327. *The Orientation of Some Veratrole Derivatives by Hydrogen Nuclear Magnetic Resonance Spectroscopy.*

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The hydrogen nuclear magnetic resonance spectra of a number of veratrole derivatives are reported. Long-range shielding by a phenyl group has been used as a criterion for orientation.

Treatment of 4,5-dichloroveratrole with ethereal methyl-lithium yields 4,5-dimethylveratrole, but only one of the chlorine atoms in 4,5-dichloro-3-phenylveratrole can be similarly replaced.[1] The orientation of the product has now been established.

The hydrogen nuclear magnetic resonance spectrum of 4,5-dichloro-3-phenylveratrole (see Table) shows methoxyl absorptions at $\tau = 6{\cdot}23$ and 6·59, the former being assigned to the 1-methoxyl group since the corresponding absorption by 4,5-dichloroveratrole is at 6·28. Similarly, 4,5-dimethyl-3-phenylveratrole gives methoxyl bands at 6·26 and 6·62, and methyl bands at 7·82 and 8·16. The absorptions at 6·26 and 7·82 are assigned, respectively, to the 1-methoxyl and the 5-methyl group, since the corresponding bands in the spectrum of 4,5-dimethylveratrole appear at 6·19 and 7·95. The presence of two methoxyl and two methyl absorptions in the spectra of the 3-phenylveratroles is ascribed to long-range shielding by the phenyl group of the substituents adjacent to it. Similar effects have been observed [2] in other systems.

The product of the reaction [1] between 4,5-dichloro-3-phenylveratrole and methyllithium shows a single methyl absorption at 7·69, which is slightly lower than that due to the 5-, but considerably lower than that due to the 4-methyl group (respectively 7·82 and 8·16) in 4,5-dimethyl-3-phenylveratrole. This indicates that the methyl group is in a relatively unshielded position, and that the compound is 4-chloro-5-methyl-3-phenylveratrole. This orientation is supported by the position of the absorption due to the 6-hydrogen atom. By taking that at 3·08 in 4,5-dichloro-3-phenylveratrole as a standard, and applying the values quoted by Diehl [3] for the shielding effect of chlorine and methyl substituents in *ortho-* and *meta*-positions, it may be predicted that the 6-hydrogen atom in 4,5-dimethyl-3-phenylveratrole should absorb at 3·37. The experimental value of 3·40 is in excellent agreement with this and indicates that Diehl's figures, determined for other compounds under different solvent and concentration conditions, are applicable to the 5,6-disubstituted 3-phenylveratrole system. Similar calculations for the 4-chloro-5-methyl and the 5-chloro-4-methyl compound predict resonances at, respectively, 3·30 and 3·15; the observed value for the chloro-methyl derivative is 3·35.

Prolonged refluxing of 3-phenylveratrole with sulphuryl chloride yields [4] the 4,5-dichloro-derivative, but a monochloro-compound can be isolated if the reaction is stopped after a short time. This product shows methoxyl absorptions at 6·27 and 6·57. The separation (0·30 p.p.m.) between these is more than that (0·25 p.p.m.) observed for 3-phenylveratrole, suggesting that the coplanarity of the rings in the monochloro-derivative is less than that in the parent compound, and that the chlorine atom has entered the 4-position. This is confirmed by a quartet at 3·15 ($\delta_{5,6} = 0{\cdot}35$) with $J \sim 9$ c./sec., characteristic [5] of an *ortho*-AB system.

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[1] Bruce and Sutcliffe, *J.*, 1956, 3824.

[2] Curtin, Gruen, Hendrickson, and Knipmeyer, *J. Amer. Chem. Soc.*, 1961, **83**, 4838; Curtin, Gruen, and Shoulders, *Chem. and Ind.*, 1958, 1205; Brownstein, *J. Amer. Chem. Soc.*, 1958, **80**, 2300; Goodwin, Shoolery, and Johnson, *Proc. Chem. Soc.*, 1958, 306.

[3] Diehl, *Helv. Chim. Acta*, 1961, **44**, 829.

[4] Bruce and Sutcliffe, *J.*, 1956, 3820.

[5] Jackman, " Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p. 85.

