SYNTHETIC STUDIES ON STEROIDAL ALKALOIDS

A THESIS PRESENTED FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

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BY

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SUMMARY

In the first part of this thesis, a brief survey of the chemistry of veratramine viz. its occurrence, isolation and structural diagnosis is given. This part also includes a review of recent work on the stereochemistry and the synthetic work of other workers on the alkaloid.

The main section describes three approaches to the synthesis of the C-Nor-D-homo ring system of the veratrum alkaloids. Howell and Taylor's acetate diester 6β-acetoxy-1β:2α di (methoxy carbonyl methyl)-9β-methyl-trans decalin prepared from 2:3:4:9:10:12-hexahydro-6-methoxy-12-methyl-2-oxophenanthrene was successfully cyclised to the potential intermediate 6β-acetoxy-1β:2α-(cyclopentan-3′-one)-9-methyl-trans decalin. The pentanone was ring extended to give a solid substance which certainly contained the steroidal ring system of veratramine but which could not be obtained in the pure form. Attempts aimed at an easier preparation of the pentanone acetate by alkylating 1-oxo-6-ethoxy-8a-methyl-1,2,3,7,8,8a hexahydro naphthalene with different alkylating agents were unsuccessful, the starting material being recovered in each case.

In a second approach, 1-(2-cyanoethyl)-2-hydroxy naphthalene

was converted to 2:3:4:9:10:12-hexahydro-6-methoxy-7-(3-bromo-propyl)-12-methyl-2-oxophenanthrene and 8-oxo-10a-methyl-1,2,3,4,5,6,8,9,10,10a-decahydro-1-oxa chrysene. The benzene nucleus of either intermediate was resistant to reduction and so they could not be used for further work.

In the last attempt, 2-benzoyloxy-1,2,3,4,5,6,7,9,10,11,12,13 dodecahydro-12-methyl-7-oxophenanthrene was prepared starting with 2-naphthol and the tricyclic enone was successfully condensed with 2,2-ethylenedioxy-5-bromo pentan-2-one in the presence of potassium t-butoxide in t-butanol. The adduct was successively reduced, reacted with methyl magnesium bromide, deketalized, acetylated, ozonised and cyclised to give an oily substance which contained the veratramine steroidal nucleus as revealed by its U.V. spectrum. The oil did not crystallize. An oil which should probably crystallize more readily could be obtained if complete reduction of the original unsaturated adduct could be accomplished.

In the attempts some new compounds were prepared. These were mainly naphthalene, phenanthrene and hydrochrysene compounds. I.R., U.V. or N.M.R. spectroscopic data were recorded for all the new compounds and for most of the known ones. Some structural formulae are repeated in the script, so as to aid the reader's comprehension.

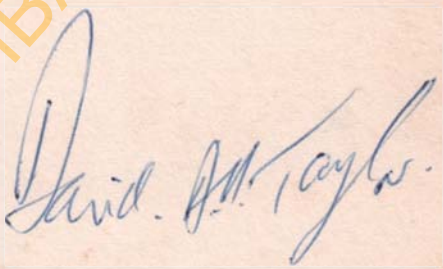
ACKNOWLEDGEMENTS

The author's sincere thanks go to Professor D.A.H. Taylor for his kind supervision and the unflinching help given throughout the whole course of study; to Professor C.W.L. Bevan for his encouragement and the general interest shown in the author's progress; and to Dr. J.W. Powell and Dr. D.E.U. Ekong for useful discussion during the time the author's supervisor was away on study leave.

The valuable service rendered by the entire technical staff of the Chemistry Department of the University of Ibadan is acknowledged.

The author is grateful to Mr. M.A. Daramola for the great care he took in the production of the thesis; to the University of Ibadan for providing a grant for the course; and finally to his wife for her understanding.

I certify that this work has been carried out by Mr. E.A. Adegoke in the Department of Chemistry, University of Ibadan.



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February, 1966.

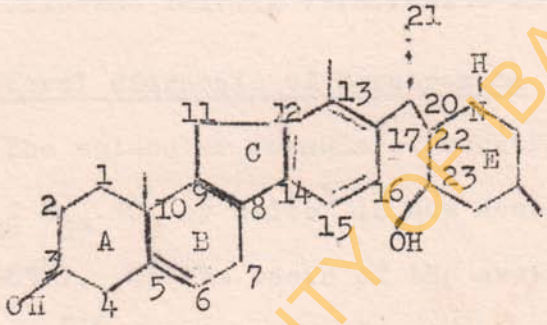
C O N T E N T S

INTRODUCTION

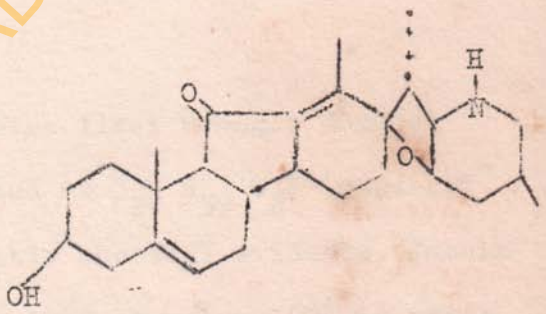
The synthesis of the unusual C-Nor-D-homo steriod skeleton existing in some of the veratrum alkaloids poses a big problem to the synthetic chemist. This account is a summary of our attempts to solve the problem. Veratramine (1) appears to be the simplest steroidal alkaloid typifying this ring system; for, unlike jervine (2) the five-membered ring C of the nucleus bears no function and unlike zygacine (3) and veracevine (4) rings A, B and D are not overloaded with substituents. We therefore sought to synthesize the steroidal skeleton portion of this alkaloid in preference to that of the other members of the family.

Although Veratrum album 'veratria' was extracted in 1819 by Pelletier and Caventou[1], it was not until 1878[2] before it was realized that it gave a mixture of alkaloids of related structures. The veratrum alkaloids, derived from the members of the Liliaceae family are now known to consist mainly of the ceveratrum group of alkamines (cevine, veracevine, zygadenine and others) and the jerveratrum alkaloids (jervine, rubijervine, veratramine and others). The jerveratrum bases and some of the ceveratrum alkaloids are obtained from V. album (European or white hellebore) while the roots and rhizomes of V. viride of U.S. and Canada (American hellebore) contain jerveratrum alkamines and glycosides as the

major components. V. Sabadilla of Mexico and West Indies, on the other hand contains only veracevine and its esters. The jeveratrum unconjugated alkaloids contain only two or three oxygen atoms and show no hypotensive activity. The ceveratrum alkaloids on the other hand contain seven to nine oxygen atoms and show high hypotensive activity. Some of the alkaloids are therefore used as hypotensive agents while the others are also useful as insecticides.



(1)



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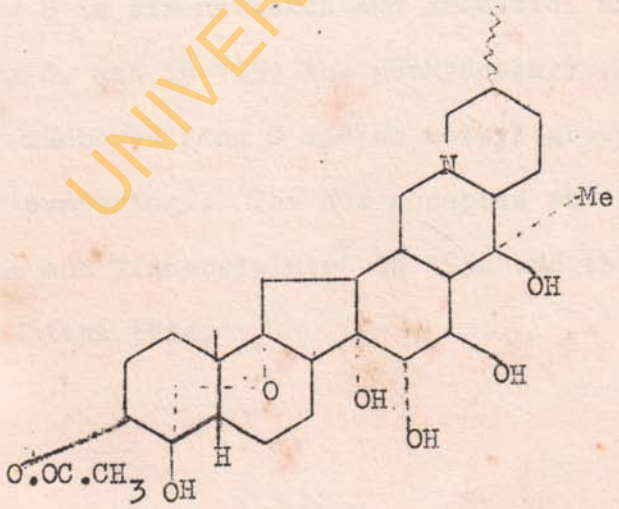

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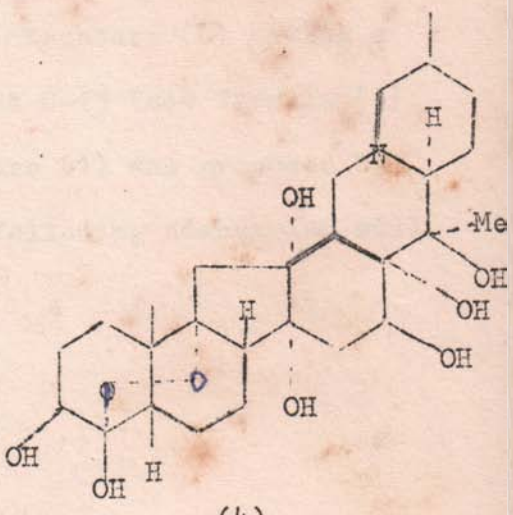
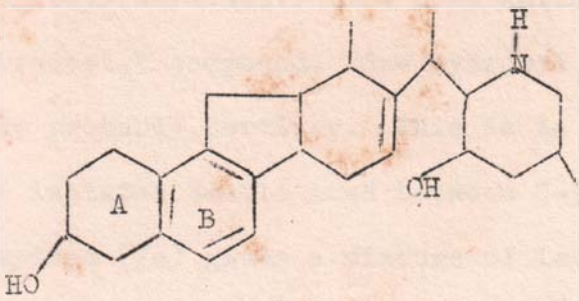


(4)

Isolation of veratramine. Kojiro and Saito[3] first isolated veratramine in 1940 from the white Hellebore (Veratrum grandiflorum Loes fil) by a rather strenuous extraction procedure excelled in simplicity by the method of Jacobs and Craig[4]. The crude alkaloid, extracted from Veratrum viride by means of benzene was converted to a mixture of jervine and veratramine sulphates, with dilute sulphuric acid. The sulphates in alcohol were converted to the free bases from which jervine was precipitated as the less soluble hydrochloride leaving veratramine in solution.

Structural diagnosis of Veratramine

The molecular formula of veratramine first wrongly deduced as $C_{26}H_{39}NO_2$ by Saito[3] is now accepted as $C_{27}H_{39}O_2N$ (m.p. 207° $(\alpha)_D$-69°). On the basis of the available chemical evidence, Jacobs and Sato[5,6] assigned to veratramine in 1949 structure (5) in which ring B is six-membered and aromatic, and the double bond is in ring D, and in 1951 the perhydrochrysene structure (6) having a six-membered ring C and no methyl group at C-13 (see formula (1) for numbering). The now accepted structure (1) was proposed by Tamm and Wintersteiner[7] in 1952 and the following discussion will establish this.



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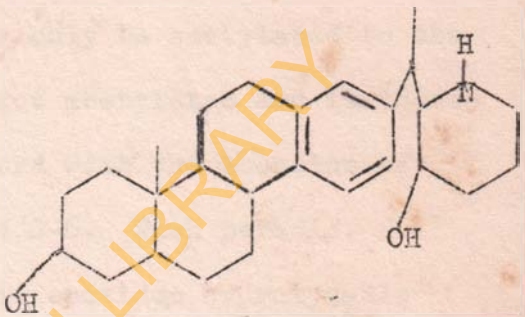
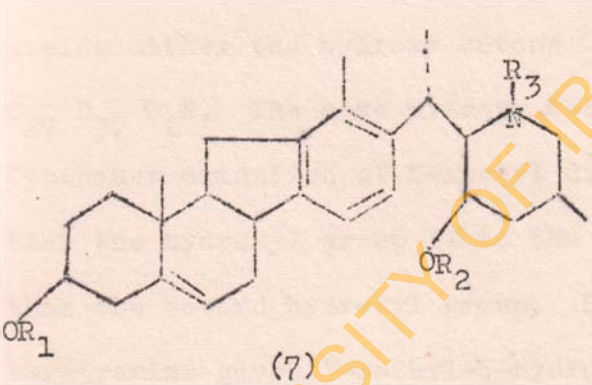


(6)

Veratramine is pentacylic unlike the Solanum alkaloids and other veratrum alkamines which are hexacylic. The two oxygen atoms are acylable and are present as secondary hydroxyls; the nitrogen atom is also secondary. Veratramine therefore gives with acetic anhydride, the O,O', N-triacetyl compound (7a) 7, $R_1 = R_2 = R_3 = Ac$ which gives on alkaline hydrolysis the N-acetyl derivative (7b). 7, $R_1 = R_2 = H$; $R_3 = Ac$. Benzoyl chloride converts the alkaloid into a tribenzoyl derivative, nitrous acid converts it to a nitroso compound and with methyl iodide in slightly basic medium it yields a quarternary methiodide.

Veratramine contains one hydrogenable double bond. It can be reduced to dihydroveratramine (8). Osmium tetroxide converts the triacetyl derivative to a diol which can only be acetylated to the tetraacetyl compound. One hydroxyl is not acetylated and is therefore probably tertiary. This is in accord with the location of the isolated double bond between C-5 and C-6. With peracid, compound (7a) gives a mixture of isomeric epoxides hydrolysable to the corresponding diols.



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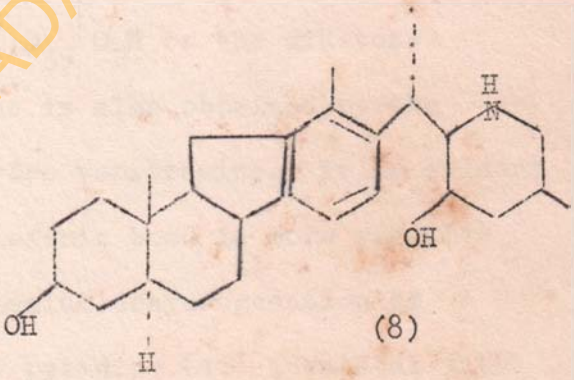
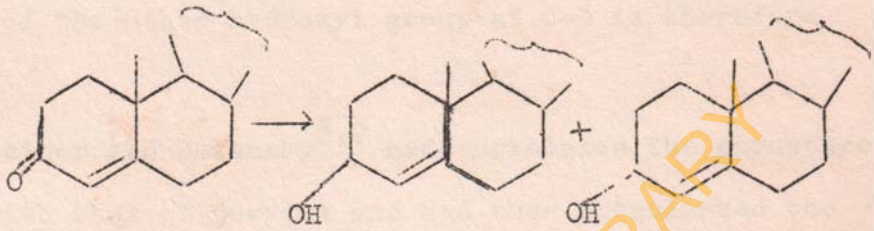


(8)

There is sufficient evidence for the existence of a β,γ - unsaturated hydroxyl. Oppenauer oxidation of the alkamine or its N-acetyl derivative yields an αβ-unsaturated ketone (9) isolable as the hydrochloride. This rules out Jacobs and Satos' structure (5). The α-β unsaturated ketone can be reduced to a mixture of epimeric alcohols (10a) and (10b) which give a positive colour reaction with trichloroacetic acid (Rosenheim test.)

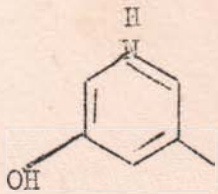
Veratramine or N-acetyl veratramine →



(9) (10a) (10b)

The two hydroxyl groups in veratramine are not equally reactive. Chromic anhydride oxidation of dihydroveratramine yields either the hydroxy ketone $C_{27}H_{39}O_2N$ or the diketone $C_{27}H_{37}O_2N$. The same hydroxy ketone is also obtained by the Oppenauer oxidation of N-acetyl dihydro veratramine. It is evident that the hydroxyl group βα to the olefinic bond is more reactive than the second hydroxyl group. Selenium dehydrogenation of veratramine gives 3-methyl-5-hydroxy pyridine (11) identical with the synthetic material.

Veratramine —Se→

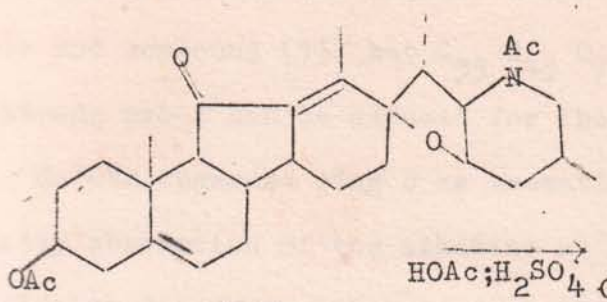


(11)

This fixes the position of the sluggishly reactive hydroxyl at C-23. Conversion of veratramine to dihydro-veratramine is accompanied by a strong positive change in optical rotation, a

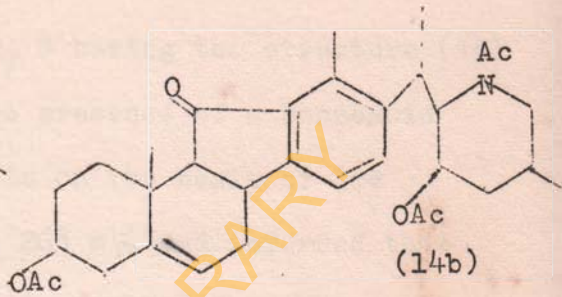
change well-known in steroid chemistry in 3 hydroxy Δ^{5-6} compounds. The location of the other hydroxyl group at C-3 is therefore plausible.

Wintersteiner and Hosansky[8,9] had correlated the structure of veratramine with that of jervine and had thus established the presence of an active methylene group in veratramine. Triacetyl dihydro veratramine (12) was oxidized with chromic oxide to yield the indanone derivative (13) which absorbed in the carbonyl region. λmax. 251 mμ (ε 10,700); 300 mμ (ε 20,000). The spectral properties were similar to those of α-tetralones and α-indanones and the ketodihydro veratramine derivative was as equally inert to carbonyl reagents as α-tetralones. The same indanone derivative was obtained by the catalytic reduction of the acetolysis product of O,N diacetyl jervine (14).



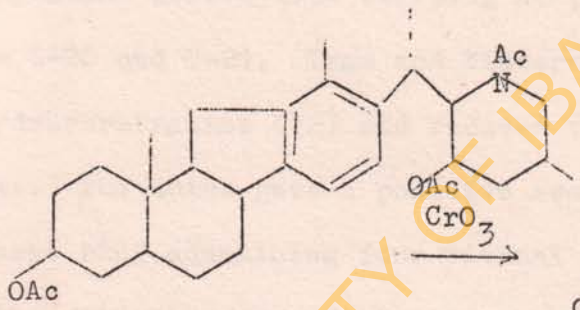
(14)

$HOAc;H_2SO_4$



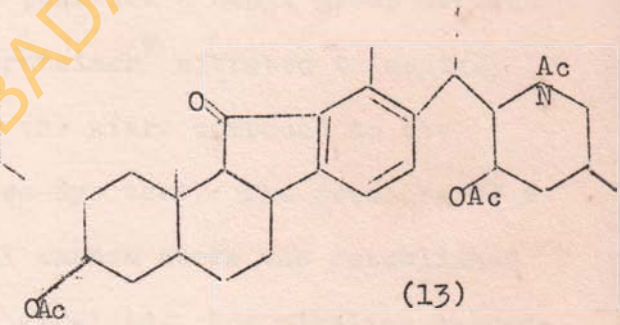
(14b)

$Pd/CaCO_3-H_2$



(12)

CrO_3



(13)

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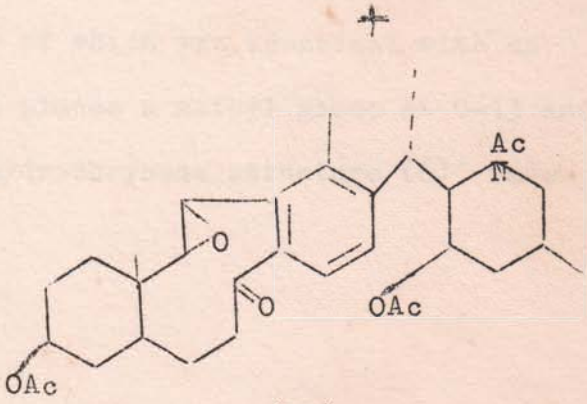
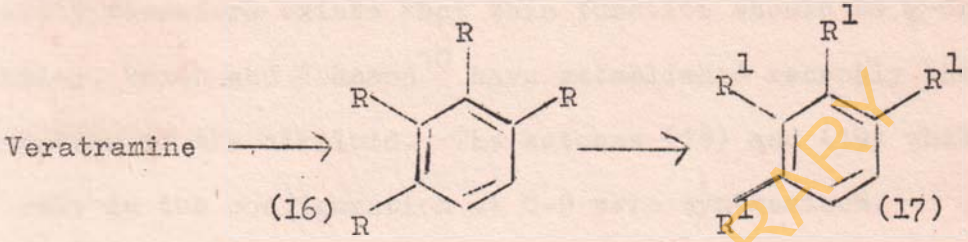


(15)

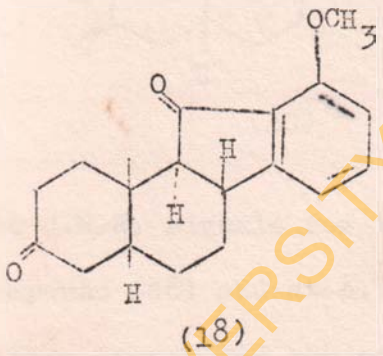
The main product from the chromic oxide oxidation of (12) was however not compound (13) but $C_{33}H_{45}O_7N$ having the structure (15)

Strong proof can be adduced for the presence of a benzenoid ring. Jacobs regarded ring D as aromatic on the basis of low intensity absorption of the alkamine at 268 mμ, and inferred that the selenium dehydrogenation product (11) resulted from the cleavage of the C(20) - C(22) bond which must have been activated by an aromatic ring. All the other jeveratrum alkaloids give rise to pyridine derivatives carrying at position 2 ethyl group derived from C-20 and C-21. Tamm and Wintersteiner[7] nitrated triacetyl dihydroveratramine (12) and reduced the nitro compound to the amine. The amine gave a positive azo-dye test. The presence of a benzene ring containing four vicinal carbon atoms was established by the oxidative degradation of the alkaloid. Hot alkaline permanganate converted veratramine to benzene -1,2,3,4-tetracarboxylic acid (16), the tetramethyl ester of which was identical with an authentic specimen. This result places a methyl group at C-13 and rules out Jacobs and Sato's perhydrochrysene structure (6) (see page 4).



R = COOH Prehnitric acid R^1 = COOMe

Since rings A and B in veratramine are constituted as in normal steroids and it is ring D which is aromatic, then ring C must be five-membered.



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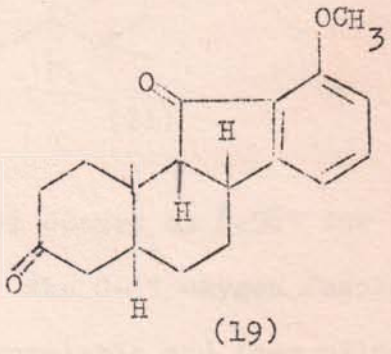


(19)

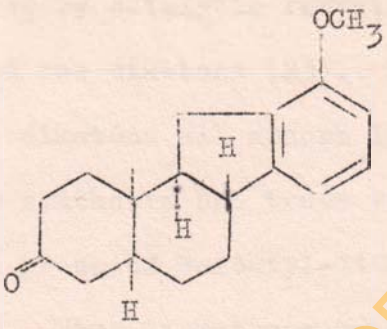
The position of the other methyl groups are in accord with their positions in normal steroids and hence veratramine is represented by structure (1). (see page 2)

The stereochemistry of veratramine

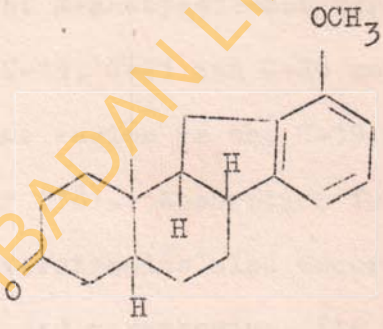
The first stereochemical assignment in the alkamine appears to be the orientation of the 3-hydroxy group. 'Veratramine and its

dihydro derivative form sparingly soluble digitonides. The possibility therefore exists that this function should be β-oriented.

Bailey, Hamon and Johnson[10] have established recently the C-9 configuration of the alkaloid. The ketones (18) and (19) which differ only in the configuration at C-9 were synthesized.

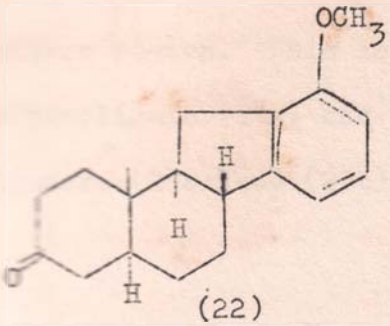


(20)



(21)

The N.M.R. signals for the C-19 methyl occurs at 8.56τ for compound (18) and at 8.14τ for (19). The C-11 oxygen function of either isomer was subjected to hydrogenolysis and then oxidation to give the ketones (20) and (21). The ketone (21) derived from substance (19) was compared with an authentic specimen of the cis-syn-cis ketone (22). Infra red data, melting point and mixed melting point revealed an identity of substances (21) and (22) and



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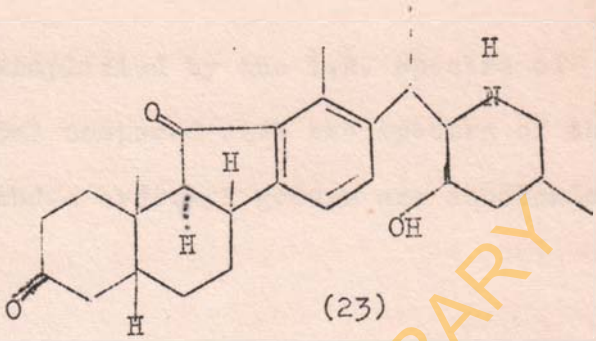
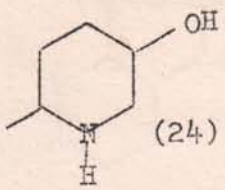


(23)

a non-identity of compounds (20) and (22). Oppenauer oxidation followed by catalytic reduction of N-acetyl-11-ketoveratramine yielded the diketone (23). The C-19, C-21 and C-26 methyl groups of the diketone all absorb in same region as the C-19 methyl group of the synthetic B/C trans epimer (18). Absorption for the C-19 methyl group of N-acetyl-11-ketoveratramine also occurs in this region. Thus 11-ketoveratramine and veratramine, its hydrogenolysis product, have the B/C trans (9-H) configuration. The above result has been confirmed recently by Masamune, Takasugi and Mori[11] in a series of transformations involving reactions that do not render C-9 readily epimerizable.

Sicher and Tichy[12] had established the relative configuration of C-22 to that of C-23 of the piperidine residue. In hydroxy piperidines, the ring nitrogen atom can only engage in H-bonding with axial hydroxyls. The I.R. spectrum of a 3-hydroxyl piperidine whose hydroxyl is axial will therefore show two concentration-independent absorptions (free OH and associated OH) around the 3

micron region. This is exemplified by the I.R. spectra of pipecolinols (24a) and (25a) compared with the spectra of the trans isomers (24b) and (25b), whose hydroxyl groups are equatorial.



(24)

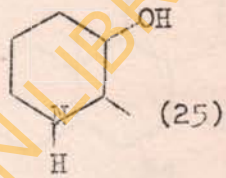
(a) cis. m.p. 49.5°

ν(OH), free, 3625 cm^{-1}

ν(OH), asso, 3532 cm^{-1}

(b) Trans m.p. 97°

ν(OH), free, 3624 cm^{-1}



(25)

(a) cis. m.p. 94.5°

ν(OH), free, 3632 cm^{-1}

ν(OH), asso, 3526 cm^{-1}

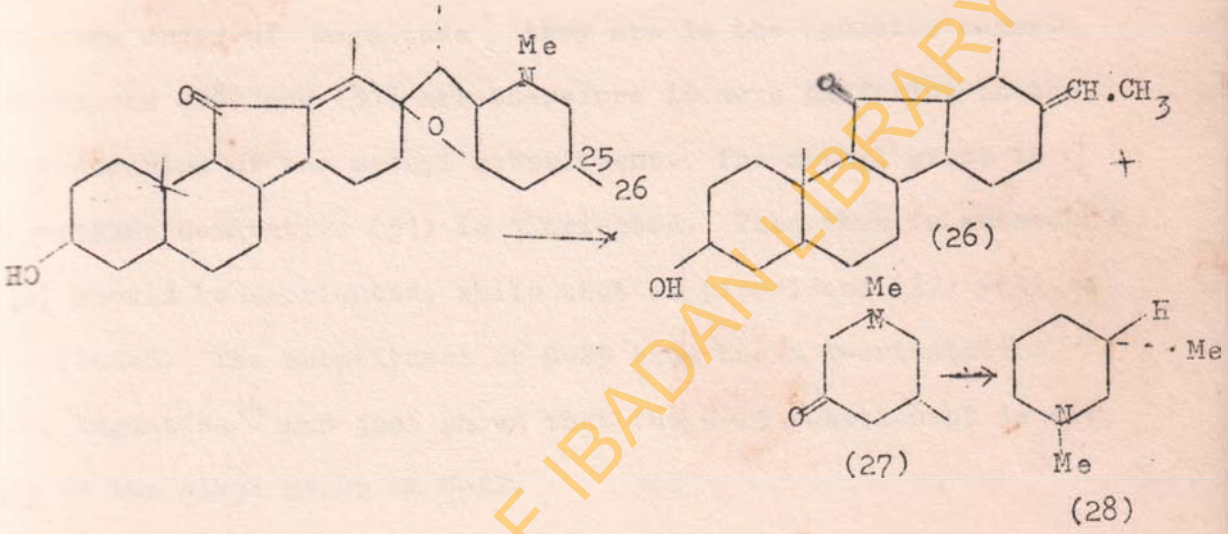
(b) Trans m.p. 139.5°

ν(OH) 3625 cm^{-1}

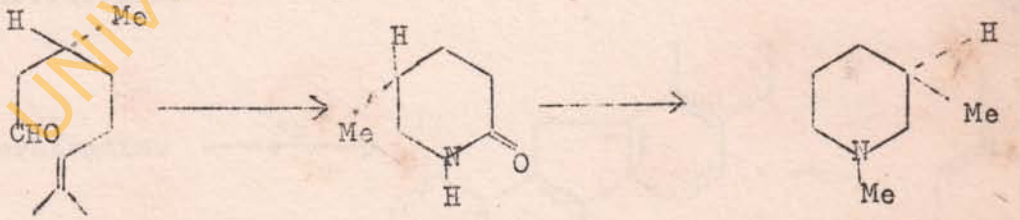
The I.R. spectrum of veratramine contains only one hydroxyl band (3619 cm^{-1}). The C-22 hydroxyl is therefore equatorial. Now the C-23 substituent determines the conformation and is therefore equatorial. The two substituents could only both be equatorial if they are trans to each other, for if they are cis, one must be equatorial and the other axial.

Okuda, Tsuda and Kataoka[13] had determined the absolute configuration at C-25. Though they worked on jervine, the result applies as well to veratramine, since both alkaloids are known to

have the same configuration of the piperidine ring.[8] N-methyl jervine was subjected to fragmentation reaction to yield the olefin (26) and 1,5, dimethyl piperidone (27).



The piperidone was subjected to Wolff-Kishner reduction to yield 1,3, dimethyl piperidine (28). 5(R)-Methyl-2-piperidone (30)

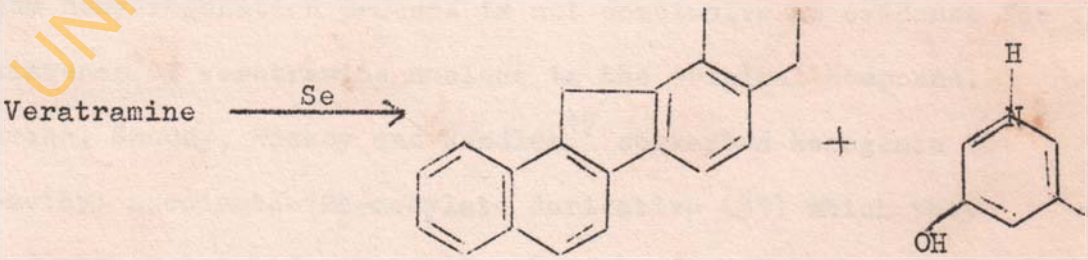


synthesized from D-(+) citronellal (29) was methylated and the product reduced to give the piperidine (31).

The picrate and hydrobromide of either piperidine have m.p. 174 - 177° and 198° - 200° respectively. Although the optical rotations of the hydrobromides at any given wavelength are numerically of the same order of magnitude they are in the opposite sense. Substances (28) and (31) are therefore isomers differing in the configuration of the methyl substituent. The methyl group in piperidine derivative (31) is β-oriented. Then that in substance (28) should be α-oriented, while that in piperidone (27) will be β-oriented. The substituent at C-25 thus has a β-orientation. R.L. Augustine[14] had just shown that the C-25 substituent is also cis to the alkyl group at C-22.

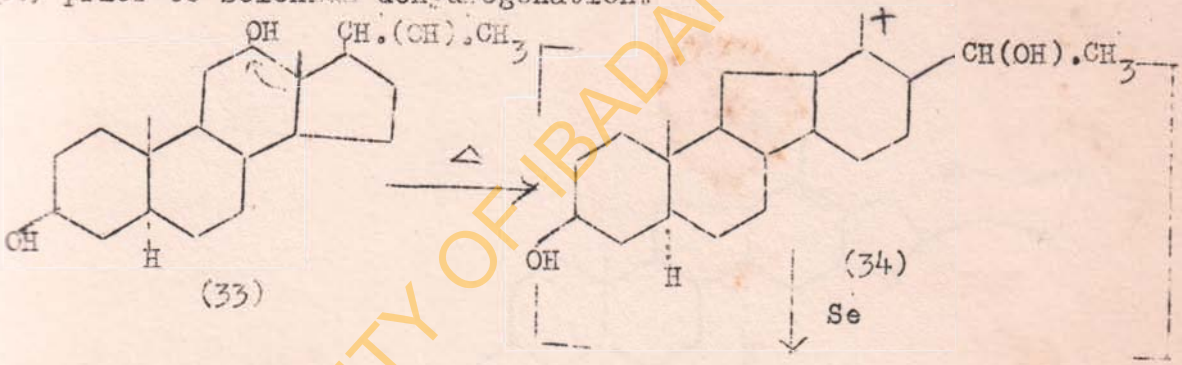
Normal-steroid rearrangement to the C-Nor-D-homo ring system

Jacobs and colleagues[5] subjected veratramine to selenium dehydrogenation and obtained the hydrocarbon (32) which was synthesized and found to be identical with 8-methyl-7-ethyl-1,2-benzfluorene.



