Macrocyclic Pyrrolizidine Alkaloid Analogues. Synthesis and Stereochemistry of (12*R*,14*S*)- and (12*S*,14*R*)-12,14-Dimethyl-1,2-didehydrocrotalanine. *X*-Ray Molecular Structure of the (12*S*,14*R*)-Isomer

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Treatment of (+)-retronecine (**1**) with *meso*-2,4-dimethylglutaric anhydride followed by lactonisation *via* the pyridine-2-thiol esters yielded (12*R*,14*S*)- (**3**) and (12*S*,14*R*)-dimethyl-1,2-didehydrocrotalanine (**4**). These pyrrolizidine alkaloid analogues were separated by column chromatography. The absolute configuration of the acid portion of each analogue was established by a sequence of two chemoselective reactions to afford optically active tetrahydro-3,5-dimethyl-2*H*-pyran-2-one. An *X*-ray crystal structure analysis confirmed the structure and stereochemistry of the (12*S*,14*R*)-isomer (**4**). The ester carbonyl groups of compound (**4**) are synparallel and directed below the plane of the macrocyclic ring.

Many pyrrolizidine alkaloids are macrocyclic diesters of (+)-retronecine (**1**).[1] These alkaloids and structurally related analogues present considerable interest as synthetic targets because of the broad range of biological activities which they exhibit, particularly hepatotoxicity. The toxicity is associated with the pyrrolizidine nucleus in combination with an allylic ester function [as in compound (**3**)].[2] Increased toxicity is usually observed with macrocyclic pyrrolizidine alkaloids. Syntheses of the 11-membered pyrrolizidine alkaloids (+)-dicrotaline,[3] (±)-fulvine, and (±)-crispatine,[4] and of the 12-membered alkaloid (±)-integerrimine[5] have been achieved. In addition, series of 11-membered[6] and 10-membered[7] analogues containing (+)-retronecine have been prepared by us. The 11-membered analogues were all made from 3,3-disubstituted glutaric anhydrides. It is believed that the steric hindrance present in many pyrrolizidine alkaloids at the α positions of the diacid portion enhances the toxicity by reducing the susceptibility of the alkaloid to detoxification by hydrolysis.[8] We therefore desired to make 11-membered pyrrolizidine alkaloid analogues containing α substituents on the diacid portion for evaluation of their toxicity.

Results and Discussion

Addition of *meso*-2,4-dimethylglutaric anhydride (**2**) to a solution of (+)-retronecine (**1**)[9] in dry 1,2-dimethoxyethane (DME) afforded a mixture of the 9-monoesters of (+)-retronecine. Lactonisation of this mixture was achieved under Corey–Nicolaou conditions utilising the pyridine-2-thiol esters.[10] The mixture of dilactones, obtained in *ca.* 1:1 ratio, was separated by careful column chromatography on basic alumina to give the two products (**3**) and (**4**) in 33 and 23% yield, respectively. The i.r. and mass spectra for the compounds (**3**) and (**4**) were analogous to those obtained for macrocyclic pyrrolizidine alkaloids. In particular, the ion at *m/z* 136 is characteristic for pyrrolizidine diesters.[11] The ^{1}H n.m.r. spectra of the two pyrrolizidine alkaloid analogues taken in deuteriochloroform were similar, with the exception of signals due to the protons at C(9) of the base portion. The chemical-shift difference between these diastereotopic protons (Δδ) is 1.28 p.p.m. for the less polar analogue (**3**), which is close to the value observed for dicrotaline (Δδ 1.24 p.p.m.[3]). These values are significantly higher than those recorded for other 11-membered diesters of retronecine (Δδ 0—0.92 p.p.m.[11]). The Δδ value of 0.07 p.p.m. for the more polar analogue (**4**) lies within this more normal range.

