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Retrorsine Hydrobromide Ethanol Solvate: A Pyrrolizidine Alkaloid

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Abstract. $C_{18}H_{26}NO_6^+.Br^-.C_2H_6O$, monoclinic, $P2_1$, $a = 13{\cdot}76\,(1)$, $b = 8{\cdot}33\,(1)$, $c = 10{\cdot}36\,(1)$ Å, $\beta = 108{\cdot}4\,(5)°$, $D_c = 1{\cdot}298$ Mg m^{-3}, μ(Cu $K\alpha$) = 255 mm^{-1}. Intensities were measured using the equi-inclination Weissenberg method; films were scanned with an automatic densitometer. The structure was solved by the heavy-atom method and refined to $R = 0{\cdot}081$. The ester carbonyls are antiparallel. The C=C–C=O grouping is *cis* with a dihedral angle of 43·7 (3)°; the central C–C bond length is 1·40 (3) Å and hence conjugated, as suggested by the long $\lambda_{\max}$ of 215 nm in the UV spectrum.

Introduction. The present analysis forms part of a structural study of pyrrolizidine alkaloids (PA's) whose structure and/or toxicity are of particular interest (Stoeckli-Evans & Crout, 1976; Stoeckli-Evans, 1979). Retrorsine, a PA derived from retronecine, is mainly found in the plant family Compositae (genus *Senecio*) (Bull, Culvenor & Dick, 1968). It is one of the many extremely toxic PA's which are important in the etiology of human and animal liver disease (Schoental, 1968; McLean, 1970; Mattocks, 1972). Like jacobine (Pérez-Salazar, Cano & García-Blanco, 1978) and swazine (Laing & Sommerville, 1972), with which it will be compared, retrorsine possesses a 12-membered macro-ring; as distinct from fulvine (Sussman & Wodak, 1973), monocrotaline (Stoeckli-Evans, 1979) and axillarine (Stoeckli-Evans & Crout, 1976), which contain 11-membered macro-rings. All six alkaloids are derived from retronecine (Bull *et al.*, 1968).

Retrorsine was isolated from *Senecio isatideus* DC. Crystals of the hydrobromide were grown by slowly cooling a saturated ethanol solution. Those suitable for X-ray analysis were sealed in Lindemann-glass tubes with a small amount of mother liquor. Layers *h*0*l*–*h*7*l* were recorded by the equi-inclination Weissenberg method using Ni-filtered Cu $K\alpha$ radiation on multiple-film packs. The films were scanned by the Science Research Council densitometer service with an Optronics P-1000 photoscan. The intensities were corrected for Lorentz–polarization effects only. 977 unique observed reflections were obtained. The structure was solved by means of Patterson and Fourier difference syntheses. Initial isotropic full-matrix least-squares refinement was followed by cycles of block-diagonal least-squares (*BLOK*) (*X-ray ARC*, 1973). Layer scales were refined separately and applied to the data after every second cycle of *BLOK*. Only the Br atom was refined anisotropically and its atomic scattering curve was corrected for anomalous dispersion. All atomic scattering curves were taken from *International Tables for X-ray Crystallography* (1974). Six reflections exhibited strong extinction and were removed from the final cycles of *BLOK*. Refinement was terminated at $R = 0{\cdot}0813$, $R_w = 0{\cdot}1022$ (average parameter shift ≤ 0·3 e.s.d.). The weighting scheme used was $\sqrt{w} = 1$ if $F_o \le 32$, otherwise $\sqrt{w} = 32/F_o$. A final difference

Table 1. *Final positional* (×10^4) *and thermal* (×10^4) *parameters and their standard deviations*

