

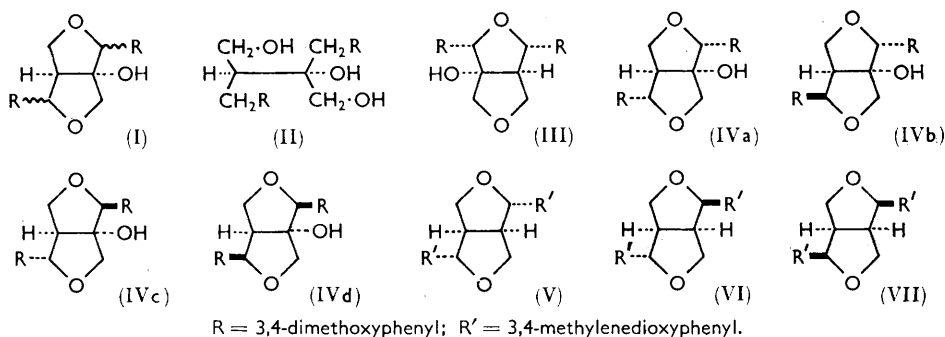
### 519. The Constitution of Gmelinol. Part IV.<sup>1</sup> Stereochemistry and Relationships to Other Lignans.

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Reduction of gmelinol and isogmelinol with sodium in liquid ammonia gives dihydro-derivatives, the reactions, rotations, and proton magnetic resonance spectra of which lead to the absolute configurations (IVb) and (IVa), respectively, for the parent compounds. Dihydrogmelinol-I is a stereoisomer of olivil dimethyl ether, a revised formula for which has been briefly reported.<sup>2</sup>

THE lignan gmelinol,  $[\alpha]_D +124^\circ$ , isolated from *Gmelina leichhardtii* has been shown<sup>1,3</sup> to have structure (I). Acid treatment of gmelinol gives, initially, isogmelinol,  $[\alpha]_D +30^\circ$ ,<sup>4</sup> which was shown to be a simple stereoisomer of gmelinol by the metal-ammonia reduction of both compounds to the same tetrahydro-derivative (II).<sup>1,3</sup> More drastic acid treatment affords the structural isomer neogmelinol (III),<sup>5</sup> and no other stereoisomers of gmelinol have so far been obtained. A compound obtained by Mentzer and his co-workers<sup>6</sup> may be the enantiomer of isogmelinol, but there is at present no proof of its structure.

There are four possible stereoisomeric structures for gmelinol and isogmelinol (IVa—d), the order of thermodynamic stability of which, on the basis of discussions<sup>7</sup> in the related pinosresinol and sesamin fields, is (IVa) > (IVb)  $\approx$  (IVc) > (IVd). Since isogmelinol is the major product from gmelinol in a homogeneous reaction mixture, it must represent a more stable structure, and the observed change in optical rotation ( $94^\circ$ ) corresponds well



with an isomerisation (IVb or c)  $\longrightarrow$  (IVa).<sup>8</sup> The corresponding rotations for the sesamin (V), asarinin (VI), and epiasarinin series (VII) are  $+71^\circ$ ,  $+120^\circ$ , and  $+385^\circ$ , respectively<sup>7</sup> (differences,  $49^\circ$  and  $265^\circ$ ). The replacement of the methoxyl groups by methylenedioxy-groups is known to make little difference to the rotations of compounds of this series.<sup>9</sup> Isogmelinol is therefore (IVa), and gmelinol (IVb) or (IVc), and the compounds have the same absolute configurations as those shown for pinosresinol and sesamin.<sup>7</sup>

Attempts to confirm the stereochemistry were based on removal of one of the

<sup>1</sup> Part III, Birch, Hughes, and Smith, *Austral. J. Chem.*, 1954, **7**, 83.

<sup>2</sup> Smith, *Tetrahedron Letters*, 1963, 991; cf. Freudenberg and Weinges, *ibid.*, 1962, 1077; Traverso, *Gazzetta*, 1960, **90**, 792, 808.

<sup>3</sup> Smith, *J. Proc. Roy. Soc. New South Wales*, 1912, **46**, 187.

<sup>4</sup> Birch and Lions, *J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 391.

<sup>5</sup> Birch, Moore, Smith, and Smith, following Paper.

<sup>6</sup> Combes, Billet, and Mentzer, *Bull. Soc. Chim. biol.*, 1959, **41**, 2014.

<sup>7</sup> Freudenberg and Sidhu, *Tetrahedron Letters*, 1960, No. 20, 3; *Chem. Ber.*, 1961, **94**, 851.

