UNIVERSITY OF GLASGOW

STUDIES IN THE CYCLOHEPTANE FIELD

By: J. R. B. Campbell, B.Sc.

Thesis submitted for the Degree of Ph.D.

Supervisor: Professor R. A. Raphael

June, 1956.

STUDIES IN THE CYCLOHEPTANE FIELD

Part I: POSSIBLE ROUTES TO AZATROPOLONES

Part II: ELABORATION PRODUCTS OF EUCARVONE

Part III: A SYNTHESIS OF THUJIC ACID

ACKNOWLEDGEMENTS

Microanalyses were carried out by Mr. J. M. L. Cameron and Miss Christie in Glasgow, and by Mr. J. G. Henry and Mr. J. Austin in Belfast. Microhydrogenations are due to Mr. J. M. L. Cameron.

Ultra-violet absorption spectra were determined by Mr. J. Austin with a Unicam SP500 Spectrophotometer and infra- red spectra by Dr. G. Eglinton with a Perkin-Elmer Model 21 Spectrophotometer.

Melting-points throughout are uncorrected.

The author wishes to thank the Department of Scientific and Industrial Research, and the Queen's University of Belfast, for providing grants which enabled this work to be undertaken.

PART ONE

POSSIBLE ROUTES TO AZATROPOLONES

HISTORICAL INTRODUCTION

According to molecular orbital theory, aromatic properties will only be shown by those rings which are planar and have $(4n + 2)\pi$ electrons, where *n* is any whole number. This rule, first propounded by Hückel[1], is obviously compatible with benzenoid derivatives and also provides a satisfactory argument for the non-aromaticity of *cyclo*öctatetraene, whose non-planarity restricts the mobility of the double bonds. Recently, it has been strikingly shown that Hückel's rule holds good for charged rings fulfilling the above criteria, as instanced by the seven-membered *cyclo*heptatrienyl, (tropylium), cation (I), and the *cyclo*pentadienyl anion (II).

The acidic properties of *cyclo*pentadiene have long been known well, and there seems little doubt that the ion, II, is a stable entity. The unusual stability of diazo*cyclo*pentadiene[40] and pyridinium *cyclo*pentadienylide[42], together perhaps with ferrocene[2,3] and its analogues, derive from this aromaticity. The possibility of the existence of the tropylium ion (I) became apparent when tropolone (III) was found to have weakly basic properties, while the parent ketone, tropone (IV) was a much stronger base.

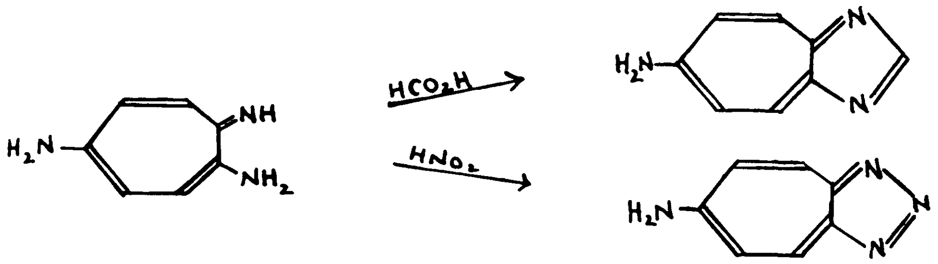
The recent preparation of salts of the parent ion (I)[4,5,32] has furnished final proof of its stable existence, though the first such salt was actually obtained by Merling in 1891[33], though its true nature was not realised. Salts of the corresponding benztropylium cation (V) have also been prepared[41].

Following on Dewar's predictions[6], that the properties of stipitatic acid and other naturally occuring substances could best be explained by assuming them to contain the hitherto unknown tropolone structure, tropolone (IV) has been synthesised[7,8,9,10], together with a large number of derivatives. The synthesis of tropone (V)[11,12] followed shortly afterwards, and the chemistry of these compounds is now quite extensive.[13] There is no theoretical reason why nitrogen containing rings analagous to tropone or *cyclo*heptatrienylium should not exist, and if prepared they would be expected to show very similar properties, (cf. benzene and pyridine).

Until very recently no such system has been reported, the nearest approaches being several pyridotropolones and azaazulenes, which have been synthesised during the past four years. VI was obtained[14] by a Skraup synthesis from 5-aminotropolone, while VII and VIII were formed by the

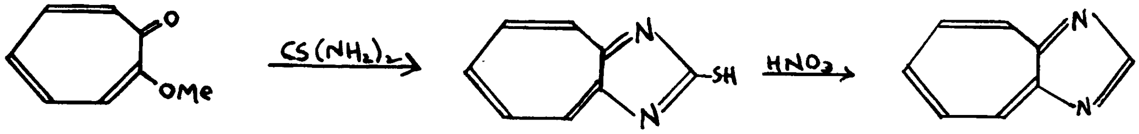
Doebner-Miller reaction of 5-aminotropolone[15], and the corresponding methyl analogue[16], with crotonaldehyde. IX was prepared[15] by condensation of ethoxyethylenemalonate and 5-aminotropolone, cyclisation occuring on further heating. The formation of aza-, diaza-, and triaza-azulenes from tropolone derivatives, has been announced recently by Nozoe and his co-workers. The syntheses of some of them are summarised below.

17

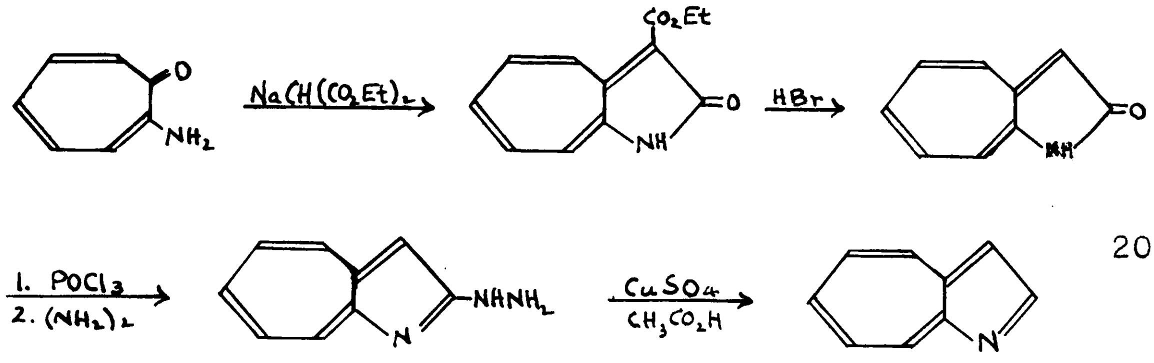


18

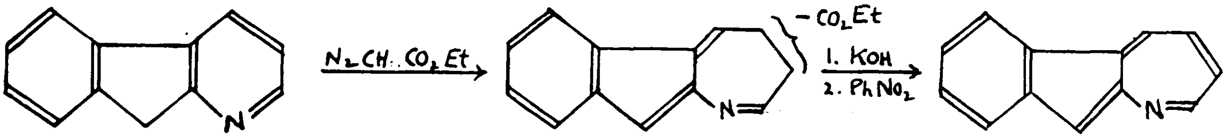
19



20



Some benzazaazulenes were prepared also by earlier workers, but some confusion still exists as to the identity of these compounds[34,35,36,37,38,39]. All of these contain a nitrogen atom in the five-membered ring. However, Treibs _et al_. in 1951[34] reacted 4-azafluorene with ethyl diazoacetate and obtained what is almost certainly a benzazaazulene with the nitrogen in the seven-membered ring, as outlined below.



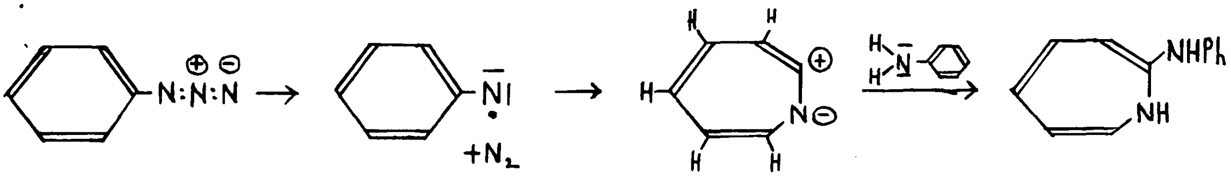
With the above single exception, in none of the aforementioned nitrogen compounds is the heterocyclic ring seven-membered, so that there is no true analogy with an aza_cyclo_heptatrienylium system.

Beckmann and Liesche[21] attempted to bring about a rearrangement of _p_-nitrosophenol(X) which exists as a tautomer, behaving partly as quinone monoxime. Since the usual acidic reagents (hydrochloric acid and phosphorus pentachloride) failed, they heated X with benzenesulphonyl chloride in pyridine and thereby obtained a product which they assumed to be XI, the tautomer, in point of fact, of an aza*iso*tropolone. It was alkali soluble, and lacked ketonic properties, typical of a tropolone. By a similar rearrangement of anthraquinone monoxime they claimed to have isolated XII, the tautomer of a dibenzaza*iso*tropolone.

Raphael and Vogel[22] reinvestigated Beckmann's product, and found that the analysis figures corresponded to $C_{12}H_{10}O_3N_2$, rather than $C_6H_5O_2N$ as reported by Beckmann. It was found, in fact, to be identical with *pp*'-dihydroxyazoxybenzene (XIII). The mechanism by which this remarkable product is formed remains obscure, since, although in a reducing medium nitroso-compounds can form azoxy-compounds, it is hard to visualise any such conditions here. The identity of the anthraquinone monoxime rearrangement product was shown to be XII, by oxidation to *o*-aminobenzophenone-*o*'-carboxylic acid, but since it formed ketonic derivatives and was alkali insoluble, it must exist almost entirely in the keto-amide form, and is thus not a true azatropolone. This lack of tropolone properties is not surprising, since the analagous dibenztropolones and dibenztropones are similar in this respect.

Leonard and Curry[23], at about the same time, published a similar investigation on Beckmann's product from nitrosophenol. In addition to isolating the azoxyphenol (XIII), they attempted the rearrangement under milder conditions, but obtained only the benzenesulphonate of p-nitrosophenol. They also proposed a mechanism to explain the formation of XIII.

Recently, Huisgen[24] has announced the characterisation of a truly aromatic, seven-membered, nitrogen containing ring. The reaction of phenyl azide on aniline was studied by Wolff[25] in 1912. The product, 'dibenzamil', he formulated as a diphenylamine derivative (XIV). Despite the fact that acylation gives a 2-acylaminodiphenylamine, the stability and unusual properties of the compound are inconsistent with this structure (XIV). Huisgen, reinvestigating the problem, obtained the amidine (XVI) by hydrogenation; the identity of this compound was confirmed by synthesis. The so-called dibenzamil is, therefore, 2-anilinotropazole (XV). The phenyl azide presumably rearranges, during decomposition, to a seven-membered ring, which then combines with aniline to give XV, as indicated below.



The origin of the system from the azide, and not from the base, is clearly shown by the fact that hydrogenation of the corresponding product from p-toluidine and phenyl azide, proceded a stage further to regenerate the free amine, together with hexamethyleneimine. Acylation of these compounds must be accompanied by a ring contraction, in order to explain the production of a phenylenediamine nucleus. Although XV and its analogues are 8-π-electron systems, whereas Hückel has predicted highest stability for the corresponding 6-π-electron nucleus, there seems little doubt that Huisgen's compounds are aromatic resonance systems, and not aliphatic trienes. In a communication to Huisgen, Doering in America has reported the formation of the same stable nucleus, by the irradiation of phenyl azide in a basic medium.

DISCUSSION

This preliminary investigation into possible routes to the nitrogen containing analogues of the tropolones, was centred on what is certainly one of the most ready sources of aza*cyclo*heptanones namely the well-known Beckmann rearrangement of substituted *cyclo*hexanone oximes to the corresponding ε-caprolactams.

A further attempt at the one step formation of 4-aza-5-hydroxytropone (XI) from nitrosophenol (X) by the use of mild conditions, was unsuccessful. The drop-wise addition of benzenesulphonyl chloride to a refluxing suspension of X in dioxan and aqueous sodium bicarbonate, according to the method of Roberts and Chalmers[26], resulted merely in the formation of the benzenesulphonate (XVII) of X.

It was therefore decided to turn to a fully saturated system, in the hope that by subsequent dehydrogenation XI could be obtained. The starting material for this work was 4-benzoxy*cyclo*heptanone (XVIII), derived from quinitol by partial esterification, and oxidation of the residual hydroxy-group. Its oxime (XIX) was found to rearrange smoothly by the simultaneous formation and decomposition of the benzenesulphonate, as described above, to give a benzoxy-substituted caprolactam (XX). Debenzoylation, by means of sodium ethoxide in ethanol, proceeded smoothly to give the free hydroxy-compound (XXI), an exceedingly water soluble solid which, although a neutral aliphatic amide, formed a stable picrate, unusual for such a compound. Any doubt about its structure, arising from this fact and from its remarkable resistance to oxidation, as described below, was removed by an examination of its infra-red spectrum. This showed that XXI was an amide, probably cyclic, and indicated the presence of a strongly hydrogen bonded hydroxyl group. Benzoylation reformed the benzoxy-compound (XX), thus putting the matter beyond reasonable doubt.

Several reagents were used in an endeavour to oxidise the hydroxy-group to a carbonyl-group, but in no case was this successful. Chromium trioxide in 2N sulphuric acid reacted very slowly, and although a small quantity of the 2:4-dinitrophenylhydrazone of a ketone was isolated, it was probably a mixture, and certainly not the derivative of the desired ketone (XXII). Chromium trioxide in either aqueous acetic acid or pyridine[27], gave heterogeneous, non-ketonic products. An attempt to bring about the oxidation with N-bromoacetamide in <u>tert</u>. butanol, resulted in the isolation of a small quantity of a solid crystalline material, non-ketonic in nature.

It is reasonable to assume, therefore, that any oxidative reaction which occured was always accompanied by complete disruption of the ring under the conditions used. A model of the hydroxy-compound (XXI) indicated that, if it were to assume the 'boat' form, the hydrogen atom of the hydroxyl group would be in close proximity to the amide oxygen, producing a strong intra-molecular hydrogen-bonded bridge structure. This is in agreement with the infra-red data, as the O-H stretching frequency is remarkably low, (3,240 cm.$^{-1}$), and the amide C=O stretching frequency also rather low, (1,640 cm.$^{-1}$), both typical of strong hydrogen bonding.

Reaction of 5-benzoxyaza*cyclo*heptan-2-one (XX) with phosphorus pentasulphide in pyridine, proceeded smoothly to the corresponding thioamide (XXIII). It was hoped that desulphurisation by means of Raney nickel would give the free amine (XXV) or its saturated analogue (XXVI), which, after debenzoylation, might well undergo oxidation to the corresponding ketone. Unfortunately, despite several attempts, the reaction products were very intractable, and attempted purification through the hydrochloride or by benzoylation, led to sticky, non-crystalline materials.

The benzoxythioamide (XXIII), when treated with sodium ethoxide in ethanol, gave the hydroxy-compound (XXIV) in good yield, and its oxidation was investigated. Treatment with either chromium trioxide in acetic acid or potassium permanganate in acetone, gave rise to a rapid reaction, but twice the theoretical quantity of reagent was consumed, sulphur was deposited, and a non-ketonic material was isolated. Initial attack would seem to be upon the C=S bond and not upon the O-H as desired.

A small scale reduction of 5-hydroxyaza<u>cyclo</u>heptan-2-one (XXI) with lithium aluminium hydride was now undertaken and, after filtration to remove the aluminium hydroxide, the residue was worked up. Benzyl alcohol was recovered from the ether layer, while evaporation of the aqueous solution gave a glass, consisting of the amino-alcohol (XXVII - ?) and lithium hydroxide. Since no picrate could be isolated, and the product was insoluble in all non-hydroxylic solvents, the mixture was benzoylated, in an attempt to obtain the dibenzoate, XXVIII, but only a dark resin was obtained, debenzoylation of which gave a non-crystalline product. A solution of the latter in methanol, deposited a small amount of crystalline material after a very long period, but an analysis showed that it was not the expected N-benzoyl-4-hydroxyaza-cycloheptane (XXIX). No nitrogen was detected by a sodium fusion, while the analysis figures are best represented by an empirical formula of $C_{13}H_{14-16}O_4$. The nature of this compound is puzzling, but in view of its small quantity, and the extended period required for its crystallisation, little importance can be attached to it.

In a final attempt to obtain workable materials, the benzoxy-amide (XX) was treated with methyl sulphate in benzene to give the imino-ether (XXX), and the crude material debenzoylated with sodium methoxide in methanol. The free hydroxy compound (XXXI), when first isolated was partially crystalline, but absorbed water very rapidly. Its deliquescence was so great, that even after distillation and standing over phosphorus pentoxide at 0.1 mm. for twelve months, crystallisation could not again be induced. A phenylurethane was therefore made for purposes of characterisation.

In view of the difficulty in working with the above materials, due to their high affinity for water and their complex behaviour towards oxidising agents, a more direct approach was tried. The Beckmann rearrangement of the monoxime (XXXII) of cyclohexane-1:4-dione should give aza*cyclo*heptane-2:5-dione (XXII) directly, dispensing with any oxidation step. *Cyclo*hexane-1:4-dione, when treated with slightly less than one mole of hydroxylamine, gave a mixture as anticipated. A small quantity of the pure monoxime was isolated which, with excess hydroxylamine, gave the known *cyclo*hexane-1:4-dioxime. It proved impracticable, however, to devise a workable, large-scale process for the separation of the monoxime from the other products. Chromatography, ion-exchange methods and fractional crystallisation failed to achieve appreciable separation, while attempted distillation resulted in decomposition. The impure product was therefore treated with benzenesulphonyl chloride as before. Soxhlet extraction of the resulting solids yielded a small quantity of a crystalline product (XXII), different from the starting material. It did not form a picrate, but was characterised by means of its 2:4-dinitrophenylhydrazone, which depressed the melting point of the derivative obtained from the oxidation product of XXI (p.13). On repetition of this experiment none of the dione (XXII) was obtained, only an amorphous polymer, together with some *cyclo*hexane-1:4-dione, being isolated. A further attempt to obtain XXII, by first forming the oxime benzenesulphonate, and then decomposing it, was likewise unsuccessful.

To sum up, it would seem that although this latter approach to aza*cyclo*heptane-2:5-dione would appear to be the more promising, efficient means both of preparing and isolating the pure monoxime, and of rearranging it to XXII, would have to be sought before any serious attempts could be made to dehydrogenate it to the desired aza*iso*tropolone (XI).

EXPERIMENTAL

4-BenzoxyCYCLOhexanone (XVIII)

Hydroquinone was hydrogenated as described by Owens and Robins[28], and the resulting quinitol partially esterified with benzoyl chloride by the method of Jones and Sondheimer[29], to give 4-benzoxy*cyclo*hexanol. This was then oxidised with chromic acid in acetic acid[29], yielding XVIII.

4-Benzoxy-1-oximinoCYCLOhexane (XIX)

4-benzoxy*cyclo*hexanone (25 gm.) and hydroxylamine hydrochloride (12 gm.) were refluxed in pyridine (150 ml.) for 2 hrs. After cooling and pouring into an excess of 2N HCl, the mixture was extracted with ether, and the extracts washed successively with 2N HCl, sodium bicarbonate, and water. Drying and removal of the solvent gave the crude oxime as an oil which solidified on standing. It was recrystallised from benzene/pet. ether (b.p. 60-80°) to give pure XIX, (23.3 gm.; 87%), as colourless needles, m.p. 105°. (Found: C, 67.15; H, 6.5; N, 6.4; $C_{13}H_{15}NO_3$ requires: C, 66.95; H, 6.5; N, 6.0%).

5-BenzoxyazaCYCLOheptan-2-one (XX)

4-benzoxy-1-oximinocyclohexane (20 gm.) and sodium bicarbonate (18.1 gm.) were dissolved in water (90 ml.) and dioxan (60 ml.). The solution was refluxed, while benzenesulphonyl chloride (18.1 gm.) in dioxan (15 ml.) was added, dropwise, during 2 hrs.[26] The mixture was then extracted continuously with ether for 24 hrs., during which time part of the product crystallised out from the ether and was set aside. The ether solution was dried and evaporated, and the combined products recrystallised from benzene/pet. ether (b.p. 80-100°) to give pure XX, (16 gm.; 80%), as colourless prisms, m.p. 133°. (Found: C, 66.95; H, 6.7; N, 6.3; $C_{13}H_{15}NO_3$ requires: C, 66.95; H, 6.5; N, 6.0%). It did not form a picrate.

5-HydroxyazaCYCLOheptan-2-one (XXI)

5-benzoxyazacycloheptan-2-one (6 gm.) and sodium (0.05 gm.) in ethanol (40 ml.) were refluxed for 3 hrs., and allowed to stand overnight. The solvent was removed and the residue extracted several times with boiling pet. ether (b.p. 60-80°), to remove ethyl benzoate. The residual solids were extracted repeatedly with boiling chloroform, until no further material could be isolated on evaporation. The resulting XXI, (2.8 gm.; 85%), white micro crystals, m.p. 140-142°, could be further purified by recrystallisation from either nitromethane or ethanol/ether, giving colourless needles, m.p. 142°, soluble in water, (giving a neutral solution), alcohols, acetic acid and pyridine, sparingly soluble in chloroform, and insoluble in all other common solvents. (Found: C, 56.2; H, 8.6; N, 11.1; $C_6H_{11}NO_2$ requires: C, 55.8; H, 8.6; N, 10.85%). Infra red spectrum (in Nujol) showed peaks at 3,240 (b.,s.), (assoc. O-H str.), 3,100 (m.), (N-H str.), 1,640 (b., v.s.), (C=O str., H bonded), 1,495 (s) (cyclic amide II?), 1,382 (m.s.), 1065cm.$^{-1}$ (s.), (O-H def; C-O str.). Benzoyl chloride in pyridine gave XX, m.p. and mixed m.p. 131-133°.

Picrate, pale yellow plates from ethanol, m.p. 152.5-153.5°. (Found: N, 15.5; $C_{12}H_{14}N_4O_9$ requires: N, 15.65%).

Attempted oxidations of XXI

(a) 5-hydroxyaza*cyclo*heptan-2-one (XXI), (1.0 gm.) in water (5 ml.) was warmed with 2N chromic acid/H_2SO_4 (6 ml.), and stood for 24 hrs. Oxidation was very sluggish. Continuous extraction with ether for 3 days gave a trace of sticky material.

2:4-Dinitrophenylhydrazone, brick red, amorphous, m.p. 159°. (Found: N, 13.72%).

(b) XXI (1.2 gm.) was warmed on a steam bath with chromic acid (0.8 gm.) in acetic acid (7 ml.) and water (1 ml.) for 60 mins. Ethanol was added to destroy the excess chromic acid, the solution neutralised with ammonia, filtered, and taken to dryness under reduced pressure. The residue partly sublimed on heating, to give a non-ketonic material of indefinite melting point.

(c) XXI, treated with chromic acid in pyridine[27], gave only a trace of a non-ketonic chloroform soluble product.

(d) XXI (0.5 gm.) and N-bromoacetamide (1 gm.) were dissolved in <u>tert</u>. butanol (20 ml.), pyridine (2 ml.), and acetic acid (0.05 ml.)[30]. After standing for 64 hrs., the solution was filtered, treated with sodium carbonate (2 gm.) in water (12 ml.), taken to dryness and extracted with boiling chloroform. Evaporation of the chloroform gave a reddish oil, partially solidifying on cooling. White needles (0.21 gm.) from acetone, m.p. 64-68°. It was non-ketonic.

5-BenzoxyazaCYCLOhepta-2-thione (XXIII)

5-benzoxyaza*cyclo*heptan-2-one (2.3 gm.) and phosphorus pentasulphide (2.6 gm.) were refluxed in pyridine (30 ml.) for 2 hrs., the solution cooled, and poured into water (400 ml.). The cinnamon coloured product was filtered off and crystallised from ethanol, after treatment with charcoal, to give XXIII, (2.0 gm.; 81%), as colourless granules, m.p. 156°. (Found: C, 62.6; H, 6.2; N, 5.75; $C_{13}H_{15}NO_2S$ requires: C, 62.5; H, 6.05; N, 5.6%)

5-HydroxyazaCYCLOhepta-2-thione (XXVI)

5-benzoxyazacycloheptan-2-thione (1 gm.) was refluxed with a trace of sodium ethoxide in ethanol (15 ml.) for 4 hrs., and the solvent removed. The residue was extracted with boiling pet. ether (b.p. 60-80°), and then several times with boiling chloroform. Evaporation of the chloroform gave XXVI as pale yellow granules, crystallising from the same solvent, after treatment with a little charcoal, as colourless granules, (0.49 gm.; 88%), m.p. 120°. Its solubility in most solvents was very low, excepting alcohols, acetic acid, pyridine, and water. (Found: C, 49.95; H, 7.95; N, 10.4; $C_6H_{11}NOS$ requires: C, 49.65; H, 7.65; N, 9.65%). Treatment with chromic acid in acetic acid resulted in a rapid oxidation with deposition of sulphur, while potassium permanganate in acetone also reacted rapidly, but in neither case was the product ketonic.

Desulphurisation of XXIII

5-benzoxyaza*cyclo*hepta-2-thione (XXIII) (2.0 gm.) and Raney nickel (7.0 gm.) were refluxed in ethanol (40 ml.) for 60 mins., then filtered through Celite. Removal of the solvent left a pale brown, foul-smelling oil (1.6 gm.), whose picrate was a liquid at room temperature. Extraction from benzene with 2N HCl, and neutralisation with sodium carbonate, gave a reddish-brown oil, chromatography of which gave several ill-defined bands, all of which, on elution with various solvents, gave traces of sticky products. From an attempt to obtain the hydrochloride, by passing dry hydrogen chloride through a solution of the basic products in ether, only a brown glass was obtained. Benzoylation in pyridine gave, on working up, a sticky, pale-brown semi-solid, which could not be induced to crystallise.

Lithium aluminium hydride reduction of XXI

5-benzoxyaza*cyclo*heptan-2-one (2.3 gm.) in benzene (20 ml.) was added during 60 mins. to lithium aluminium hydride (0.5 gm.) in ether (100 ml.). After refluxing for

90 mins. the excess hydride was decomposed by dropwise addition of water, the ether layer separated, and the aqueous layer extracted with ether. Drying and removal of the solvent gave benzyl alcohol, (1.0 gm.; 91%). (p-nitrobenzoate, colourless needles from aq. ethanol, m.p. and mixed m.p. 83-84°). The aqueous layer was filtered from alumina, the latter dried and extracted with boiling ethanol, and the extracts added to the filtrate. Evaporation under reduced pressure gave a pale yellow glass containing lithium hydroxide, extraction of which with benzene, chloroform or ethyl acetate yielded no material. It did not form a water insoluble picrate.

The glass was refluxed in pyridine for 30 min. with 3.0 moles of benzoyl chloride, and the solution poured into excess 2N HCl. Extraction with ether gave, on working up, a dark brown resin. This was refluxed in ethanol with a trace of sodium for 3 hrs., the solvent removed, and the product extracted with boiling pet. ether, and then with boiling chloroform. Removal of the chloroform gave a pale brown sticky mass which would not crystallise. After standing in a little methanol for over 12 months, a small quantity of a crystalline solid was deposited, giving colourless plates from benzene, m.p. 137.5°. No nitrogen was detected by a sodium fusion test. (Found: C, 66.2; H, 6.15; $C_{13}H_{16}O_4$ requires: C, 66.1; H, 6.85; $C_{13}H_{14}O_4$ requires:C, 66.65; H, 6.05%).

2-Methoxy-5-hydroxy-azaCYCLOhept-1-ene (XXXI)

Methyl sulphate (2.7 gm.) in benzene (5 ml.) was added during 60 mins. to a refluxing solution of 5-benzoxyazacycloheptan-2-one (5 gm.) in benzene (30 ml.)[31]. Refluxing was continued for 12 hrs., the solution cooled, and anhydrous potassium carbonate (1.45 gm.) in water (3.0 ml.) added. The vessel was shaken for 60 mins., and the precipitated potassium methyl sulphate filtered off through Celite. The benzene layer was separated, dried, and evaporated, to give 2-methoxy-5-benzoxyazaCYCLOhept-1-ene (XXX) as an almost colourless, viscous oil (4.9 gm.; 92%).

Crude XXX (4.8 gm.) and sodium (0.04 gm.) in methanol (30 ml.) were refluxed for 5 hrs., left overnight, and the solvent removed. The ethyl benzoate was removed by pet. ether as before (pp.20,23), and the residue extracted several times with boiling chloroform. Removal of the solvent gave crude XXXI, (2.3 gm., 82%), as a pale, straw-coloured oil, miscible with water, alcohols, chloroform and acetic acid, partially solidifying to a white solid, which absorbed moisture very rapidly, becoming again entirely liquid. Dilute acid or alkali, and even sodium chloride solution, hydrolysed XXXI to 5-hydroxyaza*cyclo*heptan-2-one (XXI), m.p. and mixed m.p. 137-140°. No apparent oxidation took place with chromic acid in acetic acid at room temperature.

Distillation was not completely successful, since partial decomposition occured with the formation of tars and ammonia, but a small quantity was collected as a colourless, viscous, liquid, b.p. 130°/0.05 mm. It did not solidify after standing over phosphorus pentoxide at 0.1 mm. for 12 months.

Phenylurethane, prepared by refluxing XXX (0.1 gm.) with an excess of phenyl*iso*cyanate in dry dioxan (4 ml.) for 4 hrs. Addition of pet. ether (b.p. 40-60°) brought down a sticky oil, crystallising on standing. White granules from benzene/pet. ether (b.p. 60-80°), m.p. 146-149°. (Found: C, 63.9; H, 6.45; N, 10.4; $C_{14}H_{18}N_2O_3$ requires : C, 64.15; H, 6.9; N, 10.7%)

Attempted rearrangement of *p*-nitrosophenol (X)

X (8 gm.) and sodium bicarbonate (13 gm.) in dioxan

(25 ml.) and water (50 ml.) were refluxed, with dropwise addition of benzenesulphonyl chloride (13 gm.) during 2 hrs. Refluxing was continued for 20 mins., then the reddish-black solid (11.2 gm.) filtered off and extracted with ethyl acetate from a Soxhlet thimble. Treatment with a little charcoal, and removal of the solvent, gave a sulphur and nitrogen containing solid. It crystallised from benzene as pale yellow prisms, (6.5 gm.; 36%), m.p. 132°, identical with *p*-nitrosophenol benzenesulphonate[23]. The residue in the Soxhlet thimble consisted of black infusible material.

