520. *The Conversion of Gmelinol into Neogmelinol.*

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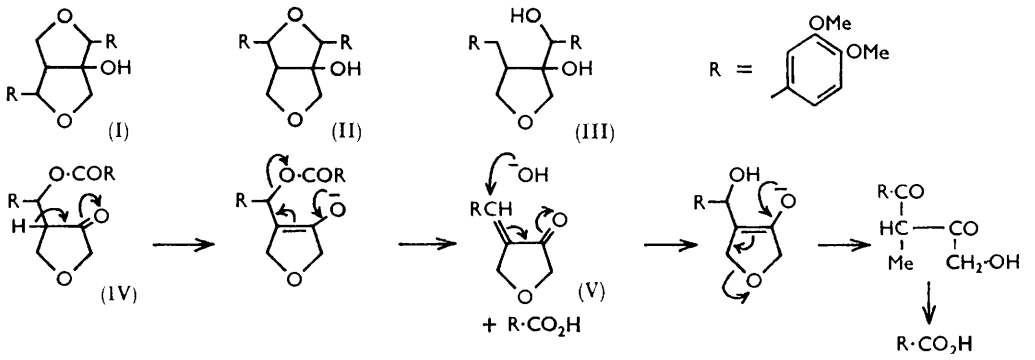
The action of perchloric acid in acetic acid on gmelinol (I) gives neogmelinol (II), the structure of which is supported by the nature and reactions of the products of chromic acid oxidation, and of metal–ammonia reduction.

Formula (I) was assigned [1] to the lignan gmelinol which has been converted by the action of acid [2] into isogmelinol, differing sterically at one or both of the centres carrying the aromatic rings.[1] Theoretically there are four such isomers, and we attempted to obtain others by acid treatment of gmelinol or isogmelinol with the object of studying their relative configurations, and ultimately of assigning a configuration to gmelinol. The best reagent for this purpose is a solution of perchloric acid in acetic acid.[3] Reaction with gmelinol gave first isogmelinol and then a third isomer, neogmelinol (II), which is, however, not one of the desired stereoisomers but a structural isomer.

Neogmelinol, $C_{22}H_{26}O_7$, contains a hydroxyl group, as shown by infrared spectroscopy and the formation of a monoacetyl derivative. The ultraviolet spectrum is identical with those of gmelinol and pinoresinol dimethyl ether. Reduction with sodium in liquid ammonia gave only a dihydro-derivative (III), in contrast to gmelinol and isogmelinol which were converted into the same tetrahydro-derivative by hydrogenolysis of both benzyl ether linkages. All isomers of gmelinol differing sterically only at the ether centres should give this tetrahydro-derivative. From this result and from the known structural requirements for ether fissions by this reagent, neogmelinol almost certainly does not contain two such benzyl ether linkages, and attempted further reduction gave only gums, apparently resulting from attack on the aromatic rings.

Dihydroneogmelinol gave rise to a diacetate, and to an isopropylidene acetal by reaction with acetone. It therefore probably contains two vicinal hydroxyl groups. This was confirmed by periodate oxidation, which, however, was very slow (incomplete after 3 days). The product contained 3,4-dimethoxybenzaldehyde and, from the infrared absorption maximum (CCl_4) at 1756 cm.$^{-1}$, a carbonyl group in a five-membered ring.



Support for structure (II) was obtained by oxidation of neogmelinol with chromic acid in acetone, to give a keto-ester, $C_{22}H_{24}O_8$ (IV), shown to be a five-membered ring ketone and an ester of an aromatic acid by infrared spectroscopy, $\nu_{max.}$ (CCl_4) 1756 and 1708 cm.$^{-1}$. It gave a 2,4-dinitrophenylhydrazone in the spectrum of which the first band was absent. Reaction of the oxidation product with 2N-methanolic potassium hydroxide under reflux

[1] (*a*) Birch, Hughes, and Smith, *Austral. J. Chem.*, 1954, **7**, 83; (*b*) Birch and Smith, preceding Paper.
[2] Birch and Lions, *J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 391; Harradence and Lions, *ibid.*, 1940, **74**, 117.
[3] Birch, Milligan, Smith, and Speake, *J.*, 1958, 4471.

gave a small amount of 3,4-dimethoxybenzaldehyde and almost two moles of 3,4-dimethoxybenzoic acid. The mechanism of this fission can be interpreted in detail in several related ways, which all depend on the fact that the substance has two oxygen atoms each β to a carbonyl group, and that, at some stage, the enol of a β-diketone is generated by conjugation of a double bond with an aromatic ring, for example, as shown. Some evidence of the ready formation of (V) was found by examining the product of chromatography of (IV) on alumina. Although this was a gum, the ultraviolet spectrum was very similar to that of methyl 3,4-dimethoxycinnamate; 3,4-dimethoxybenzoic acid was formed simultaneously.

