited no hydroxylic absorption ($3200-3500 \text{ cm}^{-1}$) in the infrared (film) but had one strong peak in the carbonyl region at 1670 cm.^{-1} ($\alpha\beta$ -unsaturated cyclohexenone). In the ultraviolet there were two maxima, λ_{\max} 241-243 (ϵ 12,000) and 249-250 mm (ϵ 15,000).

The Monoketal (CXVII).-

β -Naphthalene sulphonic acid monohydrate (50 mg.) was dissolved in refluxing benzene (70 ml.) and the water removed by azeotropic distillation. The resulting solution was filtered and added to a mixture of ethylene glycol (500 mg.) and the ene-dione (CXVI) (700 mg.) in benzene (20 ml.). The benzene solution was refluxed under a "Dean and Stark" water separator for 4 hrs. The cooled solution was filtered through a short column of activated alumina (grade V), removal of solvent then

affording the monoketal (CXVII) (800 mg.) as an oil, b.p. $128^{\circ}/0.6$ mm. (Found: C, 69.8; H, 7.6. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.15%), λ_{\max} . 250 m μ (ϵ 12,500), ν_{\max} . (film) 1770 cm^{-1} ($\alpha\beta$ -unsaturated cyclohexenone).

Attempted Condensations of the Monoketal (CXVII) with Methyl Vinyl Ketone.-

The monoketal was recovered unchanged (infrared and ultraviolet spectra) from the following experiments:-

- (i) The monoketal (280 mg.), redistilled methyl vinyl ketone (108 mg.; 1.2 mol.), and potassium (20 mg.) were dissolved in *t*-butanol and kept at room temperature (under nitrogen) for 20 hrs.
- (ii) The monoketal (280 mg.) and potassium (20 mg.) were dissolved in dry *t*-butanol (12 ml.) and pure methyl vinyl ketone (270 mg.; 3 mol.) in *t*-butanol (10 ml.) was added dropwise with stirring. The solution was then kept under nitrogen at room temperature for 20 hrs.
- (iii) The monoketal (300 mg.) and potassium (55 mg.) were dissolved in dry *t*-butanol (15 ml.). The amino-ketone (CXIII) (250 mg.; 1.2 mol.) in *t*-butanol (20 ml.) was added with stirring over 8 hrs. The solution was then kept at room temperature under nitrogen for a further 8 hrs.
- (iv) The monoketal (180 mg.), freshly distilled methyl vinyl ketone (70 mg.; 1.2 mol.), and three drops of a solution of *N*-benzyl-trimethyl ammonium methoxide (40%) in methanol were refluxed in methanol (15 ml.) for 18 hrs.
- (v) The monoketal (280 mg.), freshly distilled methyl vinyl ketone (90 mg.; 1 mol.), and sodium (10 mg.) were dissolved in dry methanol (20 ml.) and kept at room temperature under nitrogen for 16 hrs.

(vi) The monoketal (240 mg.), freshly distilled methyl vinyl ketone (100 mg.; 1.3 mol.), the amino-ketone (CXIII) (200 mg.; 1.3 mol.), and sodium (15 mg.) were dissolved in dry methanol (20 ml.) and the solution refluxed in an atmosphere of nitrogen for 18 hrs.

Condensation of the monoketal (CXIII) with Acrylonitrile.-

(i) The monoketal (220 mg.), freshly distilled acrylonitrile (55 mg.; 1 mol.), and "Triton B" (3 drops of a 40% aqueous solution) were dissolved in a mixture of *t*-butanol (20 ml.) and benzene (10 ml.) (127). The solution was kept at 35° under nitrogen for 16 hrs. The solvents and unreacted acrylonitrile were removed at the water pump and the residue was dissolved in ethyl acetate (20 ml.). This extract was washed with saturated sodium chloride solution (3 x 10 ml.) and dried. Removal of the ethyl acetate afforded an oil (200 mg.) which had $\lambda_{\text{max.}}$ 249 m μ (ϵ 10,000), $\nu_{\text{max.}}$ (film) 1670 (strong) ($\alpha\beta$ -unsaturated cyclohexenone), 1710 (weak) (cyclohexanone), and 2250 cm.⁻¹ (very weak) (nitrile).

(ii) The monoketal (150 mg.), freshly distilled acrylonitrile (145 mg.; 3 mols.), and "Triton B" (6 drops of a 40% aqueous solution) were dissolved in a mixture of *t*-butanol (10 ml.) and benzene (5 ml.) and sealed in a Carius tube under nitrogen. The tube was then kept at 50° (in a thermostatically controlled water-bath) for 10 hrs. The contents of the tube, on work up as in (i) above, afforded an oil (150 mg.) which had $\lambda_{\text{max.}}$ 249 m μ (ϵ 2,000), $\nu_{\text{max.}}$ (film) 1670 (strong) ($\alpha\beta$ -unsaturated cyclohexenone), 1710 (strong) (cyclohexanone), and 2250 cm.⁻¹ (weak) (nitrile)

(iii) The condensation was repeated as in (ii) above except that the tube was kept at 50° for 48 hrs. The product was an oil (180 mg.) which had $\nu_{\text{max.}}$ (film) 1705 (cyclohexanone) and 2250 cm.⁻¹ (nitrile), but which

exhibited neither infrared absorption at 1670 cm.^{-1} nor ultraviolet absorption at $249\text{ m}\mu$. This oil, which could not be made to crystallise, was refluxed with potassium hydroxide (100 mg.) in water (5 ml.) for 8 hrs. The cooled solution was neutralised with dilute aqueous hydrochloric acid. Extraction with ether (2 x 10 ml.) and evaporation of solvent from the dried ether extract afforded an oil (94 mg.) ($v_{\text{max.}}$ (film) 1700 (carboxyl) and $2700\text{--}3200\text{ cm.}^{-1}$ (hydroxyl of carboxyl)) which did not crystallise.

The Hydroxymethylene-derivative (CXVIII).--

Dry freshly distilled ethyl formate (4g.; 5.4 mol.) was added to a suspension of freshly prepared sodium methoxide (from 0.7 g.; 3 mol. of sodium) in dry benzene (10 ml.) (128). The mixture was allowed to stand under nitrogen, with occasional swirling, at room temperature for 10 mins. and then the monoketal (CXVII) (2.2 g.; 1 mol.) in dry benzene (10 ml.) was added. The solution was kept under nitrogen at room temperature for 20 hrs. during which time a colourless gelatinous precipitate separated. A phosphate buffer solution was added (50 ml.; pH 8) with shaking. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 50 ml.). Removal of solvents from the combined dried extracts afforded the hydroxymethylene-compound as a red oil (1.8 g.) which had $v_{\text{max.}}$ (film) 2700-3500 (weak), 1710 (weak), 1640 (very strong), and 1570 cm.^{-1} (strong) and which was used, without purification, in the production of the methylaniline-derivative.