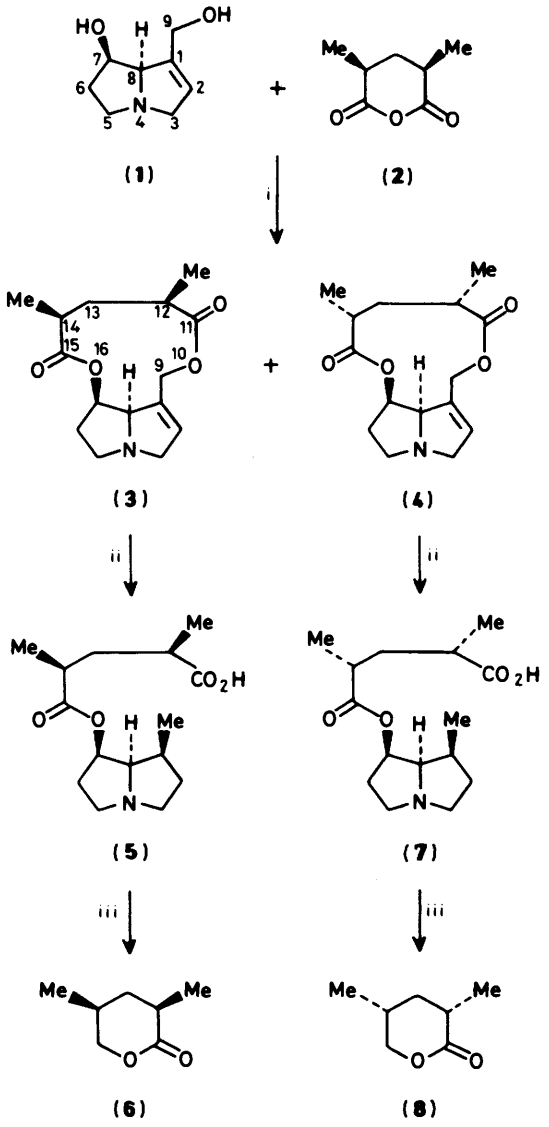
In order to assign the absolute configuration of the acid portion in each analogue, a sequence of two chemoselective reactions was carried out on each diastereoisomer to yield optically active samples of lactones (**6**) and (**8**) of known absolute configuration[12,13] (Scheme). Hydrogenolysis of the allylic ester in the less polar analogue (**3**) gave the retronecanyl ester (**5**). This ester was reduced with lithium borohydride, a reagent known to reduce esters in the presence of acids,[14] to yield the (3*R*,5*S*)-pyrone (**6**) with an optical purity of *ca.* 90%. This lactone was characterised as the benzhydrylamide (diphenylmethylamide). The enantiomeric excess (e.e.) of this derivative was estimated to be >95%, because addition of 0.05 equiv. of the chiral shift reagent Eu(hfc)$_3$† gave no detectable doubling of the signals in the ^{1}H n.m.r. spectrum. When 10% of racemic derivative was added and the ^{1}H n.m.r. spectrum was rerun, additional doublets were observed near each original methyl doublet. The racemic benzhydrylamide of compound (**6**) exhibited doubling of the methyl signals in the ^{1}H n.m.r. spectrum due to the two diastereoisomeric complexes formed on addition of 0.05 equiv. of Eu(hfc)$_3$.

In a similar manner, the more polar pyrrolizidine alkaloid analogue (**4**) was degraded into the (3*S*,5*R*)-pyrone (**8**) with an optical purity of 80%, and an estimated e.e. of 80%. A small amount of doubling of the methyl signals in the ^{1}H n.m.r. spectrum of the benzhydrylamide was observed on addition of Eu(hfc)$_3$, corresponding to the presence of *ca.* 10% of the (3*R*,5*S*)-isomer.

An *X*-ray analysis of a crystal of the analogue (**4**) grown from hexane was undertaken in order to confirm the assignment of stereochemistry and to provide information about the conformation of the macrocycle [suitable crystals could not be prepared for the other analogue (**3**)]. The crystal structure was determined by direct phasing procedures and the atomic parameters were adjusted by full-matrix least-squares calculations.

The molecular structure of compound (**4**) is shown in the Figure and the torsion angles defining the conformation are in Table 1. The conformation of the macrocycle is very similar to that of fulvine,[15] monocrotaline,[16] and related pyrrolizidine alkaloids.[17] The carbonyl bonds of the ester functions are nearly synparallel; the angle between these bonds is 20.4° while in fulvine,[15] monocrotaline,[16] and the α- and β-epoxide of monocrotaline,[17] the corresponding angles are 12.0, 15.2, 19.1, and 26.4°. The transannular distance O(10)···C(15) is 2.68 Å

† Eu(hfc)$_3$ = europium tris(heptafluorocamphorate).



