Studies in the Lignan and Terpene Fields.

THOMAS GILCHRIST, B.Sc.

THESIS

Submitted to the University of Glasgow

for the Degree of Ph.D.

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SUMMARY of Ph.D. THESIS

T. GILCHRIST, B.Sc.

Lignan Section.

Otoba fat has been shown to contain a hydroxy otobain and a mixture of phenols in addition to otobain. A structure is proposed for otobain, on the basis of its degradation products and its nuclear magnetic resonance spectrum.

(The Structure of Otobain. T. Gilchrist, R. Hodges, and A.L.Porte. J., 1780 (1962).).

The 1-phenylnaphthalenes, 7,8 : $7^1,8^1$ - tetradehydropiperocyclolignan and 3,4 : $2^1,3^1$ - bis-methylenedioxy-7,8 : $7^1,8^1$ - tetradehydro-cyclolignan, which are related to tetradehydro - otobain, have been synthesised from piperonal type precursors. Attempted syntheses of tetradehydro-otobain are also reported.

Terpene Section

Synthetic routes to aromatic diterpenoids have been investigated which involved suitably substituted phenylcyclohexanones as precursors.

2,6,6-Trimethyl-2-phenylcyclohex-3-enone was prepared from o-hydroxydiphenyl but proved resistant to external attack on its carbonyl function.

Several routes to this compound possessing a side chain suitably substituted for internal attack on the hindered ketone were also investigated.

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LIGNAN SECTION.

The Structure of Otobain.

TERPENE SECTION.

Synthetic Routes to the Aromatic Tricyclic Diterpenoids.

LIGNAN SECTION.

INTRODUCTION

The term lignan was first used by Haworth[1] to describe a family of natural products which are characterised by the carbon skeleton (1) formed by fusion through the β carbon atoms of two molecules of n-propylbenzene. In some cases, the side chains are further modified by cyclisation to form tetrahydrofuran and tetrahydronaphthalene derivatives. All lignans so far investigated have been found to contain hydroxyl and or methoxyl, and or methylenedioxy groups in both benzene rings. In addition, the side chains of these compounds usually contain two or three oxygenated functions either in the form of alcohol, aldehyde, ether or carboxylic functions.

The lignans are of wide distribution in the plant kingdom e.g. they have been isolated from the roots, seeds, foliage oils and fruits of a wide variety of species and in particular they are frequently encountered in the heartwoods and exuded resins of Coniferae. A large group of aromatic compounds found in nature is characterised by a chain of three carbon atoms attached to a benzene nucleus e.g. the eugenol, safrole types, coniferyl alcohol, cinnamic and ferulic acids, the many coumarins and the amino acids β - phenylalanine and tyrosine. The lignans are considered to be a dimer stage between such monomeric propylphenol units and lignin.

The general background of lignan chemistry which is relevant to this research topic is best discussed under three main sections.

(i) The manner in which the various naturally occurring lignans have been classified.

(ii) By choosing a particular example typical of each class, showing the methods used for complete structure elucidation.

(iii) The general methods which are available for the synthesis of each class of lignans.

The lignans have been classified[2] into five principal groups on the basis of the various structural arrangements of the side chains of the two combining units of propylbenzene. Trivial names apart, the nomenclature used in this thesis is essentially that of Freudenberg and Weinges[3] who have based their system of notation on the oxygen equivalents in the benzene rings and side chains of the basic hydrocarbons designated as lignan (1) and cyclolignan (2).

Group One : 1,4 - Diarylbutane derivatives

The chemistry of this class of lignans is typified by guaiaretic acid (3 ; R=H), i.e. 4,4' - dihydroxy - 3,3' - dimethoxy-lignen - 7'. Such a system can be considered as the dimer formed from the coupling of the β-carbon atoms of two isoeugenol units. Schroeter[4] postulated the structure (3 ; R=H) for this compound using the following information. The compound contained two phenolic groupings, and afforded guaiacol (4) and pyroguaiacin (5) on distillation[5]. Cyclisation of guaiaretic acid dimethyl ether (3 ; R=CH_3) using iodine and mercuric chloride gave the naphthalene derivative dehydroguaiaretic acid dimethyl ether (6).

Synthetic verification of these results was given by Haworth[6] who achieved the successful synthesis of racemic guaiaretic acid dimethyl ether. 3', 4' - Dimethoxyphenylacetonitrile (7) was condensed with methyl - 3', 4' - dimethoxyphenyl - 2 - methylpropionate (8) to give the cyano-ketone (9). Hydrolysis and decarboxylation of this material then gave the ketone (10) which on treatment with methyl magnesium iodide and subsequent dehydration furnished guaiaretic acid dimethyl ether identical with the natural material. An identical synthesis[7] of the corresponding diethyl ether (3 ; R=CH_2CH_3) from 3' - methoxy - 4' - ethoxyphenylacetonitrile and methyl - 3' - methoxy - 4' - ethoxyphenyl - 2 - methylpropionate confirmed the placement of the phenolic hydroxyl groups in guaiaretic acid.

The related lignan, nordihydroguaiaretic acid (13 ; R=H) i.e. 3, 4 : 3', 4' - tetrahydroxy lignan, which is nowadays of practical importance as an antioxidant, had been prepared[4] from dihydroguaiaretic acid dimethyl ether many years before it was encountered as a natural product[8]. A successful synthesis of this lignan was devised by Liebermann[9] who dimerised the Grignard reagent from isosafrole hydrogen bromide to furnish piperolignan (11) which was then converted into the carbonyldioxy compound (12) by treatment with phosphorus pentoxide and sodium carbonate solution. Acid hydrolysis of this material then afforded the synthetic lignan nordihydroguaiaretic acid.

Group Two : 2,3 - Dibenzylbutyrolactone derivatives.

The structure (17) i.e. 3,4 : 3', 4' - bis - methylenedioxy lignan - lactone (9,9') was assigned by Keimatsu[10] to hinokinin, a typical member of this group, on the basis of analytical data and reactions which were in agreement with the presence of one lactone function and two methylenedioxy phenyl groups per twenty carbon atoms. Keimatsu[11] confirmed this postulated structure by a successful synthesis of hinokinin which utilised a reaction scheme of general application in this field. Catalytic reduction of dipiperonylidenesuccinic acid (14) gave the dicarboxylic acid (15) which was then converted via the corresponding anhydride (16) into the desired lactone by treatment with aluminium amalgam.

Group Three : Tetrahydrofuran derivatives

An example of this group is the lignan galbacin (18) i.e. 7, 7' - epoxy - piperolignan which was shown by Hughes and Ritchie[12] to be a 2,5 - diaryltetrahydrofuran from analytical and spectroscopic data and from oxidative degradations with nitric acid which yielded a dinitroderivative as well as 4,5 - dinitro-methylenedioxybenzene. These authors found that isomerisation of galbacin to the phenylnaphthalene (19) did not occur readily and in fact required treatment first with perchloric acid and then with palladium-charcoal to effect this aromatisation.

The corresponding lignan galgravin (20) i.e. 3,4 : 3', 4' - tetramethoxy - 7, 7' - epoxy - lignan on the other hand readily gave dehydroguaiaretic acid dimethyl ether (6) simply on treatment with palladium - charcoal. Nitric acid treatment likewise gave a dinitroderivative and 4, 5 - dinitroveratrole. The relationship of these two lignans was finally demonstrated by the conversion of galbacin into an optically active form of galgravin by cleavage of the methylenedioxy groups of the former with sodium methoxide in methanol at 180° followed by methylation.

Group Four : Tetrahydrofurofuran derivatives

A typical member of this series, pinoresinol i.e. 4, 4' - dihydroxy - 3, 3' - dimethoxy - (7.9') (9.7') - bis - epoxy - lignan was shown to have the structure (22) by Erdtman[13]. Oxidation with nitric acid gave known veratrole derivatives in addition to bis (hydroxymethyl) succinic acid lactone. Racemic pinoresinol was synthesised by Freudenberg[14] in the following manner. Ferric chloride catalysed dimerisation of ferulic acid followed by reduction with lithium aluminium hydride gave the butanediol (21) which, when subjected to high vacuum distillation, dehydrated to form the desired lignan.

Group Five : 4 - Aryltetrahydronaphthalene derivatives

The chemistry of two members of this lignan group namely podophyllotoxin (23) i.e. 3, 4, 5 - trimethoxy - 3', 4' - methylenedioxy - 7' - hydroxy - cyclolignan - lactone (9, 9') and its

stereoisomer picropodophyllin (24) has been extensively investigated. Gensler[15,16] carried through a total synthesis of picropodophyllin and more recently[17] he has reported the interconversion of picropodophyllin to podophyllotoxin whose derivatives are of interest in connection with cancer chemotherapy.

Hughes and Ritchie[12] have investigated two further members of this group, the closely related lignans galbulin (27) i.e. 3,4 : 3', 4' - tetramethoxy - cyclolignan and galcatin (28) i.e. 3,4 - methylenedioxy - 3', 4' - dimethoxy - cyclolignan, and have shown that they are 4 - aryltetrahydronaphthalene - 2, 3 - dimethyl derivatives.

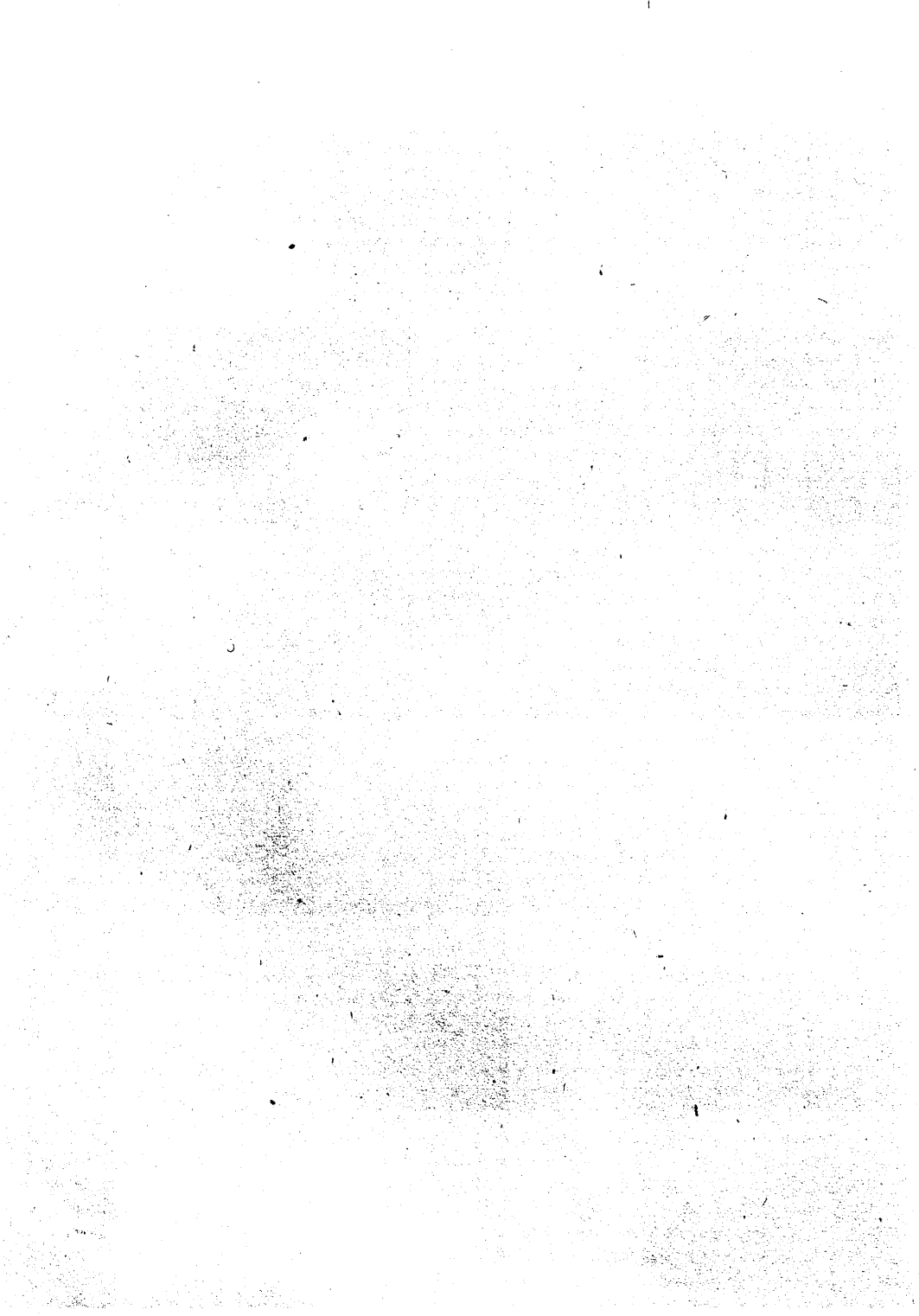
The structure of galbulin was determined from the analytical and spectroscopic data and the dehydrogenation over palladium - charcoal which gave the known phenylnaphthalene dehydroguaiaretic acid dimethyl ether (6). Potassium dichromate oxidation afforded 2 - veratroylveratric acid but no crystalline derivatives were obtained from nitric acid oxidations, a result which is characteristic of phenyltetralin lignans. Two independent syntheses of galbulin have been reported[18,19] from ∝- conidendrin dimethyl ether (25). Lithium aluminium hydride reduction afforded the diol (26 ; R=H) which was converted into the corresponding bistosylate (26 ; R=tosyl), and again reduced with lithium aluminium hydride to give the desired galbulin.

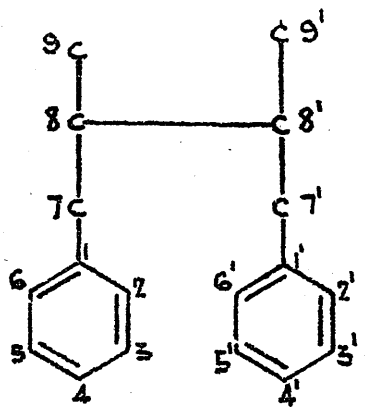
Galcatin has different substituents on the benzene rings and the position of the four oxygen atoms was demonstrated by dehydrogenation over palladium - charcoal to the corresponding naphthalene. An additional product was a phenol, formed by the rupture of the methylenedioxy ring, which on methylation gave dehydroguaiaretic acid dimethyl ether. The position of the methylenedioxy group was finally clarified by reductive opening of the methylenedioxy ring with sodium in liquid ammonia and potassium permanganate oxidation of the resulting phenol which gave veratric acid.

Schizandrin (29) is a lignan of unusual structure which does not fit into any of the above groups. The structure was proposed by Kochetkov[20] on the basis of spectroscopic data coupled with the isolation of a known oxidation product (30).

The biogenetic formation of the lignan skeleton probably occurs by the oxidative fusion of two n- propenylbenzene units through the β - carbon atoms of the side chains. The known oxidation of phenols by one-electron transfer oxidising agents to give peroxides, diphenyl ethers, 2, 2' or 4, 4' - dihydroxydiphenyls has been recognised as an important step in the biogenesis of diverse types of natural product[21]. The oxidation process involves a radical coupling reaction and, since the β - carbon atom in the side chain of a p- hydroxy - propenylbenzene can acquire this character through the extended conjugation, an analogous coupling can be expected.

One possible biological pathway (see Biosynthetic Scheme) involves the reduction of the carboxyl function and the deamination of 3, 4 - dihydroxy - phenylalanine to give the precursor (B.1). A one-electron oxidation followed by dimerisation of the radical (B.2) affords the intermediate (B.3) which has the general structure and oxygen pattern of the lignans.





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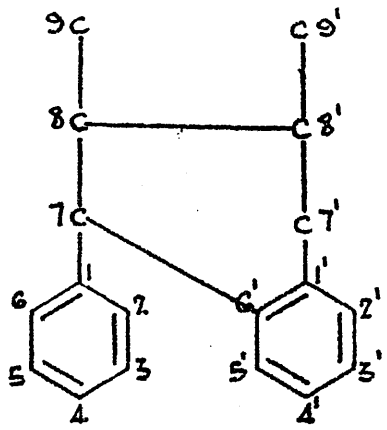

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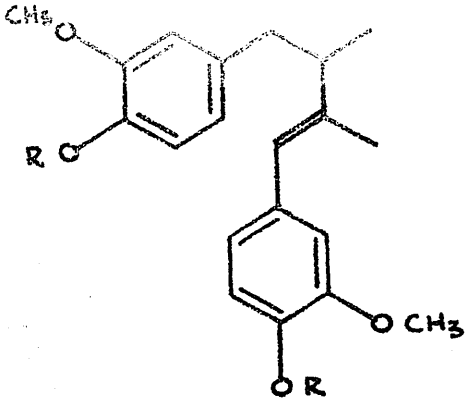
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R O
O CH3
O R

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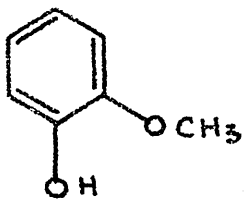
O CH3
O H

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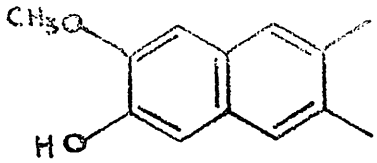
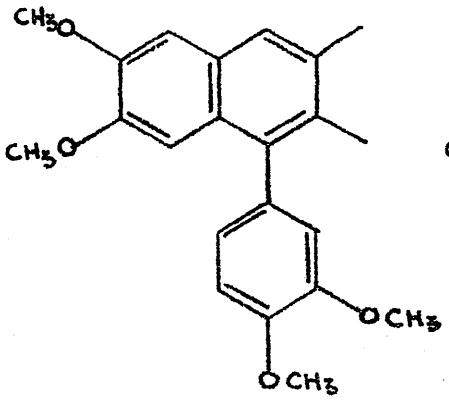

CH3O
H O

(5)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CH3O
O CH3
O CH3

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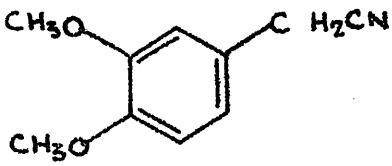
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C H2CN
CH3O

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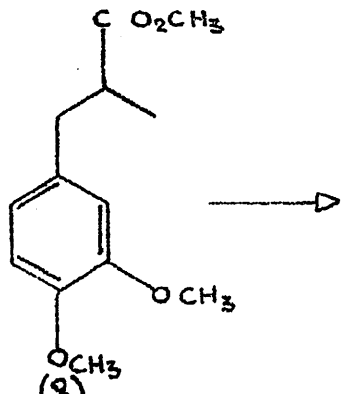
C O2CH3
O CH3
O CH3

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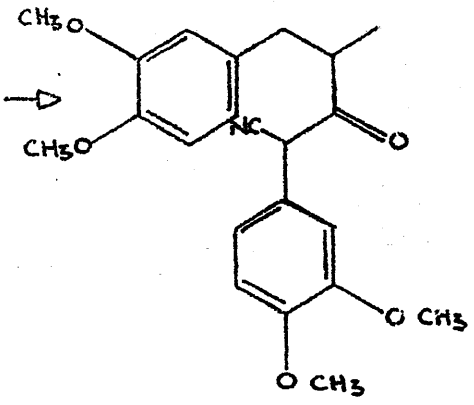
CH3O
CH3O
NC
O
O CH3
O CH3

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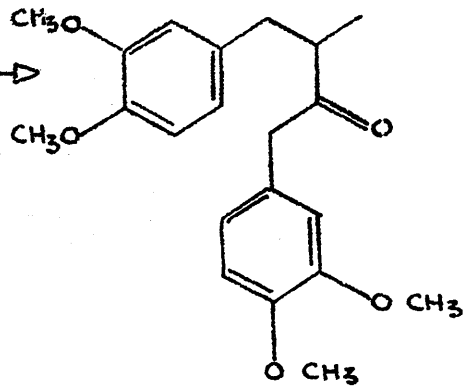
CH3O
CH3O
O
O CH3
O CH3

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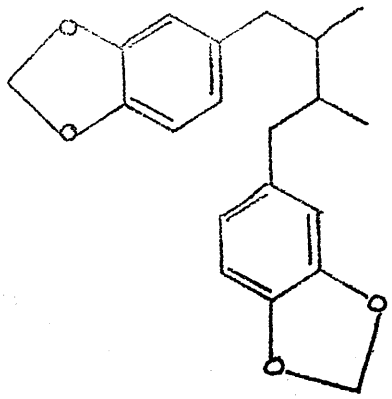

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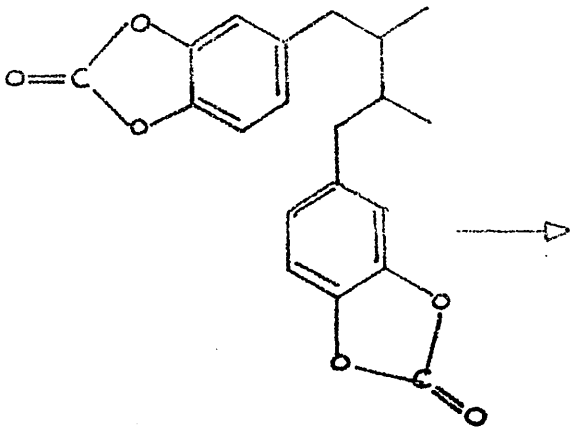

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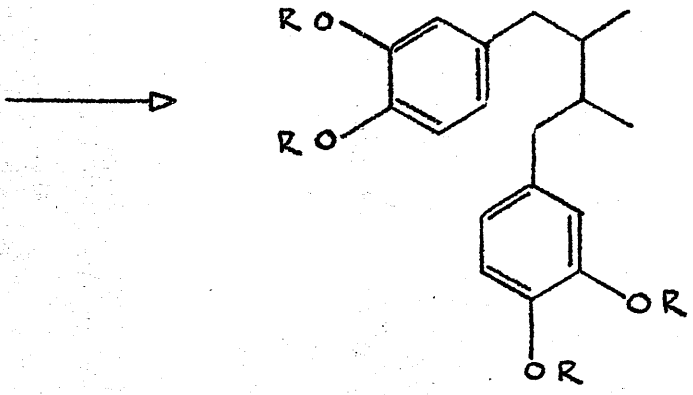

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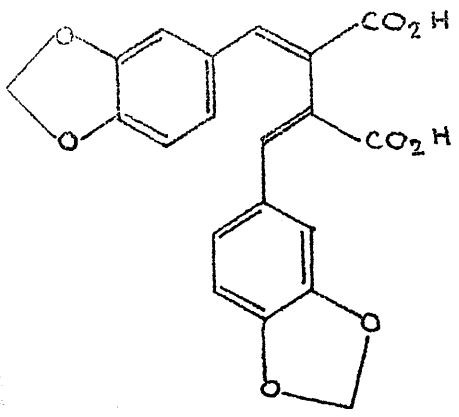

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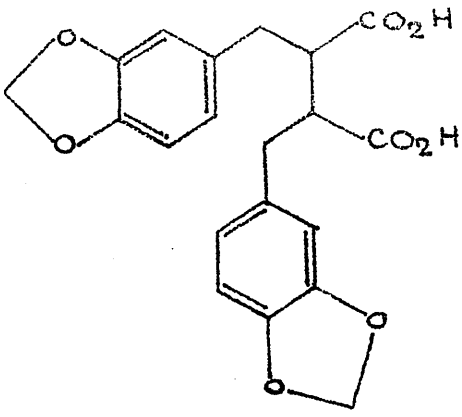

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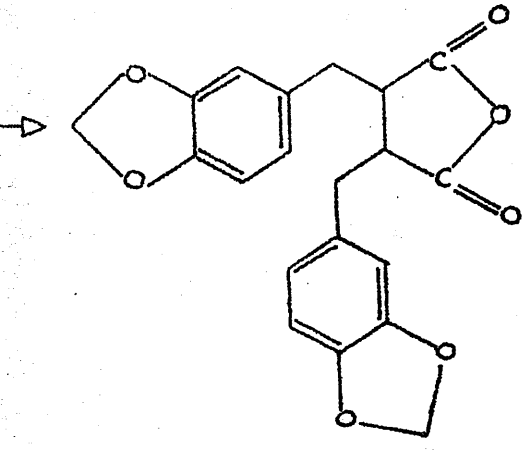

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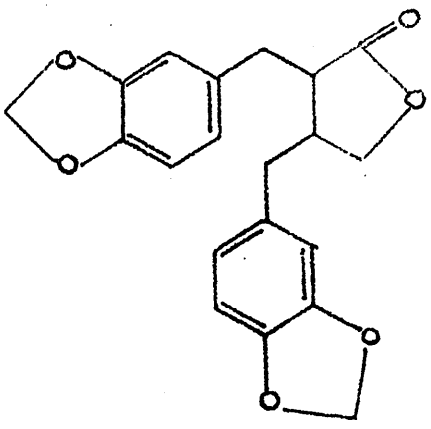

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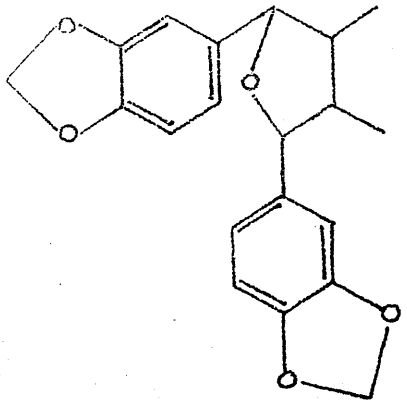

