A Thesis

entitled

'Terpene Syntheses employing Aromatic Precursors'

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by J. Carnduff, B.Sc.

Chemistry Department

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

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References

Part I.

Synthetic Approaches to Totarolone.

Summary of the thesis entitled

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submitted in July, 1963 by John Carnduff, B.Sc., to the University of Glasgow for the degree of Doctor of Philosophy in the Faculty of Science.

The thesis comprises two parts.

In Part I, a review, complete to March, 1963, is given of all known aromatic diterpenes having an octahydrophenanthrene ring system and in particular of the compound totarolone. Aspects of their biogenesis and synthesis are discussed. An account is given of an investigation of a number of naphthalene derivatives which could function as precursors for a synthesis of totarolone.

In an attempt to prepare 1,2,3,4-tetrahydro-5-isopropyl-2-keto-6-methoxy-1-methylnaphthalene, 2,6-dimethoxynaphthalene, 1-isopropyl-2-methoxynaphthalene and 1-isopropyl-2,6-dimethoxynaphthalene were synthesised.
2,6-Dimethoxynaphthalene could be reduced to the 1,4-dihydro-derivative but attempts to methylate this product at the 1-position failed.
1-Isopropyl-2-methoxynaphthalene underwent an abnormal nitration reaction giving an α-nitroketone with loss of the O-methyl group.
5-Bromo-6-hydroxytetralin was converted to 5-isopropyl-6-methoxytetralin which has now been converted, elsewhere to totarolone.
Methyl 2-hydroxy-1-naphthoate was converted to 1-isopropenyl-2-naphthol and 1-isopropyl-2-naphthol. The latter, however, proved to be much more readily available by direct alkylation of sodium 2-naphthoxide.
The mechanism of this process is discussed.
1-Isopropyl-2-naphthol showed a remarkable propensity for oxygen absorption, being rapidly converted in air to 1,2-dihydro-1-hydroperoxy-1-isopropyl-

cont'd.

2-keto-naphthalene. Since an autoxidation is possibly a key step in the biogenesis of totarol, this reaction was studied in some detail and comparison made of the reactivity of 1-isopropyl-2-naphthol with that of 1-methyl-2-naphthol and 3-isopropyl-2-naphthol, the latter being prepared from 2-hydroxy-3-naphthoic acid.

In Part II, the structures, biogenesis and published syntheses of all known iridoid monoterpenes are reviewed. An account is given of a reinvestigation of a synthetic approach to these substances from suitably substituted indanes.

Condensation of para-cresol with ethyl acetoacetate gave 4,6-dimethyl-coumarin which was converted to 3-(2-methoxy-5-methylphenyl)butyric acid. Cyclisation of this with polyphosphoric acid gave a methoxyindanone which on Clemmensen reduction and demethylation gave 7-hydroxy-1,4-dimethylindane. This phenol was also obtained by rearrangement of the 3,4-dihydro-derivative of the above coumarin to a hydroxyindanone and reductive removal of the carbonyl group of the latter by the Clemmensen procedure.
The degradation of this phenol to nepetalinic acid has been investigated.
By a route similar to the first one above, 5,7-dihydroxy-1,4-dimethylindane has been prepared from 4-methylresorcinol and ethyl acetoacetate.
It should be possible to convert this relatively simply to nepetalinic acid and research on this subject is continuing.

Aromatic Diterpenes - Structures and Syntheses.

Natural Occurrence of Octahydrophenanthrene Diterpenes.

A fairly large number of diterpenes is now known which possess an octahydrophenanthrene ring system with ring C aromatic. These must arise by rearrangement or degradation of the basic tricyclic skeleton of the ion (1) which is produced directly by cyclisation of four isoprene units (probably as shown) and which, without rearrangement, can give rise to naturally occurring but non-aromatic compounds such as pimaric acid (2).

The aromatic compounds can be grouped according to their skeletal structure and the extent of the rearrangement or degradation.

At present, examples of five such skeletons with an aromatic ring C are known, namely those exemplified by the compounds podocarpic acid (4), nimbiol (6), picrosalvin (7), ferruginol (9) and totarol (14).

The basic skeleton, 1,1,12-trimethyl-1,2,3,4,9,10,11,12-octahydrophenanthrene has been called podocarpane[1] and the numbering shown in (3) will be used for the following survey.

The only naturally occurring example of the first type is podocarpic acid itself (4) which carries oxygen functions at C-15 and C-6, but 6,7-dihydroxypodocarpane (5) has been identified as a pyrolysis product of maytenone[1].

The sole example of the second class is nimbiol (6) with oxygen functions at C-6 and C-9.

The third class is represented only by the recently discovered lactone, picrosalvin, which almost certainly has the structure (7)[2].

In contrast, the ferruginol skeleton is common and a number of acids and phenols is known. Dehydroabietic acid (8), oxygenated at C-15, occurs in Pinus palustris and is readily produced by heating or dehydrogenating any of the abietic acids. Oxygen functions at C-6 occur in ferruginol (9), 9,10-dehydroferruginol, sugiol (10) and xanthoperol (11) and a C-2 function, so common in the steroid field, occurs in hinokione (12) and the corresponding alcohol, hinokiol. The structure (13) has been proposed very recently for the compound cryptojaponol[3]. It shows the same 5,6-dioxy pattern as picrosalvin.

Until 1960, the only example of the fifth group was totarol (14) but recently other totarols have been found which correspond in oxygenation pattern to most of the known ferruginol types.

The hydroxytotarol isolated by Brandt and Thomas[4] has been shown[5,6] to have the structure (17) with a C-15 hydroxyl group and the corresponding aldehyde[6,7] and acid[7,8] have also been found naturally. Another hydroxytotarol identified by Hodges[9] as (15) occurs as a mixture of epimers at C-9 and is analogous to sugiol (10).

In 1960, the totarol analogue (16) of hinokione (12) was isolated, together with its 3,4-dehydro-derivative, from Tetraclinis articulata (Vahl, Masters) by Chow and Erdtman[10]. The structure of this totarolone, the synthesis of which was the aim of part of the research described below, was established as follows.

It had the formula $C_{20}H_{28}O_2$ and on Clemmensen reduction gave totarol in good yield. Its infra-red and ultra-violet spectra indicated the presence of a keto group unconjugated with the aromatic ring. This ketone function was proved to be adjacent to the gem-dimethyl group by conversion to the hydroxy-ether (18) and degradation of this with, successively, phosphorus pentachloride, osmium tetroxide and lead tetraacetate to the trisnor-ketone (19) and acetone. Optical rotatory dispersion data and molecular rotation differences were similar to those of hinokione and of 3-keto-5α,10β-steroids.

Thus most oxygenation patterns known in the 7-isopropyl-podocarpane series have found analogues in the 8-isopropyl series.

Biogenetic Theories.

As mentioned above a probable intermediate in the biogenesis of all these compounds is the ion (1) which has a quaternary carbon atom in ring C. The possible modifications of this ion are numerous and several are summarised in scheme A.

Without carbon - carbon bond shifts, it can give rise to products of the pimaric acid type. Cyclisation with or without bond shift can give the skeletons of phyllocladene or stachenone[11]. Loss of a proton gives the pimaradiene structure which on reprotonation and methyl shift in either of the possible directions gives rise to the skeletons of picrosalvin and of ferruginol. Hydration of the vinyl group of the pimaradiene and retroaldol-type fission as shown would give the skeleton of nimbiol as suggested by Wenkert[12].

A less plausible idea of Wenkert is that the degradation leading to podocarpic acid procedes by a series of Friedel-Crafts-type reactions involving fission of ring B, recyclisation and 'extrusion' of the isopropyl group[13]. In a similar manner he depicts a rearrangement of ferruginol to totarol as shown (scheme B) as a biogenetic route to the latter. A simpler extension of scheme A which would lead to totarol is not easily formulated. Johnson[1] has suggested that this compound is produced by a rearrangement similar to that which appears to occur in the pyrolysis of maytenone.

All these aromatic compounds except the totarols and dehydroabietic acid carry an oxygen function at C-6. Its introduction may be an integral part of the biosynthesis of the aromatic ring. The other oxygen functions occur at C-2 (by cyclisation of geranylgeraniol where the electrophile R^+ is OH^+ or its equivalent) or at C-5 or C-9 (probably as a result of free radical oxygenation of the primary phenol, e.g. ferruginol, at the free ortho position or the para benzylic methylene). Similar oxygenation of the other ortho position of ferruginol would lead to a hydroxy- or hydroperoxy-cyclohexadienone and reduction and rearrangement of this as in scheme D would give totarol.

None of the above schemes have any experimental basis other than analogies and, while those leading to nimbiol, picrosalvin and ferruginol agree with current biogenetic theories, the nature of the biogenesis of podocarpic acid and particularly of totarol remains an intriguing problem.

Syntheses of Octahydrophenanthrene Diterpenes.

Total syntheses of most of the diterpenes mentioned above have now been achieved, generally following one of three distinct construction schemes, E,F or G, as shown. Examples of method E are syntheses of 6-methoxypodocarpane[14] and of ferruginol[15]. Route F is exemplified by the beautifully stereospecific synthesis of dehydroabietic acid recently described by Ireland[27]. Method G includes as the key step in the construction of the phenanthrene ring system a Robinson-Michael condensation of methyl or ethyl vinyl ketone with a 1-methyl-β-tetralone. This step has the advantage of introducing into the podocarpane skeleton the 2-oxo substituent found in many of the terpenes and a reactive centre at C-1 which can be modified to introduce alkyl or carboxyl groups.

The β-tetralones have, in a number of cases, been obtained from the corresponding α-tetralones which can quite easily be made by oxidation of the activated methylene group of the parent tetralin or by a Friedel-Crafts-type ring closure. Treatment of the α-tetralones with excess methyl Grignard reagent gives the 1-methyl-3,4-dihydronaphthalenes which can be oxidised by a variety of methods to the 1-methyl-β-tetralones.

This last reaction was first described in 1943 by English and Cavaglieri[16] who converted 1-methyl-3,4-dihydronaphthalene (21) to 1-methyl-2-keto-1,2,3,4-tetrahydronaphthalene (22) with perbenzoic acid followed by acid hydrolysis. In 1944, Ghosh and Robinson[17] independently developed a similar technique to convert (23) to (24) for a thebaine synthesis. The procedure was again used by the Merck group[18] to build an intermediate (25) to be used in a synthesis of 11-keto-steroids.

The first examples of the application of this route to the total synthesis of octahydrophenanthrene diterpenoids were in 1956. In that year Stork and Schulenberg[19] published their synthesis of dehydroabietic acid (8). They built up the known 2-isopropylnaphthalene (26) to 1-methyl-2-oxo-6-isopropyl-1,2,3,4-tetrahydronaphthalene (27) which would give the required substituent in the aromatic ring C. Condensation of this with ethyl vinyl ketone, two-step introduction of the carboxyl group and removal of the ketone gave dehydroabietic acid as shown.

In the same year, Raman and Rao[20] published a synthesis of 6-methoxypodocarpane which was later modified[21] to provide a complete synthesis of the naturally occurring ferruginol (9) as shown.

In 1958, the preparation of β-tetralones and phenanthrenes from α-tetralones was reviewed by Howell and Taylor[22] who prepared the ketones (28)(R = R' = H; R = MeO, R' = H; R = H, R' = MeO; R = R' = MeO) and applied the Robinson-Michael cyclisation to all of them to give the corresponding ketohexahydrophenanthrenes (29).

Subsequent to this and to the start of this research programme, the method has been used to provide syntheses of the natural products nimbiol, as its methyl ether (30)[23] and hinokione, as its methyl ether(31)[24] and of 7,8-dimethoxypodocarpane (32)[25].

The research described in this part of the thesis was undertaken to investigate the synthesis of the β-tetralones (33) and (34) and their elaboration by the above technique to abietic acid and 3-ketototarol respectively. Work was, however, terminated by the recent publication by Taylor[26] of a synthesis of (34) and its elaboration to 3-ketototaryl methyl ether (42) by the method we proposed to use.

His method is summarised on page 67. 1-Bromo-2-methoxynaphthalene was elaborated, by reacting its Grignard derivative with acetone, to the isopropenylnaphthalene (36). This could be hydrogenated with Adams' catalyst to the isopropyl compound (37) and the unsubstituted ring hydrogenated over Raney nickel under pressure to give the tetralin (38). This was then oxidised to the α-tetralone (39). The overall yield of α-tetralone was 28% from bromomethoxynaphthalene without isolation of intermediates. Treatment of (39) with two moles of methyl magnesium bromide gave the dihydronaphthalene (40) which was oxidised with per-benzoic acid in chloroform and refluxed with aqueous methanolic sulphuric acid to give the β-tetralone (34). This with 4-chlorobutanone and sodium hydride gave 36% of 2,3,4,9,10,12-hexahydro-8-isopropyl-7-methoxy-12-methyl-2-oxophenanthrene (41) which could be dimethylated using methyl iodide and potassium tertiary butoxide and the unconjugated enone hydrogenated to a mixture of alcohols and hydrocarbon ethers. Mild oxidation of this and chromatography gave inter alia totaryl methyl ether and 3-ketototaryl methyl ether (42) with infra-red spectra identical to those of the natural materials.

DISCUSSION - SUBSTITUTED NAPHTHALENES AS PRECURSORS.

When the structure of totarolone was published in December 1960, I had been working with 2,6-dimethoxynaphthalene as a possible starting material for a synthesis of abietic acid and it was decided to modify this scheme to provide a synthesis of totarolone. For the reasons given in the Review section, a route was chosen which involved the preparation of a substituted β-tetralone and a number of methods of achieving this had been investigated when a synthesis of totarolone was published[26] which proceeded via a compound already synthesised by me and by the sequence of reactions which I had proposed to use. Work on the synthesis was therefore stopped but the investigations made had involved the preparation of many new compounds related to the hitherto unknown 1-isopropyl-2-naphthol, and this part of the thesis describes the preparation and properties of these compounds and a number of unexpected reactions discovered in their synthesis.

The initial aim of this research programme was the synthesis of the β-tetralones (33) and (34). The first route proposed for their synthesis involved the preparation of 2,6-dimethoxynaphthalene and 1-isopropyl-2,6-dimethoxynaphthalene, Birch reduction of these to the corresponding 1,4-dihydronaphthalenes, methylation of the latter at the 1-position and hydrolysis which would give the desired tetralones.

The preparation of 2,6-dihydroxynaphthalene (52) or its ethers requires the introduction into the 6-position of 2-naphthol or one of its simple derivatives of a substituent which can be converted to a hydroxyl group. Two distinct methods of doing this have been reported

and the investigation of a third is described below. The earliest involves sulphonation to give 6-hydroxynaphthalene-2-sulphonic acid, Schaefer's acid (51) and the alkali-fusion of this to give (52)[28]. It was subsequently found that 2-naphthol can readily be converted to 6-bromo-2-naphthol[29]; French and Sears[30] made the methyl ether of this compound and converted it to 6-methoxy-2-naphthol (54) in poor yield by air oxidation of the Grignard derivative. Gates and Webb[31] have improved the yield considerably by hydrolysing the 6-bromo-2-methoxy-naphthalene directly with alkali and copper turnings in an autoclave. Neither of the last two methods seemed particularly convenient and the availability of a quantity of Schaefer's acid (generously gifted by Imperial Chemical Industries, Ltd.) persuaded us to use the first method.

The dry sodium salt of Schaefer's acid was fused with potassium hydroxide and worked up as described by Fieser[32] who claimed a 55% yield, but we have been unable to achieve yields of more than 50%.

Attempts were made to make the melt more mobile by the addition of sodium hydroxide. This facilitated mixing but did not improve the yield. Attempts to use the potassium salt led to lower yields and the recovery of much unchanged Schaefer's acid.

Recently Clarke and Martini[33] obtained 60% crude yield using pure potassium hydroxide and a nickel crucible to avoid traces of iron. They do not state what effect iron has on the reaction but it is presumably deleterious. We had used a stainless-steel beaker for the fusions and this may account for the poorer yields.

2,6-Dimethoxynaphthalene was obtained by methylation with dimethyl sulphate and potassium carbonate in dry acetone or by addition of aqueous sodium hydroxide to a methanolic solution of the phenol and dimethyl sulphate. This order of addition is desirable owing to the ready autoxidation of the phenol in alkaline solution.

It is obvious that this route via the sulphonic acid is not suited to the rapid production of 2,6-dimethoxynaphthalene in quantity. The batch size was severely limited by the capacity of the fusion-crucible; there is a theoretical loss in weight of 40% from sodium salt to phenol; and the yield was only moderate.

We therefore considered other methods of introducing a 6-oxygen function into 2-methoxynaphthalene. It is known that acetylation can be effected at the 6-position and Baeyer-Villiger oxidation of the resultant ketone should give 6-acetoxy-2-methoxynaphthalene.

6-Acetyl-2-methoxynaphthalene (56) was prepared by acetylation of 2-methoxynaphthalene according to the method of Robinson and Rydon[34], using acetyl chloride and aluminium chloride in nitrobenzene in the cold to minimise acetylation in the 1-position. It was found, however, that both isomers were formed and the yield of 6-acetyl-2-methoxynaphthalene after purification was about 40%. Some 2-methoxynaphthalene was always recovered but an attempt to remedy this by the use of larger proportions of the reagents led to lower yields of the desired ketone and a much larger undistillable residue. The crude 1-acetyl-2-methoxynaphthalene (57) obtained as a by-product was kept and a sample purified by crystallisation had an infra-red spectrum identical to that of an authentic sample made by a different technique[35].

No Baeyer-Villiger oxidations of naphthyl ketones appear to have been reported. A number of small-scale experiments were therefore performed to investigate the oxidation of 6-acetyl-2-methoxynaphthalene with peracetic, perbenzoic, monoperphthalic and trifluoroperacetic acids.

In all cases the crude product was dark red, possibly owing to oxidation of the 2,6-dioxygenated naphthalene to a quinonoid structure and it was generally found that the recovery of water-insoluble material was considerably less than theory and was lower the higher the percentage of acetate in the recovered material. It would appear that the ketone is subject to a competing oxidation, such as hydroxylation[36], which leads to water-soluble products and is accelerated by the same factors as accelerate the normal Baeyer-Villiger reaction. Attempts to exclude this side-reaction by using only one equivalent of reagent led to recovery of much unchanged ketone.

The results of the pilot experiments are summarised in Table 1, page 13. When peracetic acid was used it was immediately obvious that the normal medium of acetic acid containing a little sulphuric acid was much too vigorous (runs 1 and 2). Omission of the sulphuric acid(3) considerably improved the percentage conversion to ester but further lowering of the acidity by adding potassium acetate(4) apparently slowed down the reaction. Use of smaller quantities of the more soluble ammonium acetate and larger concentrations of oxidising agent (5,7,10) gave fairly good yields provided the mixture was not left too long (6). The best procedure found was the use (13) of about two moles of peracetic acid in slightly buffered solution at low temperature for a longer time. These yields, however, were never attained on larger batches.

If the reaction was carried out in ethyl acetate instead of acetic acid, long reaction times were required and the percentage conversion was never very high (16,17,18). Perbenzoic acid in chloroform (8,9) caused marked colouration and poor conversion. Monoperphthalic acid in ether (11,12,19) brought about no conversion except after a long reaction time. Trifluoroperacetic acid (20) under conditions which give good yields in Baeyer-Villiger reactions on aliphatic ketones[37] caused intense colouration but produced virtually no ester.

It was accordingly decided that peracetic acid was the best reagent to use for the oxidation since it was convenient to prepare and gave the best yields. A number of larger batches of the ketone were therefore treated under the conditions which had proved most satisfactory on a small scale. In most cases the acetate was hydrolysed without purification since the phenol was easily separated from the neutral ketone and acetate. Since it was previously unknown, however, a sample of pure 6-acetoxy-2-methoxynaphthalene (58) was isolated from one batch and characterised. It could be hydrolysed to give pure phenol in nearly quantitative yield. The phenol was identical to a sample isolated from the partial methylation of 2,6-dihydroxynaphthalene. The yields in the oxidation step were, however, only moderate and this, coupled with the relatively low yield of 6-acetyl-2-methoxynaphthalene in the acetylation, excluded this route as a satisfactory one for the preparation of 2,6-dimethoxynaphthalene. The Schaefer's acid method was therefore used to prepare sufficient of the latter for the subsequent experiments.

TABLE 1

Run No.	g. (56) used	ml. solvent used	other subst. added	reagent	molar ratio	time	temp	% recy.	% ester
1	2.0	20ml HOAc	2.5ml H_2SO_4	2ml A	1:1	12hr	RT	small	0
2	2.0	5ml "	"	4ml A	1:2	"	RT	"	0
3	0.5	5ml "	nil	1ml A	1:2	"	RT		55
4	0.5	5ml "	5g KOAc	1ml A	1:2	"	RT		40
5	0.5	10ml "	1g NH_4OAc	3ml A	1:6	"	RT	50	70
6	0.5	10ml "	"	3ml A	1:6	36hr	RT	30	50
7	0.4	10ml "	"	3ml A	1:7	14hr	RT	53	70
10	0.4	10ml "	3g "	1.5ml A	1:3	20hr	RT	95	50
13	0.4	5ml "	1g "	0.8ml A	1:2	14days	5°	95	70
16	0.4	10ml EtOAc	nil	1ml A	1:2	10days	RT	45	45
17	0.4	10ml "	nil	1ml A	1:2	10days	5°	85	20
18	0.4	10ml "	0.25g NH_4OAc	2ml A	1:4	10days	RT	45	50
8	0.4	30ml $CHCl_3$	nil	3.2mmole B	1:1.6	12hr	RT		50
9	0.4	20ml "	nil	1.6 " B	1:0.8	15hr	RT	87	20
11	0.4	5ml EtOAc 10ml ether	nil	3ml P	1:1	12hr	RT	95	0
12	0.4	10ml EtOAc 10ml ether	nil	6ml P	1:2	12hr	RT	95	0
19	0.4	10ml EtOAc	nil	6ml P	1:2	10days	RT	65	50
20	2.0	10ml CH_2Cl_2	6.5g Na_2HPO_4	2.5ml $(CF_3CO)_2O$ 0.4ml 90% H_2O_2		30mins	40°		0

A = peracetic acid, about 40%
B = perbenzoic acid
P = monoperphthalic acid, 0.7molar
RT = ambient room temperature

The last two columns give the total recovery of material and the %age of this which was ester. The ratio quoted is the molar ratio of ketone to oxidising agent.

The proposed synthesis of totarolone required the preparation of 1-isopropyl-2,6-dimethoxynaphthalene (61). The first method investigated for its synthesis started with 1-acetyl-2-methoxynaphthalene which was available as a minor product in the acetylation of 2-methoxynaphthalene which had just been studied, and involved the sequence 57 - 59 - 60 - 61.

1-Acetyl-2-methoxynaphthalene, on treatment with excess methyl Grignard reagent and working up with mineral acid gave a good yield of isopropenylmethoxynaphthalene. Hydrogenation of this was slow but gave 1-isopropyl-2-methoxynaphthalene (59) in good yield. These were then the first examples known of a 2-naphthol derivative with a branched alkyl substituent at C-1. Their physical properties and the hydrogenation behaviour are discussed later.

The next step required the introduction of a nitro group into the 6-position. The closest analogy to be found in the literature is the nitration of 1-formyl-2-methoxynaphthalene to give a 92% yield of 1-formyl-2-methoxy-6-nitronaphthalene[38]. To provide a model for the reaction conditions and the spectra of the product, a sample of 2-methoxynaphthalene was nitrated in acetic acid under very mild conditions to give 2-methoxy-1-nitronaphthalene. The reaction was clean and the product had the expected spectra. Similar conditions were therefore used to nitrate 1-isopropyl-2-methoxynaphthalene in which the most nucleophilic unsubstituted carbon atom is C-6.

Attempts to perform the nitration with nitric acid in acetic acid or in benzene all led to a yellow oil whose infra-red spectrum indicated the presence of an unsaturated carbonyl group, a conjugated double bond and an unconjugated nitro group and the absence of methoxyl or hydroxyl groups. Its ultra-violet spectrum was compatible with its having a chromophore similar to that of cinnamaldehyde (c.f. Table 2, page 34).

All attempts to purify the crude oil led to its decomposition and a sample satisfactory for analysis was not obtained. It was shown, however, by thin layer chromatography (T.L.C.) on silica to consist almost entirely of one substance. On attempted distillation under vacuum, it decomposed to oxides of nitrogen and a solid material which showed hydroxyl absorption in the infra-red. On treatment with aqueous sodium hydroxide or Brady's reagent it gave only red tars. On the basis of its origin and spectra, it was assigned the structure 1-isopropyl-1-nitro-2-keto-1,2-dihydronaphthalene (62).

It thus appears that the 1-isopropyl and 2-methoxyl substituents so activate the 1-position that electrophilic attack by the nitronium ion or its equivalent takes place at that point even at the ultimate expense of the aromatic resonance energy of that ring. The intermediate mesomeric cation (63) could then be stabilised either by S_N2 attack by solvent on the methyl group (path a) or by acquisition of a hydroxyl group or its equivalent (path b) to give a hemiketal which would readily lose methanol in the acid medium.

Subsequently, when a sample of 1-isopropyl-2-naphthol was obtained it was found that treatment of it with nitric acid under similar conditions gave the same product (identical infra-red spectra and T.L.C. behaviour).

It has been known for a long time that 1-methyl-2-naphthol gives 1,1-disubstituted 2-keto-1,2-dihydronaphthalenes on treatment with reagents which normally cause aromatic substitution. For example, with chlorine it gives (64) and with 'nitrous acid gas' in ether the nitroketone (65)[39] which is a low melting solid which decomposes above 100° with evolution of nitrogen oxides. The production of (62) from 1-isopropyl-2-naphthol is thus not unexpected but its formation from the corresponding methyl ether appears to be unprecedented.