Scheme. *Reagents:* i, 2,2′-dithiodipyridine, Ph_3P; ii, H_2–PtO_2–AcOH; iii, $LiBH_4$

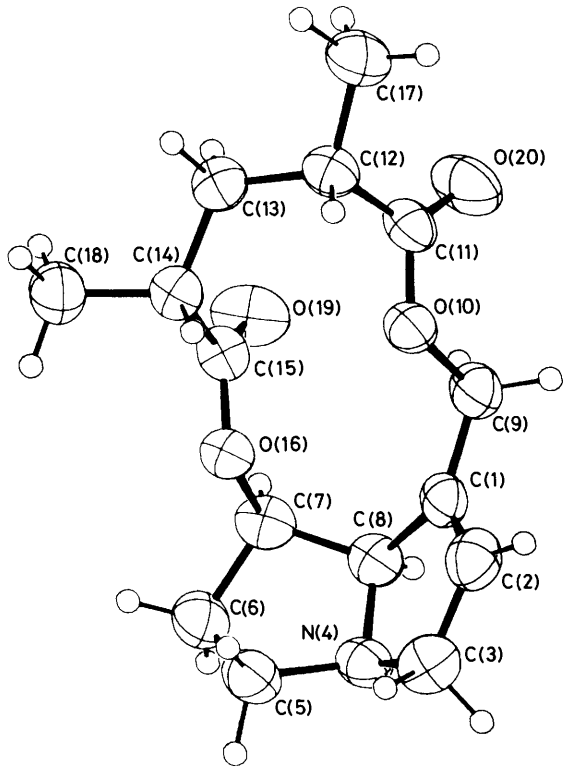


Figure. The molecular structure of compound (**4**). The thermal ellipsoids of the C, N, and O atoms are drawn at the 50% probability level. The H atoms are represented by spheres of radius 0.1 Å

atoms and the degree of magnetic non-equivalence of these atoms in ^1H n.m.r. spectra has been reviewed by Stoeckli-Evans and Crout.[18] When one of the 9-H atoms is close to both the plane of the unsaturated ring and the plane of the ester function while the other 9-H atom is remote from both, the shielding effects are additive and the Δδ value is large. Conversely, when one of these H atoms is close to the plane of the unsaturated ring and the other H atom is close to the plane of the ester function, both H atoms are shielded to about the same extent and the Δδ value is small (*e.g.*, for junceine, Δδ 0.13 p.p.m.).[19] For com-

Table 1. Torsion angles (°) for compound (**4**) with e.s.d.s in parentheses

C(8)–C(1)–C(2)–C(3)	−2.0(4)	O(20)–C(11)–C(12)–C(13)	101.1(5)	C(5)–C(6)–C(7)–O(16)	−80.6(4)
C(2)–C(1)–C(8)–N(4)	3.6(4)	O(20)–C(11)–O(10)–C(9)	−5.7(4)	C(6)–C(7)–C(8)–N(4)	−16.8(3)
C(2)–C(1)–C(9)–O(10)	−80.9(5)	C(17)–C(12)–C(13)–C(14)	−173.6(5)	O(16)–C(7)–C(8)–C(1)	−21.3(3)
C(8)–C(1)–C(9)–O(10)	102.1(5)	C(12)–C(13)–C(14)–C(18)	163.2(5)	O(16)–C(7)–C(8)–N(4)	96.6(4)
C(1)–C(2)–C(3)–N(4)	−0.4(4)	C(13)–C(14)–C(15)–O(19)	−32.7(4)	C(1)–C(8)–N(4)–C(5)	118.8(4)
C(2)–C(3)–N(4)–C(8)	2.8(4)	C(18)–C(14)–C(15)–O(19)	90.9(5)	C(7)–C(8)–N(4)–C(5)	−9.1(3)
N(4)–C(5)–C(6)–C(7)	−42.3(4)	O(19)–C(15)–O(16)–C(7)	−0.9(4)	C(12)–C(11)–O(10)–C(9)	174.1(5)
C(5)–C(6)–C(7)–C(8)	36.2(4)	C(2)–C(1)–C(8)–C(7)	122.7(5)	O(10)–C(11)–C(12)–C(17)	157.1(5)
C(6)–C(7)–C(8)–C(1)	−134.7(5)	C(9)–C(1)–C(2)–C(3)	−179.5(6)	O(20)–C(11)–C(12)–C(17)	−23.1(4)
C(6)–C(7)–O(16)–C(15)	−142.9(4)	C(9)–C(1)–C(8)–C(7)	−59.8(4)	C(11)–C(12)–C(13)–C(14)	62.3(4)
C(8)–C(7)–O(16)–C(15)	105.6(4)	C(9)–C(1)–C(8)–N(4)	−178.9(5)	C(12)–C(13)–C(14)–C(15)	−75.3(4)
C(1)–C(8)–N(4)–C(3)	−3.8(3)	C(2)–C(3)–N(4)–C(5)	−115.5(5)	C(13)–C(14)–C(15)–O(16)	149.6(4)
C(7)–C(8)–N(4)–C(3)	−131.7(4)	C(6)–C(5)–N(4)–C(3)	151.3(5)	C(18)–C(14)–C(15)–O(16)	−86.8(4)
C(1)–C(9)–O(10)–C(11)	−166.0(5)	C(6)–C(5)–N(4)–C(8)	31.9(4)	C(14)–C(15)–O(16)–C(7)	176.8(4)
O(10)–C(11)–C(12)–C(13)	−78.6(4)				