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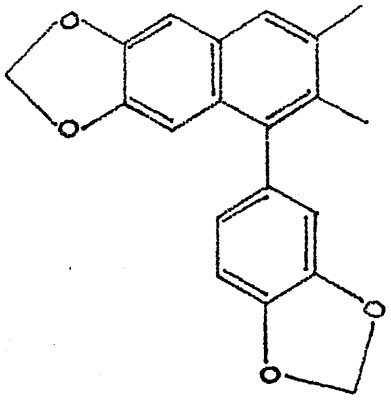

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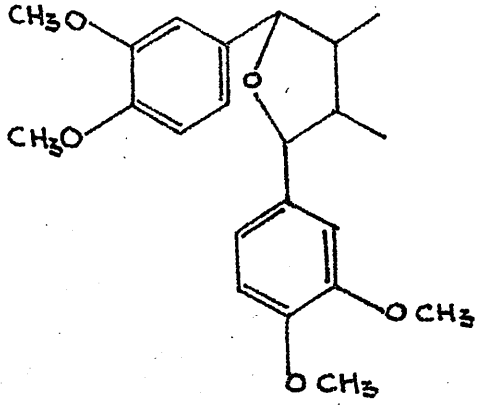

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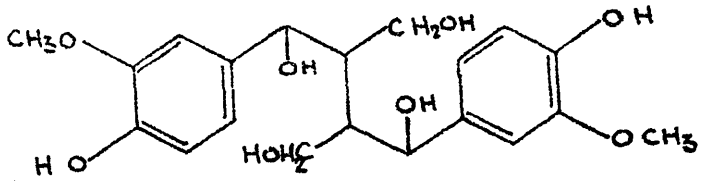

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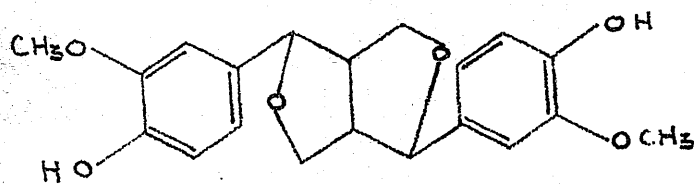

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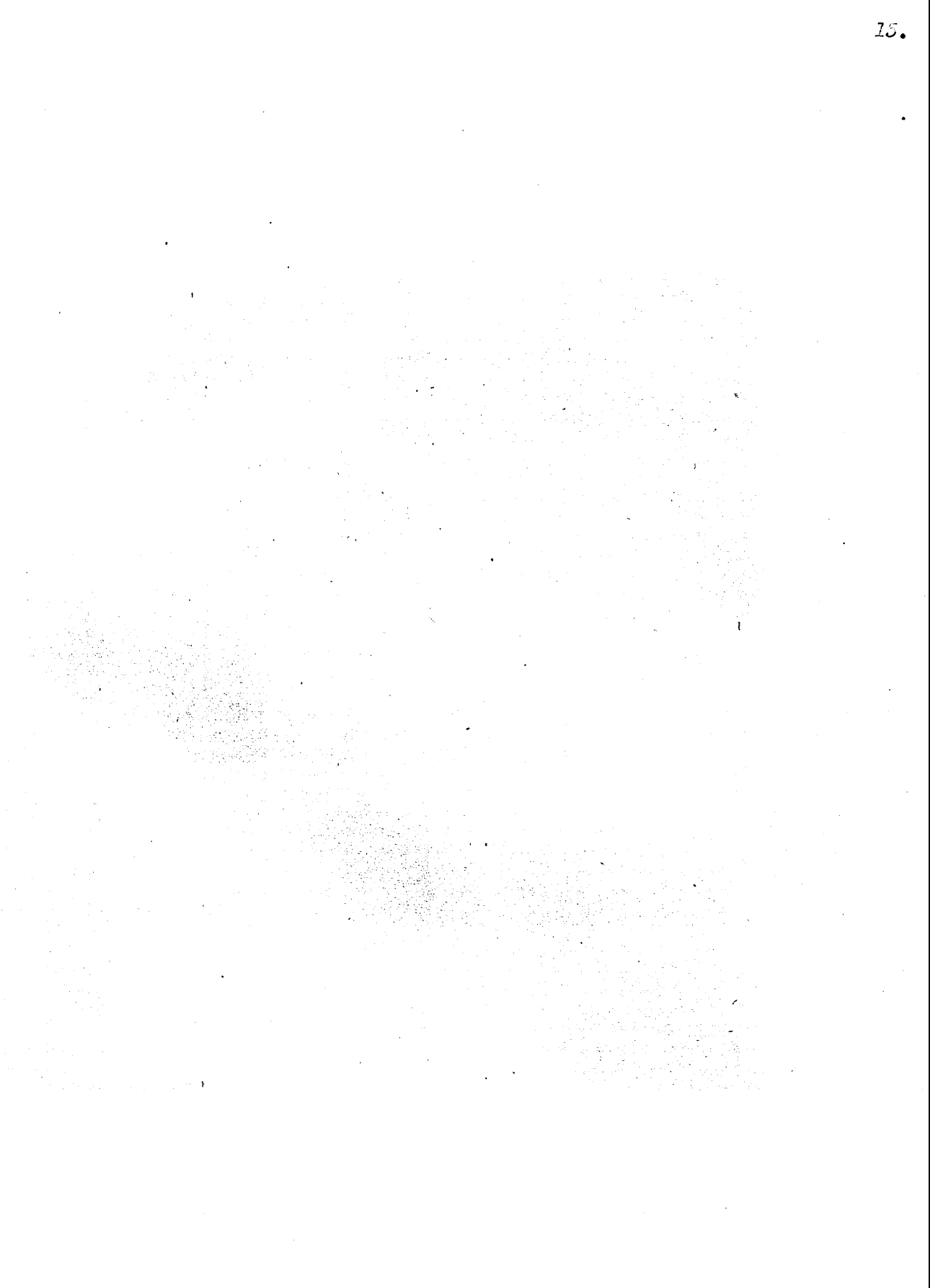

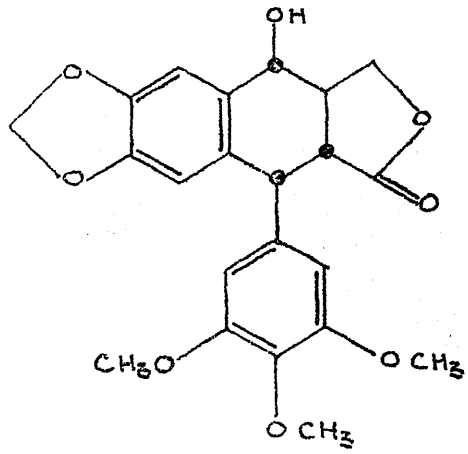

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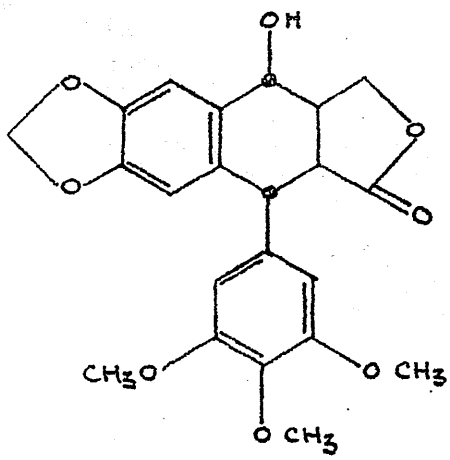

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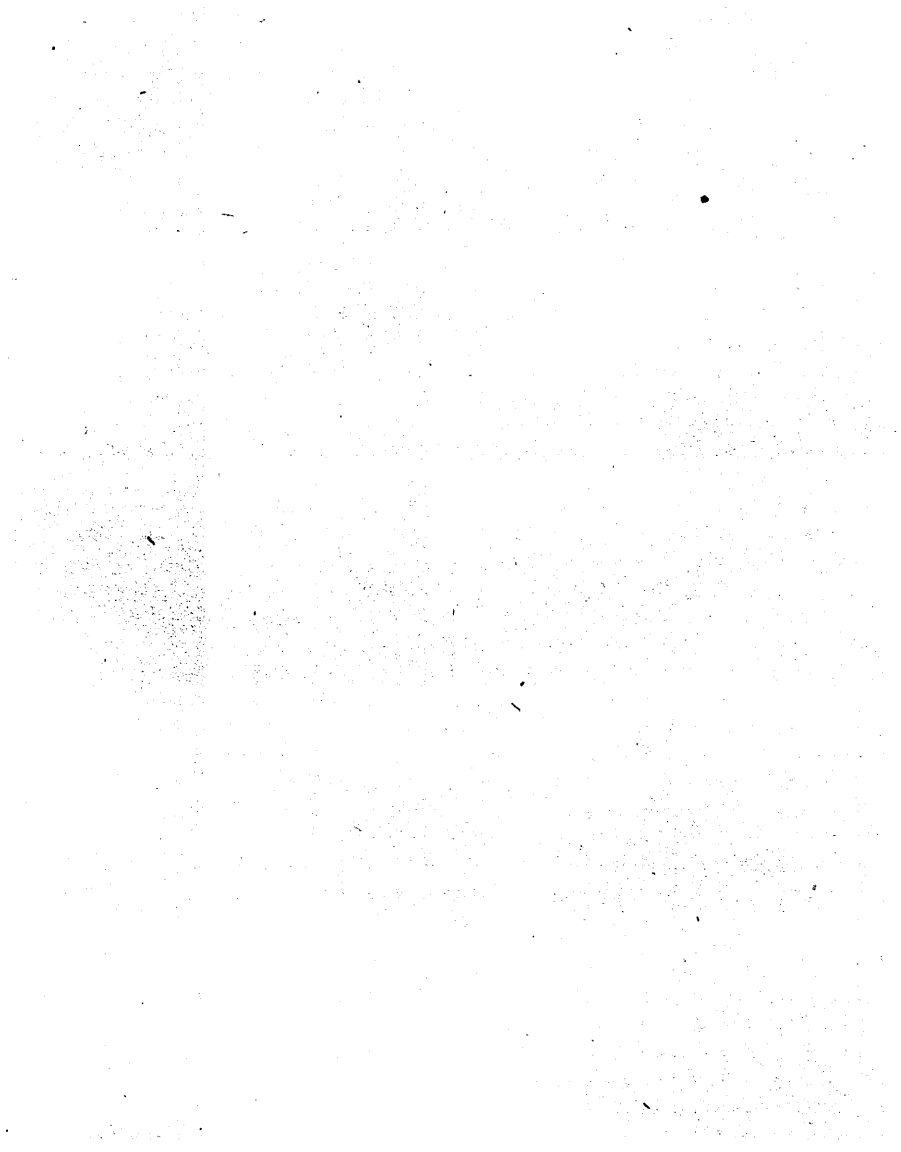

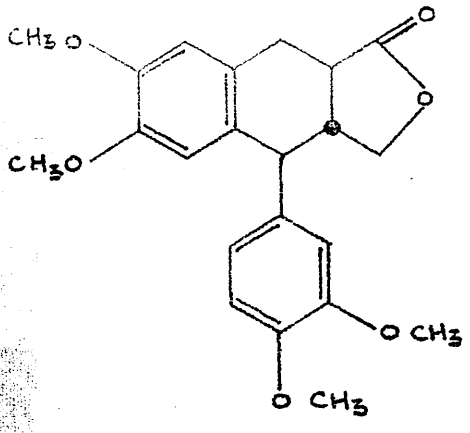

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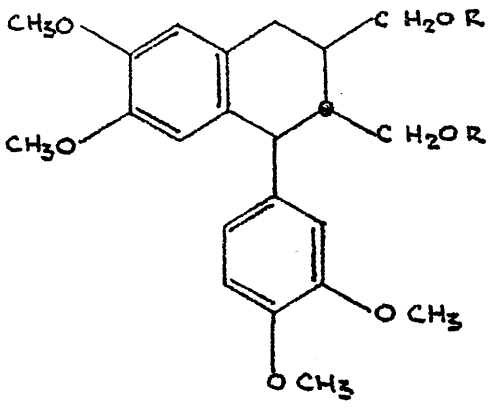

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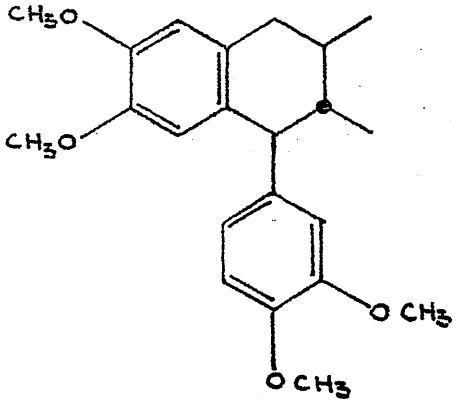

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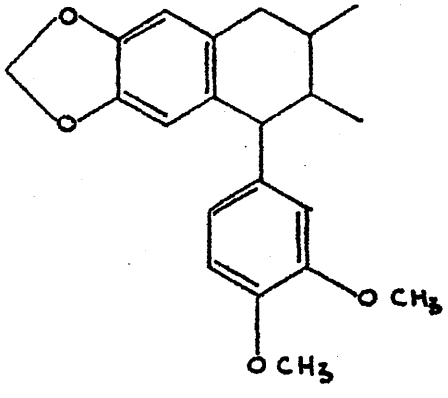

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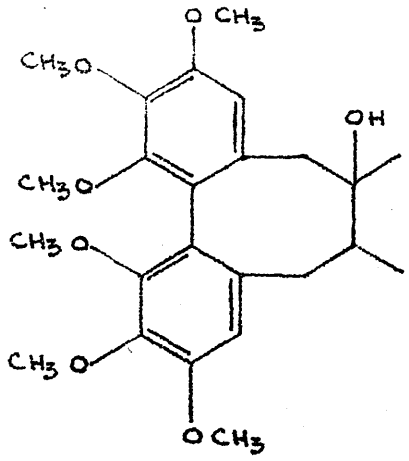

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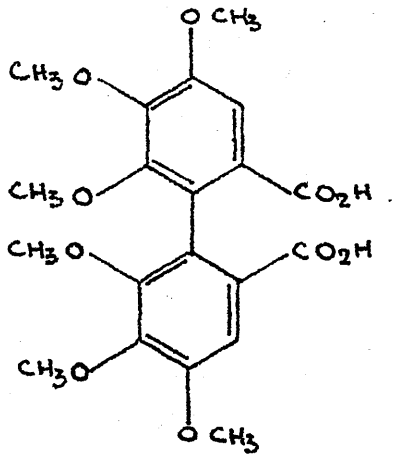

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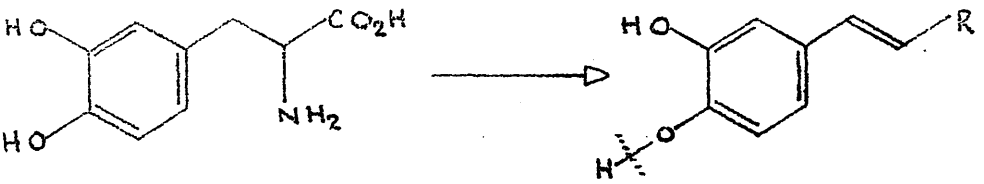
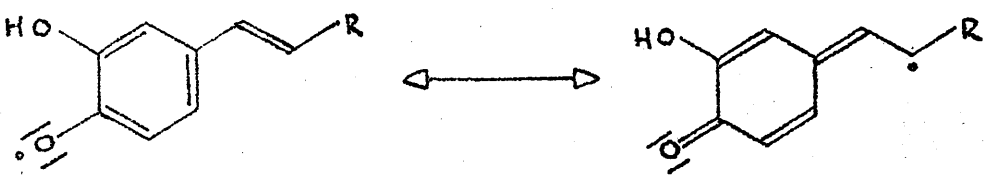
Biosynthetic Scheme

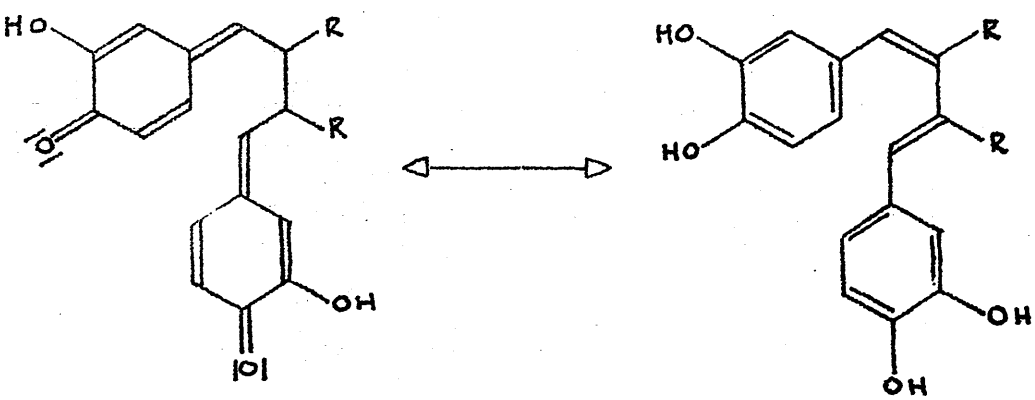


(B.1)

R = CH_2OH, CHO, CH_3



(B.2)



(B.3)

DISCUSSION

Part One: The Structure of Otobain

The expressed oil from the fruits of Myristica otoba was examined by Baughman[21] who showed that it contained two crystalline compounds, otobite and iso-otobite, to which he gave the formula $C_{19}H_{17}O_3 \cdot OCH_3$ and $C_{20}H_{20}O_4$. No structural determination on these compounds has been reported. For this reinvestigation, otoba fat was hydrolysed with ethanolic potassium hydroxide and the neutral water-insoluble products were chromatographed on alumina. The less polar fractions yielded otobite which has been renamed otobain to conform with accepted lignan nomenclature. From the more polar fractions a hydroxyotobain ($C_{20}H_{20}O_5$) and a mixture of isomeric phenols ($C_{19}H_{19}O_3 \cdot OCH_3$) was isolated.

Otobain did not contain a hydroxyl, carboxyl, or methoxyl group and was recovered unchanged after fusion with potassium hydroxide, distillation with zinc dust, or prolonged heating with methanolic hydrogen chloride. It had ultraviolet absorption ($\lambda_{max.}$ (in EtOH) 234, 286 mμ ; ε 9800, 7100) similar to that of galbulin[12], so it was assumed, as a working hypothesis, that the four oxygen atoms in the otobain molecule were present as two methylenedioxy-groups.

Hydroxyotobain did not react with chromic acid in acetone or acetic anhydride and pyridine at room temperature. Heating it with acetic anhydride and sodium acetate, or treating it with

aqueous toluene-*p*-sulphonic acid gave didehydro-otobain which had an ultraviolet spectrum ($\lambda_{max.}$ (in EtOH) 216, 231, 274, 283 ; ε 23,900, 23,600, 13,000, 11,800) suggestive of the partial structure (31). Hydrogenation of dehydro-otobain furnished a mixture from which otobain could be isolated. Dehydrogenation by dichlorodicyanobenzoquinone produced the same tetradehydro-otobain as was obtained by reaction of otobain with palladium-charcoal. Hence, hydroxyotobain must contain the same basic skeleton as otobain with the addition of a tertiary hydroxyl group situated either α or β to an aromatic ring.

No pure products were isolated on oxidation of otobain or dehydro-otobain with chromic acid, nitric acid, or potassium permanganate under a variety of conditions. A similar inability to obtain pure degradation products has been described during the oxidation of galcatin,[12] a compound containing a methylenedioxy-group. To surmount this difficulty, otobain was hydrogenolysed by

reaction with sodium in liquid ammonia.[22] Two isomeric phenols, A and B ($C_{19}H_{20}O_3$), were produced, which, it was hoped, would be more susceptible to oxidation. However, again no aromatic carboxylic acids could be isolated. On the other hand, oxidation of their methyl ethers gave p- and m-methoxy-benzoic acid, respectively. Hence, otobain must contain the partial structure (32) which has given almost equal proportions of the two possible hydrogenolysis products. Similar oxidation of tetradehydro-otobain furnished benzenepentacarboxylic acid, isolated as its pentamethyl ester.

In view of the close botanical relationship of the Myristicaceae to the Himantandraceae family from which galcatin was isolated, it seemed reasonable to postulate structure (33) for otobain. To confirm this, dipiperonylidenesuccinic anhydride[23] was dehydrogenated, yielding an anhydride (34) which was isolated as the derived dimethyl ester (35; R=CO_2CH_3) and converted through the diol (35; R=$CH_2 \cdot OH$) into compound (35; R=CH_3).

This compound (35; R=CH_3) was also synthesised using isosafrole as the progenitor. Lieberman[9] had obtained piperolignan by the dimerisation of the Grignard reagent from isosafrole hydrogen bromide and this same Grignard reagent was reacted with piperonyl methyl ketone, which had also been derived from isosafrole, to yield 7, 8 - didehydro - piperolignan which was cyclodehydrogenated to compound (35; R=CH_3). This synthetic product was not identical with tetradehydro-otobain. The unlikely possibility that the

cyclisation of dipiperonylidenesuccinic anhydride and of 7, 8 - didehydro - piperolignan had given, not (34), but (36) was ruled out by the analogous cyclodehydrogenation of guaiaretic acid dimethyl ether to dehydroguaiaretic acid dimethyl ether and also by the close similarity of the ultraviolet spectra of compound (35; R=CH_3) and dehydroguaiaretic acid dimethyl ether (see Fig.1). Hughes and Ritchie had obtained this phenylnaphthalene (34) m.p. 168°, as a degradation product of galbacin and recently Stevenson[24] had repeated this work and obtained the compound, m.p. 171-172°.

However the ultraviolet spectrum of tetradehydro-otobain is compatible with a 1-phenylnaphthalene structure and this suggested that it might be represented by structure (37) and that otobain might therefore be represented by structure (38). These structures are substantiated and confirmed by proton magnetic resonance spectroscopic studies of the two compounds.

The high-resolution proton magnetic resonance spectrum of tetradehydro-otobain is shown in Fig. 2. The τ values of the observed peaks and their assignments to functional groups are given in Table 1. These assignments are based on arguments involving the τ values known to be characteristic of these functional groups,[25] on the geometry of the averaged conformation of the molecule, and on the effects of the aromatic ring currents of this averaged conformation on the proton chemical shifts. The assignment of the methylene-dioxy-group of ring A to positions 5 and 6, rather than to positions 7 and 8, or 6 and 7, is based on the fact that two methylenedioxy-

TABLE 1.

Peak	τ	Assignment	Peak	τ	Assignment
1	7.98	3-Me	7	2.95)	
2	7.65	2-Me	8	2.80)	$H_{(7)}$, $H_{(8)}$
3	4.23	CH_2 (on ring A)	9	2.68)	
4	3.95	CH_2 (on ring C)	10	2.55)	
5	3.24)				
6	3.15)	Aromatic protons of ring C	11	2.35	$H_{(1)}$

peaks separated by 0.28 τ unit are observed. Had the methylenedioxy-group on ring A been on either of these last two sets of positions then the chemical shifts of the two methylenedioxy - groups would have been identical and only one peak, of weight equivalent to four protons, would have been observed. Placing the methylenedioxy-group on positions 5 and 6 must restrict the rotation of ring C about the 4,11-bond and by using an appropriate molecular model for an averaged molecular conformation, in which the plane of ring C lies at right angles to that of rings A and B, it is easy to show[26,27] that the proton magnetic resonance absorption peak of the CH_2 on ring A should be about 0.3 τ unit to higher applied fields than that of the CH_2 on ring C. Further, in this conformation, the 3-methyl peak should lie about 0.3 τ unit upfield from that of the 2-methyl peak. The observed separation between the methyl resonances is 0.33 τ unit. The characteristic aromatic peaks, 5-11, of the observed spectrum of tetradehydro-otobain are also accounted for by structure (37) and further substantiate both the structure and the averaged conformation mentioned above. Peaks 7-10 form a typical AB spectrum in which the coupling constant is 8.4 c.p.s. and the chemical shift between the A and B nuclei is 0.22 p.p.m. These can only arise from two protons, ortho to one

another, on an aromatic ring as on positions 7 and 8 of ring A. Peaks 5 and 6 are consistent with the spectrum expected from 2^1 -, 5^1 -, and 6^1-protons, and the τ value of peak 11 is that expected from $H_{(1)}$. The proton magnetic resonance spectrum obtained from tetradehydro-otobain is completely accounted for by formula (37).

The above reasoning is confirmed and formula (38) substantiated by the high-resolution proton magnetic resonance spectrum of otobain. This is shown in Fig. 3 and the τ values of the observed peaks and their assignments to functional groups are listed in Table 2. In the otobain spectrum the resonance absorption peaks of the methyl groups have moved upfield to positions whose τ values are characteristic of alicyclic methyl groups. Peaks characteristic of a benzylic CH_2 group and of a doubly benzylic CH group are present in the otobain spectrum. Hence in otobain ring B is reduced.

TABLE 2.

