Rosmarinine: a Pyrrolizidine Alkaloid

Andrew A. Freer,* Henry A. Kelly and David J. Robins

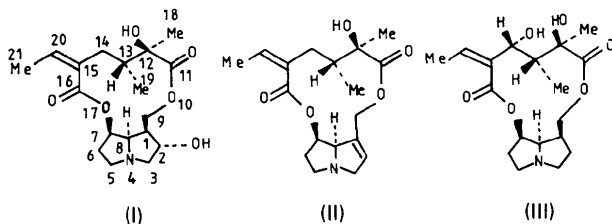*Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, Scotland*

Abstract. $C_{18}H_{27}NO_6$, $M_r = 353.4$, tetragonal, $P4_32_12$, $a = 8.033$ (2), $c = 54.979$ (5) Å, $V = 3547.8$ Å^3, $Z = 8$, $D_x = 1.32$ g cm^{-3}, $\lambda(Cu\,K\alpha) = 1.5418$ Å, $\mu = 7.79$ cm^{-1}, $F(000) = 1520$, $T = 291$ K, final $R = 0.058$ for 2751 unique observed reflections. The conformations of the pyrrolizidine ring system and the 12-membered macrocyclic ring are similar to the conformations observed in all other hepatotoxic and non-hepatotoxic 12-membered macrocyclic pyrrolizidine alkaloids, *viz* the pucker of the pyrrolizidine nucleus is *exo* and the ester carbonyl bonds are antiparallel. There is an intermolecular hydrogen bond between the hydroxyl group at C(2) and the N atom, N(4)···O(2) 2.735 (6) Å.

Introduction. Most crystallographic studies on pyrrolizidine alkaloids have been carried out on the hepatotoxic macrocyclic diesters of (+)-retronecine such as senecionine (II). Rosmarinine (I) is present in a number of *Senecio* species (family Compositae) (Robins, 1982). It was first isolated from *S. rosmarinifolius* and the structure (I) was elucidated by hydrolysis to yield the base portion, rosmarinecine, and senecic acid (de Waal, 1940, 1941). Alkaloids containing rosmarinecine should not be hepatotoxic as they do not contain a double bond at the 1,2 position in the pyrrolizidine nucleus (Mattocks & White, 1971). For this study, rosmarinine was isolated from *S. pleistocephalus* S. Moore (Kunec & Robins, 1986), and an X-ray analysis was carried out to compare the conformations of the pyrrolizidine nucleus and the macrocyclic ring with those of the corresponding 12-membered-ring diesters of retronecine, such as senecionine (II).

Experimental. Pale-yellow plate-shaped crystal grown from water, crystal *ca* 0.6 × 0.5 × 0.2 mm used in data collection, CAD-4 diffractometer. Preliminary Weissenberg photographs indicated crystals to be tetragonal, either $P4_32_12$ or $P4_12_12$. Density not measured. 3496 independent intensities, θ limit 65°, $\omega/2\theta$ scan. Two standard intensities used to monitor variations in intensity data: <3% variation observed. Least-squares technique based on 25 reflections, $\theta > 20°$, used to refine lattice parameters. No absorption corrections. $|h|$ 0 to 9, $|k|$ 0 to 9, $|l|$ 0 to 64, *hkl* and *hkl̄* collected. Structure solution by direct methods with *MITHRIL* (Gilmore, 1984). Space-group ambiguity was resolved as $P4_32_12$ since the absolute configuration of the rosmarinecine base was known (Dry, Koekemoer & Warren, 1955). Full-matrix least-squares refinement on F of coordinates and anisotropic thermal parameters for all non-H atoms converged to R and wR of 0.058 and 0.075 with $w = 1.0$. H-atom coordinates, located from difference Fourier map, included in structure-factor calculations but not refined. 2751 reflections (including Friedel pairs), $I > 3.0\sigma_I$, used. $\Delta_{max}/\sigma = 0.46$; max. and min. heights in final difference Fourier synthesis = 0.33 and −0.28 e Å^{-3}. Scattering factors from *International Tables for X-ray Crystallography* (1974). All calculations on a Gould SEL 32/27 computer using Glasgow *GX* package (Mallinson & Muir, 1985).

Discussion. Final positional and equivalent isotropic thermal parameters are given in Table 1.† Bond lengths and angles with their standard deviations are given in Table 2. An *ORTEP* (Johnson, 1976) diagram, Fig. 1, illustrates the numbering scheme and absolute configuration of the molecule.

The extent of *exo*-buckling of the pyrrolizidine nucleus is less than that so far observed for similar alkaloid analogues. The *exo*-ring pucker angle between planes defined by atoms C(5), C(6), C(7) and C(5),

(I)   (II)   (III)

---

* To whom correspondence should be addressed.

