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The Nature of Some Derivatives of Leucodrin

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Abstract

The structures of *O*-isopropylideneleucodrin aryl methyl ether and leucodrin nor-aldehyde have been revised on the basis of spectroscopic studies of these compounds and their acetyl derivatives.

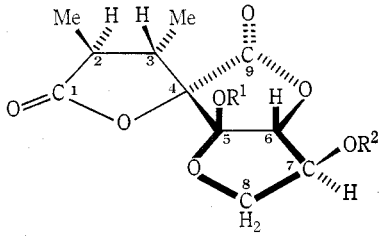
In the course of studies[1] on the absolute stereochemistry of piptoside (1) we have prepared a number of derivatives of leucodrin (2), isolated from *Leucodendron adscendens* by the method of Rapson.[2]

Leucodrin (2) may be converted into an *O*-isopropylidene derivative which may in turn be methylated to the corresponding aryl methyl ether. Murray and Bradshaw[3] found that, on treatment with two equivalents of alkali followed by excess of sodium metaperiodate, *O*-isopropylideneleucodrin aryl methyl ether consumed only one molecular proportion of periodate. They treated the reaction mixture with mineral acid to cleave the acetal, neutralized the reaction mixture with sodium carbonate, and evaporated the resulting mixture to dryness. Extraction of the solid residue with ethanol, removal of solvent from the extract, and subsequent treatment of the oily residue with *p*-nitrophenylhydrazine sulphate gave the *p*-nitrophenylosazone of glycolaldehyde. On the basis of these results they claimed that this isopropylidene derivative was 5,8-*O*-isopropylideneleucodrin aryl methyl ether.

Formation of a seven-membered *O*-isopropylidene ring is unusual and would be particularly surprising in this instance where the hydroxyl groups at C 7 and C 8 appear to be ideally situated for formation of the usual five-membered ring derivative. P.m.r. spectral results suggest strongly that these compounds are in fact 7,8-*O*-isopropylideneleucodrin (3) and its aryl methyl ether (4). In the p.m.r. spectrum of 7,8-*O*-isopropylideneleucodrin aryl methyl ether (4), the doublet of doublets at δ 4·8 collapses to a doublet after exchange with deuterium oxide. The splitting of this doublet is reproduced twice in the doublet of doublets at δ 3·5 assigned to H 6. The other reproduced splitting in the doublet of doublets at δ 4·8 is the same as that of the doublet at δ 4·4 which is replaced by an HOD peak after exchange. The doublet of doublets at δ 4·8 must then be assigned to H 5 coupled to both H 6 and the proton of the hydroxyl group at C 5.

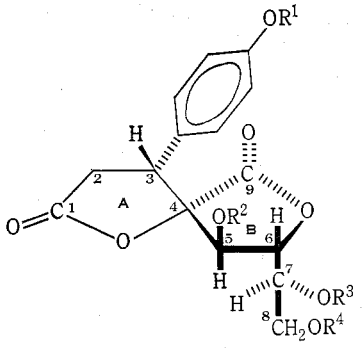
[1] Lowry, J. B., McAlpine, J. B., and Riggs, N. V., *Aust. J. Chem.*, 1975, **28**, 109.
[2] Rapson, W. S., *J. Chem. Soc.*, 1938, 282.
[3] Murray, A. W., and Bradshaw, R. W., *Tetrahedron*, 1967, **23**, 1929.

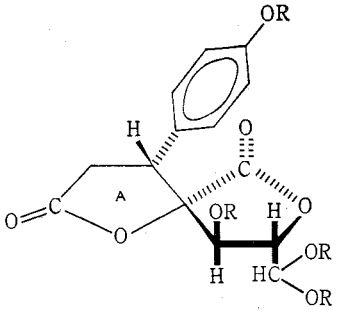
The assignment of the doublet of doublets at δ 3·5 to H 6 requires comment. This is the only hydrogen atom in the molecule attached to a carbon bearing an acyloxy group and as such it may have been expected to resonate considerably further downfield. Models in which the lactone rings have been puckered slightly in such a way as may be expected to reduce non-bonded interactions have this hydrogen very close to and in the shielding region of the aromatic ring attached to C 3. This shielding effect is seen as accounting for the relatively upfield position of the signal of H 6.