Peak	τ	Assignment	Peak	τ	Assignment
1	3.30	$H_{(7)}$ $H_{(8)}$	8	6.53	$H_{(4)}$
2	3.38	$H_{(2')}$, $H_{(5')}$, $H_{(6')}$	9	6.69	$H_{(4)}$
3	4.12	CH_2 (on ring C)	10	7.44	CH_2 (1)
4	4.32	CH_2 (on ring A)	11	7.54	CH_2 (1)
5	4.34	CH_2 (on ring A)	Unresolved peaks from 8.6-9.0		$H_{(2)}$, $H_{(3)}$
6	4.41	CH_2 (on ring A)	12	9.16	$2\text{-}CH_3$, $3\text{-}CH_3$
7	4.43	CH_2 (on ring A)	13	9.23	$2\text{-}CH_3$, $3\text{-}CH_3$

Both the configuration and the conformation of ring B in otobain are unambiguously defined by the proton magnetic resonance spectrum

shown in Fig. 3. As is to be expected from formulae (37) and (38), the chemical shift of the CH_2 on ring C is only slightly different in the two compounds. However, that part of the spectrum which arises from the methylenedioxy-protons attached to ring A is markedly different. In otobain, this part of the spectrum is a typical AB spectrum in which the coupling constant is 1.2 c.p.s. and the chemical shift is 0.09 τ unit. This is to be expected from formula (38) provided that the conformation of ring B is the pseudo-chair form (39) and that in this conformation the phenyl group is equatorial. It is only in this conformation that ring C is sufficiently close to the CH_2 on ring A to account for the observed chemical shift of 0.25 τ unit between the two methylenedioxy-groups and at the same time be such that the protons of the CH_2 group on ring A are not symmetrically placed with respect to the π electron current of ring C; i.e. in this conformation these protons constitute an AB system in otobain in contrast to the A_2 system in tetradehydro-otobain. The coupling constant of 1.2 c.p.s. within this AB system is about ten times as small as that usually observed within alicyclic CH_2 groups,[28] but is similar to that which has been reported for other methylene dioxy-systems.[29] The unusually small CH_2 coupling constant is due to the distortion, by the oxygen atoms, of the electron density within the CH_2 group so that the overlap of the σ-electron densities in the neighbourhood of the hydrogen atoms on which the proton-

proton coupling depends, is much reduced in this case.

An unambiguous assignment of the relative configurations of the substituents on ring B of otobain now follows from a comparison of the coupling constants $J_{3,4}$, $J_{2,1\alpha}$, and $J_{2,1\beta}$ observed in Fig. 3 with the corresponding values predicted by Karplus's equation.[30] The appropriate data are given in Table 3. The predicted coupling constants are those to be expected when ring B

TABLE 3.

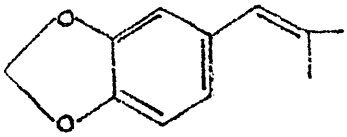
	Observed coupling constants (c.p.s.)	Coupling constants expected from (39)(cps)
$J_{3,4}$	9.6	~ 9
$J_{2,1\alpha}$	6.0	~ 7
$J_{2,1\beta}$	6.0	~ 7

is in the pseudo-chair form (39) with the phenyl and the two methyl substituents all equatorial and transtrans to one another. Only this conformation and configuration are consistent with the proton magnetic resonance data.

Ring B is not quite rigid: this is indicated by the observation that peaks 8-13 in Fig. 3 are broadened in comparison to the very sharp peaks 1-7, but it does not change readily into any other conformation.

The phenolic mixture from otoba fat could not be separated by recrystallisation, further chromatography, or by counter-current distribution between light petroleum and methanol. However,

methylation gave only one product, $C_{19}H_{18}O_2(OCH_3)_2$, which had ultraviolet absorption ($\lambda_{max.}$ (in EtOH) 235, 286 mμ; ε 12,400, 8100) similar to that of otobain. Because of the limited amount of this ether, no attempt has yet been made to establish its relation to otobain. The physical constants (m.p.106-108°, $(\alpha)_D$+5°) suggest that it may be iso-otobite (m.p. 106-108°, $(\alpha)_D$ +5.3°) despite the reported lack of a methoxyl group in this compound.



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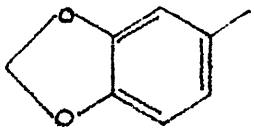

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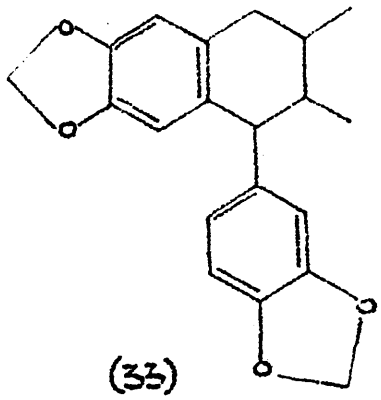

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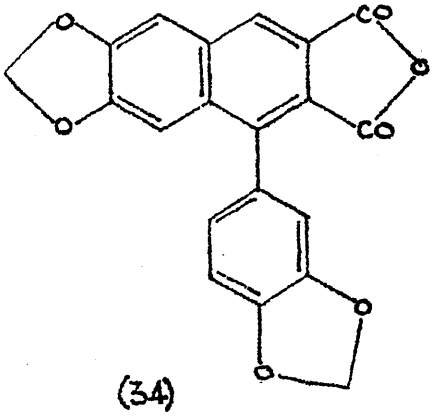

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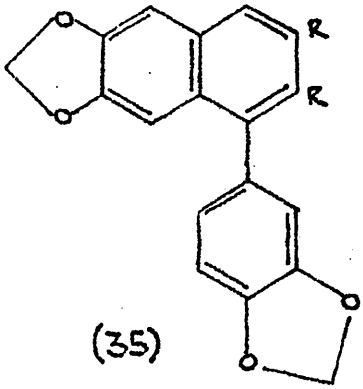

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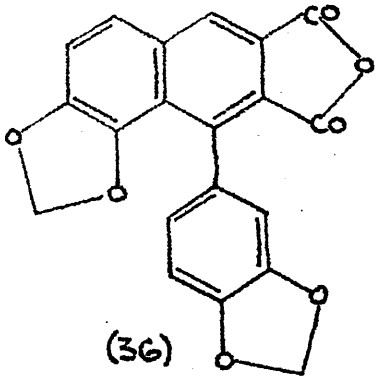

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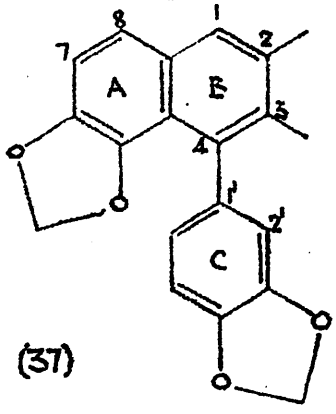

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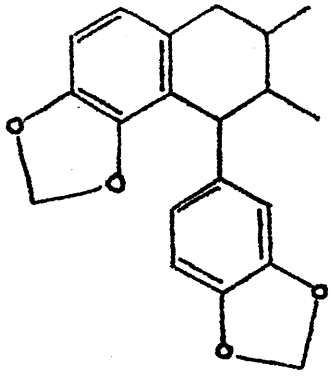

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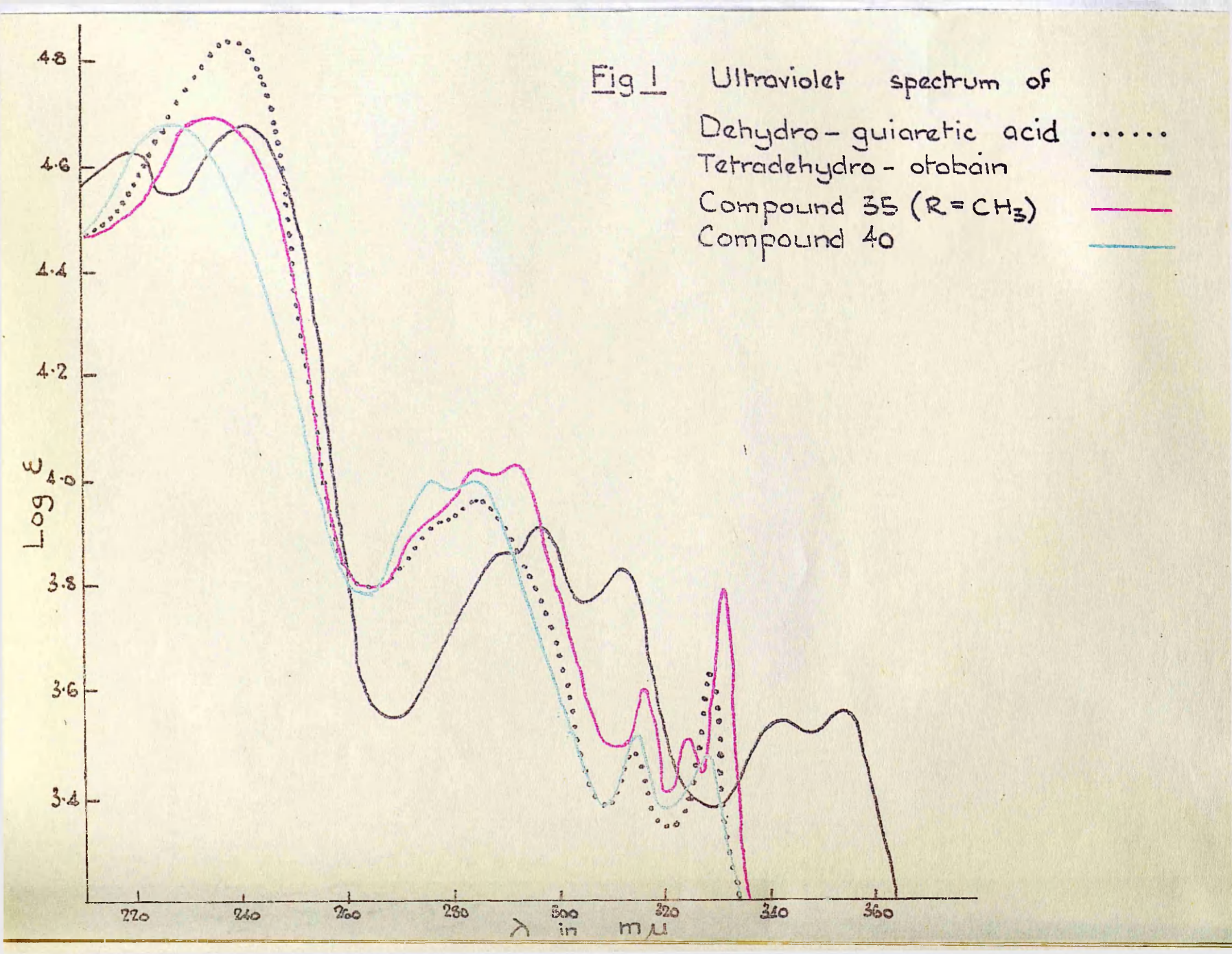
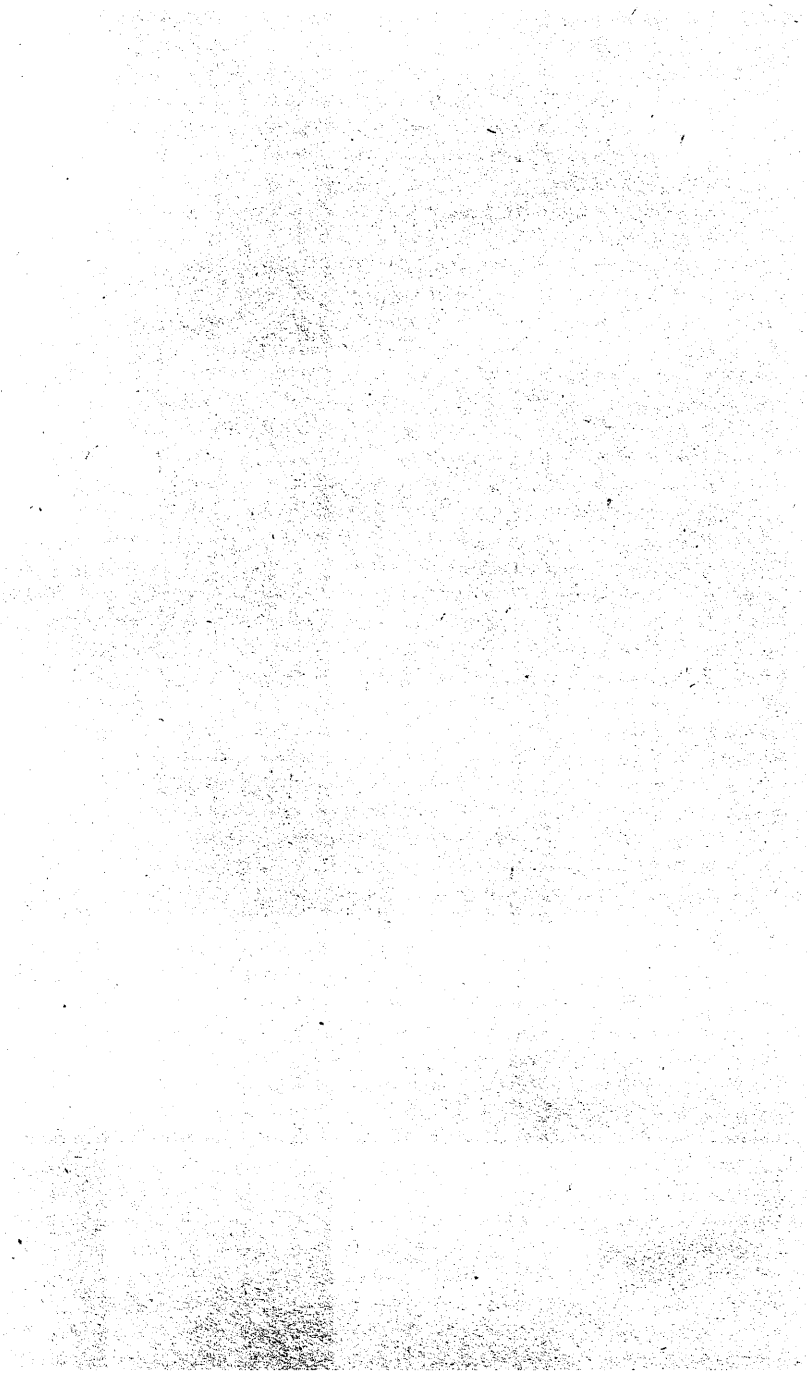


Fig 1 Ultraviolet spectrum of
Dehydro-guiaretic acid .....
Tetradehydro-otobain
Compound 35 (R = CH3)
Compound 40
Log ε
4·8
4·6
4·4
4·2
4·0
3·8
3·6
3·4
220
240
260
280
300
320
340
360
λ in mμ



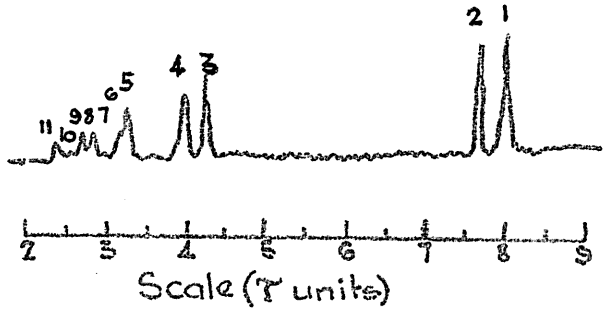


Fig. 2

Proton magnetic resonance spectrum of tetradehydro - otobain

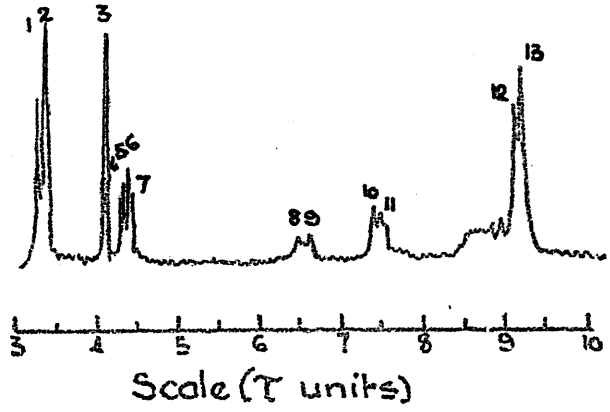
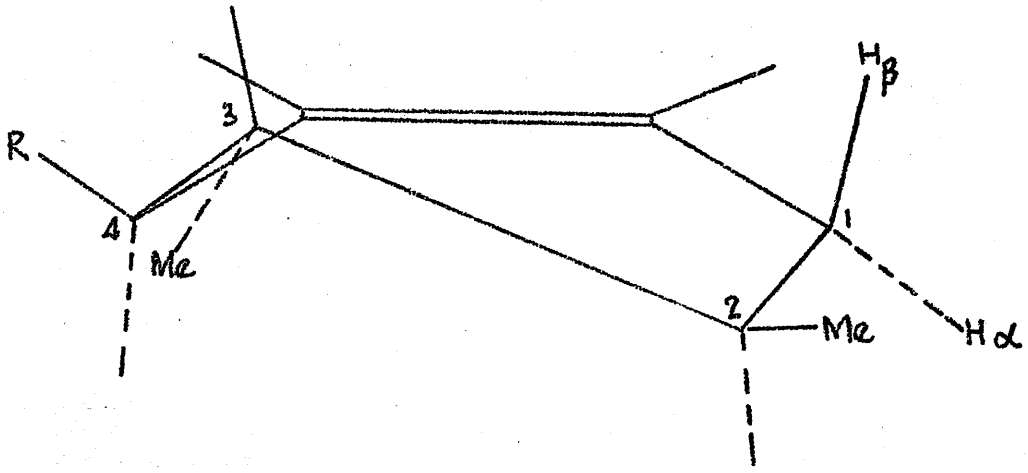


Fig. 3

Proton magnetic resonance spectrum of otobain



(39)

PART TWO

Synthetic Approaches to 1-Phenylnaphthalenes related to Otobain

In the course of the structural investigation of otobain (38), an aromatic hydrocarbon was isolated as a dehydrogenation product. This compound, which proved to be of crucial importance in determining the constitution of otobain, was later shown (see Part One) to be 3, 4, : 4^1, 5^1 - bis - methylenedioxy - 7,8 : 7^1, 8^1 - tetradehydro-cyclolignan (37) from examination of its proton magnetic resonance spectrum.

At the onset of this synthetic work however, three possible structures (35), (37) and (40), were considered for this substituted 1-phenylnaphthalene. It was decided to attempt to prepare authentic samples of each of these compounds for comparison with the otobain derivative.

Synthesis of 7,8 : 7^1, 8^1 - tetradehydro-pipero-cyclolignan (35)

As briefly indicated in Part One, this compound was prepared by two alternative pathways.

1) Piperonal was condensed in a Stobbe condensation[23] with diethyl succinate which gave after hydrolysis the dicarboxylic acid (41). The corresponding anhydride (42) was cyclodehydrogenated with palladium-charcoal in diphenyl ether and then subjected to basic hydrolysis followed by esterification with diazomethane to give

dimethyl - 7,8 : 7^1, 8^1 - tetradehydro - pipero - cyclolignan - 8, 8' - dicarboxylate (43). Lithium aluminium hydride reduction of (43) gave the corresponding diol which was then hydrogenolysed over palladium-charcoal in ethyl acetate to give authentic 7,8 : 7^1, 8^1 - tetradehydro - pipero - cyclolignan (35). This hydrocarbon had previously been obtained from galbacin.[12,24] As mentioned in Part One, this product was not identical with tetradehydro-otobain.

ii) Isosafrole (44) was converted[32] into piperonyl methyl ketone (46) via the epoxide (45). This ketone was then treated with the Grignard reagent from isosafrole hydrogen bromide[9] (47) to give directly 7,8 - didehydro-piperolignan (48). Cyclodehydrogenation over palladium-charcoal then gave the desired 1-phenylnaphthalene (35) identical in all respects with the sample obtained as above.

Synthesis of 3,4 : 2^1,3^1 - bis-Methylenedioxy-7,8 : 7^1,8^1 - tetradehydro-cyclolignan (40).

The synthetic route to this hydrocarbon envisaged the condensation of the Grignard reagent from 3,4 - methylenedioxy - 1 - bromobenzene (49) with 2,3 - dimethyl - 5,6 - methylenedioxy - α - tetralone (50). Dehydration (of the resultant tertiary alcohol) would then afford the dihydronaphthalene (51) which on dehydrogenation would furnish the required 1 - phenylnaphthalene. 3,4 - Methylenedioxy - 1 - bromobenzene was prepared from piperonal by two pathways.

i) Piperonylic acid nitrile (52) was prepared[33] from piperonal by treatment of the corresponding oxime with acetic anhydride. Treatment of (52) with alkaline hydrogen peroxide readily afforded the amide (53) which was converted into 3,4 - methylenedioxyaniline (54) by standard Hofmann reaction conditions.[34] The diazonium bromide from this amine (54) was then treated[35] with sodium hypophosphite and copper sulphate solution to give 3,4 - methylenedioxy-1-bromobenzene (49).

ii) A better method of preparing the required bromocompound (49) involved the conversion of piperonylic acid (55) into 3,4 - Methylenedioxy - 1,2 - dibromobenzene (56) by treatment of a solution of this acid in sodium carbonate with bromine.[36] The dibromo - compound (56) on catalytic hydrogenolysis furnished methylenedioxy benzene (57) which was then treated with bromine in glacial acetic acid to give 3,4 - methylenedioxy - 1 - bromobenzene (49).

Having successfully prepared one of the reactants for this synthesis we now turned our attention to the synthesis of the tetralone (50). o-Piperonylic acid i.e. 2,3 - methylenedioxy benzoic acid (58) was converted into 2,3 - methylenedioxy benzyl bromide (60) by treatment of the corresponding alcohol (59) with aqueous hydrogen bromide. This compound was then added to a suspension of the sodium salt of methyl diethyl malonate in benzene. The crude reaction product was subjected to basic hydrolysis followed by thermal decarboxylation to give 2',3' - methylenedioxy - 2 -

benzyl propionic acid (61). This acid was treated with oxalyl chloride and the crude product reacted directly with diazoethane. A mixture of the resultant diazoketone (62) in benzyl alcohol and γ - collidine[37] was heated to give crude benzyl ester which hydrolysed with base to yield $2^1,3^1$ - methylenedioxy - 3 - benzyl - 2 - methylbutyric acid (63) as a viscous oil. An intramolecular acylation catalysed by stannic chloride[38] was then effected using the acid chloride corresponding to (63) and afforded after chromatography 2,3 - dimethyl - 5,6 - methylenedioxy - α - tetralone (50) as a crystalline solid.

The envisaged synthesis was completed by preparing the Grignard reagent from (49) and refluxing it, with the tetralone (50) in tetrahydrofuran. Isolation of the product by chromatography gave a solid whose analytical figures were intermediate between those required for the alcohol (64) and the olefin (51). This material (25 mg.) was dehydrogenated over palladium-charcoal and the product isolated via chromatography to give the required 3,4 : $2^1,3^1$ - bis - methylenedioxy - 7,8 : $7^1,8^1$ - tetradehydro - cyclolignan (40) as a crystalline solid. The infrared and ultraviolet absorption spectra (see Fig. 1) of this compound (m.p. 138-141°) were similar but not identical with those recorded for tetradehydro-otobain (m.p. 183-185°).

Attempted Syntheses of Tetradehydro-otobain.

Three attempts were made to synthesise

3,4 : $4^1,5^1$ - bis - methylenedioxy - 7,8 : $7^1,8^1$ - tetradehydro - cyclolignan (37). Haworth[39] effected the cyclodimerisation of $3^1,4^1$ - dimethoxy phenyl propiolic acid (65) to the anhydride (66) by treatment with acetic anhydride. Accordingly it was thought that dimerisation of 2^1 - bromopiperonyl - propiolic acid (69) would furnish the dibromo-anhydride (70) which on catalytic hydrogenolysis followed by elaboration of the anhydride ring to methyl groupings would yield tetradehydro-otobain. The bromine functions would act in a blocking fashion to preclude cyclisation in an undesirable manner.

Therefore, 6-bromopiperonal[36] (67) was converted[40] into the cinnamic acid (68) which was then converted into the corresponding acetylene (69) by bromination and dehydrobromination. Unfortunately cyclodimerisation of this compound could not be effected under a wide variety of reaction conditions.

An alternative approach to this hydrocarbon using the blocking procedure outlined above, envisaged the preparation of the dicarboxylic acid (71) from a Stobbe condensation between 6-bromopiperonal (67) and diethyl succinate. Cyclodehydrogenation of the anhydride from this acid followed by removal of the bromine atoms and elaboration of the anhydride ring to methyl groups should then have

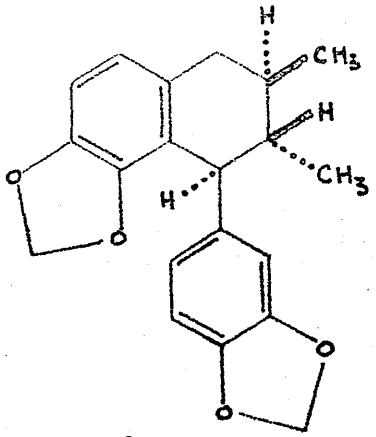
afforded tetradehydro-otobain. Unfortunately it was found that the sole product (72) from such Stobbe condensations was that formed from the condensation of one mole of 6-bromopiperonal with diethyl succinate.