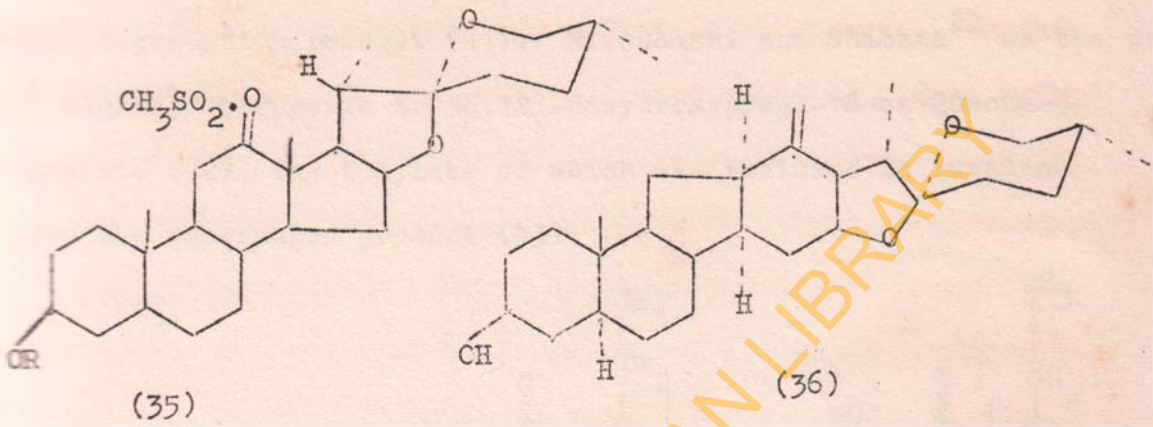
(32) (11)

This would have constituted an indisputable evidence for the presence of the C-Nor-D-home ring system in veratramine, except that Hiroshi Mitsuhashi and Shimizu[15] have obtained Jacobs hydrocarbon (32) from selenium dehydrogenation of the steroid 3β, 12β, 20β-trihydroxy-5α-pregnane (33). This is certainly a rearrangement reaction. The pyrolytic removal of the 12β-hydroxyl group initiated the steroid (33) to rearrange to the unusual ring system (34) prior to selenium dehydrogenation.

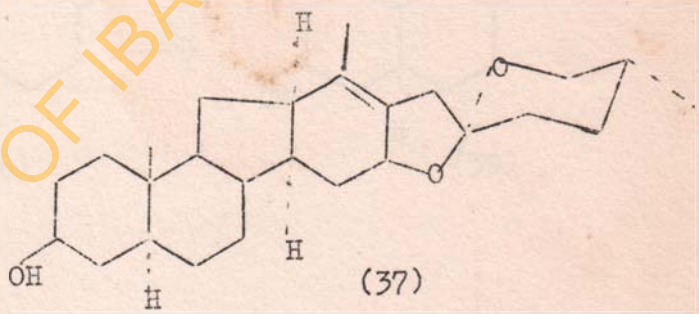


Veratramine ⟶ Jacob's hydrocarbon (32)

It is clear, that an encounter of Jacob's hydrocarbon[16] as a selenium dehydrogenation product is not conclusive an evidence for the existence of veratramine nucleus in the original compound. Hirschmann, Snoddy, Hiskey and Wendler[17] converted hecogenin to its 3-methyl succinate-12β-mesylate derivative (35) which they refluxed with t-butoxide in t-butanol. The steroid isomerized to a mixture of olefins characterized as substances (36) and (37).



(35) (36)



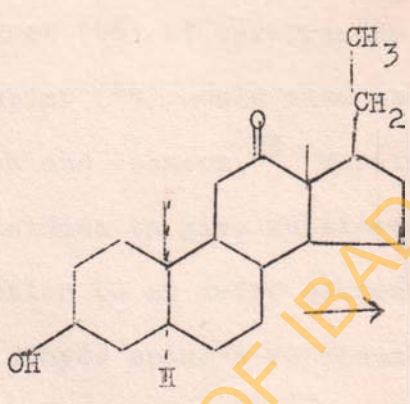
(37)

The above rearrangement was effected by Phillips, Taylor and Wyman[18] almost at the same time.

Of particular interest are the products obtained by Mitsuhashi and Shimizu[19,20] from such rearrangements. 3β-Acetoxy-5α-pregane-12-one (38) prepared from hecogenin was subjected to bromination and then hydrolysis to give the keto-diol (39). The hydrazone of (39) was heated with sodium ethylene glycolate to give the rearranged product (40) which was successively acetylated, oxidized

and reduced to give a product identical with Fried and Klingsbergs,[21] jervine degradation product (41). Mitsuhashi and Shibata[22] on the other hand degraded hecogenin to 3β,12β-dihydroxypregn-16-en-20-one-3-monoacetate (42), the tosylate of which was refluxed in pyridine to give the rearranged product (43).

Hecogenin ⟶



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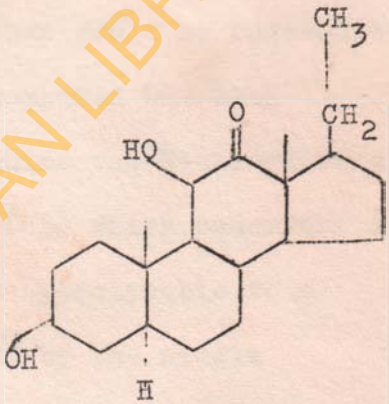

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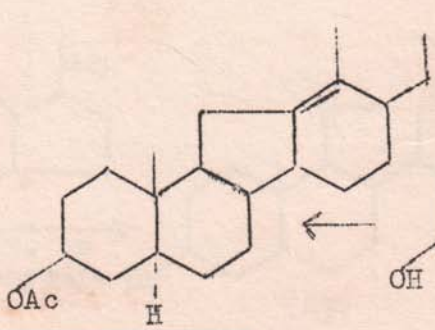

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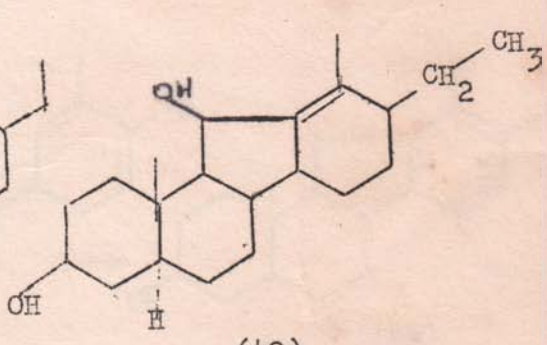
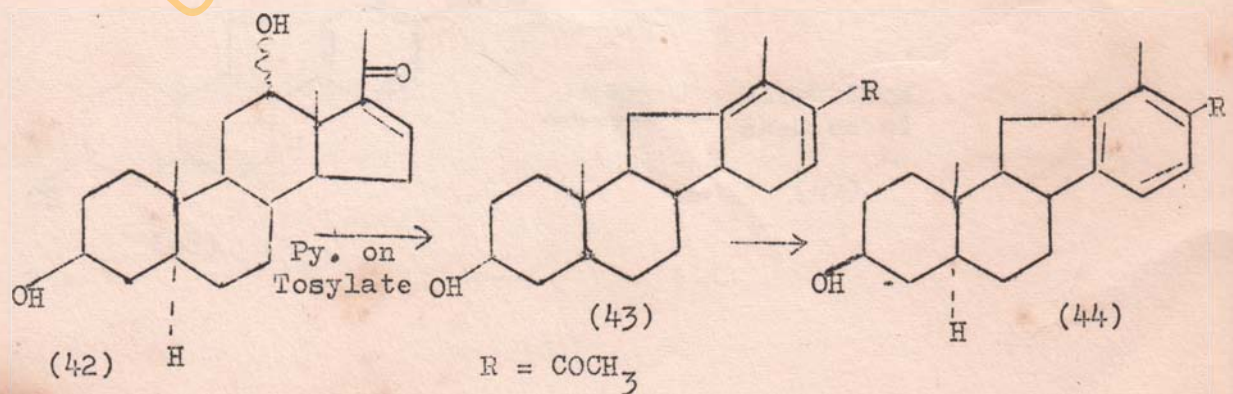


(40)

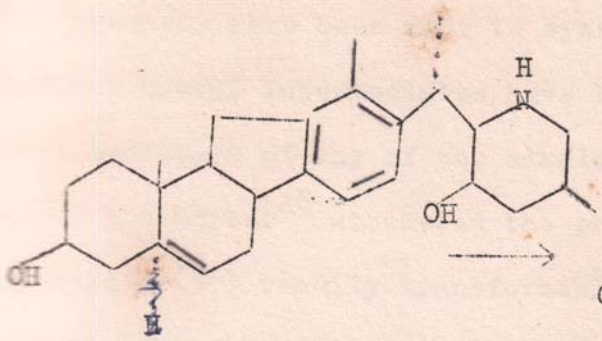
The $\alpha\beta$-unsaturated ketone could not be isolated since its ring D readily aromatized to give the aryl ketone (44) which could serve as a relay substance for the total synthesis of 5,6-dihydroveratramine (8). The aryl ketone (44) is of course identical with the dihydroveratramine degradation product of Masamune and Takasugi. A degradation product (48) of veratramine that could be reduced to a substance with which (44) could also be compared has been described by Franck and Johnson.[23] Veratramine was N-chlorinated with N-chlorosuccinimide to give substance (45) which underwent a fragmentation reaction to an imino compound hydrolysable to a mixture of C-20 aldehyde epimers represented by the single structure (47). Nitrosation and deformylation with n-butyl nitrite and a solution of sodium in n-butanol converted the aldehyde to the oxime of the ketone (48) which could also be obtained by the chromic oxide oxidation of the morpholine enamine of the aldehyde. Steroid rearrangements to the unusual ring system under

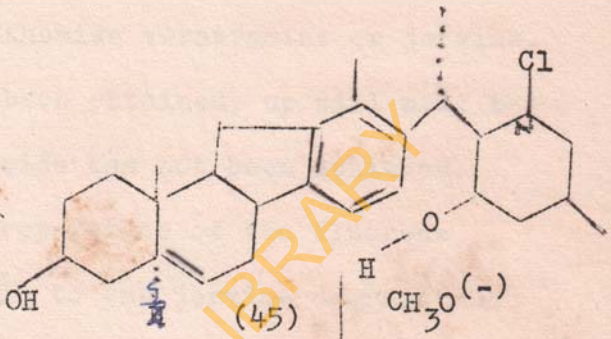


(42) (43) (44)

R = $COCH_3$

consideration had been encountered by other workers.[24-27]





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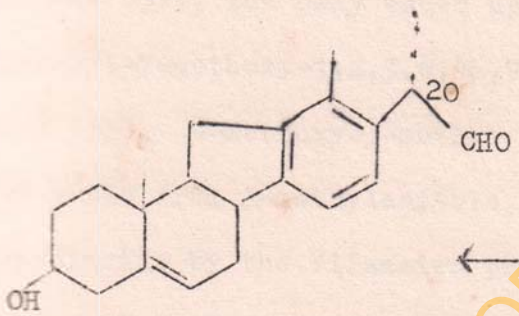

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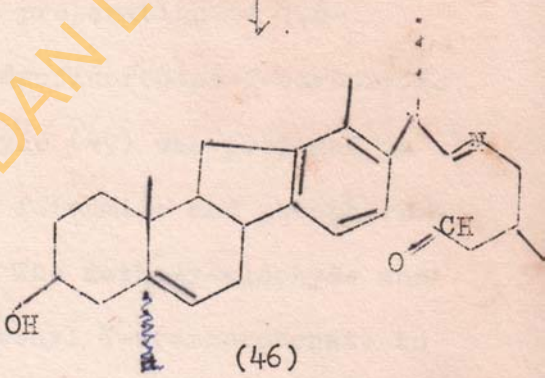

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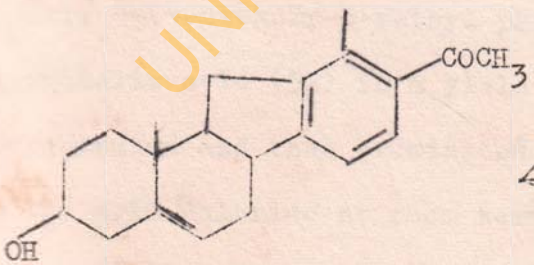
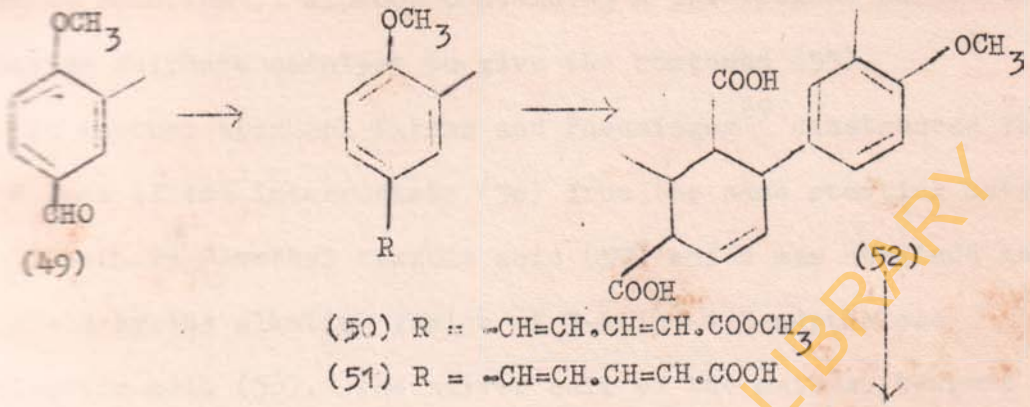


(48)

CrO_3 ← Morpholine enamine of (47)

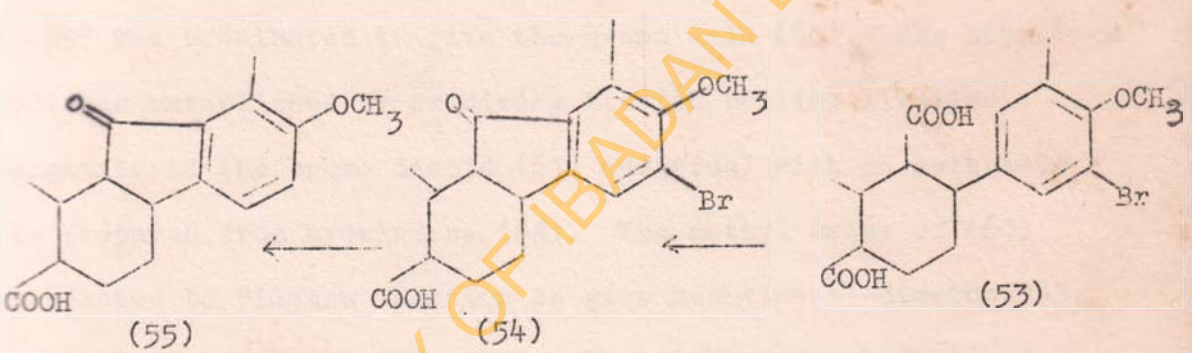
Previous synthetic studies on veratramine and allied alkamines

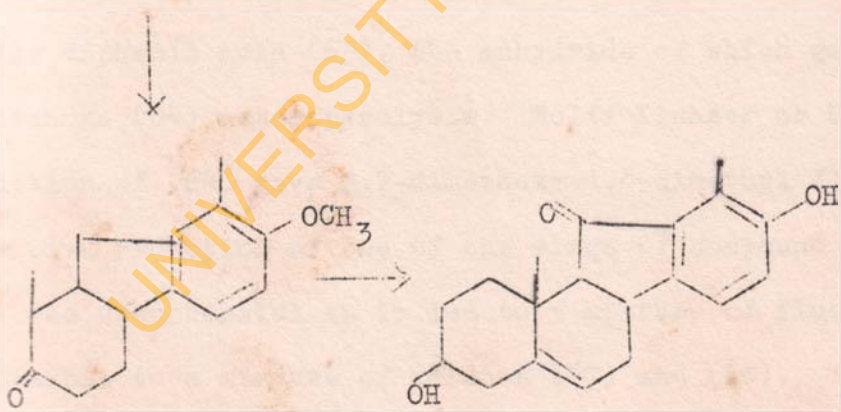
Attempts have been made to synthesize veratramine or jervine. Although useful intermediates have been obtained, up till now, the total synthesis of any of the alkaloids has not been achieved. Barnes and Gerber[28] attempted the preparation of the fluorene derivative (56) readily transformable to the jervine degradation product (57), but only ended up with the preparation of 1,8-dimethyl-7-methoxy-1,2,3,4,4a,9a,-hexahydrofluorenone-2-carboxylic acid (55). 4-Methoxy-3-methyl benzaldehyde (49) was prepared in 44% yield from 2-methylanisole, dimethyl formamide and phosphorous oxychloride by the Vilsmeier procedure. The methoxy-aldehyde was subjected to Reformatsky reaction with methyl γ-bromocrotonate to give methyl-4-methoxy-3-methyl styrylacrylate (50) hydrolysed to give the corresponding acid (51). 4-Methoxy-3-methyl styrylacrylic acid (51) was subjected to hydroquinone-catalyzed Diels-Alder reaction with crotonic acid in refluxing tetralin to give as the adduct, 4-(4-methoxy-3-methyl phenyl)-2-methyl-1,2,3,4-tetrahydro isophthalic acid (52) in a yield of 20-26%. The diacid was hydrogenated and then brominated to give (53) which was converted to the acid chloride at room temperature by phosphorous pentachloride. Cyclisation by means of aluminium chloride afforded the fluorenone (54) debrominated by catalytic hydrogenation in a



(50) R = -CH=CH.CH=CH.COOCH$_3$

(51) R = -CH=CH.CH=CH.COOH

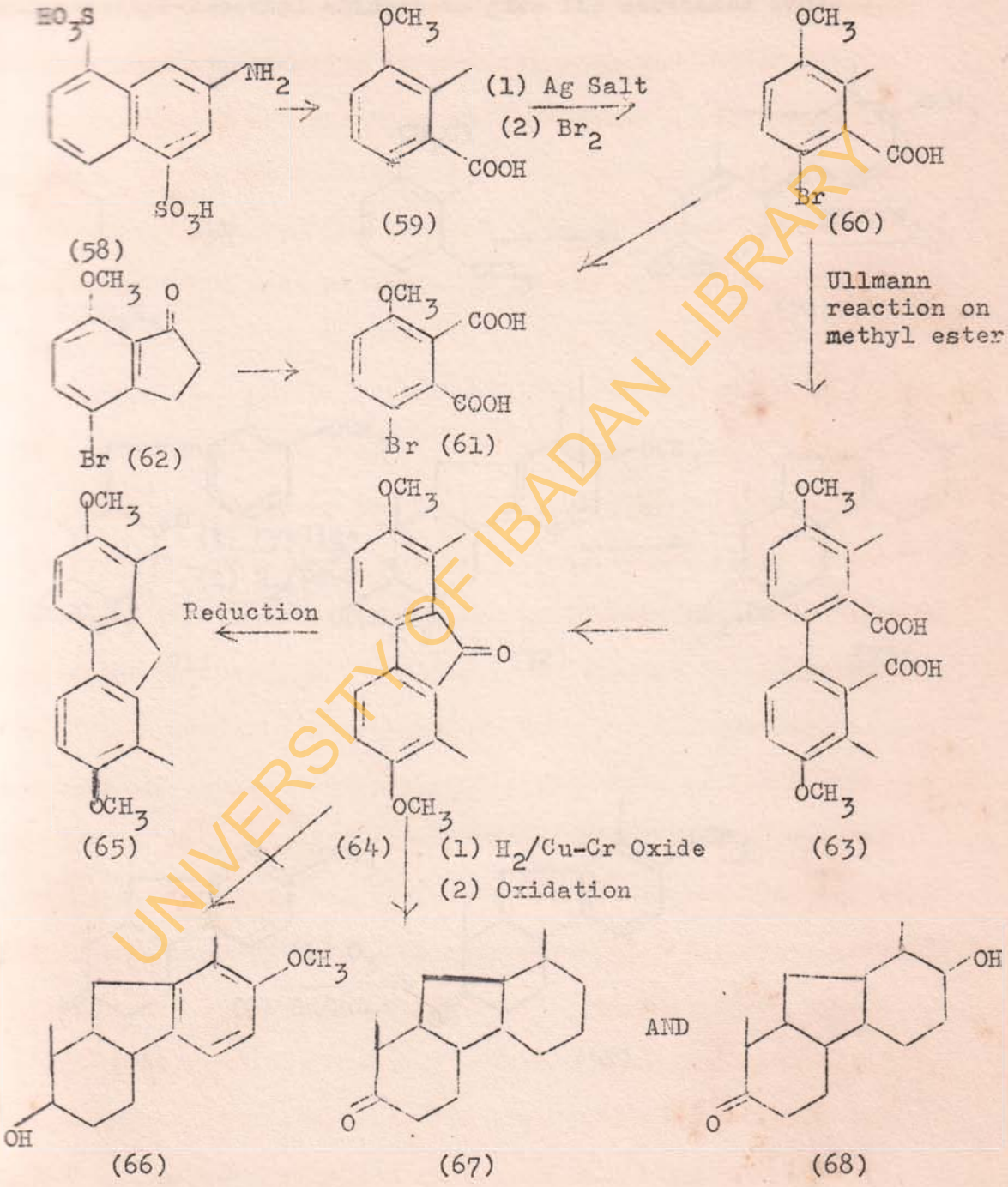




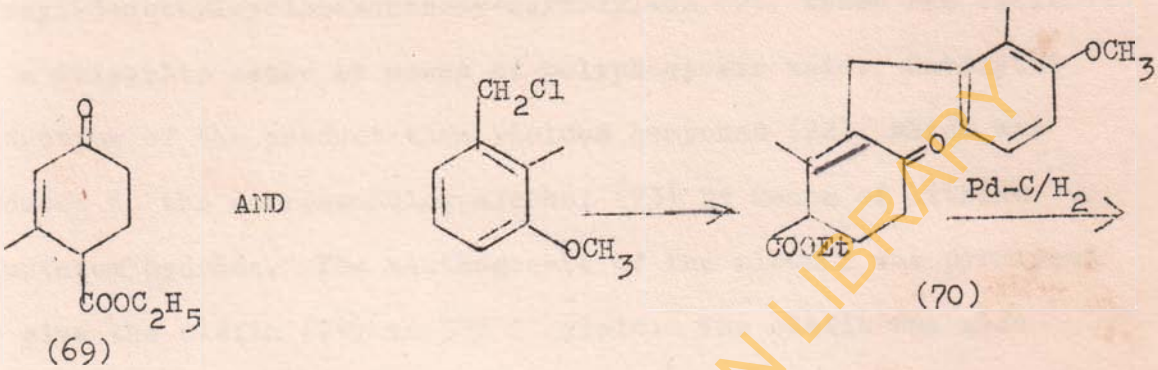
alkaline solution of alcohol containing a pre-reduced palladium-on-barium sulphate catalyst to give the compound (55).

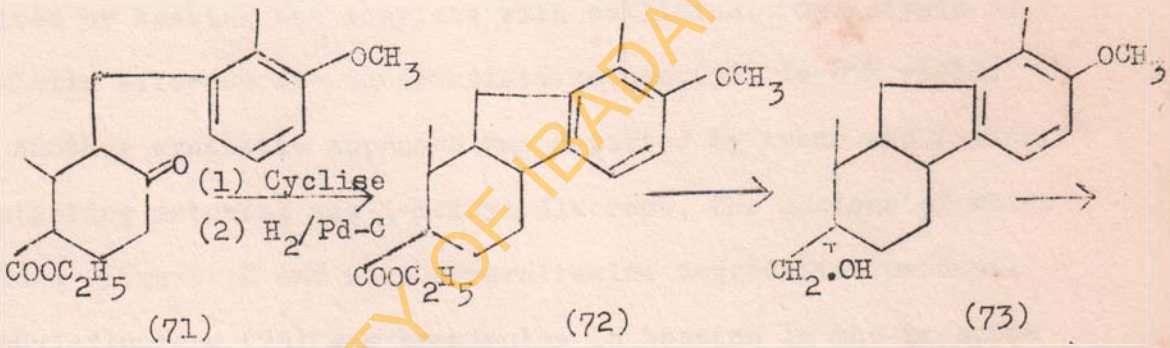
In another approach Barnes and Faessinger[29] constructed the two halves of the intermediate (56) from the same starting material viz, 3-methoxy-2-methyl benzoic acid (59) which was obtained in 30% yield by the alkaline fusion of 3-amino-1,5-napthalene disulphonic acid (58). The silver salt of the methoxy benzoic acid (59) was brominated to give the bromo acid (60). The structure of (60) was established by oxidizing it with boiling alkaline permanganate to the bromo diacid (61) identical with an authentic sample prepared from hydrindone (62). The methyl ester of (60) was subjected to Ullmann reaction to give methyl-4-4'-dimethoxy-3, 3'-dimethyl diphenate in 85% yield. The diester was hydrolysed to the diphenic acid (63), the anhydride of which gave the fluorenone (64) after pyrolysis. Wolff-Kishner or Clemmensen reduction of (64) gave 2,7-dimethoxy-1,8-dimethyl fluorene (65). Selective reduction of one of the rings of compound (64) to obtain (66) was unsuccessful as it led to a mixture of fluorene derivatives, oxidizable to a mixture of ketones (67) and (68).

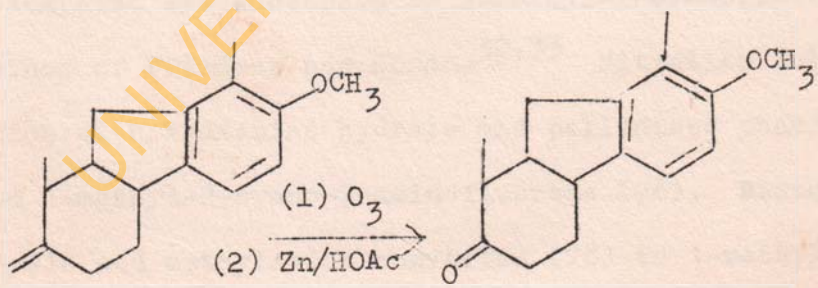
The successful synthesis of 1,8,-dimethyl-7-methoxy-1,2,3,4, 4a,9a,-hexahydro fluoren-2-one (56) was achieved by Barnes and Sedlak[30] in 1962. Hagemann's ester (69) was alkylated with



3-chloromethyl-2-methyl anisole to give the substance (70).



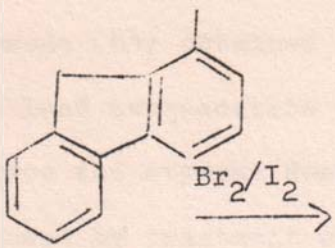




Catalytic hydrogenation of (70) yielded 2-(3'-methoxy-2'-methyl) benzyl-3-methylcyclohexanone-4-carboxylate (71) which was cyclised to a tricyclic ester by means of polyphosporic acid. Catalytic reduction of the product then yielded compound (72), which was reduced to the corresponding alcohol (73) by means of lithium aluminium hydride. The xanthogenate of the alcohol was pyrolysed to give the olefin (74) in 30% yield. The olefin was also obtained by heating the tosylate with collidine. Ozonolysis of the olefin afforded the intermediate ketone (56) in 81% yield.

Another synthetic approach was reported by Arene and Taylor.[31] The starting material was 1-methyl fluorene, the nucleus of which provided rings B, C and D of a veratramine degradation product. 1-Methyl fluorene (75) was brominated in benzene in the presence of iodine as catalyst to give 1-methyl-2-bromofluorene (76). The bromo compound was converted to 1-methyl-2-cyano~~bromo~~fluorene (~~75~~ 77) by the method of Friedman and Newan.[32,33] Nitration followed by reduction with hydrazine hydrate and palladised charcoal in ethanol yielded 1-methyl-2-cyano-7-aminofluorene (78). Diazotisation, hydrolysis and methylation converted (78) to 1-methyl-2-cyano-7-methoxyfluorene (79). Smooth hydrolysis of the nitrile to the corresponding carboxylic acid (80) was effected with potassium hydroxide in boiling ethylene glycol. The corresponding methyl

ester was reduced to the alcohol (81) which on Birch reduction afforded 7,8-dimethyl-1,2,3,4,4a,9a-hexahydrofluoren-2-one (82) in very poor yield. The poor yield discouraged further work.



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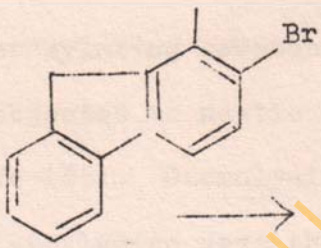

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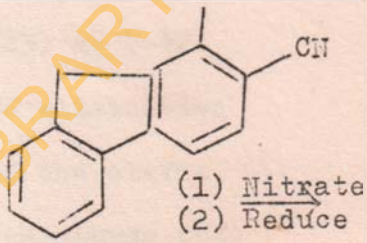

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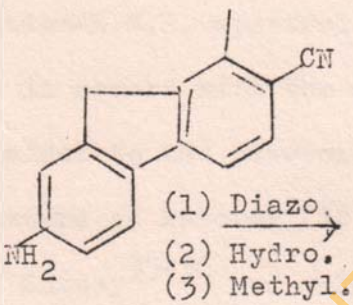

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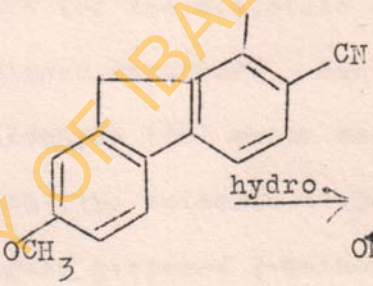

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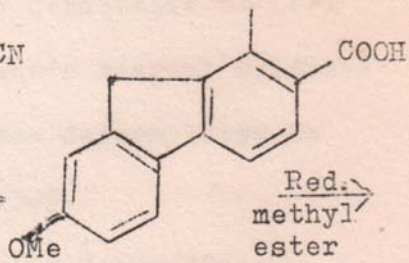

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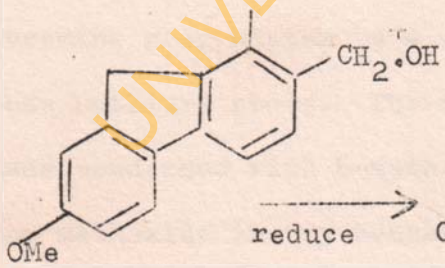

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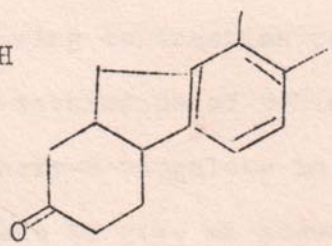
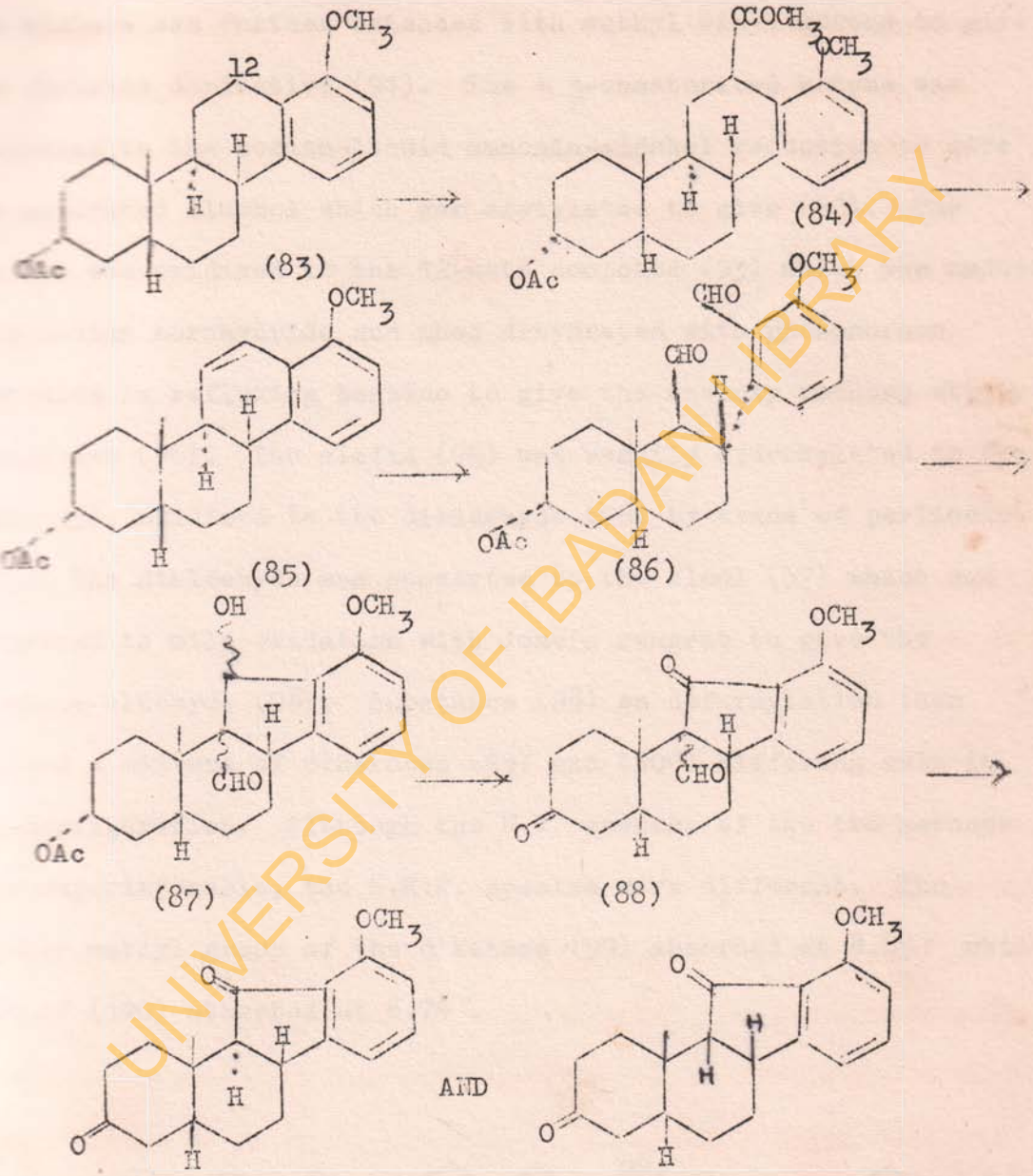


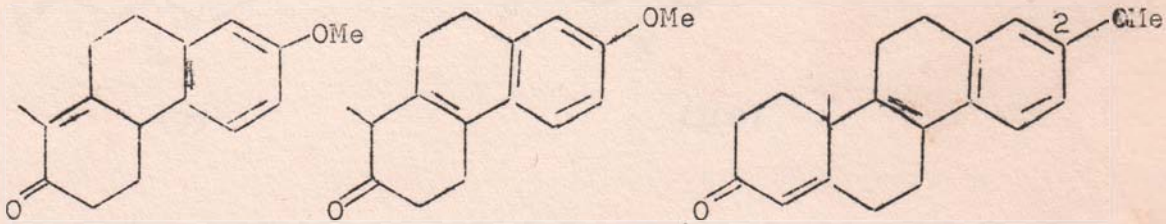
(82)

Schiess, Bailey and Johnson[34] have effected ring-C contraction of a chrysene derivative to give a product containing the novel veratramine nucleus. Acetoxy-methoxy methyl dodecahydro chrysene (84) obtained by acetoxylating compound (83) at C-12 with lead tetraacetate was subjected to acetic acid elimination to give the styrene derivative (85). Ozonolysis of the olefin followed by treatment with diethylamine gave the dialdehyde (86) which aldolized to (87) in refluxing methanolic sodium hydroxide solution. N.M.R. spectral data for the diacetate derivative of (87) were in accord with the assigned structure. Jone's reagent oxidized the aldol to the diketone-aldehyde (88) which was deformylated to a mixture of ketones (18) and (19) epimeric at C-9.

