Conformations of Eleven-membered Dilactone Rings in Pyrrolizidine Alkaloid Analogues. *X*-Ray Crystallographic Studies of *meso*-2,4-Dimethylglutaryl, 3,3-Tetramethyleneglutaryl, and 3,3-Dimethylglutaryl Derivatives of Synthanecine A

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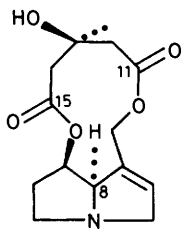
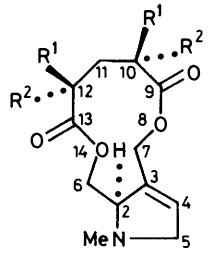
The pyrrolizidine alkaloid analogues (2*R*,10*R*,12*S*)- and (2*S*,10*S*,12*R*)-6,7-*O*,*O*-(*meso*-2,4-dimethylglutaryl)synthanecine A (**2**), (±)-6,7-*O*,*O*-(3,3-tetramethyleneglutaryl)synthanecine A (**4**), and (±)-6,7-*O*,*O*-(3,3-dimethylglutaryl)synthanecine A (**5**) have been characterized by *X*-ray crystal structure analysis. The 11-membered dilactone ring in compound (**2**) has an unsymmetrical conformation in which both ester carbonyl groups are directed above the plane of the macrocycle. The dilactone rings in compounds (**4**) and (**5**) have conformations that approximate closely to C_2 symmetry with the ester carbonyl groups *anti*-parallel. N.m.r. data suggest that the conformations persist in solution.

Pyrrolizidine alkaloids are widespread and many are hepatotoxic.[1] The most toxic have 1,2-unsaturation in the pyrrolizidine nucleus (retronecine) and contain a macrocyclic dilactone system as in dicrotaline (**1**). Robins *et al.* have reported the synthesis of a variety of these alkaloids and analogues in order to delineate the structure–activity relationships.[2] Several of the synthetic compounds incorporate a monocyclic analogue of retronecine, synthanecine A, *e.g.* the 11-membered macrocyclic diesters (**2**)—(**7**).[3]

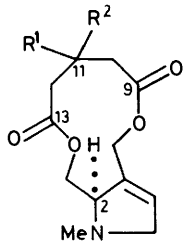


(**1**)



(**2**) R^1 = Me, R^2 = H

(**3**) R^1 = H, R^2 = Me

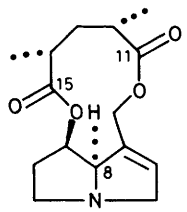


(**4**) R^1 R^2 = $[CH_2]_4$

(**5**) R^1 = R^2 = Me

(**6**) R^1 = R^2 = H

(**7**) R^1 R^2 = $[CH_2]_5$



(**8**)

The absence of the constraints imposed by the additional five-membered ring in compound (**1**) should increase the range of conformations accessible to the 11-membered rings in compounds (**2**)—(**7**). Accordingly, we undertook *X*-ray crystallographic studies of compounds (**2**), (**4**), and (**5**) to characterize their conformations and to compare these with the conformations of 11-membered pyrrolizidine alkaloids containing retronecine.

The crystal structures were determined by direct phasing procedures[4] and the atomic parameters were adjusted by full-matrix least-squares calculations that converged at *R* 0.044 for compound (**2**), 0.059 for compound (**4**) and 0.034 for compound (**5**). The molecule structures are illustrated in Figures 1—3, with the numbering system of Barbour and Robins.[3] The torsion angles defining the conformations of the 11-membered rings are listed in Table 1; they differ from those in 11-membered pyrrolizidine alkaloids containing retronecine and define new conformations for the dilactone ring.

Compound (**2**) adopts a conformation in which the ester carbonyl bonds are directed to the same side of the plane of the macrocycle. *X*-Ray results show that most 11-membered pyrrolizidine alkaloids and analogues containing retronecine have the ester carbonyl bonds directed to the same side of the plane of the macrocycle, *e.g.* fulvine,[5] monocrotaline,[6] and (12*S*,14*R*)-12,14-dimethyl-1,2-didehydrocrotalanine (**8**).[7] In these compounds, the ester carbonyl bonds and the C–H bond at C(8) are directed towards the same side of the macrocycle plane, whereas in compound (**2**) the ester carbonyl bonds are directed towards the other side of the macrocycle plane from the analogous C–H bond at C(2).