The Methylaniline-derivative (CXIX).--

The hydroxymethylene-derivative (CXVIII) (1.8 g.) and redistilled methylaniline (4 g.) were kept in dry methanol (10 ml.) at room temperature for 3 days (128). The residual oil from evaporation of the methanol was

chromatographed over activated alumina (grade V). Light petroleum eluted unreacted methylaniline and benzene-1% ether the methylaniline-derivative (CXIX) as an oil which slowly crystallised from benzene-light petroleum as large yellow plates m.p. 113-115° (Found: C, 74.3; H, 7.45; N, 4.1.

$C_{21}H_{25}O_3N$ requires C, 74.3; H, 7.4; N, 4.15%), ν_{max} . (film) 1645 (strong), 1600 (weak), 1550 (strong), and 1500 cm^{-1} (strong), λ_{max} . 264 (ϵ 13,500) and 378-379 μ (ϵ 14,000).

Condensation of the Methylaniline-derivative with Acrylonitrile.-

The methylaniline-derivative (CXIX) (700 mg.), freshly distilled acrylonitrile (2 g.; 20 mol.), and "Triton B" (0.5 ml. of a 40% aqueous solution) were dissolved in a mixture of t-butanol (20 ml.) and benzene (10 ml.) (127). The solution was sealed in a Carius tube under nitrogen and the tube was immersed in a thermostatically controlled (at 50-55°) water-bath for 5 days. Water (5 ml.) and ethyl acetate (30 ml.) were added to the residue from removal of the solvents. The organic layer was removed and washed with saturated sodium chloride solution (2 x 15 ml.). The ethyl acetate was evaporated from the dried extract leaving an oil (1 g.) which did not crystallise.

This oil was refluxed with potassium hydroxide (1 g.) in water (10 ml.) for 10 hrs. under nitrogen. The cooled aqueous layer was washed with ethyl acetate and then exactly neutralised with dilute aqueous hydrochloric acid. Extraction with ethyl acetate (2 x 10 ml.) and evaporation of solvent from the dried extracts afforded a yellow oil (405 mg.) which was treated with ethereal diazomethane and then refluxed with concentrated aqueous hydrochloric acid (4 drops) in methanol (20 ml.) for 1 hr. The solution was concentrated (to about 5 ml.) and water (10 ml.) added.

Extraction with ethyl acetate (4 x 20 ml.), washing the extract with saturated sodium chloride solution and then evaporating the solvent afforded an oil (400 mg.) which was chromatographed over activated alumina (grade III). No separation was effected, all the fractions having infrared spectra nearly identical with that of the oil which had been placed on the column (ν_{max} . (film) 1600 (weak), 1660 (weak), 1705 (strong), and 1740 (strong).

5-oxohexano-2-carboxylic acid (CXXXV).--

Ethyl acetoacetate (CXXXII) (276 g.) was dissolved with stirring in dry methanol (70 ml.) containing sodium (2.4 g.) (cf. ref. 129). Freshly distilled methyl methacrylate (CXXXIII) (213 g.) was added during 2 hrs. with stirring and heating on the steam-bath. Heating and stirring were continued for 30 min. after this addition had been completed. The methanol was removed at the water-pump and the residual mixture acidified with dilute sulphuric acid. The resulting solution, on saturation with ammonium sulphate separated into two layers. The organic layer was removed, after dilution with ether (500 ml.), and the aqueous layer was extracted with ether (4 x 500 ml.). The combined ether extracts were washed with saturated ammonium sulphate solution (2 x 500 ml.), dried and the solvent was then removed. The residual oil was distilled (b.p. $96^{\circ}/0.2$ mm.) and afforded the diester (CXXXIV) as a colourless oil (395 g.).

This oil (390 g.) was refluxed in 5N-sulphuric acid for 9 hrs. The cooled solution was saturated with ammonium sulphate, extracted with ether (5 x 500 ml.) and the combined ether extracts were washed with saturated ammonium sulphate solution and dried. Evaporation of the ether yielded a dark yellow oil which was distilled and afforded two main fractions; the first was the methyl ester (CXXXVI), a colourless oil (109 g.), which had

b.p. $48^{\circ}/0.15$ mm., n_D^{21} 1.4290 (Found: C, 60.7; H, 8.95. $C_8H_{14}O_3$ requires C, 60.75; H, 8.9%), ν_{\max} . (film) 1705 (ketone) and 1725 cm^{-1} (ester).

The second fraction was the corresponding acid (CXXXV), the expected product, which distilled as a colourless oil (132 g.) b.p. $96^{\circ}/0.1$ mm., n_D^{24} 1.4432, ν_{\max} . (film) 1700 (superimposed ketone and carboxyl) and $2500-3500$ cm^{-1} (hydroxyl of carboxyl). A small portion formed the corresponding methyl ester (CXXXVI) (infrared spectrum), on treatment with ethereal diazomethane.

The first fraction (106 g.) was converted into the acid (63 g.) by heating in excess N-potassium hydroxide solution for 1 hr., acidifying with dilute hydrochloric acid, saturating with ammonium sulphate and extracting with ether as above.

5-Hydroxy-hexane-2-carboxylic acid lactone (CXXXVII).-

The keto-acid (0.5 g.) in "AnalaR" ethyl acetate (25 ml.) was hydrogenated over Adams catalyst (10 mg.). Removal of solvent yielded an oil ν_{\max} . (film) 1700 (superimposed ketone and carboxyl) and $2500-3500$ cm^{-1} (superimposed hydroxyl and hydroxyl of carboxyl). This oil gradually deposited crystals of the lactone on standing at room temperature. This solid was collected and sublimed for analysis at $50-60^{\circ}/0.1$ mm. and formed colourless plates m.p. $49-56^{\circ}$ (Found: C, 65.05; H, 9.45. $C_7H_{12}O_2$ requires C, 65.6; H, 9.45%), ν_{\max} . (in carbon tetrachloride) 1730 cm^{-1} (δ -lactone).

