Syntheses of Fused Ring Compounds Related to the Steroids and Dicyclic Sesquiterpenes.

T H E S I S

presented for the degree

of

Doctor of Philosophy

by

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at the

University of Glasgow.

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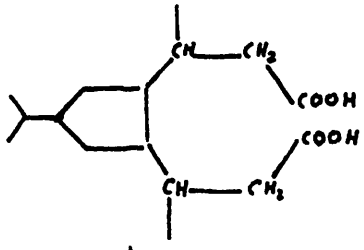
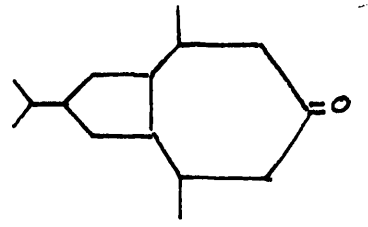
S U M M A R Y.

PART I. An attempted synthesis of tetrahydro-β-vetivone, shown by St. Pfau and Plattner to be (B), led to the preparation of a number of stereochemically pure cyclopentane derivatives related to this compound, and particularly to a stereochemically pure sample of 1-isopropyl-cyclopentane-3:4 bis (β-butyric acid) (A).

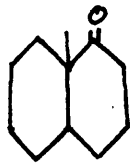


A



B

PART II. A new synthetic route to 9-methyl-1-decalone (C) by the use of a novel Reformatsky reaction between 2-methylcyclohexanone and methyl γ-bromocrotonate is described. A ketone, believed to be 1-keto-13-methyl-$\Delta^{11:12}$-dodecahydrophenanthrene (D), has also been obtained. The constitution of a ketone (E) or (F), obtained by a "Stobbe condensation" between 2-methylcyclohexanone and diethyl succinate, followed by cyclisation, decarbethoxylation, and hydrogenation, is discussed.



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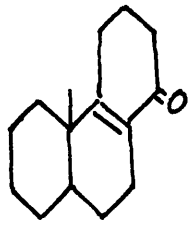

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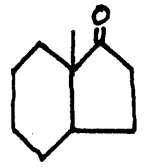
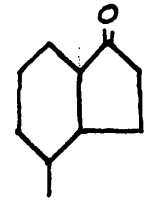
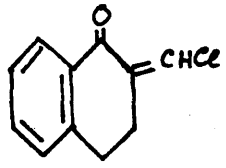


E

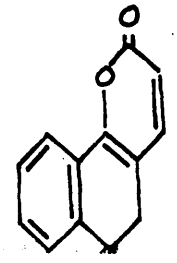


F

PART III. A projected steroid synthesis using 2-chloromethylene-1:2:3:4-tetrahydronaphthalene (G) as an intermediate led to the syntheses of various hydrocoumarin derivatives (H).



G

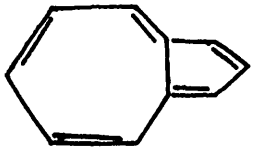


H

I N D E X.

P R E F A C E.

The azulenes are blue, violet, or green hydrocarbons present in certain essential oils or obtained from them by high temperature dehydrogenation. Synthetic and degradative studies by a number of workers, but mainly St. Pfau and Plattner[1,2,3], Plattner and Wyss[4,5] and other collaborators have demonstrated that the azulenes contain a fused five and seven membered ring system containing five double bonds:-



(I)

In 1936 St. Pfau and Plattner[1] isolated a new azulene, vetivazulene, by dehydrogenation of Java vetiver oil with selenium. Later the same authors[6] succeeded in isolating in pure form ketones, designated by them α- and β-vetivone, which yielded, among other products, vetivazulene on dehydrogenation. The elucidation of the structure of one of these ketones proves the presence of a fused five- and seven-membered ring system in a naturally occurring reduced azulene derivative.

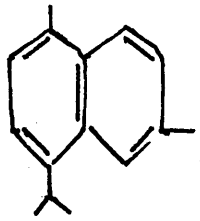
INTRODUCTION.

Vetivone.

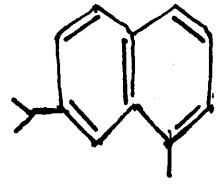
Vetiver oil, one of the essential oils, is expensive, its low volatility and high fragrance rendering it valuable in perfumery. The oil is obtained by distillation of the root derived from vetiver grass (Vetiveria zizanioides, Stapf.), a plant cultivated in Rajputana and Chutia Nagpur, Ceylon, Fiji, the Philippine Islands, Malay States, Java, West Indies, Brazil, in the Seychelles and at Réunion.

The yield of oil varies, Java root yielding 2 - 3%, while Manila root yields about 0.25%. The examination of the oil proved to be extremely difficult. Most of the constituents are of high boiling point, and liable to be changed by heat treatment or by prolonged steam distillation. Early investigators were also hampered by the lack of uniformity of samples obtained from different sources and the absence of a schematic method of procedure for treatment of the various fractions. Genvresse and Langlois[7] examined a Bourbon oil by steam distillation. They found a sesquiterpene, $C_{15}H_{24}$, called vetivene - first separated by Gladstone[8] - a mixture of esters which yielded an alcohol, vetivenol $C_{15}H_{26}O$ on saponification, and the residue in the flask contained a mixture of acids, $C_{15}H_{24}O_4$. These authors attributed the odour of the essence

to the vetivenol esters of these acids. Bacon[9] was unable to confirm the acids obtained by the above authors but found that the neutral oils remaining after saponification of the essence had a strong odour of vetiver. The first mention of the isolation of ketonic material from the oil occurs in a German patent by Fritzche and Cie[10]. These authors claimed to have isolated several ketones from vetiver oil through intermediate amorphous semicarbazones or oximes. To these compounds, called "vetirones" or "vetiverones", they assigned the formula $C_{13}H_{22}O$ and gave the boiling point of the fractions. The existence of these ketones was disputed by St.Pfau and Plattner[6] who were unable to obtain ketonic material such as described by Fritzche and Cie. Semmler, Risse and Schröter[11] also examined the oil. The most comprehensive statement on the constituents of the oil was made by Ruzicka, Capata and Huyser[12]. They detected a dicyclic compound, vetivene, $C_{15}H_{24}$, an isomer of cadinene; this was accompanied by a tricyclic vetivene. Among the alcohols a tricyclic primary vetivenol, $C_{15}H_{24}O$, two primary dicyclic vetivenols, one of the cadalene type (II), the other of the eudalene type (III), and finally a dicyclic tertiary vetivenol of the cadalene type, accompanied by other tertiary alcohols. No mention was made of ketonic constituents.



(II)



(III)

In a paper by Sabetay[13] on "A simplified procedure for the analytical oximation of aldehydes and ketones", very brief mention is made of the fact that essence of vetiver contains 12.5% of "vetiverone", a figure obtained by a titration method and not based on any quantitative isolation of solid derivatives.

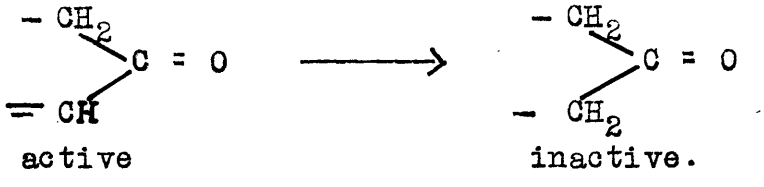
Although it was now clear that vetiver oil contained large amounts of alcohols, either primary or tertiary or a mixture of both, the existence of carbonyl constituents was still in some doubt. In 1939, two different groups of workers published conclusive evidence of the existence of ketones in the oil. Sabetay and Trabaud[14] by treatment of Bourbon vetiver oil with Girard's reagent[15] obtained water-soluble derivatives which decomposed to give an oil which furnished eventually a semicarbazone, m.p. 210°. Similar results were obtained with a Java vetiver oil. Regeneration of the carbonyl constituents from the crude semicarbazones gave an oil of composition $C_{15}H_{22}O$. A brief note by the authors added that the ketone, which they called "vetiverone", could be reduced with sodium and alcohol to

give an alcohol which could be estimated by acetylation and tritylation.

Simultaneously with the above publication, St. Pfau and Plattner[6] published the results of their researches on vetiver oil. In a very painstaking and brilliant investigation ketones were obtained in a high state of purity and work was well advanced towards a solution of their constitution. A preliminary examination of the oil was made by fractional distillation. After separation of the alcohols attention was concentrated on the neutral material obtained after removal of the phenols. Eventually, by using the odour of vetiver as a rough guide, they obtained a fraction which had the most intense odour. On treatment with semicarbazide hydrochloride a positive result was obtained. Several crystallisations of the amorphous derivatives gave a crude mixture of semicarbazones from which, by treatment with phthalic acid, an oil of characteristic odour was obtained. In an attempt to find an easier route to the carbonyl constituents the crude vetiver oil was extracted with Girard's reagent. By the use of this technique the tedious and wasteful distillation process was eliminated. The purification of the crude semicarbazones proved to be difficult, but, by fractional crystallisation, two semicarbazones were eventually obtained, a laevo-rotary compound, m.p. 228° - 229°, and a cruder dextro-rotary material,

m.p. 210-212°. Results of analysis indicated a formula $C_{16}H_{25}ON_3$ for the semicarbazones, corresponding to a substance of composition $C_{15}H_{22}O$. Evidence of the ketonic, as opposed to aldehydic nature of these compounds, was provided by the fact that they did not restore the colour to Schiff's reagent; also on oxidation no acid was obtained, reduction with sodium and alcohol yielding alcohols. The ketone from the laevorotary semicarbazone was designated β-vetivone and that from the dextro-rotary material, α-vetivone. Molecular refraction measurements indicated a dicyclic formula and the exaltation suggested that one of the double bonds was conjugated with the carbonyl function. If the vetivones were dicyclic, then their formula would indicate the presence of two double bonds. Reduction of β-vetivone with platinum gave a tetrahydro-β-vetivol. The tetrahydro compound could be oxidised to a tetrahydrovetivone, which gave a dibenzylidene derivative, thus indicating the presence of two unsubstituted methylene groups on either side of the ketonic function. If the reduction of β-vetivone was carried out with sodium and absolute alcohol, or, catalytically, with nickel, dihydro-β-vetivols were formed. Later the interesting fact was noted that while the reduction of optically active natural β-vetivone with sodium and alcohol gave a mixture of stereoisomeric dihydro-β-vetivols, the optical activity being preserved, catalytic reduction with nickel gave a

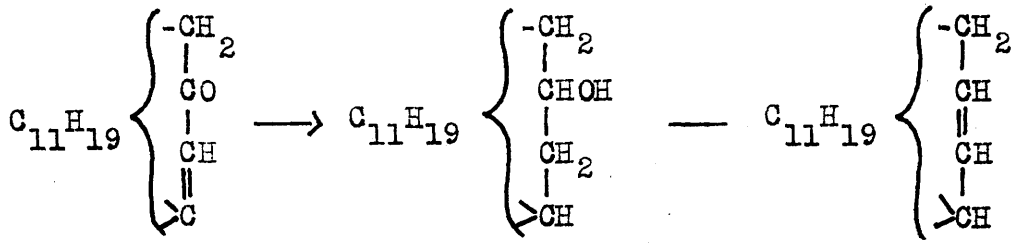
single isomer which was optically inactive. If the hydrogenation was stopped after the absorption of one molecule of hydrogen, a mixture of unchanged β-vetivone, dihydro-β-vetivone, and dihydro-β-vetivol was obtained. The separated dihydro-β-vetivone gave an inactive dibenzylidene derivative and its semicarbazone, purified with some difficulty, showed almost negative activity, this activity decreasing as purification was further effected by crystallisation. These facts, in combination with other facts, allowed the authors, as will be seen later, to draw important conclusions as to the structure of β-vetivone. It is sufficient to record, for the moment, that the reduction of one double bond, which was probably conjugated with the ketonic group in optically active β-vetivone under conditions where racemisation was unlikely, gave a single optically inactive isomer.



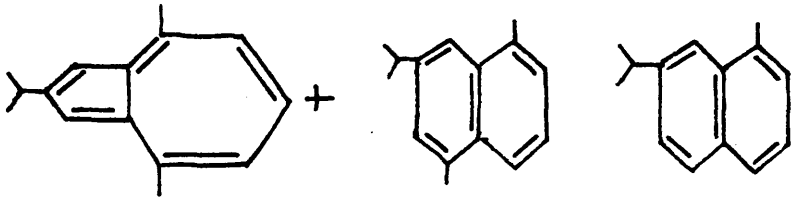
The investigation was continued by St. Pfau and Plattner[24] by a study of the products of dehydrogenation both of stereochemically pure β-vetivone and the mixture of stereoisomeric ketones, "isovetivones", which had been recovered from the residual crude mixture of semicarbazones. Results of the many dehydrogenation experiments gave

inconclusive data as to the identity of the fundamental ring system in the vetivones.

Dehydrogenation of a hydrocarbon, $C_{15}H_{24}$ (VI) obtained by dehydration of the mixture of dihydrovetivols (V) formed by the reduction of the isovetivones (IV) gave three hydrocarbons: an azulene, $C_{15}H_{18}$ (VII), a naphthalene derivative, $C_{15}H_{18}$, called vetivalene (VIII) by the authors, and a small quantity of eudalene (1-methyl-7-isopropylnaphthalene) (III). The presence of the isopropyl group in vetivalene was indicated by the isolation of cumene on treatment of the hydrocarbon with aluminium bromide in presence of benzene. The hydrocarbon (VIII) was identified as 1,5-dimethyl-7-isopropylnaphthalene by a fortuitous synthesis of this compound by Ruzicka and co-workers[16].



(IV) (V) (VI)



(VII) (VIII) (III)

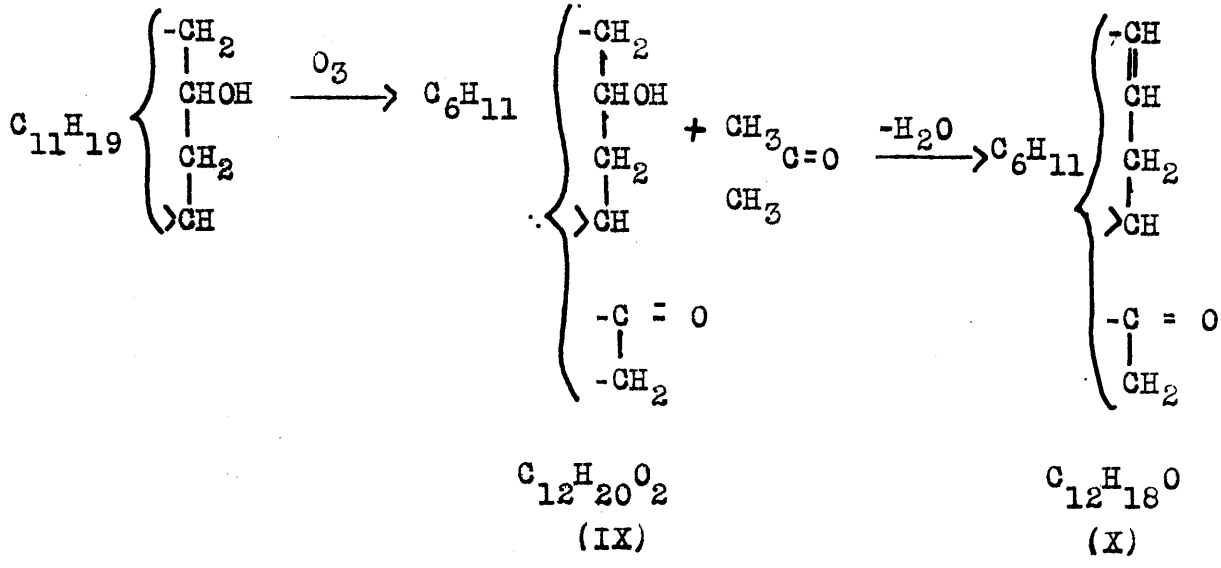
The products were always the same no matter what dehydrating agents were used in transforming (V) to (VI) or whether sulphur or selenium was used as the dehydrogenating agent. A repetition of these experiments with the dihydro-β-vetivols obtained from β-vetivone, rather than from the crude isovetivones, gave similar results although the formation of eudalene was not established with certainty.

Dehydrogenation of the Wolff-Kishner reduction product of vetivone, $C_{15}H_{24}$, gave, with either sulphur or selenium, vetivazulene and eudalene, no vetivalene being detected. Direct dehydrogenation with either sulphur, selenium or palladised charcoal of the isovetivones gave no naphthalene hydrocarbons but a mixture of phenols, one of which was eventually identified as 1-methyl-7-isopropyl-3-hydroxy-naphthalene. Analogous results were obtained with β-vetivone.

To summarise the results: the simultaneous production of naphthalene and azulene derivatives in all the cases examined did not allow any strict conclusion to be drawn as to whether the fundamental ring system was of the naphthalene or azulene type, although the dicyclic nature of the ketones had received confirmation.

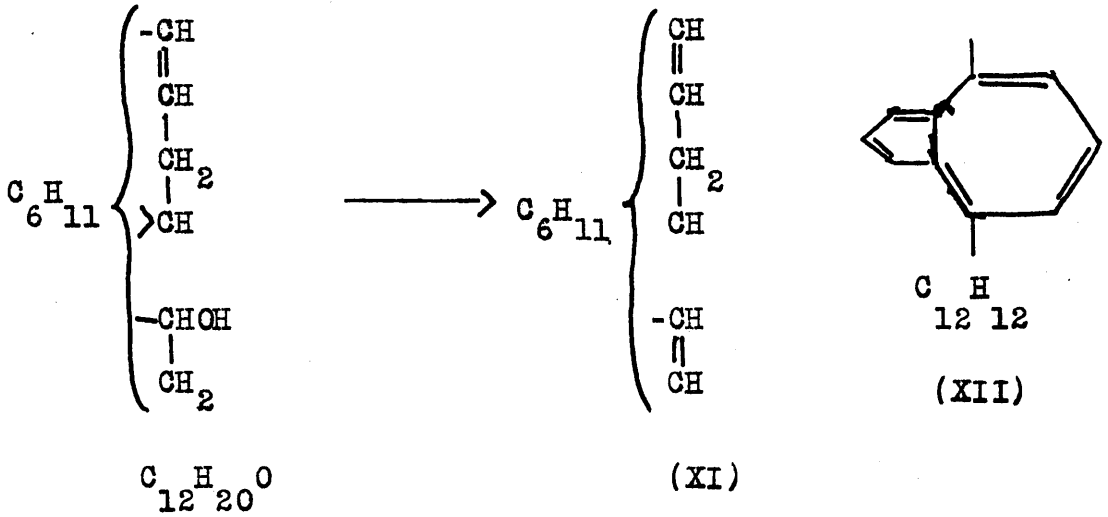
Attention was, therefore, directed to the degradation of β-vetivone. Ozonisation gave a molecule of acetone,

indicating the presence of an isopropylidene group. A repetition of the experiment using the mixture of dihydro-β--vetivols, obtained by reduction of the pure ketone with sodium and alcohol, also gave acetone, thus indicating that the double bond conjugated with the ketonic group in β-vetivone is not the site of the isopropylidene radical since the formation of a dibenzylidene derivative by the dihydro compound had shown that this conjugated bond had been reduced. A hydroxy-ketone, $C_{12}H_{20}O_2$ (IX), was also isolated from the products of ozonisation. This was dehydrated to a ketone, $C_{12}H_{18}O$ (X), which, when purified through the semicarbazone, showed a normal molecular refraction, thus demonstrating the absence of any conjugation between double bond and carbonyl function:-



Reduction of the unsaturated ketone (X) with sodium and alcohol gave an alcohol, $C_{12}H_{20}O$, which, when dehydrated

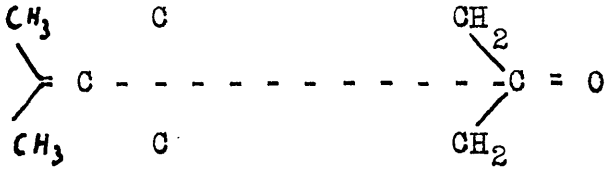
with potassium bisulphate, gave a hydrocarbon, $C_{12}H_{18}$ (XI). This hydrocarbon gave a violet coloured azulene, $C_{12}H_{12}$ (XII), when dehydrogenated with selenium.



$C_{12}H_{20}O$ (XI) $C_{12}H_{12}$ (XII)

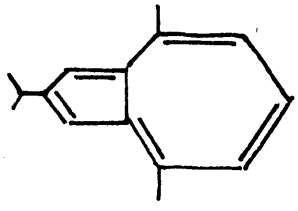
The formation of the azulene (XII) was a matter of considerable interest since it provided the first evidence (at the time the experiments were performed - 1936) of the existence of azulenes containing less than fifteen carbon atoms. To confirm the formation of this important compound and to study it and the products of ozonisation in some detail, without the troublesome interference of stereoisomers, it was decided to submit the stereochemically pure dihydro-β-vetivol, obtained by catalytic reduction of β-vetivone, to the above series of reactions. The ketone (X), obtained by the dehydration of the hydroxy-ketone (IX), gave a semicarbazone which did not depress the melting point of the optically active semicarbazone obtained by fractional

crystallisation of the ketonic derivatives from the stereoisomeric mixture; furthermore, this new semicarbazone was inactive. Intrigued by this inactivity the authors made a careful examination of the specific rotations of all the compounds prepared. Every substance obtained from catalytic dihydro-β-vetivone or dihydro-β-vetivol was found to be inactive, the others active; also the hydrogenation products were themselves inactive. The significance of this change, occurring with the reduction of a double bond conjugated with the ketonic group, was not lost to the authors. If racemisation was ruled out as the cause of this inactivation, and it appeared unlikely, the dihydro-vetivone and its derivatives must represent "meso" forms. The molecule should, therefore, possess a plane (or centre) of symmetry - as in tartaric acid - and be inactive by internal compensation: dihydro-β-vetivone, a dicyclic ketone, with an isopropylidene side-chain, must, therefore, embrace the following symmetrical scheme:-



If this reasoning is admitted, then the normal product of dehydrogenation could not be a naphthalene hydrocarbon. The other hydrocarbon, vetivazulene (XIII), would, therefore, appear to be the true product of dehydrogenation, representing the fundamental ring system.

Sufficient evidence had been adduced[1,2,3,4,5] to represent the azulene ring as a bicyclo- 0,3,5 -decapentaene structure (I) and the synthesis of vetivazulene (XIII) (it would appear to be at a later date to the actual experimental work here) by St. Pfau and Plattner[3] leaves no doubt as to the nature of this fundamental structure. The carbon skeleton of the dehydrogenation product (and synthetic product) was in complete accord with the symmetrical arrangement suggested for β-vetivone. In the light of these facts, therefore, the authors proposed formula (XIV) for the dicyclic ketone.



