"Homoerythrina" Alkaloids from *Schelhammera pedunculata* F. Muell. (Family Liliaceae)

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THERE has recently been considerable interest in the alkaloids from *Kreysigia multiflora* (family Liliaceae), because of the occurrence in that plant of both homoaporphine and homomorphine alkaloids.[1] These and related alkaloids[2] are considered to be derived by oxidative coupling from 1-phenylethyl-1,2,3,4-tetrahydroisoquinoline precursors. A further addition to the known types of these biosynthetically linked alkaloids has been found in three new alkaloids isolated from *Schelhammera pedunculata* F. Muell., which belongs to the same tribe Uvularieae of the family Liliaceae, as *K. multiflora*. The new alkaloids are the first members of the "homoerythrina" group, and two major alkaloids, schelhammerine (Ia) and schelhammeridine (IIa), and a minor alkaloid, schelhammericine (Ib), make up 75% of the total alkaloids of *S. pedunculata*. The structures of the three alkaloids and the relative stereochemistry at all centres other than C-2 in (Ia) were determined from a study of the 100 Mc./sec. n.m.r. spectra by double irradiation, and the complete structure and absolute stereochemistry of (Ia) were obtained from an *X*-ray crystal structure analysis of schelhammerine hydrobromide.

Schelhammerine (Ia), m.p. 173—174°, $[\alpha]_D$ + 186° ($CHCl_3$), has the molecular formula $C_{19}H_{23}NO_4$ (M^+ at *m/e* 329). The n.m.r. spectrum of (Ia) in $CDCl_3$ solution (Table) shows signals assigned to two *para* aromatic protons, a methylenedioxy-group, a methoxy-group, and one olefinic proton. The presence of an alcohol group is shown by the formation of an *O*-acetyl derivative (Ic), m.p. 143—144°, $[\alpha]_D$ + 242° ($CHCl_3$), M^+ 371, ν_{max} ($CHCl_3$) 1720 cm.$^{-1}$, three-proton singlet at δ 2·04. Chemical shift data and coupling constants are set out in the Table, and form the basis of the stereochemical assignments indicated for (Ia). The

Nuclear magnetic resonance spectra[a]

Proton	δ values (Me_4Si, δ 0·00) 1	2	3*eq*	4*eq*	4*ax*	7	15	18	O·CH_2O	O·CH
(Ia)	5·62(d)	4·06(m)	3·50(m)	2·60(q)	2·06(q)		6·71	6·52	5·82(s)	2·77
(Ib)	5·54(m)		3·68(m)	2·90(q)	1·79(q)		6·86	6·56	5·87(d), 5·85(d)	2·76
(Ic)	5·59(d)	5·25(m)	3·55(m)	2·95(q)	1·86(q)		6·68	6·53	5·83(s)	2·78
(Id)	5·72(d)	4·50(m)					6·62	6·53	5·82(s)	2·66
2-*epi*-(Id)	5·72(d)	4·66(m)					6·72	6·51	5·82(s)	3·13
(IIa)[a]	6·13(d)	5·63(q)	3·40(m)	3·13(q)	1·85(q)	5·44(q)	6·51	6·40	5·25(d), 5·14(d)	2·71
			3*ax*							
(IIb)[a]	6·36(q)	5·71(q)	3·66(m)	3·04(q)	1·80(t)	5·76(m)	6·60(s)	6·40(s)	5·82(s)	
(IIc)	6·44(q)	5·66(q)	4·86(m)	3·12(q)	1·92(t)	5·82(m)	6·60(s)	6·42(s)	5·87(d), 5·83(d)	

Coupling constants (*c./sec.*)

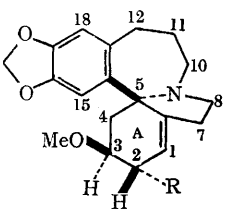
	$J_{1,2}$	$J_{2,3eq}$	$J_{3eq,4ax}$	$J_{3eq,4eq}$	$J_{4ax,4eq}$	J_{OCH_2O}
(Ia)	2·8	~3	3·2	5·0	13·9	
(Ib)			3·1	4·8	13·8	1·5
(IIa)	9·4	5·0	4·5	~1	13·0	1·5
		$J_{1,3ax}$	$J_{2,3ax}$	$J_{3ax,4ax}$	$J_{4ax,4eq}$	
(IIb)	9·5	2·5	~1	12·0	12·0	

[a] All spectra measured in $CDCl_3$ except (IIa) in C_6D_6 and (IIb) in $CDCl_3/CD_3OD$ (1 : 1). Abbreviations: *ax*, axial; *eq*, equatorial; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

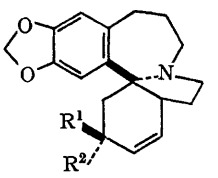
magnitude of the C-2–H, C-3–H coupling ($J \sim 3$ c./sec.) did not permit the configuration at C-2 to be assigned.

The structure and absolute stereochemistry (2*S*, 3*S*,5*S*) of (Ia) were determined by an *X*-ray crystal structure analysis of schelhammerine hydrobromide, m.p. 276°, which crystallizes in the orthorhombic space group $P2_12_12_1$ with $a = 21{\cdot}22$, $b = 9{\cdot}64$, $c = 8{\cdot}92$ Å. The bromide ion was located from the Patterson function, and the light atoms from successive electron density and difference maps. The absolute configuration as shown in (Ia) was determined by Bijvoet's method using Co-K_α radiation. The absolute stereochemistry at C-5 is therefore the same as in β-erythroidine[3] and erythratine,[4] and both (Ia) and erythratine have ring A in the half-chair form, but the C-2 and C-3 substituents are *trans*-diaxial in (Ia) whereas they are *trans*-diequatorial in erythratine.