Since none of the desired 6-nitronaphthalene (60) could be obtained using nitric acid, attempts were made to perform the nitration with urea nitrate or cupric nitrate in acetic anhydride. Separation of the crude product showed that most of the naphthalene did in fact react under the mild conditions used but the products showed complex carbonyl absorption in the infra-red and no useful material with satisfactory spectra could be isolated at all.

This route to 1-isopropyl-2,6-dimethoxynaphthalene was therefore abandoned.

Attention was then turned to the introduction of an isopropyl group into 2,6-dimethoxynaphthalene which was available in moderate quantity.

Direct Friedel-Crafts alkylation failed completely. This may be due to the hindered nature of the 1-position in this particular naphthalene and the size of the isopropyl group. Attempts using isopropanol and boron trifluoride etherate in refluxing tetrahydrofuran or isopropyl iodide and aluminium chloride in methylene chloride led to a high recovery of the starting naphthalene.

Friedel-Crafts acetylation was then investigated and it was found that about 70% conversion (estimated from the infra-red spectrum of the crude product) to an aryl ketone could be attained using acetic anhydride and aluminium chloride. The use of iodine as catalyst and no solvent as used by Dominiguez et al.[35] to acetylate 2-methoxynaphthalene also gave a high conversion but is not convenient for this ether since the mixture is liquid only above 150°. A quantity of the dimethoxy-naphthalene was therefore acetylated by the former procedure.

For electronic reasons, acetylation should occur at the 1-position rather than at the 3- or 4- positions, and the infra-red and ultra-violet spectra of the product confirmed that it was 1-acetyl-2,6-dimethoxynaphthalene (66).

Treatment of the ketone with excess methyl Grignard reagent and work-up with mineral acid gave 1-isopropenyl-2,6-dimethoxynaphthalene (67) which was hydrogenated fairly readily to give the desired 1-isopropyl-2,6-dimethoxynaphthalene (61).

While this work was in progress, experiments were started to investigate the conversion of 2,6-dimethoxynaphthalene to 6-methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydronaphthalene (33). This compound was known[22,40] and its elaboration to a hexahydrophenanthrene had been successfully carried out[22]. The synthesis we proposed was the reduction of 2,6-dimethoxynaphthalene to the 1,4-dihydro-compound (71) and methylation of this to give the enol ether (72) of the desired tetralone. We were confident that similar reduction of 1-isopropyl-2,6-dimethoxynaphthalene would occur in the less substituted ring since the electron releasing isopropyl group would discourage addition of electrons to the 1-position.

The reduction of 2,6-dimethoxynaphthalene had already been investigated by Weygand and Robinson[41] who obtained a dihydro-compound, m.p. 84°, in unstated yield by reduction with sodium in isopentanol, but did not prove which of the two possible isomers (70) and (71) it was. A much more convenient method for reducing naphthalenes is that of Rowe[42] using sodium and ethanol in refluxing xylene. Applying this method, Sneeden[40] obtained an isomeric dihydro-compound, m.p. 40°, which on treatment with alkoxides gave Robinson's compound. This lower melting isomer is the 1,4-dihydronaphthalene (71) which is the initial product in the reduction and isomerises to the more stable (70) under the conditions of the sodium/pentanol reduction. We have confirmed these structure-allocations from the spectra of the isomers.

The higher melting isomer absorbed strongly at 1630 cm^{-1} which is characteristic of a normal conjugated double bond, its intensity raised

by the vinylic methoxyl group. This isomer has λ_{max} at 272 mμ(logε 4.2) which is in good agreement with published values for similarly substituted styrenes (c.f. Table 2)

The lower melting isomer showed an unusual infra-red absorption with peaks at 1680 and 1645 cm^{-1}. The strong double bond absorption at high frequencies appears to be typical of 1,4-dihydrobenzene ethers (e.g. dihydroresorcinol dimethyl ether, ν_{max} at 1680(s) cm^{-1})

The Rowe reduction gave the unconjugated isomer in almost quantitative yield. The enol ether of 6-methoxy-β-tetralone was thus readily available. Sneeden had shown[40] that methylation of the tetralone itself gave mixtures of partially methylated products which could not be satisfactorily separated, though he had obtained a small amount of the semicarbazone of the monomethyl-ketone. We hoped to avoid this difficulty by methylating the unconjugated enol ether which, by analogy with dihydroresorcinol dimethyl ether, should alkylate in the 1-position.

Treatment with potassium amide in liquid ammonia gave a red solution which indicated that anion formation had occurred. Methyl iodide was added causing immediate disappearance of the colour but work-up with ammonium chloride gave either 2,6-dimethoxynaphthalene or 3,4-dihydro-2,6-dimethoxynaphthalene. A number of experiments were performed using also potassium tertiary butoxide or sodamide in xylene but in no case could any of the 1-methyl-β-tetralone be obtained as judged by spectra and semicarbazone formation.

In view of the failure of this route to (33) no attempt was made to reduce 1-isopropyl-2,6-dimethoxynaphthalene.

An entirely new approach to 6-methoxy-1-methyl-5-isopropyl-2-keto-1,2,3,4-tetrahydronaphthalene (34) was required and this was sought in two attempts to synthesise the corresponding tetralin (38) which could be elaborated to (34) by the method outlined in the Review section and performed already for the simpler case of (33) by Howell and Taylor[22].

The first route tried (via 1-isopropyl-2-naphthol) encountered difficulties due to autoxidation and led to further experiments in this field. A second route to (38) was therefore planned and its successful prosecution is described first.

It was decided to synthesise the tetralin from the commercially available 1,2,3,4-tetrahydro-6-naphthol (73) which is obtained by hydrogenation of 2-naphthol. This method would avoid the hydrogenation of a naphthalene and separation of the two possible tetrahydro-naphthalenes as the last step. Conversion of (73) to (38) requires the introduction of a substituent into the 5-position (75). A priori one would expect the tetralol to undergo substitution in the 7-position for both steric and electronic reasons. A survey of the literature revealed a surprising and inexplicable variety in its behaviour with different reagents. On nitration, sulphonation, reaction of its sodium salt with carbon dioxide or Claisen rearrangement of its allyl ether, it is substituted in the 7-position, while on bromination or reaction with benzene diazonium salts, with chloroform and alkali, with hydrogen cyanide and zinc chloride or with ethyl acetoacetate, substitution occurs at the 5-position.

The bromotetralol (75, X = Br) seemed to provide a route to (38) by a Grignard reaction and so its synthesis was investigated.

The only recorded preparation of this compound is by Schroeter[43] who had studied the substitution reactions of (73) and claimed that on treatment with one mole of bromine in carbon tetrachloride only the 5-bromo-compound was obtained. This seems unlikely but the assignment of structure was supported by interrelation with other substituted tetralins and has been accepted by Arnold[44] who used the substance without describing how he obtained it.

I have repeatedly found that bromination under Schroeter's conditions gave a mixture of compounds which could be purified (but not separated) by sublimation and which analysed exactly for the desired bromotetralol. It was therefore a mixture of isomers. The mixture melted over a wide temperature range and could not be effectively separated by distillation or by chromatography. Repeated fractional crystallisation from petrol led to the isolation of a fair amount of pure 5-bromotetralol with melting point the same as that quoted by Schroeter, and strong infra-red absorption at 800 cm^{-1} (1,2,3,4-tetra-substituted benzene). The other component was not obtained pure but presumably was the 7-isomer since the mixtures showed strong absorption at 850 cm^{-1} (1,2,4,5-tetrasubstituted benzene) while the pure 5-bromo-phenol showed no absorption at this frequency.

Methylation of the pure 5-bromotetralol with dimethyl sulphate proceeded in good yield to give the same methyl ether as Arnold[44] obtained.

Attempts to prepare a Grignard reagent from this ether and to react it with acetone were initially unsuccessful. Use of magnesium in ether or in refluxing tetrahydrofuran and with iodine or methyl iodide as initiator led only to isolation of 6-methoxy-1,2,3,4-tetrahydronaphthalene. Success was eventually achieved by entrainment of the tetralin with ethyl bromide as used in the closely similar case of 1-bromo-2,5-dimethoxy-3,4,6-trimethylbenzene by Smith et al.[45]. Treatment of the Grignard solution with an excess of acetone and work-up with dilute mineral acid gave a mixture of the olefin (76) and the tertiary alcohol (77) which after refluxing with concentrated aqueous toluenesulphonic acid and chromatography gave a good yield of 5-isopropenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (76). When the Grignard reaction was worked up with ammonium chloride the product was the alcohol (77). Hydrogenolysis of this alcohol over platinum in acetic acid and chromatography and distillation of the product gave the desired 5-isopropyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (38) which was an intermediate in Taylor's subsequently published synthesis of totarolone but which was not isolated or characterised by him.

While this work was in progress, an investigation was made into the synthesis of 1-isopropyl-2-naphthol (79) and its conversion to (38) by hydrogenation and methylation.

Stork[46] has shown that 2-naphthol itself can be readily and fairly specifically hydrogenated in the unsubstituted ring and so we sought a short synthesis of (79) from materials available in quantity.

The obvious starting material was 2-naphthol and it has been reported[47] that this undergoes an extremely facile Kolbe reaction to give 2-hydroxy-1-naphthoic acid in high yield. We found that by simply passing carbon dioxide through a suspension of sodium 2-naphthoxide in refluxing toluene for some hours, excellent yields of the acid were obtained. The repetition of the preparation on a large scale was made unnecessary by the gift of a quantity of the acid by I.C.I.

The conversion of the acid to its methyl ester has been shown[48] to be very difficult. Hunsberger[49] has proved that this is due to strong intramolecular hydrogen bonding and the readiness of the acid to decarboxylate on mild heating and has found that the only satisfactory method of esterification is the use of diazomethane.

The methyl ester was made in high yield by this method and treated with excess methyl magnesium iodide to give 1-isopropenyl-2-naphthol(73) This was obtained as a viscous orange oil and all attempts to crystallise it failed. It was, however, over 90% pure (estimated from its ultraviolet and infra-red spectra). Distillation only intensified the colour. Many attempts were made to hydrogenate the crude product but, owing either to inherent steric reasons or to impurities, no uptake of hydrogen could be achieved. Even after treatment with charcoal, Raney-nickel or successive quantities of palladium catalysts and hydrogen which it was hoped would remove any catalyst poisons, the crude phenol would absorb no hydrogen. It was therefore converted to its acetate which could be easily purified by distillation. Hydrolysis of the pure acetate gave back the phenol again as a red oil.

The pure acetate was hydrogenated over 10% palladium on charcoal to give 2-acetoxy-1-isopropylnaphthalene (80). The hydrogenation was very slow. A sample of this acetate was converted directly to the corresponding methyl ether (59) by treatment with aqueous methanolic potassium hydroxide and dimethyl sulphate. The ether was identical (infra-red spectrum and mixed melting point) with the material obtained from 1-acetyl-2-methoxynaphthalene (page 14).

A number of attempts to convert the acetate (80) to the free phenol by alkaline hydrolysis or by reduction with lithium aluminium hydride all led to a fairly high melting crystalline compound which showed infra-red absorption characteristic of a conjugated enone. It was found that if the hydrolysis and recrystallisation of the product were carried out with rigorous exclusion of oxygen, a sample of the desired 1-isopropyl-2-naphthol could be obtained which gave fairly good analysis figures. The phenol showed a remarkable ability to absorb oxygen and the enone was formed rapidly whenever the phenol was left exposed to the air.

It was decided to investigate this autoxidation in more detail and for this purpose larger quantities of the phenol were required. The route by which it had first been obtained (above) is obviously long and laborious and we sought a new and much more direct preparation in the procedure recently described by Wenkert[50] for the C-alkylation of 2-naphthol. He found that by refluxing a suspension of dry sodium 2-naphthoxide in toluene with an alkyl halide, moderate yields of 1-alkyl-2-naphthols were obtained along with the isomeric ethers.

Using methyl iodide, he obtained 39% of 1-methyl-2-naphthol and 25% of methyl 2-naphthyl ether and, with n-butyl bromide, 40% of 1-n-butyl-2-naphthol and 57% of n-butyl 2-naphthyl ether.

To gain experience of the method I repeated his methylation experiment and obtained 1-methyl-2-naphthol(34%), 1,1-dimethyl-2-keto-1,2-dihydronaphthalene(6%), 2-methoxynaphthalene(15%) and unchanged 2-naphthol. The first two were of considerable value as models for subsequent work with 1-isopropyl-2-naphthol.

We hoped to repeat the alkylation using isopropyl iodide which would give the desired phenol (79) directly. Wenkert reports no cases of alkylation with secondary alkyl halides and in view of the bulk of the isopropyl group, the possible side reactions and the complete failure of attempts to achieve the mechanistically and sterically similar isopropylation of 2,6-dimethoxynaphthalene under Friedel-Crafts conditions (page 17) no better than a poor yield was expected.

The reaction was carried out exactly as for methylation. The crude product was a mixture and because of the cryptophenolic nature of the alkylnaphthol, no satisfactory separation could be achieved by extraction with base. The 'acidic' fraction contained both 2-naphthol and 1-isopropyl-2-naphthol and the 'neutral' fraction the latter plus isopropyl 2-naphthyl ether. Thin layer chromatography of the crude material showed that the alkylphenol was the main component and that there was only a moderate amount of 2-naphthol and very little of the ether. Distillation and crystallisation led to the isolation of a 55% yield of fairly pure 1-isopropyl-2-naphthol (in one step).

The mechanism of this alkylation and the importance of degree of heterogeneity and of solvent polarity in determining the ratio of the products are as yet not clearly established[51,56]. It is generally assumed that the reaction occurs at the surface of an aggregate of ion-pairs or a crystallite of the metal alkoxide and we may picture the C-alkylation process as occurring via a cyclic transition state as shown (83) in which one of the sodium ions associated with the alkoxide oxygen atom in the crystallite becomes associated with the incipient halide ion formed in the heterolysis of the alkyl halide[57,54,51]. No charge separation or increase in electrostatic potential energy occurs. This would not be true of O-alkylation (84) where, because of the requirement for a linear O-C-I arrangement in the S_N2 substitution, the sodium ion of the lattice is left with no near negative charge and the incipient halide ion with no near positive charge. The preference for C-alkylation in non-polar media or under heterogeneous conditions can thus be explained.

The high proportion of alkyl phenol found using isopropyl iodide (c.f. yields with methyl iodide etc. above) is in agreement with a number of generalisations about alkylation of ambident anions which have been published recently. Curtin and Fraser[55] find that the ratio of C-alkylation to O-alkylation increases with the tendency of the alkyl halide to react by an S_N2 mechanism and Kornblum[53] has found the ratio to be increased by increased steric hindrance in either the anion or the alkyl halide, so much so, in fact, that even in homogeneous solution potassium 2,6-di-t-butylphenoxide and isopropyl

iodide give exclusively 4-isopropyl-2,6-di-t-butylphenol. No ether is formed at all under these conditions but only 28% of the halide undergoes substitution, elimination of hydrogen iodide accounting for the remainder.

A method was thus available for the rapid and direct preparation of quantities of 1-isopropyl-2-naphthol.

The high proportion of C-alkylation occurring with isopropyl iodide tempted us to investigate the analogous alkylation with tertiary butyl chloride. 1-t-butyl-2-naphthol is unknown and might react with oxygen even more readily than the isopropyl analogue. The reaction was tried using an excess of t-butyl chloride at about 50° for two days. Unfortunately the predominant reaction was elimination rather than substitution. The solution became strongly acid and the product was almost entirely unchanged 2-naphthol. The bulk of this was removed by extraction with a small amount of base and and a sample of the less acidic material was separated by T.L.C. and shown to contain eight compounds, some of which were probably self condensation products of isobutene.

Attention was then turned to the autoxidation of 1-isopropyl-2-naphthol. All the early attempts to prepare this phenol had led to the isolation of a crystalline solid, m.p. 133° which could be sublimed unchanged at 100°/0.05 mm. and which showed infra-red absorption characteristic of an aromatic system with a hydroxyl group and a conjugated enone group and ultra-violet absorption similar to that of 1,1-dimethyl-2-keto-1,2-dihydronaphthalene (81) and similar systems (c.f. Table 2). Its analysis figures fitted $C_{13}H_{14}O_3$, i.e. 1-isopropyl-2-naphthol plus two oxygen atoms. Its formula and mode of formation suggested it might be a hydroperoxide and this was confirmed by its instantaneous oxidation of ferrous thiocyanate. In order to explain these data the compound must be regarded as 1-isopropyl-1-hydroperoxy-2-keto-1,2-dihydronaphthalene (85).

In solution in carbon tetrachloride it showed absorption at 3505 and 1678 $cm.^{-1}$, unaltered by dilution, while under the same conditions 1,1-dimethyl-2-keto-1,2-dihydronaphthalene absorbed at 1666 cm^{-1}. The hydroperoxide would thus appear to be intramolecularly hydrogen bonded as shown (85) but to have its carbonyl frequency considerably increased by the presence of the α-oxygen atom.

The hydroperoxide was amazingly stable to heat (c.f. sublimation above) and acids, being recovered unchanged from treatment with p-toluene sulphonic acid or boron trifluoride which might plausibly have caused a rearrangement similar to that of cumene hydroperoxide to phenol and acetone. The reaction of the phenol with oxygen was extremely rapid. Even a sample wrapped in tin foil and in an evacuated drying pistol autoxidised partly over a few days. If air were bubbled through a

benzene solution of the phenol, the hydroperoxide crystallised out in a virtually pure state after some hours.

The ease of hydroperoxidation of 1-isopropyl-2-naphthol suggested that a similar autoxidation might be a step in the biogenesis of totarol. A possible path for the isomerisation of ferruginol has been outlined in the Review section and a sequence of this type has also been suggested by Johnson[1]. We hoped to simulate the rearrangement using a suitable stable hydroperoxide. 1-Hydroxy-1-isopropyl-2-keto-1,2-dihydronaphthalene cannot rearrange by the desired route but 3-hydroxy-3-isopropyl-2-keto-2,3-dihydronaphthalene (87) might and we decided to try to prepare this via the corresponding hydroperoxide (86). This synthesis gave the opportunity to investigate the chemistry of 3-isopropyl-2-naphthol (88) and related substances and to compare them with the isomeric series just studied.

The only investigation in this group of compounds was by Lammer[58] who treated methyl 2-hydroxy-3-naphthoate with methyl magnesium iodide and obtained the tertiary alcohol (89) which on treatment with acetic anhydride gave the unsaturated acetate (90). We repeated his work and obtained the compounds described by him. We found that the acetate could by hydrogenated very readily to give the saturated acetate (92). The rapidity of this reaction is in marked contrast to the slowness of hydrogenation of the isomeric 1-isopropenyl-2-naphthol derivatives (four minutes compared with four hours of more). Lammer reported that he was unable satisfactorily to dehydrate the alcohol (89) to 3-isopropenyl-2-naphthol (91). We were also unable to prepare the

phenol by this route. Refluxing with p-toluene sulphonic acid in benzene gave orange foams from which the only isolable material was unchanged alcohol. In view of the difficulties apparently inherent in the isolation of the phenol (c.f. the intractibility of 1-isopropenyl-2-naphthol, page 23) we prepared it by reduction of its acetate with lithium aluminium hydride. By this method we obtained crystalline material with the desired infra-red spectrum but it could not be obtained in a state fit for analysis. The saturated phenol (88) was obtained by hydrogenolysis of the alcohol (89) and was a stable, easily crystallisable solid giving correct analysis figures.

We were now able to compare the behaviour on autoxidation of 1-isopropyl-2-naphthol, 1-methyl-2-naphthol and 3-isopropyl-2-naphthol. The first had already been shown to give a hydroperoxide extremely readily. The second (which had been prepared by methylation of sodium 2-naphthoxide) is apparently stable for long periods in air although Fries[59] has reported that a sample kept in an unsealed bottle for eight years had been converted to the extent of 45% to the hydroxy ketone (quinol)(93), with no trace of hydroperoxides. He noticed that this oxidation was more rapid in benzene solution, the quinol being observed after four weeks with access of air, and that 6-bromo-1-methyl-2-naphthol was oxidised much more slowly, and 3,6-dibromo-1-methyl-2-naphthol not at all under the same conditions.

3-Isopropyl-2-naphthol was not expected to hydroperoxidise readily because of the small part that the canonical structure (95) will play in the resonance of the intermediate radical.

To determine more quantitatively the reactivities of the three phenols, samples of each in benzene solution were irradiated by two twenty watt fluorescent tubes emitting white light, the solutions being contained in 'Pyrex' tubes while oxygen was bubbled slowly through. The extent of the autoxidation was estimated from the infra-red spectra of aliquots removed intermittently.

In the case of 1-isopropyl-2-naphthol it was found that conversion to the hydroperoxide was over 50% complete after one hour, over 90% after three hours and complete after thirteen hours. This experiment was repeated with exclusion of light from the sample. After fifteen hours conversion was 80% complete and after sixty one hours virtually complete.

Under similar conditions with irradiation, 1-methyl-2-naphthol was quite unchanged after fourteen hours, but after three days it also gave a hydroperoxide.

3-Isopropyl-2-naphthol on irradiation with oxygen as before was quite unchanged after thirteen hours but after sixtyone hours the infra-red spectrum showed the development of a small peak at 1700 cm^{-1}. After one hundred hours this had increased slightly in intensity and the reaction was stopped. Thin layer chromatography showed the crude material to contain 3-isopropyl-2-naphthol plus three other compounds in moderate yield. One of these was yellow and more polar than the starting phenol and might have been the desired hydroperoxide, but no sign of the requisite absorption was observed in the spectra of the crude material(which were identical to those of 3-isopropyl-2-naphthol

except for the 1700 cm^{-1} peak) and an attempt to isolate it by chromatography of the bulk was quite unsuccessful.

It was therefore impossible to test the proposed totarol biogenesis using this model and that problem remains unsolved.

The three phenols showed considerable diffences in their rate of reaction with oxygen. The mechanism of the process is probably as shown. It involves an initial homolysis of the phenol to give the mesomeric radical (97) which can pick up oxygen to give the peroxy-radical (98). This continues the chain reaction by abstracting a hydrogen atom from another molecule of phenol. In general, step 2 is fast but in the case of 3-isopropyl-2-naphthol this step is probably very slow due to the energy required to set up the non-aromatic system (96). Normally, step 3 is rate-determining and is accelerated by factors stabilising (97) and by electron release from the phenol since the peroxy radical is electron attracting [60].

The importance of electron release into the incipient radical is borne out by the lower reactivity of the bromomethylnaphthols(c.f. above) compared with 1-methyl-2-naphthol and of toluene compared with ethyl-benzene and cumene. This factor, however, cannot satisfactorily explain the much greater reactivity of 1-isopropyl-2-naphthol compared with 1-methyl-2-naphthol, since, while isopropyl has a slightly greater inductive electron release than methyl, hyperconjugative release from it is less and the two effects might be of comparable importance. It is possible that the reactivity of the isopropyl compound is due to the release of the steric strain in the planar aromatic system (79) when C-1 becomes sp^3 hybridised as it is in the hydroperoxide (85).

APPENDIX

This investigation has led to the preparation of a number of closely related compounds. Their infra-red spectra are unexceptional and support published generalisations[61]. All the ultra-violet spectra of compounds prepared, along with a number of spectra published elsewhere, are collected in Table 2 for easy comparison.

The close similarity between the ultra-violet spectra of many of the isopropyl- and the corresponding isopropenyl-derivatives is striking. For example the spectra of 1-isopropyl- and 1-isopropenyl-2-methoxy-naphthalene and of 5-isopropyl- and 5-isopropenyl-6-methoxytetralin differ by amounts which are probably less than the experimental error. This similarity is also observed in the corresponding acetates and phenols. Apparently the olefinic double bond is not effectively conjugated with the aromatic system in these cases and this is almost certainly due to steric compression which forces the isopropenyl group out of the plane of the ring. The same effect has been observed by Ramart-Lucas[62] in the spectra of anisole and 2-isopropenylanisole. It is noteworthy that in the 3-substituted series the similarity in the spectra of saturated and unsaturated compounds is less marked than in the 1-substituted isomers. This is doubtless due to the hydrogen atom or atoms in the 8-position of the latter group which will accentuate the steric crowding.

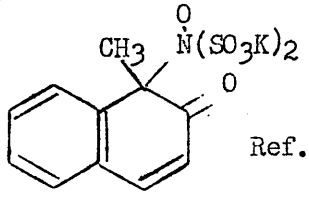
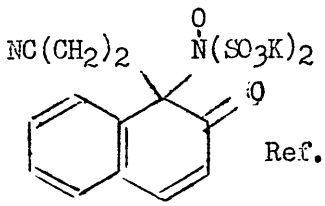
As mentioned in the discussion, the hydrogenation of all the 1-isopropenyl-2-naphthol derivatives was slow, while that of the 3-substituted isomers was rapid. This can be seen as another result of the non-coplanarity of the double bond with the ring which hinders adsorption on the catalyst surface.

TABLE 2.