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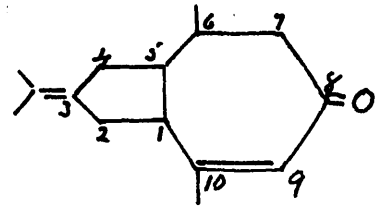


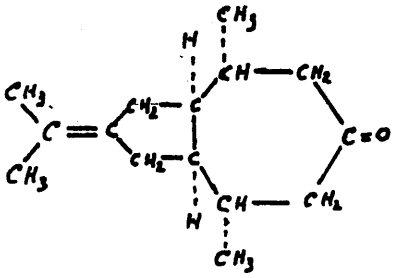
(XIV)

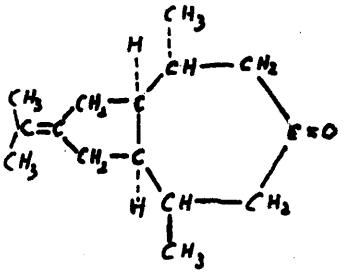
The authors add that this arrangement explains all the experimental facts if we make the following provisos (the results of dehydrogenation experiments are discussed later):-

1. The two rings are fused "cis" to one another: a "trans" linkage in dihydro-β-vetivone would rule out the possibility of obtaining "meso" forms.

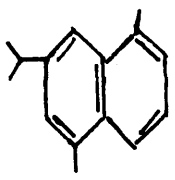
2. On catalytic hydrogenation of β-vetivone, the methyl group on carbon atom 10 becomes oriented in the same direction as the methyl group on 6 with respect to the cyclopentane ring, while on reduction with sodium and

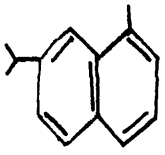
alcohol the methyl group on 10 is oriented partly in the opposite direction.

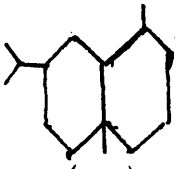




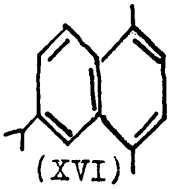
The production of vetivalene (VIII) and eudalene (III) by dehydrogenation of the vetivones or their derivatives cannot be directly reconciled with this formula deduced for vetivone.







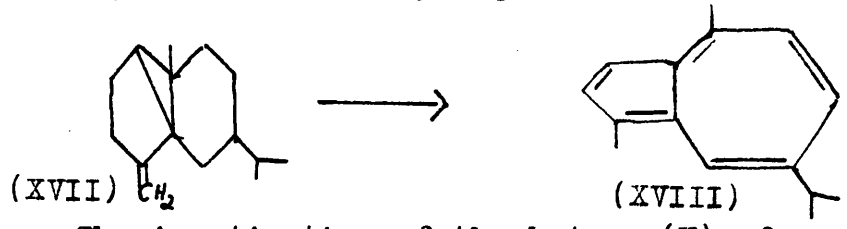
(XV)



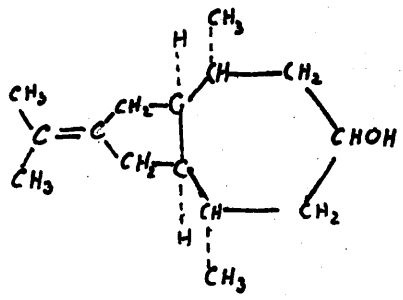
(XVI)

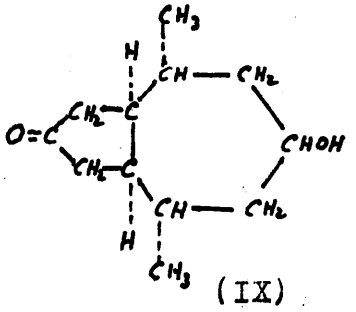
Indeed, the formation of these compounds might be interpreted as indication of a eudesmol skeleton (XV) for vetivone, but St.Pfau and Plattner have pointed out that this is incompatible with the fact that fully reduced compounds of the eudesmol type give no azulene on dehydrogenation; also, the reduction of a compound with the eudesmol structure would not give rise to "meso" forms since the molecule possesses no centre of symmetry. The authors were, therefore, forced to the conclusion that the naphthalene hydrocarbons must have been formed by ring re-arrangement, and, in the case of vetivalene, by migration of a methyl group. In 1936 St.Pfau and Plattner[1] obtained

mixtures of naphthalene hydrocarbons by passing the vapour of S-guaiazulene over silica gel at 300° under vacuum, showing the probability of migration of alkyl groups. Dehydrogenation of the product obtained by treatment of guaiol with hydrogen iodide and red phosphorus gave, after separation of azulene, 1:4-dimethyl-6-isopropyl naphthalene (XVI). Komppa[17,18] and co-workers have also observed the simultaneous formation of azulenes and naphthalene hydrocarbons during dehydrogenation of tricyclic terpene products, e.g., ledol. It is perhaps not irrelevant, although hardly adding to the argument, to add that aromadendrene (XVII) (Radcliffe and Short[19]; Naves and Perrotet[20]) yields guaiazulene (XVIII) and not a derivative of naphthalene on dehydrogenation.

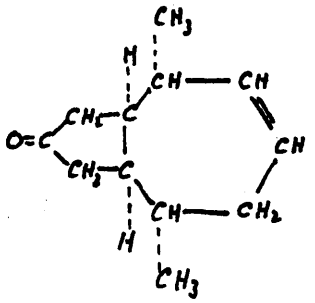


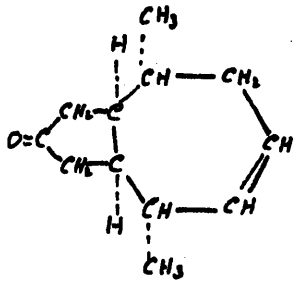
The inactivation of the ketone (X), formed as a result of ozonising the catalytic dihydro-β-vetivol, is explained by the authors in the following way:-





(IX)

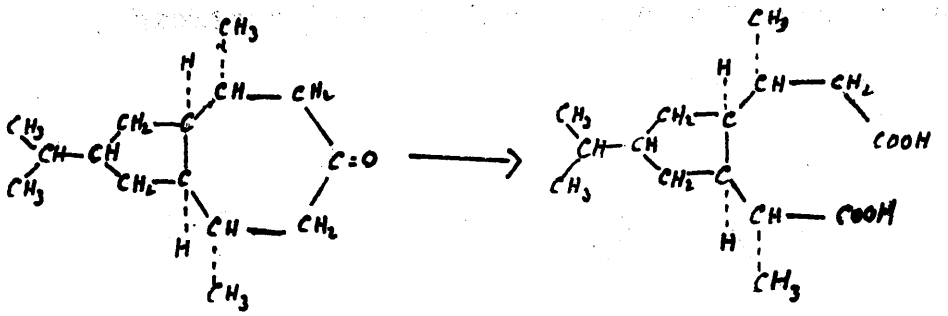




(X)

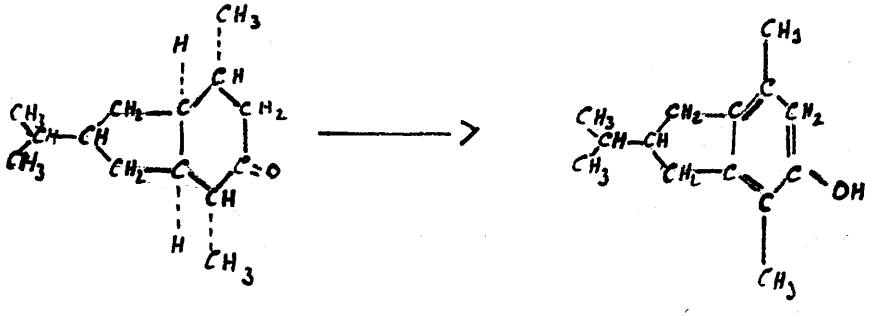
Dehydration of (IX) to (X) can proceed in two directions giving rise to antipodes: the ketone is, therefore, an inactive racemate. The production of dimethylazulene, $C_{12}H_{12}$, (XII) from (X) by reduction, dehydration and dehydrogenation, also receives a satisfactory explanation with the acceptance of the five and seven membered ring structure for β-vetivone.

Confirmation of the proposed formula was obtained by oxidative degradation. Treatment of tetrahydro-β-vetivone (XIX) with chromic acid gave a dibasic racemic acid, $C_{15}H_{26}O_4$, (XX).



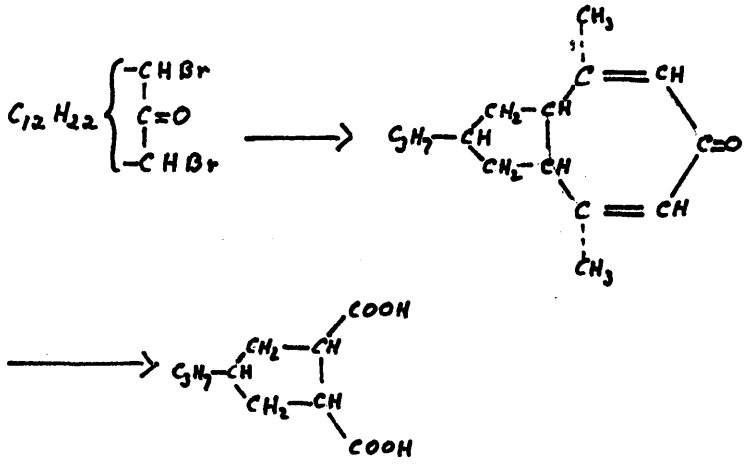
(XIX) (XX)

Distillation of this acid with acetic anhydride furnished a ketone, $C_{14}H_{24}O$, shown to be (XXI) by its dehydrogenation to 2-isopropyl-4:7-dimethyl-5-hydroxy-hydrindene (XXII), the last named compound being identified by synthesis.



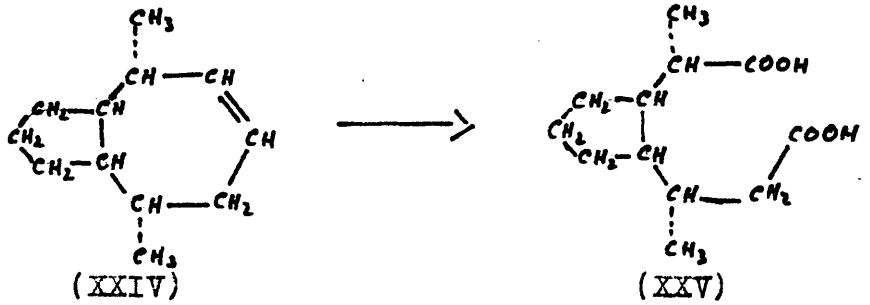
(XXI) (XXII)

The hydrindanone (XXI) is possibly identical with the pure isomer prepared by Coats and Cook[23] and re-described in this thesis. An attempt to obtain an acid (XXIII) by bromination of tetrahydro-β-vetivone, removal of hydrobromic acid and oxidation was unsuccessful.



(XXIII)

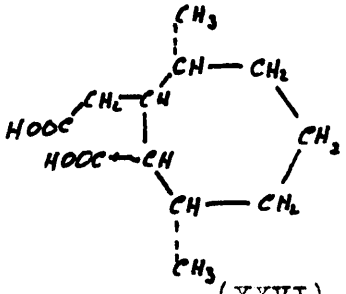
St. Pfau and Plattner next examined the unsaturated ketone (X). Wolff-Kishner reduction of the semicarbazone gave a hydrocarbon(XXIV) which was oxidised to a dicarboxylic acid (XXV):-



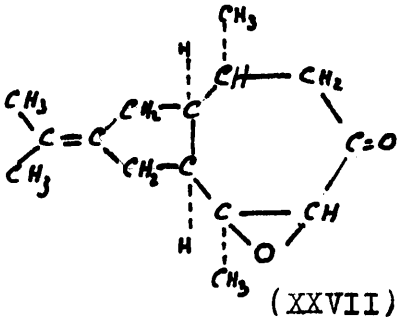
(XXIV) (XXV)

Finally, catalytic reduction of the same ketone (X),

followed by ozonisation gave a dicarboxylic acid (XXVI). As would be expected, no ketone could be obtained on distillation with acetic anhydride.



(XXVI)



(XXVII)

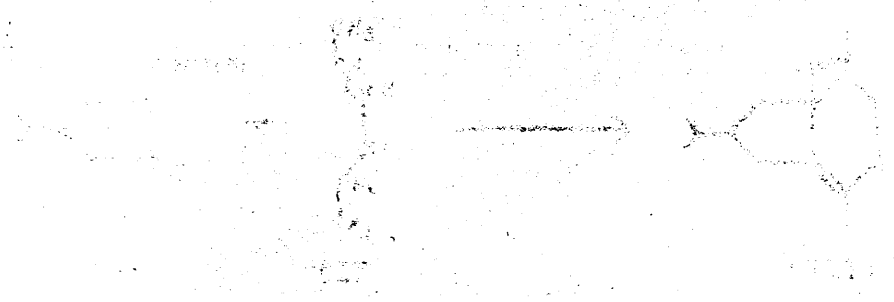
The preparation of an oxide (XXVII) of β-vetivone by the procedure of Weitz[21] confirmed the presence of a double bond conjugated with the ketonic group.

Thus, with these results in agreement with, and confirming the proposed structure (XIV), St.Pfau and Plattner concluded their research.

The work was continued by Naves and Perrotet[22] with a comparison of the chemical and physical characteristics of α- and β-vetivone, obtained from their respective semicarbazones. Both ketones gave different colourations with alcoholic sodium hydroxide and with Legal's reagent (sodium nitroprusside).

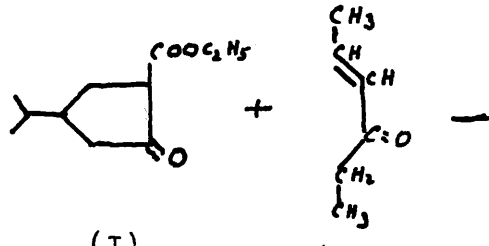
Dehydrogenation of both compounds gave similar yields of eudalinol and vetivazulene, thus indicating the probability of an identical carbon skeleton in the ketones with the carbonyl group in the same position. Ozonolysis of α- and

β-vetivone and of the corresponding α- and β-vetivanes with the formation of acetone, formaldehyde and formic acid indicated the position of the double bond. Finally, the Raman spectra of the ketones, parachors, refraction dispersions and dipole moments were measured and recorded; ultra-violet absorption curves were also obtained. The authors concluded that α- and β-vetivones are stereo-isomers and have the same plane projection formula.

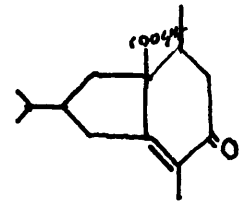


Synthetic Approaches to Tetrahydrovetivone.

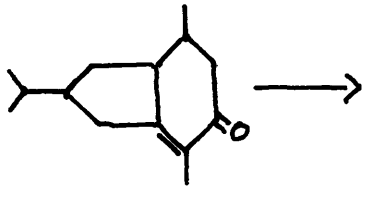
In the synthesis of vetivazulene by Coats and Cook[23] a condensation between ethyl-4-isopropylcyclopentanone-2-carboxylate (I) and Δ^{β}-hexen-δ-one (II) gave an intermediate keto-ester (III), which was converted by decarbethoxylation and then reduction to a mixture of dicyclic ketones represented by the structure (V). These authors succeeded in isolating, by way of the semicarbazone, a pure constituent of the mixture: the melting point of this semicarbazone was not very different from that of the same derivative of 4:7-dimethyl-2-isopropyl-5-hydrindanone (V) obtained by St. Pfau and Plattner[24] by degradation of tetrahydro-β-vetivone (VI) obtained from natural β-vetivone. It was proposed to prepare a further quantity of this dicyclic ketone (V) and to explore various methods which might lead to a synthesis of tetrahydro-vetivone (VI).



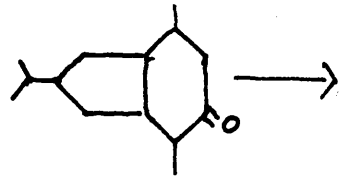
(I) (II)



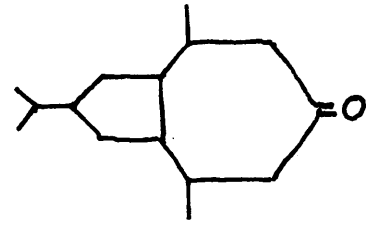
(III)



(IV)

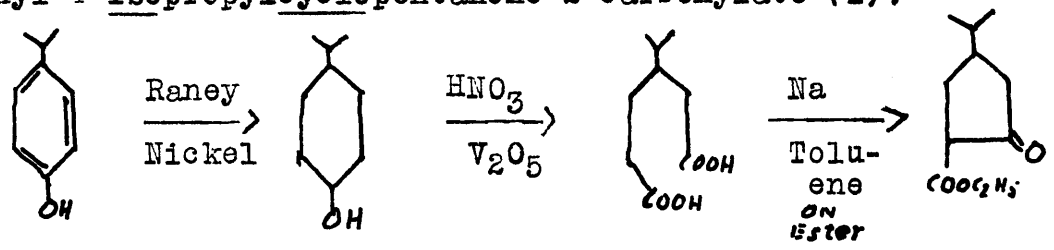


(V)



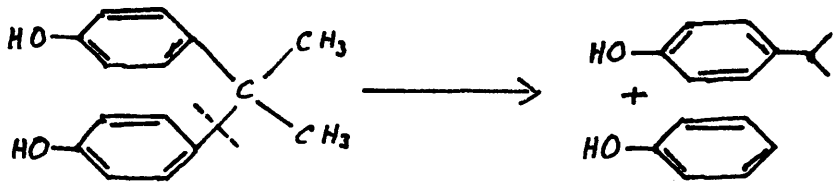
(VI)

The synthesis required the preparation of a large quantity of p-isopropylphenol (VII) which could be converted, in the manner described by Coats and Cook[23] to ethyl-4-isopropylcyclopentanone-2-carboxylate (I):



(VII)

A literature survey of the methods available for the preparation of this intermediate suggested an alternative method to that used by the above authors and which might be more labour-saving. This consisted in condensing phenol with acetone, isolating the condensation product (VIII), and by hydrogenolysis, cleaving the carbon to carbon linkage to obtain either p-isopropyl phenol or p-isopropylcyclohexanol.



(VIII)

V. Braun[25] prepared both p-isopropylcyclohexanol and p-isopropylphenol by using different nickel catalysts, but in the paper cited he makes no mention of the type of catalyst he employed or its method of preparation. Claims in several patents[26,27] indicated that the method could

be worked with a variety of catalysts and in one case[26] a mixed catalyst (nickel-manganese-kieselguhr) was prepared and the hydrogenation investigated. The results, however, did not justify a continuation of this method and the trouble in preparing the required quantities of supported catalyst would have been considerable. Raney nickel[28] gave poor results in cleaving the compound so it was decided to investigate the use of "copper chromite", although there was no encouraging evidence that it could be used to cleave carbon to carbon bonds[29,30]. High temperature and pressure hydrogenation of the crude condensation product with or without alcohol as solvent did, in fact, cleave the compound sufficiently to justify using the method for preparatory purposes. ββ'-bis-(p-hydroxyphenyl) propane (VIII) was cleaved to the extent of 60-70% giving a 30-35% yield of p-isopropylphenol based on the crude condensation product (m.p. ca 100°). More than a kilogram of p-isopropylphenol was prepared in this way. Rehydrogenation over Raney nickel gave p-isopropylcyclohexanol[23]. The alcohol was oxidised to β-isopropyl adipic acid by the method used by Coats and Cook[23,31]; in the case of the author, the acid was obtained as a solid in 78% yield. Ring closure by the Dieckman procedure gave the required keto-ester (I). The unsaturated ketone, Δ^{β}-hexen-δ-one (II) required for the Robinson condensation[23,49], was

found difficult to prepare by the Blaise reaction[32,33] and, after performing a few troublesome reactions, it was decided to prepare a block of zinc from arsenic-free zinc rods and mill this down as required. This procedure gave good results. The reaction can be initiated by adding one cc. of pyridine, per half mol. of propionitrile.

Condensation between the keto ester (I) and the unsaturated ketone (II) to give the compound (III) was carried out in dry alcoholic sodium ethoxide and the unsaturated product (III) isolated and distilled. Decarbethoxylation was accomplished by the method used by Coats and Cook.

The unsaturated ketone (IV) gave a semicarbazone and oxime which were homogeneous, and the quantitative preparation of the semicarbazone indicated that the condensation product consisted of one isomer. Distillation with oxalic acid in steam gave the pure unsaturated ketone (IV). Hydrogenation of the material over palladium gave a mixture of stereoisomeric ketones (V) and one pure component (isomer A) was isolated through its semicarbazone with a yield comparable to that obtained by Coats and Cook, who hydrogenated the crude material. In dealing with the main bulk of unsaturated material, therefore, hydrogenation was effected without preliminary purification of the unsaturated ketone (IV) by way of the semicarbazone.

The stereochemically pure 4:7-dimethyl-2-isopropyl-5-hyndrindanone was obtained by steam distillation of the semicarbazone with 20% sulphuric acid. Similar treatment of the gummy mixture of semicarbazones, obtained by diluting the aqueous mother liquors from which the pure derivative had been obtained, gave a crude mixture of stereoisomeric ketones.

Hydrogenation of the unsaturated ketone (IV) with a palladium strontium carbonate catalyst under pressure gave a mixture of stereoisomeric ketones which, on treatment with semicarbazide hydrochloride and potassium acetate, gave, after some difficulty, a crystalline derivative melting sharply, 175-176°*.

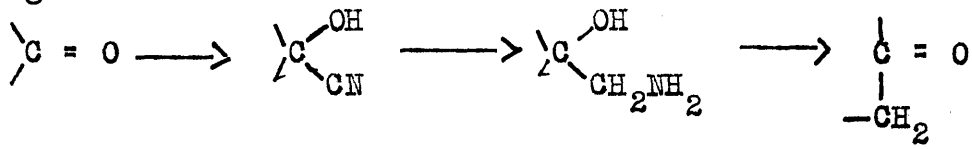
By steam distillation of this semicarbazone with 20% H_2SO_4 another pure isomer of (V) (isomer B) was obtained. Reconversion to the semicarbazone gave a compound with the same melting point as before.

The problem, at this stage, was to find the most suitable way whereby the six-membered ring could be enlarged either by a direct re-arrangement or by oxidative or other methods of degradation followed by rebuilding, to form a

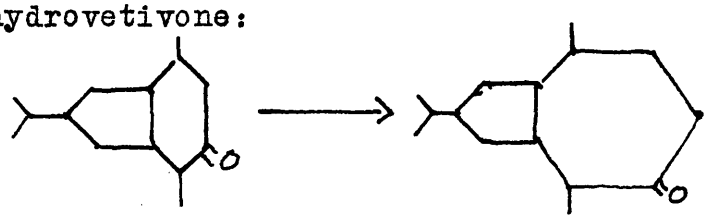
---

* This derivative has been found to give no depression in melting point on admixture with the semicarbazone of m.p. 167-168° of the isomer obtained by Coats and Cook on treatment of isomer A with diazomethane.

seven-membered ring with the keto group oriented symmetrically with respect to the rest of the molecule. Coats and Cook attempted to achieve such an enlargement by the action of diazomethane, but the ketone which they isolated proved to be an isomer of (V), although the isolation of vetivazulene from the products of dehydrogenation indicated that some ring enlargement had, in fact, taken place. An attractive method of ring enlargement was considered: this involved the preparation of the cyanhydrin, its reduction by platinum to the hydroxy-amine, and by treatment with nitrous acid to obtain the homologous cyclic ketone by rearrangement



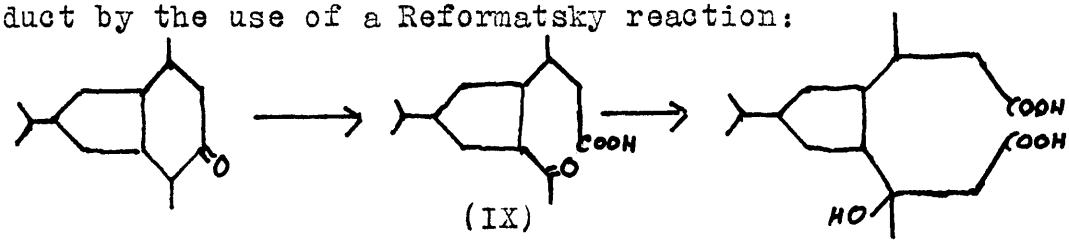
It was thought, however, that, by analogy with known examples[34,35,36], the above method would give a ketone with the carbonyl function oriented differently from that in tetrahydrovetivone:



The method was, therefore, not attempted.

