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confertifolin, which had previously been isolated[3] in minute

SOME SESQUITERPENOIDS FROM DRIMYS WINTERI F.

INTRODUCTION The "Canelo" tree of Chile (Drimys winteri, D. chilensis and D. andina) is common from the province of Valparaiso south and from the coast to the Cordillera. A sub-species (D. confertifolia) occurs also on the islands of Juan Fernandez.

The first chemical analysis of the tree was performed by Henry[6] in 1819. Other investigations have been reported [7, 8, 9] but a systematic study was not begun until Appel and his co-workers analysed the extracts obtained by petrol extraction of the bark [3, 4, 5].

In 1948, drimenol, a sesquiterpene alcohol was isolated [4, 5]. The structure of this alcohol (1)[1], together with that of the subsequently isolated drimenin (5)[2, 3] was of sufficient biogenetic interest to render a more detailed examination of the bark extracts of Drimys species desirable. Such an examination is here described.

There resulted the isolation of five new sesquiterpenoid compounds, isodrimenin (2), 7-hyroxyconfertifolin (8), 12-hydroxyconfertifolin (6), 7, 12 dihydroxyconfertifolin (7) and winterin (3). In addition to this, confertifolin, which had previously been isolated[3] in minute quantity from D. confertifolia was obtained in more substantial amounts from D. winteri.

The structure of isodrimenin (2) was elucidated in these laboratories by Dr. J. D. Connolly [10]. The chemical and spectroscopic investigations involved in obtaining the structures of compounds (3, 4, 6, 7 and 8) will be discussed below. Prior to this, there will be included a short review of related work and of sesquiterpenoid biogenesis.

THE BICYCLOFARNESOL SESQUITERPENES

Iresin and the Farnisiferols The structure and stereochemistry (other than absolute stereochemistry) of iresin as (18), initially proposed by Djerassi on chemical evidence [12,13,14,15,16], has been confirmed unequivocally by an X-ray structure analysis of the di p-bromobenzoate (18, R = p-BrC_6H_4CO) by Rossman and Lipscomb[17]. The absolute configuration of iresin depends on the fact that the optical rotatory dispersion curve (O.R.D.) of the dibromoenone (19) is antipodal to that of 2α, 6β-dibromo-4-methyl-testosterone[22] (part structure 20). In addition, the O.R.D. curve of the 13-nor-3-ketone (21) from iresin has the opposite sign to that of the 4-methyl-3-keto-5α-steroids (part structure 22). It is, perhaps, worth noting the somewhat curious fact that while (19) and (20) give antipodal O.R.D. curves, (21) and (22) do not.

Farnisiferols A, B and C were isolated from Asa Foetida by Jeger and his colleagues [19]. Only farnisiferol A has the bicyclofarnesol skeleton immediately relevant to our purpose, but farnisiferols B and C are worthy of brief comment because of their possible importance in the biogenesis of farnisiferol A. Farnisiferol A, $C_{24}H_{30}O_4$ ($\nu_{max.}$ 3590, 1725 and 1615 (coumarin), 1645 and 890 (exomethylene double bond) cm^{-1}) gave umbelliferone on vigorous acid hydrolysis, a monoacetate on acetylation with acetic anhydride in pyridine and a ketone on oxidation. Dehydrogenation of this ketone over selenium gave 1, 2, 5, 6-tetramethylnaphthalene (25) and 1, 5, 6-trimethyl-2-naphthol (26).

The umbelliferone moiety was removed by hydrogenolysis and the resulting saturated diol (27) was oxidised to a keto acid (28, R = H). This was converted to the diketone (34) by the transformations outlined in the flowsheet. Since (34) was shown to be the enantiomer of (35), a diketone derived from α amyrin[21], the absolute stereochemistry of farnisiferol is defined as in (23). The nature of the double bond

was/

was confirmed by chromic acid oxidation of (23) to (36), ozonolysis of which led to decarboxylation and formation of the bisnor diketone (37). Wolff - Kishner reduction of (28, R = H) gives the desoxy acid (38, R = H) the methyl ester of which (38, R = Me) is not enantiomeric to (39, R = Me) an acid prepared from oleanolic acid[11], either before or after equilibration in base. This requires a β C_8 methyl and, hence α face hydrogenation. To accommodate this latter, the C_9 group is assigned the configuration as in (23).

Farnisiferols B and C have been assigned structures (40) and (41) respectively on chemical and spectroscopic evidence [20]. The absolute configuration of the former rests on O.R.D. measurements made on the compound (42) and compared with analogous 3-keto-5α-steroids.

Drimenol, Drimenin and Isodrimenin

Drimenol (1) was established as the first example of a bicyclofarnesol sesquiterpene, possessing the same absolute configuration as the triterpenes, by oxidation of drimanol (10) to the acid (9) which was identical in all respects to a known degradation product of oleanolic acid and ambrein [11]. The position of the double bond in drimenol was indicated by its ultraviolet (U.V.) end absorption characteristics (ϵ_{210} 2140; ϵ_{215} 950; ϵ_{220} 250;) and infrared absorption ($\nu_{max.}$ 814 cm^{-1}) and confirmed by the chromic acid oxidation of drimenol to nor drimenone (11) the structure of which was confirmed by further oxidation to the known compound (12).

The spectroscopic properties of drimenin (5)[2] indicated the presence of a lactone ($\nu_{max.}$ 1780 cm^{-1}) and a triply substituted double bond ($\nu_{max.}$ 1670 and 808 cm^{-1}). Reduction with lithium aluminium hydride produced, in agreement with the presence of a lactone, a diol (13) the spectra of which gave further evidence for the presence of a triply substituted double bond ($\nu_{max.}$ 834 cm^{-1}, ϵ_{208} 2000; ϵ_{212} 920; ϵ_{220} 125). Hydrogenation of (13) using Adam's catalyst in acetic acid gave drimanol (10). Since drimenin is not a conjugated lactone, the carboxyl function of the lactone must have been on the

position now occupied by the surviving hydroxyl. Confirmation of structure (5) for drimenin was provided by chromic acid oxidation to (14) and subsequent transformations of this as outlined to the keto - acid (17) previously obtained from drimenol [1].

Isodrimenin, as well as occurring naturally, is produced from drimenin by treatment with base or concomitantly with hydrogenation (Adam's catalyst in acetic acid). Since it is clearly an unsaturated lactone (ν max. 1766, 1671 cm^{-1} and λ max. 218 mμ , ϵ 10000), isodrimenin must be as represented in (2).

SESQUITERPENOID BIOGENESIS

From the simple original concept of the construction of terpenes from isoprene units [27, 28, 29], Ruzicka [23, 25], using the concepts of physical organic chemistry, proposed more detailed schemes of cyclisation and rearrangement. His ideas have been developed and extended in the sesquiterpenoid field by Hendrickson[33] whose work derives also from Barton [34].

The detailed conclusions of Hendrickson need not be reproduced here, but a number of basic features will be noted and stressed. Thus, in every case, cyclisation of cis - or trans - farnesol is initiated by ionisation of the allylic hydroxyl group, assisted by one of the double bonds through a non-classical carbonium ion. The stereochemistry of the ions and, hence of the subsequent rearrangements, is considered to be governed by the requirements of "maximum π overlap and minimum steric interference". Assistance of ionisation by the central double bond is possible only in cis farnesol.

These considerations cannot be applied, without modification, to the formation of the bicyclofarnesol sesquiterpenes. These, it is reasonable to suppose, will arise by a cyclisation generally similar to that which produces the triterpenes from squalene[23] as (43) to (44). The allylic hydroxyl is not here involved and the double bonds require to be juxtaposed in such a way as to permit the necessary trans anti planar electron movements to occur with greatest ease.

The bicyclofarnesols, being distinct from the other classes of sesquiterpenes, and, further, being related in their mode of genesis to the higher terpenes, are biogenetically quite unique. Their interest is still further hightened by the existence of two classes differing only in their absolute stereochemistry. Since iresin (18), dihydroiresone [16] (62), isoiresin [16] (51) and farnisiferol A (23) all possess an oxygen substituent at C_3, while drimenol (1), drimenin (5) and isodrimenin (2) do not, Djerassi [35] was led to suggest that "the stereochemical requirements of the enzyme system promoting ring closure/

closure of the open chain - - - precursor by OH^+ - - - are such as to yield the 5 β 10 α absolute configuration". As is pointed out, this may apply also to the diterpene field where cafestol [35, 36] (45) and darutigenol (46) also have the wrong absolute configuration. Notwithstanding this suggestion, the co-occurrence of the three farnisiferols might reasonably be supposed to have biogenetic significance.

The presence of farnisiferols B and C might suggest that cyclisation to farnisiferol A occurred stepwise rather than by a fully concerted mechanism. If the configuration at C_9 in farnisiferol A is correct, this would further imply that the precursor was cis-farnesol[36]. A possible rationalisation is then that the sesquiterpenoids with the "wrong" absolute stereochemistry arise by a stepwise cyclisation of cis farnesol while the drimys sesquiterpenes are produced by a fully concerted cyclisation of trans farnesol. This mechanism is in accord with the greater interactions present in cis farnesol when the chain is folded in a manner suitable for cyclisation. The epimerisation at C_9 which would be required in the formation of iresin is unexceptional if a carbonyl function is formed at C_{12} at any stage. A possible analogy for this part of the postulated biogenesis may be found in the recently observed transformation of polygodial[38] (from Polygonum hydropiper and Drimys lanceolata) (47) in base to isoconfertifolin (48).

A number of investigations into the <u>in vitro</u> cyclisations of farnesol have been reported [36, 39, 40, 41, 42, 43, 44]. These indicate that the production of bicyclofarnesol derivatives is the favoured mode of cyclisation. A synthesis of racemic drimenol was achieved by this means[43]. While these cyclisation studies are of considerable intrinsic interest, the case of squalene [23, 37] gives warning of the pitfalls involved in applying conclusions from <u>in vitro</u> cyclisations to those occurring <u>in vivo</u>. A recent review of this subject exists[10].

THE CHEMISTRY OF CONFERTIFOLIN AND SOME RELATED SESQUITERPENES FROM DRIMYS WINTERI F.

The examination of a large number of bark extracts of trees, mainly D. winteri but including D. confertifolia and D andina, collected from several regions of Chile has indicated that drimenol and confertifolin are widely encountered and frequently occur together. Isodrimenin is of less frequent occurrence. In only one case have substantial quantities of all three compounds been obtained from a single extract. Those extracts which were examined in some detail did contain all three but one (in the particular extracts in question, this was drimenol) was present in traces only. The most surprising feature to emerge is the scarcity of drimenin. To date, this compound has been isolated from one extract only[3] and, despite a careful search, has not been re-encountered. The isolation conditions do not appear to rearrange drimenin to isodrimenin[2] and in this case also, the explanation may lie in the quantity present in the extracts.

The isolation of the compounds (3), (6) and (7) presented some difficulties. The crystalline mixture originally obtained from the extract melted in the range 155 - 170°C i.e. above the melting point of the major constituent, confertifolin. Further, the initial attempts to purify the mixture were made on a pilot scale involving approximately 30 - 40 mgms. At this level, virtually all of the material appeared to elute from a column in benzene/petrol as confertifolin. It was at first thought, therefore, that the major component of the mixture was isoconfertifolin (48) and that this was isomerised on alumina to confertifolin (4). However, on increasing the scale of chromatography, the imbalance between starting material and recovered confertifolin quickly became clear and elution with more polar solvents yielded 11-hydroxyconfertifolin (eluted in chloroform/ethyl acetate), 7, 11-dihydroxyconfertifolin (glacial acetic acid) and winterin (aqueous acetic acid). The tenacity with these compounds adhere to the alumina would indicate that they are bound to that substance in the

ring opened forms.

7-hydroxyconfertifolin was isolated from another extract in a somewhat similar manner. However its elution from alumina in solvents of less extreme polarity made its isolation, in spite of the small quantity available, relatively straightforward.

P - methoxycinnamic acid (49) has been obtained independently from D. winteri species growing in Tierra del Fuego by Dr. Appel and his colleagues[45]. From this same extract, these workers have also isolated 7, 11-dihydroxyconfertifolin[45]. Their isolation of this latter compound preceded ours in time.

Confertifolin [2, 3] (4) The spectral properties ($\nu_{max.}$ 1769 (butenolide) 1677 (double bond) 783 cm^{-1}; $\lambda_{max.}$ 217 mμ ϵ 11,750) of confertifolin and its occurrence with drimenol and isodrimenin (vide supra), suggest (4) or (48) as probable structures. The spectral similarity to iresin, isoiresin and isodrimenin is in accord with this conclusion. That (4) is the more probable structure was indicated by the reduction of confertifolin with lithium aluminium hydride to 11, 12-dihydroxydrim-8-ene (50) identical with that obtained by similar reduction of isodrimenin[2] (2). This identity also demonstrates that confertifolin possesses the same absolute stereochemistry as isodrimenin and, hence, of drimenol. Confertifolin was reduced, using Adam's catalyst in acetic acid, to cis-dihydroconfertifolin (52) and lithium aluminium hydride reduction of this gave the 11, 12-dihydroxydrimane (55) previously obtained by a similar route from drimenin. The behaviour of confertifolin on catalytic reduction is in contrast to the complete failure of isodrimenin to reduce under similar conditions. Since iresin, isoiresin and drimenin all hydrogenate smoothly, it has been suggested[2] that only the $\Delta^{7,8}$ double bond in these compounds can be reduced and that the reduction of a $\Delta^{8,9}$ bond requires prior isomerisation. In the case of isodrimenin such an isomerisation would remove the double bond from conjugation with the carbonyl group and would therefore be ener[illegible]/

energetically unfavourable. That double bond migration under the relevant conditions is possible is shown by the formation of isodrimenin from drimenin. Of interest is the observation that confertifolin will not hydrogenate when ethyl acetate is used as a solvent. If these views are correct, the hydrogenation of the unsaturated diol (50) to the saturated diol (55) might indicate that the driving force provided by the formation of two C-H bonds is sufficient to overcome the energetically unfavourable shift of the double bond from a tetra to a tri-substituted position.

Base treatment of cis-dihydroconfertifolin gave, smoothly, trans-dihydroconfertifolin (53). This transformation is analogous to the isomerisation of dihydroiresin (56) to isodihyroiresin (57). The enantiomer of (53), viz. (58) has been prepared from iresin by removal of the oxygen functions at C_3 and C_{14} [14]. Unfortunately, the physical constants of the two compounds were not in agreement ((58) has m.p. 90 - 96°C and $[\alpha]_D = -71$) and (58) was not available for comparison. However, the molecular rotation changes[46] noted in the transformations isoiresin diacetate - isodihydroiresin diacetate (51, R = Ac) - (57, R = Ac) $\Delta[M]_D = +245$) and confertifolin - isodihydroconfertifolin ((4) - (53) $\Delta[M]_D = -216$) show the expected correspondence.

Reduction of iso- (trans-) dihydroconfertifolin (53) with lithium aluminium hydride gave a new diol, 8α, 9β , -drimane-11, 12-diol (54).

Confertifolin is inert to oxidation under normal conditions and can be recovered unchanged after treatment with Beckman's mixture under conditions which readily convert drimenin and isodrimenin into oxoisodrimenin [2, 10].

The nuclear magnetic resonance (n.m.r.) spectrum of confertifolin and, more particularly, of cis- and trans-dihydroconfertifolin, provide models which aid in the interpretation of the spectra of related compounds (vide infra). Their study in some detail is, therefore, germane to our purpose.

The n.m.r. spectrum of confertifolin (Fig. 1) has a triplet centred/

centred at 5.36 τ . This is assigned to the methylene protons on C_{11} which in the planar butenolide ring must be magnetically equivalent or almost so. Their single signal is split, by a long range coupling through the double bond, by the non-equivalent protons on C_7. A similar coupling through a double bond occurs in angelic acid and methyl angelate[47] and the coupling constant there observed (1.5 c.p.s.) is in accord with that for the C_7 - C_{11} splitting in confertifolin (3 c.p.s.). The signal from the C_7 protons themselves forms an inadequately resolved multiplet at approximately 7.73 τ . The signal at 8.13 τ is assigned to the proton on C_5 while the three strong sharp singlet peaks at 8.82 τ , 9.03 τ and 9.06 τ are attributed to the allylic C_{10} methyl and the two methyls on C_4 respectively.

In trans dihydroconfertifolin (Fig. 2), the C_{11} protons are no longer equivalent and there is now a proton on C_9 with which they can couple. The low field absorption then taken the form, in accordance with expectation, of the AB part of an ABX spectrum [48, 49, 51] with J_{AB} = 10 c.p.s. and, to a first approximation, $J_{AX} = J_{BX}$ = 6 c.p.s. The two central lines (4 and 5 numbering from l. to r.) have merged to a single peak. The multiplet is centred at 5.94 τ and the absorption frequencies of the two protons are estimated to be 5.8 τ and 6.1 τ which indicates a slightly greater shielding than is observed in γ-butyrolactone[50]. The region between 7.5 τ and 8.9 τ is extremely complex and any assignments must be tentative. The sharp peak at 8.42 τ which appears to be a distorted triplet probably arises from the methine proton at C_5. The sharp singlet peaks at 9.15 τ , 9.13 τ and 9.03 τ are assigned to the three quaternary methyl groups.

In cis-dihydroconfertifolin (Fig. 3), assignment of peaks is made difficult because, in the AB part of the ABX multiplet, arising from the splitting of the C_{11} and C_9 protons, several peaks have coalesced. It is not possible to determine either J_{AB} or the absorption frequencies

of/

of the two protons. The multiplet is centred at approximately 5.9 τ . As for the trans compound, the three sharp singlet peaks at 9.10 τ , 9.15 τ and 9.18 τ are assigned to the quaternary methyl groups.

11-Hydroxyconfertifolin. (6) The spectral properties of this compound ($\nu_{max.}$ 3360 (bonded hydroxyl; KCl disc) 1769 (butenolide) and 1680 (double bond) (chloroform) cm^{-1}; $\lambda_{max.}$ 221mμ ϵ, 10,300) are, apart from the hydroxylic absorption in the infrared, closely similar to those of confertifolin, isodrimenin, iresin and isoiresin. Concentrated solutions of 11-hydroxyconfertifolin in carbon tetrachloride absorbed in the carbonyl region of the infrared at 1780 and 1749 cm^{-1}. The intensities of these peaks were markedly concentration dependent, the 1749 band disappearing completely at high dilution. Clearly they represent intermolecular hydrogen bonding between the hydroxyl and carbonyl groups.

That the hydroxyl group was attached to the butenolide ring was indicated by the ultraviolet spectrum measured in basic solution ($\lambda\lambda_{max.}$ 228, 257mμ $\epsilon\epsilon_{max.}$ 5,000, 10,300) which differed from that of confertifolin ($\lambda_{max.}$ 232mμ $\epsilon_{max.}$ 4350) and iresin ($\lambda_{max.}$ 228mμ $\epsilon_{max.}$ 3,600). Further, the n.m.r. spectrum displayed a peak (1 proton) at 3.85 τ which can reasonably be interpreted as arising from an allylic proton on a carbon carrying two oxygen functions. This would establish 11-hydroxyconfertifolin as 11-hydroxy drim-8-ene 12, 11-olide (6) or as 12-hydroxy-drim-8-ene 11.12-olide (59). That (6) was in fact correct was suggested by the markedly different absorption intensity of the unsaturated carboxylate anion chromophore in isodrimenin (2) as compared with confertifolin (4) (isodrimenin in EtOH/KOH has $\lambda_{max.}$ 230 mμ $\epsilon_{max.}$ 11,000) and confirmed by the following chemical evidence.

Reduction of 11-hydroxyconfertifolin with lithium aluminium hydride gave drim-8-ene 11, 12-diol (50) thus confirming the carbon skeleton and suggesting the absolute stereochemistry. On catalytic hydrogenation with Adam's catalyst in acetic acid, 11 hydroxyconfertifolin underwent/

underwent hydrogenolysis and reduction of the double bond to give cis dihydroconfertifolin (52). This result eliminates structure (59). Chemical proof that the hydroxyl is located at C_{11} and not at C_7 was provided by the smooth oxidation of 11 hydroxy confertifolin to winterin (3) with chromium trioxide in acetic acid.

Since the lactol ring of 11-hydroxyconfertifolin can readily tautomerise to the hydroxy - aldehyde form and almost certainly does so during work up, the C_{11} hydroxyl group will exist in the thermodynamically more stable configuration. In 11-hydroxyconfertifolin this is most probably the α configuration.

Winterin (3). It was immediately clear from the infrared spectrum ($\nu_{max.}$ 1847, 1776 (unsaturated 5 membered ring anhydride) 1668 (double bond) cm^{-1}) that the three oxygen atoms present in this molecule formed an anhydride function. The precise nature of this function became readily apparent from the resemblance of the ultraviolet spectrum ($\lambda_{max.}$ 257 mμ $\epsilon_{max.}$ 3820) to that of methyl ethyl maleic anhydride ($\lambda_{max.}$ 250 mμ $\epsilon_{max.}$ 4000 in ether)[53]. Dr. J. K. Sutherland (Imperial College, London) has kindly informed us that he has observed similar U.V. spectral properties for the substituted maleic anhydride derivatives byssochlamic acid and glauconic acid[52]. The accommodation of a maleic anhydride grouping on the drimane skeleton (assumed for the moment) defines winterin as drim-8-ene 11, 12-dicarboxylic acid anhydride (3). In accord with this, the n.m.r. spectrum has no signal at a lower field than 7.54 τ .

Chemical confirmation of structure (3) for winterin was obtained by reducing it with lithium aluminium hydride to drim-8-ene 11 12-diol (50), indicating (See p. 15) also the absolute stereochemistry.

7, 11-Dihydroxyconfertifolin. The ultraviolet spectra of this compound both in neutral ($\lambda_{max.}$ 217 mμ $\epsilon_{max.}$ 6500) and in basic solution ($\lambda_{max.}$ 233 mμ $\epsilon_{max.}$ 5050; $\lambda_{max.}$ 258 mμ $\epsilon_{max.}$ 6150) provided compelling evidence for the presence of the unsaturated lactol ring first observed in 11-hydroxy confertifolin. Since the infrared/

infrared spectrum ($\nu_{max.}$ 3604, 3475 (free and bonded hydroxyl), (chloroform) 1767 (Lactol) 1687 (double bond) (carbon tetrachloride) cm^{-1}) contained no novel peaks in the carbonyl region, the remaining oxygen function is most probably a hydroxyl or an ether. The presence in the n.m.r. spectrum of peaks at 3.85 τ (cf. 11 hydroxyconfertifolin) and 5.33 τ (cf. confertifolin) fixes the position of this oxygen function as allylic to the double bond. On the drimane template, these facts lead to 7, 11-dihydroxy drim-8-ene 12, 11-olide (7) as the required structure.

By analogy with 11-hydroxyconfertifolin it would be expected that at least the lactol hydroxyl of (7) would hydrogenolyse on catalytic reduction. In practice, this proved to be so, and treatment of 7, 11-dihydroxyconfertifolin with Adam's catalyst in acetic acid produced cis-dihydroconfertifolin. This suggests (See p.15) the absolute stereochemistry, confirms that the fourth oxygen function is indeed allylic and that it is a hydroxyl and not an ether function.

Oxidation of (7) does not proceed smoothly. However, on treatment with chromium trioxide in acetic acid, it was possible to isolate a small quantity of a compound which, on the basis of its spectroscopic properties, ($\nu_{max.}$ 1787, 1778, 1765, broad $\nu_{max.}$ anhydride, 1680 (eneone) 1660 (double bond(eneone) 1660 (double bond) cm^{-1} KCl disc; $\lambda_{max.}$ (EtOH) $\lambda_{max.}$ 238, 278 (EtOH) $\lambda_{max.}$ 238, 278 $\epsilon_{max.}$ 2780, 3710) is te the structure (60) as drim-8-ene-7-one-11, 12-dicarboxylic acid anhydride.

The stereochemistry of the hydroxyl group at C_7 is not known. Two sets of observations bear on this point. In very dilute solution, all absorption in the infrared attributable to bonded hydroxyl (3300 - 3400 cm^{-1}) disappears. The absence of intramolecular hydrogen bonding thus favours an axial 7α hydroxyl group. In addition, one possible interpretation of the hydrogenolysis results obtained with 11-hydroxyconfertifolin, 7, 11-dihydroxyconfertifolin and 7-hydroxyconfertifolin (futronolide, vide infra) would also favour a 7 α hydroxyl group in 7, 11-dihydroxyconfertifolin. Those comments made above concerning the stereochemistry of the 11 hydroxyl function in 11-hydroxyconfertifolin will apply to that function in 7, 11-dihydroxyconfertifolin also.

7-Hydroxyconfertifolin/

in/

7-Hydroxyconfertifolin (Futronolide) Only 5 mgms. of this compound were available for study and the structure proposed (8) is, since it was not possible to convert futronolide into a known compound, based on assumption that futronolide has the drimane skeleton.

The molecular weight, determined on the mass spectrometer, of 250 shows futronolide to be isomeric with 11-hydroxyconfertifolin. That the extra oxygen is not, in this case, involved in a lactol ring was clearly shown by the close similarity of the ultraviolet spectrum both in neutral ($\lambda_{max.}$ 218 mμ $\epsilon_{max.}$ 10,7000) and in basic solution ($\lambda_{max.}$ 231mμ $\epsilon_{max.}$ 5,100) to that of confertifolin. Further confirmation of this point was derived from the absence of any signal at 3.35 τ from the n.m.r. spectrum. The further absence from the n.m.r. spectrum of absorption due to olefinic protons makes a tetra-substituted double bond mandatory. On the drimane template this can be accommodated only between positions 7 and 8. The multiplet between 5 and 6 τ has a weight of three protons and takes the form of two doublets centred at 5.26 τ and 5.55 τ each with J = 5 c.p.s. The two peaks of the latter doublet are each split to a triplet (J = 1.2 c.p.s.), that at lower field being slightly better resolved. These observations can be completely accommodated with futronolide as 7-hydroxy-drim-8-ene-12, 11-olide (8). The magnetically equivalent protons at C_{11} (cf. confertifolin) split by the single proton on C_7 through the double bond are assigned to the 5.26 doublet. The C_7 proton is similarly split to a doublet by the C_{11} protons; each limb of which is split further to a triplet by the C_6 methylene protons, thus accounting for the multiplet centred at 5.55 τ . The high field signals at 8.89 τ 9.05 τ are assigned to the C_{10} angular methyl and to the C_4 gem dimethyl groups respectively. The infrared spectrum of futronolide ($\nu_{max.}$ 3605, 3500 (latter peak very broad; free and bonded hydroxyl) 1758, 1749 (butenolide) 1669 (double bond) cm^{-1}) exhibits a concentration independent bifurcation of the carbonyl band which is probably due to Fermi resonance (see page 12) and confirms the presence of a hydroxyl group. Hydrogenation of futronolide with Adam's

Adam's catalyst in acetic acid resulted in a new compound whose infrared spectrum ($\nu_{max.}$ 3609, 3508 (free and bonded hydroxyl) 1768 (γ-lactone) (chloroform) cm^{-1}) and transparency in the ultraviolet are in accord with structure (61). The failure of the hydroxyl group to hydrogenolyse in contrast to the behavious of 7, 11-dihydroxyconfertifolin can be explained only if it is assumed that the C_7 hydroxyl groups in the two compounds are epimeric and that futronolide has the 7β configuration. No conclusive evidence on this point could be obtained. Although a study of the hydroxyl region of the infrared spectrum of futronolide did indicate some residual hydrogen bonding at low concentrations, the effect was too small to be convincing. It may be observed, however, that the present tentative assignments place the C_7 hydroxyl of 7, 11 dihydroxyconfertifolin on that side of the molecule (α) which is attacked by hydrogen, while the hydroxyl in futronolide is on the opposite side. The ready reduction of the tetrasubstituted double bond of futronolide is good evidence that the compound is a derivative of confertifolin and not of isodrimenin.

Since no rotations have been measured for the known transformation products drim-8-ene 11, 12 diol and cis dihydroconfertifolin from the sesquiterpenes (3), (6) and (7), the absolute stereochemistry of these latter cannot be regarded as rigidly determined. However, the failure to observe any melting point depression during the identification of (50) and (52), on admixture with authentic material would be surprising if the absolute stereochemistry of (3), (6) and (7) were other than that suggested.

The drimys sesquiterpenes described here, taken together with drimenol[1], drimenin, isodrimenin[2] and the recently discovered polygodial (47) and isoconfertifolin (48) present an impressive and novel variety of oxygenation pattern. Whether this signifies that the relevant enzyme system has as much difficulty in achieving specific oxidations in vivo as had the author (see page 79) in vitro or that the drimys tree has a highly economic metabolism utilising one template for many purposes, remains for further investigation.

THE ULTRAVIOLET SPECTRA OF LACTONES, LACTOLS AND ANHYDRIDES

The utility of the ultraviolet spectra and, in particular, the differences between spectra obtained in neutral and basic solutions has already been alluded to in the above discussion. The subject is of sufficient intrinsic interest, however, as to merit further comment.

Several examples are extant of red shifts in the U.V. spectra of hydroxybutenolides of general structure (62), [13, 56, 57, 58, 59, 60] in the simplest of these [56] (63), the absorption* shifts from ($\lambda_{max.}$ 226 mμ $\epsilon_{max.}$ 4000) in neutral to ($\lambda_{max.}$ 261 mμ $\epsilon_{max.}$ 2000) in base. An example from the chemistry of iresin is (64, R = H). This has an absorption of ($\lambda_{max.}$ 240 mμ $\epsilon_{max.}$ 7900) in neutral and ($\lambda_{max.}$ 274 mμ $\epsilon_{max.}$ 10,700) in base. A point of interest is that (64, R = Ac) absorbs at ($\lambda_{max.}$ 218 mμ $\epsilon_{max.}$ 10,500) in neutral solution which value is in accord with those observed for the lactols (6) and (7).

Our own observations permit a clear cut distinction between the butenolide and the hydroxybutenolide of general structure (65) to be made by U.V. spectroscopy. Coupled with the above mentioned results, they permit also of a distinction between the types (62) and (65). The nature of the chromophore producing the bands at 230 mμ and 257 mμ from (6) and (7) in alkaline solution is not known. However, possibilities such as (66) are made improbable by the observation that succinic anhydride shows no high intensity U.V. absorption in alkaline solution in the required region. Since the maximum at 230 mμ occurs also in the spectra of the corresponding lactones (2), (4), (8) and (18) it is reasonable to attribute it to the unsaturated carboxylate anion. An equilibrium concentration of a species such as (67) would explain its occurrence in the spectra of the lactols (6) and (7). The 257 mμ peak may then be due to the opened aldehydo acid as (68). In agreement with this, the absorption maximum of drim-8-ene-7-one-11-oic acid[1] in basic solution is 260 mμ [64].

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*All spectra measured in ethanol.

The red shift of approximately 45 mμ produced by substitution in maleic anhydrides is unusually large. Assuming the normal rules for alkyl substitution effects in enone systems, a shift of ca. 35 mμ would be expected. A further anomaly is that, in basic solution, maleic anhydride undergoes a red shift to 220 mμ while the substituted maleic anhydride (3) undergoes a blue shift to 245 mμ. These facts indicate that the electron deficiency of the excited state is more pronounced in the unsubstituted than in the substituted case and that, further, the mechanism whereby electrons are supplied to the excited state of the substituted anhydride is operative also in basic media.

EXPERIMENTAL

M.p.s. were determined on the Kofler block. Infrared solution and KCl disc spectra were kindly recorded by Mrs. F. Lawrie with a Unicam S.P. 100 double beam infrared spectrometer and are accurate to $\pm$ 1 cm^{-1}. Ultraviolet spectra were recorded in ethanol solution on a Perkin-Elmer model 137 - U.V. spectrometer unless stated to the contrary. Microanalyses are by Mr. J. M. L. Cameron and his staff. For chromatography, Woelm alumina deactivated to the appropriate Brockmann[65] grade is used unless specified to the contrary. Chromatoplates were prepared using apparatus supplied by Messrs. Camlab Ltd. and based on the technique reported by Stahl[65]. The absorbent used was "Kieselgel G" supplied by Merck A. G. Darmstadt. Routine nuclear magnetic resonance spectra were kindly recorded by Miss M. Mackay on an A.E.I. 2 n.m.r. spectrometer. Detailed n.m.r. spectra were taken on a Varian A.60 spectrometer through the courtesy of Dr. A. Melera (Varian A. G., Basle). Dessication and extraction of the bark was kindly carried out by Mr. J. Olivares (U.T.F.S.M.). Light petroleum refers to that fraction of boiling point 60 - 80°C unless otherwise stated.

Bark samples are named according to the region of Chile from which they were obtained. The dried powdered bark was exhaustively extracted with light petrol (b.p. 70 - 80°C) in a soxhlet apparatus and the solvent subsequently removed. The normal method used to analyse the resulting extracts will be illustrated in detail for the isolation of isodrimenin, confertifolin and the oxygenated confertifolins and the results obtained by applying these methods in other cases will be indicated. The examination of two other extracts in more detail will also be reported.

Isolation of Isodrimenin. A Loncoche (D. winteri) extract (529 gms.) was steam distilled and the steam involatile fraction washed and dried. This latter was then distilled at 3mm Hg and three fractions with boiling/

boiling ranges (i) 180 - 195°C (ii) 195 - 210°C (iii) 210 - 215°C were collected. After a short delay, all three fractions crystallised. From fraction 1, after filtration and recrystallisation of the residual crystals from petrol, drimenol (1.6 gms.) was isolated and identified by m.p. (93 - 95°C) and mixed m.p. Similar treatment of fraction 3 gave, after recrystallisation from petrol, confertifolin also identified by m.p. (151 - 152°C) and mixed m.p. The crystals present in fraction 2 after filtration, were recrystallised thrice from petrol and once from methanol. There resulted isodrimenin (2) (3 gms.) m.p. 132°C $[\alpha]_D$ +87 (c. 2.02 in $CHCl_3$), +78 (c. 0.80 in C_6H_6), (Found: C 76.55; H, 9.5; $C_{15}H_{22}O_2$ requires C, 76.90; H, 9.45;).

Isolation of Confertifolin. A Valdivia (D. winteri) extract (350 gms.) was steam distilled and the steam involatile fraction worked up in the usual way. On distillation under a reduced pressure varying from 5 to 8 mm. of Hg. three fractions were collected in the boiling ranges (i) 220 - 250°C (ii) 250 - 280°C (iii) 280 - 300°C. From the third fraction, large quantities of crystals separated during distillation. When fractions 2 and 3 were diluted with petrol, refrigerated and filtered, they yielded confertifolin m.p. (after two recrystallisations from petrol) 152 - 153°C, undepressed on admixture with the compound isolated by Appel and Dohr[3] from a D. confertifolia extract, (13 gms.) $[\alpha]_D$ +72 (c. 2.00 in $CHCl_3$), +93 (c.2.10 in benzene) ($\nu_{max.}$ 1769, 1677 cm^{-1} in CCl_4), ($\lambda_{max.}$ 217 mμ $\epsilon_{max.}$ 11,750) (Found: C, 76.75; H, 9.65; $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.45;)

Isolation of Futronolide (7-Hydroxyconfertifolin). A Lago Ranco-Futrono extract (D. winteri) (250 gms.) was distilled, directly, under a reduced pressure of 10^{-2} mm. Hg. and three fractions were collected in the boiling ranges (i) 160 - 200°C (ii) 200 - 240°C (iii) 240 - 300°C. From the central fraction, substantial quantities of crystals formed on addition of hexane and cooling. These, on isolation by filtration (3 gms.), proved to have a m.p. much dependent on the mode of/

of recrystallisation. Chromatography on alumina (grade III) and elution with benzene in hexane (1:4 v/v) gave confertifolin (3 gms.) identified by m.p. (152°C) and mixed m.p. After the confertifolin, eluting in the same solvent mixture, a further small crystalline fraction was isolated. Frequent recrystallisation of this from methylene chloride/hexane gave prisms of futronolide (8) m.p. 215 - 217.5°C (5 mgms.) ($\nu_{max.}$ 3604, 3476, 1758, 1749, 1669 cm^{-1} in $CHCl_3$) ($\lambda_{max.}$ 218 mμ $\epsilon_{max.}$ 10,000 in EtOH) ($\lambda_{max.}$ 231 mμ $\epsilon_{max.}$ 5,100 in EtOH/KOH) (Mol. wt. (mass spectrometer) 250).

Isolation of 11-Hydroxyconfertifolin, 7, 11-Dihydroxyconfertifolin and Winterin (Drim-8-ene 11, 12-dicarboxylic Acid Anhydride).

A Valdivia (D. winteri) extract (400 gms.) was distilled, directly, under a reduced pressure varying from 10^{-4} to 0.3 mm. Hg. and four fractions were collected in the boiling ranges 130 - 180°C, 180 - 210°C, 210 - 240°C and 240 - 260°C. The fractions 2 and 3 on washing with petrol gave crystalline material (10.4 gms.) melting over the range 155 - 170°C. Chromatography of this on alumina (grade III, 210 gms.) and elution with petrol to chloroform produced confertifolin (8.6 gms.) identified by m.p. (153°C) mixed m.p. and infrared spectrum. Elution with ethyl acetate in chloroform (1:4 v/v) to pure ethyl acetate gave a fraction (439.1 mgms.) repeated recrystallisation from benzene of which gave 11-Hydroxyconfertifolin (6) as white prisms m.p. 177.5 - 178°C (217.6 mgms.) (yield 0.05% based on extract) $[\alpha]_D$ +111 (c. 1.18 in $CHCl_3$) ($\nu_{max.}$ 3360 (KCl disc) 1769, 1679 cm^{-1} ($CHCl_3$) ($\lambda_{max.}$ 221 mμ $\epsilon_{max.}$ 10,400 (neutral) $\lambda_{max.}$ 228, 257 mμ $\epsilon_{max.}$ 5,000, 10,300) (Found: C, 71.91; H, 8.68; $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86;) (mol. wt. (mass spectrometer) 250).