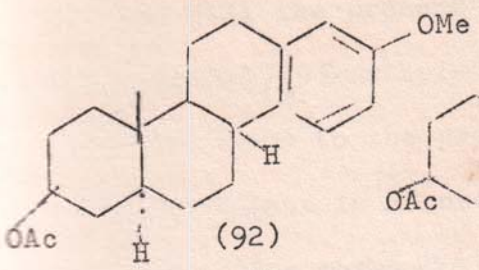
Kutney[35-36] and colleagues prepared 2-methoxy-8-oxo-10a-methyl-5,6,8,9,10,10a,11,12-octahydro-chrysene (91) starting with 6-methoxy-2-tetralone and have just reported its conversion to the veratramine ring system by a ring contraction procedure similar to the one outlined above. The methiodide of 5-Diethylaminopentan-3-one was condensed with 6-methoxy-2-tetralone in the presence of sodium methoxide in dry benzene to give an adduct which cyclised to a mixture of tricyclic enones (89) and (90).



The mixture was further extended with methyl vinyl ketone to give the chrysene derivative (91). The α,β-unsaturated ketone was subjected to the sodium-liquid ammonia-alcohol reduction to give the saturated alcohol which was acetylated to give (92). The acetate was oxidized to the 12-keto compound (93) which was reduced with sodium borohydride and then dehydrated with phosphorous pentoxide in refluxing benzene to give the acetoxy methoxy styrene derivative (94). The olefin (94) was readily hydroxylated to the diol (95), oxidized to the dialdehyde (96) by means of periiodic acid. The dialdehyde was converted to the aldol (97) which was subjected to mild oxidation with Jone's reagent to give the diketone-aldehyde (98). Substance (98) on deformylation then yielded a mixture of diketones (99) and (100) differing only in C-9 configuration. Although the U.V. spectra of the two ketones were superimposable, the N.M.R. spectra were different. The angular methyl group of the diketone (99) absorbed at 8.85τ while that of (100) absorbed at 8.74τ.



(89) (90) (91)



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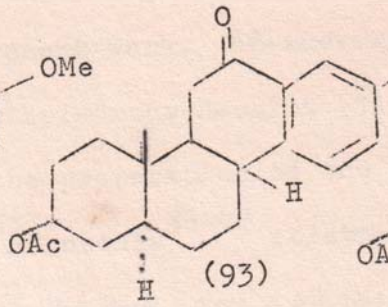

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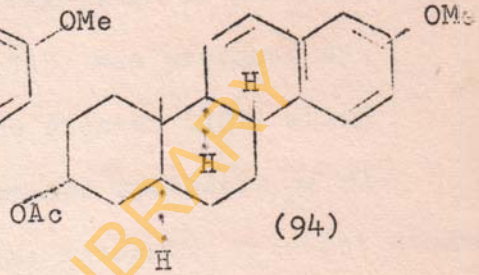
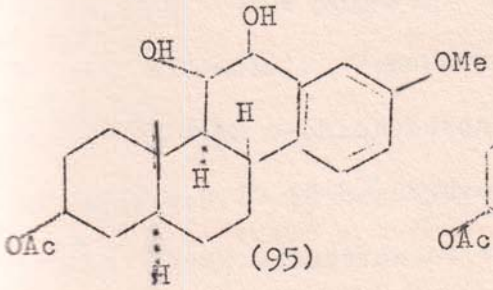


(94)



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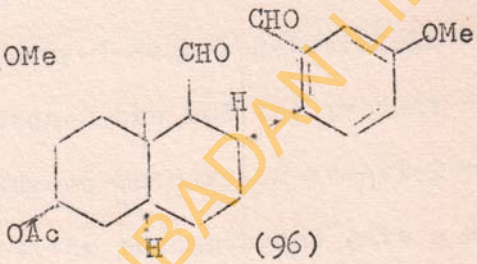

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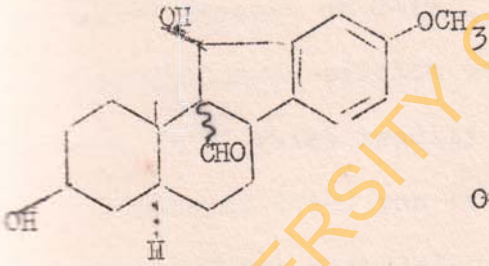

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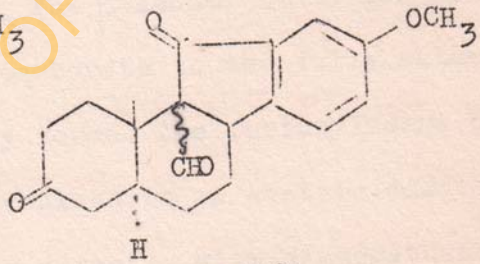
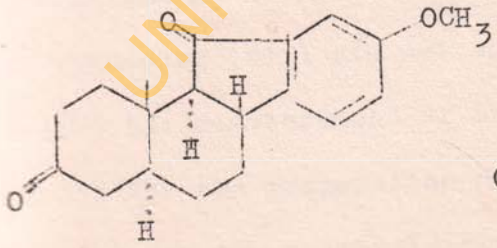


(98)



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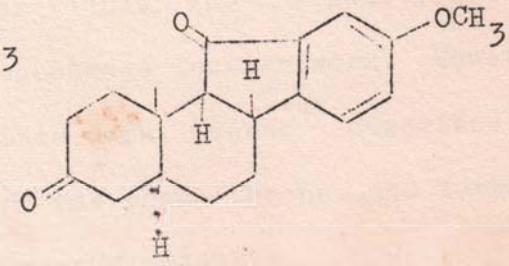
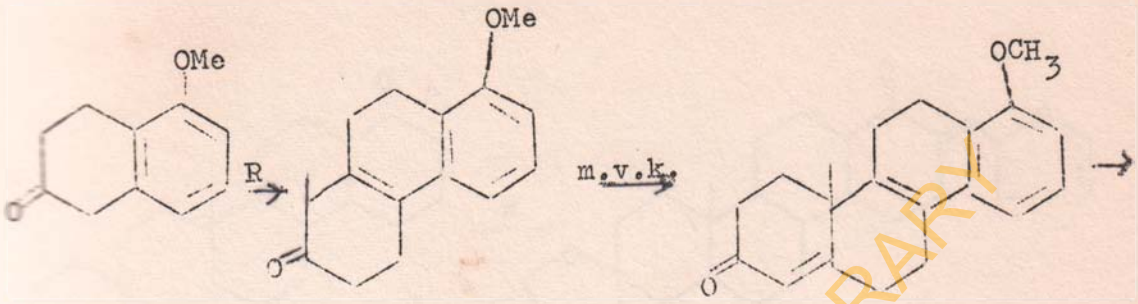


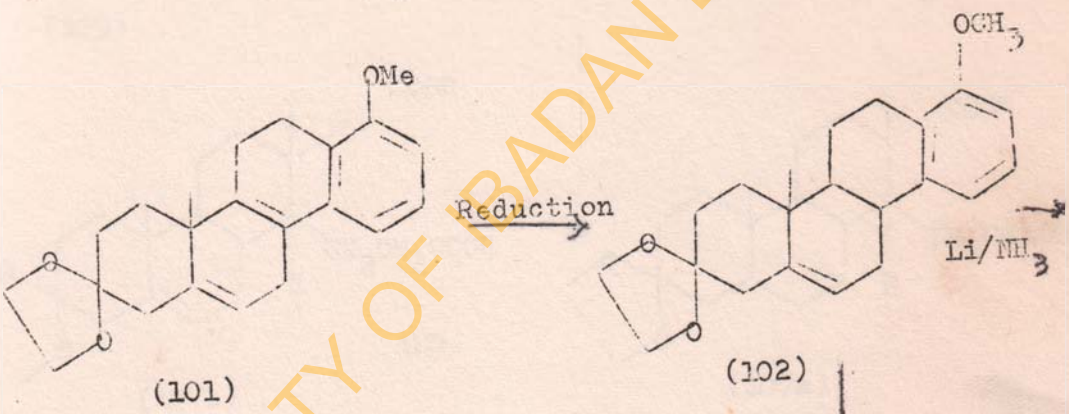
(100)

Howell and Taylor's[37] synthetic pathway is of interest in connection with the present work. 6β-Acetoxy-1β-2α-di(methoxy carbonyl methyl)-9β-methyl-trans-decalin (115) was prepared by a route analogous to the preparation of the diester (107) which is an intermediate in Johnson's[38-46] celebrated synthesis of dl-testosterone (See pages 27A & B for a scheme involving relevant stages of the synthesis). 7-methoxy-1-methyl-2-tetralone (110) was alkylated with 4-chlorobutan-2-one and the product cyclised to give 2,3,4,9,10,12-hexahydro-6-methoxy-12-methyl-2-oxophenanthrene (111). Birch reduction of the phenanthrone gave a mixture of keto alcohols epimeric at C-14. The β-isomer (112) was hydrogenated over palladium-on-calcium carbonate to the fully saturated keto-alcohol (113) which readily formed the furfurylidene derivative. The acetate of (114) was ozonised to an acetate diacid which was not isolated but methylated directly with diazomethane to the corresponding acetate diester (115). The difficulty encountered in obtaining (111) did not encourage further work. However, before the commencement of this work, Kuehne[47] described an easier method for the preparation of the phenanthrone, and further progress on the synthesis appeared possible.

In the present account, three synthetic pathways aimed at obtaining suitable intermediates for the total synthesis of

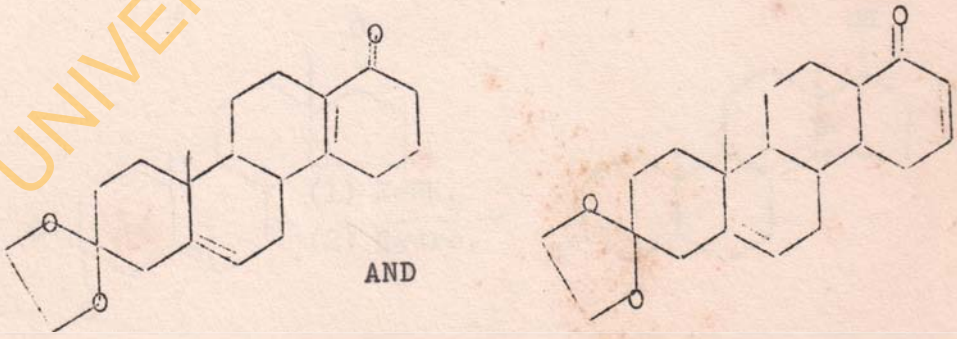


R = 1 - diethyl amino-3-pentanone



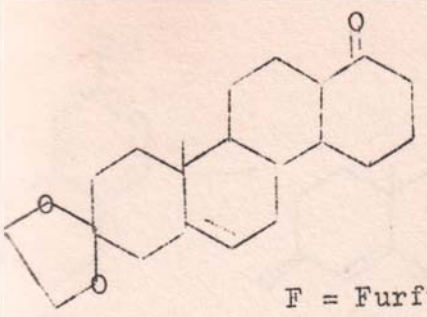
(101)

(102)



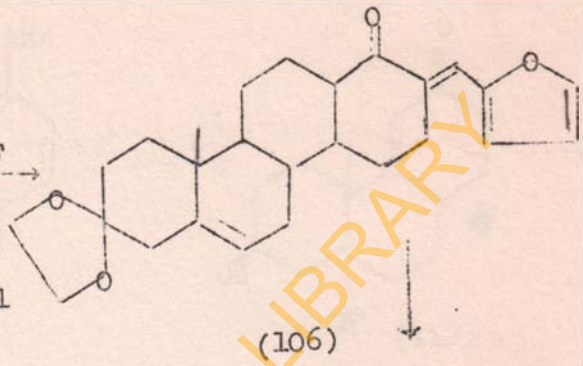
(103)

(104)

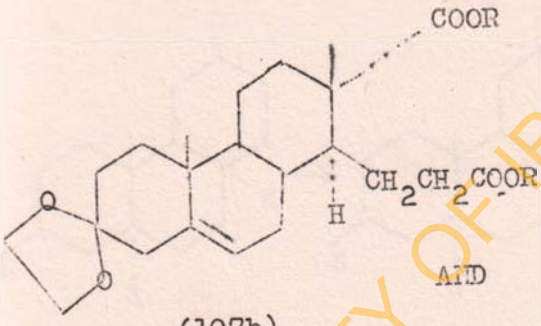


F = Furfural

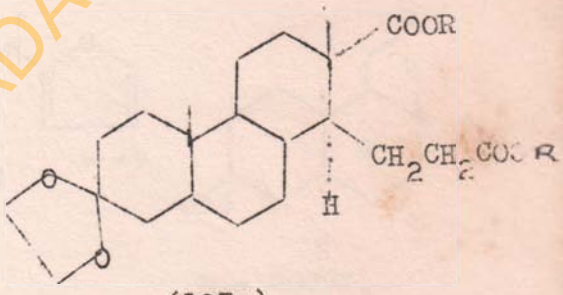
(105)



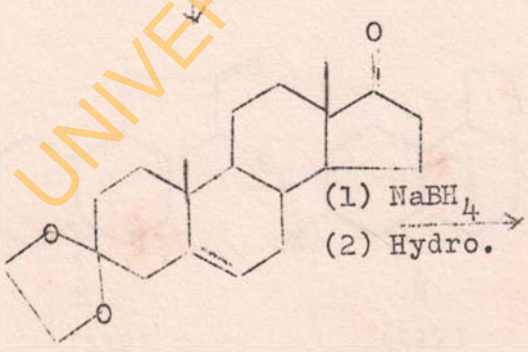
(106)



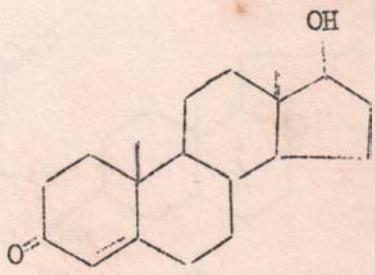
(107b)



(107a)

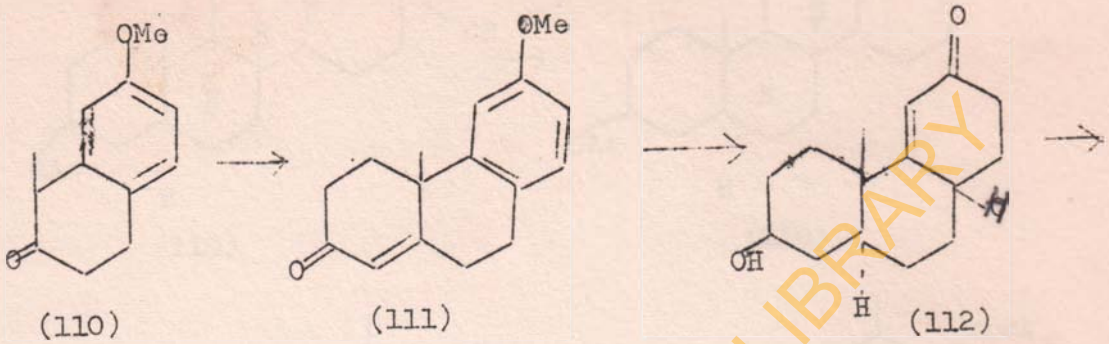


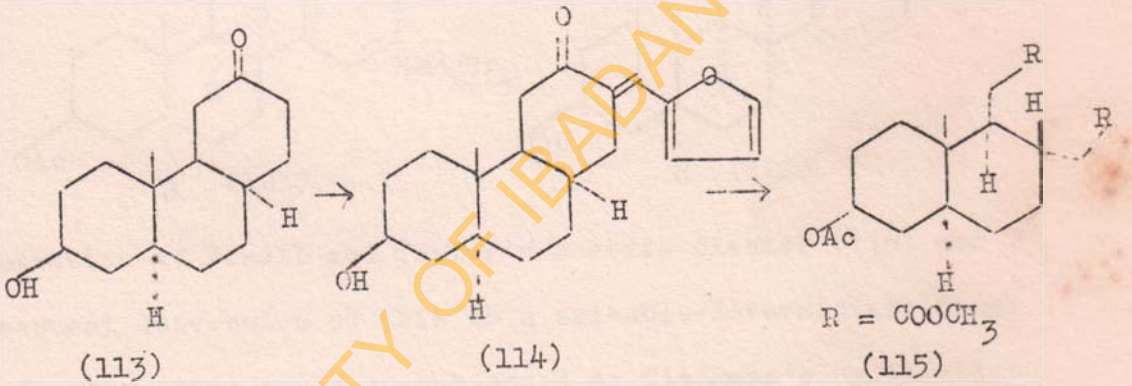
(108)

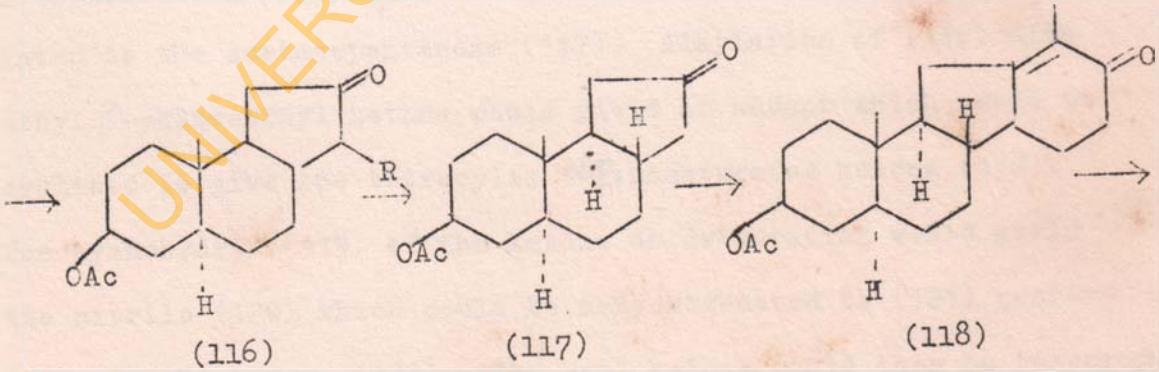


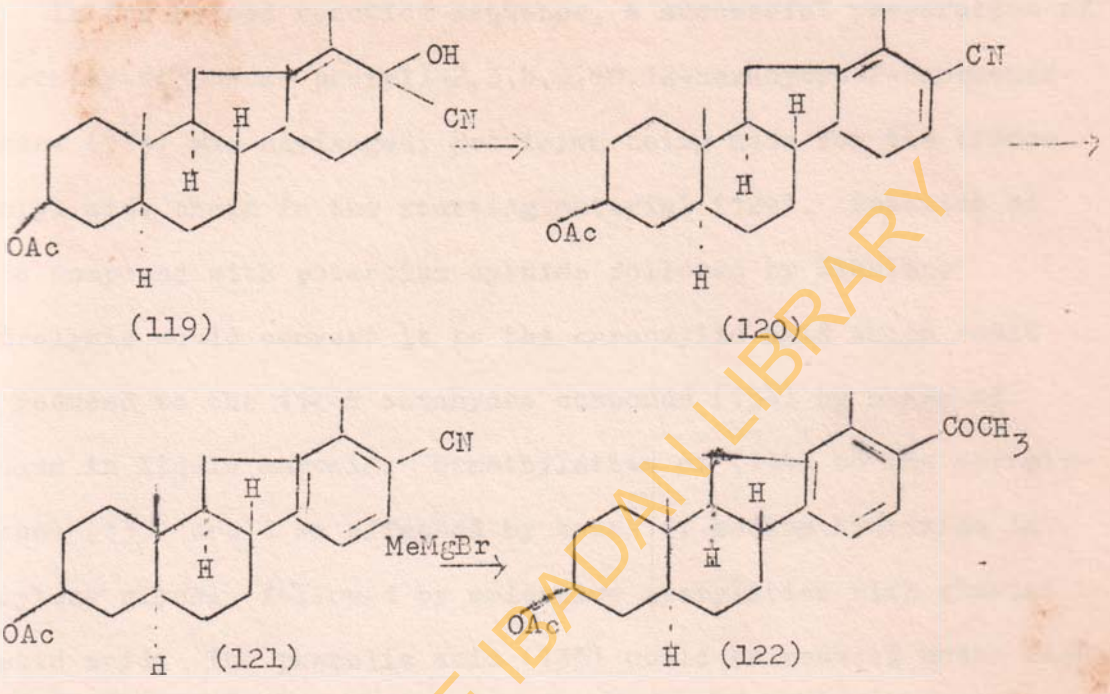
(109)

veratramine are attempted. The first pathway involves the





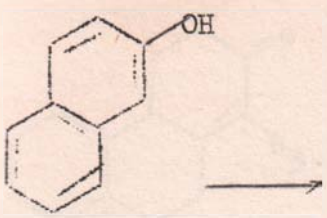




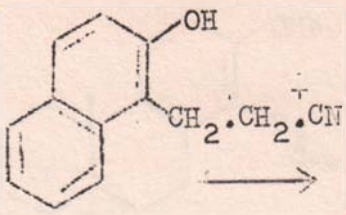
preparation of Howell and Taylor's acetate diester (115) and subsequent conversion of this to a suitable intermediate thus: the diester (115) could be subjected to Dieckman's cyclisation procedure to give the β-keto ester (116) which might be decarboxylated to the acetatepentanone (117). Alkylation of (117) with ethyl β-chloroethyl ketone would yield an adduct which could be cyclised to give the tetracylic αβ unsaturated ketone (118). The cyanohydrin (119) of the ketone on dehydration would yield the nitrile (120) which could be dehydrogenated to (121) convertible to the ketone (122). The aryl ketone could then be compared with Masamune and Takasugi's dihydroveratramine degradation product (44).

In the second reaction sequence, a successful preparation of 7-methoxy-8(3-bromo propyl)-2,3,4,9,10,12-hexahydro-2-oxophenanthrene (133) was envisaged, provision being made for the bromopropyl side chain in the starting material (124). Reaction of this compound with potassium cyanide followed by alkaline hydrolysis would convert it to the carboxylic acid which could be reduced to the 11α-H octahydro compound (134) by means of sodium in liquid ammonia. Demethylation of (134) to the acetate-phenol (135) could be effected by means of sodium hydroxide in ethylene glycol, followed by selective acetylation with glacial acetic acid. The phenolic acid (135) could be reduced under high pressure to the fully reduced phenanthrene derivative (136) which could be oxidized to the ketone (137) by means of chromic acid. C(7) - C(8) bond cleavage of the olefin (138) obtained by the grignard reaction of methyl magnesium bromide on the preceeding ketone could be achieved via ozonolysis. The diketone (139) could be cyclised to give (140) in which a simultaneous creation of rings C and D is involved. The useful substance (140) can then be converted by a two-stage sequence of dehydrogenation and reaction with methyl lithium to the relay substance (44).

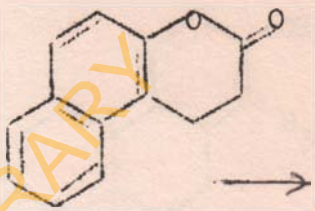
In the last synthetic approach, a suitable phenanthrene derivative was sought, and a side chain which together with the



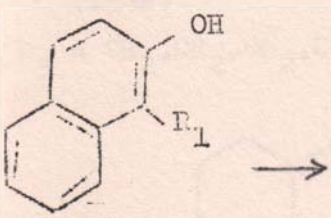
(123)



(124)



(125)



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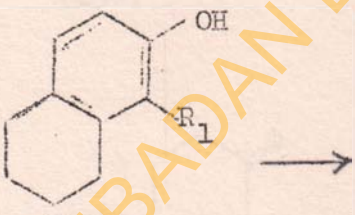
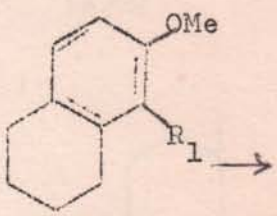


(127)

$R_1 = CH_2 \cdot CH_2 \cdot CH_2 \cdot OH$



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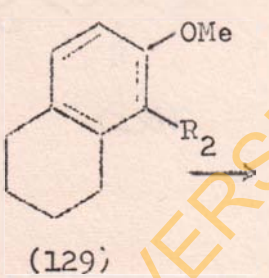
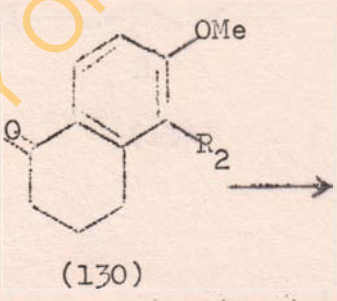
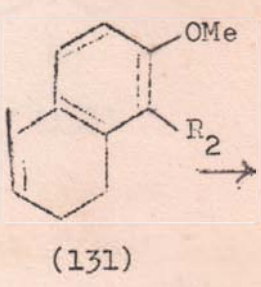


(129)

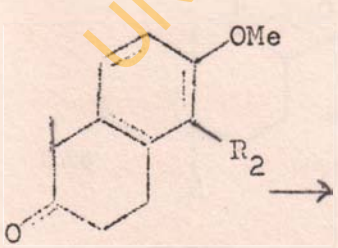


(130)

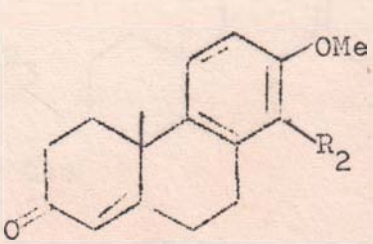
$R_2 = CH_2 \cdot CH_2 \cdot CH_2 \cdot Br$



(131)

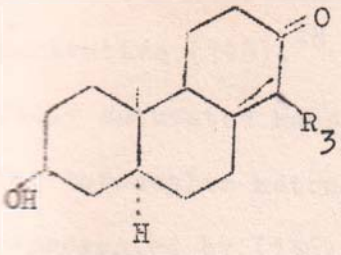


(132)



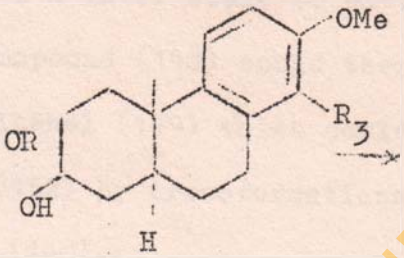
(133)

(1) KCN
(2) OH^-
(3) $Na/NH_3/MeOH$



(134a)

R_3 = $CH_2 \cdot CH_2 \cdot CH_2 \cdot COOH$



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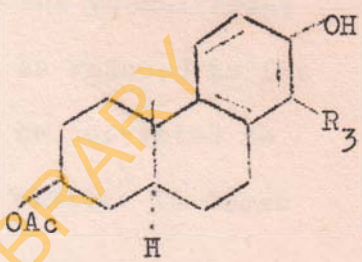

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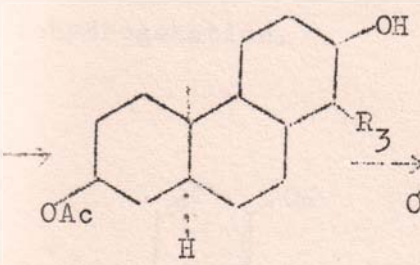

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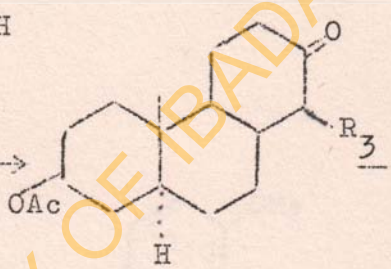

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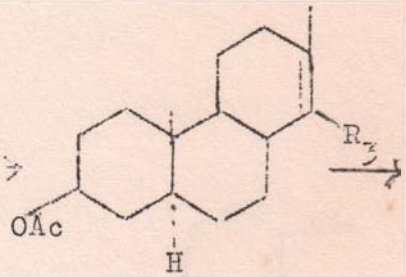

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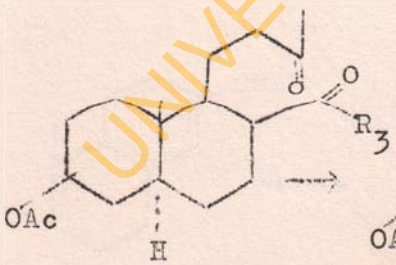
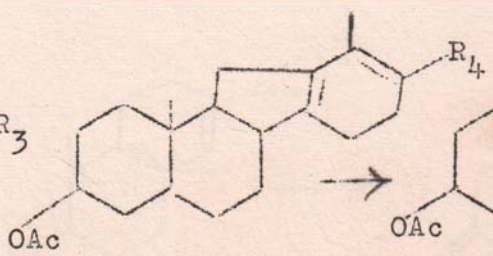
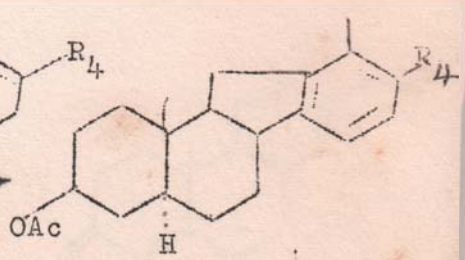


(139)



(140)

R_4 = COOH

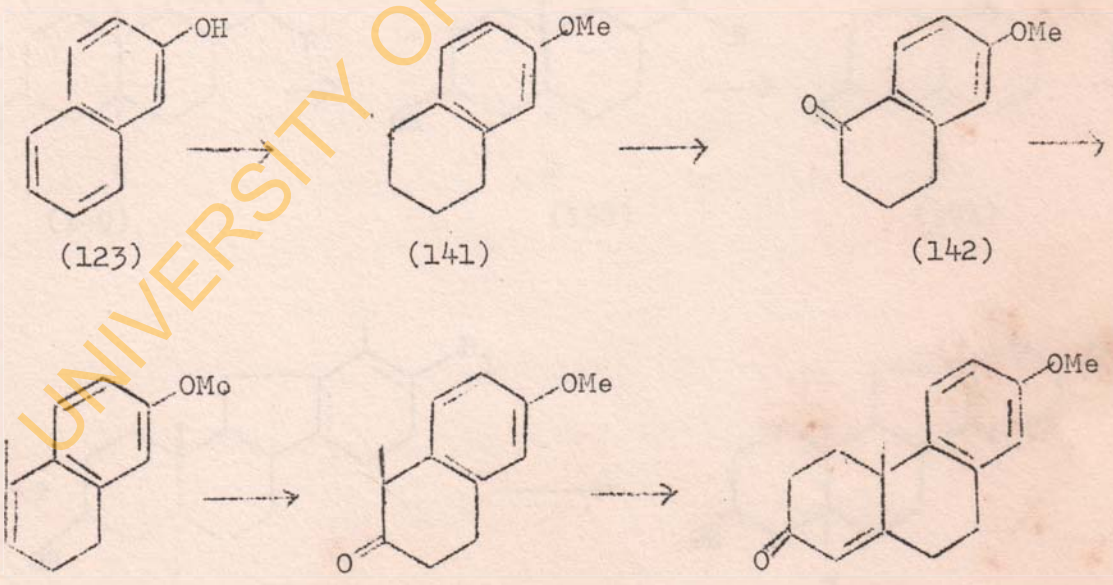


(140a)

(44)

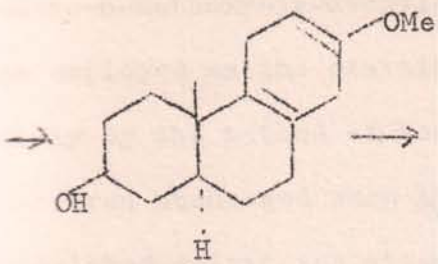
ring C opened would later provide ring C and D of the veratramine nucleus, was attached at a later stage to give the phenanthrene derivative (148).[48] Compound (148) could then be reduced to the fully saturated keto-alcohol (149) which could be converted to the tetracylic ketone (152) by transformations similar to those represented by (136) - (140).

The αβ-unsaturated ketone would yield Masamune and Takasugi's dihydroveratramine degradation product (44) on selenium dehydrogenation.