4-OximinoCYCLOhexanone

*Cyclo*hexane-1:4-dione (6.1 gm.), hydroxylamine hydrochloride (3.3 gm.), and anhydrous sodium acetate (7.6 gm.) were dissolved in water (25 ml.) and ethanol (5 ml.). After heating for 2 hrs. on a steam bath, the solution was taken to dryness under reduced pressure. Soxhlet extraction of the solids with benzene gave a brown product (5.5 gm.) on evaporation. This was extracted repeatedly with boiling pet. ether (b.p. 80-100°), reducing each portion to small bulk, and collecting the crystalline material deposited (4.5 gm.; m.p. from 80 to 100°). The material from the second extraction, m.p. 99-100°, was recrystallised from the same solvent as colourless needles, m.p. 101-102°, of the pure monoxime. (Found: C, 56.75; H, 6.65; N, 11.05; $C_6H_9NO_2$ requires: C, 56.7; H, 7.15; N, 11.0%). Treatment with excess hydroxylamine hydrochloride and sodium acetate in cold aqueous solution, gave the dioxime, m.p. and mixed m.p. 188-189°. The monoxime became dark and formed tars on standing in air.

Attempts to obtain the pure monoxime by fractional crystallisation from various solvents were unsuccessful, while on distillation, only <u>cyclo</u>hexane-1:4-dione, b.p. 97-103°/20mm., was obtained, the oxime decomposing into black involatile tars. Chromatography on alumina gave only the dione on elution, whereas on Celite no separation occured. On passing the crude material in water down a De-acidite 'F' column, the dione was separated cleanly, but an attempt to recover the oxime by elution with sodium carbonate gave only a minute quantity of an oil.

<u>AzaCYCLOheptane-2:5-dione (XXII)</u>

Impure 4-oximino<u>cyclo</u>hexanone (1.4 gm.) and sodium bicarbonate (2.0 gm.), in water (15 ml.) and dioxan (5 ml.), were refluxed, while benzenesulphonyl chloride (2.0 gm.) in dioxan (5 ml.) was added during 30 mins. Refluxing was continued for 30 mins., then the dark solution taken to dryness at the pump, and the residue extracted with chloroform from a Soxhlet thimble. Removal of the solvent gave a pale brown sticky solid, giving cream-coloured prisms of XXII, (0.1 gm.; 7%), from acetone. Treatment with charcoal gave a pure product, white prisms from acetone, m.p. 134-135°. (Found: C, 56.6; H, 6.9; N, 11.2; $C_6H_9O_2N$ requires: C, 56.7; H, 7.15; N, 11.0%). It did not form a picrate.

2:4-Dinitrophenylhydrazone, yellow micro-crystals from ethanol, m.p. 216-218°. (Found: N, 22.9; $C_{12}H_{13}N_5O_5$ requires: N, 22.8%).

On repetition of the above preparation, none of XXII was isolated. Extraction of the crude material with pet. ether (b.p. 80-100°), gave unchanged *cyclo*hexane-1:4-dione, while the sticky residue gradually decomposed into a brown polymer, m.p. $> 300°$. An attempt to bring about the rearrangement by first forming the oxime benzenesulphonate with benzenesulphonyl chloride and pyridine, as described by Roberts and Chalmers[26], was unsuccessful. Only *cyclo*hexane-1:4-dione together with an oil, was obtained and, on attempting to decompose the latter by heating with aqueous acetic acid[26], no crystalline material could be isolated.

REFERENCES

1. Hückel; Z. Physik, 1931, 70, 204.
2. Kealy and Pauson; Nature, 1951, 168, 1039.
3. Miller, Tebboth and Tremaine; J., 1952, 632.
4. Doering and Knox; J. Amer. Chem. Soc., 1954, 76, 3203.
5. Johnson and Tisler; Chem. and Ind., 1954, 1427.
6. Dewar; Nature, 1945, 155, 50, 141.
7. Cook, Gibb, Raphael and Somerville; Chem. and Ind., 1950, 427.
8. Doering and Knox; J. Amer. Chem. Soc., 1950, 72, 2305.
9. Haworth and Hobson; Chem. and Ind., 1950, 441.
10. Nozoe, Seto, Kitahara, Kunori and Nakayama; Proc. Jap. Acad., 1950, 26, No. 7, 38.
11. Daubens and Ringold; J. Amer. Chem. Soc., 1951, 73, 876.
12. Doering and Detert; loc. sit.
13. Pauson; Chem. Reviews, 1955, 55, 9.
14. Cook, Loudon and Steel; Chem. and Ind., 1952, 562.
15. Slack and Attridge; ibid., 1952, 471.
16. Akroyd, Haworth, and Jefferies; J., 1954, 286.
17. Nozoe, Seto, Ito, Matsui and Matsuda; Proc. Jap. Acad., 1953, 29, 565.
18. Nozoe, Ito and Matsui; ibid., 1954, 30, 313.
19. Nozoe, Mukai and Murata; J. Amer. Chem. Soc., 1954, 76, 3352.

20. Nozoe, Seto, Matsumura and Terasawa; Chem. and Ind., 1954, 1356, 1357.

21. Beckmann and Liesche; Ber., 1923, 56, 12.

22. Raphael and Vogel; J., 1952, 1958.

23. Leonard and Curry; J. Org. Chem., 1952, 17, 1071.

24. Huisgen; Angew. Chem., 1955, 67, 757.

25. Wolff; Ann., 1912, 394, 59.

26. Roberts and Chalmers; J. Amer. Chem. Soc., 1951, 73, 3176.

27. Poos, Arth, Beyler and Sarett; ibid., 1953, 75, 424.

28. Owens and Robins; J., 1949, 320.

29. Jones and Sondheimer; J., 1949, 615.

30. Sarrett; J. Amer. Chem. Soc., 1949, 71, 1165.

31. Benson and Cairns; Org. Syn., 31, 72.

32. Dewar and Pettit; Chem and Ind., 1955, 199.

33. Merling; Ber., 1891, 24, 3108.

34. Treibs, Barchet, Bach and Kirchhof; Ann., 1951, 574, 54.

35. Treibs; ibid., 1952, 576, 110.

36. Anderson and Tazuma; J. Amer. Chem. Soc., 1952, 74, 3455.

37. Treibs, Steinert and Kirchhof; Ann., 1953, 581, 54.

38. Lloyd; Chem. and Ind., 1953, 1889.

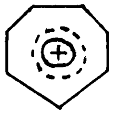
39. Muth, Steiniger, and Papanastassiou; J. Amer. Chem. Soc., 1955, 77, 1006.

40. Doering and De Puy; Abstracts, 123rd Amer. Chem. Soc. Meeting, 1953, 10M.

41. Rennhard, Heilbronner and Eschenmeser; _Chem. and Ind_. 1955, 415.

42. Lloyd and Sneezum; _ibid_., 1221.

FORMULAE.

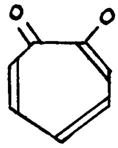


$[C_7H_7^{\oplus}]$

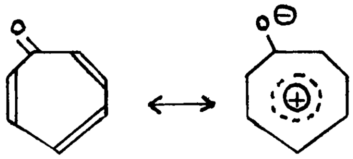
I

$[C_5H_5^{\ominus}]$

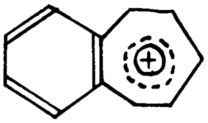
II



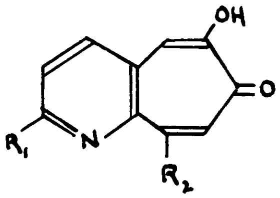
III



IV



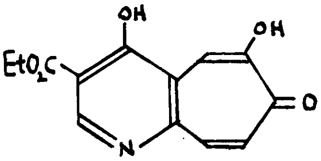
V



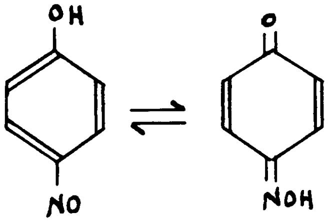
VI, $R_1 = R_2 = H$

VII, $R_1 = Me$; $R_2 = H$

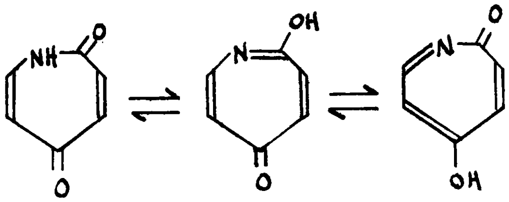
VIII, $R_1 = R_2 = Me$



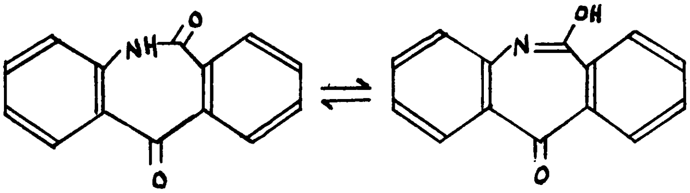
IX



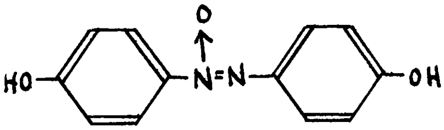
X



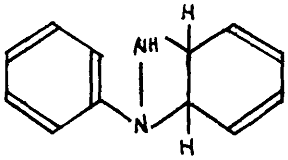
XI



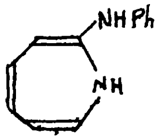
XII



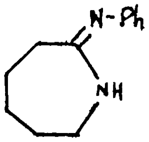
XIII



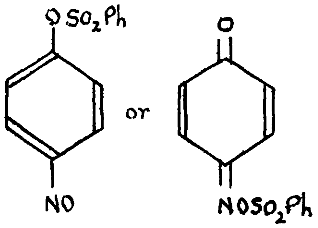
XIV



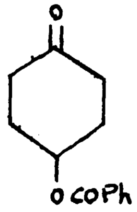
XV



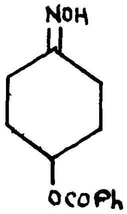
XVI



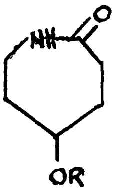
XVII



XVIII

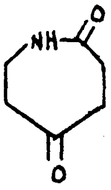


XIX

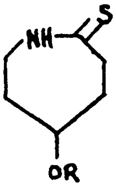


XX, R = COPh

XXI, R = H

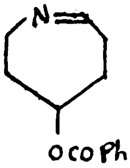


XXII

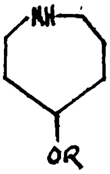


XXIII, R = COPh

XXIV, R = H

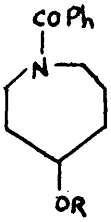


XXV



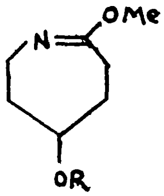
XXVI, R = COPh

XXVII, R = H



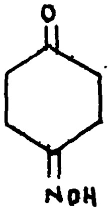
XXVIII, R = COPh

XXIX, R = H



XXX, R = COPh

XXXI, R = H



XXXII

PART TWO

ELABORATION PRODUCTS OF EUCARVONE

HISTORICAL INTRODUCTION

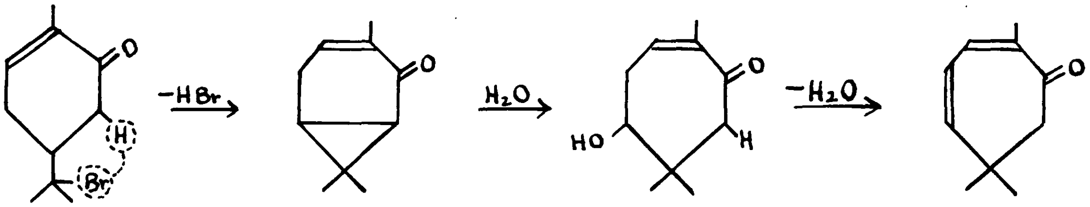
Eucarvone (I), a terpenoid trimethyl*cyclo*heptadienone, was first obtained by Baeyer[1] in 1894 from carvone hydrobromide (III) and methanolic potash. Although classified as a terpene by its derivation, and by its conformity with the isoprene rule, it was not known to occur in nature until many years afterwards. Kabu and his collaborators[2,3] in 1931 isolated I from the essential oil of *Ascarum sieboldi*, the only natural source hitherto discovered.

Baeyer found that eucarvone, isomeric with carvone, was optically inactive although prepared from dextro-rotatory carvone (II) and that at its boiling point, I was isomerised to carvacrol (IV)[1,4]. Since the new ketone had different properties from III he initially suggested that carvone possessed structure VI, eucarvone being the isomeric *cyclo*hexadienone, V; both these postulates were later proved wrong. Under the same conditions as he used in the preparation of eucarvone, Baeyer obtained from dihydrocarvone (VIII), a further ketone, carone[5] (VII), which, like VIII, gave carveol (IX) on treatment with sulphuric acid. Baeyer established the correct structure for carone[6,14], and later suggested the analagous carenone formula, X[7], for eucarvone, produced by elimination of hydrogen bromide from III to give a *cyclo*propane ring.

Reduction of eucarvone with sodium in ethanol gave a dihydroeucarvol, now known to be XI, oxidisable by chromic acid to the ketone, XII[1,5,9]. Wallach, investigating the oxidation of XII, obtained a keto-glycol (XIII), and by further oxidation a dione[9], whose structure is still uncertain. He also described the benzylidene derivatives of eucarvone itself[10, 11].

Baeyer, continuing his investigations, noted that although carone gave caronic acid on oxidation, both eucarvone and the dihydro-compound (XII) gave $\alpha\alpha$-dimethylsuccinic acid, showing that the *gem*-dimethyl group of I is still present in its reduction product[7]. (It is of interest to note that the prefix '*gem*' was first suggested in this paper to describe this type of structure.) Reduction of the oximes of either I or XII with sodium in ethanol gave a dihydroeucarvylamine (XIV) whereas eucarvoxime was reduced by zinc and hydrochloric acid to tetrahydroeucarvone, XV[7,14]. An oxidation of XV gave a keto acid, forming $\beta\beta$-dimethylpimelic acid, when treated with hypobromite, thus establishing the presence of a seven-membered ring therein[7]. The chloro-compound from dihydroeucarvol(II) and phosphorus pentachloride was dehydrochlorinated to give a hydrocarbon, 'euterpene'. Bromination and subsequent treatment with zinc and hydrochloric acid yielded, according to Baeyer, 1:2-dimethyl-4-ethylbenzene, and thus euterpene is represented by XVI or XVII[7]. No further work has, however, been done in order to clarify these somewhat doubtful assumptions. Klages and Kraith [12] in 1899 obtained 2-chlorocymene (XVIII) by treating eucarvone with phosphorus pentachloride and refluxing the product with quinoline, whereas from dihydroeucarvone (XII), by the same method, an isomer of XVIII and a chlorine free product were obtained, both as yet uncharacterised.

Harries and Stähler[13] in 1904, obtained a hydroxylaminoeucarvoxime by treating I with excess hydroxylamine. On reduction, a diamine (XIX?) was formed, whose phosphate on dry distillation yielded p-cymene. They noted that had eucarvone the structure X, as proposed by Baeyer, m-cymene would be the expected product by analogy with his own results[14] on the dry distillation of carylamine (XX) hydrochloride, to give carvestrene (XXI) and thence m-cymene by dehydrogenation. This doubt regarding Baeyer's formula for eucarvone was carried to its conclusion by Wallach, who showed that tetrahydroeucarvol (XXII) could be obtained by direct reduction of eucarvone, and that eucarvoxime, similarly, could give a mixture of the corresponding amine (XXIII), and the ketone itself (XV)[15]. Since the seven-membered ring of XV was already established there could be no reasonable doubt that I also contained a cycloheptane skeleton, since the above reductions leave no scope for any conceivable rearrangement process. He confirmed the production of ββ-dimethyl-pimelic acid from XV obtaining *gem*-dimethyl*cyclo*hexanone by pyrolysis of its calcium salt. Wallach proposed the now accepted formula for eucarvone, and suggested that it was formed from III, via Baeyer's compound (X), which then underwent hydration and dehydration to form eucarvone, as shown below.



Of the remaining uncertainties, perhaps the most outstanding was the position of the residual double bond in dihydroeucarvone. Later work by Wallach and his co-workers showed that eucarvone, on catalytic hydrogenation, gave the tetra-hydro ketone as anticipated[16], whereas from the oxime, in addition to tetrahydroeucarvoxime, a dihydro-derivative was also obtained, whose parent ketone (XXIV) was different from the dihydroeucarvone (XII) already known[17]. The new ketone could not be nitrosated successfully[18], in contradistinction to XII[5,8]. Oxidation gave ββ-dimethyladipic acid[17], proving it to be XXIV, and thus Baeyer's dihydroeucarvone, which had been oxidised to αα-dimethylsuccinic acid[7], must have the structure XII. They were therefore designated β-dihydro- and α-dihydro-eucarvone, respectively[18]. Reduction of β-dihydroeucarvoxime with sodium in ethanol gave the amine, XXIII[19], identical with that previously obtained from eucarvoxime[15]. Naves and Ardigio[20] have more recently obtained XXIV by a controlled hydrogenation of eucarvone itself.

Wallach also reported[19] a hydroxytetrahydroeucarvone (XXV or XXVI?), formed by bromination of XV and subsequent hydrolysis, which reduced to give a glycol. From a dibromo-derivative of XV, a steam volatile acid was obtained in the same way. β -dihydroeucarvone reacted with bromine[21] and treatment of the product (XXVII?) with alkali gave a ketone and α-_cyclo_geranic acid (XXVIII).

Eucarvane (XXIX), the parent hydrocarbon of the series, was prepared in 1936 by Ruzicka and Seidel[22] by Wolff-Kishner reduction of XV. Dehydrogenation by selenium gave a mixture of 1-methyl-4-ethylbenzene and 1:2:3-trimethylbenzene, whereas eucarvene (XXX?) formed by dehydration of the alcohol (XXII), yielded 1-isopropyl-3-methylbenzene.

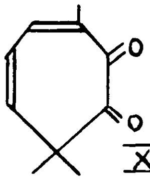
The elucidation of the structure of eucarvone has, throughout, been assisted by physical measurements. Brühl's[23] calculation of the molecular volume and molecular refraction of α-dihydroeucarvone helped to establish the presence of a double bond. Kanonnikoff[24] published measurements of the molecular density of eucarvone itself, and Auwers[25,26] recorded its molecular refraction. In recent years, polarographic measurements have been made by Csuros, Fodor and Hajos[27]. Any remaining doubts regarding the structures of eucarvone and its dihydro-derivatives, were removed by Gillam and West[28] in 1942. The ultraviolet spectra of the three ketones and their semicarbazones, were shown to be in perfect agreement with their accepted structures, as assigned by Wallach almost forty years previously[15,17]. (But cf. p.134 for further discussion.)

Apart from the two papers mentioned below, no other work on eucarvone derivatives had been reported until the present studies commenced. Rupe and Kerkovius[29], reacting eucarvone with methyl magnesium iodide obtained a very unstable alcohol, dehydrating on distillation to a tetramethyl*cyclo*heptatriene (XXXI), reducable by sodium in ethanol to di- and tetra-hydro analogues. Alder[30] reported a maleic anhydride adduct of eucarvone, to which West[31] tentatively assigned the structure XXXII.

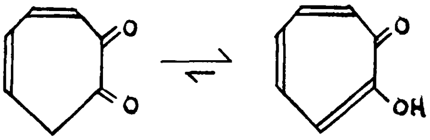
From the preparative point of view, Baeyer's original method of producing eucarvone remains unchallenged. Rabe and Weilinger[32] condensed carvone with ethyl acetoacetate in the presence of hydrogen chloride obtaining, presumably, XXXIII, which, when treated with potassium hydroxide, gave a mixture of eucarvone and a compound, $C_{13}H_{20}O_2$, of unknown structure. From carvone and potassium cyanide Clarke and Lapworth[33] prepared cyanodihydrocarvone (XXXIV), the hydrobromide of which gave β-cyanocarone (XXXV) on alkali treatment. In an attempt to hydrolyse further, eucarvone was obtained, together with a solid of unknown constitution. No total synthesis of eucarvone has yet been achieved, but recently tetrahydroeucarvone (XV) has been prepared by Dolejs, Novotny, Herout, and Sorm[34]. They obtained it from $\alpha\beta'\beta'$-trimethylsuberic acid (XXXVI) by pyrolysis with barium hydroxide and iron powder. It was identical with the product of hydrogenation of eucarvone.

DISCUSSION

The normal course of oxidation of a carbonyl compound by selenium dioxide, consists in an attack on the adjacent methylene group, leading to an α-diketone. The oxidation of eucarvone (I) on these lines should give the corresponding α-diketone, XLIV, a structure in which the *gem*-dimethyl group blocks enolisation to a true tropolone.



XLIV



The work that follows was initiated in an attempt to prepare XLIV, and thereafter to examine the possibility of rearrangement of the structure to a true tropolone by methyl group migration.

The oxidation, when carried out, was complicated by severe contamination with colloidal and combined selenium. It led chiefly to a solid product, of empirical formula $C_{10}H_{14}O_2$. This compound formed a phenylurethane and its ultra-violet absorption spectrum, (λmax. 2,290A^{o}) was consistent with that of an $\alpha\beta$-unsaturated ketone, but not for a conjugated dienone, (cf. eucarvone, λmax. 3,000A°; β-dihydroeucarvone, λ max. 2,380A°). The infra-red absorption indicated clearly the presence of a hydroxyl group, and also suggested the existence of a cyclopropane ring adjacent to the carbonyl group by strong absorption in the 1,050-990 cm.$^{-1}$ region and the abnormally low value (1,642 cm.$^{-1}$) of the C=O stretching frequency, (cf. Josien and Fuson[37]).

Mild oxidation by manganese dioxide in petroleum ether, gave the corresponding dione, showing the allylic nature of the hydroxyl group, since this reagent is specific for such compounds[38,39]. This fact was verified spectroscopically, the resulting diketone absorbing at a somewhat higher wavelength (λmax. 2,400A°) than the hydroxyketone. The spectrum of its bis-2:4-dinitrophenylhydrazone (λmax. 4,080A°) is compatible only with a completely conjugated system. Oxidation of the hydroxy-compound with chromium trioxide in acetic acid gave the same dione. These facts suggest that the oxidation product has the carenolone formula, XXXVII, the corresponding dione being the carenedione, XXXVIII.

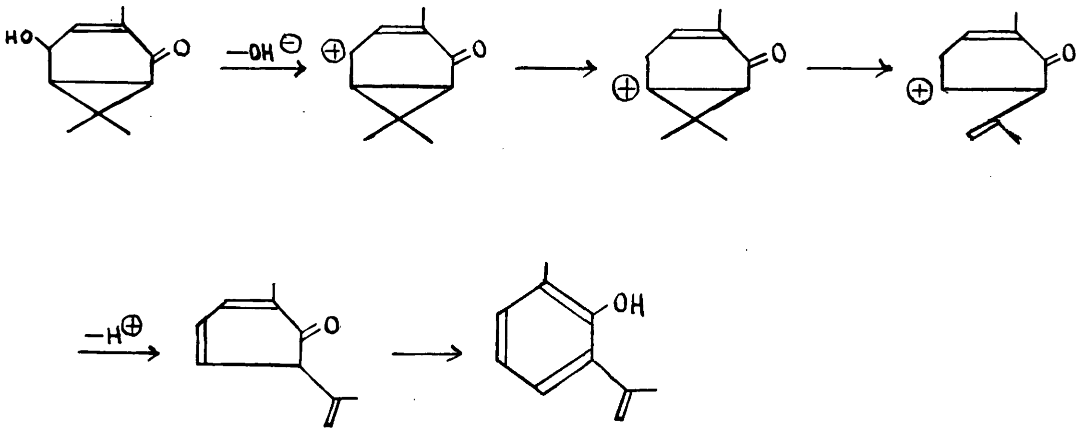
A preliminary communication published at this time by Corey and Burke[35] on a similar investigation was fully in concordance with this conclusion, and provided further proof by describing the oxidation of XXXVIII to cis caronic acid. This and a later note[36] cover, to a certain extent, the same ground, albeit with a different objective in view. Selenium dioxide oxidation of eucarvone gave a hydroxycarone, XXXVII, oxidisable further by manganese dioxide to the dione, XXXVIII. Treatment of XXXVIII with permanganate gave cis caronic acid, thus establishing its structure, verified by spectral evidence. The action of butyl nitrite on eucarvone in the presence of sodium ethoxide, gave an oximino-ketone (XXXIX) whose dioxime was the same as that of XXXVIII. These results were taken by Corey as proof that eucarvone, in some if its reactions, behaves as the carenone, X, and although no evidence of its presence in appreciable quantity could be obtained from the ultra-violet spectrum, a deuteration indicated three replaceable hydrogen atoms. The later paper [36] describes the preparation of the enol-acetate of eucarvone (XL) by the reaction of acetic anhydride on the sodioketone. It was shown to retain the triene system, by the use of the new technique of nuclear magnetic resonance, backed up by its ultra-violet and infra-red absorption, although ozonolysis yielded a large quantity of cis caronic acid. Methylation of XL gave, somewhat surprisingly, the bis gem-dimethyl ketone, XLI, by reversion to the carane skeleton. The nature of XLI was confirmed by its nuclear magnetic resonance (N.M.R.) spectrum and its ozonolysis to caronic acid. Reduction of eucarvone with sodium borohydride gave eucarvol (XLII) which dehydrated to the triene, XLIII. Rupe's triene[29] (XXXI) was also prepared and its structure verified.

In a full report, just published[68,69], Corey and his co-workers describe, in addition to the above results, the preparation of other enol esters of eucarvone, which exist in the monocyclic form. Benzylidene-eucarvone is probably a carene derivative, while the bisbenzylidene compound can best be formulated as the bicyclic ether, XLIV. An attempt to prepare the carenone isomer, X, of eucarvone by the action of acetic acid on sodio-eucarvone was without success.

A catalene model of eucarvone showed that the gem-dimethyl group exerts a considerable blocking effect on the methylene group, rendering attack by the reagent difficult. The inertness of this α-position to chemical attack is amply borne out by the later investigations, and seems to be a feature common to the eucarvone series. The accepted mechanism of formation of eucarvone through the carenone (X) as intermediate, suggests that the energy barrier between these two molecules is sufficiently low to allow eucarvone to react in this form, making available an active and unhindered methylene group at which oxidation takes place. The fact that the oxidation does not proceed extensively beyond the hydroxylation stage, is probably due to the large quantity of reagent destroyed by complex formation, again a common feature in the eucarvone series.

The crude oxidation products were distilled in an attempt to purify them, but a partial dehydration of XXXVII occured, as evidenced by the appearance of water in the distillate. Extraction with alkali proved the presence of phenols formed by this dehydration. A phenylurethane was obtained from this fraction which did not, however, appear to be pure, since recrystallisation tended to lower the melting point. On heating with iodine, the phenolic fraction became viscous, and from the products, 2'-hydroxy-2:4:4:8:3'-pentamethylflavan (XLV) was isolated in rather low yield. This compound was previously obtained in like manner by Baker, Curtis and McOmie[40], and by an earlier worker[41], from 2-methyl-6-*iso*propenylphenol (XLVI). Admixture with a genuine sample, kindly supplied by Professor Wilson Baker, failed to lower the melting point, the acetyl derivatives being likewise identical.

The formation of XLVI by dehydration is conceivable via the mechanism depicted below, the alternative rearrangement of the intermediate cation to give carvacrol (IV), being less favourable. On hydrogenation, the phenolic product absorbed 0.9 mole of hydrogen, to give what was assumed to be essentially 2-methyl-6-isopropylphenol (XLVII). A phenylurethane, seemingly quite pure, and



different from carvacrol phenylurethane, was prepared, but on attempting to form the phenoxyacetic acid, a product was isolated which was quite different from the derivative of XLVII previously described[44,45,70]. This acid was not carvacryloxyacetic acid, while its analysis figures, best represented by $C_{12}H_{12}O_4$, indicate that an extra oxygen atom had in some way entered the molecule. While the nature of this derivative remains obscure, the refractive indices of both phenols (XLVI, XLVII) are in good agreement with those reported by Guillaumin[45] and by Carpenter and Easter[70]. The infra-red spectra of the original phenolic fraction and its reduction product are compatible with 1:2:3 substitution, but the additional presence of other substitution patterns cannot be discounted. The removal of the olefinic double bond is well illustrated by the two spectra.

Dehydration of the hydroxyketone (XXXVII) by the boric acid technique[42,43] also led to a phenolic product. Its phenylurethane melted at a higher temperature than that of the thermal dehydration product, but on admixture, no depression was observed. The analysis figures for this derivative were unsatisfactory, due, presumably, to the presence of some impurity which could not satisfactorily be removed by recrystallisation. Hydrogenation of the phenolic product took place readily, 1.0 mole of hydrogen being absorbed, but lack of material prevented a comparison of the phenylurethane of the product with that previously obtained. Heating with a trace of iodine gave a resin, and a small quantity of the flavan, XLV, was isolated therefrom.

Thus, although the presence of 2-methyl-6-_iso_propenylphenol, probably as the major constituent, amongst the dehydration products of XXXVII, has been virtually proved, it is unlikely that this is the sole product. Other phenols were almost certainly present, but shortage of material prevented any further investigation into their nature.

The non-phenolic distillation products were separated into two main fractions, together with a small forerun, consisting of eucarvone and unidentified, low molecular weight products. The first major fraction was unchanged eucarvone, while the second separated on standing into a solid and a liquid component, the former being identical with the diketone, XXXVIII. The liquid was evidently a mixture of mono- and di-oxygenated components as indicated by the analysis figures and the infra-red spectrum, which showed the presence of a conjugated carbonyl group, one or more double bonds, a quantity of a hydroxy-compound, and possibly aromatic impurities. The ultra-violet spectrum, also clearly that of a mixture had a maximum at 2,480A^{o} typical of a O=C-C=C-C=O system. A bis-2:4-dinitrophenylhydrazone was prepared whose light absorption, (λmax.4050A^{o}), verified its conjugated nature. The somewhat high figure for the absorption maximum of the liquid could perhaps be caused by the presence of an aldehyde group, and treatment with dimedone, did in fact give a somewhat indefinite derivative. The routine tests for an aldehyde, although positive, are not significant, since eucarvone itself, and most of its derivatives, reduce both Fehling's solution and ammoniacal silver nitrate.