whereas the O(16) ··· C(11) distance is 3.83 Å. The short O(10) ··· C(15) distances in fulvine and monocrotaline are 2.77 and 2.74 Å.

A correlation between the positions of the C(9)-hydrogen

pound (**4**), the torsion angle H(9)–C9–C(1)–C(8) is −10° for H(9A) and −143° for H(9B), and the angle H(9)–C(9)–O(10)–C(11) is −45° for H(9A) and 75° for H(9B). Although the angles appropriate to H(9A) deviate from the ideal in-plane

values of 0° and 180° less than the angles appropriate to H(9B), the Δδ for the C(9) proton is small at 0.07 p.p.m.

The toxicity of these new pyrrolizidine alkaloid analogues can now be established.

Experimental

M.p.s were measured with a Kofler hot-stage apparatus and are uncorrected. Organic solutions were dried with anhydrous $MgSO_4$, and solvents were evaporated off under reduced pressure below 40 °C. N.m.r. spectra were recorded with a Bruker WP-200 SY spectrometer operating at 200 MHz for ^1H. Spectra were recorded for solutions in deuteriochloroform (unless otherwise stated) with tetramethylsilane as internal standard. Mass spectra were obtained with A.E.I. MS 12 or 902 spectrometers. Optical rotations were measured with an Optical Activity Ltd. AA-10 Polarimeter. T.l.c. of the bases was carried out on Kieselgel G plates of 0.25 mm adsorbent thickness developed with chloroform–methanol–conc. ammonia (85:14:1), and the bases were located by oxidation with *o*-chloranil, followed by treatment with Ehrlich's reagent.[20] DME was dried by distillation from potassium hydroxide and then from sodium-benzophenone under argon immediately prior to use.

(+)-*Retronecine* (**1**).—Extraction of *Senecio isatideus* plants yielded retrorsine, from which (+)-retronecine (**1**) was obtained by alkaline hydrolysis.[9]

