338. *The Structure of Otobain.*

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Otoba fat has been shown to contain a hydroxyotobain and a mixture of phenols in addition to otobain. Structure (VIII) is proposed for otobain, on the basis of its degradation products and its nuclear magnetic resonance spectrum.

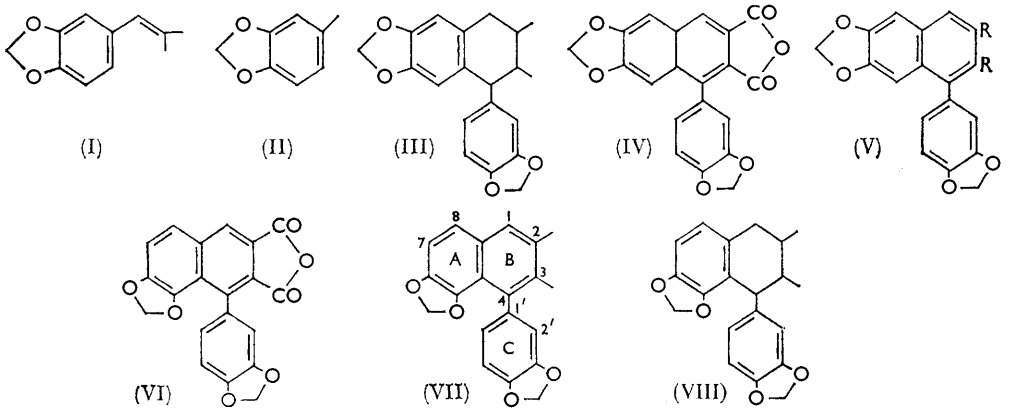
The expressed oil from the fruits of *Myristica otoba* was examined by Baughman *et al.*[1] who showed that it contained two crystalline compounds, otobite and iso-otobite, to which they gave the formula $C_{19}H_{17}O_3 \cdot OMe$ and $C_{20}H_{20}O_4$. No structural determination on these compounds has been reported. For this reinvestigation, otoba fat was hydrolysed with ethanolic potassium hydroxide and the neutral water-insoluble products were chromatographed on alumina. The less polar fractions yielded otobite which has been renamed otobain to conform with accepted lignan nomenclature. From the more polar fractions a hydroxyotobain ($C_{20}H_{20}O_5$) and a mixture of isomeric phenols ($C_{19}H_{19}O_3 \cdot OMe$) was isolated.

Otobain did not contain a hydroxyl, carboxyl, or methoxyl group and was recovered unchanged after fusion with potassium hydroxide, distillation with zinc dust, or prolonged heating with methanolic hydrogen chloride. It had ultraviolet absorption [$\lambda_{max.}$ (in EtOH) 234, 286 mμ; ε 9800, 7100] similar to that of galbulin,[2] so it was assumed, as a working hypothesis, that the four oxygen atoms in the otobain molecule were present as two methylenedioxy-groups.

Hydroxyotobain did not react with chromic acid in acetone or acetic anhydride and pyridine at room temperature. Heating it with acetic anhydride and sodium acetate, or treating it with aqueous toluene-*p*-sulphonic acid gave didehydro-otobain which had an ultraviolet spectrum [$\lambda_{max.}$ (in EtOH) 216, 231, 274, 283; ε 23,900, 23,600, 13,000, 11,800] suggestive of the partial structure (I). Hydrogenation of dehydro-otobain furnished a

[1] Baughman, Jamieson, and Brauns, *J. Amer. Chem. Soc.*, 1921, **43**, 200.
[2] Hughes and Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.

mixture from which otobain could be isolated. Dehydrogenation by dichlorodicyanobenzoquinone produced the same tetradehydro-otobain as was obtained by reaction of otobain with palladium–charcoal. Hence, hydroxyotobain must contain the same basic skeleton as otobain with the addition of a tertiary hydroxyl group situated either α or β to an aromatic ring.



No pure products were isolated on oxidation of otobain or dehydro-otobain with chromic acid, nitric acid, or potassium permanganate under a variety of conditions. A similar inability to obtain pure degradation products has been described during the oxidation of galcatin,[2] a compound containing a methylenedioxy-group. To surmount this difficulty, otobain was hydrogenolysed by reaction with sodium in liquid ammonia.[3] Two isomeric phenols, A and B ($C_{19}H_{20}O_3$), were produced, which, it was hoped, would be more susceptible to oxidation. However, again no aromatic carboxylic acids could be isolated. On the other hand, oxidation of their methyl ethers gave *p*- and *m*-methoxybenzoic acid, respectively. Hence, otobain must contain the partial structure (II) which has given almost equal proportions of the two possible hydrogenolysis products. Similar oxidation of tetradehydro-otobain furnished benzenepentacarboxylic acid, isolated as its pentamethyl ester.