Since cis caronic acid was the only isolable product from permanganate oxidation, the carenone aldehyde structure, XLVIII, is postulated as the dione component of the high boiling fraction although the evidence is insufficient for its definite identification. A hydrogenation experiment was marred by the presence of residual selenium, uptake being, in consequence, exceedingly slow: 1.9 mole hydrogen were eventually taken up, but this figure could easily be explained by the break-down of a cyclopropane ring, or by partial reduction of an aldehyde group, during the protracted period. The analysis figures for the hydrogenation product come close to those for a formula of $C_{10}H_{16}O$, but the presence of a dione component was shown by the preparation of a bis-2:4-dinitrophenylhydrazone whose light absorption, (λmax. 3,590A^{o}), indicated that no conjugation now existed between the carbonyl groups, and thus they cannot be adjacent to one another, which is in agreement with the lack of reaction shown towards periodic acid. An attempt to obtain an acid product by silver oxide oxidation was abortive, since although a reaction occured, no workable product was isolable.

The reaction between eucarvone and selenium dioxide is therefore not along the normal lines. It leads instead to the carenolone, XXXVII, together with a much smaller quantity of the corresponding dione, XXXVIII, and other unidentified products, including possibly the keto-aldehyde, XLVIII.

The nitrosation of eucarvone, were it to proceed normally, should give an α-oximinoketone, hydrolysable to the desired α-diketone, XLIV. A low yield of an oximino compound was in fact obtained by reacting I with amyl nitrite in ether saturated with hydrogen chloride. The parent diketone, prepared from the oxime by warming with formalin and hydrochloric acid, was found to be identical with XXXVIII as obtained from the selenium dioxide experiment. Corey's papers[35,68] also describe the preparation of oximinoeucarvone (XXXIX) and its identification as the monoxime of XXXVIII.

The direct preparation of the α-diketone, XLIV, from eucarvone being fruitless, attention was now turned to the partially hydrogenated analogue, α-dihydroeucarvone (XII), which, were it to react normally with selenium dioxide would give the α-diketone, XLIX, from which XLIV could probably be obtained by an indirect dehydrogenation. The oxidation, in fact, gave two isomeric liquids of empyrical formula, $C_{10}H_{16}O_2$, differing widely in boiling point. Both were hydroxyketones, forming crystalline phenylurethanes.

The low-boiling isomer was non-conjugated, since no major ultra-violet maximum was present, although micro-hydrogenation indicated the presence of one double bond. The infra-red spectrum clearly demonstrated the hydroxyl group, probably intramolecularly bonded, (3,460 cm.$^{-1}$, sharp), the non-conjugated carbonyl group, the gem-dimethyl group, and a cis CH=CH bond. An interesting feature of this compound is that the true 2:4-dinitrophenylhydrazone could not be obtained, the derivatives varying with the medium in which they were prepared. The analysis figures showed that the hydroxyl group was attacked by the solvent to give an O-acetyl 2:4-dinitrophenylhydrazone from acetic acid solution, an O-methyl from methanol, and an O-ethyl from ethanol. A further complication seemingly occured concurrently, since the absorption maxima of these derivatives, (λmax. 3710-3750A^{o}), are more consistent with those of a conjugated ketone. The hydrogenated ketone (XXV), (cf. Wallach[19], from bromotetrahydroeucarvone), also gave an O-methylated derivative, (λmax. 3,590A$^{\circ}$), but an attempt to form its oxime in order to correlate it to Wallach's compound was unsuccessful on the small scale used.

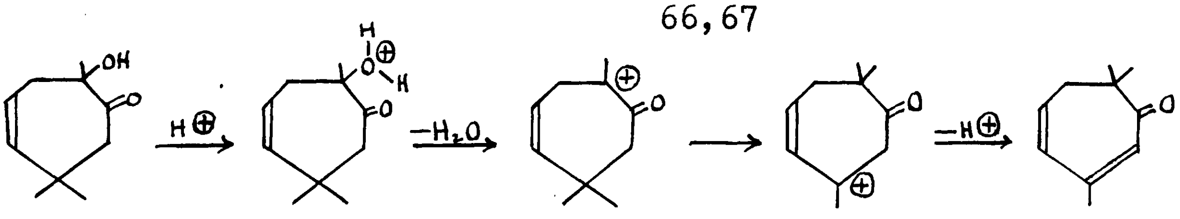
A possible explanation for the conjugated nature of the above derivatives of L, is that they were formed in the acidic medium by an anionotropic replacement rearrangement to the corresponding substituted derivatives of the isomeric hydroxyketone, LVI. In an attempt to confirm this the 2:4-dinitrophenylhydrazone of LVI was acetylated with acetic anhydride, but the product was different from the acetylated derivative mentioned above, although the absorption maximum, (λmax. 3,735A$^{\circ}$), is very similar. In a further experiment, L was treated with acetyl chloride and the product converted to 2:4-dinitrophenylhydrazone, which yielded two compounds on chromatography. The first consisted of the above ethylated derivative, formed presumably by interaction with the reaction solvent, while the second, in much smaller quantity, was different from both the above acetylated derivatives, but could not be the true O-acetyl 2:4-dinitrophenylhydrazone of L, since its absorption maximum, (λmax. 3,835), is obviously that of a conjugated ketone. Too much reliance cannot be placed on these results since molecular rearrangements may well have occured, and the compound obtained from LVI 2:4-dinitrophenylhydrazone could have been acetylated on either the O or the N atom, or both.

The free ketone consumed one mole of periodic acid, typical of an acyloin, but did not reduce bismuth oxide in acetic acid[46,47], which is regarded as a specific reaction of α-hydroxyketones. This can best be explained by assigning the structure L to this ketone, the hydroxy-group being tertiary, and therefore not attacked by the mild oxidant. The alternative structure, LI, is not, of course, disproved, and remains a distinct possibility, especially since α-dihydroeucarvone itself could conceivably have the alternative $\Delta^{3:4}$ structure as discussed in Part III of this thesis (p.134). The postulated structure was verified beyond reasonable doubt by a quantitative oxidation with chromium trioxide in acetic acid: 0.5 mole of oxygen was consumed, by the splitting of the acyloin structure, giving a product (LII?) which was acidic and gave a strong iodoform reaction. Oxidation with alkaline permanganate gave $\alpha\alpha$-dimethylsuccinic acid.

Dehydration of L by pyrolysis with boric acid[42,43], gave rise to an unexpected complication. Instead of the anticipated eucarvone (I), the product obtained was a different compound, isomeric with I. The ultra-violet absorption maximum, (λmax. 2,990A^{o}), is practically identical with that of eucarvone while that of the 2:4-dinitrophenylhydrazone (λmax. 3,960A^{o}) is a little higher. The infrared spectrum indicates a conjugated carbonyl group and a *gem*-dimethyl group, and is sufficiently similar to that of I to rule out any possibility of an entirely different ring system. Both permanganate oxidation and ozonolysis gave αα-dimethylsuccinic acid as the ultimate product, and since no formaldehyde was present amongst the ozonolysis products, the exocyclic methylene analogue, LIII, of eucarvone can no longer be considered. The non-volatile material from the ozonolysis, after hydrogenation, gave an iodoform reaction and a mauve colour with sodium nitroprusside in acetic acid. Further oxidation by means of chromium trioxide in acetic acid yielded αα-dimethylsuccinic acid, as mentioned above. An ozonolysis of eucarvone, which was run concurrently as a control, led to identical results.

The possibility of a ring-contraction to a six-ring aldehyde, such as safranal (LIV) was now considered. No dimedone derivative could be obtained and a Schiff's test was negative. Positive reactions with Fehling's solution and ammoniacal silver nitrate were obtained, but have little significance since eucarvone itself gave these tests. The refractive index of the dehydration product of L is much lower than those recorded for the two known isomeric gem-dimethylcyclohexadienals[48,49], so there seems to be little likelihood of the product having such a structure.

Hydrogen uptake over palladium-charcoal was equivalent to two double bonds per molecule. The reduction product did not form a nitroso derivative and its 2:4-dinitrophenylhydrazone was different from those of tetrahydroeucarvone (XV) and carone (VII), but the ketone displays in its infra-red spectrum, a considerable similarity to that of XV, though its gem-dimethyl peaks are well-defined, those of XV being, unexpectedly, masked. The only feasable explanation for the structure of the dehydration product would seem to lie in some form of transannular rearrangement such as is illustrated below.

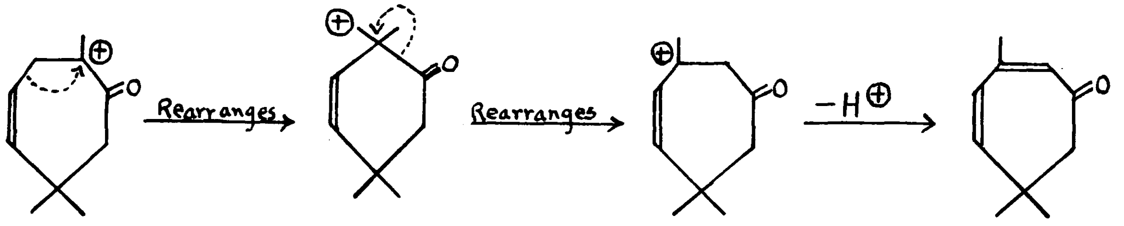


L

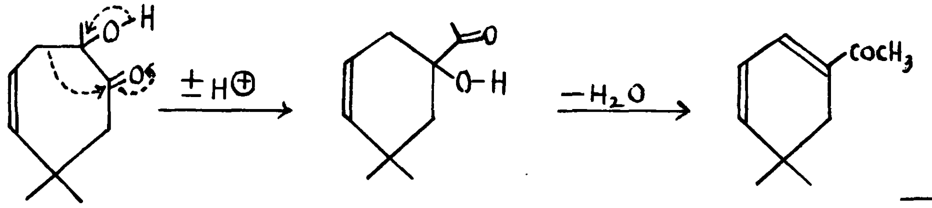
LV

The tetrahydro-derivative of perhaps the most likely product, LV, has been synthesised by Eschenmeser, Schinz, Fischer and Colonge[50], but a specimen of the 2:4-dinitrophenylhydrazone of their ketone, which was kindly supplied for the purpose, depressed the melting point of the corresponding derivative of the above reduction product.

A further possible product is that from a Wagner-Meerwein type of rearrangement, as shown below. Unfortunately, neither the unsaturated ketone, LVa, nor its tetrahydro-derivative are known, so that this possibility could only be explored by a synthesis of the tetrahydro-ketone involved. Another possible rearrangement process, outlined below, was suggested by Professor Barton, by analogy with



LVa



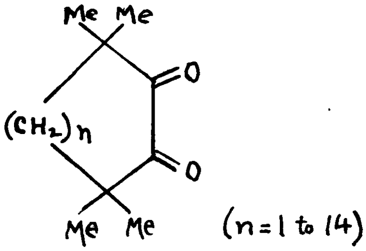
LV b

the D-homosteroid ring enlargement. The product, LVb, would, however, be expected to give an iodoform reaction, whereas the dehydration product did not. The problem, therefore, remains unsolved, and a series of larger scale degradations may be necessary before the structure of the dehydration product of L can be fully designated.

The higher-boiling product from the selenium dioxide oxidation of α-dihydroeucarvone has the absorption spectrum, (λmax. 2,370A^{o}), of a conjugated ketone. A somewhat unstable 2:4-dinitrophenylhydrazone, decomposing on neutralised alumina, and a phenylurethane were obtained. Microhydrogenation verified the presence of a double bond, while the infra-red spectrum, although lacking in any unambiguous double bond absorption, showed plainly the presence of the hydroxy-group and the conjugated keto-group. Neither periodic acid nor bismuth oxide were appreciably attacked, but oxidation by manganese dioxide in petroleum ether, or by chromium trioxide in acetic acid, led to the same liquid diketone. The parent hydroxy-compound must therefore be allylic in nature[38,39], this being in agreement with the light absorption of the dione (λmax. 2,440A^{o}) and its bis-2:4-dinitrophenylhydrazone (λmax. 3,970A^{o}). The above facts strongly suggest the hydroxylated β-dihydroeucarvone structure, LVI, for the compound, the dione being LVII. The formation of LVI would presumably be due to an initial isomerism of α-dihydroeucarvone to the β-isomer, under the acidic conditions of the oxidation.

The product of dehydration of LVI was eucarvone, as anticipated, being identical with I in its derivatives and its infra-red spectrum, but some doubt on the validity of the assumed structure for LVI was cast by a series of oxidation experiments. Permanganate, chromic acid and nitric acid all gave αα-dimethylsuccinic acid as the only major product, instead of ββ-dimethylglutaric acid as might be expected. In an attempt to settle this uncertainty, the hydroxyketone (LVI) was hydrogenated over palladium-charcoal. Uptake was slow due to the presence of residual selenium and ceased finally at a value corresponding to 1.1 double bonds. The crude product was oxidised with chromium trioxide in acetic acid, and converted to a bis-2:4-dinitrophenylhydrazone. The ultra-violet spectrum of this latter (λmax. 3,590A^{o}) showed the expected drop in wavelength due to the rupture of the conjugation, eliminating the α-diketone formula, LVIII, as a possible structure for the original dione.

To obtain comparitive data for the above argument, the ultra-violet spectra of the three isomeric cyclohexanediones were measured. Whereas all three have maxima between 3,480 and 3,590A°, the spectrum of the 1:2-isomer exhibits a subsidiary maximum at 3,920A°, indicating that a proportion of the molecules are oriented so as to allow the conjugative effect to occur. Di-acetyl bis-2:4-dinitrophenylhydrazone, being relatively unhindered, displays a single maximum at 3,880A°. The cycloheptane-1:2-dione derivative, as reported by Cook, Raphael and Scott[72], has a single maximum at 3,520A° and only an inflexion at 3,900A°, showing that the molecule is even less favourable to conjugation than the six-membered analogue. These results show an interesting similarity to those of Leonard and Mader[73], who studied the series of 1:2-diketones represented by the general formula below.



(n = 1 to 14)

They were able to correlate the shift in the high wavelength absorption maximum with the angle between the planes of the two carbonyl groups. As this angle increased from 0° in the five-membered ring, (n=1), to about 90° in the seven-membered ring compound, the absorption maximum decreased in wavelength due to resonance inhibition, then as the angle tended towards 180° in the larger rings, the wavelength again increased as the resonance became less inhibited.

In order to obtain further spectral evidence, an attempt was made to use the absorption spectra of phenylurethanes as a source of information on the structure of the parent hydroxy-compounds. Measurements were made on the derivatives of both the above oxidation products, (L and LVI), of the carenolone (XXXVII), of eucarvol (Section III of this thesis) and of cyclohexanol. Subtraction of the curve of the cyclohexanol derivative from that of XXXVII failed to give the curve of XXXVII itself, due to the exceedingly intense absorption of the substituted aromatic system, (ϵ = 16,000 for cyclohexanol phenylurethane), thus invalidating the method. It was, however, noted that the intensity of absorption of the phenylurethane of the tertiary alcohol, L, is very much lower, (ϵ = 6,400), than that of the higher-boiling oxidation product, LVI, (ϵ = 28,000), and those of the other derivatives examined. This is presumably due to a purely steric effect, the adjacent methyl group blocking the auxochromic-OCONH-group responsible for the greatly enhanced absorption intensity.

The ultimate proof of the identity of the higher boiling hydroxyketone with LVI, came from an ozonolysis. The hydrogenated ozonide gave an iodoform reaction, and was oxidised further by chromium trioxide in acetic acid to ββ-dimethylglutaric acid.

Both products from selenium dioxide oxidation of α-dihydroeucarvone (XII) are thus characterised, neither being the desired dione, XLIX, since the reagent acts preferentially on the tertiary hydrogen, rather than on the methylene group. The second product is formed by initial prototropic rearrangement, and subsequent attack on the now activated γ position, rather than on the somewhat hindered α-methylene group. The great difference in volatility between L and LVI, is readily explicable by the difference in hydrogen-bonding, that of L being intra-molecular and that of LVI inter-molecular.

A second possible source of the desired diketone, XLIX, lay in the nitroso-α-dihydroeucarvone previously described by Baeyer[5,8]. It was prepared in low yield by condensation of XII with amyl nitrite in sodium ethoxide solution. The structure of this derivative was expected to be either LIX or LX depending on whether substitution occurs preferentially at the tertiary position. Two further structures, LXI and LXII also had to be considered, lest double bond migration be possible under the conditions of the experiment. The infra-red spectrum of the nitrosation product showed strong absorption at 3,555 and 3,260 $cm.^{-1}$ due to an NO-H group, thereby eliminating structure LIX. The ultra-violet spectrum had a single maximum at 2,770A^{o}, explicable only by means of a completely conjugated system such as in LXI or LXII. Conversion of the oxime to a liquid dione, $C_{10}H_{14}O_2$, occured readily on warming with formalin and dilute acid. The ultra-violet spectra of this dione, (λmax. 2445A^{o}), and of its <u>bis</u>-2:4-dinitrophenylhydrazone, (λmax. 4110A^{o}), provide fairly conclusive evidence for the presence of a conjugated O=C-C=C-C=O system in the molecule. Two mono-2:4-dinitrophenylhydrazones were also obtained, neither of which, nor the above <u>bis</u> derivative, were the same as the corresponding derivatives of the isomeric dione, LVII. The infra-red spectrum of the dione showed a conjugated carbonyl absorption, (1674 $cm.^{-1}$, v.s.), and a double bond stretching peak at 1613 $cm.^{-1}$. The <u>gem</u>-dimethyl peaks, if present, were very weak and indistinct, a fact previously noted in the spectrum of the parent oximino-compound.

Semi-micro hydrogenation proved the presence of one double bond, the product forming a bis-2:4-dinitrophenylhydrazone whose ultra-violet absorption (λmax. 3,600A^o) indicated the removal of the conjugation. The unsaturated dione formed neither a quinoxaline nor a dimedone derivative, was unaffected by periodic acid, did not dissolve in sodium hydroxide solution and gave no colour with ferric chloride. The dione therefore is unlikely to be based on any of the above mentioned oximino-compounds, since the above tests show that it is not an α-diketone, while its non-identity with LVII eliminates the structure, LXII for the oximino compound, so long as no rearrangement occured during hydrolysis. Neither does it seem to be a β-diketone from its insolubility in alkali and its failure to give a colour with ferric chloride. Since no dimedone derivative was obtained, it is also unlikely to be a keto-aldehyde. A positive iodoform test and a colour with sodium nitroprusside were given both by the dione and by the parent oximino compound, in contra-distinction to eucarvone and other members of the series, suggesting the presence of a CH_3CO- group.

The main product of a permanganate oxidation was a crystalline acid, m.p. 108-111°, which was shown to be different from αα-dimethylsuccinic acid, methylsuccinic acid, *iso*propylsuccinic acid and ββ-dimethylglutaric acid by admixture with authentic specimens. Analysis figures showed the acid to be impure and the presence of a keto-acid could not be discounted, although iodoform and nitroprusside tests were negative. The structure of nitroso-α-dihydrydroeucarvone, therefore, still remains unknown, but it seems certain from the above work, that its formation must involve a molecular rearrangement, probably accompanied by ring contraction. The positive iodoform test is probably due to an exocyclic CH_3CO- grouping in the derived diketone, but further degradative work on a larger scale would be necessary to settle the structures conclusively.

In order to complete the series of selenium dioxide oxidations, runs were made on β-dihydroeucarvone and tetrahydroeucarvone. In neither case were satisfactory results obtained.

β-dihydroeucarvone (XXIV) might well be expected to yield the same product, LVI, as did the α-isomer (XII). In working up the reaction mixture a recently announced technique[51] of freeing the product of selenium, was adopted with slight modification. Refluxing with mercury, instead of silver powder[52] as before, gave a cleaner product, although still not entirely selenium free. A preponderance of starting material was unexpectedly recovered, leaving a higher boiling, complex mixture which failed to yield a pure 2:4-dinitrophenylhydrazone. Treatment with phenyl isocyanate gave a small quantity of the phenylurethane of LVI, although its formation could be explained by the presence of a trace of α-dihydroeucarvone in the starting material, as previously indicated by its infra-red spectrum (Part III of this thesis, p. 150).

The oxidation of tetrahydroeucarvone, also gave a complexity of products which could not be satisfactorily separated, either by distillation, or by chromatography. The only identifiable fraction was the most volatile, consisting of impure α-dihydroeucarvone, (XII), characterised by means of its 2:4-dinitrophenylhydrazone. A trace of the β-isomer (XXIV) was also probably present. Since none of XII could be detected by chromatography of the 2:4-dinitrophenylhydrazone of the starting material, it must have arisen during the oxidation, or the subsequent working up. This is remarkable, since any dehydrogenation would normally be expected to occur in the α-β position to give XXIV, which would also be formed by dehydration of any α-hydroxyketone formed in the oxidation. Attempts to obtain crystalline derivatives from the residual material were, almost without exception, unsuccessful and no phenylurethanes were obtainable. Periodate estimation gave a variety of results, the highest uptake being 0.49 mole.

Hence, from a preparative point of view, oxidation of either tetrahydroeucarvone or β-dihydroeucarvone with selenium dioxide is useless, in contrast to the oxidations of eucarvone and α-dihydroeucarvone, which give well-defined products.

As a precursor to a final attempt to obtain the α-diketone, XLIV, from eucarvone, the enol-acetate, XL, was prepared by treatment with isopropenyl acetate. An excellent yield was obtained of a material, identical in properties with that recently described by Corey[36,68]. It was converted to crude α-iodoeucarvone (LXIII?) by reaction with N-iodosuccinimide in dioxan, in accordance with the useful new technique of Djerassi and his co-workers[53]. Since the crude product decomposed on attempted distillation, it was treated with aqueous ferric chloride in an attempt to obtain the dione in one step[54]. The only isolable product, however, was probably aromatic in nature, and lacking in ketonic properties. The residue consisted of intractable resins.

An alternative route to XLIV is via the acetoxyketone, LXIV, made from the crude iodoketone. Refluxing LXIII with potassium acetate in acetic acid, gave rise to a large quantity of tars, together with some volatile material, isomeric with LXIII, probably aromatic in nature. A modification of this preparation, whereby the iodide is reacted with tetraethylammonium acetate[55], as described in Part III of this thesis, (pp.140,163), was envisaged, but the time available did not permit its accomplishment. It is hoped to attempt this step at a later date.

It is clear from the above discourse, that much work still remains to be done, before all the structural problems involved in the identification of the eucarvone derivatives described can be completed, and in addition, many of the compounds obtained by the earlier workers in their studies still await identification. Nevertheless, enough has been accomplished so far, to show that the chemistry of eucarvone and its elaboration products is both complex and intriguing, because of its seemingly unpredictable nature.

EXPERIMENTAL

Eucarvone (I)

Carvone was treated with a 40% solution of HBr in acetic acid, and the resulting crude hydrobromide refluxed with methanolic KOH, as described by Wallach[11,15]. The product was redistilled to give pure XII, (65% from carvone), b.p. 82-84°/8 mm., η_D^{25} 1.5065. Light absorption[28,35] in methanol, λmax. 3,000A°, (log ϵ, 3.82). Infra-red spectrum, illustrated (p. 171).

2:4-Dinitrophenylhydrazone[28], by adding I to reagent in ethanol and conc. HCl. Purified by chromatography on neutralised alumina, eluting with benzene. Red plates from ethanol/ethyl acetate, m.p. 151-152°. Light absorption in chloroform, λmax. 3,880A°, (log ϵ, 4.44).

Selenium dioxide oxidation of eucarvone (I). I (30 gm.) and selenium dioxide (22.2 gm.) in ethanol (550 ml.) and water (20 ml.) were refluxed for 60 hrs. Solvent was removed by distillation until about 100 ml. remained, then the solution filtered from deposited selenium and poured into N H_2SO_4 (1,000 ml.). The selenium weighed only a fraction of the theoretical, but refluxing during the final 24 hrs. had failed to increase the quantity. The acidified mixture was extracted several times with chloroform, and the extracts washed, dried, and evaporated. The residue was taken up in benzene (250 ml.) and refluxed for 18 hrs. with silver powder[52] (30 gm.; prepared by adding the theoretical quantity of zinc dust to 30% aqueous silver nitrate, standing for 2 hrs., filtering and washing free from oxide with ammonium hydroxide). Filtration and removal of the benzene gave a viscous, foul-smelling, red oil, which solidified on standing. A small portion, after charcoal treatment, and several crystallisations from pet. ether (b.p. 60-80°) and from water, gave pure car-2-en-4-olone[35,68] (XXXVII) as elongated prisms, m.p. 85-86°. Light absorption in methanol, λ max. 2,290A°, (log ϵ, 4.04). (Found: C, 72.3; H, 8.4; $C_{10}H_{14}O_2$ requires: C, 72.25; H, 8.5%). Infra-red spectrum, illustrated (p.173). No stable 2:4-dinitrophenylhydrazone could be obtained, only tars being formed.

Phenylurethane, prepared by refluxing XXXVII with excess phenyl isocyanate in pet. ether (b.p. 80-100°) for 2 hrs. Colourless, rectangular prisms from pet. ether (b.p. 80-100°), m.p. 157°[68]. Light absorption in methanol, λmax. 2,340A°, (log ϵ, 4.47). (Found: C, 71.5; H, 6.7; $C_{17}H_{19}NO_3$ requires: C, 71.55; H, 6.7%).

The bulk of the crude product was distilled and found to be heterogeneous; b.p. 40-180°/0.1 mm., (2.3 gm.). A quantity of non-volatile, selenium containing residue remained in the flask. Dehydration took place as the distillation proceeded, water collecting in the liquid-air trap. Pet. ether, (b.p. 40-60°), (40 ml.) was added to the distillate, and the lemon-yellow crystals (4.7 gm.) filtered off after standing at -10° for 7 days. Colourless prisms from pet. ether (b.p. 60-80°), m.p. 85-86°, identical with the XXXVII isolated before distillation.

The residual solution was extracted several times with 10N sodium hydroxide, and the alkaline extracts acidified with conc. HCl and extracted with ether. The ether solution was washed with sodium bicarbonate solution and with water, dried, and freed from solvent. Fractional distillation gave a colourless phenol (5.9 gm.), b.p. 86-87°/10 mm., n^{25} 1.5392[41,45,57], together with some high-boiling, impure, material. Light absorption in methanol, λmax. 2,780A°, (log.ϵ , 3.28). (Found: C, 80.4; H, 7.9; $C_{10}H_{12}O$ requires: C, 81.0; H, 8.2%) Infra-red spectrum of a thin film showed peaks at 3,500 (s.), 3,400 (m.), (O-H str.); 3,050 (m.), (=C-H str.); 1,940, 1,840, 1,695 (w.) (1:2:3 subn.?); 1,630 (m.), ($C=CH_2$ str.); 1,595 (m.s.), (C=C str.); 910 $cm.^{-1}$ (s.), ($C=CH_2$ def.). A greenish-brown colour was given with alcoholic ferric chloride, an orange-red with conc. H_2SO_4, and a mauve with aqueous sodium hydroxide and chloroform.

Phenylurethane, colourless rosettes from pet. ether (b.p. 80-100°), m.p. 125-126°. Further recrystallisation tended to lower the melting point. (Found: C, 76.1; H, 6.2; N, 5.8; $C_{12}H_{17}NO_2$ requires: C, 76.4; H, 6.4; N, 5.25%.)

The solution of non-phenolic material was washed, dried, freed from solvent and fractionated. After a small forerun, (0.9 gm.) (b.p. 65-75°/8 mm., n_D^{25} 1.4872-1.5056), two major fractions were collected. The first, a very pale yellow oil (1.9 gm.), b.p. 80-82°/8 mm., n_D^{25} 1.5085, consisted of unchanged eucarvone. It formed a 2:4-dinitrophenylhydrazone, red plates from ethanol/ethyl acetate, m.p. 153-154°, undepressed by admixture with an authentic sample, and an oxime, colourless plates from aqueous ethanol, m.p. 104-105°, mixed with eucarvoxine, m.p. 104-105°.

The second fraction, a pale yellow oil, (3.1 gm.), b.p. 115-120°/9 mm., n_D^{25} 1.5103-1.5140, partially solidified on standing. It was cooled to -30° in its own volume of pet. ether (b.p. 40-60°) for 60 mins., and filtered. The solid recrystallised from pet. ether (b.p. 80-100°) as massive yellow prisms, (1.2 gm.), m.p. 91-92°, mixed with

XXXVIII (p. 81), m.p. 91-92^o. The residual liquid was redistilled, giving a pale yellow oil (1.7 gm.), b.p. 112-115^o/9 mm., η_D^{25} 1.5095. Light absorption in methanol, λ max. 2,480A^o, (log.ϵ, 3.70), irregular curve. (Found: C, 77.7; H, 8.6%.) Infra-red spectrum of a thin film showed peaks at 3,400 (m.), (O-H str.); 3,070 (w.), (=C-H str.); 1,660 (s.), (conj. C=O str.); 1,620 (w.), (C=C str.); 1,408, 1,392 cm.$^{-1}$ (m.), ($C<^{Me}_{Me}$, def.); and also at 1,580, 1,515 cm.$^{-1}$ (m.), (aromatic?). Fehling's and silver mirror tests were given, but the colour was not restored to Schiff's reagent. Iodoform and sodium nitroprusside[56] tests were negative. No quinoxaline derivative was obtained by refluxing with o-phenylenediamine in ethanol for 60 mins. Shaking overnight with dimedone in aqueous methanol gave a small quantity of a solid, recrystallising from aqueous ethanol as a buff, amorphous powder, m.p. 89-91^o. Periodate estimation gave a value of 0.44 moles consumed during 2 days.

2:4-Dinitrophenylhydrazones. Treatment of the above liquid with Brady's reagent, gave a mixture of products, consisting chiefly of a bis-derivative, isolated by removing all benzene and ethyl acetate soluble material. Scarlet prisms from nitrobenzene (at 150-160^o), m.p. 309^o (dec.), mixed with the derivative of LVII, m.p. 265-270° (dec.). Light absorption in chloroform, λmax. 4050A°, (log. ϵ, 4.59). (Found: C, 50.95; H, 3.8; N, 21.49; $C_{22}H_{20}N_8O_8$ requires: C, 50.4; H, 3.85; N, 21.35%).