	x	y	z	$U_{\rm iso}$ (Å^2)
Br	955 (2)	2500	1068 (3)	*
C(1)	8731 (14)	4777 (27)	2346 (20)	225 (28)
C(2)	9227 (17)	3984 (33)	3448 (24)	385 (59)
C(3)	9280 (14)	2110 (27)	3202 (19)	281 (52)
N(4)	8870 (10)	2093 (20)	1656 (14)	173 (37)
C(5)	8113 (18)	710 (35)	1192 (25)	432 (63)
C(6)	7176 (14)	1510 (28)	42 (21)	246 (48)
C(7)	7200 (12)	3273 (24)	563 (18)	125 (39)
C(8)	8343 (12)	3672 (25)	1111 (17)	98 (37)
C(9)	8533 (14)	6506 (28)	2187 (20)	218 (46)
O(10)	7599 (9)	6979 (15)	2486 (12)	198 (31)
C(11)	7679 (14)	7117 (28)	3780 (20)	257 (48)
C(12)	7609 (11)	7676 (33)	4033 (16)	181 (39)
C(13)	5782 (14)	6577 (29)	3155 (21)	242 (48)
C(14)	6011 (14)	4753 (28)	3593 (20)	234 (47)
C(15)	5370 (13)	3680 (26)	2400 (18)	168 (42)
C(16)	5737 (13)	3469 (28)	1295 (19)	201 (44)
O(17)	6780 (8)	3373 (17)	1621 (12)	172 (29)
O(18)	5212 (11)	3523 (21)	89 (16)	397 (40)
O(19)	8450 (11)	6821 (19)	4713 (15)	349 (38)
O(20)	6828 (8)	7502 (26)	5432 (12)	281 (28)
C(21)	6505 (17)	9404 (32)	3612 (24)	386 (59)
O(22)	7424 (11)	10334 (21)	4155 (16)	426 (41)
C(23)	4756 (15)	7107 (28)	3353 (21)	305 (53)
C(24)	4506 (14)	3018 (25)	2489 (19)	248 (50)
C(25)	3799 (18)	2007 (32)	1399 (25)	470 (69)
C(26)	8477 (33)	3479 (63)	6841 (44)	1267 (159)
C(27)	8665 (26)	1846 (46)	7498 (36)	885 (113)
O(28)	7942 (16)	737 (30)	7056 (22)	816 (66)

* U_{11} 425 (9), U_{22} 400 (13), U_{33} 699 (13), U_{12} −78 (19), U_{13} 299 (9), U_{23} −132 (21).

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synthesis revealed no peaks higher than possible H atoms; no attempt was made to locate them. Final positional and thermal parameters are given in Table 1.*

Discussion. Bond distances and angles and their standard deviations are given in Table 2. A comparison of the torsion angles in the macrocyclic rings of jacobine, swazine and retrorsine is given in Table 3. Fig. 1 shows the atom-labelling scheme used. The absolute configuration of retrorsine was assigned by comparison with that of jacobine bromohydrin (Fridrichsons, Mathieson & Sutor, 1963), as both are derived from the same pyrrolizidine nucleus retronecine (Bull *et al.*, 1968). The geometry of retrorsine is similar to that of jacobine and swazine. Structural features of interest are:

(*a*) The pyrrolizidine nucleus exists in the *exo*-puckered form (Bull *et al.*, 1968) with a puckering angle of 31·5 (5)° between the planes defined by C(5), C(6), C(7) and C(5), N(4), C(8). In jacobine this angle is 37° and in swazine 51°.

(*b*) Unlike the 11-membered macrocyclic PA's, such as monocrotaline, C(1), C(2), C(3), N(4), C(8) and C(9) are not coplanar; deviations as large as 0·1 Å are found for certain atoms, owing to the different orientation of the C(9) ester function (see *e*).

(*c*) The angle between the least-squares planes defined by C(1), C(2), C(3), N(4), C(8) and C(5), N(4), C(8), C(7) of the pyrrolizidine nucleus is 123·7 (5)°, compared to 127° in jacobine and 125° in swazine.

(*d*) The pyrrolizidine-ring-fusion distance N(4)—C(8) is 1·52 (2) Å, compared to 1·51 Å in jacobine and 1·50 Å in swazine.

(*e*) The carbonyl bond of the C(7) ester function of retronecine-derived PA's is always directed below the plane of the macro-ring. The direction of the carbonyl bond of the C(9) ester function varies according to the size of the macro-ring. In 12-membered macro-ring PA's, such as retrorsine, it is directed above the plane of the macro-ring, while in 11-membered macro-ring PA's, such as monocrotaline, it is directed below.

(*f*) The *R*HC=C—C=O grouping is *cis* with a central C—C bond length of 1·40 Å, and a dihedral angle of 43·7 (3)°. In swazine the same grouping has a central C—C bond length of 1·49 Å, and a dihedral angle of 54°; while in senkerkine (Birnbaum, 1974) the central C—C bond length is 1·48 Å and the dihedral angle 39°.