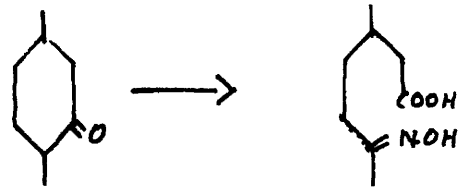
The oxidation of the hydrindanone (V) to β (2-acetyl-4-isopropylcyclopentyl) butyric acid (IX) had been investigated by Coats and Cook[23] and it was hoped that, by varying the experimental conditions, a method might be

obtained which would give a suitable yield of keto-acids - two stereoisomeric keto-acids were obtained by oxidation of the mixture of stereoisomeric ketones. From one of these acids it might be possible to obtain the desired product by the use of a Reformatsky reaction:

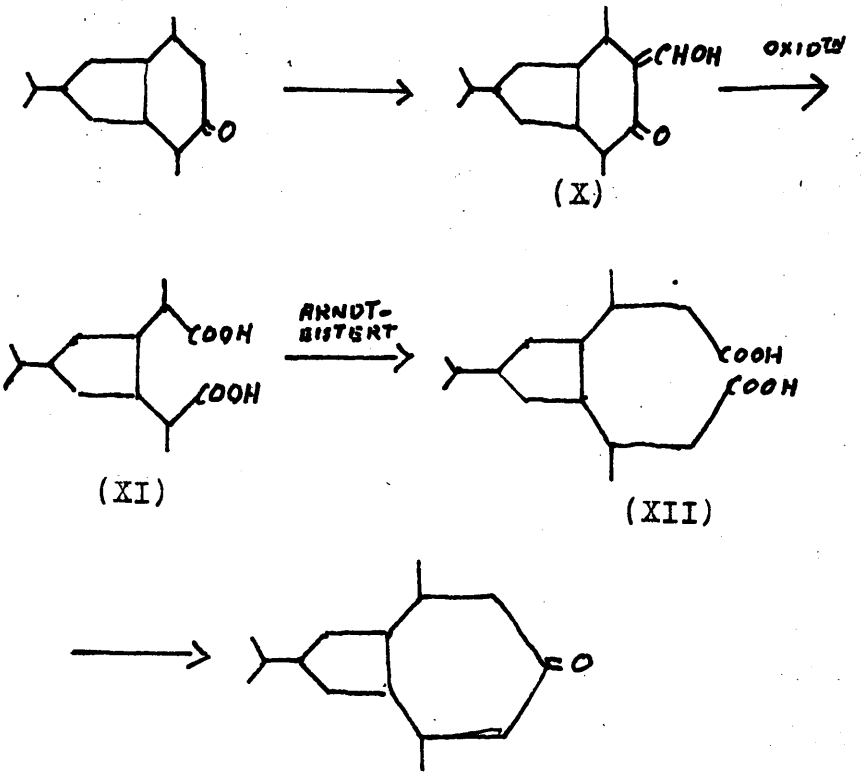


(IX)

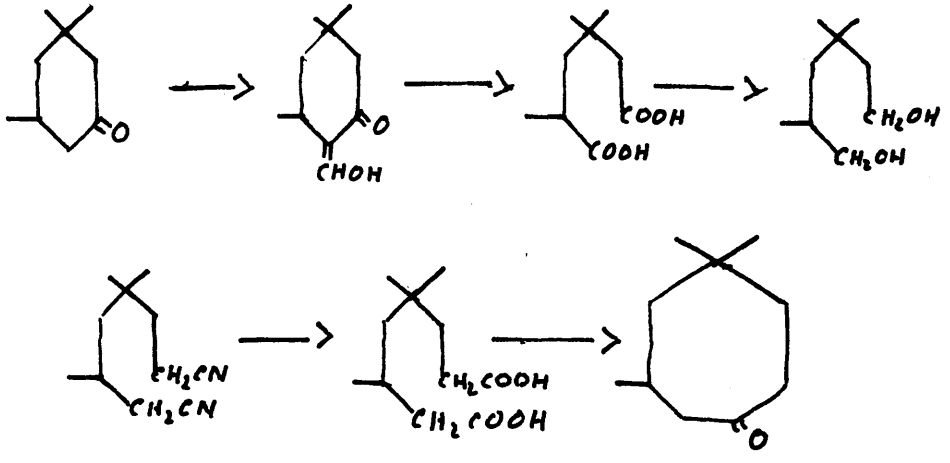
Oxidation experiments with chromic acid, varying the concentration, temperature and time of reaction on the pure ketone and on the crude mixture of ketones gave results comparable to those obtained by Coats and Cook, but no improvement in yield could be obtained. A method of oxidation described by Triebs[37] with hydrogen peroxide and vanadium pentoxide catalyst gave practically no keto-acid. The free acid was isolated in small yield, when an attempt was made to obtain the oxime of the keto-acid by the action of amyl nitrite and concentrated hydrochloric acid: such an experiment gave promising results with tetrahydrocarvone[38].



In view of the unpromising nature of these attempts, oxidation experiments were at this stage suspended and the following scheme attempted:-

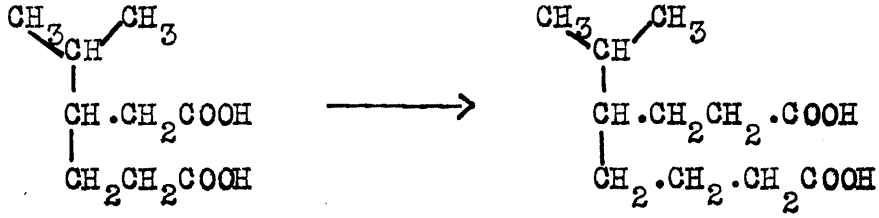


Several analogies are available[39,40,44], e.g., Ruzicka, Schinz and Seidel[39] prepared 1,1,6-trimethyl-cycloheptane-4-one (XIII) by a somewhat similar series of reactions from dihydro-isophorone



(XIII)

Adipic acid has been converted to suberic acid and sebacic acid to decane-1-10-dicarboxylic acid through the bis diazo ketones in the Arndt-Eistert procedure[41], thus introducing two methylene groups into a dicarboxylic acid in one operation[42,43]. It was hoped that 1-isopropyl-cyclopentane-3:4-bis(β-butyric acid) (XII) could be obtained by this method. A trial Arndt-Eistert with β-isopropyl adipic acid gave eventually a small amount of crystalline γ-isopropyl suberic acid (XIV)



(XIV)

The preparation of the hydroxymethylene compound (X) presented some difficulty, not mitigated by the relatively small amount of pure isomer available with which to conduct exploratory experiments. Poor results were obtained with sodium wire with benzene or toluene as solvents or by using alcohol free sodium ethoxide in ether. By using a large excess of both atomised sodium and ethyl formate, and with ether as solvent, good results were obtained with 1 gram quantities, both of the stereochemically pure ketone and the crude mixture of stereoisomeric ketones, but experiments with larger quantities of the mixed ketones gave varying results. The hydroxymethylene derivative from the

pure ketone (isomer A) was soluble in alkali and gave an intense violet colouration with ferric chloride. It formed a yellow, slightly viscous, oil which did not crystallise even after standing for several months (although a twice distilled sample kept in a refrigerator for a long period has shown some tendency to solidification). During the preparation of the hydroxymethylene compound a solid product separated at the interface of the ether-alkali mixture. The same compound was also obtained on recovery of the ketone from the neutral fraction of the experiment, distilling at a slightly higher temperature than the ketone and crystallising out from the last compound on standing. It crystallised in colourless glistening flakes from dilute acetic acid, in large flat diamond shaped crystals from more concentrated acetic acid, and had m.p. 69-70°; samples of the compound developed a reddish colouration on standing. Analysis figures indicated that the substance is isomeric with the hydroxymethylene compound. A similar compound was isolated during the preparation of the hydroxymethylene derivative of isomer B. This compound did not depress the melting point of the material obtained from isomer A and gave a semicarbazone, m.p. 206-208°. Results of analysis of this semicarbazone are unfortunately not available at the moment, (cf. page 64a).

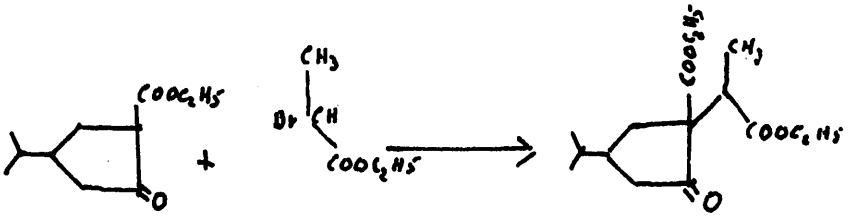
The oxidation of the hydroxymethylene compound (isomer A) was carried out with both chromic acid in acetic

acid and potassium permanganate in ice-cold alkaline solution. The solid dibasic acid, m.p. 156° (XI), crystallised well and gave correct analytical figures. It was further characterised by the preparation of a bis (p-phenylphenacyl) ester. The same acid, m.p. 153°, softening 143°, was isolated in minute yield from the gummy mixture of acids obtained by oxidation of the hydroxymethylene derivatives from the crude mixture of stereoisomeric ketones. Oxidation of the hydroxymethylene compound obtained from isomer B, gave an acid which could not be obtained solid. The p-phenylphenacyl derivative did not melt sharply but repeated crystallisation from absolute alcohol gave a product of m.p. 132-146°, unchanged by further crystallisation from alcohol and showing practically no depression on admixture with the p-phenylphenacyl ester (m.p. 154°) of the acid from the isomer A series (mixed m.p. 130-146°).

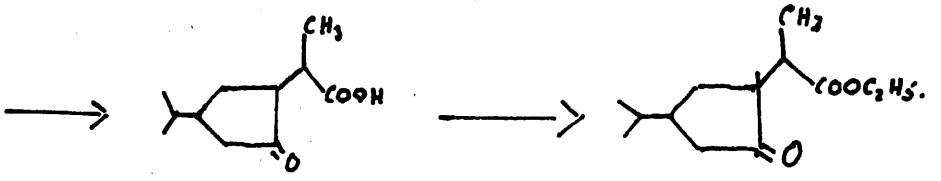
Treatment of the acid chloride of the crystalline acid (XI) with diazomethane gave a crystalline bis diazo ketone which re-arranged to a diamide which was not purified. Hydrolysis with aqueous alkali gave the required dibasic acid (XII), crystallising well from dilute acetic acid. Distillation of the thorium salt of this acid, neutralised with standard sodium hydroxide and precipitated in aqueous alcoholic solution with thorium nitrate, gave a minute

amount of red-brown distillate (metal-bath 250-300°/.2 mm.) with a ketonic odour. An attempt to obtain a crystalline semicarbazone was unsuccessful.

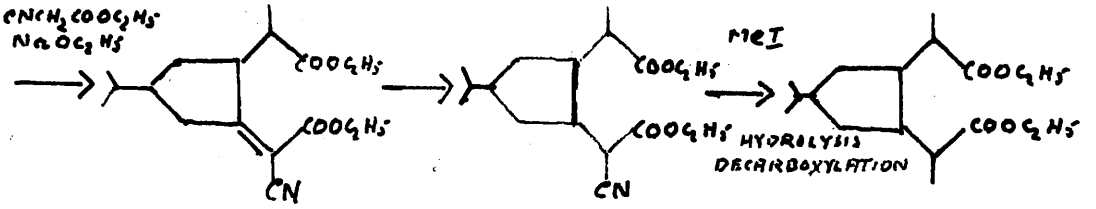
At this stage, it was decided to attempt the preparation of the necessary dibasic acid (XI) by another scheme. This envisaged the following reactions:-



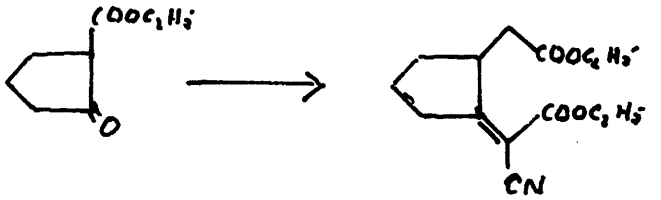
(XV) (XVI)



(XVII) (XVIII)



A similar scheme was used by Linstead and Meade[45] to obtain (XIX)



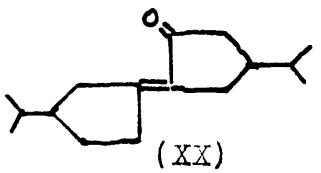
(XIX)

A condensation of a similar type (I ⟶ XVIII) using α-bromo propionic ester has also been carried out by Ruzicka[48].

The success of such a scheme in our own case would depend upon the quantity of stereochemically pure ester (XVIII) obtained as indicated by a quantitative preparation of a crystalline semicarbazone.

Condensation between the keto-ester (I) and ethyl α-bromopropionate (XV), was carried out at -15°C in alcoholic sodium ethoxide and the neutral fraction from the condensation isolated and distilled. Two ill-defined fractions were oftained after removal of lower boiling material. The major fraction was hydrolised and decarboxylated by boiling for 6 hours with concentrated hydrochloric acid. Following the procedure of Linstead and Meade, the crude product was esterified by allowing it to stand overnight at room temperature with absolute alcohol saturated with hydrochloric acid, and the ester isolated by distillation. A semicarbazone was easily obtained, crystallising well in long colourless blades, but in disappointingly low yield. Analysis figures were not good in spite of repeated crystallisation and indicated perhaps some contamination by a small amount of another ketonic constituent. The product, formed by the hydrolysis with concentrated hydrochloric acid, was further investigated. Acidic material

was separated with sodium carbonate and formed an oil which could not be obtained solid and did not form a semicarbazone. A neutral liquid remained which, when boiled with aqueous methanolic sodium hydroxide, gave a solid. This compound crystallised in glistening plates, m.p. 72-74° from aqueous methyl alcohol and gave a red precipitate with 2:4-dinitrophenylhydrazine. Analysis, melting-point, and appearance suggested that the compound was di-isopropyl cyclopentylidene cyclopentanone (XX) which was also obtained as a bye-product in a condensation by Coats and Cook.



(XX)

The condensation between the keto ester and ethyl α-bromopropionate was also carried out with atomised sodium and benzene as solvent, and the product isolated by distillation and hydrolised and decarboxylated as before. In this case α (2-keto-4-isopropylcyclopentyl)-propionic acid (XVII) was isolated as a solid, crystallising well and giving correct analytical figures, but not in sufficiently good yield to justify pursuing this scheme.

The attempt was, therefore abandoned and attention directed on the mixture of acids (XI) which had accumulated from numerous oxidations of the hydroxymethylene derivatives (X) obtained from the various mixtures of stereoisomeric

ketones (V). This gummy material successfully underwent the Arndt-Eistert homologation process giving the final crude acidic product (XII) in good yield. Treatment of the gum with freshly precipitated thorium hydroxide, roughly dried on a porous plate, gave, after heating and drying the mixture in vacuo, a brown amorphous solid. Pyrolysis of this salt in vacuo gave a dark brown viscous distillate with an intense plant-like ketonic odour. This liquid was dissolved in ether, the ether washed with sodium carbonate, and the product re-distilled, from an air-bath. Two fractions were obtained: the first, a light brown mobile oil and the second, a brown viscous liquid. Treatment of both fractions with 2:4-dinitrophenylhydrazine in an attempt to obtain a crystalline derivative, gave only unhomogeneous gummy red precipitates. A dull-red amorphous, low melting solid (m.p. 60-74°) was eventually obtained from an alcoholic solution but it could not be obtained in a state of analytical purity. The powder is possibly a mixture of isomeric 2:4-dinitrophenylhydrazones of the required tetrahydrovetivone (VI). Owing to shortage of stereochemically pure dicyclic ketone (V), the research has not been carried beyond this point. It had been hoped that the experimental work leading to the production of the stereochemically pure 1-isopropyl-cyclopentane-3:4 bis (β-butyric acid) (XII) could be repeated, in the hope of obtaining a larger quantity of this acid, but

the unfortunate course of a hydrogenation of the intermediate unsaturated ketone (IV) with a palladised strontium carbonate catalyst giving rise to different stereoisomers of 4:7-dimethyl-2-isopropyl-5-hydrindanone prevented this from being carried out. The synthetic difficulties, combined with the problem of stereoisomers, makes the construction of a molecule of the β-vetivone type a matter of considerable interest, and the author looks forward to the publication of the results of other workers in this field.

E X P E R I M E N T A L.

ββ'-bis (p-hydroxyphenyl) propane (VIII).

The method used by Zincke[46] was found to be superior to that indicated by J. v. Braun[25].

A product suitable for hydrogenation was obtained by allowing commercial phenol (1050 g.), acetone (150 - 160 g.), and fuming hydrochloric acid (105 g.; S.G. 1.19), to stand for 2 - 3 days at 36°C in a tightly stoppered Winchester. The product was stirred with dilute acetic acid (1000 cc. of 30%), filtered, pressed well with suction, washed with a further quantity of acetic acid (500 - 700 cc.), pressed well, then washed with water (1500 cc.). In this way 400 - 500 g. of glistening white needles, m.p. ca. 100°, were obtained. Two crystallisations from benzene gave a product of m.p. 159 - 160°.

Hydrogenation of condensation product.

1. With Nickel-Manganese-Kieselguhr catalyst.

Preparation of Catalyst:-

A solution of analar nickel chloride (42 g.) and manganese chloride (4.5 g.) in distilled water (80 cc.) was added to kieselguhr (50 g.) - previously purified with concentrated nitric acid - and the resultant thin green paste ground by hand in a mortar for 60 minutes. The mixture, which flowed like lubricating oil, was poured into a beaker and a warm solution of sodium bicarbonate (34.8 g., in

water, 150 cc.) added. The paste was stirred briskly, then filtered and washed with water, suspended in distilled water several times, and finally washed with large quantities of distilled water. The green mass was dried at 110 - 120° overnight, when a light brown powder was obtained.

Hydrogenation:-

The above powder (12 g.) was reduced in a stream of hydrogen for 1 hour at 450°, in an electric furnace. The black-brown powder was transferred (in an atmosphere of hydrogen) to the autoclave (previously filled with carbon dioxide). To the catalyst was added the crude acetone-phenol condensation product (215 g.) and the bomb filled with hydrogen to a pressure of 110 atmospheres. After heating at 200° for 4 hours the bomb was cooled, a sample of product extracted, and the hydrogenation repeated by adding a further quantity of catalyst (30 g.). Heating was carried out this time for 5 hours at 180°. The total absorption of hydrogen corresponded roughly to 105 litres.

The contents of the autoclave were washed out with acetone, the acetone removed and the mobile liquid residue distilled in vacuo. Initially three fractions were obtained:-

(1) B.p. 95 - 125°/30 mm. 60 g.

(2) B.p. 120° - 200°/30 mm. 8 g.

(3) Above 200° a very viscous material started to distil.

It cooled to a hard glass, m.p. ca. 40°, and was soluble to some extent in sodium hydroxide.

Fraction (1) was redistilled to obtain:

1) a b.p. 73 - 93°/14 mm. 30 g.

2) a b.p. 103 - 107°/14 mm. 15 - 16 g.

Fractions (2) and 2(a) appeared to consist essentially of p-isopropyl cyclohexanol.

2. Hydrogenation with Raney Nickel.

Preparation of Catalyst.

Pure sodium hydroxide (50 - 55 g.) was dissolved in distilled water (900 cc.), and the nickel-aluminium alloy (50 g.) added to the ice-cooled, well stirred, solution over a period of 2 hours. The solution was allowed to reach room temperature (1 hour), then heated on a steam-bath, with stirring, until evolution of hydrogen had ceased (3 - 4 hours). The catalyst was transferred to a clean beaker and washed by decantation with large quantities of distilled water, then twice with rectified spirits, twice with absolute alcohol, and stored under absolute alcohol.

Hydrogenation:

The crude acetone-phenol condensation product (212 g.) was placed in the autoclave with Raney nickel (20 - 25 g.). Absorption of hydrogen started about 80°, initial pressure 95 atmospheres, and continued as temperature rose to 228°. The temperature was held at over 200° for 4 hours,

when 60 litres of hydrogen were absorbed. Filtration of catalyst and removal of wash-solvents gave a viscous liquid. Vacuum distillation at 24 mm. gave two fractions:-

(1) Up to 95° - 45 g.

(2) 95 - 130°, mainly 127 - 130° - 34 g.

A third fraction, b.p. 203 - 230°/15 mm. was the main fraction and consisted of a sticky viscous material setting to a hard glass: it was not further investigated.

Redistillation of fraction (2) gave a colourless, mobile liquid (20 g.), b.p. 105 - 116°/14 mm., and by smell and boiling point was, presumably, p-isopropyl cyclohexanol.

3. Hydrogenation with "Copper Chromite".

(Preparation of 'Copper Chromite' catalyst[50]).

The crude diphenolic condensation product (380 g.) was hydrogenated without solvent in presence of copper chromite (38 g.). The initial pressure was 100 atmospheres and rose to 180 atmospheres at 222°C (2 hours), then fell gradually, the temperature being maintained 220 - 230°C for 5 hours. Absorption of hydrogen corresponded roughly to 70 - 75 litres. Distillation of the viscous product, after removal of catalyst, gave two fractions:

(1) B.p. 88 - 100°/15 mm. 120 - 130 g.

(2) B.p. 100 - 125°/15 mm. 100 g.

Fraction (2) began to crystallise almost immediately giving white glistening needles, m.p. 62 - 63°, and consisting essentially of p-isopropyl phenol.

Hydrogenation of p-isopropyl phenol over Raney nickel.

This was performed as directed by Coats and Cook[23] with comparable results. Higher fractions (345 g.) from the "chromite" hydrogenations, consisting essentially of p-isopropyl phenol, with a Raney nickel catalyst (20 g.), at 160-180° and 100 atmospheres gave p-isopropyl cyclohexanol (240 g.), b.p. 90-110°/11 mm. *

Oxidation of p-isopropyl cyclohexanol to β-isopropyl adipic acid.

p-Isopropyl cyclohexanol was oxidised according to Coats and Cook[23,31] using nitric acid with ammonium vanadate as catalyst. By very slow addition of the p-isopropyl cyclohexanol, and by keeping the internal temperature rigidly between 50-55°, a 78% yield of solid, m.p. (crude) ca. 70° was obtained on cooling reaction mixture in refrigerator.

Diethyl β-isopropyl adipate.

The crude solid β-isopropyl adipic acid was esterified with absolute alcohol and dry hydrogen chloride as indicated by Coats[33]. The ester had b.p. 152-153°/15 mm.