Attempted Formation of the Enol Acetate of the Keto-acid (CXXXV).-

The keto-acid (2.3 g.) and fused potassium acetate (100 mg.) were refluxed in "AnalaR" acetic anhydride (25 ml.) for 2 hrs. (131). A portion (10 ml.) of the solvent was then distilled out and the remainder refluxed for 16 hrs. The solvent was removed and the residue refluxed in water

(10 ml.) for 30 min. to destroy any mixed anhydrides present. The cooled solution was extracted with ethyl acetate (3 x 10 ml.) and the combined extracts were washed with saturated ammonium sulphate solution (2 x 10 ml.) and dried. Removal of solvent afforded starting material (1.7 g.) (identified by its b.p. and infrared spectrum).

The Enol Lactone of the Keto-acid (CXXXV).-

Oxalyl chloride (37 g.) was added to the keto-acid (42 g.) in dry benzene (50 ml.) with ice-cooling, the solution being then kept at room temperature for 16 hrs. Removal of the solvent afforded a mobile oil which distilled through a short upright Vigreux column at a steady temperature (60°/0.7 mm.) (36 g.) and was not the expected keto-acid chloride but was shown to be the enol lactone (CXXXVIII), redistilled for analysis it had b.p. 32°/0.2 mm. n_D^{22} 1.4602 (Found: C, 66.05; H, 7.45. $C_7H_{10}O_2$ requires C, 66.65; H, 8.0%), ν_{max} . (in carbon tetrachloride) 1755 cm^{-1} .

The Semithioketal of the Keto-acid (CXXXIV).-

The keto-acid (36 g.), 2-mercaptoethan-1-ol (19.5 g.), and β -naphthalene sulphonic acid (0.25 g.) were refluxed in benzene (100 ml.), the water liberated being collected by the use of a "Dean and Stark" apparatus. After 6 hrs. the solution was allowed to cool and the catalyst crystallised and was collected. Removal of solvent and distillation of the residual oil afforded the semithioketal (CXXXIX) (43 g.) as a colourless viscous oil b.p. 114°/0.2 mm., n_D^{19} 1.4890 (Found: C, 52.65; H, 8.1. $C_9H_{16}O_3S$ requires C, 52.95; H, 7.9%), ν_{max} . (film) 1700 (carboxyl) and 2500-3500 cm^{-1} (hydroxyl of carboxyl).

Attempted Preparation of the Acid Chloride of the Semithioketal.-

(i) Oxalyl chloride (3 ml.) was added, with ice-cooling, to the semithioacetal (CXXXIX) (1 g.) in dry benzene (15 ml.). The solution was kept at room temperature for 3 hrs. and the solvent was then removed. The residual red oil had ν_{\max} . (film) 1760 (strong), 1700 (strong), and 1560 cm.^{-1} (weak). The oil was then treated with a further amount of oxalyl chloride (3 g.) as before and the product was again a red oil, ν_{\max} . (film) 1760 (strong), 1700 (strong), and 1560 cm.^{-1} (strong), which polymerised on attempted distillation at 0.1 mm.

(ii) Oxalyl chloride (0.64 g.) was added, with ice-cooling, to a mixture of the dried (at $110^{\circ}/0.05$ mm.) sodium salt of the semithioacetal acid (1.08 g.), dry pyridine (3 drops), and dry benzene (10 ml.). The mixture was kept at room temperature for 10 min. and the solid which had separated was collected. Removal of solvent from the filtrate afforded an oil ν_{\max} . (film) 1700 (strong) and 1560 cm.^{-1} (weak), no absorption in the 2500-2800 cm.^{-1} region (hydroxyl of carboxyl).

Methyl 5-Ethylenedioxy-hexane-2-carboxylate (CXL).-

The keto-acid (CXXXV) (5.75 g.) was treated with excess ethereal diazomethane and afforded the corresponding methyl ester (CXXXVI) which was refluxed with ethylene glycol (3 g.; 1.2 mol.) and β -naphthalene sulphonic acid in dry benzene (20 ml.) for 6 hrs., the water formed being collected in a "Dean and Stark" water separator. The cooled solution was diluted with ethyl acetate (20 ml.) and then washed with saturated sodium bicarbonate solution (2 x 20 ml.) and saturated sodium chloride solution (20 ml.). Removal of solvents from the dried solution and distillation of the residual oil afforded the ketal (CXL) (6.2 g.) as a colourless mobile oil b.p. $68-72^{\circ}/0.04$ mm., n_D^{22} 1.4388 (Found: C, 59.1; H, 8.85. $\text{C}_{10}\text{H}_{18}\text{O}_4$ requires

C, 59.4; H, 8.95%), ν_{\max} . (film) 1720 cm.^{-1} (ester).

5-Ethylenedioxy-hexane-2-carboxylic Acid (CXLI).-

The ketal ester (CXL) (3.91 g.) was heated, with stirring, on the steam-bath with 1N-sodium hydroxide solution (50 ml.) for 1 hr. 1N-Hydrochloric acid (49 ml.) was added to the cooled solution. Extraction with ether (6 x 50 ml.) and evaporation of solvent from the dried combined extracts afforded the ketal acid (CXLI) as a mobile colourless oil (3.25 g.) ν_{\max} . (film) 1700 (carboxyl) and 2500-3500 cm.^{-1} (hydroxyl of carboxyl) and which could be reconverted to the ketal ester (identified by the infrared spectrum) with ethereal diazomethane.

6-Ethylenedioxy-3-methyl-2-oxoheptane (CXLII).-

A solution of methyl-lithium (2 mols.) in ether was added quickly to the ketal acid (CXLI) (10 g.) in dry ether (250 ml.) under nitrogen (132). A waxy solid separated immediately, which gradually dissolved when the mixture was heated and stirred vigorously (without this stirring the yields of the monoketal (CXLII) were very poor (et. ref. 132)). After refluxing for 1 hr., the solution was cooled and water (250 ml.) added slowly with shaking. The ether layer was removed and washed with water (3 x 100 ml.), these washings being extracted with ether (250 ml.) and this extract was washed as before. The solvent was removed from the dried combined ether extracts and the residual oil (6 g.) chromatographed over activated alumina (grade V) (150 g.), benzene eluting the monoketal (CXLII) as a colourless mobile oil (4.4 g.) b.p. 71-72^o/0.8 mm., n_D^{22} 1.4442 (Found: C, 64.25; H, 9.45. $\text{C}_{10}\text{H}_{18}\text{O}_3$ requires C, 64.5; H, 9.75%), ν_{\max} . (film) 1710 cm.^{-1} (ketone).

Elution of the column with ethyl acetate afforded the tertiary

alcohol (CXLIII) as an oil (1.3 g.) b.p. 80-81°/0.7 mm., n_D^{25} 1.4528, ν_{max} . (film) 3400 cm^{-1} (hydroxyl).