In view of the close botanical relationship of the Myristicaceae to the Himantandraceae family from which galcatin was isolated, it seemed reasonable to postulate structure (III) for otobain. To confirm this, dipiperonylidenesuccinic anhydride [4] was dehydrogenated, yielding an anhydride (IV) which was isolated as the derived dimethyl ester (V; R = CO_2Me) and converted through the diol (V; R = CH_2·OH) into compound (V; R = Me). This synthetic product was not identical with tetradehydro-otobain. The unlikely possibility that the cyclisation of dipiperonylidenesuccinic anhydride had given, not (IV), but (VI) was ruled out by the close similarity of the ultraviolet spectra of compound (V; R = Me) and dehydroguaiaretic acid (see Fig. 1).

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

The high-resolution proton magnetic resonance spectrum of tetradehydro-otobain is shown in Fig. 2. The τ values of the observed peaks and their assignments to functional groups are given in Table 1. These assignments are based on arguments involving the τ values known to be characteristic of these functional groups,[5] on the geometry of the

[3] Birch, *J.*, 1947, 102.
[4] Haworth and Woodcock, *J.*, 1938, 1985.
[5] Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.

averaged conformation of the molecule, and on the effects of the aromatic ring currents of this averaged conformation on the proton chemical shifts. The assignment of the

TABLE 1.

Peak	τ	Assignment	Peak	τ	Assignment
1	7·98	3-Me	7	2·95	$H_{(7)}$, $H_{(8)}$
2	7·65	2-Me	8	2·80	
3	4·23	CH_2 (on ring A)	9	2·68	
4	3·95	CH_2 (on ring C)	10	2·55	
5	3·24	Aromatic protons of ring C	11	2·35	$H_{(1)}$
6	3·15				

methylenedioxy-group of ring A to positions 5 and 6, rather than to positions 7 and 8, or 6 and 7, is based on the fact that two methylenedioxy-peaks separated by 0·28 τ unit are observed. Had the methylenedioxy-group on ring A been on either of these last two sets of positions then the chemical shifts of the two methylenedioxy-groups would have been

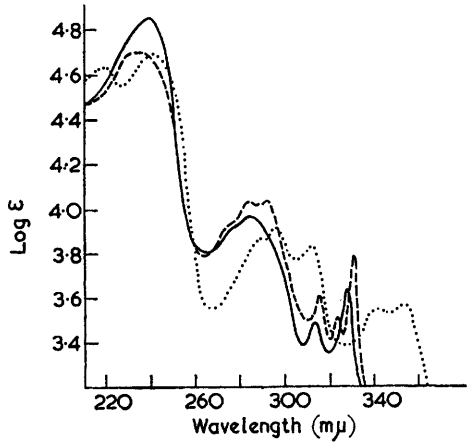


FIG. 1. Ultraviolet spectrum of dehydroguiaretic acid, (· · ·) tetradehydro-otobain, and (– – –) compound (V; R = Me).

identical and only one peak, of weight equivalent to four protons, would have been observed. Placing the methylenedioxy-group on positions 5 and 6 must restrict the rotation of ring C about the 4,1′-bond and by using an appropriate molecular model for an averaged molecular conformation, in which the plane of ring C lies at right angles to that of rings A and B, it is easy to show [6,7] that the proton magnetic resonance absorption peak of the CH_2 on ring A should be about 0·3 τ unit to higher applied fields than that of the CH_2 on ring C. Further, in this conformation, the 3-methyl peak should lie about 0·3 τ unit upfield from that of the 2-methyl peak. The observed separation between the methyl resonances is 0·33 τ unit. The characteristic aromatic peaks, 5—11, of the observed spectrum of tetradehydro-otobain are also accounted for by structure (VII) and further substantiate both the structure and the averaged conformation mentioned above. Peaks 7—10 form a typical AB spectrum in which the coupling constant is 8·4 c.p.s. and the chemical shift between the A and B nuclei is 0·22 p.p.m. These can only arise from two protons, *ortho* to one another, on an aromatic ring as on positions 7 and 8 of ring A. Peaks 5 and 6 are consistent with the spectrum expected from 2′-, 5′-, and 6′-protons, and the τ value of peak 11 is that expected from $H_{(1)}$. The proton magnetic resonance spectrum obtained from tetradehydro-otobain is completely accounted for by formula (VII).

