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THE STRUCTURE OF ISOLAPACHENOLE

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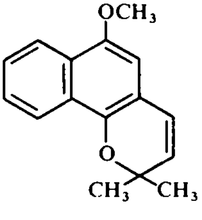
Abstract—PMR spectra show previously proposed structures for the acid catalysed dimer of lapachenole[1] to be incorrect. The dimerization has been carried out in deuterosulphuric-deuteroacetic acid with the incorporation of one atom of deuterium. A probable mechanism is described, and this together with the PMR data is compatible with the proposed structure of iso-lapachenole.

Livingstone and Whiting[1] showed that the naturally occurring compound 2,2-dimethyl-6-methoxy-7,8-benzochromen (lapachenole; I) dimerizes under acid conditions to isolapachenole, for which they suggested structure II. By analogy with the dimerization of the allylic diol III,[2] Barnes *et al.*[3] inferred that isolapachenole would have structure IV.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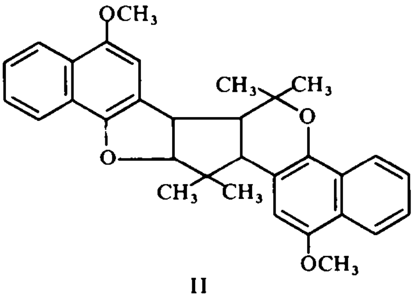
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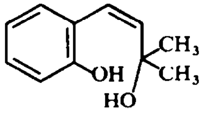
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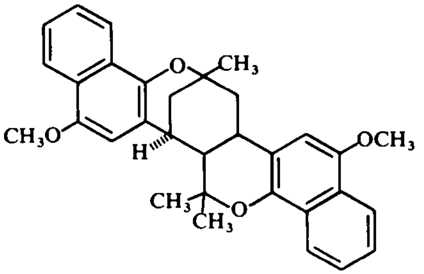
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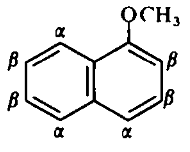

V

PMR spectrum of isolapachenole (60 Mc/s)

In this spectrum, (Fig. 1) the integral shows that there is an intensity ratio of 4:5 between the two groups of aromatic protons at 1·7–2·1 τ and 2·4–2·8 τ respectively, and an extra proton under the Me resonances 8·3–8·7 τ. In addition to the two OMe groups (5·94 and 6·08 τ) and the four Me groups (8·4, 8·52, 8·6 and 8·75 τ) there is a total of five single protons: one in the 8·5 τ region; two in a multiplet 7·58–7·84 τ; one in a multiplet 6·6–6·95 τ; and one in a doublet (J = 7·4 c/s) at 5·31 τ.

In naphthalene, β-protons resonate at a higher field than α-protons.[4] Further, an α-OMe substituent is known to exert high field *ortho-* and low field *peri-*shifts,[5] so that the distribution of shifts in α-methoxynaphthalene (V) should be comparable with those in naphthalene. Thus isolapachenole must possess a total of four α- and five β-aromatic protons, together with four C-Me groups. This eliminates the previously suggested structures II and IV for isolapachenole, since both contain ten aromatic hydrogen atoms and IV has only three C-Me groups.

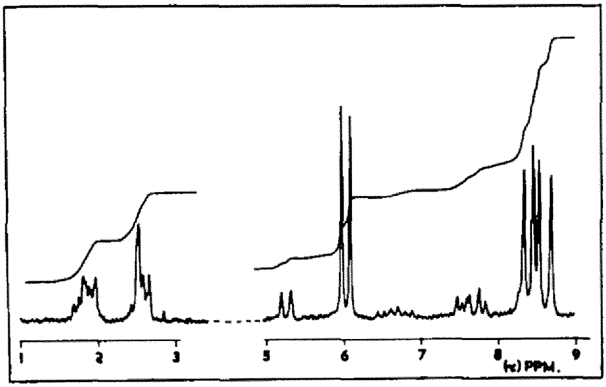


Fig. 1

Spectrum of isolapachenole (100 Mc/s)

Comparison with the 60 Mc/s spectrum enables the following conclusions to be drawn:

(a) The doublet, intensity one proton, at 5·3 τ has a separation of 7·4 c/s at both frequencies, and must arise from a single chemical shift.