Ethyl-4-isopropylcyclopentanone-2-carboxylate.

The keto ester was prepared by the Dieckman reaction in toluene according to Coats[33].

* Acid Phthalate (Cis and Trans mixture) m.p. 90-98°

Yield, 65-70%, b.p. 128-132°/12 mm.

Δ^{β}-Hexen-δ-one.

Allyl bromide, propionitrile, and zinc were reacted according to Coats[33] by the method of Blaise[32]. The yield was greatly improved by the use of zinc milled from a block of the metal made from arsenic free rods. One c.c. of pyridine (per half mol. of propionitrile) initiates the reaction.

2-Isopropyl-4:7-dimethyl-5-keto Δ^{4}-tetrahydrohydrindene (IV).

The dicyclic unsaturated ketone was prepared according to Coats and Cook by condensing ethyl-4-isopropyl-cyclopentanone-2-carboxylate with Δ^{β}-hexen-δ-one in presence of sodium ethoxide and decarbethoxylating the fraction b.p. 170-193°/10 mm. with boiling aqueous alcoholic potassium hydroxide. The unsaturated ketone (5.2 g.), semicarbazide hydrochloride (5 g.), potassium acetate (6 g.) in aqueous alcohol gave a crude semicarbazone (5 g.) which on recrystallisation from aqueous alcohol gave colourless needles, m.p. 198-204° (3.4 g.).

A sample for analysis had m.p. 204°.

Found: C, 68.47; H, 9.27; N, 16.10.

$C_{15}H_{25}ON_3$ req.: C, 68.44; H, 9.50; N, 15.98.

Several further crystallisations of the analysis sample gave long needles (saw-shaped edges under microscope), m.p. 208-210°.

An oxime was also obtained by refluxing the ketone with hydroxylamine hydrochloride in pyridine solution. The analysis sample had m.p. 172.5-173.5° and formed small white needle clusters from alcohol.

Found: C, 1. 76.01; H, 1. 9.67; N, 6.45
2. 76.16; 2.10.16;

$C_{14}H_{23}ON$ req.: C, 76.01; H, 10.40; N, 6.34.

Steam distillation of the semicarbazone, m.p. 198-204° (3.4 g.) with oxalic acid gave the pure unsaturated ketone as a colourless mobile oil (2 g.) which distilled from an air-bath at 88° /.15 mm. (air-bath temperature).

4:7-dimethyl-2-isopropyl-5-hydrindanone.

The above oil (2 g.), hydrogenated in absolute alcohol (18 cc.) with Pd black (0.7 g.), absorbed 190 cc. of hydrogen in six hours. Treatment with semicarbazide hydrochloride gave a crude semicarbazone (0.4 g.), m.p. ca. 170°. Three recrystallisations from absolute alcohol gave colourless needles, m.p. 201°. Concentration of the filtrates from which this semicarbazone had been obtained gave another amorphous semicarbazone which, after a further two crystallisations from alcohol, had m.p. 156-164°, depressed to 150° by admixture with material m.p. 201°. Steam distillation of the semicarbazone m.p. 201° with sulphuric acid (20%) gave the pure saturated ketone (isomer A).

In this, and in other experiments on a much larger

scale, the crude mixture of stereoisomeric ketones was recovered by steam distillation with 20% sulphuric acid of the aqueous alcoholic mother liquors from which the pure semicarbazone had been obtained.

Typical Experiment: Oxidation of the Crude Mixture of Stereoisomeric Ketones (V).

A stirred solution of the mixture of ketones (20 g.), recovered by steam distillation of the alcoholic mother liquors from which semicarbazone m.p. 201° had been obtained, in purified acetic acid (145 cc.) was treated, drop by drop, with chromic anhydride (11.7 g.) in 80% acetic acid (30 cc.). The addition required an hour. The mixture was left overnight, poured into water (600 cc.) and extracted three times with ether. The aqueous solution was made alkaline with solid sodium carbonate and heated on the water-bath. Acidification gave a gum (6.8 g.). Treatment with potassium acetate (8 g.), semicarbazide hydrochloride (6 g.) in alcohol (150 cc.) and water (50 cc.) gave solid semicarbazone derivatives (2.9 g.). Recrystallised from alcohol there

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The main bulk of this compound (isomer A) was prepared according to Coats and Cook by going directly from the unsaturated ketone to the saturated material without preliminary isolation of the pure unsaturated compound by way of its semicarbazone, as it was obvious from the figures given above that no advantage could be gained by this preliminary treatment.

was obtained:

Crop I m.p. 168-170° 0.88 g.

Crop II m.p. 168-170°

Recrystallisation gave satin white rosettes, m.p. 175°, softening 168°. Mixed m.p. with Professor Cook's sample of semicarbazone (m.p. 181°) of β(2-acetyl-4-isopropyl cyclopentyl)butyric acid was 175-177°.

Crop III - m.p. 163-167° - plate-like material,

Crop IV - m.p. 161-165° - softening 155°. 0.7 g.

Mixed m.p. Crop III with Crop I, m.p. 158-162°

Mixed m.p. Crop IV with Professor Cook's sample (m.p. 150-155°) was 150 - 160°.

Hydrogenation of Unsaturated Ketone (IV) with a Palladised Strontium Carbonate Catalyst.

(Hydrogenation was performed by Mr. Cameron).

The dicyclic ketone (50 g.), absolute alcohol (500 cc.) and palladised strontium carbonate (20 g.) were placed in the autoclave under a pressure of 112 atmospheres of hydrogen. The bomb was heated to 50° and maintained there for six hours. Absorption of hydrogen was approximately 12 litres. After filtration of catalyst and distillation of some of the alcohol, the solution was treated with semicarbazide hydrochloride and potassium acetate. An oil precipitated. The oil was separated, washed with water, ether extracted, and the ether distilled. The

aqueous alcoholic solution was concentrated, diluted with water and ether extracted. The recovered gummy mixture of semicarbazones was dissolved in alcohol when, eventually, two crops of solid crystalline derivatives were obtained. Crystallisation of a sample from each crop gave the same semicarbazone. The two crops were, therefore, combined and after four crystallisations a crystalline semicarbazone (7.9 g.), m.p. 162-164°, was obtained. Hydrolysis of this material by steam distillation with 20% sulphuric acid gave a liquid ketone - isomer B (5.8 g.), b.p. 85°/3 mm. (air-bath temperature):

Found: C, 80.82; H, 11.39.

$C_{14}H_{24}O$ req.; C, 80.77; H, 11.53.

Reconversion of a sample of the pure ketone to semicarbazone gave material m.p. 162-164°. Further recrystallisation of the above semicarbazone gave glistening platelets, melting sharply 175-176°.

Found: 1. C, 67.39; H, 10.07. 2. C, 67.74; H, 10.36.

$C_{15}H_{27}ON_3$ req.: C, 67.91; H, 10.20.

Steam distillation with 20% sulphuric acid of the aqueous alcoholic mother liquors from which the above derivative had been prepared gave a crude mixture of stereoisomeric ketones.

A sample of the above semicarbazone m.p. 162-164° showed no depression of melting point on admixture with the semicarbazone m.p. 167-168° obtained by Coats and Cook by the action of diazomethane on the pure dicyclic ketone (isomer A).

Oxidation of Crude Mixture of Stereoisomeric Ketones (V) with Hydrogen Peroxide.

A catalyst was prepared by adding hydrogen peroxide (0.2 cc. of 30%) to vanadium pentoxide (0.05 g.). A violent reaction took place and a voluminous green brown precipitate resulted. To the above catalyst a mixture of the stereoisomeric ketones (2 g.) and methyl alcohol (16 cc.) was added: hydrogen peroxide (4 cc. of 30%) was then added drop by drop. A vigorous reaction took place, the solution becoming red and warming to reflux point, when water cooling was applied. After fifteen hours the solution was heated on the water-bath and the alcohol distilled, the mixture turning green. The residue was poured into sodium carbonate solution, the mixture extracted with ether, and the alkaline liquors made acid and again ether extracted. An acidic fraction (0.6 g.) was obtained as a gum which gave only a trace of semicarbazone on treatment with semicarbazide hydrochloride and potassium acetate in aqueous alcohol.

Action of Amyl Nitrite and Hydrochloric Acid on the Pure Dicyclic Ketone (isomer A).

Isolation of β(2-acetyl-4-isopropyl cyclopentyl) butyric acid (IX).

The pure ketone (1 g.) was mixed with amyl nitrite (0.6 g.), the mixture cooled in ice and concentrated hydrochloric acid (0.5 cc.) added gradually with shaking. The

solution became green, then greenish blue with separation of white semi-solid material. After 9 hours the solution was poured into aqueous sodium carbonate, extracted with ether and the ether washed with sodium hydroxide. The sodium hydroxide washings, on acidification, gave practically no organic material. Acidification (dilute hydrochloric acid) of the carbonate washings caused the slow deposition of fern-like needles, m.p. ca. 64°. Crystallisation from hexane or cyclohexane (more soluble in latter solvent) gave long colourless needles, m.p. 71-72°, which did not depress the melting point of a sample of the above keto-acid supplied by Professor Cook.

Found: C, 69.90; H, 10.03.

$C_{14}H_{24}O_3$ req.: C, 69.97; H, 10.03.

6-Hydroxymethylene-4:7-Dimethyl-2-isopropyl-5-hydrindanone (X)

a). Stereochemically Pure Ketone (V) - Isomer A.

The ketone (1 g.) was added to atomised sodium (1 g.) in absolute ether (25 cc.) and ethyl formate (5.5 cc.) added. A fairly vigorous reaction followed, the colour of the solution changing from yellow to red. After standing for twenty four hours at room temperature, the reaction mixture was poured into ice-water (300 cc.) and extracted with ether. A white solid separated at the interface of the ether-alkali layer. This solid was removed by filtration, the ether layer separated, and the cold aqueous alkaline solution

acidified with dilute hydrochloric acid. Ether extraction, drying (sodium sulphate) and distillation of the ether gave a brown-red viscous oil. This was distilled from an air-bath to give a light golden yellow viscous liquid (0.6-0.65g.) b.p. 98-105°/.2 mm., (air-bath temperature). The same procedure with the crude mixture of stereoisomeric ketones gave a slightly lower yield of a golden yellow viscous oil, b.p. 120-140°/.25 mm. (air-bath temperature). The hydroxy-methylene derivative gave an intense violet colouration with ferric chloride.

The ethereal extract of neutral material from the experiment with the pure ketone gave a distillate (0.2 - 0.3 g.), b.p. 90-120°/.4 mm. (air-bath temperature), which slowly deposited large crystals which had m.p. ca. 64° when pressed on porous plate. The substance, which was identical with the material filtered off in the earlier stages of the experiment, crystallised from dilute acetic acid in white glistening flakes, m.p. 69-70°, or from more concentrated acetic acid in large flat diamond shaped crystals. On standing the samples developed a reddish colouration, probably due to an impurity. The substance gave an intense violet colouration with ferric chloride. Treatment with semicarbazide gave a semicarbazone. Results of analysis indicate that the substance may be an isomer of the hydroxy-methylene derivative.

Found: C, 76.17; H, 9.82.

$C_{15}H_{24}O_2$ req.: C, 76.27; H, 10.16.

b). Crude mixture of ketones.

An ice-cold mixture of the ketones (6 g.) in dry benzene (50 ccs), containing sodium (0.67 g.), in the form of wire, was treated with ethyl formate (2.8 cc.). A sluggish reaction started and the colour of the solution changed from yellow to red. After standing at room temperature for 40 hours the dark red reaction mixture was poured into water and the solution extracted with ether. Acidification of the aqueous layer precipitated an oil which was extracted with ether. Removal of the ether left a dark red viscous gum. Distillation of this material from an air-bath gave a slightly viscous, yellow liquid (1.1-1.2 g.), b.p. 120-140°/.2 mm. (air-bath temperature).

c). Mixture of Ketones.

Sodium (0.3 g.) was atomised in toluene and suspended in toluene (10 cc.). The mixture of ketones (2 g.), ethyl formate (1 cc.), and toluene (10 cc.) were added with cooling. A sluggish reaction started and was allowed to continue for some 24 hours. The alkali soluble fraction was worked up as before and on distillation from an air-bath gave a yellow slightly viscous liquid (0.4-0.5 g.), b.p. 125-145°/.2-.3 mm.

Hydroxymethylene Derivative from Isomer B.

Treatment of pure dicyclic ketone (1 g.), from isomer B, with ethyl formate (5 cc.) in absolute ether (30 cc.) containing atomised sodium (1 g.) gave the hydroxymethylene derivative (0.6 g.), b.p. ca. 100° (air-bath temperature), as a slightly yellow viscous oil. As in the experiment with isomer A, a solid separated at the interface of the ether-alkali layer. It was also obtained in the neutral fraction containing unchanged ketone. Crystallisation of this material from dilute acetic acid gave glistening flakes, m.p. 69-70°, undepressed on admixture with the compound obtained in the experiment with isomer A (page 49). The substance gave an intense violet colouration with ferric chloride, and formed a semicarbazone, m.p. 206-208°.

Found: C, 58.42; H, 8.54.

$C_{17}H_{30}O_2N_6$ req.: C, 58.28; H, 8.57.

Hydromethylene Derivative from the Crude Mixture of Stereoisomeric Ketones from which Isomer B had been removed.

Several experiments using the mixture of ketones (6 g.) in ether (50-30 cc.) and atomised sodium (1-1.2 g.) and ethyl formate (5-5.5 cc.) and allowing to stand for 24 hours at room temperature gave crude alkali-soluble fractions (4.5-4.2 g.) which, distilled from an air-bath,

gave hydroxymethylene derivatives (3.2-2.9 g.), b.p. 114°/ .4 mm. (air-bath temperature).

1-Isopropyl Cyclopentane 3:4 bis (α-Propionic Acid) (XI).

a) Oxidation with Potassium Permanganate.

The hydroxymethylene derivative (0.5 g.) prepared from the stereochemically pure dicyclic ketone (V), isomer A, in 10% sodium hydroxide (1.5 cc.) was treated drop by drop with an ice-cold solution of potassium permanganate (1.0 g. in 38 cc. water) at 0°. After standing for several hours in ice-water, when the colour of the permanganate had completely disappeared, the solution was filtered and the filtrate extracted with ether. Acidic material was removed with sodium bicarbonate solution and extracted with ether. Drying of the ether solution (sodium sulphate) and distillation gave a light yellow gum (0.45 g.) which became semi-solid in a vacuum desiccator. Crystallisation from water, after removal of unsolidified material with n-hexane, gave a solid acid which separated from hexane in colourless cubes or from a large volume of water in glistening white needles, m.p. 154-156° (Yield: 0.2 g.).

Found: C, 1). 65.60; H, 1). 8.72,
2). 65.59; 2). 9.03.

$C_{14}H_{24}O_4$ req.: C, 65.62; H, 9.37.

The residual gum (0.2 g.), obtained from the hexane mother liquors, was treated with p-phenylphenacyl bromide

(400 mg.) in aqueous alcohol with sufficient carbonate to neutralise the acid and sufficient dilute hydrochloric acid to make the solution acid to litmus. After refluxing a solid separated: several crystallisations from alcohol (absolute) gave the bis-p-phenylphenacyl ester of above acid as colourless microscopic needle tufts, m.p. 153-153.5°.

Found: C, 78.00; H, 7.05.

$C_{42}H_{44}O_6$ req.: C, 78.25; H, 6.83.

Oxidation of the crude mixture of stereoisomeric ketones by the procedure outlined above gave a gum which, after standing for several months, became partially crystalline. Trituration with light petroleum gave a small quantity of an acid which crystallised from dilute acetic acid in microscopic needles, m.p. 153°, softening at 143°.

Oxidation of Hydroxymethylene Derivative from Isomer B.

Oxidation of the hydroxymethylene derivative with ice-cold alkaline permanganate, under similar conditions to that used for the material from isomer A, gave acidic material as a gum which could not be obtained solid. The crude p-phenylphenacyl ester had m.p. ca. 125°; repeated crystallisation gave white microscopic needles, m.p. 132-146°. Mixed with a sample of the ester (m.p. 154°) of acid of isomer A series, m.p. 130-146°.

b). With Chromic Acid.

Stereochemically pure hydroxymethylene derivative (0.4 g.) from dicyclic ketone - isomer A - in purified acetic acid (20 cc.) was treated with chromic anhydride (0.68 g.) in acetic acid (68 cc.). The solution was allowed to stand overnight, the excess chromic acid destroyed by the addition of a little methyl alcohol, then, after concentration in partial vacuum to about 2 cc., the residue was diluted with water, and ether extracted. The ethereal solution was extracted with sodium bicarbonate solution, the bicarbonate solution acidified (dilute hydrochloric acid), and again ether extracted. Evaporation of the ether gave a gum which, on treatment with methyl alcohol and on prolonged standing, gave white solid material, m.p. 130-135°.

1-Isopropyl Cyclopentane-3:4-bis (β Butyric Acid) (XII).

The acid (XI) m.p. ca. 150° (0.75 g.) was treated with purified thionyl chloride (2 cc.) at 0°C and the mixture left for 20 hours. The excess thionyl chloride was removed in vacuo and the solution stripped, once with ether and once with benzene. A brownish viscous liquid remained. This was dissolved in ether (12 cc.) and added, drop by drop, to an ethereal solution of diazomethane (from 9 g. of nitrosomethylurea) at 0°C. After standing overnight the solution was concentrated in a partial vacuum, when a light lemon yellow, crystalline powder, m.p. 111-111.5° softening

110°, precipitated.

The diazoketone (0.3-0.4 g.) was filtered and the ethereal filtrate again concentrated, when a gummy lemon-yellow semi-solid was obtained. This was dissolved in ether (10 cc.) and left in the refrigerator, when a further small quantity of crystalline solid separated.

The diazo-ketone crystallised from n-hexane as almost white, cream-coloured micro-needles, m.p. 111-111.5°.

Analysis was performed after standing for several weeks at room temperature, when the sample may have deteriorated to some extent.

Found: C, 63.79; H, 7.66.

$C_{16}H_{24}O_2N_4$ req.:C, 63.16; H, 7.89.

Re-arrangement of the Bis Diazo Ketone.

The cream coloured powder (0.30 g.) was dissolved (and suspended: not too soluble!) in dioxan (20 cc.), heated on the water-bath, then treated with aqueous ammonia (1.5 cc. of 20%) and silver nitrate (0.3 cc. of 10%). The solution became brown and opaque. It was heated for one and a half hours, then filtered, giving a clear yellow filtrate which when concentrated (10 cc.), deposited a small amount of brown microcrystalline needles (probably unchanged diazo-compound). The solution was filtered, taken to dryness, when a gum was obtained. This solidified completely under hexane (micro-needles). The brown solid,

presumably the diamide, was hydrolised by refluxing with methanolic potassium hydroxide (0.4 g. KOH in 6 cc. water) for several hours until evolution of ammonia had ceased. Concentration of the solution in vacuo, cooling, ether extraction, followed by acidification (dilute hydrochloric acid) of the aqueous layer gave a gum which solidified on stirring to give a brown microcrystalline solid, m.p. 160-161°, softening at 155° (yield 0.120 g.). The acid recrystallised (twice) from dilute acetic acid as slightly brown fluffy needles, m.p. 172-173°.

Found: C, 1). 68.13; H, 1). 10.20,
2). 68.24; 2). 10.17.

$C_{16}H_{28}O_4$ req.: C, 67.61; H, 9.86.

Starting material:

$C_{14}H_{24}O_4$ req.: C, 65.67; H, 9.37.

$C_{15}H_{26}O_4$ req.: C, 66.61; H, 9.70.

Pyrolysis of the Thorium Salt of 1-Isopropyl Cyclopentane-3:4-Bis (β-Butyric Acid).

The acid (0.08 g.) was treated with sodium hydroxide (2 cc. of .2727 N) followed by the theoretical amount of thorium nitrate dissolved in aqueous alcohol. Distillation of the precipitated light brown thorium salt gave a minute amount of brown-red distillate with a pleasant ketonic odour, metal-bath 250-300°/.2 mm.

An attempt to obtain a crystalline semicarbazone was unsuccessful.

β-Isopropyl Adipoyl Chloride.

β-isopropyl adipic acid (4 g.) was treated in the cold with thionyl chloride (4 cc.) and left overnight. The brown reaction mixture was heated in vacuo to remove thionyl chloride. Distillation of the residue from an air-bath, 2 mm., external temperature 104°, gave the acid chloride (3.9 g.).

Diazo Ketone.

The acid chloride in absolute ether (30 cc.) was added to a solution of diazomethane - from nitrosomethyl-urea (20 g.) - in ether (250 cc.). There was a slight effervescence and a fluffy precipitate appeared. After leaving for 36 hours the ether was removed in a partial vacuum to give a brown-red viscous gum which could not be obtained crystalline.

Re-arrangement and Isolation of γ-Isopropyl Suberic Acid (XIV).

The red viscous gum was dissolved in dioxan (40 cc.) and the solution heated on the water-bath. To the hot solution was added ammonia (15 cc. of 20%), followed by silver nitrate (3 cc. of 10%). A mild effervescence followed, becoming very brisk, and ceasing after ten minutes. Heating was continued for one hour and the solution filtered.

Removal of the dioxan in vacuo gave a red gum which did not solidify on chilling or under solvents. The gum was refluxed with potassium hydroxide (3 g. in 30 cc. water). After three hours boiling the evolution of ammonia ceased. Acidification of the hot solution (dilute hydrochloric acid) gave a gum. On cooling the hot mother liquors, decanted from gum, deposited fern-like needles, m.p. 50-54°. Recrystallised from hexane these formed colourless needles, m.p. 69.5-71°, depressing the melting point of the starting material to 61°.

Found: C, 60.89; H, 9.00

$C_{11}H_{20}O_4$ req.: C, 61.11; H, 9.25.

Starting material:

$C_9H_{16}O_4$ req.: C, 57.44; H, 8.51.

Pyrolysis of the Thorium Salt obtained from the Residual Gum.

The thorium salt (1 g.), obtained from a portion of the above gum (which had solidified under petroleum ether) by dissolving in sodium hydroxide (0.5 N) and alcohol, neutralising with dilute nitric acid, and treating with thorium nitrate, was heated at 300-350°/.3-.4 mm. At 320°, a small quantity of mobile, clear light-red liquid, smelling of violets, was obtained. This gave a semicarbazone, m.p. 140-141°, softening 121°. Repeated crystallisation of the small quantity available failed to give a sample suitable for analysis.

Condensation of ethyl-4-isopropyl-cyclopentanone-2-carboxylate with ethyl ∝-bromopropionate.

A solution of sodium ethoxide was obtained by dissolving sodium (2.3 g.) in absolute alcohol (50 cc.). The solution was cooled to -15°C, and the keto-ester, ethyl isopropyl cyclopentanone carboxylate (20 g.) added. After 1½ hours the bromo-ester (18.1 g.) was added, drop by drop, with occasional stirring of the sludgy white paste of sodio compound. The solution was heated for 6 hours at 50°, after leaving for 30 hours at room temperature. After pouring the mixture on to ice, the neutral material was ether extracted, dried (sodium sulphate) and distilled. The main fraction was obtained as a colourless, slightly viscous liquid (15 g.), b.p. 155-185°/13 mm.