Confirmation of many of the structural features was obtained by means of proton magnetic resonance (p.m.r.) spectroscopy (see Table). The spectrum of neogmelinol shows a one-proton singlet at 5·30 τ and a one-proton doublet at 5·45, 5·39 τ, demonstrating

Proton magnetic resonance spectra.

τ	Multiplicity *	No. of protons	Assignment
	Neogmelinol (II)		
2·95—3·15	m	6	Aromatic CH
5·30	s	1	O·CHR·C
5·45, 5·59	d	1	O·CHR·CH
5·91, 6·48	m	4	CHO_2
6·14	s	12	Aromatic OCH_3
7·15	s	1	OH †
7·35	m	1	Methine CH
	Keto-ester (IV)		
2·64	m	2	Aromatic H *ortho* to COR
2·95—3·25	m	4	Aromatic CH
4·93, 5·09	d	1	O·CHR·CH
5·39, 5·47	d	2	$CO·CH_2O$
5·72, 5·91	d(?)	2	CH_2O
6·11, 6·18; 6·16	d + m	12	Aromatic OCH_3
7·11	m, br	1	Methine CH
	Dihydro-compound (III)		
3·02—3·25	m	6	AromaticCH
5·26	s	1	O·CHR·C
5·83—6·48	m	4	CH_2O
6·16	s	12	Aromatic OCH
6·85	s	1	OH
7·00—7·63	m	3	Benzyl CH_2 and methine CH
8·93	m	1	OH
	O-*Isopropylidene dihydroneogmelinol* (VIIIa)		
3·06—3·30	m	6	Aromatic CH
5·03	s	1	O·CHR·C
5·97—6·56	m	4	CH_2O
6·10	s	12	Aromatic OCH_3
6·85—7·58	m	3	Benzyl CH_2 and methine CH
8·51	s	2	$C(CH_3)_2$
8·79	s	3	$C(CH_3)_2$

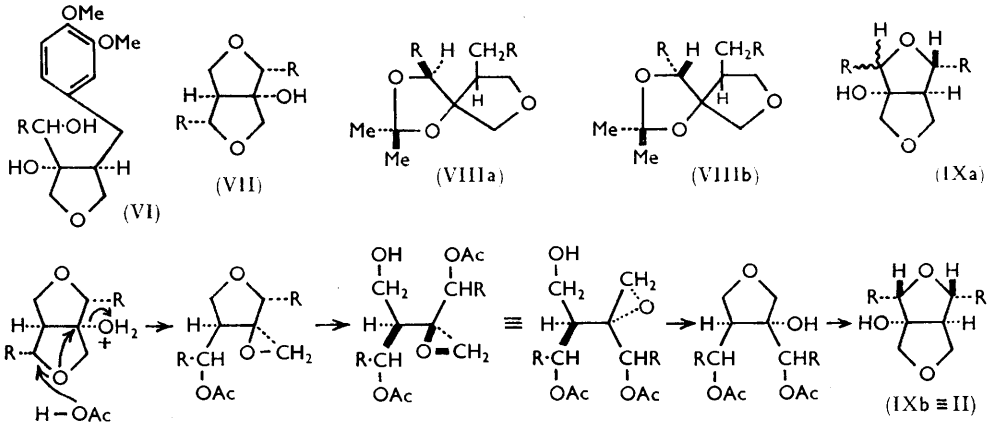
* s, singlet; d, doublet; m, multiplet; br, broad. † Checked by deuterium exchange.

the two types of benzyl ether hydrogen atom (ref. 1*b*). The rest of the spectrum is in accord with the proposed structure. The spectrum of dihydroneogmelinol shows a one-proton singlet at 5·26 τ, indicating that the suggested mode of fission of the dibenzyl ether linkage is correct. The high resonance position of the benzyl hydroxyl group (8·93 τ) may be due to hydrogen-bonding to the other aromatic ring (VI). The spectrum of oxidised neogmelinol is again in accord with the proposed structure. The presence of a one-proton doublet at 4·93, 5·09 τ indicates which of the benzyl positions has been oxidised.