(b) The doublet, intensity six protons, at 6·0 τ has a separation of 6·5 c/s at 60 Mc/s and 11 c/s at 100 Mc/s, and has been assigned to two OMe groups of different chemical shifts.

(c) The four Me groups at 8·4, 8·52, 8·6 and 8·75 τ are distinct and are not coupled to any other protons; since their separations at 60 Mc/s and 100 Mc/s are in the ratio 6:10. These Me resonances have been assigned to two *gem*-dimethyl groups.

Spin-decoupling experiments at 100 Mc/s

Frequency-sweep spin-decoupling confirms (Fig. 2) that there is an extra proton under the Me peaks, which is not coupled to these Me groups. The isolapachenole molecule must, therefore, possess four Me groups, two OMe groups, nine aromatic protons divided in the ratio 4:5 between α- and β-naphthalenic protons and five other non-aromatic hydrogen atoms. The following spin-decoupling experiments enable the relative disposition of these five protons to be found.

Comparison (Fig. 2) of the 7·7 τ region of the undecoupled spectrum (a) with the same region of a decoupled spectrum in which the proton 5·3 τ is irradiated shows (b) that there is a coupling of 7·4 c/s between $H_{(5\cdot3\,\tau)}$ and $H_{(7\cdot68\,\tau)}$. Since the doublet (c) collapses to a singlet (d) when the decoupling irradiation is centred at 232 c/s, $H_{(5\cdot3\,\tau)}$ cannot be significantly coupled to any other proton, whereas (b) shows that $H_{(7\cdot68\,\tau)}$ has another coupling of 10 c/s; (f) shows that this must be to the proton with the chemical shift 6·76 τ.

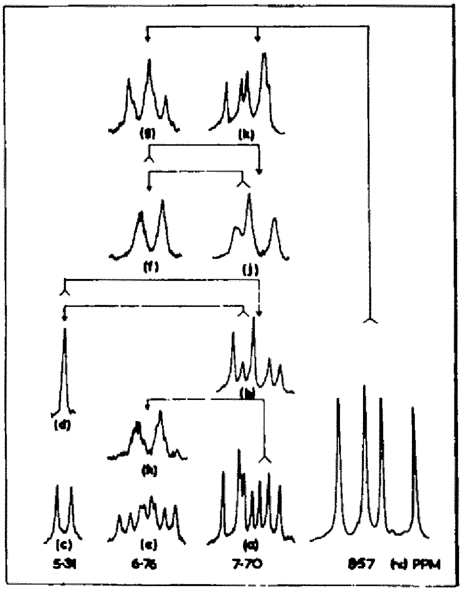
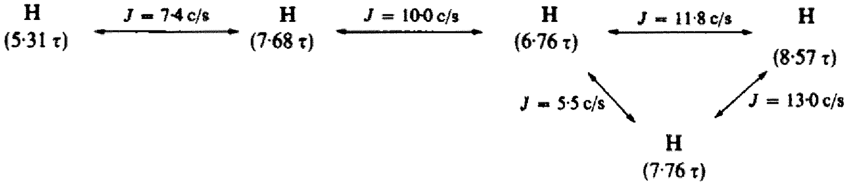


Fig. 2

The eightfold multiplicity of the $H_{(6\cdot76\,\tau)}$ resonance (e) suggests that it is coupled to three protons. One, $H_{(7\cdot68\,\tau)}$, has been referred to; comparison of (g) and (e) shows that another must be $H_{(8\cdot57\,\tau)}$. The third coupling of $H_{(6\cdot76\,\tau)}$ must be to $H_{(7\cdot76\,\tau)}$ since irradiation at 324 c/s causes both $H_{(7\cdot76\,\tau)}$ and $H_{(7\cdot68\,\tau)}$ signals to collapse (j). The $H_{(6\cdot76\,\tau)}$ signals obtained by irradiation at 224 c/s and 232 c/s are similar broadened doublets with a separation of 11·8 c/s; evidently, irradiation at either frequency almost completely erases both couplings, so that $J_{H8\cdot57\,\tau-H6\cdot76\,\tau}$ is 11·8 c/s. In the undecoupled spectrum $H_{(7\cdot76\,\tau)}$ appears as a pair of doublets with separations of 5·5 and 13·0 c/s; since irradiation at 143 c/s produces a collapsed form (k) then the larger couplings is $J_{H8\cdot57\,\tau-H7\cdot76\,\tau}$ and $J_{H7\cdot76\,\tau-H6\cdot76\,\tau}$ must be 5·5 c/s.