The spectra, except those for which the reference is given, were measured on a Perkin-Elmer 137UV spectrometer or, if marked (U), on a Unicam SP 500 spectrometer and are quoted in bands as λ_{max}(mμ)(log ε)
(e = ethanol, h = hexane, c = cyclohexane)

2-Naphthol (50)(Ref. 66)	c	227(4.85)	263 272(3.70) 285	313(3.25) 329(3.35)
2-methoxynaphthalene(55)	e	227 (4.97)	262(3.64) 272(3.68) 282.5(3.50)	314(3.20) 328.5(3.33)
"	h	226.5(4.90)	262(3.66) 271.5(3.68) 282.5(3.52)	313.5(3.27) 328(3.47)
2,6-Dihydroxynaphthalene (52)(Ref. 64)	e	228(4.86)	260(3.66) 269(3.60) 279(3.43)	340(3.42) 349(3.44)
6-Methoxy-2-naphthol (54)	e	229.5(4.90)	259(3.72) 267.5(3.69) 277(3.33)	336(3.43) 347(3.46)
6-Acetoxy-2-methoxy-naphthalene (58)	h	228.5(4.79)	260(3.68) 269.5(3.69) 278(3.47)	319(3.23) 333(3.33)
2,6-Dimethoxynaphthalene (53)	h	231(4.88)	257(3.76) 265(3.74)	329(3.44) 339(3.43) 344.5(3.55)
6-Acetyl-2-methoxy-naphthalene (56)	h	214(4.23)	240(5.02) 248(4.97) 258(4.97)	301.5(4.09)
1-Acetyl-2-methoxy-naphthalene (57)	h	226(4.70)	283 - 293 (3.60)	335.5(3.43)
1-Acetyl-2,6-dimethoxy-naphthalene (66)	e	233.5(4.63)		352(3.54)
1-Isopropyl-2,6-dimethoxy-naphthalene (61)	h (U)	233(4.89)	265(3.71) 274(3.75) 283(3.54)	336(3.52) 346(3.49) 352(3.48)
1-Nitro-2-methoxy-naphthalene	e	227.5(4.83)	257(3.64) 267(3.64) 279(3.63) 290.5(3.53)	319(3.32) 332(3.41)

1-Methyl-2-naphthol (Ref. 63)	MeOH	230(4.88)	277(3.68) 290(3.60)	318(3.25) 334(3.40)
1-Isopropenyl-2-naphthol (78)	e	228(4.80)	267(3.60) 277(3.69) 288(3.61)	332(3.44)
1-Isopropyl-2-naphthol (79)	e	232.5(4.87)	269(3.61) 281(3.72) 291(3.63)	325(3.37) 335(3.40)
1-Isopropenyl-2-methoxy-naphthalene	h	231(4.80)	282(3.73) 293.5(3.66)	337(3.43)
1-Isopropyl-2-methoxy-naphthalene (59)	h	232(4.80)	282(3.69) 293(3.60)	322(3.27) 337(3.34)
1-Isopropenyl-2-acetoxy-naphthalene	h	224(4.93)	269(3.79) 277(3.85) 287(3.73)	318(2.73)
1-Isopropyl-2-acetoxy-naphthalene (80)	h (U)	225(5.00)	270(3.80) 278(3.86) 288(3.72)	320(2.78)
5-Isopropenyl-6-methoxy-tetralin (76)	h	207(4.57)	282(3.35)	288(3.34)
5-Isopropyl-6-methoxy-tetralin (77)	h	206(4.60)	279(3.27)	288(3.27)
3-Isopropenyl-2-naphthol (91)	e	235(4.72)	268(3.70) 277(3.71) 287(3.62) 298(3.32)	322(3.25) 334(3.34)
3-Isopropyl-2-naphthol (88)	e (U)	229(4.87)	258(3.46) 267(3.61) 277(3.64) 288(3.47)	317(3.31) 330(3.42)
3-Isopropenyl-2-acetoxy-naphthalene (90)	h (U)	228(4.72) 232(4.70)	272(3.76) 278(3.75)	
3-Isopropyl-2-acetoxy-naphthalene	h (U)	225(4.69)	261(3.60) 268(3.69) 277(3.70) 287(3.51)	305(2.70) 318(2.76)
3-(2-Hydroxyprop-2-yl)-2-naphthol (89)	e	230(4.86)	257(3.49) 266(3.60) 277(3.64) 287(3.46)	318(3.25) 330(3.36)

2,6-Dimethoxy-3,4-dihydronaphthalene (70)	h	271(4.26)	345(2.27)	
2,6-Dimethoxy-1,4-dihydronaphthalene (71)	h	278(3.66)	344(2.38)	
3,4-Dihydronaphthalene (Ref. 66)	h	261(4.0)	297(2.7)	
1,4-Dihydronaphthalene (Ref. 66)	h	267(2.9)	273(2.9)	
6-Methoxy-3,4-dihydronaphthalene (Ref. 65)	e	272(4.0)		
p-Chlorostyrene (Ref. 66)		258(4.2)		
β-Iodostyrene (Ref. 66)		265(4.3)		
1-Isopropyl-1-nitro-2-keto-1,2-dihydronaphthalene(62)	e	235-8(4.18)	283(3.65)	322(3.75)
1-Hydroperoxy-1-isopropyl-2-keto-1,2-dihydronaphthalene (85)	h	234(4.17) 240(4.19)		313(3.92)
1,1-Dimethyl-2-keto-1,2-dihydronaphthalene (81) (Ref. 50)	e	230(4.38)		310(3.75)
1-Methyl-1-dichloromethyl-2-keto-1,2-dihydronaphthalene (Ref. 50)	e	239(4.08)		314(3.96)
 Ref. 63	H_2O	240(4.2)		330(3.88)
 Ref. 63	H_2O	238(4.2)		322(3.88)

EXPERIMENTAL

M.p.s were observed on a Kofler microscope hot stage. Infra-red absorption spectra (on Nujol mulls of solids and films of liquids) were measured on a Perkin-Elmer Infracord spectrometer. All ultra-violet (U.V.) spectra measured are given in Table 2 and not in the Experimental section. 'Worked up in the usual manner' means washed with saturated brine, dried with magnesium sulphate and the solvent removed, usually under vacuum.

2,6-Dihydroxynaphthalene (52)

Schaefer's acid (224 g.) and sodium hydroxide (80 g.) were stirred with water (200 ml.) and evaporated to dryness giving the dry di-sodium salt (280 g.) This salt (80 g.) and potassium hydroxide (200 g.) were heated to 320° in a 300 ml. steel beaker and kept at 320 - 340° for 20 min. The melt was poured into conc. hydrochloric acid (500 ml.) containing ice. The yellow precipitate was filtered off, dissolved in ether, poured into hot water and allowed to crystallise yielding 2,6-dihydroxynaphthalene (20 g.; 42%) m.p. 212 - 213°. A sample of pure white phenol obtained by sublimation had m.p. 222° (lit.[28] 220 - 223°).

2,6-Dimethoxynaphthalene (53)

Method a :- 2,6-Dihydroxynaphthalene (8 g.) was dissolved in methanol (50 ml.). Dimethyl sulphate (14 g.) was added and a solution of sodium hydroxide (6 g.) in water (50 ml.) added dropwise over 20 min. with stirring. The solution was then refluxed for 90 min. The precipitate was extracted into benzene and this solution washed with aq. sodium hydroxide and worked up in the usual manner to give 2,6-dimethoxy-

naphthalene (5.1 g.; 54%) which crystallised from benzene-petrol as pale yellow rhombs, m.p. 145 - 149°. Part of this was purified by sublimation and part by steam-distillation. Both samples had m.p. 151 - 152° (lit.[28] 151 - 152°),

In one experiment, the alkaline washings of the crude product were acidified and the precipitate purified by sublimation at 200°/0.1 mm. to yield a small amount of the monomethyl ether, 6-methoxy-2-naphthol, m.p. 150 - 151° (lit.[31] 150 - 151°), $\nu_{max.}$ 3250 (OH), 1020 (methyl ether) $cm.^{-1}$.

Method b :- 2,6-Dihydroxynaphthalene (54.3 g.) was dissolved in dry acetone (1 litre) containing Analar potassium carbonate (200 g.). Dimethyl sulphate (100 g.) was added over 2 hr. to the refluxing solution. The solution was allowed to reflux overnight, cooled and filtered and the filtrate worked up to give 2,6-dimethoxynaphthalene (33 g.; 52%), m.p. 151°.

6-Acetyl-2-methoxynaphthalene (56)

2-Methoxynaphthalene (156 g.) was added to a solution of aluminium chloride (162 g.) in dry nitrobenzene (900 ml.). The red solution was cooled in ice and freshly distilled acetyl chloride (90 ml.) was added over 20 min. with stirring. The flask was kept cooled in ice for 2 hr., the ice was then allowed to melt and the stirring continued at room temperature for a further 36 hr. The green solution was then poured onto a mixture of ice (1 Kg.), water(300 ml.) and conc. hydrochloric acid (300 ml.) The nitrobenzene layer was separated, washed twice with water and steam-distilled. When all the nitrobenzene had

been removed, the flask was allowed to cool, the supernatant water poured off and the dark residue transferred to a smaller flask and distilled under vacuum. After a forerun containing water and nitrobenzene, two fractions were taken of b.p. 120 - 160°/0.4 mm. (20 g.) and b.p. 160 - 180°/0.4 mm. (130 g.). An involatile residue (40 g.) always remained. Crystallisation of the higher boiling fraction from methanol gave 6-acetyl-2-methoxynaphthalene (73.5 g.; 38%), m.p. 107 - 108.5°. Four crystallisations from methanol gave a pure sample, m.p. 108 - 108.5° (lit.[34] 104 - 105°), $\nu_{max.}$ 1680 (carbonyl), 865 and 825 cm.$^{-1}$ (1,2,4-trisubstituted benzene rings).

The lower boiling fraction contained 2-methoxynaphthalene and 1-acetyl-2-methoxynaphthalene and was difficult to crystallise. one sample on crystallisation from methanol had m.p. 45 - 50° and an infra-red spectrum identical to that of an authentic specimen of 1-acetyl-2-methoxynaphthalene. Chromatography of this low melting material gave a small quantity of the pure ketone, $\nu_{max.}$ 1685 (carbonyl) 820 (two adjacent aromatic Hs) and 750 cm.$^{-1}$ (four adjacent Hs).

The experiment was repeated using 2-methoxynaphthalene (158 g.) aluminium chloride (200 g.) in nitrobenzene (1 litre) and acetyl chloride (102 ml.) added over 1 hr. Only 72 g. of crude distillate was obtained and there was a much larger residue.

Baeyer-Villiger Oxidations.

The small scale pilot experiments were carried out using the conditions and quantities given in Table 1 and worked up by pouring into water, filtering and washing and drying the solid whose composition was estimated from its infra-red spectrum. The peracetic acid was prepared by the method of Greenspan[67] and was assumed to be about 40% CH_3CO_3H, the perbenzoic acid (0.2 N) by that of Kergomard and Philibert-Bigou[68] and the trifluoroperacetic acid by that of Emmons[37].

6-Acetoxy-2-methoxynaphthalene (58)

6-Acetyl-2-methoxynaphthalene (10 g.) in acetic acid (75 ml.) containing ammonium acetate (5 g.) was treated with 40% peracetic acid (20 ml.) and left in the refrigerator (about 0°) for 60 hr. The solution was poured into water and the precipitate filtered off and crystallised from methanol to give 6-acetoxy-2-methoxynaphthalene (3.5 g.; 32%) as white needles, m.p. 104 - 106°. A sample purified by further crystallisation from methanol had m.p. 106 - 107°, $\nu_{max.}$ 1770 $cm.^{-1}$ (ester carbonyl), (Found: C, 72.14; H, 5.86%. $C_{13}H_{12}O_3$ requires C, 72.21; H, 5.59%).

6-Methoxy-2-naphthol (54)

6-Acetoxy-2-methoxynaphthalene (0.5 g.) in ethanol (20 ml.) was mixed with a solution of potassium hydroxide (0.5 g.) in water (5 ml.) and the solution refluxed for 2 hr. and then poured into water. There was no precipitate. The solution was acidified and filtered and the solid dried to give 6-methoxy-2-naphthol (377 mg.; 94%), m.p. 153°. Its infra-red spectrum was identical to that of a sample made from Schaefer's acid (page 38).

1-Isopropenyl-2-methoxynaphthalene.

A solution of 1-acetyl-2-methoxynaphthalene (5 g.) in ether (20 ml.) was added to a solution of methyl magnesium iodide from magnesium(3.5 g.) and methyl iodide (9.5 ml.) in ether (150 ml.) After 2 hr., water and dil. hydrochloric acid were added carefully and the ether layer was separated, washed with dil. sodium bicarbonate solution and saturated brine, dried and evaporated to yield a yellow oil (4.7 g.) which showed no hydroxyl absorption in the infra-red. Chromatography on alumina (180 g., Grade 'H') and elution with petrol and petrol-benzene(10:1) gave 1-isopropenyl-2-methoxynaphthalene (4.23 g.; 85%) as a colourless oil, n_D^{25} 1.6108. Part of this oil was purified by repeated distillation on a sublimation block at 100 - 120°/0.6 mm. It then had n_D^{25}1.6112, $\nu_{max.}$ 1640 (m)(C=C), 900cm.$^{-1}$ (s)(CH_2=C<), (Found: C, 84.59; H, 6.91. $C_{14}H_{14}O$ requires C, 84.81; H, 7.12%). Addition of a saturated alcoholic solution of picric acid to a sample of the oil in a little ethanol gave an immediate precipitate of a bright red picrate, crystallising from methanol as needles, m.p. 129 - 130°. No pure sample of this could be obtained since drying under even slight vacuum or overnight open to the air led to partial loss of the naphthalene and the production of crystals of picric acid. Drying over phosphorus pentoxide did not satisfactorily remove the solvent. The complex thus appears to dissociate easily even in the solid state and is completely dissociated in solution which is pale yellow.

1-Isopropyl-2-methoxynaphthalene (59)

1-Isopropenyl-2-methoxynaphthalene (3.79 g.) in petrol (250 ml.) was hydrogenated at room temperature and pressure over palladised charcoal (10%, 500 mg.). The uptake was extremely slow and showed no clear endpoint. Hydrogenation was stopped after 19 hr. when the uptake had reached 470 ml. (theory 430 ml.). Filtration and evaporation of the filtrate gave an oil which was distilled to give 1-isopropyl-2-methoxynaphthalene (3.29 g.; 86.5%) in three arbitrary fractions boiling in the range 74 - 87°/0.08 mm. but with identical infra-red spectra. Each of the fractions solidified on standing in the refrigerator to a soft white solid, m.p. 30 - 40°. A sample was crystallised twice from ethanol in a 'Dricold' bath yielding white flakes, m.p. 45 - 46.5°(lit.[26] 48 - 49°) $\nu_{max.}$ 805 (s), 740 (s) cm.$^{-1}$, (Found: C, 83.66; H, 8.22. $C_{14}H_{16}O$ requires C, 83.96; H, 8.05%). A sample of this naphthalene in a little ethanol, on treatment with excess of a saturated solution of picric acid in ethanol, gave the corresponding picrate as red needles m.p. 138 - 140° from methanol. This picrate also dissociated slowly on standing in air and could not be purified for analysis.

Nitration of 2-Methoxynaphthalene.

Conc. nitric acid (1 ml.) was added to a solution of 2-methoxynaphthalene (316 mg.) in glacial acetic acid (5 ml.) with stirring at room temperature. After 1 hr. the mixture was poured into water and extracted with ether to give 1-nitro-2-methoxynaphthalene as yellow crystals from benzene-petrol, m.p. 127 - 128° (lit.[69] 130°), $\nu_{max.}$ 1630(m), 1600(m), 1510(s) and 1350(s) (nitro), 1280(s) and 1080(s)(ArOMe), 810(s)(2 adjacent Hs), 750(s) cm.$^{-1}$.

Nitration of 1-isopropyl-2-methoxynaphthalene.

a) With Nitric Acid:- Conc. nitric acid (0.5 ml.) was added dropwise to a stirred solution of 1-isopropyl-2-methoxynaphthalene (200 mg.) in glacial acetic acid (5 ml.). The solution became green but there was very little rise in temperature. After 1 hr. the solution was poured into water and extracted with ether. The ether layer was washed with aq. sodium hydroxide, dried and evaporated leaving a yellow oil, $\nu_{max.}$ 3080(w)(=CH), 1675(s)(enone), 1615(m), 1600(m), 1540(s) and 1340(nitro)cm.$^{-1}$ The same product was obtained using fuming nitric acid in acetic acid or conc. nitric acid in benzene with vigorous stirring and also under the above conditions for only one minute.

b) With Urea Nitrate:- A mixture of urea nitrate (250 mg.), 1-isopropyl-2-methoxynaphthalene (200 mg.) and Analar acetic anhydride (10 ml.) was stirred at room temperature overnight. The yellow solution was then treated with water to hydrolyse the anhydride and extracted with ether. The ether was washed with aq. sodium hydroxide and with brine and dried. Evaporation left an oil whose infra-red spectrum was very similar to that of 1-isopropyl-2-methoxynaphthalene except for new peaks of relatively low intensity at 1780, 1650 and 1570 cm.$^{-1}$.

The experiment was repeated using cupric nitrate trihydrate (124 mg.) in place of the urea nitrate. After stirring overnight, the mixture was treated with water (10 ml.) shaken till homogeneous, poured into water and neutralised with sodium hydroxide till cupric hydroxide just began to precipitate. The solution was worked up as before and gave a yellow oil (240 mg.) whose infra-red spectrum was very similar to that

of the urea nitrate product. It was chromatographed on alumina (Grade 'H', 10 g.). Petrol eluted a small amount of unchanged isopropyl-methoxynaphthalene. Petrol-benzene (10:1) eluted a yellow solid (100 mg.) and then smaller quantities of material showing hydroxyl absorption in the infra-red. The yellow solid had $\nu_{max.}$ 1650(m), 1610(m), 1600(m), 1520(s), 1340(s) $cm.^{-1}$. Recrystallisation was difficult but a small amount was obtained as yellow needles from petrol in the cold, m.p. 125 - 130° with charring. The intensity of the 1520 cm^{-1} peak was, however, much reduced.

1-Isopropyl-1-nitro-2-keto-1,2-dihydronaphthalene (62)

(From 1-isopropyl-2-naphthol):- Conc. nitric acid (310 mg.) in glacial acetic acid (1 ml.) was added with stirring and ice-cooling to a solution of 1-isopropyl-2-naphthol (233 mg.) in acetic acid (5 ml.). The mixture was stirred for 2½ hr. during which it was allowed to warm to room temperature. Dilution with ether, washing with water and work-up in the usual way gave an orange oil (280 mg.) whose infra-red absorption was closely similar to that of 1-isopropyl-1-nitro-2-keto-1,2-dihydro-naphthalene obtained by nitration of 1-isopropyl-2-methoxynaphthalene Samples from both preparations on thin layer chromatography on silica eluted with benzene showed a spot of $R_f = 0.55$. The sample from the ether showed no other significant spots while that from the phenol showed a small spot of $R_f = 0.11$.

Attempted isopropylation of 2,6-dimethoxynaphthalene.

a) With isopropanol:- 2,6-Dimethoxynaphthalene (190 mg.) was dissolved in tetrahydrofuran (5 ml.) and boron trifluoride etherate (1 ml.) added. To the resulting yellow solution was added Analar isopropanol (70 mg.)

in ether (1 ml.) and the mixture was refluxed for 3 hr. (internal temperature 62°). No colour change occurred. The solution was poured into water and extracted with ether, and this washed with sodium hydroxide solution and dried. Evaporation gave a quantitative recovery of dimethoxynaphthalene.

b) With isopropyl iodide :- 2,6-Dimethoxynaphthalene (188 mg.), aluminium chloride (400 mg.) and freshly distilled isopropyl iodide (243 mg.) were dissolved in methylene chloride (7 ml.) and the solution left standing for 70 hr. at room temperature. A similar work-up again gave unchanged starting material in high yield.

1-Acetyl-2,6-dimethoxynaphthalene (66)

Method a) :- 2,6-Dimethoxynaphthalene (5 g.) and aluminium chloride (8 g.) were dissolved in methylene chloride (75 ml.) and acetic anhydride (3 g.) added with ice cooling. The solution was stirred for 65 hr. at room temperature then refluxed for 30 min. The infra-red spectrum of a sample showed 70% conversion to ketone. The bulk was poured into water and the organic layer washed with sodium bicarbonate and brine, dried, treated with charcoal and evaporated to give a yellow solid. Chromatography of this on alumina (Grade 'H', 150 g.) with benzene gave dimethoxynaphthalene (1.25 g.) and 1-acetyl-2,6-dimethoxynaphthalene (3.13 g.; 52%, or 69% allowing for recovered ether. Crystallisation of the ketone from benzene-petrol gave white plates, m.p. 74 - 74.5°, $\nu_{max.}$ 1680(s), 860(s), 820 and 800(s)(doublet)(1,2,3,4- and 1,2,4- substituted benzenes)$^{cm^{-1}}_{b}$ (Found: C, 73.28; H, 6.15. $C_{14}H_{14}O_3$ requires C, 73.02; H, 6.13%).

Method b) :- Dimethoxynaphthalene (188 mg.), acetic anhydride (113 mg.) and iodine (5 mg.) were heated together in an oil bath at 160° for 3 hr. The black solid was extracted with methylene chloride and this was washed with sodium hydroxide and sodium bisulphate solutions and dried and evaporated to give a grey solid which was estimated (from its infra-red spectrum) to contain about 80% of the desired ketone.

1-Isopropyl-2,6-dimethoxynaphthalene (61)

A solution of methyl magnesium iodide was prepared from methyl iodide (1.9 ml.) and magnesium (720 mg.) in ether (50 ml.). 1-Acetyl-2,6-dimethoxynaphthalene (2.3 g.) was added and the mixture refluxed for 1 hr. Aq. sulphuric acid was added and the ether layer worked up as usual to give a solid which still contained ketone. This was treated with a further 0.03 mole of methyl magnesium iodide and worked up as before to give a brown solid, m.p. 48 - 56°. A sample of this on crystallisation from methanol gave 1-isopropenyl-2,6-dimethoxynaphthalene as white rhomboid plates, m.p. 58.5 - 59°, $\nu_{max.}$ 1630(m) and 900(s) (>C=CH_2) $cm.^{-1}$ which was not further characterised. The crude bulk was hydrogenated over palladised charcoal (10%, 450 mg.) in ethyl acetate. After 4 hr., uptake had virtually ceased and 221 ml. of hydrogen had been absorbed. The solution was filtered through celite and evaporated and the residue crystallised from methanol to give 1-isopropyl-2,6-dimethoxynaphthalene (1.43 g.; 65% from the ketone) as white rhomboid plates, m.p. 55 - 59°. A pure sample had m.p. 59.5 - 60°, $\nu_{max.}$ 1615(m), 1600(s), 1500(s), 1250(s), and 1040(s)(ArOMe), 860(s), 830 and 805(s) $cm.^{-1}$ (Found: C, 78.16; H, 7.62. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%).

1,4-Dihydro-2,6-dimethoxynaphthalene (71)

Sodium (0.64 g.) was added to a hot solution of 2,6-dimethoxynaphthalene (1 g.) in pure dry xylene (20 ml.). The suspension was refluxed and vigourously stirred. Dry ethanol (1.5 ml.) was added dropwise over 1 min. and stirring and refluxing continued for 15 min. The solution was cooled, water added and the xylene layer separated, washed, dried and evaporated under vacuum to give a pale yellow solid which was recrystallised from methanol at 0° to give 1,4-dihydro-2,6-dimethoxynaphthalene (0.8 g.; 80%) as white flakes, m.p. 37 - 37.5°. A sample purified by repeated crystallisation from methanol in a 'Dricold' bath had m.p. 38 - 40°, $\nu_{max.}$ 1680(s), 1645, 1600, 1580, 1500 cm.$^{-1}$, (Found: C, 75.90; H, 7.34. $C_{12}H_{14}O_2$ requires 75.76; H, 7.42%).

3,4-Dihydro-2,6-dimethoxynaphthalene (70)

a) By reduction of dimethoxynaphthalene:- 2,6-Dimethoxynaphthalene (1 g.) was dissolved in isopentanol (25 ml.), sodium (2.5 g.) added and the mixture refluxed for 2 hr. A further 12 ml. of isopentanol was added and refluxing continued for 6 hr. Part of the solvent was distilled off and the residue separated between benzene and water. The organic layer was distilled to dryness and the residue crystallised from methanol to give 3,4-dihydro-2,6-dimethoxynaphthalene (0.37 g.; 36%) as plates m.p. 79 - 82° (lit.[41] 83 - 84°). Sublimation gave material of m.p. 82 - 83°, $\nu_{max.}$ 1630(m), 1600, 1580, 1500 cm^{-1}.

b) By isomerisation:- 1,4-Dihydro-2,6-dimethoxynaphthalene (136 mg.) was dissolved in a solution of sodium (0.6 g.) in dry isopentanol (40 ml.) and the mixture refluxed for 4½ hr. After cooling, the solution was

washed with water and evaporated under vacuum to leave 3,4-dihydro-2,6-dimethoxynaphthalene which crystallised from methanol as plates, m.p. 86 - 87° identical to the product from route a) above.

Bromination of 6-hydroxytetralin.

A stirred solution of 6-hydroxy-1,2,3,4-tetrahydronaphthalene (74 g.) in carbon tetrachloride (160 ml.) was treated dropwise with a solution of bromine (81 g.) in carbon tetrachloride (150 ml.). The addition was complete in 1 hr. When the solution was again pale brown and most of the hydrogen bromide had evaporated, the solution was washed with water, with aq. sodium bicarbonate and with brine and the organic layer worked up to give a solid (111 g.; 98%), m.p. 50 - 65°.

A sample of this mixture was sublimed at 100°/0.1 mm to give white crystals, m.p. 49 - 55° (Found: C, 52.98; H, 4.72; Br, 35.10. $C_{10}H_{11}OBr$ requires C, 52.88; H, 4.88; Br, 35.19%). Part of the mixture was distilled. 77% of the sample boiled between 96 and 102°/0.08 mm,; the distillate still melted over a wide range. The first and last fractions had identical infra-red spectra.