The third attempt to synthesise tetradehydro-otobain followed closely the pathway employed for the synthesis of (40) and envisaged the condensation of the Grignard reagent from 3,4 - methylenedioxy-1-bromobenzene (49) with 2,3 - dimethyl - 7,8 - methylenedioxy - α - tetralone (75).

$3^1,4^1$ - Methylenedioxy —3 - benzyl - 2 - methylbutyric acid (73) was prepared from piperonal by an identical route to that employed for the preparation of $2^1,3^1$ - methylenedioxy -3-benzyl-2-methylbutyric acid (63). Cyclisation of the corresponding acid chloride could have proceeded in two directions to yield the α - tetralone (74) or the desired (75). To overcome this problem, the acid (73) was brominated to give $3^1,4^1$ - methylenedioxy -6^1-bromo-3 - benzyl - 2 - methylbutyric acid (76) whose acid chloride readily cyclised to furnish 2,3 - dimethyl-5-bromo - 7,8 - methylenedioxy - α - tetralone (77), as a crystalline solid.

The bromotetralone (77) was unaffected by treatment with either the Grignard reagent from (49) or the lithium derivative under a variety of conditions. The sole products isolated were the starting materials and methylenedioxy - benzene. This last result coupled

with the successful synthesis of (40) by a similar route seems to imply that the lack of success at this stage is due to the strong buttressing effects of the methylenedioxy and methyl groups flanking the carbonyl in the tetralone.



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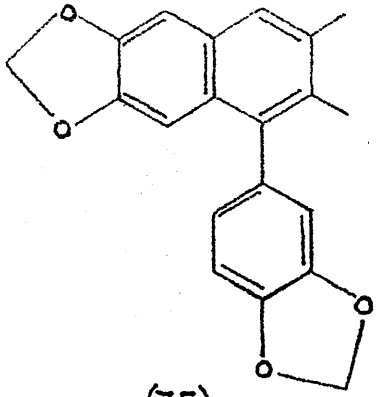

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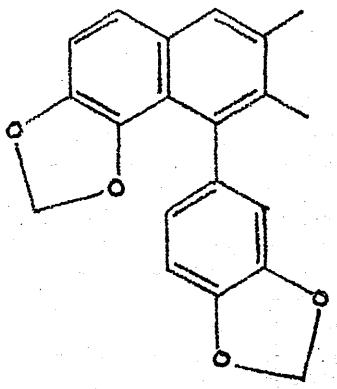

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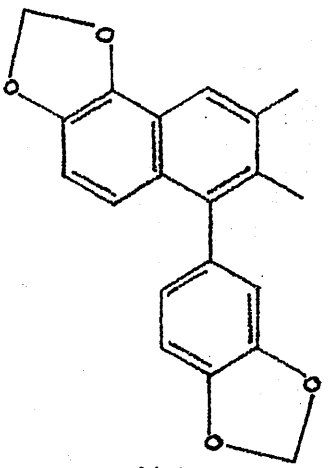

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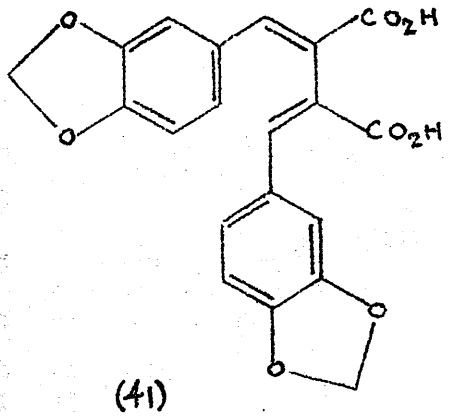

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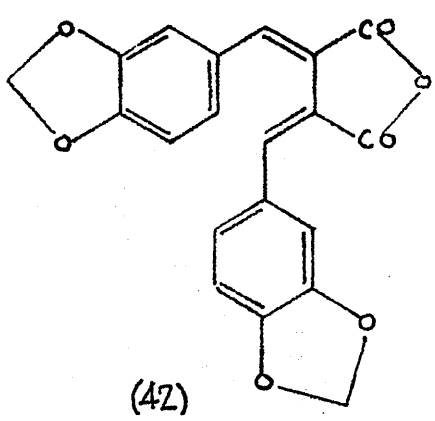

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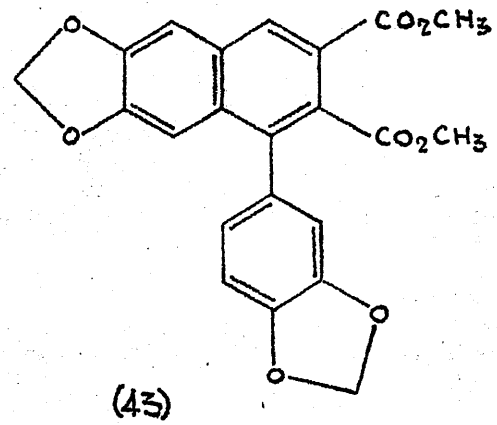

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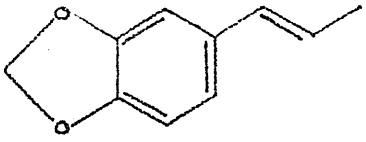

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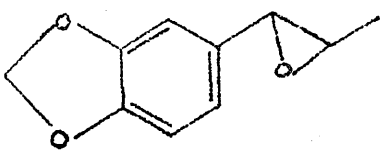

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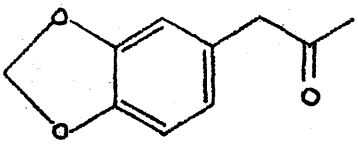

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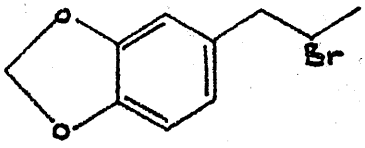

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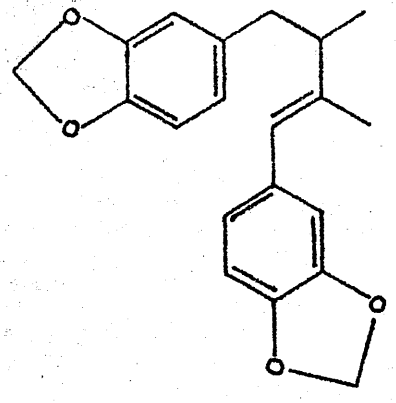

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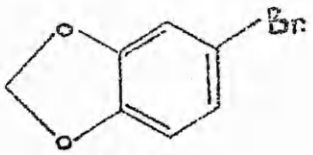

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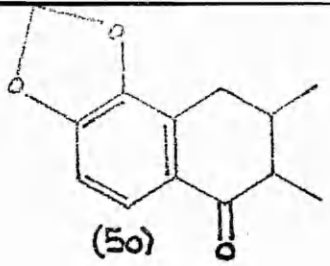

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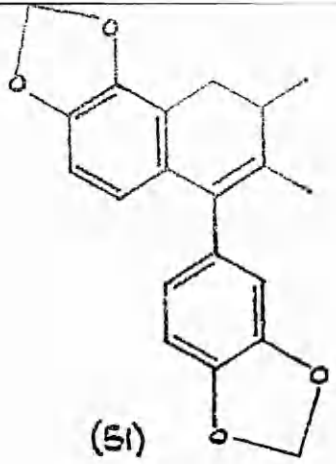

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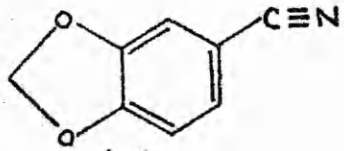

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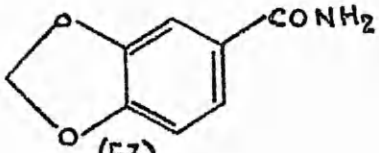

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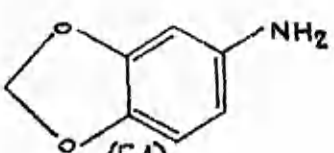

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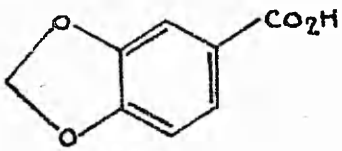

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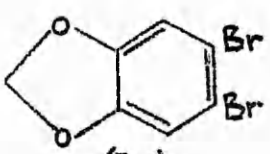

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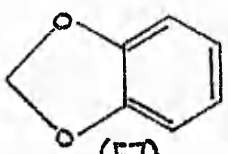

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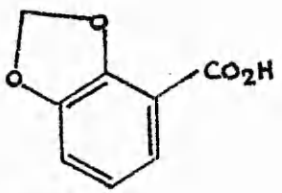

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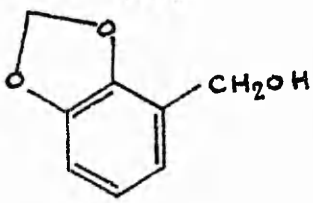

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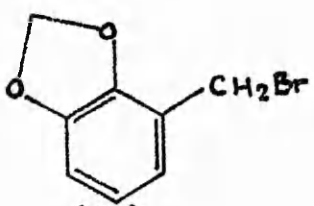

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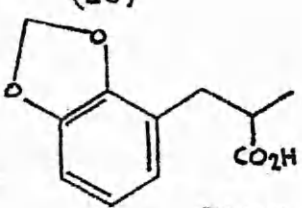

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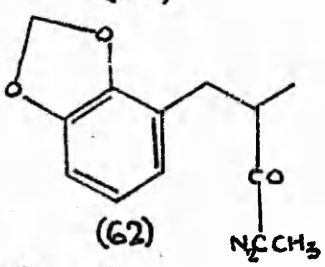

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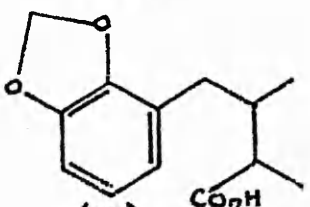

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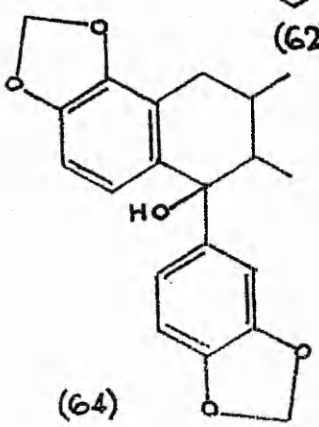

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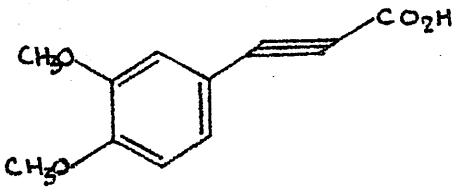

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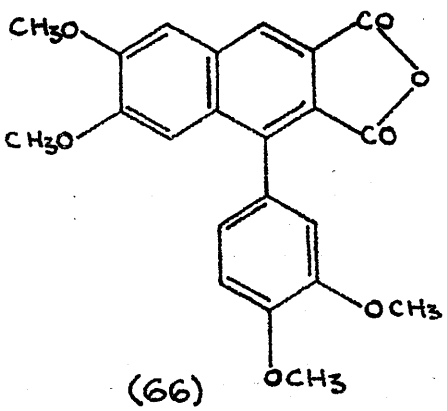

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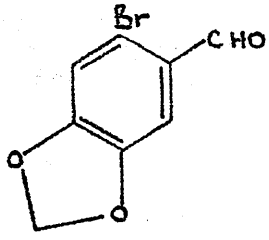

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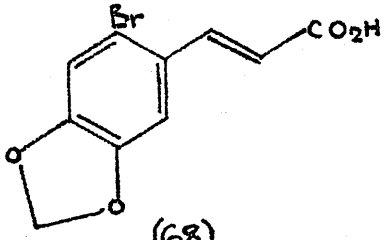

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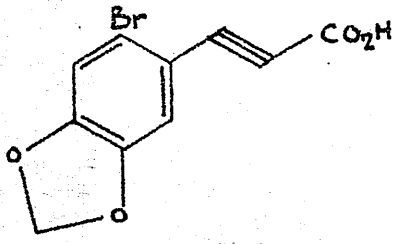

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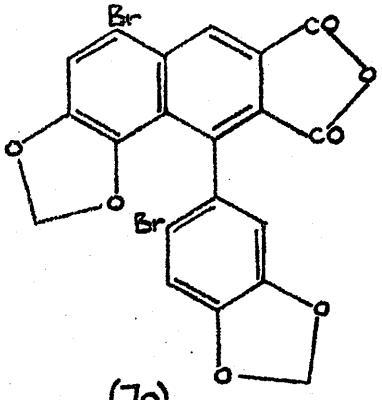

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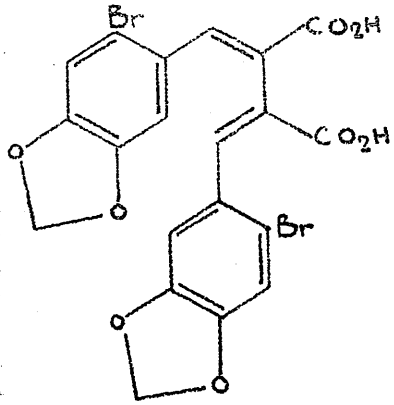

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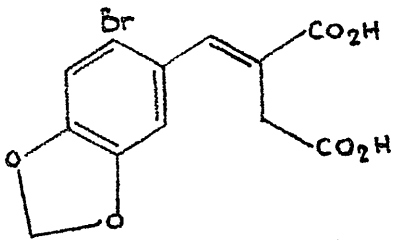

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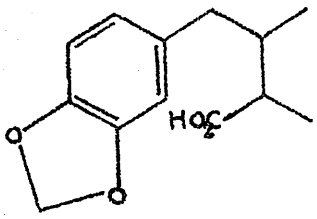

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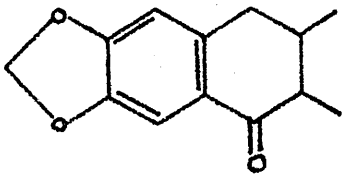

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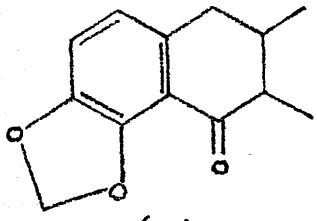

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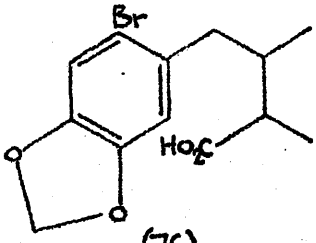

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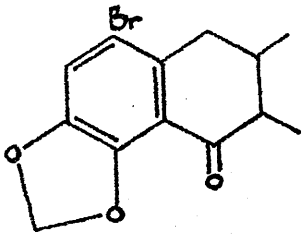


(77)

EXPERIMENTAL.

Rotations were measured for chloroform solutions at room temperature. M.p.s. were determined on a Kofler block and are corrected. Alumina of activity II was employed for chromatography, and the light petroleum used for elution had b.p. 60 - 80°.

The proton magnetic resonance absorption spectra of otobain and of tetradehydro-otobain were recorded at 23° in O.C.M. deuterochloroform solution on an A.E.I. R.S.2 spectrometer operating at an applied radiofrequency of 60 Mc./sec.

Isolation of Otobain - Otoba fat (250 g.) was heated under reflux for 30 min. with potassium hydroxide (150 g.) in ethanol (500 ml.). Dilution with water, followed by repeated extraction with ether, gave a yellow oil (60 g.) which was adsorbed from light petroleum on alumina (2 kg.) and eluted in the following sequence. (a) Light petroleum gave an oil (30 g.) which appeared to be a mixture of unsaturated sesquiterpene hydrocarbons. (b) Crystallisation of the benzene eluate from light petroleum yielded otobain (15.4 g.), m.p. 136-137°, $[\alpha]_D$ -43° (c, 0.8) (lit.,[21] m.p. 137-138°, $[\alpha]_D$-35.7°) (Found: C,74.15; H,6.35. Calc. for $C_{20}H_{20}O_4$: C,74.05; H,6.2%). (c) Washing the column with ether-methanol (19 : 1) gave a brown oil which was reabsorbed from benzene on alumina deactivated with 8% of 10% acetic acid. Elution with benzene yielded hydroxyotobain as prisms (4.5 g.) (from methylene chloride-light petroleum), m.p. 116 - 117°, $[\alpha]_D$ -28° (c 0.8) (Found: C,70.85; H,5.6. $C_{20}H_{20}O_5$ requires C,70.55; H,5.9%). Benzene-ether (1 : 1) eluted a phenol which crystallised from light petroleum-methylene chloride as needles (260 mg.), m.p. 119-132° (Found: C,73.85; H,6.85; OMe, 9.25. $C_{20}H_{22}O_4$ requires C,73.6; H,6.8; OMe,9.5%). Further elution with benzene-ether (1 : 1) gave β-sitosterol (385 mg.).

Didehydro-otobain.- Hydroxyotobain (270 mg.) was heated under reflux with sodium acetate (500 mg.) and acetic anhydride (5 ml.) for 2 hr. The product crystallised from light petroleum as needles (170 mg.) of didehydro-otobain, m.p. 129.5-130.5°,

$[\alpha]_D$ + 43° (c 0.7) (Found: C,74.4; H,5.95. $C_{20}H_{18}O_4$ requires C,74.5; H,5.65%). The same product was obtained in higher yield by heating hydroxyotobain in benzene under reflux with 10% aqueous toluene-p-sulphonic acid for 4 hr. Hydrogenation of didehydro-otobain (35 mg.) in ethyl acetate in presence of 10% palladium-charcoal gave otobain (6 mg.; after repeated crystallisation from methanol and light petroleum).

Tetradehydro-otobain.- Didehydro-otobain (41 mg.) was heated under reflux with dichlorodicyanobenzoquinone (29 mg.) in xylene (10 ml.) for 5 min. The resulting mixture was filtered through alumina and crystallised as prisms (32 mg.) of tetradehydro-otobain, m.p. 183-185° (Found: C,75.1; H,4.85. $C_{20}H_{16}O_4$ requires C,75.0; H,5.05%). Dehydrogenation of otobain with 10% palladium-charcoal in diphenyl ether under reflux for 4 hr. also yielded tetradehydro-otobain.

Hydrogenolysis of Otobain.- Otobain (440 mg.) in ether (20 ml.) was added to a solution of sodium (500 mg.) in ammonia (50 ml.) stirred under reflux. After 5 min. sufficient ammonium chloride was added to discharge the blue colour and the solvents allowed to evaporate. The products were adsorbed from benzene on alumina deactivated with 5% of 10% acetic acid. The first fractions eluted with benzene-ether (19 : 1) crystallised from chloroform-light petroleum as prisms (160 mg.) of phenol B, m.p. 162-164°, $[\alpha]_D$ -31° (c 1 : 1) (Found: C,76.75; H,6.95.

$C_{19}H_{20}O_3$ requires C,77.0; H,6.8%). Further elution gave phenol A as needles (195 mg.) (from chloroform-light petroleum), m.p. 197-199°, $[\alpha]_D$ -33° (c 0.9) (Found: C,76.95; H,7.1%).

These two phenols were treated with dimethyl sulphate and aqueous sodium hydroxide. Methyl ether A crystallised from methanol as prisms, m.p. 105-106°, $[\alpha]_D$ -32° (c 1.0) (Found: C,77.6; H,7.15. $C_{20}H_{22}O_3$ requires C,77.4; H,7.15%). Methyl ether B formed prisms (from ethanol), m.p. 67-69° (Found: C, 77.65; H,7.05%).

Permanganate Oxidations.- The general method employed was to heat a solution of the organic compound in aqueous pyridine on a steam-bath with potassium permanganate, until removal of the pyridine gave a water-soluble product. This was then heated with aqueous permanganate until reaction was complete. The excess of permanganate was destroyed with methanol, and manganese dioxide removed by filtration. Evaporation of the aqueous solution and acidification gave p-methoxybenzoic acid (25%), m-methoxybenzoic acid (18%), and benzenepentacarboxylic acid (isolated as its pentamethyl ester) (8%) from methyl ether A, methyl ether B, and tetradehydro-otobain, respectively.

Methylation of Phenolic Mixture from Otoba Fat.- The crude phenols (m.p. 119-132°) (55 mg.) in 10% aqueous sodium hydroxide (10 ml.) were heated under reflux with dimethyl sulphate (1 ml.), added during 2 hours. The product formed needles of a dimethyl

ether (48 mg.) (from light petroleum), m.p. 106-108°, $[\alpha]_D$ + 5° (c 0.7) (Found: C,74.35; H,7.1; OCH_3, 17.9. $C_{21}H_{24}O_4$ requires C,74.1; H,7.1; OCH_3, 18.25%).

Synthesis of 7,8 : 7^1, 8^1 - Tetradehydro-piperocyclolignan (35).

Route (a)

7,8: 7^1, 8^1 - Tetradehydro-piperolignan-8, 8^1-dicarboxylic acid anhydride (42).

This was prepared by the method developed by Haworth[29] when piperonal (15 g.) was condensed with diethyl succinate (8.3 g.) in the presence of sodium ethoxide. The dicarboxylic acid (41) isolated from the reaction mixture was then treated with acetic anhydride to give the required anhydride (5.6 g.) which crystallised from benzene in yellow plates, m.p. 208-210° (lit., m.p. 210°).

Dimethyl - 7,8: 7^1,8^1 - tetradehydro-pipero-cyclolignan - 8, 8^1 - dicarboxylate (43).

A mixture of the anhydride (42) (3.1 g.), palladium-charcoal (10%, 200 mg.) and diphenyl ether (10 g.) was heated under reflux for 5 hours then cooled, diluted with chloroform, filtered, and the solvent removed in vacuo. The residue was heated under reflux with an excess of aqueous ethanolic potassium hydroxide (10%) for 1 hour then diluted with water and extracted with ether. The alkaline aqueous layer was acidified with dilute hydrochloric

acid and extracted with chloroform. The required dicarboxylic acid was then isolated by washing the chloroform layer with sodium bicarbonate solution and subsequent acidification of the bicarbonate extract. The corresponding dimethyl ester, prepared by diazomethane treatment was adsorbed on alumina from benzene. Elution with chloroform-benzene (3 : 7) gave dimethyl-7,8 : 7^1, 8^1 - tetradehydro-pipero-cyclolignan-8,8^1-dicarboxylate[41] (1 g.) which crystallised from chloroform-ethanol as prisms, m.p. 216-219°, (Found: C,64.75 ; H,4.4. $C_{22}H_{16}O_8$ requires C,64.7 ; H,3.95%).

7,8: 7^1,8^1 - Tetradehydro-pipero-cyclolignan-9,9^1 - diol.

The foregoing ester (173 mg.) was heated under reflux with lithium aluminium hydride (200 mg.) in tetrahydrofuran for 3 hours. The cooled reaction mixture was treated with ethyl acetate to destroy the excess lithium aluminium hydride and then poured into water, acidified with dilute hydrochloric acid and extracted with chloroform. After drying and removal of the solvent, the residue was adsorbed on alumina from benzene-chloroform (1 : 1). Elution with chloroform-methanol (99 : 1) gave 7,8 : 7^1, 8^1 - tetradehydro-pipero-cyclolignan-9,9^1-diol (91 mg.) which crystallised from methanol as prisms, m.p. 185-187°, (Found: C,68.65 ; H,4.95. $C_{20}H_{16}O_6$ requires C,68.2 ; H,4.6%).

7,8 : 7^1,8^1 - Tetradehydro-pipero-cyclolignan (35).

Catalytic hydrogenolysis of the foregoing diol (58 mg.) in ethyl acetate over palladium-charcoal (10%) yielded the desired 7,8 : $7^1 8^1$ -tetradehydro-pipero-cyclolignan (41 mg.) which crystallised from ethanol-chloroform in needles, m.p. 173.5 - 175°, (lit., m.p. 168°,[12] 171-172°[24]) (Found: C,74.9 ; H,5.35. $C_{20}H_{16}O_4$ requires C,75.0 ; H,5.05%).

Route (b)

Isosafrole Hydrogen Bromide (47).

Hydrogen bromide in glacial acetic acid (160 g. 50%) was added dropwise to a stirred solution of safrole (81 g.) in glacial acetic acid (200 ml.) at 0°. After the addition was complete the stirring was continued for a further 6 hours at 0° and finally overnight at room temperature. The reaction mixture was then poured into ice-cold sodium carbonate solution and the whole extracted with ether. The combined ethereal extracts were washed with sodium hydroxide solution, water, dried over potassium carbonate and then evaporated. Fractional distillation of the residual oil (115 g.) gave the desired isosafrole hydrogen bromide (80 g.), b.p. 122-124°/0.4 mm., n_D^{20} 1.5602.

Isosafrole (44)

Safrole (32 g.) was stirred under reflux with powdered potassium hydroxide (3 g.) for 1 hour. The crude product was then

distilled to give isosafrole (28 g.) as a colourless oil, b.p. 90°/0.2 mm., n_D^{18} 1.5758.

Piperonyl Methyl Ketone (46).