Attempts to obtain pure materials from the forerun of the above distillation were unsuccessful. The 2:4-dinitrophenylhydrazones were chromatographed, yielding chiefly the derivative of I, together with a yellow, amorphous, benzene insoluble product, m.p. 196° (dec.).

Hydrogenations

(a) The phenolic fraction (0.9648 gm.) in ethanol (20 ml.) was hydrogenated over 10% palladium-charcoal (0.4gm.): 638 ml. at 15° and 764 mm. were absorbed during 25 mins., corresponding to 0.90 double bonds. After filtering from the catalyst, which was washed with hot ethanol, the solvent was removed. Distillation gave a colourless oil, (0.89 gm.; 91%), b.p. 94-98°/10 mm., n_D^{25} 1.5212[45,57]. Light absorption in methanol, λmax. 2,730A°, (log ϵ, 3.22). (Found: C, 80.25; H, 9.5; $C_{10}H_{14}O$ requires: C, 79.95; H, 9.4%.) Infra-red spectrum of a thin film showed peaks at 3,490(m.s.), (O-H str.); 3,030 (w.), (=CH str.); 1,595 (m.), (C=C str.), 848 (w.), 819 (m.), 777 (m.s.), 745 cm.$^{-1}$ (s.), (C-H out of plane, 3 or more adjacent H atoms). A yellow-green colour was given with alcoholic ferric chloride, an orange-yellow with conc. H_2SO_4 and a mauve with chloroform and aqueous sodium hydroxide.

Phenylurethane, colourless needles from pet. ether (b.p. 80-100°), m.p. 159°, mixed with carvacrol phenylurethane, (feathery needles from the same solvent, m.p. 136-137°), m.p. 115-124°. (Found: C, 75.8; H, 6.75; N, 5.4; $C_{17}H_{19}NO_2$ requires : C, 75.8; H, 7.1: N, 5.2%.)

Phenoxyacetic acid(?), colourless needles from benzene/pet. ether (b.p. 60-80°), feathery needles from water, m.p. 15 0-151°, mixed with carvacryloxy acetic acid, (needles from benzene/pet. ether, m.p. 141-143°), m.p. 112-115°. (Found: C, 65.85; H, 5.1; $C_{12}H_{16}O_3$ requires: C, 69.2; H, 7.75; $C_{12}H_{16}O_4$ requires : C, 65.45; H, 5.5%.)

(b) The eucarvone fraction (0.455 gm.) in ethanol (10 ml.) was hydrogenated over palladium-charcoal (0.2 gm.), absorption being equivalent to 1.90 double bonds. Working up as above, and distillation, gave a colourless oil, b.p. 87-90°/15 mm., n_D^{25} 1.4572, yielding a 2:4-dinitrophenylhydrazone, orange prisms from pet. ether (b.p. 80-100°) m.p. 134-136°, mixed with the derivative of tetrahydroeucarvone, m.p. 135-137°.

(c) <u>The high boiling fraction</u> (0.3936 gm.) in ethanol (7 ml.) was hydrogenated over 10% palladium-charcoal (0.25 gm.). Absorption was very slow, fresh catalyst being added from time to time until no further uptake was recorded. In all, 112 ml. at 18.5° and 745 mm. were absorbed, equivalent to 1.91 double bonds. Working up as before gave a colourless, mobile liquid, b.p. 110-112°/10 mm., η_D^{25} 1.4810. (Found: C, 78.65; H, 10.55%.) Infra-red spectrum of a thin film showed peaks at 3,400 (m.s.), (O-H str.); 1,700 (v.s.), (C=O str.); 1408, 1394 (s.), ($\mathrm{C}{<}^{\mathrm{Me}}_{\mathrm{Me}}$ def.); 1,137, 1,115 (s.), ($\mathrm{C}{<}^{\mathrm{Me}}_{\mathrm{Me}}$ skel.), 1070 cm.$^{-1}$ (s.), (C-OH str.?) and also at 1,612, 1,588, 1,512 cm.$^{-1}$ (m.s.), (aromatic?). Fehling's and silver mirror tests were positive, while a periodate estimation showed a consumption of only 0.105 mole during 48 hrs.

Treatment with silver nitrate in aqueous methanol, followed by dropwise addition of 2N sodium hydroxide[58], caused immediate blackening of the precipitated silver oxide. After shaking for 18 hrs., filtering, and washing the solids with hot water, the solution was acidified, neutralised with potassium carbonate and extracted with chloroform. The aqueous solution was re-acidified and extracted with ether. These extracts failed to yield a crystalline product, only a sticky intractable material being isolated.

2:4-Dinitrophenylhydrazones. Treatment with Brady's solution gave an inseparable mixture of mono-derivatives, but on warming with 2:4-dinitrophenylhydrazine in 90% acetic acid, a bis-derivative was slowly deposited. A better yield of this latter was obtained by refluxing with the reagent in ethanol and sulphuric acid for 60 mins.; small orange-yellow prisms from xylene/nitromethane (10:1), m.p. 244 - 245° (dec.), mixed with the corresponding derivative from the hydrogenation of LVII, m.p. 240-242° (dec.). Light absorption in chloroform, λ max. 3,580A°, (log ϵ, 4.66). (Found: C, 50.4; H, 4.0; N, 21.05; $C_{22}H_{24}N_8O_8$ requires: C, 50.0; H, 4.6; N, 21.2%.)

Dimerisation of the phenolic fraction[40]

The phenolic dehydration product (0.5 gm.) and iodine (5 mg.) were heated together at 60° for 30 mins., taken up in ether and washed with sat. sodium bisulphite, and with water. After drying and removal of the solvent, the residual viscous material was distilled, yielding a forerun of volatile phenols and a pale yellow resin, b.p. 150-160°/ 2×10^{-5} mm. Prolonged steam distillation gave a purer product, solidifying on standing. Crystallisation from pet. ether (b.p. 60-80°) gave colourless prisms, m.p. 68-70°, mixed with an authentic sample of 2'-hydroxy-2:4:4:8:3'-pentamethylflavan, m.p. 69-70°.

Acetyl derivative. By refluxing the above with acetic anhydride in benzene and a trace of pyridine for 12 hrs., the acetyl derivative was obtained. Plates from aqueous methanol, m.p. 101-102°, mixed with an authentic specimen, m.p. 102°.

Oxidation of higher-boiling ketonic fraction

This material (0.25 gm.) and water (5 ml.) were stirred, and a solution of potassium permanganate (2.0 gm.) in water (30 ml.) was added, while carbon dioxide was passed through the solution. Working up as described in Part III of this thesis (p.155), gave a dark semi-solid which was purified by charcoal treatment in benzene. On cooling, crystals were deposited which were recrystallised from the same solvent giving *cis*-caronic acid as colourless prisms, m.p. 173-176°, (mixed with dimethylmalonic acid, m.p. 155-160°). An attempted micro-sublimation at 160-180° gave an oil, solidifying to a white solid, the anhydride, m.p. 50-54°. No other product could be isolated from the oxidation.

Oxidation of carenolone (XXXVII)

(a) XXXVII (0.1 gm.) and activated manganese dioxide[59] (0.5 gm.) in pet. ether (3 ml.) and acetic acid (0.5 ml.) were shaken for 6 days at room temperature. After filtration and washing the solids with chloroform, the solution was washed with sodium bicarbonate solution, the solvents removed and the residual solid recrystallised from pet. ether (b.p. 60-80°), giving pale yellow prisms (0.086 gm.; 83%) of carenedione (XXXVIII), m.p. 91-92° [35,68].

(b) XXXVII (0.1 gm.) in acetic acid (2 ml.) and water (2 ml.) was added to a 1% solution of chromium trioxide in 50% aqueous acetic acid (4.1 ml.). After standing for 36 hrs., a few drops of ethanol were added to destroy the excess chromic acid. The acetic acid was neutralised with solid sodium carbonate, the solution filtered, and extracted with ether. The extracts were washed, dried, and evaporated, and the residual solid recrystallised from water, and from pet. ether (b.p. 60-80°) to give XXXVIII (0.075 gm.; 73%) as pale yellow prisms, m.p. 92°, mixed with the previous product, m.p. 91-92°. Light absorption in methanol, λ max. 2,400A°, (log ϵ, 4.12). (Found: C, 73.6; H, 7.4; $C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.35%.) Infra-red spectrum of a Nujol mull shows peaks at: 3,015 (w.), (=C-H str.);

1660 (v.s.), (conj. C=O str.); 1376, 1340 (m.s.), ($\mathrm{C}{<}^{\mathrm{Me}}_{\mathrm{Me}}$ def.); 1142, 1130 (m.), ($\mathrm{C}{<}^{\mathrm{Me}}_{\mathrm{Me}}$ skel.); 1,008, 1,000 $\mathrm{cm.}^{-1}$ (m.), ($\triangle$?).

Mono-2:4-dinitrophenylhydrazone, by treatment with Brady's solution, orange-red plates from benzene/ethanol, m.p. 171-173°. (Found: N, 16.2; $C_{16}H_{18}N_4O_5$ requires: N, 16.25%.)

Bis-2:4-dinitrophenylhydrazone, separated slowly from a hot solution of the reagent in 95% acetic acid, but addition of about 30% by volume of Brady's solution caused rapid precipitation. Scarlet needles from nitrobenzene (at 150-160°), m.p. $>$ 360° (chars at 245-255°). Light absorption in chloroform, λ max. 4,080A°, (log ϵ, 4.70). (Found: C, 50.3; H, 3.95; N, 21.25; $C_{22}H_{20}N_8O_8$ requires: C, 50.4; H, 3.85; N, 21.35%.)

Oximinoeucarvone (XXXIX)[35, 68]

Amyl nitrite (12 gm.) in dry ether (70 ml.) was cooled to 0°. Eucarvone (10 gm.) in ether (80 ml.) was added dropwise, with stirring, during 2hrs., while dry HCl was passed into the solution. The stirring and passage of HCl was continued for a further 30 mins., then the flask was stoppered and left at 0° overnight. The yellow hydrochloride was filtered off, dissolved in a little hot water, and treated with saturated sodium bicarbonate to bring the pH to 8. The oxime separated on cooling, and was recrystallised from water to give oximinoeucarvone, (1.3 gm.; 11%) as colourless needles, m.p. 154-155°. (Found: C, 67.0; H, 7.4; N, 8.15%; $C_{10}H_{13}NO_2$ requires: C, 67.0; H, 7.3; N, 7.8%.)

Carenedione(XXXVIII)

Oximinoeucarvone (0.2 gm.), 40% formalin (2 ml.) and 2N HCl (4 ml.) were refluxed for 60 mins., and extracted with chloroform. The extracts were washed, dried, and freed from solvent, giving a dark solid residue which was extracted several times with boiling pet. ether (b.p. 60-80°). The solution was treated with charcoal, and evaporated to small bulk. On cooling, the dione separated, and was recrystallised from the same solvent giving carenedione (0.15 gm.; 80%), m.p. 89-90°, mixed with that previously obtained, m.p. 90-91°.

Dehydration of carenolone

Carenolone (1.0 gm.) and boric acid (0.4 gm.)[42,43] were heated together over a bare flame, and the wet distillate taken up in ether. The ether solution was extracted several times with 5N sodium hydroxide, the extracts acidified and re-extracted with ether. After washing with sodium bicarbonate, drying, and removing the solvent, the residual phenolic oil was distilled to give a colourless liquid, (0.28 gm.; 32%), b.p. 82-84°/8 mm., n_D^{25} 1.5378.

Phenylurethane, colourless needles from pet. ether (b.p. 80-100°), m.p. 148°, (sinters at 143-145°), mixed with derivative of phenols from distillation of selenium dioxide oxidation products, m.p. 135-137°, mixed with carvacrol phenylurethane, m.p. 109-114°.

Dimerisation. The above phenol (0.25 gm.) and iodine (3 mg.) were heated at 60° for 30 mins., and the crude product isolated as before (p. 79). Steam distillation for 2 hrs. and extraction of the distillate with ether, gave, after drying and removal of solvent, a colourless, very viscous oil, which could not be induced to crystallise. Chromatography on alumina, eluting with pet. ether (b.p. 60-80°) gave, after a forerun of oily material, the pure dimer in small quantity as a colourless solid, crystallising from pet. ether (b.p. 40-60°) as colourless prisms, m.p. 68-70°, mixed with 2'-hydroxy-2:4:4:8:3'-pentamethylflavan, m.p. 69-70°.

Semi-micro hydrogenation

The above phenol (33.2 mg.) in ethanol (2 ml.) was hydrogenated over 10% palladium-charcoal. Uptake was rapid, ceasing after 10 mins. 5.05 ml. at 16° and 774 mm. were absorbed, corresponding to 0.97 double bonds.

Selenium dioxide oxidation of α-dihydroeucarvone

The α-dihydroeucarvone (XII) was prepared by lithium aluminium hydride reduction of eucarvone, as described in Part III of this thesis (pp. 145,146).

XII (20 gm.) was refluxed with selenium dioxide (15.2gm.) in ethanol (300 ml.) and water (10 ml.) for 16 hrs. Deposition of selenium was not quantitative, but was not increased by prolonging the reaction period. The crude product was isolated, and partially freed from selenium, as described under the oxidation of eucarvone, (p. 71). The residual viscous red-brown oil was distilled, separating into two distinct fractions; b.p. 75-105°/8 mm., (9.5 gm.; 43%); b.p. 80-110°/0.1 mm., (6.0 gm., 27%). The residue (3.4 gm.) consisted of selenium containing tars. The two products were further purified by fractionation. Neither gave a ferric chloride coloration.

The low-boiling material consisted of <u>3:3:7-trimethyl-</u>

CYCLOhept-4-en-7-olone (L), a colourless, mobile, liquid, b.p. 88-90°/8 mm., n_D^{18} 1.4845. Light absorption in methanol showed only a low peak, (λmax. 3010A°), due to impurities. (Found: C, 71.95; H, 9.25; $C_{10}H_{16}O_2$ requires: C, 71.4; H, 9.6%.) Micro-hydrogenation gave a value of 1.1 double bonds. Infra-red spectrum, illustrated, (p. 174).

Phenylurethane, colourless, elongated prisms, from pet. ether (b.p. 80-100°), m.p. 131°. Light absorption in methanol, λ max. 2,250A°, (log ε, 3.81). (Found: C, 70.9; H, 7.45; $C_{17}H_{21}NO_3$ requires: C, 71.05; H, 7.35%.)

O-Ethyl-2:4-dinitrophenylhydrazone (?), formed by adding to a solution of the reagent in ethanol and sulphuric acid; pale orange plates from ethanol/ethyl acetate, m.p. 150°. Light absorption in chloroform, λ max. 3,750A°, (log ε, 4.43). (Found: C, 57.55; H, 6.35; N, 14.7; $C_{18}H_{24}N_4O_5$ requires: C, 57.45; H, 6.45; N, 14.9%.)

O-Methyl-2:4-dinitrophenylhydrazone (?), formed as above, replacing the ethanol by methanol, pale red tablets from ethanol/ethyl acetate, m.p. 157.5-158°. Light absorption in chloroform, λ max. 3,740A°, (log ε, 4.38). (Found: C, 56.2; H, 6.3; N, 15.6; $C_{17}H_{22}N_4O_5$ requires: C, 56.35; H, 6.1; N, 15.45%.) The same derivative was obtained, in less pure condition, by using Brady's solution.

O-Acetyl-2:4-dinitrophenylhydrazone (?), formed by heating with the reagent in acetic acid at 100° for 60 mins., and isolated by pouring into water; yellow plates from ethanol/ethyl acetate, m.p. 179-180°. Light absorption in chloroform, λmax. 3,710A°, (log ϵ, 4.45). (Found: C, 55.1; H, 5.85; N, 14.6; $C_{18}H_{22}N_4O_6$ requires: C, 55.4; H, 5.7; N, 14.35%.) By heating at 140° for 2 hrs. or by crystallisation from a hot solvent, this compound was obtained in a red form, identical in its light absorption with the yellow form. When crystallised from a cold solvent it reverted to the yellow modification. During the determination of its melting point the yellow crystals gradually became red.

Attempts to form the true 2:4-dinitrophenylhydrazone. L was refluxed with 2:4-dinitrophenylhydrazine in pyridine[60] for 4 hrs., but on pouring into water, only unchanged reagent was recovered. Treatment of L with a saturated solution of the reagent in 2N HCl, gave a heterogeneous product which decomposed on attempted chromatography.

Attempted formation of true O-acetyl-2:4-dinitrophenylhydrazone. L (70 mg.) was refluxed with acetyl chloride (40 mg.) and pyridine (50 mg.) in benzene (1 ml.), for 2 hrs., pyridine hydrochloride being deposited. Ether was added, and the solution washed with dilute HCl and with water, dried, and evaporated to give an almost colourless oil, (7-acetoxy-3:3:7-trimethyl*cyclo*hept-4-enone?). The crude product was added to a solution of 2:4-dinitrophenylhydrazine in ethanol and sulphuric acid, to give, on standing, a mixture of 2:4-dinitrophenylhydrazones, separable by chromatography on neutralised alumina, eluting with benzene/pet. ether (b.p. 60-80°), (1:3).

The lower band yielded a small amount as scarlet plates from ethanol, m.p. 156-158°, mixed with above acetyl-2:4-dinitrophenylhydrazone, m.p. 140-144° and with eucarvone 2:4-dinitrophenylhydrazone, m.p. 139-143°. Light absorption in chloroform, λmax. 3,835A$^\circ$, (log ϵ, 4.39).

The upper band gave a larger quantity as pale red plates from ethanol, m.p. 147-148°, consisting of the above ethyl-2:4-dinitrophenylhydrazone, (mixed m.p. 152°). Light absorption in chloroform, λmax. 3,735A$^\circ$, (log ϵ, 4.43). (Found: C, 57.2; H, 6.35; N, 14.85; $C_{18}H_{24}N_4O_5$ requires: C, 57.45; H, 6.45; N, 14.9%.)

The high-boiling product consisted of *3:3:7-trimethyl-CYCLOhept-6-en-5-olone* (LVI), a pale yellow viscous liquid, b.p. 78-81°/0.08 mm., n_D^{18} 1.5004. It was slightly contaminated with selenium, but deposited most of it on standing for several weeks. Light absorption in methanol, λ max. 2,370A^{o}, (log ϵ, 3.81). (Found: C, 71.45; H, 9.25; $C_{10}H_{16}O_2$ requires: C, 71.4; H, 9.6%.) Microhydrogenation gave a value of 0.96 double bonds. Infra-red spectrum, illustrated, (p.174). No quinoxaline derivative could be obtained by refluxing with *o*-phenylenediamine in ethanol. The uptake of perbenzoic acid was only 0.22 mole during 20 hrs.

Phenylurethane, colourless elongated prisms from pet. ether (b.p. 80-100^{o}), m.p. 141-141.5^{o}. Light absorption in methanol, λ max. 2,370A^{o}, (log ϵ, 4.45). (Found: C, 70.8; H, 7.55; $C_{17}H_{21}NO_3$ requires: C, 71.05; H, 7.35%.)

2:4-Dinitrophenylhydrazone, by treating with Brady's solution, crimson prisms from ethanol/ethyl acetate, m.p. 152^{o}, decomposing on a column of neutralised alumina. Light absorption in chloroform, λ max. 3,735A^{o}, (log ϵ, 4.41). (Found: C, 55.15; H, 5.75; N, 15.9; $C_{16}H_{20}N_4O_5$ requires: C, 55.15; H, 5.75; N, 16.1%.) An attempt to obtain a derivative using acetic acid as medium was unsuccessful.

Acetylation of above derivative. The 2:4-dinitrophenylhydrazone (10 mg.) and acetic anhydride (100 mg.) in benzene (2 ml.), were refluxed for 90 mins., then ethanol (0.5 ml.) added and refluxing continued for a further 15 mins. to destroy the excess acetic anhydride. Evaporation under reduced pressure gave the crude product, which crystallised from pet. ether (b.p. 60-80^{o}) as orange-red granules, m.p. 139-142^{o}, mixed with starting material, m.p. 108-112^{o}, with acetyl-2:4-dinitrophenylhydrazone of L, m.p. 130-134^{o}, and with the unidentified 2:4-dinitrophenylhydrazone from acetylation of L, m.p. 125-130^{o}. Light absorption in chloroform, λmax. 3,735A^{o}, (log ϵ, 4.41).

<u>CYCLOhexanol phenylurethane</u>, clusters of needles from pet. ether (b.p. 60-80^{o}), m.p. 82-83^{o}. Light absorption in methanol, λmax. 2,340A^{o}, (log ϵ, 4.20).

<u>Bismuth oxide oxidations</u>[46,47]

Both the above products (L, LVI), (0.05 gm.) were separately dissolved in acetic acid (0.5 ml.) and water (0.25 ml.). Solid carbon dioxide was added to free the test tubes from air, and when it had evaporated, bismuth oxide (0.05 gm.) was introduced rapidly, the tubes loosely corked, and heated on a steam bath for 2 hrs. In neither case was any significant blackening apparent, whereas in a control using benzoin, the solid was quite black after 20 mins.

Periodate estimations

Both L and LVI (70 to 90 mg.) were weighed into separate conical flasks, and periodic acid, approx. 0.2M, (3 ml.), (previously standardised against sodium arsenite), was added, together with sufficient methanol to maintain a homogeneous solution. After standing for 30 hrs. at 30°, alongside a blank, the contents of the flasks were washed into larger vessels. Saturated sodium bicarbonate solution (1 to 2 ml.), standard sodium arsenite, approx. 0.05M (10 ml.), and 10% potassium iodide (0.5 to 1 ml.) were added and the mixtures stood for 15 mins. then titrated with a standard iodine solution. Calculating from the results obtained, less the blank value, L had consumed 0.91 mole periodic acid, and LVI, 0.11 mole. A control, using benzoin, showed a consumption of 0.94 mole.

Potassium permanganate oxidations

Carbon dioxide was passed through stirred suspensions of L and of LVI (0.5 gm.) in water (5 ml.) while a solution of potassium permanganate (2.5 gm.) in water (40 ml.) was added during 60 mins. The passage of carbon dioxide was continued for a further 3 hrs. and the mixtures stood overnight. After acidification with conc. HCl and passage of sulphur dioxide to obtain clear solutions, they were extracted several times with ethyl acetate, and the extracts dried. Removal of the solvent left, in both cases, a solid material which was treated with charcoal in benzene and recrystallised from the same solvent. Both L and LVI gave colourless prisms, (50-60 mg.), m.p. 139-141°, mixed with synthetic αα-dimethylsuccinic acid, m.p. 139-141°. The sample for comparison was prepared by condensation of acetone and ethyl cyanoacetate, followed by decarboxylation as described by Smith and Horwitz[61]. It melted at 140-142°.

Chromic acid oxidation of LVI

LVI (0.2 gm.) in water (2 ml.) was warmed on a steam bath, and chromium trioxide (0.5 gm.) in water (5 ml.) and conc. H_2SO_4 (1 ml.) added gradually. The reaction was quite rapid, almost all the oxidant being consumed after 2 hrs. The excess was destroyed with ethanol, sodium carbonate added until the mixture was alkaline and the solids filtered off, and washed with hot water. The filtrate was extracted with chloroform, and then acidified and extracted several times with ether. Evaporation of the ether gave a gum, yielding colourless prisms, from benzene, m.p. 135-138°, mixed with αα-dimethylsuccinic acid, m.p. 137-141°.

Nitric acid oxidation of LVI. LVI (0.05 gm.), conc.

HNO_3 (0.4 ml.) and water (0.1 ml.) were heated for 2 hrs. on a steam bath and then evaporated to dryness under reduced pressure, destroying the final traces of acid by addition of ethanol and again evaporating. The residual sticky solid was recrystallised twice from benzene, giving colourless prisms, m.p. 132-136°, mixed with $\alpha\alpha$-dimethylsuccinic acid, m.p. 135-138°.

Ozonolysis of LVI

LVI (0.185 gm.) in ethyl acetate (5 ml.) was cooled to -30° and ozonised oxygen (0.6% O_3) passed for 4 hrs., trapping any volatile products formed in a water trap. The solution was then hydrogenated over 10% palladium-charcoal (0.5 gm.), uptake being almost theoretical. The contents of the water trap were tested for traces of formaldehyde both by chromotropic acid in 75% H_2SO_4 and by carbazole in conc. H_2SO_4[62]. None was present. No iodoform reaction was observed, and no colour was obtained with sodium nitroprusside[56], while shaking with 2:4-dinitrophenylhydrazine in 2N HCl gave no precipitate. The hydrogenated solution was freed from solvent under reduced pressure, collecting the volatile material in a trap at -70°. Again the above tests were negative. The solid residue gave a strong iodoform reaction, and a deep blue colouration was produced in sodium nitroprusside and sodium hydroxide on acidification with acetic acid. The bulk of the solids were refluxed with chromic acid (0.35 gm.) in water (5 ml.) and acetic acid (5 ml.) for 2 hrs. The excess chromic acid was destroyed with ethanol and the product isolated as before (p.92). Recrystallisation from benzene/pet. ether (b.p. 60-80°) gave ββ-dimethylglutaric acid, as colourless elongated prisms, m.p. 97-101°, mixed with a genuine specimen, m.p. 98-103°.

Manganese dioxide oxidation of LVI

LVI (0.2 gm.) and activated manganese dioxide[59] (2.0 gm.) were shaken together in dry pet. ether (b.p. 40-60°) (25 ml.) for 4 days. The solids were filtered off and washed with hot benzene, the solvents removed, and the residual pale yellow oil (0.195 gm.; 97%) partially converted to a mono-2:4-dinitrophenylhydrazone of 3:3:7-trimethylCYCLOhept-6-ene-1:5-dione by treatment with Brady's reagent; orange needles from ethanol/ethyl acetate, m.p. 190-191°. Light absorption in chloroform, λmax. 3,745A°, (log ϵ, 4.46). (Found: C, 55.6; H, 5.2; N, 16.0; $C_{16}H_{18}N_4O_5$ requires: C, 55.5; H, 5.25; N, 16.2%.)

BIS-2:4-dinitrophenylhydrazone, by warming with the reagent in 90% acetic acid, red needles, m.p. 289° (dec.). Light absorption in chloroform, λmax. 3,970A°, (log ϵ, 4.71). (Found: C, 49.8; H, 4.3; N, 21.0; $C_{22}H_{22}N_8O_8$ requires: C, 50.2; H, 4.2: N, 21.3%.)

Oxidations with chromic acid in acetic acid

(a) 3:3:7-trimethyl*cyclo*hept-4-en-7-olone (L), (0.5 gm.) and chromium trioxide (0.2 gm.) were dissolved in acetic acid (5 ml.) and water (5 ml.). After standing at room temperature for 12 hrs., an aliquot portion was titrated with standard ferrous ammonium sulphate solution. The quantity of oxidising agent consumed was found to be 96% of that calculated for the splitting of an α-*tert*.-hydroxy-ketone. The bulk of the solution was treated with methanol, to destroy excess chromic acid, neutralised with sodium carbonate, filtered, and extracted with benzene. The benzene extracts contained only a trace of organic material. The aqueous layer was evaporated to a smaller volume (10 ml.) and was found to give a strong iodoform reaction.

(b) 3:3:7-trimethyl*cyclo*hept-6-en-5-olone (LVI), (0.5 gm.) was treated as above, the benzene extracts yielding, on evaporation, a pale yellow oil, (0.41 gm.; 81%), which was distilled, to give pure *3:3:7-trimethylCYCLOhept-6-ene-1:5-dione*

(LVII) b.p. 110-112°/9 mm., $n_D^{18.5}$ 1.4948. Light absorption in methanol, λ max. 2440A°, (log ϵ, 3.95). (Found: C, 71.8; H, 8.7; $C_{16}H_{14}O_2$ requires: C, 72.2; H, 8.5%.) Infra-red spectrum of a thin film showed peaks at: 1672 (v.s.), (conj. C=O str.); 1620 (s.), (C=C str.); 1,372 (s.), 1,120 (m.), ($C\langle^{Me}_{Me}$?; doublets not resolved); 834 cm.$^{-1}$ (w.), ($\rangle C{=}C\langle^{H}$ def.). No colour was given with ferric chloride solution. Fehling's solution and ammoniacal silver nitrate were reduced, but it was found that eucarvone, α and β -dihydroeucarvones, L, and LVI also gave these reactions. Both a mono- and a <u>bis</u>-2:4-dinitrophenylhydrazone were obtained as above (p.94), identical with the derivatives previously obtained.

BIS-2:4-dinitrophenylhydrazones of the CYCLOhexanediones etc.

The derivatives of *cyclo*hexane-1:4-dione and of *cyclo*hexane-1:3-dione were prepared directly, and that of *cyclo*hexane-1:2-dione by refluxing nioxime in Brady's solution for 60 mins. The properties were as follows:-

1:4-dione*, dark yellow, m.p. 244° (dec.), λmax. 3,590A°, (log ϵ, 4.67)
1:3-dione*, brick-red, m.p. 211° (dec.), λmax. 3,570A°, (log ϵ, 4.58)
1:2-dione, scarlet, m.p. 228° (dec.), λmax. 3,480; 3920A°, (log ϵ, 4.47, 4.36)

Also:
Di-acetyl, brick-red, m.p. 317° (dec.), λmax. 3,880A°, (log ϵ, 4.56)

Cycloheptane-1:2-dione, (Cook, Raphael and Scott)[72], λmax. 3,520A° (log ϵ, 4.53); inflexion at 3,900A°, (log ϵ, 4.44).

(* - not previously mentioned in the literature.)

Hydrogenations

(a) L (0.4 gm.) in methanol (10 ml.) was hydrogenated over 10% palladium-charcoal (0.1 gm.). 63 ml. at 17° and 772 mm. were absorbed during 60 mins., corresponding to 1.13 double bonds. Working up in the normal way (see p. 76) gave 3:3:7-trimethylCYCLOheptan-7-olone[19] as a colourless oil, b.p. 93-94°/12 mm., n_D^{25} 1.4592.

An attempt to prepare the oxime on a small scale by the normal procedure was unsuccessful, only an oil being formed. All attempts to render this crystalline, including chromatography on powdered silica gel, failed.