Four fractional crystallisations of the crude mixture from low boiling petrol led to the isolation of 5-bromo-6-hydroxy-1,2,3,4-tetrahydronaphthalene as fine white needles, m.p. 75 - 76° (lit.[43] 74°), $\nu_{max.}$ 3300, 1600(w), 1580(w), 800(s)(1,2,3,4-tetrasubstituted benzene)$cm.^{-1}$. The amount of this, the less soluble component, which could be isolated pure was only about 15% of the total crude mixture. The remaining material was still a mixture of wide melting range and was shown by its infra-red spectrum still to contain considerable amounts of the desired

phenol but no more could be isolated by crystallisation. 4g. of the crude mixture were chromatographed on alumina (Grade 'H', 150 g.) which had been treated with acetic acid (10%, 7 ml.). Elution with 1:1 benzene-petrol gave pure 5-bromophenol (0.4 g.) m.p. 73 - 75°. Elution with benzene and with benzene-chloroform gave mixtures melting about 50 - 53° containing gradually increasing amounts of the second component. Pure chloroform eluted a mixture, m.p. 46 - 50° containing about equal amounts of the two isomers. No material containing a higher percentage of the second isomer was ever obtained.

A study of the infra-red spectra of the mixtures obtained from this chromatography showed the gradual diminution in intensity of the 800 cm^{-1} peak characteristic of the 5-bromophenol and development of new peaks at 3450(sharp)(unbonded OH), 1200 and 850(1,2,4,5-tetrasubstituted benzene) $cm.^{-1}$, due to the isomeric phenol.

5-Bromo-6-methoxy-1,2,3,4-tetrahydronaphthalene

5-Bromo-6-hydroxy-1,2,3,4-tetrahydronaphthalene (20 g.) was dissolved in a solution of sodium hydroxide (8 g.) in water (200 ml.). Dimethyl sulphate (20 ml.) was added dropwise with stirring. After 30 min., sodium hydroxide (8 g.) in water (50 ml.) was added and the mixture stirred overnight. Extraction with ether and work-up in the usual way gave 5-bromo-6-methoxy-1,2,3,4-tetrahydronaphthalene which was crystallised from aqueous methanol in the refrigerator as pale yellow prisms (17.7 g.; 83%), m.p. 35 - 36° (lit.[44] 38 - 39°), $\nu_{max.}$ 1280, 1080 and 1060 (ArOMe), 800 (1,2,3,4-tetrasubstituted benzene) $cm.^{-1}$

5-Isopropenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (76)

5-Bromo-6-methoxy-1,2,3,4-tetrahydronaphthalene (1 g.) and ethyl bromide (0.45 ml.) were dissolved in dry ether (10 ml.) and this solution was added dropwise over 45 min. to a suspension of magnesium (280 mg.) in ether (2 ml.), the mixture being kept refluxing gently. After the addition was complete, refluxing was continued for 1 hr. and then a mixture of dry acetone (5 ml.) and ether (5 ml.) added gradually. The solution was then refluxed overnight, cooled, diluted with ether and treated with dil. hydrochloric acid. Work-up of the ether layer in the usual way gave a brown oil which was shown by its infra-red spectrum to contain both alcohol and olefin. It was therefore warmed on a steam-bath for 90 min. with conc. aq. toluene sulphonic acid and toluene. The toluene layer was worked up in the usual way and the product chromatographed on alumina (Grade 'H', 37 g.). Elution with petrol gave 5-isopropenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (0.60 g.; 72%) as a pale yellow oil. A sample purified by distillation at 70°/0.02 mm. in a sublimation tube was an almost colourless oil, n_D^{26} 1.5475, $\nu_{max.}$ 3100(w), 1645(m), 1260(s), 1090(s), 1070(s), 900(s), 800(s) cm.$^{-1}$, (Found: C, 83.14; H, 8.99. $C_{14}H_{18}O$ requires C, 83.12; H, 8.97%).

5-Isopropyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (38)

The above Grignard reaction was repeated using 5-bromo-6-methoxy-1,2,3,4-tetrahydronaphthalene (12.05 g.), ethyl bromide (5 ml.), magnesium (3.36 g.) and acetone (15 ml.). After refluxing gently overnight, it was worked up in the usual way but using saturated ammonium chloride solution.

The ether layer after drying and evaporation yielded a yellow oil (15 g.) whose infra-red spectrum showed strong absorption due to hydroxyl and conjugated carbonyl groups(the latter due to self condensation of the acetone). 6 g. of this crude alcohol was hydrogenated over platinum oxide (180 mg.) in acetic acid (50 ml.). Absorption was erratic and did not stop completely. After about 450 ml. of hydrogen had been absorbed, the crude product was isolated and chromatographed on alumina (Grade 'H', 150 g.). Elution with petrol gave a colourless oil which was distilled to give 5-isopropyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (3 g.; 73%) as a clear oil, b.p. 76 - 78°/0.02 mm., n_D^{21} 1.5335, $\nu_{max.}$ 1590(m), 1250(s). 1105(s), 1045(s), 800(s) cm.$^{-1}$, (Found: C, 82.33; H, 9.78. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%).

2-Hydroxy-1-naphthoic Acid.

2-Naphthol (5 g.) and sodium (1.3 g.) were refluxed in toluene (150 ml.) till the sodium had dissolved. Carbon dioxide was passed through the suspension for 4 hr. Water and dilute sulphuric acid were added and the mixture was extracted with ether. The acid was extracted into sodium bicarbonate solution and this reacidified to give 2-hydroxy-1-naphthoic acid (4 g.; 61%), $\nu_{max.}$ 1645(hydrogen bonded conjugated carbonyl), 830(2 adjacent Hs) and 745(4 adjacent Hs) cm^{-1}.

Methyl 2-hydroxy-1-naphthoate.

To a solution of 2-hydroxy-1-naphthoic acid (47 g.) in ether were added batches of diazomethane in ether until further addition produced no effervescence. The yellow solution was washed with aq. sodium bicarbonate and water, dried and evaporated to give an orange solid

which on crystallisation from aq. ethanol gave methyl 2-hydroxy-1-naphthoate (46.2 g.; 91%) as white needles, m.p. 78 - 79°(lit.[49] 78 - 79°), $\nu_{max.}$ 1650(hydrogen bonded conjugated carbonyl), 1050 and 1030(methyl ester), 830 and 750 $cm.^{-1}$.

1-Isopropenyl-2-naphthol (78)

To a solution of methyl magnesium iodide from magnesium (36 g.) and methyl iodide (94 ml.) in dry ether (1 litre) was added dropwise a solution of methyl 2-hydroxy-1-naphthoate (37 g) in ether (250 ml.) at such a rate as kept the ether refluxing gently. There was no precipitation. The solution was stirred overnight and a large precipitate formed. Ethanol was added to decompose the excess reagent and the mixture was then stirred with dil. aq. sulphuric acid till two clear layers formed. The ether layer was separated, washed with water, aq. sodium bicarbonate and brine and the solvent evaporated to give a red oil (34 g.) whose infra-red spectrum showed it to be largely 1-isopropenyl-2-naphthol. It could not be induced to crystallise. Neither distillation nor chromatography provided a satisfactory method of purification. Repeated distillation of a small amount in a sublimation tube at 80°/0.02 mm. gave a fairly pure sample of the phenol as a yellow oil, n_D^{25} 1.6297, $\nu_{max.}$ 3500(OH), 3050($=CH_2$), 1620(C=C), 910($C=CH_2$), 815, 750 $cm.^{-1}$

1-Isopropenyl-2-acetoxynaphthalene

The crude 1-isopropenyl-2-naphthol (30 g.) was warmed on a steam-bath for 2 hr. with acetic anhydride (30 ml.) and pyridine (5 ml.). It was allowed to stand at room temperature overnight, poured into water

and extracted with ether. The crude ether solution was run through a column of alumina (Grade 'H', 100 g.) and the eluate evaporated under vacuum to give an orange oil, which on distillation gave 1-isopropenyl-2-acetoxynaphthalene as a pale yellow oil, b.p. 106 - 110°/0.1 mm., n_D^{20} 1.5838, $\nu_{max.}$ 3050, 1770(s), 1630(m), 910(s), 885(s), 810(s), 760(s), 740 cm.$^{-1}$ (Found: C, 80.17; H, 6.69. $C_{15}H_{14}O_2$ requires C, 79.62; H, 6.24%) After standing about a month in the refrigerator the acetate had crystallised and a sample recrystallised from petrol in the cold as white plates had m.p. 35 - 36°.

A sample of pure acetate was hydrolysed with aq. methanolic potassium hydroxide under nitrogen at room temperature for 5 days. The phenol was obtained as an orange oil with infra-red spectrum identical to that of purer samples of the original preparation.

1-Isopropyl-2-acetoxynaphthalene (80)

Pure solid 1-isopropenyl-2-acetoxynaphthalene (7.0 g.) was hydrogenated over palladised charcoal (10%, 480 mg.) in ethanol (500 ml.) containing acetic acid (5 ml.). After 60 hr. at room temperature and pressure, 770 ml. of hydrogen had been absorbed. The solution was filtered, the solvent removed under vacuum and the residue crystallised from petrol to give 1-isopropyl-2-acetoxynaphthalene (4.5 g.: 65%) as white rhombs, m.p. 65 - 67°. A sample recrystallised twice from petrol had m.p. 69 - 70°, $\nu_{max.}$ 1750(s), 950(m), 870(s), 765(s), 740(m) cm.$^{-1}$, (Found: C, 79.14; H, 7.18. $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.05%).

1-Isopropyl-2-methoxynaphthalene (59)(from (80))

1-Isopropyl-2-acetoxynaphthalene (0.5 g.) and potassium hydroxide (1 g.) were dissolved in 50% aq. methanol (10 ml.) and allowed to stand in a stoppered flask overnight. Dimethyl sulphate (1 ml.) was added and the mixture stirred for 30 min. Ether extraction and work-up in the usual way gave a mixture of two solids. This was extracted with petrol leaving yellow rhombs, m.p. 126 - 133° which were later shown to be 1-isopropyl-1-hydroperoxy-2-keto-1,2-dihydronaphthalene. Evaporation of the petrol washings and crystallisation of the residue from methanol in a 'Dricold' bath gave 1-isopropyl-2-methoxynaphthalene. (0.13 g.) as white flakes, m.p. 47 - 49°, mixed m.p. with a sample(m.p. 45 - 46.5°) prepared from 1-acetyl-2-methoxynaphthalene 45.5 - 47°

1-Isopropyl-2-naphthol (79) (from (80))

1-Isopropyl-2-acetoxynaphthalene (0.5 g.) and potassium hydroxide (1 g.) were dissolved in 50% aq. methanol (10 ml.), warmed on a steam-bath under nitrogen for two hr., cooled, poured into water and acidified. Extraction with ether and usual work-up and crystallisation of the product from petrol gave 1-isopropyl-2-naphthol as pale yellow rods, m.p. 59°. A sample purified by repeated crystallisation from petrol under nitrogen consisted of colourless rods, m.p. 59.5 - 60.5°, ν max. 3300(s), 1600(m), 1500(m), 1250(s), 1090(s), 1015(m), 930(s), 800(s), 745(s) cm^{-1}, (Found: C, 83.33; H, 7.32. $C_{13}H_{14}O$ requires C, 83.83; H, 7.58%. The sample apparently contained a little of the hydroperoxide by the time the analysis was carried out.)

Methylation of 2-naphthol

Analar 2-naphthol (10 g.) was dissolved in a solution of sodium (1.6 g.) in dry ethanol (50 ml.) and the solvent removed under vacuum. Dry toluene (50 ml.) was added and removed by distillation under vacuum. This process was repeated. The dry sodium salt was broken up and toluene (40 ml.) and methyl iodide (20 ml.) were added and the suspension refluxed for 19 hr. Chromatography of the total organic product on alumina (Grade 'H') and elution with a range of solvent mixtures from petrol through benzene, ether, chloroform and methanol resulted in the isolation of the following components, identified by infra-red spectroscopy and m.p.- 2-methoxynaphthalene (1.61 g.; 14.7%); 1,1-dimethyl-2-keto-1,2-dihydro-naphthalene (0.73 g.; 6%), as an oil, $\nu_{max.}$ 1680 cm.$^{-1}$, dinitrophenyl-hydrazone, m.p. 227 - 229° (lit.[50] 230 - 231°); 1-methyl-2-naphthol (3.75 g.; 34%); 2-naphthol (2.3 g.; 23%).

Isopropylation of 2-naphthol.

Dry sodium 2-naphthoxide (from 2-naphthol (10 g.) as described above) was refluxed gently under nitrogen for 20 hr. with a solution of toluene (40 ml.) and isopropyl iodide (37 ml.). After cooling, the solution was decanted and the residue (NaI) washed with benzene. Combination of the organic layers and evaporation of the solvent gave a brown oil (13.3 g.) which solidified on seeding with authentic 1-isopropyl-2-naphthol. Thin layer chromatography of a sample of the crude product with benzene-petrol(1:1) on silica showed that it contained 2-naphthol 1-isopropyl-2-naphthol and isopropyl 2-naphthyl ether in the ratio of about 2:5:1. The bulk of the crude material was distilled and

the fraction, b.p. 100°/0.06 mm. crystallised from petrol to give fairly pure 1-isopropyl-2-naphthol (7.1 g.; 55%) as needles, m.p. 55 - 60°.

Reaction of sodium 2-naphthoxide with t-butyl chloride.

Dry sodium 2-naphthoxide (from 2-naphthol (10 g.) as above) was refluxed gently for 65 hr. in a solution of toluene (40 ml.) and t-butyl chloride (45 ml.). The suspension was cooled and washed with water. The aqueous layer was strongly acidic. A sample of the organic material was shown by thin layer chromatography to consist almost entirely of 2-naphthol. The crude product (in toluene) was washed with 4N sodium hydroxide and the remaining 'neutral' layer dried and evaporated to give a brown oil whose infra-red spectrum was similar to that of 1-isopropyl-2-naphthol but which gave eight spots on a silica plate run in benzene-petrol (1:1) and an attempted chromatographic separation of the bulk failed completely.

1-Hydroperoxy-1-isopropyl-1,2-dihydronaphthalene (85)

1-Isopropyl-2-acetoxynaphthalene was hydrolysed as described above, p. 54, but without exclusion of air. The crude product was crystallised several times from benzene-petrol again with access of air to yield 1-hydroperoxy-1-isopropyl-2-keto-1,2-dihydronaphthalene as pale yellow rhombs or needles, m.p. 133 - 134°. A sample was sublimed at 100°/0.05 mm. to give clear yellow prisms, m.p. 133°, $\nu_{max.}$ (Nujol) 3300(m)(sharp), 1650(s), 1600(m), 1550(m), 1230(m), 1210(m), 1020(m), 820(s), 765(s), 750(m) cm.$^{-1}$, (0.002 M in CCl_4) 3505, 1678 cm.$^{-1}$(unaltered on dilution). (Found: C, 71.32; H, 6.31. $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47%) The compound gave an immediate colouration when treated with ferrous thiocyanate and a brown colouration with starch-iodide paper after about 30 sec.

Ethyl 2-hydroxy-3-naphthoate.

2-Hydroxy-3-naphthoic acid (50 g.) was dissolved in dry ethanol (800 ml.), conc. sulphuric acid (10 ml.) added and the solution refluxed for 2 hr. and then left standing overnight. Most of the ethanol was removed under vacuum and the residue poured into water. Extraction with ether and work-up in the usual way gave ethyl 2-hydroxy-3-naphthoate (51 g.; 89%) as yellow chunky crystals from benzene-petrol, m.p. 80 - 81°, (lit,[70] 85°).

3-(2-hydroxyprop-2-yl)-2-naphthol (89)

A solution of ethyl 2-hydroxy-3-naphthoate (37 g.) in dry benzene (100 ml.) was added dropwise over 1 hr. to a solution of methyl magnesium iodide from magnesium (20 g.) and methyl iodide (52 ml.) in dry ether (600 ml.) Ether (200 ml.) was added and the solution stirred at room temperature under nitrogen for 18 hr. The reaction was worked up in the usual manner with acetic acid to give a crude yellow solid (36 g.), m.p. 120°. Crystallisation from benzene-petrol gave 3-(2-hydroxyprop-2-yl)-2-naphthol (20.3 g.; 59%) as pale yellow needles, m.p. 137 - 8°.
A sample sublimed at 120°/0.05 mm. as white crystals, m.p. 137 - 8° (lit.[58] 140 - 141°), $\nu_{max.}$ 3300(m)(sharp), 3100 - 2800(broad), 1610(m) 1590(m), 1220, 1190, 1150(s), 1050(m), 940(s), 890(s), 870(s), 840(m) 750(s), 720(m).cm.$^{-1}$.

2-Acetoxy-3-isopropenylnaphthalene (90)

A solution of 3-(2-hydroxyprop-2-yl)-2-naphthol (3 g.) in acetic anhydride (35 ml.) containing sodium acetate (3 g.) was refluxed for 4 hr., then poured into water and shaken till the excess anhydride was

hydrolysed. The solid precipitate was extracted into ether, worked up in the usual way and crystallised from aq. methanol to give 2-acetoxy-3-isopropenylnaphthalene (2.9 g.; 86%) as pale yellow plates, m.p. 68 - 68.5° (lit.[58] 68 - 69°), $\nu_{max.}$ 1760(s), 1615(w), 1200(s), 1150(s), 1050(s), 925(s), 895 and 885(s) 750(s)cm^{-1}.

2-Acetoxy-3-isopropylnaphthalene (92)

2-Acetoxy-3-isopropenylnaphthalene (1 g.) in ethanol (60 ml.) containing palladised charcoal (10%, 185 mg.) was shaken with hydrogen at room temperature and pressure. After 4 min., 104 ml. had been absorbed and uptake stopped completely. The solution was filtered, the solvent evaporated and the residue crystallised from aq. methanol to give 2-acetoxy-3-isopropylnaphthalene (0.86 g.; 85%) as colourless plates, m.p. 60 - 63°. A sample recrystallised from methanol had m.p. 62.5 - 63.5°, $\nu_{max.}$ 1750(s), 1200(s), 1140(m), 1045(m), 925(m), 905(m), 890(m), 750(s) $cm.^{-1}$, (Found: C, 79.11; H, 7.27. $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06%)

3-Isopropenyl-2-naphthol (91)

Lithium aluminium hydride (0.18 g.) was suspended in dry ether (15 ml.) and a solution of 2-acetoxy-3-isopropenylnaphthalene (1 g.) in ether (7 ml.) added dropwise with stirring. The solution was then refluxed for 15 min., cooled and treated with dil. sulphuric acid. Work-up of the ether layer in the usual way and crystallisation of the residue from low boiling petrol gave 3-isopropenyl-2-naphthol as pale yellow chunky prisms, m.p. 45 - 49°, $\nu_{max.}$ 3200(m), 1630(m), 1200(s), 1175(s) 1060(m), 900(s), 870(m), 750(s)cm^{-1}. No sample satisfactory for analysis

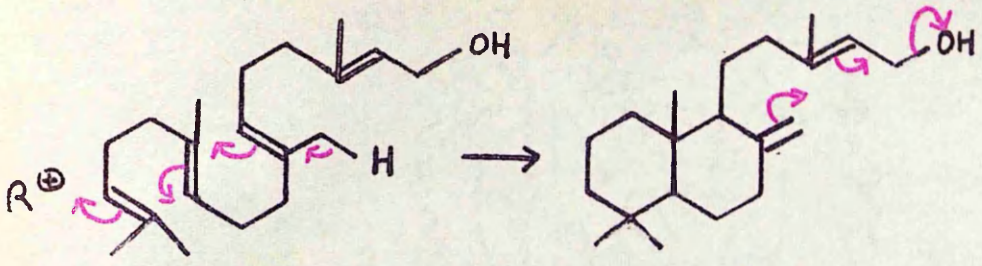
could be obtained. When dried under vacuum at room temperature, the crystals melted and resolidified on removal from the drying pistol.

3-Isopropyl-2-naphthol (88)

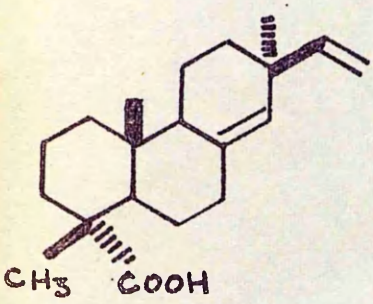
3-(2-hydroxyprop-2-yl)-2-naphthol (2.02 g.) in ethanol (100 ml.) containing a few drops of aq. perchloric acid and palladised charcoal (10%, 200 mg.) was shaken with hydrogen till 240 ml. had been absorbed The solution was filtered and evaporated and the residue chromatographed on silica (40 g.). The material eluted with benzene was crystallised from petrol to give 3-isopropyl-2-naphthol (0.92 g.; 50%) as pale yellow rhombs, m.p. 77 - 79°. A sample was recrystallised from hexane as colourless rods, m.p. 80 - 81°, $\nu_{max.}$ 3200(s), 1620(m), 1600(m), 1210(s), 1180(s), 945(m), 890(m), 870(s), 840(m), 815(m), 750(m), $cm.^{-1}$ (Found: C, 83.90; H, 7.40. $C_{13}H_{14}O$ requires C, 83.83; H, 7.58%).

Autoxidation Experiments

These are described in the Discussion section.



Geranyl geraniol



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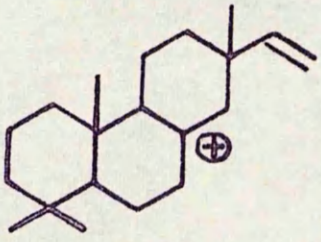

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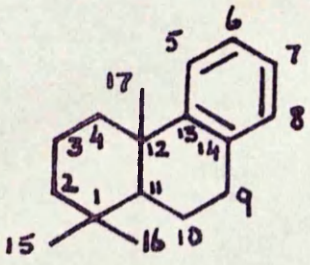
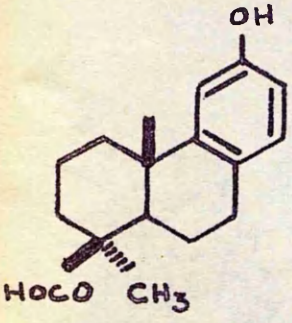


Podocarpane (3)



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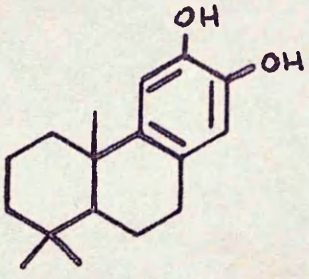

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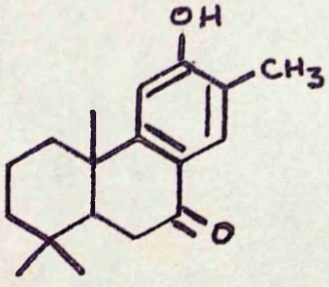

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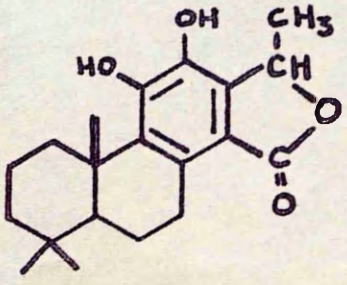

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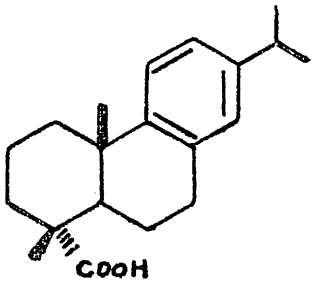

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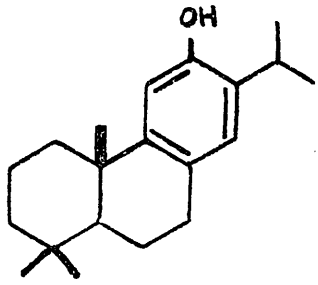

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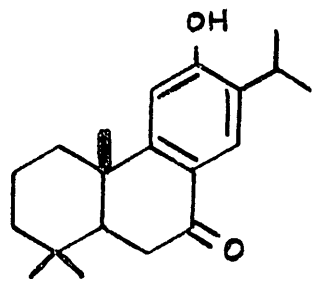

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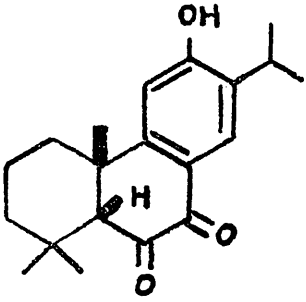

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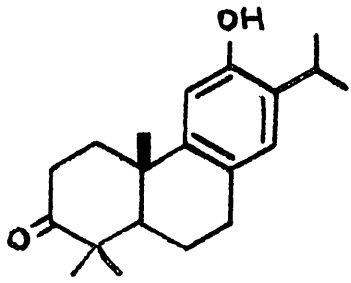

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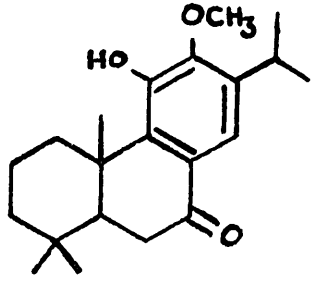

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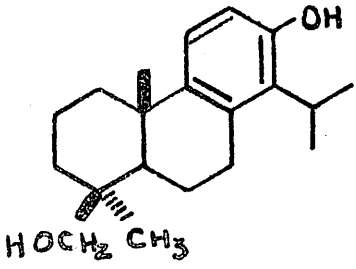

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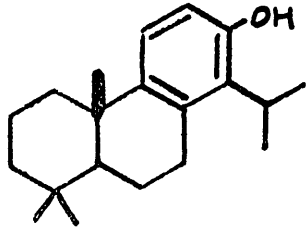
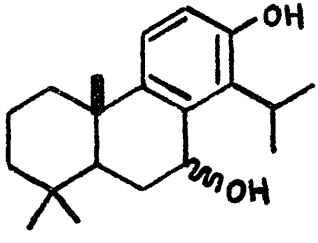


Totarol (14)