Compounds (**4**) and (**5**) have essentially identical macrocycle conformations; corresponding torsion angles differ by 0.0—3.8°, with a mean difference of only 1.1°. In these molecules the ester carbonyl bonds point to opposite sides of the macrocycle plane, a situation that has been recorded in 1,2-didehydrocrotalanine

Table 1. Conformational details of the eleven-membered dilactone rings

Torsion angle (°) about bond	Compound (2)	(4)	(5)
C(2)–C(3)	−47	−57	−56
C(3)–C(7)	−43	69	67
C(7)–O(8)	174	−158	−160
O(8)–C(9)	−169	169	169
C(9)–C(10)	97	−116	−112
C(10)–C(11)	−77	48	48
C(11)–C(12)	65	46	45
C(12)–C(13)	−133	−122	−122
C(13)–O(14)	173	168	168
O(14)–C(6)	−107	−159	−159
C(6)–C(2)	96	74	75

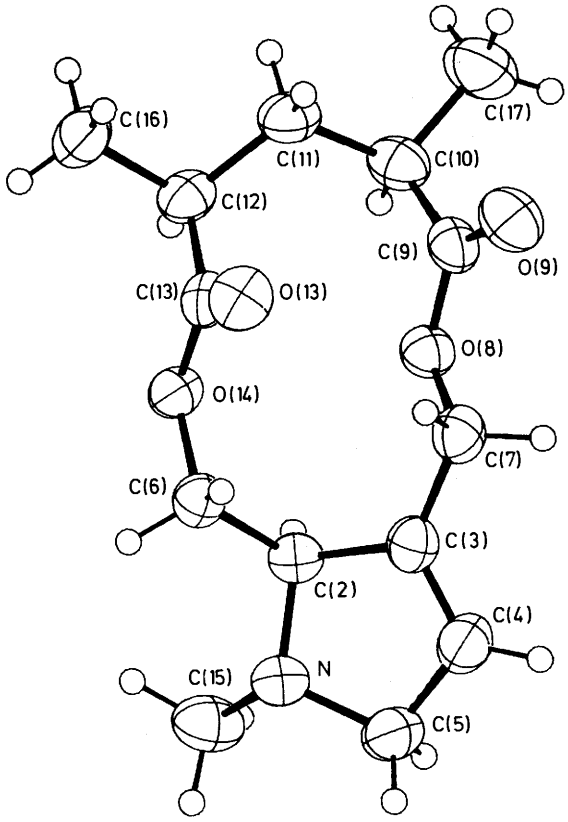


Figure 1. The molecular structure of compound (**2**). The thermal ellipsoids of the C, N, and O atoms are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å

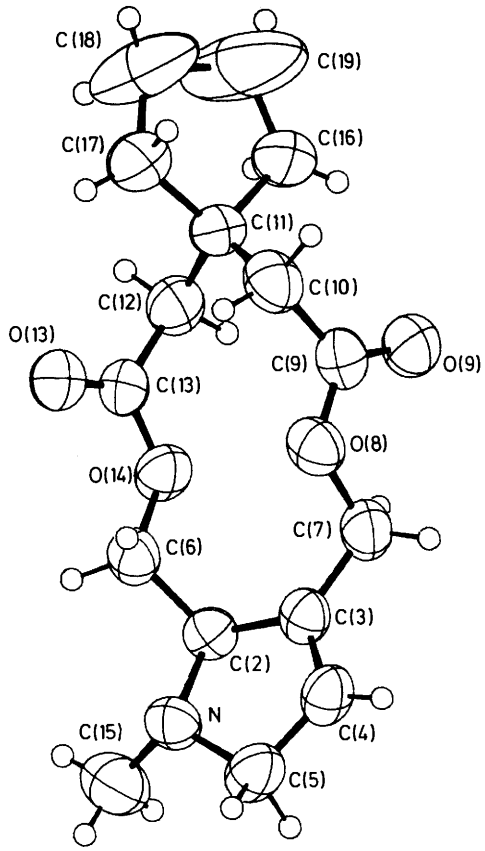


Figure 2. The molecular structure of compound (**4**). The thermal ellipsoids of the C, N, and O atoms are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å

picrate[8] and trichodesmine.[9] In the latter compounds, however, the left-hand carbonyl group C(15)=O is orientated in the same direction as C(8)–H, whereas in compounds (**4**) and (**5**) it is the right-hand carbonyl group C(9)=O that is orientated in the same direction as C(2)–H.