Elution with glacial acetic acid, partition of the resulting fraction between ether and water and work up in the usual way, gave a semi-crystalline oil (807 mgms.). Repeated recrystallisation of this from, first benzene and subsequently methylene chloride/petrol gave 7, 11-Dihydroxyconfertifolin (7) as prisms m.p. 170 - 172°C (155.1 mgms.). This was shown to be identical by m.p. and mixed m.p. to the compound "fuegin/

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"fuegin II" isolated by Dr. Appel and his associates from a D. winteri tree obtained from Tierra del Fuego. $[\alpha]_D$ +76 (c. 1.12 in $CHCl_3$) ($\nu_{max.}$ 3345, 1748, 1672, cm^{-1} (KCl disc) 3582, 3340, 1764, 1680 cm^{-1} ($CHCl_3$) ($\lambda_{max.}$ 217 mμ $\epsilon_{max.}$ 6500 (EtOH), $\lambda\lambda_{max.}$ 233, 258 mμ $\epsilon\epsilon_{max.}$ 5050, 6150) (Found: C, 67.85; H, 8.02; $C_{15}H_{22}O_4$ requires C, 67.64; H, 8.33) (mol. wt. (mass spectrometer) 266). Elution with aqueous acetic acid and work up of the fraction as above gave a crude crystalline material (697.5 mgms.). Recrystallisation to constant m.p. of this from ether gave Winterin (3) as large well-formed plates m.p. 158°C (156.4 mgms.). $[\alpha]_D$ + 109 (c. 2.52 in $CHCl_3$) ($\nu_{max.}$ 1847, 1776, 1668 cm^{-1} (CCl_4)) ($\lambda_{max.}$ 257 mμ $\epsilon_{max.}$ 3820 (neutral) $\lambda_{max.}$ 245 mμ $\epsilon_{max.}$ 8900 (EtOH/KOH)) (Found: C, 72.43; H, 8.06; $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12;) (mol. wt. (mass spectrometer) 248).

The following is a cross section of the extracts examined. The variation in content from tree to tree is especially remarkable.

Lago Ranco (Futrono) (138 gms.) From the fraction boiling at 165 - 180°C @ 14 mm Hg., confertifolin (5 mgms.) was obtained.

Lago Ranco (Futrono) (100 gms.) From the fraction boiling at 220 - 240°C @ 9 mm. Hg., confertifolin (1.25 gms.) was obtained. From the fraction b.p. 180 - 220°C, drimenol (0.8 gms.) was isolated.

Lago Ranco (Futrono) (132 gms.)

Fraction b.p. 220 - 300°C @ 5 mm. Hg. yielded confertifolin (1.25 gms.)

Fraction b.p. 150 - 220°C @ 5 mm. Hg. yielded drimenol (6.6 gms.)

Lago Ranco (Futrono) (90 gms.)

Fraction b.p. 185 - 200°C @ 8 mm. Hg. yielded drimenol (9.4 gms.)

Valdivia (350 gms.)

Fraction b.p. 250 - 300°C @ 8 mm. Hg. yielded confertifolin (13 gms.)

Loncoche (280 gms.)

Fraction b.p. 185 - 220°C @ 4 mm. Hg. yielded confertifolin (2.6 gms.) and drimenol (traces)

Loncoche/

Loncoche (406 gms.)
Fraction b.p. 70 - 170°C @ 4 mm. Hg. yielded drimenol (22 gms.)
Fraction b.p. 170 - 200°C @ 4 mm. Hg. yielded confertifolin (900 mgms.)
Loncoche (496 gms.)
Fraction b.p. 177 - 190°C @ 4 mm. Hg. yielded isodrimenin (1.25 gms.) and drimenol (3 gms.)
Los Lagos (360 gms.)
Fraction b.p. 180 - 200°C @ 4 mm. Hg. yielded drimenol (22 gms.)
Fraction b.p. 200 - 210°C @ 4 mm. Hg. yielded confertifolin (3.1 gms.)
Juan Fernandez (D. confertifolia) (29 gms.)
Fraction b.p. 190 - 260°C @ 4 mm. Hg. yielded confertifolin (Traces).
All the compounds referred to in the above series were identified by m.p. and mixed m.p.

Detailed examination of a Loncoche extract.

An ethereal solution of the extract (10 gms.) was separated into acid and neutral fractions in the usual way. Acidification of the bicarbonate solution and extraction into ether yielded, after drying and removal of ether, a semi crystalline mass (85 mgms.) from which needles melting at 150 - 170°C could be obtained on addition of benzene. Sublimation of these followed by several recrystallisations from benzene finally produced long white needles of p - methoxycinnamic acid (49) m.p. 170 - 171°C (23.2 mgms.) ($\nu_{max.}$ 1688, 1630 cm^{-1} ($CHCl_3$)) (Found: C, 67.4: H, 5.61; $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.62;). Esterification of this acid with diazomethane and recrystallisation of the product from hexane gave plates of methyl p-methoxycinnamate m.p. 84 - 88°C ($\nu_{max.}$ 1720, 1645, 1610 cm^{-1}). The neutral portion of the extract (9.7 gms.) was chromatographed on alumina (grade III, 300 gms.). Elution with benzene in ether (1:1 v/v) gave isodrimenin (1.811 gms.) melting, at 133 - 135 undepressed by authentic material. Ether eluted confertifolin (727 mgms.) identified by m.p. (153°C) and mixed m.p.

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A fraction (700 mgms.), eluting in ether/methanol (1:1 v/v) ($\nu_{max.}$ 3400, 1760, 1730, 1675 cm^{-1} liquid film) was rechromatographed (grade V alumina) and that fraction eluting in hexane (171 mgms: $\nu_{max.}$ 3400, 1760, 1720, 1680 cm^{-1}) was treated with dinitrobenzoyl chloride (198 mgs.) in pyridine (5 mls.) and worked up in the usual way. Chromatography of the product (170 mgms.) and elution with benzene/ether (3:1 v/v) gave 30 mgms. of confertifolin identified by m.p. (153 - 154°C) and mixed m.p.

A second fraction of the original chromatogram eluting in ether/methanol (1:1 v/v) (1.6 gms.) was separated into carbonyl and non carbonyl fractions using Girard's reagent "P". Work up, isolation and distillation of the non carbonyl fraction yielded in the portion b.p. 110 - 130°C @ 10^{-3} mm. Hg. a trace of drimenol, identified by m.p. (91 - 93°C) and mixed m.p.

Hydrogenation of Confertifolin. Confertifolin (23.4 mgms.) was hydrogenated at atmospheric pressure and room temperature with Adam's catalyst (22 mgms.) in acetic acid (5 mls.). After 4 hours, 1.18 moles of hydrogen had been absorbed. The reaction was stopped, filtered and the acetic acid removed under reduced pressure. Recrystallisation of the product from petrol gave cis dihydroconfertifolin (52) as needles m.p. 134 - 135°C $[\alpha]_D$ ±0 (c. 4.28 in $CHCl_3$) ($\nu_{max.}$ 1781 cm^{-1} (CCl_4)) (Found: C, 76.4; H, 10.0; $C_{15}H_{24}O_2$ requires C, 76.25; H, 10.15;). When ethyl acetate was used as solvent in place of acetic acid, no hydrogen was absorbed and confertifolin was recovered unchanged.

Lithium Aluminium Hydride Reduction of Confertifolin. Confertifolin (343 mgms.) was added in ethereal solution (25 mls.) to a stirred slurry of lithium aluminium hydride in refluxing ether over a period of two hours. The reaction was allowed to stand overnight. Excess reducing agent was destroyed with ethyl acetate, dilute hydrochloric acid was added and the ethereal solution was worked up in the usual way. The oily semi crystalline product (387 mgms.) on two recrystallisations/

recrystallisations from petrol gave drim-8-ene 11, 12 diol as plates m.p. 121 - 123°C $[\alpha]_D$ +119 (c. 1.78 in benzene) (153 mgms.) undepressed on admixture with authentic material from reduction of isodrimenin. The infrared spectrum ($\nu_{max.}$ 3320, 1640, 1028 and 982 cm^{-1} (KCl disc)) was identical to that of authentic material. From the mother liquors, a further 61.2 mgs. of this compound were obtained. The oily mother liquors (133 mgms.) appeared from the infrared spectrum to be a mixture of diol and confertifolin.

Reduction of cis-Dihydroconfertifolin with Lithium Aluminium Hydride.

Cis dihydroconfertifolin (63 mgms.) in tetrahydrofuran (4 mls.) was slowly added to a slurry of lithium aluminium hydride (150 mgms.) in the same solvent. The reaction was refluxed for two hours and then worked up in the usual way. There was obtained 75 mgms. of a crude product which, after one recrystallisation from hexane gave crystals m.p. 130 - 145°C. Sublimation of 29 mgms. of this material (0.1 mm Hg., 120 - 130°C) gave 8β, 9β-drimane-11, 12-diol (55) m.p. 151 - 153°C $[\alpha]_D$ + 24 (c. 1.04 in $CHCl_3$) undepressed on admixture with authentic material from reduction of drimenin. Identical infrared spectra ($\nu_{max.}$ 3300, 1052 and 1025 cm^{-1} (KCl)).

Isomerisation of cis-Dihydroconfertifolin. Cis dihydroconfertifolin (30.5 mgms.) was dissolved in methanol (1 ml.) containing potassium hydroxide (31.6 mgms.) and allowed to stand for 48 hours. Acidification and extraction into chloroform gave, on removal of solvent, a crude crystalline product (30.8 mgms.). Two recrystallisations from hexane gave isodihydroconfertifolin (53) m.p. 121 - 123°C $[\alpha]_D$ -9 (c. 1.1 in $CHCl_3$) (21.9 mgms.) ($\nu_{max.}$ 1792 cm^{-1} (CCl_4)) (Found: C, 76.28; H, 9.91; $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24;). From the mother liquors, a further 9.4 mgms. melting at 118 - 120°C were recovered.

Reduction of Isodihydroconfertifolin with Lithium Aluminium Hydride.

Isodihydroconfertifolin/

trioxide (5.12 mgms., 1.54 equivalents of O) in acetic acid (4 mls.) and allowed to stand overnight. Ether was then added and washed with bicarbonate solution and water. Removal of solvent, drying and recrystallisation of the resulting material from ether gave winterin (3) m.p. 154 - 157°C (10.8 mgms.) undepressed on admixture with authentic material. The two compounds showed identical mobility on a chromatoplate.

Hydrogenolysis of 11 Hydroxyconfertifolin.

11 hydroxyconfertifolin (9.6 mgms.) was shaken for 16 hours with Adam's catalyst (13.6 mgms.) in acetic acid (5 mls.) and in an atmosphere of hydrogen. During this time 0.97 mls. (= 1.05 moles) of hydrogen were absorbed. The reaction was stopped and a further quantity of catalyst (10 mgms.) was added. Shaking in an atmosphere of hydrogen was then continued for two days. Filtration and removal of solvent gave 26.1 mgms. (extra weight shown to be due to silicone grease) of product. Chromatography of this on alumina (600 mgms. grade III) gave, on elution with petrol benzene (1:1 v/v) cis-dihydroconfertifolin (10.0 mgms.), identified by m.p. (133 - 135°C), mixed m.p. and superposibility of infrared spectra.

Reduction of 11 Hydroxyconfertifolin with Lithium Aluminium Hydride.

11 hydroxyconfertifolin (33.3 mgms.) was dissolved in dry ether and the solution added slowly to a slurry of lithium aluminium hydride (118 mgms.) in ether. When the addition was complete, the reaction was refluxed for ca. 0.5 hours and then allowed to stand at room temperature for a further two hours. Ethyl acetate and water were used to destroy excess reducing agent. The ether was washed with N hydrochloric acid and repeatedly with water. Removal of solvent and drying gave drim-8-ene-11, 12-diol (23.4 mgms.) identified by m.p. (120 - 122°C), mixed m.p. and infrared spectrum.

Hydrogenolysis of 7, 11 Dihydroxyconfertifolin.

7, 11-dihydroxyconfertifolin (9.0 mgms.) was dissolved in acetic acid (5 mls.) and shaken with Adam's catalyst (53 mgms.) in an atmosphere of hydrogen. After two days, 1.94 mls. (2.39 moles) of hydrogen had been absorbed. A further 12 mgms. of Adam's catalyst

were/

were then added and the mixture hydrogenated for a further 12 hours. Work up in the usual way yielded 8.1 mgms. of an oily material from which on chromatography on alumina (600 mgms. grade III) were obtained, in the petrol benzene (1:1 v/v) eluates, crystals of cis-dihydroconfertifolin (4.1 mgms.) identified by m.p. (132 - 134°C), mixed m.p. and infrared spectra.

Oxidation of 7, 11-Dihydroxyconfertifolin.

7, 11-Dihydroxyconfertifolin (36.5 mgms.) was dissolved in acetic acid (2 mls. - AR. and redistilled over CrO_3) in a flask fitted with efficient stirring. A solution of chromium trioxide (19.5 mgms. = 2.14 equivalents of [O]) in acetic acid (10 - 15 mls. prepared as above) was then run dropwise into the stirred solution. When all the oxidant had been added the stirring was stopped and the solution allowed to stand overnight at room temperature. Excess reagent was destroyed with methanol. Water and ether were added and the ether was repeatedly washed with water. Removal of solvent and drying gave 33.2 mgms. of impure feathery crystals. Repeated recrystallisation from chloroform gave drim 8 ene 7 one 11, 12 dicarboxylic acid anhydride (5 mgms.) (60) m.p. 147 - 150°C ($\nu_{max.}$ 1780 (v broad) 1689, 1641, 1395, 1385 cm^{-1} (KCl disc)) ($\lambda_{max.}$ 230 mμ $\epsilon_{max.}$ 7750 (neutral) $\lambda_{max.}$ 238, 278 mμ $\epsilon\epsilon_{max.}$ 2780, 3710 (base)).

Hydrogenation of Futronolide.

Futronolide (3.5 mgms.) in acetic acid (5 mls.) was shaken with Adam's catalyst (17.0 mgms.) in an atmosphere of hydrogen for 7 hours. A further 21.9 mgms. of Adam's catalyst was then added and the hydrogenation continued for a similar period. Filtration and removal of solvent left a gum (5.9 mgms.) which was chromatographed on alumina (grade III). Elution with chloroform gave solid material crystallising in both needles and prisms. Rechromatography and elution with benzene/chloroform (4:1 v/v) gave 7 hydroxydihydrocon-fertifolin (61) as needles m.p. 164 - 165°C (ca. 1 mgm.) ($_{max.}$ 3609, 3508, 1768 ($CHCl_3$) cm^{-1}).

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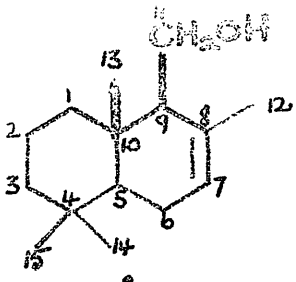
* I am indebted to Dr. A. I. Scott for a manuscript copy of his book before publication.



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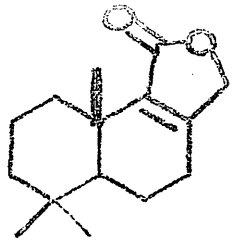

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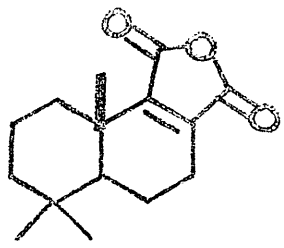

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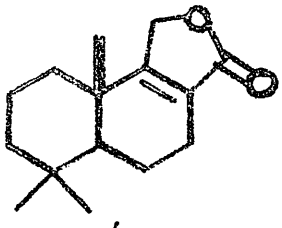

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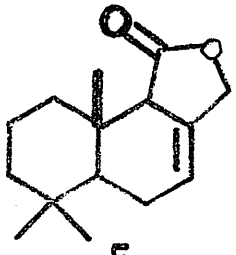

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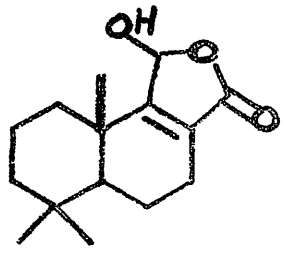

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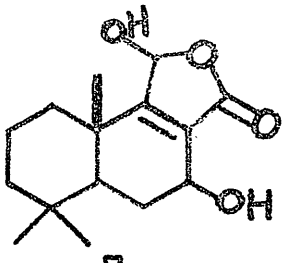

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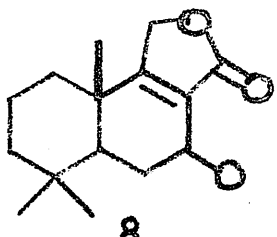

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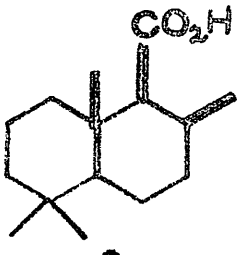

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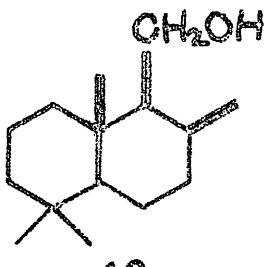

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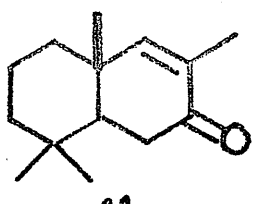

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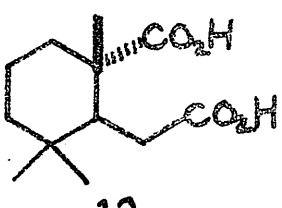

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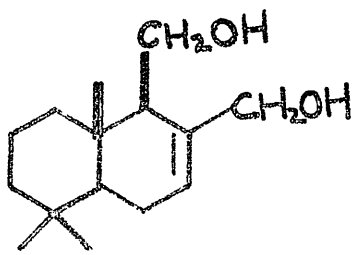

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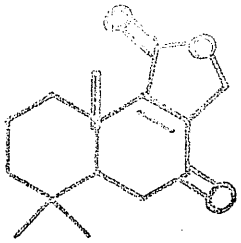

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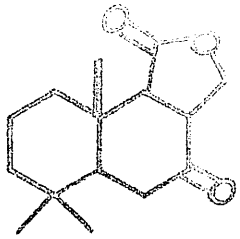
Zn/Acetic acid →



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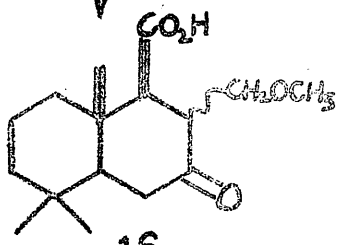

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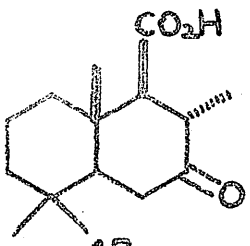

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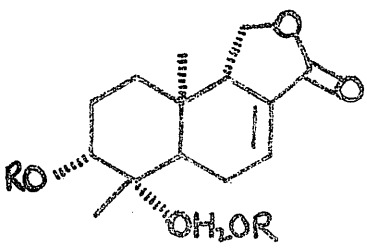

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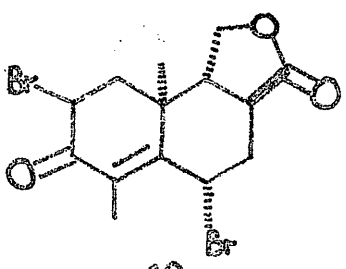

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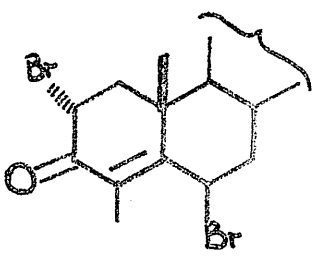

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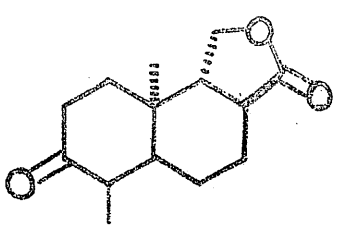

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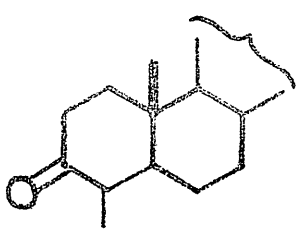

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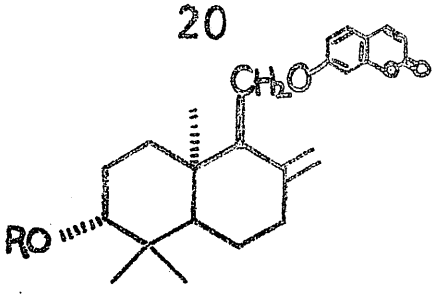

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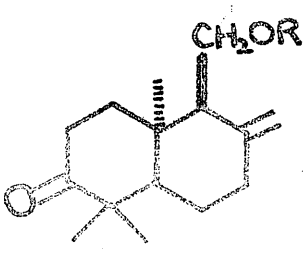

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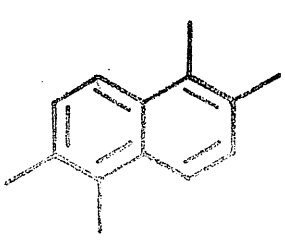

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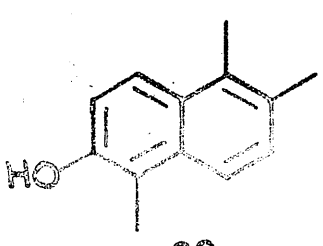

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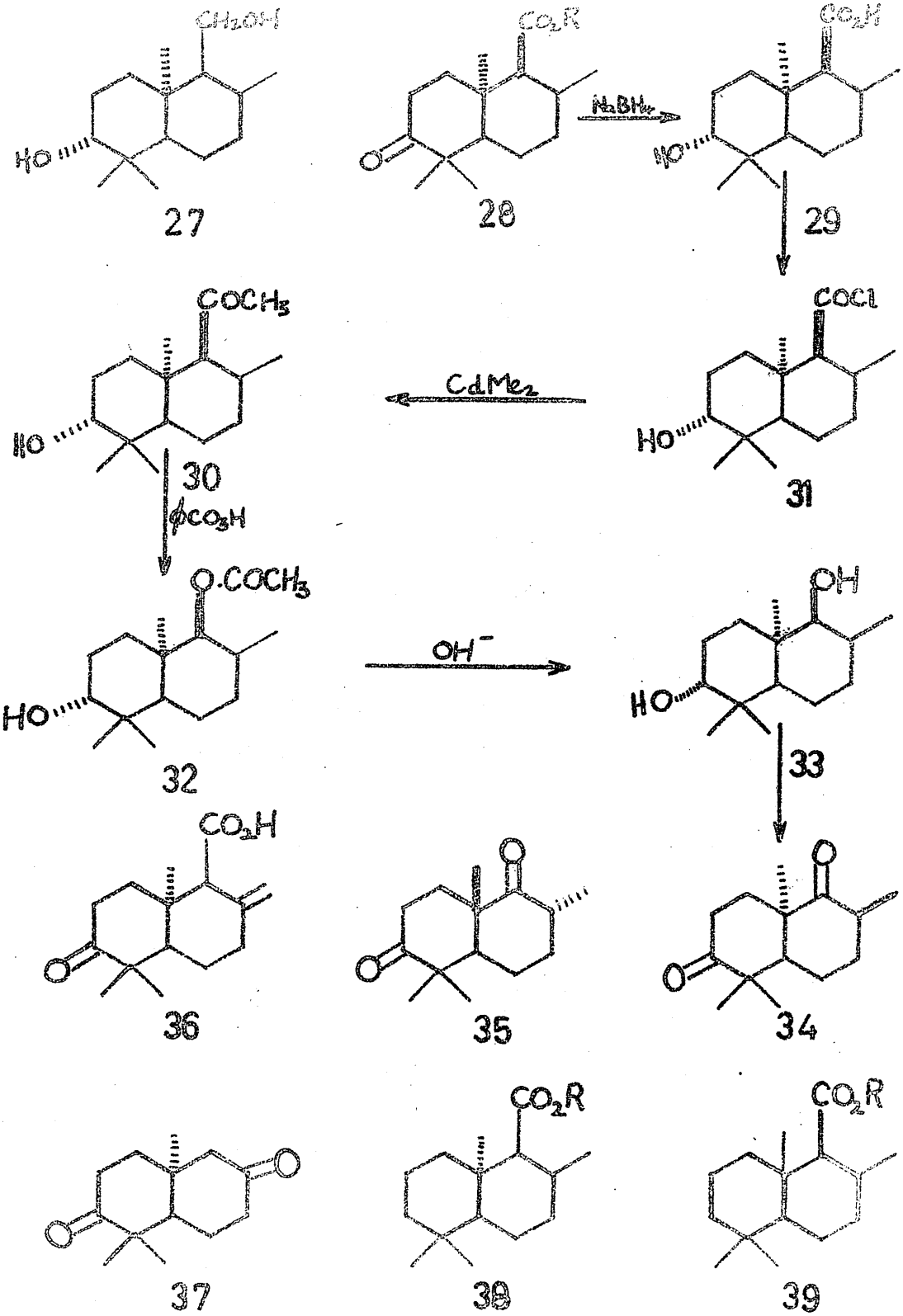
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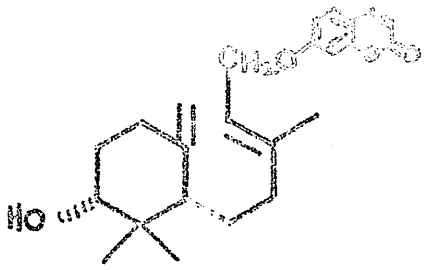

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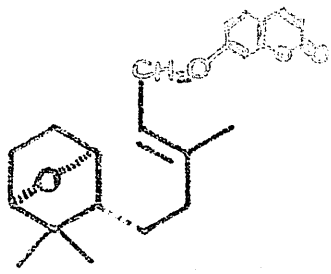

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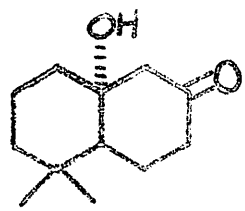

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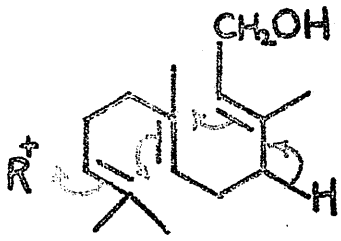

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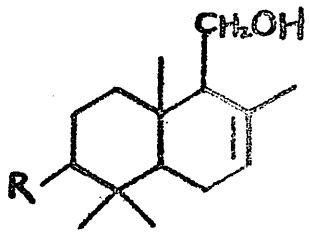

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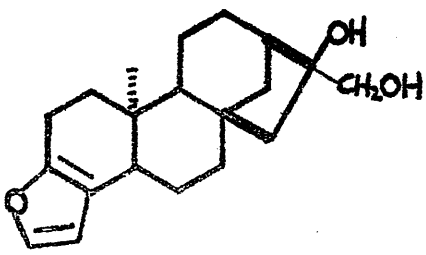

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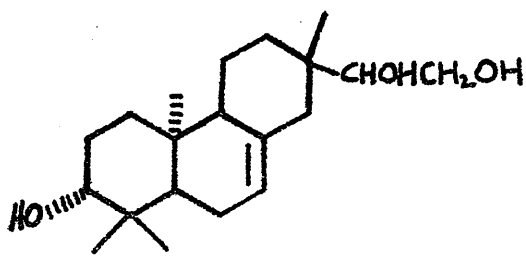

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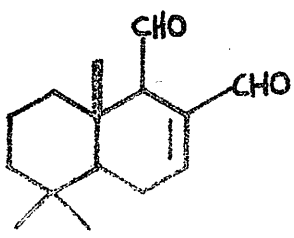

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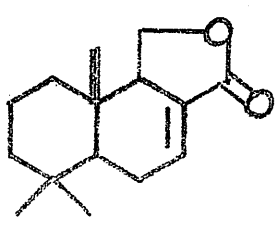

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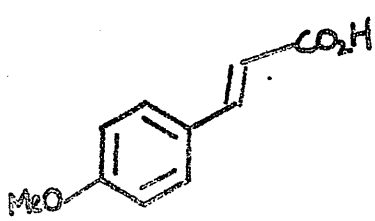

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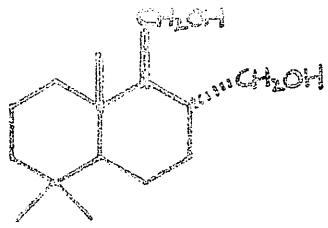

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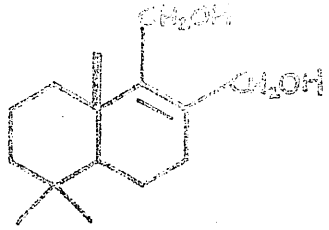

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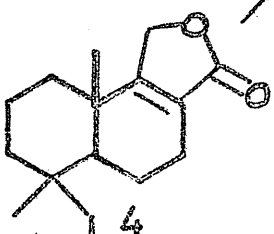

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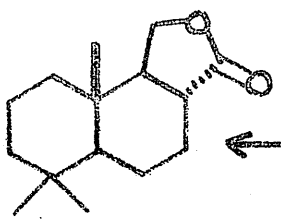

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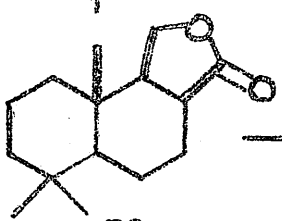

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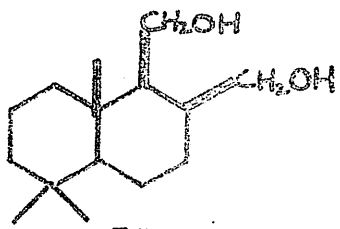

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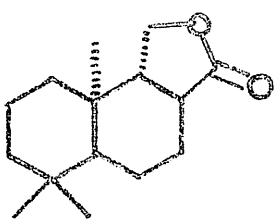

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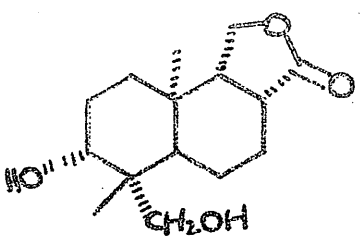

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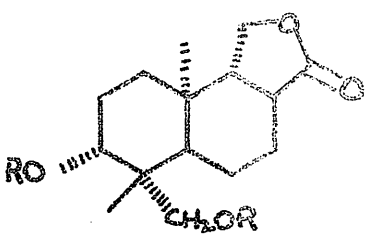

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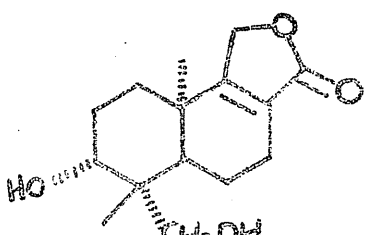

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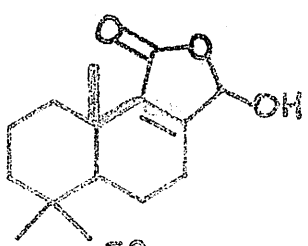

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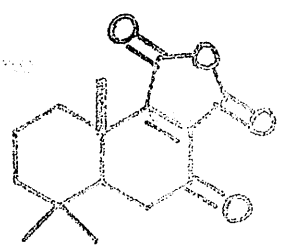

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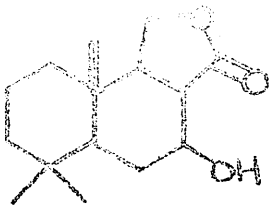

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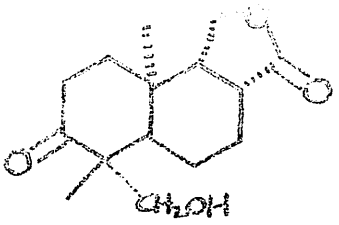

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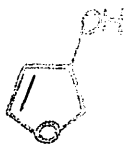

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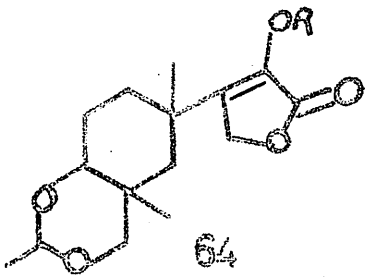

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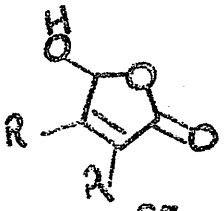

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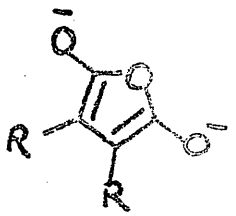

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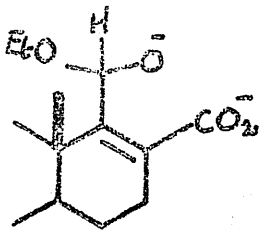

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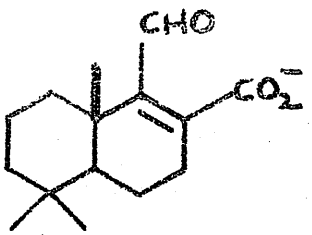

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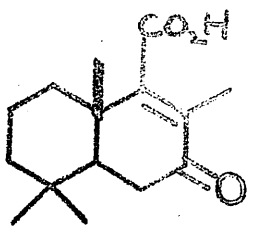

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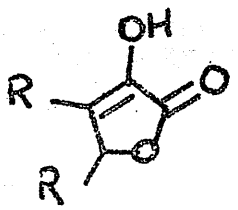