The above reasoning is confirmed and formula (VIII) substantiated by the high-resolution proton magnetic resonance spectrum of otobain. This is shown in Fig. 3 and the τ values of the observed peaks and their assignments to functional groups are listed

[6] Pople, *J. Chem. Phys.*, 1956, **24**, 1111.
[7] Porte, Gutowsky, and Hunsberger, *J. Amer. Chem. Soc.*, 1960, **82**, 5057.

in Table 2. In the otobain spectrum the resonance absorption peaks of the methyl groups have moved upfield to positions whose τ values are characteristic of alicyclic methyl groups. Peaks characteristic of a benzylic CH_2 group and of a doubly benzylic CH group are present in the otobain spectrum. Hence in otobain ring B is reduced.

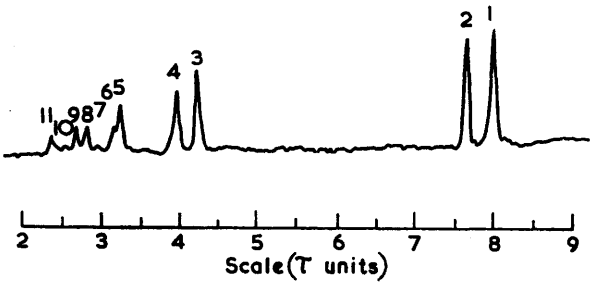


FIG. 2. Proton magnetic resonance spectrum of tetradehydro-otobain.

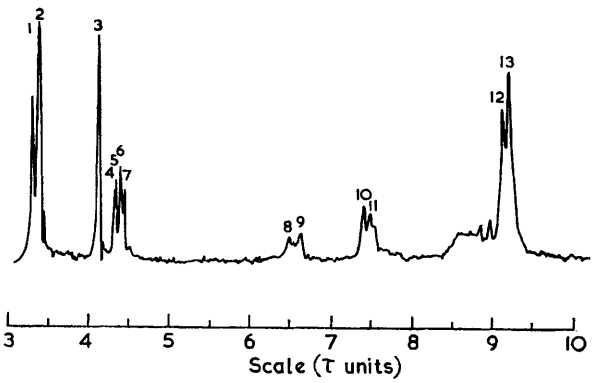
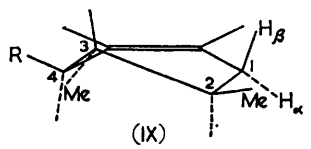


FIG. 3. Proton magnetic resonance spectrum of otobain.

TABLE 2.

Peak	τ	Assignment	Peak	τ	Assignment
1	3·30	$H_{(7)}$, $H_{(8)}$	8	6·53	$H_{(4)}$
2	3·38	$H_{(2')}$, $H_{(5')}$, $H_{(6')}$	9	6·69	
3	4·12	CH_2 (on ring C)	10	7·44	$CH_{2(1)}$
4	4·32	CH_2 (on ring A)	11	7·54	
5	4·34		Unresolved peaks from 8·5—9·0		$H_{(2)}$, $H_{(3)}$
6	4·41		12	9·16	2-CH_3, 3-CH_3
7	4·43		13	9·23	

Both the configuration and the conformation of ring B in otobain are unambiguously defined by the proton magnetic resonance spectrum shown in Fig. 3. As is to be expected from formulæ (VII) and (VIII), the chemical shift of the CH_2 on ring C is only slightly different in the two compounds. However, that part of the spectrum which arises from the methylenedioxy-protons attached to ring A is markedly different. In otobain, this part of the spectrum is a typical AB spectrum in which the coupling constant is 1·2 c.p.s. and the chemical shift is 0·09 τ unit. This is to be expected from formula (VIII) provided that the conformation of ring B is the pseudo-chair form (IX) and that in this conformation the phenyl group is equatorial. It is only in this conformation that ring C is sufficiently close to the CH_2 on ring A to account for the observed chemical shift of 0·25 τ unit between the two methylenedioxy-groups and at the same time be such that the protons of the CH_2 group on ring A are not symmetrically placed with respect to the π-electron current of ring C; *i.e.*, in this conformation these protons constitute an AB system in otobain in



(IX)

contrast to the A_2 system in tetradehydro-otobain. The coupling constant of 1·2 c.p.s. within this AB system is about ten times as small as that usually observed within alicyclic CH_2 groups,[8] but is similar to that which has been reported for other methylenedioxy-systems.[9] The unusually small CH_2 coupling constant is due to the distortion, by the oxygen atoms, of the electron density within the CH_2 group so that the overlap of the σ-electron densities in the neighbourhood of the hydrogen atoms on which the proton–proton coupling depends, is much reduced in this case.