(12R,14S)-12,14-*Dimethyl*-1,2-*didehydrocrotalanine* (**3**) *and* (12S,14R)-12,14-*Dimethyl*-1,2-*didehydrocrotalanine* (**4**).—*meso*-2,4-Dimethylglutaric anhydride (**2**) (50.2 mg, 0.353 mmol) was added to a stirred solution of (+)-retronecine (**1**) (52.2 mg, 0.336 mmol) in dry DME (10 ml) under argon. After the mixture had been kept for 16 h at ambient temperature, 2,2′-dithiodipyridine (88 mg, 0.399 mmol) and triphenylphosphine (106 mg, 0.404 mmol) were added, and the mixture was vigorously stirred for a further 16 h until a homogeneous yellow solution was obtained. This solution was added during 3 h by syringe to dry DME (50 ml) heated at reflux under argon, and after addition was complete the mixture was heated for a further 24 h. The cooled solution was concentrated to a gum under reduced pressure, and the residue was dissolved in chloroform (15 ml). The chloroform solution was extracted with 1M-HCl (3 × 5 ml). The acid extracts were washed with chloroform (5 × 15 ml), and basified with conc. ammonia. The basic solution was extracted with chloroform (4 × 15 ml). The extracts were dried and concentrated to afford a yellow oil which was shown to contain two major components by t.l.c. (R_F 0.50 and 0.55). These products were separated by application to a basic alumina column and elution with 25% v/v chloroform in dichloromethane. The first compound eluted was (12R,14S)-12,14-*dimethyl*-1,2-*didehydrocrotalanine* (**3**) (31 mg, 33%); R_F 0.55; fine needles, m.p. 197—198 °C (from benzene–hexane); $[\alpha]_D^{18}$ −0.2° (*c* 1.45 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 735 cm^{-1}; δ_H 1.11 (3 H, d, *J* 7 Hz, Me), 1.14 (3 H, d, *J* 7 Hz, Me), 1.55 (1 H, m, 13-H), 1.83 (1 H, m, 13-H), 2.25 (2 H, m, 6-H_2), 2.38 and 2.55 (2 H, complex, 12- and 14-H), 2.75 (1 H, m, 5-H), 3.4—3.7 (2 H, complex, 3- and 5-H), 4.10 (1 H, br d, *J* 12 Hz, 9-H), 4.20 (1 H, m, 3-H), 4.43 (1 H, br s, 8-H), 5.24 (1 H, br s, 7-H), 5.38 (1 H, d, *J* 12 Hz, 9-H), and 5.90 (1 H, s, 2-H); δ_C (50 MHz) 17.5 and 18.5 (C-17 and -18), 34.1 (C-6), 36.6 and 37.3 (C-12 and -14), 38.4 (C-13), 53.5 (C-5), 59.5 and 61.1 (C-3 and -9), 74.2 and 76.4 (C-7 and -8), 128.9 (C-2), 132.6 (C-1), and 175.2 and 175.5 (C-11 and -15); *m/z* 279 (M^+), 206, 137, 136, 120, 119, 94, 93, and 80 (Found: M^+, 279.1474. $C_{15}H_{21}NO_4$ requires *M*, 279.1470).

Further elution of the column then gave a mixture of compounds (**3**) and (**4**) (4.6 mg, 5%), followed by pure (12S,14R)-12,14-*dimethyl*-1,2-*didehydrocrotalanine* (**4**) (22 mg, 23%); R_F 0.5, needles, m.p. 103—104 °C (from benzene–hexane); $[\alpha]_D^{18}$ +9.6° (*c* 0.67 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 740 cm^{-1}; δ_H 1.13 (3 H, d, *J* 7 Hz, Me), 1.14 (3 H, d, *J* 7 Hz, Me), 1.23 (1 H, m, 13-H), 1.90—2.25 (3 H, complex, 13-H and 6-H_2), 2.45 (2 H, m, 12- and 14-H), 2.75 (1 H, m, 5-H), 3.38—3.65 (2 H, complex, 3- and 5-H), 4.10 (1 H, m, 3-H), 4.47 (1 H, d, *J* 12 Hz, 9-H), 4.54 (1 H, d, *J* 12 Hz, 9-H), 4.65 (1 H, br s, 8-H), 5.50 (1 H, br s, 7-H), and 5.97 (1 H, s, 2-H); δ_C (50 MHz) 17.7 and 19.6 (C-17 and -18), 33.4 (C-6), 39.1 (C-13), 39.2 and 39.4 (C-12 and -14), 53.8 (C-5), 58.1 and 60.4 (C-3 and -9), 72.5 and 77.9 (C-7 and -8), 132.8 (C-1), 133.4 (C-2), and 175.0 and 176.4 (C-11 and -15); *m/z* 279 (M^+), 206, 137, 136, 120, 119, 94, 93, and 80 (Found: M^+, 279.1470).

Assignment of Stereochemistry at C-12 *and* C-14 *of Macrocycle* (**3**).—(1R,7S,8R)-*Hexahydro*-7-*methyl*-1H-*pyrrolizin*-1-*yl Hydrogen* (2S,4R)-2,4-*Dimethylglutarate* (**5**). Platinum(IV) oxide (5 mg) was added to a solution of the (−)-dilactone (**3**) (30 mg, 0.107 mmol) in acetic acid (10 ml) and the mixture was stirred for 24 h under 1 atmosphere of hydrogen. The catalyst was filtered off, and the filtrate was concentrated to yield (1*R*,7*S*,8*R*)-*hexahydro*-7-*methyl*-1H-*pyrrolizin*-1-*yl hydrogen* (2S, 4R)-2,4-*dimethylglutarate* (**5**) as an oil (30 mg, 99%); $\nu_{max.}$(film) 3 200 and 1 735 cm^{-1}; δ_H(CD_3OD) 1.14, 1.16, and 1.2 (each 3 H, d, *J* 7 Hz, Me); *m/z* 283 (M^+) (Found: M^+, 283.1780. $C_{15}H_{25}NO_4$ requires *M*, 283.1782).