O-Methyl-2:4-dinitrophenylhydrazone, formed by treating with the reagent in methanol and sulphuric acid, orange prisms from ethanol, m.p. 170-171°. Light absorption in chloroform, λmax. 3,590A°, (log ϵ, 4.35). (Found: C, 55.7; H, 6.05; N, 15.15; $C_{17}H_{24}N_4O_5$ requires: C, 56.05; H, 6.65; N, 15.4%.)

(b) LVI (0.520 gm.) in ethanol (15 ml.) was hydrogenated over 10% palladium charcoal (0.25 gm.). Absorption was sluggish, ceasing at 69 ml. at 26° and 764 mm., equivalent to 1.1 double bonds. Working up in the normal way, followed by distillation, gave 3:3:7-trimethylCYCLOheptan-5-olone, (0.31 gm.; 60%), as a colourless oil, b.p. 155-158°, together with involatile solids.

The reduction product (0.2 gm.) was treated with a solution of chromium trioxide (0.08 gm.) in acetic acid (2 ml.) and water (2 ml.). After standing for 24 hrs., and working up as before (p. 95), a pale yellow liquid was obtained, (3:3:7-trimethylCYCLOheptane-1:5-dione), which was not further purified.

BIS-2:4-dinitrophenylhydrazone, by heating with the reagent in 94% acetic acid at 100°, dark orange microcrystals from anisole, m.p. 238-239° (dec.). Light absorption in chloroform, λ max. 3,558A°, (log ϵ, 4.65). (Found: C, 50.2; H, 4.15; N, 21.1; $C_{22}H_{24}N_8O_8$ requires: C, 50.0; H, 4.6; N, 21.2%.)

Dehydrations

(a) L (1.5 gm.) and boric acid (0.55 gm.)[42,43] were heated over a bare flame until no further distillate could be obtained. Working up as before, (pp. 83/84), but omitting the sodium hydroxide extraction, then distillation gave a pale yellow oil, (1.02 gm.; 74%), b.p. 88-89°/11 mm., η_D^{15} 1.5040. Light absorption in methanol, λ max. 2990A°, (log ϵ, 3.70). (Found: C, 79.4; H, 9.5; $C_{10}H_{14}O$ requires: C, 79.95; H, 9.4%.) Infra-red spectrum, illustrated, (p. 171). Positive Fehling's and silver mirror tests were given, but the colour was not restored to Schiff's reagent. No iodoform test was given, and no dimedone derivative could be obtained.

2:4-Dinitrophenylhydrazone, crimson needles from ethanol/ethyl acetate, m.p. 172-173°, mixed with eucarvone 2:4-dinitrophenylhydrazone, m.p. 123-129°. Light absorption in chloroform, λ max. 3960A°, (log ϵ, 4.45). (Found: C, 58.1; H, 5.9; N, 16.8; $C_{16}H_{18}N_4O_4$ requires: C, 58.15; H, 5.5; N, 16.95%.)

Semicarbazone, colourless plates from aqueous ethanol, m.p. 119-122°.

(b) LVI (0.5 gm.) and boric acid (0.2 gm.) were heated together as above. Distillation of the product gave a pale yellow oil, (eucarvone), b.p. 81-82°/8 mm., η_D^{17} 1.5160. Infra-red spectrum almost identical with that of eucarvone (p. 171).

2:4-Dinitrophenylhydrazone, red tablets from ethanol/ethyl acetate, m.p. 146-147°, mixed with eucarvone 2:4-

dinitrophenylhydrazone, m.p. 148-150°. Light absorption in chloroform, λ max. 3,875A°, (log ϵ, 4.44).

Oxime, shimmering plates from aqueous ethanol, m.p. 103-104°, mixed with eucarvoxime, m.p. 103-104°.

Oxidations of product of dehydration of L

(a) The dehydration product (0.185 gm.) was warmed at 100° with a solution of chromium trioxide (0.8 gm.) in water (5 ml.) and conc. H_2SO_4 (1 ml.) for 3 hrs. Working up as before (p. 92) gave a gum, which deposited crystals from benzene; colourless prisms from the same solvent, m.p. 135-138°, mixed with $\alpha\alpha$-dimethylsuccinic acid, m.p. 137-140°.

(b) The dehydration product (0.165 gm.) in ethyl acetate (5 ml.) was ozonised for 4½ hrs. by the procedure previously described, (p. 93). The solution was hydrogenated over 10% palladium-charcoal (0.5 gm.), uptake being only 70% of that required by theory for 2 double bonds, due to rapid decomposition of the ozonide. No significant quantity of formaldehyde was detectable[62] amongst the volatile products, nor was any precipitate obtained with 2:4-dinitrophenylhydrazine. The solid products gave a strong iodoform test, and a deep mauve colouration was given by sodium nitroprusside[56]. Further oxidation with chromic acid in acetic acid gave a crystalline acid, colourless prisms from benzene, m.p. 134-138°, mixed with $\alpha\alpha$-dimethylsuccinic acid, m.p. 137-141°.

Ozonolysis of eucarvone (0.2 gm.) by the same procedure gave almost identical results at each stage. Hydrogenation uptake was 75% of theory, and a fluorescent blue colour was given by sodium nitroprusside. The iodoform test was positive and the final oxidation gave, as above, $\alpha\alpha$-dimethylsuccinic acid.

Hydrogenation of product of dehydration of L

The dehydration product (0.343 gm.) in methanol (10 ml.) was hydrogenated over 10% palladium-charcoal (0.2 gm.), 93 ml. at 20° and 758 mm. being absorbed during 12 mins., corresponding to 2.00 double bonds. Working up gave a colourless oil, (0.29 gm.; 83%), b.p. 90/15 mm., n_D^{25} 1.4520. Infra-red spectrum, illustrated, (p. 172).

2:4-Dinitrophenylhydrazone, orange plates from pet. ether (b.p. 80-100°), m.p. 115-118° (sintered at 97-100°), mixed with 2:2:6-trimethylcycloheptanone 2:4-dinitrophenylhydrazone[50], m.p. 80-95°. Light absorption in chloroform, λmax. 3,640A°, (log ϵ, 4.34). (Found: C, 56.7; H, 6.2; $C_{16}H_{22}N_4O_4$ requires: C, 57.45; H, 6.65%.)

An attempt to prepare a nitroso-derivative by adding a trace of conc. HCl, (in ethanol), to a mixture of the ketone and amyl nitrite, and standing overnight at 0°, gave no solid product.

Nitrosotetrahydroeucarvone[18] was formed under the same conditions, from XV; colourless plates from aqueous acetone, m.p. 103-104°.

Oximino-α-dihydroeucarvone

α-dihydroeucarvone (10 gm.) was added to a warm solution of sodium ethoxide, (from sodium (2 gm.) in dry ethanol (40 ml.)). After standing for 15 mins., the liquid was cooled to 0°, amyl nitrite (8 gm.) was added, and the cherry-red solution left at 0° for 48 hrs., shaking occasionally. Glacial acetic acid (6 ml.) in water (60 ml.) was then added, and the mixture extracted several times with ether. The ether solution was extracted six times with small portions of a solution of sodium hydroxide (5 gm.) and sodium carbonate (5 gm.) in water (50 ml.). The alkaline extracts were brought to p H 6 with acetic acid and re-extracted with ether. After washing with sodium bicarbonate solution, and with brine, the extracts were washed, dried and evaporated. The crude oximino-α-dihydroeucarvone[5,8] crystallised from benzene/pet. ether (b.p. 80-100^{o}), (1:3), in white rosettes, (4.5 gm.; 39%), m.p. 121-124^{o}. Light absorption in methanol, λ max. 2,770A^{o} (log ϵ, 4.10). (Found: C, 66.5; H, 8.3; N, 7.5; $C_{10}H_{15}NO_2$ requires: C, 66.25; H, 8.35; N, 7.75%.) Infra-red spectrum, illustrated, (p.172). Further experiments were carried out under varying conditions, but no improvement in yield could be achieved. A positive iodoform reaction and a mauve colour with sodium nitroprusside were observed.

Conversion of oximino-α-dihydroeucarvone to a diketone. The oximinoketone (3 gm.) was warmed on a steam bath for 15 mins. with 40% formalin (20 ml.), 2N HCl (40 ml.), and ethanol (30 ml.). Working up as previously described, (p. 83), gave a red oil which was distilled to give a pale yellow, mobile, liquid, (2.0 gm.; 73%), b.p. 115^{o}/12 mm., n^{17} 1.4928. Light absorption in methanol, λ max. 2,445A^{o}, (log ϵ, 3.98). Analysis figures suggested the presence of a more highly oxygenated impurity. Infra-red spectrum of a thin film showed peaks at: 1,668 (v.s.), (conj. C=O str.); 1618 (m.), (C=C str.); 1,372 (m.), 1,355 (w.), ($C<^{Me}_{Me}$ def.?); 834 cm.$^{-1}$ (w.); ($>C=C<^{H}$ def.?). The product gave no colour with ethanolic ferric chloride, and was insoluble in 5N sodium hydroxide. It did not form a quinoxaline derivative or a dimedone derivative. Periodate consumption was 0.07 mole after 48 hrs. It gave a positive iodoform test, (eucarvone, and α-dihydroeucarvone did not), and a greenish-brown colour with sodium nitroprusside.

Mono-2:4-dinitrophenylhydrazones. Treatment with Brady's solution, and chromatographic separation of the crude product gave two isomeric derivatives. The first formed yellow needles from ethanol/ethyl acetate, m.p. 192-193°, mixed with the corresponding derivative of LVII, m.p. 182-186°. Light absorption in chloroform, λ max. 3,750A°, (log ϵ, 4.46). (Found: C, 55.8; H, 5.55; N, 16.15; $C_{16}H_{18}N_4O_5$ requires: C, 55.5; H, 5.25; N, 16.2%.) The second formed orange tablets from the same solvent, m.p. 181-182°, mixed with the above, m.p. 155-160°. Light absorption in chloroform, λmax. 3,735A°, (log.ϵ, 4.53). (Found: C, 55.4; H, 5.6; N, 16.0; $C_{16}H_{18}N_4O_5$ requires: C, 55.5; H, 5.25; N, 16.2%.)

BIS-2:4-dinitrophenylhydrazone, by warming with the reagent in acetic acid, crimson needles, m.p. 284-286° (dec.), mixed with the corresponding derivative of LVII, m.p. 271-274° (dec.). Light absorption in chloroform, λ max. 4,110A°, (log ϵ , 4.72). (Found: C, 50.4; H, 4.45; N, 21.25; $C_{22}H_{22}N_8O_8$ requires: C, 50.2; H, 4.2; N, 21.3%.)

Permanganate oxidation of diketone from oximino-α-dihydroeucarvone

The diketone (0.5 gm.) in water (10 ml.) was stirred and treated with a solution of potassium permanganate (1.60 gm.) in water (30 ml.), while passing carbon dioxide through the mixture, as outlined previously (pp. 91,92). Working up gave a gum which, after charcoal treatment, gave colourless prisms from benzene, m.p. 108-112°, together with a smaller quantity of a lower melting acid mixture. No gas evolution took place on heating to 200°. Mixed with αα-dimethylsuccinic acid, m.p. 90-96°, with methylsuccinic acid, m.p. 80-90°, with *iso*propylsuccinic acid, m.p. 85-95°, with ββ-dimethylglutaric acid, m.p. 75-80°. (The *ISOpropylsuccinic* acid for comparison was prepared from *iso*butyraldehyde, ethyl cyanoacetate, and potassium cyanide, by the method of Smith and Horwitz[61], and the *methylsuccinic acid* from methyl crotonate and sodium cyanide, as described by Brown[63].) The acid gave neither an iodoform reaction nor a colour with sodium nitroprusside and no precipitate was formed on standing with 2:4-dinitrophenylhydrazine in 2N HCl. (Found: C, 52.6; H, 6.3%.)

Semi-micro hydrogenation of diketone from oximino-α-dihydroeucarvone

The diketone (34.1 mg.) in acetic acid (5 ml.) was hydrogenated over 10% palladium-charcoal (50 mg.), 4.8 ml. at 20° and 743 mm. being absorbed during 15 mins., corresponding to 1.0 double bonds. The catalyst was filtered off and washed well with hot acetic acid, and the solvents reduced in bulk. The solution together with a few drops of water was warmed with 2:4-dinitrophenylhydrazine giving the BIS-2:4-dinitrophenylhydrazone as orange micro-crystals, m.p. 230° (dec.). Light absorption in chloroform, λ max. 3,595A°, (log ϵ, 4.68). (Found: C, 50.1; H, 4.45; N, 20.8; $C_{22}H_{24}N_8O_8$ requires: C, 50.0; H, 4.58; N, 21.2%.)

Selenium dioxide oxidation of β-dihydroeucarvone

The β-dihydroeucarvone (XXIV) was prepared by isomerisation of the α-isomer in ethanol and sulphuric acid, as described in Part III of this thesis (p. 150).

XXIV (10 gm.) and selenium dioxide (7.6 gm.) were refluxed for 16 hrs. in ethanol (150 ml.) and water (5 ml.). The solvent was evaporated until about 40 ml. remained, then the solution was filtered and poured into N H_2SO_4 (400 ml.). The mixture was extracted with ether and the extracts washed with aqueous sodium bicarbonate, dried and evaporated. The residual dark oil was refluxed overnight with mercury[51] (125 gm.) in pet. ether (b.p. 60-80°), (100 ml.) with rapid stirring. The atomised mercury was filtered off and washed with ether, then the filtrate was freed from solvent and distilled, yielding a mixture of products, b.p. 35-105°/0.08 mm., and a non-volatile selenium containing residue.

Fractionation gave mainly XXIV, (6.5 gm.; 65% recovery), as a colourless liquid, b.p. 78-79°/7 mm., n_D^{25} 1.4773. 2:4-dinitrophenylhydrazone, scarlet plates from ethanol/ethyl acetate, m.p. 195°, mixed with β-dihydroeucarvone 2:4-dinitrophenylhydrazone, m.p. 194-195°. Semicarbazone, colourless needles from aqueous ethanol, m.p. and mixed m.p. 203-205° (dec.), (sealed tube).

The higher-boiling material (2.1 gm.) was not homogeneous; b.p. 71-85°/0.1 mm., n_D^{25} 1.4946-1.5163. 2:4-dinitrophenylhydrazones, red amorphous powder from ethanol, m.p. 80-90°, could not be resolved by chromatography. Phenylurethane, colourless elongated prisms, (small quantity), from pet. ether (b.p. 80-100°), m.p. 138-139°, mixed with corresponding derivative of LVI, m.p. 139-140°.

Selenium dioxide oxidation of tetrahydroeucarvone

The tetrahydroeucarvone (XV) was prepared by hydrogenation of eucarvone, as described in Part III of this thesis (p. 161).

XV (18.5 gm.) and selenium dioxide (14.6 gm.) were refluxed for 30 hrs. in ethanol (300 ml.) and water (10 ml.). The products were isolated and partially freed from selenium, as described under eucarvone (pp.71,72). Distillation gave a complex mixture (13.2 gm.) b.p. 40-200°/0.05 mm., and a large quantity of selenium containing residue. No satisfactory separation was achieved by fractionation.

The lowest-boiling fractions, b.p. 90-96°/18 mm., n_D^{25} 1.4653-1.4672, consisted essentially of α-dihydroeucarvone. 2:4-dinitrophenylhydrazones from acetic acid as medium, gave, after chromatography, yellow prisms from ethanol, m.p. 112-115°, mixed with the derivative of XII m.p. 117-120°. A trace of β-dihydroeucarvone 2:4-dinitrophenylhydrazone was also obtained as orange prisms from ethanol/ethyl acetate, m.p. 182-186°, mixed with the derivative of XXIV, m.p. 185-188°. No α-dihydroeucarvone could be detected in the starting material by chromatography of its 2:4-dinitrophenylhydrazone.

The middle fractions, b.p. 108-120°/18 mm., n_D^{25}

1.4703-1.4728, gave a mixture of 2:4-dinitrophenylhydrazones which could not be separated by chromatography.

The high-boiling fractions, b.p. 140-170°/18 mm., n_D^{25} 1.4848-1.4920, gave a similar, inseparable mixture of non-crystalline derivatives.

No phenylurethanes could be isolated from any of the above fractions. Periodate estimations showed a progressively higher consumption with increase in boiling-point, ranging from 0.01 mole to 0.49 mole. Bismuth oxide tests (see p. 90) were substantially negative, a slight greying being observed with the high-boiling material.

An attempt to separate the products by chromatography on alumina, was unsuccessful. Elution with a range of solvents from pet. ether to methanol, gave several fractions, the first consisting of impure α-dihydroeucarvone, b.p. 85-88°/14 mm., n_D^{25} 1.4666-1.4688, identified by its 2:4-dinitrophenylhydrazone. The later fractions, many resinous in nature, were not pure compounds, but from one of them, b.p. 108-112°/14 mm., n_D^{25} 1.4750, a small quantity of a crystalline 2:4-dinitrophenylhydrazone was obtained, (red prisms from ethanol, m.p. 114-119°), together with amorphous material.

Enol acetate of eucarvone (XL)[36,68]

Eucarvone (25 gm.), *iso*propenyl acetate (150 ml.) and *p*-toluenesulphonic acid (2 gm.) were heated in a flask fitted with a 12" Vigreux column and condenser[64]. Heating was adjusted so as to maintain a slow distillation of acetone and *iso*propenyl acetate during 15 hrs., while *iso*propenyl acetate (100 gm.) was added slowly to keep the volume in the flask above 100 ml. The temperature at the top of column rose from 60° to 90° during the first three hours, indicating the removal of most of the acetone from the system. Solid sodium bicarbonate (20 gm.) was added, and the excess *iso*propenyl acetate evaporated under vacuum. The residual dark oil was taken up in ether, filtered from the solids and washed with aqueous sodium bicarbonate. After drying and freeing from solvent, distillation gave XL, (28.7 gm.; 90%) as a colourless liquid, b.p. 110°/10 mm., n_D^{25} 1.4926. Light absorption in hexane[36], λ max. 2,680A°, (log ϵ, 3.43). (Found: C, 74.95; H, 8.05; $C_{12}H_{16}O_2$ requires: C, 74.95; H, 8.4%.) Infra-red spectrum[36] of a thin film showed peaks at: 1,750 (v.s.), (ester C=O str.); 1,670, 1,637, 1,560 (w.), (C=C str.); 1,368 (s.), ($\mathrm{C}{<}^{\mathrm{Me}}_{\mathrm{Me}}$ def.); 1,090, 1,065 (s.), (C-O str.?); 848 (w.), (${>}\mathrm{C}{=}\mathrm{C}{<}^{\mathrm{H}}$ def.); 824 cm.$^{-1}$ (w.), ($\mathrm{C}{<}^{\mathrm{Me}}_{\mathrm{Me}}$ skel.).

α-iodoeucarvone (LXIV?)

The N-iodosuccinimide was prepared from silver succinimide and iodine, as described by Djerassi and Lenk[53].

Eucarvone enol-acetate (12 gm.) was added to a solution of N-iodosuccinimide (16 gm.) in sodium-dried dioxan (150 ml.), and the mixture left in the dark at room temperature for 36 hrs. A certain amount of iodine was released. Excess 50% potassium iodide was introduced, followed by sufficient 10% sodium thiosulphate to destroy the free iodine, then the mixture was immediately extracted with ether. (Excess thiosulphate should be avoided, as it quite rapidly reacts with the product, perhaps forming Bunté salts[65]?) The extracts were washed, dried, and evaporated at the pump, to give crude LXIV as a viscous reddish-brown oil (7.8 gm.; 79%). Attempted distillation of a portion at 10^{-4} mm. led to rapid decomposition.

Attempted conversion of LXIV to the diketone (XLIV). Crude α-iodoeucarvone (7.8 gm.) in water (100 ml.) was stirred vigorously at 95-100°, while a solution of ferric chloride hexahydrate (14 gm.) in water (10 ml.) was added during 30 mins.[54] Stirring was continued for a further 15 mins., then the mixture cooled, and ammonium sulphate (12 gm.) added. After stirring for 3 hrs., the mixture was extracted with ether, the extracts washed with 10% sodium thiosulphate and with water, dried, and the solvent removed. Distillation of the residual red-brown viscous material gave only a small quantity (1.1 gm.) of volatile material, accompanied by iodine. Treatment with thiosulphate and redistillation, gave a colourless, non-ketonic oil, b.p. 66-68°/0.5 mm., η_D^{25} 1.4938. Light absorption in methanol, λmax. 2,695, 2,630A° (log ϵ, 2.85, 2.82). (Found: C, 73.7; H, 7.9%.)

Attempted conversion of LXIV to α-acetoxyeucarvone (LXV)

Crude α-iodoeucarvone (15 gm.), anhydrous potassium acetate (10 gm.), acetic acid (25 ml.), acetic anhydride (1 ml.) and pyridine (0.1 ml.) were refluxed for 6 hrs., and poured into water. The tarry product was separated and extracted several times with boiling pet. ether (b.p. 40-60°). After charcoal treatment and removal of the solvent, the clear red viscous liquid was distilled, yielding a non-ketonic, colourless, mobile liquid (1.65 gm.), b.p. 56°/0.1 mm., η_D^{25} 1.4948. Light absorption in hexane, λmax. 2,700, 2,615, 2,555A°, (log ϵ, 2.88, 2.89, 2.88). (Found: C, 75.4; H, 8.5; $C_{12}H_{16}O_2$ requires: C, 74.95; H, 8.4%.)

A second fraction (1.4 gm.) in the form of an amber resin, b.p. 150-160^{0}/10^{-3} mm., was also obtained, the residue being undistillable.

REFERENCES

1. Baeyer; Ber., 1894, 27, 810.
2. Kabu and Kondo; J. Pharm. Soc. Japan, 1931, 51, 8.
3. Kabu, Cho and Orita; ibid., 862.
4. Dormaar; Rec. Trav. chim., 1904, 23, 394.
5. Baeyer; Ber., 1894, 27, 1915.
6. Baeyer and Ipatiev; ibid., 1896, 29, 2797.
7. Baeyer; ibid., 1898, 31, 2067.
8. idem., ibid., 1895, 28, 639.
9. Wallach; ibid., 1895, 28, 2703.
10. idem., ibid., 1896, 29, 1595.
11. Wallach and Löhr; Ann., 1899, 305, 223.
12. Klages and Kraith; Ber, 1899, 32, 2550.
13. Harries and Stähler; Ann., 1904, 330, 275.
14. Baeyer; Ber., 1894, 27, 3485.
15. Wallach and Köhler; Ann., 1905, 339, 94.
16. Wallach; ibid., 1911, 381, 51.
17. idem., Nachr. K. Ges. Wisr. Gottingen, 1913, 236.
18. Wallach, Albright and Klein; Ann., 1914, 403, 73.
19. Wallach and Standacher; Ann., 1918, 414, 367.
20. Naves and Ardigio; Helv. Chim. Acta, 1949, 32, 329.

21. Wallach and Standacher; *Ann.*, 1919, *418*, 53.

22. Ruzicka and Seidel; *Helv. Chim. Acta*, 1936, *19*, 419.

23. Brühl; *Ber.*, 1899, *32*, 1222.

24. Kannonnikoff; *J. Russ. Phys. Chem. Soc.*, 1901, *33*, 95.

25. Auwers and Eisenlohr; *J. Pr. Chem.*(2), 1911, *84*, 37.

26. Auwers; *Ann.*, 1918, *415*, 98.

27. Csuros, Fodor and Hajos; *Acta Chim. Acad. Sci. Hung.*, 1952, *2*, 961.

28. Gillam and West; *J.*, 1942, 483.

29. Rupe and Kerkovius; *Ber.*, 1911, *44*, 2702.

30. Alder and Stein; *Ann.*, 1935, *515*, 165.

31. West; *J.*, 1940, 1162.

32. Rabe and Weilinger: *Ber.*, 1903, *36*, 234.

33. Clarke and Lepworth; *J.*, 1910, 11.

34. Dolejs, Novotny, Herout and Sorm; *Chem. Listy*, 1954, *48*, 586.

35. Corey and Burke; *J. Amer. Chem. Soc.*, 1954, *76*, 5257.

36. Corey, Burke and Remers; *ibid.*, 1955, *77*, 4942.

37. Josien and Fuson; *Compt. Rend.*, 1950, *231*, 1511.

38. Ball, Goodwin and Morton; *Biochem. J.*, 1948, *42*, 516.

39. *Ann. Reports*, 1952, 142.

40. Baker, Curtis and McOmie; *J.*, 1952, 1774.

41. Guillaumin; *Bull. Soc. chim.*, 1910, (4), *7*, 374.

42. Brandenberg and Galat; J. Amer. Chem. Soc., 1950, 72, 3275

43. O'Connor and Nace; ibid., 1955, 77, 1578.

44. Béhal and Tiffenau; Bull. Soc. chim., 1910, (4), 7, 330.

45. Guillaumin; ibid., 332.

46. Rigby; J., 1951, 793.

47. Holden and Rigby; ibid., 1924.

48. Fischer and Löwenburg; Ann., 1932, 494, 263.

49. Kuhn and Winsterstein; Ber., 1934, 67, 354.

50. Eschenmeser, Schinz, Fischer and Colonge; Helv. Chim. Acta, 1951, 34, 2329.

51. Jacques, Ourisson and Sandris; Bull. Soc. chim., 1955, 1293.

52. Fieser and Ourisson; J. Amer. Chem. Soc., 1953, 75, 4404.

53. Djerrassi and Lenk; ibid., 3493.

54. Inhoffen and Kramer; Ber., 1954, 87, 488.

55. Owen and Smith; J., 1951, 4035.

56. Feigl; Spot Tests, Vol. II, Organic; Elsevier Press, New York, 1954; p. 160.

57. Béhal and Tiffenau; Bull. Soc. chim., 1908, (4), 3, 730.

58. Delepine and Bonnet; ibid., 1909, (4), 5, 883.

59. Attenburrow, Cameron, Chapman, Evans, Hems, Jansen and Walker; J., 1952, 1094.

60. Braude and Timmons; ibid., 1953, 3131.

61. Smith and Horwitz; *J. Amer. Chem. Soc*., 1949, *71*, 3418.

62. Feigl; Spot Tests, Vol. II, Organic; Elsevier Press, New York, 1954; pp. 241, 242.

63. Brown: Org. Syn., Coll. Vol. II, 615.

64. Moffet and Weisblat; *J. Amer. Chem. Soc*., 1952, *44*, 2183.

65. Bunté; *Ber*., 1874, *7*, 646.

66. Nametkin and Brüssoff; *Ann*., 1927, *459*, 144.

67. *idem*.; *J. Pr. Chem*., (2), 1932, *135*, 155.

68. Corey and Burke; *J. Amer. Chem. Soc*., 1956, *78*, 174.

69. Corey, Burke and Remers; *ibid*., 180.

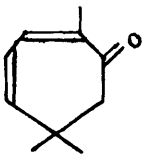
70. Carpenter and Easter; *J. Org. Chem*., 1955, *20*, 401.

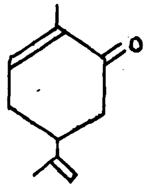
71. Spica; *Gazz. chim. ital*., 1882, *12*, 552.

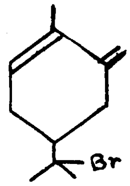
72. Cook, Raphael and Scott; *J*., 1952, 4416.

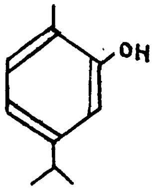
73. Leonard and Mader; *J. Amer. Chem. Soc*., 1950, *72*, 5388.

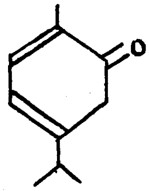
FORMULAE.