Treatment of the Condensation Product.

The main fraction was refluxed with concentrated hydrochloric acid (100 cc.) for 6 hours. After cooling, the solution was extracted with ether and the ether dried. Distillation of the ether gave a brown oil which was directly esterified with absolute alcohol and dry hydrochloric acid. After standing overnight at room temperature, the solution was poured into water, extracted with ether and the ether layer washed with a solution of sodium carbonate, then water. Distillation of the dried ethereal extract gave an oil which was vacuum distilled. The main fraction (7 g.)

distilled as a colourless liquid, b.p. 141-150°/15 mm. Treatment of this oil in aqueous alcohol with potassium acetate and semicarbazide hydrochloride gave a semicarbazone which after several crystallisations from aqueous methyl alcohol formed long colourless blades, m.p. 163-165°, sintering at 159°. A further crystallisation gave materials m.p. 164-166.5°. The poor analytical figures may be, despite repeated crystallisations, due to the presence of di-isopropyl cyclopentylidene cyclopentanone (XX); see next experiment.

Found: C, 60.04; H, 8.75; N, 14.24.

$C_{14}H_{25}O_3N_3$ req.: C, 59.37; H, 8.83; N, 14.84.

Found: C, 59.63; H, 8.8.

Hydrolysis of Condensation Product and Isolation of Di-isopropyl Cyclopentylidene Cyclopentanone (XX).

The main fraction (15 g.), from condensation of keto-ester and α-propionic ester, was boiled for 6 hours with concentrated hydrochloric acid (100 cc.) and the acidic material separated with sodium carbonate solution, the alkaline liquors acidified (dilute hydrochloric acid) and ether extracted. Evaporation of the ether gave an acid (9 g.) which could not be obtained solid. It did not form a semicarbazone. The neutral material from the hydrolysis, when boiled with aqueous methyl alcoholic potash (50 cc. of

10%) gave a solid which crystallised from aqueous methyl alcohol as glistening plates, m.p. 72-74°. It gave a red precipitate with 2:4 dinitrophenylhydrazine. Analysis and melting point indicated that the compound is di-iso-propyl cyclopentylidene cyclopentanone, obtained also by Coats and Cook[23]x.

Found: C, 82.12; H, 10.8.

$C_{16}H_{26}O$ req.: C, 82.06; H, 11.11.

Condensation in Benzene.

Sodium (1.2 g.) was atomised in toluene, the toluene decanted and benzene (40 cc.) added. The keto-ester (10 g.) was added and the white sodio compound heated at reflux point for 2 hours. The reaction mixture was cooled and the bromo compound (10 g.) added. After heating on the steam bath for 6 hours, the solution was poured into water and ether extracted, the ether-benzene layer dried (sodium sulphate) and distilled. The main fraction (8.8 g.) distilled as a colourless oil, b.p. 140-180°/10 mm.

Hydrolysis of Main Fraction: Isolation of α-(2-keto-4-isopropyl cyclopentyl) propionic acid (XVII).

The main fraction was boiled with concentrated hydrochloric acid (60 cc.) for 6 hours. The resultant

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x A sample of the material obtained by Coats is unfortunately not available for a mixed melting-point.

mixture was ether extracted and the ether layer washed with sodium carbonate. Acidification of the alkaline liquors, and ether extraction of the precipitated oil, followed by drying and distilling the ether layer, gave a gum (4-5 g.) which gradually became semi-solid. Addition of petroleum ether and filtering gave a solid acid forming small, colourless needles, m.p. 97-103°. Crystallisation from n-hexane (three times) gave an acid of m.p. 109-110°.

Found: C, 66.63; H, 9.30.

$C_{11}H_{18}O_3$ req.: C, 66.67; H, 9.10.

The material, insoluble in carbonate (3.1 g.), a brown oil with a strong terpene-like odour, gave an unhomogeneous 2:4 dinitrophenylhydrazone, separated by crystallisation from alcohol into reddish plates sparingly soluble in alcohol, m.p. 80-110° and more soluble light orange plates, m.p. 120-125°. It was not further investigated.

Arndt Eistert Chain Lengthening of Mixture of Acids (XI) Obtained from Mixture of Stereoisomeric Ketones (V).

The ice-cold mixture of acids (7.4 g.) was treated with thionyl chloride (6 cc.). A reaction soon started and continued until the gum had disappeared and a dark brown solution was obtained (2½ hours). After warming (40-60°) on the water-bath for about 30 minutes, the thionyl chloride was removed in vacuo. Benzene (10 cc.) was added

and then removed; finally, absolute ether was added, distilled off, and the residual gum heated in a partial vacuum for a short time. The brown acid chloride was dissolved in dry ether (70 cc.) and then added, drop by drop, to an ethereal solution of diazomethane (from nitrosomethylurea (41 g.)). A brisk reaction started immediately. The solution was left for 18 hours at room temperature, then the ether and excess diazomethane removed in a partial vacuum. The residue (a dark brown viscous liquid) was dissolved in dioxan (50 cc.), the solution warmed to 50° on water-bath, then ammonia (17 cc. of 20%) added, followed by a silver nitrate solution (3 cc. of 10%). A vigorous reaction started with reflux. The solution was heated for three-quarters of an hour then left overnight. After filtration the dioxan solution was boiled with charcoal, filtered, and evaporated in vacuo. A thick brown, almost solid gum remained. To this was added a solution of potassium hydroxide (6 g. in 36 cc. of water) and the solution boiled until evolution of ammonia ceased. The cooled solution was extracted with ether and the brown aqueous layer acidified (dilute hydrochloric acid). A brown gummy amorphous semi-solid material precipitated. It was extracted with ether, and the ether dried (sodium sulphate) and distilled, when a dark brown almost solid gum (6.5 g.), presumably the required mixture of 1-isopropyl-

cyclopentane-3:4 bis (β-butyric acids), was obtained.

Pyrolysis of the Thorium Salt of the Mixture of Crude Acids (XII).

The crude mixture of acids (6.5 g.) was treated with freshly precipitated thorium hydroxide (made from thorium nitrate (8 g.) and ammonium hydroxide, and quickly drying the washed precipitate on heated porous plate) and the mixture heated under vacuum on the water-bath. The resultant amorphous brown powder was quickly heated with a bunsen flame at .2 - .5 mm. pressure. A viscous brown distillate (1.5 g.), with a plant-like odour, was obtained. The oil was dissolved in ether, washed several times with saturated carbonate solution, then water. Evaporation of the ether gave a brown oil which was redistilled.

Fraction I: b.p. 85-95°, mainly 85°/.1-.15 mm. (air-bath temperature) - light brown mobile oil.

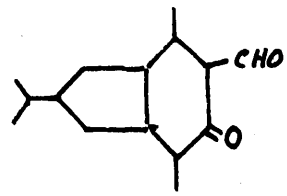
Fraction II: b.p. 105-113°/.1-.15 mm. (air-bath temperature) - brown viscous oil.

Both fractions gave red gummy precipitates with 2:4 dinitrophenylhydrazine. An alcohol solution of the derivatives from fraction I gave a dull-red amorphous solid, m.p. 60-74°.

Note:- All melting points are uncorrected.

Addendum.

The analysis for the semicarbazone (referred to on page 30) is now available (page 51). These figures, taken in combination with the analysis for the solid product itself, suggest that the derivative is a disemicarbazone. Although no rigid proof is advanced, it would appear possible that the solid which was insoluble in the ice-cold alkaline solution, represents the "aldehydo" form of the hydroxymethylene derivative;



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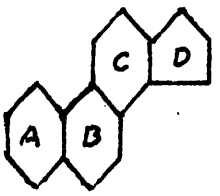
PART II.

Syntheses of Fused Ring Compounds Related to Steroids.

Syntheses of Fused Ring Compounds Related to Steroids.

Many novel synthetic methods have recently led to further developments in the field of synthesis of the natural hormones. Equilenin and oestrone have been the most attractive goals because they present less complex stereochemical difficulties than the completely reduced hormone structure. There are many methods of approach to the synthesis of the cyclopentenophenanthrene carbon skeleton (I).



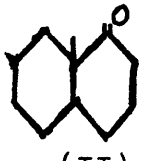
(I).

In general, these methods can be roughly divided into two, the first based on the building up of ring D in the early stages of the synthesis and the completion of the middle rings at some later point, or the second, which attempts the construction of the five-membered ring on to the completed system A - B - C.

The present work is concerned with the second method of approach to the problem, viz., the preliminary building of the system A - B - C. In a synthesis of oestrone, where ring A is aromatic, and in equilenin, where both A and B are aromatic, the absence of angular methyl substituents simplifies the problem, and furthermore, use can be made of

the reactivity of the aromatic nucleus and the para directing influence of the methoxy group. The non-benzenoid hormones present a much more difficult problem, with the introduction of the angular methyl substituents and the increasing number of stereoisomers complicating the problem of purification and consequently, identification.

A compound which would be useful as an intermediate in the synthesis of a molecule of the androstane type (IV) is 9-methyl-1-decalone (II). Several considerations make this compound desirable as an intermediate: its ease of purification and identification, the reactive nature of the carbonyl function permitting further synthetic operations, and, furthermore, the fact that a method of synthesis of this compound from 2-methyl cyclohexanone could, thereotically, be repeated using 9-methyl-1-decalone itself to obtain, ultimately, 1-keto-13-methyl-perhydrophenanthrene (III).



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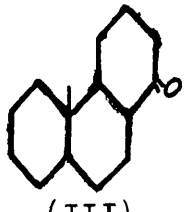
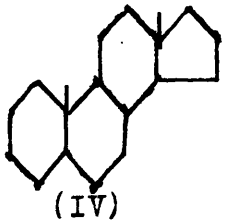


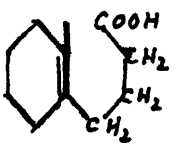
(III)



(IV)

A survey of the literature reveals a variety of processes whereby 9-methyl-1-decalone (II) can be obtained.

All the reported methods, with the exception of the procedure whereby the angular methyl group is directly introduced into decalone[1,2], centre on the preparation of methylcyclohexenyl butyric acid (V) which is cyclised according to the Darzens reaction as modified by Cook and Lawrence[4,5] to the corresponding chloro ketone (VI) which, after removal of hydrochloric acid, yields the unsaturated ketones (VII) or (VIII) or a mixture of both.



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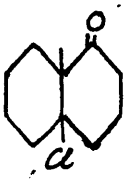
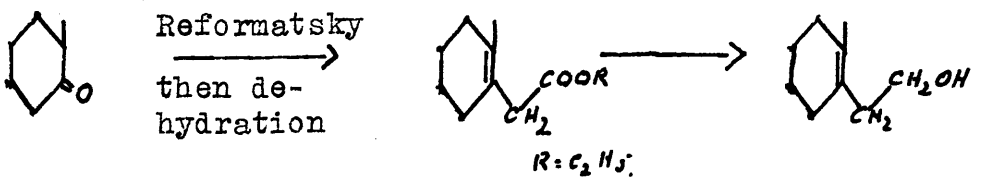


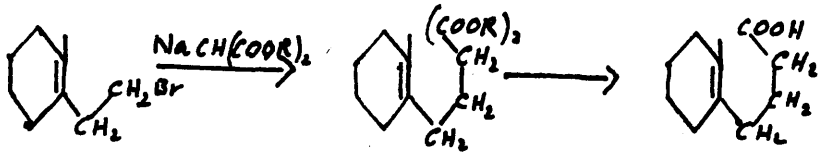
(VI)

(VII)

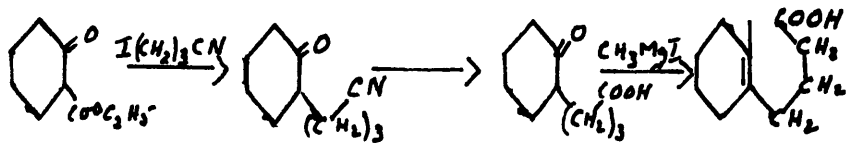
(VIII)

Primarily the problem is the preparation of the substituted butyric acid (V) since the cyclisation procedure has been well tried and the reported yields are good. This acid has been synthesised by several methods. Chuang, Tien and Ma[6], following a method elaborated by Cook and Lawrence[4] in the synthesis of decalone, obtained the acid by the following scheme:-

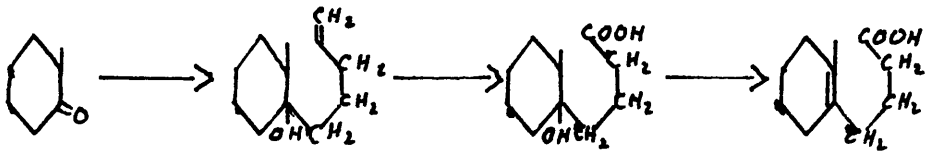




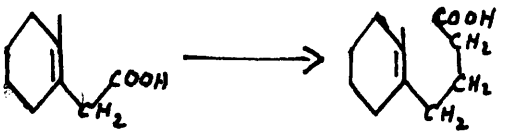
These authors anticipated to some extent the work of Cook and Lawrence[5] who now reported a different route to the butyric acid:



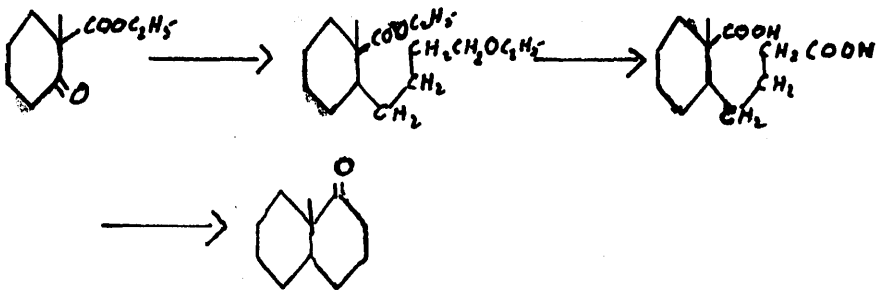
Elliot and Linstead[7], in the following year, reported an ingenious though somewhat involved method of obtaining this intermediate. This consisted in reacting 2-methylcyclohexanone with a Grignard reagent prepared from Δ^4-n-pentenyl bromide, oxidising the product to a hydroxy acid and dehydrating to the required unsaturated compound:-



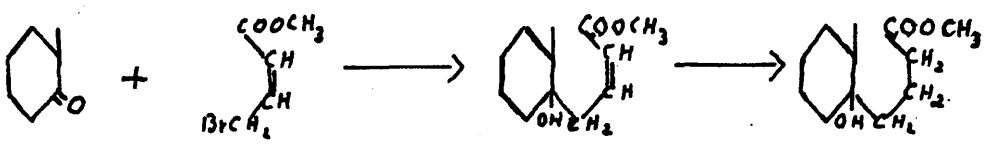
A more recent method of preparation of γ-(2-methyl-Δ^1-cyclohexenyl) butyric acid (V), due to Plentl and Bogert[8], consists in the elongation of the side-chain of methyl cyclohexenyl acetic acid by two successive Arndt-Eistert reactions.



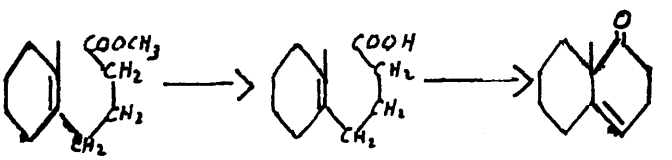
9-Methyl-1-decalone has also been synthesised by Kon, Linstead and Simons[31] by a Grignard reaction between methyl cyclohexanone carboxylate and γ-ethoxy butyl bromide, oxidising the product to a dibasic acid and ring closing the ester.



The first objective of this research was to synthesise 9-methyl-1-decalone (II) by the use of a novel Reformatsky reaction with methyl γ-bromo crotonate (IX) envisaging the following scheme:



(IX) (X) (XI)



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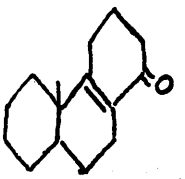
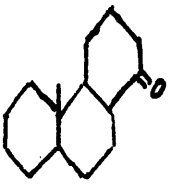


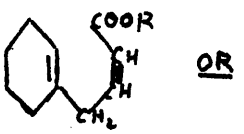
(XIV)



(XV)

If the method could be thus successfully realised it was proposed to extend the same series of reactions to 9-methyl-1-decalone itself in the hope of obtaining 1-keto-13-methyl- $\Delta^{11:12}$-dodecahydrophenanthrene (XIV) or 1-keto-13-methyl-perhydrophenanthrene (XV).

The vinylogues of the α-haloesters appear to have been first used by Fuson, Arnold and Cooke[10] who condensed γ-iodocrotonate with cyclohexanone and zinc to obtain (XVI)



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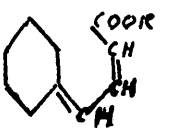
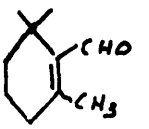


(XVI) (XVI)



(XVII)

The same group of workers[11], also Sobotka and co-workers[12,13] have sought to utilise the reaction in polyene synthesis, reacting β-methyl-γ-bromo crotonic ester with β-cyclocitral (XVII) to obtain Vitamin A intermediates.

Still more recently in this laboratory Cook and Schoental[14] have successfully utilised γ-bromo crotonic ester in a hydroxy chrysene synthesis.

The method gained in importance with the finding of

Ziegler[15,16] that methyl crotonate could be directly brominated in the allyl position with n-bromo succinimide in good yield.

In the scheme which has been outlined above, 9-methyl-1-decalone has now been synthesised in an overall yield of 20% from 2-methyl cyclohexanone; and by essentially the same series of reactions, a ketone has been obtained, characterised by its 2:4-dinitrophenylhydrazone, which is, presumably, the required 1-keto-13-methyl-$\Delta^{11:12}$-dodecahydrophenanthrene (XIV).

By using zinc, prepared by milling down a zinc block made from arsenic free zinc rods, and activated by amalgamation[17] (the author is indebted to Dr. Schoental for this observation), 2-methyl cyclohexanone reacted with γ-bromo crotonic ester (IX) to give methyl-γ-(1-hydroxy-2-methyl cyclohexyl) crotonate (X) in 50% yield. The distilled product was hydrogenated with palladium black as catalyst, the intake of hydrogen ceasing after the theoretical amount required for one double bond had been absorbed. The procedure adopted at this stage was to dehydrate the hydroxy ester (XI), hydrolise the crude product (XII) with aqueous methanloic sodium hydroxide, and judge the utility of the process by the methyl cyclohexenyl butyric acid (XIII) formed. Several methods of dehydration of the hydroxy-ester were studied. Poor results were obtained with

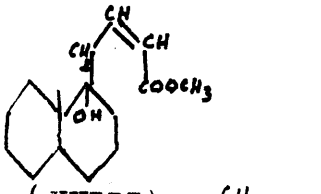
thionyl chloride and pyridine, the acidic material showing no tendency to solidify. Dehydration with sodium bisulphate, followed by hydrolysis gave an alkali soluble fraction which slowly deposited, in small yield, crystals of the required acid. However, by heating the hydroxy ester gently with a crystal of iodine and hydrolising the crude product, an alkali soluble viscous liquid was obtained which rapidly solidified at room temperature to a white mass of flakes of γ-(2-methyl-Δ^{1}-cyclohexenyl)-butyric acid (XIII). The crude material was cyclised to the chloro ketone and hydrochloric acid removed with dimethylaniline, to give 9-methyl-$\Delta^{4:10(\text{or } 5:10)}$-1-octalone (VII) or (VIII), identified by m.p. (and mixed m.p.) of the semicarbazone. Hydrogenation with palladium black was slow, but by using a large excess of catalyst, 9-methyl-1-decalone, (mainly the cis product) was obtained. It was identified by comparison with an authentic sample of methyl decalone semicarbazone. For preparatory purposes on a somewhat larger scale, hydrogenation of the octalone was satisfactorily effected byusing a palladised strontium carbonate catalyst at 50° and 115 atmospheres pressure. The distilled product, which was identified by its semicarbazone, was used directly in the subsequent stages of the synthesis.

The dicyclic ketone, prepared as indicated, reacted vigorously with methyl γ-bromo crotonate and zinc activated as before. In working up the reaction mixture, although

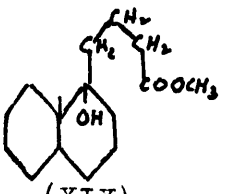
distillation was carried out on a small scale from an air-bath, no attempt was made to distil products on a large scale since it was essential to prevent dehydration of the methyl γ-(1-hydroxy-9-methyl decalyl) crotonate (XVIII).

Hydrogenation with palladium black, in several different experiments, indicated, by the amount of hydrogen absorbed, that the unsaturated hydroxy ester (XVIII) had been formed in 40 - 50% yield (although no allowance is made for any methyl decalol which may have been formed with 9-methyl-1-decalone during the hydrogenation with palladised strontium carbonate). The crude product was dehydrated as before by heating with a crystal of iodine. Attempted distillation of the product at this stage gave unchanged methyl decalone and indefinitely boiling higher fractions which distilled with considerable decomposition leaving a large dark residue in the flask. Hydrolysis of the methyl ester (XX) was, therefore, effected with aqueous methanolic sodium hydroxide, without preliminary purification. Ether extraction of the diluted aqueous methanolic sodium hydroxide gave a 40 - 50% recovery of 9-methyl-1-decalone (based on weight of semicarbazone). From the alkaline liquor a brown gum was obtained by acidification. Extraction with ether, drying and distillation gave a dark brown viscous material. By its behaviour towards hot and cold alkali it appeared to consist mainly of lactone, possibly (XXII), with a small

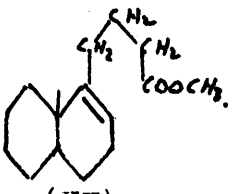
amount of acid (XXI)



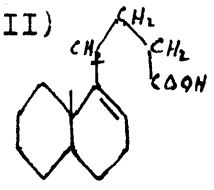
(XVIII)



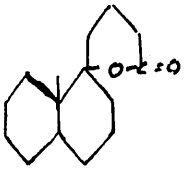
(XIX)



(XX)



(XXI)

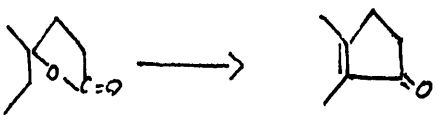


(XXII)

Some of the above gum was treated with thionyl chloride and pyridine in ethereal solution, and the product cyclised with stannic chloride according to the procedure of Cook and Lawrence[4,5]. On decomposition of the brown complex which separated from the carbon disulphide reaction mixture, an insoluble gum, presumably mainly the starting material, was recovered. On standing under aqueous alcohol, the gum solidified to a brown crusty solid. This dissolved in alcohol and on standing deposited a fawn-coloured amorphous powder. The behaviour of the powder suggested that it was a lactone, possibly (XXII). Treatment of the material soluble in carbon disulphide with dimethyl-aniline and distillation of the product gave a fairly mobile light yellow liquid which darkened very slightly after standing for some time at room temperature. The substance gave a brilliant red 2:4 dinitrophenylhydrazone which was homogeneous and crystallised easily and well from glacial acetic acid:

results of analysis indicated that it is the derivative of the required 1-keto-13-methyl- $\Delta^{11:12}$-dodecahydrophenanthrene (XIV)[x].