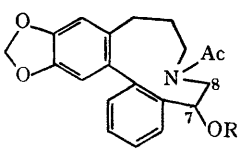
Schelhammeridine (IIa), m.p. 118°, $[\alpha]_D$ − 108° ($CHCl_3$), has the molecular formula $C_{19}H_{21}NO_3$ (M^+ 311). A detailed double-resonance study of the 100 Mc./sec. n.m.r. spectrum in C_6D_6 solution leads to the assignments shown in the Table. In refluxing 10% hydrochloric acid, the 3β-methoxy-group of (IIa) is displaced to give as a major product the 3α-hydroxy-derivative (IIb), m.p. 233—235°, $[\alpha]_D$ + 20° ($CHCl_3$), M^+ 297, which in



(I) a; R=OH
b; R=H
c; R=OAc
d; R=Cl



(II) a; R^1=OMe, R^2=H
b; R^1=H, R^2=OH
c; R^1=H, R^2=Ac



(III) a; R=Ac
b; R=H

acetic anhydride–pyridine at room temperature forms the *O*-acetyl derivative (IIc), m.p. 103—105°, $[\alpha]_D$ + 48° ($CHCl_3$), M^+ 339, three-proton singlet at δ 1·97, ν_{max} ($CHCl_3$) 1630 cm.$^{-1}$. The assignment of the relative stereochemistry at C-3 in (IIa), (IIb), and (IIc) can be made from comparison of the coupling constants for the C-4 axial proton, as this signal appears as a quartet ($J_{4ax,4eq}$ 13·0

† Physical constants are not recorded as (Id) was not obtained entirely free from the C-2 epimer.

c./sec., $J_{4ax,3eq}$ 4·5 c./sec.) in the n.m.r. spectrum of (IIa) and as triplets ($J_{4ax,4eq}$ 12·0 c./sec., $J_{4ax,3ax}$ 12·0 c./sec.) in the spectra of both (IIb) and (IIc).

To establish the relationship of schelhammeridine (IIa) to schelhammerine (Ia), the reaction of (Ia) with methanesulphonyl chloride in pyridine was studied. Schelhammeridine is formed in approximately 20% yield in this reaction, the other products being two chloro-compounds, (Id)† and the C-2 epimer of (Id), of which the latter (m.p. 195—196°, $[\alpha]_D$ − 58° in $CHCl_3$, isotopic molecular ions at *m/e* 347, 349) is predominant. Schelhammeridine (IIa) therefore has the same absolute configuration at C-3 and C-5 (3*S*,5*S*) as (Ia), and its closest analogue among the 1-benzyl-1,2,3,4-tetrahydroisoquinoline-derived *Erythrina* alkaloids is erythraline[5] which has a similar diene system and the same absolute configuration at C-5, but the opposite at C-3.

Reaction of (IIa) with acetic anhydride at reflux temperature leads to aromatization of ring A, with the formation of (IIIa), m.p. 108—110°, $[\alpha]_D$ − 28° ($CHCl_3$), M^+ 381, ν_{max} ($CHCl_3$) 1640, 1730 cm.$^{-1}$, three-proton singlets at δ 1·97 and δ 1·89 (NAc and OAc), a pair of one-proton doublets at δ 5·89 and δ 5·91 (nonequivalent protons of methylenedioxy-group), one-proton singlets at δ 6·65 and δ 6·74 (C-18–H and C-15–H), a four-proton multiplet between 700—760 c./sec. (ABCD aromatic proton system) and an ABX quartet at δ 5·72 (C-7 proton, J_{AX} 5·0, J_{BX} 10·0 c./sec.). Hydrolysis of (IIIa) gives (IIIb), m.p. 269—270°, $[\alpha]_D$ − 45° ($CHCl_3$), M^+ 339, which on oxidation with MnO_2 affords the corresponding ketone, m.p. 203—204°, $[\alpha]_D$ ± 0° ($CHCl_3$), M^+ 337, ν_{max} ($CHCl_3$) 1690 (ArCO), 1650 cm.$^{-1}$ (NAc), a three-proton singlet at δ 1·82 (NAc), AB doublets (*J* 16·0 c./sec.) at δ 2·64 and δ 4·36 (C-8 protons). The formation of an optically inactive ketone on oxidation of (IIIb) shows that the optical activity of (IIIb) can be attributed to the new asymmetric centre at C-7 and not to diphenyl asymmetry, and indicates that the conversion of (IIa) into (IIIa) takes place by a fully concerted mechanism.

The third and minor alkaloid, schelhammericine, m.p. 76—77°, $[\alpha]_D$ + 122° ($CHCl_3$), M^+ 313, was characterized as (Ib) from the n.m.r. data (Table). This structure was confirmed and the absolute configuration (3*S*,5*S*) established by the formation of (Ib) identical with schelhammericine, as a product of the catalytic hydrogenation of (IIa) in acetic acid solution.

(*Received, July 2nd,* 1968; *Com.* 878.)

[1] (a) A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 450; (b) J. Fridrichsons, M. F. Mackay, and A. McL. Mathieson, *Tetrahedron Letters*, 1968, 2887; N. K. Hart, S. R. Johns, J. A. Lamberton, and J. K. Saunders, *ibid.*, p. 2891; A. R. Battersby, M. H. G. Munro, R. B. Bradbury, and F. Šantavý, *Chem. Comm.*, 1968, 695.

[2] A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, 1965, 228, and other papers cited in reference 1a.

[3] A. W. Hanson, *Acta Cryst.*, 1963, **16**, 939.

[4] V. Boekelheide and M. Y. Chang, *J. Org. Chem.*, 1964, **29**, 1303; D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *Chem. Comm.*, 1966, 294.

[5] W. Nowacki and G. F. Bonsma, *Z. Krist.*, 1958, **110**, 89.