The selective reductive fission of only one of the two benzyl ether linkages in neogmelinol must be related to the presence of the hydroxyl group. Inhibition of fission of the adjacent ether link by alkoxide formation is unlikely to be the reason, since the reaction can be carried out in the presence of ethanol. It is possible that fission of the opposite link is facilitated by cyclic donation of the hydroxyl proton.

It has been observed qualitatively that isomerisation of gmelinol into isogmelinol (VII) (for mechanism see ref. 3) is much more rapid than into neogmelinol, and no isomerisation similar to the formation of neogmelinol occurs in compounds lacking the hydroxyl group, *e.g.*, eudesmin or pinoresinol. Direct acid-fission of both benzyl ether groups, followed by rotation about the central bond and re-closure of the ether rings, would lead to the extremely unlikely strained *trans*-fusion of the rings in neogmelinol; such a molecule

would have ample opportunity under the reaction conditions to change into a more stable molecule such as a phenyltetralin. If the ring junction in (II) is *cis*, there must be inversion at an asymmetric centre in the carbon backbone, a process indicative of a special mechanism, probably involving the hydroxyl group. The process shown is suggested as a possibility. Probably equilibration of the ether centres is also involved. A considerable amount of gum, of unassigned structure, was also produced. The configuration was assigned on the assumption that neogmelinol is the most stable isomer, since equilibration can obviously occur. Some support for the configuration (IXb) can be obtained from a



consideration of the p.m.r. spectrum of *O*-isopropylidenedihydroneogmelinol, which shows no abnormally shielded benzyl CH_2 protons. Of the two possible stereoisomers (VIIIa and b), models of the latter show that the 3,4-dimethoxyphenyl group of the benzyl ether is held very close to the benzyl CH_2 adjacent to the second dimethoxyphenyl group, and this isomer can therefore be discounted. On this basis neogmelinol must be (IXa) with the configuration of one 3,4-dimethoxyphenyl group undefined. This must be α (IXb ≡ II) if it is in the stable configuration as expected.

Experimental

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

Neogmelinol (II).—Gmelinol (10 g.) was dissolved by warming in glacial acetic acid (30 ml.), the solution cooled, and perchloric acid (70%; 3 ml.) added. After 3 days the brown solution was diluted with water (200 ml.) and extracted with ethyl acetate (3 × 100 ml.). The combined extracts were washed with sodium hydrogen carbonate solution and dried ($MgSO_4$). The solution was passed through a column of alumina to remove most of the colour, and the solvent was evaporated. The gummy residue was dissolved in hot methanol (30 ml.), a little water added, and the solution left to crystallise. *Neogmelinol* (3·6 g.) was obtained as colourless prisms, m. p. 161—163° (from methanol), $\lambda_{max.}$ (EtOH) 232, 279 mμ (log ε 3·58, 3·03), $\nu_{max.}$ (Nujol) 3410 $cm.^{-1}$ (OH) (Found: C, 65·4; H, 6·3. $C_{22}H_{26}O_7$ requires C, 65·7; H, 6·5%).

Neogmelinol (100 mg.), acetic anhydride (2 ml.), and pyridine (2 ml.) were heated on a steam-bath for 2 hr., the solvent was removed under reduced pressure, and the residue taken up in ether. Working up in the usual way and sublimation at 180°/0·1 mm. gave *O-acetylneogmelinol* (107 mg.) as a yellow gum (Found: C, 64·65; H, 6·3. $C_{24}H_{28}O_8$ requires C, 64·85; H, 6·35%), $\nu_{max.}$ (CCl_4) 1746 $cm.^{-1}$ (O·COMe).