(123) (141) (142)

(143) (144) (145)



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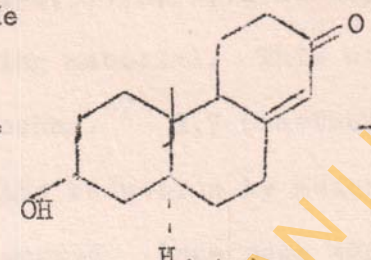

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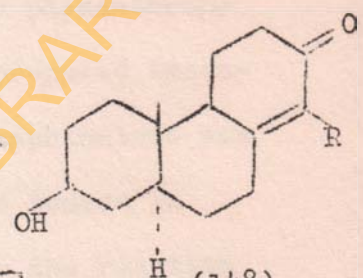
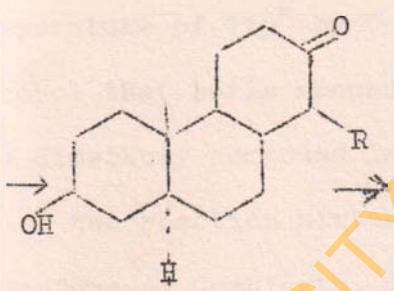


(148)

R = $CH_2 \cdot CH_2 \cdot CH_2 \cdot C(CH_3) \cdot CH_3$



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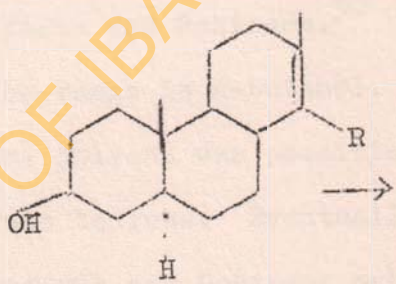

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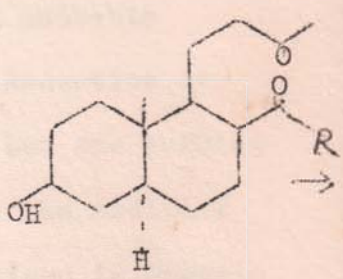
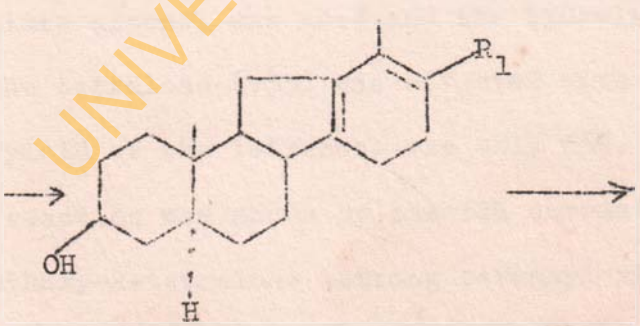
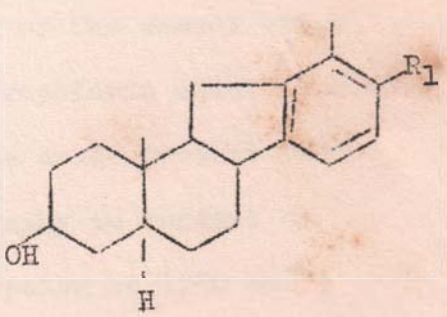


(151)



(152)

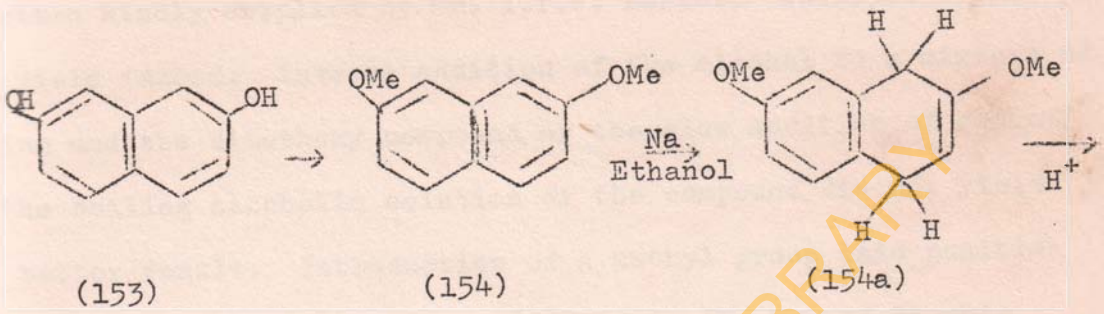
$R_1 = COCH_3$



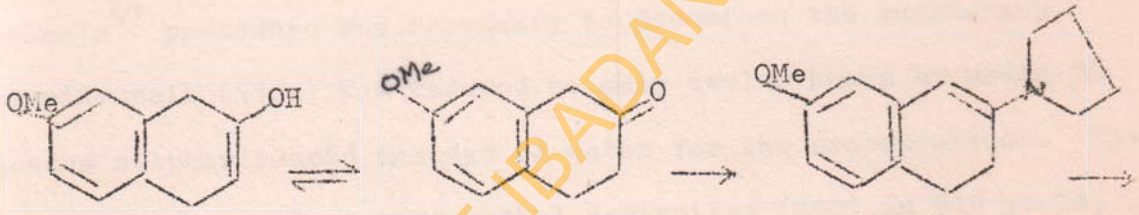
(44)

DISCUSSION

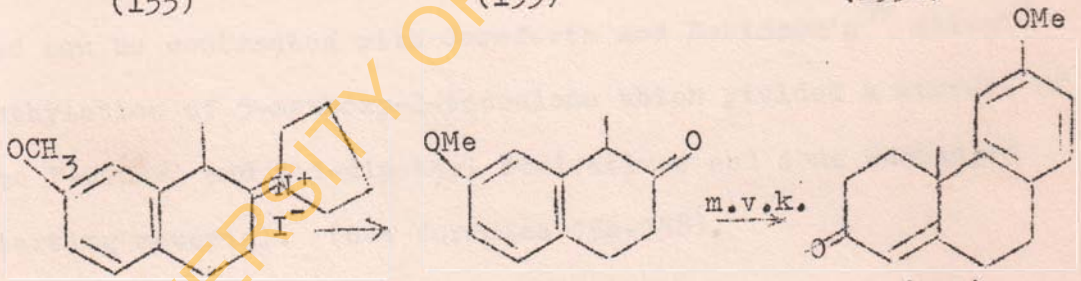
In order to prepare a suitable intermediate for the total synthesis of veratramine by the first scheme just discussed, 2-keto-6-methoxy-12-methyl-2,3,4,9,10,12-hexahydro phenanthrene was employed as the starting material. This was prepared essentially by the method of Kuehne.[47] 2,7-Dimethoxy naphthalene was recovered unchanged when its reduction by means of sodium in methylated spirit was attempted. (see page 32A for the reaction sequence) A similar reduction had been carried out at a bath temperature of 115° by Cornforth and Robinson.[50] A suitable alcohol that boils around the range is n-butanol. Reduction of the dimethoxy compound in the solvent was possible but the working up of the reaction mixture was tedious. Eventually the modified procedure of Cornforth, Cornforth and Robinson outlined in Organic Syntheses[51] for the preparation of 2-tetralone was followed. Absolute alcohol was used and the hydrolysis of the dienol ether to the tetralone (155) was effected with hydrochloric acid. However, the yield of the tetralone was only 25%. The crude product from the reaction was shown by careful chromatography to consist of 7-methoxy-2-tetralone (strong carbonyl absorption at 1760 cm^{-1}) 2,7,dimethoxy naphthalene (m.p. 139°) and 6-methoxy tetralin, the I.R. spectrum of which was identical with that of an authentic



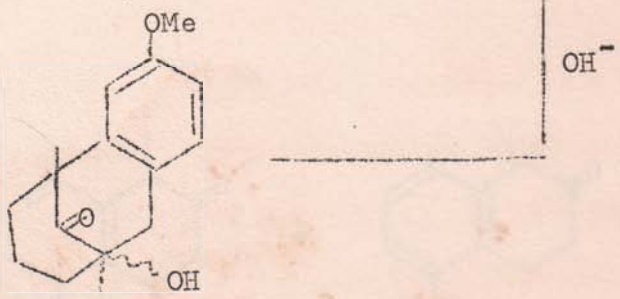
(153) (154) (154a)



(155) (155) (155a)

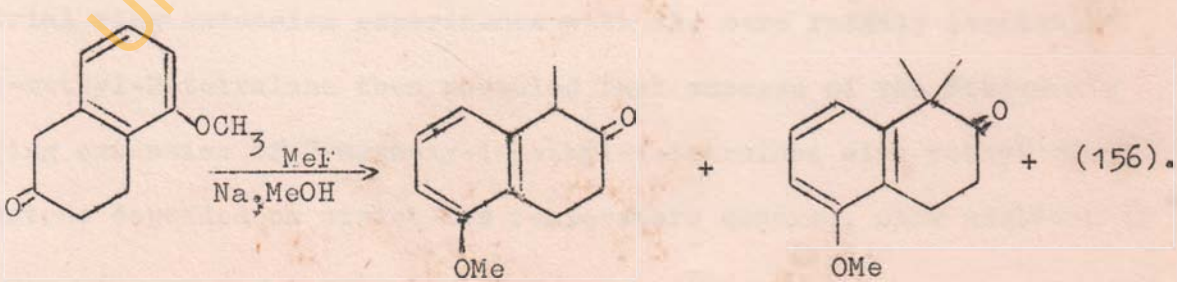


(110a) (110) (111)



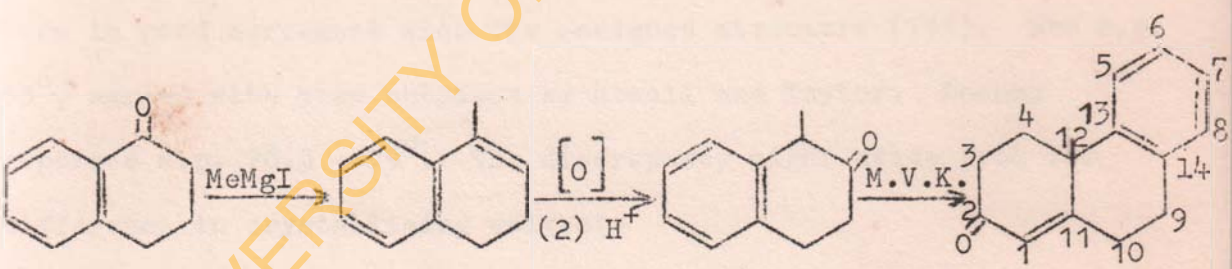
(111a)

specimen kindly supplied by Mr. I.T.U. Eshiet. Attempts to improve the yield failed. Inverse addition of the alcohol to a mixture of sodium and the dimethoxy compound or the slow addition of sodium to the boiling alcoholic solution of the compound did not yield any better result. Introduction of a methyl group into position (1) of the tetralone (155) was effected by the use of Stork's enamine slkylation method.[52-55] The period of five days which in Kuehne's[47] procedure was necessary to decompose the quartenary ammcnium salt (110a) was reduced to only twelve hours by using 5% aqueous sulphuric acid instead of water for the decomposition. The procedure gave a clean mono methyl derivative (110) in 91% yield, and can be contrasted with Cornforth and Robinson's[56] direct methylation of 5-methoxy-2-tetralone which yielded a mixture of the 1-methyl and 1:1-dimethyl derivatives and some unchanged starting material. (See formulas 156-158).



(156) (157) (158)

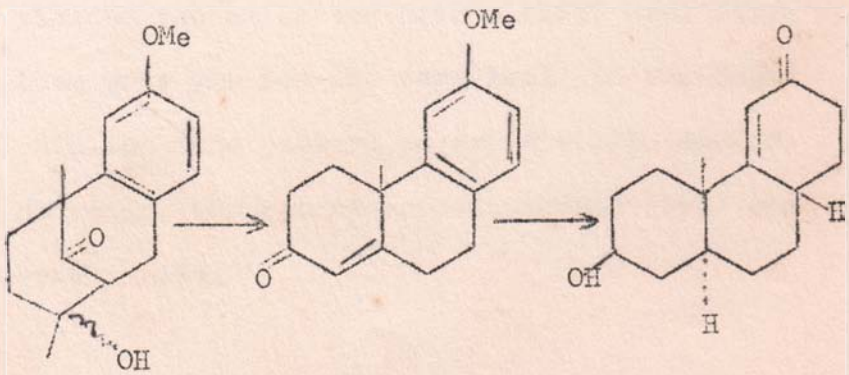
First attempt to obtain the tricyclic ketone (111) by homoannelation of 7-methoxy-1-methyl-2-tetralone (110) with methyl vinyl ketone was unsuccessful. As a check of Kuehne's synthetic pathway to the preparation of the ketone (111),[28] 1-methyl-2-tetralone (161) was prepared by two different methods. 1-Tetralone (159) prepared by Friedel Craft's acylation of benzene with γ-butyrolactone[57] was converted to 1-methyl-3,4-dihydro naphthalene (160) by the action of methyl magnesium iodide. The dihydro naphthalene was oxidized with perbenzoic acid[58-59] to give 1-methyl-2-tetralone, the I.R. spectrum of which was identical with the enamine alkylation product of 2-tetralone.



(159) (160) (161) (162)

Trial ring extension experiments with the more readily available 1-methyl-2-tetralone then revealed that success of the Robinson's ring extension of 7-methoxy-1-methyl-2-tetralone with methyl vinyl ketone depended on strict low temperature control, slow addition of

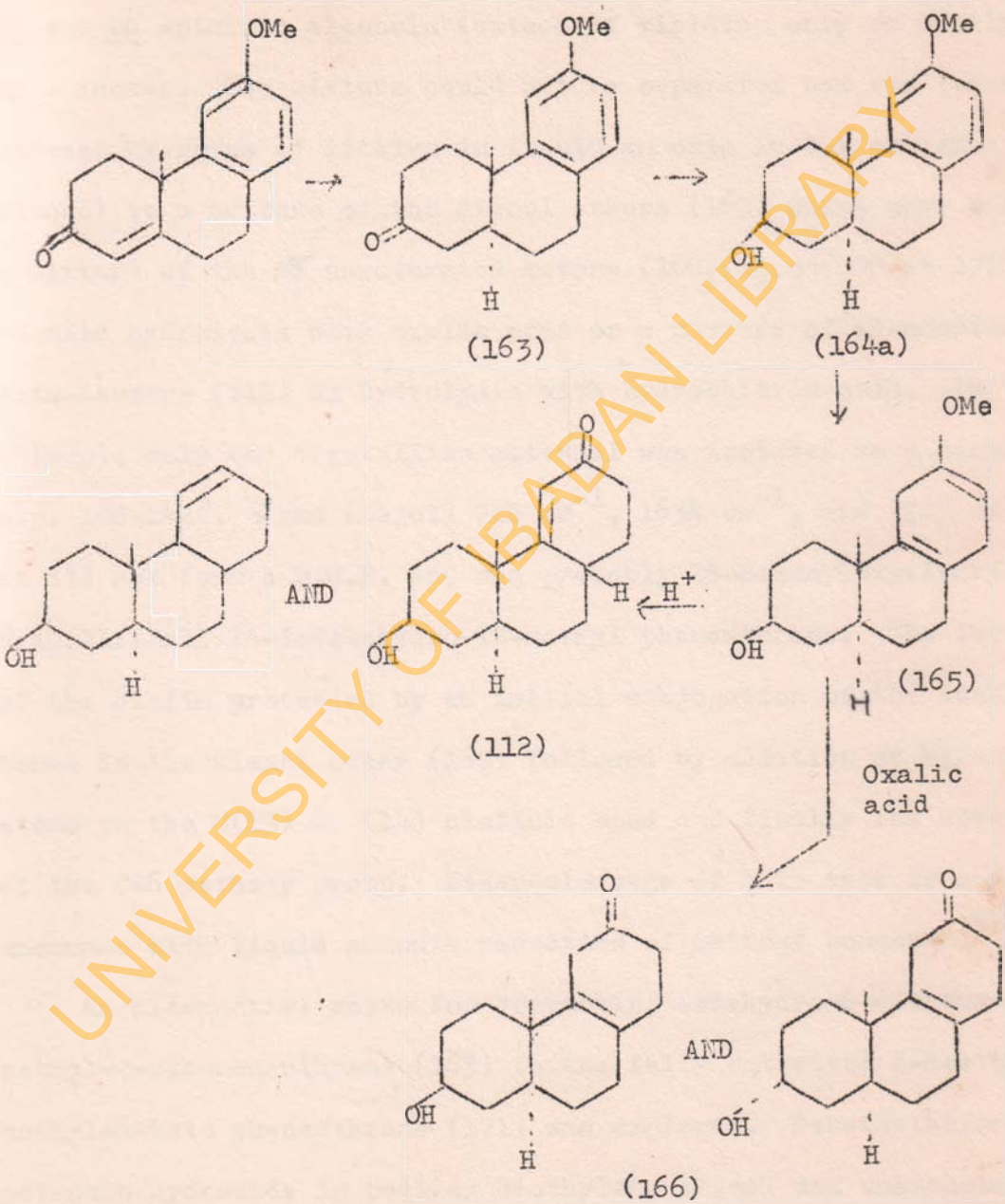
the reagent and on absolute exclusion of oxygen from the reaction system. The actions are necessary as a result of the reversibility, and exothermicity of the reaction. High temperature favoured retrogression[60] and presence of oxygen promoted complex oxidation side reactions. The use of an atmosphere of butane gas instead of the commercial nitrogen which is not completely free from oxygen solved the last difficulty. In this way, the tricyclic methoxy enone (111) (see the formulas below) was obtained in 52% yield taking into account the recovered starting material. It gave very good elemental analysis and its I.R. and U.V. spectra, (ν max. 1575 cm^{-1}, 1616 cm^{-1} and 1670 cm^{-1}. λ max. 205 mμ (ϵ 12,540), λ max. 228.5 mμ (ϵ 18670) were in good agreement with the assigned structure (111). The m.p. 63°, agreed with that obtained by Howell and Taylor. Kuehne reported m.p. 78.5 - 79°. The discrepancy might arise from the difference in crystallising solvent.



(111a) (111) (112)

Of interest was the isolation of the keto-alcohol (111a) (ν max. 1750 cm and 3570 cm^{-1}) which was a precursor of the unsaturated ketone 111. Smooth dehydration of the alcohol to the unsaturated ketone was effected in boiling methanolic solution of potassium hydroxide.

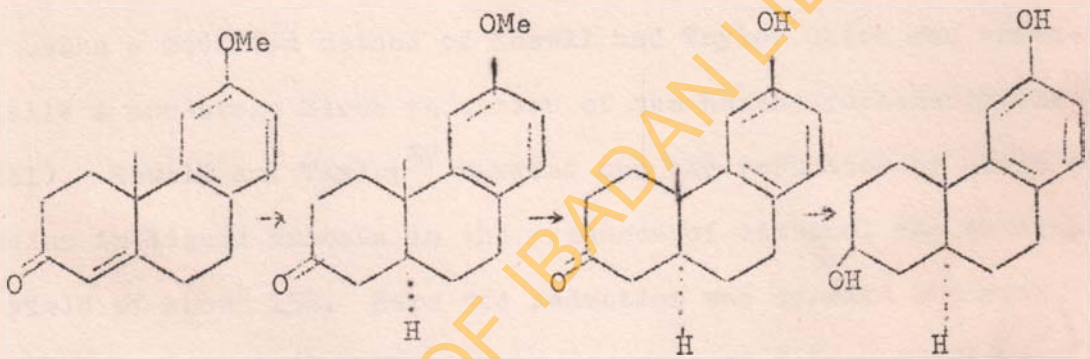
With the preparation of the starting material under control attention was directed towards its conversion to the αβ-unsaturated 6-keto compound (112). The problem then was threefold. The C-2 carbonyl must be converted to the corresponding 2β-secondary hydroxyl. The C-11 olefinic function must be reduced in a way to confer on rings A and B a trans-fusion arrangement and the benzene nucleus should be reduced to a form in which the C-6 methoxy would be transformable into a function which could be used in a controlled contraction of ring C. The first attempt was a stepwise reduction of the tricyclic ketone. Selective reduction of the double bond by means of lithium in liquid ammonia followed by an addition of ammonium chloride[59] yielded the saturated ketone (163) m.p. 129.5 - 130° in 78% yield. (See page 36A for the formulas). In the hope that reduction should follow same pattern as for the allo series of the conventional steroids, the octahydrophenanthrene (163) was reduced with sodium borohydride.



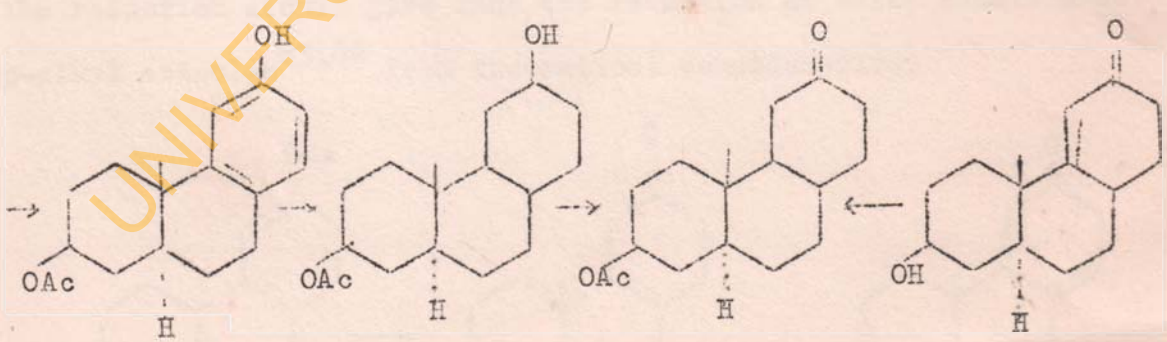
The reduction was not stereospecific but yielded a mixture of the 2α and 2β epimeric alcohols instead of yielding only or mostly the 2β - isomer. The mixture could not be separated but was further reduced by means of lithium in liquid ammonia in the presence of alcohol to a mixture of the dienol ethers (165) which gave either a mixture of the β,γ unsaturated ketone (166)(strong CO at 1710 cm^{-1}), on mild hydrolysis with oxalic acid or a mixture of αβ-unsaturated keto-isomers (112) on hydrolysis with hydrochloric acid. In the attempt, only one crystalline material was isolated as a benzoate m.p. 140-142°, ν max (Nujol) 720 cm^{-1}, 1634 cm^{-1}, and 1725 cm^{-1}. It did not form a D.N.P. and was probably 2β-Benzoyloxy:1:2:3:4:7:9:8:10:11:12:13:14-dodecahydro-12-methyl phenanthrene. The formation of the olefin proceeded by an initial conjugation of the double bonds in the dienol ether (165) followed by addition of hydrogen atoms to the C(13) - (14) olefinic bond and finally the cleavage of the C-6 methoxy group. Ether-cleavage of this type is not uncommon with liquid ammonia reduction of methoxy benzenes.[61-62]

An alternative route for converting octahydro-6-methoxy-12-methyl-2-oxophenanthrene (163) to the fully saturated 2-acetoxy-12-methyl-6-keto phenanthrene (171) was explored. Demethylation with potassim hydroxide in boiling diethylene glycol was unsuccessful. The phenolic ketone (167) m.p. 174° obtained by the action of

hydriodic acid in refluxing acetic acid on compound (163) was reduced by means of sodium borohydride to a mixture of the α and β phenolic alcohols (168) which on selective acetylation with glacial acetic acid yielded presumably the phenolic - 2β-acetoxy compound (169) m.p. 144-146°. The overall poor yield of the phenolic acetate based on the methoxy ketone (163) justified the reluctance to



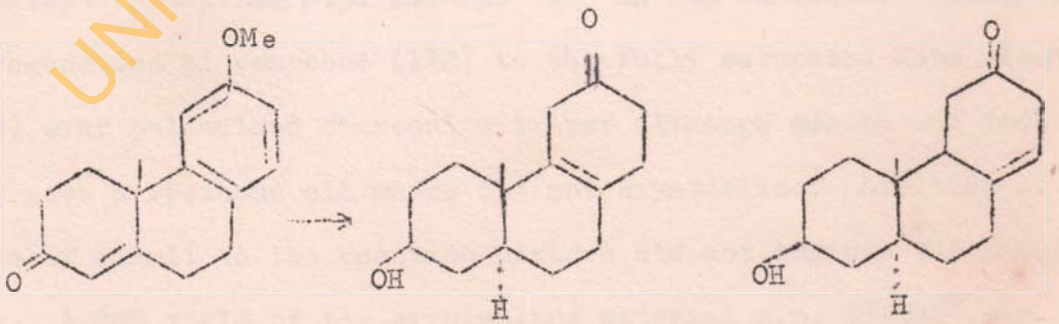
(111) (163) (167) (168)



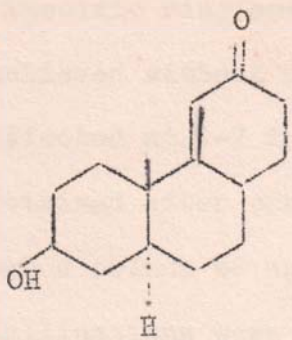
(169) (170) (171) (112)

continue with the scheme. Had the yield been higher, high pressure hydrogenation followed by chromic acid oxidation of substance (169) should yield the fully saturated acetoxy ketone (171) which on hydrolysis should give the reduction product of compound (112).

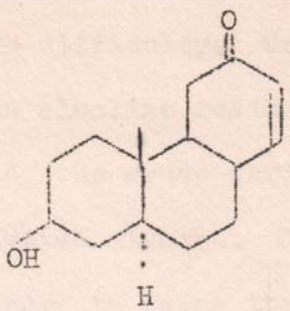
The preparation of the unsaturated ketone (112) was realized by using a modified method of Howell and Taylor which was essentially a one-stage Birch reduction of the hexahydrophenanthrone (111). Howell and Taylor[37] carried out the reduction by means of sodium in liquid ammonia in the presence of methanol and obtained a yield of about 15%. Here the reduction was carried out with lithium in same medium but in the presence of a less reactive alcohol viz, n-propanol, in 31% yield. It was felt that this yield was reasonable in the light of the complex mixture of isomers the reduction should give like the reduction of other substituted p-alkyl anisoles[63,64] from theoretical consideration.



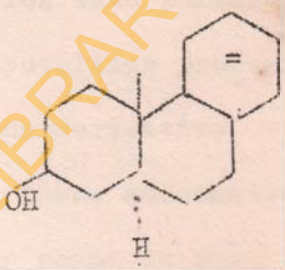
(111) (a) (b)



(c)



(d)

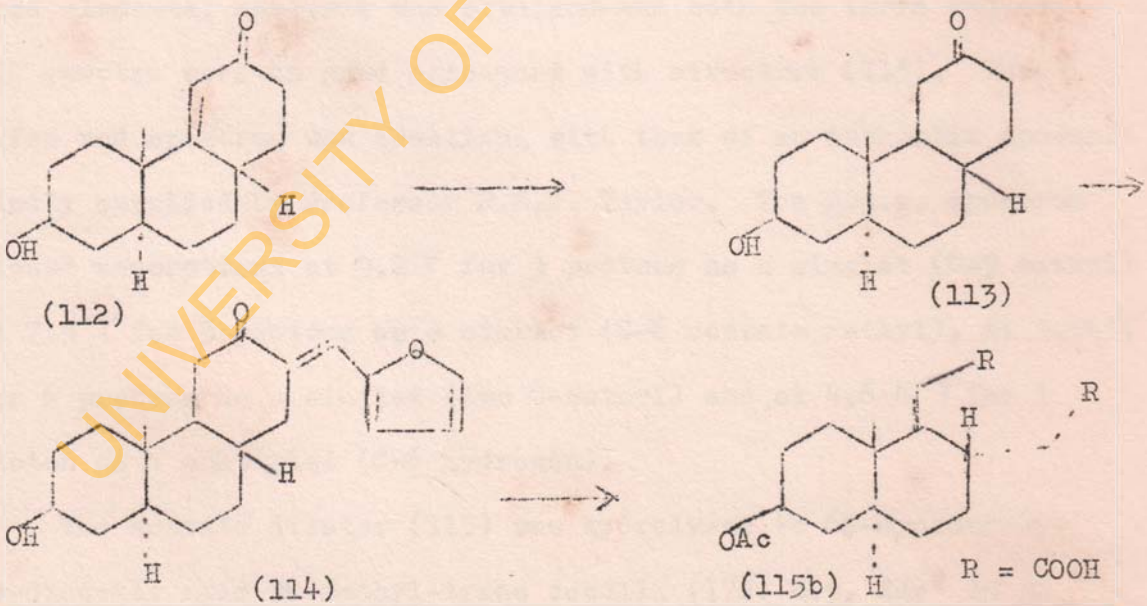


(e)

Infra red spectral analysis of components obtained by passing the mixture through a column suggested that among other things substances (a) - (e) might be present in the reduction product in agreement with the experience of Johnson and collaborators.[44] The unsaturated keto-alcohol (112) which was of interest was isolated crystalline m.p. 118-120° and as its benzoate. Catalytic hydrogenation of compound (112) to the fully saturated keto alcohol (113) over palladised charcoal catalyst although smooth and fast only gave a resinous oil which did not crystallize. Addition of trace of alkali to the reaction mixture did not improve the situation. A 60% yield of the crystalline material m.p. 98-102° was

however obtained when palladised calcium carbonate catalyst was used.

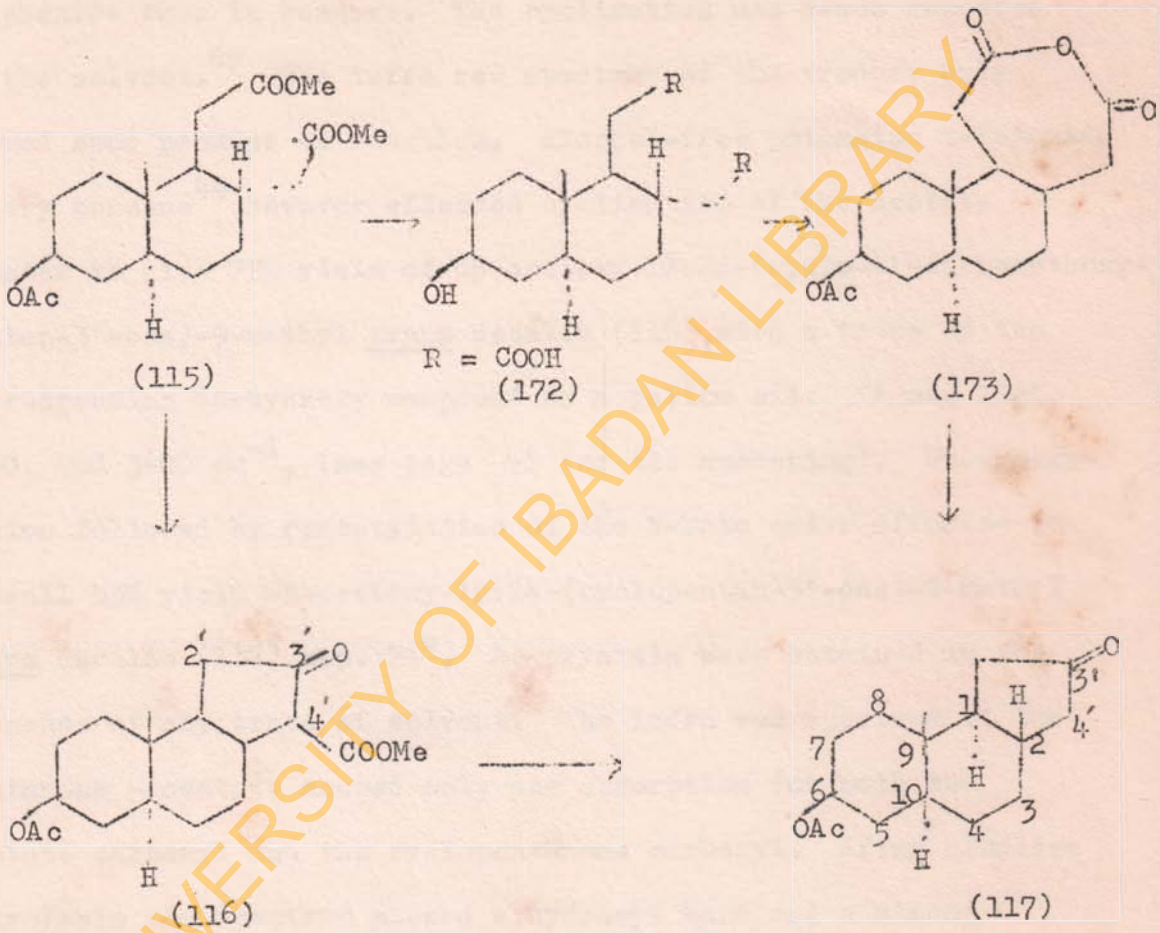
Specific ring opening of compound (113) between C-6 and C-7 was achieved without much difficulty. Condensation with furfural was effected at C-7 in an alkaline medium. A crystalline product was obtained after passing the crude furfurylidene derivative through a column of activated alumina. However, three successive crystallisations were needed to raise the melting point to the value of 204° obtained by Howell and Taylor.[37] Alkaline peroxide oxidation of the acetate of trans-antitrans-7-furfurylidence perhydro-2-hydroxy-6-oxo-phenanthrene (114) resulted in no



oxidation but in extensive hydrolysis of the acetate. This would have been a very suitable oxidation procedure for a large scale run.

Complete ozonolysis of only one gm. of the furfurylidence acetate in ethyl acetate was not achieved quickly at - 20°. Ozonolysis in same solvent or in methylene chloride at - 78° (acetone-solid carbondioxide bath) was complete within three hours. Acid hydrogen peroxide oxidation of the ozonide gave an acetate diacid (115b) m.p. 200° which gave an impure acetate diester after esterification with crude diazomethane. I.R. spectrum of the product showed that the diester was contaminated with nitrosomethyl urea. Methylation of the diacid with redistilled diazomethane gave a very pure product m.p. 103° in agreement with the literature value. Good elemental analysis was obtained and both the infra red and NMR spectra were in good agreement with structure (115). The infra red spectrum was identical with that of an authentic specimen kindly supplied by Professor D.A.H. Taylor. The n.m.r. spectrum showed absorptions at 9.2τ for 3 protons as a singlet (C-9 methyl) at 7.5τ for 3 protons as s singlet (C-6 acetate methyl), at 5.54τ for 6 protons as a singlet (two O-methyl) and at 4.6-4 τ for 1 proton as a multiplet (C-6 hydrogen).

