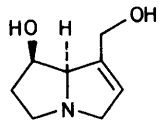
Pyrrolizidine Alkaloid Analogues. Synthesis of Macrocyclic Diesters of (±)-Synthanecine A from (±)-3-Chloromethyl-2-hydroxymethyl-1-methyl-2,5-dihydropyrrolium Chloride

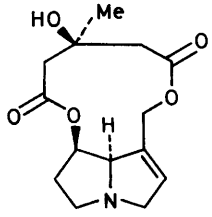
Robert H. Barbour and David J. Robins*
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

Reaction of 2,3-bis(hydroxymethyl)-1-methyl-2,5-dihydropyrrole [(±)-synthanecine A] (**3**) with thionyl chloride produces (±)-3-chloromethyl-2-hydroxymethyl-1-methyl-2,5-dihydropyrrolium chloride (**11**), which was treated with a series of anhydrides and base at room temperature to give the corresponding 6-monoesters of (±)-synthanecine A. Intramolecular nucleophilic substitution of the chlorine by carboxylate anion in the presence of base (DBU) gives the corresponding macrocyclic diesters of (±)-synthanecine A. The pyrrolizidine alkaloid analogues [(**6**), (**7**), and (**16**)—(**20**)] are prepared in better yields than using Corey–Nicolaou lactonisation conditions. A range of new 10-membered [(**8**)—(**10**) and (**12**)—(**14**)] and 11-membered [(**15**) and (**21**)] macrocyclic diesters of (±)-synthanecine A has been prepared.

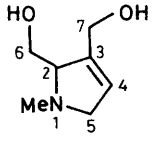
The synthesis of pyrrolizidine alkaloids and structurally related compounds is of considerable interest because of the broad range of biological activities they exhibit. The main danger to livestock grazing on plants containing these alkaloids is hepatotoxicity. The most toxic pyrrolizidine alkaloids contain (+)-retronecine (**1**) as the base part of a macrocyclic diester



(**1**)



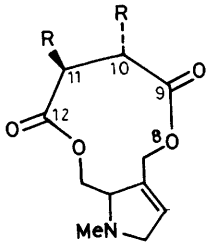
(**2**)



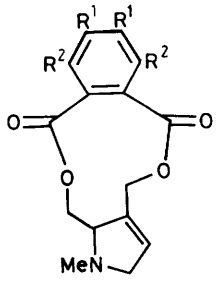
(**3**)

system.[1,2] The 11-membered pyrrolizidine alkaloid dicrotaline (**2**),[3] and a series of 11-membered[4,5] and 10-membered[6] alkaloid analogues containing (+)-retronecine have been prepared by us. Each macrocyclic dilactone was made by treatment of (+)-retronecine (**1**) with the appropriate anhydride to yield the corresponding monoester, which was lactonised *via* the pyridine 2-thiol ester (Corey–Nicolaou route).[7] The range of macrocyclic pyrrolizidine alkaloid analogues available for biological evaluation was extended recently by using 2,3-bis(hydroxymethyl)-1-methyl-2,5-dihydropyrrole (**3**) (synthanecine A), which is a monocyclic analogue of retronecine. A number of 11-membered[8] and 10-membered[9] [(**4**)—(**6**)] macrocyclic diesters of (±)-synthanecine A were synthesised by the Corey–Nicolaou procedure. The metabolism and toxicity of some of these macrocyclic dilactones incorporating synthanecine A have been investigated.[10]

The yields of the phthalate dilactones incorporating synthanecine A or retronecine obtained by the Corey–Nicolaou route were both *ca.* 15%. These yields were too low to prepare sufficient quantities of these analogues for biological evaluation. A solution to this problem was provided when an alternative route to 7,9-*O*,*O*-phthaloylretronecine was established.[11] (+)-Retronecine (**1**) was converted into the allylic chloride hydrochloride, and this was treated with phthalic anhydride and two equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), to give a much improved yield (57%) of the phthaloylretronecine. A number of new pyrrolizidine alkaloid analogues containing retronecine were made in this way.[11] We have now used this procedure to improve the yield of the corresponding phthaloylsynthanecine A (**7**) and to prepare new macrocyclic pyrrolizidine alkaloid analogues containing (±)-synthanecine A.



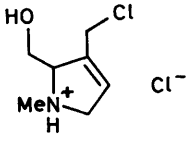
(**4**) R = H
(**5**) R = Me
(**6**) R, R = $(CH_2)_4$



(**7**) $R^1 = R^2 = H$
(**8**) R^1 = Cl, R^2 = H
(**9**) $R^1 = R^2$ = Cl
(**10**) $R^1 = R^2$ = Br

Results and Discussion

Treatment of (±)-synthanecine A (**3**)[8,12] with thionyl chloride gave a chloro compound isolated as the hydrochloride. The structure was assigned as the allylic chloride (**11**) by consideration of n.m.r. spectra, including comparison with those of the corresponding retronecine derivative, and use of 2D homonuclear (^1H–^1H) and heteronuclear (^{13}C–^1H) correlation



(**11**)