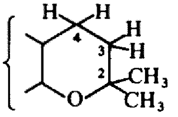
From their relative intensities, the peaks due to $H_{7\cdot76\,\tau}$ and $H_{7\cdot68\,\tau}$ (a) are not coupled to each other, so that, despite their similarity in shift, they do not form a pair of geminal protons.

Thus the chemical shifts (τ values) and coupling constants (c/s) of the five single non-aromatic protons are as follows:–



The observed spectrum would be obtained from a system which possessed a terminal methylene connected to three methine groups. The methylene protons will be $H_{(8\cdot57\tau)}$ and $H_{(7\cdot76\tau)}$ and, since the smallest $\Delta\nu/J$ ratio is six, then the spectrum is approximately first order and has been considered as such when obtaining J values.

The PMR spectra of 2,2-dimethylchroman and 2,2-dimethyl-5,6-benzochroman (VI) have pairs of broadened triplets centred at 7·25 and 8·25 τ and 7·0 and 8·1 τ respectively. The appearance of the spectra indicate the presence of an A_2B_2 system ($J_{AB} = 7$ c/s) and this, coupled with the existence of a single Me resonance suggests that there is rapid conformational inversion of the hetero-ring. Coupling from the aromatic system broadens the low field triplet, so that the high field triplet corresponds to the C-3 methylene group.



VI

The corresponding H_4—H_5 geminal protons in isolapachenole (X) are centred at 7·76 and 8·57 τ indicating that there is no longer the same degree of conformational mobility, but the mean value 8·16 τ agrees well with the experimental average for the C-3 methylene resonance of 2,2-dimethylchroman and 2,2-dimethyl-5,6-benzochroman.

Isolapachenole-d_1. Lapachenole when treated with a mixture of deuterosulphuric and deuteroacetic acids, dimerised to give monodeuteroisolapachenole. (Isolapachenole-d_1).

Spectrum of isolapachenole-d_1 (60 Mc/s)

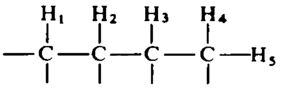
The integral shows that the compound has one hydrogen atom fewer than isolapachenole and that one of the five non-aromatic single hydrogens has been replaced by deuterium.

Although only four single protons are now present, they produce resonance at the same positions as the five single protons of isolapachenole: one proton appears as a doublet ($J = 7\cdot4$ c/s) at 5·3 τ, one as a pair of quartets ($J = 10$ c/s and 12 c/s; $J = 10$ c/s and 5·5 c/s) at 6·67 τ, another as a quartet ($J = 10\cdot0$ and 7·4 c/s) at 7·68 τ and the final proton is divided equally between a broadened doublet ($J = 5\cdot5$ c/s) at 7·75 τ and a resonance hidden beneath the four C-Me peaks.

The change in the splitting of the multiplet centred at 6·67 τ and the half-proton intensities of the resonance at 7·75 τ and 8·5 τ suggest that isolapachenole-d_1 is composed of a pair of epimers. The deuterium atom must be present in the geminal methylene group and the epimer mixture is formed since each of the methylene protons have been replaced equally by deuterium.

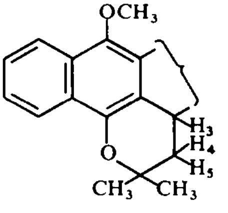
The structure of isolapachenole

The PMR spectral data has indicated that isolapachenole contains two *gem*-dimethyl groups (confirmed by the presence of a doublet at 1380 cm^{-1} in the IR spectrum), the four carbon fragments VII, and nine aromatic protons (four α- and five β-). The UV spectrum[1] of isolapachenole is very similar to that of 3,4-dihydrolapachenole and comparison of extinction coefficients suggests the presence of two dihydronaphthopyrans moieties in isolapachenole. The chemical shifts of the H_4H_5 protons place this methylene group adjacent to a *gem*-dimethyl and the observed spin-spin coupling between H_3, H_4 and H_5 put these protons in the same dihydronaphthopyran moiety VIII.