The acetate diester (115) was hydrolysed to 6β-Hydroxy-1β-2α-diacetic acid-9β-methyl-trans decalin (172) m.p. 224° in an attempt to convert the diacid to the anhydride (173) the pyrolysis[65]



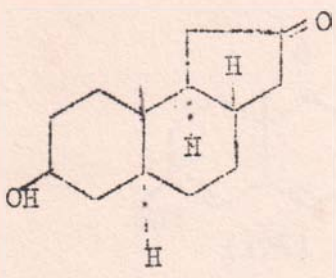
of which should give the pentanone (117). However, attention was directed towards obtaining substance (117) by the Dieckman's cyclisation procedure which appeared simpler than the pyrolysis method. Cyclisation[66] of the acetate diester in benzene by means of sodium hydride gave the starting material with the C-6 acetate

group hydrolysed. Sodium hydride is a stronger base in dimethyl sulphoxide than in benzene. The cyclisation was hence repeated in the solvent.[67] The infra red spectrum of the product only showed some promise of reaction. Alcohol-free potassium t-butoxide in dry benzene[44] however effected cyclisation of the acetate diester to give 77% yield of 6β-acetoxy-1β:2α-(cyclo-4'-carbomethoxy-pentan-3'-one)-9-methyl trans decalin (116) with a trace of the corresponding 6β-hydroxy compound as a yellow oil. ν max 1725, 1760, and 3400 cm^{-1}, (see page 43 for the numbering). Decarboxylation followed by reacetylation of the β-keto ester afforded in overall 53% yield 6β-acetoxy-1β:2α-(cyclopentan-3'-one)-9-methyl trans decalin (117) m.p. 74°. No crystals were obtained in the presence of any trace of solvent. The infra red spectrum of the pentanone - acetate showed only one absorption for both the acetate carbonyl and the cyclopentanone carbonyl. After alkaline hydrolysis the spectrum showed a hydroxyl band and a strong carbonyl absorption due to the cyclopentanone keto group. The N.M.R. signals were significant. There were signals at 8.9 τ for 3 protons as a singlet (C-9 methyl), at 8.32 - 8.2 τ for 4 protons as a doublet (2' and 4' methylenes) at 7.51 τ for 3 protons as a singlet (C-6 acetate methyl), and at 4-4.5 τ for 1 proton as a multiplet (C-6 hydrogen). A very useful intermediate for the

synthesis of veratramine was therefore obtained.

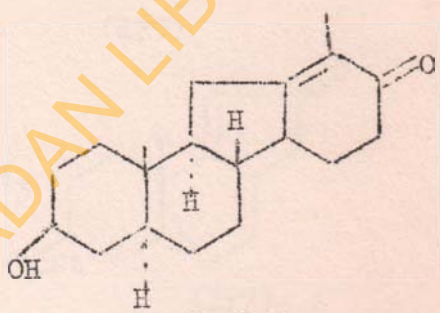
The cyclopentanone carbonyl in the intermediate (117) is flanked on both sides at C-2' and C-4' by active methylene groups. It was evident that ring extension of the pentanone to the αβ-unsaturated ketone (118) typifying the unusual C-Nor-D-homo ring system must involve an initial selective alkylation of the pentanone-acetate. As a model for this reaction, 6-Methoxy-1-tetralone and 5-methoxy hydrindone-1 (prepared by methylating 5-indanol with dimethyl sulphate followed by chromic acid oxidation[68] of the ether) were each formylated according to the procedure of Johnson, Anderson and Shelber.[68] 2-Hydroxy methylene-6-methoxy-1-tetralone and 2-hydroxy methylene-5-methoxy-1-hydrindone were each alkylated with ethyl β-chloro-ethyl ketone in the presence of sodium methoxide in methanol. The cyclised products from the two exploratory experiments were oils which had identical infra red spectra characterized by triplet absorptions around the 6-micron region. Alkylation of the formyl derivative of compound (117) yielded a similar ring extension product. A crystalline enamine of the pentanone was not obtained and so ring extension by Stork's procedure was not attempted. Direct ring extension of the pentanoneacetate, with β-chlorodiethyl ketone and sodium ethoxide in ethanol however, gave a substance m.p. 134° (decomposed).

Although the substance had the expected U.V. absorption at 251 mμ it gave a very poor elemental analysis for $C_{19}H_{28}O_2$ which is the formula for the tetracyclic compound (118a).



(117)

R

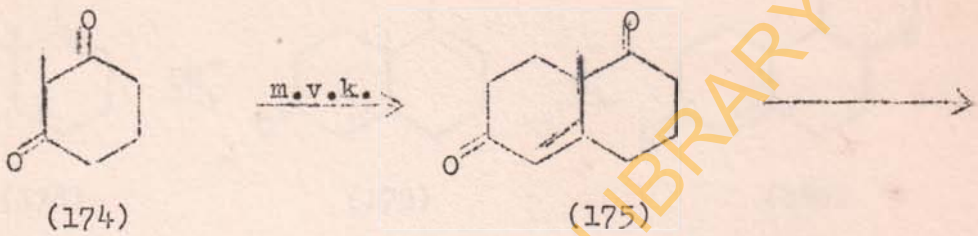


(118a)

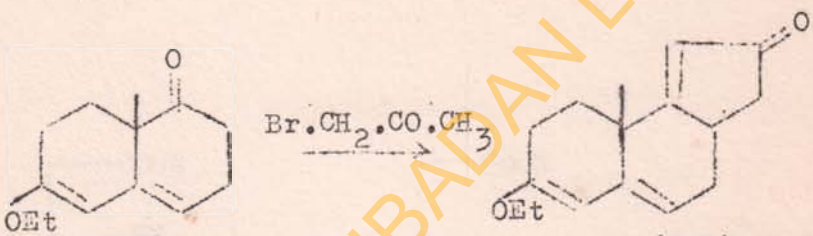
R = $Cl.CH_2.CH_2.CO.CH_2.CH_3$

The acetate of the substance absorbed at 248 mμ (ε 4,660) but also gave poor analysis. The U.V. absorption is however in fair agreement with that obtained for the same acetate encountered by Mitsuhashi and Kawahara[69] in a recent degradation work, although their ε-value of (18,100) showed the present sample as far from being pure.

It was clear, that if the pentanone acetate (117) could be obtained in a larger quantity it should be possible to obtain a cleaner ring extension product. A shorter route to the preparation of substance (117) was sought.

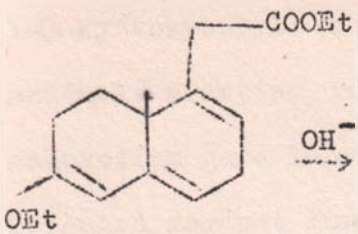


(174) (175)

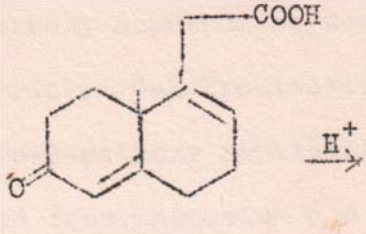


(176) (177)

High pressure hydrogenation of resorcinol[70-71] gave dihydroresorcinol which was methylated to 2-methyl-1,3 cyclohexane-dione (174) in high yield. The dione was ring extended with methyl vinyl ketone to 1,2,3,4,6,7,8,8a-octahydro-8a-methyl-1,6-naphthalene-dione[72] (175) which was etherified to the ethoxy derivative (176) according to the procedure of Swaminathan and Newman.[73] Alkylation of the 1-oxo-6-ethoxy compound with bromo acetone[74] gave unchanged starting material. Reformatsky reaction of (176) with ethyl bromo acetate was unsuccessful. This would have given the adduct (178) convertible to compound (184) by the reaction sequence represented by (178) - (184).



(178)



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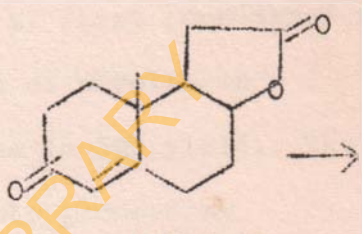
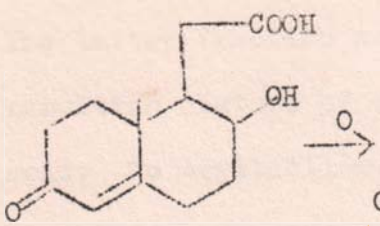
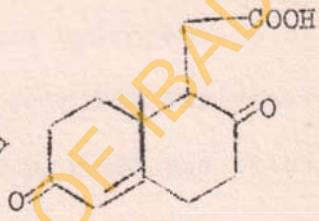


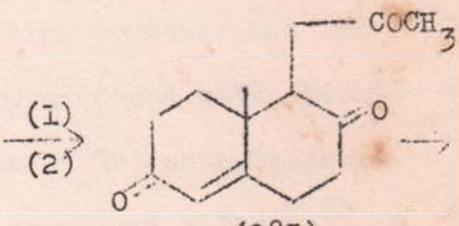
(180)



(181)



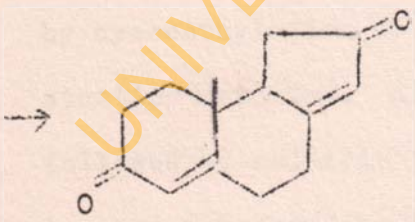
(182)



(183)

(1) Protection

(2) Methyl lithium.

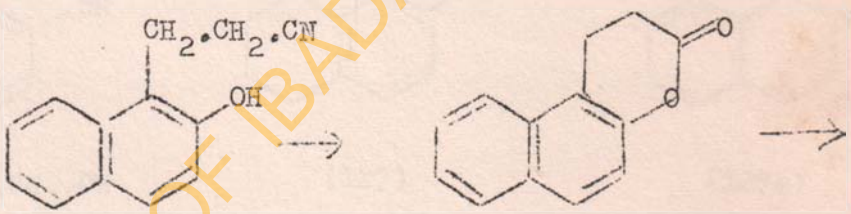


(184)

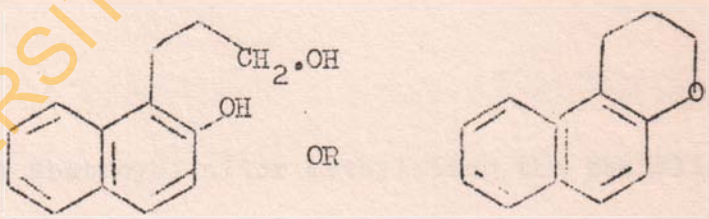
Since attempts to obtain the pentanone acetate (117) by a shorter reaction sequence failed, the first synthetic pathway was abandoned.

For the second synthetic pathway (see page 30A for the chart). 1-(4-Hydroxybutyl)-2 methoxy naphthalene was at first considered a suitable starting material. C-1 Bromination of nerolin in chloroform gave 1-bromo-2-methoxy naphthalene in 59% yield. The Grignard reagent formed from magnesium and the preceeding bromonaphthalene was treated with γ-butyrolactone. The product consisted mainly of 2-methoxy naphthalene and a fraction which was a mixture of saturated and αβ-unsaturated carbonyl compounds. The latter fraction was hydrogenated at high pressure and the resulting mixture of tetralin derivatives oxidized with chromic acid. No crystalline product was obtained. The same Grignard reagent was reacted with β-carbomethoxy propionyl chloride[75] in an endeavour to obtain 1-(δ-carbomethoxy propionyl)-2-methoxy naphthalene but the product was mainly 2-methoxy naphthalene. However, 1-(2-Cyanoethyl)-2-hydroxy naphthalene[76] (124) prepared by cyanoethylation of 2-naphthol was found as an alternative starting material. Alkaline hydrolysis of the phenolic nitrile followed by acidification with concentrated hydrochloric acid yielded 5,6-benzdihydrocoumarin (125) m.p. 52-54° and an unidentifiable acidic substance of formula $C_{13}H_{12}O_5$. The dihydrocoumarin only solidified when completely free from solvent. It gave very good elemental analysis and its infra red spectrum

(ν max. 1582 cm^{-1}, 1632 cm^{-1} and 1762 cm^{-1}) was in accord with structure (125). Reduction of the dihydro coumarin with lithium aluminium hydride yielded the crystalline diol (126) m.p. 135° in quantitative yield. The diol (ν max. 1587.5, 1625, 3150 and 3410 cm^{-1}) gave a green colour with ferric chloride solution and could not be the cyclic ether (126a), a fact confirmed by the IR spectrum of the diol, and by C, H-analysis.



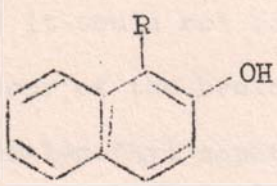
(124) (125)



(126) (126a)

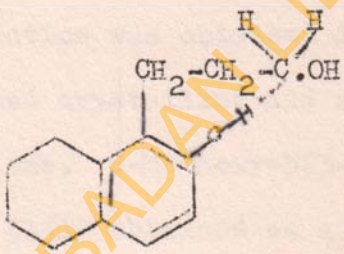
High pressure hydrogenation of the phenolic alcohol over neutral Raney nickel catalyst gave a mixture of 1-(3-hydroxy propyl)-2 hydroxy-5,6,7,8-tetrahydronaphthalene (127) m.p. 65-70° in 78% yield and a neutral fraction presumably 1-(3-hydroxy propyl)-2 hydroxy-1,2,3,4-tetrahydronaphthalene (127a). The infra red

spectrum of the former is of interest. Two hydroxy absorptions (3233 cm^{-1} and 3550 cm^{-1}) around the 3 micron region suggested extensive hydrogen bonding[12] in the molecule as represented in formula (127).

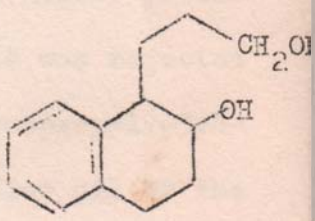


R = $CH_2 \cdot CH_2 \cdot CH_2 \cdot OH$

(126)



(127)

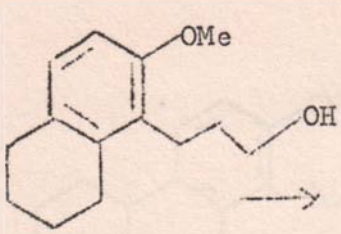


(127a)

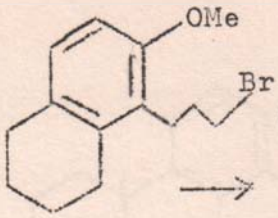
The bonding was destroyed after methylating the phenolic alcohol with dimethyl sulphate, there being only one hydroxyl absorption (3400 cm^{-1}) in its spectrum. Bromination of the methoxy alcohol (128) with phosphorous tribromide in benzene gave a poor yield of the bromide. (See page 30A). When the reaction was however repeated in dry diethyl ether a 65% yield of 1-(3-bromopropyl)-2-methoxy-5,6,7,8-tetrahydronaphthalene (129) was obtained. Chromic acid oxidation of the preceeding tetralin derivative afforded

5-(3-bromopropyl)-6-methoxy-1-tetralone m.p. 92-94° in only 32% yield; a good analysis was obtained. The major oxidation product was an acidic substance which was not investigated further. Attempt to improve the yield by controlling the reaction temperature failed. Although the closely similar acetoxy compound 5-(3-acetoxy-propyl)-6-methoxy-1-tetralone prepared by acetylation of (128) followed by chromic acid oxidation was obtained in a higher yield of 50% it could not be obtained crystalline and so it was rejected in favour of the bromo tetralone. 6-Methoxy-5(3-bromopropyl)-3:4-dihydro-1-methyl naphthalene (131) obtained as a yellow oil by the reaction of methyl magnesium bromide on the 1-tetralone (130) was converted to the corresponding 2-tetralone (132) by perbenzoic acid[77] epoxidation of the C1-C2 olefinic bond followed by acid hydrolysis.

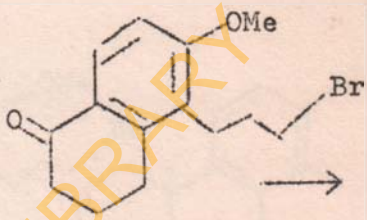
Robinson ring extension of 1-methyl-5(3-bromopropyl)-6-methoxy-2-tetralone by means of methyl vinyl ketone in the presence of potassium hydroxide gave the oily tricyclic compound (185) with the side chain bromide hydrolysed to the alcohol.



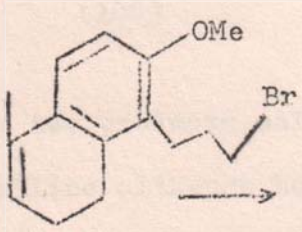
(128)



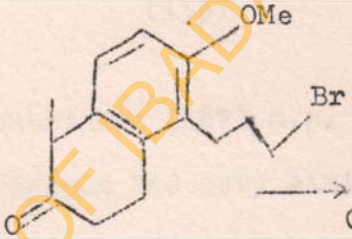
(129)



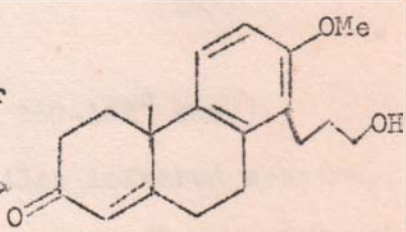
(130)



(131)

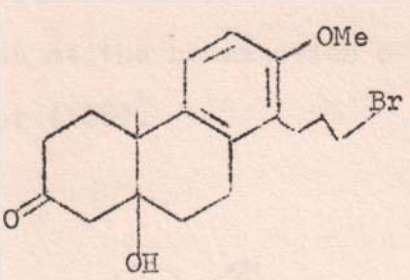


(132)

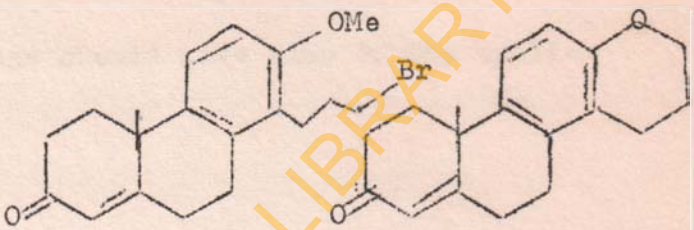


(185)

The tetralone was condensed with methyl vinyl ketone in the presence of potassium hydroxide to give the adduct (186) which was isolated as an oil (ν max. 1710 cm^{-1} and 3400 cm^{-1}). The milder base, potassium carbonate, effected smooth dehydration of the adduct to a mixture of enones (133) and (187) separable only by chromatography.



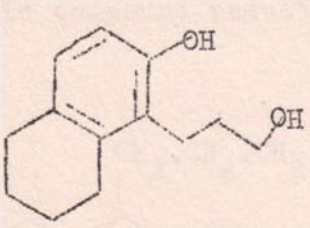
(186)



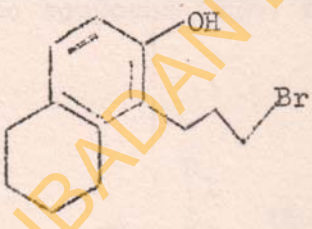
(133) (187)

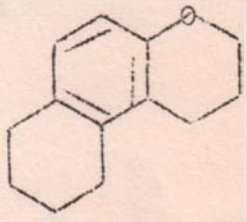
Of the two products, only substance (187) m.p. 160-162° was crystalline although both enones had very similar infrared spectra. The ultra violet of the solid showed two absorptions (λ max. 207 mμ and 234 mμ) and the infra red spectrum showed absorptions at νmax. 1587.5 cm^{-1}, 1616 cm^{-1} and 1650 cm^{-1}. C, H-analysis was in fair agreement with formula $C_{18}H_{20}O_2$ and its N.M.R. spectrum agreed with structure (187). There were absorptions at 8.04 τ for 3 protons as a singlet (C-9 methyl), at 6.96-6.6 τ for six protons as a multiplet (2xAr. $CH_2\underline{CH_2}$ and CO $\underline{CH_2}$), at 5.04-4.48 τ for 2 protons as triplet ($\underline{OCH_2}$), at 2.88 τ for one proton as a singlet (C-5 olefinic hydrogen) and at 1.96-1.24 τ for two protons as a quintet (two aromatic hydrogens). Further support for the structure was obtained from its inertness towards alcoholic

potassium cyanide. The formation of the cyclic ether is still not very clear. One possibility is that it might originate from incomplete methylation of the phenolic hydroxyl compound (127) which at the bromination stage should give rise to the cyclic ether (188).



(127)

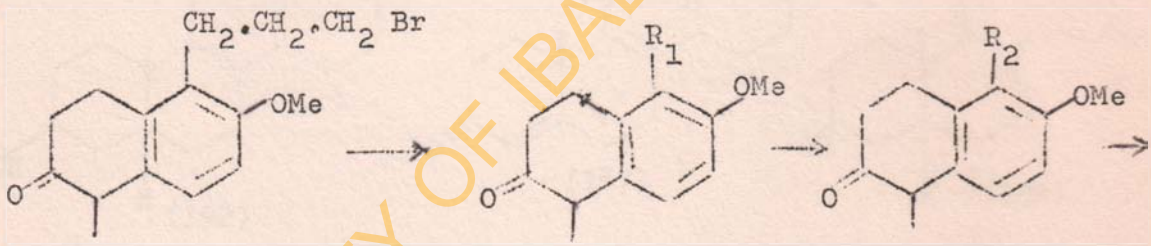




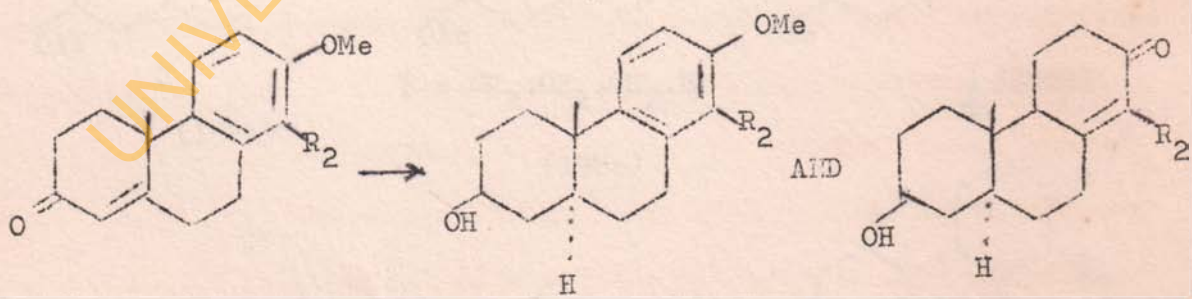
(188)

This is very unlikely in view of the chemical separational procedure involved in the preparation of the methoxy compound (129), the chromic acid oxidation product of which was crystalline and analysed very well for carbon, hydrogen and bromine. On the other hand demethylation might occur during the perbenzoic acid oxidation of the dihydronaphthalene derivative (131) by an obscure mechanism. A third and likely possibility is that easy demethylation of the methoxy group during the ring extension of the tetralone (132) by potassium hydroxide might be due to an

activation effect imposed by a benzene nucleus carrying four vicinal substituents. Alkaline cleavage of phenolic ether of this type is not unprecedented in the literature.[78] Attempt to convert the 2-tetralone derivative (132) to the corresponding carboxylic acid (190) which it was hoped should be crystalline and serve as a purer starting material for the preparation of a tricyclic compound reducible to compound (134) failed.



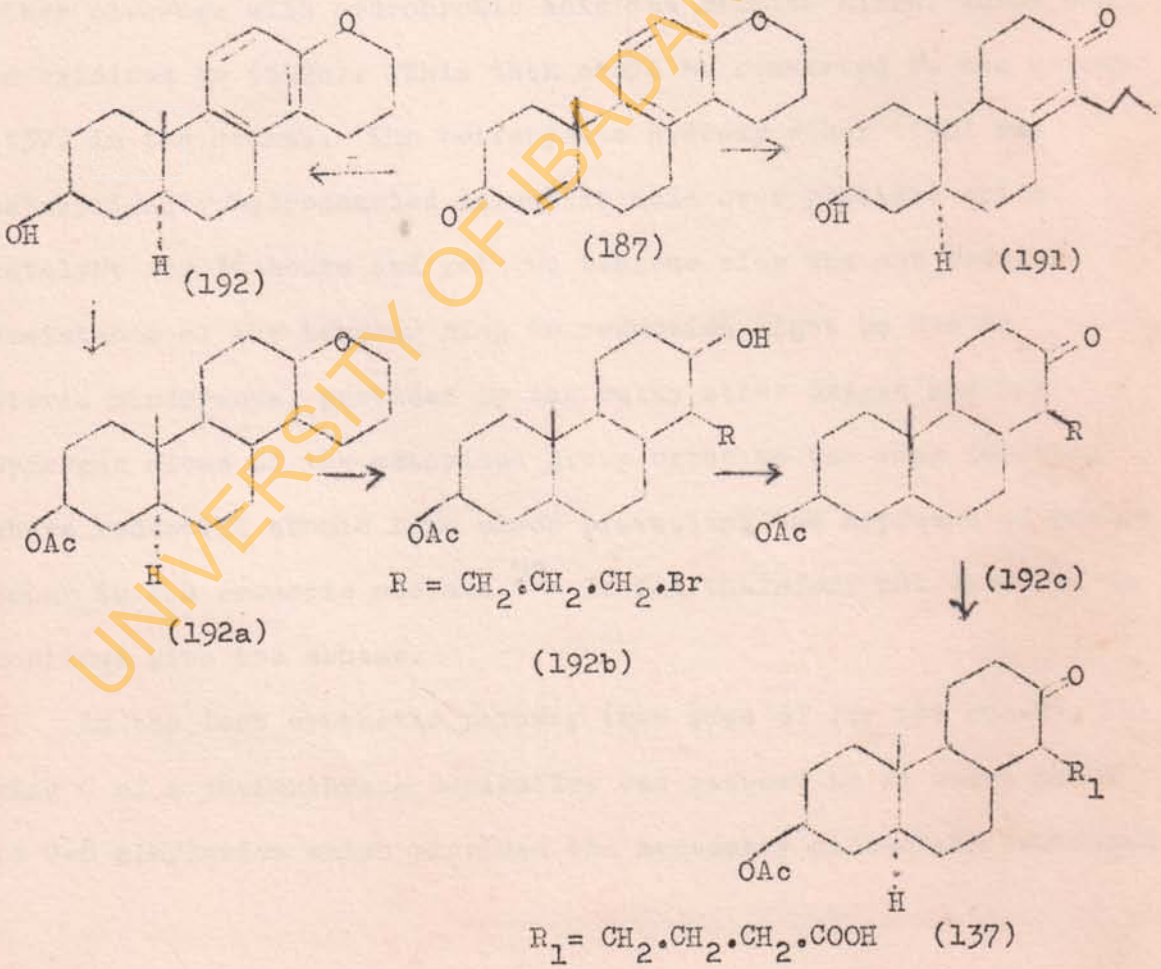
(132) R_1 = $CH_2.CH_2.CH_2.CN$ (189) R_2 = $CH_2.CH_2.CH_2.COOH$ (190)



(134) (134a)

The acid was obtained as an oil.

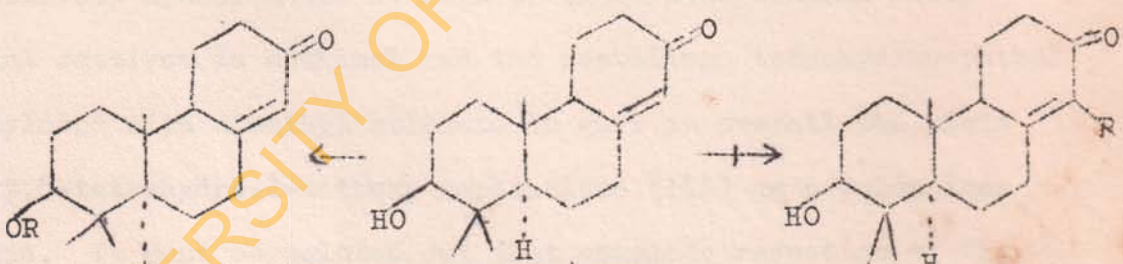
Now the crystalline tetracyclic enone (187) should give on Birch reduction followed by acid hydrolysis the αβ-unsaturated keto-alcohol (191). It should then be possible for the carboxylic acid obtained by reacting the bromide (133) with potassium cyanide followed by alkaline hydrolysis of the resulting nitrile to give, on Birch reduction, the enone (134a) instead of the octahydrophenanthrene derivative (134).



The enone (187) was therefore reduced with seventy equivalents of lithium in liquid ammonia in the presence of methanol. Instead of obtaining the αβ-unsaturated keto alcohol (191) however, only the double bond and keto group were reduced, and 8β-Hydroxy-10a-methyl-1,2,3,4,5,6,6a ,7,8,9,10,10a-dodecahydro-1-oxa-chrysene (192) m.p. 128° was obtained. The structure is in agreement with the I.R. spectrum. If on the other hand the benzene nucleus of (192) could be fully reduced, then it would give on acetylation followed by ether cleavage with hydrobromic acid the bromide (192b) which can be oxidized to (192c). This then could be converted to the ketone (137) in the scheme. The tetracyclic hydroxy ether (192) was catalytically hydrogenated in acetic acid over platinum oxide catalyst for 36 hours and yet the benzene ring was not reduced. Resistance of the benzene ring to reduction might be due to steric hinderance, provided by the bulky ether oxygen and the hydrogen atoms of the methylene group ortho to the ring junction where reduction should take place preventing the approach of proton donor to the aromatic nucleus.[79] It was therefore not possible to continue with the scheme.

In the last synthetic pathway (see page 31 for the chart) ring C of a phenanthrene derivative was reduced to an enone prior to C-8 alkylation which provided the necessary side-chain envisaged

in the preceeding pathway. Exploratory alkylation experiments were carried out on 1,2,3,4,5,6,7,9,10,11,12,13-dodecahydro-1, 1,-dimethyl-2β-hydroxy-12-methyl-7-oxophenanthrene (193) again supplied through the kindness of Professor D.A.H. Taylor. γ -Bromo butyric acid[80] was prepared from a mixture of γ-Butyrolactone and 60% hydrobromic acid. Esterification[81] of the crude acid with methanol gave a mixture of butyrolactone, unreacted acid and the required methyl ester. The contaminants were water-soluble and were therefore removed from the mixture with water.



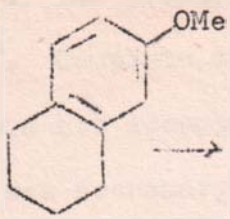
(194) (193) (195)

Condensation of the tricyclic enone (193) with γbromo methyl butyrate b.p. 186-187° in boiling xylene in the presence of sodium hydride gave the unchanged starting material. Although t-butoxide in t-butanol effected condensation, this took place at the wrong centre and in the presence of quite a large excess of bromo ester. The I.R. spectrum of the yellow substance m.p. 100° had ν max. 1625,

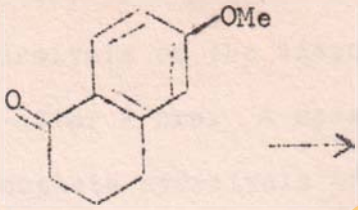
1666, 1725 cm^{-1} and no γ-OH and it absorbed at 242 mμ in the U.V. The starting material also absorbed at 242 mμ. The substance was presumably compound (194). In an endeavour to force alkylation to go at C-8, condensation was attempted on the benzoate of the substrate. Yet there was no reaction. The most plausible reason is that the bromoester probably cyclised back to γ-butyrolactone before it had time to react with the alkali salt of the enone.

The next phase of the work was the preparation of 1,2,3,4,5,6,7,9,10,11α,12,13 dodecahydro-12-methyl-2β-hydroxy-7-oxophenanthrene (147). The unsubstituted benzene ring of 2-naphthol was selectively hydrogenated at high pressure over neutral Raney nickel catalyst in methanol and the resulting tetrahydronaphthol methylated with dimethyl sulphate to give in overall 54% yield 5,6,7,8-tetrahydro-2-methoxy naphthalene (141) as a colourless liquid. It must be pointed out that complete reduction of the 2-naphthol to the 2-tetralol (i,e. until hydrogen uptake completely ceased) was necessary to avoid complication at the isolation stage. Introduction of an oxygen function to the C-5 benzene - activated position of the methoxy tetralin was accomplished by oxidizing it with chromic acid to give a 46% yield of 6-methoxy-1-tetralone (142). Here, too, isolation of the product was sometimes very tedious due to bad temperature control during the addition stage

of chromic acid solution to the substrate. Reaction of methyl magnesium bromide with the tetralone afforded in 90% yield 1-methyl-3,4-dihydro-6-methoxy naphthalene (143). For the oxidation of a large amount of the dihydro naphthalene, a large quantity of a suitable peracid was required. Although perbenzoic acid[77] was used for similar oxidations described earlier in this account, the yield of about 28% usually obtained in its preparation did not encourage its use for a large scale operation. Monoperphthalic acid was found as a suitable alternative since it could be obtained in a yield as high as 90% by a procedure outlined in Vogel's Practical Organic Chemistry[82] and modified by Professor D.A.H Taylor. If strict conditions for the experiment were not adhered to a very low yield was obtained in the oxidation. When exactly one equivalent or a little less than one equivalent of perphthalic acid was added at a low temperature to the dihydronaphthalene, completely free from its precursor 6-methoxy-1-tetralone, a yield of 50% of 6-methoxy-1-methyl-2-tetralone was obtained. 6-Methoxy-1-methyl-2-naphthol was isolated as a by-product in the reaction, a result consistent with the experience of Howell and Taylor[59] on the oxidation of same compound.



(141)



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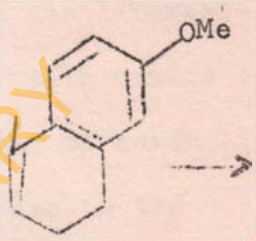
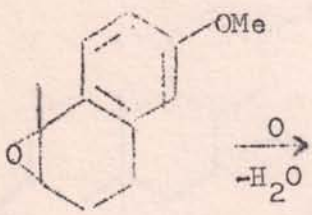


(143)



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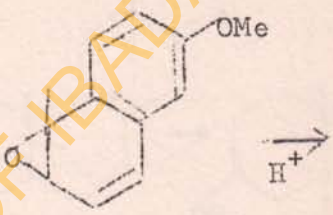

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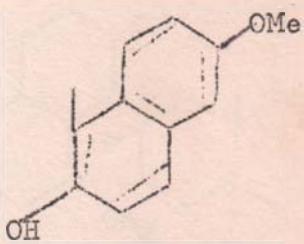
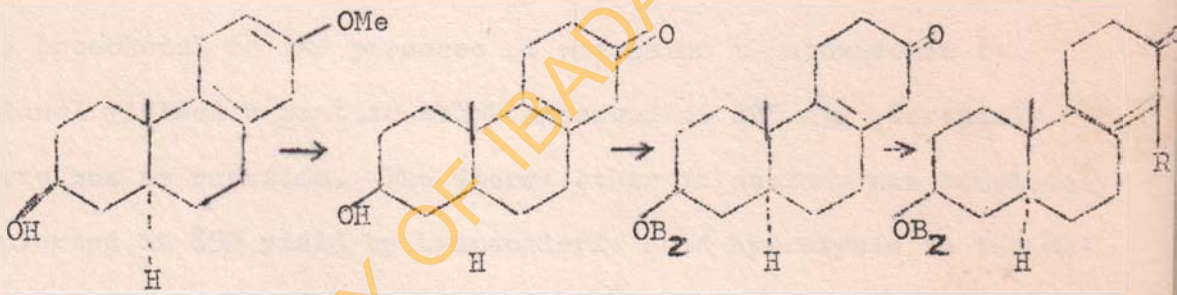


(198)

A reasonable mechanism for the oxidative formation of the phenol from the dihydro compound is indicated by structures (196)-(198). Robinson ring extension of 6-methoxy-1-methyl-2-tetralone by means of methyl vinyl ketone afforded in 50% yield 7-methoxy-12-methyl-2,3,4,8,10,12-hexahydro-2-oxophenathrene (145). Complete reduction of the enone in liquid ammonia to the dihydro ether (146) could not be achieved even with 28 equivalents of lithium in the presence of

n-propanol. However, it was possible to isolate in pure form 50% yield of the product as against 74% yield reported in the literature[48]. Complete mild hydrolysis of the dienol ether with oxalic acid was not accomplished after 2 hrs. A reaction time of seven hours was necessary for complete hydrolysis of the ether to the β,γ-unsaturated keto-alcohol (199) m.p. 93-95°. λ max. 228 mμ.