70

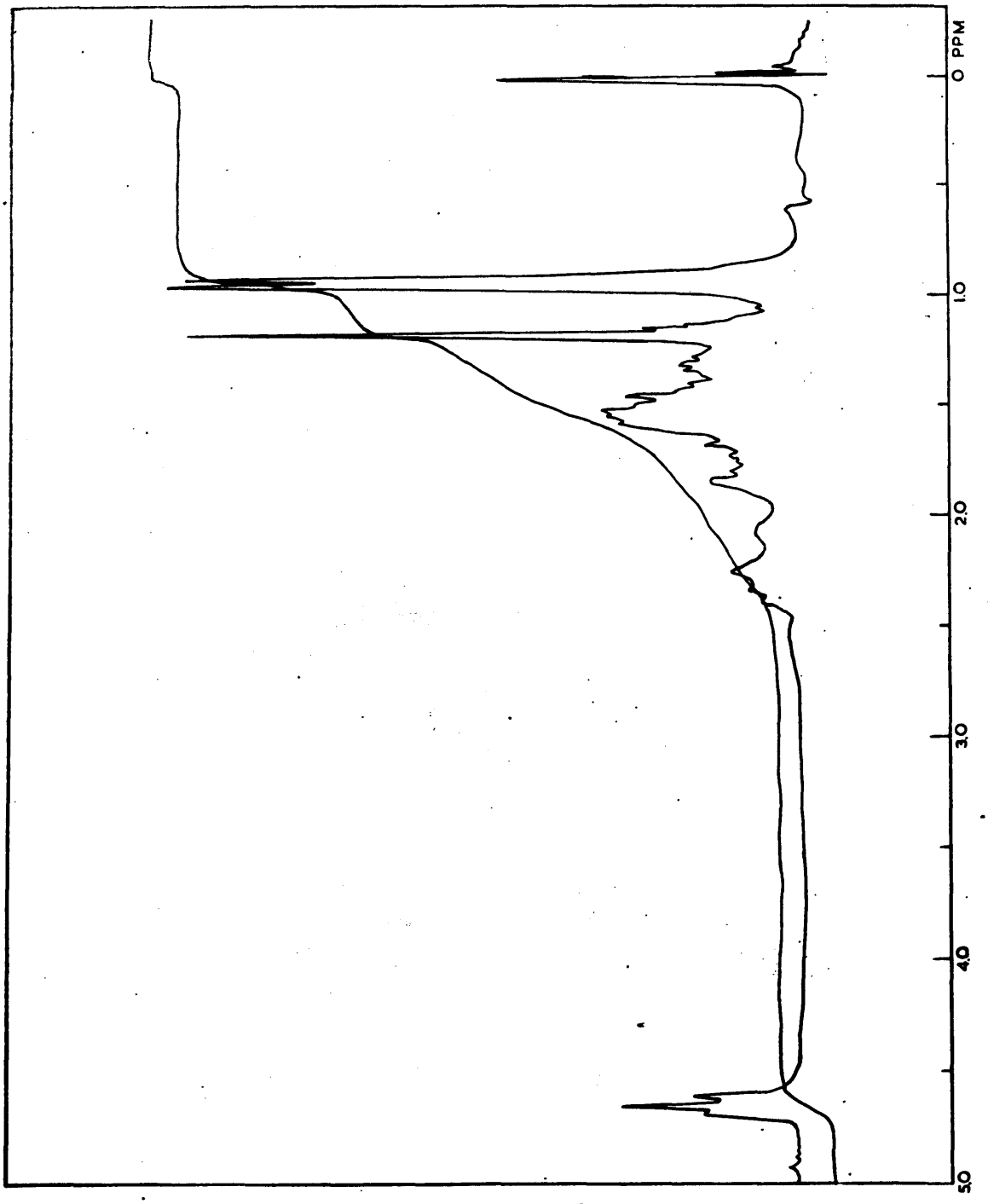

FIGURE I

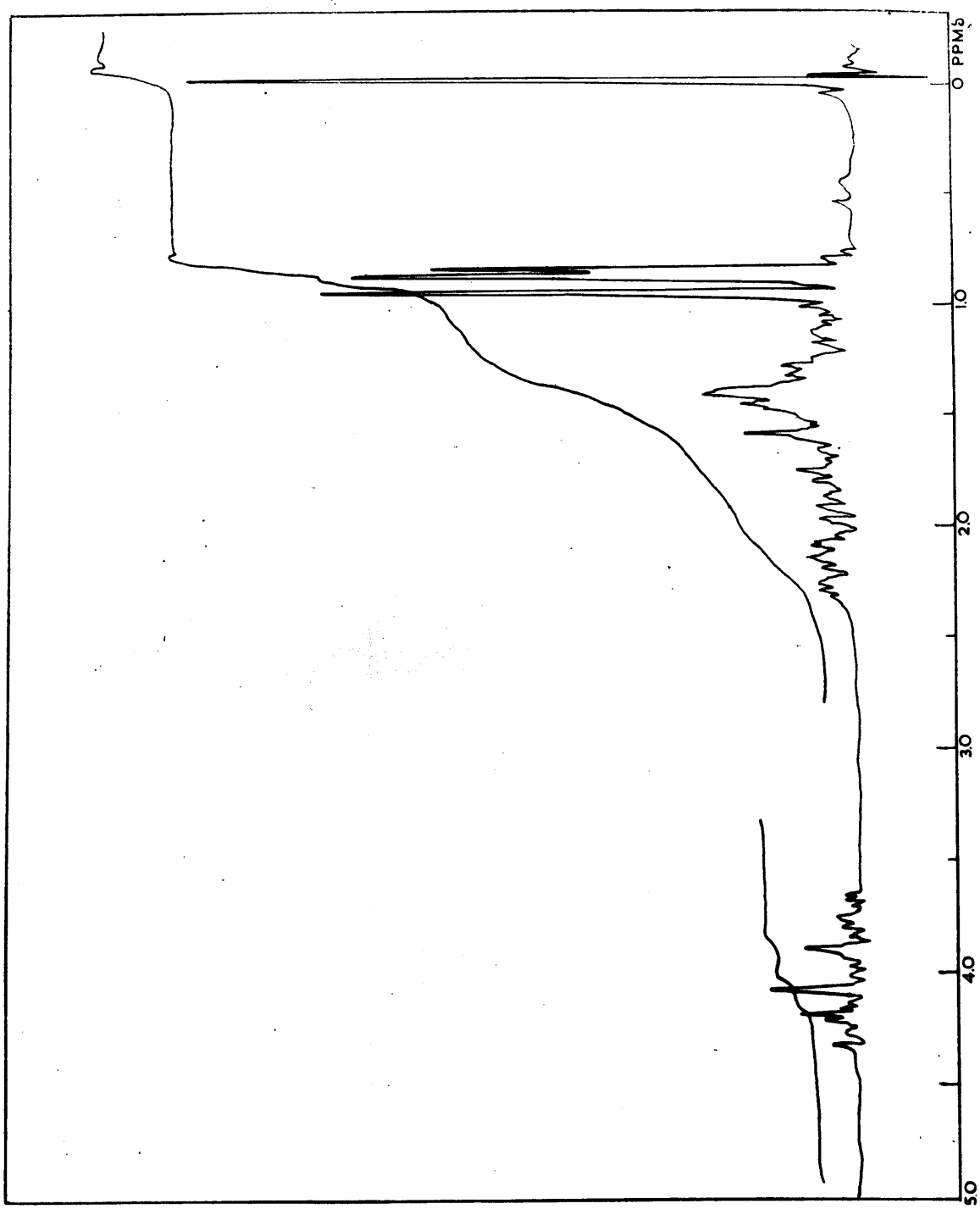

FIGURE 2

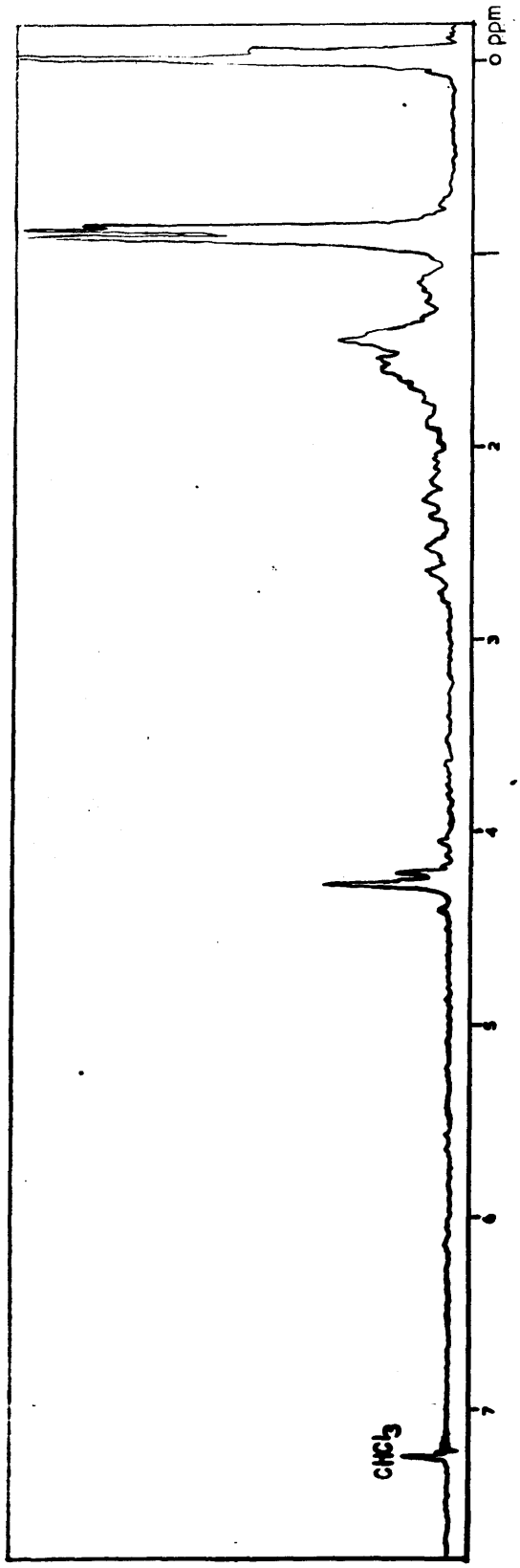

FIGURE 3

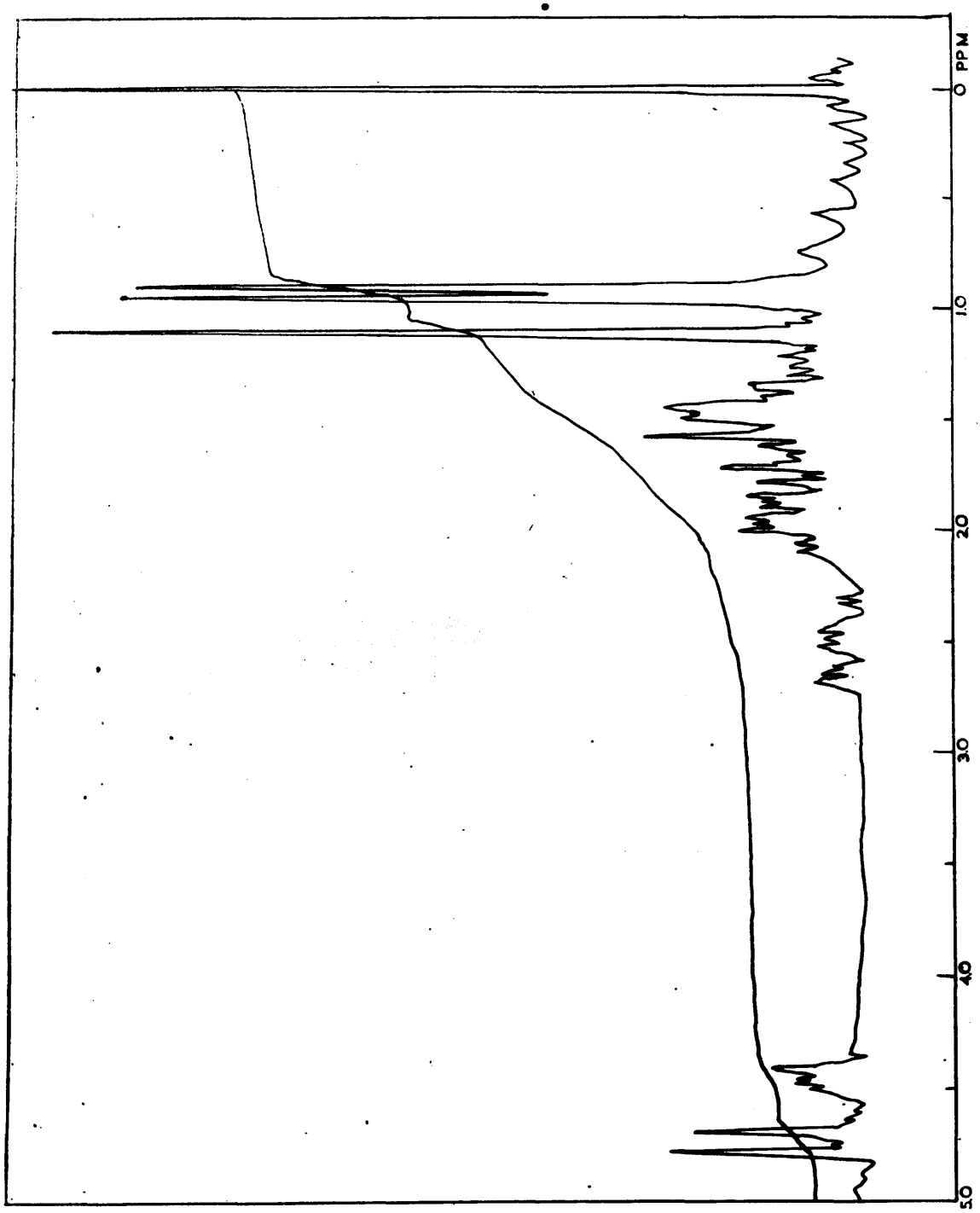

FIGURE 4

THE PHOTOCHEMISTRY OF CONFERTIFOLIN

INTRODUCTION: The photochemical literature records no detailed study of the simple α,β-unsaturated γ-lactone system [38, 39, 43]. That the behaviour of such a system might prove of interest has been indicated by a preliminary study of the photolysis of digitoxinin[1]. These facts, coupled with the observation, made early in these investigations, that crystalline confertifolin (1) on prolonged exposure to bright Chilean sunlight, acquires a yellow colouration and has its m.pt. markedly lowered and the melting range widened, indicated that a systematic study of the photochemistry of confertifolin would be of value.

THE MECHANISM OF PHOTOCHEMICAL REACTIONS

The vast compendium of fact and physico-chemical theory which gives to ground state organic chemistry its powerful predictive and interpretative powers cannot be applied to the chemistry of molecules in the excited state. The interaction of a molecule with light quanta not only raises the energy levels of the electrons, it also alters the electronic distribution and the geometry of the molecule. In short, the excited state of a molecule is a new chemical species.

In no photochemical reaction are the intermediates and their reaction modes fully understood. A considerable literature of physical studies of such reactions exists but the experimental difficulties, arising from the short lifetime of the intermediates and the large number of variables involved, have prevented any clear cut conclusions being drawn.

It seems likely that in this, as in ground state chemistry, the empirical approach of the Organic Chemist will provide useful correlations to guide the physical chemical interpretations of such reactions. The guiding principles which theoretical chemistry can supply to aid in mechanistic interpretation of photoreactions may be summarised briefly as follows.

Since unexcited organic molecules exist almost exclusively in the singlet state, absorption of light should, in theory, produce a singlet excited state i.e. with no resultant electronic spin. Spin-orbit interactions are sufficiently significant, however, in complex molecules to permit crossing to a triplet state[2], though with low probability.

It is normally difficult to ascertain whether a photochemical reaction is proceeding through a singlet or a triplet excited state. Evidence has been presented favouring a singlet intermediate in the photolytic decomposition of cyclopentanone[11], while the reduction of carbonyl compounds by alcohols[12], the isomerisation of olefins[2, 13] and the sensitised dimerisation of olefins[14] appear to occur via a triplet state. The application of e.p.r. spectroscopy to the study of photochemical reactions[15] will no doubt make definitive identification of the/

the triplet state much simpler. It should be emphasised that, while the distinction between the two possible intermediates is mechanistically important, they may not differ greatly in chemical properties.[65] The singlet state though not possessing resultant electronic angular momentum, can nevertheless, behave as a diradical [65, 11]. The longer lifetime of the triplet state, arising from the low probability of its transition to the singlet, can have important chemical consequences especially in solution.

Photochemical excitation of an electron will, by the "aufbau" principle, place that electron in an antibonding orbital. The general electronic properties of the excited state may thus be inferred from a knowledge of these properties in the ground state of the molecule and from the nature of the antibonding orbitals[9]. Experimental requirements[16] in performing photochemical reactions will normally limit our consideration of electronic transitions to those of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ type. In those cases which have both transitions available, that utilised will depend on reaction conditions and on facilities for reaction through the relevant excited states. It would seem reasonable to suppose, however, that, other things being equal, the lower energy $n \rightarrow \pi^*$ transition would be the more favoured. The large number of carbonyl compounds which undergo photochemical rearrangement [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27] on irradiation in pyrex apparatus[16] would seem to support this supposition. Different reaction modes arising from the different electronic transitions in the same compound have been demonstrated experimentally by Hata [28, 29] and Hammond[30].

Together with electronic excitation, molecules normally acquire considerable vibrational energy on interaction with light quanta. This is a result of the Franck-Condon principle. The possession of vibrational energy and the ease or otherwise with which it is lost can control the mode of decomposition or rearrangement.[26, 39] The geometry of an excited molecule can only be obtained by a detailed analysis of the emission spectrum of that molecule, or by a theoretical analysis using, for example, the L.C.A.O. method. Where this has been done[31], the/

the results have given some insight into the chemical behaviour of the species [14, 32, 33, 34]. In general, the nature of the products will give some indication of the way in which the geometry of the excited state is altered with respect to the ground state. It is here that the empirical approach of the organic chemist can be used to best advantage in elucidating the pathways of these reactions.

The photochemical literature has been reviewed in recent years[2, 3, 4, 6. 8, 16, 35, 36, 37, 38], with an adequacy which makes a comprehensive survey unnecessary here. Only material which is germane to the present topic will be considered, together with work of particular note which has appeared since the last review[35].

The mode of reaction most frequently observed in the photolysis of $\alpha\beta$-unsaturated carbonyl compounds is that involving the formation of carbon-carbon bonds by the mutual saturation of the double bond of the $\alpha\beta$-unsaturated carbonyl with a second unsaturated system. There are many examples of this and, for the purposes of discussion, they will be divided into intermolecular and intramolecular reactions.

Intermolecular light catalysed reactions of $\alpha\beta$-unsaturated ketones, esters and acids to give cyclobutanoid dimers are well known and the earlier examples have been reviewed by Mustafa[37].

Methyl cyclohexenone [37, 39, 40], thymoquinone [38, 41], coumarin [37, 38, 42, 64] and Δ^4 3keto steroids [38, 43] dimerise on irradiation to give compounds (2,3,4,5 and 6) respectively.

The cinnamic acids similarly dimerise to give α truxillic (7) acid and β truxinic (8) [4, 5] acid. The disposition of the monomer units about the cyclobutane ring is partly dependent on the physical state of the cinnamic acid. As has been pointed out [38], there appears to be no simple pattern to the stereochemistry of these reactions which would enable predictions to be made in a given case. A cis stereochemistry about the central ring may be inferred in those cases where a "double dimerisation" occurs. Thus 2, 6, dimethylbenzoquinone (9) has been shown to give (11) via (10)[45]. Dibenzylidene acetone is photochemically dimerised in the presence of uranyl salts to (12)[37].

In/

In contrast, methyl α ketopentadiene dicarboxylate gives (13) on direct irradiation. More recently, the photodimerisation of some furocoumarins, a process exactly analogous to that for the simple coumarins, has been reported[47]. Chapman and Smith have finally established the structure of α-lumicolchicine as the dimer (15) of β-lumicolchicine (14).

The transformation of (10) into (11)[45] may be regarded as an intramolecular attack of one conjugated double bond on another of the same kind. This, together with the analogous reaction of 2, 6 dimethylpyrone which presumably follows a similar path is, to the author's knowledge, the sole intramolecular representative of this type of reaction. In intramolecular photolyses, mutual saturation (vide supra) to form a system no longer capable of absorbing light is achieved by the interaction of the double bond which is conjugated with the carbonyl, with an isolated double bond. The best known example of this is the conversion of (16, R = COOH) into the quadricyclene derivative (17, R = COOH). Dauben has shown that the analogous reaction can be produced in norbornadiene (16, R = H) itself [34], while Hammond has also produced quadricyclene (17, R = H) from nor bornadiene using diketones as photosensitisers [14]. A similar reaction to produce the cage structure (19) from the Diels-Alder adduct (18) of cyclopentadiene and benzoquinone has been reported by Cookson[50]. A number of examples are known (see e.g. reference 38, page 392) where molecules with cage-like structures result from the irradiation of substances which have suitably juxtaposed double bonds not conjugated with carbonyl functions, but carrying chlorine substituents.

In contrast to the above intramolecular reactions which involve molecules of rigid structure and suitably placed interacting groups, transformations are known which appear to follow similar mechanistic pathways but which require that a marked change in the geometry occurs between the ground and excited states. Thus, the production of carvone camphor (22) from carvone (20) must involve an intermediate such as (21)[22]. The isomerisation of verbenone (23) to

chrysanthenone/

chrysanthenone (24)[52] is closely related mechanistically although not itself representative of the reaction type under discussion.

The synthesis of bicyclo (3:2:0) heptenones from cycloheptadienones represents an analogous bond forming reaction where one of the new bonds is formed between two carbon atoms already joined by a single bond. Interesting transformations of this type have been observed with eucarvone (25) and may be represented as shown (25 - 26 - 27 and 28). [89, 90] Buchi[89] has pointed out that a rearrangement of chrysanthenone analogous to the rearrangement of (26) to (27) would produce (30). Similarly, we may observe that a rearrangement of chrysanthenone analogous to that producing the trimethylbicycloheptenone (28) would give rise to the spiro structure (31). Neither of these transformations has yet been observed, however. Apart from eucarvone, several other cycloheptadienones have been studied [53, 55, 56, 57] and the interaction of the unsaturated groups to form cyclobutane derivatives has been shown to be a general phenomenon. There is one exception which is worthy of particular note. Chapman and his associates [56] obtained, on irradiating 3, 5 cycloheptadienone (32, R = H) in ether, carbon monoxide and a mixture of isomeric 1, 3, 5 hexatrienes. They have interpreted this as indicating that the normal interaction to form bicyclo (3:2:0) heptenes does not occur and that the decomposition is a direct process. Ample analogy exists, however [11, 53, 54, 57] to suggest that the diene system, whether activated by the carbonyl or not, would interact [53, 54] to give the ketone (33, R = H) and that this would decompose [11, 57] irradiatively to give 1:3:5 hexatriene and carbon monoxide. This latter decomposition may occur directly via the diradical (34) or indirectly by way of bicyclo (2:2:0) hexene (35). The former is the more probable as it is likely that the latter reaction is thermal rather than photochemical. Similar effects have been observed with and similar comments apply to the photolysis of 2 methyl 3, 5 cycloheptadienone (32, R = Me et seq.).

The recently reported cyclisation of citral (36) with U.V. light to give 2-isopropenyl-5-methyl cyclopentylaldehyde (38) fits into the pattern/

pattern of reactions under discussion if the intermediacy of a species such as (37) is assumed.

The production, photochemically, of the diketone (42) from cyclohexene (39) and acetylacetone reported recently by de Mayo[59] provides an intermolecular analogy, hitherto lacking, for the photochemical reaction between isolated and enone double bonds.

It is of interest to note the bond forming reactions observed with dienes when photosensitised by diketones[14]. This, together with earlier work by the same authors[13] makes it probable that such bond forming reactions proceed through a triplet excited state. Photochemical dimerisation reactions may also involve a triplet species since the probability of intermolecular reaction will increase as the lifetime of the reactive intermediate increases.

In interpreting certain of the interesting and unusual transformations of dienones, Barton[36] has suggested the entity (part structure 44A) as a possible intermediate. Such a structure can be envisaged as arising by an interaction, between one double bond and the enone system, analogous to the reactions discussed above. This is in accord with the known spectroscopic properties of dienones [63]. A very similar intermediate for dienone rearrangements, based on theoretical considerations similar to those outlines at the beginning of this discussion, has been put forward by Zimmerman[10].

THE PHOTOCHEMISTRY OF CONFERTIFOLIN

RESULTS AND DISCUSSION: Irradiation of a cyclohexane solution of confertifolin with U.V. light and chromatography of the product gave cis-dihydroconfertifolin, together with four other crystalline compounds which were designated lumi-X_1, X_2, X_4 and X_5.

Analysis and mass spectrometric molecular weight determination of lumi-X_1 indicated it to be isomeric with confertifolin. In apparent contradiction to this, the spectral properties of the compound ($\nu_{max.}$ 1763 cm^{-1} * no high intensity U.V. absorption above 200 mμ) were suggestive of a saturated γ-lactone. The stability of lumi X_1 to acid demonstrated that these anomalies did not arise through the formation, during the photolysis, of a cyclopropane ring [67]. Analogies in the literature suggest [37, 38, 64, 45, 47, 48, 49] that, the molecular weight information apart, these facts would be accommodated by assuming that confertifolin had formed a dimer, probably involving a cyclobutane ring. Such a dimer could decompose thermally[45] or by electron impact to monomer units in the mass spectrometer, thus giving an apparent molecular weight one half of the true value. Such an interpretation would also explain the very high melting point observed for lumi-X_1. That such a rationalisation represented the situation correctly was shown in the following way.

Reduction of lumi-X_1 with lithium aluminium hydride in ether gave a product (melting range 199 - 209°C) which was difficult to purify. Treatment of this material with hydrogen chloride in chloroform produced a compound (m.p. 256 - 259°C) whose infrared spectrum ($\nu_{max.}$ 1395, 1360 (gem-dimethyl) 1005 (ether) cm^{-1}) indicated it to be an ether. Mass spectrometric examination of this compound gave a value of 444 for the molecular weight. This value corresponds to two molecules of confertifolin diol (70) with the elimination of two molecules of water (240 + 240 - 36). The dimeric nature of lumi X_1 itself was confirmed/

*This value is somewhat lower than that normally observed for a saturated γ-lactone. The transparency in the U.V. makes the assignment reasonable however. The effect is probably due to the unusual steric environment in which the lactone must be placed (vide infra).

confirmed by a determination of the molecular weight using the thermistor drop technique[68]. This gave a value of 450 ± 20 (confertifolin dimer has a molecular weight of 468). Further confirmation of these conclusions was obtained when pyrolysis of lumi-X_1 at 540°C in an atmosphere of nitrogen gave an approximately 60% yield of confertifolin. The possibility that the two monomer units might be joined by an ether bridge arising from the γ-lactone group of one of them was excluded by integrating the areas of the infrared carbonyl bands of lumi-X_1 and cis-dihydroconfertifolin. The carbonyl intensity per monomer unit was of the same order of magnitude in both cases. Bridging of the monomer units by carbon-carbon bonds is therefore mandatory, and lumi X_1 must be a cyclobutanoid dimer.

The nuclear magnetic resonance (n.m.r.) spectrum of Lumi X_1 (fig.) has three sharp singlet peaks at 9.21 τ 9.15 τ and 9.10 τ each having a weight of six protons. These peaks are assigned to the six methyl groups of the dimer (cf. cis and trans dihydroconfertifolin). The occurrence of only three peaks requires that the magnetic environment of the methyl groups does not change between one monomer unit and its companion. The octuplet between 6.15 τ and 5.45 τ arises from the two protons on C_{11}[70] (cf. cis and trans dihydroconfertifolin). The observed multiplicity can be interpreted either (a) as the superposition of two AB quadruplets with identical coupling constants (J_{AB} = 10.8 c.p.s.) but differing slightly in the chemical shifts of the two protons; or (b) as the AB part of an ABX spectrum with J_{AB} = 10.8 c.p.s. and $J_{AX} = J_{BX}$*.

If interpretation (a) is correct, the dimer must have formed across the site of the double bond in confertifolin. The six possible structures for such a dimer are represented by the formulae (63, 64, 65, 66, 67, 68). Structures (63, 65, 67 and 68) involve considerable molecular overcrowding and their formation is inherently improbable. This applies also to (64) which, in addition, has one methyl group (arrowed) in a magnetically unique environment. The remaining structure/

*The presence of a quadruplet in the 7.9 - 8.5 region which would be required by interpretation (b) cannot be confirmed or refuted because of the complexity of the spectrum in this region.

structure (66) is the most favoured mechanistically since its formation involves that mode of mutual approach of monomer units which sets up fewest non-bonded interactions. The high symmetry of structure (66) makes it difficult, however, to explain the slight difference in chemical shift between the C_{11} protons on the two monomer units, required by the n.m.r. spectrum. In view of the size of the shift involved (ca. 0.1 p.p.m.) this does not, however, constitute evidence of sufficient weight as to exclude the structure (66).

Interpretation (b) of the n.m.r. spectrum would require that dimerisation be preceded by a photochemically induced migration of the double bond to position 7, § [38, 76]. The possible structures resulting from dimerisation in this position, including those which involve inversion of configuration at C_9, are given in the formulae (45 - 62 inclusive). This somewhat formidable list can be substantially reduced if it is assumed that the intramolecular overcrowding in the structures (47, 48, 49, 50, 53, 54, 55, 58, 60 and 61) makes their formation improbable. Further elimination is made possible by the following argument. For the octuplet between 6.15 τ and 5.43 τ to be the AB part of an ABX spectrum requires that all the variables which control the form of the spectrum be single valued (δ_A δ_B, J_{AB}, J_{AX} and J_{BX}). The disposition of the C_{11} protons relative to the C_9 methine proton must therefore be the same in both units of the dimer. Reference to the Newman projections (taken along the $C_9 - C_{11}$ bond) in figures* shows that structures (51, 52, 56, 57, and 62) may be dismissed from consideration. Only structures (45, 46, and 59), therefore, are mechanistically feasible and fit the available physical data. Since only one dimer is formed in the photolysis, it may be supposed that lumi-X_1 arises from the energetically most favoured path. Such a view would prefer (45) as the structure of lumi X_1.

The weight of n.m.r. evidence preferring, as it does, structure (45) over (66) is nicely balanced by the scarcity of analogy for photochemically induced double bond shifts. The available evidence is insufficient to distinguish between the two possibilities. On the basis/

*Figures (3 - 7)

basis of these structures, the ether produced by acid treatment of the lithium aluminium hydride reduction product of lumi X_1 will have the structures (71) or (72). The homo acid resulting from fusion of lumi X_1 with potassium cyanide is tentatively assigned the structures (73) or (74).

Lumi-X_2 ($C_{21}H_{34}O_2$) appeared to have arisen by addition of cyclohexane to confertifolin. Its spectroscopic properties ($\nu_{max.}$ 1774 cm.$^{-1}$, no high intensity U.V. absorption above 200 mμ) indicated it to be a γ-lactone. The mass spectrum gave a molecular weight of 318, in accord with the analytical data and the cracking pattern showed a base peak at 236, indicating ready loss of C_6H_{10}. The n.m.r. spectrum of lumi X_2 has peaks at 9.21τ and 9.16τ attributable to the three methyl groups of the confertifolin unit. The multiplet centred at approximately 5.96τ must arise from the C_{11} protons. The peaks are not well resolved but appear to form an AB spectrum with ($\delta_A - \delta_B$) small. This would be in accord with the addition of a cyclohexyl residue at C_9 as in (69) which is the structure to be expected on mechanistic arguments (vide infra). The stereochemistry at positions 8 and 9 cannot be ascertained on the available evidence.

The remaining two compounds, lumi-X_4 and lumi-X_5 are isomeric with lumi-X_2. Both are saturated γ-lactones (X_4 $\nu_{max.}$ 1760 cm^{-1}, X_5 $\nu_{max.}$ 1779 cm^{-1}) and both have base peaks in the mass spectra at 236. It is very probable that these compounds are stereoisomers of lumi-X_2 but they are formed in low yield and were not examined in detail.

The photolytic reduction of an $\alpha\beta$-unsaturated carbonyl compound in a hydrocarbon solvent is sufficiently novel to call for further comment.

Photochemically induced intermolecular hydrogen transfer is well authenticated [61, 78, 79, 62, 80, 81, 82] and has been interpreted for carbonyl compounds as involving the triplet state of the n transition.[61, 62] Quinones are readily reduced photochemically in the presence/

presence of hydrogen donors[82], and a recent publication[83] describes a case where saturated hydrocarbons fulfill the latter function. However, the results obtained indicate that hydrogen attached to tertiary carbon is necessary for reduction to proceed. The many intramolecular reactions in which ketones can abstract a suitably placed hydrogen atom [84, 85, 86] demonstrates that the lack, hitherto, of an intermolecular analogy is not due to the absence of a suitable mechanism. The formation of lumi-X_2 may be regarded as the intermolecular and vinylogous analogue of the formation of methylbutanol from 2 pentanone[84]. Though intramolecular analogies for the hydrogen abstraction reaction make the first step in the reduction plausible, there remains to be explained why the resulting cyclohexyl radical couples with the ground state monoradical in one case (to give lumi X_2) and donates a hydrogen atom to it in the other (formation of cis dihydroconfertifolin). A possible rationalisation is depicted in scheme 1. The initially formed cyclohexyl radical may either (a) couple (step 3) or (b) eliminate hydrogen to form a cyclohexenyl radical[87]. The confertifolin radical then abstracts hydrogen from this latter to give cyclohexadiene[88] and dihydroconfertifolin (step 5).

also from hexane, rose to 191 - 193°C (25

tetrachloride 1774 cm^{-1}) (Found: C, 73.33;

H, 10.76;) (mol. wt. (mass spect

EXPERIMENTAL

For general proceedures see page 18

Photolyses. Irradiations were performed with an ordinary fan-cooled mercury arc lamp. The excess heat from the lamp was sufficient to reflux the cyclohexane solvent.

Photolysis of Confertifolin. (i) Confertifolin (523.3 mgms.) was dissolved in "spectrosol" cyclohexane and irradiated for 24 hours under reflux. The reaction was followed by the disappearance of the 217 m chromophore in the U.V. spectrum. Removal of solvent under reduced pressure gave a yellow-brown oil of distinctive and pleasant odour (681 mgms.). This was chromatographed on neutral alumina (grade III). On eluting with benzene in hexane (3:1 v/v), a highly crystalline material of m.p. 270°C was obtained (108 mgms.). Recrystallisation from hexane gave needles m.p. 291° - 294°C of lumi X_1 $[\alpha]_D$ -63 (C. 1.07 in $CHCl_3$) (ν max. (carbon tetrachloride) 1763 cm^{-1} (strained lactone)) (Found: C, 76.63; H, 10.14; $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46; mol. wt. (mass spectrometer), 234; (thermistor drop[68]), 450 ± 20.)

Another crystalline fraction of m.p. 175 - 185°C was obtained by elution with benzene in hexane (1:3 v/v) (124 mgms.). These were combined with an identical fraction from a companion irradiation and the total material (165 mgms.) was rechromatographed on grade III neutral alumina.

Elution with hexane produced crystals of lumi X_2 melting at 175 - 180°C (96.1 mgms.) $[\alpha]_D$ -25 (C. 1.04 in $CHCl_3$) which, on recrystallisation, also from hexane, rose to 191 - 193°C (25 mgms.). (ν max. carbon tetrachloride 1774 cm^{-1}) (Found: C, 79.32; H, 10.78; $C_{21}H_{34}O_2$ requires C, 79.19; H, 10.76;) (mol. wt. (mass spectrometer) 318).

Further purification by sublimation brought the m.p. to 196 - 198.5°C but the analysis was unaffected.

In/

In the range of solvent polarity from benzene in hexane (1:9 v/v) to benzene in hexane (1:3 v/v), there was eluted an oil (79 mgms.) which, after sitting in a little hexane for some time, crystallised spontaneously. Recrystallisation from hexane gave needles m.p. 163 - 165°C of lumi X_4. ($\nu_{max.}$ 1760 cm^{-1} (KCl disc)) (Found: C, 78.96; H, 10.54; $C_{21}H_{34}O_2$ requires C, 79.19; H, 10.76;).

Finally there eluted from benzene in hexane (2:3 v/v) a crude crystalline fraction m.p. 108 - 120°C (38.5 mgms.). Recrystallisation to constant m.p. from hexane gave a small quantity of colourless needles m.p. 135 - 135.5°C undepressed on admixture with authentic dihydro-confertifolin (m.p. 134 - 135°C). The infrared spectra of the two compounds were identical.

All fractions, other than those referred to were oils and were not further examined.

(ii) A repetition of the above irradiation procedure on confertifolin (550.6 mg.) gave 679 mg. of the pleasant smelling oil. Chromatography of this on 20 g. of neutral Grade III alumina gave, as before, lumi X_1, m.p. 289 - 291°C (33.6 mg.), and lumi X_2, m.p. 190 - 193°C (24.9 mg.) on elution with benzene in hexane (3:1 v/v) and benzene in hexane (1:3 v/v) respectively.

Elution with benzene in hexane (1:1 v/v) and two recrystallisations of the resulting material (22.5 mg.) from hexane gave needles, m.p. 156 - 160°C. On admixture with lumi X_4 this depressed to 135 - 154°C. The analytical specimen melted at 158 - 161°C. This compound was designated lumi X_5. ($\nu_{max.}$ (carbon tetrachloride) 1779 cm^{-1}) (Found: C, 78.81; H, 10.42; $C_{21}H_{34}O_2$ requires C, 79.19; H, 10.76;).

As before, all other fractions were oils.

Attempts to isomerise Lumi X1 in Acid Media. Unchanged starting material was recovered in essentially quantitative yield from the following experiments.

(i) Lumi-X_1 (1.8 mgms.) was dissolved in acetic acid (1 ml) containing sulphuric acid (concentrated, 0.2 ml.) and refluxed overnight. Water and/

and ether were added and the ethereal solution worked up in the usual way.

(ii) Lumi-X_1 (2.5 mgms.) was dissolved in acetic acid (1 ml.) containing hydrogen chloride (concentrated acid, 0.15 mls.) and treated as above.

(iii) Lumi-X_1 (2.8 mgms.) was dissolved in chloroform (5 mls.) ethanol (5 mls.) and hydrochloric acid (concentrated, 1.5 mls.) and shaken for 1 week. The organic solvents were washed with water and worked up as before.

Pyrolysis of Lumi-X_1. Lumi X_1 (58.6 mgms.) was vaporised into a stream of nitrogen and passed through a tube heated to 540°C. The products were recovered from a trap (32.9 mgms.) cooled in acetone/drikold and by extraction of the pyrolysis tube (38 mgms.). The latter crystallised and, after recrystallisation from petrol, was identified, by m.p. (154 - 155°C), mixed m.p. and infrared spectrum, as confertifolin.

Reduction of Lumi X_1 with Lithium Aluminium Hydride. (i) A saturated solution of lithium aluminium hydride in ether (15 - 20 mls.) was added over a period of five minutes to a well stirred solution of lumi X_1 (9.8 mgms.) in ether cooled in a bath of acetone/drikold. The reaction was then allowed to come to room temperature and was kept thus overnight. Excess reducing agent was destroyed with ethyl acetate, water was added, the ethereal solution separated, washed and dried. The product (9.8 mgms.) was analysed by means of alumina impregnated paper in 10 gm. aliquots. This indicated the presence of at least three components. (ii) A solution of lumi X_1 (19.7 mgms.) in tetrahydrofuran was run into a stirred slurry of lithium aluminium hydride in the same solvent. When the addition was complete, the reaction was refluxed for 1½ - 2 hours. Excess reducing agent was destroyed with ethyl acetate, ether and water were added and the ethereal solution worked up as before. The product ($\nu_{max.}$ 3600, 3350 (free and bonded hydroxyl) 1390, 1365 (gem dimethyl) cm^{-1}) was chromatographed on alumina (grade V).

That/

That fraction eluting in benzene (17 m mg.) was crystalline and began to melt at ca. 229°C but solid still remained at 300°C. In chloroform in benzene (1:1 v/v) there eluted a small quantity of a further crystalline compound which, after recrystallisation from hexane melted at 202 - 210°C ($\nu_{max.}$ 3600 (free hydroxyl) 3350 (bonded hydroxyl) 1390, 1365 (gem dimethyl) cm^{-1}).

(iii) By duplication of the previous procedure, 20 mgms. of crude reduction product were obtained from lumi X_1 (22 mgms.). On chromatography on grade V alumina and elution with benzene there were obtained 16 mgms. of material m.p. 199 - 209°C ($\nu_{max.}$ 3600, 3350, 1390, 1365 cm^{-1}). Treatment of this with hydrochloric acid in chloroform and recrystallisation of the product from hexane gave prisms m.p. 256 - 259°C ($\nu_{max.}$ 1395, 1360, 1005 (saturated ether) cm^{-1}). (mol. wt. (mass spectrometer) 444).

(iv) Reduction of lumi X_1 with lithium aluminium hydride (80 mgms.) in tetrahydrofuran at reflux gave 26 mgms. of product after work up in the usual way. Addition of a little ethyl acetate to this, filtration, and recrystallisation of the residue from the same solvent gave needles m.p. 220 - 221°C (with a few crystals remaining in the liquid melt until 237°C) (8.9 mgms.). Acetylation of these with acetic anhydride (12 drops) in pyridine (10 drops) overnight gave an oil (11.1 mgms.) ($\nu_{max.}$ 1740 (acetate carbonyl) 1390, 1365, 1240 (acetate)).

(v) Lumi-X_1 (11.4 mgms.) was dissolved in pyridine and lithium aluminium hydride powder added directly (118.4 mgms.). After the initial vigorous reaction had subsided, the flask was stoppered and allowed to stand for three hours. The reaction mixture was thrown into dilute hydrochloric acid and the resulting aqueous suspension extracted with ether. Work up in the usual way gave a semi-crystalline solid (10.8 mgms.) chromatography of which on silica gel and elution with chloroform in benzene (1:4 v/v) gave a fraction (3.2 mgms.) from which prisms m.p. 255 - 257°C were obtained after a further separation on a preparative scale chromatoplate. The chromatoplate/

chromatoplate indicated the presence of two other compounds, one of which was starting material.

Saponification of Lumi-X_1. Lumi X_1 (15 mgms.) was refluxed overnight in ethanol (20 mls.) containing sodium hydroxide (200 mgms.) The solution was taken to dryness under reduced pressure and the residue partitioned between ether and water. Standard work up of the ether gave lumi X_1 (14.7 mgms.) identified by m.p. (290 - 294°C) and mixed m.p.

In a control experiment, performed under similar conditions, only 1.9 mgms. of cis-dihydroconfertifolin was recovered from the saponification of 11 mgms.