Table 1. *Final atomic parameters and equivalent isotropic thermal parameters* (Å^2) *with e.s.d.'s in parentheses*

$$U_{eq} = \tfrac{1}{3}\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	U_{eq}
O(2)	−0·4340 (5)	−0·0687 (5)	−0·1363 (1)	0·052
O(10)	−0·6842 (4)	−0·0493 (4)	−0·0773 (1)	0·034
O(11)	−0·7478 (7)	0·0994 (5)	−0·1103 (1)	0·071
O(12)	−0·7544 (5)	0·3850 (4)	−0·0839 (1)	0·051
O(16)	−0·4026 (5)	−0·0967 (5)	−0·0147 (1)	0·054
O(17)	−0·3584 (4)	−0·0785 (4)	−0·0548 (1)	0·033
N(4)	−0·1991 (5)	−0·2906 (5)	−0·0926 (1)	0·036
C(1)	−0·4869 (6)	−0·2318 (6)	−0·1007 (1)	0·032
C(2)	−0·3848 (6)	−0·0907 (6)	−0·1119 (1)	0·036
C(3)	−0·2048 (7)	−0·1483 (8)	−0·1097 (1)	0·057
C(5)	−0·0814 (7)	−0·2780 (7)	−0·0718 (1)	0·047
C(6)	−0·1831 (7)	−0·3199 (7)	−0·0492 (1)	0·047
C(7)	−0·3568 (6)	−0·2606 (6)	−0·0556 (1)	0·034
C(8)	−0·3706 (6)	−0·3147 (6)	−0·0824 (1)	0·033
C(9)	−0·6628 (6)	−0·1966 (6)	−0·0925 (1)	0·039
C(11)	−0·7329 (7)	0·0877 (7)	−0·0887 (1)	0·042
C(12)	−0·7801 (7)	0·2326 (6)	−0·0712 (1)	0·041
C(13)	−0·6700 (7)	0·2372 (6)	−0·0480 (1)	0·041
C(14)	−0·4839 (7)	0·2516 (6)	−0·0534 (1)	0·040
C(15)	−0·3820 (6)	0·1734 (6)	−0·0334 (1)	0·037
C(16)	−0·3836 (6)	−0·0126 (6)	−0·0324 (1)	0·036
C(18)	−0·9650 (7)	0·2064 (7)	−0·0652 (1)	0·056
C(19)	−0·7244 (9)	0·3797 (8)	−0·0314 (1)	0·069
C(20)	−0·2987 (7)	0·2594 (7)	−0·0168 (1)	0·045
C(21)	−0·1896 (8)	0·1896 (9)	0·0033 (1)	0·062

N(4), C(8) of 29·2 (4)° is smaller than that observed for its closest analogue, hygrophylline (Mackay, Mitrprachachon & Culvenor, 1985) (III), 34·8 (4)°, or the 13-membered-ring alkaloid bulgarsenine (Stoeckli-Evans, 1980), 34·3 (4)°. The *endo* pucker angle, 163·8 (5)°, between the planes defined by atoms C(1), C(2), C(3) and C(3), N(4), C(8) also differs slightly from those found in hygrophylline and bulgarsenine, 158·5 (5) and 156·2 (5)° respectively. The dihedral angle between the planes defined by atoms C(1), C(8), N(4), C(3) and C(5), N(4), C(8), C(7) is 126·9 (6)° and is similar to values found in retronecine-based alkaloids.

The macrocyclic ring mimics hygrophylline very closely; the largest torsional-angle difference, 6·2 (5)°, occurring at C(7)—C(8)—C(1)—C(9). Further conformational similarities of this non-hepatotoxic analogue to other 12-membered-ring alkaloids are also seen in senecionine (Mackay & Culvenor, 1982), anacrotine (Mackay, Sadek & Culvenor, 1984) and retrorsine hydrobromide (Stoeckli-Evans, 1979). The carbonyl bonds of the ester function are antiparallel as observed for all other 12-membered-ring alkaloids so far reported. The angle between the carbonyl bonds of the essentially planar primary and secondary ester groups is 22·5 (6)° compared to 26·5 (6)° in hygrophylline, 16·8 (3)° in senecionine, 17·2 (7)° in retrorsine hydrobromide, 18·8 (3)° in jacobine (Rohrer, Karchesy & Deinzer, 1984), 14·0 (5)° in anacrotine and 24·7 (4)° in bulgarsenine.