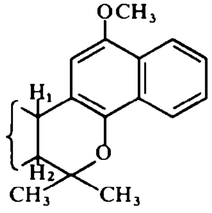


$$-\underset{|}{\overset{\overset{H_1}{|}}{C}}-\underset{|}{\overset{\overset{H_2}{|}}{C}}-\underset{|}{\overset{\overset{H_3}{|}}{C}}-\underset{|}{\overset{\overset{H_4}{|}}{C}}-H_5$$

VII

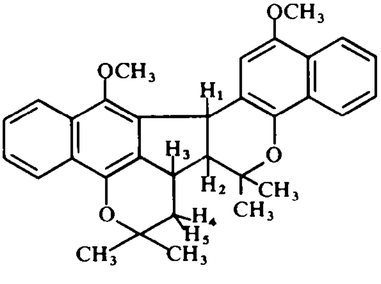


VIII

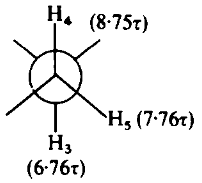


IX

The other fragment IX contains protons H_1 and H_2 and since H_2 is strongly coupled to H_3 then VIII and XI must be joined to produce the basic ring structure of isolapachenole X.



X

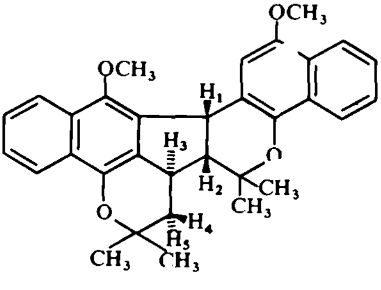


XI

The detailed stereochemistry of the four carbon fragment VII remains unknown, but it may be determined by the use of Dreiding models and consideration of chemical shifts and coupling constants obtained from the PMR spectra. The coupling constants of the H_3, H_4, H_5 protons indicate that H_3 lies outside the *gem*-protons (XI).[6] If the dihydropyran ring assumes the half-chair conformation, then H_4 will have an axial and H_3 a pseudoaxial orientation. In this orientation there is a strong H_3—CH_3 1,3-diaxial repulsion which would lead to considerable Van-der Waals deshielding[6] of H_3. The chemical shift of H_3 (6·76 τ) is lower by 0·3 ppm than the usual benzylic proton and is further evidence for the pseudoaxial nature of H_3.

The observed difference (0·8 ppm) in chemical shift between the geminal protons (H_4,H_5) is to be expected when the conformation of the dihydropyran ring is locked. The equatorial proton H_5 is deshielded relative to the axial proton H_4 by the anisotropy of the neighbouring C—C and C—O single bonds[7] by about 0·6 ppm and by the anisotropy of the aromatic system by a further 0·2 ppm.[8] The methine proton H_2 has a chemical shift and environment similar to that of H_5, so that its probable orientation will be equatorial, and there will be an anti-relationship between protons H_2 and H_3.

Only the configuration of the atom bearing H_1 remains in doubt and there are two possible isomers for isolapachenole one with H_1 H_2 *cis* and the other with H_1 H_2 *trans*. Dreiding models showed that the *trans*-isomer could not exist, as the 'cyclopentene' ring is locked in a near planar conformation and adjacent *trans* bonds in a dihydropyran ring cannot be coplanar. The model of the *cis*-isomer XII showed that the structure has little ring strain, is not strongly destabilised by Van der Waal's repulsions and fits the physical data.