Treatment of Lumi X_1 with Potassium Cyanide[91]. Lumi X_1 (33 mgms.) was intimately mixed with powdered potassium cyanide (2.4668 gms.) and the mixture placed in a pyrex tube. The tube was evacuated, sealed and then heated to 360°C for four hours. On opening, the contents were partitioned between ether and water. The neutral fraction (5 mgms.) then obtained by work up of the ether was not further examined. Acidification and re-extraction of the aqueous phase yielded 18.3 mgms. of a semi-crystalline solid exhibiting an infrared spectrum characteristic of a carboxylic acid. This product was hydrolysed by refluxing overnight in 45% potassium hydroxide solution (5 mls.). Acidification and work up in the usual way yielded a brown gum (20 mgms.). Addition of ethyl acetate and several recrystallisations from the same solvent gave white needles (2 mgms.) m.p. 209 - 211°C. These also had absorption in the infrared typical of carboxylic acids ($\nu_{max.}$ 1710 cm^{-1}). Treatment of the mother liquors of this acid with acetic anhydride and sublimation of the product at 10^{-3} mm. Hg. gave a mixture of substances ($\nu_{max.}$ 3100, 2650 (carboxyl OH) 1805, 1750 (strain - free anhydride) 1710 (carboxyl) cm^{-1}).

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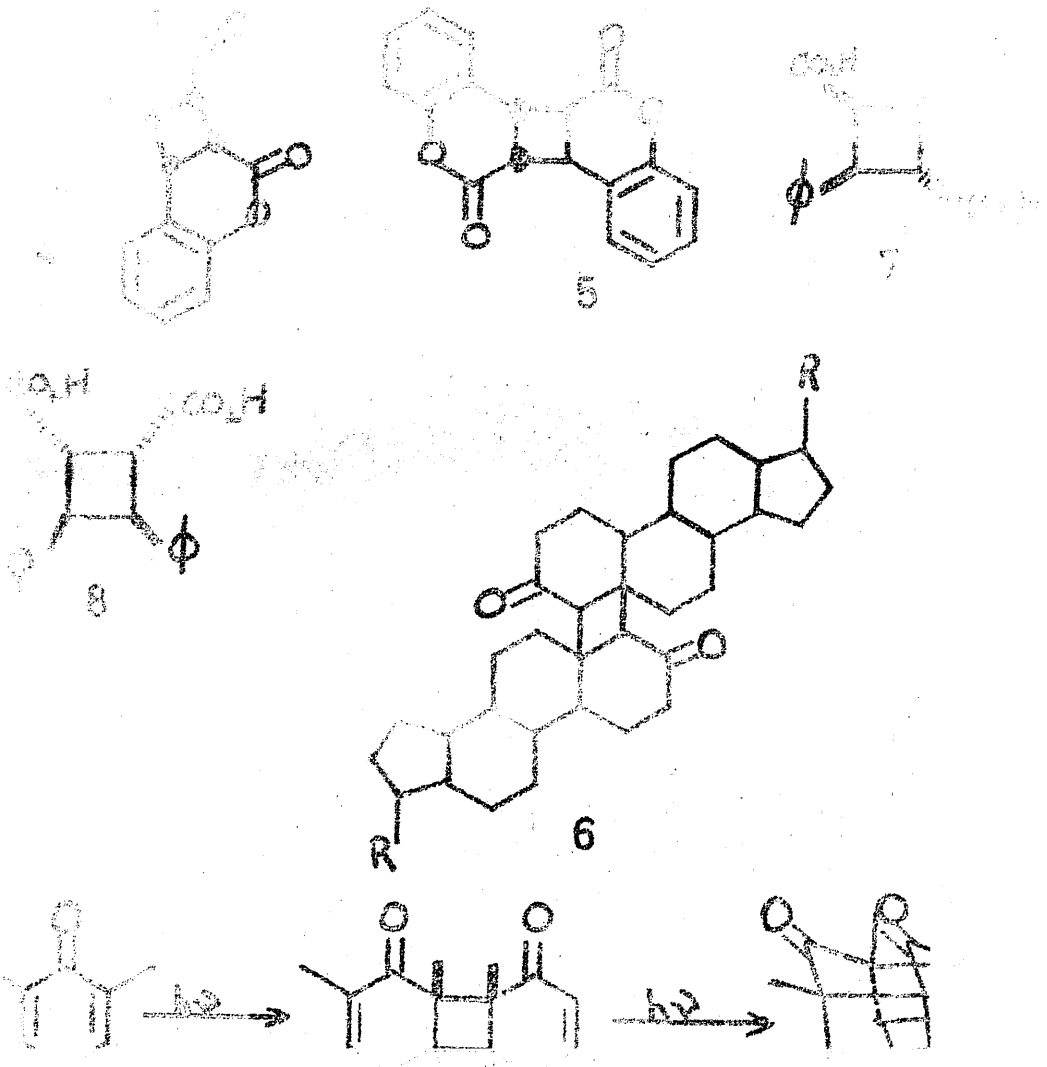

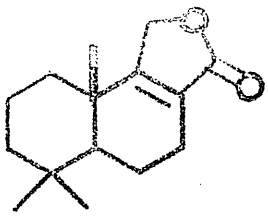

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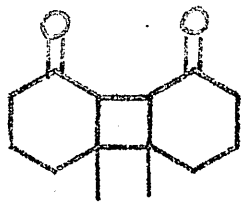

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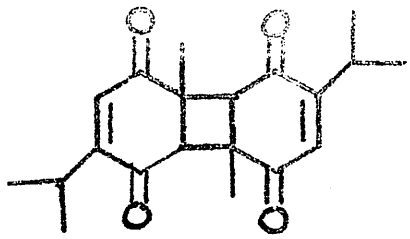

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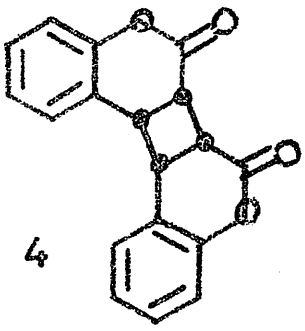

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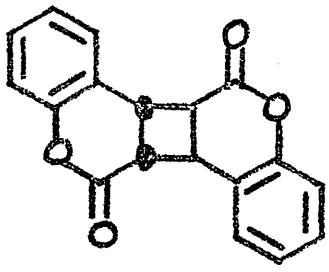

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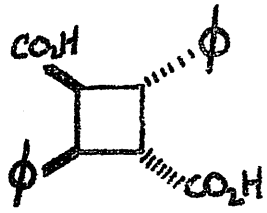

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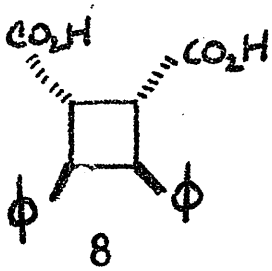

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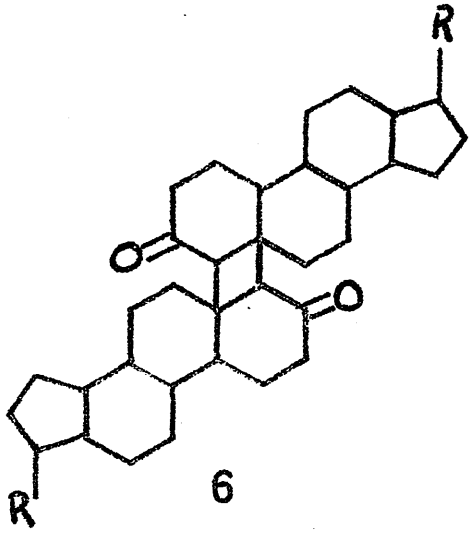

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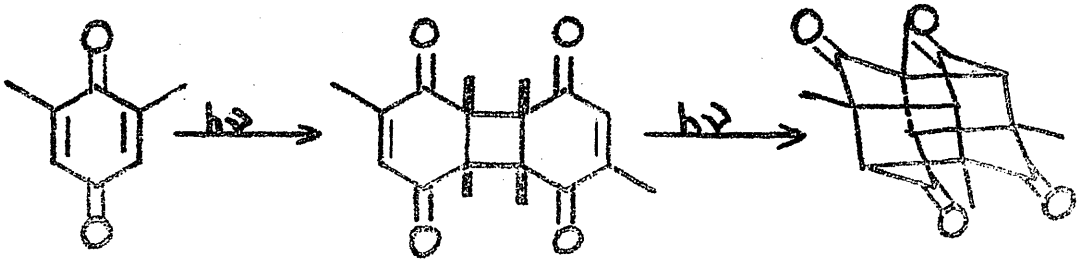

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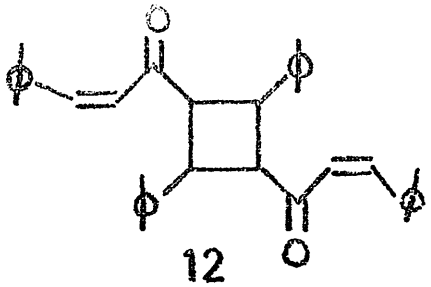

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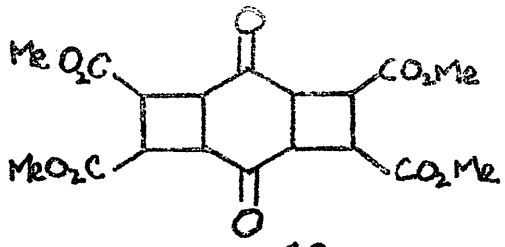

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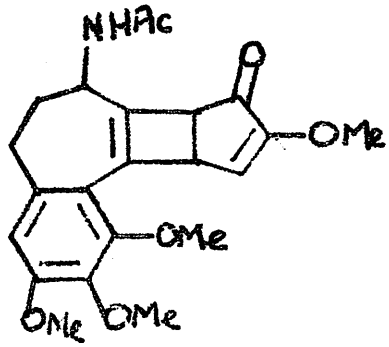

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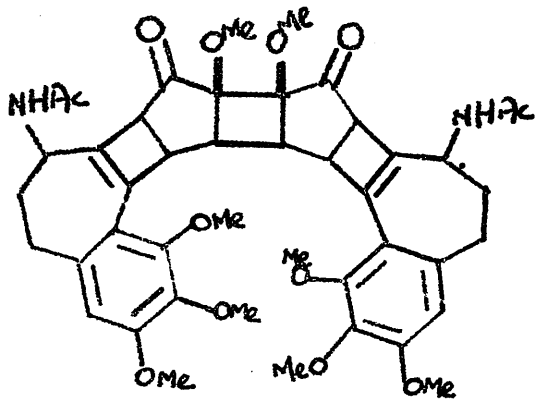

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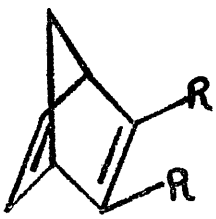

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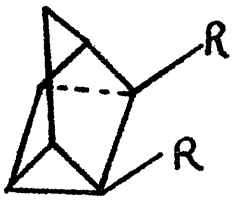

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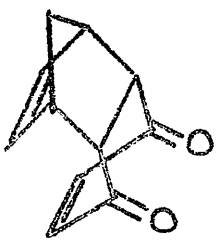

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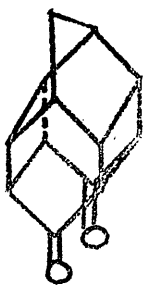

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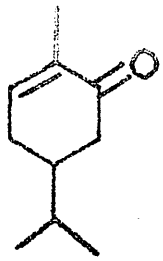

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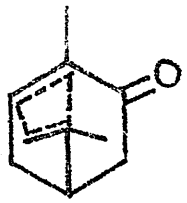

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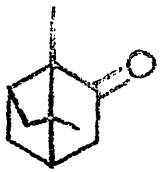

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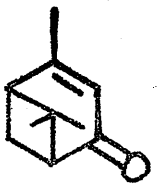

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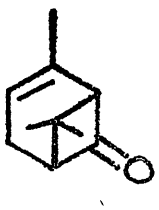

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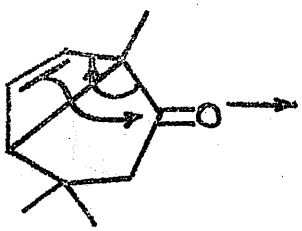

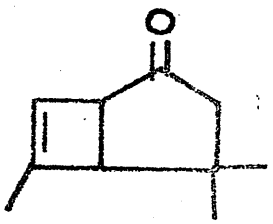

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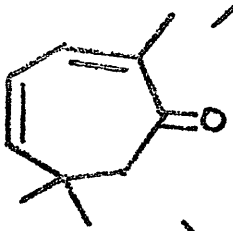

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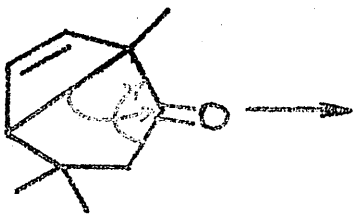

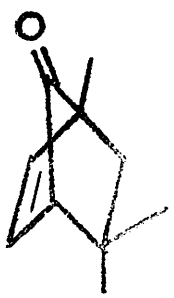

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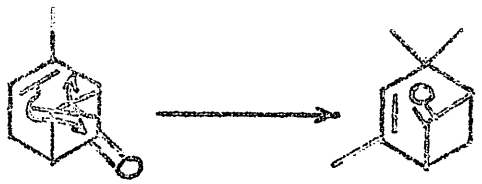

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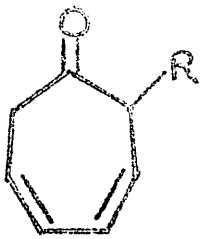

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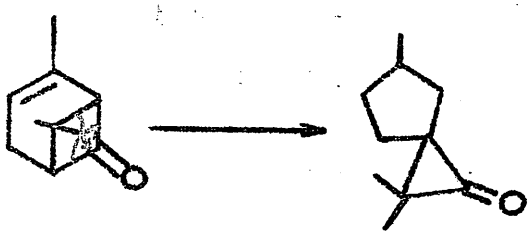

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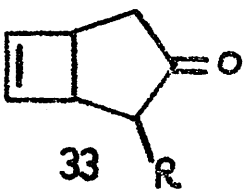

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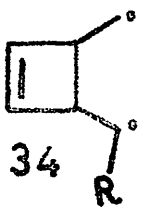

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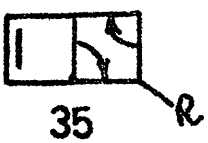

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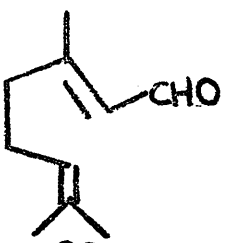

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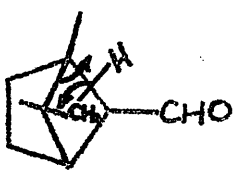

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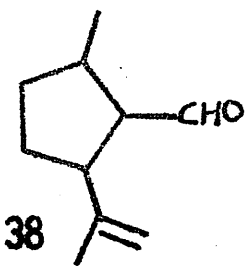

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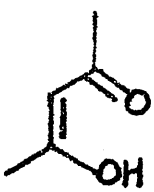

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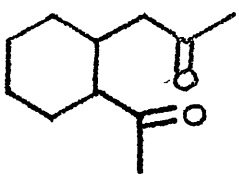

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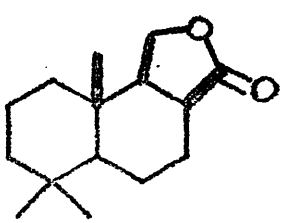

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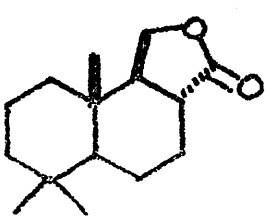

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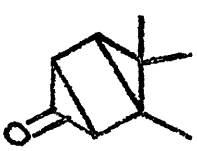

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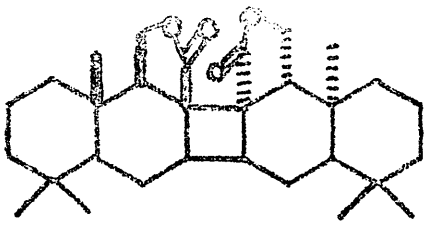

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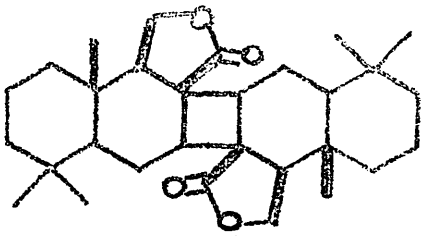

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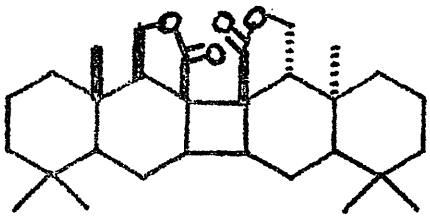

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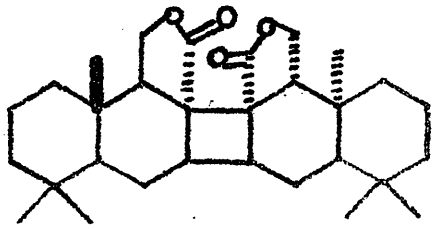

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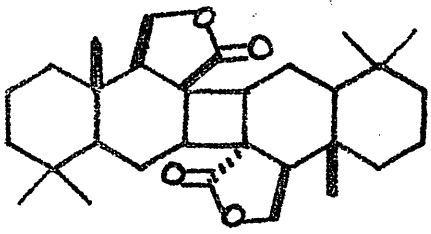

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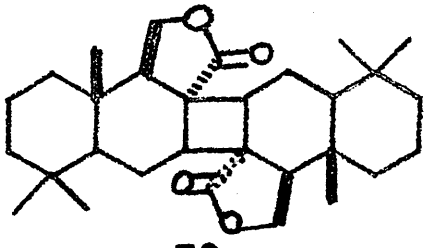

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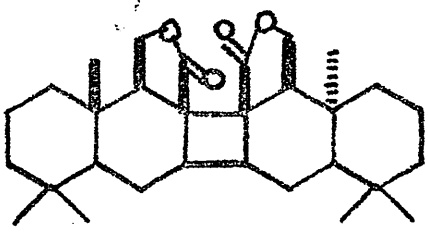

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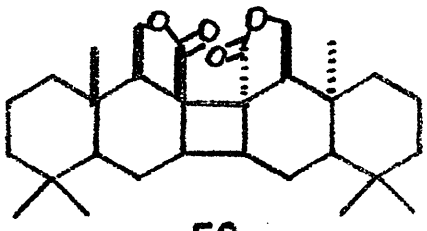

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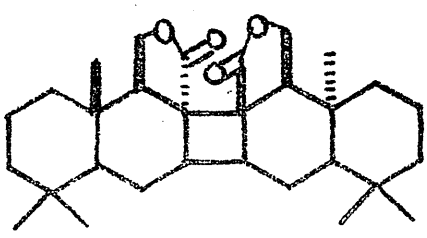

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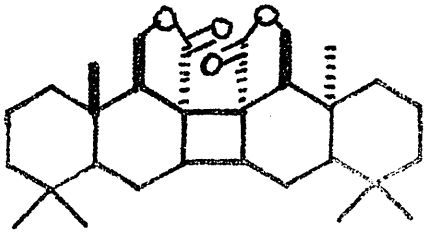

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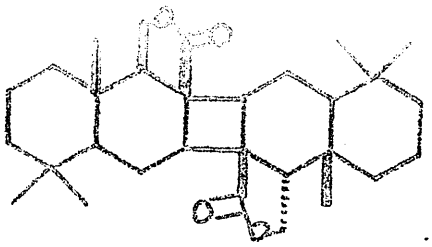

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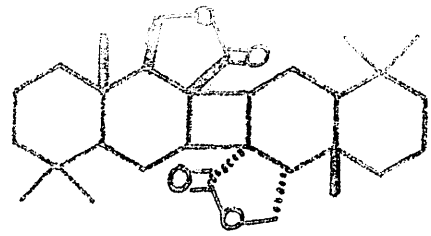

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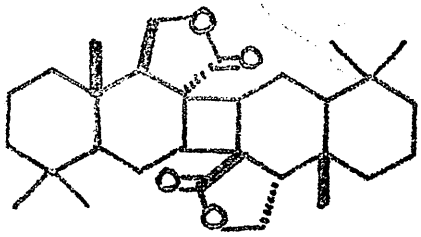

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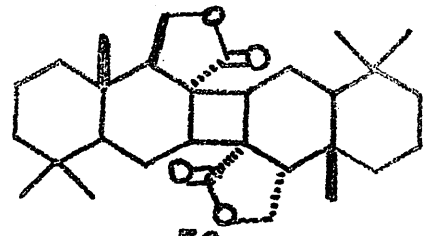

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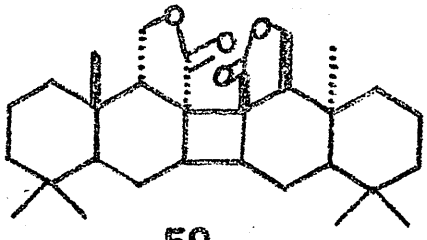

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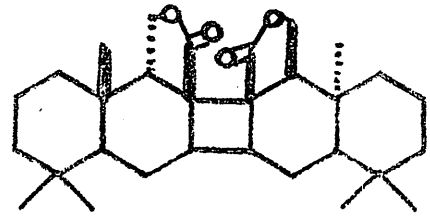

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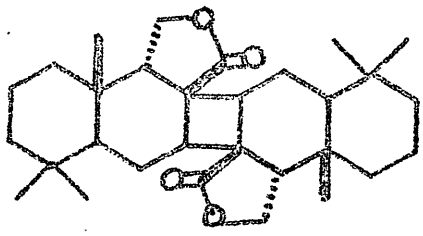

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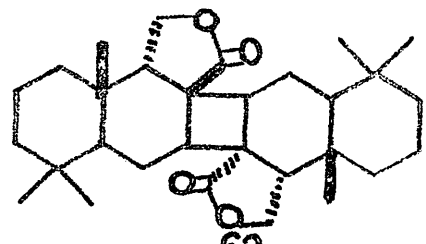

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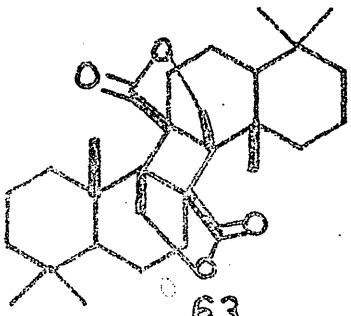

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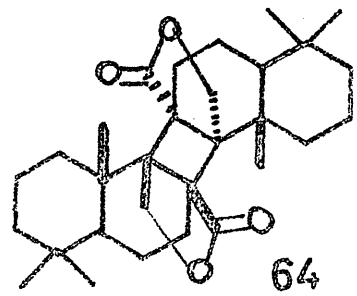

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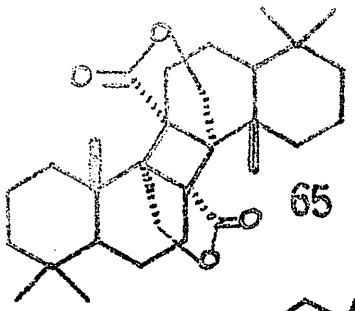

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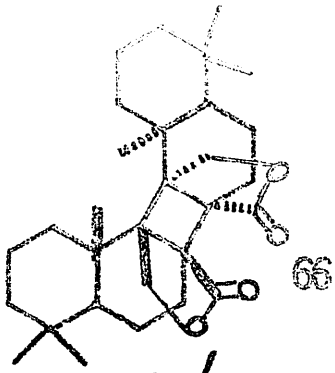

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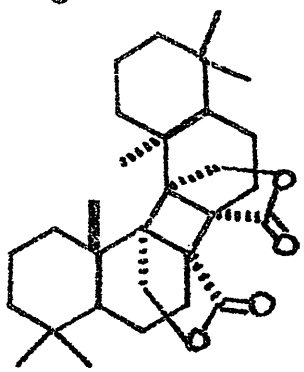

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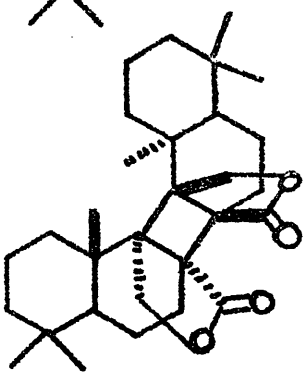

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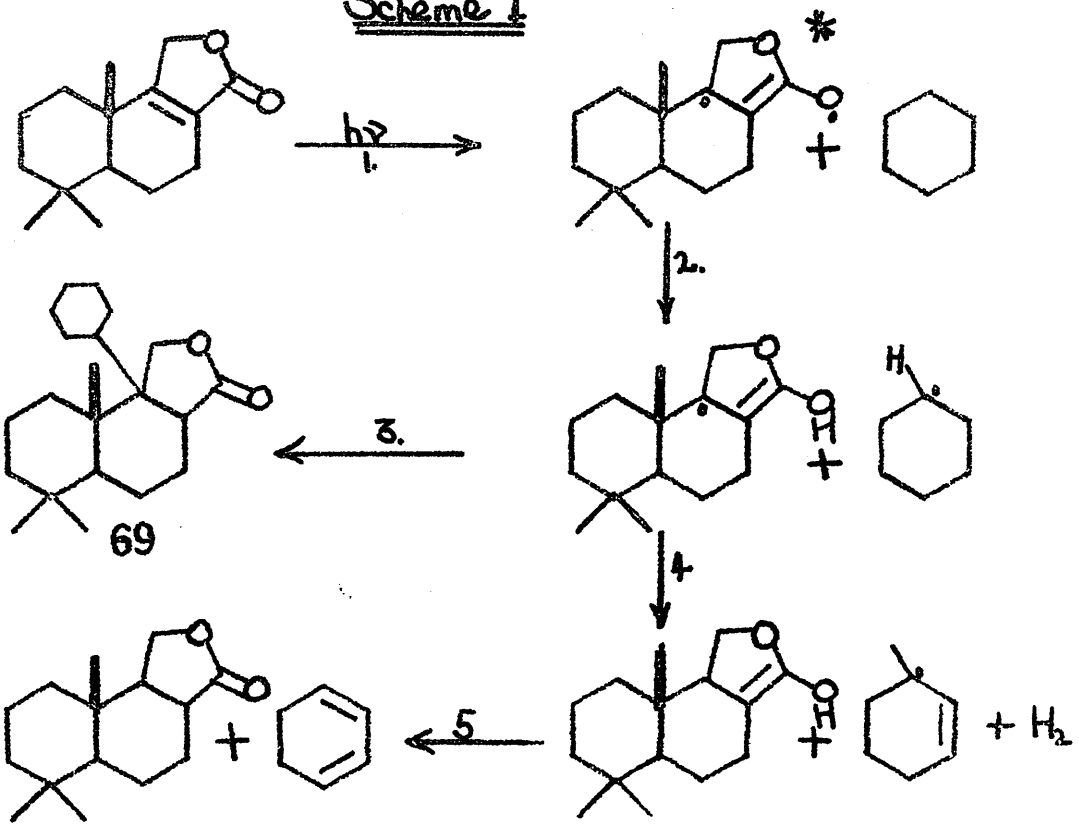
Scheme I



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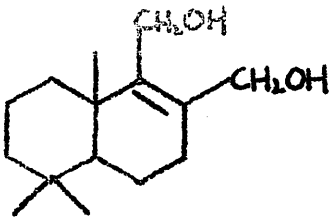

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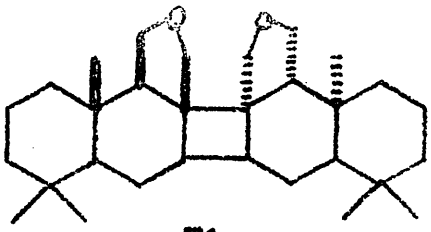

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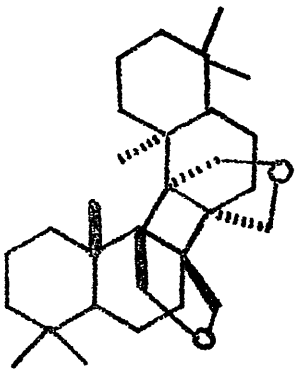

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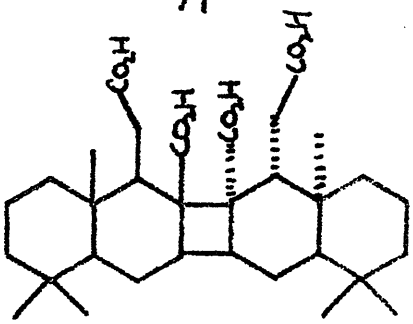

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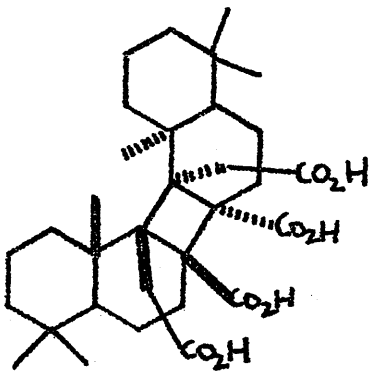

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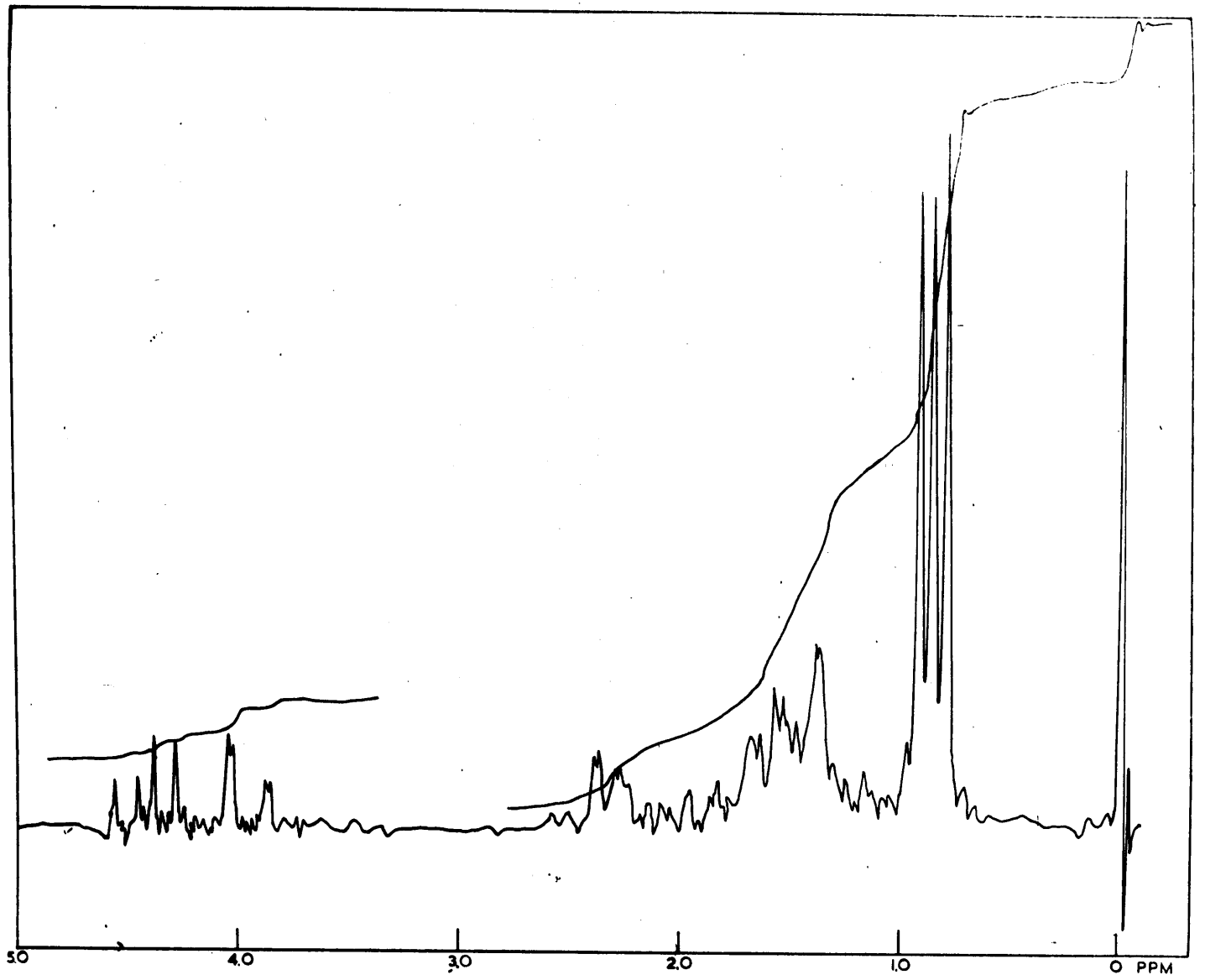


FIGURE 1

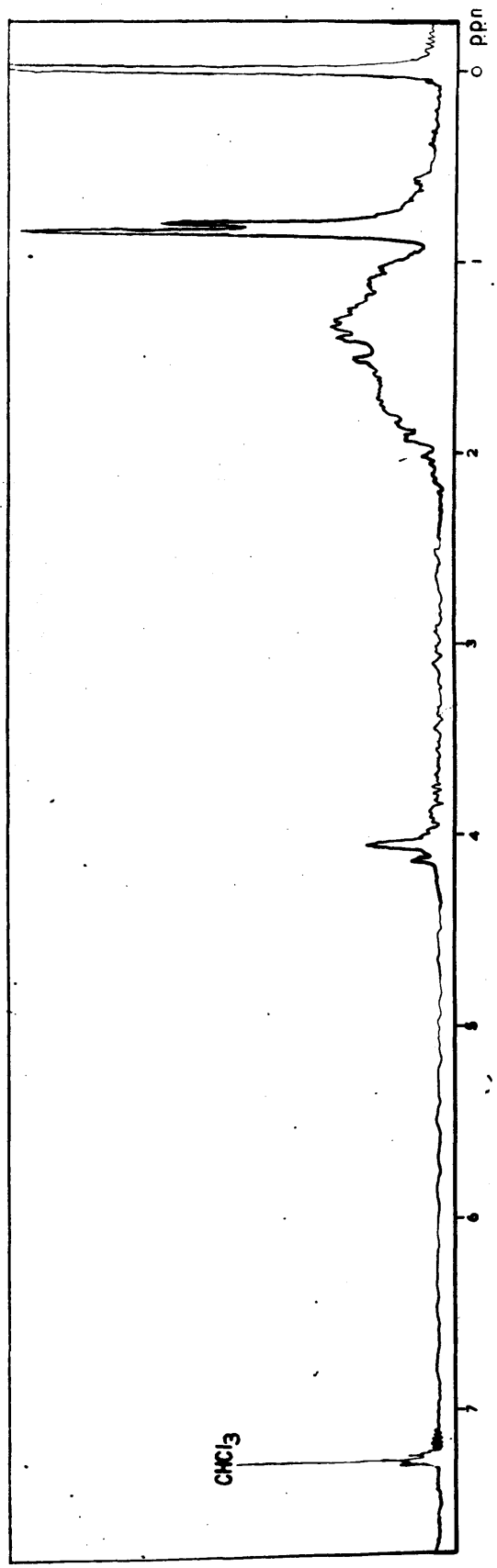
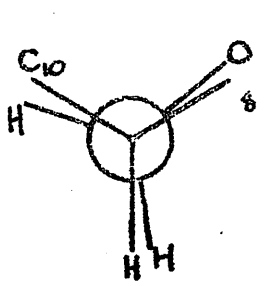


FIGURE 2



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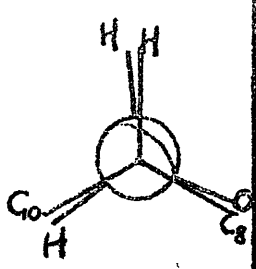

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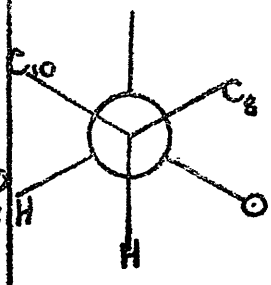

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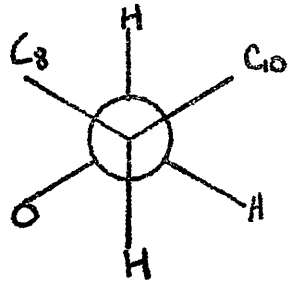

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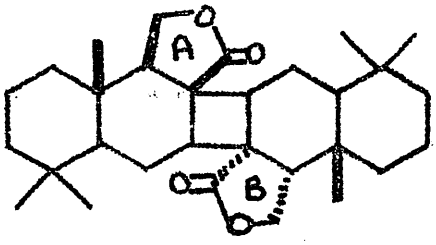

Figure 3

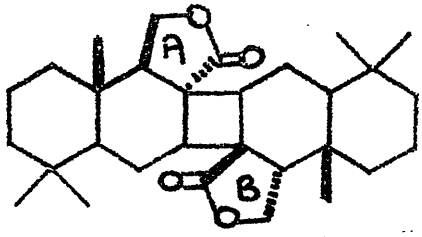

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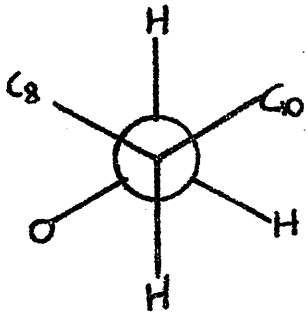
Figure 4



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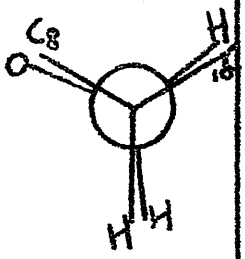

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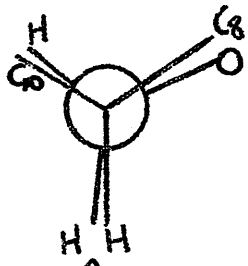

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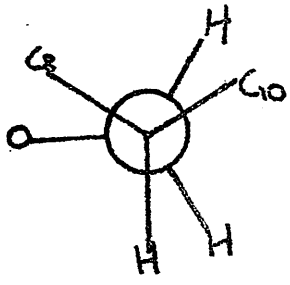

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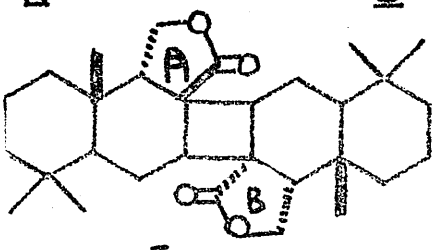

Figure 5

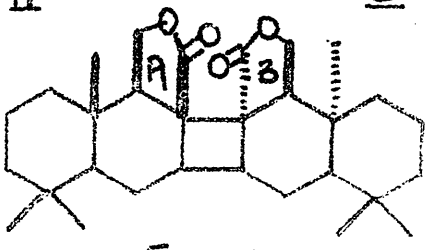

Figure 6

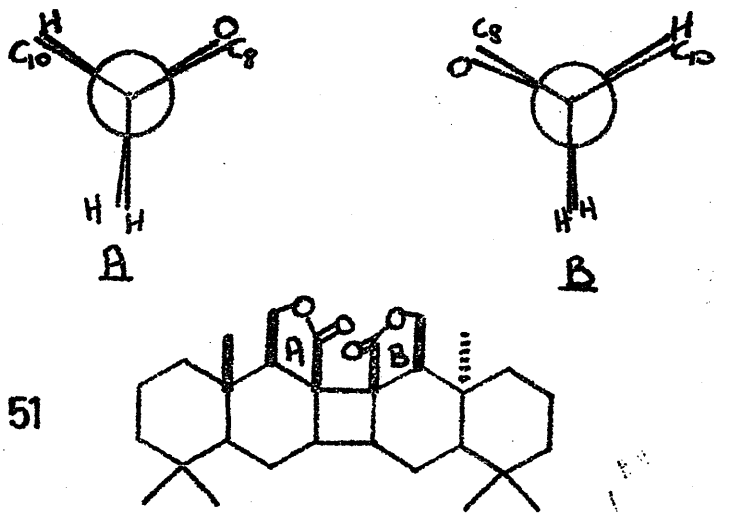

Figure 7

APPROACHES TO THE SYNTHESIS OF CONFERTIFOLIN

INTRODUCTION. This investigation was instituted as a result of certain natural disasters in Chile.