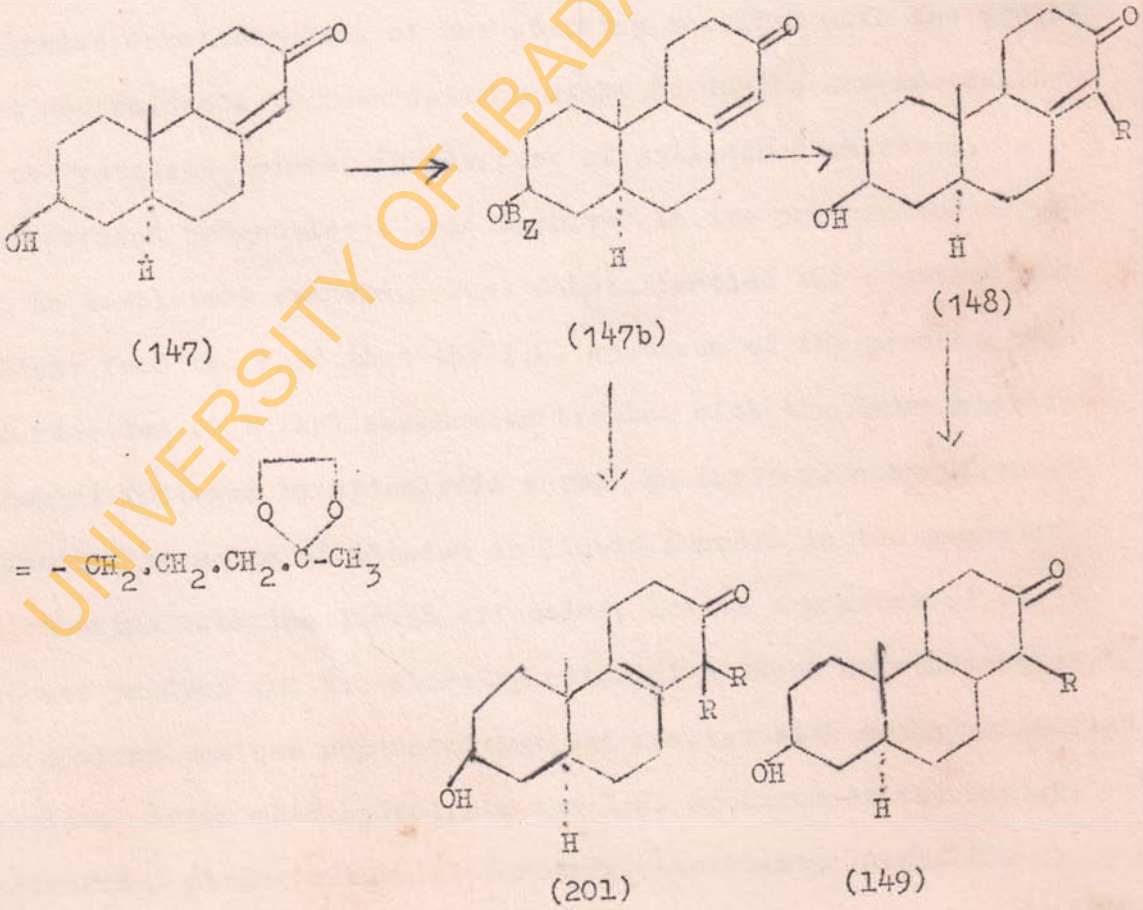


(146) (199) (200)

Monoalkylation of β,γ-unsaturated ketone with simultaneous double bond isomerization had been achieved in the course of studies on structure of Cassaic acid[83] and other related work[84]. The procedure applied to the alkylation of the benzoate (200) with α-bromo methyl butyrate in the presence of potassium t-butoxide in t-butanol gave back the starting material λ max. 228 mμ. 5-Bromo-2-pentanone, prepared by the action of aqueous hydrobromic

acid on α-acetobutyro lactone according to the procedure outlined for the preparation of 5-chloro-2-pentanone in Organic Syntheses[85] was converted to the ethylene ketal by the usual procedure. The bromo ketal reported crystalline in the literature[86] was obtained as an oil in fairly good yield, the by-product being presumably acetyl trimethylene. It was deketalized when passed through a column. It however gave fairly good elemental analysis for C, H and Br. Alkylation of the non-conjugated keto benzoate (200) with the bromoketal in the presence of potassium t-butoxide in t-butanol yielded a mixture which absorbed at 225 mμ. Certainly there was no reaction. The dienol ether in acetone was completely converted in 85% yield by hydrochloric acid hydrolysis to the αβ-unsaturated ketone (147) m.p. 123-124°. ν max. 1616, 1666 and 3400 cm^{-1}. λmax. 242 mμ (ε,17,000). The spectral properties were in agreement with those reported in the literature.[48] Attempt to alkylate its benzoate (147b) (m.p. 177-179°) with bromo methyl butyrate failed as before. Although some Japanese workers[48] effected condensation between the benzoate and 2,2-ethylene dioxy-5 bromo-pentan-2-one in boiling xylene containing sodium hydride, attempt to repeat this also failed. This might be due to the poor quality of the sodium hydride. Inverse addition of the benzoate to a boiling xylene solution of sodium hydride and

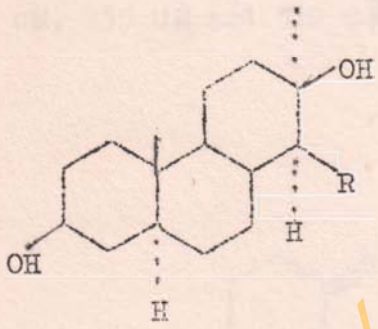
the bromo ketal gave a mixture which after alkaline hydrolysis absorbed at 210 mμ and 250 mμ and contained some of the right stuff. When, on the other hand the alkylation was carried out in t-butanol in the presence of excess potassium t-butoxide the product, after alkaline hydrolysis, absorbed at 213 mμ and 225 mμ. This indicated dialkylation of the enone to give a product of the type (201).



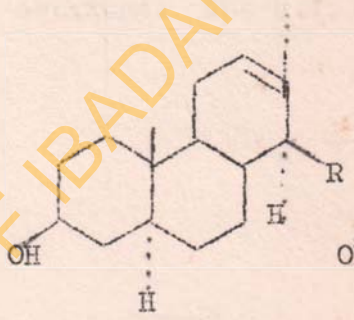
A very clean mono alkylation product (148) λmax. 250 mμ was however obtained when an excess of the bromo ketal was used in the presence of an exactly ONE equivalent of potassium t-butoxide in t-butanol, followed by alkaline hydrolysis of the condensation product.

Attempt to reduce by catalytic hydrogenation the αβ-unsaturated ketone (148) to the fully saturated keto alcohol (149) over palladised charcoal or palladium-on-calcium carbonate resulted in extensive deketalization of the starting material with the double bond not reduced. Deketalization might be due to non-neutrality of the catalyst, since, in the case of palladised charcoal, concentrated hydrochloric acid involved in its preparation might not be completely removed. That deketalization had occurred was evident from the fact that the I.R. spectrum of the product from the reaction of methyl mangnesium bromide with the hydrogenated material followed by hydrolysis showed no carbonyl absorption. Reduction by means of lithium in liquid ammonia in the presence of ammonium chloride though effective, led to a mixture of the reduced product and the starting material without deketalization. The mixture was not separated but was reacted with methyl magnesium bromide. After acid hydrolysis the I.R. spectrum of the mixture indicated a strong saturated carbonyl absorption. Among the

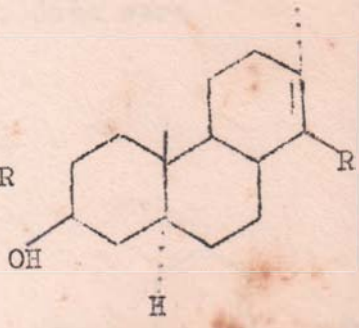
possible products that could be present in the mixture are substances (202), (203) and (150). Important signals in the N.M.R. spectrum of the mixture occurred at 6.04 τ (C<u>H</u> OH), at 6.96 τ, (CH_3 CO $C\underline{H}_2$-) at 7.404 τ ($\underline{CH}_3$-C(=O)-), at 8.5 τ ($\underline{CH}_3$-C-OH) and at 8.96 τ ($\underline{CH}_3$-C-).



(202)



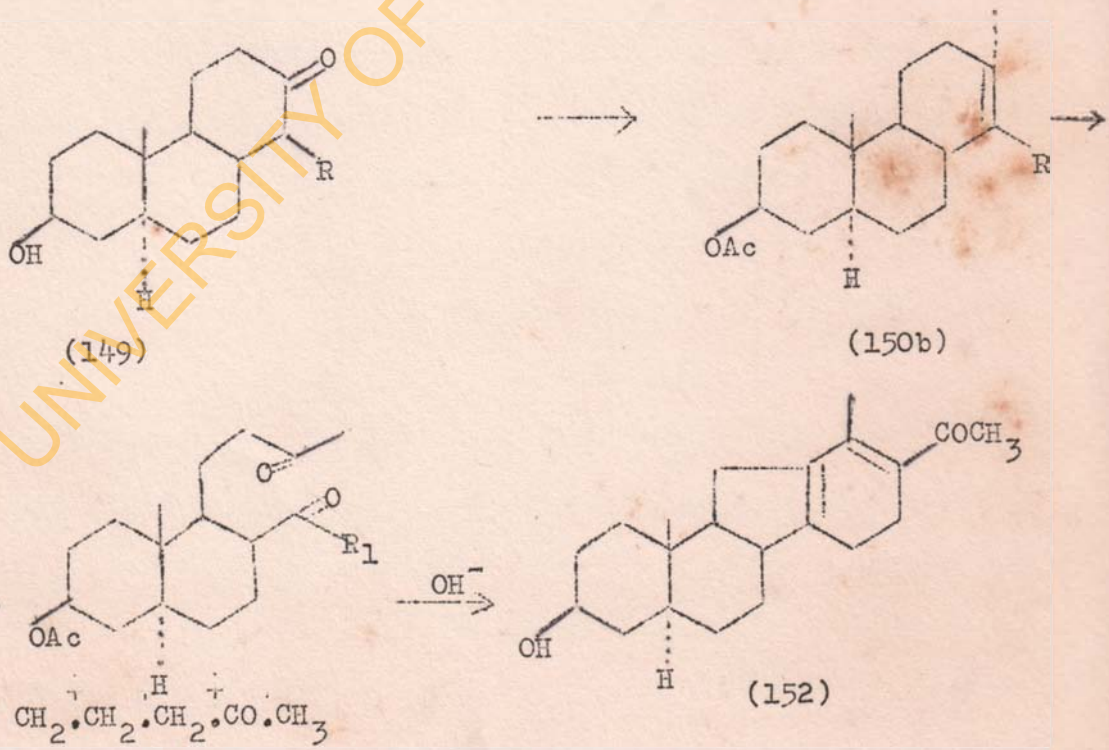
(203)



(150)

If substance (203) was a component of the mixture, then an absorption due to C-6 olefinic hydrogen should be present at 4.4 τ. The signal was conspicuously absent. The mixture was acetylated with boiling acetic anhydride. The IR. spectrum showed a strong acetate carbonyl absorption and no hydroxyl band, hence the mixture did not contain the tertiary alcohol (202). Any olefin in the mixture resulting from the action of methyl magnesium bromide on the fully saturated ketone (149) should therefore be the olefin (150)

After acetylating with boiling acetic anhydride, the mixture in ethyl acetate was treated with ozone at - 61° in a bath of chloroform in liquid air and the ozonide reduced immediately by shaking the solution with acetic acid and zinc powder. The mixture which should contain the triketone (151) was refluxed with methanolic 2N sodium hydroxide. After careful chromatography, 10 mg. of an oil which had low intensity U.V. absorptions at 225 mμ, 255 mμ and 310 mμ was obtained. The U.V. data were



in fair agreement with structure (152). Better agreement would certainly be achieved if this was crystalline. The oil did not crystallize, which was not unusual with C-nor-D-homo ring systems. In fact Kawahara and Mitsuhashi[69] had recently concluded from their experience on the synthesis of C-nor-D-homo epiandrosterone that the C-nor-D-homo steroid systems proved to be generally more difficult to obtain crystalline than the normal steroid derivatives. The oil was however, not sufficient for further purification by physical methods.

EXPERIMENTAL

Melting points were determined by means of soft-glass capillary tubing unless otherwise stated. I.R. and U.V. spectra were recorded on a Perkin Elmer model 137 and U.V. measurements were taken in methanol solutions. N.M.R. spectra were recorded on a Varian A56/60 spectrometer. In all cases deutero-chloroform was the solvent. Act. alumina type H of act. 1 - 11 was used and was sometimes deactivated by 5% its weight of a 10% aq. solution of acetic acid.

2,7 Dimethoxy naphthalene: 2,7 dihydroxy naphthalene was methylated according to the procedure of Cornforth and Robinson[49] used for the methylation of 1,6-dihydroxy naphthalene: 2,7 dihydroxy naphthalene (200 g; 1.25 mole) was dissolved in 2N sodium hydroxide (1120 c.c.) in a one-necked 5-litre flask and dimethyl sulphate (250 ml; 2.7 mole) added at once. The mixture was shaken and prevented from actually boiling by immersion in an ice-bath until reaction had subsided. 2N sodium hydroxide (560 c.c.) and then dimethyl sulphate (125 ml; 1.3 mole) were then added. When the second reaction slackened excess of dimethyl sulphate was destroyed by warming with frequent shaking for half an hour on a water-bath. The warm liquid was acidified with conc. hydrochloric acid and was

extracted with chloroform. The chloroformic extract was washed with 2N sodium hydroxide and then evaporated. The crude dimethoxy compound (220 g; 93.6%) crystallized from methylated spirit as plates m.p. 139°. Literature value 139°.

7-Methoxy-2-tetralone: 2,7 dimethoxy naphthalene was reduced according to the modified method of Cornforth and Robinson[51] outlined in Org. Syn. for 2-tetralone: 2,7 dimethoxy naphthalene (220 g; 1.17 mole) was dissolved in 95% ethanol (1900 c.c.) in a 5-litre three-necked flask fitted with a mechanical stirrer, a double-surface condenser, and a Y-shapped adaptor to allow for the introduction of both sodium and nitrogen. The apparatus was flushed thoroughly with nitrogen and its flow reduced as soon as the solution began to boil. The sodium (190 g; 6.3 g. atoms) was added in small portions. More ethanol (400 c.c.) was added as soon as the liquid became viscous and the addition of sodium continued. When all the metal had dissolved, water (600 c.c.) was cautiously added and most of the alcohol removed under diminished pressure. The residue was mixed with more water (300 c.c.) and the lower aqueous layer was separated as far as possible and extracted twice with a little dioxan which was then united with the oily layer. To this was added water (250 c.c.) and then conc. hydrochloric acid (100 c.c.; d. 1.18) to Congo red. More acid (30 c.c.) was

added and the liquid kept on a water-bath for 30 minutes. The lower oily layer was diluted with water (1 litre), separated from more oil and extracted thrice with small quantities of chloroform.

Sodium bisulphite adduct of the 2-tetralone. The crude tetralone in chloroform was shaken with a cold solution of sodium metabisulphite (250 gm.) in water (500 ml.) until crystals began to appear. Next day, the mass was triturated with ether, the solid was collected and washed with ether until almost colourless.

Decomposition of the bisulphite adduct. The solid dissolved in hot water (2-3 litres) was treated with solid sodium carbonate until no more oil separated. The solution was extracted with chloroform; the chloroformic extract washed once with 10% hydrochloric acid and then severally with water until the washings were neutral to litmus paper. The organic solvent was removed and the residual oil redistilled under reduced pressure. The oil distilled between 130-140°/5 mm. to give 66 gm. (25.6%) of 7-methoxy-2-tetralone. ν max. 1760 cm^{-1} (strong carbonyl). B.W. Horrom and H. Zaugg[87] reported b.p. 123-125° (4 mm). G.B. Diammond and M.D. Soffer[88] reported same. M. Kuehne[47] reported a yield of 65% b.p. 130-140 (0,3 mm).

Identification of the non-ketonic portion. Thin plate chromatography of the oil revealed three spots, two of which had R.F. values

corresponding to 7-methoxy-β-tetralone and 2,7 dimethoxy naphthalene. The mixture was then passed through a column of activated alumina. Petroleum ether eluted 7-methoxy tetralin. Pet. ether containing 10% benzene eluted 2,7 dimethoxy naphthalene while benzene eluted a trace of 7-methoxy-2-tetralone.

7-Methoxy-1-methyl-2-tetralone. 7-Methoxy-2-tetralone was methylated by a modified procedure of M. Kuehne[47]. Butane gas (purified by first passing it through conc. sulphuric acid) was passed through a solution of 7-methoxy-2-tetralone (14 gm; 0.079 mole) in dry benzene (150 c.c.) in a 500 c.c. two-necked flask. Then pyrrolidine (7 gm; 0.099 mole) was added and while still in an atmosphere of butane the mixture was refluxed with a water-separator for 3 hours on a water-bath. After concentration in vacuo, the residual oil in methanol (100 ml.) was treated with methyliodide (14 c.c.) while cooling. The mixture was then refluxed on a water-bath for 2 hrs. 20 c.c. of 5% solution of con. sulphuric acid in water was added and the mixture refluxed for further 12 hrs. on the water-bath. The mixture was diluted with water, the oil which separated was removed and the aqueous mother-liquor extracted with chloroform. Both the oil and the chloroformic extracts were united, washed neutral with water, dried over anhydrous magnesium sulphate and the organic solvent removed.

Redistillation in vacuo gave 7-methoxy-1-methyl-2-tetralone, (12.1 gm; 80%) as light yellow oil, b.p. 160-170°/15 mm. Reported b.p. 123-4° (0.25 mm.) in 91% yield. This has also been obtained by the perbenzoic acid oxidation of 7-methoxy-1-methyl-3,4-dihydro naphthalene[59].

1-Tetralone was prepared by the procedure essentially that of Truce and Olson modified by C.E. Olson and A.R. Bader[57]. A 3-1 three-necked flask was fitted with a mercury-sealed stirrer, an efficient condenser capped by a drying tube filled with calcium chloride and a wide-bore rubber tube leading to a 1-litre Erlenmeyer flask. One litre of dry thiophene-free benzene and γ-butyrolactone (104 g.; 1.21 mole) were placed in the three-litre flask. Anhydrous aluminium chloride (600 g; 4.5 moles) was placed in the flask and was added to the stirred reaction mixture at such a rate to make the reaction mixture reflux smoothly, (about 2 hours). The mixture became dark brown, refluxed gently and evolved hydrogen chloride. After the addition of all the catalyst, the mixture was heated on a steam-bath with continued stirring for 16 hrs. It was then cooled to room temperature and poured onto 3 Kg. of crushed ice drenched with 500 c.c. of conc. hydrochloric acid. The lower aqueous layer was separated and extracted with about 500 ml. of toluene. The brown organic upper

layer and the toluene extract were combined, washed successively with water, 20% potassium hydroxide solution and water and distilled under reduced pressure to remove benzene, toluene and traces of water. Distillation of the residue in a Claisen flask yielded 1-tetralone (160 g.; 91%), b.p. 143-145°/20 mm. ν max. 1760 cm^{-1} (co). Reported yield 91-96% b.p. 75-85°/0.3 mm. Semicarbazone (m.p. 216-217°) was quantitative.

1-Methyl-3:4-dihydro naphthalene. A dry five-litre three-necked flask was equipped with a dry stirrer, a condenser and a 250 ml. separatory funnel. Both the double-surface condenser and the separatory funnel carried tubes of absorbent cotton wool. In the flask magnesium, (22 gm; 0.92 mole) covered with ether (400 ml.) was placed, and methyl iodide (60 ml.) was added. The reaction started spontaneously and was complete when all the magnesium had reacted. It was then refluxed for fifteen more minutes. 1-Tetralone (84 gm.; 0.58 mole) in ether (500 ml.) was added slowly with stirring. After stirring for one hour on a water-bath, saturated ammonium chloride solution (120 gm. in 240 ml. of water) was added to the cooled mixture. The ethereal layer was separated and evaporated after drying over anhydrous magnesium sulphate. The oil solidified on cooling to give 1-methyl-1,2,3,4-tetrahydro-1-naphthol m.p. 89° ν max. (chloroform) 3400 cm^{-1} (OH). Reported[89]

m.p. 88-89°. Fused potassium hydrogen sulphate (100 g) was heated with all the carbinol obtained from above in an oil bath maintained at 120-130° for 2 hrs. After cooling to room temperature and separating the hydrated potassium hydrogen sulphate the water-potassium bisulphate was extracted with ether and the oil and ether extracts were united and dried. After evaporating the ether, the residue was fractionated IN VACUO to give 1-methyl-3:4-dihydronaphthalene b.p. 84°/5 mm: n_D^{21} 1.5761. Reported b.p. 84°/5 mm.

1-Methyl-2-tetralone Method A. This was prepared by the method of Howell and Taylor[59]. 1-Methyl-:3:4-dihydro naphthalene (130 g; 0.90 mole) was added slowly with shaking to perbenzoic acid (130 g; 0.94 mole) in acetone (1 litre) at 0°C. After 12 hrs. the solvent was evaporated and ether added. The solution was washed until neutral and the ether evaporated. The residue was then refluxed for 4 hrs. with methanol (800 ml.), conc. sulphuric acid (100 ml.), and water (600 ml.). The mixture was cooled, extracted with ether, the ether washed neutral with water and the organic solvent evaporated. 1-Methyl-2-tetralone (100 g; 69.2%) was collected at 168°/30 mm. and had n_D^{20} 1.5568. Semicarbazone m.p. 191°C (Found; C, 81.60; H, 7.42% $C_{11}H_{12}O$ requires C, 82.46 H, 7.55%) ν max. 1725 cm^{-1} (co). Reported b.p. 128°/14 mm. n_D^{20} 1.5568; semicarbazone m.p. 187-189.

Method B.

Methyl-β-naphthyl ether was reduced by means of sodium in boiling 95% ethanol to 2-tetralone as outlined in Organic Syntheses. 2-Tetralone (70 gm; 0.48 mole) was refluxed in benzene (200 ml.) with pyrrolidine (40 gm; 0.56 mole) with azeotropic removal of water for 3 hrs. Concentration in vacuo gave enamine of 2-tetralone m.p. 80°. The enamine in methanol (500 c.c.) was refluxed for 2 hrs. with methyl iodide (80 c.c.). The quartenary amine salt was decomposed by refluxing with 100 c.c. of 5% sulphuric acid for 12 hrs. The reaction mixture was diluted with water, the aqueous solution extracted with chloroform and the chloroformic extracts washed neutral and dried over anhydrous magnesium sulphate. After evaporation of the organic solvent the residue was distilled in vacuo b.p. 168°/30 mm. Semicarbazone had m.p. 191° same as for semicarbazone of 1-methyl-2 tetralone prepared by method A.

2:3:4:9:10:12-Hexahydro-12-methyl-2-oxo-phenanthrene.

This was prepared by a modified method of Kuehne[47]. 1-Methyl-2-tetralone (20 g; 0.13 mole) was dissolved in methanol (200 ml.) in a three-necked 500 ml. flask equipped with a stirrer, a condenser carrying a separatory funnel and a gas-lead. Butane gas purified with conc. sulphuric acid was passed through the flask which was immersed in a cold-bath. When the temperature of the solution had

fallen to 0°C, potassium hydroxide (8.5 g; 0.15 mole) in water (15 ml.) was added to the solution by removing the gas-lead for a short while. The well-stirred solution was cooled to - 20°, and then methyl vinyl ketone (8.75 g; 0.125 mole) in methanol (10 ml.) was added dropwise over one hour. It was stirred for a further one hour. The system was dismembered and two of the three necks of the flask securely stoppered. The third neck was fitted with an adaptor carrying a clipped rubber-tubing containing a tiny hole. The reaction was then left overnight. Butane gas was again passed through the solution which was refluxed on a water-bath for 3 hrs. The three necks of the flask were corked while hot, and the flask was cooled in ice-water. The cold contents of the flask were quickly poured onto crushed ice containing conc. hydrochloric acid (12.8 ml; d. 1.18). The solution was extracted with chloroform, the chloroformic extracts were washed with water and dried over anhydrous magnesium sulphate and the organic solvent removed. The residue was redistilled in vacuo. Fraction b.p. 150-168°/30 mm. was 1-methyl-2-tetralone. Fraction b.p. 168-210°/30 mm. was the required phenanthrone. The viscous oil was diluted with 1:1 benzene-pet. ether and filtered through a short column of activated alumina. The solvent was removed and the oil crystallized from pet. ether (40-60), m.p. 89-90°. (Found: C, 84.84; H, 7.61 $C_{15}H_{16}O$

requires C, 84.87; H, 7.60) ν max. (Nujol) 1666 cm^{-1}, 1634 cm^{-1} λmax. 211 mμ (ϵ 14330). λ max. 235 mμ (ϵ 19442). Reported m.p. 90°;

2:3:4:9:10:12-Hexahydro-6-methoxy-12-methyl-2-oxophenanthrene.

7-Methoxy-1-methyl-2-tetralone (20 gm., 0.105 mole) in methanol (200 ml.) was condensed with methyl vinyl ketone (8 gm; 0.105 mole) in methanol (40 ml.) in the presence of potassium hydroxide (8 gm; 0.143 mole) in water (16 ml.) using the procedure for 2:3:4:9:10:12-hexahydro-12-methyl-2-oxophenanthrene outlined above. Fraction b.p. 160-180°/30 mm. was mainly 7-methoxy-1-methyl-2-tetralone (5 gm). The phenanthrone was collected as viscous oil b.p. 180 - 220°/30 mm. It was diluted with benzene and filtered through a column of activated alumina. The benzene was removed and the residual oil treated with ether-pet. ether to give 10 gm. of yellow crystals m.p. 63°. The yield was 52.3% taking into account the recovered starting material. (Found: C, 79.25; H, 7.25. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49). ν max. 1575 cm^{-1}, 1616 cm^{-1} 1670 cm^{-1} λ max. 205 mμ (ϵ 12,540) λ max. 228.5 mμ (ϵ 18,670). Howell and Taylor[59] reported m.p. 63°, yield 50% K. Kaman and P.N. Rao[90] reported a yield of 62% (oil) and M. Kuehne[47] reported m.p. 78.5-79° (ethanol) and a yield of 71%. In one run, the uncyclised intermediate adduct m.p. 92° (ν max. 1750 cm^{-1}, 3570 cm^{-1}) was isolated and cyclised to the phenanthrone m.p. 63°.

1:2:3:4:9:10:11:12: Octahydro-6-methoxy-12-methyl-2-oxophenanthrene.

2:3:4:9:10:12 hexahydro-6-methoxy-12-methyl-2-oxophenanthrene (10 gm; 0.041 mole) in tetrahydro furan (200 ml.) was added to liquid ammonia (400 ml.) containing lithium (1 gm; 0.142 mole). After five minutes, ammonium chloride (16 g; 0.301 mole) was added. Water and ether were added. The ethereal layer was separated, washed neutral with water, dried over anhydrous magnesium sulphate and the ether evaporated. The oil crystallized from methanol to give plates (7.8 gm; 78%) m.p. 130°. Literature value[47,59] m.p. 129.5°-130°; (34%).

Trans-2β-hydroxy-1:2:3:4:9:10:11:12 octahydro-6-methoxy-12-methyl phenanthrene.

1:2:3:4:9:10:11:12 octahydro-6-methoxy-12-methyl-2-oxophenanthrene (3 gm; 0.012 mole) was dissolved in T.H.F. (tetrahydrofuran) (10 ml.) and added to methanol (50 ml.). Sodium borohydride (0.75 gm.; 0.02 mole) in 2N sodium hydroxide (1 ml.) and diluted with water (8 c.c.) was added dropwise and very slowly to the methanolic solution which was stirred mechanically and cooled in ice. After the addition the ice-bath was removed and stirring continued for 45 mins. The solvent was removed on a water-bath and the residue after dilution with water was extracted with ether, the ether washed with water, dried over anhydrous magnesium sulphate

and evaporated. The alcohol was obtained as a colourless oil. This did not crystallise and was probably a mixture of the 2β and 2-α isomeric alcohols.

Lithium-liquid ammonia-alcohol reduction of Trans-2β-hydroxy-1:2:3:4:9:10:11:12 octahydro-6-methoxy-12-methylphenanthrene.

The alcohol (2.5 g; 0.01 mole) in ether (100 ml.) was added to liquid ammonia (300 ml.) containing lithium (0.5 g; 0.07 mole). Methanol was added dropwise until the blue colour was discharged. More lithium (0.5g x 3) was added and the colour discharged with methanol. The solvent was allowed to evaporate, the residue diluted with water and extracted with chloroform, to give the corresponding dienol ether.

(a) The dienol ether (17.9 gm; 0.072 mole) suspended in methanol (100 ml.) was treated with a solution of oxalic acid (4 gm; 0.037 m) in water (5 ml.). The mixture was left at room temperature for 2 hrs, diluted with water and extracted with ether. The ethereal layer was washed with water and evaporated. The oil mostly trans-2β-hydroxy-1:2:3:4:5:6:7:8:9:10:11:12: dodecahydro-12-methyl-6-oxo-phenanthrene did not crystallise though it showed strong hydroxy and carbonyl absorptions νmax. 1710 cm^{-1} (non. conj. co); 3430 cm^{-1} (hydroxyl).

(b) The dienol ether (2.5 gm; 0.01 mole) was refluxed for 3 hrs. with ethanol (150 ml.), water (25 ml.) and conc. hydrochloric acid (25 ml.). It was diluted with water, extracted with chloroform and the chloroformic extracts washed with water, dried over anhydrous magnesium sulphate and evaporated. The oil was passed through a column of activated alumina. It did not crystallize. It was benzoylated in pyridine with benzoyl chloride. The benzoate (m.p. 140°-142°) which did not form a D.N.P. was trans-2β-Benzoloxy: 1:2:3:4:7:8:9:10:11:12:13:14-dodecahydro-12-methylphenanthrene. νmax. (Nujol) 720 cm^{-1}, 1587 cm^{-1}, 1634 cm^{-1} and 1725 cm^{-1}.

1:2:3:4:9:10:11:12 Octahydro-6-hydroxy-12-methyl-2-oxophenanthrene

1:2:3:4:9:10:11:12 octahydro-6-methoxy-12-methyl-2-oxophenanthrene (1 gm; 0.004 mole) in acetic acid (20 ml.) and 4 ml. 55% hydriodic acid (previously refluxed over red phosphorous) were refluxed for 2 hrs. by direct heating. Ether and water were added and the ether layer washed with aqueous solution of sodium metabisulphite and then with water. The ethereal solution was dried and evaporated to give an oil which solidified over pet. ether (60-80°) and was crystallised from aqueous ethanol. The phenol had m.p. 174° and went brown with a drop of ferric chloride solution ν max. (Nujol) 1700 cm^{-1}, and 3400 cm^{-1}.

Sodium-borohydride reduction of 1:2:3:4:9:10:11:12-octahydro-6-hydroxy-12 methyl-2-oxophenanthrene.

Sodium borohydride (0.1 gm; 0.02 mole) was dissolved in 2N sodium hydroxide (1 ml.) and the solution diluted with water (1 ml). The phenolic ketone (1 gm; 0.004 mole) was dissolved in tetrahydro furan (10 ml.) and the solution diluted with methanol (10 ml). The resulting solution was cooled below $0^{\circ}C$ and the borohydride solution added to it dropwise. After the addition it was allowed to stand for 1 hr., and the solvents evaporated at ordinary pressure on a water-bath. The residue was diluted with water and extracted with ether. The ether was washed neutral and dried over anhydrous magnesium sulphate. After evaporating the ether, the residue was crystallized from a mixture of ether and cyclohexane. Product had m.p. $108-118^{\circ}$ and was probably a mixture of the epimeric alcohols. The mixture was acetylated by refluxing it with glacial acetic acid (10 ml.) for 4 hrs. Excess acetic acid was removed in vacuo. The residue was crystallised from cyclohexane and then from aqueous ethanol, to give 6-hydroxy-2-acetoxy-12 methyl-1:2:3:4:9:10:11:12-octahydro phenanthrene as an amorphous solid m.p. $144-146^{\circ}$ ν max. (Nujol) 1700 cm^{-1} and 3400 cm^{-1}. (Found: C, 74.32%; H, 7.65. $C_{17}H_{22}O_3$ requires C, 74.42%; H, 8.08%). The methanolic solution of the product went brown with a drop of

ferric chloride solution

1:2:3:4:6:7:8:9:10:11 α:12:14β-Dodecahydro-2β hydroxy-12-methyl-6-oxophenanthrene.