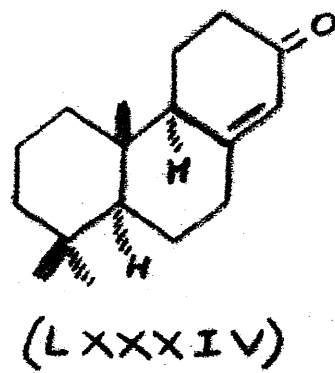
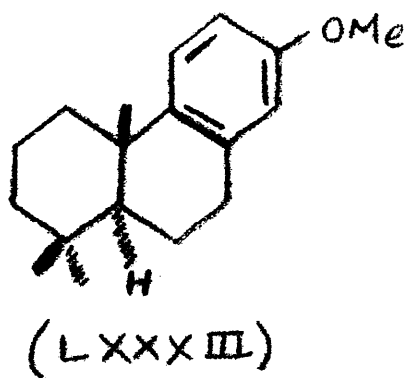
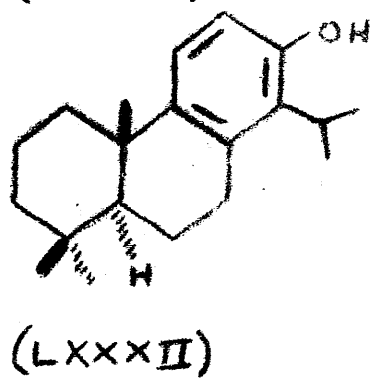
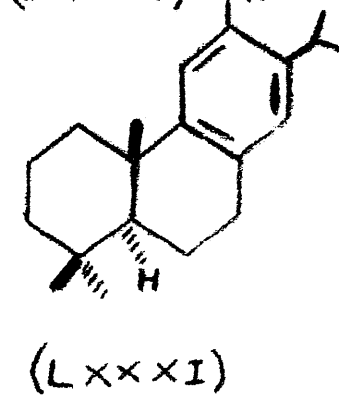
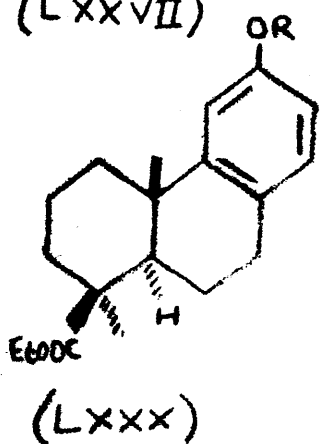
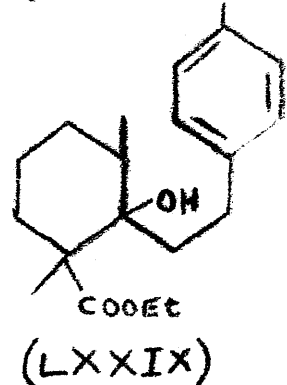
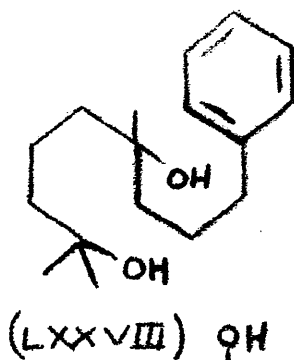
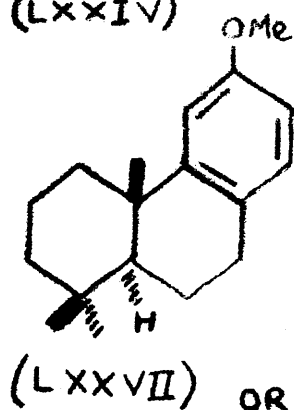
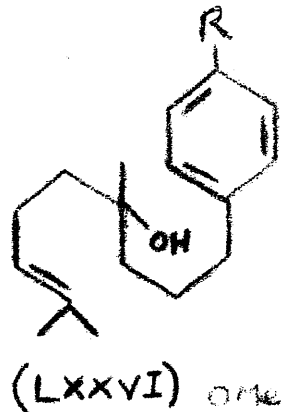
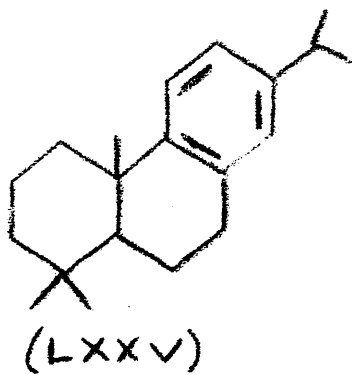
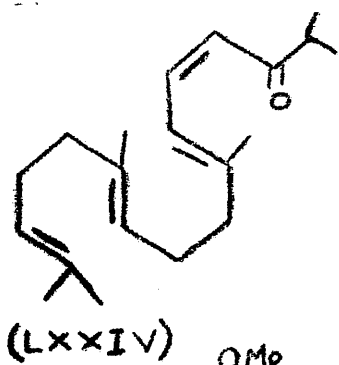
Condensation of the Monoketal (CXLII) with N,N'-Tetraethylmethylenediamine (CXLIV).-