The Br atom is 3·1 Å from $N^{i}(4)$, and the hydroxyl group of the molecule of ethanol of crystallization is 2·9 Å from O(22), and hence hydrogen bonded. There is a short intramolecular hydrogen bond between the C(12) hydroxyl substituent and the carbonyl oxygen O(19), the distance O(20)—O(19) being 2·63 Å, compared to 2·68 Å in swazine, 2·71 Å in jacobine and 2·68 Å in senkerkine. This situation causes a displacement of the —OH IR stretching frequency (Bull *et al.*, 1968). It does not occur in 11-membered macro-ring PA's, such as monocrotaline, because the C(9) carbonyl group is directed below the plane of the macro-ring and hence away from the C(12) hydroxyl substituent.

Table 2. *Bond distances* (Å) *and bond angles* (°)

C(1)—C(2)	1·31 (3)	C(12)—O(20)	1·41 (2)
C(1)—C(8)	1·53 (3)	C(12)—C(21)	1·50 (4)
C(1)—C(9)	1·46 (3)	C(13)—C(14)	1·59 (3)
C(2)—C(3)	1·59 (4)	C(13)—C(23)	1·55 (3)
C(3)—N(4)	1·52 (2)	C(14)—C(15)	1·55 (3)
N(4)—C(5)	1·53 (3)	C(15)—C(16)	1·40 (3)
N(4)—C(8)	1·52 (2)	C(15)—C(24)	1·34 (3)
C(5)—C(6)	1·60 (3)	C(16)—O(17)	1·37 (2)
C(6)—C(7)	1·56 (3)	C(16)—O(18)	1·23 (2)
C(7)—C(8)	1·53 (2)	C(21)—O(22)	1·44 (3)
C(7)—O(17)	1·40 (2)	C(24)—C(25)	1·50 (3)
C(9)—O(10)	1·47 (3)	C(26)—C(27)	1·51 (6)
O(10)—C(11)	1·32 (2)	C(27)—O(28)	1·33 (4)
C(11)—C(12)	1·51 (3)	Br—$N^{i}(4)$	3·13
C(11)—O(19)	1·21 (2)	O(22)—$O^{i}(28)$	2·88
C(12)—C(13)	1·60 (3)	O(20)—O(19)	2·63

C(2)—C(1)—C(8)	112·0 (13)	C(11)—C(12)—C(13)	108·4 (15)
C(2)—C(1)—C(9)	128·5 (13)	C(11)—C(12)—O(20)	108·8 (10)
C(8)—C(1)—C(9)	119·6 (9)	C(11)—C(12)—C(21)	109·7 (15)
C(1)—C(2)—C(3)	113·2 (13)	C(13)—C(12)—O(20)	109·7 (14)
C(2)—C(3)—N(4)	99·1 (8)	C(13)—C(12)—C(21)	109·9 (11)
C(3)—N(4)—C(5)	109·2 (8)	O(20)—C(12)—C(21)	110·2 (16)
C(3)—N(4)—C(8)	111·0 (7)	C(12)—C(13)—C(14)	109·5 (11)
C(5)—N(4)—C(8)	109·8 (10)	C(12)—C(13)—C(23)	111·0 (13)
N(4)—C(5)—C(6)	103·3 (7)	C(14)—C(13)—C(23)	110·0 (14)
C(5)—C(6)—C(7)	102·1 (6)	C(13)—C(14)—C(15)	108·1 (9)
C(6)—C(7)—C(8)	103·9 (11)	C(14)—C(15)—C(16)	117·5 (2)
C(6)—C(7)—O(17)	111·0 (9)	C(14)—C(15)—C(24)	118·4 (11)
C(8)—C(7)—O(17)	109·2 (6)	C(16)—C(15)—C(24)	124·1 (10)
C(1)—C(8)—N(4)	102·1 (7)	C(15)—C(16)—O(17)	115·2 (7)
C(1)—C(8)—C(7)	119·2 (12)	C(15)—C(16)—O(18)	125·2 (13)
N(4)—C(8)—C(7)	105·3 (10)	O(17)—C(16)—O(18)	119·1 (11)
C(1)—C(9)—C(10)	112·6 (14)	C(7)—O(17)—C(16)	118·2 (6)
C(9)—O(10)—C(11)	116·2 (10)	C(12)—C(21)—O(22)	110·0 (14)
O(10)—C(11)—C(12)	114·1 (11)	C(15)—C(24)—C(25)	124·1 (11)
O(10)—C(11)—O(19)	124·4 (16)	C(26)—C(27)—O(28)	118·0 (23)
C(12)—C(11)—O(19)	121·5 (15)		

Table 3. *Torsion angles* (°) *in the macrocyclic ring for retrorsine, jacobine and swazine*