<sup>8</sup> Cf., Freudenberg and Weinges, *Tetrahedron*, 1961, **15**, 115.

<sup>9</sup> Schrecker and Hartwell, *J. Amer. Chem. Soc.*, 1955, **77**, 432.

asymmetric benzyl ether centres. Partial reduction of gmelinol with sodium in liquid ammonia gave a mixture of two dihydro-compounds and the tetrahydro-compound (II). One of the dihydro-compounds, dihydrogmelinol-I, crystallised from a solution of the crude reaction product in ethanol. The other, dihydrogmelinol-II, was not obtained in a crystalline form but was isolated as the crystalline isopropylidene acetal by treatment of the crude mixture, after crystallisation of dihydrogmelinol-I, with acetone and toluene-*p*-sulphonic acid, followed by chromatography on alumina. Acid hydrolysis of the isopropylidene derivative afforded dihydrogmelinol-II as a gum. Spectral studies showed that no isomerisation occurred during these reactions. Similar partial metal-ammonia reduction of isogmelinol gave only dihydrogmelinol-II, showing that gmelinol and isogmelinol differ in stereochemistry at only one of the benzyl ether linkages.

Partial reduction of the gmelinol-type molecule (I) can give two distinct dihydro-derivatives, each of which can exist in two stereoisomeric modifications. The possibilities are (VIIIa and b) and (IXa and b). It is possible to distinguish between structures (VIII) and (IX) by the use of proton magnetic resonance (p.m.r.) spectroscopy. Many examples show that hydrogen atoms on the benzyl carbon atom of benzyl ethers of the above general type normally absorb in the region 4.5—5.5  $\tau$ . In structures (VIII), C-3 carries no hydrogen, so the benzyl ether hydrogen attached to C-2 will appear as a singlet. In structure (IX), C-3 carries one hydrogen and the benzyl ether hydrogen should show as a doublet.

The 60 Mc. p.m.r. spectrum of dihydrogmelinol-I (see Table) shows a one-proton doublet at 4.48  $\tau$  ( $J = 5$  c./sec.), which means that this compound must have structure

## Proton magnetic resonance spectra.

$\tau$	Multi- plicity *	No. of protons	Assignment	$\tau$	Multi- plicity *	No. of protons	Assignment
<i>Olivil dimethyl ether (IXa)</i>				<i>Dihydrogmelinol-I (IXb)</i>			
2.95—3.14	m	6	Aromatic CH	3.04, 3.12	d	6	Aromatic CH
5.22, 5.35	d	1	O-CHR-CH	4.40, 4.50	d	1	O-CHR-CH
5.85—6.43	m	4	CH <sub>2</sub> O	5.65—6.52	m	4	CH <sub>2</sub> O
6.12	s	12	Aromatic OCH <sub>3</sub>	6.11	s	12	Aromatic OCH <sub>3</sub>
7.02	s, br	2	Benzyl CH <sub>2</sub>	6.94	s	2	Benzyl CH <sub>2</sub>
7.55	s + m	3	2OH + methine CH	7.67	m, br	1	Methine CH
				7.82	s	1	Tertiary OH †
				8.58	m, br	1	Primary OH
<i>O-Isopropylidenedihydrogmelinol-II (XII)</i>				<i>Dihydrogmelinol-II (VIIIa) ‡</i>			
2.98—3.28	m	6	Aromatic CH	3.08—3.22	m	6	Aromatic CH
5.33	s	1	OCHR-C	5.14	s	1	O-CHR-C
5.55—6.52	m	4	CH <sub>2</sub> O	6.15	s	12	Aromatic OCH <sub>3</sub>
6.12, 6.13	d	12	Aromatic OCH <sub>3</sub>				
6.75—7.55	m	3	Benzyl CH <sub>2</sub> + methine CH				
8.63	s	3	C-CH <sub>3</sub>				
9.23	s	3	C-CH <sub>3</sub>				

\* s, singlet; d, doublet; m, multiplet; br, broad. † Checked by deuterium exchange. ‡ Only three assignments made.

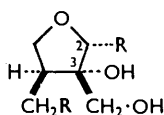
(IXa) or (IXb). The other structure will represent olivil dimethyl ether,<sup>2</sup> a conclusion which was readily verified by the conversion of dihydrogmelinol-I into cyclo-olivil dimethyl ether (X) by the action of acid. Comparison of the p.m.r. spectra of these two compounds (see Table) reveals that certain CH<sub>2</sub>O and OH protons are more highly shielded in dihydrogmelinol-I than in olivil dimethyl ether, and, by analogy with known examples,<sup>10</sup> the 2-3',4'-dimethoxyphenyl group and the 3-hydroxymethyl group are placed *cis* to one another in dihydrogmelinol-I, which therefore has structure (IXb). Olivil dimethyl ether has the absolute configuration (IXa).<sup>2</sup>

<sup>10</sup> E.g., Riggs and Stevens, *Austral. J. Chem.*, 1962, **15**, 305.