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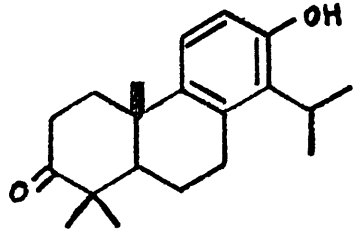

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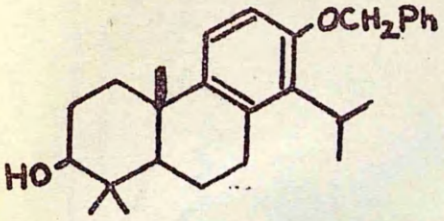

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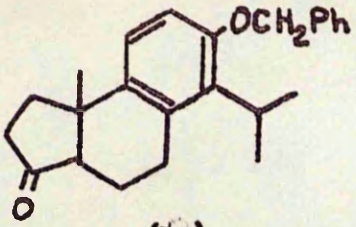

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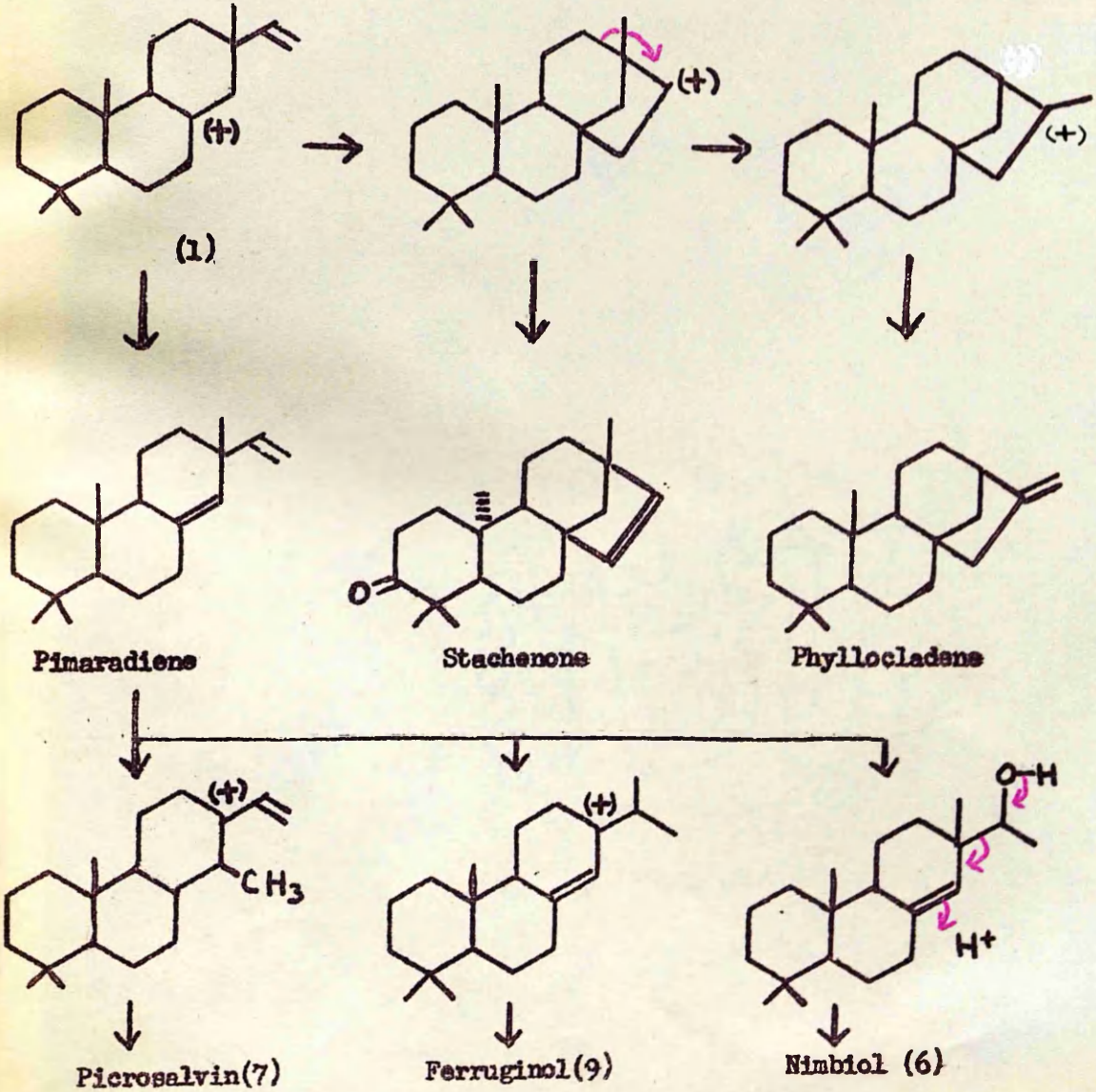
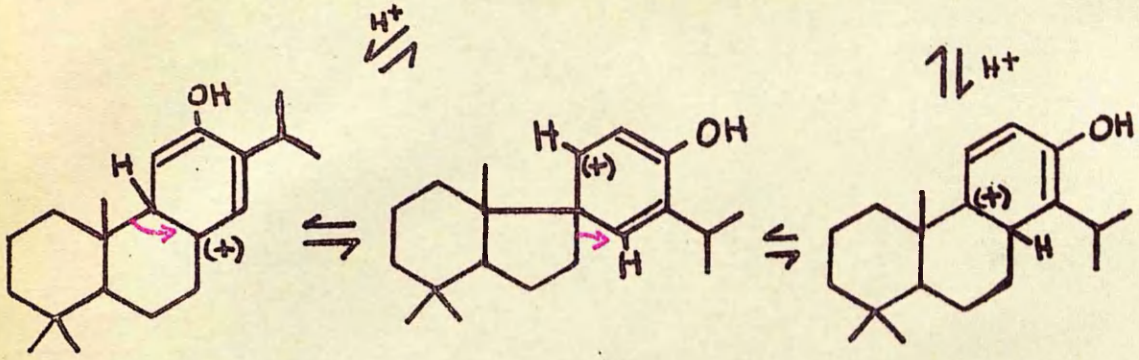
Scheme A



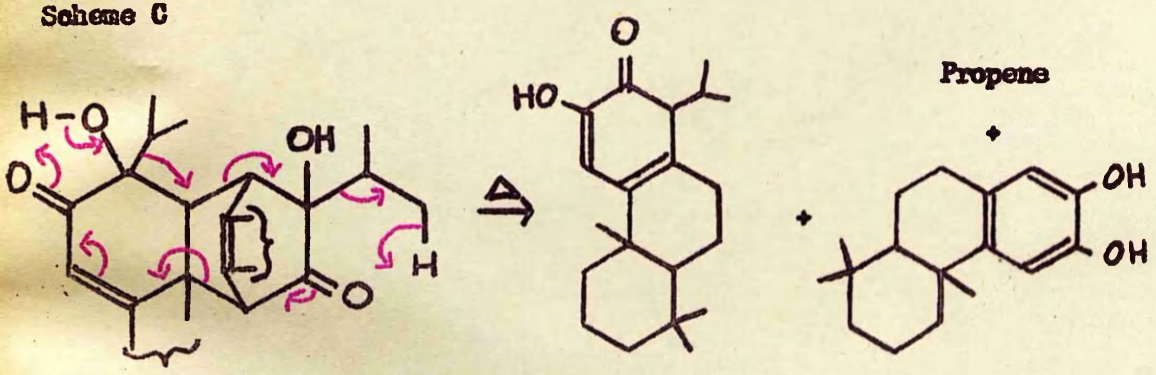
Scheme B

Ferruginol (9)

Totarol (14)



Scheme C



Maytenone

6-Hydroxytotarol

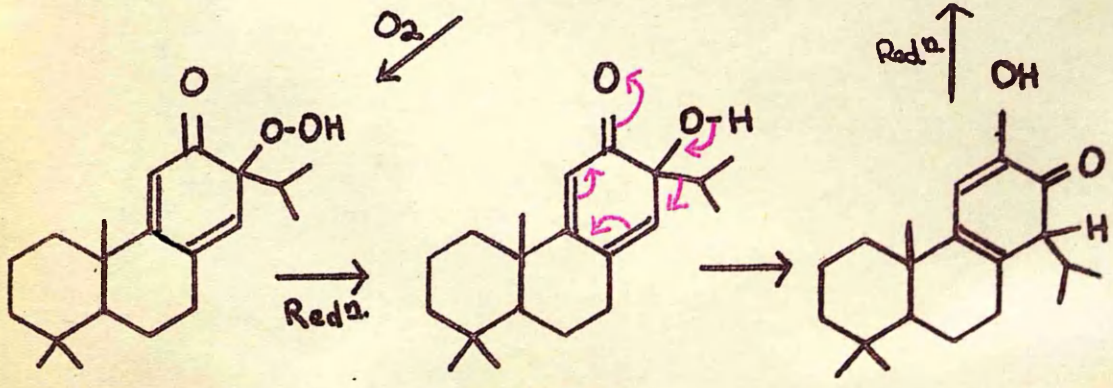
Podocarpane diol (5)

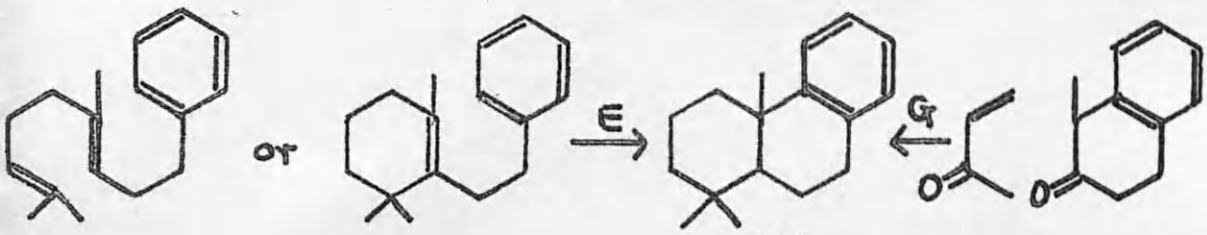
Rings A and B of the two ferruginol units are attached at the points marked }.

Scheme D

Ferruginol (9)

Totarol (14)





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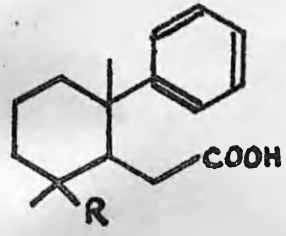

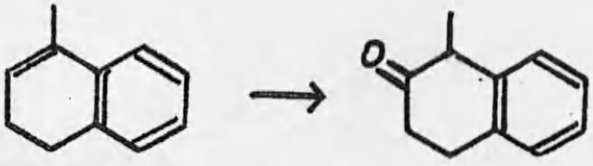

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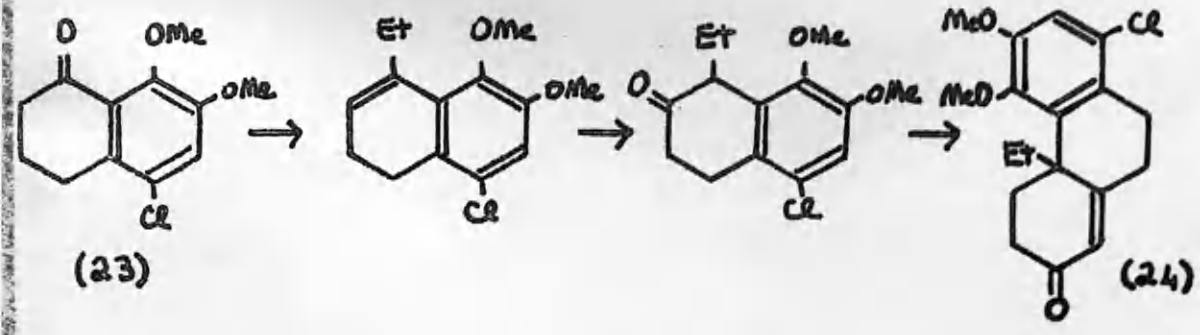

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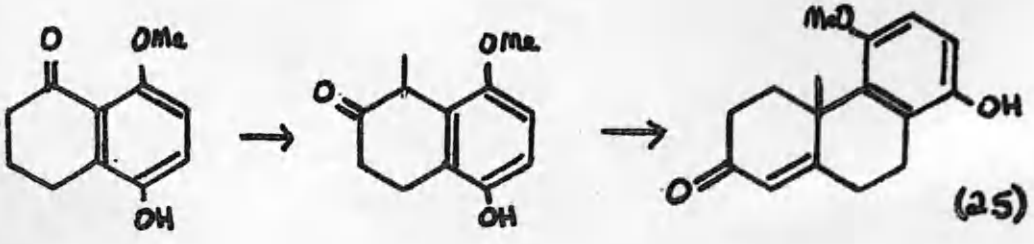

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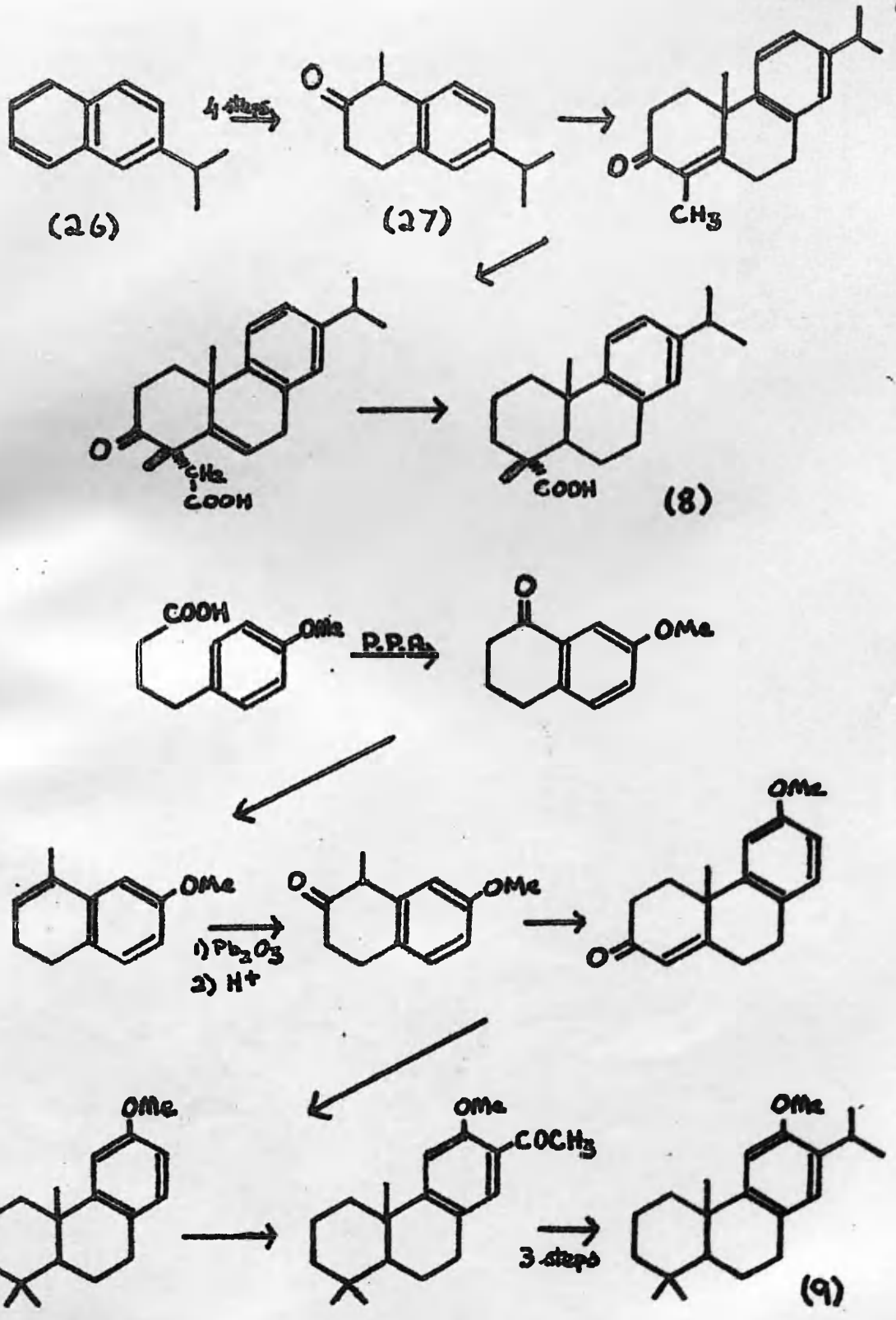
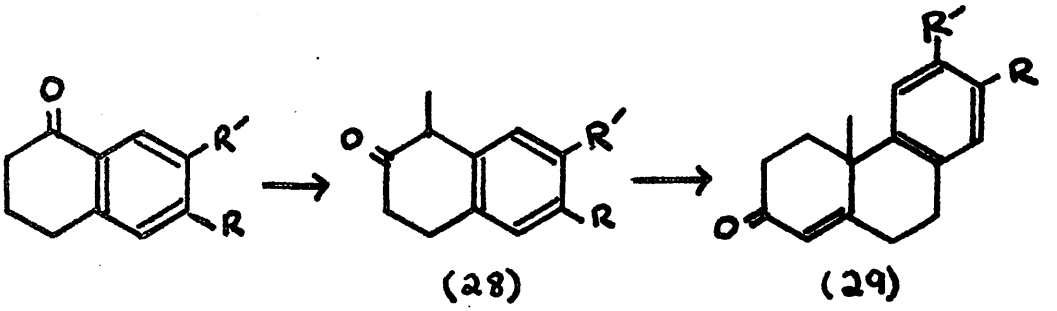

4 steps
(26)
(27)
CH3
COOH
(8)
COOH
OMe
P.P.A.
OMe
OMe
OMe
1) Pb2O3
2) H+
OMe
OMe
OMe
COCH3
3 steps
(9)



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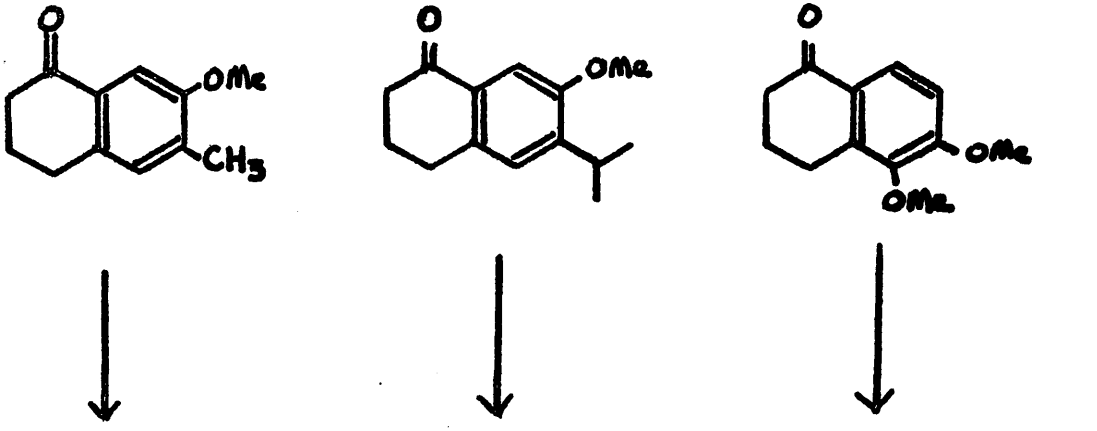

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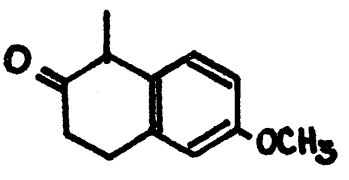

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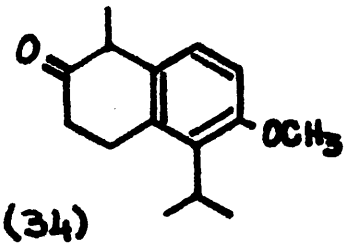

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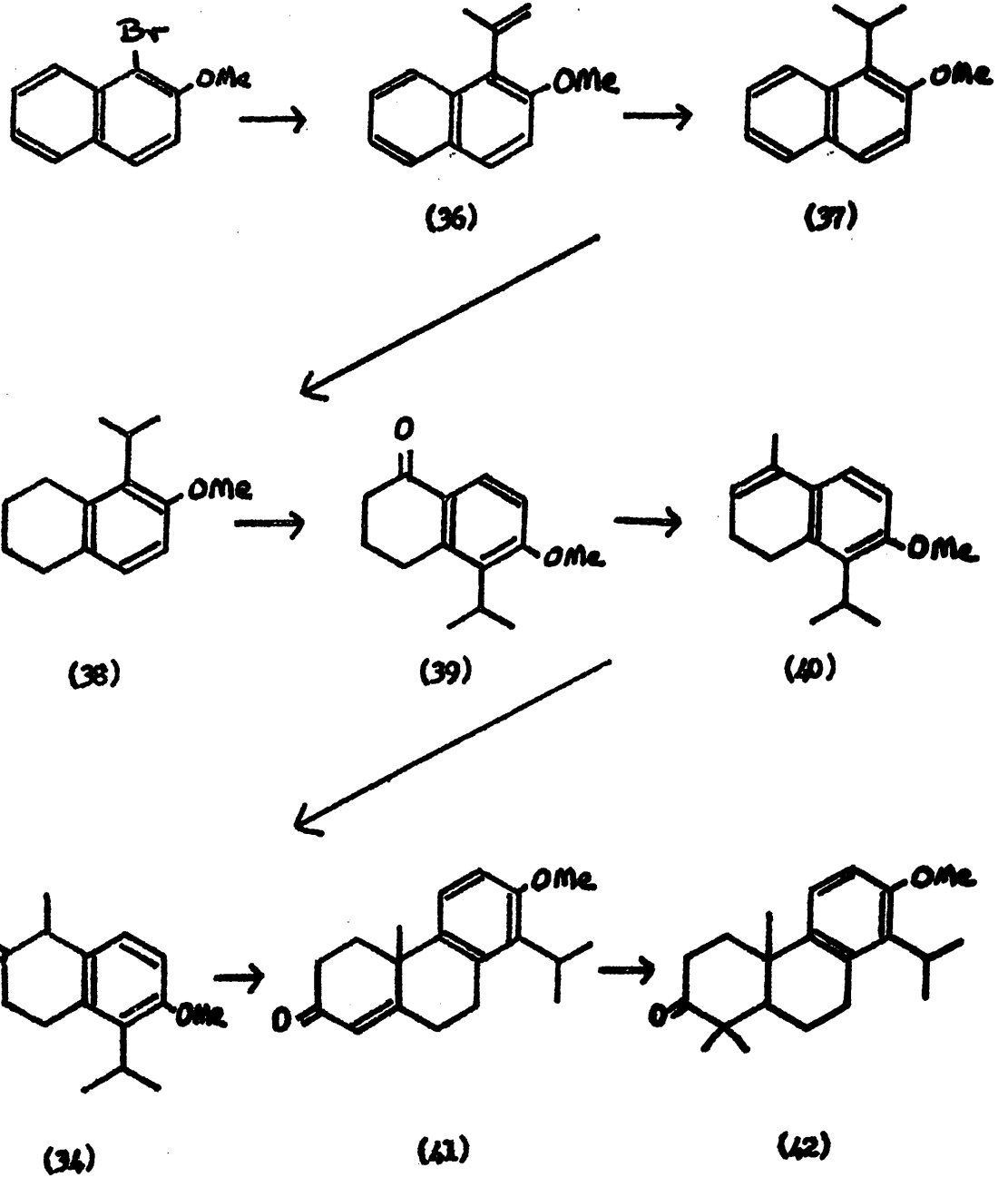
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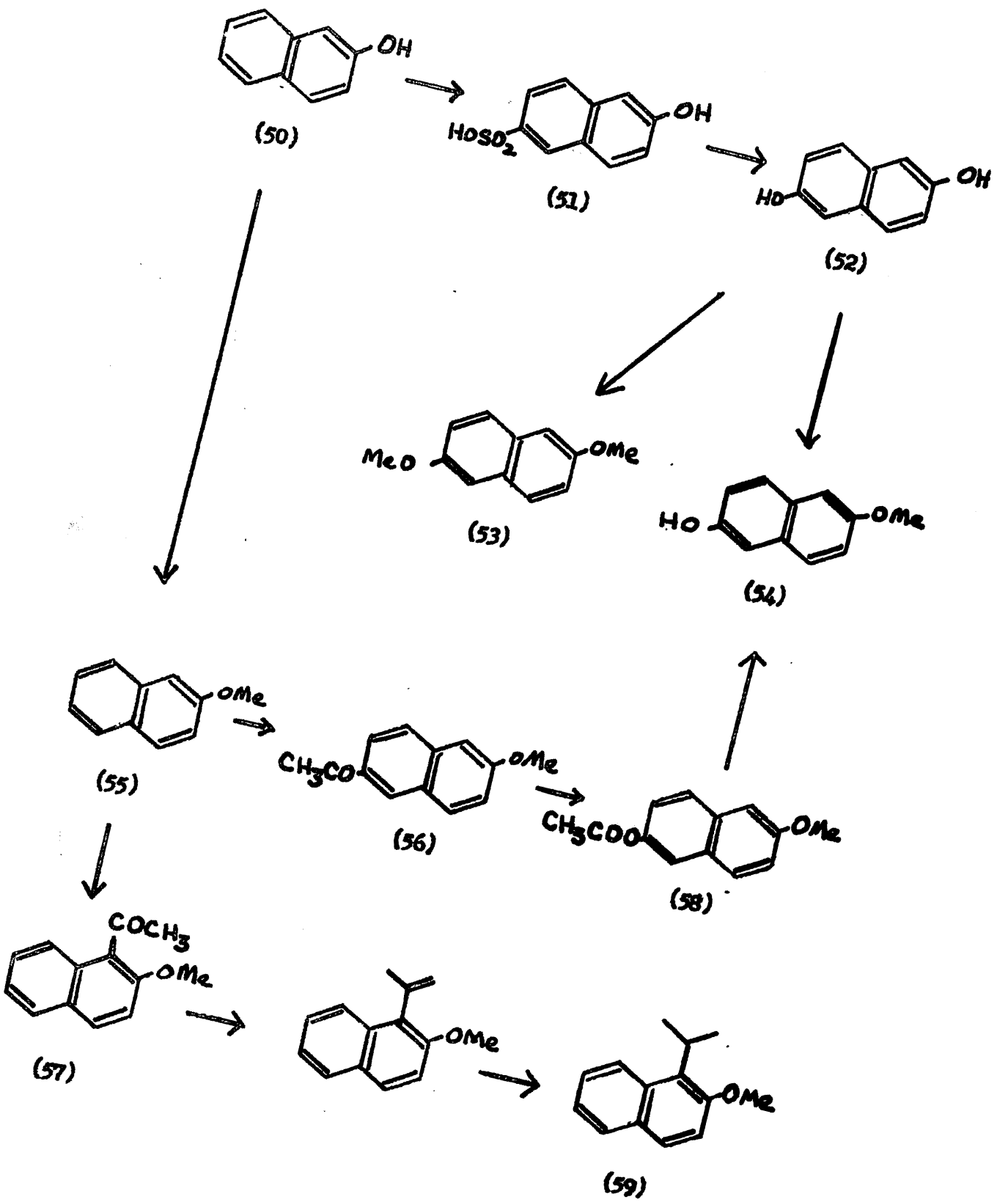
OMe
OMe
OMe
(36)
(37)
OMe
O
OMe
OMe
(38)
(39)
(40)
O
OMe
OMe
O
OMe
(34)
(41)
(42)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OH
(51)
HO
OH
(52)
MeO
OMe
(53)
HO
OMe
(54)
OMe
(55)
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(56)
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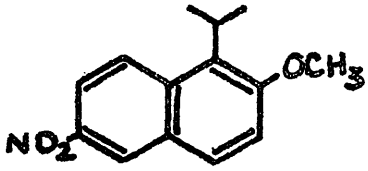
OMe
(57)
OMe
OMe
(59)