Lithium (4 gm; 0.57 atom.) was dissolved in liquid ammonia (1 litre). After five minutes, 2:3:4:9:10:12-hexahydro-6-methoxy-12-methyl-2-oxophenanthrene (5 gm; 0.021 mole) in purified tetrahydro furan (200 ml.) was added to the lithium solution. After another five minutes n-propanol was added dropwise until the blue colour was discharged (about 75 ml.). This was followed by an addition of lithium (3 gm) and then n-propanol. The process was repeated until in all 10 gm. of lithium had been added. The ammonia was allowed to evaporate and the residue diluted with water, was extracted with chloroform. The chloroformic extracts were washed with water, and dried over anhydrous magnesium sulphate. The solvent was removed to give the corresponding crude dienol ether as a viscous oil. The oil in methanol (150 ml.) was treated with conc. hydrochloric acid (25 ml.) and water (25 ml.) and was refluxed for 3 hrs. The reaction mixture was diluted with water and isolated with chloroform. The oil was passed through a column of deactivated alumina. Pet-ether, pet. ether - benzene, and benzene eluted non-ketonic fractions. Benzene containing 30% and 50% diethyl ether

eluted 1:2:3:4:6:7:8:9:10:11 α:12:14β dodecahydro-2β hydroxy-12-methyl-6-oxophenanthrene. m.p. 118-120° (diethyl-ether). The yield was 1.5 gm. (31%). (Found: C, 76.78, H, 9.65 $C_{15}H_{22}O_2$ requires C, 76.88: H, 9.46). ν max. (chloroform) 1610 cm^{-1}, 1666 cm^{-1} (conj. carbonyl) and 3430 cm^{-1} (hydroxy) λ max. 238 mμ (ε 17,160). The benzoate m.p. 174° had ν max, (Nujol) 717 cm^{-1}, 1616 cm^{-1} 1666 cm^{-1} and 1725 cm^{-1}. Howell and Taylor[37] used sodium instead of lithium used here and methanol instead of n-propanol. Reported m.p. 118-120° (15%).

Catalytic hydrogenation of 1:2:3:4:6:7:8:9:10:11 α:12:14β dodeca-hydro-2β-hydroxy-12-methyl-6-oxophenanthrene.

The procedure followed was that of Howells and Taylor[37]. The unsaturated ketone (0.5 g; 0.002 mole) in purified ethanol (20 ml.) was placed in a hydrogenation flask and shaken up with hydrogen in the presence of palladium-on-calcium carbonate catalyst (0.25 g.) until the hydrogen up-take completely ceased. The solution was filtered from the catalyst and the ethanol completely removed in vacuo. The oil crystallised slowly from dry diethyl ether to give the fully saturated keto alcohol (0.3 gm; 60%) as colourless prisms m.p. 98-102°. (Found: C, 76.18, H, 10.42 $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.2).

Literature value m.p. 98-102°. Instead of palladium-on-calcium carbonate palladium-on-carbon was also used. Hydrogenation proceeded smoothly but the product did not crystallize.

Trans-anti-trans-7-Furfurylidene Perhydro-2-hydroxy-6-oxophenanthrene.

This was prepared by the method of Howells and Taylor[37]. The fully saturated hydroxy phenanthrone, (120 mg; 0.0005 mole) was kept overnight under nitrogen with furfuraldehyde (100 mg; 0.001 mole) in the presence of 33% sodium hydroxide (2.0 ml.). The mixture was diluted with water and extracted with chloroform. The chloroformic extracts were washed with water, and dried over anhydrous magnesium sulphate. The chloroformic solution was filtered through a short column of activated alumina. The solvent was evaporated when yellow solid m.p. 196-198° was left behind. The product crystallized from methanol to give 120 mg. (75.8%) of trans-anti-trans-7-furfurylidene perhydro-2-hydroxy-6-oxophenanthrene m.p. 204°. Literature value 197-207° (Found: C, 76.25; H, 8.43. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3) ν max. (Nujol) 747 cm^{-1}, 1584 cm^{-1} 1666 cm^{-1}, 3570 cm^{-1} λ max (methanol) 324 mμ (ε 24,220).

6β-Acetoxy-1β;2α-di(methoxy carbonyl methyl)-9β-methyl-trans decalin

Trans-anti-trans-7-Furfurylidene perhydro-2-hydroxy-6-oxophenanthrene (6 gm; 0.019 m.) in pyridine (50 ml.) was treated with acetic anhydride (7 ml; 0.07 mole) and allowed to stand for 2 days. The solution was diluted with water and the product isolated with chloroform to give the acetate of the furfurylidene derivative m.p. 154-156° ν max. (Nujol) 780 cm^{-1}, 1584 cm^{-1}, 1666 cm^{-1}, 1725 cm^{-1}. (Found: C, 73.94; H, 7.63 $C_{22}H_{28}O_4$ requires C, 74.13, H, 7.92)

(a) Attempted alkaline hydrogen peroxide oxidation of the acetate of the furfurylidene derivative.

Nitrogen was passed through a solution of 0.2 gm. (.0005 mole) of the furfurylidene ketone acetate in 20 ml. of ethanol. Then 20 ml. of a solution of sodium (6 gm; 0.26 at) in ethanol (170 ml.) was added followed by 30% hydrogen peroxide (4 ml.). The thick paste was stirred until homogeneous and again 20 ml. of the ethoxide solution was added followed by 10 ml. of 30% hydrogen peroxide solution and the paste was again stirred until homogeneous. The mixture was stirred overnight, concentrated in vacuo at 50° on a water-bath, and the residue diluted with water. The alkaline solution after being washed with chloroform was acidified with dil. sulphuric acid and extracted with chloroform.

The chloroformic extract was washed with water, and dried over anhydrous magnesium sulphate. The solvent was removed to give a residue whose infra red spectrum was identical with the hydroxy furfurylidene ketone. i.e. hydrolysed starting material.

(b) Ozonolysis of the furfurylidene ketone acetate.

The furfurylidene ketone acetate (200 mg.; .0005 mole) in methylene chloride (40 ml.) was treated with ozone at -70° in a bath of acetone-solid carbon dioxide, until a persistent blue colouration was obtained. It was then ozonised for further one hour; and allowed to stand at room temperature until the blue colour was discharged. The solvent was completely removed and to the residue was added glacial acetic acid (20 ml.), water (5 ml.) and 30% hydrogen peroxide (2 ml.). The vessel was then corked and allowed to stand overnight. The solution was diluted with water and then extracted with ether. The ether extract was washed free of acetic acid with water and extracted with 40 ml. of 10% aqueous potassium carbonate. The alkaline solution was washed twice with little ethyl acetate and acidified with dil. hydrochloric acid. The product was taken up in chloroform, the extract washed with water and dried over anhydrous magnesium sulphate. The residue after evaporating the organic solvent crystallized from a little ether to give 133 mg. (71%) of the acetate diacid m.p. 200°. The acetate

diacid (133 mg; .0004 mm) in methanol was treated with distilled diazo-methane and the solution allowed to stand for 20 mins and then concentrated when 132 mg. (92%) of colourless crystal of the acetate dimethyl ester m.p. 103° was obtained. The infra-red spectrum of this ester was completely identical with that of an authentic specimen kindly supplied by Professor D.A.H. Taylor. (Found: C, 64.54; H, 8.50 $C_{19}H_{30}O_6$ requires C, 64.38; H, 8.53). Literature[37] m.p. 103°. The N.M.R. spectrum showed significant absorptions at 9.2τ for 3 protons as a singlet (C-9 methyl), at 7.5 τ for 3 protons as a singlet (C-6 acetate methyl), at 5.54τ for 6 protons as a singlet (two O-methyl) and at 4.6-4 τ for 1 proton as a multiplet (C-6 hydrogen).

6β Hydroxy-1β:2α-diacetic acid-9β-methyl-trans decalin.

The preceeding acetate diester (200 mg.; .0005 m) in methanol (20 ml.) was treated with potassium hydroxide (200 mg; .0035 m) in water (0.5 ml.) and the mixture refluxed for two hours. The alcohol was removed under reduced pressure. The residue was diluted with water, acidified with dil. hydrochloric acid, saturated with sodium chloride and the resulting mixture extracted with ether. After evaporating the solvent the residue crystallized from a little ether to give 6β-hydroxy-1β:2α-diacetic acid-9β-methyl-trans decalin m.p. 224° in quantitative yield.

6β-Acetoxy-1β,2α-(cyclopentan-3' -one)-9 methyl-trans decalin.

Potassium (0.5 g; 0.013 atom) was dissolved in t-butanol (redistilled over calcium hydride at ordinary pressure) and excess alcohol removed under reduced pressure. The solid t-butoxide was covered with benzene and the benzene removed at ordinary pressure. Addition with consequent removal of benzene was repeated three times. The alcohol-free potassium salt was then covered with dry benzene (40 ml.) and the flask equipped with a hot and dry condenser carrying a cotton-wool tube. The solution in an atmosphere of nitrogen was heated under reflux in an oil-bath maintained at 100°C. Then, the preceeding acetate dimethyl ester, (0.5 g; 0.0014 mole) in dry benzene (10 ml.) was added through the condenser to the boiling solution, and the reflux continued for 4 hrs. with occasional shaking of the flask. It was cooled, acidified with con. sulphuric acid (1 c.c.) in water (25 ml.). The organic layer was separated, the aqueous layer extracted with ether and the combined organic solution was washed with water. The organic solvent was removed to give the alcohol ketoester (0.35 gm; 76.9%) as a yellow viscous oil (νmax. 1725 cm^{-1}, 1760 cm^{-1} and 3400 cm^{-1}). The β-keto ester (0.35 gm; .001 m) in glacial acetic acid (20 ml.) was treated with conc. hydrochloric acid (7 ml.) and water (2 ml.) and the solution was refluxed for one hour over naked flame. The solution was

evaporated to dryness under reduced pressure at 40° on a water-bath. To the oil in methanol (20 ml.) was added 5% sodium hydroxide (15 ml.) and the solution was refluxed for a further one hour. The alcohol was removed under reduced pressure. The residue diluted with water was thoroughly extracted with ether. The ethereal solution was dried over anhydrous magnesium sulphate and was then evaporated to give the pentanone-alcohol as an oil. (ν max. 1750 cm^{-1} (co) and 3400 cm^{-1} (OH)). The oil in pyridine was treated with acetic anhydride (0.5 ml.) and the solution allowed to stand overnight. The solvent was removed under reduced pressure and the oil in ether was washed successively with 0.1N sodium hydroxide, 2N hydrochloric acid and water. It was dried over anhydrous magnesium sulphate and the solvent removed to give an oil which solidified on cooling. m.p. 62-66°. The crude pentanone-acetate was passed through a column of activated alumina and the column was eluted with pet. ether-diethyl ether mixtures. 1:1 Pet. ether-ether eluted most of the product as an oil which solidified on cooling and scratching to give, 0.2g. (69%) of 6β-Acetoxy-1β:2α-(cyclopentan-3′-one)-9 methyl-trans decalin. m.p. 74° (Yield of 53.7% based on acetate dimethyl ester).
(Found: C, 72.66; H, 9.15 $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15).
ν max. 1760 cm^{-1} (for both CO pentanone and CO acetate). Alkaline

hydrolysis of the acetate regenerated the pentanone-alcohol (ν max. 1750 cm^{-1} (CO-petanone) and 3400 cm^{-1} (OH)). The only important signals in the N.M.R. spectrum occurred at 8.9τ for 3 protons as a singlet (C-9 methyl), at 8.32-8.2 τ for 4 protons as a doublet (2 methylene and 4 methylene), at 7.51τ for 3 protons as a singlet (C-6 acetate methyl), and at 4-4.5τ for 1 proton as a multiplet (C-6 hydrogen).

Formylation of 6β-Acetoxy-1β:2α-cyclopentanone-9β methyl-trans decalin and related ketones viz: 6-methoxy 1-tetralone and 5-methoxyhydrindone-1 (prepared by methylating 5-indanol with dimethyl sulphate followed by chromic anhydride oxidation of the ether).

A solution of sodium methoxide prepared from sodium (0.5 at) and methanol was evaporated under diminished pressure to dryness. It was finally heated in vacuo in an oil bath maintained at 160 - 165°. The solid after being cooled in an atmosphere of butane was broken up and covered with dry benzene (160 ml). Then ethyl formate (0.5 mole) was added and the mixture stirred under butane for one hour. The mixture cooled in ice was treated with the ketone (0.25 mole) in benzene (100 ml.) and stirring continued for two days. (Five hours stirring was sufficient in the case of 5-methoxy-hydrindone-1). The mixture was treated with ice-cold dil. sulphuric acid and the aqueous layer was extracted with ether-benzene mixture.

The combined organic extracts were shaken with excess ice-cold 2% potassium hydroxide and the alkaline layer washed well with ether. The aqueous solution was acidified with dil. hydrochloric acid and extracted with benzene-ether mixture. The organic extract was washed with water, dried and evaporated to give formyl derivature of the pentanone acetate as a yellow oil (64%) or 2-hydroxy methylene-6-methoxy-1-tetralone (m.p. 62°) (93%) or 2-hydroxymethylene-5-methoxy-1-hydrindone m.p. 138-138.5° (98%). They all imparted characteristic colours to ferric chloride solution.

Alkylation of the preceeding formyl ketones.

The formyl ketone, (0.01 mole) in methanol (60 ml.) was added to a solution of sodium (0.75 gm, .033 at) in methanol (40 ml). The resulting solution was treated with ethyl β-chloro-ethyl ketone (1.2 gm; .01 mole) in methanol (8 ml.) and the solution left at room temperature overnight. It was refluxed for one hour on a water-bath and cooled. The solution was added to crushed ice containing conc. hydrochloric acid and the aqueous acidic mixture was extracted with chloroform. The organic layer was washed with water, dried and evaporated. Each of the three formyl ketones gave a yellow oil which did not crystallize. The oils all had identical infra-red spectra viz. triplet absorptions around the 6-micron region.

Direct alkylation of 6-β methoxy-1β:2α cyclopentanone-12β-methyl trans decalin.

The pentanone-acetate (264 mg; .001 mole) in absolute ethanol (10 ml.) was added to a solution of sodium (25.3 mg; .001 atom) in absolute ethanol (1 ml.) and the mixture brought to reflux. Ethyl β-chloro-ethyl ketone (120 mg; .001 m) in absolute ethanol (1.2 ml) was added and the reflux continued. After one hour, more sodium (50.6 mg; .002 atom) in absolute ethanol (2 ml.) was added and after 10 more minutes, more ethyl β-chloro-ethyl ketone (240 mg; .002m) was added and the mixture refluxed for half an hour. The mixture was cooled and worked up as above. The oil after being passed through alumina crystallized from a mixture of ether and pet. ether (40-60°) to give a substance m.p. 128-134° (decomp.) λmax. 251.5 mμ (Found: C, 75.95; H, 8.85 $C_{19}H_{28}O_2$ requires C, 79.12; H, 9.97). The acetate after passing through alumina had m.p. (78-86°), λmax. 248 mμ (ε 4,660) literature value for acetate m.p. 163-165°. λmax. (247 mμ) (ε 18,100).

2-Methyl-1,3,cyclohexane-dione.

The procedure outlined in Organic Syntheses[71] was followed. Resorcinol (110 gm., 1 mole) was suspended in a solution of sodium hydroxide (48 gm; 1.2 mole) in water (168 ml.) in a hydrogenation bomb. After Raney nickel (20 gm.) had been added, the mixture was

hydrogenated for six hours at an initial pressure of 85 atmospheres and a set temperature of 45°. After filtering off the catalyst, the solution in a litre round-bottomed flask was treated with conc. hydrochloric acid (16.8 ml.). Then dioxane (72 ml.) and iodo-methane (168 gm) were added and the mixture refluxed overnight over a heating - mantle. The mixture was cooled in an ice-bath for four hours, crystals were collected in a sinstered glass funnel and were washed with cold water until the washings were almost colourless. The product crystallized from methylated spirit to give slightly yellow crystals m.p. 207-210° (dec.). Literature value m.p. 206-208° (dec.).

1,2,3,4,6,7,8,8a. Octahydro-8a-methyl 1,6,naphthalenedione.

The procedure in Org. Syntheses[72] was followed. A mixture of 2-methyl-1 ,3-cyclohexane-dione (21 g; .16 mole), methyl vinyl ketone (17.5g.; 0.25 mole), potassium hydroxide (about 0.08g; 1 pellet), and 250 ml. of methyl alcohol (dried over calcium hydride) were refluxed in a 500 ml. round-bottomed flask fitted with a reflux condenser and a cotton-wool tube. The mixture was refluxed for 3 hrs. when all the dione went into solution. Then methanol and excess methyl vinyl ketone were removed at 70° on a water-bath under reduced pressure (650 mm.). The residual liquid was dissolved in dry benzene (83 ml.) and 7 ml. of the solvent was

removed with a water-separator. To the well-cooled solution was added pyrrolidine or piperidine (1 ml.) and the mixture held at reflux for 30 mins., during which time about 3 ml. of water collected in the trap. Refluxing was continued for an additional 15 mins. after the separation of water had ceased. The water collected was removed and 16 ml. of the solvent was distilled. The reddish reaction mixture was cooled to room temperature and diluted with 50 ml. of ether. The solution was washed with 33 ml. of distilled water containing 5 ml. of 10% hydro-chloric acid and then with 33 ml. of water. The aqueous extracts were extracted twice with 25 ml. of ether and the combined organic layers were washed with three 33 ml.-portions of water, then with saturated salt solution and dried over magnesium sulphate. The solvents were removed and the residue distilled b.p. 117-145°/0.5-1 mm. The distillate was crystallized from ether-pet. ether mixture and washed with a little cold ether to give colourless plates m.p. 46-48° (25%). Reported m.p. 47-50° (63-65%).

1-Oxo-6 ethoxy-8a-methyl 1,2,3,7,8,8a-hexahydronaphthalene.

This was prepared according to the procedure of S. Swaminathan and M.S. Newman[73]. A mixture of 5 gm. (.028m.) of the preceeding octahydro-8a methyl naphthalene dione, 4.8 g. (0.0324 m.) of

triethyl orthoformate, 30 ml. of dry benzene and 1.3 ml. of 5% anhydrous ethanolic hydrochloric acid was refluxed for 2 hrs. The dark mixture was cooled, neutralized with 5% alcoholic sodium hydroxide solution and taken up in ether. The ether-benzene solution was successively washed with 20 ml. of water, 25 ml. of 5% sodium hydroxide solution, 20 ml. of water and saturated sodium chloride solution and then dried over sodium sulphate. Distillation under reduced pressure afforded 4.6 g. (79.4%) of a lemon yellow liquid. ν max. 1675 cm^{-1}, and 1721 cm^{-1}.

Attempted Alkylation of 1-oxo-6 ethoxy-8a-methyl-1.2.3.7.8.8a. hexahydronaphthalene with bromo-acetone.

The ethoxy ketone (20.6 g; 0.1 mole) in dry methanol (100 ml.) was treated with a solution of sodium (4.6 gm.) dissolved in dry methanol (minimum amount). To the solution was added 14.7 gm. (0.1 m.) of bromoacetone (prepared according to the procedure in Organic Syntheses). The mixture was refluxed for 2 hrs. and then concentracted under diminished pressure. The mixture was diluted with water, the product isolated with ether, and the solvent evaporated when the starting material was recovered. The experiment was repeated using 2 equivalents of potassium in dry t-butanol and yet there was no reaction.

Attempted condensation of 1-oxo-6 ethoxy-8a-methyl-1,2,3,7,8,8a hexahydronaphthalene with ethyl bromoacetate.

Ethyl bromoacetate (16.7 g; 0.1 mole) in tetrahydro furan (40 ml.) and zinc wool (6.5 g; purified by washing successively with 2% hydrochloric acid, plenty of water, alcohol, acetone and ether and drying at 110 for 30 mins.) were placed in a 500 ml. three-necked flask equipped with a mechanical stirrer, a reflux condenser and a dropping funnel. A trace of iodine was added and the mixture was stirred on a water-bath until nearly all the zinc had dissolved. To the Grignard reagent was added the ethoxy ketone (20.6 g; 0.1 mole) and stirring and refluxing continued for 2 hrs. More zinc wool (6.5 g; 0.1 mole) with a trace of iodine was added followed after 30 mins. by more ethyl bromo acetate (16.7 g; 0.1 mole) and stirring and refluxing were continued for further 2½ hrs, to make a total reaction time of 5 hrs. The solvent was removed and the cooled Grignard complex was diluted with water and decomposed with 10% sulphuric acid. The organic layer was washed successively with water, dilute sodium carbonate solution and then water. The solvent, dried in the usual way was evaporated when the starting material was recovered.

1-Bromo-2 methoxy-naphthalene

Nerolin (250 g; 1.58 m.) in dry chloroform (1 litre) was stirred until dissolved. Very slowly and with stirring bromine (80 ml.) was added. The stirring was continued for additional 15 mins. The solvent was removed in vacuo and the residue was treated with 20 gm. (0.5 m) of sodium hydroxide, and heated for half-an-hour on a steam-bath. The residue was decanted from sodium hydroxide or any water, diluted with one litre of pet-ether (b.p. 100-120°) and the mixture stirred until crystals began to form. It was allowed to cool and the voluminous crystals were filtered at the pump. The product was dried by distillation in vacuo, to give 220 g. of solid m.p. 80° (58.7%).

Attempted preparation of 1-(δ-Hydroxy butanoyl)-2-methoxynaphthalene

Magnesium (6 gm; the magnesium was washed with sodium-dried ether and dried at 110-120°) in tetrahydro furan (100 ml.) was treated with ethyl bromide (0.5 c.c.). When the reaction had started, 1-brome-2-methoxy naphthalene (35 g; 0.15 mole) in tetrahydro furan (200 ml.) was added while the mixture was stirred. To the clear solution was added butyrolactone (15 g; 0.174 mole) while stirring and refluxing continued. It was refluxed for further 3 hrs and the magnesium complex was decomposed with aqueous hydrochloric acid. The organic layer was separated and washed with

water. The solvent was removed and the residue distilled in vacuo. First fraction (25 gm.) came off at 160-180°/60 mm. and crystallized from methanol to give 2-methoxy naphthalene m.p. 72°. Second fraction (5 gm.) b.p. 190-250°/60 mm. consisted of both saturated and unsaturated carbonyl compounds. The residue might probably be a hydrocarbon.

1-(2-Cyanoethyl)-2-hydroxy naphthalene

A mixture of benzene (825 c.c.), 2-naphthol, (430 g; 2.99 mole), exactly 133.4 gm. (3.33m) of sodium hydroxide and acrylonitrile (200 gm. or 250 ml.; 3.77 mole) was heated on a water-bath under reflux for 4 hrs. Then cold water (1500 ml.) was added and the mixture stirred until all the alkali had dissolved. The aqueous layer was separated and acidified with acetic acid. The product was filtered and crystallized from methylated spirit and allowed to stand overnight in the solvent. The product was filtered and washed with a little methylated spirit until colourless i.e. until all the pink colouration was removed. 530 gm. (90%) of slightly yellow crystals m.p. 145° were obtained. ν max. (Nujol) 1575 cm^{-1}, 1616 cm^{-1}, 2250 cm^{-1} and 3333 cm^{-1}. Reported[76] m.p. 142°.

5,6-Benzdihydrocoumarin.

1-(2 Cyanoethyl)-2 hydroxy naphthalene (3.94 g.; .02 mole) and a solution of sodium hydroxide (2.4 g; .06 m.) in water (12 ml.) was refluxed on a heating mantle for about 5 hrs. (i.e. until no more ammonia was evolved). It was then refluxed for a further one hour. The reaction mixture was diluted with water to dissolve the precipitate formed and was acidified with conc. hydrochloric acid to Congo red. The reaction mixture was then refluxed until nearly all the solid precipitate had been converted to oil. The oil was separated while the mixture was still very hot and was allowed to cool. It was then diluted with ether and the ethereal solution was thoroughly washed with sodium carbonate solution, and then with water. After drying the organic extract over anhydrous magnesium sulphate, it was evaporated. The residual oil was treated with dry benzene and the benzene removed at ordinary pressure. This was repeated thrice. Traces of benzene were then completely removed in vacuo and the oil was cooled to below 0° with stirring when it solidified to give 3.14 g. (80%) of 5,6 benzdihydrocoumarin m.p. $52-54^{\circ}$. ν max. (Nujol) 1582 cm^{-1}, 1632 cm^{-1} and 1762 cm^{-1} (Found: C, 78.77; H, 5.05 $C_{13}H_{10}O_2$ requires C, 78.77; H, 5.09).

1-(3 Hydroxy propyl)-2 hydroxy-naphthalene.

Lithium aluminium hydride (10 g.; 0.26 m.) in sodium-dried ether (300 c.c.) was placed in 2-litre three-necked flask equipped with a stirrer, a reflux condenser and a separatory funnel. Then slowly and with stirring, 5.6-benzdihydrocoumarin (70 g.; 0.36 mole) in dry ether (200 c.c.) was added. After the addition it was stirred for a further one hour. Ethyl acetate (24 ml.) was added rapidly to decompose excess lithium aluminium hydride followed by ice-cold water and then dil. hydrochloric acid. The ethereal layer was separated and the aqueous layer was extracted thrice with small portions of ether. The combined organic extracts were washed with water severally, dried over magnesium sulphate and then evaporated. The resulting solid crystallized from methanol to give quantitatively colourless crystals of 1-(3 hydroxy propyl)-2 hydroxy naphthalene m.p. 135°. The phenol in methanol imparted yellowish green colour to a drop of ferric chloride solution. ν max. (Nujol) 1587.5 cm^{-1}, 1625 cm^{-1} 3150 cm^{-1} and 3410 cm^{-1}. (Found: C, 77.23; H, 6.90 $C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98).

1-(3 hydroxy propyl)-2 hydroxy-5,6,7,8 tetrahydro-naphthalene.

1-(3 hydroxy propyl)-2 hydroxy naphthalene (50 g.; .024m.) in methanol was hydrogenated over Raney nickel (6 g.; 0.102 at)

at an initial pressure of 65 atmospheres and a set temperature of 120° until the hydrogen up-take was complete (about 7 hrs). The catalyst was filtered off and the methanol was removed completely on a water-bath under reduced pressure. The residue, taken up in ether, was thoroughly extracted with 10% sodium hydroxide solution. The alkaline solution was washed with ether and then acidified with dil. hydrochloric acid. The resulting solution was extracted with ether, the ethereal solution dried and evaporated. To the oil benzene was added and removed at ordinary pressure. This was repeated several times. Traces of benzene were removed completely under reduced pressure. The oil was then recrystallized in small portions from pet. ether (30-40°). After drying overnight in a vacuum desicator 40 gm. (78.4%) of 1-(3-hydroxypropyl)-2 hydroxy-5,6,7,8 tetrahydro naphthalene. m.p. 65-70° was obtained. The product in methanol gave a green colour with a drop of ferric chloride solution. νmax. 1587 cm^{-1}, 3233 cm^{-1} and 3550 cm^{-1}. (Found: 75.9; H, 8.80. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80).

1-(3 hydroxy propyl)-2 methoxy-5,6,7,8 tetrahydro naphthalene.

1-(3 hydroxy propyl)-2 hydroxy-5,6,7,8 tetrahydro naphthalene (206 g.; 1 mole) in water (400 ml.) containing sodium hydroxide (42 g.; 1.05 m.) was stirred until dissolved in a three-necked

flask equipped with a condenser and a separatory funnel. The solution was cooled below 10° in an ice-salt bath and dimethyl sulphate 126 g. (94 ml.; 1 mole) was added dropwise while the mixture was stirred. After the addition, the mixture was stirred for 30 mins. and water (200 ml.) containing sodium hydroxide (21g.; .53 m.) was added and the mixture stirred for a further 30 mins. The mixture was refluxed on a water-bath for 2 hrs., cooled, and was then diluted with water. The oil was separated and the aqueous layer was extracted with ether. The oil and ether extracts combined were washed successively with dil. sodium hydroxide, dil. hydrochloric acid and water. The ethereal solution was dried over magnesium sulphate and the solvent was evaporated to give 178.8 gm. (81.3%) of 1-(3 hydroxy propyl)-2-methoxy-5,6,7,8-tetrahydro naphthalene as a colourless oil. ν max 800 cm^{-1}, 1256 cm^{-1}, 1600 cm^{-1} and 3400 cm^{-1}.

1-(3 Bromo propyl)-2 methoxy-5,6,7,8 tetrahydro naphthalene.

The preceeding methoxy propanol (15.4 g.; 0.07 m.) in sodium-dried diethyl ether (50 c.c.) was cooled to 0° in an ice-salt bath. While stirring, phosphorous tribromide (2.68 ml.) in ether (10 ml.) was added dropwise at such a rate that the temperature was kept as near zero as possible. After the addition, stirring was continued for further 30 mins. Then both the bath and the reaction

mixture were allowed to warm to room temperature overnight. The mixture was diluted with ether, and sodium carbonate solution was added. It was successively washed with water, dil. hydrochloric acid and then water. The ethereal solution after being dried over magnesium sulphate was evaporated to give 12.9 g. (65%) of 1-(3-Bromopropyl)-2-methoxy-5,6,7,8-tetrahydro naphthalene as a colourless oil ν max. 800 cm^{-1}, 1266 cm^{-1} and 1600 cm^{-1}.

5-(3 Bromopropyl)-6 methoxy-1-tetralone.

The preceeding methoxy bromide (283 g.; 1 mole) in glacial acetic acid (856 ml.) was cooled to 5° in an ice-salt bath. A solution of chromic anhydride (153 g.; 1.53 mole) in water (55 ml.) and glacial acetic acid (428 ml.) was added at such a rate that the temperature was held at about 20°, while the mixture was vigorously stirred. The mixture was allowed to warm to room temperature overnight and was then diluted with water. The oil was separated and the aqueous layer was extracted severally with diethyl ether. The oil and organic extracts were combined and washed successively with water, C. IN sodium hydroxide, dil. hydrochloric acid and with water. The organic solution was dried and evaporated to give a viscous oil which crystallized from pet. ether (30-40°) or a little diethyl ether to give 94 g. (31.6%) of 5-(3-bromopropyl)-6 methoxy-1-tetralone m.p. 92-94°. (Found: C, 56.83; H, 5.74,

Br, 26.8 $C_{14}H_{17}O_2Br$ requires C, 56.75; H, 5.70; Br, 27.0%)
ν max. (Nujol) 1587.5 cm^{-1}, 1666 cm^{-1}.

6-Methoxy-5(3-Bromopropyl)-3:4 dihydro-1-methyl naphthalene.

To a grignard solution prepared in ether from magnesium (120 g.; 5 atoms) and an excess of bromo methane (sufficient to react all the magnesium turnings) was added the preceeding ketone (294 g.; 0.99 mole) in tetrahydro furan. After the addition it was stirred under reflux for a further 2 hrs. The complex was decomposed by the careful addition of dil. hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with chloroform. The organic solutions were separately washed neutral with water, and were united. The organic solution was dried and evaporated, to give 228.6 g. (77%) of 6-methoxy-5(3-Bromopropyl)-3:4-dihydro-1-methyl naphthalene as a yellow oil. The I.R. spectrum had no carbonyl absorption.

1-Methyl-5(3-bromopropyl)-6 methoxy-2-tetralone.

The preceeding dihydro naphthalene (295 g.; 1 mole) dissolved in chloroform (320 ml.) was oxidized with perbenzoic acid (134 g.; 0.97 mole) in chloroform (1760 c.c.) at 0°. After storage overnight in the refrigerator, the red solution was washed with dil. sodium hydroxide and then water; and the solvent removed under reduced

pressure. The residue was refluxed for 1½ hrs. with conc. sulphuric acid (206 ml.), methanol (1380ml.) and water (1100 ml.) and the product isolated with ether. After being washed and dried the solution was evaporated, to give 252.8 g. (80.9%) 1-methyl-5 (-3 bromopropyl)-6 methoxy-2-tetralone as a yellow oil. ν max. 1600 cm^{-1} and 1720 cm^{-1}.

Ring extension of 1-methyl-5(3 bromopropyl)-6-methoxy-2-tetralone.

The preceeding tetralone (6 g.; .019 mole) in methanol (100 ml. was cooled to 0° in an atmosphere of purified butane. Potassium hydroxide (1.6 g.; .02 mole) in water (3.2 mole) was added and the solution cooled to - 20°. The mixture was stirred vigorously for 30 mins and then methyl vinyl ketone (1.7 ml.) in methanol (5 ml.) was added dropwise and slowly. After the addition, stirring was continued for a further one hour. Stirring was discontinued and the mixture was allowed to stand overnight at room temperature under trapped butane. It was acidified with dil. hydrochloric acid containing crushed ice and extracted with chloroform. The organic solvent was washed, dried and evaporated, to give a viscous oil. The oil (5 g.) in methanol (100 ml.) was treated with potassium carbonate (3 g.) in water (3 ml.) and the mixture refluxed for 3 hrs. The reaction mixture was cooled, poured onto ice containing conc. hydrochloric acid and the mixture extracted with

chloroform. The organic solution was washed, dried and evaporated to give an oil which was passed through activated alumina. Various mixtures of pet. ether and benzene eluted nothing. Second benzene fraction was mainly the product viz. 2:3:4:9:10:12-hexahydro-6-methoxy-7(3-bromopropyl)-12-methyl-2-oxophenanthrene as an oil. ν max. 1587 cm, 1616 cm and 1650 cm^{-1}. Third and fourth fractions consisted of an oil which crystallized from a little ether to give 8-Oxo-10a-methyl-1,2,3,4,5,6,8,9,10,10a-decahydro-1-oxa-chrysene m.p. 160-162°. ν max. 1587.5 cm, 1616 cm, 1650 cm^{-1}. λmax. 207.5 mμ (ϵ 37,180). λmax. 234 mμ (ϵ 37,520) (Found: C, 80.16; H, 7.52 $C_{18}H_{20}O_2$ requires C, 80.56; H, 7.51). The N.M.R. spectrum showed absorption at 8.04 τ for 3 protons as a singlet (C-9 methyl), at 6.96-6.6 τ for six protons as a multiplet (2x Ar $CH_2\underline{CH_2}$ and CO.$\underline{CH_2}$), at 5.04-4.48 τ for 2 protons as a triplet (OCH_2), at 2.88 τ for one proton as a singlet (C-5 olefinic hydrogen) and at 1.96-1.24 τ for two protons as a quintet (two aromatic hydrogens).

8β-Hydroxy-10a-methyl-1,2,3,4,5,6-6a-α-7,8,9,10,10a, dodecahydro-1-oxa-chrysene.

Lithium (1 gm.; 0.14 atom) was dissolved in liquid ammonia (200 ml.). After 5 mins, the preceeding tetracylic enone-ether (0.6 gm.; .002 mole) in tetrahydro furan (20 ml.) was added.

After shaking the solution for five minutes, the blue colour was discharged by a dropwise addition of methanol. This was followed by an addition of more lithium (0.5 g.) and then methanol, and then lithium (0.5 g.) and again methanol until in all 2 gm. of lithium had been added. The solution was allowed to evaporate overnight, and was diluted with water. The aqueous solution was extracted with chloroform. The organic solution, after drying over magnesium sulphate was evaporated to give an oil which crystallized from a little ether or acetone to give 8β-Hydroxy-10a-methyl-1,2,3,4,5,6, 6aα-7,8,9,10,10a decahydro-1-oxa-chrysene m.p. 128°. ν max.(Nujol) 1587.5 cm and 3440 cm^{-1}. The preceeding hydroxy-ether in acetic acid was hydrogenated over platinum oxide at room temperature and atmospheric pressure for 36 hrs. A compound m.p. 45-50° was obtained νmax. 1587.5 cm^{-1}, and 3440 cm^{-1} and was perhaps the starting material.