The largest methoxyl separation (0·46 p.p.m.) is observed with 4-(2,3-dimethoxyphenyl)cinnoline, the deviation from coplanarity of the rings being increased by interaction of the hydrogen atoms at positions 6 and 5 of, respectively, the dimethoxyphenyl and the cinnoline nuclei, but a direct comparison with the 3-phenylveratroles cannot be made as the ring currents in the phenyl and the cinnolinyl groups are probably different. Interactions which lead to loss of coplanarity are most severe in 4,5-dichloro-3-(5,6-dichloro-2,3-dimethoxyphenyl)- and 3-(2,3-dimethoxy-5,6-dimethylphenyl)-4,5-dimethylveratrole, but here the methoxyl separations are, respectively, only 0·23 and 0·28 p.p.m. Estimation of the shielding of the methoxyl group is complicated by the possibility of rotation about the C–OMe bond which may lead to different motional averaging of the shielding effects as the rings become less coplanar. Comparison of the methyl-group separations (0·34 and 0·50 p.p.m., respectively) in 4,5-dimethyl-3-phenyl- and 3-(2,3-dimethoxy-5,6-dimethylphenyl)-4,5-dimethyl-veratrole supports this view.

Hydrogen nuclear magnetic resonance spectra of veratrole derivatives.

	OMe			
Veratrole	(τ)	Separation (p.p.m.)	Me (τ)	6-H (τ)
4,5-Dichloro-[4]	6·28	—	—	3·24
3,4,5-Trichloro-	6·23, 6·27	0·04	—	3·17
4,5-Dichloro-3-iodo-[4]	6·18, 6·25	0·07	—	3·07
4,5-Dichloro-3-(5,6-dichloro-2,3-dimethoxyphenyl)-[4]	6·15, 6·38	0·23	—	3·01
4,5-Dimethyl-[1]	6·19	—	7·95	3·50
3-Phenyl-[6]	6·27, 6·52	0·25	—	(*a*)
4,5-Dichloro-3-phenyl-[4]	6·23, 6·59	0·36	—	3·08
4,5-Dimethyl-3-phenyl-[1]	6·26, 6·62	0·36	7·82, 8·16 (*b*)	3·40
3-(2,3-Dimethoxy-5,6-dimethylphenyl)-4,5-dimethyl-[1]	6·27, 6·55	0·28	7·82, 8·32 (*c*)	3·42
4-Chloro-5-methyl-3-phenyl-[1]	6·27, 6·61	0·34	7·69	3·35
4-Chloro-3-phenyl-	6·27, 6·57	0·30	—	(*d*)
6-Methoxy-3-phenyl-[6]	6·24, 6·30, 6·42	—	—	(*e*)
4-Phenyl-	6·29, 6·33	0·04	—	(*f*)
3-(4-Cinnolinyl)-[7]	6·08, 6·54	0·46	—	(*g*)
4-(4-Cinnolinyl)-[7]	6·02, 6·04	0·02	—	(*h*)

(*a*) ABC-type spectrum due to 4,5,6-H_3; most intense line at 3·17. (*b*) Separation 0·34 p.p.m. (*c*) Separation 0·50 p.p.m. (*d*) AB-type quartet centred at 3·15, due to 5,6-H_2; $\delta_{5,6} = 0·35 \pm 0·04$; $J_{5,6} = 8·7 \pm 0·5$ c./sec. (*e*) AB-type quartet centred at 3·28, due to 4,5-H_2; $\delta_{4,5} = 0·31 \pm 0·04$; $J_{4,5} = 8·7 \pm 0·5$ c./sec. (*f*) ABC-type spectrum due to 3,5,6-H_3; most intense lines at 2·90, 3·06, 3·23, 3·38. (*g*) ABC-type spectrum due to veratrole 4,5,6-H_3 not distinguished. (*h*) ABC-type spectrum due to veratrole 3,5,6-H_3 not distinguished.

That the separation between the methoxyl absorptions of the above compounds is at least in part due to long-range shielding is supported by the fact that the bands in the spectra of 4-phenylveratrole and 4-(3,4-dimethoxyphenyl)cinnoline are separated by, respectively, only 0·04 and 0·02 p.p.m. However, the introduction of a 6-methoxyl group into 3-phenylveratrole reduces the overall separation, suggesting that other effects may be involved.