The low yield of products obtained in the photolysis of confertifolin (see page 53) meant that these investigations required a considerable investment of material. Our original stock of confertifolin was in any case small, and the events in S. America led us to fear that we would be unable to obtain further supplies for some time.

The availability of more liberal supplies of drimenol (1) led us to investigate methods of synthesising confertifolin from this compound as a possible solution to the problem. The first part of the work described in this section is, therefore, a search for a practical, high yield, synthesis of confertifolin from drimenol. Such a conversion would constitute a formal total synthesis of confertifolin[57]. When it became clear that this objective would not be accomplished, we had acquired a little experience and a considerable interest in the synthetic applications of nitrite photolyses. The latter part of this section represents, therefore, an investigation into the scope and applicability of the Barton reaction[32] as applied to a simple system such as drimenol (9, R = H), offering two alternative sites for reaction.

OBSERVATIONS ON INTRAMOLECULAR HYDROGEN ABSTRACTION REACTIONS.

Of recent years, a number of reactions, which may be classified as hydrogen abstraction reactions, have joined the older Hoffman - Loffler - Freytag reaction [23, 24, 25, 26, 27, 28] as aids to the synthetic organic chemist for the introduction of functional groups on unactivated saturated carbon atoms. The thermal decomposition of diazo ketones[29], the lead tetra-acetate induced cyclisation of alcohols[30, 31], the photolysis of nitrite esters[32, 33, 34, 35], the photolysis of hypochlorites[36], the photolysis of alkyl[37] and acyl[38] azides, and the photolysis of ketones[39, 40], have all been utilised in elegant partial syntheses of unusually functionalised natural products such as aldosterone[35] and connessine[37]. These reactions have all been shown to be critically dependent on the steric juxtaposition of the activating group and the site to be activated [25, 26, 32, 34, 39].

Given this, a mechanistic point of some interest arises from the observation that the specific intramolecular hydrogen abstraction in the reactions of nitrite esters and alkyl and acyl azides occurs only when the reaction is photochemically induced and not at all in the corresponding thermal reaction [32, 34, 38]. A reasonable explanation of the effect has been advanced by Edwards for the case of alkyl and acyl azides[38]. He suggests that the nitrene, which can be produced thermally or photolytically, undergoes, in the latter case, a transition to a triplet state which species then reacts with the appropriate C - H bond. Objection might be raised to this explanation on the grounds that Smolinsky[41] has adduced evidence for the intermediacy of triplet nitrene in the thermal decomposition of some aryl azides. In fact, Smolinsky[41] and Smith and Brown[42] have observed thermally activated intramolecular hydrogen abstraction reactions, e.g. the transformation of o - azido - cumene (26) to 3-methyl-2, 3,-dihydroindole (27) and of o-azido-phenylcyclohexane (28) to hexahydrocarbazole (29), analogous to the photochemically induced reactions of azides reported by Barton[37]. The discrepancies/

discrepancies in the results of these various authors can be rationalised if it is supposed that the magnetic currents associated with the π electron system of the aromatic ring in (26) and (28) facilitate spin orbit interaction [43, 44] in the nitrene intermediate and thus increase the probability of singlet-triplet transitions.

In support of this postulate, it may be noted that while most carbenes[45] behave in a manner to be expected of a singlet species,[47, 48] it has been suggested that diphenylcarbene exists as a triplet[46].

To explain the corresponding superiority of photochemical over thermal activation in the reactions of nitrite esters, Barton has suggested that nitrite photolyses involve an "activated" alkoxyl radical produced by O-N bond fission[34]. The nature of the "activation" is not specified but, since these reactions occur in pyrex vessels, it cannot be electronic in nature for no suitable transition is available within the permitted energy range. Vibrational activation is, of course, possible, but it is very difficult to see why a similar effect could not be produced thermally. In addition, the observation, by Mills and Petrov[58] that 6α-methyl-androstane-3β, 17β-diol-6β hypochlorite-3, 17-diacetate (30) could be rearranged to the 19-chloro-6β ol (31) with azobisisobutyronitrile in cyclohexane under nitrogen, renders the concept of an "activated" alkoxyl radical unnecessary. That an alkoxyl radical is an intermediate in these reactions is beyond dispute. The alternative reactions which have been shown to occur (C-C bond fission, disproportionation, reaction with other radicals etc. see reference 32 page 52) are typical of such species[49].

Given that the observed hydrogen abstraction reactions are sterically favoured, the known dissociation energies [49, 50] of C-H and O-H bonds suggest that abstraction of a primary H atom by an alkoxyl radical would be exothermic to the extent of about 1 - 6 Kcals. per mole. The failure of the thermal reaction must therefore be kinetic and due to the absence of the requisite activation energy (3 - 7 Kcals. per mole. for C-H bond fission[49]). Further, in the thermal reaction, the system must/

must be unable to invoke mechanisms capable of lowering this activation energy. With these considerations in mind, the following mechanism is proposed.

Orgel has attributed the absorption band of nitrites in the 400 mμ region to an $n \rightarrow \pi^*$ transition involving the lone pair electrons on the nitrogen[51]. Accepting this, the initial step in the photolysis (see scheme I) will be the promotion of a non-bonding electron into an antibonding orbital between N and O. The other O-N bond may then fission in the manner shown to reconstitute the lone pair on nitrogen. A singlet - triplet transition of the photo-excited NO entity is now envisaged to produce an energised diradical. It is likely that the triplet NO has a lifetime relatively short for such species since otherwise reaction with solvent would be anticipated[52]. Nevertheless, the existence of an intermediate in the reaction scheme with a finite lifetime satisfactorily rationalises those reactions involving alternative schemes of decay for the alkoxyl radical (vide supra)[32, 53]. The nature of the step (IV) - (V) and the influence of the triplet species requires some comment. The effect here operative is considered to be an "assistance" of C-H bond homolysis by the paramagnetic influence of the triplet NO. Such an effect is not dissimilar to that noted for paramagnetic species in cis trans isomerisation[68, 69, 70]. More immediately analogous in the present case are the catalytic effects noted for ortho substituted iodo [72] and sulphide [54] groups in the decomposition of tertiary butyl perbenzoates (35, R = I, CH_3S or C_6H_5S). The effect in (35, R = I) has been ascribed to the inhomogeneous magnetic field associated with heavy atoms[71] which catalyses singlet triplet transitions in the O-O bond. For the case of (35, R = CH_3S and C_6H_5S), the concept of "anchimeric assistance of bond homolysis" has been invoked. Evidence for such a concept from considerations of activation entropy has been presented [54].

The effect of triplet NO on the C-H bond is not anchimeric assistance but is more accurately described as second order homolytic substitution/

substitution. As written in (IV), the process is almost certainly fully concerted with transfer of the hydrogen atom to the alkoxyl radical. Thus the overall effect of the triplet NO entity (and hence the influence of irradiation) is to make available a mechanism with a low activation energy for the step:

RO H-C ROH C.

In what has come to be regarded as the normal mode of reaction, (V) will collapse to the ground state by any one of the normal mechanisms[43] to produce a hydroxy nitroso compound or equivalent (as VI).

In those reactions (*e.g.* 36 37, see reference 32 page 48) which have been reported to involve alternative modes of decay for the hydrocarbon radical[32], the intermediacy of (V) now provides an alternative explanation of their mechanism. These reactions[32] involve carbonyl groups and it would be surprising indeed if these were not themselves photoactivated. The mechanisms may then be written as in schemes II and III. Since there is good evidence for the existence of carbonyl triplets during photolyses (see section 2 for leading references) these reactions would be expected to be expecially favoured for they offer to the two triplet species a non radiative mode of collapse to the singlet state by mutual interaction.

Results and Discussion. The conversion of (1) into (2) involves, essentially, the oxidation of a methyl group attached to a double bond. An obvious difficulty is that the C_6 methylene group provides an alternative site for oxidative attack. In the beginning, our hopes rested on the possibility that the C_4 gem-dimethyl grouping would provide a steric shielding effect sufficient to permit preferential oxidation at the C_{12} methyl. We were encouraged in this hope by the examples provided by the oxidation of lupene-1 (3) to lupenal-1 (4)[7] and of (5) to (6)[8], both with selenium dioxide[4, 5, 6, 9].

Treatment of drimenol (1, R = H) with selenium dioxide in benzene and of drimenyl acetate (1, R = Ac) with selenium dioxide in acetic acid/dioxan solution produced intractable oils with discouragingly complex infrared spectra. These, together with the failure of the oils to resolve, to any marked extent, on chromatography, indicated that these reactions had not exhibited the anticipated specificity.

Although there is, to the author's knowledge, no example of tertiary butyl chromate[10, 12, 13, 14] having been used to oxidise a primary allylic position to an aldehyde, we were attracted next to this reagent by virtue of its, necessarily, considerable steric bulk. This, it was hoped, would accentuate the difference in ease of approach to positions 6 and 12 of drimenol (1) referred to above.

The product resulting from treatment of drimenyl acetate (1, R = Ac) with tertiary butyl chromate in acetic acid and acetic anhydride[12] was again a mixture of some complexity. No attempt was made to separate this mixture. Instead, it was oxidised immediately with moist alkaline silver oxide and the resulting product was separated into acid and neutral fractions. The former appeared to no longer possess unsaturated linkages (no ultraviolet absorption above 200 mμ). That the carboxyl group had not arisen from oxidation at C_{12} was demonstrated by the failure of the acidic material to lactonise on base hydrolysis and treatment of the hydrolysate with hydrochloric acid in chloroform. The ultraviolet spectrum of the neutral product would suggest/

suggest that the double bond had migrated to the $\Delta^{8,9}$ position and that C_7 had subsequently been oxidised. The production of piperitenone (33) from tertiary butyl chromate oxidation of limonene (32) provides analogy for such a shift[14]. The intensity of absorption in the ultraviolet, the complexity of the infrared spectrum and the chromatoplate evidence all clearly show that the oxidation was not straightforward.

Reaction of drimenyl acetate (1, R = Ac) with N-bromosuccinimide, a reagent frequently used to introduce bromine to positions allylic to double bonds[1], gave, as expected, a compound containing halogen. The infrared spectrum of this material ($\nu_{max.}$ 3430 (hydroxyl) 1730 (acetate) 1680 (enecne) cm^{-1} (liquid film)) suggested, however, that concomitant hydrolysis and other side reactions had occured. Mild Hydrolysis removed the halogen but the resulting material was resistant to oxidation with either manganese dioxide or Jones's reagent[59]. It seems probable, therefore, that the bromine has substituted at C_9, the energetically favoured point of attack.

Manganese dioxide is not normally used directly to functionalise allylic positions but rather to oxidise allylic alcohols to the corresponding carbonyls[2]. That it can also fulfill the former function was indicated by other work in these laboratories[15].

As judged from infrared evidence, ($\nu_{max.}$ 3500 (hydroxyl) 1730 (acetate) 1680 (enecne) cm^{-1} (liquid film)) some oxidation occurred when drimenyl acetate was shaken with manganese dioxide in petrol solution. The observed changes were considerably enhanced when the reaction was performed under an atmosphere of oxygen. The resulting oil contained starting material and two other constituents. The ultraviolet and infrared spectra of the mixture ($\nu_{max.}$ 3500 (hydroxyl) 1730 (acetate) 1680 (enecne) cm^{-1} (liquid film); $\lambda_{max.}$ 227, 248 $m\mu$ (both shoulders in the end absorption band)) suggested that the two unknown compounds might have the structures (7) and (8)[16]. That no oxidation had occurred at C_{12} was demonstrated by separation

of/

of the non-hydroxylic component of the mixture (by distillation) and treating it with silver oxide. No acidic material could be isolated. it is unlikely that a hydroxyl group could survive as such on C_{12} during treatment with manganese dioxide.

Applications of the Barton Reaction to Drimenol. Treatment of drimenol (1, R = H) with nitrosyl chloride in pyridine, using conditio similar to those described by Barton and Beaton[17] provided drimenyl nitrite (1, R = NO) as an unstable yellow oil ($\nu_{max.}$ 1650, 1600, 80 (all nitrite) cm^{-1}). It was found convenient to irradiate this material directly without further purification as attempts to purify it proved futile. Chromatography of the product resulting from irradiation of (1, R = NO) gave, as the sole crystalline product, drimenol (1, R = H). The more polar fractions from the chromatograph were combined, hydrolysed with laevulinic acid and hydrochloric acid and then treated with moist silver oxide. The stereochemical requirements of photolytic oximation (vide supra) are such that, had any oxime been produced, this reaction sequence would have converted it to a lactone. The non-appearance of such a compound indicates, therefore, that if any oxime resulted from the irradiation, it was not a major product.

Studies on the Photolysis of 8β Drimanyl Nitrite. During our experiments on the irradiation of drimenyl nitrite, the possibility of using the reduced compound, drimanol (9, R = H) as a model for further studies on nitrite photolysis was conceived. The compound was considered to be well suited to this purpose since it has two methyl groups suitably placed sterically to undergo the Barton reaction but differing in that one is attached to a tertiary site and the other to a fully substituted carbon.

8β Drimanyl nitrite (9, R = NO) ($\nu_{max.}$ 3500, 1650, 1600, 800 (last three peaks due to nitrite) cm^{-1} $\lambda_{max.}$ 233, 334, 344, 356, 370, 384 mμ) was prepared from drimanol (9, R = H) with nitrosyl chloride in pyridine. Residual traces of unchanged alcohol (3500 cm^{-1} peak in infrared) were removed by chromatography and the purified material/

material was irradiated in benzene solution. There crystallised spontaneously from the resulting oil, an oxime ($\nu_{max.}$ 3623, 3584 and very broad absorption between 3400 and 3100 cm^{-1}) subsequently shown to be 13-oximinodriman-12-ol (13). This was quantitatively converted to the corresponding acetoxy nitrile (10, R = Ac) ($\nu_{max.}$ 2230 (nitrile), 1735 (acetate), 1395 and 1365 (gem-dimethyl)) with refluxing acetic anhydride. The acetoxy nitrile was a colourless oil. Hydrolysis of this oil in aqueous potassium hydroxide afforded the hydroxy nitrile (10, R = H) in 77% yield. This, on further hydrolysis with concentrated hydrochloric acid in ethanol gave, in high yield, the imino lactone (11) ($_{max.}$ 3700 (NH) 1680 (C=N) cm^{-1}) which was smoothly converted to driman-13, 12-olide (12) ($\nu_{max.}$ 1770 cm^{-1} (γ-lactone)) on further mild hydrolysis with dilute hydrochloric acid. The lactone (12) could also be prepared quantitatively from (10, R = H or R = Ac) by hydrolysis with 50% sulphuric acid.

The structure of (12) is based on its mode of genesis, the spectroscopic properties given above and, more particularly, its nuclear magnetic resonance spectrum (figure 1). The existence of the methyl at C_{11} on a carbon also carrying hydrogen is convincingly demonstrated by the doublet centred at 9.09τ(J = 6.6 c.p.s.). The singlet at 9.07 occurs in the same range as do the methyl protons in cis and trans dihydroconfertifolin (14 and 15 respectively) and must be due to the equatorial methyl at C_4. The axial methyl at C_4 has a signal at 8.83τrepresenting a deshielding of approximately 0.3 p.p.m. from the equivalent grouping in (14) and (15). This accords well with structure (12) in which the axial methyl at C_4 is so placed relative to the carbonyl at C_{13} as to be magnetically deshielded by the anisotropy of the latter[18, 19]. The lowest peak occurring in the complex absorption between 7.5$\tau$and 8.8τin (12) has a shift of 7.8τ which is higher than the corresponding value for (14) and considerably higher than that for (15). The absence of a proton to carbonyl is therefore indicated, but the point cannot be made unequivocally since trans-space anistropic effects of the carbonyl

may lead to anomalies here also. The low field absorption of the C_{11} methylene groups centered at 5.8 takes the form of an AB spectrum with $J_{AB}/\delta_{AB} > 1$, with the C_9 proton coupling with only one C_{11} proton to form a secondary doublet (J = 2.4 c.p.s.). The AB coupling constant (J_{AB} = 5 c.p.s.) is lower than would be expected[19] and lower than the coupling constant in trans dihydroconfertifolin (15). Low values of J_{AB} have been observed for other systems [21, 22] but the explanations there offered would not be applicable to the present case.

The materials produced along with (13, R = H) in the irradiation were examined carefully by various analytical techniques in an endeavour to establish their nature. The original irradiation product was a dark brown oil and the colouration persisted through all the fractions collected on column chromatography. It could, however, be removed by vapor phase chromatography, suggesting that the colour was due to polymeric materials of high molecular weight and low volatility.

By partition of several fractions from column chromatography on a vapour phase chromatograph, the presence of drimanol in a number of them was established. The fact that drimanol is present in chromatographic fractions collected over a wide range of solvent polarity suggests that it occurs not only as such but as a derivative or derivatives capable of decomposing to drimanol on standing or on being vapourised in the vapour phase chromatograph. Those fractions similar in chromatographic polarity to (13) were refluxed in acetic anhydride and the product examined for nitrile absorption in the infrared. In one case, a small peak was observed at 2250 cm^{-1} but subsequent reactions designed to produce the lactone and chromatographic analysis of the product failed to produce evidence of dihydroconfertifolin. That the desired irradiation product is not present as the nitroso-dimer is evidenced by the absence of absorption above 250 mμ in the ultraviolet spectra of any of the chromatographic fractions, by the failure to produce the monomer thermally under the conditions of vapour phase chromatography and by the failure of refluxing with hydrochloric acid in ethanol to produce/

produce any change in a representative number of chromatographic fractions[58].

Complementary to the vapour phase chromatography studies, several attempts were made to reduce dihydroconfertifolin (14) to the hydroxy-aldehyde (16, R = O) in order that, by converting this to the oxime (16, R = NOH), we should have had available a reference compound to aid these studies. Several reagents of reported subtlety were tried. Thus, bis-3-methyl-2-butylborane [59, 60], sodium borohydride, diborane[61] and lithium aluminium hydride in triethylamine[62] were tried in turn and produced the diol (34), starting material (14) or both. In the case of lithium aluminium hydride in triethylamine a product having an infrared carbonyl band at the position expected for an aldehyde was obtained. The subsequent behaviour of this compound makes it likely that it was a mixture of cis dihydroconfertifolin and the diol (34). The infrared carbonyl absorption may have been affected by intermolecular hydrogen bonding.

These results, while not conclusive, indicate that no 11-oximino-drimanol (16, R = NOH) is formed during the photolysis of drimanyl nitrite (9, R = NO). Since, on paper, the methyl groups at C_{11} and C_{13} are sterically equivalent with respect to the nitrite function, the non-appearance of (16, R = NOH), or the equivalent nitroso-dimer, must be due either to subtle conformational effects or to an alternative mode of decay for the carbon radical (or its equivalent - see section on mechanism) at C_{11}.

That some conformational distortion should arise as a result of the 1:3 diaxial interactions between the methyl groups on C_4, C_{10} and C_8 seems likely. A similar, single, 1:3 diaxial interaction between the methyl groups on C_5 and C_9 of friedelanone (17) has been assumed to cause a conformational distortion large enough to destabilise the 4 α methyl epimer and prevent its formation during base equilibration [55, 56]. The distortions required to minimise these interactions in drimanol would produce a significant distinction in the positions of carbon atoms 11 and 13 relative to that of 12 only when their magnitude

was such as to give ring B a "boat" or at least a "skew" conformation. The invocation of such a conformation for ring B has no analogy in decalin systems not containing a carbonyl function. The complete absence of (16) would therefore be difficult to rationalise on purely conformational arguments.

The cleavage of the C-H bond at C_8 would produce an electronically favoured tertiary radical. Studies by the Schering group[32], however, have shown that steric considerations are much more important than are electronic in nitrite photolyses. However, if we invoke the intermediacy of an initially formed triplet C-nitroso entity (18, vide supra) a mode of decay alternative to physical energy loss (to give the C-nitroso compound and hence the oxime 16, R = NOH) such as indicated in (18) - (19) might be envisaged. The conformational factors referred to above can be considered to provide the driving force for this route, which, of course, is not available to the triplet C-nitroso species formed at C_{13} en route to (13). The initially produced $\Delta^{8,12}$ drimenol might survive as such or utilise the mechanistic path shown to form nor-drimene (20).

In the case of drimenyl nitrite, the most stable conformation is such as to render attack on C_{13} unlikely. Attack on C_{11} would be expected, because of the allylic character of the resulting radical (or equivalent) and of the known relative stabilities of primary and secondary radicals, to undergo subsequent rearrangement. A possible route is outlined in the formulae (22) - (24). Attack on C_1 is also sterically feasible.

The production of confertifolin from 8 drimanyl nitrite during a reaction occurring under uncontrolled conditions (unfiltered radiation, very high temperature, large temperature gradient) has not been repeated under conditions where the phenomena occurring are better understood.

EXPERIMENTAL

For general experimental proceedures see page 18 .

Attempts to Oxidise Drimenol.

Treatment of Drimenol with Selenium Dioxide in Benzene. Drimenol (1.142 gms.) and selenium dioxide (resublimed, 0.7428 gms.) were refluxed together in benzene for two hours. The solution, after cooling, was filtered and the filtrate freed of solvent under reduced pressure. There resulted a yellow mobile oil (1.5154 gms.) (ν max. 3450, 1800, 1760, 1710 and 1680 cm^{-1} (liquid film)). Chromatography of this oil on alumina (grade III) failed to produce a clean separation and the infrared spectra of the individual fractions indicated them to be complex mixtures.

Treatment of Drimenyl Acetate with Selenium Dioxide. Drimenyl acetate prepared as previously described[63], (1.095 gms.) was refluxed with selenium dioxide (0.8893 gms.) in a mixture of dioxan (100 mls.) and acetic acid (glacial, 100 mls.) for 1 hour. The solvents were then removed under reduced pressure, the residue was taken up in ether, filtered, and treated with precipitated silver to remove selenium. Removal of the ether yielded a yellow oil (1.0378 gms.) (ν max. 3400, 1730, and a complex series of shoulders from 1680 to 1550 cm^{-1}). Chromatography of this on alumina (grade V) gave, apart from drimenyl acetate (277 mgms.) eluting in carbon tetrachloride and identified by its infrared spectrum, a series of fractions with a minimum of 4 peaks in the carbonyl region of the infrared. Only material eluting in benzene in carbon tetrachloride (1:4 v/v) (90.1 mgms.) gave a simpler spectrum (ν max. 1730, 1680 cm^{-1}) but a series of shoulders between 1650 and 1550 cm^{-1} indicated that this, too was a complex mixture.

Treatment of Drimenyl Acetate with Tertiary Butyl Chromate. Drimenyl acetate (753.7 mgms.) was dissolved in carbon tetrachloride (5 mls.) and this solution was heated to reflux. A solution of acetic acid (2.25 mls.) acetic anhydride (1 ml.) and tertiary butyl chromate (7.5 mls.)/

(7.5 mls.) was added dropwise over a period of ½ hour. The reaction was stirred overnight at reflux temperature. Oxalic acid was then added in water with ice cooling and vigorous stirring. More water and carbon tetrachloride were added and the two layers separated. Emulsification provided some difficulty at this stage but the emulsion was effectively broken up by slow filtration through celite. The organic layer was worked up in the usual way and, on removal of solvent, gave a yellow oil (335 mgms.) ($\nu_{max.}$ 3430, 1800, 1730, 1690, 1680 cm^{-1}). This oil was added dropwise in ethanol solution to an alkaline suspension of silver oxide (5 mls. of 20% sodium hydroxide solution 290 mgms. silver nitrate in 5 mls. of water) and the reaction was stirred under reflux for one hour. Filtration and removal of solvents followed by partition between bicarbonate and ether gave, after normal work up, 52.6 mgms. of neutral product and 130.4 mgms. of acidic material. A chromatoplate analysis indicated that the neutral product had 4 components and the acidic material had 2. The neutral product had ($\nu_{max.}$ 3500, complex carbonyl region with peaks at 1705 and 1680 cm^{-1}; $\lambda_{max.}$ 243 mμ $\epsilon_{max.}$ 2,000) and the acidic material had (extremely broad complex OH and carbonyl regions, no ultraviolet absorption above 200 mμ). Basic hydrolysis of the acid fraction (ethanolic sodium hydroxide) followed by treatment with hydrochloric acid in chloroform failed to produce any lactonic material.

Treatment of Drimenyl Acetate with Manganese Dioxide. Drimenyl acetate (517 mgms.) and manganese dioxide (2.3 gms.) were shaken together in petrol for 48 hours. Filtration, trituration of the manganese dioxide, and removal of solvent gave a product which had two peaks of low intensity in the infrared at 3500 and 1680 cm^{-1} superimposed on the spectrum of drimenyl acetate. Treatment of the product for a further 24 hours with manganese dioxide produced little further change. The material now recovered was once more dissolved in petrol and excess manganese dioxide added. This slurry was then shaken under a small positive pressure of pure oxygen in a hydrogenation apparatus. Work up as above yielded material whose absorption in the infrared/

inflexed at 3500 and 1680 cm^{-1} was considerably enhanced. The ultraviolet spectrum had two shoulders at (in the strong end absorption) 227 and 248 mμ. Chromatoplate analysis indicated the presence of 3 major components, one of which was starting material.

Distillation under reduced pressure (10^{-3} mm. Hg.) separated the mixture into hydroxylic and non hydroxylic fractions. The non-hydroxylic fraction was treated with alkaline silver oxide in ethanol for two hours, worked up in the usual way and separated into acid and neutral portions. The neutral fraction gave semi-crystalline material (m.p. over a range to 200°C) ($\nu_{max.}$ 3600, 1680 cm^{-1}). The acid fraction was negligible.

Treatment of Drimenyl Acetate with N-Bromo-Succinimide. Drimenyl acetate (236 mgms.) was dissolved in carbon tetrachloride and placed in a quartz flask. A suspension of N-bromo-succinimide (145 mgms.) in carbon tetrachloride (8 mls.) and a trace (ca. 10 mgms.) of benzoyl peroxide were added. The mixture was irradiated with ultraviolet light for 5 minutes and then allowed to stand overnight. Filtration, to remove succinimide and N-bromo-succinimide, and removal of solvent gave a light yellow oil (226 mgms.) giving a positive Beilstein test; ($\nu_{max.}$ 3450, 1730, 1680 cm^{-1}). This oil was dissolved in dry ether and solid silver carbonate (excess) was slowly added to the stirred solution at 0°C. The slurry was briefly refluxed, cooled and filtered. Removal of solvent gave an oil still giving a positive Beilstein test. The silver carbonate treatment was repeated with a little water being added to the slurry. This afforded an oil with a negative reaction to the Beilstein test. ($\nu_{max.}$ 3400, 1730, 1680 cm^{-1}).

Treatment of this oil with manganese dioxide in chloroform (shaken for 24 hours) or with Jones's reagent[59] (chromium trioxide, sulphuric acid, acetone) at room temperature produced material whose infrared spectrum did not differ significantly from that of starting material.

Applications of the Barton Reaction to Drimenol.

Treatment/

Treatment of Drimenol with Nitrosyl Chloride.

(i) Drimenol (1.1381 gms.) was dissolved in pyridine, the solution cooled in an ice brine bath and vigorously stirred while nitrosyl chloride (prepared by the method of Morton and Wilcox[64]) was allowed to condense into the solution. After approximately 4 hours, water was carefully added to the solution followed by ether and the two layers were allowed to separate. The ether layer was washed with water, very dilute hydrochloric acid, sodium bicarbonate and water and dried over sodium sulphate. On removing solvent, drimenyl nitrite (1, R = NO) ($\nu_{max.}$ 3500, 1650, 1600 and 1550 cm^{-1}) was obtained. An attempt to purify this nitrite by distillation under reduced pressure led to severe tarring and loss of material.

(ii) Drimenyl nitrite (1.0732 gms.) ($\nu_{max.}$ 1650, 1600 and 800 cm^{-1}, negative Beilstein test) was prepared as above from drimenol (1.2052 gms.). Chromatoplate analysis indicated the presence of 5 components.

Irradiation of Drimenyl Nitrite. Drimenyl nitrite (0.5 gms.) was dissolved, without further purification, in benzene (20 mls.) and irradiated at 10°C in an atmosphere of nitrogen with a Hanovia ultra-violet lamp fitted with a pyrex filter sleeve. The irradiation was continued until the infrared spectrum (taken on aliquots removed from the reaction) showed no further changes (disappearance of the two bands at 1650 and 1600 cm^{-1}). This required ca. 19 hours. Solvent was then removed and the resulting dark brown oil chromatographed on silica gel (standardised to grade V according to the proceedure of Hernandez et al[65]). Hexane eluted an oil (194.1 mgms.) having a spot pattern on a chromatoplate identical to that of the irradiation product. Benzene in hexane (1:4 v/v) eluted crystalline drimenol (148.4 mgms.) identified by m.p. (93 - 95°C), mixed m.p. and infrared spectrum. Fractions eluted in more polar solvents to chloroform showed little variation one from another in infrared spectra. These were, accordingly, combined (127 mgms.) ($\nu_{max.}$ 3400, 1810, 1710, 1680, 1640 and 1530 cm^{-1}).

In view of the difficulty of purifying this latter oil, it was submitted/

submitted to the following reactions in order to ascertain whether or not any of its components corresponded to the desired oxime.

The oil was heated on the steam bath for 3 hours with N hydrochloric acid (1 ml.) and aqueous laevulinic acid (5 mls.). The product from this reaction, obtained by work up in the usual way, was oxidised with silver oxide (180 mgms.) on the steam bath for 2 hours. There resulted an acid (20 mgms.) and a neutral (9.0 mgms.) fraction neither of which gave any indication from their infrared spectra of containing a lactone function.

Applications of the Barton Reaction to 8β Drimanol.

Preparation of 8 β-Drimanyl Nitrite. 8 β-Drimanol (1.859 gms.) was dissolved in dry pyridine (50 mls.) and stirred in a flask cooled intermittently with drikold/acetone. Nitrosyl chloride was allowed to distil into the flask until a yellow colour persisted. Water and ether were then immediately added, the two layers separated and the ether washed with dilute (2N) hydrochloric acid (to remove most but not all of the pyridine), water and then dried over sodium sulphate. Solvent and excess pyridine were then removed at room temperature under reduced pressure. Drimanyl nitrite was thus obtained as a yellow oil ($\nu_{max.}$ 3500, 1650, 1605 and 800 cm^{-1}; $\lambda_{max.}$ 233, 334, 344, 356, 370 and 384 mμ), contaminated with drimanol. The presence of this latter was confirmed by chromatoplate analysis. The mixture was chromatographed on alumina (grade III, basic) and the material eluted in petrol (1.1827 gms.) was used for the subsequent irradiation. 8 β Drimanol (132.6 mgms.) was recovered from the column by elution with benzene.

Irradiation of 8 Drimanyl Nitrite.

(i) The nitrite ester prepared as described above (1.1827 gms.) was dissolved in benzene (400 mls.) and irradiated for 5½ hours under conditions similar to those used for drimenyl nitrite. The course of the irradiation was followed by the disappearance of the nitrite bands (1650, 1600 and 800 cm^{-1}) in the infrared. Removal of the solvent under reduced pressure gave a dark brown oil (1.3409 gms.) which began

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to crystallise on addition of petrol. The crystals were filtered off and the filtrate was chromatographed on silica gel (grade V). Further quantities of crystalline material were obtained from this eluting in ethyl acetate in benzene (1:6 v/v) (fractions 8 and 9 of chromatography), other fractions were oils and are discussed below.

The solid material thus obtained (543 mgms. crude) was recrystallised 4 times from methylene chloride/hexane and sublimed at 130 - 140°C (1.24×10^{-4} mm. Hg.). There resulted 13-oximino-driman-12-ol as prisms m.p. 134.5 - 136°C (37.5 mgms. of this m.p. from 120 mgms. crude). The compound had a double m.p., the lower being at ca. 115°C ($\nu_{max.}$ 3623, 3584 and broad absorption between 3400 and 3100 cm^{-1}); Found: C, 70.78; H, 10.59%; $C_{15}H_{27}NO_2$ requires C, 71.10; H, 10.74%.

(ii) A further sample of drimanyl nitrite (1.6678 gms.) was irradiated for 21 hours and the product chromatographed on alumina (grade V). The details of this are recorded below.

Examination of the other Products produced from Irradiation of Drimanyl Nitrite. The results of the chromatographic separations performed on the products from irradiation of drimanyl nitrite are recorded in the following tables.

[illegible] as obtained by chromatoplate analysis.

Table 1

Chromatography of the product of irradiation (i) of drimanyl nitrite.

Fraction No.	Eluent	Weight (mgms.)	No. of components*	Relevant infrared peaks (cm^{-1})
1	petrol	263.4	7	3600(w),2680(m),1770(m),1750(m), 1730(s),1630(s)
2	petrol	63	5	3600(m),2680(w),1770(w),1730(m), 1630(v.s.)
3	10% C_6H_6	23.8	6	3600(m),2680(w),1770(w),1730(m), 1700(w),1630(vs)
4	10% C_6H_6	26	4	3600(m),1770(vw),1730(w),1700(vw), 1630(s)
5	20% C_6H_6	43.4	6	3600(m),1770(vw),1730(m),1630(s)
6	75% C_6H_6	56.6	5	3600(m),1770(vw),1730(m),1630(m)
7	10% EtAc	176.4	4	3650(m),3300(m),1710(m),1680(m)
8	15% EtAc	236	cryst.	
9	15% EtAc	85.4	cryst.	
10	25% EtAc	79.1	2	
11	50% EtAc	36	2	3780(w),3680(w),3400(m),3250(m), 1710(m)
12	75% EtAc	29	2	
13	MeOH	94.5	1	3600(w),3300(m),1700(m)

*As obtained by chromatoplate analysis.

Table 2

Chromatography of the product from irradiation (ii) of drimenyl nitrite.

Fraction No.	Eluent	Weight (mgms.)	No. of components.	Relevant infrared and ultra-violet peaks (cm^{-1} and mμ)
1	CCl_4	58.9	5	3520(w),2700(s),1760(m),1710(s), 1630(m), $E^{1\%}_{1cm}$(210mμ) 70
2	CCl_4	784.0	7	3600(m),2700(w),1760(w),1730(m), 1710(m),1630(m), $E^{1\%}_{1cm}$ (210 mμ) 62.8; sh.237 $E^{1\%}_{1cm}$ 35.2
3	10% C_6H_6	96.3	1	$E^{1\%}_{1cm}$ (210 mμ) 64.8; $\lambda_{max.}$ 237mμ $E^{1\%}_{1cm}$ 51.2
4	20% C_6H_6	9.3	3	3550(m),1710(m),1630(m), $E^{1\%}_{1cm}$ (210 mμ) 93 $\lambda_{max.}$ 237 mμ $E^{1\%}_{1cm}$ 64.5
5	40% C_6H_6	13.4	3	
6	50% C_6H_6	5.9	3	
7	60% C_6H_6	16.8	3	$\lambda_{max.}$ 237 mμ $E^{1\%}_{1cm}$ 160
8	80% C_6H_6	9.6	2	
9	80% C_6H_6	29.5	2	$\lambda_{max.}$ 237 mμ $E^{1\%}_{1cm}$ 115
10	90% C_6H_6	6.2	2	3600(m),3300(m),1700(m)
11	C_6H_6	53.3	2	No high intensity U.V. above 210 m
12	20% $CHCl_3$	13.2	-	
13	$CHCl_3$	33	-	

Table 3

Vapour phase chromatography of fractions from column chromatography of the products from irradiations of drimanyl nitrite.

Fraction No.	Irradiation No.	Retention times of major peaks (minutes)
1	(i)	50.7; 19.2; 11.8
4	(i)	47.3; 19.3
5	(i)	54.4; 24; 19.1
7	(i)	18.5
2	(ii)	48.5; 21; 16.6
2	(ii)	51.2; 21.9; 17.1
3	(ii)	48.5; 20.5; 16.25; 7.5
4	(ii)	47.6; 20; 16; 7.5

These results were obtained on an analytical vapour phase chromatography unit* using a stationary phase of 10% polyethyleneglycol adipate on celite at a temperature of 166°C. Gas flow rate was 25 _ 3 mls. per minute, detector volts, 1250 with a sensitivity 10.