A solution of isosafrole (25 g.) in acetone (90 ml.) was added dropwise over 20 minutes to a stirred mixture of hydrogen peroxide (25 g. 30%) and formic acid (11.4 g 80%) with the temperature maintained at 40°, and the stirring continued overnight. After removal of the solvent under vacuum, the residue was heated under reflux with a mixture of methanol (25 ml.) and sulphuric acid (140g. 15%) for 3 hours. The cooled reaction mixture was then extracted with ether, the combined ethereal extracts washed with sodium hydroxide solution (5%), water and then dried. Evaporation of the solvent furnished a mixture (22 g.) of the desired ketone (46) and isosafrole.

This mixture was adsorbed on alumina, and elution with light petroleum gave, after a fore run of isosafrole (12.5 g.), piperonyl methyl ketone (7 g.) as a colourless oil, b.p. 76-80°/0.45mm. The corresponding semicarbazone crystallised from ethanol as needles m.p. 162-163° (lit.[32], m.p. 161-163°).

7,8 - Didehydro-piperolignan (48).

A solution of piperonyl methyl ketone (4.5 g.) in anhydrous ether (25 ml.) was added dropwise in a nitrogen atmosphere to a stirred solution of the Grignard reagent of isosafrole hydrogen

bromide (from isosafrole hydrogen bromide (7 g.) and magnesium (0.7 g.)) in ether (50 ml.) held at 0°. The reaction mixture was then heated under reflux for 2 hours and poured onto saturated ammonium chloride solution. Ether extraction followed by water washing, drying and removal of the solvent gave a liquid product which was adsorbed on alumina (Woelm Grade II) from light petroleum. Elution with the same solvent gave 7,8 - didehydro-piperolignan (250 mg.) as a solid which crystallised from light petroleum as prisms, m.p. 73-74°, (Found: C,73.9 ; H,6.05. $C_{20}H_{20}O_4$ requires C,74.05 ; H,6.20%). λ_{max} 236 mμ (ε 7,500), 286 mμ (ε 7,100).

7,8 : $7^1,8^1$ - Tetradehydro-pipero-cyclolignan (35).

7,8 - Didehydro-piperolignan (100 mg.) was heated under reflux with palladium-charcoal (50 mg. 10%) in diphenyl ether (2 g.) for 4 hours. The mixture was cooled, diluted with chloroform (15 ml.) and filtered to remove the palladium-charcoal. The chloroform was removed, water (25 ml.) added and the diphenyl ether steam distilled out of the mixture. The aqueous residues were ether extracted, the combined extracts dried and evaporated to give a thick gum which was adsorbed on alumina from light petroleum, and eluted with benzene-ether (4 : 1) to give 7,8 : $7^1,8^1$ -tetradehydro-pipero-cyclolignan (15.3 mg.) which crystallised from light petroleum in needles, m.p. 173-175° undepressed on admixture with the sample prepared by the alternative synthetic pathway.

Synthesis of 3,4 : $2^1,3^1$ -bis-Methylenedioxy-7,8 : $7^1,8^1$-tetradehydro-cyclolignan (40)

Part (1) Synthesis of 3,4-Methylenedioxy-1-bromobenzene (49).

Route (i) Piperonylic Acid Nitrile (52).

This was prepared, as described by Marcus,[33] by the condensation of piperonal (150 g.) with hydroxylamine (33 g.) to give piperonyloxime (160 g.) which crystallised from hot water in needles, m.p. 109-110° (lit., m.p.110°). Piperonyloxime (80 g.) was then heated under reflux with acetic anhydride to yield the desired piperonylic acid nitrile (70 g.) which crystallised from water in needles, m.p. 95° (lit., m.p. 95°).

3,4 - Methylenedioxyaniline (54).

This was obtained by the method of Rupe.[34] Piperonylic acid nitrile (50 g.) was converted by the action of hydrogen peroxide in weakly alkaline solution to piperonylic acid amide (45 g.) which crystallised from water in needles, m.p. 167-168° (lit., m.p. 169°). This amide (53) (45 g.) was degraded under the Hofmann conditions of bromine in sodium hydroxide solution to give 3,4-methylenedioxyaniline (12 g.) which crystallised from light petroleum in needles, m.p. 45-46° (lit., m.p. 44-46°).

3,4 - Methylenedioxy-1-bromobenzene (49).

This was prepared, as described by Manneli,[35] when the diazonium bromide from 3,4-methylenedioxyaniline (12 g.) was decomposed

with sodium hypophosphite and copper sulphate solution. Fractional distillation of the oil obtained from the reaction furnished 3,4-methylenedioxy-1-bromobenzene (5.5 g.) as a pale yellow liquid, b.p. 100-102°/16 mm., n_D^{19} 1.5830.

Route (ii) 3,4-Methylenedioxy-1,2-dibromobenzene (56).

This was obtained, as described by Robinson,[36] by adding bromine water to a sodium carbonate solution of piperonylic acid (55) (100 g.). The crude product was filtered off and crystallised from ethanol to give 3,4-methylenedioxy-1,2-dibromobenzene (42 g.) as needles, m.p. 86° (lit., m.p. 86°).

1,2 - Methylenedioxybenzene (57).

When a solution of the dibromide (56) (10 g.) in methanol containing potassium hydroxide (5 g.) was hydrogenated over palladium-charcoal (10%, 2 g.) an uptake of 1610 ml. of hydrogen (2 equivalents) was recorded. The reaction mixture was filtered, evaporated to small bulk, dissolved in ether (50 ml.) and washed with water. The ethereal solution was then dried and evaporated furnishing methylenedioxybenzene[41] (4 g.) as a volatile oil, b.p. 78-80°/16 mm.

3,4 - Methylenedioxy-1-bromobenzene (49).

1,2-Methylenedioxybenzene (4 g.) in glacial acetic acid (25 ml.) was treated with bromine (2.7 g.) in glacial acetic acid (5 ml.) and left to stand overnight. The reaction mixture

was neutralised with sodium bicarbonate solution, ether extracted and the combined ethereal extracts washed with sodium carbonate solution and water, dried and evaporated. The residue was fractionally distilled to yield 3,4-methylenedioxy-1-bromobenzene (4.5 g.) as a pale yellow oil b.p. 101-102/16 mm., n_D^{18} 1.5832.

Part (2) Synthesis of 2,3-Dimethyl-5,6-methylenedioxy-α-tetralone (50).

2,3 - Dihydroxybenzoic Acid (o-pyrocatechuic acid)

This compound was prepared by the reaction sequence described by Perkin.[42] 2-Hydroxy-3-methoxybenzaldehyde (o-vanillin) (150g.) was heated under reflux with dimethyl sulphate in methanolic potassium hydroxide solution to give 2,3-dimethoxybenzaldehyde (o-veratraldehyde) (160 g.) in needles, m.p. 54° (lit., m.p. 54-55°). The above aldehyde (83 g.) in aqueous acetone solution was oxidised with an aqueous solution of potassium permanganate (10%) affording 2,3-dimethoxybenzoic acid (o-veratric acid) (80g) as needles, m.p. 122° (lit., m.p. 122°), which was heated at 135° with freshly distilled hydrogen iodide to give 2,3-dihydroxybenzoic acid (51 g.) which crystallised from water in needles, m.p. 202-204° (lit., m.p. 204°).

2,3-Methylenedioxybenzoic Acid (o-piperonylic acid) (58).

A solution of methylene iodide (50 g.) in ethanol (120 ml.) was added dropwise with stirring, in a nitrogen atmosphere, to a warm mixture of 2,3-dihydroxybenzoic acid (60 g.), copper-bronze turnings (15 g.) and potassium hydroxide (90 g.) in aqueous

ethanol. The reaction mixture was then heated under reflux with vigorous stirring, additional portions of methylene iodide (25 g.) and copper-bronze turnings (8g.) added after 3 hours and again after 6 hours, and the mixture refluxed overnight. The cooled solution was filtered, washed with ether and the alkaline aqueous layer acidified with dilute hydrochloric acid. Ether extraction furnished a crude sample of the desired acid (62 g.) which was then sublimed and crystallised from methanol to give 2,3-methylenedioxybenzoic acid (43 g.) as needles, m.p. 224-226° (lit., m.p. 227°).

2,3-Methylenedioxybenzyl Alcohol (o-piperonyl alcohol) (59).

A solution of 2,3-methylenedioxybenzoic acid (8 g.) in dry tetrahydrofuran (100 ml.) was slowly added to a stirred suspension of lithium aluminium hydride (5 g.) in tetrahydrofuran (100 ml.). The mixture was heated under reflux for 1 hour, cooled and ethyl acetate (5 ml.) in tetrahydrofuran (10 ml.) cautiously added. The reaction mixture was then poured into dilute hydrochloric acid and extracted with ether. The combined ethereal extracts were washed with dilute sodium hydroxide solution and water, dried and the solvent removed to give 2,3-methylenedioxybenzyl alcohol (6 g.) which crystallised from light petroleum in needles, m.p. 33-35° (lit.[49], m.p. 34-35°).

2,3-Methylenedioxybenzyl Bromide (o-piperonyl bromide) (60).

2,3-Methylenedioxybenzyl alcohol (5 g.) was stirred with a saturated aqueous solution of hydrogen bromide, the reaction mixture diluted with water and the crude bromide which precipitated was collected. Recrystallisation from light petroleum gave 2,3-methylenedioxybenzyl bromide (7 g.) as needles, m.p. 63-64° (Found: C,44.75 ; H,3.25. $C_8H_7O_2Br$ requires C,44.7 ; H,3.3%).

$2^1,3^1$ - Methylenedioxy-2-benzylpropionic Acid (61).

Methyl diethyl malonate (8 g.) in dry benzene (50 ml.) was added to a stirred suspension of sodium hydride (2.4 g. of a 50% suspension in oil) in dry benzene (40 ml.) and the mixture gently heated until evolution of hydrogen gas ceased. A solution of 2,3-methylenedioxybenzyl bromide (8.6 g.) in benzene (100 ml.) was added, the mixture refluxed for 90 minutes, cooled and aqueous methanol added to destroy the excess sodium hydride. After removal of the benzene in vacuo, the residue was heated under reflux with potassium hydroxide (10 g.) in aqueous ethanol (100 ml.) for 1 hour, diluted with water and washed with ether. The aqueous solution was acidified with dilute hydrochloric acid, extracted with ether, the combined ethereal extracts washed with water, dried and the solvent evaporated to give a colourless oil which was heated at 210-220° until evolution of carbon dioxide ceased. The residue then solidified and was recrystallised from methanol

to give $2^1,3^1$-methylenedioxy-2-benzylpropionic acid (5.2 g.) in prisms, m.p. 65-66° (Found: C,63.85 ; H,6.25. $C_{11}H_{12}O_4$ requires C,63.45 ; H,5.8%).

$2^1,3^1$-Methylenedioxy-3-benzyl-2-methylbutyric Acid (63).

Treatment of the above acid (5.4 g.) with oxalyl chloride (8 ml.) in dry benzene gave the corresponding acid chloride (6g.) which was allowed to stand overnight with an ethereal solution of diazoethane (excess). After evaporation of the solvent, the residue was adsorbed on alumina from benzene. Elution with the same solvent gave the desired diazoketone (6.5 g.) as a viscous red oil (ν_{max} (liquid film) 2080 cm^{-1}). A mixture of the diazoketone in freshly distilled γ-collidine (30 ml.) and freshly distilled benzyl alcohol (30 ml.) was heated rapidly to 170-190° by immersing the reaction flask in a preheated oil bath. After a short induction period the reaction proceeded with a vigorous evolution of nitrogen. The heating was continued for a further 5 minutes and the reaction mixture cooled, diluted with ether (100 ml.) and washed with dilute hydrochloric acid. The residue obtained on evaporation of the ether was dissolved in methanol (30 ml.) and heated under reflux with potassium hydroxide (13.5g) in water (30 ml.) for 3 hours then cooled, washed with ether and the alkaline aqueous layer acidified with dilute hydrochloric acid and thoroughly extracted with ether. The combined ethereal extracts were washed with water, dried, the solvent removed and the residual oil adsorbed on silica gel from benzene. Elution

with benzene-ether (1 : 1) gave $2^1,3^1$-methylenedioxy-3-benzyl-2-methylbutyric acid as a viscous oil (3.3 g.).

2,3-Dimethyl-5,6-methylenedioxy-α-tetralone (50).

Stannic chloride (1.6 g.) was added slowly to a stirred solution of the acid chloride (1.2 g.), derived from $2^1,3^1$-methylenedioxy-3-benzyl-2-methylbutyric acid (1 g.), in dry benzene (50 ml.) cooled in an ice bath to 0°, and the mixture then stirred at room temperature for 1 hour. The reaction mixture was then poured into 10% hydrochloric acid solution, the benzene layer separated, washed with sodium hydroxide solution and water, dried and the solvent evaporated under vacuum. The residue was adsorbed on alumina from benzene-light petroleum (1 : 1) and eluted with benzene to give 2,3-dimethyl-5,6-methylenedioxy-α-tetralone (630 mg.) as a white solid which crystallised from light petroleum in needles, m.p. 110° (Found: C,52.3 ; H,4.25. $C_{15}H_{14}O_3$ requires C,52.55 ; H,4.4%).

Part (3) 3,4 : $2^1,3^1$-bis-Methylenedioxy-7,8-didehydrocyclolignan (51).

A crystal of iodine (0.5 mg.) and 3,4-methylenedioxy-1-bromobenzene (100 mg.) were added in an atmosphere of nitrogen (dry and oxygen free) to a stirred suspension of fine magnesium turnings (60 mg. previously washed with ether and dried at 100°) in tetrahydrofuran (5 ml.). The vigorously stirred mixture was maintained under refluxing conditions by the dropwise addition of 3,4-methylenedioxy-1-bromobenzene (350 mg.) in tetrahydrofuran

(15 ml.) and the whole then heated under reflux for 90 minutes. The cooled reaction mixture was treated with 2,3-dimethyl-5,6-methylenedioxy-α-tetralone (115 mg.) in tetrahydrofuran (10 ml.) and the mixture heated under reflux overnight. The cooled reaction mixture was poured into saturated ammonium chloride solution, the aqueous mixture thoroughly ether extracted and the combined ethereal extracts washed with water and dried. After evaporation of the solvent, the residual oil was adsorbed on alumina from light petroleum and elution with light petroleum-chloroform (3 : 2) gave 3,4:2^1,3^1-bis-methylenedioxy-7,8-didehydro-cyclolignan (43 mg.) which crystallised from chloroform-methanol in needles, m.p. 107.5-110° (Found: C,73.25 ; H,6.15. $C_{20}H_{18}O_4$ requires C,74.5 ; H,5.6%).

3,4:2^1,3^1-bis-Methylenedioxy-7,8:7^1,8^1-tetradehydro-cyclolignan (40).

3,4:2^1,3^1-bis-Methylenedioxy-7,8-didehydro-cyclolignan (25 mg.) was heated with palladium-charcoal (10%, 12 mg.) for 5 hours at 180-190°, cooled, then diluted with chloroform and the solution filtered. The solvent was removed and the residue adsorbed from light petroleum on alumina and eluted with light petroleum-chloroform (4 : 1) to give a gummy solid (14 mg.) which was sublimed then dissolved in light petroleum-chloroform (7 : 3) and filtered through a short column of alumina to yield 3,4:2^1,3^1-bis-methylenedioxy-7,8:7^1,8^1-tetradehydro-cyclolignan

(2.5 mg.) crystallised from chloroform-light petroleum as needles m.p. 138-141°. λ_{max} (in EtOH) 226, 273, 283 ; ε 48,000, 11,200, 11,200.

Attempted Syntheses of Tetradehydro-otobain

(1) 6-Bromo-3,4-methylenedioxycinnamic Acid Methyl Ester.

6-Bromopiperonal was prepared by the method of Robinson[36] when piperonal (100 g.) was treated with bromine in glacial acetic acid overnight and the reaction mixture poured into water. The crude bromo compound was filtered off and crystallised from chloroform-light petroleum to give 6-bromopiperonal (125 g.) as needles, m.p. 125-126° (lit., m.p. 124-126°). The bromopiperonal (46 g.) was condensed, by the method of Haworth,[40] with malonic acid (21 g.) in the presence of pyridine and piperidine to yield 6-bromo-3,4-methylenedioxycinnamic acid (36 g.) which crystallised from acetic acid in prisms, m.p. 249-250° (lit., m.p. 249-251°). This acid (27 g.) was then heated under reflux for 2 hours with methanolic hydrogen chloride solution to give the required 6-bromo-3,4-methylenedioxycinnamic acid methyl ester (25 g.) which crystallised from methanol in needles, m.p. 138-140° (lit., m.p. 138-140°).

$3^1,4^1$-Methylenedioxy-3-phenyl-2,3,6^1-tribromopropionic Acid Methyl Ester

The foregoing methyl ester (10 g.) in glacial acetic acid (40 ml.) was treated with a solution of bromine (8 g.) in glacial

acetic acid (10 ml.) and left to stand overnight. The mixture was poured into water and the solid tribromo ester (14 g.) collected and crystallised from chloroform-light petroleum in prisms, m.p. 138.5-140° (Found: C,29.85 ; H,2.35, $C_{11}H_9O_4Br_3$ requires C,29.7 ; H,2.05%).

$3^1,4^1$-Methylenedioxy-6^1-bromo-3-phenylpropiolic Acid (69).

The above methyl ester (30 g.) was heated under reflux with potassium hydroxide (17 g.) in ethanol (120 ml.) for 4.5 hours, the ethanol removed under vacuum and water (300 ml.) added to the reaction mixture. The crystalline precipitate was filtered off, dissolved in glacial acetic acid and poured into dilute sulphuric acid. The required propiolic acid (69) (7.2 g.) was collected and crystallised from benzene-acetone as needles, m.p. 190-191° (with decomposition) (Found: C,44.4 ; H,2.1. $C_{10}H_5O_4Br$ requires C,44.6 ; H,1.9%).

The mother liquors of the reaction mixture were left to stand overnight when a second crop of crystals was deposited. These were dissolved in acetic acid and poured into dilute sulphuric acid to give the corresponding dibromo olefinic acid (1.1 g.) which crystallised from benzene-acetone in needles, m.p. 216-218° (Found: C,34.35 ; H,1.85. $C_{10}H_6O_4Br_2$ requires C,34.3 ; H,1.75%).

(2) Stobbe Condensation[46] between 6-Bromopiperonal and Diethyl Succinate

A solution of diethyl succinate (8.3 g.) and 6-bromopiperonal (22 g.) in dry tetrahydrofuran (50 ml.) was added to a vigorously

stirred suspension of freshly prepared, alcohol free sodium ethoxide (6.4 g.) in tetrahydrofuran at -18° and the reaction mixture stirred for 12 hours at a temperature of -14° to -10°. The temperature was then raised to 0° and the mixture kept at this temperature for 7 days then poured into water and the tetrahydrofuran removed. The aqueous alkaline residues were refluxed for 1 hour, cooled, washed with ether and then acidified to yield crude product which was dissolved in chloroform and re-extracted with potassium hydroxide solution. The product precipitated on acidification with dilute hydrochloric acid was repeatedly crystallised from glacial acetic acid to furnish $3^1,4^1$-methylenedioxy-6^1-bromobenzylidenesuccinic acid (72) (4.2g.) as needles, m.p. 239-242° (Found: C,44.3 ; H,2.7. $C_{12}H_9O_6Br$ requires C,43.8 ; H,2.75%). The corresponding acid anhydride crystallised from glacial acetic acid in needles, m.p. 265-266° (Found: C,46.7 ; H,2.7. $C_{12}H_7O_4Br$ requires C,46.35 ; H,2.3%).

(3a) Synthesis of 2,3-Dimethyl-5-bromo-7,8-methylenedioxy-α-tetralone (77).

3,4-Methylenedioxybenzyl Alcohol (piperonyl alcohol)

The alcohol was prepared, as described by Davidson[47] by the Cannizzaro reaction of formaldehyde on piperonal (50 g.) in methanolic sodium hydroxide solution. 3,4-Methylenedioxybenzyl alcohol (35 g.) crystallised from light petroleum in needles, m.p. 58° (lit., m.p. 58°).

3,4-Methylenedioxybenzyl Bromide (piperonyl bromide)

This was obtained, as described by Robinson,[45] by shaking piperonyl alcohol (10 g.) with a saturated aqueous solution of hydrogen bromide, adding water and filtering off the crude bromide. Recrystallisation from petrol afforded piperonyl bromide (13 g.) as needles, m.p. 49° (lit., m.p. 49°).

$3^1,4^1$-Methylenedioxy-2-benzylpropionic Acid.

This was prepared, as described for $2^1,3^1$-methylenedioxy-2-benzylpropionic acid, by the condensation of piperonyl bromide (16 g.) with methyl diethyl malonate (15 g.) in the presence of sodium hydride followed by hydrolysis of the diester thus formed to the corresponding diacid which was then heated to 220° to give $3^1,4^1$-methylenedioxy-2-benzylpropionic acid (7.3 g.) which crystallised from methanol in needles, m.p. 80.5-81° (Found: C,63.3 ; H,6.4. $C_{11}H_{12}O_4$ requires C,63.45 ; H,5.8%).

$3^1,4^1$-Methylenedioxy-3-benzyl-2-methylbutyric Acid (73).

A mixture of the foregoing propionic acid (1.3 g.) and oxalyl chloride (2 ml.) in dry benzene (25 ml.) was left to stand overnight, the benzene evaporated under vacuum and the acid chloride (1.4 g.) obtained as a brown coloured oil, treated overnight with an excess ethereal solution of diazoethane. The residue obtained on evaporation of the ether was adsorbed from benzene on alumina and eluted with benzene to give the corresponding diazoketone

(1.25 g.) as a red oil (ν_{max} 2075 cm^{-1}.). A mixture of the diazoketone in freshly distilled γ-collidine (5 ml.) and freshly distilled benzyl alcohol (5 ml.) was rapidly heated to 170-190° by immersing the reaction flask in a preheated oil bath. Reaction proceeded with vigorous evolution of nitrogen. The mixture was heated for 5 minutes at 190°, cooled, diluted with ether (30 ml.) and washed with dilute hydrochloric acid. The residue obtained on evaporation of the ether was taken up in methanol (5 ml.) and heated under reflux with aqueous potassium hydroxide solution (45%) for 3 hours, cooled, washed with ether and acidified with dilute hydrochloric acid. The aqueous mixture was extracted with ether and the combined ethereal extracts washed with water, dried and evaporated to give a gummy residue which was adsorbed from benzene on silica gel and eluted with benzene-ether (1:1) to give the acid (73) (630 mg.) as a thick gum.

$3^1,4^1$-Methylenedioxy-6^1-bromo-3-benzyl-2-methylbutyric Acid (76).

A mixture of the acid (73) (1.2 g.) and bromine (0.4 g.) in glacial acetic acid was left to stand overnight and the residue obtained on evaporation of the acetic acid was adsorbed from benzene on silica gel. Elution with benzene-ether (9 : 1) gave the required bromoacid (76) (1.15 mg.) which crystallised from chloroform-light petroleum in needles, m.p. 110° (Found: C,49.95; H,3.95. $C_{13}H_{15}O_4$ Br requires C,49.5 ; H.4.8%).

2,3-Dimethyl-5-bromo-7,8-methylenedioxy-α-tetralone (77).

A mixture of bromoacid (76) (1 g.) and oxalyl chloride (2 ml.) in dry benzene (25 ml.) was left to stand overnight and the benzene then evaporated to give the corresponding acid chloride (1.3 g.) as a brown oil. Stannic chloride (1.7 g.) was slowly added to a stirred solution of the acid chloride in dry benzene at 0°. The reaction mixture was brought to room temperature, stirred for 1 hour and then poured into dilute hydrochloric acid. The benzene layer was separated, washed with sodium hydroxide solution and water, dried and evaporated to give a residue which was adsorbed from benzene on alumina and eluted with benzene-chloroform (3 : 1) to give 2,3-dimethyl-5-bromo-7,8-methylenedioxy-α-tetralone (720 mg.) which crystallised from chloroform-light petroleum in needles, m.p. 156-157° (Found: C,52.7 ; H,4.6. $C_{13}H_{13}O_3Br$ requires C,52.55 ; H,4.4%).

(3b) Attempted Grignard Condensation of 3,4-Methylenedioxy-1-bromobenzene with 2,3-Dimethyl-5-bromo-7,8-methylenedioxy-α- tetralone.

A crystal of iodine (0.5 mg.) and 3,4-methylenedioxy-1-bromobenzene (100 mg.) were added in an atmosphere of nitrogen (dry and oxygen free) to a stirred suspension of fine magnesium turnings (60 mg. previously washed with ether and dried at 100°) in tetrahydrofuran (5 ml.). The vigorously stirred mixture was maintained under refluxing conditions by the dropwise addition of 3,4-methylenedioxy-1-bromobenzene (350 mg.) in tetrahydrofuran (15 ml.) and the whole then heated under reflux for 90 minutes.