An unambiguous assignment of the relative configurations of the substituents on ring B of otobain now follows from a comparison of the coupling constants $J_{3,4}$, $J_{2,1\alpha}$, and $J_{2,1\beta}$ observed in Fig. 3 with the corresponding values predicted by Karplus's equation.[10] The appropriate data are given in Table 3. The predicted coupling constants are those to be

TABLE 3.

	Observed coupling constants (c.p.s.)	Coupling constants expected from (IX) (c.p.s.)
$J_{3,4}$	9·6	~9
$J_{2,1\alpha}$	6·0	~7
$J_{2,1\beta}$	6·0	~7

expected when ring B is in the pseudo-chair form (IX) with the phenyl and the two methyl substituents all equatorial and *trans-trans* to one another. Only this conformation and configuration are consistent with the proton magnetic resonance data.

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

The phenolic mixture from otoba fat could not be separated by recrystallisation, further chromatography, or by counter-current distribution between light petroleum and methanol. However, methylation gave only one product, $C_{19}H_{18}O_2(OMe)_2$, which had ultraviolet absorption [$\lambda_{max.}$ (in EtOH) 235, 286 mμ; ε 12,400, 8100] similar to that of otobain. Because of the limited amount of this ether, no attempt has yet been made to establish its relation to otobain. The physical constants (m. p. 106—108°, $[\alpha]_D$ +5°) suggest that it may be iso-otobite (m. p. 106—108°, $[\alpha]_D$ +5·3°) despite the reported lack of a methoxyl group in this compound.

EXPERIMENTAL

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

Isolation of Otobain.—Otoba fat (260 g.) was heated under reflux for 30 min. with potassium hydroxide (150 g.) in ethanol (500 ml.). Dilution with water, followed by repeated extraction with ether, gave a yellow oil (60 g.) which was adsorbed from light petroleum on alumina (2 kg.) and eluted in the following sequence. (*a*) Light-petroleum gave an oil (30 g.) which appeared to be a mixture of unsaturated sesquiterpene hydrocarbons. (*b*) Crystallisation of the benzene eluate from light petroleum yielded otobain (15·4 g.), m. p. 136—137°, $[\alpha]_D$ −43° (*c*, 0·8) (lit.,[1] m. p. 137—138°, $[\alpha]_D$ −35·7°) (Found: C, 74·15; H, 6·35. Calc. for $C_{20}H_{20}O_4$: C, 74·05; H, 6·2%). (*c*) Washing the column with ether–methanol (19 : 1) gave a brown oil which was reabsorbed from benzene on alumina deactivated with 8% of 10% acetic acid. Elution with benzene yielded *hydroxyotobain* as prisms (4·5 g.) (from methylene chloride–light petroleum), m. p. 116—117° $[\alpha]_D$ −28° (*c* 0·8) (Found: C, 70·85; H, 5·6. $C_{20}H_{20}O_5$ requires C, 70·55; H, 5·9%). Benzene–ether (1 : 1) eluted a *phenol* which crystallised from light petroleum–methylene chloride as needles (260 mg.), m. p. 119—132° (Found: C, 73·85; H, 6·85; OMe, 9·25. $C_{20}H_{22}O_4$

[8] Ref. 5, p. 85.
[9] Goodwin, Shoolery, and Johnson, *Proc. Chem. Soc.*, 1958, 306.
[10] Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

requires C, 73·6; H, 6·8; OMe, 9·5%). Further elution with benzene–ether (1 : 1) gave β-sitosterol (385 mg.).

Didehydro-otobain.—Hydroxyotobain (270 mg.) was heated under reflux with sodium acetate (500 mg.) and acetic anhydride (5 ml.) for 2 hr. The product crystallised from light petroleum as needles (170 mg.) of *didehydro-otobain*, m. p. 129·5—130·5°, $[\alpha]_D$ +43° (*c* 0·7) (Found: C, 74·4; H, 5·95. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·65%). The same product was obtained in higher yield by heating hydroxyotobain in benzene under reflux with 10% aqueous toluene-*p*-sulphonic acid for 4 hr. Hydrogenation of didehydro-otobain (35 mg.) in ethyl acetate in presence of 10% palladium–charcoal gave otobain (6 mg.; after repeated crystallisation from methanol and light petroleum).