Dihydroneogmelinol (III).—To neogmelinol (400 mg.), in ethanol (5 ml.) and liquid ammonia (70 ml.), was added sodium (140 mg.) in small pieces. After the disappearance of the blue colour, water (5 ml.) was cautiously added and the ammonia evaporated. The residue was extracted

with ether, and afforded *dihydroneogmelinol* (315 mg.) as colourless plates, m. p. 146—149° (from aqueous ethanol) $\nu_{max.}$ (Nujol) 3420 cm.$^{-1}$ (OH) (Found: C, 65·25; H, 7·05. $C_{22}H_{28}O_7$ requires C, 65·3; H, 6·9%).

The dihydro-compound (93 mg.) was acetylated as for neogmelinol, and gave *di-O-acetyldihydroneogmelinol* (83 mg.) as a gum (Found: C, 63·9; H, 6·8; OAc, 15·9. $C_{26}H_{32}O_9$ requires C, 63·8; H, 6·55; 2OAc, 17·6%), $\nu_{max.}$ (CCl_4) 1741 cm.$^{-1}$ (O·COMe).

Dihydroneogmelinol (260·5 mg.) in pure acetone (15 ml.) was treated with a small crystal of toluene-*p*-sulphonic acid and set side at room temperature overnight. After making the solution alkaline by addition of sodium methoxide solution, the acetone was removed under reduced pressure, and the residue treated with water (20 ml.) and extracted with chloroform (3 × 20 ml.). This gave *O-isopropylidenedihydroneogmelinol* (VIIIa) (267·0 mg.) as colourless needles, m. p. 123—124° (from ethanol), $\nu_{max.}$ (CCl_4) 1375, 1385 cm.$^{-1}$ (CMe_2) (Found: C, 67·3; H, 7·05. $C_{25}H_{32}O_7$ requires C, 67·5; H, 7·25%).

Oxidation of Dihydroneogmelinol.—Dihydroneogmelinol (105 mg.), in dioxan (25 ml.) and water (20 ml.), was treated with sodium metaperiodate (62·2 mg.) in water (10 ml.) and 5N-aqueous sulphuric acid (1 ml.). After 3·5 days at room temperature, an excess of sodium arsenite was added and the mixture steam-distilled. The steam-distillate afforded 3,4-dimethoxybenzaldehyde (3·5 mg.), isolated by ether extraction, with infrared spectrum identical with that of an authentic sample. The steam-distillation residue, after cooling, was extracted with ether, and afforded a yellow gum (95·7 mg.). The infrared spectrum of this showed it to consist mainly of starting material, but also had a medium intensity band (CCl_4) at 1758 cm.$^{-1}$.

Oxidation of Neogmelinol.—Neogmelinol (98·2 mg.) in pure acetone (20 ml.) containing anhydrous magnesium sulphate (2 g.) was treated, with swirling, with 0·8N-chromic acid (2 ml.), added during 5 min. Propan-2-ol was added to destroy the excess of chromic acid, the mixture was filtered, and the solvent evaporated. The green residue was treated with water (30 ml.) and extracted with chloroform (3 × 15 ml.). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution (10 ml.), and dried ($MgSO_4$), and afforded the ***keto-ester*** (IV) (94·1 mg.) as a yellow gum which formed colourless prisms, m. p. 106—107° (from ethanol), $\lambda_{max.}$ (EtOH) 265, 284 mμ (log ε 3·42, 3·23), $\nu_{max.}$ ($CHCl_3$) 1767, 1719 cm.$^{-1}$ (Found: C, 63·35; H, 5·75. $C_{22}H_{24}O_8$ requires C, 63·4; H, 5·8%).

The *2,4-dinitrophenylhydrazone*, purified by chromatography on bentonite–kieselguhr (3 : 1) in chloroform–ethanol (1 : 1), formed needles, m. p. 165—168° (from ethanol), $\lambda_{max.}$ ($CHCl_3$) 350 mμ (log ε 3·38), $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$ (Found: C, 56·4; H, 4·55. $C_{28}H_{28}N_4O_{11}$ requires C, 56·5; H, 4·7%).

The keto-ester (40 mg.) in tetrahydrofuran (1 ml.) and N-aqueous sodium hydroxide solution (4 ml.) was refluxed for 30 min., diluted with water, and extracted with ether. The aqueous solution was acidified and extracted with chloroform, to give 3,4-dimethoxybenzoic acid (22 mg.), m. p. 181—184° (from water), undepressed by an authentic specimen.

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