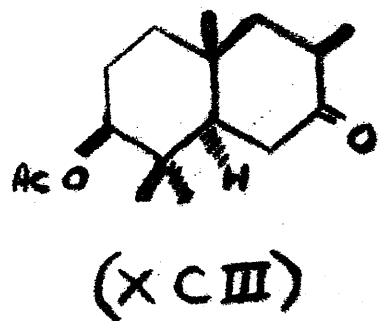
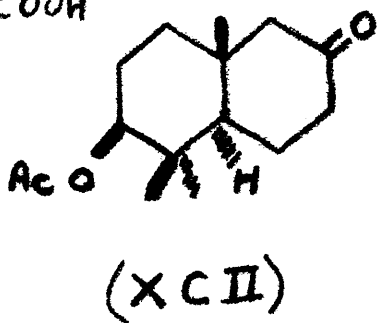
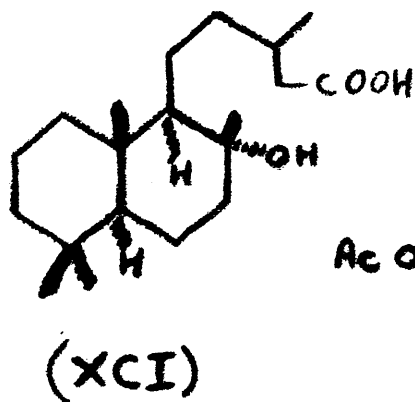
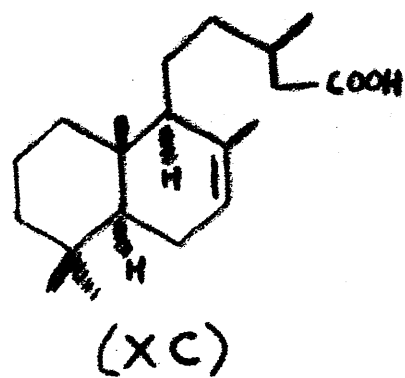
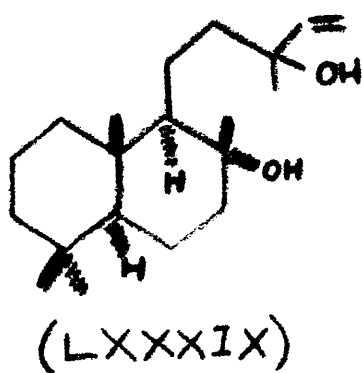
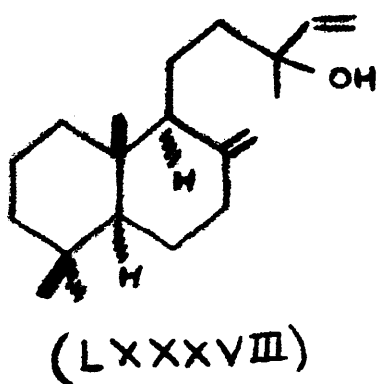
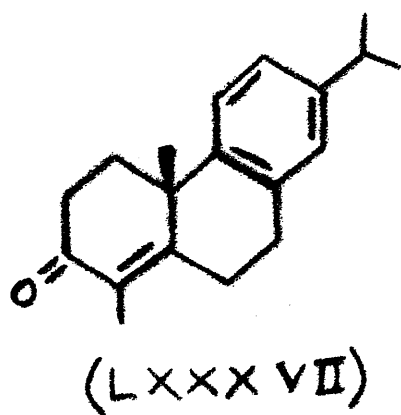
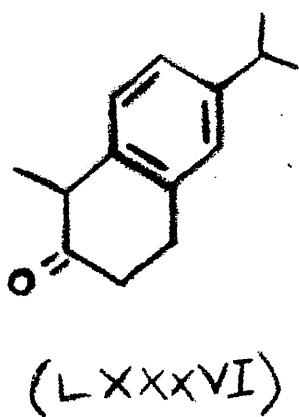
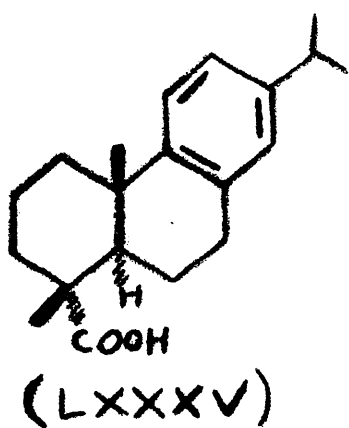
The monoketal (400 mg.) and the diamine (CXLIV) (135) (400 mg.) were heated on the steam-bath with dimethylamine hydrochloride (200 mg.) for 10 hrs. Potassium hydroxide (140 mg.) in water (5 ml.) was added and the resulting mixture extracted with ether (20 ml.). Removal of solvent, diethylamine and unreacted diamine (at the water-pump) from the dried ether extract afforded the amino-ketone (CXLV) as a viscous oil (520 mg.) which exhibited infrared absorption at 1705 cm^{-1} (ketone) and 2800 cm^{-1} (present in the spectrum of 1-diethylaminopentan-3-one). The oil was distilled (at 125-130°/0.1 mm.) in an attempt to obtain a specimen suitable for analysis but the distillate showed a new peak in the infrared (at 1680 cm^{-1} ($\alpha\beta$ -unsaturated ketone)) and in the ultraviolet (λ_{max} . 213 m μ (ϵ 3,000)). Redistillation strengthened these two peaks (λ_{max} . 213 m μ (ϵ 4,200)).

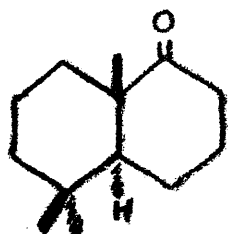
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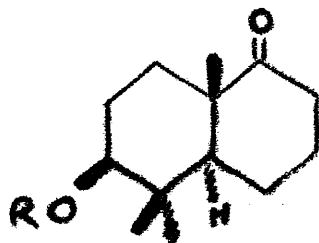
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- (135) Mannich and Ritsert, Ber., 1924, 57, 1116.



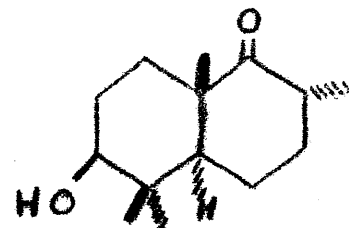




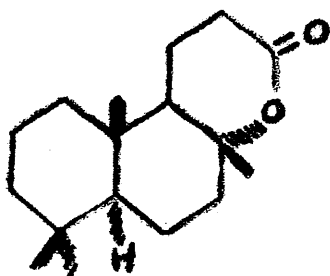
(XCIV)