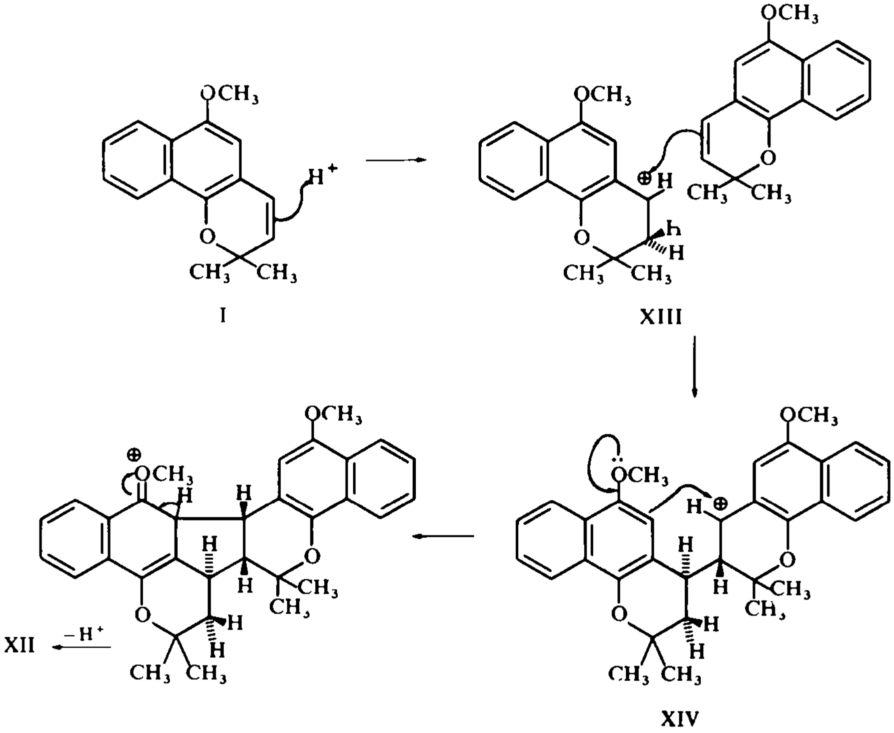


XII

From the model of XII dihedral angles of the four carbon fragment VII were measured and coupling constants estimated using the modified Karplus equation.[9] Although this equation may not be strictly followed in a molecule of this complexity and the effect of the electronegativity of substituents has been ignored, the calculated and experimental coupling constants are in good agreement.

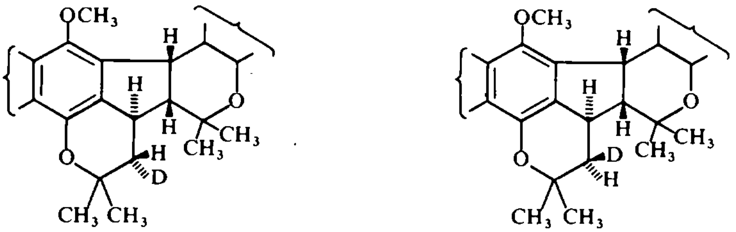
	Dihedral angle $\phi°$	J calc. c/s	J observed c/s
H_1H_2	33	7·0	7·4
H_2H_3	160	10·5	10·0
H_3H_5	57	3·0	5·5
H_3H_4	177	12·0	11·8

The proposed mechanism leads to isolapachenole XII with the required sterochemistry and no other isomer could be formed via this route. Initially there is protonation of the C_3—C_4 olefinic bond of isolapachenole which produces the stable 'benzylic' carbonium ion XIII. This cation attacks the C_3—C_4 bond in a second lapachenole molecule to give another carbonium ion XIV, which gives Isolapachenole by a Friedel–Crafts type of cyclization. Isolapachenole is produced as a racemate of a single isomer due to the restrictions placed on the cyclization step by carbonium ion XIV.



When the acid catalysed dimerization of lapachenole is carried out with deuterons instead of protons, then the initial deuteration step will produce the racemic carbonium ion XIII-d_1, since attack of these double bond can take place equally from both sides. When these cations complete the proposed reaction sequence, each will produce a racemate and an enantiomer from one dl-pair will be the epimer of one of the enantiomers from the other racemate. (XII-d_1).

XIII-d



XII-d$_1$

EXPERIMENTAL

PMR spectra were recorded on Varian A60, A60A and HA100 spectrometers, using $CDCl_3$ as solvent and TMS as internal standard.

Isolapachenole-d$_1$ (XII-d$_1$). Lapachenole (0·136 g) was dissolved in a mixture of deuteroacetic-d$_4$ (1·836 g) and deuterosulphuric-d$_2$ (0·425 g) acids and left to stand. After 24 hr the reaction was complete and the the precipitated product (0·139 g m.p. 251–253°) was filtered off, recrystallized from EtOAc to yield XII-d$_1$ (0·093 g, 67%: m.p. 256°).

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