(3R,5S)-3,5-*Dimethyltetrahydro*-2H-*pyran*-2-*one* (**6**).—An aqueous solution of the retronecanyl ester (**5**) (30 mg, 0.106 mmol) was neutralised with 0.1M-lithium hydroxide (1.1 ml), and the solution was freeze-dried. The lithium salt was dissolved by being stirred in dry tetrahydrofuran (5 ml) overnight, and then a 1M-solution of lithium borohydride in dry diethyl ether (200 μl) was added, and the solution was refluxed for 2 h. Methanol (120 μl) was added and the solution was refluxed for a further 30 min. Water (1 ml) was added and the organic solvents were removed under reduced pressure. The pH of the aqueous solution was adjusted to 8 and the solution was continuously extracted for 18 h with chloroform to remove boric acid. The aqueous solution was acidified to pH 2 and extracted with chloroform for 24 h. These extracts were dried and concentrated under reduced pressure and the residue was taken up in methanol and concentrated (5 ×) to remove traces of boric acid.

The (3*R*,5*S*)-pyrone was obtained as an oil (7.0 mg, 51%); $[\alpha]_D^{18}$ −35.2° (*c* 0.14 in $CHCl_3$) (lit.,[12] $[\alpha]_D^{20}$ −39.1°). This material was identical (t.l.c., i.r. and ^1H n.m.r. spectra) with a synthetic sample of the (±)-lactone (**6**). The benzhydrylamide had m.p. 128—130 °C. Addtion of Eu(hfc)$_3$ gave no detectable doubling of the signals in the ^1H n.m.r. spectrum.

Assignment of Stereochemistry at C-12 *and* C-14 *of Macrocycle* (**4**).—Hydrogenolysis of (**4**) and treatment of the product (**7**) with lithium borohydride was carried out as described for compound (**3**) to give the (3*S*,5*R*)-pyrone (**8**) as an oil, $[\alpha]_D^{18}$ +31.8° (*c* 0.1 in $CHCl_3$) (lit.,[12] $[\alpha]_D$ +39.1°). This material was identical (t.l.c., i.r. and ^1H n.m.r. spectra) with the synthetic (±)-lactone (**6**). The benzhydrylamide had m.p. 127—129 °C. Addition of Eu(hfc)$_3$ showed some doubling of the signals in the ^1H n.m.r. spectrum, corresponding to *ca.* 10% of the (3*R*,5*S*)-isomer.

(±)-cis-3,5-*Dimethyltetrahydro*-2H-*pyran*-2-*one* (**6**) *and* (**8**).—*meso*-2,4-Dimethylglutaric anhydride (**2**) (1.39 g) was treated with excess of ethanol (5 ml), triethylamine (5 ml), and a catalytic amount of 4-dimethylaminopyridine in dry DME (100 ml) overnight. The solvents were removed under reduced pressure, and the residue was dissolved in 2M-hydrochloric acid (50 ml). The acidic solution was extracted with dichloromethane (4 × 50 ml). The extracts were dried, filtered, and concentrated

Table 2. Fractional atomic co-ordinates for compound (4) with e.s.d.s in parentheses