Symmetrical and unsymmetrical conformations must be considered in any general assessment of possible conformations of the 11-membered dilactone ring in analogues of pyrrolizidine alkaloids. When the ester carbonyl bonds point to opposite sides of the macrocycle plane, a C_2 conformation of the 11-membered ring would have a symmetry axis passing through C(11) and the midpoint of the C(3)–C(3) bond [see numbering in (**2**) and (**4**)]. When the ester carbonyl bonds point to the same side of the macrocycle plane, a C_s conformation would have a symmetry plane passing through C(11) and the midpoint of the C(2)–C(3) bond. Comparison of appropriate pairs of torsion angles, *e.g.* C(2)–C(3)–C(7)–O(8) and C(3)–C(2)–C(6)–O(14), C(3)–C(7)–O(8)–C(9) and C(2)–C(6)–O(14)–C(13), *etc.* reveals differences of 1.1—5.8°, mean 3.2°, in compound (**4**) and differences of 0.6—9.4°, mean 4.6°, in compound (**5**). The dilactone rings in compounds (**4**) and (**5**) approximate closely to C_2 symmetry. In compound (**2**), on the other hand, appropriate pairs of torsion angles show differences of 4.4—66.8°, mean 34.6°, and the angle C(6)–C(2)–C(3)–C(7) is −47° rather than the C_s value of 0°. The dilactone ring in compound (**2**) does not approximate to C_s symmetry. This distinction between symmetrical and unsymmetrical conformations for the dilactone ring with *anti*-parallel and *syn*-parallel orientations of the carbonyl bonds arises because C_s geometry does not define a minimum-energy form, requiring an eclipsed conformation about the C(2)–C(3) bond.

The ^{1}H n.m.r. spectra of compounds (**2**) and (**3**) show some differences from the spectra of compound (**4**)—(**7**) in solution in deuteriochloroform. Thus, the chemical-shift differences of the protons at C(6) are δ 0.51 for compound (**2**), δ 0.48 for compound (**3**), and δ 0.07, 0.17, 0.07, and 0.13 for compounds (**4**), (**5**), (**6**), and (**7**), respectively. Barbour and Robins suggested therefore that the conformations of the macrocyclic rings in compounds (**2**) and (**3**) may differ from those in compounds (**4**)—(**7**).[3] This is consistent with the *X*-ray results for compounds (**2**), (**4**), and (**5**) and suggests that the conformations observed in the crystals persist in deuteriochloroform solution. The ^{13}C n.m.r. signals for C(10) and C(12) in these compounds are at 39.2, 40.5 p.p.m. for compound (**2**), 38.8, 40.6 p.p.m. for compound (**3**), 42.7, 42.7 p.p.m. for compound (**4**), 44.2, 44.3 p.p.m. for compound (**5**), 33.7, 34.1 p.p.m. for compound (**6**), and 41.8, 41.8 p.p.m. for compound (**7**).[3] The slightly larger chemical-shift differences δC(12) − δC(10) in compounds (**2**) and (**3**) are consistent with a conformational difference between compounds (**2**) and (**3**) on the one hand and compounds (**4**)—(**7**) on the other. The differences, moreover, are consistent with the conformation of compounds (**2**) and (**3**) being less symmetrical than the conformation of compounds (**4**)—(**7**), in agreement with the *X*-ray results. The chemical-shift differences are small, however, and could not be used with confidence to deduce conformations. Additional structural and n.m.r. data are required to improve our knowledge of the conformational properties of pyrrolizidine alkaloid analogues.