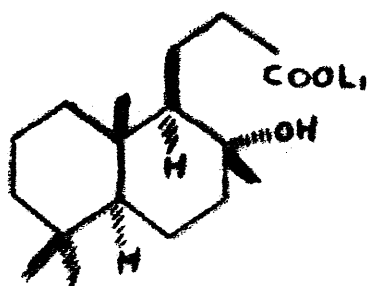
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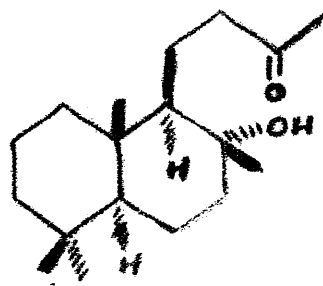
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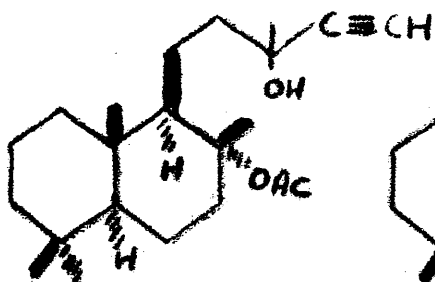
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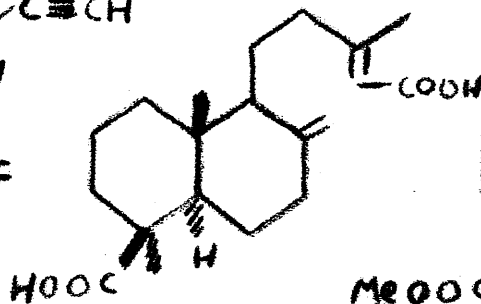
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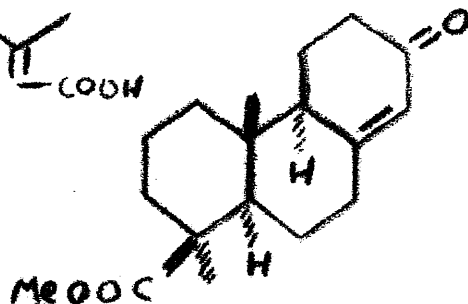
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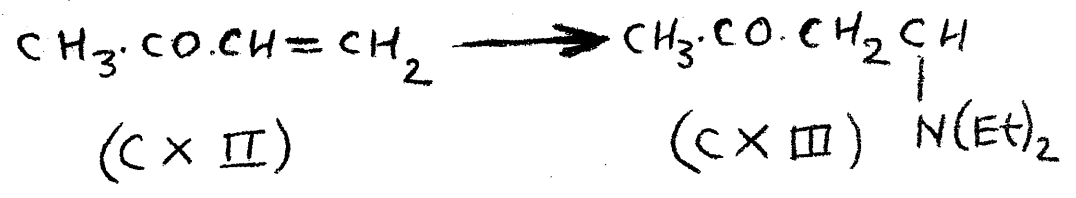
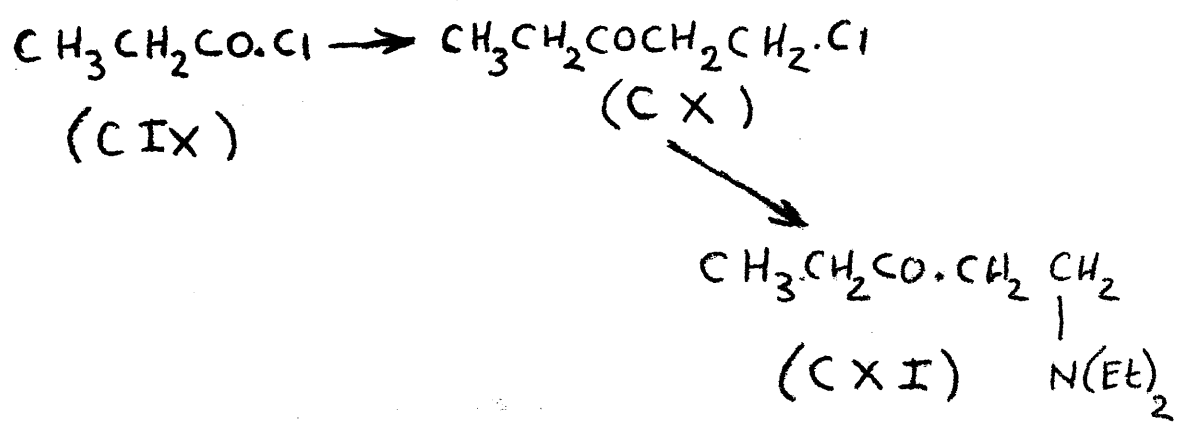
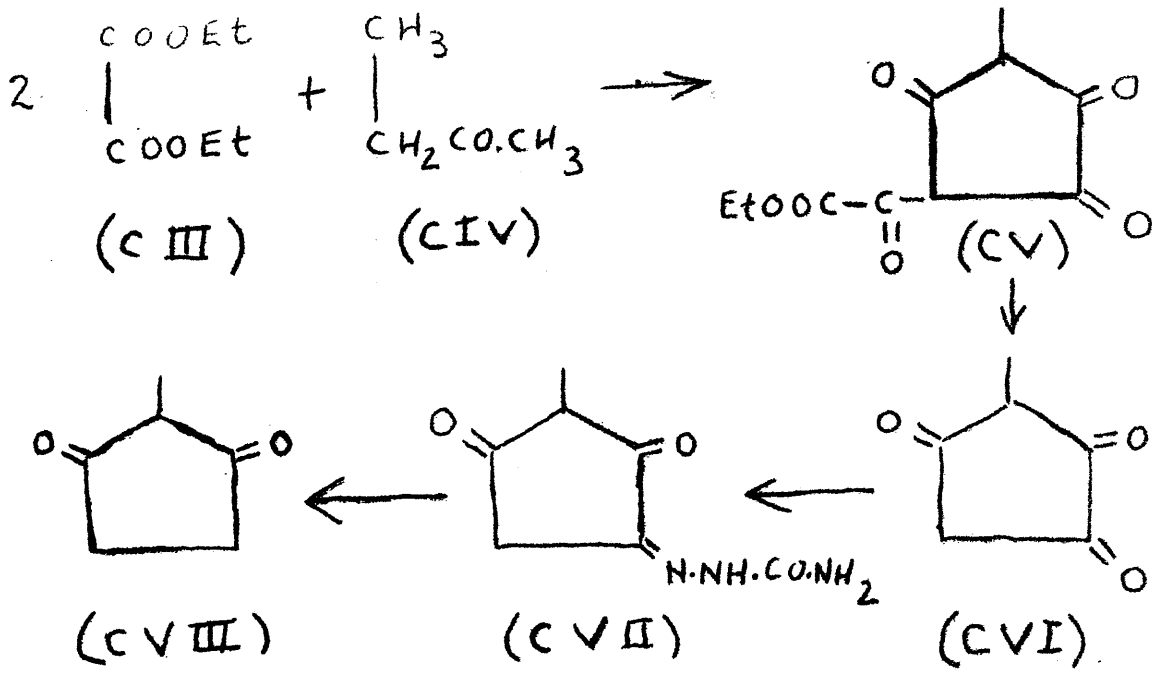
(C)