	Retrorsine	Jacobine	Swazine
C(2)—C(1)—C(9)—O(10)	−87·0 (5)	−106·2	−108·3
C(1)—C(9)—O(10)—C(11)	79·5 (9)	88·4	97·3
C(9)—O(10)—C(11)—C(12)	177·5 (7)	179·2	−177·6
O(10)—C(11)—C(12)—C(13)	50·3 (2)	51·6	63·3
C(11)—C(12)—C(13)—C(14)	59·3 (3)	63·0	60·3
C(12)—C(13)—C(14)—C(15)	−157·5 (2)	−158·8	−152·5
C(13)—C(14)—C(15)—C(16)	78·6 (1)	59·8	64·9
C(14)—C(15)—C(16)—O(17)	36·3 (5)	50·7	28·4
C(15)—C(16)—O(17)—C(7)	−175·7 (3)	−175·8	−173·0
C(16)—O(17)—C(7)—C(8)	163·5 (5)	167·2	175·5
O(17)—C(7)—C(8)—C(1)	−27·5 (2)	−29·3	−30·9
C(7)—C(8)—C(1)—C(9)	−74·6 (1)	−75·3	−68·4
C(8)—C(1)—C(9)—O(10)	93·6 (5)	85·6	69·3
O(18)—C(16)—C(15)—C(24)	43·7 (3)	–	54·1

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34624 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

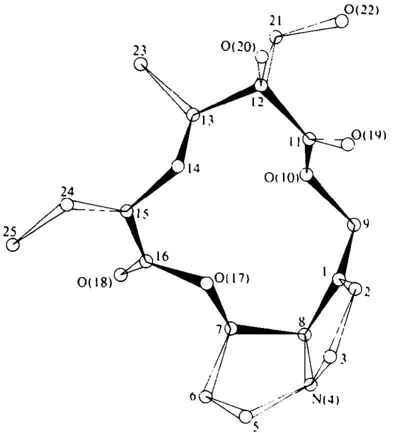

Fig. 1. A perspective view of the molecule showing the numbering scheme. The macrocyclic ring is shaded.

The carbonyl bonds are nearly parallel in all three PA's. The angle between the planes defined by C(7)—O(17)—C(16)—O(18) and C(9)—O(10)—C(11)—O(19) is 12·2 (2)° in retrorsine and 15° in jacobine, but 25° in swazine. This difference is explained by the slightly different conformation of the macro-ring, and also accounts for the shorter intramolecular distance O(10)—O(17) in swazine. In retrorsine and jacobine these distances are 3·23 and 3·25 Å respectively, with dihedral angles C(9)—O(10)—C(11)—C(12) of 177·5 (7)° and 179°. In swazine the corresponding distance is 3·16 Å and the dihedral angle is −178°.

It has been suggested that the potency of these alkaloids depends in some way on the accessibility to attack of the C(1)—C(2) double bond, regarded in terms of the size of the C(2)—C(1)—C(9)—O(10) dihedral angle (Sussman & Wodak, 1973). This angle is −87·0 (5)° in retrorsine, −106° in jacobine, 108° in swazine, −64° in fulvine, −63° in monocrotaline, −88° in axillarine and −12° in heliotrine (Wodak, 1975), a monoester PA. A direct comparison of the toxicity of all these alkaloids is a difficult and costly study. However, one should note that for retrorsine and axillarine which have similar dihedral angles (*ca* −88°) the former is by far the more toxic. Also, retrorsine, which contains two hydroxyl substituents and has a dihedral angle of −87·0 (5)°, is twice as toxic as jacobine (Bull *et al.*, 1968) which is less water soluble (containing only one hydroxyl substituent) and has a larger dihedral angle of −106°.

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The Structure of Colchiceine Ethyl Acetate–Water Solvate

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Abstract. $C_{21}H_{23}NO_6.C_4H_8O_2.H_2O$, monoclinic, $P2_1$, $Z = 2$, $a = 8{\cdot}329\ (1)$, $b = 12{\cdot}795\ (1)$, $c = 12{\cdot}571\ (1)$ Å, $\beta = 106{\cdot}57\ (1)°$, $M_r = 492{\cdot}5$, $D_m = 1{\cdot}26\ (1)$, $D_x = 1{\cdot}273$ Mg m^{-3} at 296 K. Cell dimensions were obtained by least-squares refinement of angles measured at $\pm\theta$. Intensity data were collected with an Enraf–Nonius