	x	*y*	*z*
C(1)	0.631 32(18)	0.480 88(80)	0.257 14(18)
C(2)	0.573 9(2)	0.328 5(6)	0.256 5(2)
C(3)	0.535 7(2)	0.313 3(9)	0.340 0(3)
C(5)	0.618 7(2)	0.360 5(10)	0.467 2(2)
C(6)	0.685 6(3)	0.521 1(10)	0.483 8(2)
C(7)	0.712 2(2)	0.581 5(7)	0.394 6(2)
C(8)	0.638 4(2)	0.600 8(8)	0.343 5(2)
C(9)	0.680 5(2)	0.537 0(9)	0.182 8(2)
C(11)	0.795 96(18)	0.379 97(80)	0.126 91(18)
C(12)	0.852 37(19)	0.176 69(75)	0.134 22(19)
C(13)	0.901 2(2)	0.200 5(9)	0.215 9(2)
C(14)	0.860 78(19)	0.188 56(71)	0.300 30(20)
C(15)	0.818 12(18)	0.418 19(69)	0.320 06(18)
C(17)	0.901 8(3)	0.163 5(12)	0.055 4(3)
C(18)	0.916 3(3)	0.139 5(11)	0.374 4(2)
O(10)	0.736 05(12)	0.342 22(57)	0.177 17(12)
O(16)	0.756 94(10)	0.374 60	0.366 72(11)
O(19)	0.838 11(16)	0.618 22(59)	0.298 73(17)
O(20)	0.801 58(16)	0.558 05(62)	0.082 65(16)
O(21)	0.5000	0.335 6(10)	1.0000
N(4)	0.578 85(16)	0.481 54(65)	0.395 38(16)

Table 3. Bond lengths (Å) and bond angles (°) for compound (4) with e.s.d.s in prentheses

(a) Bond lengths

C(1)–C(2)	1.314(6)	C(1)–C(8)	1.510(5)
C(1)–C(9)	1.493(5)	C(2)–C(3)	1.482(6)
C(3)–N(4)	1.475(6)	C(5)–C(6)	1.493(7)
C(5)–N(4)	1.479(5)	C(6)–C(7)	1.517(5)
C(7)–C(8)	1.521(5)	C(7)–O(16)	1.457(5)
C(8)–N(4)	1.489(5)	C(9)–O(10)	1.457(6)
C(11)–C(12)	1.501(6)	C(11)–O(10)	1.341(4)
C(11)–O(20)	1.208(6)	C(12)–C(13)	1.537(5)
C(12)–C(17)	1.522(6)	C(13)–C(14)	1.513(4)
C(14)–C(15)	1.507(6)	C(14)–C(18)	1.532(6)
C(15)–O(16)	1.332(4)	C(15)–O(19)	1.207(5)

(b) Bond angles

C(2)–C(1)–C(8)	110.0(3)	C(2)–C(1)–C(9)	125.4(4)
C(8)–C(1)–C(9)	124.5(4)	C(1)–C(2)–C(3)	112.8(4)
C(2)–C(3)–N(4)	104.4(4)	C(6)–C(5)–N(4)	103.2(4)
C(5)–C(6)–C(7)	102.9(3)	C(6)–C(7)–C(8)	103.2(3)
C(6)–C(7)–O(16)	106.2(4)	C(8)–C(7)–O(16)	111.0(3)
C(1)–C(8)–C(7)	120.1(4)	C(1)–C(8)–N(4)	104.2(3)
C(7)–C(8)–N(4)	106.5(3)	C(1)–C(9)–O(10)	106.9(4)
C(12)–C(11)–O(10)	111.3(4)	C(12)–C(11)–O(20)	126.3(4)
O(10)–C(11)–O(20)	122.3(4)	C(11)–C(12)–C(13)	111.2(4)
C(11)–C(12)–C(17)	111.0(4)	C(13)–C(12)–C(17)	111.2(4)
C(12)–C(13)–C(14)	117.4(3)	C(13)–C(14)–C(15)	112.6(4)
C(13)–C(14)–C(18)	111.6(3)	C(15)–C(14)–C(18)	107.9(4)
C(14)–C(15)–O(16)	111.7(3)	C(14)–C(15)–O(19)	124.3(4)
O(16)–C(15)–O(19)	123.9(4)	C(9)–O(10)–C(11)	117.1(4)
C(7)–O(16)–C(15)	117.9(3)	C(3)–N(4)–C(5)	113.6(4)
C(3)–N(4)–C(8)	108.5(3)	C(5)–N(4)–C(8)	106.5(3)

under reduced pressure to give the monoethyl ester as an oil (1.69 g, 92%); $\nu_{max.}$(CHCl$_3$) 1 710 and 1 725 cm^{-1}; δ_H 1.2 (6 H, d, *J* 7 Hz, and 3 H, t, *J* 7 Hz), 1.3—2.7 (4 H, complex), and 4.15 (2 H, q, *J* 7 Hz); *m/z* 171 (M^+ − 17), 170, 143, 142, 115, 114, 102, 87, 74, and 69.