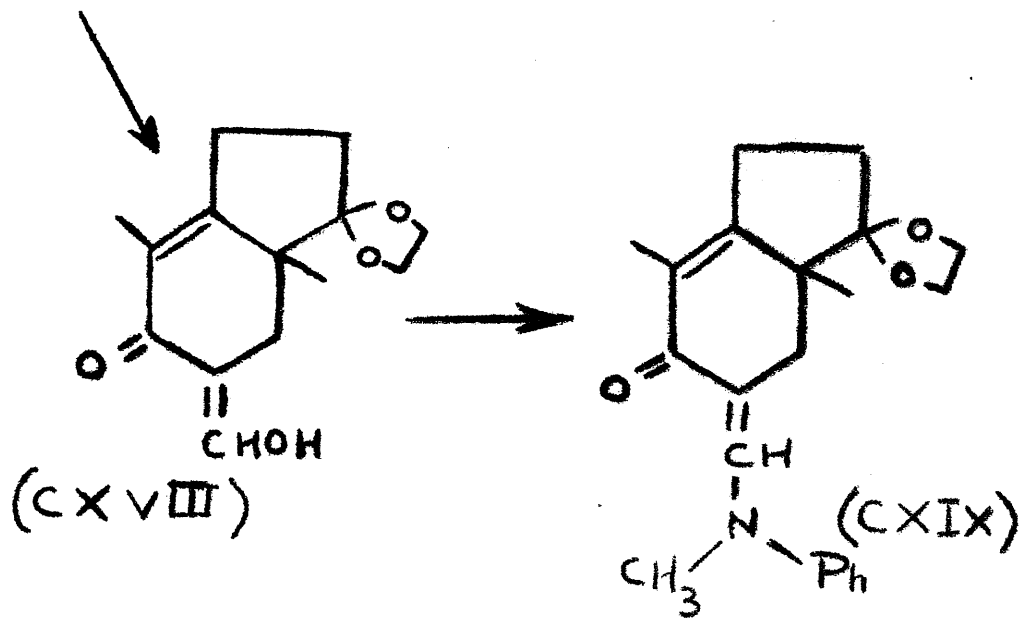
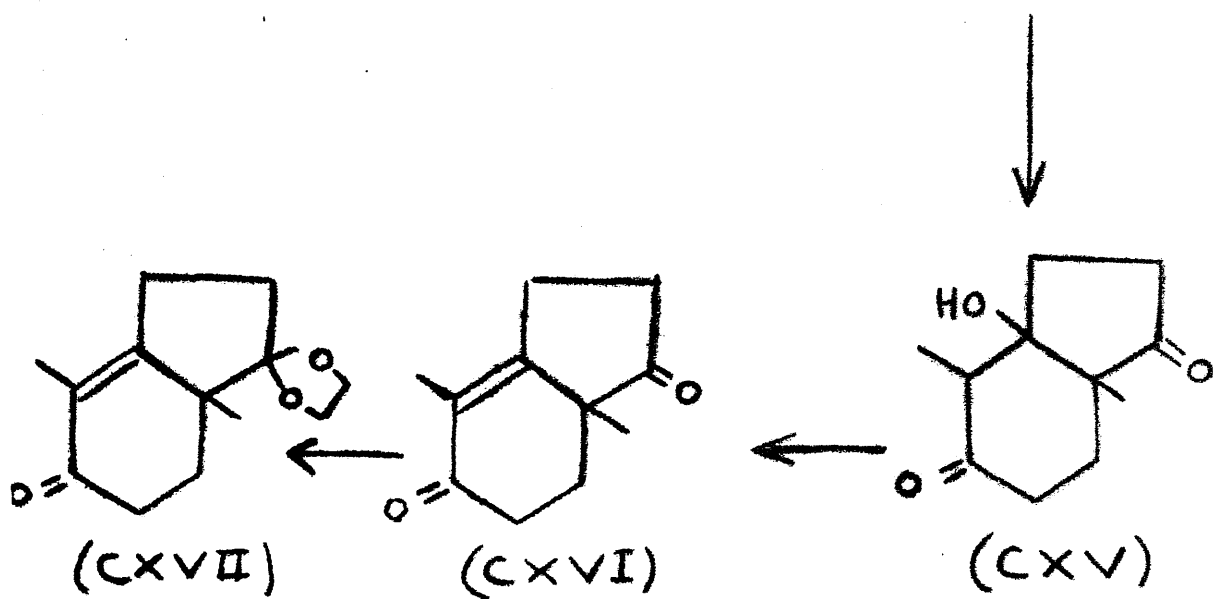
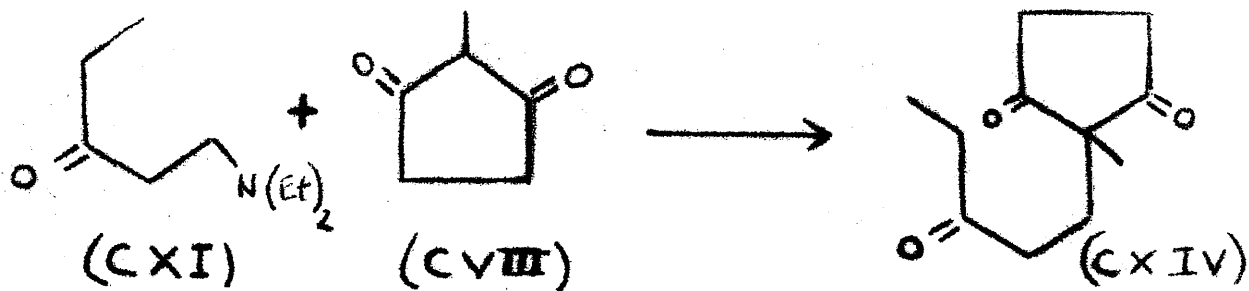


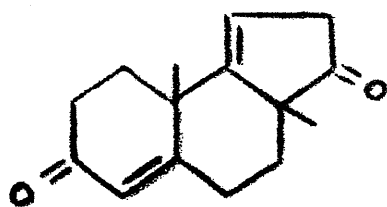
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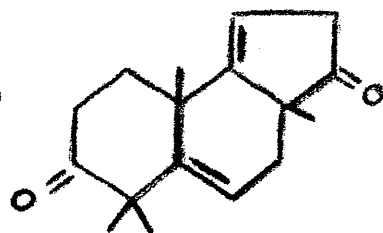
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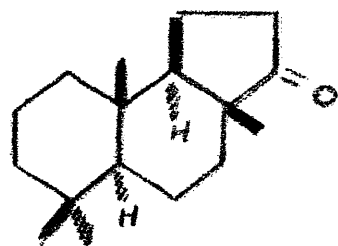




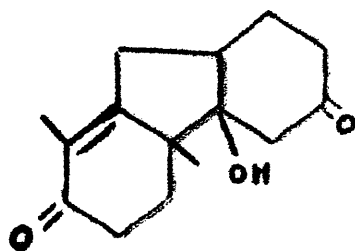
(CXX)