Experimental

Crystal Data.—(2*R*,10*R*,12*S*)- and (2*S*,10*S*,12*R*)-6,7-*O*,*O*-(*meso*-2,4-Dimethylglutaryl)synthanecine A (**2**), $C_{14}H_{21}NO_4$,

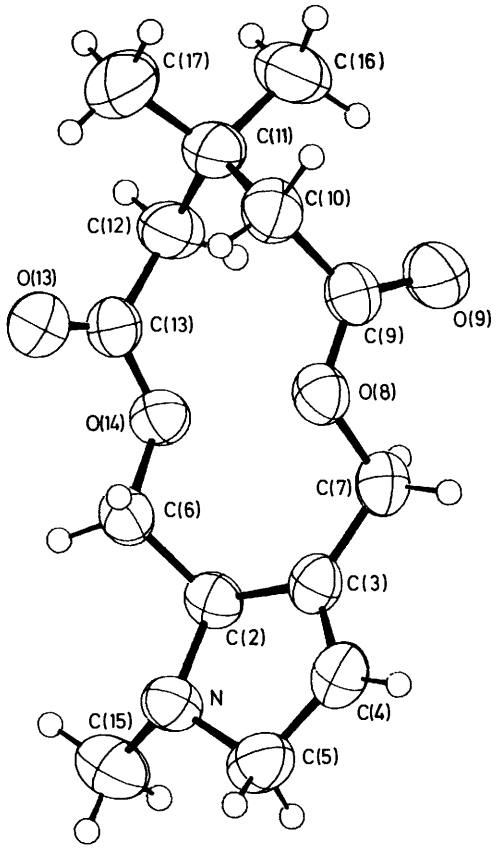


Figure 3. The molecular structure of compound (**5**). The thermal ellipsoids of the C, N, and O atoms are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å

M = 267.35, triclinic, a = 4.981(1), b = 10.554(2), c = 14.232(3) Å, α = 105.88(1), β = 92.62(1), γ = 99.81(1)°, V = 706 Å^3, D_c = 1.26 g cm^{-3}, Z = 2, $F(000)$ = 288, μ(Mo-K_α) = 0.99 cm^{-1}, space group P$\bar{1}$.

(±)-6,7-*O*,*O*-(3,3-Tetramethyleneglutaryl)synthanecine A (**4**), $C_{16}H_{23}NO_4$, M = 293.39, monoclinic, a = 12.676(4), b = 10.602(2), c = 13.006(7) Å, β = 115.71(2)°, V = 1 575 Å^3, D_c = 1.24 g cm^{-3}, Z = 4, $F(000)$ = 632, μ(Mo-K_α) = 0.95 cm^{-1}, space group $P2_1/c$.

(±)-6,7-*O*,*O*-(3,3-Dimethylglutaryl)synthanecine A (**5**), $C_{14}H_{21}NO_4$, M = 267.35, monoclinic, a = 12.650(3), b = 10.760(4), c = 10.794(3) Å, β = 91.04(1)°, V = 1 469 Å^3, D_c = 1.21 g cm^{-3}, Z = 4, $F(000)$ = 576, μ(Mo-K_α) = 0.95 cm^{-1}, space group $P2_1/a$.

Crystallographic Measurements.—Cell dimensions were derived from least-squares analysis of the setting angles of 25 reflections measured on an Enraf-Nonius CAD4 diffractometer with Mo-K_α radiation. For compound (**2**), 4 072 reflections were surveyed in the range $\theta < 27°$ and after merging 1 602 observations to get 619 independent intensities (merging R = 0.015), 2 659 independent reflections satisfied the criterion $I > 3.0\sigma(I)$. For compound (**4**), 3 424 reflections were surveyed in the range $\theta < 26°$ and after averaging 142 pairs of equivalent reflections (merging R = 0.020), 2 022 independent reflections satisfied the criterion $I > 2.5\sigma(I)$. For compound (**5**), 2 855 reflections were surveyed in the range $\theta < 25°$ and after averaging 127 pairs of equivalent reflections (merging R = 0.025), 1 718 independent reflections satisfied the criterion $I > 2.5\sigma(I)$.