*Pye Argon Gas Chromatogram fitted with a strontium 90 ionisation detector.

The separations achieved by analytical vapour phase chromatography (V.P.C.) were capable of reproduction on an instrument designed to fractionate milligram quantities. Fraction 2 of irradiation (ii) was separated in this way and 3 fractions with retention times 48.5, 21, and 16.6 minutes were collected. Six runs were required to collect ca. 2 mgms. of the material having a retention time of 48.5 minutes and lesser quantities of the other components.

The ubiquitous peak of retention time 48.5 minutes on collection crystallised spontaneously and was readily identified as 8 β drimanol by m.p. and mixed m.p.

The compound of retention time 16.6 minutes collected as an oil and had no absorption in the OH or carbonyl region of the infrared.

The compound of retention time 21 minutes was also an oil and had ($\nu_{max.}$ 1752, 1728, 1707 and 3532 cm^{-1} (all very weak)).

Further Reactions performed on Fraction 7 of Irradiation (i)

Fraction 7 (176.7 mgms.), which immediately precedes 12-oximinodrimanol on elution from the column, was dehydrated by refluxing briefly with acetic anhydride. A very weak C=N peak could be detected in concentrated solutions in the infrared. Basic hydrolysis and treatment with 50% sulphuric acid (see below) produced material absorbing at 1770 cm^{-1} (weak) in the infrared but neither chromatoplate analysis nor column chromatography produced evidence of dihydroconfertifolin.

Further Reactions performed on the Fractions 10, 11 and 12 from Irradiation (i). Fractions 10, 11, 12, which appeared to be identical in composition (chromatoplates and infrared) were combined (164 mgms.) and dehydrated by refluxing with acetic anhydride. The product had ($\nu_{max.}$ 1730 and 1680 cm^{-1}) but exhibited no OH and no C = N absorption. These properties were not changed by dehydration with acetic anhydride in the presence of sodium acetate.

Acid Treatment of Fractions from Chromatography of the Irradiation Product. Aliquots of fractions 1, 3, 5, 7 and 10 of irradiation (i) and/

and fractions 1, 3, 5, 7 and 10 of irradiation (i) and fractions 2 and 11 of irradiation (ii) were refluxed for ca. 1 hour in ethanol containing 2N hydrochloric acid. The products obtained, after work up in the usual way, had infrared spectroscopic and chromatoplate mobility characteristics not distinguishable from those of the starting materials.

Dehydration of 13-Oximino-driman-12-ol. 13-Oximino-driman-12-ol (50 mgms.) was dissolved in acetic anhydride (7 mls.) and the solution refluxed for 1 hour. Excess acetic anhydride was removed under reduced pressure on the steam bath. There remained 13-cyano- drimanyl acetate (10, R = Ac) (52.3 mgms.) as a clear colourless oil ($\nu_{max.}$ 2230 (w. C ≡ N), 1735 (s. acetate) cm^{-1}).

Hydrolysis of 13-Cyano-drimanyl Acetate in Base. 13-Cyano-drimanyl acetate (18.5 mgms.) was treated with 5% aqueous potassium hydroxide, containing just enough dioxan to give a homogeneous solution, for 1 hour at reflux. After acidification, most of the solvent was removed under reduced pressure and water and ether were added. Work up of the ether solution in the usual way gave 13-cyano-driman-12-ol as needles m.p. (after 1 recrystallisation from petrol (boiling range 40 - 60°C)) 95°C (14.2 mgms.) ($\nu_{max.}$ 3620 (hydroxyl) 2220 (C ≡ N) cm^{-1}). The analytical sample had m.p. 95 - 97°C (Found: C, 76.81; H, 10.23; N, 5.85; $C_{15}H_{25}ON$ requires C, 76.54; H, 10.71; N, 5.95).

Hydrolysis of 13-Cyano-drimanyl Acetate with Sulphuric Acid. 13-Cyano-drimanyl acetate (33.8 mgms.) was dissolved in the minimum amount of absolute ethanol. To this solution, 50% aqueous sulphuric acid (10 mls.) was added and the whole solution was refluxed for 12 hours. The reaction mixture, after cooling was poured into water at 0°C. The resulting turbid solution was extracted with ether. The ethereal solution was repeatedly washed with water and, after removal of solvent, azeotroped to dryness with benzene. There resulted crystals of driman-13, 12-olide (12) m.p. after 1 recrystallisation from petrol (40/60), 93 - 95°C. (16.7 mgms.)

Neutralisation of the aqueous portion from the above extraction with/

with ostorium hydroxide and re-extraction yielded a further 16 mgms. of driman-13, 12-olide. The sample submitted for analysis had m.p. 101 - 105°C ($\nu_{max.}$ 1770 (γ-lactone) cm^{-1}) (Found: C, 76.0: H, 10.46: $C_{15}H_{24}O_2$ requires C, 76.22: H, 10.24).

Hydrolysis of 13-Cyano-drimanol with Sulphuric Acid.

(i) 13-Cyano-drimanol (4.6 mgms.) was dissolved in a small quantity (2 - 3 drops) of ethanol and 50% aqueous sulphuric acid (4 mls.) was added. This was refluxed for 10 hours and then poured onto ice and extracted with ether. Work up of the ethereal solution in the usual way gave crystals m.p. 94 - 96°C (2.8 mgms.). Basification and re-extraction of the aqueous washings gave a further 1.6 mgms. of the same material (m.p., mixed m.p.). This substance was shown, by m.p., mixed m.p. and infrared spectrum to be unchanged starting material.

(ii) 13-Cyano-drimanol (17.2 mgms.) was dissolved in a little ethanol, treated with 65% aqueous sulphuric acid and refluxed for 3½ hours. Substantial charring occurred during this time. Work up as above yielded 6.1 mgms. of semi-crystalline material exhibiting lactonic absorption at 1770 cm^{-1} in the infrared. This was chromatographed on alumina (grade III). Material eluting in benzene/petrol (1:4 v/v) was shown to be identical to driman-13, 12-olide by m.p., mixed m.p. and infrared spectrum. Unchanged 13-cyano-drimanol was similarly identified on elution with benzene in petrol (4:1 v/v).

Isomerisation of 13-Cyano-drimanol to the Imino Lactone. 13-Cyano-drimanol (18.2 mgms.) was refluxed for 15 minutes with ethanol (2.5 mls.) and concentrated hydrochloric acid (0.5 mls.). The mixture was then poured onto ice and ether and sodium bicarbonate solution were added. Standard work up of the ether layer furnished the imino lactone (14.2 mgms.) as an oil ($\nu_{max.}$ 3700 (NH), 1680 (C=N) cm^{-1}).

Hydrolysis of the Imino Lactone. The imino lactone (14.2 mgms.) was dissolved in 2N hydrochloric acid and allowed to stand at room temperature for 12 hours. Partial neutralisation and extraction into ether yielded, after work up, driman-13, 12-olide (10 mgms.) identified by m.p., mixed m.p. and infrared spectrum.

Note/

Note on some Preliminary Irradiation Experiments. In a preliminary irradiation of drimanyl nitrite, the system of cooling used was to immerse the reaction flask, which had the U.V. lamp and filter sleeve fixed within it, in a bath of acetone/drikold. The resulting temperature gradient caused the (pyrex) filter sleeve to crack and considerable charring occurred in the solution. The product from this irradiation was chromatographed and the crude crystalline oxime without further purification was submitted to dehydration, base hydrolysis and, finally, acid hydrolysis in 50% aqueous sulphuric acid, the detailed conditions being as described above. The final product from this series of reactions was chromatographed on alumina (grade III). Benzene in carbon tetrachloride (1:9 v/v) eluted driman 13, 12-olide identified in the usual way. There were obtained, on eluting with benzene in carbon tetrachloride (1:1 v/v), crystals melting at 151 - 154°C (after one recrystallisation from petrol) undepressed on admixture with authentic confertifolin and having an identical rate of travel on a chromatoplate. The intermediates in this reaction sequence were characterised only by their infrared spectra. These, however, do not differ significantly from the spectra obtained in subsequent experiments as described above. The obtention of confertifolin has not, however, been repeated.

Attempted Reduction of cis Dihydroconfertifolin.

(i) With 3-Methyl-2-butyl-borane[59, 60] 2-Methyl-2-butene (342 mgms.) and sodium borohydride (78.4 mgms.) were placed in a well stirred flask in dry redistilled tetrahydrofuran solution at 0°C and under an atmosphere of nitrogen. Boron trifluoride etherate (341 mgms.) was added in tetrahydrofuran (10 mls.) with vigorous stirring and the reaction mixture was allowed to stand for 1 hour. The flask was allowed to warm to room temperature. A solution of cis dihydroconfertifolin (41 mgms.) was then quickly run in and the total reaction mixture allowed to stand for 15 hours. Alkaline hydrogen peroxide (pH 8) was then added until a clear solution resulted. The solvents/

solvents were removed under reduced pressure and ether and water added. The ether was washed and worked up in the usual way. Chromatoplate analysis of the product (47.9 mgms.) indicated the presence of 3 components one of which corresponded to starting material. Chromatography on alumina (grade III) gave unchanged starting material (35.4 mgms.) eluted with carbon tetrachloride (identified by m.p. and mixed m.p.) and an oil showing B-H bands in the infrared. This latter was not further investigated.

(ii) With 3-Methyl-2-butyl-borane. The reagent was prepared in tetrahydrofuran as before using 714.5 mgms. of 2-methyl-2-butene, 145.2 mgms. of sodium borohydride and 791 mgms. of boron trifluoride etherate. After sitting for 2 hours in ice, it was allowed to warm to room temperature and cis dihydroconfertifolin (246.4 mgms.) was added. The reaction was left for 13 hours at room temperature followed by 2 hours refluxing. After addition of alkaline hydrogen peroxide, and then palladium charcoal to destroy excess peroxide, work up was as before. The product (270 mgms.) spontaneously crystallised. It showed only lactonic and very weak OH absorption in the infrared. Chromatoplate analysis, however, indicated the presence of 7 components. Repeated recrystallisation (from petrol) led to high recovery of starting material (181 mgms.) identified as before. The residual material revealed no significant carbonyl absorption other than saturated lactone.

(iii) With sodium borohydride. Cis dihydroconfertifolin (66 mgms.) was dissolved in a methanol/water solvent adjusted just to form a homogeneous solution. Sodium borohydride (77.9 mgms.) was added. This was allowed to stand for 2 days and then poured into dilute hydrochloric acid at 0°C. Ether extraction and work up in the usual way gave starting material quantitatively.

(iv) With Lithium Aluminium Hydride in Triethylamine. Cis dihydroconfertifolin (94.6 mgms.) in triethylamine (redistilled) was added gradually at room temperature to a stirred slurry of lithium aluminium hydride (116 mgms.) in the same solvent. After refluxing briefly,/

briefly, the solution was allowed to stand overnight at room temperature. Excess reducing agent was destroyed with ethyl acetate, water was added and the mixture was then poured into ice and hydrochloric acid. Ether extraction of the resulting aqueous suspension gave, after standard work up, a semi-crystalline oil (88 mgms.) chromatoplate analysis of which showed the presence of starting material, driman-11, 12-diol (34) and 3 components of intermediate polarity. Rough chromatography on alumina (grade V) gave an oil (47.8 mgms.) ($\nu_{max.}$ 3650, 3550, 1740 cm^{-1}) which appeared to be the desired hydroxyaldehyde, eluting in petrol. In more polar eluents, (34) was obtained and identified by m.p., mixed m.p. and infrared spectrum.

The oil was treated with hydroxylamine hydrochloride (56.6 mgms.) and 5% potassium hydroxide in aqueous ethanol (2 ml.) on the steam bath for two hours. Extraction with ether and work up in the usual way gave crystalline diol (34) identified as before (16.8 mgms.). No other material could be recovered even after acidification and re-extraction.

(v) With Diborane. Diborane, produced in a generator from boron trifluoride etherate and sodium borohydride was passed through a solution of cis dihydroconfertifolin (268 mgms.) in tetrahydrofuran for 6 hours. Work up by partition between ether and water gave a quantitative recovery of starting material.

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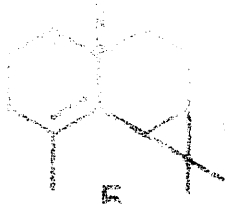

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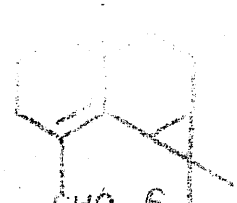

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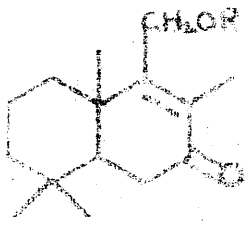

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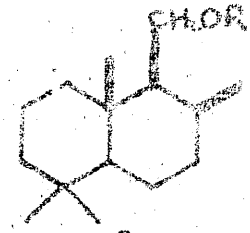

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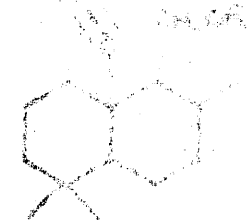

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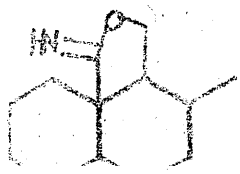

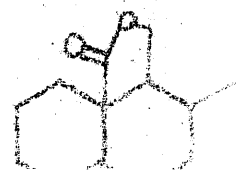

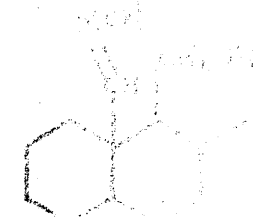

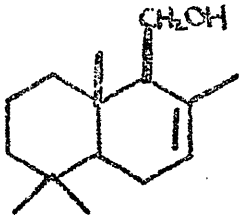

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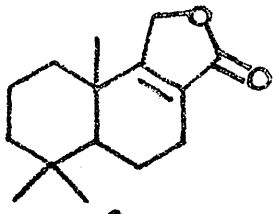

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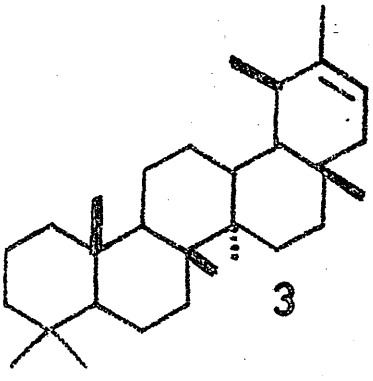

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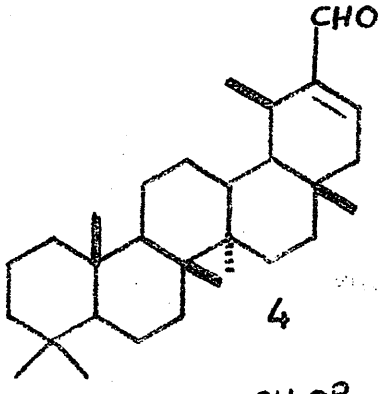

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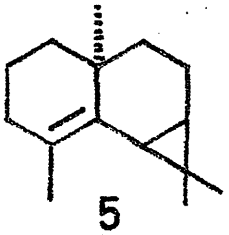

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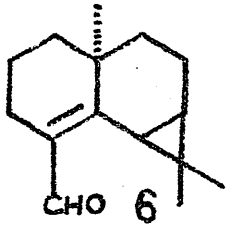

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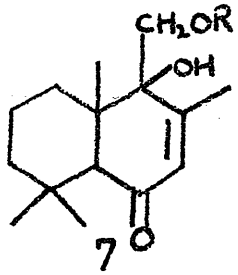

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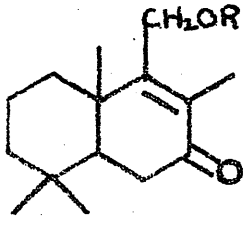

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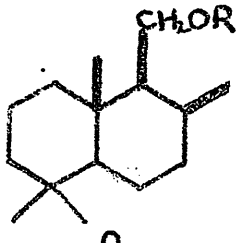

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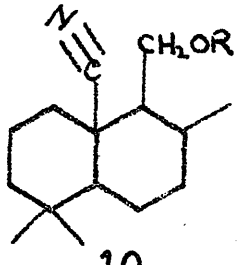

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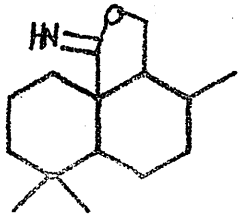

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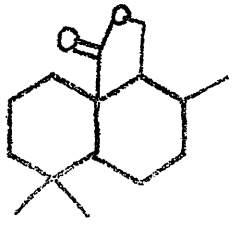

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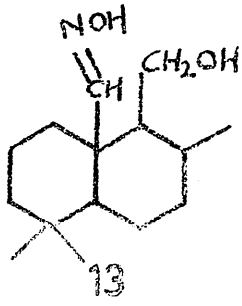

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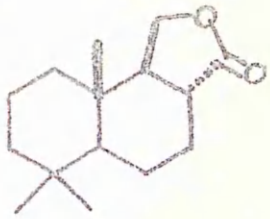

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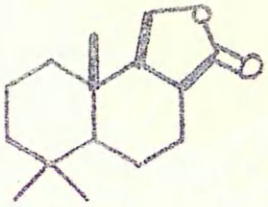

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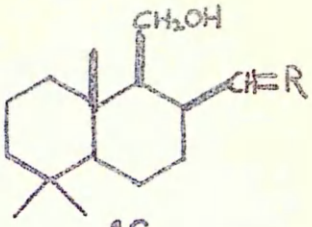

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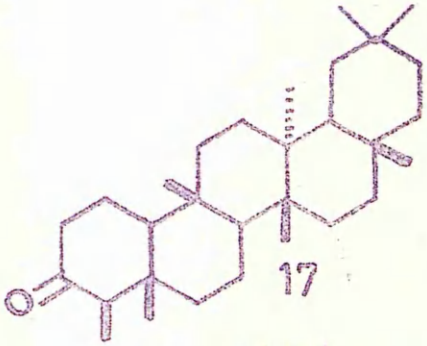

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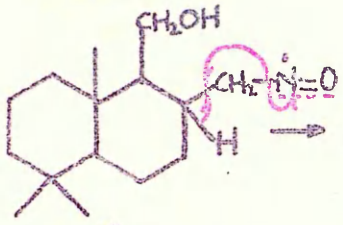

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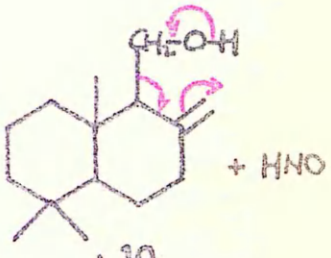

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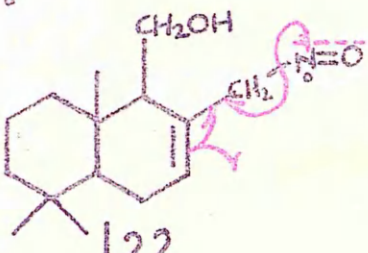

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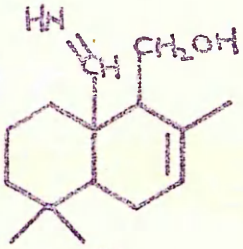

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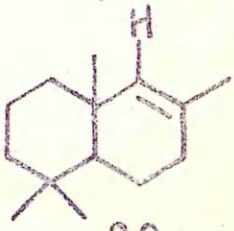

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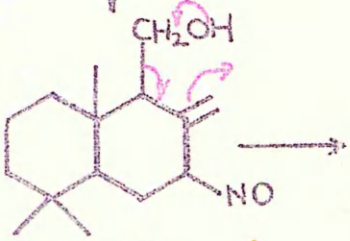

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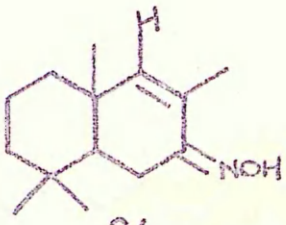

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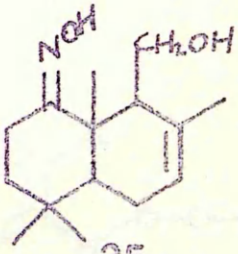

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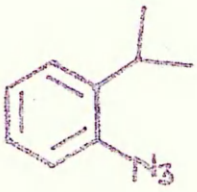

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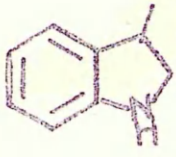

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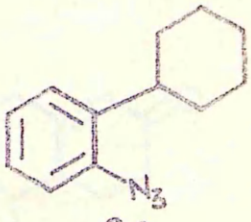

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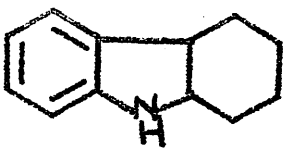

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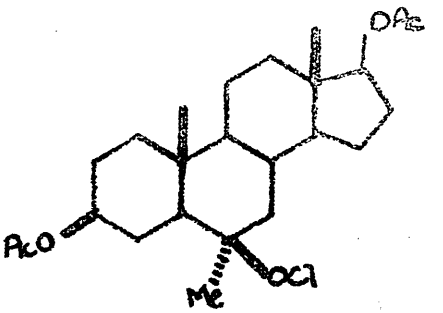

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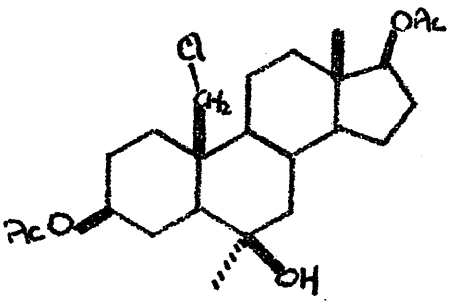

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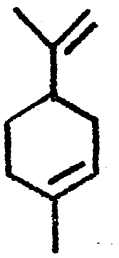

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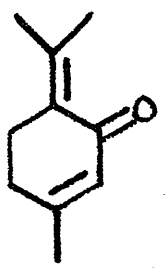

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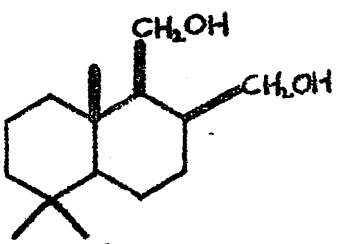

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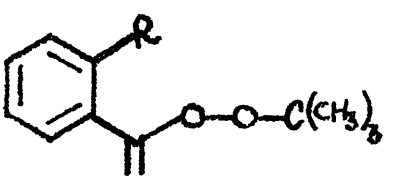

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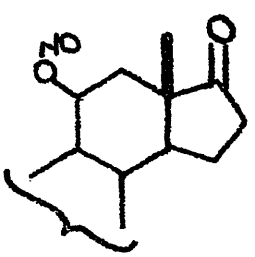

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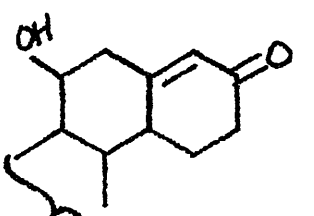

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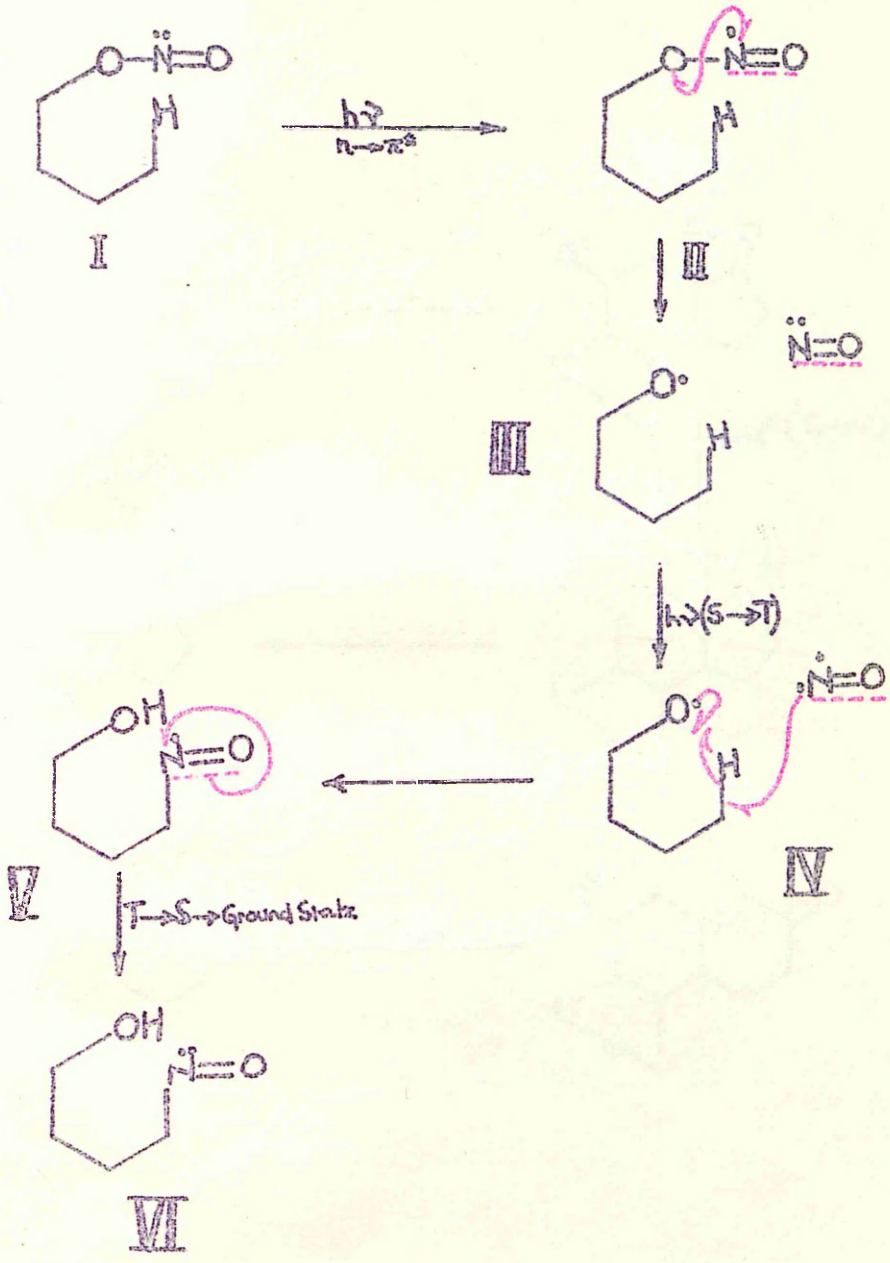
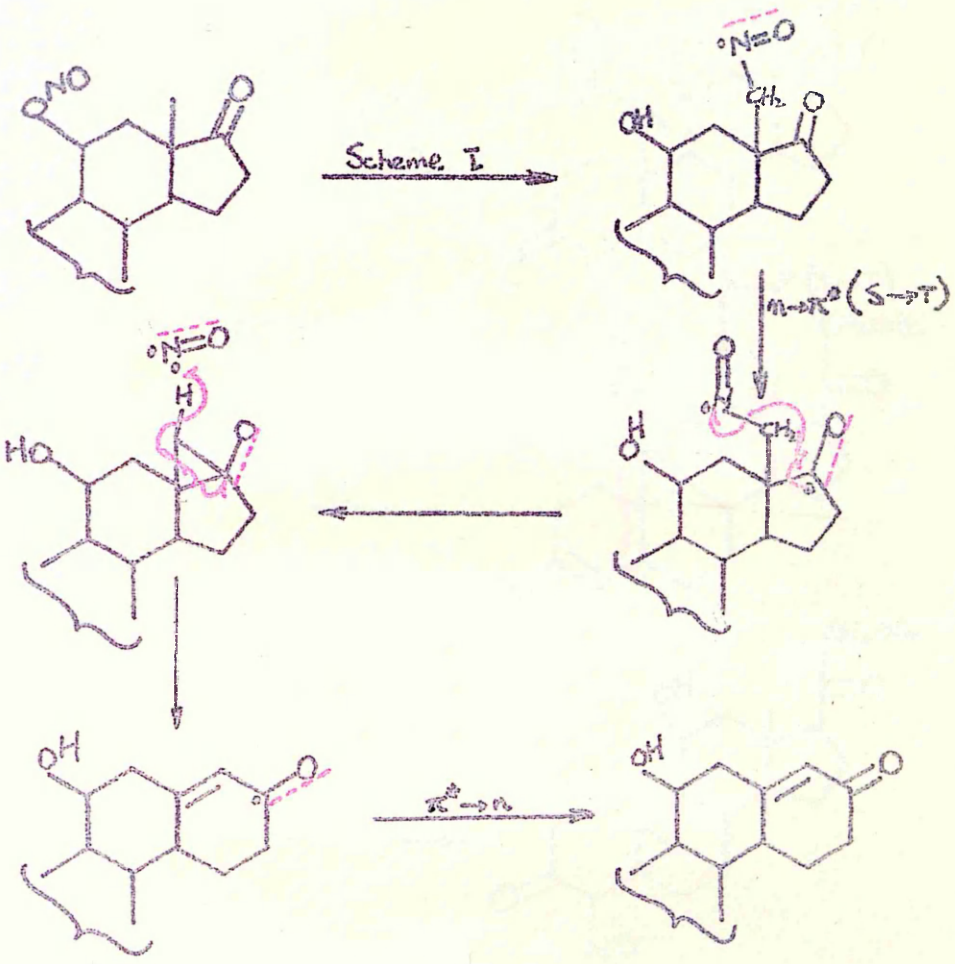
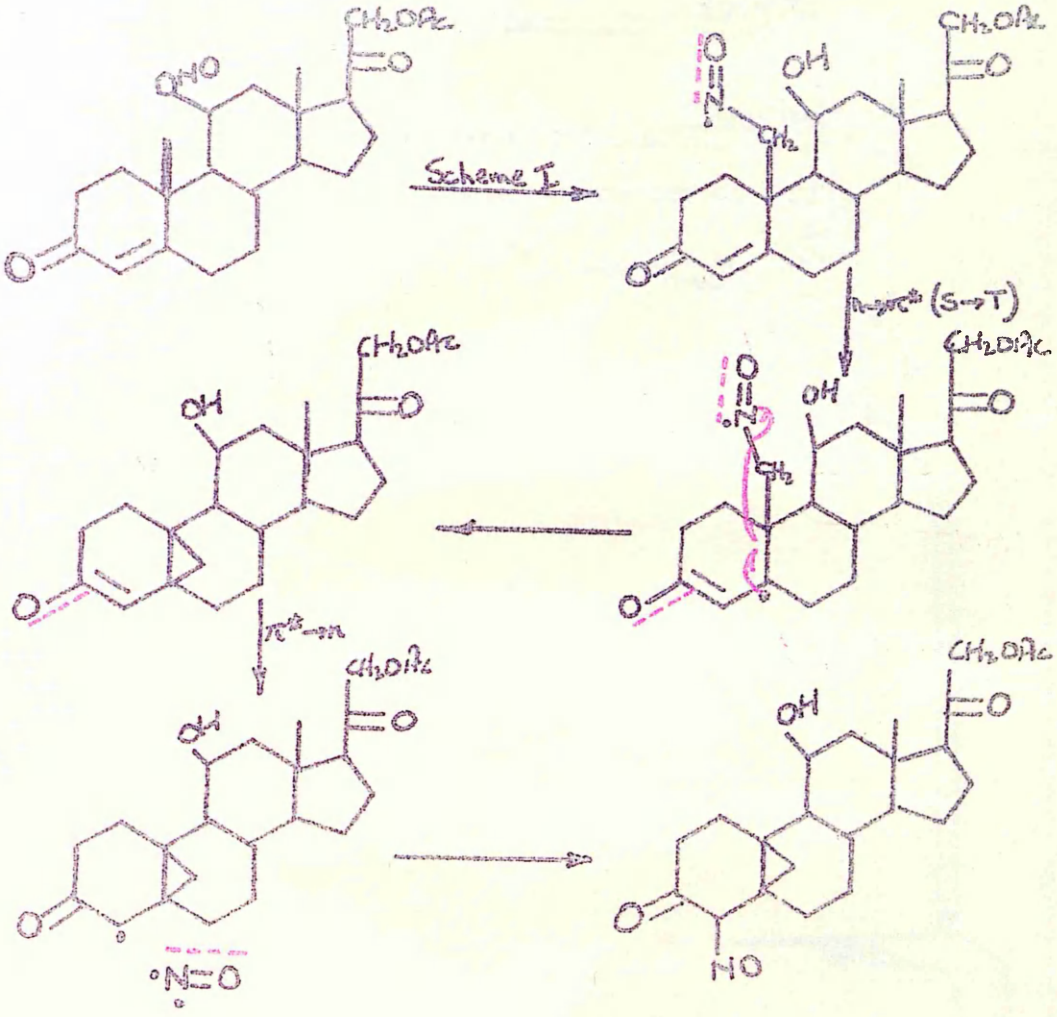
Scheme I



Scheme II



Scheme III.



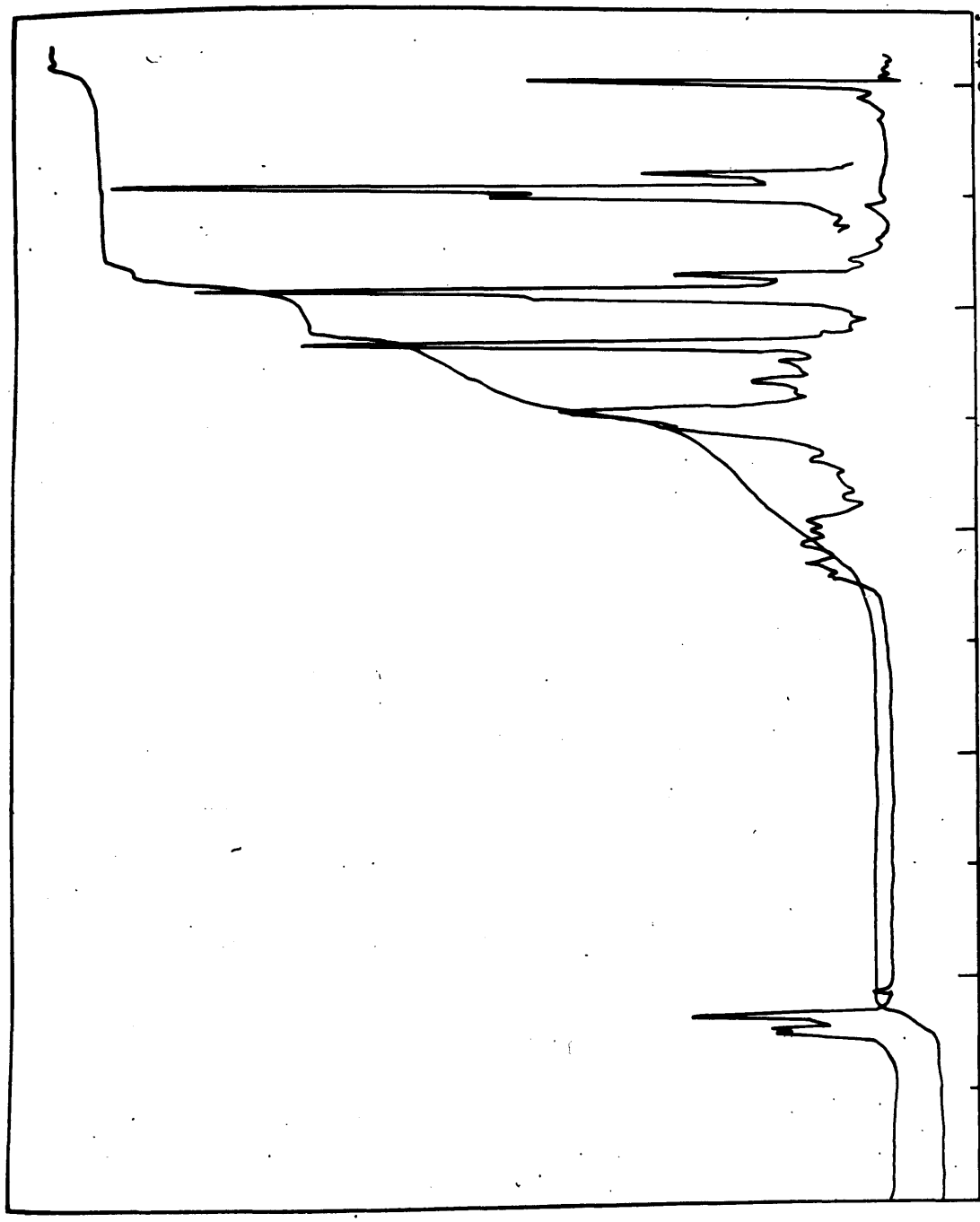


FIGURE 1

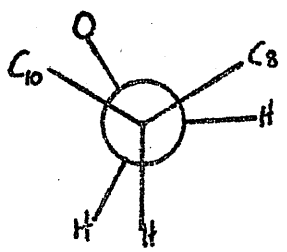


Figure 2.

(Newman Projection along $C_9 - C_{11}$ bond in 12)

UNUSUAL EFFECTS IN THE INFRARED SPECTRA OF LACTONES

INTRODUCTION The work here presented represents a continuation and extension of that of Jones and his colleagues on the twinned carbonyl absorption bands of lactones[24]. This phenomenon, attributed by Jones to Fermi resonance has been shown to display a solvent dependence in accord with this interpretation. The effect has also been shown to be, in the series studied, general though not invariable. In contrast to Jones's results it is here noted that several saturated lactones exhibit multiplet carbonyl bands. It is also suggested that the number of overtones available for Fermi-type perturbation is, in some cases, greater than one.

REVIEW

The great utility of infrared spectroscopy to organic chemistry lies in the concept of group frequencies. The common functional groups of organic molecules absorb infrared radiation at frequencies which are relatively insensitive to the nature of the rest of the molecule. Development of the method has enabled the chemist to take diagnostic advantage of such small sensitivity to molecular environment as can be detected. This is particularly well exemplified in the case of the carbonyl groups, for the application of infrared spectroscopy to the study of which, a vast literature exists[1, 2, 3].