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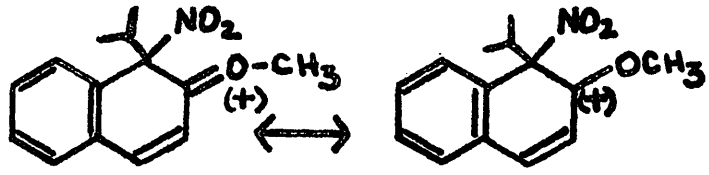

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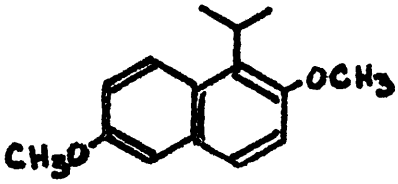

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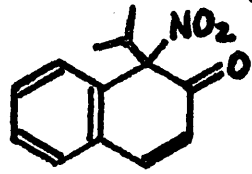
a b



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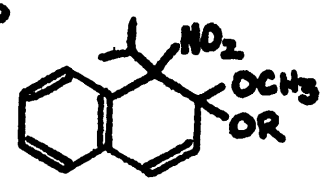

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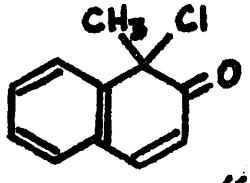

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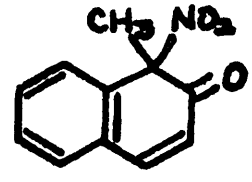

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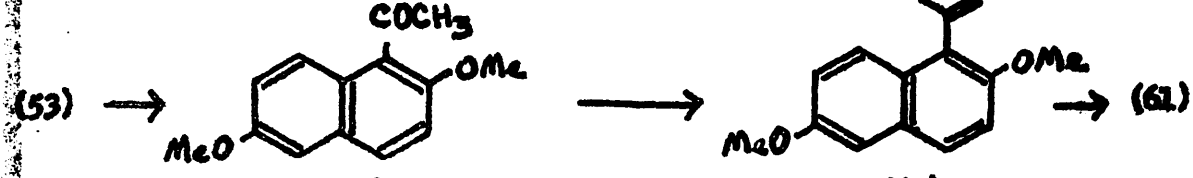

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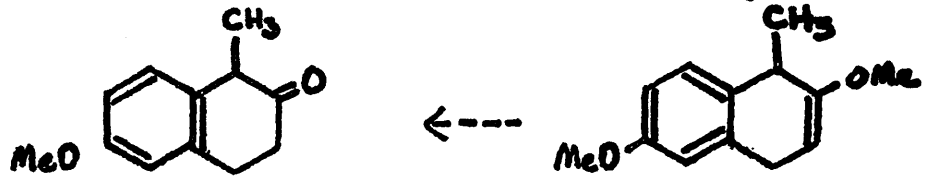

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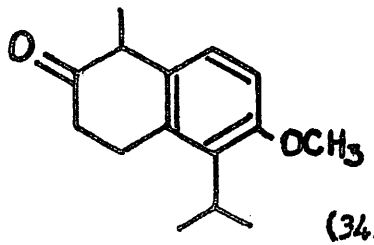

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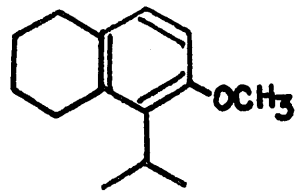

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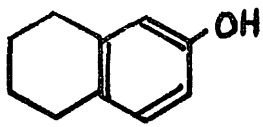

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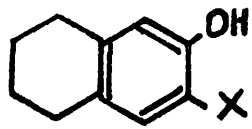

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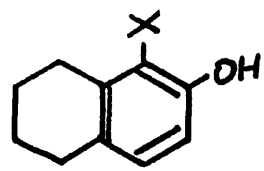

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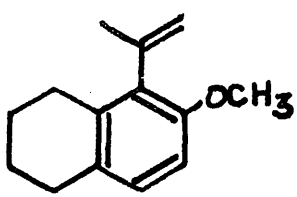

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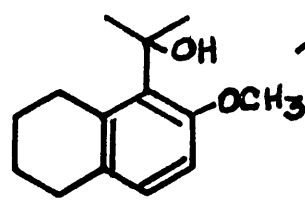

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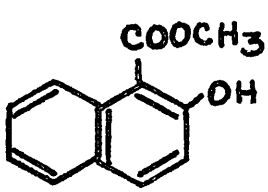

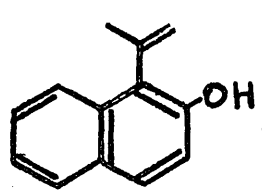

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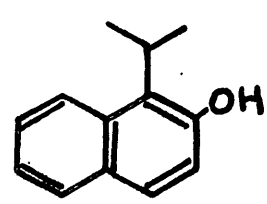

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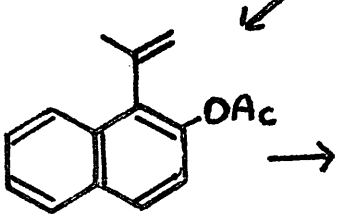

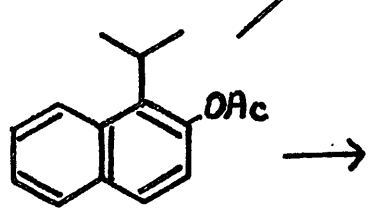

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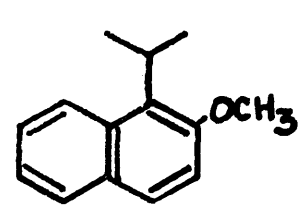

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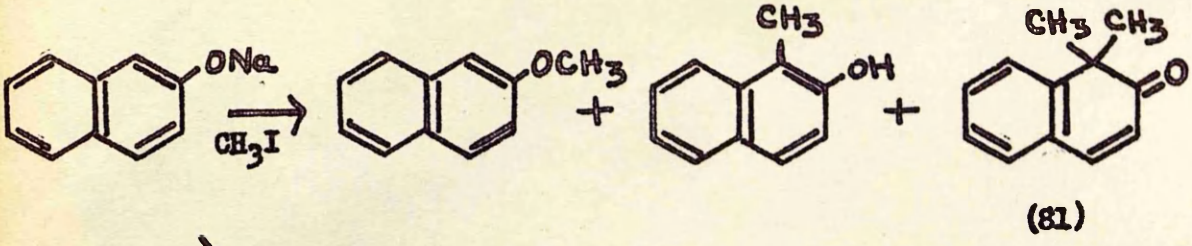

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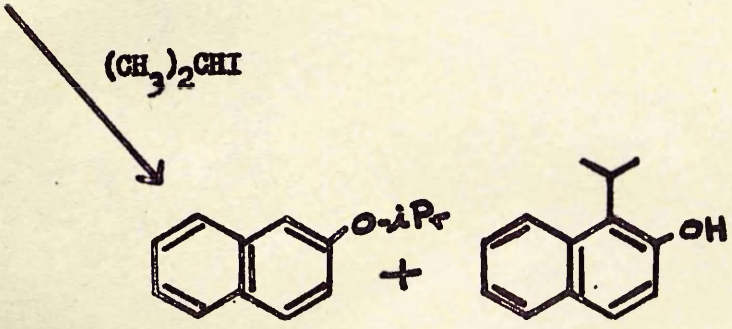

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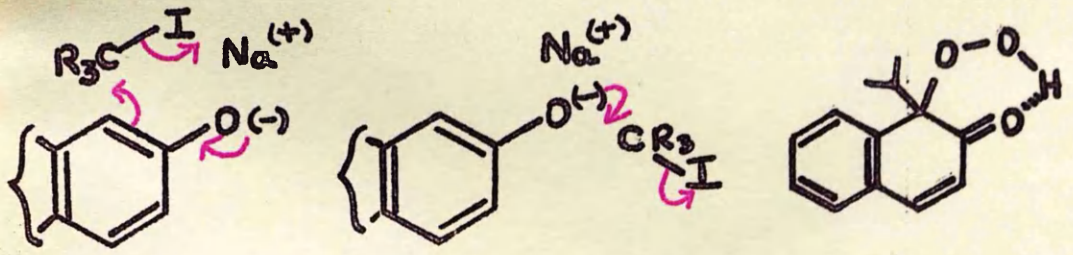

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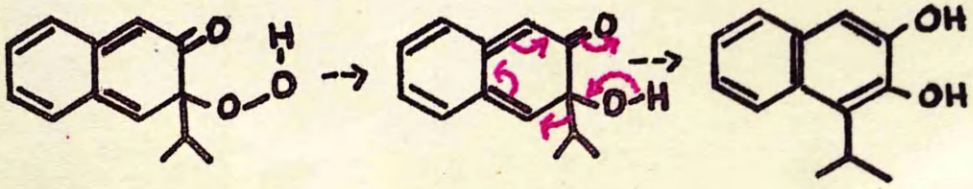

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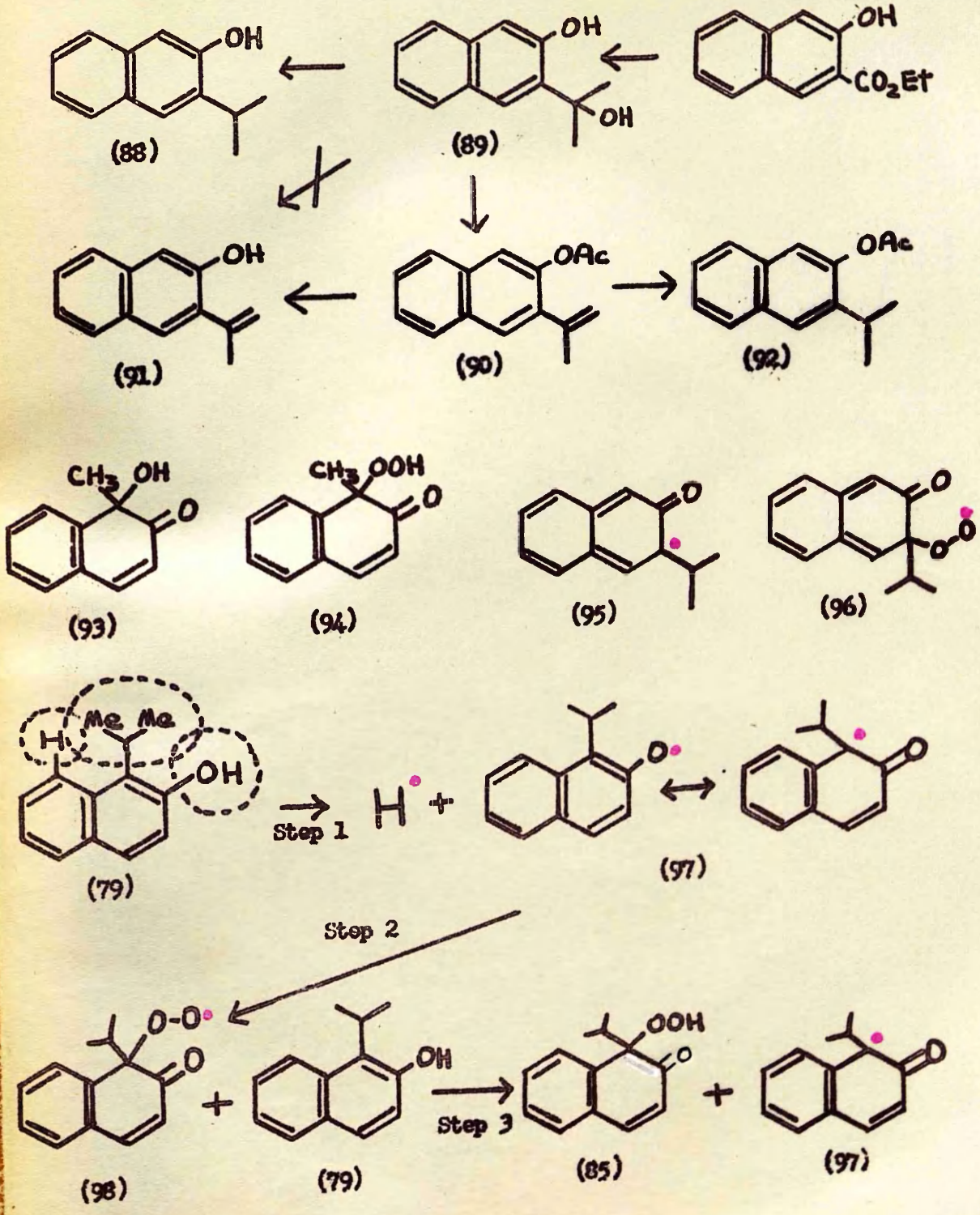
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(88)
OH
OH
(89)
OH
CO2Et
OH
(91)
OAc
(90)
OAc
(92)
CH3 OH
O
(93)
CH3 OOH
O
(94)
O
(95)
O
O
O
(96)
H
Me Me
OH
(79)
Step 1
H
O
(97)
Step 2
O-O
O
(98)
OH
(79)
Step 3
OOH
O
(85)
O
(97)

Part II.

Synthetic Approaches to Iridoid Monoterpenes.

The Iridoid Monoterpenes.

The term 'iridoid' has been coined by Briggs[71] to describe that group of monoterpenes which possess the carbon skeleton (101). Although natural products containing a five membered carbocyclic ring are relatively rare and until recently very few monoterpenes showing this feature were known, it has become apparent in the last five years that a fairly large group of monoterpenes exists which are characterised by the possession of this unusual isopropyl-dimethyl-cyclopentane skeleton.

Examples of this group have been isolated from both plant and animal sources and their very varied biological effects have resulted in a marked intensification of interest in their structure and synthesis. Thus, nepetalactone from catnip is an attractant to cats. The ant extractives, iridomyrmecin, isoiridomyrmecin, iridodial and dolichodial have lacrymatory, repellant, insecticidal and antibiotic properties. The more complex iridoid glucosides are often responsible for the blackening on standing of the leaves of certain plants and have therefore been collectively named pseudoindicans. Aucubin is known to increase the rate of excretion of uric acid.[91]

Interconversions of the different substances are many and have been of considerable value in structure determination. In particular, the allocation of structure and stereochemistry to the more complex compounds has often depended on a relationship with nepetalactone or its degradation products.

Nepetalactone (102) was isolated from catnip, Nepeta cataria, in 1936[72]. On alkaline hydrolysis it yields the two epimeric nepetalic acids (103) which can be reconverted to the lactone on pyrolysis. Oxidation of the aldehyde function gives a nepetalinic acid (104) or nepetonic acid (105) which can be further degraded with sodium hypoiodite to nepetic acid (106). The evidence leading to the structure and stereochemistry of these compounds has been summarised by Cavill[73]. All the possible nepetic acids (106) have been synthesised and identified[74]. Comparisons with samples made from natural sources andcyclisations and epimerisations observed with the natural materials enabled McElvain[75] to allocate to nepetalactone the stereochemistry shown in (102). Its absolute configuration as (102) follows from degradation of the cyclopentane ring to L-(+)-α-methylsuccinic acid[76].

In 1949, Pavan[77] isolated from the ant Iridomyrmex humilis a monoterpene lactone named iridomyrmecin. Subsequently Cavill has discovered the closely related substances isoiridomyrmecin and iridodial[78] and dolichodial[81] in other species of ant. Iridomyrmecin and isoiridomyrmecin also occur in the Japanese plant Actinidia polygama[107, 73]; these two are collectively known as the iridolactones.

Iridomyrmecin is epimerised by base to isoiridomyrmecin[79]. Iridomyrmecin on oxidation gives one of the nepetalinic acids derivable without epimerisation from nepetalactone while isoiridomyrmecin gives the C-8 epimer[79]. The lactones are therefore epimeric and epimerisable at C-8 and must have the structures (107).

Very recently, X-ray studies[83] have confirmed proposals by Sorm[84] and Cavill[73] that iridomyrmecin is (108) and isoiridomyrmecin (109). In the solid state at low temperatures the methyl group in both cases is equatorial to a half-boat lactone ring. The monomethyl ester (104a) obtainable from nepetalactone has been converted by reduction with lithium aluminium hydride to isoiridomyrmecin[85].

Iridodial undergoes an internal Cannizzaro reaction with base giving inter alia isoiridomyrmecin. On oxidation, it gives a mixture of nepetalinic acids. Its infra-red spectrum suggests that it exists largely as the enol-hemiacetal. It is therefore best represented as an equilibrium mixture (110)[80].

Dolichodial has been assigned the structure (111)[82]. It gives iridodial (110) on hydrogenation and formaldehyde on ozonolysis and has an ultra-violet spectrum typical of an α-monosubstituted acrolein.

Treatment of iridodial bis-dinitrophenylhydrazone with acid gives actinidine (112)[80], which occurs naturally in Actinidia polygama[107]. It is interesting that both isoiridomyrmecin and actinidine are attractive to cats, while iridomyrmecin is not. This may be due to the fact that the molecules of the first two substances, like that of nepetalactone, are almost planar while that of iridomyrmecin is not[83].

The iridoid skeleton occurs in more reduced state in the alkaloid skytanthine (113)[86] and in more highly oxygenated form in genipin (114)[87] and the closely related β-D-glucosides asperuloside (115)[1], verbenalin (116)[88] and loganin (117)[89]. In catalposide (118)[90] and

in aucubin (119)[91] and its p-hydroxybenzoate, agnuside[92], decarboxylation has occured while in plumieride (120)[93] and plumericin (121)[94] an acetoacetate unit has been added.

Biogenesis.

The most probable biogenetic precursor of all of these compounds is citral (122) which has been isolated from at least one species of ant and which on retroaldol cleavage would give 6-methylhept-5-ene-2-one which occurs together with iridodial in many Iridomyrmex and Dolichoderus species. It has been suggested that stereospecific reduction to L-(-)-citronellal, oxidation of the terminal allylic methyl group to a second aldehyde function and Michael-type internal cyclisation would give iridodial which on disproportionation would give the iridolactones, on oxidation nepetalactone and on cyclisation with ammonia and oxidation or reduction actinidine or skytanthine[95, 73].

A similar reaction sequence on citral itself without reduction to citronellal could give the structure (123). This would appear to be a possible precursor of all the more oxygenated iridoids since the extra oxygen functions, e.g. in asperuloside (115), occur at all the allylic positions while loganin (117) and catalposide (118) would require hydration or epoxidation of the double bond. The structures (118) and (119) would result from decarboxylation of the β-formyl carboxylic acid system. The oxygenation might alternatively occur at the allylic positions of citral prior to cyclisation.

Synthesis.

Because of the potential use of iridoids as antibiotics and insecticides there has been considerable interest in their synthesis and routes have now been devised which constitute total syntheses of nepetalactone, actinidine and all the ant extractives. The most noteworthy is that of Robinson[95] which simulates the proposed biogenetic route and which has yielded iridodial and isoiridomyrmecin. L-Citronellal (125) was converted to its ethylene acetal and this was oxidised by selenium dioxide to the aldehyde (126). Mild acid hydrolysis gave a mixture of cyclic and acyclic dialdehydes which could be separated by distillation. The cyclic aldehyde was found to be identical with natural L-iridodial and could be converted by disproportionation to L-isoiridomyrmecin. The value of this scheme lies in its stereospecificity, its brevity and its relation to the proposed biosynthesis. The yields are, however, only fair.

A variation of this route to provide dolichodial has been described by Cavill[96]. D-Citronellal ethylene acetal was degraded by hydroxylation of the double bond and cleavage to the tris-nor-aldehyde (127). Condensation of this with ethyl cyanoacetate gave an analogue (128) of Robinson's aldehyde (126) with an extra functional group at C-9 which would become the exo-methylene group of dolichodial. Acid catalysed cyclisation, modification of the side chain and finally removal of the ethylene acetal gave a mixture of dialdehydes which was shown to contain D-iridodial (129) and an isomer (130).

Various routes from non-natural sources have been investigated by Korte and co-workers.[97] In the first of these 3-methylcyclopentanone was converted by Reformatski reaction with ethyl α-bromopropionate, dehydration and hydrolysis to a mixture of unsaturated acids (131). The conjugated isomer was removed by distillation and the mixture of unconjugated ones submitted to a Prins reaction with formaldehyde which gave a mixture of unsaturated lactones from which, after hydrogenation and seeding with the natural compound, (±)-iridomyrmecin could be isolated. The yields are moderately good but the formation of isomers and the difficulty in separating them caused considerable loss of material. It is noteworthy that the formaldehyde adds from that side of the cyclopentene ring trans to the adjacent methyl group and that the subsequent hydrogenation gives that isomer with the hydrogen atoms at C-2, C-4 and C-8 all cis.

A different route has led to (±)-isoiridomyrmecin[98]. Homocatechol (132) on hydrogenation, cleavage and cyclisation gave a 1:1 mixture of isomeric methyl cyclopentene aldehydes. This was separated by preparative gas chromatography in one millilitre batches. The required 1-formyl-5-methylcyclopentene (133) was heated in an autoclave with cis-1-(n-propoxy)-propene, prepared from propanol and propanal followed by fractional distillation to separate the cis-isomer. The enol acetal (134), obtained in 42% yield, was hydrogenated and the saturated acetal hydrolysed, oxidised and lactonised. (±)-Isoiridomyrmecin was isolated from the resultant mixture.

An interesting route to nepetalactone which avoids the structural and some of the stereochemical ambiguities of Korte's procedures has been reported briefly by Sakan et al.[99]. 2-Ethoxycarbonyl-5-methylcyclopentanone was alkylated with 3-bromobut-1-yne and the resultant acetylenic ester hydrated, hydrolysed and decarboxylated to the diketone (135) which was cyclised and hydrogenated to the dimethyl-bicyclo-[3,3,0]-octanone (136) in which the rings must be cis-fused. The product was mainly the cis,trans-isomer shown. Condensation with benzaldehyde, reduction of the ketone and acetylation gave a separable mixture of stereoisomeric acetates (137) one of which on ozonolysis, hydrolysis and periodate cleavage gave a nepetalic acid(138) which on pyrolysis gave (±)-nepetalactone with an infra-red spectrum identical to that of the natural material.

No satisfactory route to the iridoid monoterpenes seems yet to have been developed involving readily available starting materials and high yields.

To this end investigations were undertaken in this department[100] to develop a synthetic route from simple aromatic precursors. Pechmann condensation of ethyl acetoacetate and pyrogallol gave the coumarin (139) which was converted via the trimethoxycinnamic acid (140) by hydrogenation and cyclisation with polyphosphoric acid to the indanone (141). This on Clemmensen reduction, chloromethylation and hydrogenolysis gave the indane (142). All attempts to degrade this or its derivatives to a substance with the skeleton of iridodial failed, however, apparently owing to the tendency of the trialkyl-

trioxygenated system to resinify. An attempt to make the simpler analogue (143) failed when the intermediate (144) could not be induced to cyclise. When p-cresol was used as starting material, the indane (145) was obtained fairly readily. This could not be reduced with lithium in liquid ammonia. No satisfactory method of demethylating it could be found; the small amounts of phenol obtained could not be oxidised with Fremy's salt. The ether was nitrated to give (146), but this could not be demethylated at all and on reduction it gave an amine whose mono- or di-acetate could not be degraded satisfactorily by ozonolysis.

Note added on July 1st. In a very recent communication[112], Cavill has described an improvement on Sakan's route[99] to the iridoids. Pulegone was converted via trans-pulegenic acid to the dimethyl-bicyclo[3,3,0]-octane (147). The neat, direct, Baeyer-Villiger oxidation of this to nepetalactone could not be effected but epoxidation of the enone and rearrangement and reduction could be made to yield a hydroxyketone or a diol which could be converted on periodate cleavage to nepetalactone or iridodial respectively, (see page 99).