The methoxyl separations, respectively 0·04 and 0·07 p.p.m., observed for 3,4,5-trichloro- and 4,5-dichloro-3-iodo-veratrole may be due to the steric effect of the 3-halogen atom which restricts the rotation of the 2-methoxyl group about its C–OMe bond, and so causes it to be more shielded by the aromatic nucleus than the 1-methoxyl group.

It is of interest that the absorptions due to the phenyl-hydrogen atoms in 4-chloro- and 4-chloro-5-methyl-3-phenylveratrole are singlets at 2·75 and 2·80, respectively,

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[6] Bruce and Sutcliffe, *J.*, 1955, 4435.

[7] Bruce, *J.*, 1959, 2366.

whereas those in the other derivatives are complex groups with centres in the 2·6—2·8 region.

EXPERIMENTAL

Nuclear magnetic resonance spectra were measured at 60 Mc./sec. with an Associated Electrical Industries model RS2 spectrometer, tetramethylsilane being used as internal standard. Solutions, of 20—35% concentration in carbon tetrachloride except for 4-(3,4-dimethoxyphenyl)cinnoline which was 20% in deuterochloroform, were contained in sample tubes of 4 mm. internal diameter. M. p.s are corrected.

3,4,5-*Trichloroveratrole.*—3-Amino-4,5-dichloroveratrole [4] (5·6 g.) in 10% hydrochloric acid (90 c.c.) was diazotised with aqueous 20% sodium nitrite, and the solution was added with stirring to cuprous chloride (4 g.) in concentrated hydrochloric acid (20 c.c.) at 0—5°. The suspension was heated during 1 hr. to 80°, then cooled, and the solid was collected and dissolved in light petroleum (60 c.c.; b. p. 60—80°), washed with aqueous 10% sodium hydroxide, then with water, and dried (Na_2SO_4). Removal of the solvent and distillation of the residue gave an oil, b. p. 90°/0·2 mm., which solidified, and on being crystallised from light petroleum (b. p. 40—60°) afforded 3,4,5-trichloroveratrole (5·4 g., 90%) as needles, m. p. 68·5° (lit.,[8] 68—69°) (Found: Cl, 44·0. Calc. for $C_8H_7Cl_3O_2$: Cl, 44·1%).

4-*Chloro*-3-*phenylveratrole.*—3-Phenylveratrole [6] (2·14 g.) was refluxed for 30 min. with freshly distilled sulphuryl chloride (10 c.c.), and the excess was then removed. The residue, in ether, was washed with aqueous 10% sodium hydroxide, then with water, and the solution was dried (Na_2SO_4). Removal of the solvent, and distillation of the residue gave an oil, b. p. 102°/0·02 mm., which solidified, and, on being crystallised from light-petroleum (b. p. 40—60°) and then from methanol gave 4-*chloro*-3-*phenylveratrole* (6-*chloro*-2,3-*dimethoxybiphenyl*) (1·3 g., 52%) as rhombic tablets, m. p. 90·5—91° (Found: C, 67·6; H, 5·1; Cl, 14·0. $C_{14}H_{13}ClO_2$ requires C, 67·6; H, 5·2; Cl, 14·3%), $\lambda_{max.}$ (in dioxan) 286 mμ (log ε 3·34); when refluxed for 8 hr. with an excess of sulphuryl chloride, it afforded 4,5-dichloro-3-phenylveratrole,[4] m. p. and mixed m. p. 90°.

4-*Phenylveratrole.*—A mixture of 1-(3,4-dimethoxyphenyl)cyclohexene [6] (0·21 g.), chloranil (0·47 g.), and sulphur-free xylene (4 c.c.) was refluxed for 7½ hr., cooled, and filtered. The filtrate was washed with aqueous 10% sodium hydroxide, then with water, and dried (Na_2SO_4). Removal of the solvent and distillation [bulb-to-bulb, 140°(bath)/0·02 mm.] gave 4-phenylveratrole (0·12 g., 58%), needles (from pentane), m. p. 70·5° (lit.,[9] 70°) (Found: C, 78·2; H, 6·4. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·5%).

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[8] Cousin, *Compt. rend.*, 1898, **127**, 759; *Ann. Chim. Phys.*, 1903, **29**, 62.

[9] Harris and Christiansen, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1934, **23**, 530.