The monoethyl ester was converted into its lithium salt which was then reduced with lithium borohydride as described above to yield (±)-*cis*-3,5-dimethyltetrahydro-2*H*-pyran-2-one (**6**) and (**8**) as an oil (1.07 g, 93%); $\nu_{max.}$(CHCl$_3$) 1 725 cm^{-1}; δ_H 0.95 (3 H, d, *J* 7 Hz, Me), 1.25 (3 H, d, *J* 7 Hz, Me), 1.5—2.3 (3 H, complex), 2.3—2.8 (1 H, m, 4-H), 3.9 (1 H, dd, *J* 8 and 11 Hz, 6-H), and 4.3 (1 H, dd, *J* 8 and 11 Hz, 6-H) (Found: M^+, 128.0838. Calc. for $C_7H_{12}O_2$: *M*, 128.0834). The *benzhydrylamide* had m.p. 131—132 °C (from benzene); $\nu_{max.}$ 3 630, 3 440, 1 665, 1 600, and 1 495 cm^{-1}; δ_H 0.9 (3 H, d, *J* 6 Hz), 1.15 (3 H, d, *J* 7 Hz), 1.2—2.1 (3 H, complex), 2.3 (1 H, s, OH), 2.2—2.6 (1 H, m), 3.35 (2 H, d, C*H*$_2$OH), 6.25 (1 H, d), 6.55 (1 H, d, NH), and 7.3 (10 H, s). Addition of 0.05 equiv. of Eu(hfc)$_3$ resulted in doubling of the methyl signals. The product had *m/z* 311 (M^+, 43), 293 (6), 182 (66), 167 (100), 106 (10), 104 (8), and 77 (7%) (Found: M^+, 311.1894. $C_{20}H_{25}NO_2$ requires *M*, 311.1902) (Found: C, 77.0; H, 8.0; N, 4.4%. $C_{20}H_{25}NO_2$ requires C, 77.4; H, 8.09; N, 4.50%).

Crystal Structure Analysis of the Pyrrolizidine Alkaloid Analogue (**4**).—*Crystal data.* Crystals were grown from a hexane solution, $C_{15}H_{21}NO_4 \cdot \frac{1}{2}H_2O$, *M* = 288.37, monoclinic, *a* = 17.603(4), *b* = 5.517(3), *c* = 15.674(4) Å, β = 90.78(2)°, *V* = 1 522 Å^3, D_c = 1.26 g cm^{-3}, *Z* = 4, *F*(000) = 620, μ(Mo-K_α) = 1.00 cm^{-1}, systematic absences *hkl*: $k + l = 2n + 1$, space group *A*2 (C^3_2, No. 5).

Crystallographic Measurements.—Cell dimensions were derived by least-squares treatment of the setting angles of 25 reflections measured on an Enraf-Nonius CAD4 diffractometer with Mo-K_α radiation. For the intensity measurements, 1 436 reflections (*hkl* and *hkl̄*) were surveyed in the range $\theta \leqslant 25°$ with Mo-K_α radiation and of these 1 125 satisfied the criterion $I > 2.5\sigma(I)$.

Structure analysis. The crystal structure was elucidated with the direct phasing procedure MITHRIL, including negative quartets.[21] After preliminary least-squares adjustment of the co-ordinates of the C, N, and O atoms of the pyrrolizidine alkaloid analogue (**4**), the O atom of the water molecule and all the H atoms were located in difference electron-density distributions. Refinement with anisotropic thermal parameters for the C, N, and O atoms and with the H atoms constrained to ideal positions with fixed thermal parameters converged at *R* 0.047, R_w 0.055 with weights $w \propto 1/\sigma^2(|F|)$. The H atoms were then included in the least-squares calculations with isotropic thermal parameters and convergence was reached at *R* 0.035, R_w 0.039. Fourier, least-squares, geometry, and ORTEP calculations were performed with the GX systems of programs.[22]

Atomic co-ordinates are listed in Table 2, and bond-lengths and angles in Table 3. Observed and calculated structure amplitudes, thermal parameters, hydrogen-atom co-ordinates, and C–H bond lengths are listed in Supplementary Publication No. SUP 56571 (5 pp.).*

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* For details of the Supplementary Publication Scheme, see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1.

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