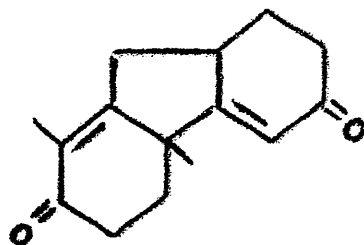
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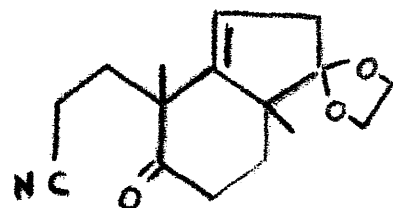
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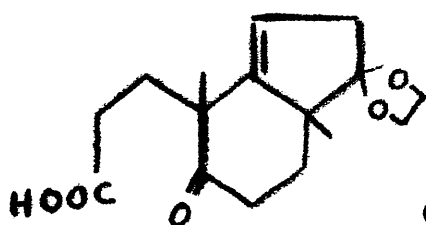
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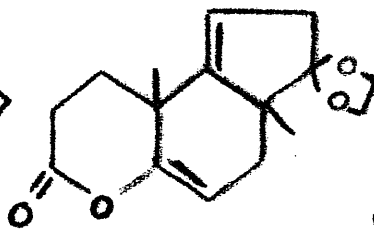
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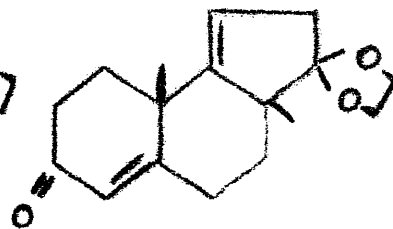
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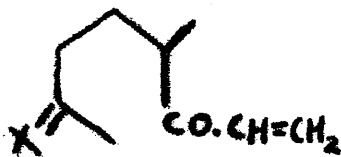
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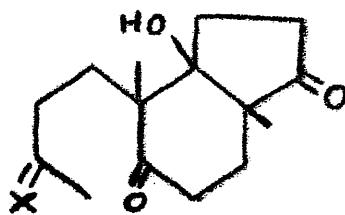
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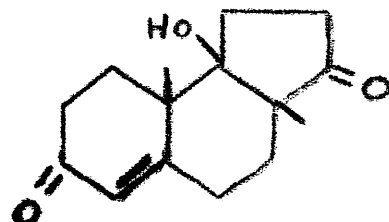
(CXXVIII)



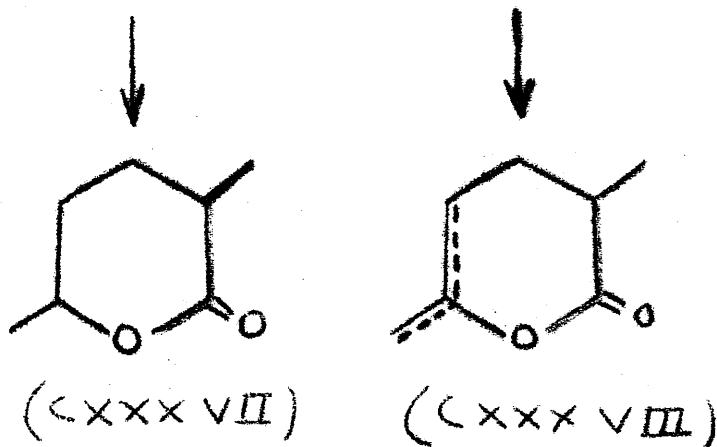
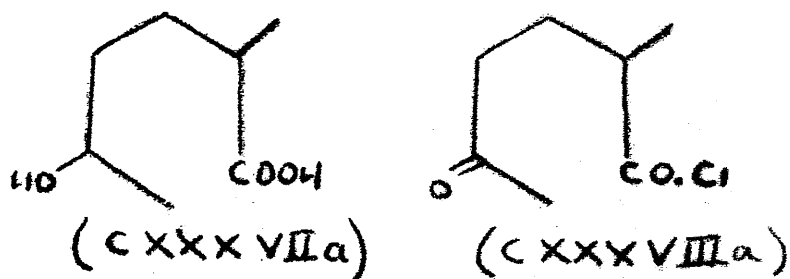
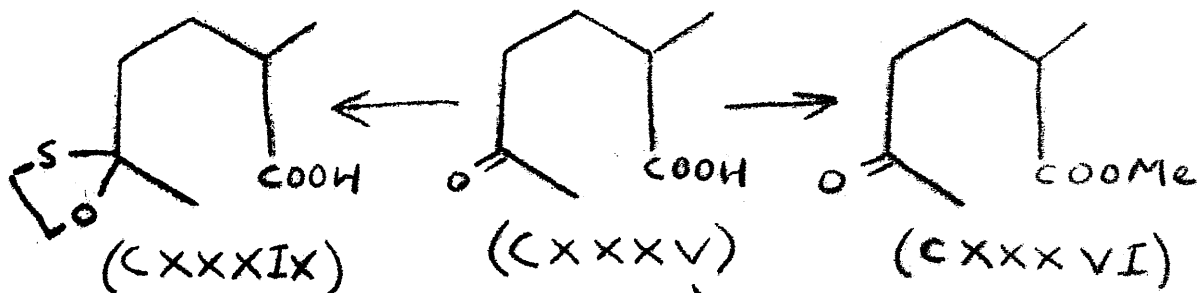
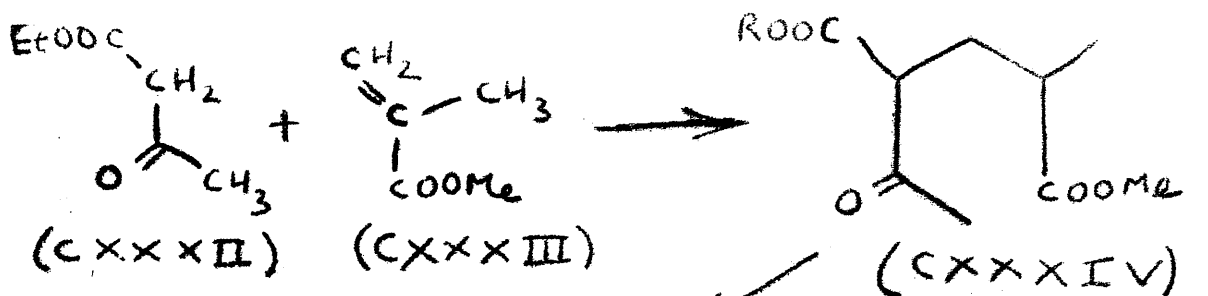
(CXXIX)



(CXXX)



(CXXXI)



R = Me or Et