5(3-Acetoxy propyl)-6-methoxy-1-tetralone.

1-(3-hydroxypropyl)-2-methoxy-5,6,7,8, tetrahydro naphthalene (2.20 g.; 0.01 mole) in dry pyridine (1 ml.) was treated with acetic anhydride (1.45 g.; 0.014 m.). The mixture was allowed to stand overnight and the product isolated in the usual way with ether. The acetate was an oil. The acetate (2.62 g. 0.01 mole) in acetic acid (8.6 ml.) was treated with chromic anhydride (1.5g; 0.015 mole)

in water (1 ml.) and glacial acetic acid (4.3 ml.) at 20°. The mixture was allowed to stand overnight and the product isolated with ether in the usual way, to give in 50% yield 5-(3-Acetoxy propyl)-6-methoxy-1-tetralone as an oil. ν max. 1575 cm^{-1}, 1666 cm^{-1} and 1725 cm^{-1}.

Attempted preparation of 6-Methoxy-5-(n-propionic acid)-1-methyl-2-tetralone.

6-Methoxy-5 (3-bromopropyl)-1-methyl-2-tetralone (3.1 g.; 0.01 mole) in methylated spirit (50 ml.) was added to a solution of potassium cyanide (0.97 g; 015 mole) in water (0.5 ml.) in a 100 ml. flask and the mixture refluxed for 20 hrs. on a water-bath. The reaction mixture was cooled and the precipitated potassium bromide was filtered off. The alcoholic filterate was diluted with water and the aqueous solution extracted with chloroform. The organic solvent was washed and evaporated to give the corresponding nitrile as an oil, νmax, 1587 cm^{-1}, 1700 cm^{-1} and 2225 cm^{-1} (nitrile). The nitrile (2.5 g; 0.01 mole) suspended in water (50 ml.) was treated with sodium hydroxide (2 g; .05 mole) and the mixture refluxed over a heating mantle for 20 hrs. It was cooled, washed with chloroform and poured onto ice containing conc. hydrochloric acid. The acid mixture was extracted with chloroform and the chloroformic solution was extracted with aqueous sodium bicarbonate.

The alkaline solution was acidified and extracted with chloroform. After drying, the organic solvent was removed to give 0.5 gm. of the acid as a semi-solid. Attempt to crystallize the substance failed. $\nu_{max.}$ 1587.5 cm^{-1}, 1710 cm^{-1}, and 2670 cm^{-1}. Attempt to prepare a D.N.P. derivative also failed.

α-Bromo methyl butyrate.

γ-Butyro lactone (43 g; 0.5 m.) and 60% hydrobromic acid (92 ml; d = 1.7) were placed in a flask equipped with a water-condenser carrying an adaptor filled with absorbent cotton wool. The mixture was refluxed over a heating mantle for 5 hrs. and excess hydrobromic acid was removed under diminished pressure on a water-bath. The residue was cooled and then taken up in ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulphate and then evaporated. The crude α-bromo butyric acid (78.9 g; 0.47 m.) in dry benzene (72 ml.) was treated with dry methanol (48 ml.) and conc. sulphuric acid (0.3 ml.). The mixture was then refluxed with a water-separator on a water bath. Water, benzene and alcohol separated and formed two layers in the separator. The lower layer (50% water-methanol mixture) was then run off. When no more water separated, more dry methanol (about 150 ml.) was added and the reflux continued for 30 minutes more. The solution was concentrated at ordinary pressure on a water-bath. The residue

was cooled and shaken up with water to dissolve unreacted γ-butyrolactone and γ-bromobutyric acid. The oil was separated from the aqueous solution, dissolved in ether and the ethereal solution dried over magnesium sulphate and evaporated. The oil was redistilled on a heating mantle. Fraction b.p. 186-187° was collected. Overall yield based on γ-butyrolactone was 80% $\nu_{max.}$ 1737 cm^{-1}. (Strong carbonyl).

Alkylation of 1,2,3,4,5,6,7,9,10,11,12,13, dodecahydro-1,1,-dimethyl-2β-hydroxy-12-methyl-7-oxophenanthrene with γ-bromomethyl butyrate.

Potassium (0.1 gm; .003 m.) was added to dry t-butanol (20 ml.) in a super-dry flask. The flask was equipped with a dry condenser carrying a cotton-wool adaptor. The solution was refluxed over a heating-mantle until all the metal had dissolved and then the hydroxy enone (0.56 g; 0.002 m.) was added and the reflux continued for 15 minutes more. γ-Bromo methyl butyrate (1 gm.; this was quite a large excess) was added and the reflux continued for 15 minutes more. The reaction mixture was cooled, diluted with water, acidified with cold dil. hydrochloric acid and extracted with ether. The organic solvent was evaporated when an oil was obtained. The oil was passed through a column of activated alumina. Different mixtures of pet. ether and benzene eluted nothing but pure benzene eluted a substance which crystallized from a little ether to give

200 mg. of a Compound m.p. 100°. ν max. 1625, 1666 and 1725 cm^{-1}. Pure ether eluted about 300 mg. of the starting material.

5,6,7,8-Tetrahydro-2-methoxy naphthalene.

β-Naphthol (500 g; 3.5 m.), was suspended in methanol and the mixture was hydrogenated over alkali-free Raney nickel (40 gm; 0.68 atom) at an initial pressure of 120 atmospheres and a set temperature of 140°. The system was replenished from time to time with hydrogen until the uptake almost ceased. The solution was filtered and the methanol removed completely over a water-bath. The residue was taken up in ether and was extracted thoroughly with 2N sodium hydroxide. The alkaline solution was methylated with dimethyl sulphate in the usual way to give 277 gm. (53.9%) of 5,6,7,8-tetrahydro-2-methoxy naphthalene after redistillation under reduced pressure over a heating mantle b.p. 140°/1 5 mm. Reported b.p. 129-131°/11 mm.

6-Methoxy-1-tetralone.

The preceeding methoxy tetralin (160 g; .99 m.) in glacial acetic acid (550 ml.) was cooled to about 15° in an ice-salt bath. A solution of chromic anhydride (130 g; 1.3 m.) in water (100 ml.) and glacial acetic acid (500 ml.) was added with stirring at such a rate that the temperature was held at about 20°. After the

addition, the reaction mixture was allowed to stand at room temperature overnight. The deep green reaction mixture was diluted with water and the mixture was allowed to stand for one hour. The aqueous layer after being decanted from the oil which separated was extracted thoroughly with diethyl ether. The oil and ether extracts were combined and washed with water. To the organic solution was added dil. sodium hydroxide. Without shaking, the aqueous layer was separated. This operation was repeated. The organic solution was extracted with dil. sodium hydroxide, washed with water and dried over magnesium sulphate. The organic solvent was removed and the residue was distilled in vacuo. (Water condenser was used and the water in the condenser was emptied as soon as fraction began to solidify). Fraction b.p. 160°/1 mm. was collected. The oil crystallized from pet. ether (30-40°), to give 80 gm. (46%) of 6-methoxy-1-tetralone as light yellow crystals m.p. 87°. $\nu_{max.}$ 1600, and 1666 cm^{-1}.

1-Methyl-3,4-dihydro-6-methoxy naphthalene.

A grignard solution was prepared by adding excess bromo methane (about 200 ml.) in cold dry diethyl ether (800 ml.) to magnesium turnings (40 g; 1.7 atoms) in dry diethyl ether (1500 ml.) contained in a five-litre three-necked flask which was equipped with a double-surface condenser, a dropping funnel and stirrer and

which was placed near an ice-salt bath for occassional cooling. After all the magnesium turnings had reacted, 6-methoxy-1-tetralone (160 g; 0.91 m.) in a minimum amount of tetrahydro furan was added while the mixture was stirred. After the addition, stirring was continued for one more hour. The complex was decomposed with dil. sulphuric acid. The organic layer was separated, washed with water, dried as usual and evaporated to give in 90% yield 1-methyl-3,4-dihydro-6-methoxy naphthalene as a light yellow oil. (No carbonyl absorption).

6-Methoxy-1-methyl-2-tetralone.

Monoperphthalic acid was prepared as follows: 125 g. of sodium hydroxide dissolved in 125 ml. of water was treated with one Kg. of ground ice. The solution was stirred and then 250 ml. of 30% hydrogen peroxide was added followed immediately by the addition of 2.5 g. of magnesium sulphate. Then all at once, 250 g. of phthalic anhydride (freshly ground) was added and the mixture stirred until all the anhydride had dissolved. (About 5 mins.). The mixture was then acidified with ice-cold 20% sulphuric acid prepared before hand. (The whole operation from the beginning to the acidification stage was done very quickly). The perphthalic acid was extracted with ether and a sample of the ether solution (1 ml.) was titrated by adding glacial acetic acid (2 c.c.),

water (20 c.c.) and potassium iodide (about 1 gm.) and titrating with decinormal sodium thiosulphate solution.

The dihydro naphthalene (174 g; 1 mole) in ether (500 c.c.) was cooled to - 10°C and then 1.9 litre of Normal monoperphthalic acid (this is a little less than one equivalent) was added slowly. After the addition, it was left in the bath for 4 hrs. and was allowed to stand at the temperature of the cold room (about 20°) overnight. The reaction mixture was diluted with aqueous sodium hydroxide. The organic layer was separated, washed with water and evaporated. To the residue in methanol (300 ml.) was added conc. sulphuric acid (30 ml.) in water (160 ml.) and the mixture refluxed for 2 hrs. The reaction mixture was diluted with water and the oil which separated was removed. The aqueous solution was extracted with chloroform. The oil and chloroformic extracts were combined and washed with dil. sodium hydroxide and then water. The solvent was evaporated and the residue distilled under reduced pressure, to give 94.4 gm. (49.7%) of 6-Methoxy-1-methyl-2-tetralone. ν max. 1724 cm^{-1} (strong carbonyl absorption).

7-Methoxy-12-methyl-2,3,4,9,10,12 hexahydro-2-oxophenanthrene.

6-Methoxy-1-methyl-2-tetralone was condensed with methyl vinyl ketone using the procedure already described for the

preparation of 6-methoxy-12-methyl,2,3,4,9,10,12-hexahydro-2-oxophenanthrene. The crude product was distilled under reduced pressure and the distillate was crystallized from a little ether to give 50% yield of 7-methoxy-12-methyl-2,3,4,9,10,12-hexahydro-2-oxophenanthrene as yellow crystals m.p. 107-109°. ν_{max}. 1600, 1625 and 1666 cm^{-1}.

Trans, 1,2,3,4,5,8,9,10,11,12-decahydro-7-methoxy-12-methyl-2β-hydroxy phenanthrene.

Lithium (4 g; 0.58 atom) was dissolved in liquid ammonia (1 litre). After five minutes, the preceeding hexahydrophenanthrene (5 g; 0.021 m) in purified tetrahydro furan (200 ml.) was added. After another five minutes, n-propanol, (75 ml.) was added dropwise until the blue colour was discharged. This was followed by an additional 3 gm. of lithium and then propanol and yet 3 gm. of lithium, followed by propanol until in all 10 gm. of the metal had been added. The solution was allowed to evaporate. The residue was diluted with distilled water and extracted with chloroform. The chloroformic extract was washed with water and dried over anhydrous sodium sulphate. The solvent was completely removed to leave an oil which crystallized from ether to give 50% yield of 1,2,3,4,5,8,9,10,11,12-decahydro-7-methoxy-12-methyl-2β-hydroxy phenanthrene m.p. 133-134°. ν_{max}. (Chloroform) 1661, 1693, and 3524 cm^{-1} Reported[48] m.p. 133-135°.

Trans-1,2,3,4,5,6,7,8,9,10,11α,12-dodecahydro-12-methyl-2β-hydroxy-7-oxophenanthrene.

The preceeding dienol ether (17.9 g; .072 m.) in methanol (100 ml.) was treated with a solution of oxalic acid (4 g; .037 m.) in water (5 ml.). The mixture was allowed to stand at room temperature overnight. The reaction mixture was diluted with water, extracted with chloroform and the organic extract washed with water. The solvent was completely removed to give a residue which crystallized from pet-ether (30-40°) to give 80% yield of the β,γ-unsaturated ketone m.p. 93-95°. ν max. (chloroform) 1700 and 3423 cm^{-1}. The benzoate had ν max. (chloroform) 713, 1600 and 1720 cm^{-1}, and λmax. 228 mμ.

1,2,3,4,5,6,7,9,10,11α,12,13 dodecahydro-12-methyl-2β-hydroxy-7-oxophenanthrene.

1,2,3,4,5,8,9,10,11,12-Decahydro-7-methoxy-12-methyl-2β-hydroxy phenanthrene (0.25 g; 0.001 m.) in acetone (20 ml.) was treated with a solution of conc. hydrochloric acid (1 ml.) in water (3 ml.) and the mixture refluxed on a water-bath overnight. The solution was cooled, diluted with water and extracted with chloroform. The solvent was completely removed to leave a residue which crystallized from ether to give 0.2 g. of the α-β unsaturated keto-alcohol m.p. 121-123°. (84.8%) νmax. (chloroform) 1616, 1666 and 3400 cm^{-1}.

λmax. 242 mμ (ϵ 17,000). Reported[37] m.p. 123-4°. The unsaturated ketone (0.5 g.) in pyridine (5 ml.) was treated with benzoyl chloride (1 ml.). The product was isolated the following day with chloroform. The oil was shaken up with 10% solution of sodium hydroxide and extracted again with chloroform. After evaporating the solvent the crude benzoate was crystallized from methanol or acetone. m.p. 177-179° ν max. (Nujol) 714, 1666, and 1716 cm^{-1}. λmax. (methanol) 235.5 mμ.

2,2-Ethylene dioxy-5-bromo-pentan-2-one.

5-Bromo-pentan-2-one was prepared according to the procedure outlined for the preparation of 5-Chloropentan-2-one in organic Syntheses Coll. Vol. IV[85]. α-Acetobutyro lactone (20 g; 0.16 m.) and water (27 ml.) were placed in a two-necked 500 ml. flask. Two or three antibumping stones were added and the flask was arranged for distillation. A water condenser was used and the receiving flask was immersed in crushed ice while the reaction flask was placed over a heating mantle. 60% Hydrobromic acid (84 ml.) was introduced through the other neck of the reaction flask and stoppered. Heating was started immediately. 5-Bromo-pentan-2-one distilled azeotropically with water at 120-122° at ordinary pressure. When about two-thirds of the reaction mixture had distilled over, more water (10 ml.) was added to the reaction mixture and distillation

was continued until only water was distilling over. The lower layer of the distillate was separated and the aqueous layer was extracted with ether. The organic liquid and ether extracts were combined and washed well with water. The organic solution was dried over anhydrous calcium chloride for 10 mins. and decanted into another dry flask containing calcium chloride. After one hour, it was again decanted into another flask and evaporated on a water-bath at ordinary pressure.

The bromo ketone (25 g.) in dry benzene (100 ml.) was treated with ethylene glycol (25 ml.) and conc. sulphuric acid (5 drops). The mixture was refluxed with a water-separator for 48 hrs. The benzene layer was separated from unreacted glycol, 0.3 ml. of pyridine was added and the organic solution was washed with dil. sodium hydroxide and then with water. After drying the organic solution in the usual way, the solvent was removed completely under reduced pressure on a water-bath. The oil was then kept in a well stoppered bottle to prevent deterioration. (Found: C, 40.40; H, 6.68, Br, 36.15% $C_7H_{13}O_2Br$ requires C, 40.20; H, 6.20; Br. 38.28%).

Alkylation of 2-Benzoyloxy-1,2,3,4,5,6,7,8,9,10,11,13,dodecahydro-12-methyl-7-oxophenanthrene with 2,2-ethylenedioxy-5-bromo pentan-2-one.

Potassium (42 mg; 001 at) dissolved at reflux in dry t-butanol was treated with the benzoate (0.3 g.; 0.001 m.). (Heating mantle was used and a very dry water-condenser carrying a cotton wool tube was provided). After five minutes, the bromo ketal (0.58 g; 0.003m.) was added and the reflux continued for 1½ hrs more. The organic solvent was completely removed, the residue was dissolved in methanol, treated with 0.58 g. of sodium hydroxide in 1 ml. of water and the mixture refluxed for 24 hrs on a water-bath. The alcohol was almost completely removed under reduced pressure. The residue was diluted with water and extracted with chloroform. The organic solvent was completely removed to leave the adduct as an oil, λmax, 250 mμ νmax. 1600, 1666 and 3425 cm^{-1}.

Reduction of the αβ-unsaturated ketone (148).

Lithium (0.2 gm; 0.02 atom) was added to liquid ammonia (400 ml.). After all the metal had dissolved (about 10 mins), the α-β unsaturated ketone (3 g; .008 mole) in tetrahydrofuran (60 ml.) was added. After 5 mins, solid ammonium chloride was added very carefully until the blue colour was discharged. The ammonia was allowed to evaporate overnight and then chloroform was added. The organic solution was then washed with water, dried over anhydrous

sodium sulphate and evaporated to give an oil (ν max. 1625, 1666, 1700 and 3400 cm^{-1}) which was a mixture of the fully saturated keto alcohol (149) and the starting material.

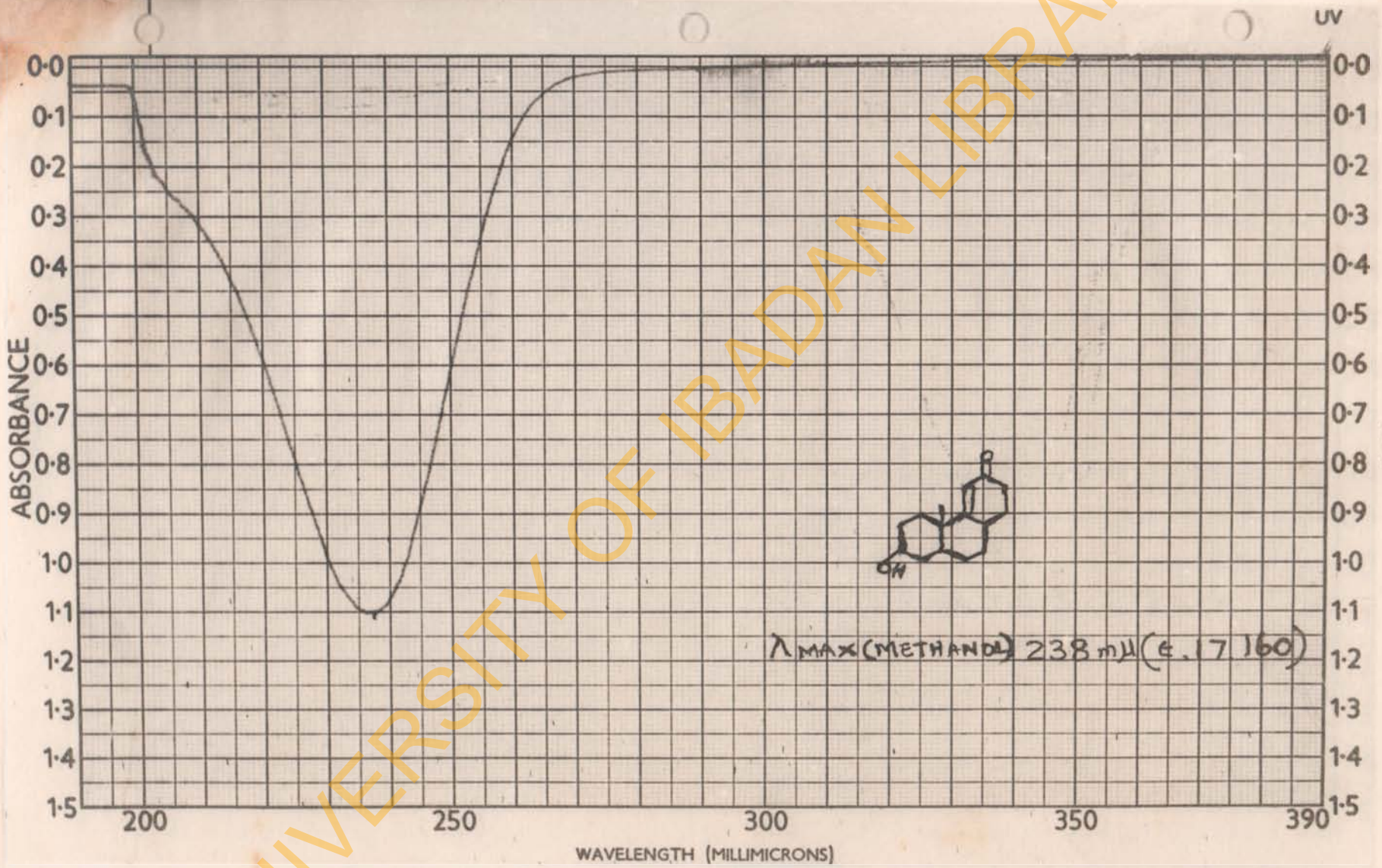
Conversion of the fully saturated keto alcohol (149) to the olefinic ketone (150).

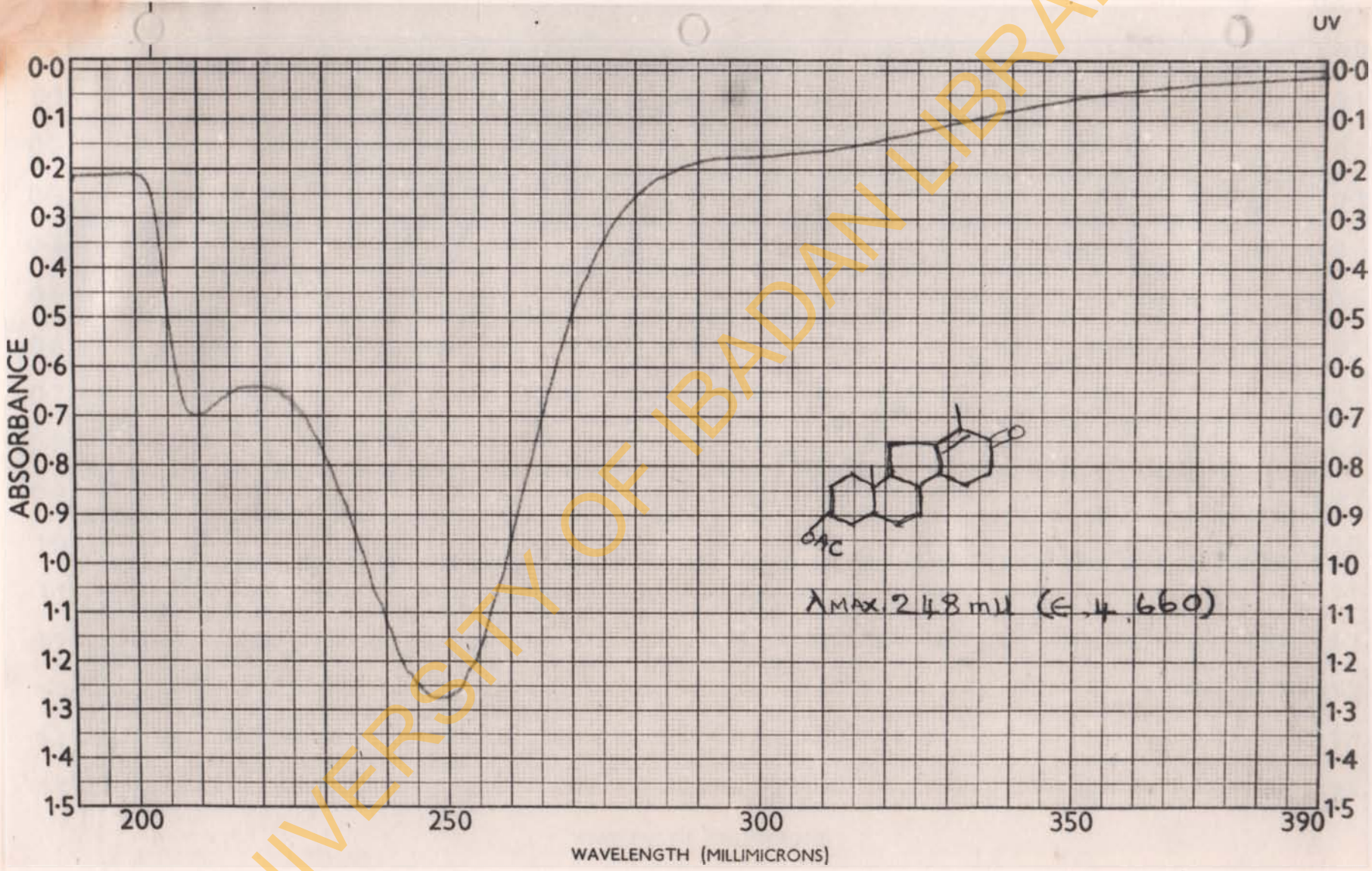
Grignard reagent prepared from magnesium turnings (4 g.) and excess bromomethane in dry ether was treated with the preceeding keto mixture (0.5 g.) in tetrahydrofuran (40 ml.) and the mixture stirred for one hour. The complex was decomposed with a solution of conc. hydrochloric acid (25 ml.) in water (50 ml.). The organic solution was washed with water, dried over sodium sulphate and evaporated, to give an oil, ν max. 1710 and 3400 cm^{-1}. λ max. 209 mμ (very strong). Significant signals in the N.M.R. spectrum occurred at 6.04 τ ($\underline{CH}$ OH), at 6.96 tau ($\underline{CH_2}COCH_3$), at 7.44 tau ($\underline{CH_3}$-C-) and at 8.5 tau (CH_3).

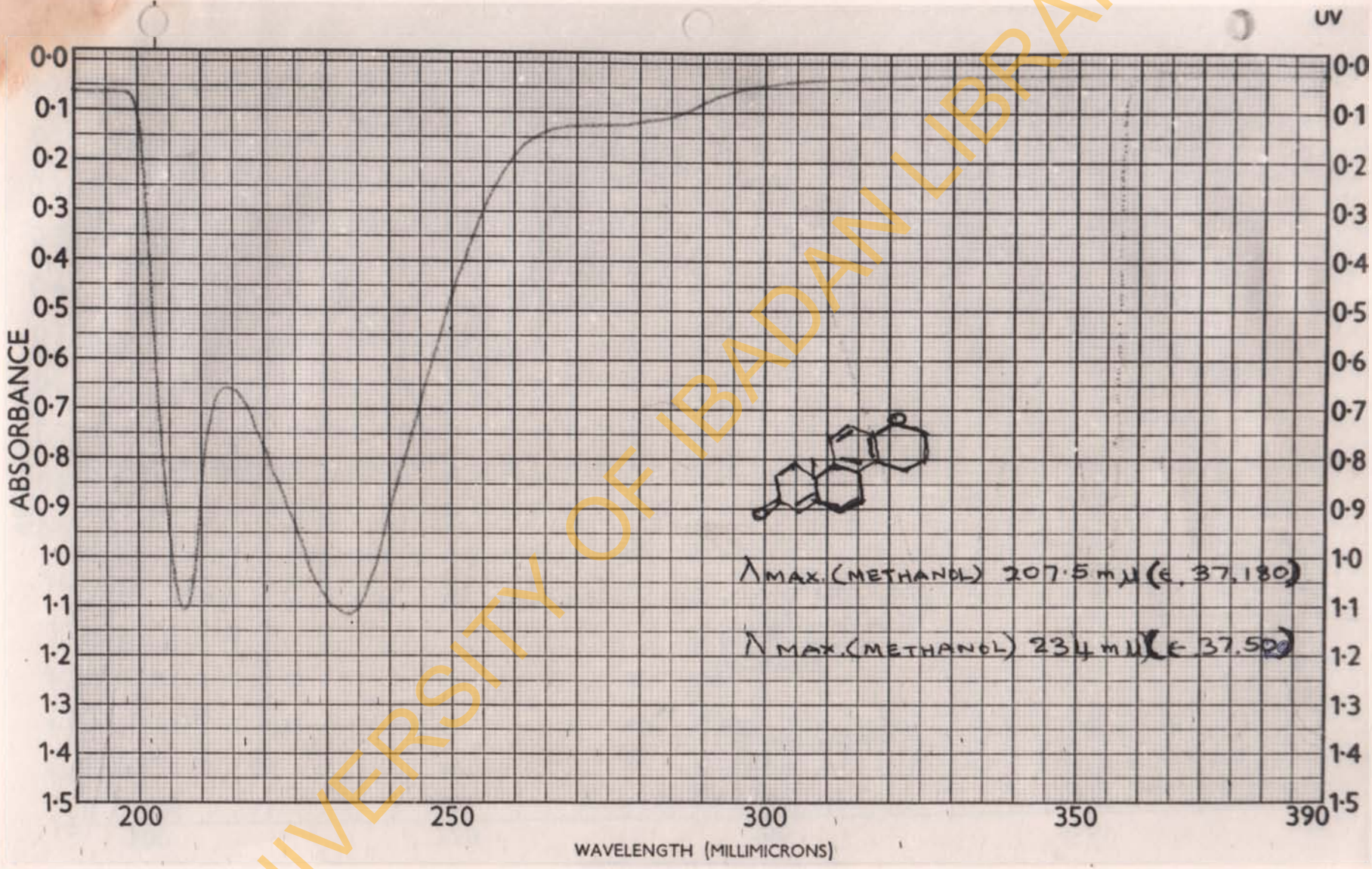
Preparation of the tetracyclic C-Nor-D-homo dieno-ketone (152).

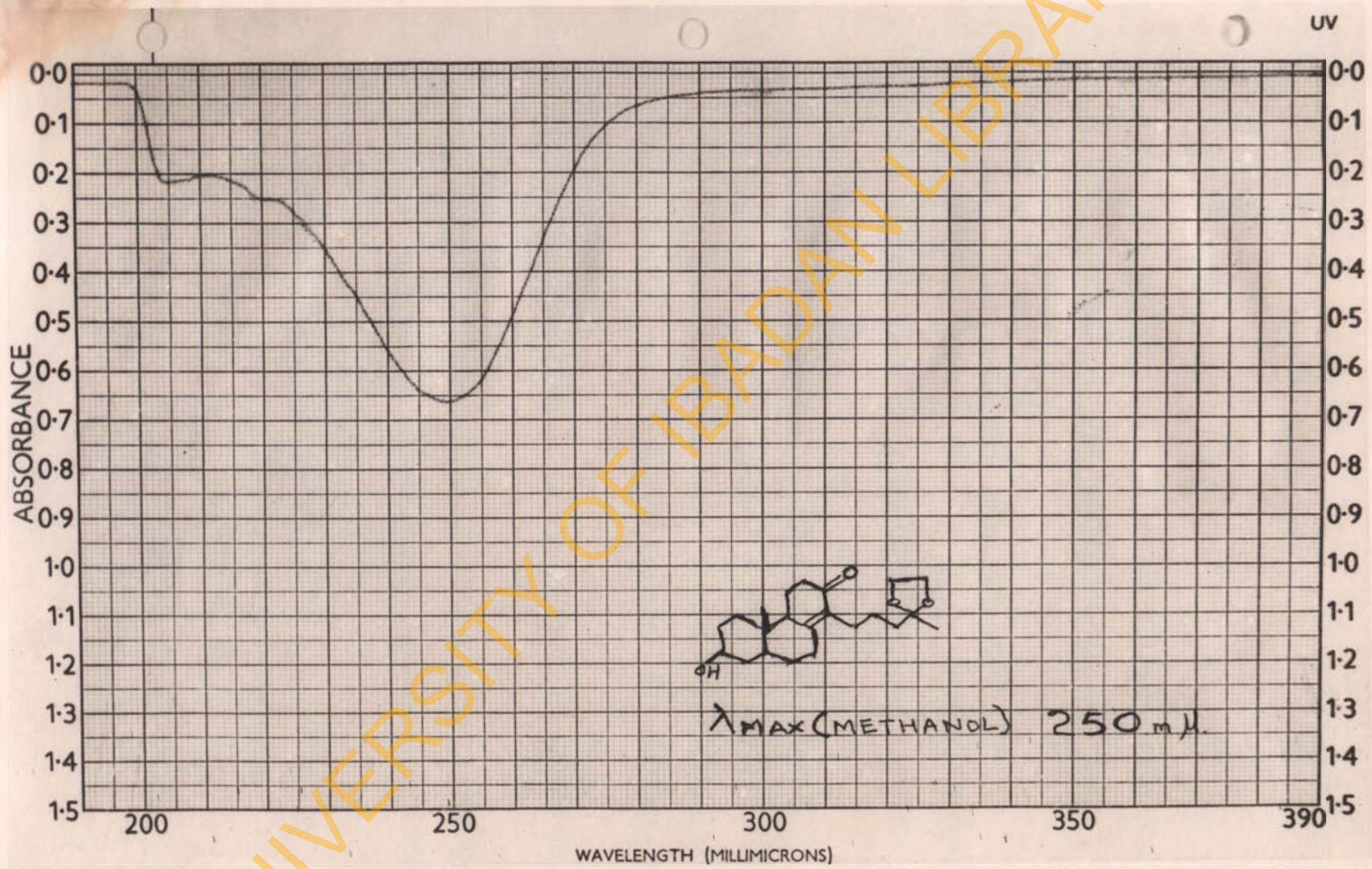
The preceeding mixture supposed to contain the olefin (150) was boiled with acetic anhydride for one hour; methanol was added and the solvents removed completely in vacuo. The resulting acetate (strong CO) was dissolved in ethyl acetate and ozonized at - 61° in a bath of chloroform and liquid air. As soon as the blue

colouration was developed glacial acetic acid and zinc powder were added to the solution. The mixture was shaken for four hours and the zinc dust filtered off. The solvents were then removed completely. The oil was refluxed with 2N methanolic sodium hydroxide for 12 hrs. The alcohol was removed, the residue diluted with water and extracted with chloroform. The organic solution was dried and evaporated. The resulting oil (λmax. 225, 255 and 310 mμ) was passed through a column of activated alumina, Pet. ether (40-60°), mixtures of pet ether and benzene, benzene, and mixtures of benzene and chloroform eluted different fractions. However, chloroform eluted 10 mg. of an oil (λmax, 225 mμ, 255 mμ and 310 mμ). The oil did not crystallize.









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