Indanes as Precursors.

The general route to iridoid monoterpenes via suitably substituted indanes which was mentioned in the Review section seemed, in spite of the early setbacks, to merit further investigation. Since 4,6-dimethylcoumarin (151) is readily available from p-cresol, its modification to provide the indanes (152) and (153) was reinvestigated. Nabney[100] had made the ether (152) and found no satisfactory method of degrading the aromatic ring. Its conversion to the free phenol (153), which should be more easily degraded, could be achieved in only poor yield. A good route to this phenol was therefore our first aim.

Using the technique of Papa, Schwenk and Whitman[101] for reduction of α,β-unsaturated acids by addition of Raney nickel-aluminium alloy to a hot alkaline solution of the acid, the coumarin (151) was smoothly and rapidly reduced. The alkaline solution on treatment with dimethyl sulphate gave the methoxyacid (154) very simply and in excellent overall yield. On heating with polyphosphoric acid, the acid readily cyclised to 4-methoxy-3,7-dimethylindan-1-one (155) and this was reduced by the Clemmensen prodedure to the parent indane (152). In both steps yields better than those reported[100] were achieved.

Nabney[100] had found that attempts to demethylate (152) using hydrogen bromide or sodamide led only to resins, while fusion with pyridine hydrochloride gave a 25% crude yield of material for which good analysis figures could not be obtained. I have found that fusion with freshly prepared pyridine hydrochloride does give the

phenol in fairly good yield but a much preferable method of demethylation is that of Johnson[102] which involves heating the ether with excess methyl magnesium iodide with no solvent. Nucleophilic attack by the methyl anion on the methoxyl carbon atom of the ether results in smooth evolution of ethane and careful acidification of the residue led, in this case, to the isolation of 7-hydroxy-1,4-dimethylindane (153) in excellent yield and requiring virtually no purification. The overall yield of the phenol from 4,6-dimethylcoumarin was 47%.

The methylation and demethylation steps were necessitated by the requirement to protect the phenol function during the internal Friedel-Crafts acylation, and are, strictly unnecessary to the synthesis. We therefore sought to repeat the scheme with the free hydroxy-compounds. 4,6-Dimethylcoumarin was therefore reduced as before and the solution acidified carefully to yield a white precipitate of 3-(2-hydroxy-5-methylphenyl)butyric acid (156). This could not be purified since on standing or warming in solvents it lactonised to (157). Treatment of the crude hydroxyacid with zinc chloride at 200° for two hours or with polyphosphoric acid at 120° for three hours also led only to the lactone. This lactone, or dihydrocoumarin, is isomeric with the desired hydroxyindanone (158) and should be convertible to the latter under sufficiently forcing Friedel-Crafts or Fries reaction conditions. Such isomerisations have reported by Loudon and Razdan[103] using aluminium chloride at high temperatures. The lactone was therefore mixed with aluminium chloride and heated

in an oil bath at about 190° for twenty minutes. Work-up of the resulting black resin gave the desired hydroxyindanone in moderate yield. Clemmensen reduction of this product gave 7-hydroxy-1,4-dimethylindane (153) identical to that obtained from the methyl ether. The overall yield from 4,6-dimethylcoumarin was 28% but it should be possible by careful selection of the isomerisation conditions to raise this to over 50%.

Attempts to degrade this phenol to nepetalic or nepetalinic acid have been, as yet, unsuccessful. Nabney[100] was unable to oxidise it with Fremy's salt and I have found that, while it can be coupled with diazotised sulphanilic acid and the azo-dye reduced to the ortho-amino-phenol hydrochloride, attempts to oxidise this material (e.g. with ferric chloride) gave only dark intractible material much of which was water-soluble. It has been reported by various workers[108, 109] that 2,4-dialkyl-6-nitrophenols, on heating with concentrated sulphuric acid are degraded to substituted muconic acids and hydroxylamine. This reaction seemed to offer an alternative to the ortho-quinone route for cleaving the aromatic ring, but attempts to perform this conversion with 2,4-dimethyl-6-nitrophenol as a model compound gave such poor results that the route was abandoned.

The most desirable degradation of the ring would be one which would result in cleavage between C-5 and C-6 as well as between C-6 and C-7 of the 7-hydroxyindane system. This would be facilitated by a further oxygen function in the 5-position. [c.f. attempts[100] to make and degrade the 5,6,7-trimethoxy- and 5,7-dimethoxyindanes (142)

and (143)]. We therefore sought to introduce a further hydroxyl group into (153) by oxidation with lead tetraacetate[110]. It was hoped that acetoxylation would occur at the 4-position giving the acetoxycyclohexadienone (148) which would rearrange to the resorcinol derivative (149) on treatment with boron trifluoride[111]. In the event, treatment of (153) with lead tetraacetate gave a small yield of material whose ultra-violet absorption indicated that it was the undesired isomeric fully conjugated dienone (150).

While the above work was in progress, a quantity of 2,4-dihydroxybenzaldehyde became available which allowed investigation of a direct route to 5,7-dihydroxy-1,4-dimethylindane (160). Clemmenson reduction of the 2,4-dihydroxybenzaldehyde gave 4-methylresorcinol and it was planned to repeat, using this starting material, the syntheses which had been carried out with p-cresol.

Pechmann condensation with ethyl acetoacetate was carried out as before. 7-Hydroxy-4,6-dimethylcoumarin (161) was formed in good yield and, as reported[104] crystallised initially in two forms, needles and prisms. By digestion with methanol or repeated crystallisation, it could all be obtained in the latter form.

In an attempt to repeat the dihydrocoumarin - hydroxyindanone rearrangement as before, the coumarin was converted to its methyl ether (162) and this reduced by the Raney alloy technique to give 3,4-dihydro-7-methoxy-4,6-dimethylcoumarin (163). Fusion of this with aluminium chloride, however, resulted only in demethylation and hydrolysis to give 3-(2,4-dihydroxy-5-methylphenyl)butyric acid (164) which was also

obtained by Raney alloy reduction of the hydroxycoumarin (161). Presumably demethylation and fission of the lactone occur to give a complex acylium ion, perhaps as shown (165), but this fails to cyclise and is simply hydrolysed during the work-up. Acylation meta to two oxygen functions as is required here is known to be very difficult (see below) but at least one case is known where an analogous alkylation was effected. 7-Methoxychromanone (166) on fusion with aluminium chloride gave, albeit in poor yield, 5,7-dihydroxyindanone (168) presumably via an intermediate such as (167)[103].

Attention was therefore turned to polyphosphoric acid cyclisation of 3-(2,4-dimethoxy-5-methylphenyl)butyric acid (169) which was made by Raney alloy reduction of the coumarin (161) and methylation. The conversion of the acid to an indanone requires the internal acylation to occur at a position meta to both the methoxyl groups. Recorded reports of similar acylations were not encouraging.[100] All attempts to cyclise 3-(2,4-dimethoxyphenyl)butyric acid (144) with sulphuric acid, hydrofluoric acid or polyphosphoric acid or to cyclise the acid chloride with aluminium chloride had failed completely, and indeed, with two notable exceptions, no cyclisation of a 2,4-dimethoxyphenyl-carboxylic acid has been reported to give more than 5% yield of the corresponding ketone[105]. Cyclisation meta to one methoxyl group can be effected in high yield, however [c.f. cyclisation of (154) in 82% yield, p. 81]. The deactivating effect of the two methoxyl groups has been attributed somewhat vaguely to inductive withdrawal of electrons from the ring and it was hoped that the electron-repelling methyl group

on the ring of (169) might help to counterbalance this. Schmid and Burger[106] have reported that while 4-(2,4-dimethoxyphenyl)butyric acid (172) on treatment with polyphosphoric acid gives only about 4% yield of the corresponding tetralone, its 2- and 3-methyl-derivatives (173) and (174) give the corresponding tetralones in over 60% yield on heating to 165° with polyphosphoric acid for a short time. No explanation was offered for this exceptional report but the conditions were rather critical and their selection had obviously required considerable trial and error investigation. It was hoped that, in spite of the better yields obtained in cyclisations to tetralones compared with those for indanones, moderate yields of 4,6-dimethoxy-3,7-dimethylindan-1-one might be obtained using such high temperature-short time techniques.

In the event, an attempt to cyclise (169) with polyphosphoric acid at between 110 and 130° for one hour led only to recovery of most of the acid. When the same reaction was carried out at 150° for three minutes, the product was a red, low-melting solid which was shown by thin layer chromatography to consist largely of the desired indanone and this was isolated in 27% yield by crystallisation from methanol. Clemmensen reduction of the indanone gave 5,7-dimethoxy-1,4-dimethyl-indane (171) which when heated with methyl magnesium iodide was demethylated to yield the desired 5,7-dihydroxy-1,4-dimethyl indane (160).

On the basis of many precedents, it should now be possible to reduce this substituted resorcinol with sodium in ethanol to the cyclo-hexa-1,3-dione (175) which on hypoiodite oxidation should give a product with the structure of nepetalinic acid (104).

Experimental.

4,6-Dimethylcoumarin (151)

This was prepared from p-cresol and ethyl acetoacetate by the usual Pechmann procedure[100].

3-(2-Methoxy-5-methylphenyl)butyric acid (154)

4,6-Dimethylcoumarin (50 g.) was dissolved in 4N aq. sodium hydroxide (500 ml.) and the solution stirred and heated on a steam-bath while Raney nickel-aluminium alloy (40 g.) was added over 2 hr. The hot solution was filtered and the filtrate cooled to room temperature and treated dropwise with dimethyl sulphate (120 ml.) over 2 hr. with vigorous stirring. After standing overnight, the solution was poured into iced conc. hydrochloric acid and extracted with ether and this dried and evaporated. The residue on crystallisation from petrol gave 3-(2-methoxy-5-methylphenyl)butyric acid (52.5 g.; 88%) as white rhombs, m.p. 60 - 61° (lit.[100] 60.5 - 61°).

4-Methoxy-3,7-dimethylindan-1-one (155)

3-(2-Methoxy-5-methylphenyl)butyric acid (12 g.) was stirred with polyphosphoric acid (180 g.) at 100 - 120° for 2 hr. It was allowed to cool, poured into water and extracted with chloroform. This was washed with sodium hydroxide solution, dried and evaporated and the red liquid residue crystallised from petrol to give 4-methoxy-3,7-dimethylindan-1-one (8.0 g.; 82%) as pale yellow spars, m.p. 52 - 54° (Nabney quotes 33 - 33.5° possibly a misprint for 53°), ν_{max} 1700(s) cm^{-1}.

7-Methoxy-1,4-dimethylindane (152)

Zinc (150 g.), amalgamated by shaking with mercuric chloride (15 g.) in water (70 ml.) containing dilute hydrochloric acid (8 ml.), was suspended in a mixture of ethanol (300 ml.), conc. hydrochloric acid (240 ml.) and water (50 ml.). The suspension was refluxed and a solution of 4-methoxy-3,7-dimethylindan-1-one (30 g.) in ethanol (250 ml.) added over 45 min. Refluxing was continued for 3½ hr. with occasional addition of conc. hydrochloric acid. After cooling, the solution was decanted, the zinc washed with methanol and the combined solutions evaporated carefully through a fractionating column. The residue was distilled to give 7-methoxy-1,4-dimethylindane (20.6 g.; 75%) as a colourless oil, b.p. 117 - 119°/15 mm., n_D^{19} 1.533 (lit.[100] n_D^{25} 1.529) ν_{max} 1260(s) and 1080(s)(ArOMe) and 800(s) cm^{-1}.

7-Hydroxy-1,4-dimethylindane (153)

A solution of methyl magnesium iodide was prepared from magnesium turnings (600 mg.) and methyl iodide (1.7 ml.) in ether (20 ml.). 7-Methoxy-1,4-dimethylindane (2.11 g.) was added and the solvent removed, finally under oil-pump vacuum. The flask was filled with nitrogen and immersed in an oil-bath at 180°. Gas evolution had ceased after 1 hr. The grey frothy residue was cooled and ether and dilute sulphuric acid were added and shaken till two homogeneous layers formed. Work-up of the ether layer in the usual way gave 7-hydroxy-1,4-dimethylindane (1.7 g.; 88%) as a colourless oil which crystallised as long fibres, m.p. about 40°, on standing. Crystallisation from petrol at -60° also gave this low-melting form. Crystallisation from petrol at 0° gave prisms, m.p. 65°,

ν_{max} 3300(s), 1260(s), 1020(m), 810(s) cm^{-1}. (Found: C, 81.18; H, 8.86. $C_{11}H_{14}O$ requires C, 81.44; H, 8.70%).

3,4-Dihydro-4,6-dimethylcoumarin (157)

4,6-Dimethylcoumarin (20 g.) was dissolved in 4N aq. sodium hydroxide (200 ml.) and the solution stirred and heated on a steambath while Raney alloy (20 g.) was added over 1 hr. When effervescence had ceased, the solution was cooled and filtered and poured into iced dilute hydrochloric acid. The white microcrystalline precipitate consisted of 3-(2-hydroxy-5-methylphenyl)butyric acid, m.p. 42.5 - 45°, ν_{max} 3500(sh), 3200 - 2700 and 1700 (COOH) cm^{-1}. It could not be purified further due to spontaneous lactonisation. The crude acid was refluxed with p-toluenesulphonic acid in toluene and water (2 ml.) collected by distillation. The toluene solution was cooled, washed with dilute aq. sodium bicarbonate, dried and evaporated to give a yellow oil which was distilled to give 3,4-dihydro-4,6-dimethylcoumarin (17.8 g.; 88%) as a clear colourless oil, b.p. 90 - 92°/0.05 mm., n_D^{23} 1.538, ν_{max} 1775 (s)(aryl ester), 1160(s) and 820(s) cm^{-1}. (Found: C, 74.68; H, 7.00. $C_{11}H_{12}O$ requires C, 74.97; H, 6.86.).

4-Hydroxy-3,7-dimethylindan-1-one (158)

3,4-Dihydro-4,6-dimethylcoumarin (5 g.) was mixed with aluminium chloride (15 g.). The mixture became warm. It was immersed in an oil-bath at 180 - 200° for 20 min., with occasional swirling, when it became fluid and black and evolved small quantities of hydrogen chloride. After cooling, the black solid was broken up and mixed with ice and dilute hydrochloric acid. The insoluble residue was dissolved in

ether and this yielded, after the usual work-up and crystallisation of the residue from petrol-chloroform or aqueous methanol, 4-hydroxy-3,7-dimethylindan-1-one (2.36 g.; 47%) as white flakes, m.p. 165 - 167°, ν_{max} 3200(s), 1680(s), 1280(s), 820(s) cm^{-1}. (Found: C, 74.99; H, 6.90. $C_{11}H_{12}O_2$ requires C, 74.97; H, 6.86%).

It could be sublimed rapidly at 140°/0.1 mm. The infra-red spectrum of the mother-liquors from the crystallisation showed them to contain more indanone plus unchanged dihydrocoumarin in about equal proportions but no more of the former could be isolated by crystallisation.

7-Hydroxy-1,4-dimethylindane (153)[from (158)]

4-Hydroxy-3,7-dimethylindan-1-one (1 g.) in ethanol (25 ml.) was added to a suspension of amalgamated zinc (10 g.) in ethanol (10 ml.) containing conc. hydrochloric acid (10 ml.). The mixture was refluxed for 3½ hr., conc. hydrochloric acid (5 ml.) being added after 2 hr. The ethanol was decanted and the zinc washed with alcohol. The combined solutions were evaporated and the residue separated between water and petrol. The petrol layer after usual work-up gave a brown oil (0.85 g.) which crystallised on standing and was largely the desired phenol. Crystallisation from petrol yielded 7-hydroxy-1,4-dimethyl indane (0.62 g.; 67%) as white prisms, m.p. 63 - 64°, identical with a sample made from the methyl ether (m.p., mixed m.p. and infra-red spectrum).

4,6-Dimethyl-7-hydroxycoumarin (161)

4-Methylresorcinol (9 g.), ethyl acetoacetate (11 ml.) and conc. sulphuric acid (15 ml.) were mixed and left overnight in an ice-bath.

The mixture was poured into water and the precipitate filtered off, washed, and digested with and finally crystallised from methanol to give 4,6-dimethyl-7-hydroxycoumarin (9.3 g.; 80%) as slightly green sugar-like prisms, m.p. 253 - 256° with regrowth starting above 200° (lit.[104] 254 - 255°), ν_{max} 3200(m), 1680(s), 1630(m), 1280(m), 1070(m) and 840(s) cm^{-1}.

7-Methoxy-4,6-dimethylcoumarin (162)

7-Hydroxy- 4,6-dimethylcoumarin (2 g.) was refluxed overnight in dry acetone (60 ml.) containing potassium carbonate (7 g.) and dimethyl sulphate (3 ml.). The solution was cooled and filtered and the filtrate evaporated and the residue crystallised from aqueous methanol to give 7-methoxy-4,6-dimethylcoumarin (2 g.; 93%) as long fine colourless needles, m.p. 183 - 185°. A sample recrystallised from methanol had m.p. 186 - 187°, ν_{max} 1710(s), 1300(s), 1060(s), 870(m) and 850(m) cm^{-1}. (Found: C, 70.73; H, 5.92. $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.92%).

3,4-Dihydro-7-methoxy-4,6-dimethylcoumarin (163)

7-Methoxy-4,6-dimethylcoumarin (1.77 g.) was dissolved in 4N aq. sodium hydroxide containing a little methanol. The solution was stirred at 100° and Raney alloy (2 g.) added portionwise over 20 min. The solution was cooled, filtered, poured onto iced conc. hydrochloric acid and extracted with ether. Work-up of the ether gave an oil which was shown by its infra-red absorption at 1780 and 1720 cm^{-1}. to be a mixture of lactone and hydroxyacid. This mixture was refluxed with p-toluene-sulphonic acid in benzene for 30 min. and the benzene solution washed with water, dried and evaporated to give 3,4-dihydro-7-methoxy-4,6-

dimethyl-coumarin (1.62 g.; 91%) as white plates, m.p. 67 - 69°. A sample recrystallised from methanol had m.p. 70.5 - 71.5°, ν_{max} 1755(s), 1250(s), 1205(s), 1160(s), 1035(s), 910(s) and 840(s) cm^{-1}. (Found: C, 69.88; H, 6.93. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84%).

3-(2,4-Dimethoxy-5-methylphenyl)butyric acid (169)

7-Hydroxy-4,6-dimethylcoumarin (8.5 g.) was dissolved in 4N aq. sodium hydroxide (85 ml.). The hot solution was treated as before with Raney alloy (8.5 g.) over 20 min. When effervescence had ceased the solution was cooled and filtered. Acidification of a sample at this stage led to isolation of 3-(2,4-dihydroxy-5-methylphenyl)butyric acid as a colourless viscous oil, ν_{max} 3600 - 2700 and 1705 cm^{-1}., which was not further characterised. Dimethyl sulphate (20 ml.) was added to the bulk of the alkaline solution and vigorous stirring under nitrogen continued overnight. The solution was then refluxed for 30 min. to hydrolyse any ester formed and then cooled and filtered to remove alumina. Acidification, extraction with ether and usual work-up gave 3-(2,4-dimethoxy-5-methylphenyl)butyric acid (8.05 g.; 76%) as a clear pale yellow viscous sticky oil which could not be induced to crystallise. A sample purified by distillation at 150°/0.05 mm. was an almost colourless oil, n_D^{22} 1.5233, ν_{max} 3300 - 2600(s), 1700(s), 1040(s) and 820(s) cm^{-1}. Its methyl ester was an oil, n_D^{20} 1.5040, ν_{max} 1740 cm^{-1}. Its S-benzylthiouronium salt crystallised from aqueous methanol as white plates, m.p. 139 - 140° (Found: C, 62.63; H, 7.12; N, 6.88. $C_{21}H_{28}N_2O_4S$ requires C, 62.36; H, 6.98; N, 6.93%).

Action of polyphosphoric acid on 3-(2,4-dimethoxy-5-methylphenyl)-butyric acid.

a) The acid (250 mg.) was mixed with polyphosphoric acid (3,5 g.) and stirred in an oil bath whose temperature was gradually raised from 100° to 135° over 1 hr. The mixture was cooled, stirred with water and extracted with chloroform. The organic layer was washed with dilute sodium hydroxide solution. Work-up of the chloroform solution gave no useful neutral material. Work-up of the alkaline extract gave unchanged acid (150 mg.; 60%).

b) The acid (1.9 g.) was stirred with preheated polyphosphoric acid (34 g.) at 150° for 3 min. The brown mixture was stirred with ice and extracted with ether. The ether after usual work-up give a low-melting red solid (1.1 g.) which was dissolved in benzene-petrol (1:1) and passed through a column of alumina (10 g., Grade '1'). The eluate was crystallised from petrol to give pale yellow needles of 4,6-dimethoxy-3,7-dimethylindan-1-one (485 mg; 27%). Recrystallisation from methanol gave colourless flat needles, m.p. 90 - 91.5°, ν_{max} 1690(s), 1300(s), 1120(s), 1050 and 1020(s), 855 and 840(s) cm^{-1}. (Found: C, 70.75; H, 7.09. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%). It is perhaps noteworthy that in both experiments much of the crude product appeared to be water-soluble.

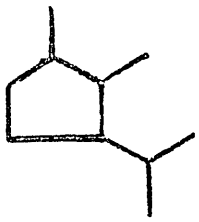
5,7-Dimethoxy-1,4-dimethylindane (171)

4,6-Dimethoxy-3,7-dimethylindan-1-one (300 mg.) in ethanol (5 ml.) was added to a suspension of amalgamated zinc (3 g.) in ethanol (5 ml) containing conc. hydrochloric acid (2 ml.). The suspension was refluxed

for 3½ hr. and then cooled. The solution was decanted and the zinc washed with more ethanol. The combined solutions were evaporated and the residue partitioned between petrol and water. The petrol layer after usual work-up gave 5,7-dimethoxy-1,4-dimethylindane (240 mg.; 85%) as a colourless oil, n_D^{20} 1.533, ν_{max} 1320(s), 1200(s), 1130(s) and 1100(s), 850(w) and 810(m) cm^{-1}., which was not further purified or characterised.

5,7-Dihydroxy-1,4-dimethylindane (160)

The crude 5,7-dimethoxy-1,4-dimethylindane obtained above (200 mg.) was added to a solution of methyl magnesium iodide, from magnesium (250 mg) and methyl iodide (0.6 ml.) in ether (20 ml.), and the solvent removed under vacuum. The residue was immersed in an oil-bath at 180° for 1 hr. 60 ml. of displaced gas were collected. (Theoretical volume of ethane 50 ml.). The flask was cooled, ether and dilute hydrochloric acid were added and the mixture was shaken till two clear layers formed. Work-up of the ether layer gave a green oil which on trituration with petrol gave a green solid (135 mg.; 78%) which was shown by T.L.C. to contain over 90% of the desired phenol. Sublimation at 140°/0.1 mm. gave 5,7-dihydroxy-1,4-dimethylindane as white polymorphic crystals, m.p. 165 - 174°, ν_{max} 3300(s), 1600(s), 1340 - 1240(multiplet)(s), 1200(m), 1100 and 1060(s) and 830(s) cm^{-1}. Thin layer chromatography in ethyl acetate-petrol (1:1) on silica showed a single spot of R_f 0.51. (Found: C, 73.82; H, 7.81. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%).