Table 2. Fractional atomic co-ordinates for (2*R*,10*R*,12*S*)- and (2*S*,10*S*,12*R*)-6,7-*O*,*O*-(*meso*-2,4-dimethylglutaryl)synanecine A (**2**) (e.s.d.s in parentheses)

	x	*y*	*z*
C(2)	0.004 3(3)	0.327 4(1)	0.169 3(1)
C(3)	0.141 7(3)	0.389 4(1)	0.095 3(1)
C(4)	0.091 5(4)	0.302 5(2)	0.006 7(1)
C(5)	−0.084 4(4)	0.175 3(2)	0.009 3(1)
C(6)	0.178 0(3)	0.343 0(1)	0.264 1(1)
C(7)	0.306 6(3)	0.527 6(1)	0.121 4(1)
C(9)	0.291 0(3)	0.741 0(1)	0.228 7(1)
C(10)	0.149 0(3)	0.814 6(1)	0.312 3(1)
C(11)	0.288 9(4)	0.812 8(1)	0.410 4(1)
C(12)	0.222 1(3)	0.681 2(1)	0.438 2(1)
C(13)	0.321 6(3)	0.568 5(1)	0.367 7(1)
C(15)	−0.314 3(4)	0.114 1(2)	0.143 1(1)
C(16)	0.353 9(5)	0.697 4(2)	0.541 4(1)
C(17)	0.158 3(6)	0.958 3(2)	0.307 9(2)
O(8)	0.159 7(2)	0.613 4(1)	0.189 7(1)
O(9)	0.499 5(3)	0.786 6(1)	0.200 2(1)
O(13)	0.549 2(2)	0.576 2(1)	0.341 2(1)
O(14)	0.128 49(19)	0.457 29(9)	0.339 93(6)
N	−0.069 6(3)	0.184 5(1)	0.114 1(1)

Table 3. Atomic co-ordinates for (±)-6,7-*O*,*O*-(3,3-tetramethyleneglutaryl)synthanecine A (**4**) (e.s.d.s in parentheses)

	x	*y*	*z*
C(2)	−1.091 7(2)	−0.205 6(2)	−0.667 8(2)
C(3)	−1.025 0(2)	−0.116 0(2)	−0.707 3(2)
C(4)	−1.076 7(3)	−0.111 3(3)	−0.820 7(2)
C(5)	−1.180 4(3)	−0.192 9(3)	−0.869 3(2)
C(6)	−1.019 4(3)	−0.304 3(2)	−0.583 6(2)
C(7)	−0.926 9(3)	−0.036 6(3)	−0.631 7(2)
C(9)	−0.745 7(3)	−0.071 9(3)	−0.469 0(3)
C(10)	−0.661 5(3)	−0.170 7(3)	−0.400 4(3)
C(11)	−0.664 3(3)	−0.198 8(3)	−0.285 2(3)
C(12)	−0.790 3(3)	−0.217 6(3)	−0.301 4(2)
C(13)	−0.861 7(3)	−0.301 3(3)	−0.399 5(2)
C(15)	−1.279 0(3)	−0.312 2(4)	−0.778 1(3)
C(16)	−0.605 8(3)	−0.093 6(3)	−0.196 9(3)
C(17)	−0.585 3(3)	−0.314 5(3)	−0.230 4(4)
C(18)	−0.515 3(5)	−0.284 6(6)	−0.111 4(4)
C(19)	−0.512 8(7)	−0.146 2(6)	−0.106 6(5)
O(8)	−0.826 99(17)	−0.117 72(17)	−0.567 19(17)
O(9)	−0.744 3(2)	0.035 4(2)	−0.441 2(2)
O(13)	−0.837 5(2)	−0.406 4(2)	−0.412 5(2)
O(14)	−0.956 39(17)	−0.242 56(28)	−0.474 14(14)
N	−1.169 34(19)	−0.271 07(21)	−0.773 70(17)