Tetradehydro-otobain.—Didehydro-otobain (41 mg.) was heated under reflux with dichlorodicyanobenzoquinone (29 mg.) in xylene (10 ml.) for 5 min. The resulting mixture was filtered through alumina and crystallised as prisms (32 mg.) of *tetradehydro-otobain*, m. p. 183—185° (Found: C, 75·1; H, 4·85. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·05%). Dehydrogenation of otobain with 10% palladium–charcoal in diphenyl ether under reflux for 4 hr. also yielded tetradehydro-otobain.

Hydrogenolysis of Otobain.—Otobain (440 mg.) in ether (20 ml.) was added to a solution of sodium (500 mg.) in ammonia (50 ml.) stirred under reflux. After 5 min. sufficient ammonium chloride was added to discharge the blue colour and the solvents allowed to evaporate. The products were adsorbed from benzene on alumina deactivated with 5% of 10% acetic acid. The first fractions eluted with benzene–ether (19 : 1) crystallised from chloroform–light petroleum as prisms (160 mg.) of *phenol B*, m. p. 162—164°, $[\alpha]_D$ −31° (*c* 1 : 1) (Found: C, 76·75; H, 6·95. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%). Further elution gave *phenol A* as needles (195 mg.) (from chloroform–light petroleum), m. p. 197—199°, $[\alpha]_D$ −33° (*c* 0·9) (Found: C, 76·95; H, 7·1%).

These two phenols were treated with dimethyl sulphate and aqueous sodium hydroxide. *Methyl ether A* crystallised from methanol as prisms, m. p. 105—106°, $[\alpha]_D$ −32° (*c* 1·0) (Found: C, 77·6; H, 7·15. $C_{20}H_{22}O_3$ requires C, 77·4; H, 7·15%). *Methyl ether B* formed prisms (from ethanol), m. p. 67—69° (Found: C, 77·65; H, 7·05%).

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

Dehydrogenation of Dipiperonylidenesuccinic Anhydride.—Dipiperonylidenesuccinic anhydride [4] (3·1 g.) was heated under reflux with 10% palladium–charcoal (200 mg.) in diphenyl ether (10 g.) for 5 hr. The mixture was hydrolysed by alkali, then treated with ethereal diazomethane. Absorption of the crude dimethyl ester from benzene on alumina, followed by elution with chloroform–benzene (3 : 7), gave the ester [11] (V; R = CO_2Me) as prisms (1·0 g.) (from chloroform–ethanol), m. p. 216—219° (Found: C, 64·75; H, 4·4. Calc. for $C_{22}H_{16}O_8$: C, 64·7; H, 3·95%).

2,3-*Dimethyl*-3′,4′ : 6,7-*dimethylenedioxy*-1-*phenylnaphthalene* (V; R = Me).—The foregoing ester (173 mg.) was heated under reflux with lithium aluminium hydride (200 mg.) in tetrahydrofuran for 3 hr. The product was adsorbed from benzene–chloroform (1 : 1) on alumina and eluted with chloroform–methanol (99 : 1) as prisms (91 mg.) of the *alcohol* (V; R = CH_2·OH) (from methanol), m. p. 185—187° (Found: C, 68·65; H, 4·95. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%). Catalytic hydrogenation of this product (58 mg.) in ethyl acetate over 10% palladium–charcoal gave *compound* (V; R = Me) (41 mg.), m. p. 173·5—175° (from ethanol–chloroform) (Found: C, 74·9; H, 5·35. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·05%).

Methylation of Phenolic Mixture from Otoba Fat.—The crude phenols (m. p. 119—132°) (55 mg.) in 10% aqueous sodium hydroxide (10 ml.) were heated under reflux with dimethyl sulphate (1 ml.), added during 2 hr. The product formed needles of a *dimethyl ether* (48 mg.) (from light petroleum), m. p. 106—108°, $[\alpha]_D$ +5° (*c* 0·7) (Found: C, 74·35; H, 7·1; OMe, 17·9. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1; OMe, 18·25%).

[11] Haworth and Kelly, *J.*, 1936, 746.

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

The authors thank Professor R. A. Raphael for advice, and the Tropical Products Institute for supplying the otoba fat.

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