The transannular distance O(10)⋯O(17) of 2·904 (5) Å is shorter than that observed for hygrophylline, 2·966 (5) Å, senecionine, 3·293 (3)'Å, and anacrotine, 3·349 (6) Å. A similar, though slightly more exaggerated twisting about the C(11)—C(12) bond than is seen in hygrophylline results in an O(11)—C(11)—C(12)—O(12) torsional angle of −30·0 (5)° [*cf.* −20 (5)° for hygrophylline and −3·8 (3) and −3·4 (5)° for senecionine and anacrotine respectively]. Likewise, the unsaturated side chain

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

O(2)—C(2)	1·412 (6)	O(10)—C(9)	1·461 (6)
O(10)—C(11)	1·328 (7)	O(11)—C(11)	1·194 (6)
O(12)—C(12)	1·423 (7)	O(16)—C(16)	1·198 (6)
O(17)—C(7)	1·463 (6)	O(17)—C(16)	1·352 (6)
N(4)—C(3)	1·482 (8)	N(4)—C(5)	1·486 (7)
N(4)—C(8)	1·499 (7)	C(1)—C(2)	1·528 (7)
C(1)—C(8)	1·526 (7)	C(1)—C(9)	1·509 (7)
C(2)—C(3)	1·523 (8)	C(5)—C(6)	1·527 (8)
C(6)—C(7)	1·517 (8)	C(7)—C(8)	1·538 (7)
C(11)—C(12)	1·558 (8)	C(12)—C(13)	1·555 (7)
C(12)—C(18)	1·536 (9)	C(13)—C(14)	1·528 (8)
C(13)—C(19)	1·528 (9)	C(14)—C(15)	1·507 (7)
C(15)—C(16)	1·495 (7)	C(15)—C(20)	1·328 (7)
C(20)—C(21)	1·517 (8)		

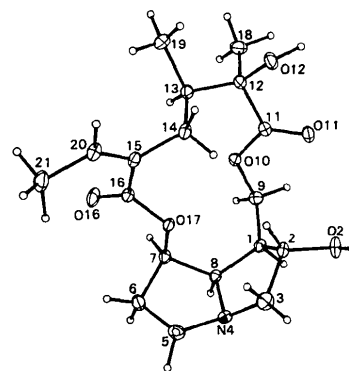|				
C(9)—O(10)—C(11)	115·7 (4)	C(7)—O(17)—C(16)	115·0 (4)
C(3)—N(4)—C(5)	117·1 (5)	C(3)—N(4)—C(8)	107·9 (4)
C(5)—N(4)—C(8)	107·9 (4)	C(2)—C(1)—C(8)	105·1 (4)
C(2)—C(1)—C(9)	118·9 (5)	C(8)—C(1)—C(9)	117·4 (4)
O(2)—C(2)—C(1)	109·0 (4)	O(2)—C(2)—C(3)	112·2 (5)
C(1)—C(2)—C(3)	104·6 (5)	N(4)—C(3)—C(2)	108·3 (5)
N(4)—C(5)—C(6)	105·7 (4)	C(5)—C(6)—C(7)	103·4 (5)
O(17)—C(7)—C(6)	108·3 (4)	O(17)—C(7)—C(8)	108·3 (4)
C(6)—C(7)—C(8)	101·7 (4)	N(4)—C(8)—C(1)	105·1 (4)
N(4)—C(8)—C(7)	104·7 (4)	C(1)—C(8)—C(7)	123·4 (4)
O(10)—C(9)—C(1)	115·6 (4)	O(10)—C(11)—O(11)	124·4 (5)
O(10)—C(11)—C(12)	113·4 (4)	O(11)—C(11)—C(12)	122·0 (5)
O(12)—C(12)—C(11)	107·7 (4)	O(12)—C(12)—C(13)	107·4 (4)
O(12)—C(12)—C(18)	111·4 (5)	C(11)—C(12)—C(13)	112·8 (5)
C(11)—C(12)—C(18)	105·5 (5)	C(13)—C(12)—C(18)	112·0 (5)
C(12)—C(13)—C(14)	113·5 (4)	C(12)—C(13)—C(19)	110·2 (5)
C(14)—C(13)—C(19)	109·9 (5)	C(13)—C(14)—C(15)	111·0 (4)
C(14)—C(15)—C(16)	116·0 (5)	C(14)—C(15)—C(20)	124·0 (5)
C(16)—C(15)—C(20)	119·9 (5)	O(16)—C(16)—O(17)	122·6 (5)
O(16)—C(16)—C(15)	126·5 (5)	O(17)—C(16)—C(15)	110·9 (4)
C(15)—C(20)—C(21)	126·9 (6)		

Fig. 1. A perspective view of the molecule showing the numbering scheme and vibrational ellipsoids (35% probability level).

C(15)=C(20)—C(21) is in a nearly *cis* arrangement, the torsional angle C(20)—C(15)—C(16)—O(16) of 44·0 (6)° agreeing well with the values of 40·5 (5) and 46·2 (3)° found for hygrophylline and senecionine respectively.