At this stage in the synthesis the work of Johnson and co-workers[18] became available. These workers prepared five-membered ring ketones by cyclisation of lactones on to alicyclic ring systems by the use of acetic anhydride and acetic acid containing a catalytic amount of fused zinc chloride[34]:



There are a few references in the literature to the cyclisation of lactones. Plattner and St.Pfau[19] prepared substituted cyclopentenones by the removal of water from γ, δ - unsaturated acids or the corresponding lactones. Cyclisations of lactones have also been described in the Patent Literature[20,21,22,23] by Bryusova and Osipova[24], and by Frank, Arvan, Richter and Vanneman[25]. The last named authors succeeded in transforming γ-methyl-γ-decanolactone (XXIII) to dihydrojasmone in 50% yield by using phosphorus pentoxide.

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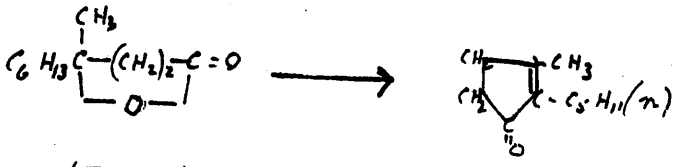
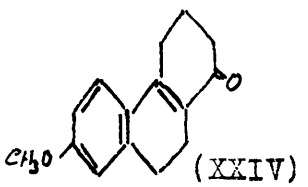
[x] An attempt to obtain a semicarbazone gave gummy material: a later test with semicarbazide on another sample of ketone appears to be much more promising.



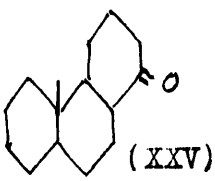
(XXIII)

It was, therefore, a matter of some interest to see if the brown powder, recovered from the cyclisation with stannic chloride, and presumably having the structure represented by (XXII) could be cyclised to the required substituted cyclohexenone by the use of the "acetic anhydride - zinc chloride" reagent. Treatment of this material with this reagent, under the conditions used by Johnson for cyclopentenones (in this particular case the reaction was not carried out in an atmosphere of nitrogen - later experiments were, however), did, in fact, give a small yield of 1-keto-13-methyl- $\Delta^{11:12}$-dodecahydrophenanthrene (XIV), characterised by the same red crystalline 2:4 dinitrophenylhydrazone as had been obtained from the product of the stannic chloride cyclisation. Consequently, in the next series of experiments the gum (probably a lactone (XXII) - acid (XXI) mixture) obtained after hydrolysis of the unsaturated ester (XX) was treated directly with the zinc chloride, acetic anhydride reagent. By this technique, and, in this case, by carrying out the reaction, in a stream of nitrogen, the acid-lactone mixture was converted to neutral ketonic material apparently consisting essentially of 1-keto-

13-methyl- $\Delta^{11:12}$-dodecahydrophenanthrene, in 38% yield. An attempt to reduce this tricyclic ketone with palladium black appeared to be only very partially successful. This was to be expected in view of the difficulty experienced by Robinson and co-workers[26] in attempting to reduce the double bond in (XXIV).



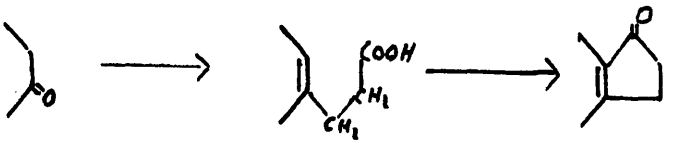
(XXIV)



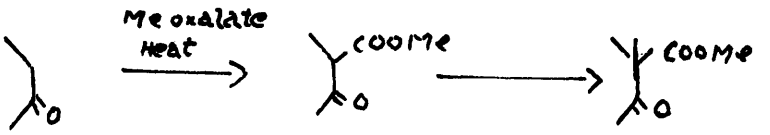
(XXV)

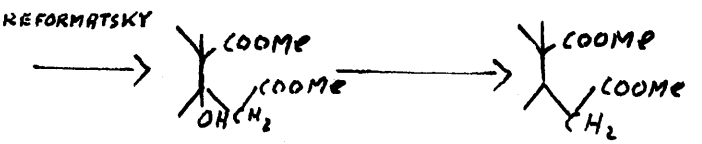
However, a mixture of 2:4-dinitrophenylhydrazones was obtained from the partially hydrogenated material. After separation of the less soluble red derivative of the starting material, a more soluble semi-crystalline orange-red substance, m.p. ca. 176°, was obtained from acetic acid. This may be the 2:4-dinitrophenylhydrazone of 1-keto-13-methyl-perhydrophenanthrene (XXV).

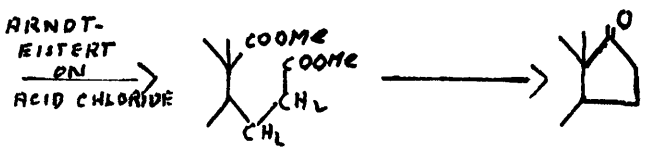
In view of the amount of unsaturated material available and the probable difficulty of obtaining, without a much larger amount of starting material, any useful quantity of (XXV), it was decided to continue the research, for the moment, by attempting the synthesis of a tetracyclic compound from the unsaturated ketone (XIV). Several methods have been elaborated for the construction of the five-membered ring with the carbonyl function in the required position:



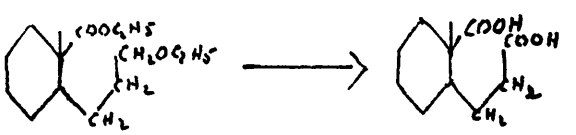
Bachman and co-workers have used the following method in the synthesis of equilenin[27] and oestrone[28], and more recently 8-methyl-1-hydrindanone[29]:





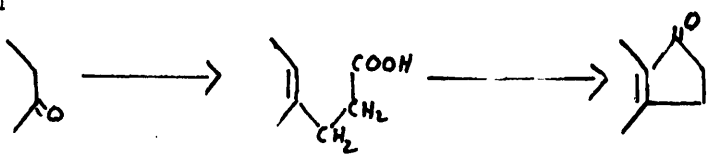


The essential feature of this and other available methods is the obtaining of a propionic acid residue at the site of the carbonyl function. Robinson and Walker[30] and Kon and Linstead[31] utilised a Grignard reaction with γ-ethoxypropyl bromide and oxidised the dehydrated and reduced product (XXVI) to the required acid:

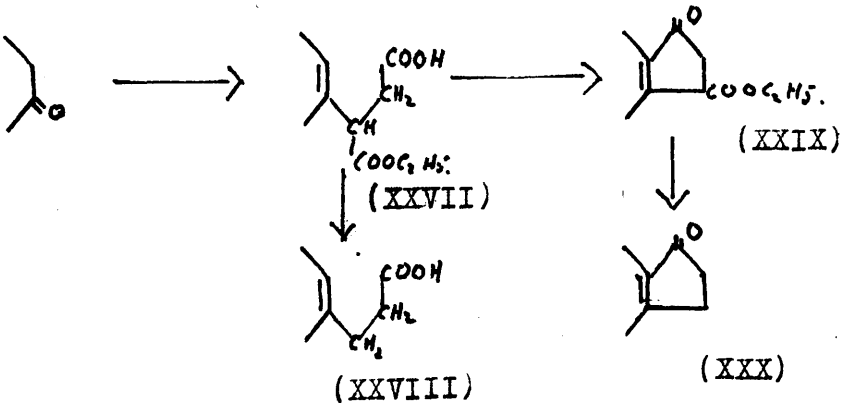


(XXVI)

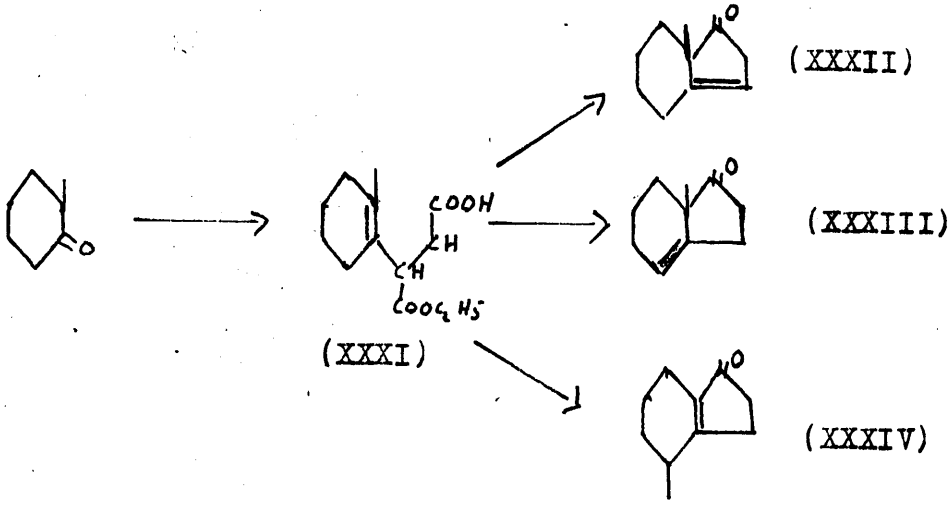
The introduction of the propionic acid residue has been achieved in one stage by Haberland and Heinrich[32] who reacted the ketone with β-bromopropionic ester and magnesium



The yield was, however, poor. An attractive method has recently been reported by Johnson and collaborators[18]. A modified "Stobbe condensation"[33] was carried out between the ketone and diethyl succinate in the presence of potassium-tertbutoxide yielding a half-ester (XXVII) in 89-94% yield. This material could be decarbethoxylated to the required propionic acid (XXVIII) or could be directly cyclised to the five-membered ring ketone by using a mixture of acetic anhydride and acetic acid containing a catalytic amount of fused zinc chloride[34]. By decarbethoxylating the product (XXIX) by boiling with concentrated hydrochloric acid, the semicarbazone of the ketone (XXX) was obtained in 58% yield.



It was decided to apply this process to the tricyclic unsaturated ketone (XIV) after carrying out preliminary experiments on the easily obtainable 2-methyl cyclohexanone:



It would also be a matter of some interest to ascertain the direction of ring closure of the half-ester under the influence of this novel reagent for cyclisation of a carboxy group into an unsaturated alicyclic nucleus. 2-Methylcyclohexanone condensed with diethyl succinate in an atmosphere of nitrogen to yield the crude acid (XXXI) in 80% yield. Distillation of a sample gave two acidic fractions. The lower boiling fraction remained liquid, but the higher boiling material solidified on addition of light petroleum and gave an acid which analysed in agreement with (XXXI). The liquid acid is possibly an isomer of (XXXI). Ring closure of the crude product with the fused zinc chloride

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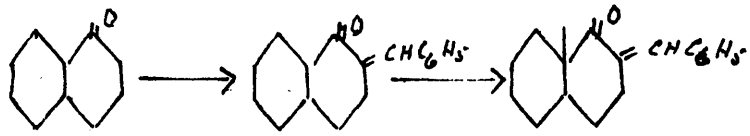
An attempt to condense methylcyclohexanone with diethyl glutarate in presence of potassium tert-butylate was unsuccessful.

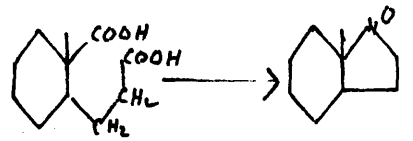
reagent and decarbethoxylating the intermediate keto-ester by refluxing with concentrated hydrochloric acid gave a ketone with the odour of bog myrtle. The substance gave a semicarbazone, m.p.240.5°: analytical data were in agreement with the expected dicyclic hydrindenone. Chuang, Tien and Ma[6], who prepared 8 -methyl-1-keto-hexahydro-indene (XXXII) or (XXXIII) by a different scheme, obtained a semicarbazone, m.p. 187°. Thus the compound arising from the ring-closure with the acetic acid, acetic anhydride, zinc chloride reagent, may be a stereoisomer of the ketone prepared by the last named authors (XXXII) or (XXXIII), the location of the double bond being different, or the two compounds might be positional isomers differing in the location of the methyl group (XXXIV). Hydrogenation of the unsaturated compounds might give rise to the same saturated ketones. The crude ketone was, therefore, hydrogenated in presence of palladium black until the absorption of hydrogen (which was very slow) had ceased. An oil was obtained which did not possess the camphor-like odour, typical of 8 -methyl-1-hydrindanone (XXXVII). A semicarbazone was obtained which, when crystallised to constant melting point (210-211°), melted only several degrees below the product obtained by Chuang, Tien and Ma (213°), but considerably lower than the values observed by later workers[29,30,31], for either the "cis" or "trans" derivatives. It was decided, therefore,

to prepare a sample of the known 8 -methyl-1-hydrindanone and compare the semicarbazones of the two ketones.

The most suitable method for our purpose appeared to be one recently elaborated by Johnson[35,36]:



(XXXV)



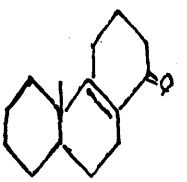
(XXXVI) (XXXVII)

In our case the intermediate (XXXV) was obtained directly from 9-methyl-1-decalone, a supply of which was available to us, instead of carrying out the preliminary methylation. Oxidation with neutral permanganate in acetone solution gave the dibasic acid (XXXVI), which ring-closed in presence of baryta, to give cis-8 -methyl-1-hydrindanone (XXXVII) as a waxy solid. The semicarbazone, which formed slowly, had m.p. 222-223°. On admixture with the semicarbazone m.p. 210-211°, there was a definite depression (m.p. 200-202°, softening 196°). This identity of this dicyclic ketone is still, therefore, up to the present, in doubt - the only clear point is that the ketone is not pure cis-8 -methyl-1-hydrindanone.

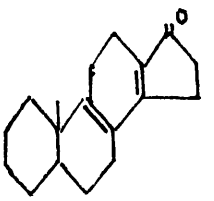
At the moment experiments on the tricyclic ketone,

1-keto-13-methyl- $\Delta^{11:12}$-dodecahydrophenanthrene are still in the preliminary stages and the following information cannot, in any way, be regarded as final.

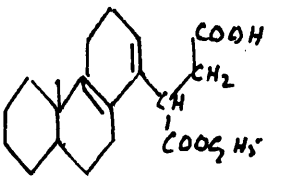
Condensation of this ketone (XXXVIII) with diethyl succinate, in a stream of nitrogen, and with potassium tert-butoxide as condensing agent, gave an acidic product as a gum which was not obtained solid. This material might conceivably be the mono-ethyl ester of 1-(13-methyl- $\Delta^{1:2:11:12}$-decahydrophenanthryl) succinic acid (XXXIX).



(XXXVIII)



(XL)

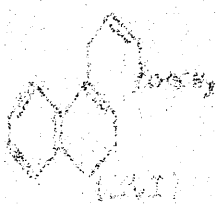


(XXXIX)

Treatment of this acidic product with acetic anhydride, acetic acid and fused zinc chloride, followed by refluxing with concentrated hydrochloric acid, in the hope of obtaining 3'-keto-13-methyl- $\Delta^{1:2:11:12}$-decahydro-1:2-cyclopentenophenanthrene (XL) gave only a trace of ketonic material. Distillation of this material from an air-bath gave a liquid distillate which formed an unhomogeneous 2:4-dinitrophenylhydrazone. Crystallisation gave only a minute amount of the 2:4-dinitrophenylhydrazone of the initial tricyclic

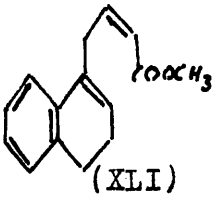
ketone (m.p. and mixed m.p.) (a certain small amount of this material had probably escaped ether extraction).

Pressure of time has prevented a repetition of these last experiments, but the author hopes to re-investigate the use of the Stobbe condensation applied to the tricyclic ketone during the remainder of his time in these laboratories.



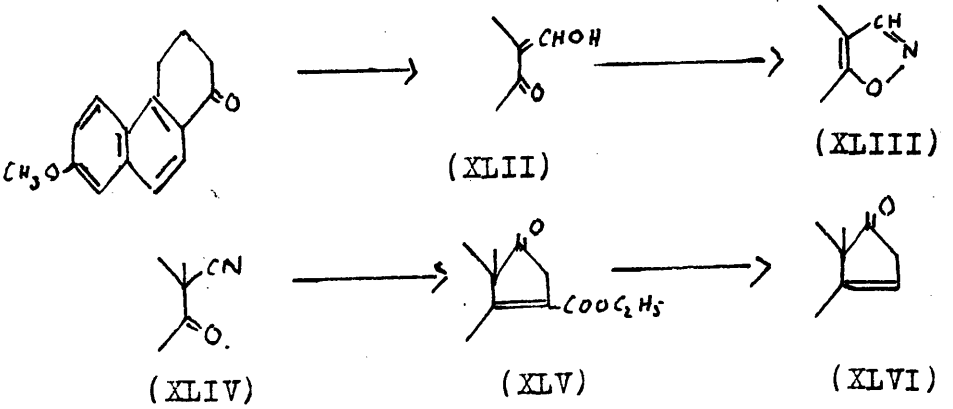
ADDENDA.

1. A preliminary attempt was made, in the course of this work, to condense γ-bromo-methyl crotonate with 6-methoxy-1-tetralone and zinc. The reaction was sluggish and only sustained by heating. Extraction of ketonic material with Girard's reagent[37] gave a yellow gum which, on trituration with methyl alcohol, gave a yellow solid, in small yield. Repeated crystallisation gave shimmering yellow rhombs, m.p. 182°. Analysis data for a compound of structure (XLI) were poor despite sublimation and repeated crystallisation:



(XLI)

2. The following interesting method of five-membered ring construction has appeared as a note in the latest available publication of J.A.C.S.[9]



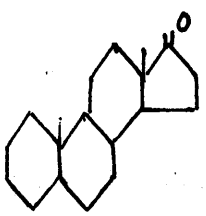
(XLII) (XLIII)

(XLIV) (XLV) (XLVI)

Treatment of the isoxazole derivative (XLIII), obtained from (XLII) with hydroxylamine hydrochloride, with sodium methoxide and methyl iodide gave (XLIV). Condensation of this cyano-ketone with diethyl succinate in presence of potassium tert-butoxide gave (XLV) in one step. The acid on heating under reduced pressure gave (XLVI).

The authors claim a synthesis of d and l equilenin by this method.

It is intended to investigate the reaction in the hope of obtaining androstanone (aetioallo-cholanone-17)[41] (XLVII) or an isomer of this compound.



(XLVII)

EXPERIMENTAL.

Succinimide was prepared according to Ma and Sah[39]. Probably a better method is outlined in Organic Syntheses[40].

Methyl Crotonate was prepared according to Purdie and Marshall[38].

N-Bromo-succinimide and methyl-γ-bromo-crotonate were prepared according to Ziegler and co-workers[15].

Methyl-γ(1-hydroxy-2-methyl cyclohexyl) crotonate (X).

Zinc (10 g.), milled from arsenic free zinc rods, was placed in a 250 cc. flask and heated over a free flame with a small quantity of mercuric chloride until a sublimate formed on the sides of the flask. Dry benzene (50 cc.) was added, the mixture heated to reflux, then allowed to cool. 2-methyl cyclohexanone (11 g.) was added to the slightly warm solution followed by methyl γ-bromo crotonate (21 g.) in one lot. The reaction started immediately (it may be exceedingly violent if the bromo compound is added to the hot mixture), and continued vigorously for 5 - 7 minutes, water cooling being applied from time to time. The flask was transferred to the steam-bath and a vigorous reflux allowed to proceed for 30 minutes. The complex formed was decomposed with ice-cold dilute hydrochloric acid and the product extracted with ether. After drying over sodium sulphate, the ether was distilled giving a residual dark

brown oil. Distillation gave as the main fraction a light yellow viscous oil (11 g.), b.p. 170-176°/15-17 mm. Several gram. of discoloured gum remained in the flask; this, when taken up in hot methyl alcohol, deposited a dark brown solid which was not further investigated.

Hydrogenation:

Methyl-γ(1-hydroxy-2-methyl-cyclohexyl) butyrate (XI).

The Reformatsky product (10 g.) in absolute alcohol (45 cc.) was hydrogenated in presence of palladium black (.1 g.) until there was no further intake of hydrogen. The substance absorbed approximately 1200 cc. of hydrogen in about 13 hours, the theoretical amount required for one double bond being 1120 cc. Distillation of the alcohol, after filtration of catalyst, gave the product which distilled as a light yellow mobile liquid (9 g.), b.p. 144-160°/12 mm.

Dehydration of Hydrogenation Product followed by Hydrolysis.

a). With Thionyl Chloride and Pyridine.

The hydrogenation product (9 g.) was dissolved in ether (63 cc.), cooled in ice and treated with pyridine (6.5 g.), followed by thionyl chloride (6 g.), drop by drop.

Note: When a similar experiment was performed using double the quantities and with no water-cooling, the product (and subsequent hydrogenation product) was less viscous and boiled some twenty degrees lower. However, this material also gave mainly the expected unsaturated butyric acid, as it solidified almost completely in a freezing mixture and cyclised to the expected ketone.

The ether was filtered, evaporated, and the residual oil distilled. The material distilled over a considerable range and was collected in two fractions which were not sharply defined:

1). B.P. 120 - 130° 15 mm.
2). B.P. 132 - 144°

Hydrolysis of Above Products.

Fraction 1) was treated with warm aqueous methanolic sodium hydroxide (20 cc. of 10%) and left at room temperature overnight. The clear solution was poured into water, ether extracted, and the aqueous layer acidified. The precipitated oil was extracted with ether and acidic material removed with sodium carbonate. An acid was obtained as a liquid which did not show any tendency to solidify. The hydrolysis was repeated with fraction 2), with similar results. The two acidic fractions were combined and distilled at 0.3 mm. from an air-bath, when the material distilled as an almost colourless slightly yellow mobile liquid (4.2 g.) at 90 - 115° (external air-bath temperature).

b). Dehydration with Iodine.

The saturated hydroxy ester (6.1 g.), with the addition of a few crystals of iodine, was heated for 30 minutes over a free flame and just under the reflux point. Water appeared on the sides of the flask.

Hydrolysis.

γ-(2-methyl- Δ'-cyclohexenyl) butyric acid (XIII).

For hydrolysis the dehydrated ester was added to slightly warm aqueous methanolic sodium hydroxide [120 cc. - made up with methyl alcohol (70 cc.), water (50 cc.), sodium hydroxide (12 g.)] and then shaken till solution was complete. After standing for 24 hours at room temperature the alcoholic mixture was poured into water and the neutral material extracted with ether. Acidification of the alkaline layer (dilute hydrochloric acid) gave an oily gum which was extracted with ether (in one small scale experiment the gum solidified after standing for several days at room temperature, giving glistening waxy flakes of the required acid). Distillation of the ether gave crude material (4.9 g.) which solidified at room temperature to a semi-solid mass of white glistening flakes. The crude product, when first pressed on porous plate, melted at 39° (Linstead[7] gives m.p. 44°).

Found: C, 72.39; H, 9.74.

$C_{11}H_{18}O_2$ req.: C, 72.52; H, 9.90.

c). Dehydration with Sodium Bisulphate.