	R^1	R^2
(1)	H	β-D-glucopyranosyl
(6)	Me	tetra-*O*-methyl-β-D-glucopyranosyl

	R^1	R^2	R^3	R^4
(2)	H	H	H	H
(3)	H	H	$-CMe_2-$	
(4)	Me	H	$-CMe_2-$	
(5)	Me	Ac	$-CMe_2-$	





(7) R = H
(8) R = Ac

To confirm these results 7,8-*O*-isopropylideneleucodrin aryl methyl ether (4) was acetylated. The product had a melting point considerably lower than that recorded by Rapson,[2] but spectral results were in complete accord with its formulation as 5-*O*-acetyl-7,8-*O*-isopropylideneleucodrin methyl ether (5). Rapson's product had a melting point almost identical with that of 7,8-*O*-isopropylideneleucodrin aryl methyl ether (4) and it is possible that he recovered starting material from his acetylation mixture. Our product showed in its infrared spectrum a very strong band at 1800 cm^{-1} arising from the two lactone carbonyls and a strong band at

1750 cm^{-1} attributable to the acetate carbonyl. The p.m.r. spectrum had a singlet of six-proton intensity at δ 1·31 assigned to the protons of the *gem*-dimethyl group, and a singlet of three-proton intensity at δ 2·30 assigned to the protons of the acetate group. The doublet of doublets at δ 3·6 is assigned to H 6, and one of the reproduced splittings here is the same as that of the doublet at δ 5·9 which is assigned to H 5. The aromatic protons give rise to rough doublets at δ 6·86 and 7·29, and the methoxyl protons give rise to a singlet at δ 3·77. The multiplet at δ 3·0 probably arises from two of the protons of ring A and the multiplet around δ 4·1 must then be assigned to the remaining proton on ring A and to the three protons attached to C 7 and C 8.

The uptake of only one mole of periodate by 7,8-*O*-isopropylideneleucodrin aryl methyl ether (4) after treatment with alkali is surprising and it may be that only ring B is opened; it is of interest that one of the lactone rings of penta-*O*-methylpiptoside (6) is not opened by dilute alkali under reflux for 5 h.[4] Other workers[5] have obtained variable results in periodate oxidation of leucodrin (2) under the given conditions. The glycolaldehyde isolated as *p*-nitrophenylosazone by Murray and Bradshaw[3] could have arisen from the expected cleavage product, glyceraldehyde, of a compound of structure (4) as the result of a retroaldol reaction during evaporation of the reaction mixture to dryness.

When leucodrin (2) was subjected to periodate oxidation according to the method described by Murray and Bradshaw[3] for production of leucodrin nor-aldehyde, the product obtained melted at 181–183° (cf. lit.[3] 178–179°) and analysed satisfactorily for $C_{14}H_{12}O_7,H_2O$. Any absorption at 1720 cm^{-1} in the infrared spectrum of our product was however very weak. Further, although the p.m.r. spectrum showed peaks at the values published,[3,6] the integrated intensities in the spectrum of our product differed from those given by Murray and Bradshaw. The p.m.r. spectrum indicates that our product was the stable *gem*-diol (7) of leucodrin nor-aldehyde. The broad singlet at δ 9·5 is exchangeable and does not therefore arise from the aldehyde proton; it is assigned here to the phenolic proton. The aromatic protons give rise to rough doublets around δ 6·6 and 7·2. Both the doublet at δ 6·4 and the triplet at δ 6·15, which integrate for a total of three protons, disappear on treatment of the sample with deuterium oxide. The triplet is considered to be a pair of overlapping doublets, and the three exchangeable doublets are assigned to the three protons of the aliphatic hydroxyl groups. The spectrum upfield of these signals is considerably simplified when the sample is treated with deuterium oxide. The multiplets at δ 4·6 and 4·9 collapse to sharp doublets with splittings of 8 and 3 Hz, respectively. These splittings are each reproduced twice in the doublet of doublets at δ 3·3 and, as the very-low-field (δ 6·8) aliphatic-proton doublet in the spectrum of leucodrin nor-aldehyde tetraacetate (8) (see below) has a splitting of 3 Hz, the signal at δ 4·9 is assigned to H 7, that at δ 4·6 to H 5, and that at δ 3·3 to H 6. The multiplet of two-proton intensity at δ 3·0 and the two lines around δ 4·2 must then be assigned to the protons of ring A. Leucodrin nor-aldehyde *gem*-diol (7) formed a syrupy acetyl derivative which could not be crystallized but whose p.m.r. and infrared spectra are fully in accord with its formulation as leucodrin nor-aldehyde tetraacetate (8).

[4] Riggs, N. V., and Stevens, J. D., *Aust. J. Chem.*, 1966, **19**, 683.
[5] Perold, G. W., Howard, A. S., and Hundt, H. K. L., *J. Chem. Soc. C*, 1971, 3136.
[6] Murray, A. W., and Bradshaw, R. W., *Tetrahedron Lett.*, 1966, 3773.

Experimental

General Procedures

General procedures followed have been previously described.[1]

Isolation of Leucodrin (2)

Air-dried leaves of *L. adscendens* male plant (470 g) were milled and extracted continuously with ethanol in a Soxhlet apparatus for 36 h. The extract was concentrated on a rotary evaporator to an almost solid residue (203 g). This was digested in water (1 l.) and treated with basic lead acetate solution (6·6%; 800 ml). After 2 h the mixture was filtered and solvent was removed from the filtrate to give a solid residue (112 g). The residue deposited crystals of leucodrin (33 g) from water. Samples were thrice recrystallized from water before use in subsequent experiments. A similar extraction of leaves (500 g) of the female plant gave leucodrin (31·9 g). Each sample gave an infrared spectrum identical with that of an authentic sample.