The cooled reaction mixture was treated with 2,3-dimethyl-5-bromo-7,8-methylenedioxy-α-tetralone (110 mg.) in tetrahydrofuran (10 ml.) and the mixture heated under reflux overnight. The cooled reaction mixture was poured into saturated ammonium chloride solution, the aqueous mixture thoroughly ether extracted and the combined ethereal extracts washed with water and dried. After evaporation of the solvent, the residual oil was adsorbed on alumina (Woelm Grade II) from light petroleum. Elution with light petroleum gave a mixture (280 mg.) of methylenedioxybenzene and 3,4-methylenedioxy-1-bromobenzene while elution with light petroleum-chloroform (3 : 2) afforded the α-tetralone (77) (100 mg.). No other reaction product was isolated.

TERPENE SECTION.

Synthetic Routes to the Aromatic Tricyclic Diterpenoids

INTRODUCTION

The known naturally occurring aromatic tricyclic diterpenoids are summarised on the first of the accompanying flow sheets and it is the intention to survey the various reported syntheses of these and related compounds.

Syntheses from Acyclic Precursors.

The postulated biosynthesis of tricyclic diterpenoids has been extensively reviewed by Barltrop[48] and is based on the cyclisation of acyclic polyisoprenoid precursors. In agreement with such natural processes, several farnesol derivatives have been cyclised under acid conditions to diterpenoid systems.[49] For example, the ketone (1) was converted by the action of phosphoric acid into the abietatriene (2) possessing the basic tricyclic diterpenoid skeleton with ring C aromatic.[50]

Syntheses from Compounds having Ring C Preformed.

Substituted benzene compounds have also been used as synthetic intermediates and cyclisation using polyphosphoric acid of suitable precursors has effected several required syntheses.[51] For example, the Grignard reagent from 3 - isopropyl - phenethyl chloride was coupled with 2,3 - dichlorotetrahydro - 3 - methylpyran to yield

the compound (3). Ring scission of this tetrahydropyran with sodium furnished the alcohol (4) which was then converted into the required tertiary alcohol precursor (5) by treatment of the Grignard reagent of the corresponding chloride with acetone. Subsequent cyclisation of the unsaturated alcohol (5) with polyphosphoric acid gave cis and trans abietatriene (2).

Nasipuri[52] prepared methyl - 5 - oxo - 8 - phenyloctanoate (6) by the alkylation of ethyl - 4:6 - dioxoheptane - 1:5 - dicarboxylate with phenethyl bromide and then allowed this ester (6) to react with an excess of methyl magnesium iodide to yield the diol (7). Cyclodehydration of this diol with polyphosphoric acid gave 1:2:3:4:9:10:11:12: - octahydro - 1:1:12 - trimethylphenanthrene (8).

These synthetic pathways have not yet been modified to give compounds with the tertiary 1 - carboxyl group characteristic of the diterpenoid acids nor do they effect control over the configurations of the A-B ring junction. The preferred use of substituted naphthalenes and phenethylcyclohexanols has led to the total synthesis of many naturally occurring tricyclic diterpenoids with more effective stereochemical control.

Syntheses from Compounds having Rings B and C Preformed

Dehydroabietic Acid (13).

A substituted naphthalene was used by Stork[53] in his elegant synthesis of dl-dehydroabietic acid. 2-Isopropylnaphthalene (9)

was sulphonated to the 6- sulphonic acid which was transformed into 6-isopropyl - 2 - naphthol by fusion with potassium hydroxide. Reduction of this naphthol with sodium in liquid ammonia gave 6-isopropyl - 2 - tetralone (10; R=H) which was monomethylated via its enamine derivative to yield the β-tetralone (10; R=CH_3). Condensation with ethyl vinyl ketone gave the tetrahydro phenanthrone (11) which underwent alkylation with bromacetic ester from the less hindered rear face of the molecule with concomitant movement of the double bond to give the ester (12). Removal of the keto group followed by catalytic hydrogenation of the corresponding free acid, which again occurred from the rear of the molecule, afforded dl-homodehydroabietic acid. Barbier-Wieland degradation of the side chain yielded the required dl-dehydroabietic acid (13).

Podocarpic Acid

Podocarpic acid and its analogues do not possess the complete diterpenoid skeleton but they have proved to be valuable intermediates in diterpene synthesis. Rao[54] synthesised trans -6-methoxypodocarpane (18) using 1 - methyl - 7 - methoxy - 3,4 - dihydronaphthalene as the precursor. This naphthalene (14) was oxidised by red lead oxide to introduce a carbonyl function at position 2. Condensation of this β-tetralone (15) with 4 - diethylaminobutanone - 2 - methiodide gave the phenanthrene (16). Alkylation with methyl iodide in the presence of potassium t-butoxide afforded the gem dimethyl compound (17) which was catalytically

reduced stereospecifically from the less hindered side of the molecule to effect a trans A-B ring junction. Clemmensen reduction of the carbonyl function gave the expected trans - 6 - methoxypodocarpane.

Syntheses from Compounds having Rings A and C Preformed

The total synthesis of dl-podocarpic acid (21) was effected by King[55] from a precursor possessing rings A and C which formed ring B by an internal Friedel-Crafts closure. A condensation between 2-carboethoxy - 2,6 - dimethylcyclohexanone and the Grignard reagent from p-methoxyphenylacetylene gave 2-carboethoxy - 1 - (p-methoxy-phenyl) ethynyl - 2,6 - dimethylcyclohexanol (19) which was catalytically reduced and then cyclised using polyphosphoric acid to the phenanthrene (20). A mixture of three stereoisomeric esters was obtained from this cyclisation, which afforded no steric control over the A-B ring junction. Hydrolysis of one of the esters gave dl-podocarpic acid (21).

Ferruginol (24; R=H)

The above route had been a modification of the author's previously reported total synthesis of dl-ferruginol[56] incorporating 2,6,6 - trimethylcyclohexanone in condensation with sodium p-methoxyphenyl acetylene to yield the alcohol (22). Reduction followed by polyphosphoric acid cyclisation of the intermediate (22) gave a phenanthrene whose trans isomer (23; R=H) was acylated at position 7

by reaction with acetyl chloride and aluminium chloride. Treatment of the resultant acetyl compound (23; R=$COCH_3$) with methyl magnesium iodide furnished a tertiary alcohol (23; R=$C(OH).(CH_3)_2$) which was dehydrated to the isopropenyl compound (23; R=$CH_3.C=CH_2$). Catalytic reduction gave the required ferruginol methyl ether (24; R=CH_3) from which dl-ferruginol was obtained by treatment with hydrogen bromide.

Rao[57] effected a stereospecific synthesis of dl-ferruginol by a standard modification of trans - 6 - methoxypodocarpane (18) which he had previously prepared as described above. An aluminium chloride catalysed acylation of the naphthalene (18) using acetyl chloride furnished the 7-acetyl derivative (23; R=$COCH_3$) which was converted into a tertiary carbinol by treatment with methyl magnesium iodide. Dehydration of this alcohol furnished an isopropenyl derivative which was catalytically hydrogenated over platinum oxide to give dl-ferruginol methyl ether which was then heated with pyridine hydrochloride to yield dl-ferruginol.

Nimbiol.

Trans - 6 - methylpodocarpane has also been modified to yield nimbiol methyl ether.[58] Oxidation with chromic acid gave the ketone (25) which was chloromethylated to the compound (26; R=Cl). This was converted via the thiouronium salt into the mercaptan (26; R=SH) which gave the desired nimbiol methyl ether (26; R=H) on Raney nickel desulphurisation.

Totarol (31)

This diterpene, which does not conform to the classical isoprene rule, was synthesised by Barltrop[59] who condensed m - methoxyphenylacetylene with 2,6, 6 - trimethylcyclohexanone to give 1 - m - methoxyphenylethynyl - 2,6, 6 - trimethylcyclohexanol (27). This compound (27) was then catalytically hydrogenated and then cyclised using polyphosphoric acid to give the phenanthrene (28). A mixture of the unsaturated ketones (29 and 30; R=H) was obtained from a Birch reduction of the methyl ether (28), each of which on alkylation with isopropyl iodide and sodium t-amyl oxide afforded a mixture of the isopropylated ketones (29 and 30; $R=CH(CH_3)_2$). Dehydrogenation of this mixture furnished the required dl-totarol as an uncrystallisable glass. A more satisfactory synthesis has recently been reported by Taylor.[60]

The Grignard reagent from 1 - bromo - 2 - methoxynaphthalene was condensed with acetone and the product catalytically hydrogenated over Adams catalyst to yield 1 - isopropyl - 2 - methoxynaphthalene. Further catalytic hydrogenation over Raney nickel gave the tetrahydronaphthalene (32; $R=H_2$) which on oxidation with chromic acid furnished the tetralone (32; R=O). Reaction of this ketone with methylmagnesium bromide gave the dihydronaphthalene (33) which on treatment with perbenzoic acid yielded the tetralone (34) which with 4 - chlorobutan - 2 - one afforded the hexahydrophenanthrene (35). Methylation of (35) with methyl iodide and potassium t-butoxide gave the gem-dimethyl derivative (36) which on hydrogen-

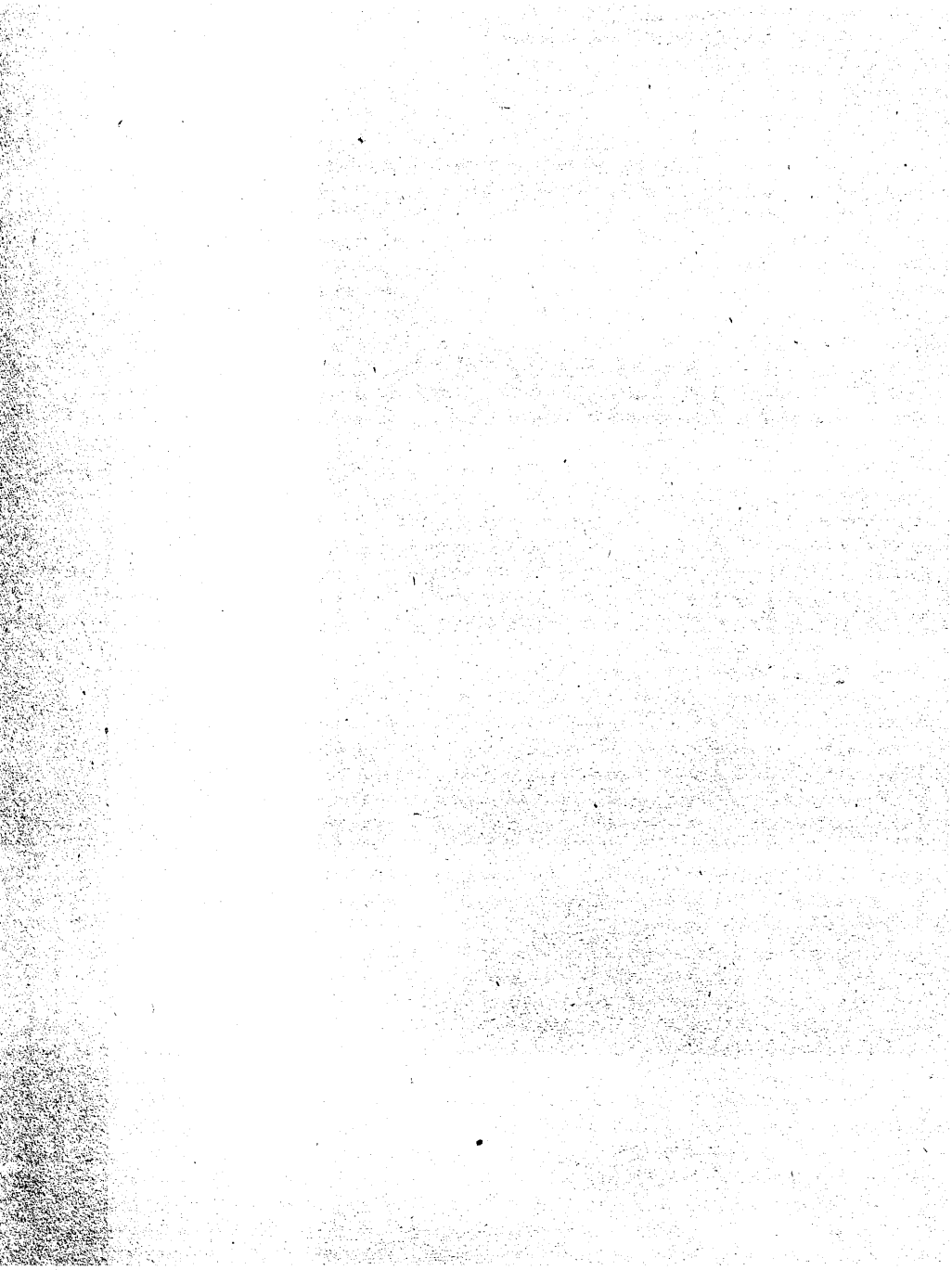
ation over palladium-charcoal gave a mixture which on reoxidation and chromatography yielded dl- 3 - oxototaryl methyl ether and also dl-totaryl methyl ether.

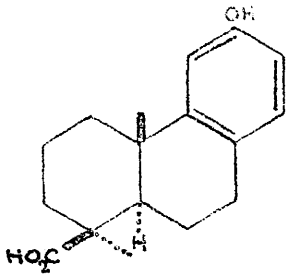
Use has been made of Stork's[61] ketone (37) in the synthesis of compounds related to the tricyclic diterpenoids. This ketone appears to exist mainly in the cis form and was used by Barltrop[62] in the synthesis of dl-trans-deisopropyldehydro - abietic ester (41). Treatment of the ketone (37) under forcing conditions with lithium acetylide in liquid ammonia gave the ethynyl alcohol (38) which was converted by boiling formic acid into the ketone (39). This unsaturated ketone was reduced with sodium in liquid ammonia to the corresponding saturated ketone whose enol acetate was converted by the action of hypobromous acid into the bromoketone (40). The bromoketone underwent the Favorskii rearrangement when heated with methanolic sodium methoxide to give a mixture of methyl esters from which a small amount of the desired dl-trans-deisopropylde-hydroabietic ester was obtained.

Stork's ketone has also been used to effect a synthesis of dl-cis-deisopropydlehydroabietic ester (45; R=H).[63] The ketone (37) was condensed with cyanoacetic ester to give the unsaturated ester (42) to which hydrocyanic acid added stereospecifically from the less hindered rear face of the molecule. The adduct (43) was hydrolysed and esterified to give the acid (44) whose silver salt was brominated to furnish the bromomethyl compound (45; R=Br) which

was reduced to give the required dl-cis-deisopropyldehydroabietic ester.

Use of a similar ketone precursor to that of Stork was made by Wenkert[64] in a further synthesis of d-podocarpic acid. The unsaturated ketone (46) was carboxylated with triphenylmethylsodium and carbon dioxide and then esterified to give a mixture from which the ester (47) was isolated. Stereospecific catalytic hydrogenation afforded the saturated ester (48) which on methylation afforded a mixture of epimers from which the keto ester (49) was obtained. The carbonyl function was removed by Clemmensen reduction and resolution of the product gave d -desoxypodocarpic acid (50; R=H). A Friedel-Crafts acetylation afforded the ketone (50; R=$COCH_3$) which was oxidised by peracetic acid to yield the acetate (50 ; R=$OCOCH_3$) of podocarpic ester. Hydrolysis then gave the desired d -podocarpic acid (21).





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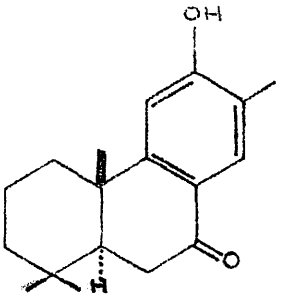

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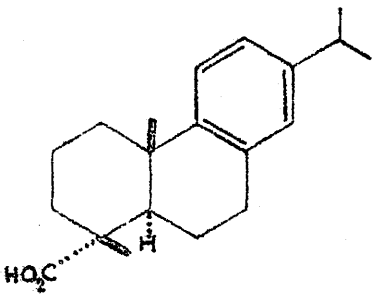

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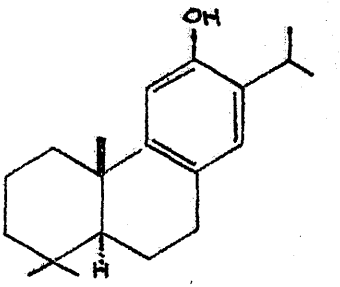

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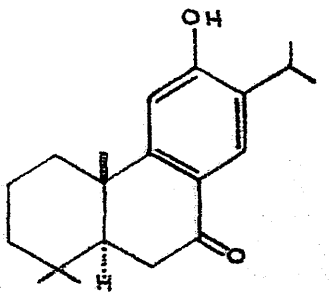

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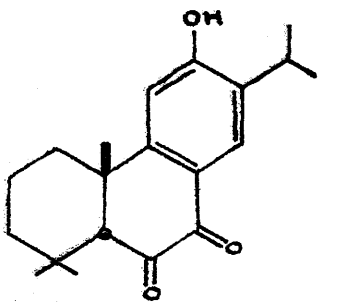

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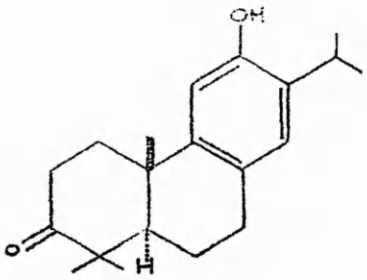

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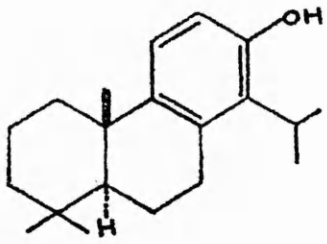
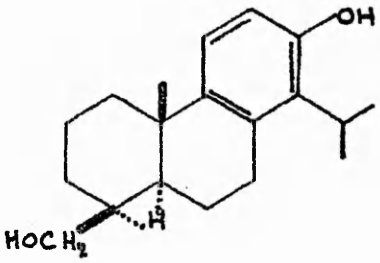


TOTAROL



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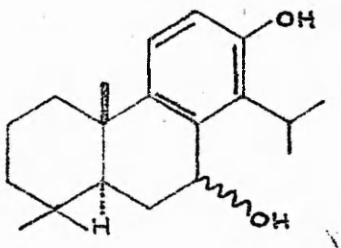

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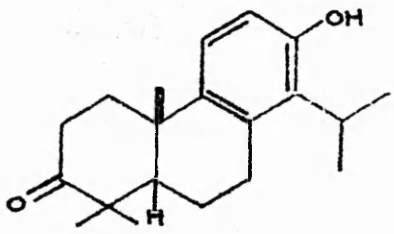

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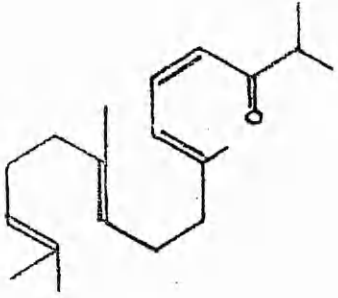

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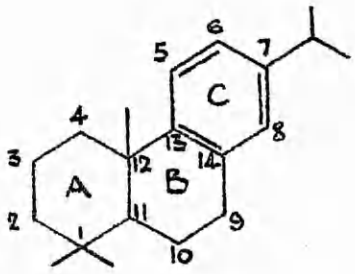

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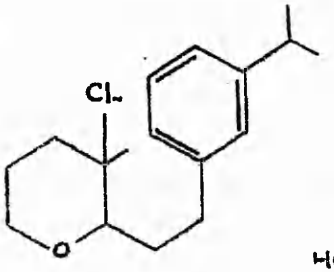

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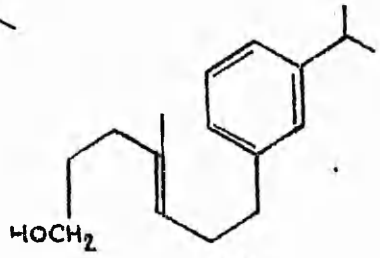

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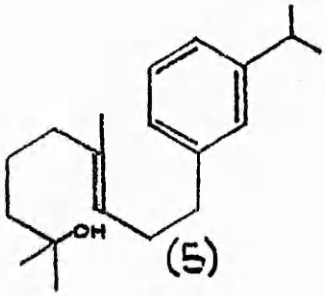

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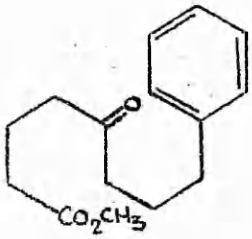

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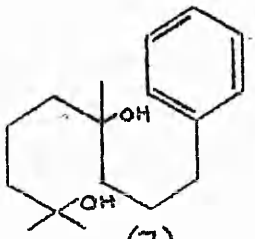

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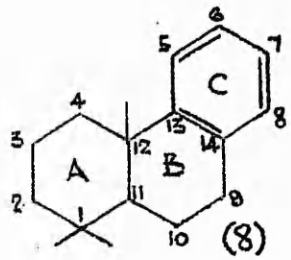

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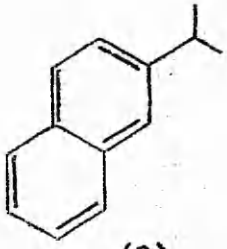

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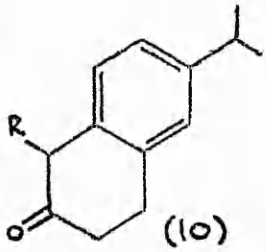

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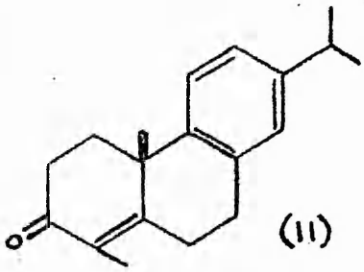

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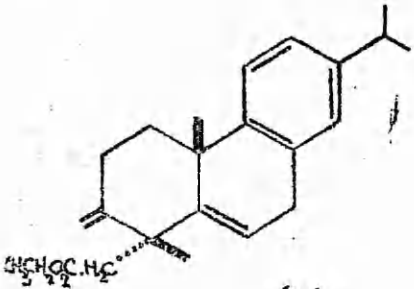

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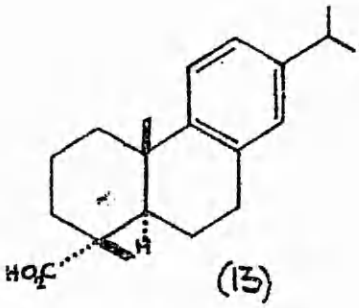

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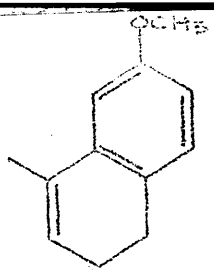

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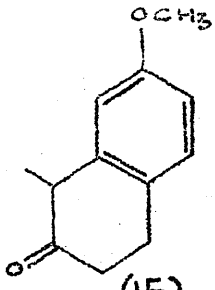

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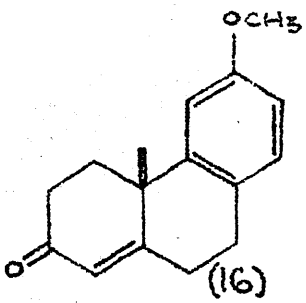

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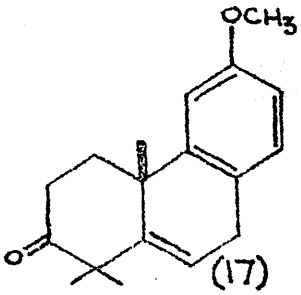

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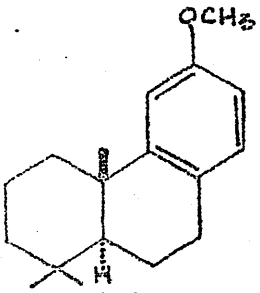

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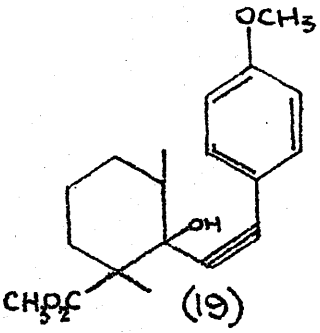

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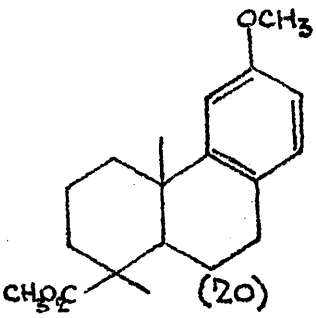

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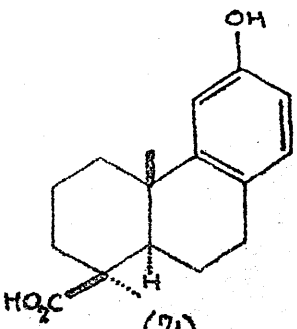

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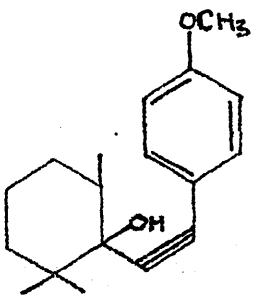

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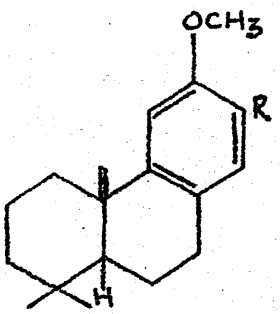