Structure Analysis.—The crystal structures were elucidated by the direct phasing program MITHRIL.[4] After preliminary least-squares adjustment of the C, N and O atoms, the H atoms were located in difference electron-density distributions and included in subsequent least-squares calculations with isotropic thermal parameters. The weighting scheme used was $w = 1/\sigma^2(|F|)$. The calculations converged at R 0.044, R_w 0.063 for compound (**2**), R 0.059, R_w 0.081 for compound (**4**), and R 0.034, R_w 0.043 for compound (**5**). The calculations were performed on our SEL 32/27 computer with the GX programs.[10]

In compound (**4**), the thermal ellipsoids of atoms C(18) and C(19) of the spiro cyclopentane ring are large and anisotropic, with the largest component perpendicular to the ring plane, and the apparent bond lengths involving these atoms are distinctly shorter than expected [C(17)–C(18) 1.447, C(18)–C(19) 1.467, C(19)–C(16) 1.371 Å]. There is clearly a disordered arrangement of half-chair and/or envelope forms averaged to

Table 4. Fractional atomic co-ordinates for (±)-6,7-*O*,*O*-(3,3-dimethylglutaryl)synthanecine A (**5**) (e.s.d.s in parentheses)

	x	*y*	*z*
C(2)	0.626 38(14)	0.206 94(16)	0.592 40(16)
C(3)	0.693 84(14)	0.115 12(15)	0.523 62(16)
C(4)	0.787 43(16)	0.107 13(19)	0.578 86(19)
C(5)	0.795 98(17)	0.188 96(21)	0.688 69(22)
C(6)	0.573 65(16)	0.305 44(18)	0.514 33(20)
C(7)	0.655 75(18)	0.037 72(17)	0.418 04(17)
C(9)	0.566 79(15)	0.073 10(17)	0.224 21(16)
C(10)	0.532 02(18)	0.170 64(21)	0.134 01(19)
C(11)	0.412 73(17)	0.203 68(19)	0.138 28(17)
C(12)	0.377 14(18)	0.226 38(24)	0.272 29(19)
C(13)	0.450 80(16)	0.306 52(21)	0.347 35(17)
C(15)	0.659 3(3)	0.310 6(3)	0.791 8(2)
C(16)	0.345 3(3)	0.096 7(3)	0.086 5(3)
C(17)	0.395 4(4)	0.319 1(3)	0.058 3(3)
O(8)	0.631 15(10)	0.117 96(10)	0.312 49(11)
O(9)	0.540 76(12)	−0.034 09(13)	0.220 50(12)
O(13)	0.478 42(15)	0.409 69(14)	0.321 44(14)
O(14)	0.485 60(10)	0.248 36(12)	0.447 86(11)
N	0.702 87(12)	0.268 27(14)	0.675 89(13)

give a planar ring with shortened C–C bonds. The remainder of the molecule is normal (see Figure 2).

Atomic co-ordinates are listed in Tables 2—4. Full details of the molecular geometries, together with thermal parameters and hydrogen atom positions, have been deposited at the Cambridge Crystallographic Data Centre.*

* For details, see section 5.6.3 of the Instructions for Authors, January issue.

Acknowledgements

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References

1 D. J. Robins, *Fortschr. Chem. Org. Naturst.*, 1982, **41**, 115.
2 K. Brown, J. A. Devlin, and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1819; M. Burton and D. J. Robins, *Ibid.*, 1985, 611; J. A. Devlin, D. J. Robins, and S. Sakdarat, *Ibid.*, 1982, 1117.
3 R. H. Barbour and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2475.
4 C. J. Gilmore, *J. Appl. Crystallogr.*, 1983, **17**, 42.
5 J. L. Sussman and S. J. Wodak, *Acta Crystallogr., Sect. B*, 1973, **29**, 2918.
6 H. Stoeckli-Evans, *Acta Crystallogr., Sect. B*, 1979, **35**, 231; S. Wang, *Sci. Sin.*, 1981, **24**, 497.
7 K. Brown, M. Burton, D. J. Robins, and G. A. Sim, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1261.
8 H. Stoeckli-Evans and D. J. Robins, *Helv. Chim. Acta*, 1983, **66**, 1376.
9 B. Tashkhodzhaev, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1979, 363.
10 P. R. Mallinson and K. W. Muir, *J. Appl. Crystallogr.*, 1985, **18**, 51.

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