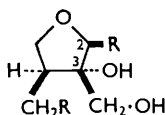
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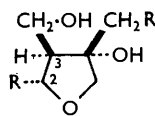
Dihydrogmelinol-II shows a one-proton singlet at 5.14  $\tau$  in the p.m.r. spectrum confirming that it has structure (VIIIa or VIIIb). The spectrum shows no abnormally



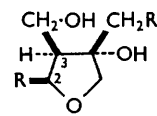
(VIIIa)



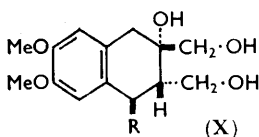
(VIIIb)



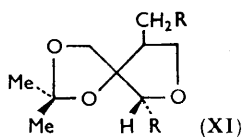
(IXa)



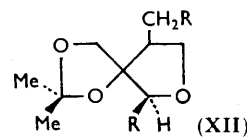
(IXb)



(X)



(XI)



(XII)

shielded  $\text{CH}_2\text{O}$  or  $\text{OH}$  protons, and the 2-3',4'-dimethoxyphenyl group is therefore placed *trans* to the 3-hydroxymethyl group in dihydrogmelinol-II, which thus has structure (VIIIa). This structure is further confirmed by the p.m.r. spectrum of *O*-isopropylidene-dihydrogmelinol-II (see Table) in which the two *C*-methyl groups are shielded to quite different extents. In structure (XI), the 2-3',4'-dimethoxyphenyl group is held at a considerable distance from these methyl groups, but in the stereoisomer (XII) it is very close to one of them and can thus give rise to the observed differential shielding. Structure (XII) corresponds to structure (VIIIa) for dihydrogmelinol-II. Under the same conditions used for the preparation of cyclo-olivil dimethyl ether from dihydrogmelinol-I, acid treatment of dihydrogmelinol-II failed to give any phenyltetralin derivative.

The above evidence confirms structure (IVa) for isogmelinol, and leads to the structure (IVb) for gmelinol. Careful examination of the metal-ammonia reduction product of isogmelinol failed to reveal the presence of any olivil dimethyl ether, the production of which would correspond to the formation of dihydrogmelinol-I in the reduction of gmelinol. The reasons for this selective fission of only one of the benzyl ether bonds are not clear. However, assuming that the hydroxyl group somehow inhibits the fission of the adjacent benzyl ether linkage, the production of two dihydro-compounds in the case of gmelinol may be due to the "axial" nature of the aromatic ring at this centre, providing a steric compression factor which would assist fission there.

## EXPERIMENTAL

P.m.r. spectra were measured on a Varian A60 spectrometer, using *ca.* 20% solutions in deuteriochloroform, with tetramethylsilane as internal standard.

**Sodium-Ammonia Reduction of Gmelinol.**—Gmelinol (401.1 mg.) in pure tetrahydrofuran (10 ml.) was added to dry redistilled liquid ammonia (100 ml.), and the stirred solution treated with sodium (70 mg.). After the disappearance of the blue colour, a little water was added to the yellow solution and the ammonia was evaporated. The residue was treated with water (100 ml.), and the mixture extracted with chloroform ( $3 \times 50$  ml.). The dried ( $\text{MgSO}_4$ ), combined chloroform extracts were filtered, and the solvent was removed, to give a pale brown gum (402.3 mg.) which was dissolved in ethanol (1 ml.) and set aside at  $0^\circ$  for 24 hr. The crude *dihydrogmelinol-I* (111.0 mg.) was obtained as colourless plates, m. p.  $192\text{--}194^\circ$  (from ethanol)  $[\alpha]_D^{21} +59.8^\circ$  (*c* 0.56 in  $\text{CHCl}_3$ ) (Found: C, 65.1; H, 6.95.  $\text{C}_{22}\text{H}_{28}\text{O}_7$  requires C, 65.3; H, 6.95%).