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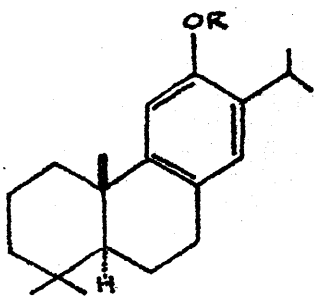

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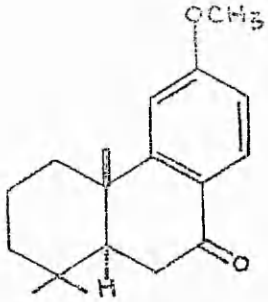

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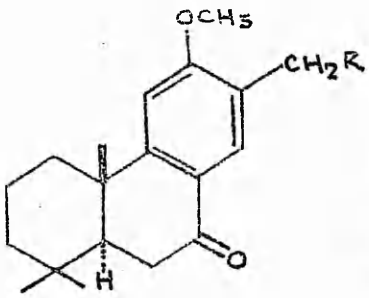

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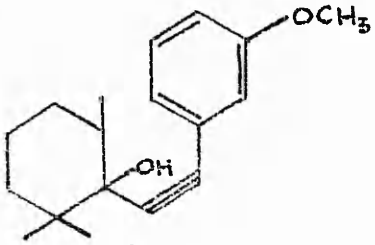

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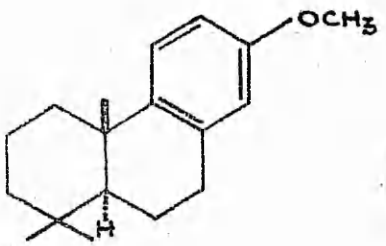

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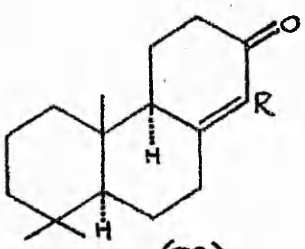

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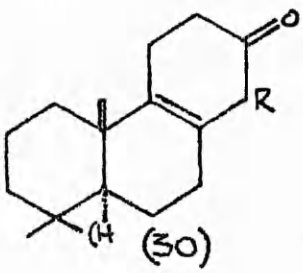

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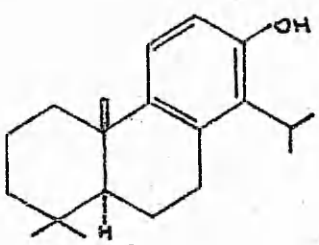

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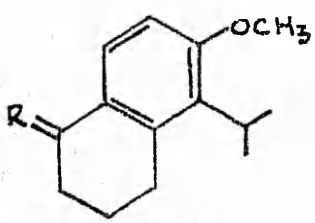

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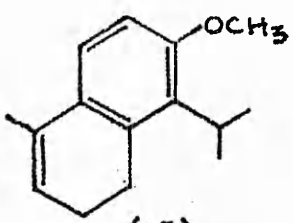

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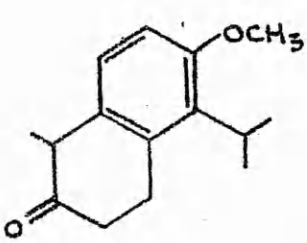

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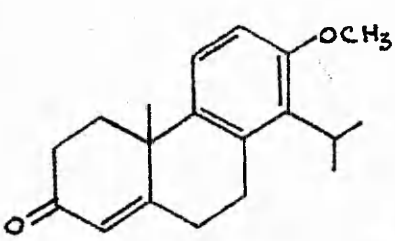

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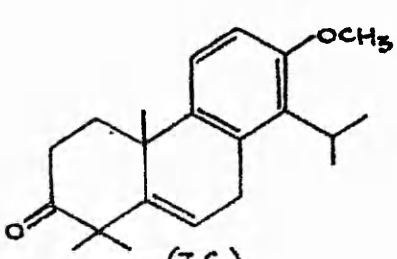

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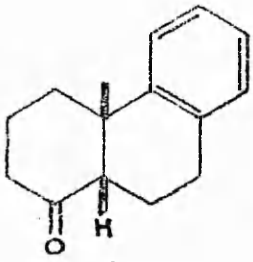

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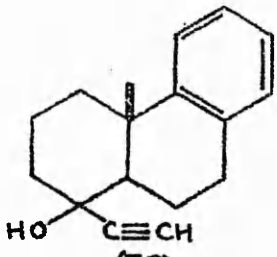

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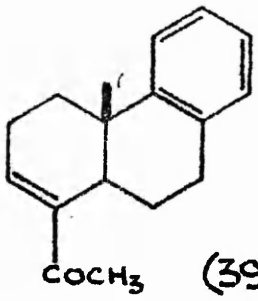

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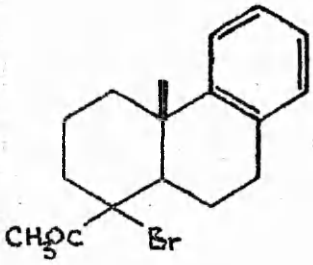

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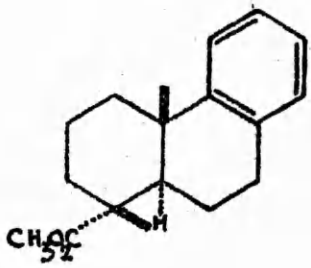

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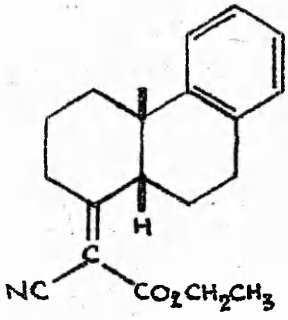

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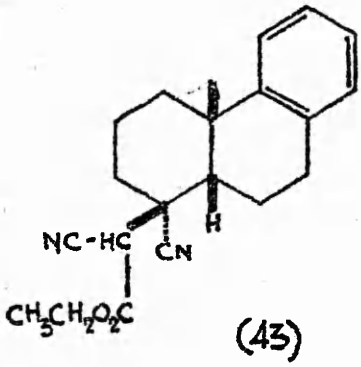

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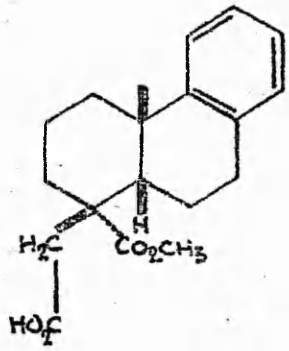

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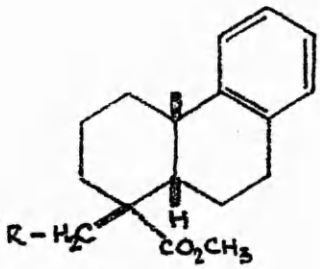

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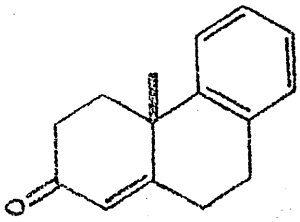

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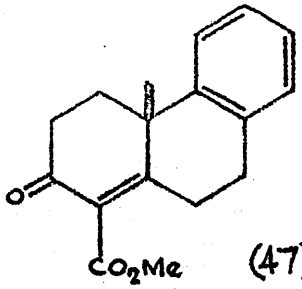

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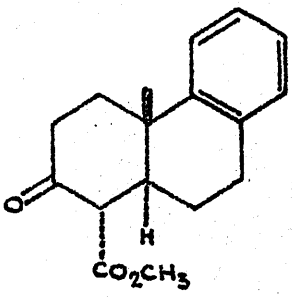

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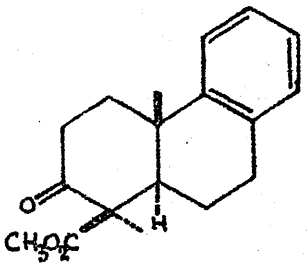

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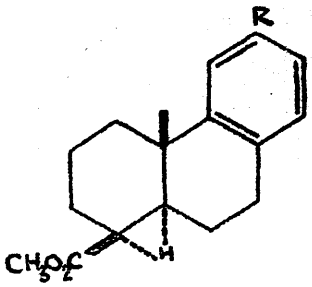

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DISCUSSION

In this field, it seemed worth investigating syntheses of aromatic tricyclic diterpenoids by a route involving a suitably substituted phenylcyclohexanone as an alternative pathway to these compounds such as to allow for elaboration of rings A and C of the fundamental skeleton (8).

In 1950, Bachmann[65] had attempted a synthesis of a tricyclic resin acid from 2-(p-isopropylphenyl) cyclohexanone. This ketone (51) was methylated with methyl iodide and sodamide to give (52) which underwent glyoxalation followed by decarbonylation to furnish the ester (53). Further methylation with methyl iodide and sodamide gave the tetrasubstituted ketone (54) which was sterically hindered to such an extent that it would not undergo a Reformatski reaction to furnish (55). The intended completion of this synthesis involved a ring closure to (56), followed by reduction of the carbonyl group and hydrolysis to yield dehydroabietic acid.

A further synthesis of 1:2:3:4:9:10:11:12 - octahydro - 1:1:12 trimethylphenanthrene (8) was envisaged with the initial formation of 2,6,6 - trimethyl - 2 - phenylcyclohexanone (57) comprising rings A and C of the tricyclic diterpenoid skeleton. Modification of this structure by a suitable addition of a two carbon fragment to the carbonyl function would yield the acid (58) which on a Friedel-Crafts cyclisation would furnish the unsaturated ketone (59).

The required phenanthrene would readily be obtained from this compound by a stereospecific reduction of the double bond from the less hindered rear face of the molecule followed by hydrogenolysis of the benzylic carbonyl function.

Accordingly the readily available o-methoxydiphenyl was subjected to a Birch reduction to give 2 - phenylcyclohex - 2 - enone (60) which on exhaustive methylation using methyl iodide and potassium t-butoxide in t-butanol[66] afforded the tetrasubstituted cyclohexanone (61). The carbonyl function in this molecule, as in (54) proved resistant to attack under Reformatski conditions.[67] However it was felt that the use of an ethynyl organometallic reagent might meet with more success.

Consequently (61) was treated under forcing conditions with sodium acetylide,[68,69] ethynyl magnesium bromide[70] and ethoxyacetylene[71] but in all cases, no reaction was observed. The feasibility of such a synthetic route has recently been demonstrated by Shimizu[72] who effected the successful addition of an acetylenic reagent to the tetrasubstituted carbonyl compound (62). Reaction of ethoxy-ethynyl - lithium with the compound (62), whose carbonyl function presumably is held more open to attack by the presence of the nitrogen bridge in the system, led to the formation of the corresponding adduct (63). This compound was modified by partial reduction and then treatment with phosphorus tribromide to give the aldehyde (64) whose corresponding saturated alcohol was cyclised using polyphosphoric acid to yield the diterpenoid alkaloid structure (65).

The failure of external attack by such reagents on this carbonyl function led to the attempted synthesis of the same partial structure containing an additional acetyl function (71) suitable for internal cyclisation to the desired ketone (59). The Grignard reagent of o-ethylbromobenzene was reacted with cyclohexanone to give, after dehydration of the tertiary alcohol, the phenylcyclohexene (66) which on treatment with mercuric acetate[73] yielded the allylic acetate (67; R=$COCH_3$). Hydrolysis readily gave the allylic alcohol (67; R=H) which was oxidised by manganese dioxide[74] to the corresponding substituted phenylcyclohexenone (68). Exhaustive methylation of this ketone (68) with methyl iodide and potassium t-butoxide in t-butanol gave the trimethyl compound (69) which was readily reduced under catalytic conditions to yield (70).

The allylic acetylation had been considered to give only the 6-substituted cyclohexene (67; R=$COCH_3$) on the precedent of the known similar substitution of phenylcyclohexene;[73] this assumption was rigidly confirmed by an independent synthesis of the cyclohexenone (68) from fluorenone. The derived lactone (72) readily gave the methyl ether carboxylic acid (73) which on treatment with lithium methyl[74] afforded the acetyl derivative (74; R=O). Wolff-Kishner reduction of the carbonyl function gave (74; R=H_2) which on Birch reduction afforded a product identical in all respects with the phenylcyclohexenone (68).

The methylation product (70) of this ketone resisted all attempts to oxidise the ethyl group to the desired acetyl function

using either chromic oxide or chromous oxide.[75] One possible way of overcoming this difficulty could be the preservation of the acetyl function in compound (74; R=O) by a ketal group during the subsequent reaction sequence as outlined above.

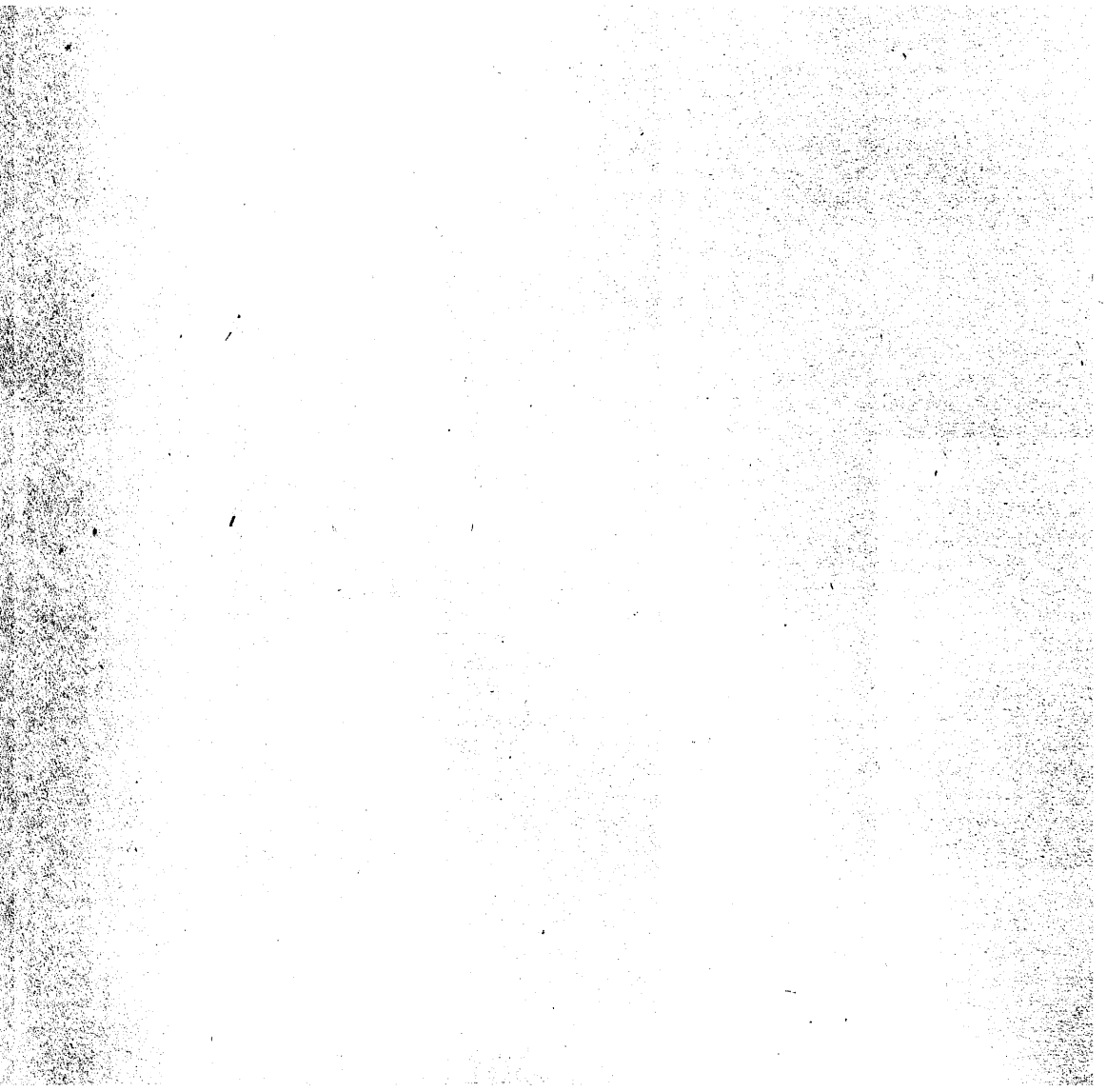
An alternative pathway to the diterpenoid skeleton using a phenylcyclohexane precursor considered the utilisation of Stetter's lactone (75) a compound readily obtainable from the condensation of dihydroresorcinol with o-bromobenzoic acid.[77] Reduction to the ketolactone (76) was envisaged, followed by exhaustive methylation to yield (77). The opening of the lactone ring and removal of the alcoholic function would afford the keto acid (78) whose ketal would readily give the desired acetyl derivative (71) on treatment with lithium methyl.

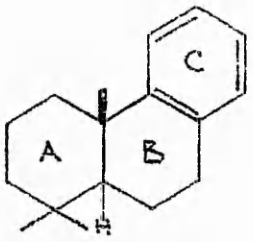
Attempts were made to reduce the double bond in the lactone (75). The lactone did not react with zinc in acetic acid or with hydrogen over palladium-barium sulphate[78] and afforded an intractable gum on treatment with lithuim aluminium hydride. Treatment of the lactone with the calculated amount of sodium borohydride afforded in poor yield the desired ketolactone (76) along with the triol (79). The compound (79) was the sole product of the reaction of an excess of sodium borohydride on the lactone (75) and could be reoxidised to the hydroxy lactone (80) by treatment with manganese dioxide and hence to the desired ketolactone (76) using chromic oxide.

Catalytic hydrogenation of (75) over platinum oxide proved too drastic and afforded a mixture of two non-aromatic lactones (81)

and (82). Reduction over palladium-charcoal left the aromatic ring unaffected but partial hydrogenolysis produced a mixture of the lactone (83) and the hydroxy lactone (80) a stereoisomer of the compound obtained by the alternative pathway.

The unpromising results of the earlier steps in this synthesis precluded any further work.





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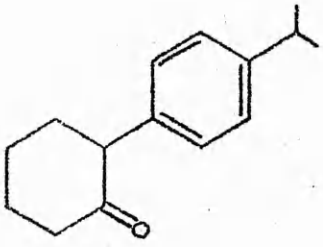

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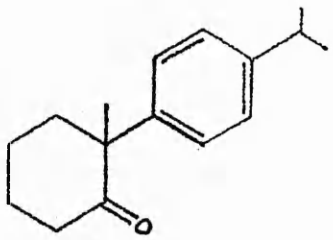

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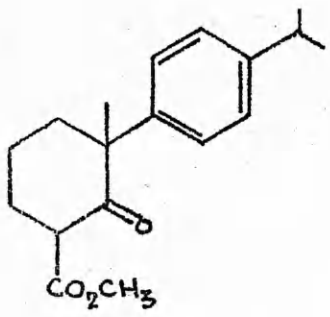

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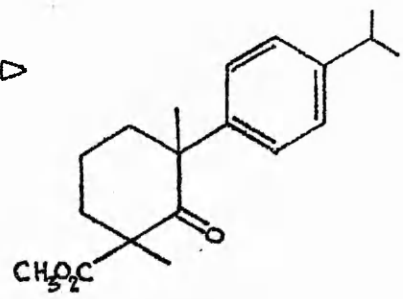

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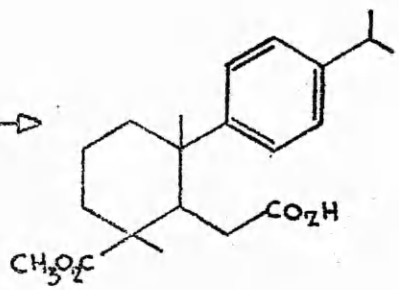

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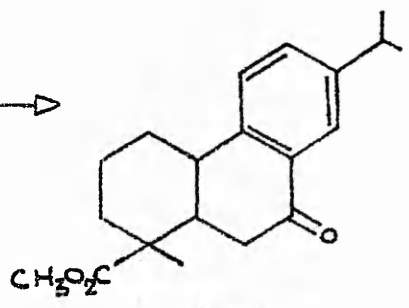

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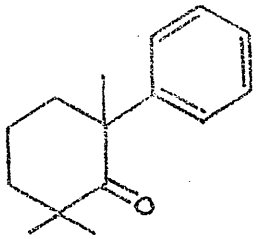

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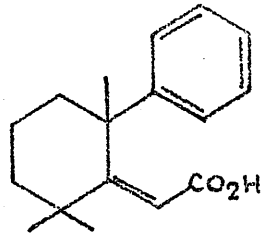

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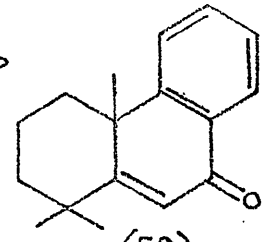

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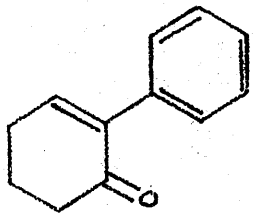

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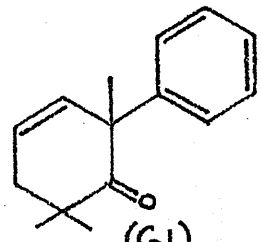

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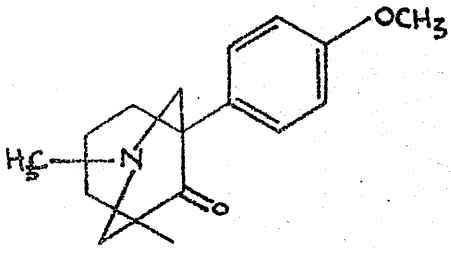

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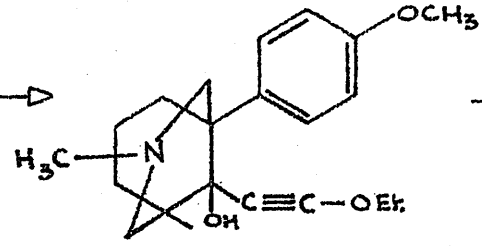

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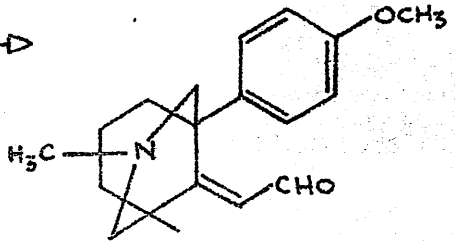

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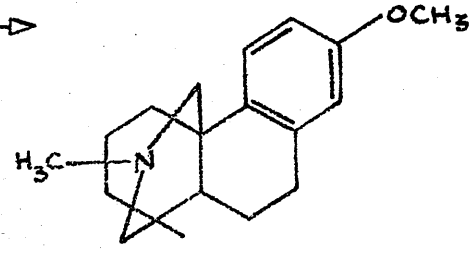

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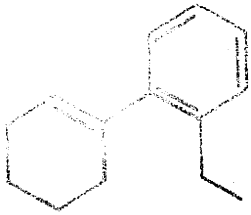

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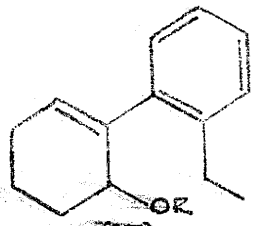

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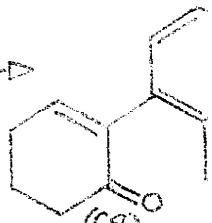

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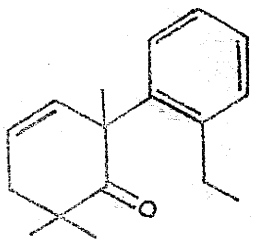

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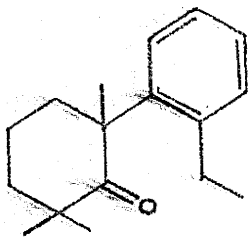

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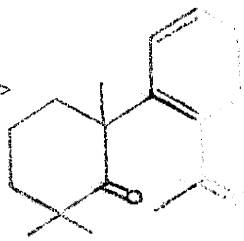

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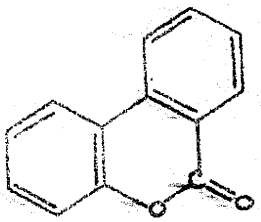

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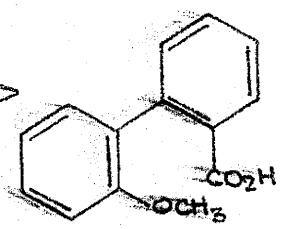

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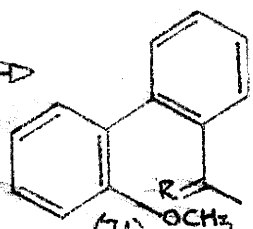

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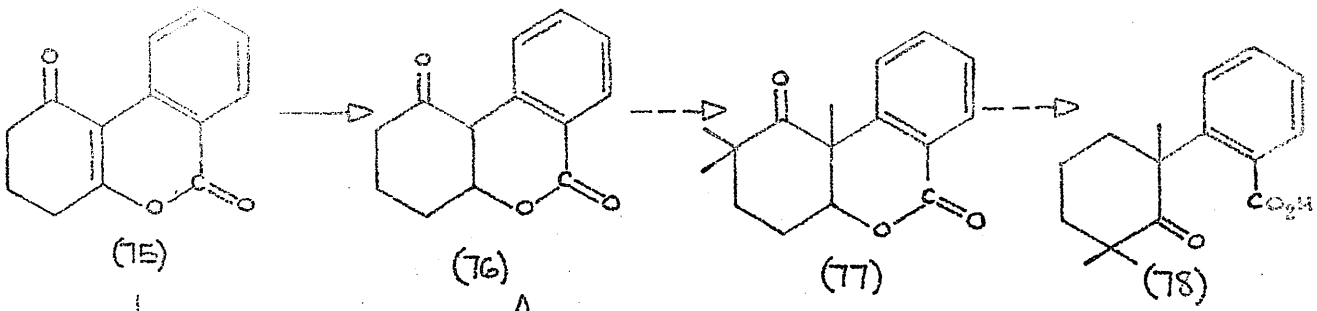
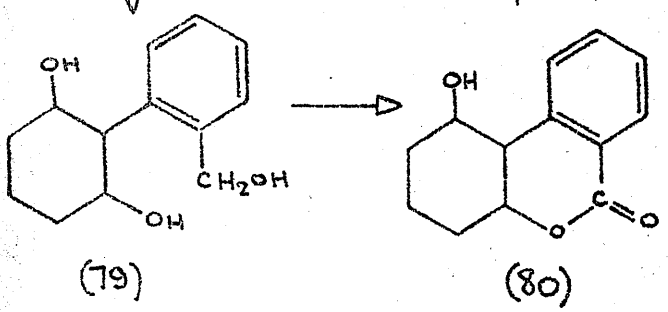


(75) (76) (77) (78)



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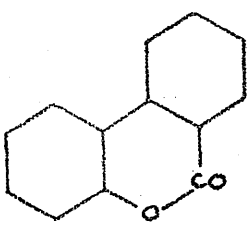

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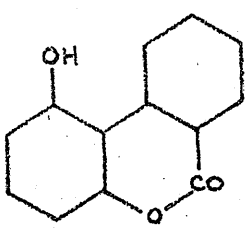

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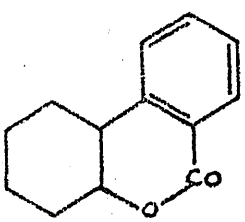

(83)

EXPERIMENTAL

2-Phenylcyclohex-2-enone (60).