The hydrogenated hydroxy ester (2.3 g.) was treated with very roughly powdered sodium bisulphate (2 g.) and heated at 180° for 30 minutes. Water appeared on the sides of the flask. The product was ether extracted, washed with

water, the ether dried (sodium sulphate) and distilled. Hydrolysis of the crude product was carried out as before with 10% aqueous methanolic sodium hydroxide at room temperature. Acidification of the aqueous layer with dilute hydrochloric acid, after dilution and ether extraction of neutral material, gave an oil which after extraction with ether distilled from an air-bath as a light brown liquid (1.3 g.). Crystals of the unsaturated butyric acid were slowly deposited after the oil had stood for some time. It did not become completely semi-solid even in a freezing mixture.

9-Methyl-$\Delta^{4:10(\text{or } 5:10)}$-1-octalone (VII) or (VIII).

The unsaturated acid (9.15 g.), obtained by dehydration with iodine, followed by hydrolysis, was treated with pyridine (5 cc.) in absolute ether (60 cc.). Thionyl chloride (5 cc.) was added drop by drop to the ice-cold solution. A little ethereal hydrochloric acid was then added. The resultant liquid was filtered through a plug of cotton wool in the side arm of the flask and distilled. After heating the liquid residue in vacuo for a short time, it was dissolved in carbon disulphide (20 cc.) and added, drop by drop, to a solution of stannic chloride (6 g.) in carbon disulphide (50 cc.) in a freezing mixture. The reaction mixture darkened and a dark brown oil separated.

After one hour in the freezing mixture and two hours at room temperature the mixture was poured on to ice, when the dark brown colour disappeared, giving an amber coloured layer of carbon disulphide. Distillation of the carbon disulphide gave a brown residual oil which was treated with dimethyl-aniline (6 g.) and heated in a metal bath at 195° for three hours. The mixture was dissolved in ether, when a solid precipitated; the whole was shaken with dilute hydrochloric acid (three times), then with water, and the ether dried (sodium sulphate). Distillation gave a brown oil with odour of camphor. This was distilled giving a clear liquid (4.5 g.), b.p. 110 - 115°/12 mm., which became yellowish-brown on standing. A dark brown gum was left in the flask. In another experiment the product was distilled from an air-bath (0.2 mm.). Three fractions were obtained (temperatures - air-bath):

1). 75-81°.

Colourless mobile liquid, darkening on standing.

2). 95-100°.

Yellow mobile liquid turning green on standing.

3). 160°.

Viscous partially crystalline brown gum.

Fraction 1) gave a semicarbazone but no such derivative was obtained from fraction 2). The semicarbazone obtained from fraction 1) had m.p. 225-226°, after recrystallisation

from absolute alcohol and formed colourless glistening prisms.

Found: C, 65.38; H, 8.54; N, 18.83.

$C_{12}H_{19}ON_3$ req.: C, 65.10; H, 8.55; N, 19.00.

There was no depression of melting point on admixture with an authentic sample of 9-methyl-1-octalone.[5] A second crop of crystals had m.p. ca. 176°, a third crop, m.p. 166 - 176°, and a fourth, 140 - 150°. Plentl and Bogert[8] report two semicarbazones, m.p. 228 - 229° and 168°.

9-Methyl-1-decalone (II).

1. Hydrogenation with palladium black.

The octalone (4.6 g.), which had been previously purified by steam distillation of its semicarbazone with oxalic acid, was hydrogenated in presence of palladium (.1 g.) and absolute alcohol (60 cc.). After 550 cc. of hydrogen had been absorbed (6 hours), the hydrogenation became sluggish. Addition of a further amount of palladium (.1 g.) caused an absorption of 125 cc. of hydrogen. The total absorption was, therefore, 675 cc. of hydrogen. Distillation of the product from an air-bath gave 9-methyl-1-decalone (3.5 g.), b.p. 97 - 107°/0.5 mm. (air-bath temperature). It formed a semicarbazone which crystallised from absolute alcohol in white needles, m.p. 222°.

Found: C, 64.71; H, 9.50.

$C_{12}H_{21}ON_3$ req.: C, 64.58; H, 9.41.

2. Hydrogenation of 9-methyl-1-octalone with a palladised strontium carbonate catalyst.

(Hydrogenation was performed by Mr. Cameron).

Methyl octalone (50 g.), absolute alcohol (500 cc.) and palladised strontium carbonate (20 g.) were introduced into the autoclave and hydrogenated for 6 hours at 50° and 115 atmospheres. The drop in pressure was 17 atmospheres. Filtration of catalyst and distillation of alcohol gave a liquid product which boiled at 108 - 112°/12 mm., 44 g. The semicarbazone formed from alcohol in white needles, m.p. 221 - 222°, depressed to 204 - 207° on admixture with a sample of methyl octalone semicarbazone.

Reformatsky Reaction with 9-methyl-1-decalone and methyl γ-bromocrotonate.

Zinc (10 g.) was amalgamated as already described and benzene (50 cc.) and 9-methyl-1-decalone (10 g.) added. To the warm solution methyl γ-bromocrotonate (20 g.) was added in one lot. A vigorous reaction began and was moderated by immersing the flask once or twice in cold water. The solution became yellow and a brown yellow complex separated. After heating on the water-bath for 30 minutes, the mixture was cooled then stirred with ice-cold dilute hydrochloric acid (3 - 5N). The complex decomposed very slowly. Excess zinc was removed by means of a rough glass wool filter and washed with ether. The ether-benzene layer

was removed and dried (sodium sulphate). Removal of the solvent under slightly reduced pressure gave a brown mobile oil (14.8 g.), presumably consisting of unchanged 9-methyl-1-decalone and methyl-γ(1-hydroxy-9-methyl-decalyl) crotonate (XVIII).

In a small scale experiment with 9-methyl-1-decalone (2 g.), the product was distilled from an air-bath. Two fractions were obtained:-

1). B.p. 84 - 100°/0.8 mm.
2). B.p. 100- 160°/0.8 mm. external temperature

Fraction 2), a viscous yellow oil, absorbed 95 cc. of hydrogen when dissolved in absolute alcohol (15 cc.) and hydrogenated with palladium black (.1 g.).

Hydrogenation of crude Reformatsky product.

The crude product was dissolved in absolute alcohol (100 cc.) and palladium (0.2 g.) added. Hydrogenation was sluggish after 500 cc. of hydrogen had been absorbed (10 - 12 hours). Addition of fresh palladium (0.1 g.) caused a further absorption of hydrogen (155 cc., 8 hours). The total intake of hydrogen was, therefore, 655 cc., corresponding roughly to about 7 g. of expected hydroxy ester (XVIII).

Treatment of Hydrogenation Product.

The catalyst was filtered and the alcohol removed, the last traces in vacuo, leaving a light brown, mobile,

pleasant-smelling liquid. To this was added a few crystals of iodine and the mixture heated gently over a free flame for 30 minutes. This material was added to warm methanolic sodium hydroxide (10%) - made with methyl alcohol (80 - 100 cc) and water (30 cc.) - and left overnight at room temperature after occasional shaking. The resultant mixture was diluted with water, the neutral material extracted with ether and the aqueous layer acidified with dilute hydrochloric acid and ether extracted. After drying (sodium sulphate), the ether was distilled, giving a residual dark brown viscous material (5.9 g.), probably consisting of a mixture of lactone (XXII) and unsaturated acid (XXI). Distillation of the ether extract of neutral material gave a brown mobile liquid which gave 9-methyl-1-decalone semicarbazone (5.5 g.) on treatment with semicarbazide.

Cyclisation of the crude Hydrolysis Product with Stannic Chloride: 1-keto-13-methyl- $\Delta^{11:12}$-dodecahydrophenanthrene (XIV).

The brown viscous material (5.9 g.) was treated with pyridine (25 cc.) and absolute ether (an amorphous gummy solid separated at this stage and was re-dissolved by heating). To the ice-cooled solution thionyl chloride (2.5 cc.) was added, drop by drop, and the mixture allowed to stand in ice-water for one hour with occasional shaking. The ether was distilled from the filtered solution and the residual brown gum,

in carbon disulphide (15 cc.), added, drop by drop, to a solution of stannic chloride (3 cc.) in carbon disulphide (21 cc.) in a freezing mixture (-15°C). After leaving for some 24 hours the mixture was shaken with ice and water. The brown-coloured carbon disulphide layer was separated, leaving a large quantity of insoluble brown gum (see next experiment). Distillation of the carbon disulphide (dried over sodium sulphate) gave a brown viscous liquid. This was treated with dimethylaniline (2 g.) and the mixture heated for 3 hours at 200°. The cooled product was shaken with dilute hydrochloric acid and the mixture extracted with ether. The ether layer was washed with dilute hydrochloric acid then water, and dried. Removal of the ether gave a dark brown viscous oil which distilled from an air-bath as a fairly mobile yellow oil (.7 g.), b.p. 120 - 128°/0.25 mm. (external temperature). Redistillation of a sample gave an oil with a very light yellowish tinge, b.p. 105 - 108°/ 0.25 mm. (external temperature).

Treatment of a sample of the product with 2:4-dinitrophenylhydrazine gave a voluminous red crystalline product which was difficultly soluble in alcohol but crystallised from glacial acetic acid in a matte of glistening red microscopic needles, m.p. 225°. (See later experiment for analysis).

Treatment of the Residual Gum from Stannic Chloride Cyclisation.

The dark brown gum, insoluble in carbon disulphide (last experiment), slowly solidified under aqueous ethyl alcohol. When pressed on porous plate and dried in a vacuum desiccator, it formed a brown amorphous powder of indefinite melting point. The compound was insoluble in cold dilute sodium carbonate and sodium hydroxide; an alcoholic solution of this material deposited a fawn-coloured amorphous product which could not be obtained crystalline. In contact with sodium hydroxide (4 - 5N) the compound slowly dissolved at room temperature, giving a brown solution which, on acidification, deposited the same brown powder. The behaviour suggests that the compound is a lactone (possibly (XXII)).

The dry powdered lactone (0.7 - 0.8 g.) was refluxed for 4¾ hours with a mixture of glacial acetic acid (10 cc.), a solution of fused zinc chloride in acetic acid (3 cc. of stock solution containing zinc chloride (5.5 g.) in acetic acid (80 cc.)), and acetic anhydride (14 cc.). Solvents were removed in a partial vacuum and the dark residue allowed to stand overnight in contact with dilute sodium hydroxide. The mixture was ether extracted, washed with water and dried (sodium sulphate). Distillation of the ether gave a small quantity of a brown viscous liquid with rather a sharp

pleasant smell. The ketone, distilled from an air-bath, slowly heated from 110 - 130°/0.25 - 0.3 mm., as a light yellow slightly viscous liquid[x]. This gave the 2:4 dinitrophenylhydrazone of 1-keto-13-methyl-$\Delta^{11:12}$-dodecahydrophenanthrene as a voluminous red crystalline precipitate, m.p. 225°, and identical with the material obtained from the stannic chloride cyclisation. The analysis was performed on the sample from this cyclisation.

Found: C, 63.73; H, 6.93; N, 14.27.

$C_{21}H_{36}O_4N_4$ req.: C, 63.32; H, 6.53; N, 14.07.

Cyclisation of the Crude Product of Hydrolysis (probably a mixture of γ-(9-methyl-decalenyl) butyric acid (XXI) and γ-(9-methyl-decalyl) butyro-δ-lactone (XXII) with acetic anhydride and fused zinc chloride in acetic acid).

The crude brown gum (6 g.) was refluxed for 4¾ hours, in a stream of nitrogen, with a mixture of acetic anhydride (112 cc.), glacial acetic acid (50 cc.) and a solution of fused zinc chloride (20 cc.) (the solutions contain 70 mg./100 cc. - zinc chloride). After cooling the dark brown solution was concentrated in a partial vacuum, leaving a viscous dark brown material. This was treated with 5% potassium hydroxide solution (120 cc.) and warmed for several hours on the water-bath (the residual lactone was, however,

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[x] Becomes dark brown on keeping.

very incompletely cleaved by this procedure - see later). The cooled alkaline solution was extracted with ether, the ether dried (sodium sulphate) and evaporated. Distillation of the residue from an air-bath gave a light yellow, slightly viscous liquid (1.7 g.), b.p. 120 - 130°/0.2 mm. (air-bath temperature). This material gave the same red 2:4-dinitrophenylhydrazone (m.p. 225°) as had been obtained in previous experiments. A condensation with diethylsuccinate was performed with this sample.

In the flask from which ketone had been distilled there remained a dark brown "glass". This material dissolved slowly (24 hours) in 5 - 8N sodium hydroxide. Ether extraction of this solution, followed by acidification, gave a brown amorphous powder (2.8 g.).

Hydrogenation of 1-keto-13-methyl-$\Delta^{11:12}$-Dodeca Hydrophenanthrene.

The distilled ketonic material (0.35 g.) was treated with palladium black (0.05 g.) in absolute alcohol (10 cc.). 30 cc. of hydrogen were absorbed in $2\frac{1}{2}$ hours. Addition of more catalyst caused no further absorption. Half of the alcoholic solution was treated with an alcoholic solution of 2:4-dinitrophenylhydrazine (which had been dissolved in concentrated sulphuric acid). An orange-red unhomogeneous gummy precipitate was obtained. Crystallisation from glacial acetic acid gave crops of crystals:

1). Red needles, m.p. 210°,

2). Red needles, m.p. ca. 200°.

3). Semi-crystalline orange plates, m.p. ca. 176°.

The smallest crop, crop 3), is possibly a derivative of 1-keto-13-methyl perhydrophenanthrene (XXV).

Condensation of 2-methyl-cyclohexanone with Diethyl Succinate: β-carbethoxy-β-(2-methyl-Δ^1-cyclohexenyl) propionic acid (XXXI).

Potassium (2.15 g.) was dissolved in tert-butyl alcohol (40 cc.) (distilled from quicklime), the solution chilled in ice, and a mixture of methyl cyclohexanone (5.6 g.) and diethyl succinate (13 g.) in tert-butyl alcohol (10 cc.) added. A brown red colour developed. The clear brown red solution was allowed to reflux for 40 minutes, in a stream of nitrogen, then left for 4 hours at room temperature, when the solution had developed a greenish colour. Acidification gave a straw-coloured solution which was concentrated in vacuo. The potassium chloride was dissolved in water, leaving a yellow brown oil in suspension. The solution was made alkaline with sodium carbonate, when a large amount of the oil dissolved. Ether extraction and acidification of the aqueous layer gave a brown yellow viscous oil (9.3 g.) which did not solidify in a vacuum desiccator. Distillation of a sample of the acid from an air-bath gave two fractions:-

1). B.p. 105-125° (air-bath temperature)/0.15 mm.,

2). B.p. 130-150° (air-bath temperature)/0.15 mm.

Fraction 1) - clear mobile liquid showing no tendency to solidify - soluble in sodium carbonate.

Fraction 2) - viscous liquid with slight greenish-blue fluorescence. On standing for several days it started to solidify. Addition of ligroin gave a colourless, crystalline acid, m.p. ca. 90°. Recrystallised from n-hexane, the acid was obtained as lustrous mother of pearl flakes, m.p. 99-100°.

Found: C, 65.09; H, 8.23.

$C_{13}H_{19}O_4$ req.: C, 65.27; H, 7.96.

8-methyl-$\Delta^{3:9(\text{or } 4:9)}$-1-hydrindenone (XXXII) or (XXXIII) or 4-methyl-$\Delta^{8:9}$-1-hydrindenone (XXXIV).

The crude acidic material (2 g.) from the last condensation was refluxed, in a stream of nitrogen, for 4 hours with a mixture of acetic anhydride (28 cc.), acetic acid (10 cc.) and a solution of fused zinc chloride in acetic acid (6 cc.) (solution contained 70 mg./cc. of fused zinc chloride). The solution became dark brown in colour. Solvents were removed in partial vacuum and the dark brown

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Note: A condensation using diethyl glutarate instead of diethyl succinate with similar quantities (in this case in absence of nitrogen) gave a negligible acidic fraction. The conditions were, otherwise, exactly the same as above.

residual oil refluxed for 40 minutes with concentrated hydrochloric acid (8.5 cc.) and glacial acetic acid (10 cc.). The acid was removed in vacuo and the residue treated with 5% potassium hydroxide solution (40 cc.). After warming for several hours on the water-bath, the solution was ether extracted, and the ether washed with water and dried (sodium sulphate). Distillation of the ether gave a light brown oil (0.3 g.). The oil was treated, in aqueous alcohol, with semicarbazide hydrochloride (0.5 g.) and potassium acetate (0.5 g.). On standing a semicarbazone was obtained as almost colourless micro-needles, m.p. 233-236° (to a brown liquid). Three crystallisations from absolute alcohol gave dull colourless, fern-like clusters of needles, m.p. 240.5°, turning brown at 230°.

Found: C, 63.42; H, 7.97; N, 20.18.

$C_{11}H_{17}ON_3$ req.: C, 63.76; H, 8.21; N, 20.28.

Hydrogenation of the Methyl Hydrindenone.

The crude ketone (0.6 g.) was hydrogenated with absolute alcohol (30 cc.) and palladium black (0.1 g.) until absorption of hydrogen had ceased. Hydrogenation was sluggish and a further quantity of palladium (0.05 g.) had to be added before approximately the necessary volume of hydrogen required for one double bond had been absorbed (8 hours). Filtration of catalyst and treatment of the solution with semicarbazide gave a semicarbazone which

crystallised from alcohol in glistening white needles, m.p. 210-211°, different in appearance from the semicarbazone, m.p. 240.5°. Mixed with a sample of cis-8-methyl-1-hydrindandone semicarbazone, m.p. 222-223° (see later experiments), it had m.p. 200-202°, softening 196°.

2-Benzal-9-methyl-1-decalone (XXXV).

Cis-9-Methyl-1-decalone (5 g.), in ethanol (50 cc.), was treated with cooled sodium hydroxide solution (15 cc. of 15%), benzaldehyde (4 g.) and water (4 cc.), with swirling, and in that order. After standing several days at room temperature an oil separated. The mixture was diluted with water, ether extracted, and the ether dried. Distillation gave a yellow liquid which became partially solid on standing. Trituration with petroleum ether gave 2-benzal-9-methyl-1-decalone (3 g.) as a solid, m.p. (crude 98°).

β-(2-carboxy-2-methylcyclohexyl)-propionic acid (XXXVI).

The acid was prepared by oxidation of the above benzal derivative with potassium permanganate according to Johnson[35], and with comparable results.

Cis-8-methyl-1-hydrindanone (XXXVII).

Prepared by pyrolysis of the above acid (2 g.) in presence of baryta (0.15 g.) at 210-300° according to Johnson[35], the semicarbazone had m.p. 222-223°. Mixed melting point with semicarbazone of last hydrogenation

product (m.p. 210-211°) was 200-202°, softening at 196°.

Condensation of 1-keto-13-methyl- $\Delta^{11:12}$-dodecahydrophenanthrene (XXIV) with diethyl succinate.

The freshly distilled ketone (1.6 g.), mixed with diethyl succinate (2.3 g.) and tert-butyl alcohol (4 cc.) was added to chilled potassium tert-butoxide, made by heating potassium (0.4 g.) with dry tert-butyl alcohol (9 cc.). A red colouration developed immediately. The solution was refluxed for 35 minutes, in a stream of nitrogen, when the solution became dark red. The solution was acidified with dilute hydrochloric acid, when a yellow oil was obtained. Solvents were removed in a partial vacuum and sodium carbonate solution added to the residual brown-red oil. The carbonate extract was ether extracted, then acidified and the precipitated oil extracted. Distillation of the ether gave a slightly viscous brown liquid (1.7 g.).

Attempted Cyclisation and Decarbethoxylation of the Acidic Condensation Product.

The acid (1.7 g.) was treated with acetic anhydride (20 cc.), acetic acid (4 cc.) and a solution of fused zinc chloride in acetic acid (5 cc.) (solution contained 0.06 g/cc.), and the mixture allowed to reflux for 4¾ hours with a stream of nitrogen passing through the solution. Water (ca. 20 cc.) was then added to the cooled solution to decompose the acetic anhydride, followed by concentrated hydrochloric acid (ca.

10 cc.) to decarbethoxylate the cyclised product. After refluxing for one hour the solvents were removed in vacuum and the dark residue treated with 5% potassium hydroxide (40 cc.), when most of the material dissolved. The mixture was warmed on the water-bath, then extracted with ether, the ether layer washed with water and dried. Distillation of the ether gave only a minute amount of neutral product which was distilled from an air-bath.

Fraction I.

B.p. 110-120° (0.15 mm.: air-bath temperature). On raising the temperature there was evidence of the distillation of a minute amount of yellow viscous material, showing signs of solidification.

Fraction I gave a 2:4-dinitrophenylhydrazone as an unhomogeneous bright red crystalline precipitate.

Crystallisation from acetic acid gave a small quantity of the 1-keto-13-methyl-$\Delta^{11:12}$-1:2:3:4-dodecahydrophenanthrene 2:4-dinitrophenylhydrazone (m.p. and mixed m.p.).

EXPERIMENTAL ADDENDA.

Reaction between 6-methoxy-1-tetralone and γ-bromocrotonic ester and zinc.

Methoxy tetralone (8.8 g.) was dissolved in benzene (30 cc.) and zinc turnings (3.5 g.) added. On addition of the bromo ester (9 g.) an extremely sluggish reaction started, and only sustained by heating. Heating was discontinued, the reaction left at room temperature for several hours, then, finally, heated for 30 minutes on a steam bath. The red complex was decomposed with cold ammonium chloride and hydrochloric acid (1-2N), the product extracted with ether, and the ether dried (sodium sulphate). Evaporation of the ether gave a red oil which was treated with Girard's reagent T[37] (8 g.) in the prescribed acetic acid (10%) alcohol mixture (75 cc.). The mixture was refluxed for 1 hour on water-bath then poured into ice-cold sodium carbonate solution (7.5 g.). The gummy red material which separated was ether extracted, washed with water, and dried (sodium sulphate). Evaporation of the ether gave a semi-solid red gum. When dissolved in absolute alcohol a lemon yellow crystalline solid precipitated, m.p. 176° (turning red) (first three crops = 0.6 g.). Crystallisation from alcohol gave glittering yellow plates, m.p. 181-183.5°, apparently contaminated with a minute amount of colourless prisms, m.p. ca. 82° (micro-melting point). Repeated crystallisation did not remove the impurity.

Found: C, 76.03; H, 7.09.

$C_{16}H_{18}O_3$ req.: C, 74.42; H, 6.98.

The compound was sublimed at 170-180°/0.2 mm., and the sublimate recrystallised from absolute alcohol. Lemon yellow glistening plates, m.p. 182-183°, were obtained.

Found: C, 75.45; H, 7.21.

$C_{16}H_{18}O_3$ req.: C, 74.42; H, 6.98.

Decomposition of the "Girard hydrazone" with cold dilute hydrochloric acid gave unchanged methoxy tetralone (3.8 g.).

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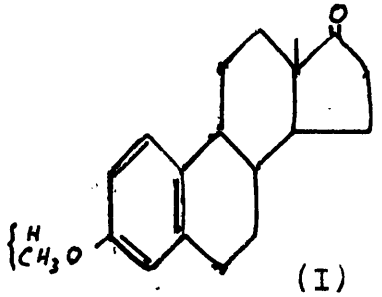
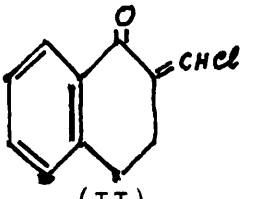
APPENDIX TO PART II.