A number of examples are known where a compound, which contains a single carbonyl group in the molecule, exhibits two or more bands in the carbonyl region of the infrared spectrum. In the majority of cases such a phenomenon is attributed to the presence of more than one absorbing species through dimerisation [4, 5], hydrogen bonding[7] or conformational equilibrium[6]. For some time, the exhibition by cyclopentanone of binate carbonyl absorption has been difficult to rationalise on the basis of these concepts.

Cyclopentanone: Since 1941[8] it has been known that cyclopentanone both as a liquid and in solution, gives rise to binate carbonyl diffusion bands in the Raman[19], the intensity maxima being at 1744 and 1727 cm^{-1}. A similar effect in the I.R. was noted by Jones in 1956[1]. Although these facts have attracted much comment and many hypotheses have been advanced to explain them, experimental data, other than mere observation of the I.R. and Raman spectra, have, until comparatively recently, been surprisingly scanty. In 1947, Gray and Taboury [10, 11], commenting on frequency differences between carbonyl bands in the I.R. and Raman, suggested that all ketones are coupled electrostatically through the carbonyl dipole and that the peculiar spectral properties of cyclopentanone are due to a similar association phenomenon involving more than 2 molecules. The idea of electrostatic antiparallel coupling of the carbonyl group has been used by a number of authors in attempting to explain/

explain the twinned carbonyl bands of cyclopentanone. Gray and Taboury revised and extended their original suggestion in 1952[12], Taboury repeated it in 1956[15] and the hypothesis was used by Baker[17] in the same year. Gray, earlier, claimed to have detected significant enolisation in cyclopentanone[13] and, accordingly, postulated a hydrogen bond between keto and enol forms. The band at 1744 cm^{-1} corresponded to free keto form and that at 1727 to the hydrogen bonded moiety. This hypothesis was, however, quickly retracted by its author[14]. The similarity between the bifurcate carbonyl bands of cyclopentanone and effects produced in the spectra of carbonyl compounds capable of conformational equilibria, (vide supra) led Josien and her collaborators[18] to suggest that cyclopentanone itself may be capable of existing in 2 interconvertible forms. They did not precisely specify the nature of the conformers.

An unusual type of hydrogen bond between the methylene group of 1 molecule and the keto group of another was suggested by Suetaka[16] in 1952 as a possible explanation of the phenomenon.

The currently held view, for which there is most experimental support, was first mooted in a thesis by Le Corff[20]. He suggested that the effect was produced by the interaction of the carbonyl band with a fortuitously positioned overtone or combination band. Such an interaction is known as a Fermi resonance[21]. This suggestion has derived considerable support from papers by Jones[22] and Meakins[23] and their collaborators. These authors have shown that the I.R. and Raman spectra of $\alpha\alpha\alpha'\alpha'$-tetradeutero cyclopentanone[22] and of octadeutero cyclopentanone[23] exhibit only one band in the carbonyl region. This they interpret as indicating that the twinning of the bands in cyclopentanone itself must arise from an internal vibrational effect. In addition, Meakins and his co-workers provide data concerning the behaviour of the bigeminate bands in various solvents which is also indicative of Fermi resonance (vide infra). It must be said, however, that the temperature variations quoted by these latter authors are

contrary/

contrary to that which would be expected from this type of perturbation.

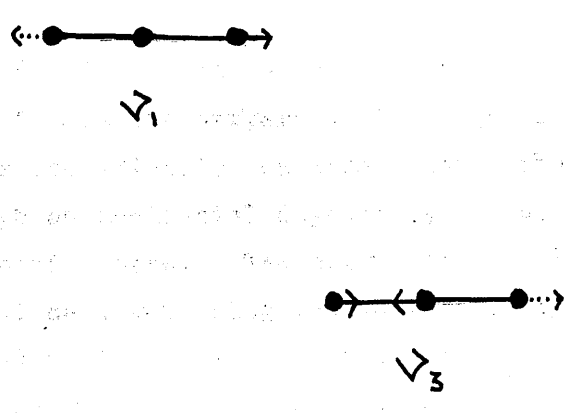
More recently, a number of other cases of double carbonyl bands [24, 25, 26] have been reported and assigned, somewhat tentatively, to

More recently, a number of other cases of double carbonyl bands [24, 25, 26] have been reported and assigned, somewhat tentatively,

ap[illegible] resonance, it is pertinent to enquire what properties can be predicted from theory for Fermi bands in I.R. and Raman spectra.

Fermi Resonance

In 1931, Fermi[21], studying the I.R. and Raman spectra of carbon dioxide, observed that, in the latter, instead of the single high intensity band due to the symmetrical vibration mode ν_1 , there was a doublet.



The frequency of the unsymmetrical mode ν_3 was known from I.R. spectrum and, using this value to obtain C-O bond force constant, Fermi then calculated an approximate value for ν_1 . Noting that this calculated value (1230 cm^{-1}) was close to the (harmonic) overtone of ν_2 ($2\nu_2$ = 1346 cm^{-1}), Fermi postulated that the two bands arose from a perturbation of ν_1 by the weak overtone of ν_2 .

The/

The eigenfunctions of the perturbed bands are linear combinations of the eigenfunctions of the unperturbed bands, weighted in such a way that the perturbation increases as the difference in frequency between the unperturbed vibrations decreases[28]. The exchange of intensity, which depends on the values of the perturbed eigenfunctions, increases as the perturbation increases.

The observable effects of such a perturbation are represented in figure (13)[28] where the energies of the perturbed bands are plotted against the separation of the unperturbed bands. As can be seen, the observed (i.e. perturbed) bands are "forced apart" relative to the theoretical unperturbed frequencies. The intensity relationships between the two bands are given by:-

$$\frac{I_2}{I_1} = \frac{\Delta + \delta}{\Delta - \delta} \quad \ldots\ldots\ldots (1)$$

where (I_2 is the intensity of the higher frequency peak

(I_1 is the intensity of the lower frequency peak

(Δ is the difference in frequency between the perturbed bands

(δ is the difference in frequency between the unperturbed bands.

We are specifically concerned with carbonyl frequencies perturbed, through an accidental degeneracy of the Fermi type, by an overtone or combination band. The origin of the latter will not be known in the general case but using the analogy of cyclopentanone, it will be assumed that it arises from C-H deformation vibrations.

The frequency of absorption of a carbonyl group, measured in solution, decreases as the polarity of the solvent increases [27, 29, 30, 31, 32, 33, 34]. In contrast, the nature of the solvent affects the C-H deformation frequencies but little. We must make the additional assumption also that solvent effects will not markedly influence the anharmonicity of the overtone.

It is now possible to examine what behaviour (of Fermi bands) under varying solvent conditions would be predicted from the above considerations

Fig./

Fig. (14a) shows an intense carbonyl band in a non-polar solvent or in the gas phase with, at a lower frequency, a very weak overtone or combination band. At this stage, they are uncoupled. Fig. (14b) represents the same compound measured in a more polar solvent. The carbonyl has shifted to lower frequencies and into the "range" of the overtone band so that perturbation has begun. The red dotted lines represent the theoretical positions of the unperturbed bands. As solvent polarity is further increased, the carbonyl band moves to still lower frequency and in fig. (14c) its frequency is coincident with that of the overtone band. Perturbation is here at a maximum and the carbonyl "donates" 50% of its intensity to the other band. As the carbonyl moves to yet lower frequencies, the perturbation passes through the stage of (14d), until finally it once again moves "out of range" of the perturbing overtone and the situation shown in (14e) then pertains. It will be noted that if the frequency of the overtone is to remain unchanged, the movement of the theoretical unperturbed carbonyl band must be followed in the perturbed bands not only by intensity variations, but also by a slight frequency shift.

Figure (15) shows how the relative positions of the bands in figs. 14(a) - (e) would appear superimposed on fig. (13).

In theory, temperature changes should not affect Fermi resonance phenomena. The effect which such changes do in fact have can be attributed to the influence of temperature on solvent polarity. Increase in temperature, by increasing the rate of orientational change of solvent dipoles, will reduce the effective polarity of a solvent and hence will raise the carbonyl frequency[24]. Decreasing the temperature increases the importance of solute-solvent-complexes[7, 33, 34], tends to "freeze" solvent cages about solute molecules and hence increases the apparent polarity. Exceptions to this latter are, however, known[33].

In practice, the solvents available for I.R. spectroscopy do not have a sufficiently wide range of polarity for the observation of the full sequence of events depicted in fig. 2.

A further method of varying the carbonyl frequency, and which is closely/

closely related to simple solvent effects, is to add a second compound, which will specifically complex to the carbonyl group, to the solution of carbonyl compound. Alcohols and phenols are most frequently used for this purpose [7, 33, 34] and they complex by means of a hydrogen bond. Although little experimental information is available, it would seem probable a priori that such complexing agents would exert observable effects on C-H deformation frequencies and, more particularly, on the anharmonicity terms of the overtones of such frequencies.

An alternative approach to the problem of varying carbonyl frequencies in Fermi resonance studies, and one which demonstrates the effect of structural variations on such phenomena, has been made by Rao [27]. To observe variations in a perturbation of the carbonyl region of benzoyl chloride, he substituted various electron donating and electron withdrawing substituents into the ring. These, of course, alter the carbonyl frequency in so far as they alter the nature of the C - O dipole. Unfortunately, the change in electronic character of the molecule inevitably influences also the vibration which gives rise to the perturbing overtone. Simple arguments such as have been used above are not, therefore, applicable without modification.

The Distinguishing Features of Fermi Resonance.

The occurrence of bifurcate carbonyl bands in the infrared spectra of compounds containing a single carbonyl function (as distinct from the twinning which occurs in (e.g. anhydrides) is likely to be caused by conformational equilibria, dipole coupling, hot transitions, Fermi resonance or solvent solute complexing. Such explanations, as intermolecular hydrogen bonding through enolic forms [13] and intramolecular hydrogen bonding to methylene groups [16] are, for normal carbonyl compounds, at variance with normal experience.

Dipole coupling and solvent solute complexing are readily distinguishable by their concentration dependence. Similarly, hot transitions would be identifiable by a marked temperature dependence[23].

Generally, doublet carbonyl bands arising from a conformational equilibrium would not be expected to show precisely the properties described/

described above for Fermi bands. It is possible to conceive, however, of a fortuitous energy relationship between conformers which would produce effects similar to those to be expected for Fermi bands. The degree of coincidence required for this to occur would, however, be very large. In any event, conformational equilibrium ought to produce twinned peaks in regions of the spectrum other than the carbonyl.

RESULTS AND DISCUSSION

The results obtained are displayed in figures 1 - 12 and are summarised in tables 1 - 4. These tables show the $\nu_{max.}$ values and the molecular extinction coefficients of the relevant peaks relative to each other ($\frac{\epsilon_1}{\epsilon_2}$). This parameter is, of course, an approximation to the values ($\frac{I_1}{I_2}$) of the relative intensities and it ignores band width effects. However, as we shall see sequentially, ($\frac{\epsilon_1}{\epsilon_2}$) is adequate for our purposes. The value $\frac{\Delta\text{solvent}_1}{\Delta\text{solvent}_2}$ represents the quotient of the frequency differences between the perturbed bands in two solvents. From what has been said in the review section, it will be seen that this should have the value unity.

Drimenin (fig. 4), confertifolin (fig. 5B) and cis dihydro-confertifolin (fig. 5C) exhibit single carbonyl bands (at 1771, 1749, 1772 cm^{-1} in $CHCl_3$ and 1781, 1769, 1781 cm^{-1} in CCl_4 respectively) although that of confertifolin is very broad and may envelope perturbations which have not been resolved.

Isodrimenin (fig. 8A, B and C) shows bigeminal carbonyl absorption in chloroform (1750, 1740 cm^{-1}), but the peak in carbon tetrachloride (1766 cm^{-1}) is symmetrical and a singlet. Conversely, dihydro campholenolactone (fig. 7B) has twin peaks in carbon tetrachloride (1783, 1774 cm^{-1}) but only a broad and somewhat unsymmetrical singlet in chloroform (1756 cm^{-1}).

The remaining lactones studies are listed in table 1. From theory, it would be expected that ($\frac{\epsilon_1}{\epsilon_2}$) would have a higher value in the less polar solvent (where subscript 1 refers to the higher frequency peak). This, indeed, is the invariably observed order. These data would not, of themselves, distinguish Fermi resonance from a conformational equilibrium but in the compounds studied, where the latter explanation is not obviously applicable, they strongly favour the former interpretation. Taken together with the observed values, discussed below, they provide very strong evidence for the operation of an internal vibrational effect.

In/

In a few cases, the term $\frac{\Delta \text{Solvent 1}}{\Delta \text{Solvent 2}}$ departs markedly from unity. This is probably due to the measurements involved having been taken on the fringe of or over too wide a range of the perturbation effect (see fig. 13), in which case, Δ is not expected to be constant.

That Δ does, indeed, remain approximately constant when the solvent polarity changes are more subtle is shown by the impressive agreement of the $\frac{\Delta \text{Solvent 1}}{\Delta \text{Solvent 2}}$ values for dihydrodrimenin (table 4) with theory. In this case, the perturbation is clearly at a maximum in chloroform since the twinned peaks have almost equal intensity in that solvent and hence most of the measurements have been taken over a favourable range. As can readily be seen from the $\frac{\epsilon_1}{\epsilon_2}$ values, all the intensity changes are in the anticipated sense. Consideration of the spectra of dihydrodrimenin (fig. 3) and in particular of fig. 3A, B and E makes it clear that without high resolution and an adventitious solvent, the perturbation effect can easily escape detection.

A detailed consideration of figures 1, 3 and 6 reveals that for coumarin, dihydrodrimenin and β-angelica lactone, more than two peaks "rise and fall" over the measured solvent ranges. Thus, for angelica lactone, there are peaks at* 1800, 1790, 1760 and 1710 cm^{-1} for coumarin at 1765, 1755, 1740, 1730 and 1710 cm^{-1} and for dihydrodrimenin at 1797, 1785, 1778 and 1763. Thus there appear to be, respectively, 4, 5 and 4 overtone bands suitable, both as to position and symmetry, for Fermi-type perturbation with the carbonyl fundamental. This observation makes the hitherto surprising [36] generality of this phenomena in lactones more readily understandable. At the same time, it indicates that an empirical search for the structural feature(s) giving rise to the necessary overtone or combination bands utilised in Fermi resonance is likely to prove unfruitful since, apparently, these are more readily available than was previously thought and can presumably/

*The figures change by 2 - 3 cm^{-1} from solvent to solvent and approximate values are given.

presumably arise from a variety of structural features.

The data presented in figure 2 and table 3 cannot be interpreted in detail with the information currently to hand. Clearly in this case, by using phenols as complexing agents to vary the frequency of the carbonyl fundamental, there is now more than one molecular species involved. There is being observed, not only Fermi resonance phenomena but spectra arising from uncomplexed molecules, 1:1 complexes and higher complexes and the attendant multiplicity of absorption peaks will become comprehensible only when detailed information of concentration dependence becomes available. It can be said, however, that the close correspondence of Δless polar / Δmore polar to unity is probably real and not fortuitous because, regardless of the nature of the absorbing species, the perturbation effects will predetermine the position of the peaks.

Although these observations on lactones are based solely on solvent dependence, the nature of this latter, together with the available analogies[23, 24, 27] makes the explanation of these multiplet bands in terms of Fermi resonance plausible.

It now seems clear that this is a much more general phenomenon than was previously thought and it is confidently predicted that as instruments of high resolving power become more readily available, many more examples may be brought to light.

EXPERIMENTAL

Materials. Coumarin (1), angelica lactone (9) and γ- butyrolactone (8) were obtained commercially and purified by distillation (8 and 9) and crystallisation (1). Campholenolactone (11) and dihydrocampholenolactone (10) were prepared in these laboratories by Dr. J. D. Connolly[37]. Their purity has been checked by vapour phase chromatography. The sesquiterpene lactones (2, 3, 4, 5, 6 and 7)[38] used were all of analytical purity. Compounds (12) and (13) were supplied by the courtesy of Professor W. S. Johnson (Stanford University)[39].

Commercial samples of p-nitro-phenol, p-methoxy-phenol, p-cresol and 2:6-dimethoxy-phenol were used and purified by recrystallisation with the exception of the strongly deliquescent p-cresol which was purified by sublimation. Carbon tetrachloride, carbon disulphide, methyl iodide and n-hexane (all AnalaR) were used without purification. Chloroform (AnalaR) was freed from ethanol by two successive passages through blue silica gel immediately prior to use. Acetonitrile was purified by successive prolonged treatments with potassium hydroxide, calcium chloride and phosphorus pentoxide followed by distillation.

Measurements. Spectra were recorded linearly in cm^{-1} as percentage transmission with a Unicam S.P. 100 double beam infrared spectrometer equipped with an S.P. 130 sodium chloride prism-grating double monochrometer (1500 lines per inch (650 - 2000 cm^{-1})) operated under dry air conditions. The cell well temperature was 29 _ 3°C. The wave number scale was calibrated against methane, water vapor, carbon dioxide and ammonia. The calibration was checked before and after each group of measurements with a solution of acetone in carbon tetrachloride (band at 1719 cm^{-1}). Measurements are believed accurate to ± 1 cm^{-1}. The theoretical spectral slit width, calculated from tables supplied by Messrs. Unicam Instruments Ltd. was ca. 4.5 cm^{-1} at 1650 cm^{-1}, 5.2 cm^{-1} at 1750 cm^{-1} and 4 cm^{-1} at 650 cm^{-1}. Carbonyl bands were scanned at 18 cm^{-1} per minute for carbon tetrachloride, carbon disulphide and chloroform solutions and at 12 cm^{-1} for n-hexane and acetonitrile solutions.

KEY TO FIGURES

Figure 1.

A Coumarin (1) in CH_3CN (——), in $CHCl_3$ (— · —) and in CH_3I (- - - -)

B Coumarin (1) in $CHCl_3$ (— · —) and in CCl_4 (——).

C Coumarin (1) in CCl_4 (——), in hexane (— · —) and in CS_2 (- - - -).

Figure 2.

A Coumarin (1) (0.1M) in CCl_4 (——) and in 0.0375M p-nitro-phenol in $CHCl_3$: CCl_4 (1:1 v/v) (- - - -).

B Coumarin (1) (0.1M) in 2:6-dimethoxy-phenol (0.2M) in CCl_4 (——) and in p-nitro-phenol (0.0375M) in $CHCl_3$: CCl_4 (1:1 v/v) (- - - -).

C Coumarin (1) (0.1M) in p-cresol (0.01M) in CCl_4 (——), in p-cresol (M) in CCl_4 (— · —) and in CCl_4 (- - - -).

Figure 3.

A Dihydrodrimenin (2) (0.01M) in hexane.

B " " in chloroform: hexane (1:99 v/v).

C " " in chloroform: hexane (1:19 v/v).

D " " in chloroform: hexane (1:9 v/v).

E " " in chloroform: hexane (1:4 v/v).

F " " in chloroform: hexane (1:1 v/v).

G " " in chloroform.

Figure 4.

A Isodrimenin (4) (0.01M) in $CHCl_3$ (——), dihydrodrimenin (0.01M) in $CHCl_3$ (— · —) and drimenin (0.01M) in $CHCl_3$ (- - - -).

B Isodrimenin (4) (0.01M) in CCl_4 (——), dihydrodrimenin (0.01M) in CCl_4 (— · —) and drimenin (0.01M) in CCl_4 (- - - -).

Figure 5./

Figure 5.

A Trans dihydroconfertifolin (7) (0.01M) in $CHCl_3$ (——) and in CCl_4 (- - -).

B Confertifolin (5) (0.01M) in $CHCl_3$ (——) and in CCl_4 (- - -).

C Cis dihydroconfertifolin (6) (0.01M) in $CHCl_3$ (——) and in CCl_4 (- - -).

Figure 6.

A β-Angelica lactone (9) (0.01M) in $CHCl_3$ (——) and in CH_3CN (— - —).

B β-Angelica lactone (9) (0.01M) in $CHCl_3$ (——) and in CCl_4 (- - -).

C β-Angelica lactone (9) (0.01M) in CCl_4 (- - -), CS_2 (——) and in hexane (- - -).

Figure 7.

A Campholenolactone (11) (0.01M) in $CHCl_3$ (——) and in CCl_4 (- - -).

B Dihydro campholenolactone (10) (0.01M) in $CHCl_3$ (——) and in CCl_4 (- - -).

Figure 8.

A Isodrimenin (4) (0.01M) in CH_3CN (——), in $CHBr_3$ (— - —) and in $CHCl_3$ (- - -).

B Isodrimenin (4) (0.01M) in CCl_4 (——), in CS_2 (— - —) and in hexane (- - -).

C Isodrimenin (4) (0.01M) in $CHCl_3$ (- - -) and in CCl_4 (——).

Figure 9.

A Drimenin (3) in CS_2 1000 cm^{-1} region.

B Dihydrodrimenin (2) in CS_2, 1000 cm^{-1} region.

C Isodrimenin (4) in CS_2 1000 cm^{-1} region.

Figure 10.

A Lactone (13) (0.01M) in $CHCl_3$ (- - -) and in CCl_4 (——).

B Lactone (12) (0.01M) in $CHCl_3$ (- - -) and in CCl_4 (——).

C γ-Butyrolactone (8) (0.01M) in $CHCl_3$ (— - —) and in CCl_4 (——).

Figure 11.

A Trans-dihydroconfertifolin (7) in CS_2, 1000 cm^{-1} region.

B/

B Cis-dihydroconfertifolin (6) in CS_2, 1000 cm^{-1} region.

Figure 12. A Confertifolin (5) in CS_2, 1000 cm^{-1} region.

B γ-Butyrolactone (8) in CS_2, 1000 cm^{-1} region.

Confertifolin (5)	1795,1781;	1788,1768;	0.[illegible];	0.[illegible];
Cis-dihydro-confertifolin (6)	1779,1758;	1771,1761;	[illegible]	[illegible]
Trans-dihydro-confertifolin (7)	1792,1777;	1781,1770;	2.13;	0.737;
[illegible]-Butyro-lactone (9)	1783,1765;	1784,1759;	1.65;	0.266;
Dihydrocon-fertifolone (11)	1783,1758;	1782,1753;	1.334;	0.285;
[illegible]lone (13)	1796,1787;	1789,1777;	1.44;	0.50;
[illegible]lone (12)	1795,1784;	1788,1780;	1.36;	0.63;
	1786,1768;	1780,1771;	1.0	1.12;
[illegible]-Butyro-lactone (8)	1795,1784;	1793,1773;	0.730;	0.229;

TABLE 1

Compound	ν max. in CCl_4	ν max. in $CHCl_3$	$\frac{\epsilon_1}{\epsilon_2}$ in CCl_4	$\frac{\epsilon_1}{\epsilon_2}$ in $CHCl_3$	$\frac{\Delta \text{ in } CCl_4}{\Delta \text{ in } CHCl_3}$
Coumarin (1)	1755,1741;	1755,1730;	0.847;	0.290;	0.560
Dihydro-drimenin (2)	1779,1758;	1771,1761;	5.56;	0.979;	2.1
Transdihydro-confertifolin (7)	1792,1777;	1781,1770;	2.13;	0.707;	1.35
β-Angelica-lactone (9)	1783,1765;	1784,1759;	1.66;	0.266;	0.72
Campholeno-lactone (11)	1783,1758;	1782,1751;	1.334;	0.288;	0.805
Lactone (13)	1796,1787;	1789,1777;	1.44;	0.50;	0.75
Lactone (12)	1795,1786;	1788,1780;	1.36;	0.63;	1.125
	1786,1766;	1780,1771;	3.5	1.12;	2.22
γ-Butyro-lactone (8)	1795,1784;	1793,1773;	0.730;	0.229;	0.55

*Acetonitrile is arbitrarily assumed to be more polar than chloroform.

TABLE 2

Compound	ν max. in less polar solvent.	ν max. in more polar solvent.	ϵ_1 in less ϵ_2 polar solvent.	ϵ_1 in less ϵ_2 polar solvent.	Ω in less polar solvent. Ω in more polar solvent.
β-Angelica lactone (9) (in CH_3CN and hexane)	1791,1762;	1785,1761;	8.1;	0.26;	1.2;
Coumarin (1) (in CCl_4 and hexane)	(1767,1757;	1768,1755;	0.342;	0.131;	0.77;
	(1757,1744;	1755,1741;	3.1;	0.85;	0.93;
in $CHCl_3$ and CH_3CN*	(1755,1730;	1755,1735;	0.29;	0.257;	1.25;
	(1730,1713;	1735,1710;	2.07;	0.885;	0.92;
in CH_3I and CS_2	1753,1741;	1754,1737;	0.77;	0.388;	0.705;
	1741,1705;	1737,1710;	19.03;	13.9;	0.97;

*Acetonitrile is arbitrarily assumed to be more polar than chloroform.

TABLE 3

Coumarin (1)	$\tilde{\nu}$ max. in less polar medium.	$\tilde{\nu}$ max. in more polar medium.	ϵ_1 in less polar medium. / ϵ_2 less polar medium.	ϵ_1 in more polar medium. / ϵ_2 more polar medium.	$\frac{D \text{ in less polar medium}}{D \text{ in more polar medium}}$
(i) 2:6 dimethoxyphenol and p-methoxyphenol	1758,1744;	1758,1746;	0.81;	0.85	1.16
	1744,1710;	1746,1717;	3.2;	0.320	1.17
(ii) 0.01 p-cresol and p-cresol	1757,1746;	1757,1744;	0.83;	0.845;	0.845
	1746,1731;	1744,1727;	2.97	0.785;	0.88
	1731,1720;	1727,1715;	1.565	1.02;	0.92
$CHCl_3$ benzene (1:∞ v/v)	1776,1764;	[illegible]	[illegible]	[illegible]	1.00
$CHCl_3$ benzene (1:1 v/v)					
$CHCl_3$ benzene (1:1 v/v) $CHCl_3$	1775,1763;	[illegible]	[illegible]	[illegible]	

TABLE 4

Dihydro-drimenin in	ν max. in less polar solvent.	ν max. in more polar solvent.	ϵ_1/ϵ_2 in less polar solvent.	ϵ_1/ϵ_2 in more polar solvent.	D in less polar solvent / D in more polar solvent
hexane $CHCl_3$ hexane (1:99 v/v)	1797,1787;	1797,1787;	0.374;	0.330;	1.00
$CHCl_3$ hexane (1:99 v/v)	(1797,1787;	1798,1786;	0.330;	0.326;	0.83
$CHCl_3$ hexane (1:19 v/v)	(1787,1763;	1786,1762;	8.28;	3.88;	1.00
$CHCl_3$ hexane (1:19 v/v)	(1798,1786;	1797,1785;	0.326;	0.326;	1.00
	(1786,1779;	1785,1778;	3.88;	0.865;	1.00
$CHCl_3$ hexane (1:9 v/v)	(1779,1762;	1778,1763;	3.38;	2.59;	1.13
$CHCl_3$ hexane (1:9 v/v)	(1797,1778;	1797,1776;	0.273;	0.165;	0.905
$CHCl_3$ hexane (1:4 v/v)	(1778,1763;	1776,1764;	2.59;	1.90;	1.36
$CHCl_3$ hexane (1:4 v/v) $CHCl_3$ hexane (1:1 v/v)	1776,1764;	1775,1763;	1.90;	1.28;	1.00
$CHCl_3$ hexane (1:1 v/v) $CHCl_3$	1775,1763;	1771,1761;	1.28;	0.92	1.20

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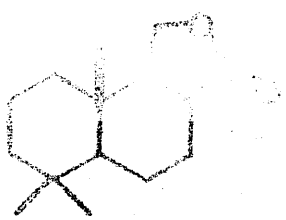

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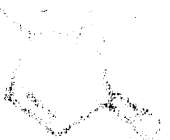

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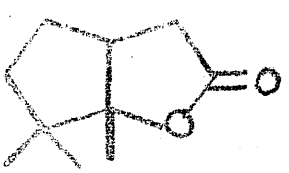

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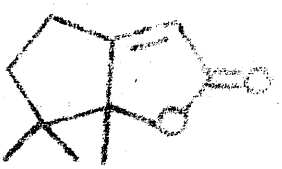

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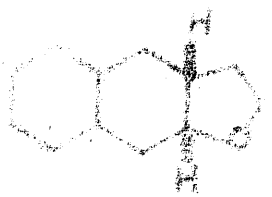

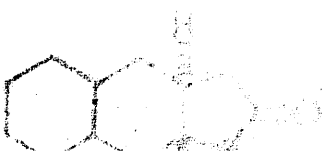

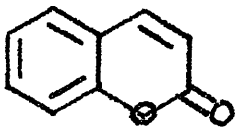

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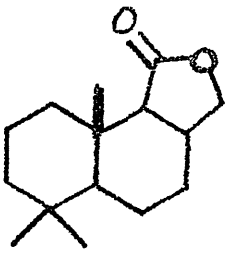

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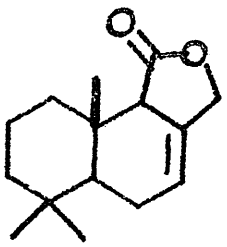

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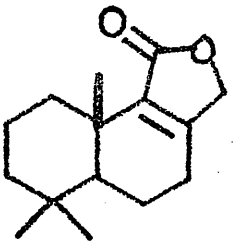

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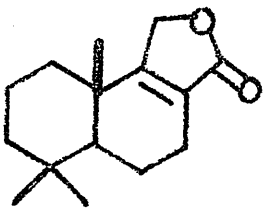

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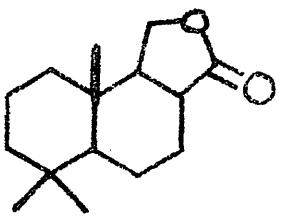

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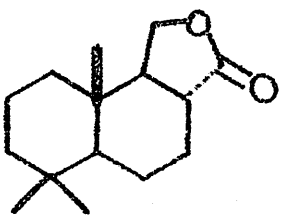

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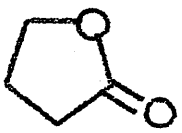

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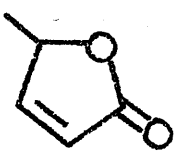

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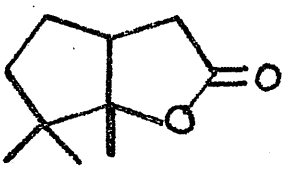

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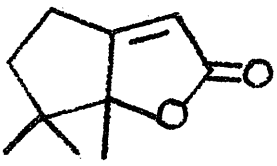

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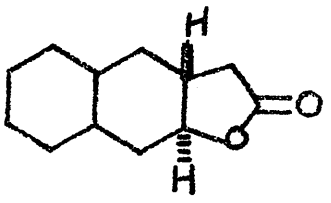

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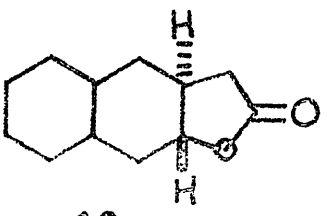

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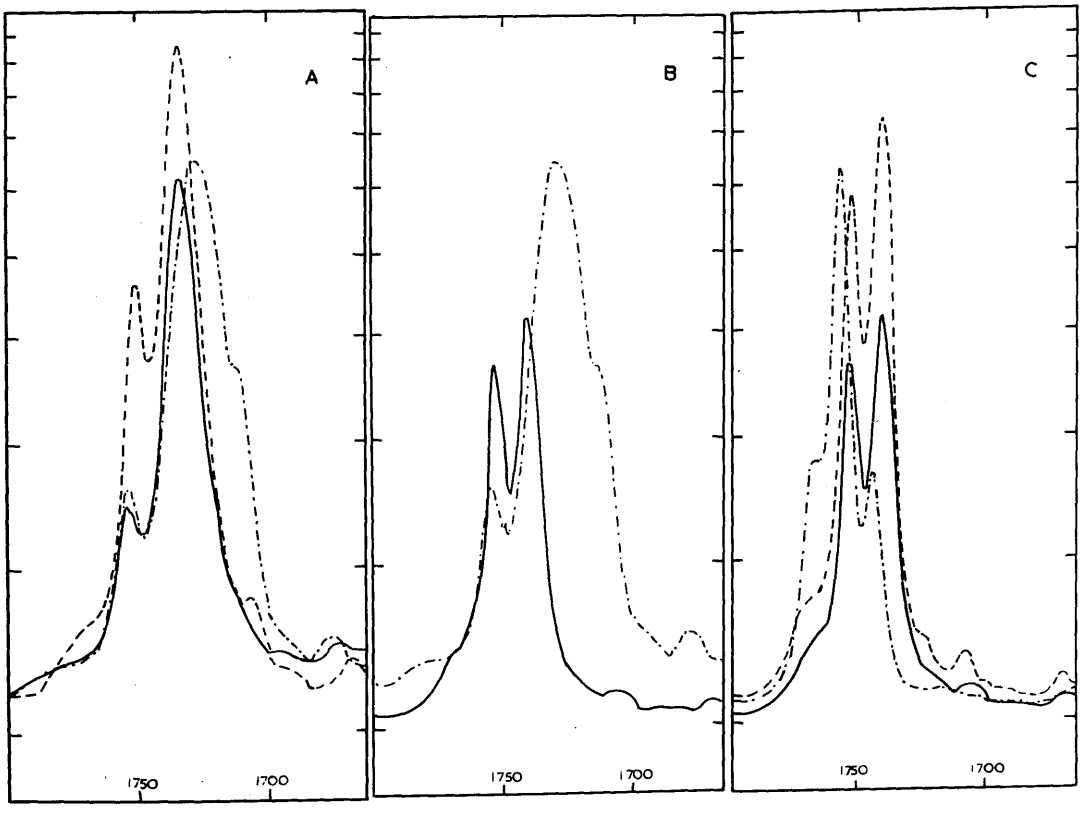


FIGURE 1

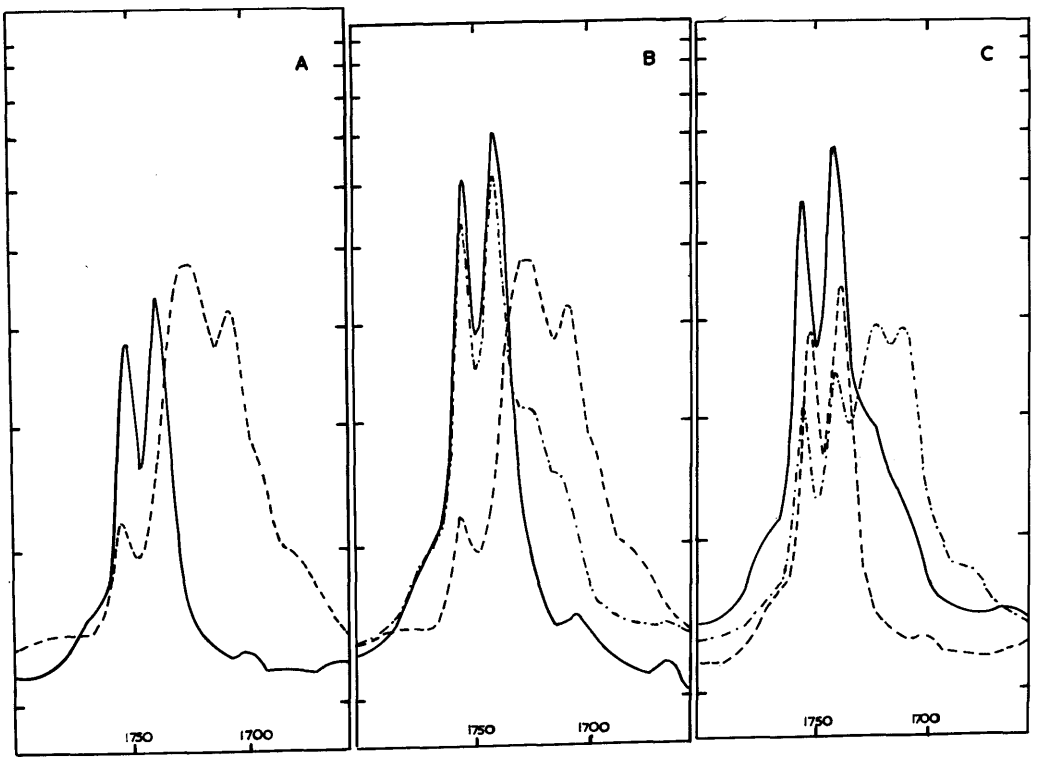
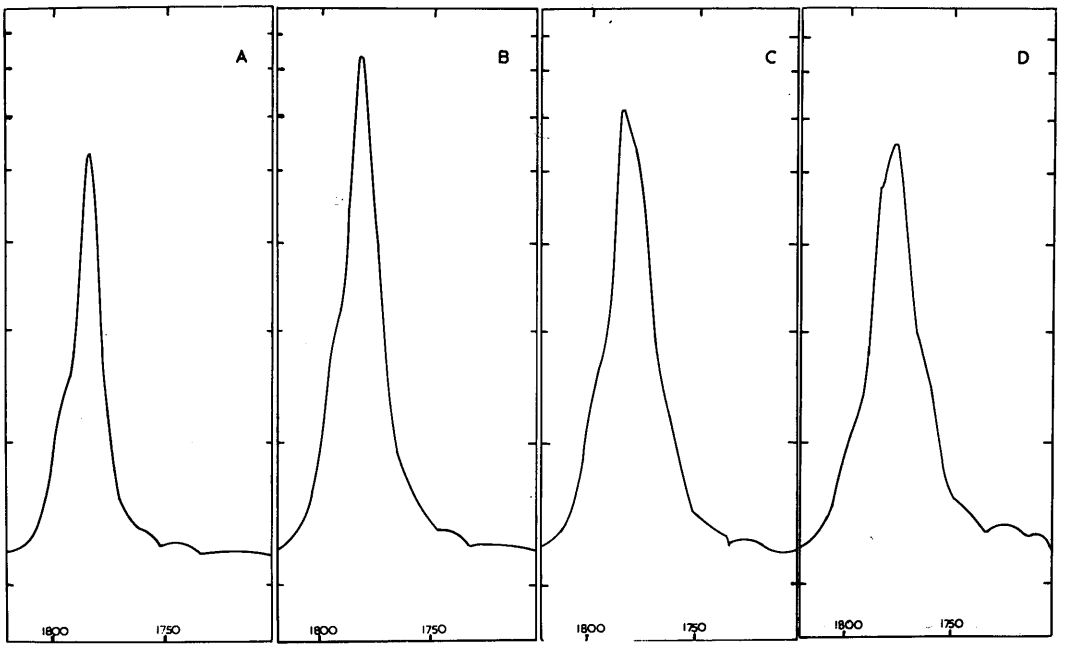