The ethanol from the above filtrate was removed *in vacuo*, and the residual gum was dissolved in pure acetone (15 ml.), treated with a small crystal of toluene-*p*-sulphonic acid, and set aside at room temperature for 24 hr. The solution was made basic by the addition of methanolic sodium methoxide solution, the acetone was evaporated, and the residue treated with water (30 ml.) and extracted with chloroform ( $3 \times 20$  ml.). The combined extracts were

washed with water (10 ml.), dried ( $\text{MgSO}_4$ ), filtered, and evaporated, to give a yellow gum which was dissolved in benzene-chloroform (9 : 1) and chromatographed on alumina (Spence grade H; 50 g.). Elution with benzene-chloroform mixtures (4 : 1 and 1 : 1) and chloroform gave colourless prisms of *O-isopropylidenedihydrogmelinol-II* (251.2 mg.), m. p. 153—156° (from ethanol),  $[\alpha]_D^{21} - 7.2^\circ$  ( $c$  0.575, in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$ . (in  $\text{CS}_2$ ) 1375, 1385  $\text{cm}^{-1}$  ( $\text{CMe}_2$ ), no OH absorption (Found: C, 67.4; H, 7.2.  $\text{C}_{25}\text{H}_{32}\text{O}_7$  requires C, 67.6; H, 7.3%). Further elution with chloroform-ethanol (49 : 1 and 19 : 1) gave a partly crystalline gum (50.7 mg.) shown by spectroscopy to be a mixture of the above isopropylidene compound and tetrahydrogmelinol. This was not investigated further.

*Hydrolysis of O-Isopropylidenedihydrogmelinol-II.*—*O*-Isopropylidenedihydrogmelinol-II (129.3 mg.) in ethanol (2 ml.) was treated with 5*N*-hydrochloric acid (1 ml.), and the mixture warmed on a water-bath to effect dissolution. The solution was cooled to room temperature, set aside for 5 min., diluted with water (15 ml.), and extracted with chloroform (3 × 10 ml.). The combined chloroform extracts were washed with saturated aqueous sodium hydrogen carbonate solution (10 ml.), dried ( $\text{MgSO}_4$ ), filtered, and evaporated, to give a pale yellow gum (115.3 mg.) which could not be purified for analysis. The infrared and p.m.r. spectra of this material were consistent with the formula proposed for dihydrogmelinol-II.

*Sodium-Ammonia Reduction of Isogmelinol.*—Isogmelinol (432.7 mg.) was reduced with sodium (59.7 mg.), as described above, to give a gum (421.9 mg.). The infrared and p.m.r. spectra showed this to be almost pure dihydrogmelinol-II, and with acetone-toluene-*p*-sulphonic acid it gave *O*-isopropylidenedihydrogmelinol-II, m. p. 153—156° (undepressed on admixture with a sample of the above material). The infrared spectrum (Nujol) and specific rotation were identical with those of the material obtained from gmelinol.

*Cyclisation of Dihydrogmelinol-I.*—Dihydrogmelinol-I (102.4 mg.) in 50% aqueous acetic acid (5 ml.) was heated at 100° for 24 hr. After cooling, water (20 ml.) was added and the mixture extracted with chloroform (3 × 10 ml.). The combined chloroform extracts were washed with saturated aqueous sodium hydrogen carbonate solution (10 ml.), dried ( $\text{MgSO}_4$ ), filtered, and evaporated. The residual gum crystallised when treated with a small amount of ethanol. The product, m. p. 100—180°,  $w_{\text{a}}$ ; dissolved in benzene-chloroform (4 : 1) and chromatographed on Florisil (12 g.). Elution with benzene-chloroform yielded small amounts of partly crystalline gums, which were not further investigated. Elution with chloroform-ethanol (19 : 1) gave, after removal of the solvent, white plates (81.1 mg.), m. p. 186—188° (from acetone), identical with an authentic specimen of cyclo-olivil dimethyl ether similarly prepared from olivil dimethyl ether.

*Attempted Cyclisation of Dihydrogmelinol-II.*—Treatment of dihydrogmelinol-II (94.2 mg.) with 50% aqueous acetic acid (1.5 ml.) by the above method afforded a gum, which was chromatographed on Florisil (10 g.). Elution with benzene-chloroform (1 : 1) and chloroform gave a colourless gum (81.2 mg.). The infrared spectrum of this was identical with that of the starting material, and a portion was converted into the *O*-isopropylidene derivative, m. p. 153—156°, in good yield. Further elution gave no other material.

We are indebted to Mrs. R. H. Cornforth and Dr. F. Lions for a gift of gmelinol, and to Professor R. D. Haworth for a specimen of olivil dimethyl ether. The work was carried out during the tenure of an Imperial Chemical Industries Limited Fellowship (M. S.).