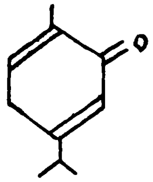

I

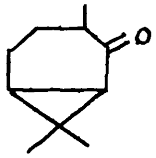

II

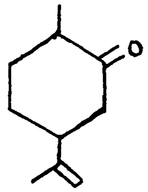

III

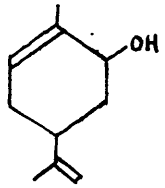

IV

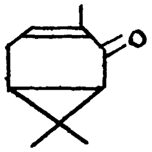

V

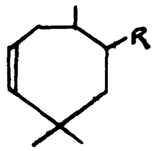

VI


VII

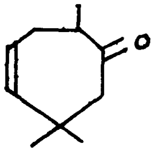

VIII

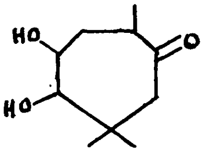

IX

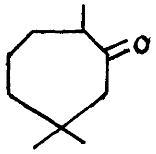

X

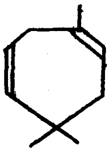

XI, R=OH

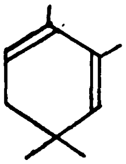
XIV, R=NH_2

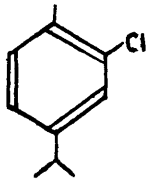

XII

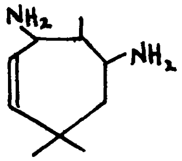

XIII

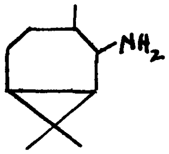

XV

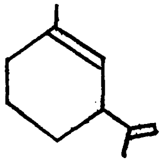

XVI

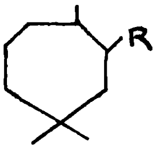

XVII


XVIII

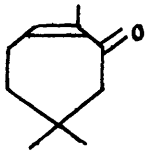

XIX

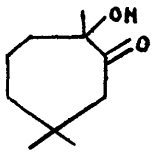

XX

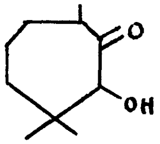

XXI

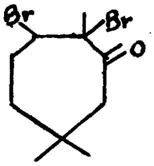

XXII, R = OH

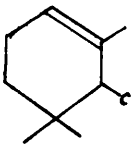
XXIII, R=NH_2


XXIV

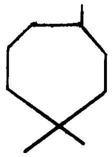

XXV


XXVI

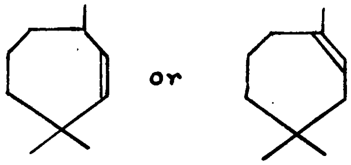

XXVII



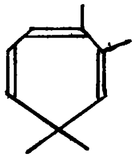
XXVIII



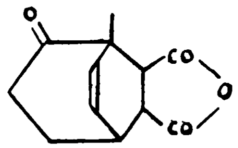
XXXIX



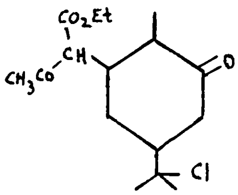
XXX



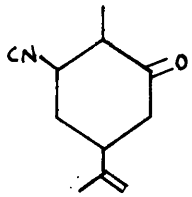
XXXI



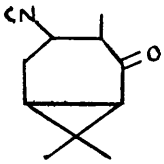
XXXII



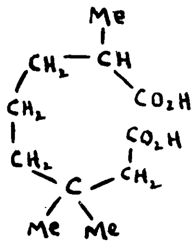
XXXIII



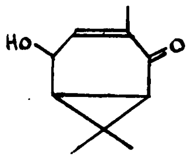
XXXIV



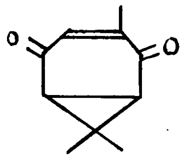
XXXV



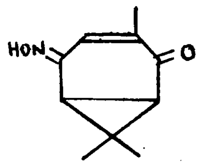
XXXVI



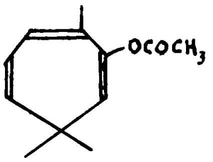
XXXVII



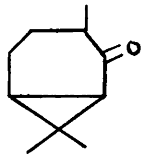
XXXVIII



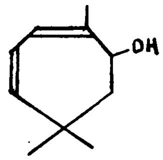
XXXIX



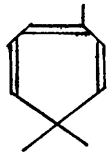
XL



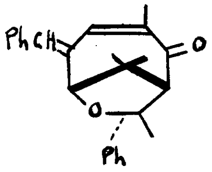
XLI



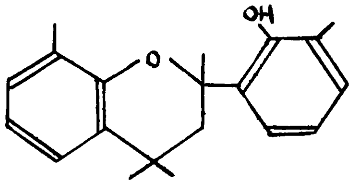
XLII



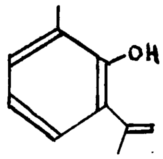
XLIII



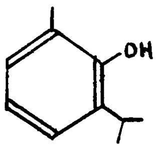
XLIV



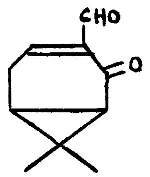
XLV



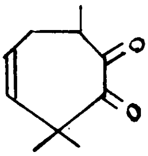
XLVI



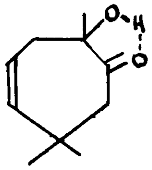
XLVII



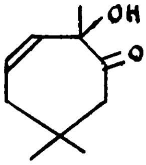
XLVIII



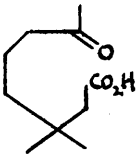
XLIX



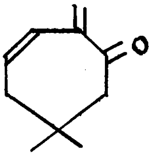
L



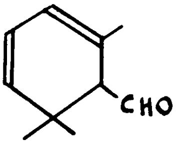
LI



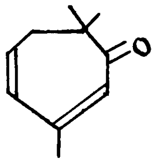
LII



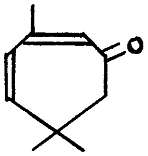
LIII



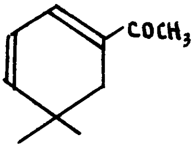
LIV



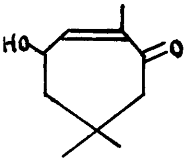
LV



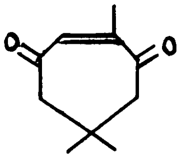
LV a



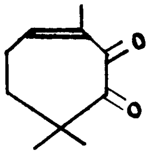
LV b



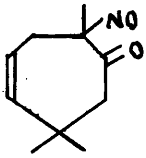
LVI



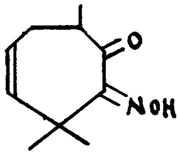
LVII



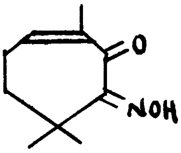
LVIII



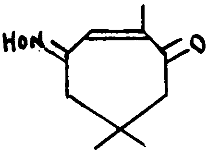
LIX



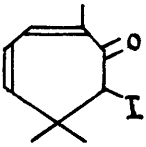
LX



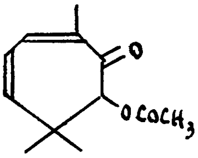
LXI



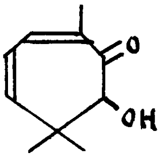
LXII



LXIII



LXIV



LXV

PART THREE

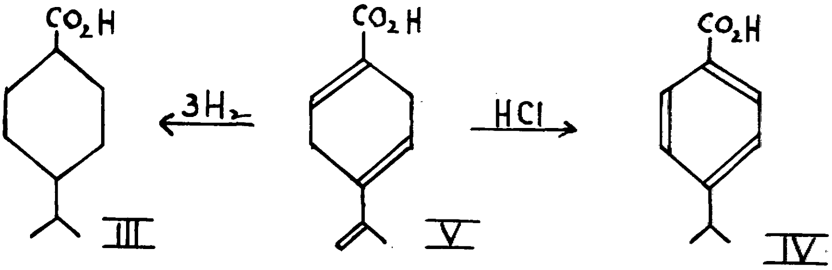
A SYNTHESIS OF THUJIC ACID

HISTORICAL INTRODUCTION

The naturally occuring compound, thujic acid, (I) is found amongst the extractives of the heartwood of the Western red cedar, (Thuja plicata, D. Don) and of other members of the same genus.

It was first isolated as early as 1907 by Blasdale[1], as a steam volatile, white, crystalline solid, displaying acidic properties. He obtained for it the empirical formula, $C_{10}H_{12}O_2$. Interest was revived some twenty years later, when it was suspected that the extreme durability of the heartwoods of some species of Cupressales might be due to the fungicidal and antibiotic nature of their constituents. In the case of the genus, Thuja, these active principles were in fact proved to be the isomeric α, β and γ-thujaplicins, (II a, b and c, resp.), which were amongst the first naturally occuring tropolones to be studied. Thujic acid itself has only feeble activity[2,4].

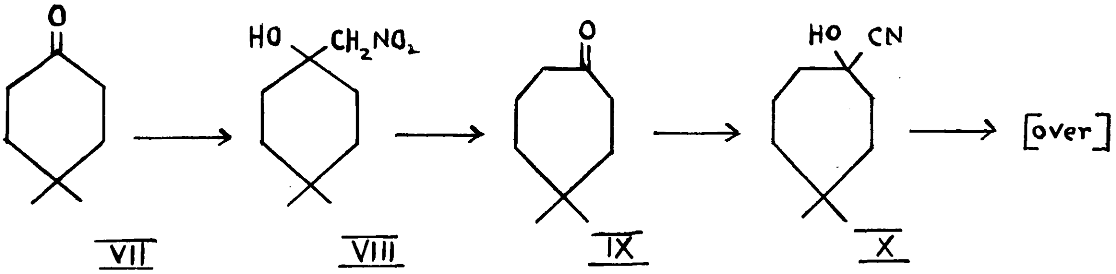
Anderson and Sherrard, in 1933[2], reported the isolation of I, and suggested a structure for the acid, based on an investigation of its properties and degradation products. They showed, by hydrogenation, the presence of three double bonds, the product being regarded as an unknown isomer of hexahydrocumic acid (III). Since ozonolysis produced formaldehyde and possibly $\beta\gamma$-diketovaleric acid, while refluxing with hydrochloric acid gave cumic acid, (IV), they suggested the formula V for the acid and named it dehydroperrillic acid.

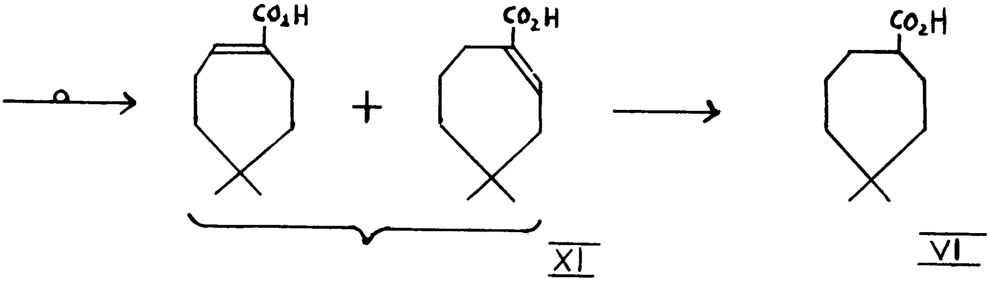


Some years later, Erdtman and Gripenberg began a systematic investigation on the constituents of *thuja plicata* heartwood, and examining the light absorption of the so-called dehydroperrillic acid[3], showed that a much greater degree of conjugation must be present than in the previously assigned structure. They also pointed out that both geometrical isomers of hexahydrocumic acid were now known, and that neither was the same as the product of hydrogenation of thujic acid[4,5]. Permanganate oxidation yielded dimethylmalonic acid, while ozonolysis gave only a trace of formaldehyde. By two independent degradations of the hexahydro-compound, Gripenberg obtained $\beta\beta$-dimethylpimelic and $\beta\beta$-dimethyladipic acids. The above facts constitute an unequivocal proof that the compound is a *cyclo*heptatriene acid of formula I, and the present name, thujic acid, was proposed. The isomerisation to cumic acid is explicable by analogy with the transformation of eucarvone to carvacrol[6], and of *cyclo*heptatriene to benzyl bromide[7].

More recently, Gripenberg announced a partial synthesis of thujic acid from its hexahydro-derivative (VI)[8]. Bromination of the latter (with N-bromosuccinimide) gave the α-bromo-acid, which was dehydrobrominated, treated with a further two moles of N-bromosuccinimide, and again dehydrobrominated. The product was thujic acid, identical with the naturally occuring material.

The same worker, in 1952[9], completed the total synthesis of I, by synthesising hexahydrothujic acid (VI). 4:4-dimethyl*cyclo*hexanone (VII) was converted into 4:4-dimethyl-1-nitromethyl*cyclo*hexanol (VIII) by condensation with nitromethane.





Reduction of VIII and treatment with nitrous acid led to 4:4-dimethyl*cyclo*heptanone (IX). Its cyanhydrin (X) was dehydrated, and the product hydrolysed to a mixture of two acids (XI), hydrogenation of which gave hexahydrothujic acid.

The difficulty of obtaining the necessary starting material (VII), coupled with the rather low overall yield of less than 1%, make it desirable to seek a simpler route, while it is also noteworthy that in Gripenberg's synthesis the bromination-dehydrobromination procedure was not unequivocal from the structural point of view. The ideal starting material would seem to be eucarvone (XII), readily available in good yield by treatment of carvone hydrobromide with methanolic potash[6]. It possesses already a seven-membered ring[10], with two of the three desired double bonds in place, and in addition has the required *gem* dimethyl-group and a third methyl group in position for conversion to the carboxyl group of I.

DISCUSSION

As will be described, a successful attempt was made to convert eucarvone (XII) into thujic acid (I), the first stage being the preparation of the parent 1:1:4-trimethyl-*cyclo*heptatriene, (XIV). From this hydrocarbon, thujic acid was obtained by suitable oxidation of the 4-methyl-group.

The expected action of lithium aluminium hydride on XII, would be to produce the alcohol, eucarvol (XIV), which on appropriate dehydration should give XIII. On carrying out these reactions, however, it was found that the conditions and the reagent employed, had a profound effect. When the reduction of XII with lithium aluminium hydride was carried out and the resulting complex decomposed after standing overnight, the sole product which could be isolated was a ketonic material. Its boiling point, refractive index, and light absorption[11], suggested that it was in fact α-dihydroeucarvone (XV), previously obtained from eucarvone by reduction with sodium in ethanol[6]. Its identity was confirmed by preparing the semicarbazone[12]. In order to verify the accepted structure of XV, its infra-red spectrum was examined, since recent discoveries have shown[13,14] that, in certain of its reactions, eucarvone tends to revert to a carane skeleton. The alternative carone structure (XVI) was, however, completely disproved by the presence of a =C-H str. peak at 3020 cm.$^{-1}$ and a cis CH=CH def. absorption at 685 cm.$^{-1}$. Microhydrogenation also showed the presence of one double bond. (But cf. p.134.)

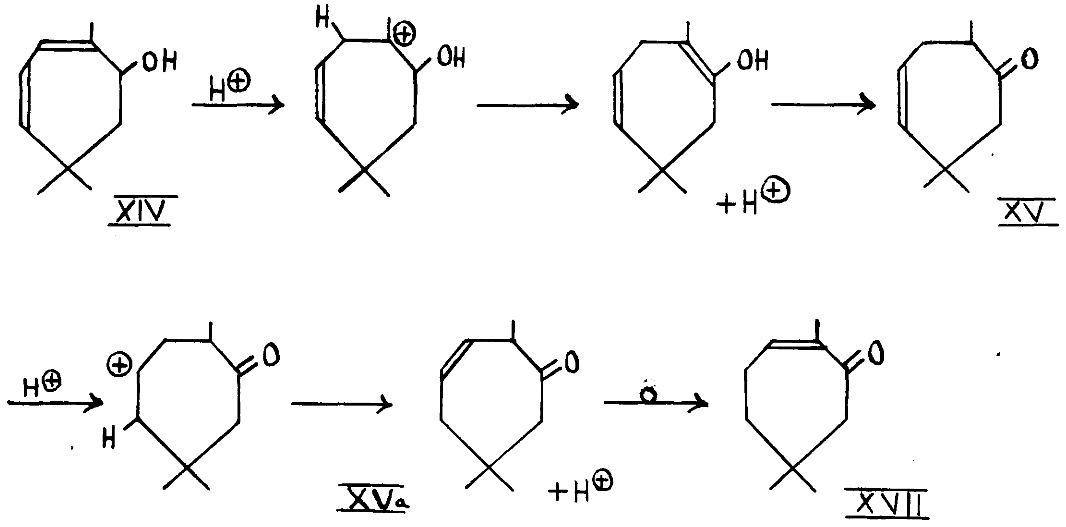
In an endeavour to prepare the 2:4-dinitrophenylhydrazone of XV, an interesting phenomenon was observed. When a derivative was prepared using 2:4-dinitrophenylhydrazine in ethanol and sulphuric acid, the product was red, m.p. 191-194°, whereas using a solution of the reagent in acetic acid, a yellow product, m.p. 120-121°, was obtained. Using hydrochloric acid in ethanol as medium, a mixture of both was precipitated. Their ultra violet spectra were examined, the red derivative showing a maximum at 3805A°, and the yellow at 3670A°. This suggests the presence of an α-β unsaturated linkage in the former case. The 2:4-dinitrophenylhydrazones of eucarvone[11] (XII), tetrahydroeucarvone (XVIII) and carone (XVI) were also prepared, and their spectra examined. The results, tabulated over, are in accordance with the measurements of Braude[15] and others and show clearly the variation of maxima with degree of conjugation. The purification of these derivatives of carone and of tetrahydroeucarvone was accomplished by passing down a column of bentonite and keiselguhr by a modification of the new method of Elvidge and Whalley[36], whereas the other 2:4-dinitrophenylhydrazones prepared were chromatographed on neutralised alumina. It is worthwhile noting that this latter gave a cleaner separation for derivatives of the eucarvone series.

Ketone	-	m.p.	Colour	λmax. ($CHCl_3$)	logϵ
Eucarvone	XII	151-152°	Red	3,880A°	4.44
β-dihydro-eucarvone	XVII	195°	Orange-red	3,805	4.40
Carone	XVI	101-102°	Orange-red	3,685	4.34
α-dihydro-eucarvone	XV	120-121°	Yellow	3,670	4.38
Tetrahydro-eucarvone	XVIII	137-137.5°	Orange	3,650	4.34

That the red product was indeed the β-dihydroeucarvone derivative, was established by preparation of the latter. A mixed melting point showed no depression. Evidently the presence of a strong mineral acid causes the migration of the γ-δ double bond of XV to the more stable α-β position of XVII.

The reduction of eucarvone with lithium aluminium hydride was found to take the expected course when the complex was broken up almost immediately after the addition of the ketone was completed. Eucarvol (XIV) is obtainable as the only product provided the working up is done promptly and carefully. It was characterised by means of the phenylurethane and showed an ultra-violet absorption maximum at 2485A° consistent with a _cyclo_heptadiene. (_Cyclo_heptadiene itself, λ max. 2480A°)[39]. The major complication in this preparation lies in the very labile nature of the free alcohol. If contact with acid during the working up is prolonged, or if the temperature is allowed to rise, rearrangement to α-dihydroeucarvone (XV) occurs very readily, accompanied by resinification. Distillation in the presence of the merest trace of acid causes a complete isomerisation to the ketone. It is interesting to note that by deliberately adopting the reaction conditions to favour the formation of the ketone, a somewhat simpler method is available for its preparation than that previously described[10].

The dehydration of eucarvol (XIV) to the triene (XIII) was also found to present difficulties, due to the labile nature of the alcohol. The products obtained by heating with potassium bisulphate at 200° were found to consist chiefly of the ketone (XV), plus a small quantity of a neutral compound, later identified as XIII. Admixture with potassium pyrosulphate and heating to 250° again resulted in a mixture of components, the greater part of which was identified as β-dihydroeucarvone (XVII) by means of its semicarbazone[16] and its ultra-violet absorption[11]. Only a trace of non-ketonic material was isolated. The formation of XVII in this manner is presumably due to acid catalysed double prototropic rearrangement of the hydroxy compound as indicated:

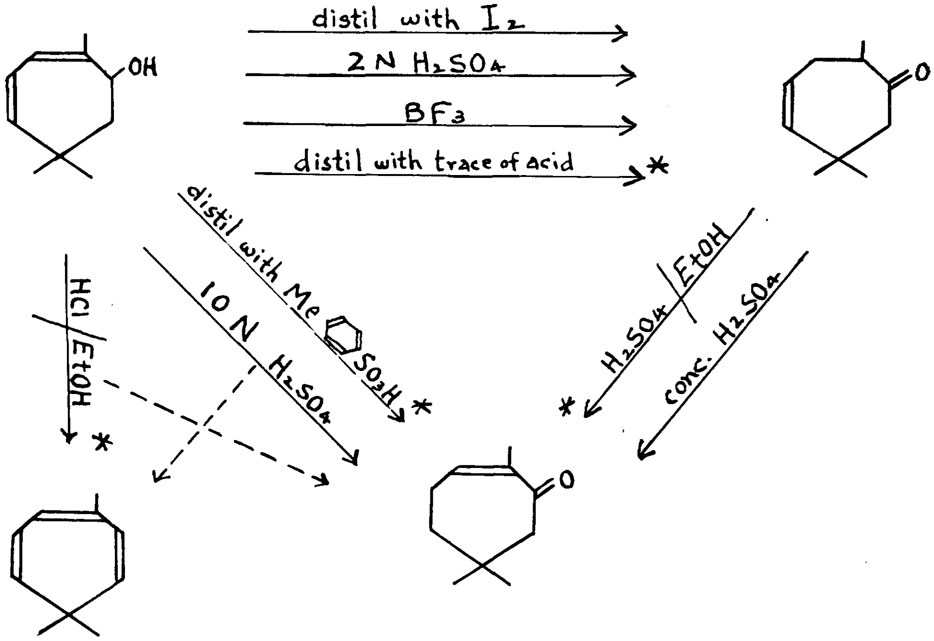


Both stages of this process have previously been noted, the first in the working up of the reduction products and in the potassium bisulphate dehydration, and the second in the formation of the 2:4-dinitrophenylhydrazone of XVII from XV. Further evidence on this subject is described later (pp. 131-134).

A much improved procedure of carrying out the dehydration involves heating XIV with boric acid[17,18]. Possibly the initial formation of the metaborate ester[18] (XIX) at a comparatively low temperature stabilises the eucarvol system, and enables the resulting pyrolysis to take place at 300° without complication. An appreciable quantity of the ketone was none the less obtained by this technique, varying considerably between experiments, and is almost certainly due to initial isomerisation in the presence of the weak acid, before ester formation is complete. The yield of hydrocarbon (XIII), identical with the small quantities previously obtained, varied from 40% to 61%.

It was decided at this point, to examine more closely the conditions favouring the isomerisation of eucarvol into the isomeric α- and β-dihydroeucarvones, in the light of the unexpected results of both the reduction, and the subsequent dehydration. It was found, that under varying acid conditions, the alcohol could be converted into either isomer at will. Distillation of XV over *p*-toluenesulphonic acid led almost entirely to β-dihydroeucarvone (XVII) together with involatile resins, whereas with a minute trace of sulphuric acid, the only isolable product was the α-isomer (XV). Boron trifluoride in ether at room temperature caused large scale resinification of the alcohol, but only a partial isomerisation to XV, while sodium ethoxide in ethanol had no appreciable effect under similar conditions. Shaking with 10 N sulphuric acid gave a complexity of products, including XVII and the triene (XIII), together with unchanged eucarvol (XIV). An experiment, wherein XIV was refluxed with hydrochloric acid in ethanol, led to a remarkably high yield (60%) of the dehydration product (XIII) accompanied by some of the β-ketone. This would seem therefore, to provide an attractive alternative to the boric acid technique for the preparation of this hydrocarbon. It is worth mentioning also that an abortive attempt to dehydrate XIV by distilling with a trace of iodine, resulted merely in an almost complete isomerisation to α-dihydroeucarvone. Shaking eucarvol in ether with 2N sulphuric acid also brought about a partial conversion to XV.

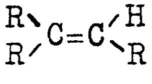
α-dihydroeucarvone was isomerised to the β-isomer (XVII) by admixture with concentrated sulphuric acid in the cold, but the yield was poor due to extensive polymerisation. On the other hand, on refluxing XV with sulphuric acid in ethanol, by analogy with the conditions favouring the isomerisation of its 2:4-dinitrophenylhydrazone, an excellent yield of β-dihydroeucarvone was obtained. This material, characterised by its spectra and by its derivatives, gave a 2:4-dinitrophenylhydrazone identical with that derived from the α-isomer under strongly acid conditions.



(*Best preparative method)

These results, summarised in the above diagram, are therefore in agreement with the postulated acid catalysed prototropic type of rearrangement, and verify the previous observation that the main deciding factor as to the product of lithium aluminium hydride reduction of eucarvone, lies in the time of contact of the reaction mixture with sulphuric acid. If this period is protracted, or if the products are not completely freed from the acid before distillation, the aforementioned rearrangement will occur. It is interesting to note that the more common base-catalysed rearrangement does not appear to take place so readily, since in the presence of sodium ethoxide, no isomerisation was detected. It is pertinent to note at this point that the alternative $\Delta^{3:4}$ structure (XVa) for α-dihydrocarvone is not excluded by its properties, and would be more acceptable in terms of the above protropic rearrangement in that its conversion to β-dihydroeucarvone (XVII) would proceed by one stage only, instead of via XVa as an intermediate as depicted in the scheme (p.130). The only evidence which led earlier workers to propose the formula XV, was a permanganate oxidation to yield αα-dimethylsuccinic acid[37], but since it has been shown in Part II of this thesis (pp. 61, 64) that such oxidations can proceed further than would be anticipated, the oxidative evidence cannot be regarded as conclusive, while the formation of the ketone by reduction of eucarvone with sodium and alcohol could well proceed by the well-known change from a $\Delta^{1:2-3:4}$ diene to the $\Delta^{2:3}$ compound. Thanks are due to Professor D. H. R. Barton for discussion on the above possibility.

In view of the initial doubt as to the structure of the dehydration product of eucarvol (see below), an attempt to remove the elements of water by indirect means was initiated. A solution of XIV in chloroform and dimethylaniline, on treatment with thionyl chloride at low temperature, gave a chloro-compound, which was seemingly homogeneous but decomposed readily on standing. It analysed for the expected eucarvyl chloride (XX), but the possibility that it was in fact the isomeric enol-chloride (XXI) of XVII, could not be ruled out on spectroscopic grounds. The ultra-violet absorption maximum at 2430A° is, however, in agreement with a <u>cyclo</u>heptadiene skeleton. Dehydrochlorination by the method of Steiner and Selving[19], consisting in shaking the halide with dry silver oxide in benzene, was unsuccessful. The product isolated was β-dihydroeucarvone, together with a smaller quantity of chlorine containing material, the light absorption of which could be explained by the presence of aromatic compounds. No further attempts were made to dehydrohalogenate the supposed eucarvyl chloride, since the product of direct dehydration was now known to be that desired.

The possibility that this hydrocarbon from the boric acid dehydration was <u>p</u>-cymene (XXII), could not at first be disregarded. The initially formed triene (XIII) might well have rearranged as does eucarvone at its boiling point to carvacrol[6], especially since both boiling points and refractive indices are similar. (XIII: b.p. 62^{o}/20 mm., n_D^{25} 1.4948; XXII: b.p. 176^{o}/760 mm., n_D^{20} 1.4908.) On treatment with bromine in carbon tetrachloride, however, the hydrocarbon discharged the colour rapidly, giving rise to a yellow precipitate, whereas a sample of XXII discharged the colour much more slowly and gave no precipitate. A sample of XIII also decolorised permanganate in acetone almost immediately, again in complete contrast to p-cymene. In an attempt to free the dehydration product from ketonic impurity by means of semicarbazide acetate, it polymerised to a glass-like mass, which could not have occured had the product been p-cymene. The ultra-violet spectrum had a single peak at 2,660A^{o} (cf. p-cymene; 4 peaks at 2120, 2590, 2650 and 2730A^{o}). This is very similar to that of *cyclo*-heptatriene itself (2650A^{o})[38], and quite different from either *cyclo*heptadiene (2480A^{o})[39] or *cyclo*hexadiene (2560A^{o}). This data would seem to rule out the possibility of a caradiene structure (XXIII) for the product. The infra-red spectrum was not inconsistent with a *cyclo*heptatriene, showing peaks identifiable with the *gem* di-methyl group, with a *cis* CH=CH and with a  $R_2C{=}C(H)R$ entity. The absence of *cyclo*-propane absorption at 1020-1000 cm.$^{-1}$ could not be taken as significant, however, since Cole[20] has stated that this absorption is not always present and cannot be taken as indicative of the system. He also showed that characteristic absorption in the 3,050-3,020 cm.$^{-1}$ region only appears when there is a methylene group in the *cyclo*propane ring. It is interesting to note that in the spectra both of XIII and of thujic acid (I) a distinct similarity to the aromatic series is shown, especially with regard to a series of bands in the 1500 to 1630 cm.$^{-1}$ region. In order to settle the structure of the dehydration product conclusively, a series of experiments was devised.

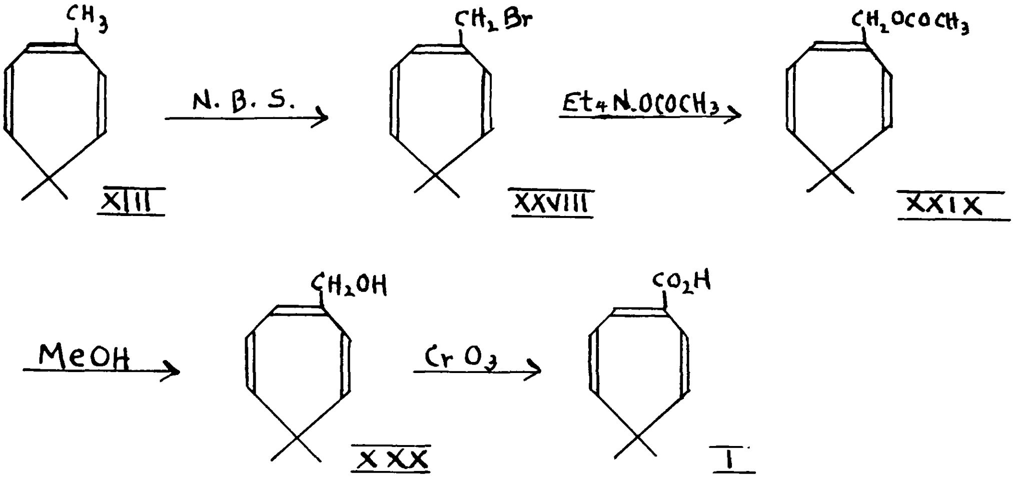
A maleic anhydride adduct was prepared, a microhydrogenation of which seemed to indicate that two double bonds remained. This can only be reconciled with the structure, XIII, for the hydrocarbon, the adduct being either of two isomers (XXIV, a or b). Some doubt is cast on this assertion, however, by the work of Alder and Jacobs[21] on the adduct from *cyclo*heptatriene itself. They claim that only one mole of hydrogen is taken up, unless an especially active catalyst is used, and furthermore, obtained caronic acid by exhaustive oxidation. Their proposed formula for the derivative (XXV) is, therefore, that based on a carane type skeleton.

Oxidation of XIII with alkaline permanganate gave, as the only detectable product, dimethylmalonic acid, only reconcilable with the triene structure for the hydrocarbon, since caradiene (XXIII) would almost certainly oxidise to caronic acid. An estimation of the double bond content with perbenzoic acid in chloroform, following the uptake over several days, gave a value of 1.8 double bonds. This low value is not without precedent, however, since <u>cyclo</u>-octatetraene under similar conditions[31] will only consume one mole of perbenzoic acid. Steric considerations make it unlikely that three epoxide rings could be accommodated on a structure such as XIII without introducing undue strain on the molecule.

The hydrogenation figures were, nevertheless, more disturbing. Double bond values were obtained, varying from 1.9 to 2.4, depending on the solvent, and in every case, signs of catalyst poisoning were apparent, as absorption was slow and ceased completely until fresh catalyst was introduced. Since these figures could not rule out the caradiene structure it was decided to isolate and characterise the hydrogenation product. It was impossible to obtain it in a solvent free condition, due to its high volatility, (a fact previously noted for eucarvane (XXVI) by Ruzicka and Seidel[22]), so a technique was adopted whereby hydrogenation was accomplished in a water miscible solvent, and the product isolated by addition of water, with subsequent washing to remove all solvent. Examination of the infra-red spectrum of the product showed definite evidence of residual unsaturation and a ketonic impurity. An effort to establish the existence of this unsaturation by means of perbenzoic acid, gave a negative result, presumably since any double bond remaining is inaccessible to the reagent. The impure material was treated with strongly acid permanganate and then extracted several times with concentrated sulphuric acid, washed, and left over alumina, in an attempt to remove the impurities. The infra-red spectrum still showed evidence of a double bond but not of carbonyl absorption, yet it was found that all catalyst poisons had now been removed, as further hydrogenation resulted in a rapid uptake, leaving a completely saturated material. Its infra-red spectrum was again measured and found to be almost identical with that of eucarvane XXVI, but quite different from that of carane (XXVII)[23]. The samples of XXVI and XXVII for comparison, were obtained from the corresponding ketones (tetrahydroeucarvone (XVIII) and carone (XVI) resp.) by the Huang-Minlon[24] modification of the Wolff-Kishner reaction. The yields in both cases were a substantial improvement on those obtained by the older technique[22,25].