EXPERIMENTS WITH CHLOROMETHYLENE COMPOUNDS.

In the course of attempts to obtain an intermediate which might be useful in a synthesis of a steroid molecule of the oestrone type (I), we had occasion to investigate the preparation and reactions of 2-chloromethylene-1-keto-1:2:3:4 tetrahydronaphthalene (II)

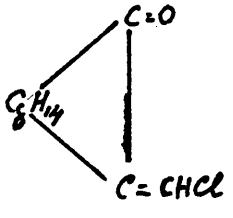


(I)

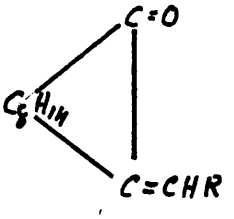


(II)

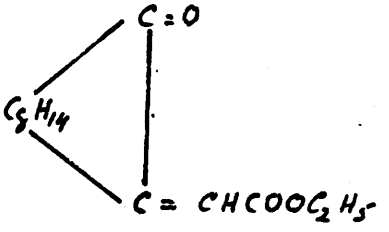
The literature contains few references to the preparation of chloromethylene derivatives. Chloromethylene camphor (III) has been prepared by Claisen[1] and Brühl[2] by the action of phosphorus trichloride or oxychloride on hydroxymethylene camphor. The chloride can, however, be prepared more conveniently by the action of thionyl chloride[3]. It reacts readily with magnesium alkyl halides to yield alkylidene camphors (IV), and this is probably the simplest method for the preparation of these derivatives of camphor[3].



(III)



(IV)



(V)

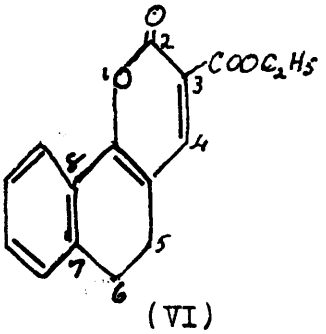
Chloromethylene camphor also reacts with the sodio derivative of aceto-acetic ester to yield an ester of structure (V)[4].

The chloromethylene derivative of diethyl succinate has been prepared by Wislicenus, Boklen and Reuthe[5]; and, recently, in these laboratories, 2(and 3)-chloromethylene-1(and 4)-keto-1:2:3:4-tetrahydrophenanthrenes have been successfully used in syntheses of pyrimidines by Cook and Thomson[6].

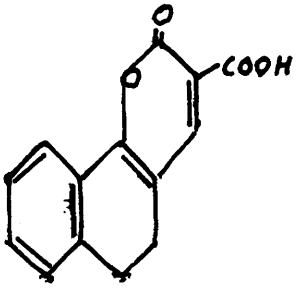
In view of the paucity of information about these compounds it was, therefore surprising to find that the required derivative (II) could be obtained extremely easily and in excellent yield from the hydroxymethylene compound by the action of thionyl chloride; moreover, it presented no trouble in purification since it distilled in vacuo without decomposition and crystallised easily and well. A condensation with the sodio derivative of diethyl malonate gave a yellow crystalline solid in good yield. The substance exhibited an intense green fluorescence in cold concentrated sulphuric acid and precipitated unchanged on the addition of water. Dilute alkali had no action on the compound in the cold but it dissolved in alcoholic sodium hydroxide, the solution becoming dark brown-red. Heating with aqueous sodium hydroxide resulted in decomposition, yielding a neutral oil, which could be extracted with ether, and a resinous mixture of acids which could not be purified. Hot concentrated hydrochloric acid gave an acid, the sodium

salt of which was sparingly soluble in water. The acid crystallised well and regenerated the original compound on esterification with absolute alcohol and concentrated sulphuric acid. An attempt to obtain an adduct with maleic anhydride, by refluxing in toluene, gave a dark brown solid which could not be purified.

The above reactions, combined with analytical data, suggest that the original condensation product is ethyl-(5:6-dihydro-7:8 benzcoumarin)-3-carboxylate (VI), and the acid, obtained by the action of hydrochloric acid, (VII)

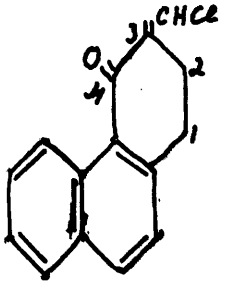


(VI)

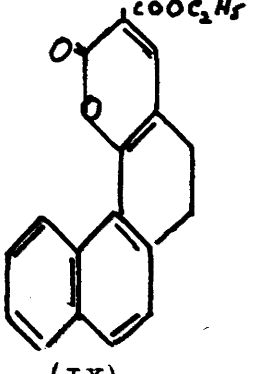


(VII)

To investigate the general applicability of the reaction a similar condensation was carried out with 3-chloromethylene-4-keto-1:2:3:4-tetrahydrophenanthrene (VIII)[6] (kindly supplied by Mr. W.H.S. Thomson).



(VIII)



(IX)

The orange-red condensation product was insoluble in aqueous sodium carbonate and hydroxide. It dissolved in alcoholic sodium hydroxide with a deepening in colour and gave a precipitate on acidification. The results of analysis are also in agreement with the lactone structure (IX).

A condensation with sodio-acetoacetic ester and 2-chloromethylene-1-keto-1:2:3:4-tetrahydronaphthalene under similar conditions to those used for the above experiments gave two neutral products: an orange-red crystalline solid, m.p. 136-137° (which gave a yellow semicarbazone which was highly insoluble in the usual solvents), together with light yellow glistening flakes, m.p. 245-246°, formed in much smaller yield than the first product. Analytical data for the first compound, and for its semicarbazone, suggest that it is 3-acetyl-5:6-dihydro-7:8-benzcoumarin (X); we were unable to interpret the results of analysis for the second product of the condensation.

The formation of these highly crystalline compounds, in good yield, is interesting in view of the recent interest in substituted coumarins and the reported Vitamin E activity[x]

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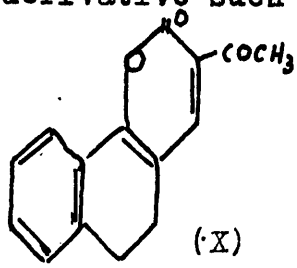
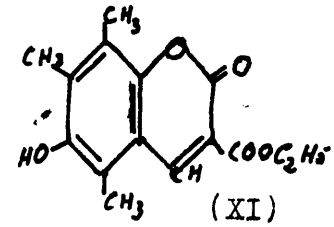
[x] Compound (XI) is prepared by Smith and Dobrovolny[15] by the reaction of duroquinone with ethyl sodiomalonate in benzene solution. This substance has apparently been dispensed in tablet form along with various food materials[16]. Smith[17,18,19,20] has made an exhaustive investigation of the preparation of 6-hydroxy-5:7:8-trimethyl coumarins substituted in the 3 position by groups such as carbethoxyl, aryl, cyano, etc.

of a derivative such as (XI)[7]



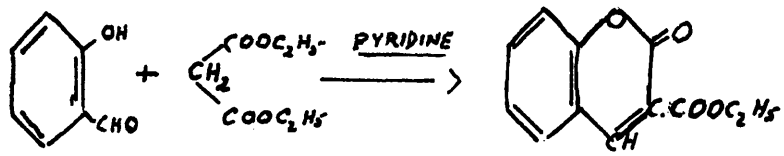
(X)



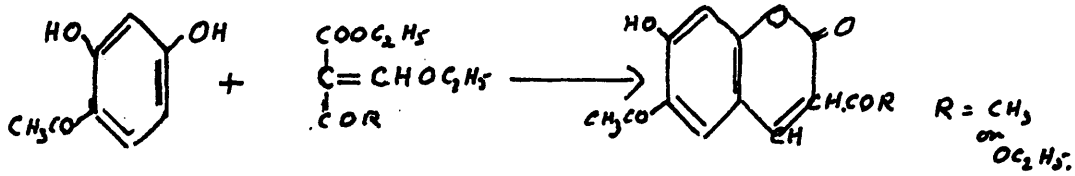
(XI)

Coumarins have been prepared by a variety of methods. Two methods which bear some relationship to the condensations carried out in this work are:-

(1). Knoevenagel's classical method[8]:

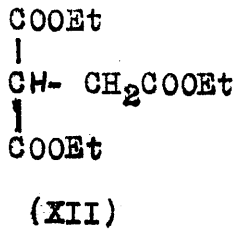


(2). A method due to Weiss and Merksammer[9] and Weiss and Kratz[10] involving ethoxymethylenemalonate or ethoxymethylene acetoacetate and resacetophenone:

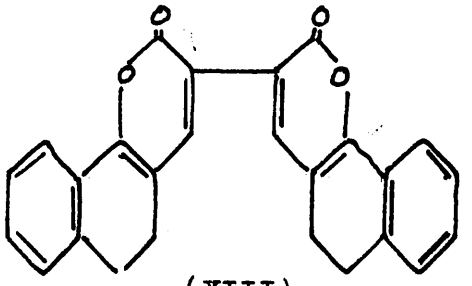


A full review of the reactions and methods of preparation of coumarins has very recently been given by Settna and Shah[11].

In yet a further attempt to obtain a suitable intermediate for a projected synthesis, the condensation between α-carbo-ethoxy diethyl succinate (XII) and 2-chloromethylene-1-keto-1:2:3:4-tetrahydronaphthalene (II) was investigated.

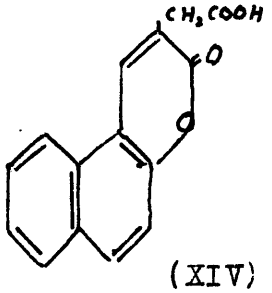


(XII)

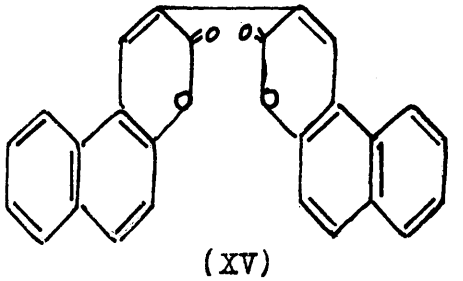


(XIII)

The main product was a gum which distilled over a considerable range and could not be obtained in a suitable state for further treatment. A bye-product of the reaction was a highly coloured, high-melting solid which crystallised well. It is tentatively suggested that the compound might be represented by structure (XIII). Such a compound is analogous to the high-melting bye-product, assigned structure (XV), obtained by Dey and co-workers[12], who prepared substituted coumarin-3-acetic acids (XIV) by a condensation between o-hydroxy aldehydes, sodium succinate, and succinic anhydride.



(XIV)



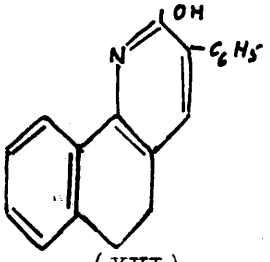
(XV)

A further condensation was carried out with the chloromethylene compound (II) and benzyl cyanide. The results are briefly summarised:-

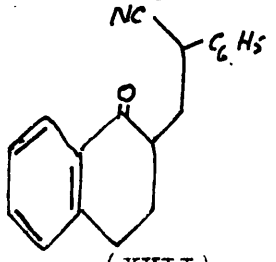
Two products were obtained,

Compound A - white needles, m.p. 182-183°, and analysing in agreement with a structure (XVI) or (XVII),

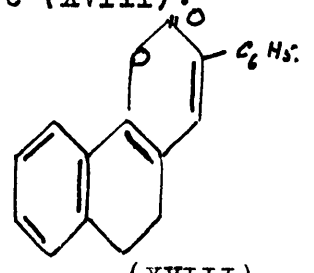
Compound B - light yellow-brown glistening rhombs, giving analytical data conforming to structure (XVIII).



(XVI)



(XVII)



(XVIII)

Compound A on treatment with concentrated sulphuric acid gave an unhomogeneous product from which was obtained an unstable, crystalline, red picrate (not given by the original compound). Decomposition of this picrate with ammonia gave a different compound, m.p. 248°, and also analysing in agreement with formulae (XVI) and (XVII).

These interesting developments of a piece of work, which arose, incidentally, to the main objects of the research, have not been investigated beyond this point, due to the pressure of time, but the results would seem to indicate that there is a considerable field for further work on the reactions and possible synthetical applications of chloromethylene derivatives.

EXPERIMENTAL.

1-Keto-1:2:3:4-tetrahydronaphthalene.[13]

1:2:3:4-tetrahydronaphthalene (tetralin) (140 g.), dissolved in purified acetic acid, was cooled below 0° and chromic anhydride (153 g.) in water (60 cc.) and glacial acetic acid (300 cc.) added with stirring. The solution was left till it acquired a greenish-violet tinge (72 hours). The acetic acid was removed and the residue diluted with water and steam distilled. 1-Keto-1:2:3:4-tetrahydronaphthalene (60 g.) distilled as a light yellow oil, b.p. 123-128°/10 mm.

2-Hydroxymethylene-1-keto-1:2:3:4-tetrahydronaphthalene.

The hydroxymethylene derivative was obtained in excellent yield (85%) by the method of Auwers and Wiegand[14].

2-Chloromethylene-1-keto-1:2:3:4-tetranaphthalene (II).

Thionyl chloride (15 cc.) was added, drop by drop, to the hydroxymethylene derivative (15 g.) and a fairly vigorous reaction occurred, the brown colour of the hydroxymethylene compound changing to dark red. The mixture was heated for a short time on the water-bath, then the thionyl chloride removed in a partial vacuum. The liquid product was poured into water, when a dark brown crusty solid was obtained. This was broken up, washed with sodium hydroxide (3N) then dissolved in ether (slight amount of brown solid, apparently

a bye-product and difficult to purify, remained undissolved). The ether was washed several times with dilute sodium hydroxide, water, followed by hydrochloric acid, then water again. Distillation of the ether gave a brown solid which distilled as a slightly yellow liquid, b.p. 115-116°/0.5 mm., solidifying immediately to an almost white crystalline mass (12.2 g.). The product crystallises from alcohol or petroleum ether (40-60°) in long stout glistening transparent prisms, m.p. 64-65°.

Found: C, 68.79; H, 4.82.

$C_{11}H_9OCl$ req.: C, 68.57; H, 4.67.

Ethyl-(5:6-dihydro-7:8-benzcoumarin)-3-carboxylate (VI).

2-Chloromethylene-1-keto-1:2:3:4-tetrahydronaphthalene (15 g.) and absolute alcohol (15 cc.) were placed in a flask with diethyl malonate (12 g.). A solution of sodium ethoxide, prepared from sodium (1.7 g.) dissolved in absolute alcohol (30 cc.) was added. The colour of the solution changed from yellow to red, and heated. A solid separated rapidly and remained after refluxing the solution for 2¾ hours. The reaction mixture was left over-night, then poured into water, when a yellow solid (18 g.), m.p. ca. 147°, separated. Recrystallisation from alcohol (80%) gave glistening yellow prisms, m.p. 150-152°.

Found: C, 71.31; H, 5.16.

$C_{16}H_{14}O_4$ req.: C, 71.11; H, 5.18.

(5:6-dihydro-7:8-benzcoumarin)-3-carboxylic acid (VII).

The carbethoxy compound (2 g.) was heated for 1 hour on the water-bath with concentrated hydrochloric acid (25 cc.). An amorphous mass was soon obtained, the crystalline form of the ester disappearing. The solution was left over-night, then poured into water, made alkaline with sodium carbonate [a certain amount of insoluble sodium salt (glistening white plates) separated], filtered and the filtrate acidified. The acid (1.5 g.) separated, and crystallised from alcohol in long glistening yellow needles with metallic lustre, m.p. 195-196°.

Found: C, 69.49; H, 4.16.

$C_{14}H_{10}O_4$ req.: C, 69.42; H, 4.13.

Reconversion of the above acid to the original product.

The acid (1 g.) was heated on the water-bath with absolute alcohol (10 cc.) and a few drops of concentrated sulphuric acid. The original ester was obtained as the neutral product (m.p. and mixed m.p.).

Treatment of Coumarin (VI) with Alkali.

The substance was unaffected by shaking for 10 hours with 2% potassium hydroxide. Complete decomposition resulted by heating with 5N sodium hydroxide, the solution becoming green-blue in colour and leaving a neutral oil which could be removed with ether. Acidification yielded resinous acidic material which could not be purified although

in one experiment a small quantity of an acid, m.p. ca. 120°, was obtained.

Condensation of Compound (VI) with Maleic Anhydride.

The compound (1 g.), maleic anhydride (.32 g.) and toluene (3 cc.) were refluxed for 2 hours, when a black tarry material was obtained. Boiling methyl alcohol left a brownish-black solid which decomposed slowly above 280°. Attempts at purification were unsuccessful.

α-Carboethoxy diethyl succinate (XII).

A solution of sodium ethoxide was prepared by dissolving sodium (6.9 g.) in absolute alcohol (160 cc.). To the sodio compound was added diethyl malonate (48 g.) followed, drop by drop, by chloracetic ester (37 g.). The reaction mixture was allowed to stand for several hours, then heated on the water-bath for 30 minutes. Some of the alcohol was distilled and the residue poured into water. After extraction with ether, drying, etc., the ether was distilled, leaving an oil. The required ester distilled as a colourless liquid (40.7 g.), b.p. 156-158°/15 mm.

Condensation of 2-chloromethylene-1-keto-1:2:3:4-tetrahydronaphthalene with α-carboethoxy diethyl succinate.

The chloro compound (10 g.) was suspended in absolute alcohol (10 cc.); the ester (12.3 g.) was added with stirring. A solution of sodium ethoxide [from Na (1.1 g.) in absolute

alcohol (20 cc.)] was added, drop by drop, with stirring. A red colour developed immediately, and stirring was continued for 15 minutes after addition. The solution was left for 1 hour at room temperature, then heated on the water-bath (1 hour). When cold, the mixture was poured into water, and ether extracted. A red amorphous powder separated at the interface of the ether-water layer. Crystallisation of this solid from chloroform and acetone gave a matte of long slender glistening orange-red needles (possibly (XIII)), m.p. 302°.

Found: C, 78.74; H, 4.46.

$C_{26}H_{18}O_4$ req.: C, 79.16; H, 4.56.

The ether was removed and a residual gum obtained. This distilled as a thick viscous gum, b.p. 265-285°/5 mm. Attempts to obtain solid material from the gum were unsuccessful.

Micro-Hydrogenation of Compound, m.p. 302° (possibly (XIII)).

The substance (3.570 mg.), with platinum oxide in acetic acid absorbed hydrogen (2.53 cc. at 769 mm. and 16.7°). Assuming a compound of structure (XIII), the amount of hydrogen absorbed corresponds to 11.88 (12) double bonds.

Condensation of 2-chloromethylene-1-keto-1:2:3:4-tetrahydronaphthalene with acetoacetic ester.

Sodium (.6 g.) was dissolved in absolute alcohol (15 cc.) and the cooled solution of sodium ethoxide added to

a mixture of acetoacetic ester (4 g.) and the chloromethylene derivative (5 g.) in absolute alcohol (20 cc.). The mixture was refluxed for 30 minutes, then left over-night at room temperature. Orange crystalline material (3.7 g.) m.p. ca. 130° filled the liquid in the morning. Crystallised from alcohol two fractions were obtained:-

(1). Light yellow glistening flakes, m.p. 245-246°.

Found: 1). C, 81.14; H, 4.90.

2). C, 80.80; H, 5.25.

We are unable to interpret the analysis.

(2). Orange-red prismatic needles, m.p. 136-137°.

Found: C, 74.93; H, 5.03.

$C_{15}H_{12}O_3$ req.: C, 75.00; H, 5.00.

The substance gave a semicarbazone, m.p. 239° (d) crystallising from a large volume of acetone as a microcrystalline yellow matte.

Found: C, 64.11; H, 5.47.

$C_{16}H_{15}O_3N_3$ req.:C, 64.61; H, 5.05.

The second compound is probably 3-acetyl-5:6-dihydro-7:8-benzcoumarin (X).

Condensation of 3-chloromethylene-4-keto-1:2:3:4-tetrahydrophenanthrene[6] with diethyl malonate.

The chloromethylene compound (0.8 g.), diethyl malonate (1 cc.), in warm absolute alcohol (10 cc.) were treated with a solution of sodium ethoxide made from sodium

(0.08 g.) in absolute alcohol (5 cc.). An immediate red colouration developed and a white precipitate (salt) appeared. After heating the mixture on the water-bath for 25 minutes with occasional shaking, it was poured into water, when a red gum separated. Addition of alcohol and trituration gave an orange-yellow solid (0.6 g.) which crystallised from rectified spirits in fine orange needles, m.p. 172-173°, and analysing in agreement with structure (IX). A further crop (0.3-0.4 g.), m.p. 168°, was obtained from the alcoholic extracts.

Found: C, 1). 73.71; H, 1). 4.57,
2). 74.93; 2). 4.93.

$C_{20}H_{16}O_4$ req.: C, 75.00; H, 5.00.

Condensation of 2-chloromethylene-1-keto-1:2:3:4 tetrahydronaphthalene with benzyl cyanide.

To a solution of sodium ethoxide made from sodium (1.5 g.) in absolute alcohol (35 cc.) was added benzyl cyanide (7.3 g.). The solution was cooled and the chloro compound (12.2 g.), dissolved in warm absolute alcohol (30 cc.), was added within a few minutes, the contents of the flask being swirled during the addition. There was an immediate reddening of the solution and heat was evolved. The mixture was heated on the water-bath for 2 hours, when a considerable quantity of salt separated. Ice-cooling of the red liquid precipitated a red gummy material which, on

trituration with alcohol, gave a brick-red solid (5.5 g.). Two crystallisations from rectified spirits (a little dilute hydrochloric acid added to the solvent removed the red colouration in the solution) gave white needles, m.p. 182-183° (XVI) or (XVII) - Compound A.

Found: 1). C, 82.24; H, 5.52.

2). C, 83.64; H, 5.32; N, 4.93.

$C_{19}H_{15}ON$ req.: C, 83.16; H, 5.49; N, 5.12.

A second crop of amorphous gummy material was obtained from the original mother liquors. Further concentration gave a third crop of material; this, crystallised from alcohol, gave glistening yellow-brown rhombs, m.p. 210°, and containing no nitrogen - Compound B.

Found: C, 83.38; H, 4.54.

$C_{19}H_{14}O_3$ req.: C, 83.22; H, 5.10.

The analysis suggests that the compound is 3-phenyl-5:6-dihydro-7:8-benzcoumarin (XVIII).

Treatment of Compound (A) with Sulphuric Acid.

A mixture of concentrated sulphuric acid (9 cc.) and water (1 cc.) was cooled in ice and compound (A) (0.5 g.) added with stirring. The substance slowly dissolved, the colour of the solution changing from yellow to brown-red. After standing for 30 minutes at room temperature it was poured on to ice and made alkaline with sodium carbonate. An amorphous yellow solid separated, m.p. below 100°. An

alcoholic solution (fluorescent-blue) of this substance was treated with picric acid. A dark red picrate (0.15 g.), m.p. 186-188°, was obtained in the form of dumb-bell shaped crystals (under microscope). Decomposition of the picrate with ammonium hydroxide gave a yellow powder, crystallising from alcohol to give microscopic pale-cream needles, m.p. 248°.

Found: C, 82.93; H, 5.49; N, 5.67.

$C_{19}H_{15}ON$ req.: C, 83.16; H, 5.49; N, 5.12.

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