Ethanol (175g.) was added dropwise to a stirred mixture of lithium (19g.) in dry liquid ammonia (1500 ml.) and o-methoxydiphenyl (100 g.) in ether (1000 ml.) until the blue colour of the mixture faded and the solution became almost colourless. The ammonia was evaporated, ammonium sulphate solution added and the aqueous mixture ether extracted. The combined ether extracts were washed with dilute sodium hydroxide solution, water and then dried and the solvent evaporated. The residual oil (85 g.) was fractionally distilled to yield 2-phenylcyclohex-2-enone (54 g.) b.p. 169-174°/ 15 mm., n_D^{22} = 1.5516. This material then solidified and was crystallised from ethanol as needles m.p. 91-94° (Lit.[79] m.p. 94-95°).

2-Methyl-2-phenylcyclohex-3-enone.

2-Phenylcyclohex-2-enone (17 g.) in dry t-butanol (200 ml.) was added in an atmosphere of nitrogen to a stirred solution of potassium (4.7 g.) in t-butanol (150 ml.) and the mixture heated under reflux for 15 minutes. Methyl iodide (86 g.) was then added and the reaction mixture heated under reflux for a further hour. The solvent was removed under vacuo, the residues diluted with water, thoroughly extracted with ether and the combined ethereal extracts washed with water, dried and the solvent removed.

The residual oil (18 g.) was fractionally distilled to yield 2-phenylcyclohex-2-enone (9.6 g.) and an impure sample of 2-methyl-2-phenylcyclohex-3-enone (3.3 g.) b.p. 82-90°/0.2 mm., n_D^{20}=1.5410 which was identified by the corresponding 2:4-dinitrophenylhydrazone which crystallised from ethanol as needles m.p. 154°(Found: C,62.35 ; H,5.4 ; N,15.35. $C_{19}H_{18}O_4N_4$ requires C,62.3 ; H,4.95 ; N,15.3%).

2,6,6-Trimethyl-2-phenylcyclohex-3-enone. (61)

2-Phenylcyclohex-2-enone (5.7 g.) in dry t-butanol (130 ml.) was added in an atmosphere of nitrogen to a stirred solution of potassium (5.2 g.) in t-butanol (130 ml.) and the solution heated under reflux for 5 minutes. Methyl iodide (28 g.) in t-butanol (30 ml.) was then added and the reaction mixture heated under reflux for 1 hour before the further addition of methyl iodide (19 g.) in t-butanol (30 ml.). This mixture was then heated under reflux for 90 minutes, the solvent removed and the cooled residues diluted with water and extracted with ether. The combined ethereal extracts were washed with water, dried and evaporated to give an oil (6 g.) which was then fractionally distilled to yield 2,6,6-trimethyl-2-phenylcyclohex-3-enone (2.3 g) as a colourless liquid b.p. 77°/0.05 mm., n_D^{20} = 1.5386 (Found : C,84.4 ; H,8.2. $C_{15}H_{18}O$ requires C, 84.1 ; H,8.45%).

Attempted Reformatsky Reaction on 2,6,6-Trimethyl-2-phenylcyclohex - 3 - enone

A mixture of 2,6,6-trimethyl-2-phenylcyclohex-3-enone (1.3g.) and ethyl bromoacetate (0.75 ml.) in anhydrous ether (15 ml.) was

added to a suspension of zinc wool (2.5 g.) in dry benzene (25 ml.). The mixture was heated under reflux and mercuric chloride (1 mg.) added to initiate reaction. Further quantities of zinc wool (7.5 g.) and ethyl bromoacetate (2.3 g.) were added in three portions over a period of two days. The reaction mixture was cooled and glacial acetic acid added to dissolve a yellow complex deposited on the zinc wool. The acid solution was thoroughly extracted with ether and the combined ethereal extracts washed with sodium carbonate solution, water and dried. Removal of the solvent afforded a mixture from which only the starting materials could be isolated in a pure state.

Attempted Condensation of 2,6,6-Trimethyl-2-phenylcyclohex-3-enone with Sodium Acetylide

Acetylene was passed for 1.5 hours into a stirred suspension of sodamide (250 mg.) in dimethylformamide (30 ml.) at -10°. A solution of the ketone (61) (1 g.) in dimethylformamide (10 ml.) was added dropwise and the stirring continued for a further 3 hours. The reaction mixture was poured on to ice, acidified with dilute sulphuric acid (50%) and thoroughly extracted with ether. The combined ethereal extracts were washed, dried and then evaporated to yield the starting ketone (950 mg.) as the sole product.

Attempted Condensation of 2,6,6-Trimethyl-2-phenylcyclohex-3-enone with Ethynyl Magnesium Bromide

A solution of ethyl magnesium bromide (prepared from magnesium (1.2 g.)) in dry tetrahydrofuran (40 ml.) was added dropwise under nitrogen to a stirred saturated solution of acetylene in

tetrahydrofuran (50 ml.). A solution of the ketone (61) (2.14g) in tetrahydrofuran (20 ml.) was then added to the reaction mixture and the whole stirred overnight at room temperature then poured into saturated ammonium chloride solution. Ethereal extraction afforded only the starting ketone (2 g.).

Attempted Condensation of 2,6,6-Trimethyl-2-phenylcyclohex-3-enone with Ethoxy Acetylene

A solution of the ketone (61) (140 mg.) in anhydrous ether (10 ml.) was added under nitrogen to a stirred solution of ethoxyacetylene (70 mg.) and boron trifluoride in ether (25 ml.) and the whole stirred for 12 hours at room temperature. The ethereal solution was then washed with water, dried and evaporated to give an oily residue from which only starting materials were isolated.

1-(o-Ethylphenyl) cyclohexene (66)

o-Ethyl bromobenzene (10 g.), prepared from o-ethyl aniline by the method of Wood,[80] and a crystal of iodine (1 mg.) were added in a nitrogen atmosphere to a stirred suspension of dry magnesium turnings (4 g.) in dry ether (20 ml.). The mixture was maintained under refluxing conditions by vigorous stirring and the dropwise addition of o-ethyl bromobenzene (20.8 g.) in ether (140ml) and then heated under reflux for a further period of 1 hour. The cooled reaction solution was treated with cyclohexanone (14 g.) in ether (40 ml.) and the mixture heated under reflux for 2 hours. The cooled reaction mixture was poured into saturated ammonium chloride solution, the aqueous mixture thoroughly ether extracted and the combined extracts washed with saturated sodium bisulphite solution, water and dried. After evaporation of the solvent, the residual oil (36 g.) was heated under reflux with naphthalene-2-sulphonic acid (1 g.) in benzene (200 ml.) for 3 hours, the benzene solution washed with dilute sodium hydroxide solution, water and then dried. The crude product (27 g.) obtained on evaporation of the solvent was distilled to give 1-(o-ethylphenyl) cyclohexene (18 g.) as a colourless liquid, b.p. 69°/0.2 mm., n_D^{20} = 1.5371 λ max. 220 (ε 7,400), (Found : C,90.25 ; H,10.0. $C_{14}H_{18}$ requires C,90.25 ; H,9.75%).

2-(o-Ethylphenyl cyclohex-2-en-1-ol (62 ; R=H).

1-(o-Ethylphenyl) cyclohexene (18 g.) in glacial acetic acid (30 ml.) was added to a stirred solution of yellow mercuric oxide

(43 g.) in glacial acetic acid (150 ml.) and the reaction mixture heated under reflux for 1 hour. The acetic acid was removed in vacuo and the residues thoroughly extracted with ether. The combined ethereal extracts were washed with dilute sodium hydroxide solution, water dried and the solvent removed to yield the crude acetate (67 ; R=$COCH_3$) as an oil (24 g.) which was heated under reflux with potassium hydroxide (30 g.) in aqueous methanol for 5 hours. The cooled solution was ether extracted, the combined extracts washed with water, dried and the ether evaporated to give the desired product as an oil (16 g.) which was adsorbed from benzene on alumina and eluted with benzene-ether (7 : 3) to yield 2-(o-ethylphenyl) cyclohex-2-en-1-ol as a colourless oil, b.p. 101°/0.05 mm., n_D^{20} 1.5510, which crystallised from light petroleum as plates, m.p. 35-36° (Found : C,83.05 ; H,9.0 $C_{14}H_{18}O$ requires C, 83.1 ; H,9.0%).

2-(o-Ethylphenyl) cyclohex-2-enone (68).

2-(o-Ethylphenyl) cyclohex-2-en-1-ol (10 g.) in light petroleum (300 ml.) was shaken with active manganese dioxide (100g. supplied by Wooley) for 90 hours, and the reaction mixture then filtered and evaporated to give an oil (9 g.) which was distilled to yield 2-(o-ethylphenyl) cyclohex-2-enone as a colourless liquid (6 g.), b.p. 108°/0.05 mm., n_D^{18} 1.5610, $\lambda_{max.}$ 228 (ε, 6,000), (Found : C,83.6 ; H,7.78. $C_{14}H_{16}O$ requires C,83.96 ; H,8.05%).

The corresponding 2:4-dinitrophenylhydrazone crystallised from chloroform-ethanol as needles m.p. 135° (Found : C,63.4 : H,4.95 ; N,14.55. $C_{20}H_{20}O_4N_4$ requires C,63.15 ; H,5.30 ; N,14.7%). The corresponding semicarbazone crystallised from aqueous ethanol as needles m.p. 170° (Found : C,70.2 ; H,7.45 ; N,16.35. $C_{15}H_{19}ON_3$ requires C,70.0 ; H,7.45 ; N,16.35%).

2,6,6-Trimethyl-6-(o-ethylphenyl) cyclohex-4-enone (69)

2-(o-Ethylphenyl) cyclohex-2-enone (2 g.) in dry t-butanol (15 ml.) was added under nitrogen to a stirred solution of potassium (2.5 g.) in t-butanol (15 ml.) and the mixture heated under reflux for 10 minutes, then cooled and methyl iodide (10 g.) in t-butanol (10 ml.) added. The mixture was stirred for 2 hours at room temperature and for 1 hour under refluxing conditions and then poured into ice and the aqueous mixture extracted with ether. The combined ether extracts were washed with water, dried, and the solvent removed to give a residual oil (2.3 g.) which was fractionally distilled to yield 2,6,6-trimethyl-6-(o-ethylphenyl) cyclohex-4-enone (700 mg.) as a viscous oil b.p. 70°/0.02 mm., n_D^{27} 1.5288 (Found: C,84.0 ; H,9.35. $C_{17}H_{22}O$ requires C,84.25 ; H,9.15%).

2,6,6-Trimethyl-6-(o-ethylphenyl) cyclohexanone (70)

2,6,6-Trimethyl-6-(o-ethylphenyl) cyclohex-4-enone (350 mg.) in glacial acetic acid (10 ml.) was catalytically hydrogenated over 10% palladium charcoal (100 mg.) with uptake of 30 ml. of

hydrogen (theory requires 32 ml.). The solution was filtered and the solvent removed under vacuo to give an oil (280 mg.) which was adsorbed from light petroleum on alumina and eluted with light petroleum-benzene (4 : 1) to give 2,6,6-trimethyl-6-(o-ethylphenyl) cyclohexanone (180 mg.) as a colourless liquid, b.p. 65°/0.05 mm., n_D^{25} 1.5570 (Found: C,83.4 ; H.9.95. $C_{17}H_{24}O$ requires C,83.55 ; H,9.9%).

o-Ethylphenylcyclohexane

1-(o-Ethylphenyl) cyclohexene (930 mg.) in ethyl acetate (50 ml.) was catalytically hydrogenated over 10% palladium-charcoal (200 mg.) with uptake of 118 ml. of hydrogen (theory requires 112 ml.). The solution was filtered and the solvent removed to give an oil (850 mg.) which was fractionally distilled to yield o-ethylphenylcyclohexane (450 mg.) as a colourless liquid b.p. 78°/0.5 mm., n_D^{21} 1.5245 (Found: C,89.25 ; H,10.95 $C_{14}H_{20}$ requires C,89.3 ; H,10.7%).

2-(o-Ethylphenyl) cyclohexanone

2-(o-Ethylphenyl) cyclohex-2-enone (200 mg.) in glacial acetic acid (30 ml.) was catalytically hydrogenated over 10% palladium-charcoal (100 mg.) with uptake of 24 ml. of hydrogen (theory requires 23 ml.). The solution was filtered and the solvent removed to give an oil which was adsorbed from light petroleum on alumina and eluted with light petroleum-benzene (4:1) to yield 2-(o-ethylphenyl) cyclohexanone (120 mg.) as a colourless oil,b.p. 114°/0.05 mm., n_D^{20} 1.5350 (Found; C.82.95 ; H,9.15. $C_{14}H_{18}O$ requires C,82.15 ; H.9.0%).

2'-Methoxydiphenyl-2-carboxylic Acid (73).

The lactone (72) (20g.), obtained from fluorenone as described by Doering,[81] was heated under reflux for 2 hours with potassium hydroxide (20g.) and dimethyl sulphate (12 ml.) in aqueous methanol. The reaction was then cooled, washed with ether and the alkaline layer acidified with dilute hydrochloric acid to give 2'-methoxydiphenyl-2-carboxylic acid (24g.) which crystallised from ethyl acetate as prisms m.p. 151° (Found: C, 73.6 ; H, 5.65. $C_{14}H_{12}O_3$ requires C, 73.65 ; H, 5.3%).

2-Acetyl-2'-methoxydiphenyl (74 ; R=O)

An ethereal solution (300 ml.) of lithium methyl, prepared from lithium (3.3g.) and methyl iodide (44g.), was added dropwise under nitrogen to a stirred solution of 2'-methoxydiphenyl-2-carboxylic acid (23g.) in benzene-ether (1:1) and the mixture heated under reflux for 45 minutes. The reaction mixture was washed with water, and dilute sodium carbonate solution, dried and then concentrated to yield 2-acetyl-2'-methoxydiphenyl (22g.) which crystallised from ethanol-light petroleum as needles m.p. 93° (Found: C,79.4 ; H,6.3. $C_{15}H_{14}O_2$ requires C,79.6 ; H,6.25%).

The corresponding 2:4-dinitrophenylhydrazone crystallised from chloroform-ethanol as needles, m.p. 170° (Found: C,61.9 ; H,4.4 ; N,13.75. $C_{21}H_{18}O_5N_4$ requires C,62.05 ; H,4.45 ; N,13.8%).

When a solution of the acid (73) (4.5g.) in ether-benzene (1:1) was added under nitrogen to a solution of lithium methyl prepared from lithium (600 mg.) and methyl iodide (9g.) and the mixture heated under reflux for 1 hour, isolation of the product by the above procedure gave a neutral mixture of products (3.5g.) which was adsorbed from light petroleum-benzene (1:1) on alumina and eluted with benzene-light petroleum (4:1) to give the ketone (74 ; R=O) (2.3g.). Elution with benzene-ether (4:1) afforded the corresponding tertiary alcohol (500 mg.) which crystallised from light petroleum as plates m.p. 78° (Found: C,79.25 ; H,7.55. $C_{16}H_{18}O_2$ requires C,79.3 ; H,7.5%).

2-Ethyl-2^1-methoxydiphenyl (74 ; R=H_2)

A mixture of 2-acetyl-2^1-methoxydiphenyl (16g.), anhydrous hydrazine (30 ml.) and diethylene glycol (200 ml.) was heated under gentle reflux at an internal temperature of 180° for 3 hours. The internal temperature was then raised to 200° by distillation of the excess hydrazine and water present, and solid potassium hydroxide (18g.) was gradually added and the reaction mixture heated under reflux for a further 3 hours then cooled, diluted with water and extracted with light petroleum. The combined extracts were dried and the solvent removed to give an oil (15g.) which was adsorbed from light petroleum on alumina and eluted with the same solvent to give 2-ethyl-2^1-methoxydiphenyl (14.5g.) which crystallised from light petroleum (b.p. 40-60°) as needles

m.p. 45.5-46° (Found: C,85.0 ; H,7.4. $C_{15}H_{16}O$ requires C,84.9 ; H,7.6%).

2-(o-Ethylphenyl) cyclohex-2-enone (68).

A solution of ethanol (8 ml.) in ether (10 ml.) was added dropwise to a stirred mixture of lithium (1.6g.) in dry liquid ammonia (150 ml.) and 2-ethyl-2^1-methoxydiphenyl (8g.) in ether (100 ml.) until the blue colouration disappeared. The ammonia was removed, ammonium sulphate and water were added, the alkaline solution extracted with ether, and the combined ethereal extracts washed with water, dried and the solvent removed to give a colourless oil (5g.). This material was adsorbed on alumina from light petroleum and eluted with the same solvent to give 2-ethyl-2^1-methoxydiphenyl (3.2g.). Elution with benzene-light petroleum (4:1) gave a mixture of ketones (0.6g.) while elution with benzene afforded 2-(o-ethylphenyl) cyclohex-2-enone (450mg.) identified as the corresponding 2:4-dinitrophenylhydrazone which crystallised from chloroform-ethanol as needles, m.p. 134-135°. This sample did not depress in melting point on admixture with a sample prepared by the alternative route.

Enol Lactone corresponding to 2-(o-Carboxyphenyl) cyclohexan - 1 : 3 - dione (75)

This was prepared from dihydroresorcinol and o-bromobenzoic acid by the method of Stetter.[77]

2-(o-Hydroxymethylphenyl) cyclohexan-1:3-diol (79).

A mixture of the lactone (75) (2g.) and sodium borohydride (2g.) in dioxan (200 ml.) and water (1 ml.) was left to stand overnight then treated with dilute hydrochloric acid and the solvent removed. The residues were diluted with water, extracted with ether, and the combined ethereal extracts dried and the solvent removed to yield 2-(o-hydroxymethylphenyl) cyclohexan - 1 : 3-diol (1.8g.) which crystallised from ethyl acetate as prisms m.p. 192° (Found: C,70.45 ; H,8.2. $C_{13}H_{18}O_3$ requires C,70.35 ; H,8.2%). λ_{max} 264(ε1,140).

The corresponding triacetate crystallised from ethyl acetate as prisms m.p. 113° (Found: C,65.65 ; H,6.9. $C_{19}H_{24}O_6$ requires C,65.5 ; H.6.95%).

2-(o-Carboxyphenyl) cyclohexan-1:3-diol Lactone (80).

A solution of 2-(o-hydroxymethylphenyl) cyclohexan-1:3-diol (1g.) in dry tetrahydrofuran (25 ml.) was shaken with active manganese dioxide (10g.) for 20 hours, and the reaction mixture then filtered and the solvent removed to give 2-(o-carboxyphenyl) cyclohexan-1:3-diol lactone (840 mg.) which crystallised from ethyl

acetate as needles, m.p. 131-132° (Found: C,71.25 ; H,6.3. $C_{13}H_{14}O_3$ requires C,71.5 ; H,6.45%). λ_{max} 233, 281 (ε 10,000, 1,600).

The corresponding acetate crystallised from ethyl acetate as prisms m.p. 153° (Found: C,69.25 ; H,5.9. $C_{15}H_{16}O_4$ requires C,69.2 ; H,6.2%).

2-(o-Carboxyphenyl)-3-hydroxycyclohexanone Lactone (76).

A solution of chromium trioxide-sulphuric acid (6.6 ml. 3.5 molar) was added dropwise to a cooled solution of 2-(o-carboxyphenyl) cyclohexan-1:3-diol lactone (5g.) in acetone (60 ml.). The reaction mixture was diluted with water and the white solid filtered off and crystallised from ethyl acetate to yield 2-(o-carboxyphenyl)-3-hydroxycyclohexanone lactone (4.6g.) as needles, m.p. 145-146° (Found: C,72.0 ; H,5.2. $C_{13}H_{12}O_3$ requires C,72.2 ; H,5.6%). λ_{max} 234, 282, 303 (ε 11,200, 2,200, 600).

This ketolactone (76) was also obtained when a mixture of 2-(o-hydroxymethylphenyl) cyclohexan-1:3-diol (2g.) in methanol (300 ml.) and sodium borohydride (500 mg.) in water (1 ml.) was left to stand overnight, treated with acetic acid and the solvent removed. The residues were diluted with water, extracted with ether and the combined ethereal extracts dried and evaporated to give crude product which on repeated crystallisation from ethyl acetate afforded 2-(o-carboxyphenyl)-3-hydroxycyclohexanone lactone (200 mg.) as needles, m.p. 147-148° (Found: C,72.25 ;

H,5.65. $C_{13}H_{12}O_3$ requires C,72.2 ; H.5.6%).

2-(2^1-Carboxycyclohexyl) cyclohexanol Lactone (81) and 2-(2^1-Carboxycyclohexyl) cyclohexan-1:3-diol Lactone (82).

The lactone (75) (2g.) in glacial acetic acid (100 ml.) was catalytically reduced over platinum oxide (200 mg.) with uptake of 700 ml. of hydrogen. The solution was filtered and the solvent removed under vacuo to give an oil (2g.) which was adsorbed from benzene on alumina and eluted with the same solvent to give 2-(2^1-Carboxycyclohexyl) cyclohexanol lactone (500 mg.) which crystallised from ethyl acetate as prisms m.p. 132° (Found: C,74.95 ; H,9.45. $C_{13}H_{20}O_2$ requires C,74.95 ; H,9.65%).

Elution with ether-benzene (4:1) gave 2-(2^1-carboxycyclohexyl) cyclohexan-1:3-diol lactone (980 mg.) which crystallised from ethyl acetate as needles m.p. 172-173° (Found:C,70.35 ; H,8.55. $C_{13}H_{18}O_3$ requires C,70.25 ; H,8.15%).

2-(o-Carboxyphenyl) cyclohexan-1:3-diol Lactone (80) and 2-(o-Carboxyphenyl) cyclohexanol Lactone (83).

The lactone (75) (2g.) in glacial acetic acid (100 ml.) was catalytically reduced over 10% palladium-charcoal with uptake of 490 ml. of hydrogen. The solution was filtered and the solvent removed under vacuo to give an oil (1.9g.) which was adsorbed from benzene on alumina and eluted with benzene-ether (9:1) to give 2-(o-carboxyphenyl) cyclohexanol lactone (800 mg.) which

crystallised from acetone-ethyl acetate as plates, m.p. 93.5° (Found: C,77.35 ; H,6.95. $C_{13}H_{14}O_2$ requires C,77.2 ; H,6.95%).

λ_{max} 235, 282 (ε 8 585, 606).

Elution with ether-methanol (9:1) afforded 2-(o-carboxyphenyl) cyclohexan-1:3-diol lactone (950 mg.) which crystallised from acetone-ethyl acetate as prisms m.p. 160-162° (Found: C,72.1 ; H,6.55. $C_{13}H_{14}O_3$ requires C,71.55 ; H,6.45%).

λ_{max} 237, 282 (ε 12,500, 2000).

The corresponding acetate crystallised from acetone-ethyl-acetate as prisms m.p. 108-109° (Found: C,68.65 ; H,6.0. $C_{15}H_{16}O_4$ requires C,69.2 ; H,6.2%).

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