The identity of the dehydration product had now been unequivocally proved, (cf. Corey *et al.*[14,26]), the difficulties of hydrogenation being explicable by the presence of impurities, plus the ready resinification of the olefin, since a certain amount of glassy material was always isolated along with the hydrogenation product. It is possible that the poisoning of the catalyst was due to the formation of a layer of this polymer over the active surface.

The second part of the thujic acid synthesis involving a step-wise oxidation of the single methyl group, could now be confidently undertaken. A selenium dioxide oxidation of 1:1:4-trimethyl*cyclo*heptatriene (XIII) was unsuccessful due to complications, but bromination with N-bromosuccinimide proceeded smoothly in carbon tetrachloride solution, to which a little chloroform and a trace of benzoyl peroxide were added. The resulting bromo-compound (XXVIII) was used in its crude state, as the possibility of allylic rearrangement could not be ignored, though XXVIII would normally be the more stable isomer. It was treated with tetraethylammonium acetate[27] to give the acetoxy derivative (XXIX), which was converted to the free alcohol (XXX) by methanolysis in the cold with sodium methoxide in methanol. This indirect, but very mild route was chosen to avoid any possible rearrangement of the resulting carbinol (XXX).



In an attempt to repeat the preparation of the above acetate (XXIX), the product was found to analyse for $C_{12}H_{16}O_4$. This could be due to peroxide formation such as in XXXIa or XXXIb, although its structure was not proved. Schenk and Ziegler[28] obtained a similar compound (XXXIII) by the action of light on a solution of the norcaradiene derivative, XXXII.

The final oxidation of the carbinol (XXX) was accomplished with an aqueous solution of chromic acid at room temperature, by the method of Heilbron~~n~~, Jones and Sondheimer[29]. Extraction with ether gave a solid acidic product which was partially steam volatile. This volatile component solidified on cooling, and was recrystallised from petroleum ether.

Its melting point (60-75°) was decidedly lower than that of natural thujic acid (87-88°) but repeated recrystallisations gave a product, m.p. 78-80°, which showed no depression on admixture with an authentic sample kindly supplied by Dr. Gripenberg. The great difficulty in purifying the oxidation product is not unexpected, since thujic acid, as isolated from *Thuja plicata*, has to be recrystallised many times before it can be obtained perfectly pure. When a small quantity of the synthetic product was heated with concentrated hydrochloric acid, as described by Gripenberg[5], a crystalline material resulted, which did not depress the melting point of genuine cumic acid (IV). The infra-red spectra of both natural and synthetic thujic acid were determined and found to be identical.

The non-volatile constituents from the chromic acid oxidation were found to consist mainly of *trans* caronic acid. This is unexpected since the alcohol (XXX) almost certainly does not contain a three-membered ring. The production of *cyclo*propane acids by the oxidation of substances not containing a three-membered ring has, however, been observed before[30,26].

The unequivocal synthesis of thujic acid from a readily available starting material has thus been accomplished with satisfactory yields throughout, except in the final oxidation. There seems no apparent reason why a more efficient procedure for this step could not be found, but even as it stands, the overall yield of 2.3% is an improvement on that of less than 1% by Gripenberg's route[8,9], while the number of stages involved is now reduced to six from the original ten.

EXPERIMENTAL

Eucarvone (XII)

This was prepared by the method of Wallach[32], from carvone hydrobromide, as outlined in Part II of this thesis. Its 2:4-dinitrophenylhydrazone, and signigicant spectral data are there described (p. 71).

Eucarvol (XIV)[14,26]

Lithium aluminium hydride (6 gm.) was powdered and refluxed in dry ether (200 ml.) for 60 mins. Eucarvone (20 gm.), in dry ether (100 ml.), was added during 30 mins., then after standing for 10 mins., the excess hydride was decomposed by gradual addition of ethyl acetate, followed by water. The solids were dissolved in ice-cold 5% H_2SO_4, the ethereal layer separated, and the aqueous layer extracted with ether. The combined ether solution was washed with sodium bicarbonate and with water, dried, and evaporated under reduced pressure.

It is essential that in the working up, the time of contact with acid be kept to a minimum, and that the temperature be kept below about 5°, in order to avoid extensive isomerisation of the product.

The residual colourless oil was distilled to give fairly pure XIV, (18.5 gm.; 92%), b.p. 94-97°/10 mm., n_D^{18} 1.4980. Light absorption in methanol, λ max. 2485A°, (log ϵ, 3.76); in hexane, λ max. 2480A°, (log ϵ, 3.56). (Found: C, 78.55; H, 10.3; $C_{10}H_{16}O$ requires: C, 78.9; H, 10.6%.) Infra-red spectrum of a thin film showed peaks at 3375 (s.), (O-H str.); 1647, 1615 (w.), (C=C str.); 1380, 1368 (m.), ($\mathrm{C}\genfrac{}{}{0pt}{}{\diagup\mathrm{Me}}{\diagdown\mathrm{Me}}$ def.); 1180, 1130 (m.), ($\mathrm{C}\genfrac{}{}{0pt}{}{\diagup\mathrm{Me}}{\diagdown\mathrm{Me}}$ skel.); 1032 cm.$^{-1}$ (s.), (C-OH str.). (In addition a C=O str. peak was always present at about 1700 cm.$^{-1}$ due to ketonic impurity.)

Phenylurethane, by refluxing with phenyl *iso*cyanate in pet. ether (b.p. 80-100°) for 6 hrs., formed colourless needles from pet. ether (b.p. 60-80°), m.p. 110-111°. Light absorption in hexane, λ max. 2,355A°, (log ϵ, 4.47). (Found: N, 5.4; $C_{17}H_{21}NO_2$ requires: N, 5.15%.)

α-Dihydroeucarvone (XV)

Eucarvone (20 gm.) was added to lithium aluminium hydride (6 gm.) in ether, as described above. When the addition was complete, the mixture was refluxed for 30 mins., then left overnight. It was worked up as above, except that after the addition of the acid, the mixture was again allowed to stand for 8 hrs. Fractionation of the products gave XV, (15.1 gm.; 75%), as a colourless oil, b.p. 78°/ 11 mm., η_D^{17} 1.4686, together with some high boiling material. Light absorption[11] in methanol, λmax. 2,900A°, (log ϵ, 1.57). Micro-hydrogenation; 4.470 mg. in acetic acid with a palladium catalyst, absorbed 0.790 cc. hydrogen during 20 mins., corresponding to 1.1 double bonds. Infra-red spectrum, illustrated (p. 174).

<u>Semicarbazone</u>[12], colourless needles from aq. ethanol m.p. 188-189°.

<u>2:4-Dinitrophenylhydrazones</u>.

(a) XV added to a solution of 2:4-dinitrophenylhydrazine in ethanol and conc. H_2SO_4, the mixture warmed for 10 mins., and stood for 6 hrs. The crude product was purified by chromatography on neutralised alumina, eluting with benzene/pet. ether (b.p. 60-80°), (1:5). Orange-red plates from ethyl acetate, m.p. 191-194°. Melting and cooling failed to alter the melting point. Light absorption in chloroform, λmax. 3805A°, (log ϵ, 4.40). (Found: C, 57.6; H, 5.85; N, 16.9; $C_{16}H_{20}N_4O_4$ requires: C, 57.8; H, 6.05; N, 16.85%.)

(b) XV added to the reagent in acetic acid, the mixture heated at 100° till clear, then stood for 6 hrs. The crude product, isolated by the addition of water, was purified by chromatography as above. Yellow prisms from ethanol, m.p. 120-121°; mixed with the above, m.p. 90-96°. Melting and cooling failed to alter the melting point. Light absorption in chloroform, λ max. 3670A°, (log ϵ, 4.38). (Found: C, 58.05; H, 6.25; N, 16.9; $C_{16}H_{20}N_4O_4$ requires: C, 57.8; H, 6.05; N, 16.85%.)

(c) From ethanol and conc. HCl as medium, a mixture of the above two compounds was obtained.

(d) No derivative could be isolated using pyridine as medium[33].

β-Dihydroeucarvone 2:4-dinitrophenylhydrazone. β-dihydroeucarvone semicarbazone (10 mg.) was boiled for 10 mins., with excess Brady's reagent and the product recrystallised as orange-red plates from ethyl acetate, m.p. 195°. Mixed with product from (a) above, m.p. 193-194°.

Isomerisations of Eucarvol (XIV)

(a) XIV (5 gm.) was mixed with p-toluene sulphonic acid (0.1 gm.) and distilled. A considerable quantity of resins remained in the flask, and the product was fractionated, giving fairly pure β-dihydroeucarvone, (3.5 gm.; 70%), b.p. 78-79°/7 mm., n_D^{25} 1.4777.

Semicarbazone[16], needles from aq. ethanol, m.p. 203-204° (dec.), (sealed tube).

(b) XIV (2 gm.) distilled in the presence of a trace of sulphuric acid, (1 drop of a 10% solution of H_2SO_4 in ethanol). The product was fractionated, giving α-dihydroeucarvone, (1.72 gm.; 86%), b.p. 74-76°/9 mm., n_D^{25} 1.4655.

Semicarbazone[12], needles from aq. ethanol, m.p. 187-189°.

(c) XIV (3 gm.) and boron trifluoride etherate (0.1 gm.) were left overnight in ether at room temperature. Working up and fractionation, gave α-dihydroeucarvone (0.45 gm.), eucarvol (1.8 gm.) and residual resins.

(d) XIV (3 gm.) was mixed with a sodium ethoxide solution, (sodium (0.5 gm.) in ethanol (10 ml.)), and worked up in the usual way. Only unchanged XIV (2.7 gm.) was obtained.

(e) XIV (3 gm.) was shaken overnight with 10N H_2SO_4 (10 ml.). Washing free of acid, drying, and fractionally distilling, gave a mixture of products (2.4 gm.) consisting essentially of 1:1:3-trimethylcycloheptatriene (XIII), (25% of distillate), β-dihydroeucarvone (40%) and unchanged XIV (35%).

(f) XIV (3 gm.) was refluxed with conc. HCl (5 ml.) and ethanol (15 ml.) for 3 hrs. After standing overnight, working up and fractionation as above gave slightly impure XIII, (1.6 gm.; 60%), b.p. 50-55°/10 mm., n_D^{25} 1.4895. Light absorption in hexane, λmax. 2685A°, (log ϵ, 3.38). It showed no ketonic properties, rapidly decolorised permanganate in acetone, and gave a yellow precipitate with bromine in carbon tetrachloride. The other products were β-dihydroeucarvone (0.4 gm.) and resins.

(g) XIV (5 gm.) in ether (50 ml.) was shaken overnight with 2N H_2SO_4 (100 ml.). Working up gave a mixture of α-dihydroeucarvone (2.2 gm.) and unchanged XIV (2.1 gm.) together with some resins.

Isomerisations of α-dihydroeucarvone (XV)

(a) XV (1 gm.) in conc. H_2SO_4 (1 ml.) were mixed and stood for three hours. The dark red solution was diluted with water, extracted with ether, and the extracts washed with bicarbonate solution and dried. Removal of the solvent and distillation, gave impure β-dihydroeucarvone, (0.62 gm.; 62%), b.p. 86-90°/13 mm., n_D^{25} 1.4768, together with dark resins.

(b) XV (10 gm.) and conc. H_2SO_4 (1 ml.) were refluxed together in ethanol (25 ml.) for 45 mins. The solution was poured into saturated sodium carbonate solution and worked up as above. Distillation gave β-dihydroeucarvone, (9.2 gm.; 92%), b.p. 86-88°/11 mm., η_D^{25} 1.4773. Light absorption[11] in methanol, λmax. 2,380A°, (log ϵ, 3.79). Infra-red spectrum, (illustrated on p.171), showed the presence of a trace of the α-isomer, (1705 $cm.^{-1}$ (w.)).

<u>2:4-Dinitrophenylhydrazone</u>, orange-red plates from ethyl acetate, m.p. 194-195°. Mixed with the derivative from XV in strong acid, m.p. 193-194°.

Dehydrations of Eucarvol (XIV)

(a) XIV (4.8 gm.) and potassium hydrogen sulphate (1.5 gm.) were heated together at 300° and the distillate collected. Fractionation of the dried product gave a volatile liquid, impure 1:1:4-trimethyl*cyclo*heptatriene (XIII), (1.2 gm.; 28%), b.p. 78-88°/30 mm., η_D^{17} 1.4915. The main product was a ketonic material α-dihydroeucarvone, (2.6 gm.), b.p. 81°/13 mm., η_D^{20} 1.4697.

<u>2:4-Dinitrophenylhydrazone</u>, yellow prisms from ethanol, m.p. 120°. Mixed with derivative of eucarvone reduction product, m.p. 120-121°.

(b) XIV (11 gm.) and potassium pyrosulphate (3 gm.) were heated together over a naked flame. Fractionation of the dried distillate gave impure XIII(1.8 gm.; 20%) and β-dihydroeucarvone (5.7 gm.), b.p. 93-95°/18 mm., η_D^{17} 1.4820. Light absorption[11] in ethanol, λmax. 2400A°, (log ϵ, 3.85).

Semicarbazone[16], needles from aq. ethanol, m.p. 200-202° (dec.), (rapid heating). Mixed with derivative from isomerisation of XIV, m.p. 201-202°.

Oxime[16], plates from aq. ethanol, m.p. 121-122°.

(c) XIV (1 gm.) and iodine (10 mg.) were heated together, gradually raising the temperature and pressure to 200°/760 mm. Since no evolution of water occured, the contents of the flask were distilled, giving a mixture of XIV and α-dihydroeucarvone.

(d) XIV (20 gm.) and boric acid (10 gm.) were gradually heated until homogeneous, when the temperature was raised fairly rapidly to 350° on a metal bath. The crude distillate was taken up in pet. ether (b.p. 40-60°), washed with water, dried, and the solvent removed. Fractionation of the crude oil gave XIII, (11 gm.; 61%), as a colourless mobile liquid, b.p. 62°/20 mm., η_D^{20} 1.4948. Light absorption in methanol, λmax. 2680A°, (log ϵ, 3.34); in hexane,

λ max. 2680A$^{\circ}$, (log ϵ, 3.40). (Found: C, 89.6; H, 10.7; $C_{10}H_{14}$ requires: C, 89.5; H, 10.5%.) A deep red colour was given by tetranitromethane in carbon tetrachloride. Infra-red spectrum of a thin film showed peaks at 1625, 1610 (m.s.), (C=C str.); 1,375, 1,360 (s.), ($C\langle^{Me}_{Me}$ def.); 1192 (m.s.), 1170 (m.), ($C\langle^{Me}_{Me}$ skel.); 816 (s.), ($^{R}_{R}\rangle C=C\langle^{H}_{R}$ def.); 664 cm.$^{-1}$ (m.), (<u>cis</u> CH=CH def.). A small amount of ketonic impurity was indicated by a peak at 1710 cm.$^{-1}$. The second fraction was α-dihydroeucarvone (4.6 gm.), b.p. 82°/12 mm., n_D^{19} 1.4699.

In an attempt to remove the traces of ketone from XIII by means of semicarbazide acetate, a large proportion polymerised to a hard glass, soluble in hot chloroform. It was also noted that after standing for a few days XIII partially polymerised to a similar material.

<u>Eucarvyl chloride (XX?)</u>

Eucarvol (5 gm.) and dimethylaniline (6 gm.) in chloroform (10 ml.) were cooled in ice, and thionyl chloride (5 gm.) in chloroform (10 ml.) was added dropwise with stirring during 30 mins. Stirring was continued for a further 30 mins., and the mixture maintained at -10° for 10 hrs. After shaking with ice-cold N HCl (50 ml.), the mixture was extracted with chloroform and the extracts washed with N HCl, with bicarbonate, and with water. After drying and freeing from solvent, the residual yellow oil was distilled, giving XX as a fragrant, colourless, mobile liquid, (3.9 gm.; 70%), b.p. 78-80°/8 mm., n_D^{18} 1.4992. Light absorption in methanol, λ max. 2,430A°, (log ϵ, 3.48). (Found: C, 70.05; H, 8.85; Cl, 20.4; $C_{10}H_{15}Cl$ requires: C, 70.35; H, 8.85; Cl, 20.8%.) An immediate white precipitate was formed with alcoholic silver nitrate. Infra-red spectrum of a thin film showed peaks at 3020 (w.), (=C-H str.), 1658 (m.s.), (C=C str.), 1400, 1395 cm.$^{-1}$ (m.), ($C\begin{smallmatrix}\diagup Me\\ \diagdown Me\end{smallmatrix}$ def.). XX decomposes on standing in air to black tars.

<u>Attempted dehydrochlorination of XX</u>. Dry silver oxide was prepared from silver nitrate (6 gm.), as described by Steiner and Selving[19], and covered with dry benzene (20 ml.). XX (3 gm.) in benzene (40 ml.) was added during 30 mins., with occasional shaking. The mixture was shaken at room temperature for 48 hrs., and the solids filtered off. Since distillation yielded only a trace of water, the solution was refluxed for 2 hrs. with more silver oxide, but no more water was formed. The benzene was removed under reduced pressure and the residual oil distilled, with considerable decomposition, to give a colourless oil (2.1 gm.), b.p. 78-80°,

η_D^{25} 1.4899. Light absorption in methanol, λ max. 2,395A°, (log ϵ, 3.68) and 2,880A°, (flat peak), (log ϵ, 3.09). It contained chlorine. (Found: Cl, 5.95%.)

2:4-Dinitrophenylhydrazone. Treatment of the above liquid with Brady's solution gave a crude product, chromatography of which yielded impure β-dihydroeucarvone 2:4-dinitrophenylhydrazone; orange-red plates from ethyl acetate, m.p. 185-188°. Mixed with an authentic sample, m.p. 188-190°.

Maleic anhydride adduct of XIII

1:1:4-trimethyl*cyclo*heptatriene (XIII), (1 gm.), and maleic anhydride (0.8 gm.), were heated together in a sealed tube for 3 hrs. at 100°. The pasty mass was extracted twice with portions (100 ml.) of the top layer of a previously shaken mixture of equal volumes of pet. ether (b.p. 60-80°), benzene, methanol and water[34]. The extracts were washed with the bottom layer, and the washings re-extracted with a further portion (100 ml.) of the top layer. After drying the combined extracts, removal of the solvents gave a yellow gum, crystallising when triturated with a little ethanol. Colourless prisms from ethanol, m.p. 112-114°. (Found: C, 71.95; H, 6.4; $C_{14}H_{16}O_3$ requires C, 72.4;

H, 6.95%.) Microhydrogenation; 5.815 mg. in acetic acid with a platinum catalyst, absorbed 1.260 cc. hydrogen at 761 mm. and 20.5°, corresponding to 2.08 double bonds. Attempts to prepare the adduct in benzene or xylene as solvent, were unsuccessful, due to the extensive formation of a white, acetone soluble polymer, m.p. 210-220°.

Permanganate oxidation of XIII

XIII (0.4 gm.) in benzene (10 ml.) and water (20 ml.) was stirred, and a solution of potassium permanganate (6.0 gm.) in water (100 ml.) added during 60 mins., while carbon dioxide was passed through the mixture. The stirring and passage of carbon dioxide were continued for a further 6 hrs., the reaction mixture left overnight, then acidified with HCl, and treated with sulphur dioxide until a clear solution resulted. Continuous extraction with ether for 2 days, gave, on working up, a straw-coloured gum which was extracted several times with boiling benzene, depositing a crystalline material on partial evaporation. The product (60 mg.), colourless plates from benzene, could be further purified by sublimation, m.p. 189-191° (dec.), (rapid heating). Mixed with dimethylmalonic acid, m.p. 188-191°. A portion was heated at 180° for 10 mins., and the resulting *iso*butyric acid isolated as its S-benzylthiouronium derivative, m.p. and mixed m.p. 141-143°.

Dimethylmalonic acid. Diethyl malonate (4 gm.) was added to a warm solution of sodium (2 gm.) in dry ethanol (15 ml.), the mixture maintained at 60° for 10 mins., and then cooled. Methyl iodide (15 gm.) was added in portions during 30 mins., cooling externally. The vessel was corked and kept in the dark for 4 days, water (25 ml.) added and the mixture acidified with dilute H_2SO_4. It was then extracted with ether and the extracts washed successively with 2N sodium hydroxide, water, sodium thiosulphate , and water. After drying and removal of the solvent, the residual oil was distilled, giving a colourless distillate, diethyl dimethylmalonate, (3.60 gm.; 75%), b.p. 78°/11 mm., n_D^{21} 1.4123. A portion of this ester was hydrolysed by shaking with excess 20% potassium hydroxide for 2 days, diluting with water, and acidifying with conc. HCl. The free acid was isolated in quantitative yield, by repeated extraction with ethyl acetate. White needles from ethyl acetate/pet. ether (b.p. 60-80°), m.p. 188-191° (dec.), (rapid heating).

Perbenzoic titration of XIII

A solution of perbenzoic acid in chloroform was prepared by adding benzoyl chloride (6.25 gm.) in cold ether (25 ml.) to sodium peroxide (7.5 gm.) in iced water (100 ml.) and ethanol (50 ml.). After stirring for 5 mins. and filtering rapidly, the mixture was acidified with iced N H_2SO_4 (180 ml.), extracted with chloroform (4 x 40 ml.) and the extracts washed with water, dried, and stored in a dark bottle at 0° [35]. The solution was standardised by adding (2 ml.) to 0.4N acetic acid (10 ml.) and saturated potassium iodide (1 ml.). The mixture was shaken and the liberated iodine titrated with 0.03N sodium thiosulphate.

To the above perbenzoic acid solution (30 ml.), XIII (0.15 gm.) in chloroform (2 ml.) was added and the solution kept in the dark at 0°. The reaction was followed by withdrawing aliquot portions (1 ml.) from time to time, estimating the unreacted perbenzoic acid by the above procedure. The reaction, at first rapid, soon became very slow, ceasing completely after 96 hrs., by which time the consumption of perbenzoic acid was equivalent to 1.8 double bonds per mole. An attempt to isolate a pure product was unsuccessful, the initial sticky product yielding only a gum after chromatography on alumina.

Hydrogenation of XIII

This was accomplished in a variety of solvents including ether, methanol, ethyl acetate, acetic acid, butanol, and diethylene glycol. The high volatility of the hydrogenated compound in low boiling solvents prevented the isolation of a solvent-free product, while in the high boiling glycol the rate of uptake was excessively slow. Only by the use of water miscible solvents, (see below), could a pure product be obtained. Both palladium-charcoal and Adam's catalyst were used, but in no case was an uptake of more than 2.4 moles observed, despite the addition of further quantities of catalyst to counteract the poisons present. A typical run is as follows:-

XIII (5.62 gm.) in methanol (15 ml.) was hydrogenated over Adam's catalyst (0.5 gm.). Absorption, at first rapid, ceased after 90 mins., and further portions of catalyst (0.1 gm.) were added from time to time, until no further uptake occured. Allowing for the uptake by the catalyst itself, 2,250 ml. at 758 mm. and 20^{o} were taken up, corresponding to 2.2 double bonds. The catalyst was filtered off and washed with methanol, water (50 ml.) was added to the filtrate, and the upper layer separated off, washed with water, dried and distilled, giving a colourless liquid

(4.45 gm.; 77%), b.p. 70°/28 mm., n_D^{24} 1.4462. A quantity of high boiling residue remained in the flask. Light absorption in hexane showed an end absorption, and a pale yellow colour was produced by tetranitromethane in carbon tetrachloride. No uptake of perbenzoic acid was detectable after 48 hrs. The infra-red spectrum displayed peaks typical of residual unsaturation, and of a ketonic impurity.

The partially hydrogenated material was shaken twice with strongly acid permanganate solution, and several times with conc. H_2SO_4 until the acid ceased to become coloured. After washing and standing over alumina for 24 hrs., the remaining product was distilled. Coloration by tetranitromethane and bands in the infra-red spectrum were still observed, indicative of unsaturation, but the carbonyl absorption was no longer visible. This material (1.32 gm.) in acetic acid (20 ml.) over Adam's catalyst (0.2 gm.) absorbed 110ml. of hydrogen at 755 mm. and 20° during 45 mins., corresponding to 0.5 double bonds. The product was isolated by pouring into water and washing with bicarbonate. Distillation gave a completely saturated product, eucarvane, (1.19 gm.; 90%), b.p. 86°/56 mm., n_D^{25} 1.4412. Light absorption in hexane was absent. (Found: C, 85.45; H, 14.4; $C_{10}H_{20}$ requires: C, 85.65; H, 14.35%.) Addition to tetranitromethane in carbon tetrachloride gave no colour. Infra-red absorption, illustrated on p.173, was almost identical with that of eucarvane.

Carane (XXVII)

Carone (5 gm.), 60% hydrazine hydrate (3.5 ml.) and sodium hydroxide (2.7 gm.) in diethylene glycol (25 ml.)[24] were refluxed for 90 mins., a thermometer in the liquid reading 137°. More hydrazine hydrate (2 ml.) was added and refluxing continued for 60 mins., the temperature now being 134°. The contents were now distilled out until the temperature reached 207°, and the distillate was set aside. The residual solution was heated under reflux for 12 hrs., combined with the distillate, diluted with water (100 ml.) and extracted with ether. The combined extracts were washed with 2N HCl and with water, dried, and the solvent removed. The residual pale yellow oil distilled to give a colourless liquid, XXVII, (2.73 gm.; 61%), b.p. 76°/43 mm., n_D^{20} 1.4575, which gave a bright yellow colour with tetranitromethane in carbon tetrachloride. Infra-red absorption[23], illustrated (p. 173).

Tetrahydroeucarvone (XVIII)

Eucarvone (5 gm.) in ethanol (20 ml.) was hydrogenated over 10% palladium-charcoal (0.5 gm.). Absorption was complete after 2½ hrs., uptake being 1,620 ml. at 765 mm. and 23°, corresponding to 2.0 double bonds. The catalyst was filtered off and washed with hot ethanol, then the filtrate freed from solvent and distilled, giving XVIII, (4.65 gm.; 91%), b.p. 79-80°/12 mm., η_D^{19} 1.4558. Infra-red spectrum, illustrated (p. 172).

2:4-Dinitrophenylhydrazone by addition to Brady's solution. Purified by chromatography on bentonite and kieselguhr[36], eluting with pet. ether (b.p. 60-80°). The crude product seemed to be a mixture of isomers. Orange plates from pet. ether (b.p. 80-100°), m.p. 137-137.5°. (Found: C, 57.7; H, 6.35; N, 16.45; $C_{10}H_{22}N_4O_4$ requires: C, 57.45; H, 6.65; N, 16.75%.) Light absorption in chloroform, λmax. 3,650A°,(log ϵ, 3.98).

Eucarvane (XXVI)

Tetrahydroeucarvone (3.5 gm.), 60% hydrazine hydrate (3.0 ml.), and sodium hydroxide (2.3 gm.), in diethylene glycol (20 ml.) treated as described for carane, above. XXVI, colourless oil, (1.80 gm.; 59%), b.p. 72-72.5°/35 mm., η_D^{15} 1.4438. Only a very faint colour was given by tetranitromethane in carbon tetrachloride. Infra-red spectrum, illustrated (p. 173).

Carone 2:4-dinitrophenylhydrazone, prepared and purified as for the tetrahydroeucarvone derivative. Orange-red needles from ethanol, m.p. 101-102°. Light absorption in chloroform, λ max. 3685A°, (logϵ, 4.34). (Found: C, 58.35; H, 6.0; N, 16.9; $C_{16}H_{20}N_4O_4$ requires: C, 57.8; H, 6.05; N, 16.85%.)

4-Bromomethyl-1:1-dimethylCYCLOheptatriene (XXVIII)

1:1:4-trimethyl*cyclo*heptatriene (1 gm.) in carbon tetrachloride (10 ml.) was treated with freshly crystallised, dry, N-bromosuccinimide (1.3 gm.) and the mixture gently refluxed for 5 hrs. No apparent change was observed, but the addition of chloroform (3 ml.) and a few crystals of benzoyl peroxide, caused the reaction to go to completion within 20 mins. (All solids now on surface of mixture.) After cooling in ice, the succinimide (0.7 gm.; 97%) was filtered off and the filtrate freed from solvents under reduced pressure. The light brown oily residue (1.5 gm.; 100%) was not purified further.

4-Acetoxymethyl-1:1-dimethylCYCLOheptatriene (XXIX)

Tetraethylammonium acetate was prepared, as described by Owen and Smith[27], by treating tetraethylammonium bromide solution with silver oxide, filtering and neutralising with acetic acid. Evaporation gave the crude acetate, crystallising from acetone at -70°. XXVIII(1.5 gm.) in acetone (10 ml.) was added slowly to tetraethylammonium acetate (5 gm.) in acetone (50 ml.), with occasional shaking and external cooling to maintain below 5°. The orange solution deposited tetraethylammonium bromide on standing overnight. The bromide was filtered off, washed with acetone till colourless, and the filtrate concentrated under reduced pressure. Dilution with water, extraction with ether and drying, gave, on removal of the solvent and distillation, XXIX, (1 gm.; 73%) as a colourless liquid, b.p. 94-97°/ 12 mm., η_D^{19} 1.5435.

On repetition of the above preparation, an oil (XXXI?) was obtained, b.p. 104°/11 mm., η_D^{18} 1.5415, which gave only trans-caronic acid, m.p. 208°, on methanolysis and subsequent oxidation (see below). (Found: C, 64.3; H, 7.2; $C_{12}H_{16}O_4$ requires: C, 64.3; H, 7.15%.)