7,8-O-Isopropylideneleucodrin (3)

Treatment of leucodrin (4·2 g) according to the method of Rapson[2] gave 7,8-*O*-isopropylideneleucodrin (3·5 g), m.p. 236–238·5° (after two recrystallizations from benzene–light petroleum) (lit.[2] m.p. 229–231·5°). P.m.r. spectrum (δ) (in C_5D_5N): 1·30, s (6H), 2·7–3·6, m (3H), 3·98 (exchangeable) superimposed on 3·8–4·9, m (total 5H), 5·17, d (1H).

7,8-O-Isopropylideneleucodrin Aryl Methyl Ether (4)

7,8-*O*-Isopropylideneleucodrin (3) (3·5 g) in methanol was treated with diazomethane in ether until t.l.c. indicated that no starting material remained. Solvent was removed and the residue was recrystallized from propanol to give 7,8-*O*-isopropylideneleucodrin aryl methyl ether (3·2 g), m.p. 161–163°. ν_{max} (Nujol): 1024, 1061, 1114, 1248, 1277, 1780, 3560 cm^{-1}. P.m.r. spectrum (δ): 1·31, s (6H), 3·0, m (2H), 3·5, d of d (1H), 3·75, s (3H), 4·0, m (4H), 4·4, d (1H), 4·8, d of d (1H), 6·83, d (2H), 7·30, d (2H). After addition of D_2O, the doublet at δ 4·4 disappeared, a singlet (HOD) appeared at δ 5·65, and the doublet of doublets at δ 4·8 collapsed to a doublet.

5-O-Acetyl-7,8-O-isopropylideneleucodrin Aryl Methyl Ether (5)

7,8-*O*-Isopropylideneleucodrin aryl methyl ether (400 mg) in pyridine (0·7 ml) and acetic anhydride (0·3 ml) was allowed to stand for 16 h and poured into iced water. The mixture was filtered and the precipitate was purified by chromatography on a preparative layer of 'Kieselgel PF 254' developed with methylene chloride. The band of highest R_F was extracted with hot ethanol. Solvent was removed from the extract and the oily residue was recrystallized from ethanol to give needles of 5-*O*-acetyl-7,8-*O*-isopropylideneleucodrin aryl methyl ether, m.p. 138–139°. ν_{max} (Nujol): 1036, 1054, 1068, 1178, 1225, 1260, 1523, 1750, 1800 cm^{-1}. P.m.r. spectrum (δ): 1·31, s (6H), 2·30, s, (3H), 3·0, m (2H), 3·6, d of d (1H), 3·77, s (3H), 3·9–4·3, m (4H), 5·90, d (1H), 6·86, d (2H), 7·29, d (2H).

Leucodrin Nor-Aldehyde gem-*Diol (7)*

Leucodrin was treated with sodium metaperiodate according to the method of Murray and Bradshaw.[3] The crude product, after several recrystallizations from water and treatment with charcoal, gave leucodrin nor-aldehyde *gem*-diol, m.p. 181–183° (Found: C, 54·0; H, 4·7. Calc. for $C_{14}H_{12}O_7,H_2O$: C, 54·2; H, 4·6%). ν_{max} (Nujol): 1045, 1081, 1117, 1198, 1227, 1263, 1272, 1770, 1802, 3333, 3460, 3497 cm^{-1}. P.m.r. spectrum (δ) [in $(CD_3)_2SO$]: 3·0, m (2H), 3·3, m (1H), 4·2, rough d (1H), 4·7, m (2H), 6·1, d and overlapping 6·2, d (2H), 6·4, d (1H), 6·6, d (2H), 7·2, d (2H), 9·5, s (1H). After addition of D_2O: 3·0, m (2H), 3·3, d of d (1H), 3·9, s (HOD peak), 4·2, rough d (1H), 4·6, d (1H), 4·9, d (1H), 6·6, d (2H), 7·2, d (2H).

Leucodrin Nor-Aldehyde Tetraacetate (8)

Leucodrin nor-aldehyde *gem*-diol (7) (135 mg) in acetic anhydride (3 ml) and pyridine (2 ml) was allowed to stand for 22 h and poured into water. The semisolid precipitate was filtered off. Attempts

to crystallize it failed even after it had been chromatographed on a silicic acid column developed with benzene : ethyl acetate (1 : 1). The oily product had ν_{max} 1020, 1050, 1200 (br), 1750 (br), 1800 cm^{-1}. P.m.r. spectrum (δ): 2·00, s and overlapping 2·01, s (6H), 2·25, s (6H), 3·0, m (2H), 3·8, d of d (1H), 4·2, rough quartet (1H), 5·9, d (1H), 6·8, d (1H), 7·2, quartet (4H).

Acknowledgments

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