FIGURE 2


A
B
C
D
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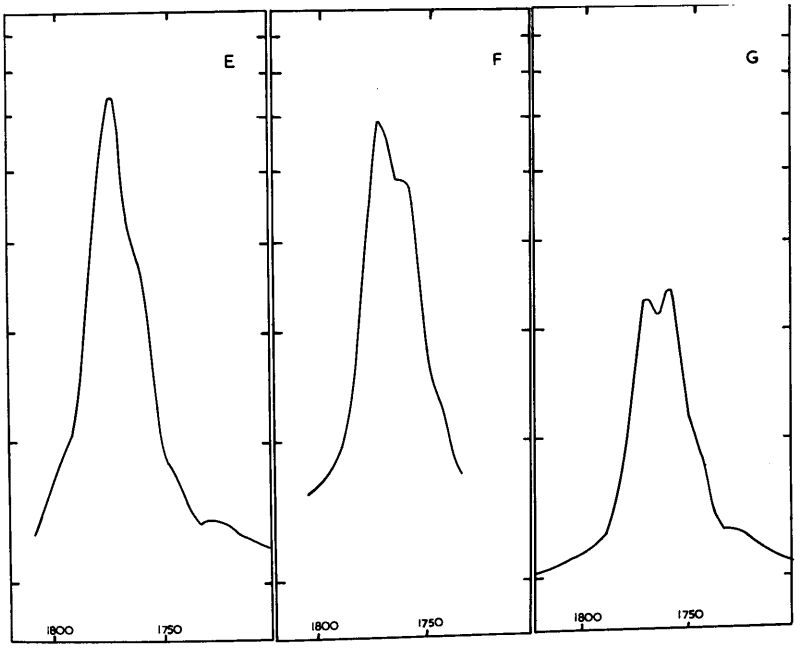
1750
1800
1750
1800
1750
1800
1750

FIGURE 3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F
G
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1750
1800
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1750

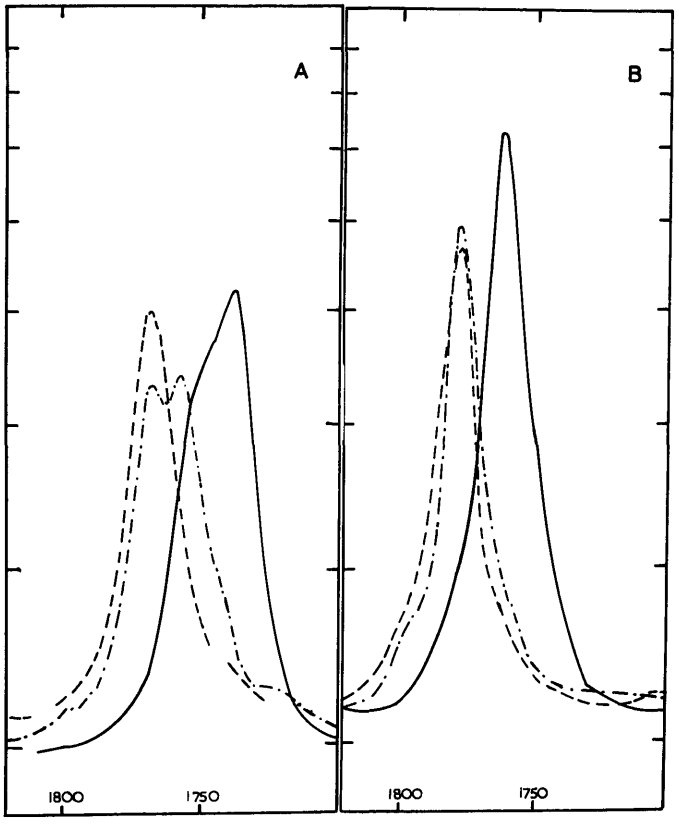


FIGURE 4

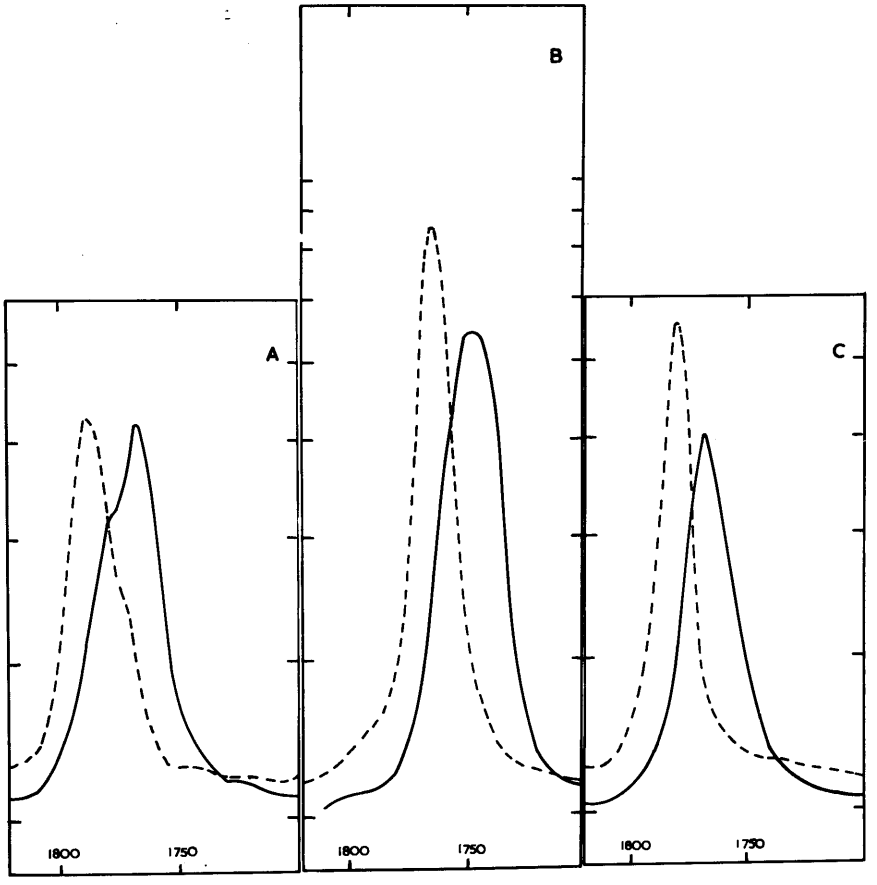


FIGURE 5

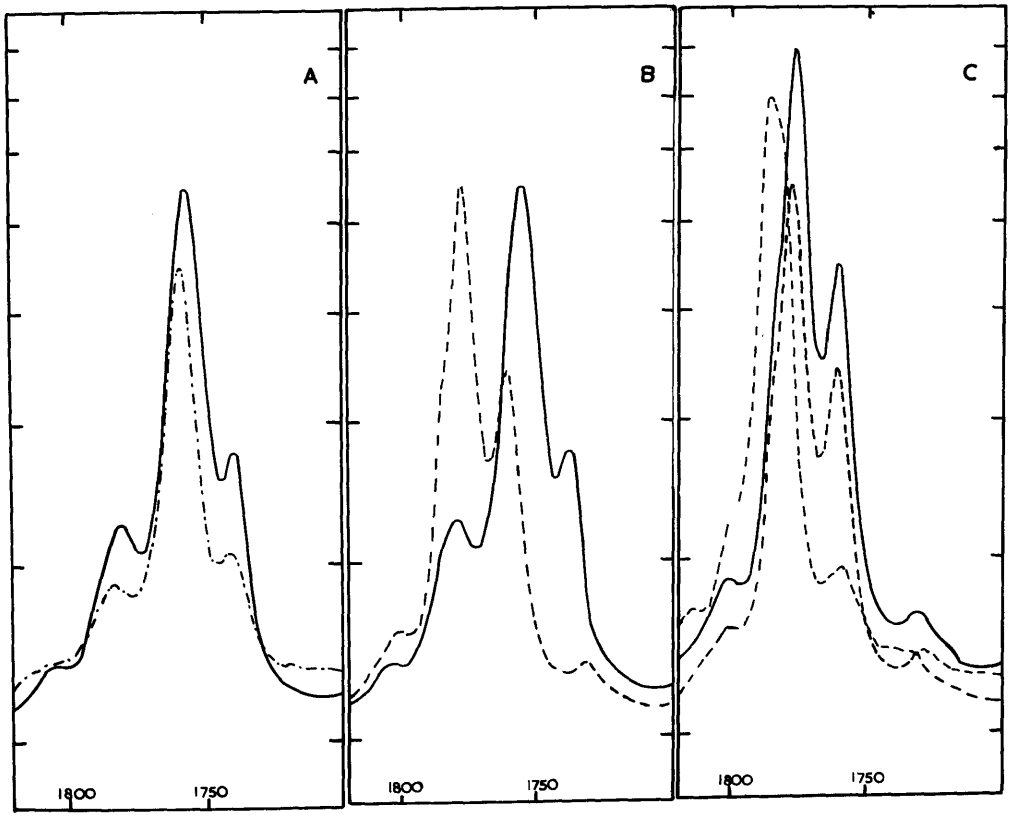


FIGURE 6

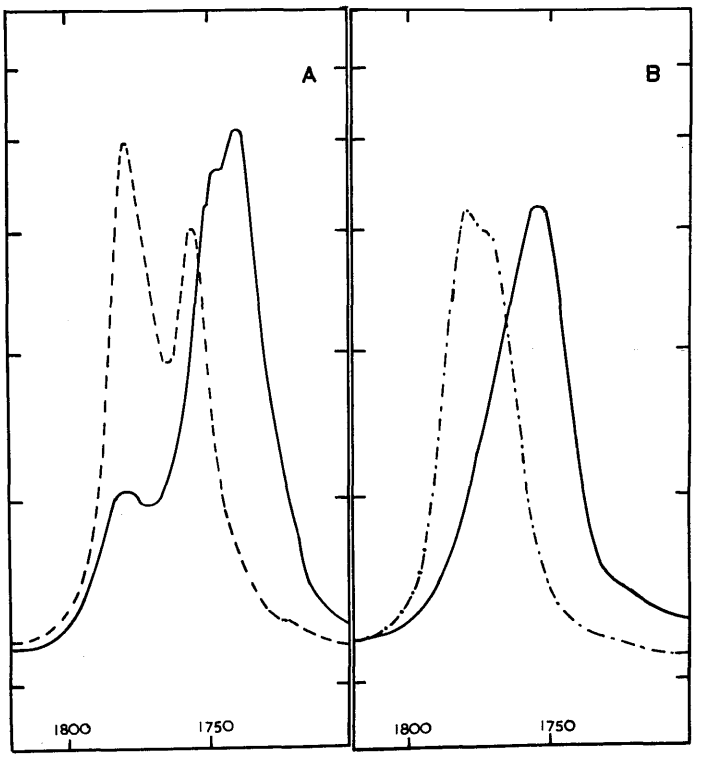


FIGURE 7

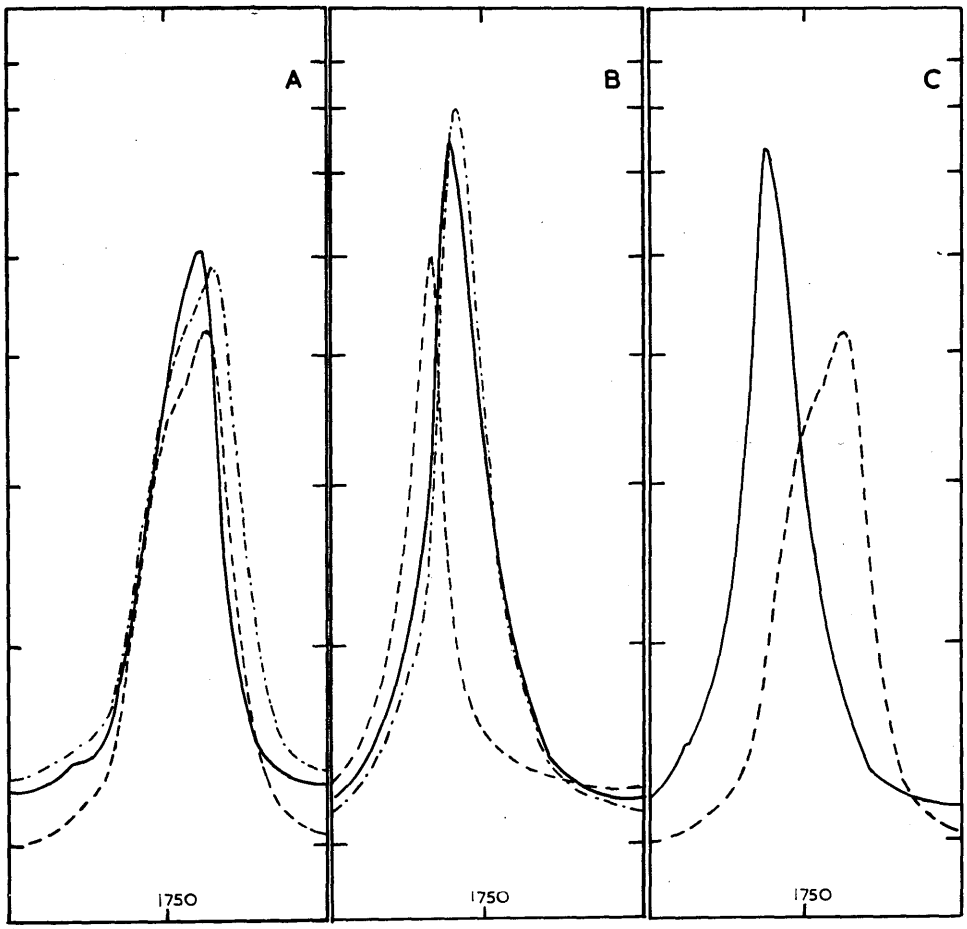


FIGURE 8

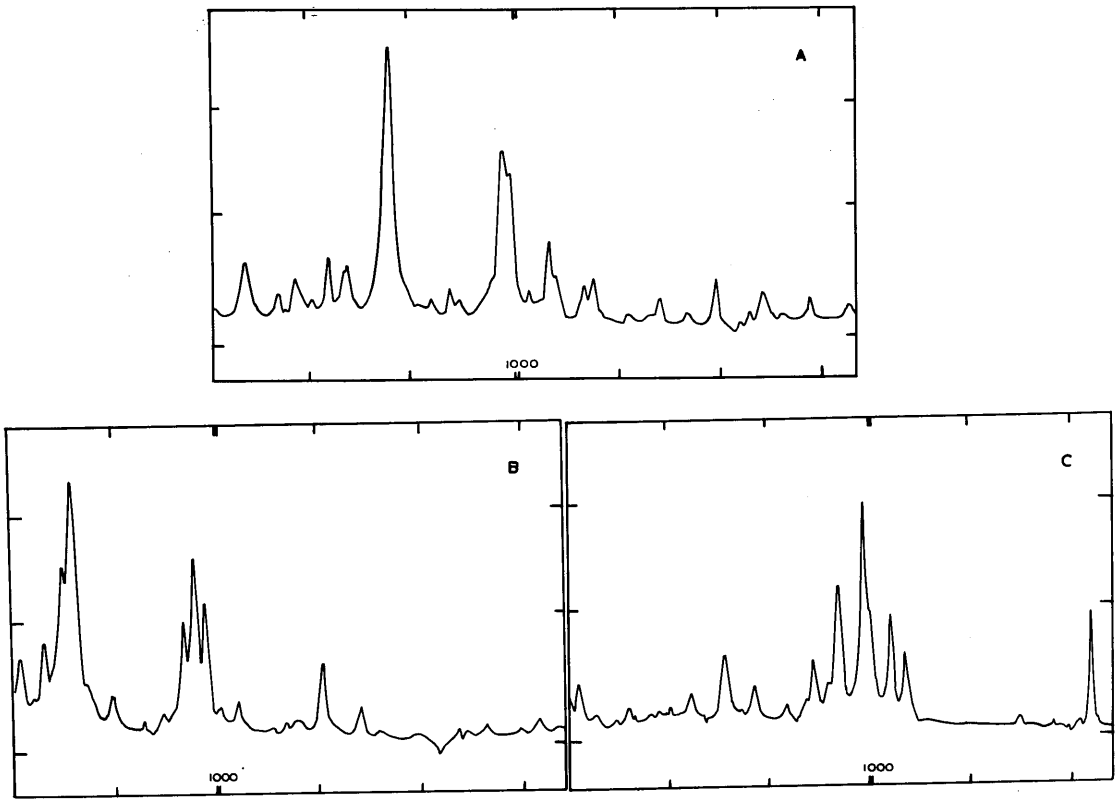


FIGURE 9

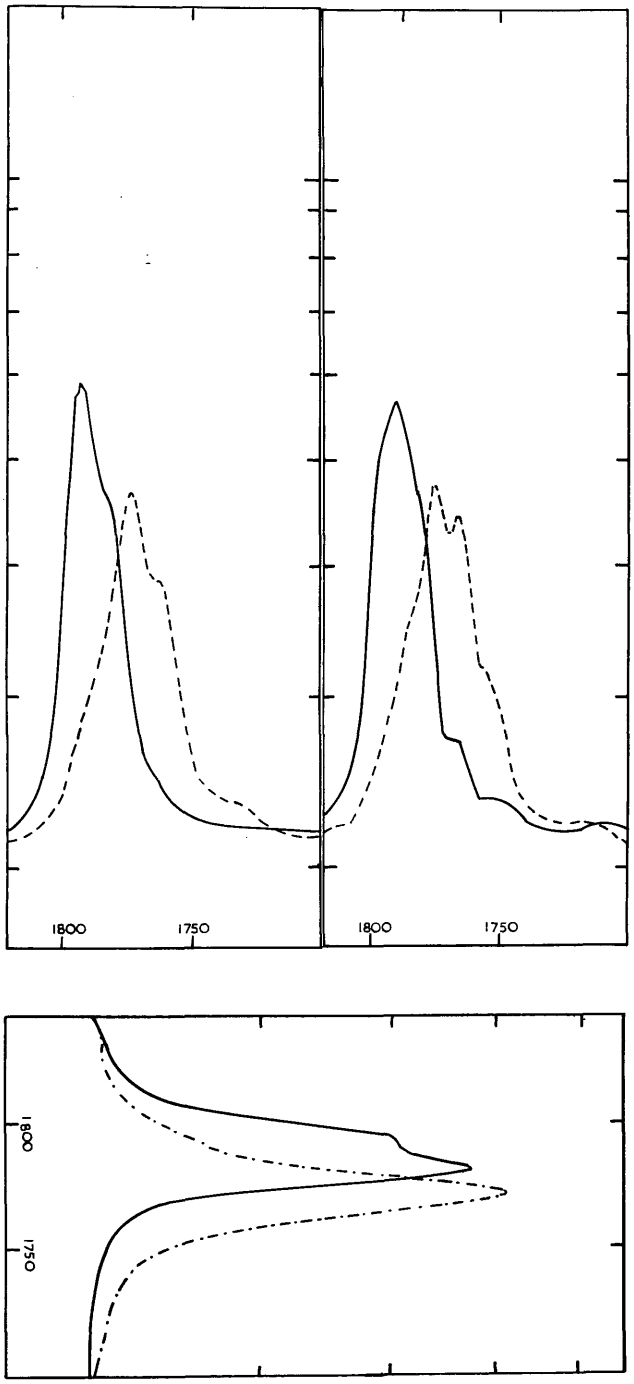
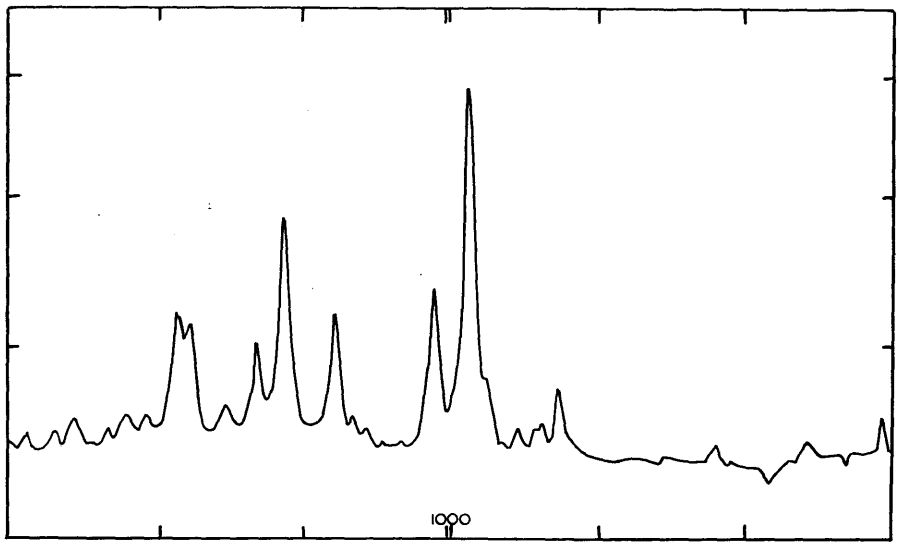


FIGURE 10



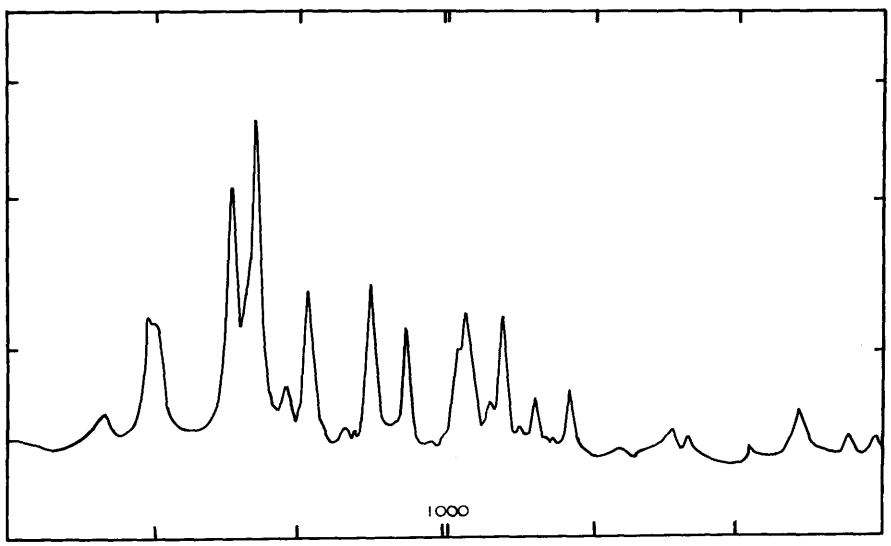


FIGURE 11

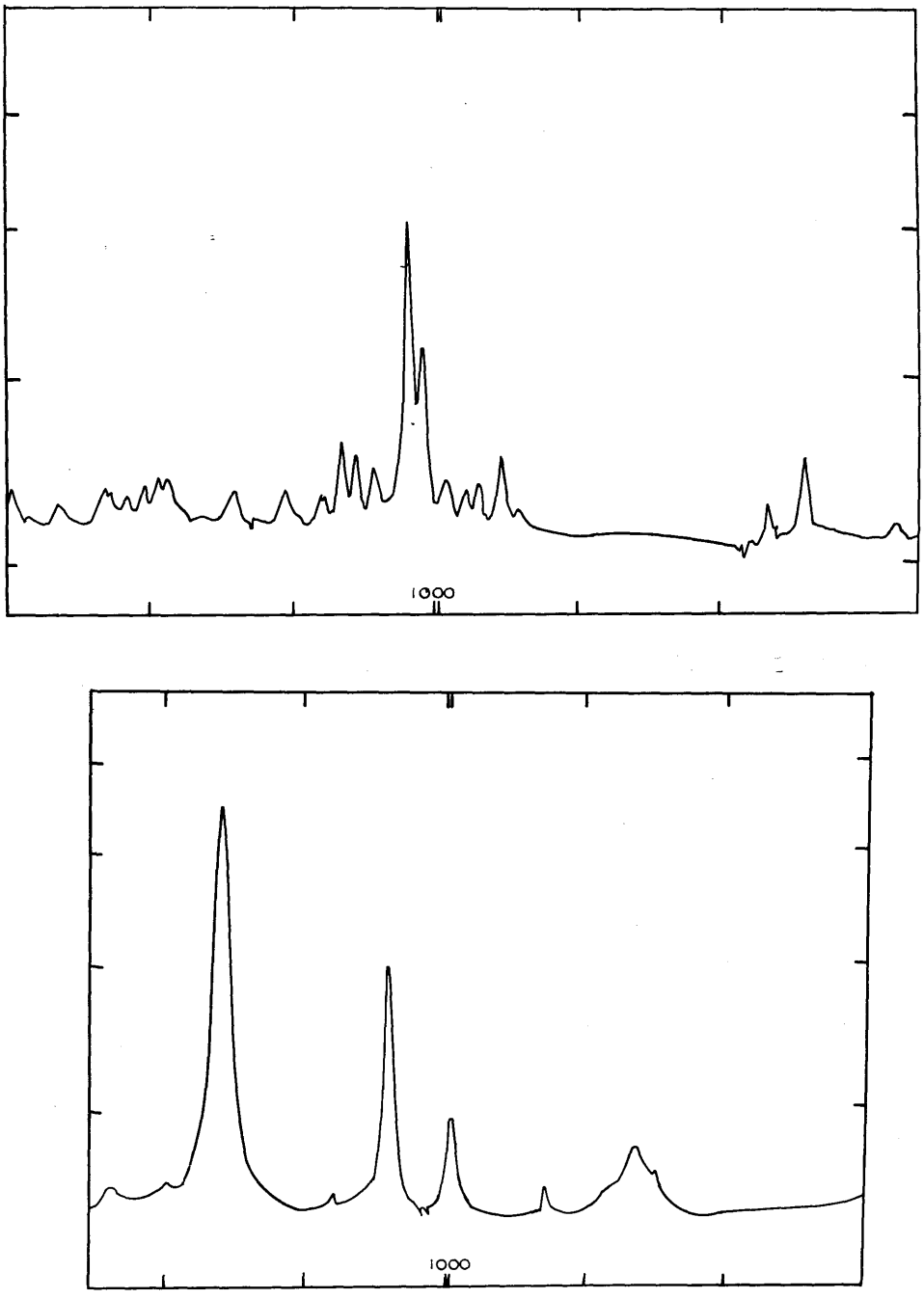


FIGURE 12

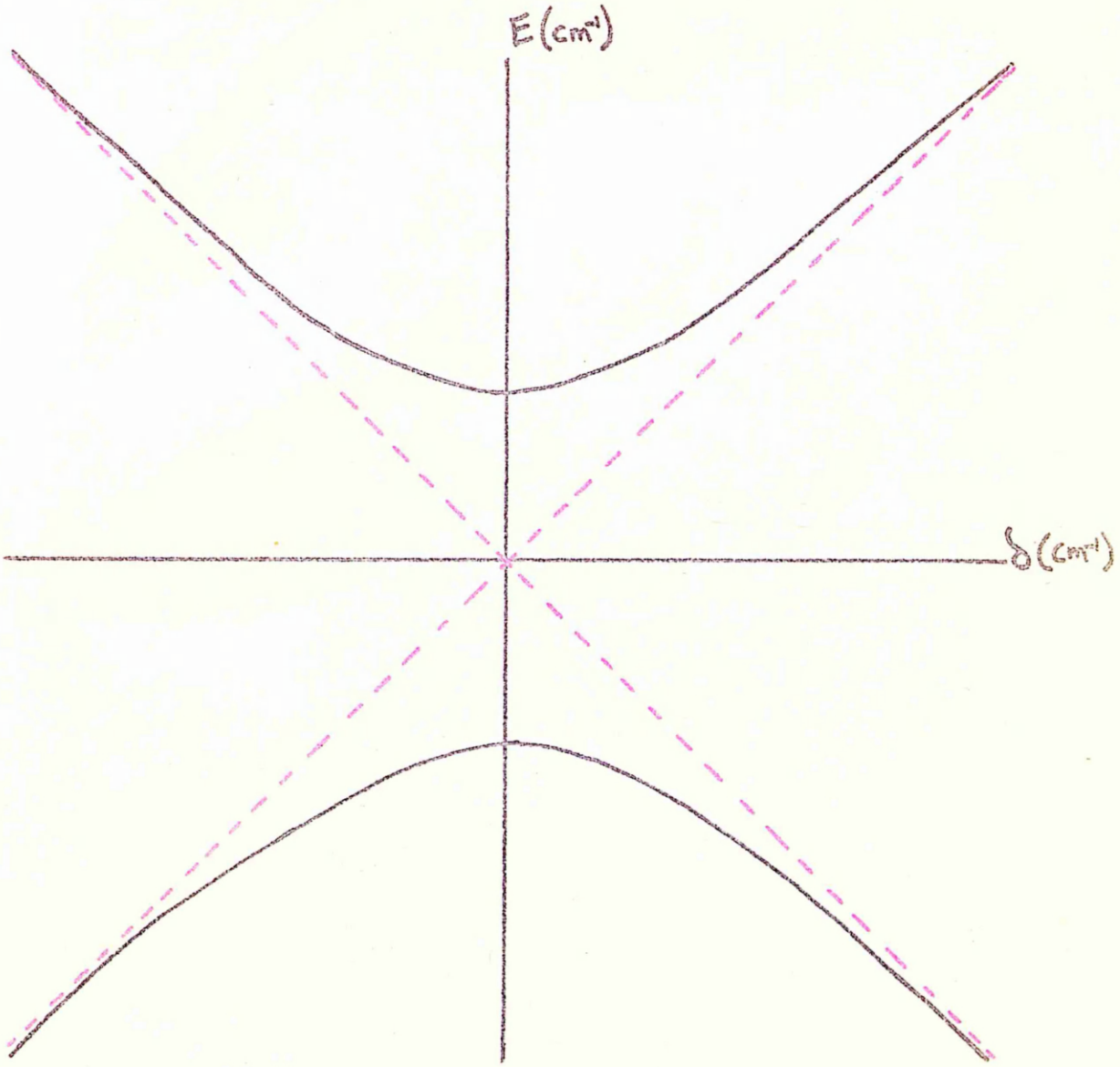


Figure 13

Plot of the energies of the perturbed functions (——) against the separation of the unperturbed functions (– – –).

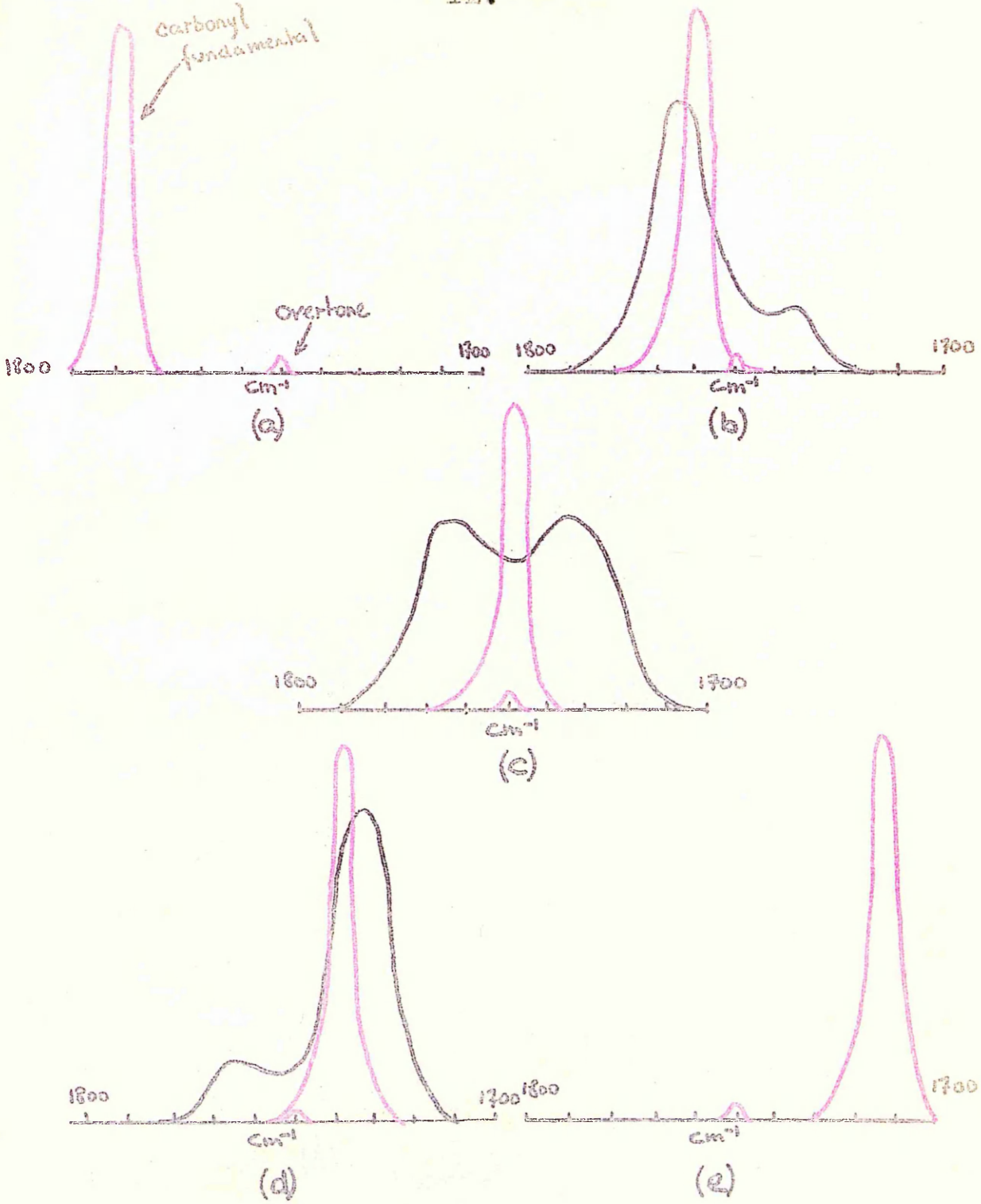


Figure 14

Perturbed bands ( ) Unperturbed bands ( )

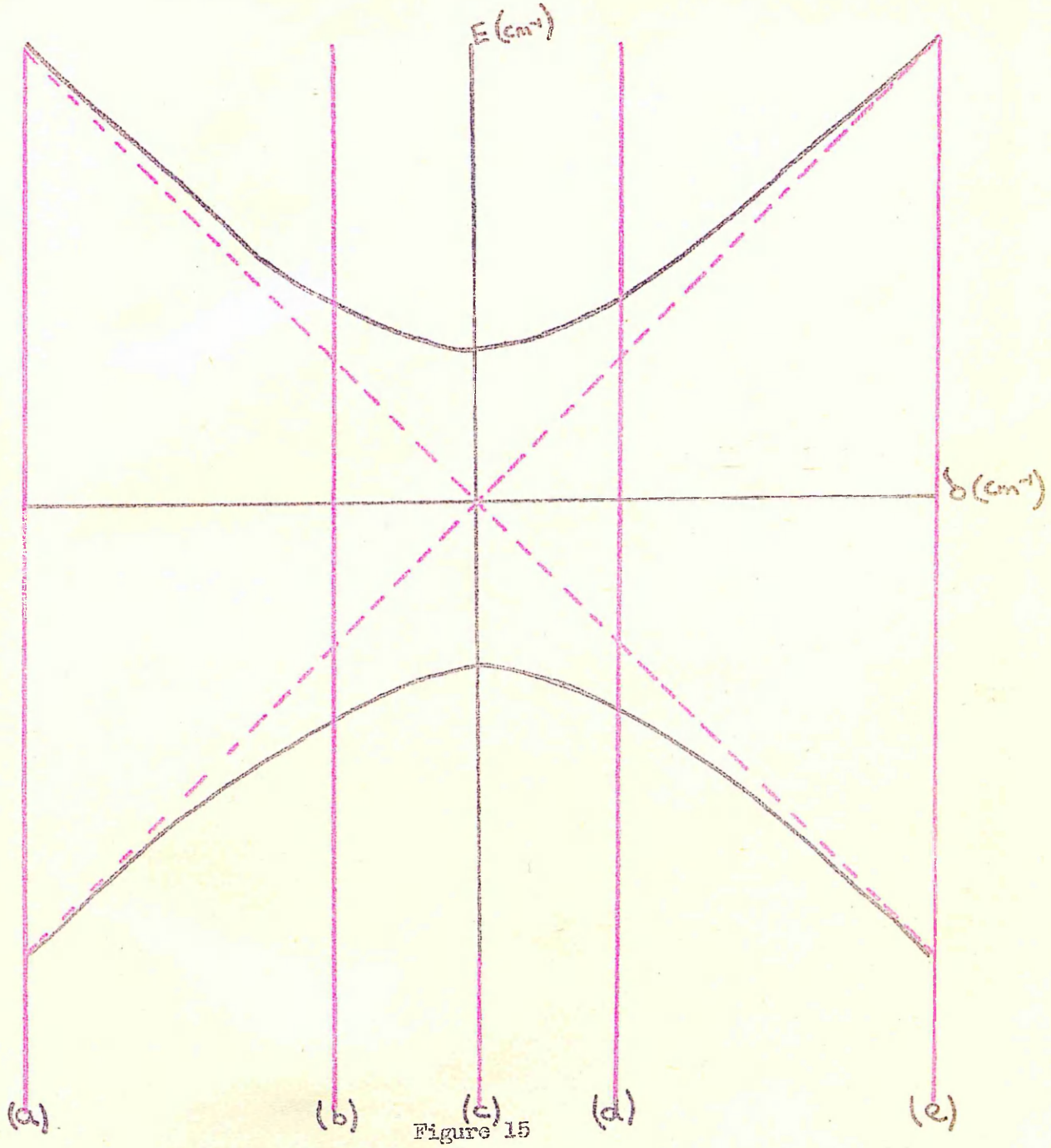


Figure 15

The perturbations represented in figure 14 superimposed on figure 13