4-Hydroxymethyl-1:1-dimethylCYCLOheptatriene (XXX)

XXIX (1 gm.) was added to a methanolic solution of sodium methoxide, (from sodium (0.1 gm.) and methanol (20 ml.)), and set aside for 18 hrs. After dilution with water, the mixture was extracted with ether, and the extracts washed with water, dried, and freed from solvent. Distillation gave XXX as a colourless oil (0.35 gm.; 51%), b.p. 100-102°/12 mm., $\eta_D^{19.5}$ 1.5200.

Thujic acid (I)

XXIX (0.35 gm.) in acetone (10 ml.), was treated with a solution of chromium trioxide (0.31 gm.) in water (20 ml.), at such a rate as to keep the temperature below 20°[29]. After shaking for 60 mins. the mixture was extracted several times with ether, and the extracts washed with sodium carbonate solution, which was then acidified. Extraction of the acid solution with ether and removal of the solvent gave a gum (80 mg.), which became crystalline on standing. The crude acids were steam distilled, and the volatile material (40 mg.) was isolated, and crystallised from pet. ether (b.p. 40-60°) as colourless needles, m.p. 60-75°. Repeated recrystallisations from the same solvent gave a purer product, I, m.p. 78-80°. Admixture with an authentic sample, (m.p. 81-82°), caused no depression. Infra-red spectrum, (illustrated on p. 175), was determined for both natural and synthetic acids, the two being practically identical.

The non-volatile material consisted mainly of <u>trans</u> caronic acid; prisms from water, m.p. 205-211°.

Isomerisation of thujic acid[5]

A portion of I was refluxed with conc. HCl for 30 mins. and, after diluting with water and cooling, the crystals were filtered off. Recrystallisation from aqueous methanol gave colourless prisms, m.p. 114-116°. Mixed with an authentic sample of cumic acid, m.p. 114-116°.

REFERENCES

1. Blasdale; J. Amer. Chem. Soc., 1907, 29, 539.
2. Anderson, and Sherrard; ibid., 1933, 55, 3813.
3. Erdtman, and Gripenberg; Nature, 1948, 161, 719.
4. idem.; ibid., 1949, 164, 316.
5. Gripenberg; Acta Chem. Scand., 1949, 3, 1147.
6. Baeyer; Ber., 1894, 27, 810.
7. Merling; Ber., 1891, 24, 3108.
8. Gripenberg; Acta Chem. Scand., 1951, 5, 995.
9. idem.; ibid., 1952, 6, 854.
10. Wallach; Ann., 1905, 339, 94.
11. Gillam, and West; J., 1942, 483.
12. Baeyer; Ber., 1894, 27, 1915.
13. Corey, and Burke; J. Amer. Chem. Soc., 1954, 76, 5257.
14. Corey, Burke, and Remers; ibid., 1955, 77, 4942.
15. Braude; J., 1945, 498.
16. Wallach, Albright, and Klein; Ann., 403, 1914, 73.
17. Brandenberg and Galat; J. Amer. Chem. Soc., 1950, 72, 3275.
18. O'Connor and Nace; ibid., 1955, 77, 1578.
19. Steiner and Selving; Helv. Chim. Acta, 1951, 34, 1176.
20. Cole; Chem. and Ind., 1953, 946; J., 1954, 3807.

21. Alder and Jacobs; Ber., 1953, 86, 1528.

22. Ruzicka and Seidel; Helv. Chim. Acta, 1936, 19, 424.

23. Pliva and Herout; Coll. Czech. Chem. Comm., 1950, 15, 160.

24. Huang-Minlon; J. Amer. Chem. Soc., 1946, 68, 2487.

25. Semmler and Feldstein; Ber., 1914, 47, 384.

26. Corey, Burke and Remers; J. Amer. Chem. Soc., 1956, 78, 180.

27. Owen and Smith; J., 1952, 4035.

28. Schenk and Ziegler; Ann., 1954, 584, 221.

29. Heilbron, Jones and Sondheimer; J., 1947, 1586.

30. Farmer and Ingold; ibid., 1920, 1362.

31. Reppe, Schinting, Klager and Toepel; Ann., 1948, 560, 1.

32. Wallach; Ann., 1899, 305, 237; ibid., 1905, 339, 94.

33. Braude and Timmons; J., 1953, 3131.

34. Anet, Lythgoe, Silk and Trippett; ibid., 320.

35. Nat. Bureau Standards; C. 440, p. 480.

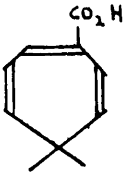
36. Elvidge and Whalley; Chem. and Ind., 1955, 589.

37. Baeyer; Ber., 1898, 31, 2067.

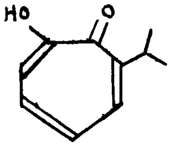
38. Dryden; J. Amer. Chem. Soc., 1954, 76, 2841.

39. Pesch and Friess; ibid., 1950, 72, 5756.

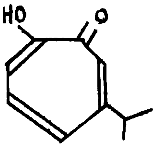
FORMULAE.



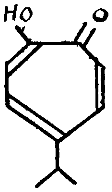
I



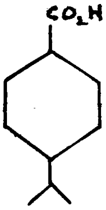
II a



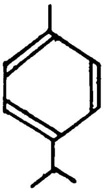
II b



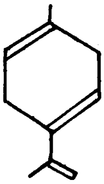
II c



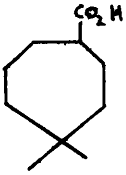
III



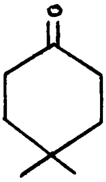
IV



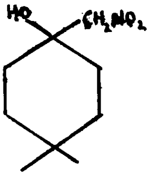
V



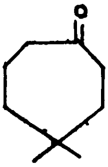
VI



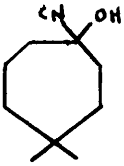
VII



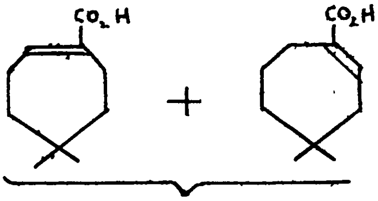
VIII



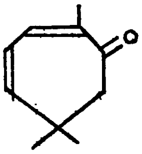
IX



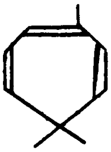
X



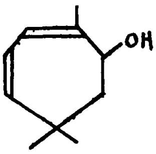
XI



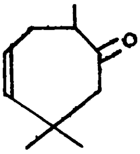
XII



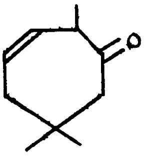
XIII



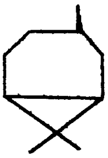
XIV



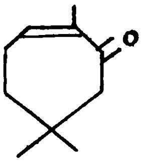
XV



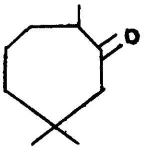
XV a



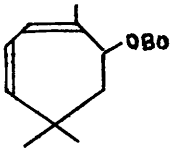
XVI



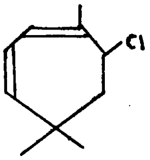
XVII



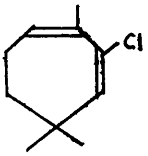
XVIII



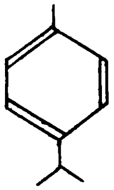
XIX



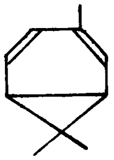
XX



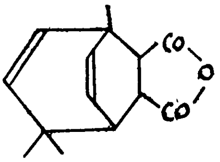
XXI



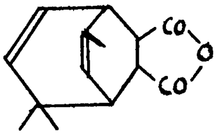
XXII



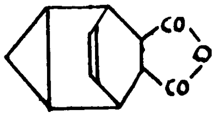
XXIII



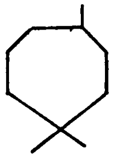
XXIV a



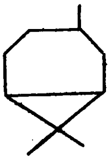
XXIV b



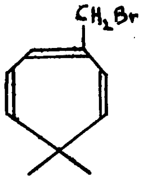
XXV



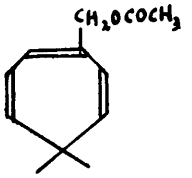
XXVI



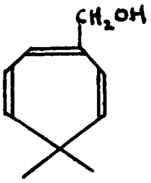
XXVII



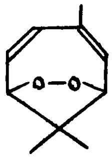
XXVIII



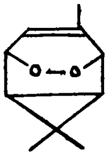
XXIX



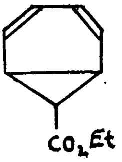
XXX



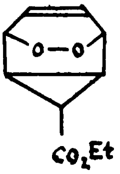
XXXI a



XXXI b



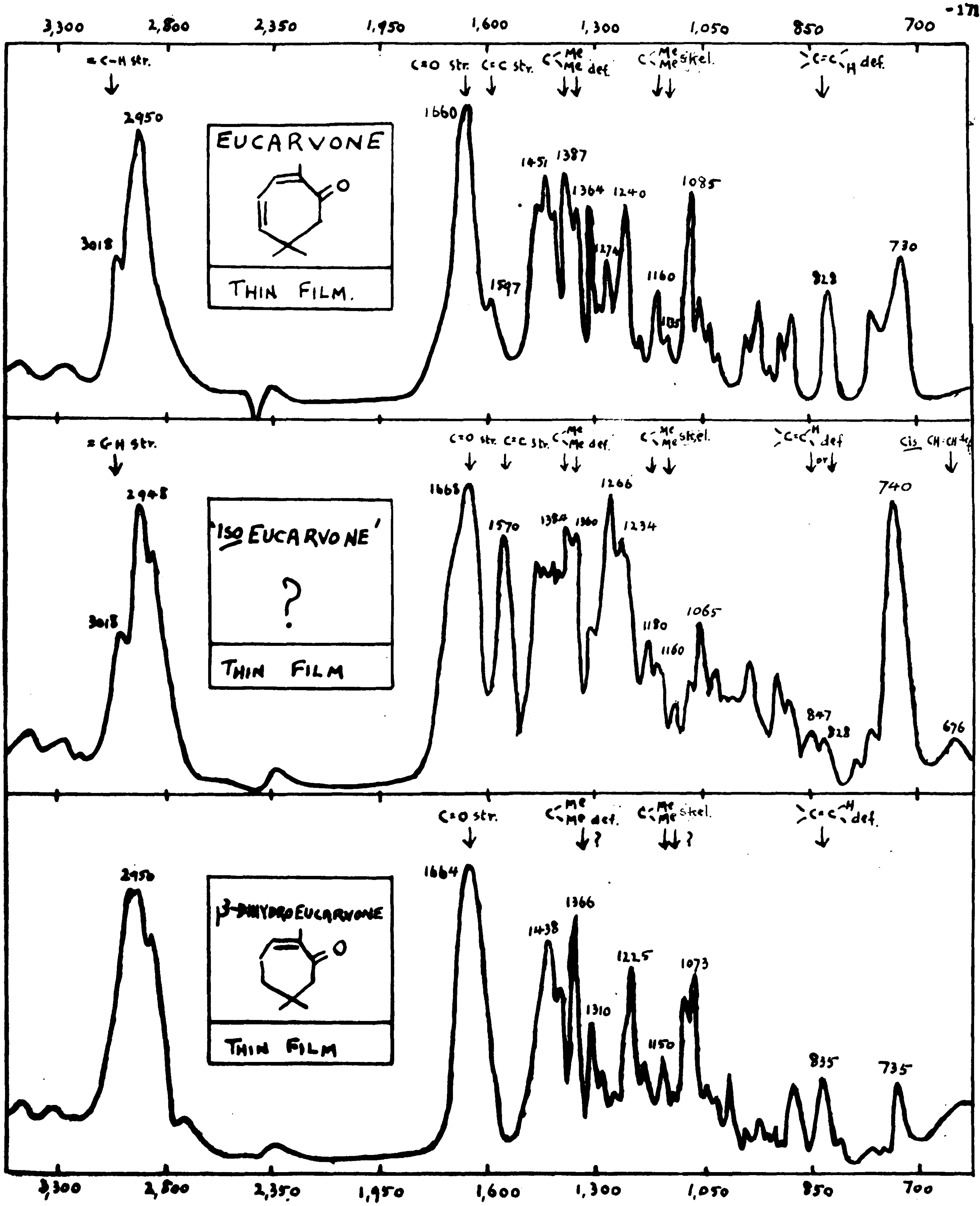
XXXII

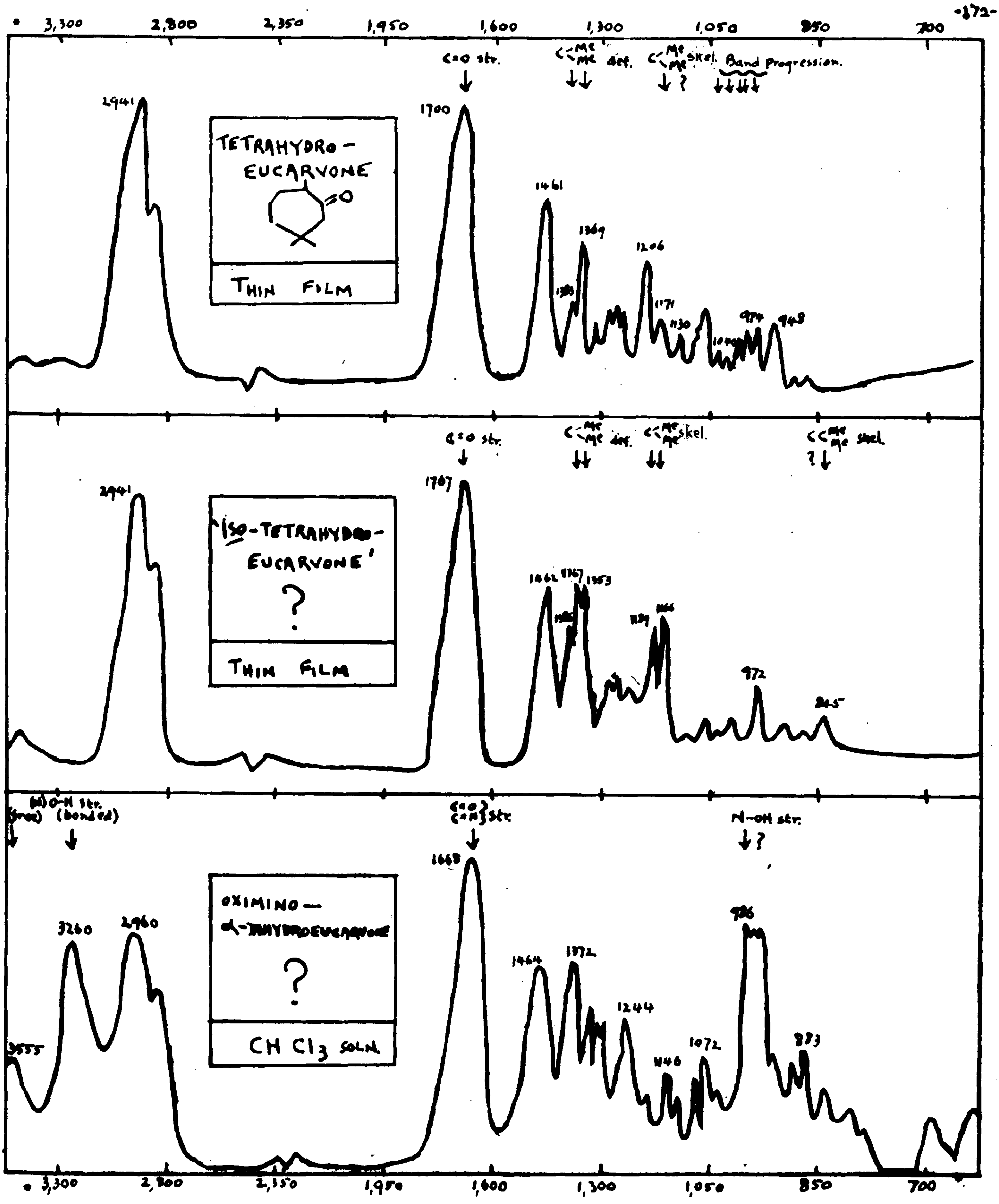


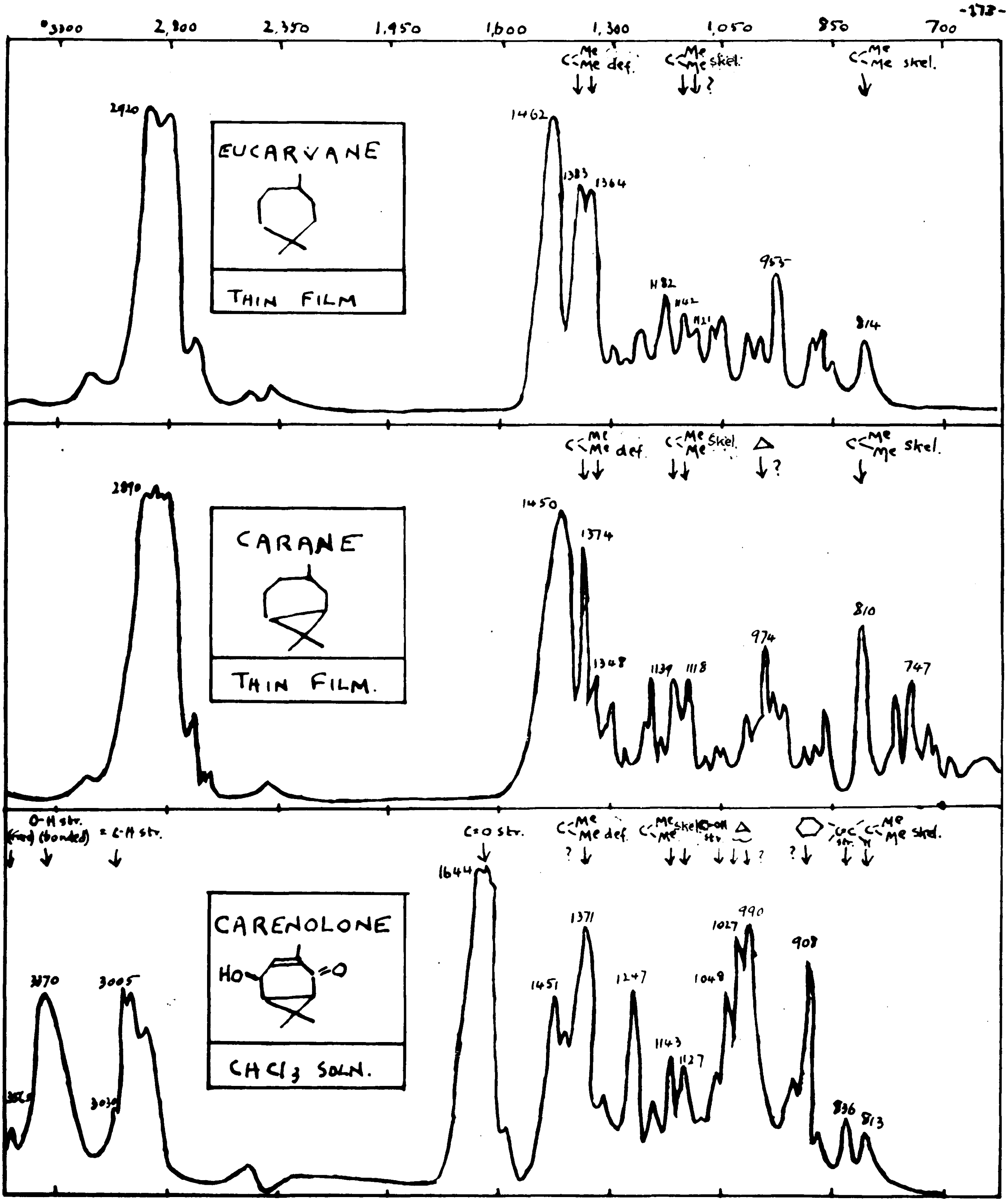
XXXIII

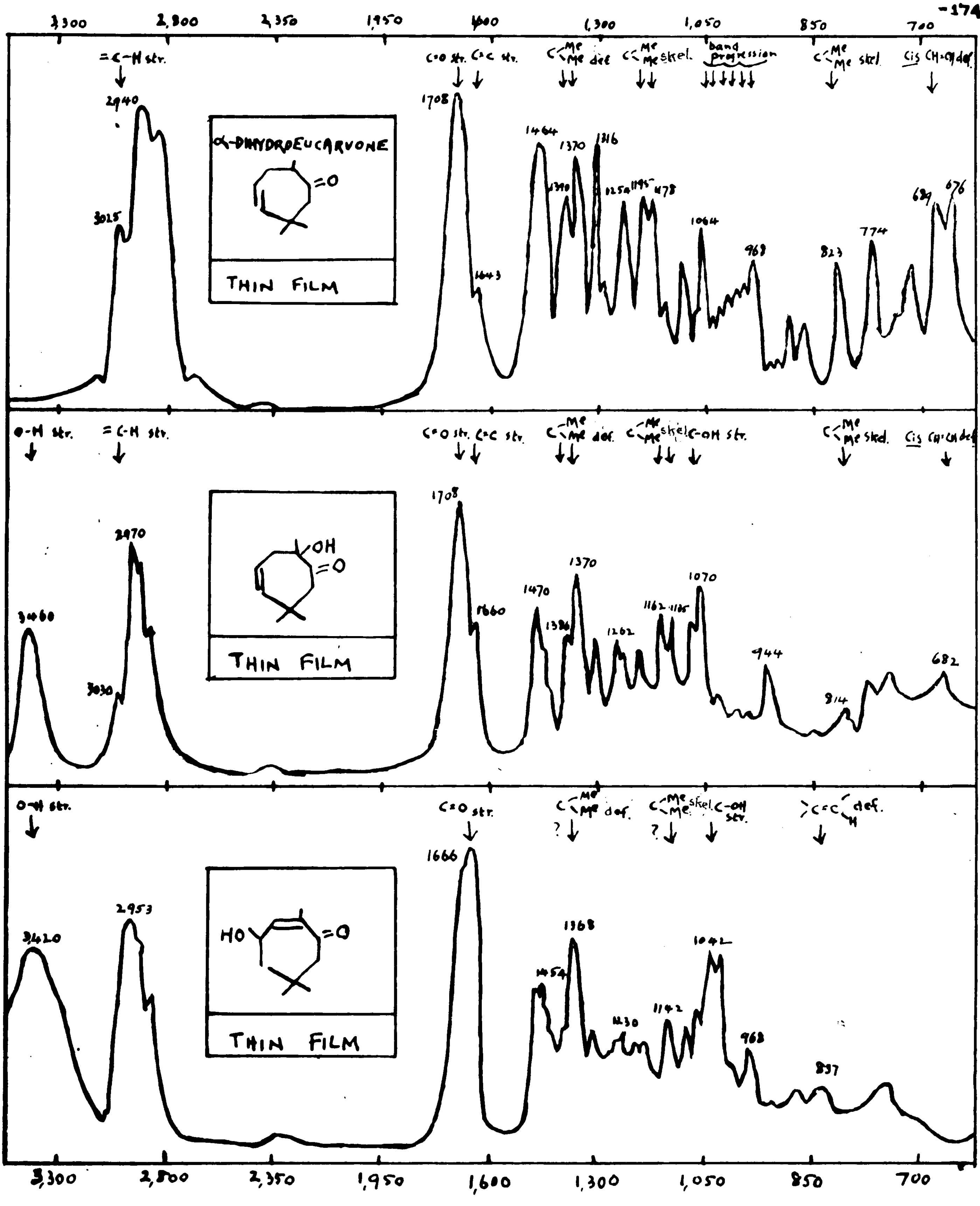
APPENDIX

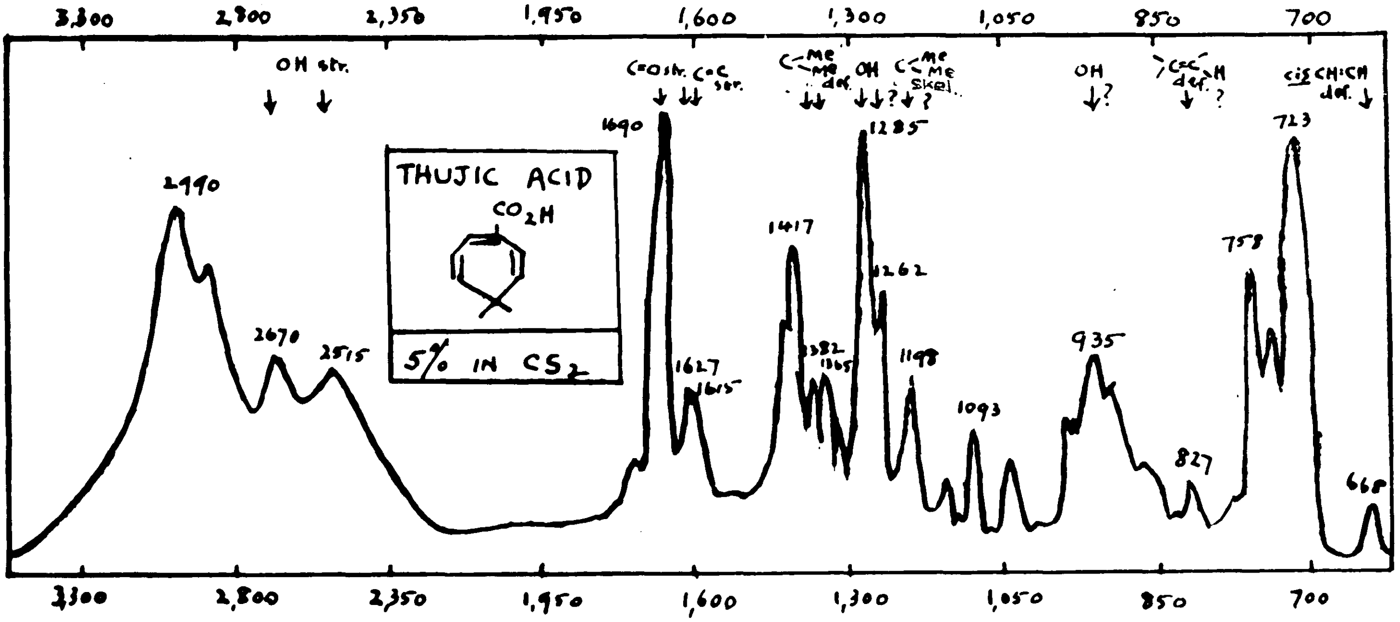
INFRA-RED SPECTRA OF SOME EUCARVONE DERIVATIVES


3,300
2,800
2,350
1,950
1,600
1,300
1,050
850
700
≡C-H str.
C=O str.
C=C str.
C<Me Me def.
C<Me Me skel.
>C=C<H def.
2950
3018
1660
1597
1451
1387
1364
1274
1240
1160
1135
1085
828
730
EUCARVONE
THIN FILM.
≡C-H str.
C=O str.
C=C str.
C<Me Me def.
C<Me Me skel.
>C=C<H def.
or
Cis CH=CH def.
2948
3018
1668
1570
1384
1360
1266
1234
1180
1160
1065
847
828
740
676
'ISO EUCARVONE'
?
THIN FILM
C=O str.
C<Me Me def.
?
C<Me Me skel.
?
>C=C<H def.
2950
1664
1438
1366
1310
1225
1150
1073
835
735
β-DIHYDROEUCARVONE
THIN FILM
3,300
2,800
2,350
1,950
1,600
1,300
1,050
850
700


3,300
2,800
2,350
1,950
1,600
1,300
1,050
850
700
C=O str.
C<Me Me def.
C<Me Me skel.
Band Progression.
2941
1700
1461
1383
1369
1206
1171
1130
1040
974
948
TETRAHYDRO-EUCARVONE
THIN FILM
C=O str.
C<Me Me def.
C<Me Me skel.
C<Me Me skel.
2941
1707
1462
1383
1367
1353
1184
1166
972
845
'ISO-TETRAHYDRO-EUCARVONE'
?
THIN FILM
(a) O-H str.
(free)
(bonded)
C=O C=N } str.
N-OH str.
3555
3260
2960
1668
1464
1372
1244
1146
1072
936
883
OXIMINO-
α-TETRAHYDROEUCARVONE
?
CH Cl3 SOLN.


3,200
2,800
2,350
1,950
1,600
1,300
1,050
850
700
C<Me Me def.
C<Me Me skel.
?
C<Me Me skel.
2920
1462
1383
1364
1182
1142
1121
953
814
EUCARVANE
THIN FILM
C<Me Me def.
C<Me Me Skel.
?
C<Me Me skel.
2890
1450
1374
1348
1139
1118
974
810
747
CARANE
THIN FILM.
O-H str.
(free) (bonded)
= C-H str.
C=O str.
?
C<Me Me def.
C<Me Me skel.
C-OH str.
?
?
C=C str.
C<Me Me skel.
1644
3070
3005
3030
1451
1371
1247
1143
1127
1048
1027
990
908
836
813
CARENOLONE
HO
=O
CHCl3 SOLN.
3,200
2,800
2,350
1,950
1,600
1,300
1,050
850
700


3,300
2,800
2,350
1,950
1,600
1,300
1,050
850
700
=C-H str.
C=O str.
C=C str.
C<Me Me def.
C<Me Me skel.
band progression
C<Me Me skel.
Cis CH=CH def.
2940
3025
1708
1643
1464
1390
1370
1316
1254
1195
1178
1064
968
823
774
689
676
α-DIHYDROEUCARVONE
=O
THIN FILM
O-H str.
=C-H str.
C=O str.
C=C str.
C<Me Me def.
C<Me Me skel.
C-OH str.
C<Me Me skel.
Cis CH=CH def.
3460
3030
2970
1708
1660
1470
1386
1370
1262
1162
1135
1070
944
814
682
OH
=O
THIN FILM
O-H str.
C=O str.
C<Me Me def.
C<Me Me skel.
C-OH str.
>C=C<H def.
?
?
3420
2953
1666
1454
1368
1230
1142
1042
968
837
HO
=O
THIN FILM
3,300
2,800
2,350
1,950
1,600
1,300
1,050
850
700


3,300
2,800
2,350
1,950
1,600
1,300
1,050
850
700
OH str.
C=O str.
C=C str.
C<Me Me def.
OH
C<Me Me skel.
?
OH ?
>C=C<H def. ?
cis CH:CH def.
2990
2670
2515
1690
1627
1615
1417
1382
1365
1285
1262
1198
1093
935
827
758
723
668
THUJIC ACID
CO₂H
5% IN CS₂