The hydroxyl group at C(2) and the N atom of a neighbouring molecule are linked by an intermolecular hydrogen bond. The O(2)···N(4), O(2)—H(3) and N(4)···H(3) distances are 2·735 (6), 0·86 and 1·88 Å and the angle O(2)—H(3)···N(4) is 171°. Similar intermolecular interactions involving a hydroxyl substituent at C(12), instead of at C(2) as in rosmarinine, are observed in senecionine, 2·827 (4), 0·77 (5), 2·07 (5) Å and 167 (3)°, and retrorsine (Coleman, Coucourakis & Pretorius, 1980), 2·85 (1), 0·98 (7), 1·90 (7) Å and 162°.

References

COLEMAN, P. C., COUCOURAKIS, E. D. & PRETORIUS, J. A. (1980). *S. Afr. J. Chem.* **33**, 116–119.

DRY, L. J., KOEKEMOER, M. J. & WARREN, F. L. (1955). *J. Chem. Soc.* pp. 59–63.

GILMORE, C. J. (1984). *J. Appl. Cryst.* **17**, 42–46.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

JOHNSON, C. K. (1976). *ORTEP.* Report ORNL-5138. Oak Ridge National Laboratory, Tennessee.

KUNEC, E. K. & ROBINS, D. J. (1986). *J. Chem. Soc. Chem. Commun.* pp. 250–252.

MACKAY, M. F. & CULVENOR, C. C. J. (1982). *Acta Cryst.* B**38**, 2754–2758.

MACKAY, M. F., MITRPRACHACHON, P. & CULVENOR, C. C. J. (1985). *Acta Cryst.* C**41**, 395–397.

MACKAY, M. F., SADEK, M. & CULVENOR, C. C. J. (1984). *Acta Cryst.* C**40**, 1073–1077.

MALLINSON, P. R. & MUIR, K. W. (1985). *J. Appl. Cryst.* **18**, 51–53.

MATTOCKS, A. R. & WHITE, I. N. H. (1971). *Nature (London) New Biol.* **231**, 114–115.

ROBINS, D. J. (1982). *Fortschr. Chem. Org. Naturst.* **41**, 115–203.

ROHRER, D. C., KARCHESY, J. & DEINZER, M. (1984). *Acta Cryst.* C**40**, 1449–1452.

STOECKLI-EVANS, H. (1979). *Acta Cryst.* B**35**, 2798–2800.

STOECKLI-EVANS, H. (1980). *Acta Cryst.* B**36**, 3150–3153.

WAAL, H. L. DE (1940). *Onderstepoort J. Vet. Sci. Anim. Ind.* **15**, 241–249.

WAAL, H. L. DE (1941). *Onderstepoort J. Vet. Sci. Anim. Ind.* **16**, 149–166.

Structure of Econazole

BY ANDREW A. FREER*

Department of Chemistry, Glasgow University, Glasgow G12 8QQ, Scotland

AND ALAN PEARSON AND EUGENE G. SALOLE

Department of Pharmacy, University of Strathclyde, Glasgow G1 1XW, Scotland

Abstract. 1-{2-[(4-Chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole, $C_{18}H_{15}Cl_3N_2O$, $M_r = 381·7$, monoclinic, $P2_1/c$, $a = 8·410$ (1), $b = 11·084$ (1), $c = 19·657$ (2) Å, $\beta = 96·24$ (1)°, $V = 1821·3$ Å^3, $Z = 4$, $D_m = 1·42$, $D_x = 1·39$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 47·08$ cm^{-1}, $F(000) = 784$, $T = 291$ K, final $R = 0·040$ for 2083 unique observed reflections. Each of the three ring systems is essentially planar, with the *p*-chlorophenyl ring twisted at an angle of approximately 60° to the other two ring systems which are almost coplanar. Intra- and intermolecular distances and angles are within the values recorded for similar compounds.

Introduction. Econazole is a prime member of the group of imidazole derivatives (Godefroi, Heeres, Van Cutsem & Janssen, 1969) which have achieved prominence as antimycotic agents (Drouhet, 1978). Like its close analogue miconazole, which differs in having an additional Cl at C(19) in the benzyloxy moiety, econazole has a wide antifungal spectrum (Thienpont, Van Cutsem, Van Nueten, Niemegeers & Marsboom, 1975) and is of particular clinical use in the topical treatment of superficial mycoses. As the racemic free-base forms of both econazole and miconazole are poorly soluble in aqueous systems, they were selected as models for a study of crystal growth in pharmaceutical semi-solid formulations (Pearson, Shankland, Salole & Johnson, 1985). Since the crystal-