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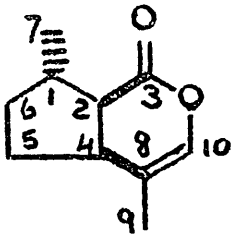

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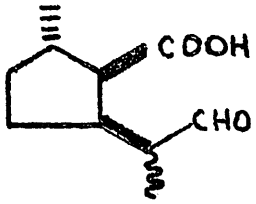
(102)



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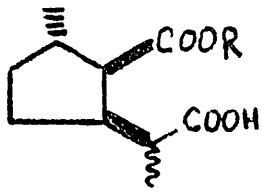
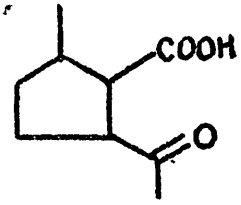


(104) R = H

(104a) R=CH_3



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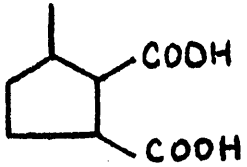

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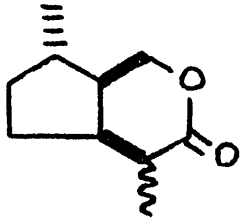

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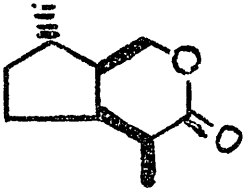
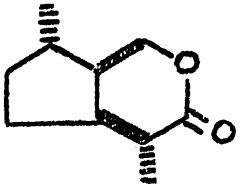


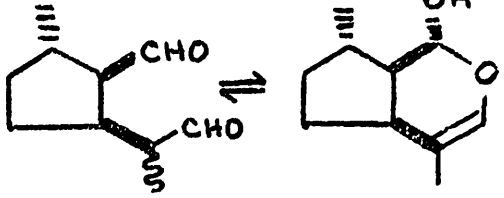
iridomyrmecin

(108)



isoiridomyrmecin

(109)



iridodial

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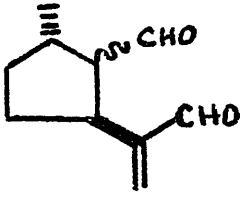

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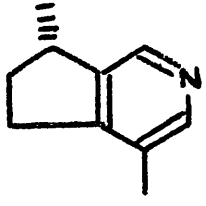

actinidine

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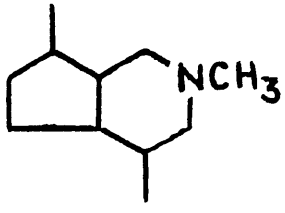

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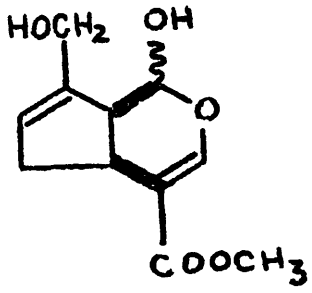

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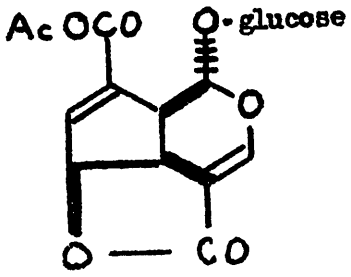

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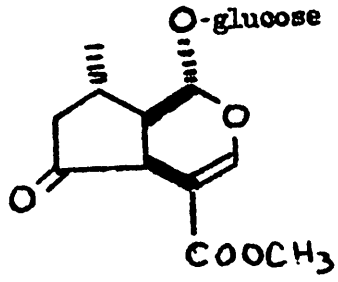

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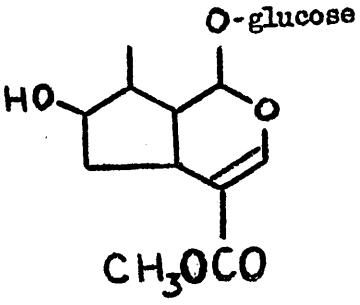

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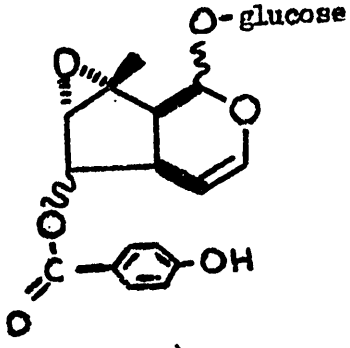

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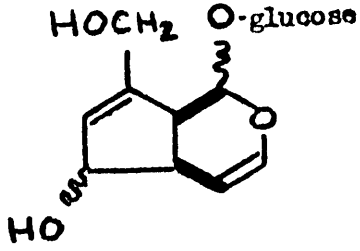

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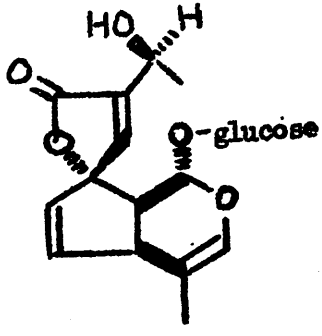

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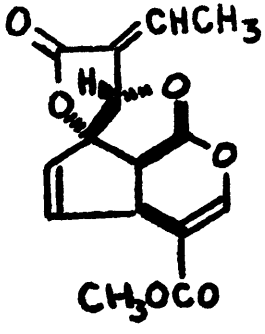

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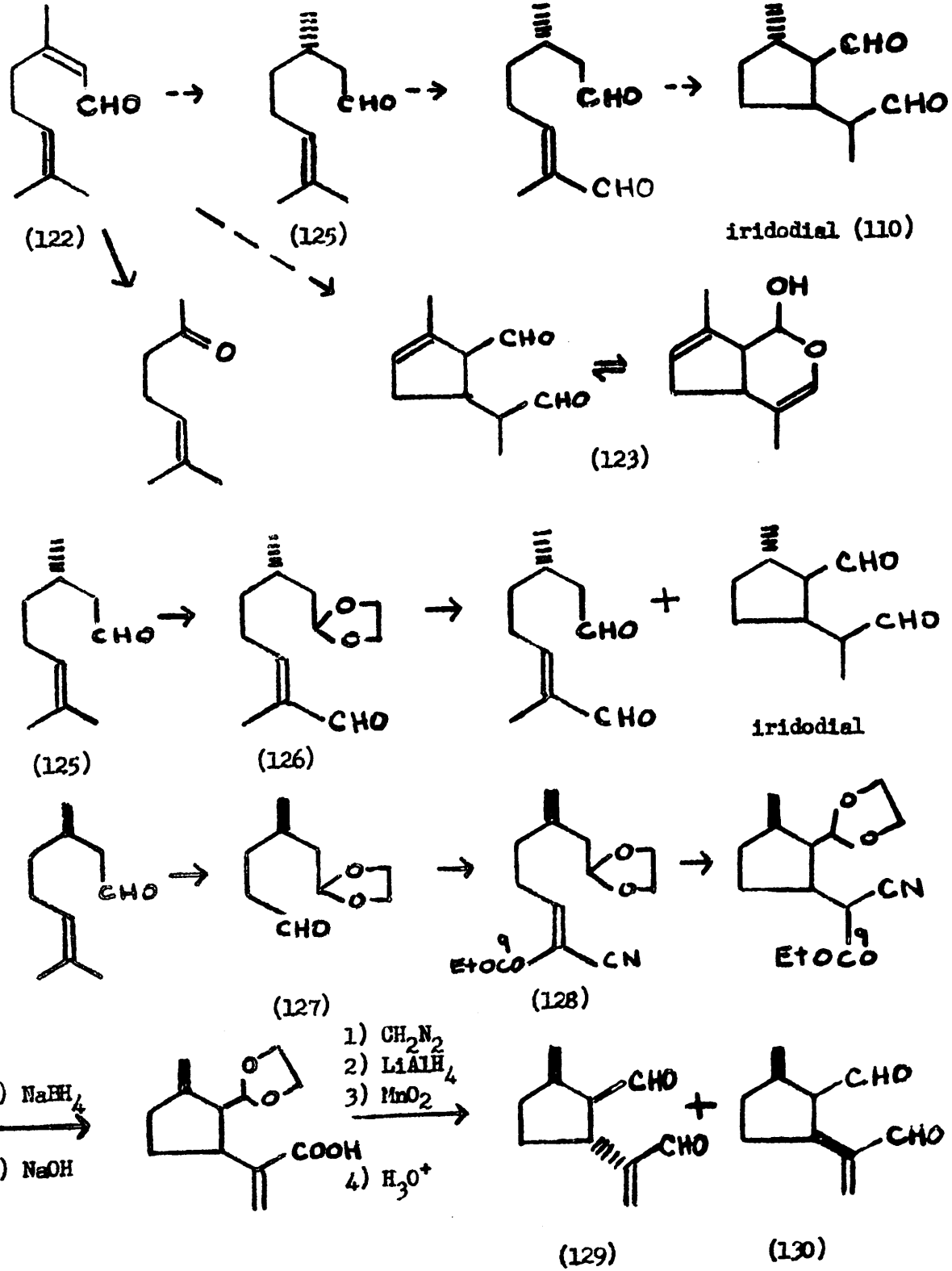
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CHO
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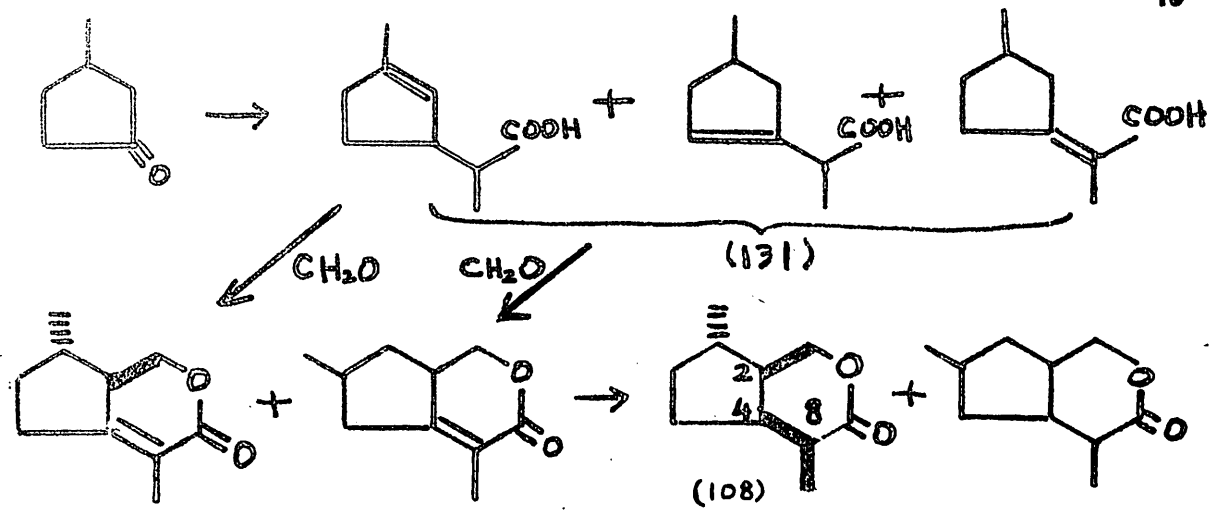
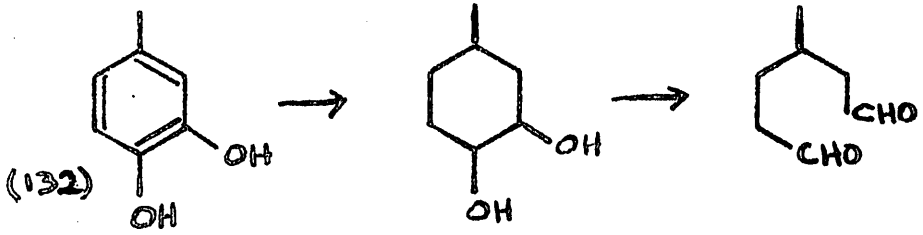
CHO
CHO
CHO
iridodial (110)
(122)
(125)
O
CHO
CHO
OH
O
(123)
CHO
CHO
CHO
CHO
CHO
CHO
iridodial
(125)
(126)
CHO
CHO
CN
EtOCO
EtOCO
(127)
(128)
1) NaBH4
2) NaOH
COOH
1) CH2N2
2) LiAlH4
3) MnO2
4) H3O+
CHO
CHO
CHO
CHO
(129)
(130)


COOH
COOH
COOH
(131)
CH₂O
CH₂O

(108)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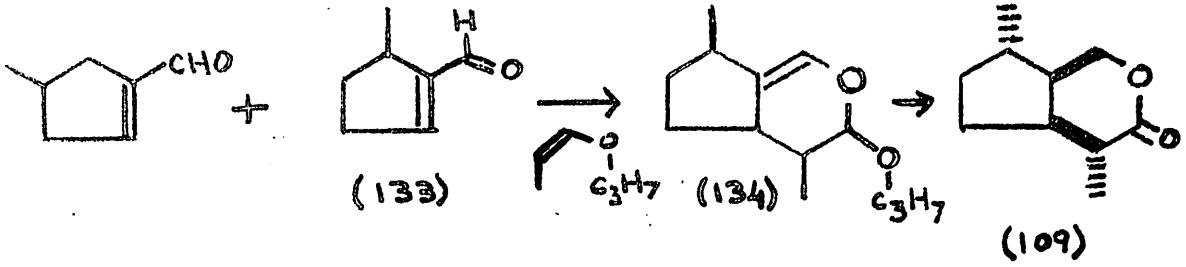
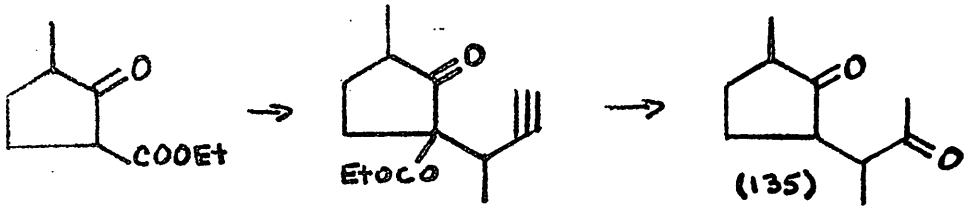
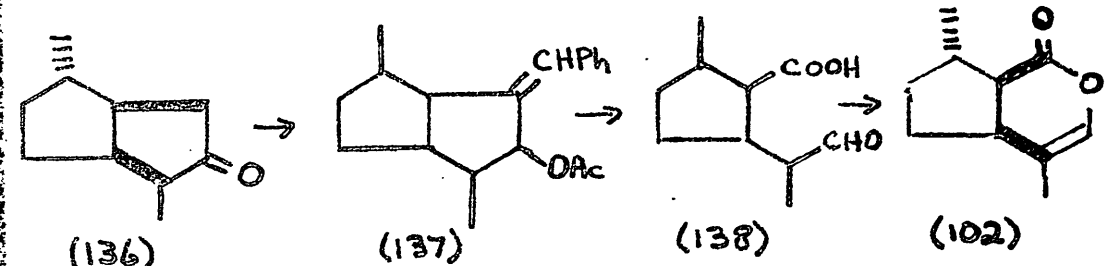
OH
OH
OH
CHO
CHO


CHO
H
(133)
C₃H₇
(134)
C₃H₇
(109)


COOEt
EtoCO
(135)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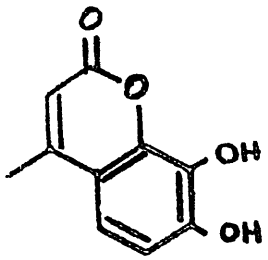
OAc
COOH
CHO
(136)
(137)
(138)
(102)



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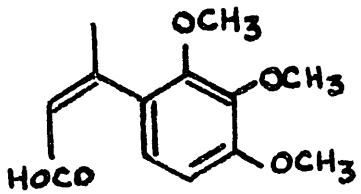

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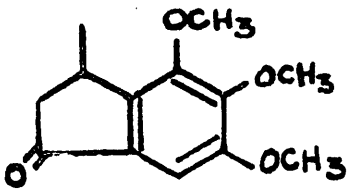

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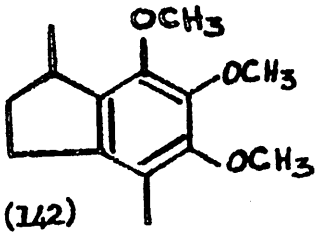

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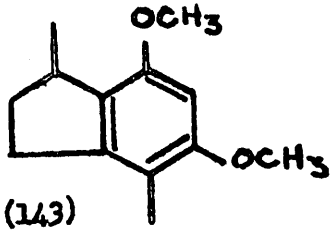

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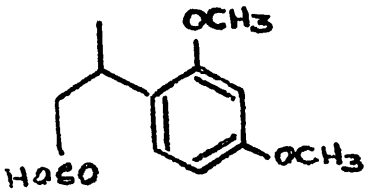

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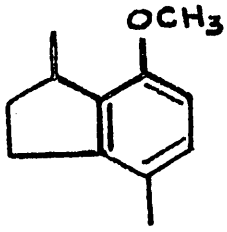

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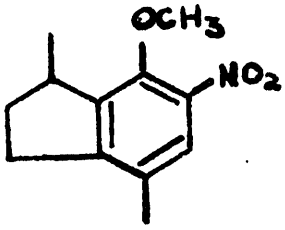

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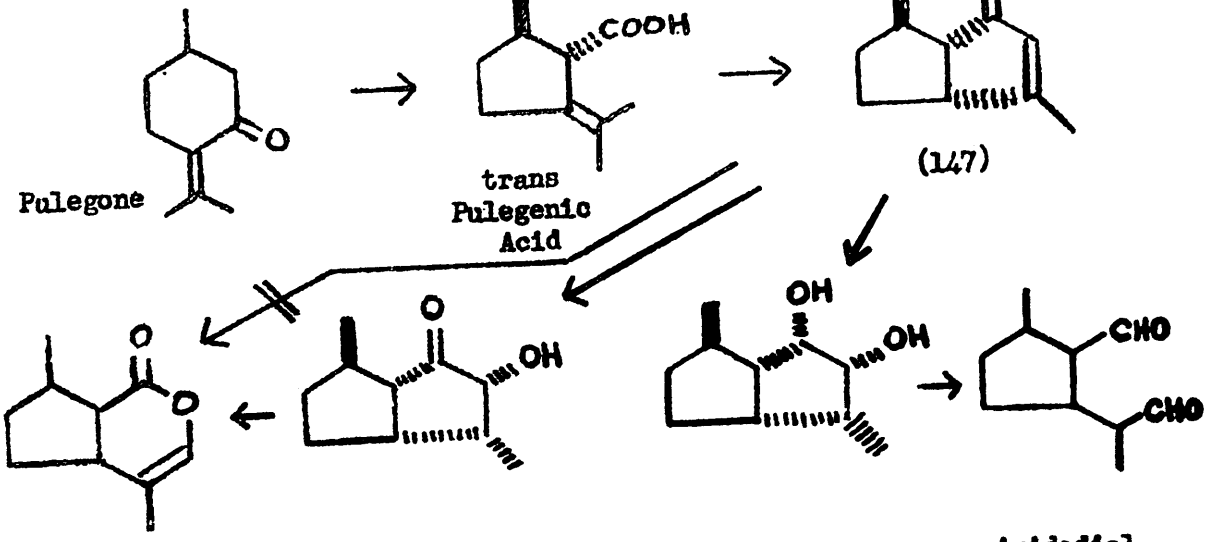
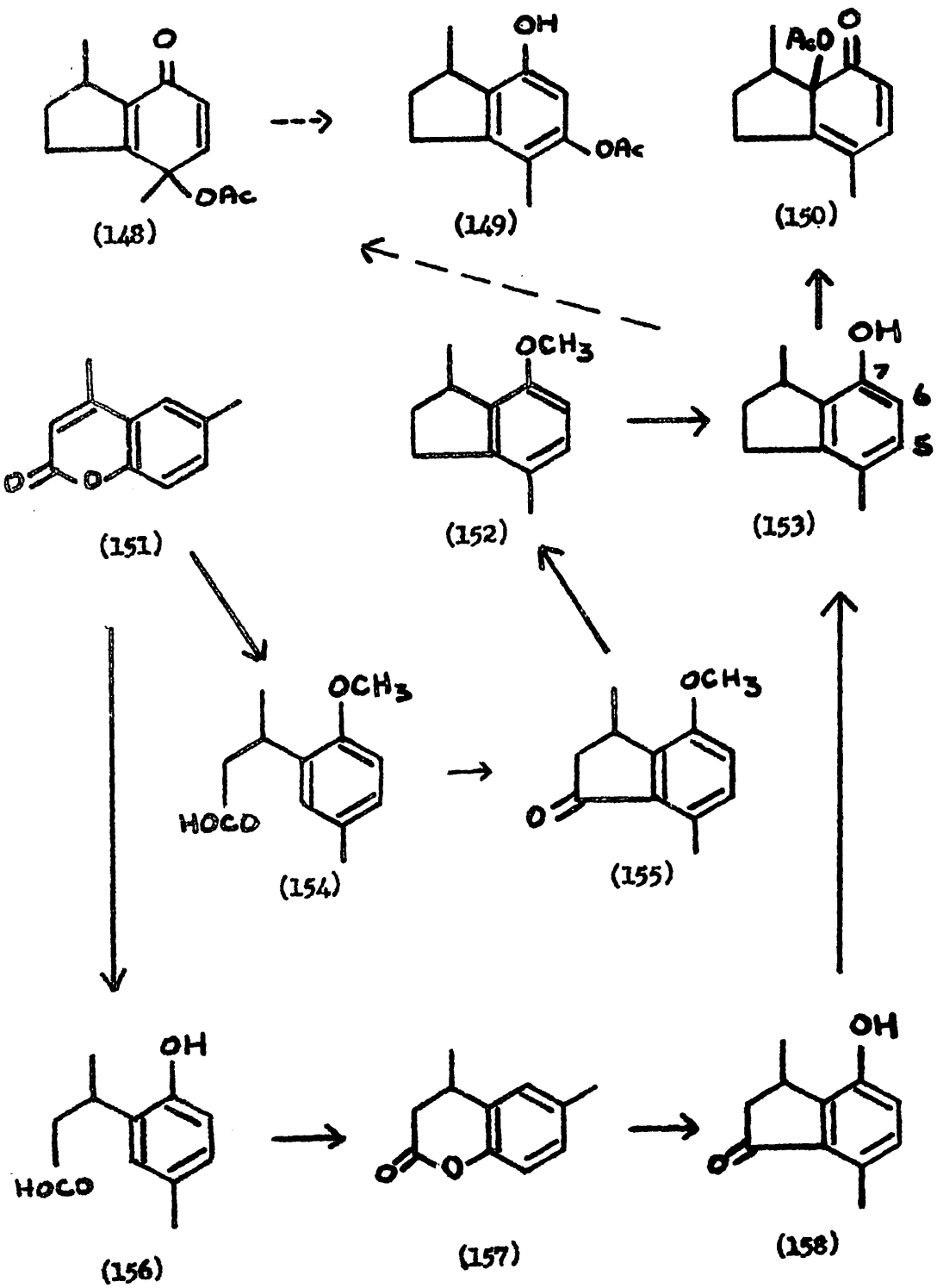
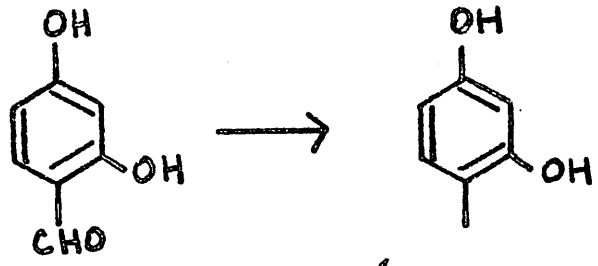
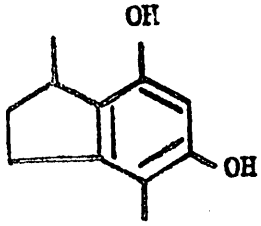



O
OAc
(148)
OH
OAc
(149)
AcO
O
(150)
OCH3
(152)
OH
7
6
5
(153)
O
O
(151)
OCH3
HOCO
(154)
OCH3
O
(155)
OH
HOCO
(156)
O
O
(157)
OH
O
(158)





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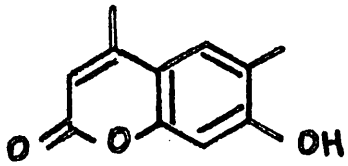

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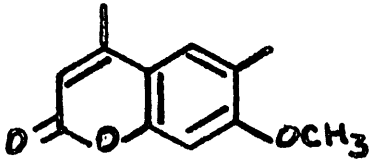

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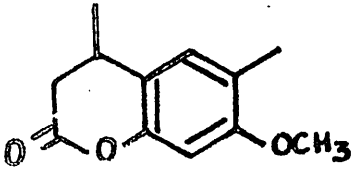

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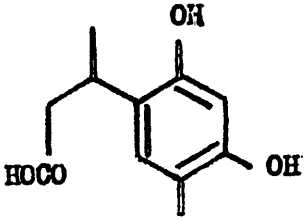

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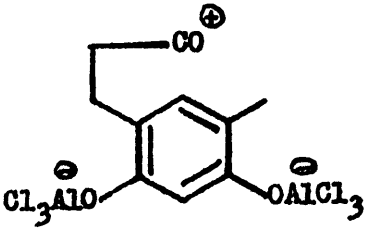

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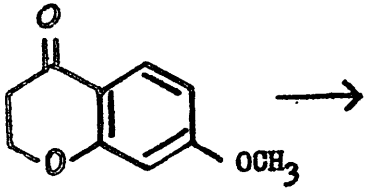

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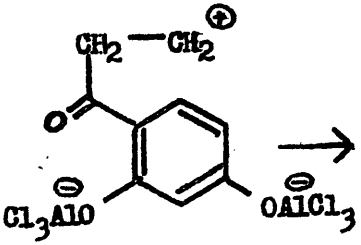

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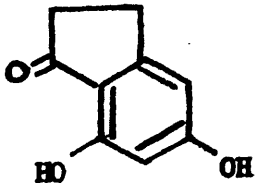

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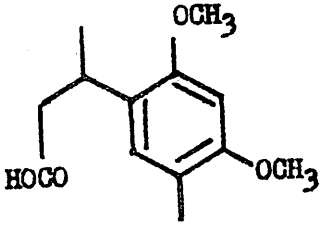

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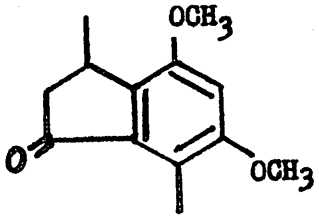

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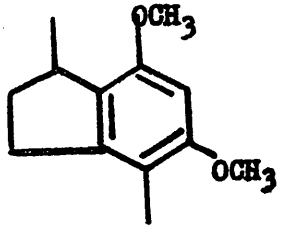

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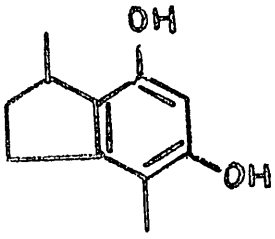

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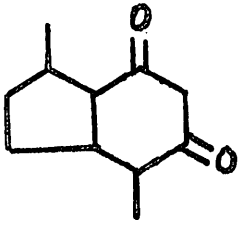

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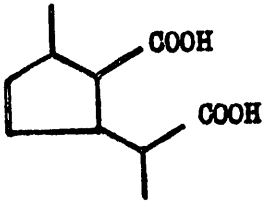

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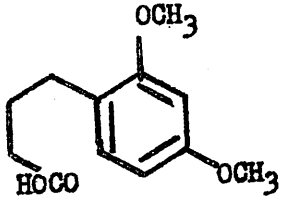

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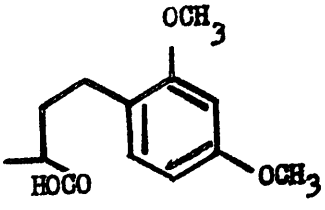

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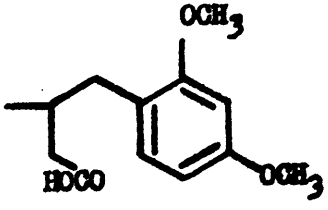

(174)

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