Table. Formation of dilactones of (±)-synthanecine A

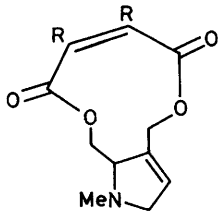
Analogue	Size of macrocycle	Yield (%) Method A[a]	Yield (%) Method B[b]	Δδ/p.p.m. C-6 protons	Δδ/p.p.m. C-7 protons
(4)	10	30[c]	10	0.42	0.68
(5)	10	32[c]	17	0.60	0.86
(6)	10	23[c]	51	*e*	*e*
(7)	10	16[c]	86	0.36	0.48
(8)	10	0	91	0.34	0.47
(9)	10		67	0.23	0.23
(10)	10		81	0.13	0.15
(12)	10	0	49	0.36	0.53
(13)	10		33	0.44	0.53
(14)	10		77	0.46	0.60
(15)	11		65	0.56	0.34
(16)	11	21[d]	37	0.07	0
(17)	11	25[d]	53	0.17	0.16
(18)	11	26[d]	66	0.13	0.13
(19)	11	20[d]	52	*e*	*e*
(20)	11	30[d]	77	0.48 0.51	0.20 0.40
(21)	11	0	44	0.05	0

[a] Corey–Nicolaou lactonisation. [b] Reaction of (±)-3-chloromethyl-2-hydroxymethyl-1-methyl-2,5-dihydropyrrolium chloride with various anhydrides using DBU as the base. [c] Ref. 9. [d] Ref. 8. [e] Mixture of diastereoisomers.

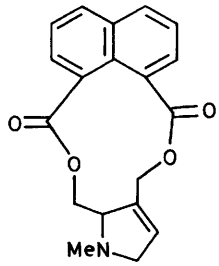
spectroscopy. It is possible that the chlorination process proceeds *via* a cyclic sulphite ester before formation of the allylic chloride (**11**). This assignment of structure is supported by the reactivity of compound (**11**) in the subsequent lactonisation reactions.

Treatment of the allylic chloride (**11**) with phthalic anhydride in the presence of two equivalents of DBU gave a much improved yield (86%) of the phthalate diester (**7**). Spectroscopic data on this compound were identical in all respects to those obtained for the material prepared earlier.[9] We had previously tried to make a macrocyclic dilactone from (±)-synthanecine A and 4,5-dichlorophthalic anhydride by the Corey–Nicolaou method but without success. Use of the allylic chloride (**11**) with this anhydride and DBU resulted in a 91% yield of the new macrocyclic diester (**8**). An accurate mass measurement on this dichloro compound (**8**) gave a molecular formula of $C_{15}H_{13}{}^{35}Cl_2NO_4$, and the mass spectral fragmentation pattern was typical for a macrocyclic dilactone containing synthanecine A.[8] In the ^{1}H n.m.r. spectrum of dilactone (**8**), the protons assigned to C-6 and C-7 were both shifted downfield relative to the corresponding signals in the spectrum of synthanecine A. The chemical shift differences (Δδ) between these protons on C-6 and C-7 are listed in the Table and are similar to those of the phthalate derivative (**7**). Reaction of the allylic chloride (**11**) with 4,5-dichlorophthalic anhydride in the presence of other bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and Hunig's base (*N*,*N*-di-isopropylethylamine) also led to formation of the cyclic diester (**8**) but in lower yields of 24 and 40%, respectively. Two more new aromatic analogues [(**9**) and (**10**)] were prepared in good yield (Table) from 3,4,5,6-tetrachloro- and 3,4,5,6-tetrabromo-phthalic anhydride using DBU as the base.

The 10-membered pyrrolizidine alkaloid analogue (**12**) with a double bond in the acid portion of the macrocycle was required for toxicity studies. However, esterification of (±)-synthanecine A (**3**) with maleic anhydride and attempted lactonisation using the pyridine-2-thiol esters did not give any cyclized product. Treatment of the allylic chloride (**11**) with maleic anhydride and DBN or Hunig's base also failed to yield the required dilactone.



(**12**) R = H
(**13**) R = Me
(**14**) R, R = $(CH_2)_4$

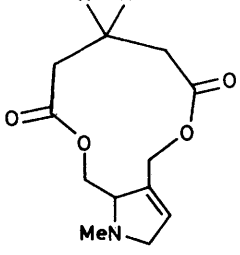


(**15**)

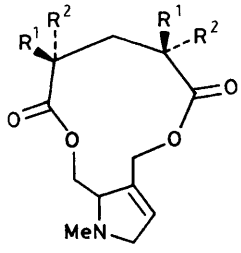
Use of DBU in this reaction gave the desired maleate diester (**12**) in 49% yield. The related analogues (**13**) and (**14**) were also prepared from 2,3-dimethylmaleic and cyclohexene-1,2-dicarboxylic anhydrides with DBU as base. The chemical shift differences for the protons at C-6 and C-7 for these new analogues are quoted in the Table. All of the 10-membered dilactones except the tetrahalogeno compounds [(**9**) and (**10**)] have relatively large chemical shift differences for the protons at C-6 (0.34—0.60 p.p.m.) and C-7 (0.47—0.86 p.p.m.). These large Δδ values are believed to arise when one of the protons on a carbon next to the oxygen is deshielded by proximity to the plane of the ester carbonyl group. An additional effect is possible if one of the C-7 protons is also close to the plane of the double bond. *X*-Ray crystal structure analysis of the succinate derivative (**4**) showed that the ester carbonyl groups are antiparallel, with the allylic ester carbonyl on the opposite side of the ring to the 2-H. It is possible, from consideration of the ^{1}H n.m.r. spectroscopic data (Table), that the other 10-membered analogues [(**5**)—(**8**) and (**12**)—(**14**)] have similar conformations of the macrocycle. It has been suggested that the conformations of a pyrrolizidine alkaloid in solution and the solid state are likely to be similar.[13] In the case of the tetrahalogeno compounds (**9**) and (**10**), the conformations may be affected by the presence of the bulky halogens.

Treatment of the allylic chloride (**11**) with naphthalene-1,2-dicarboxylic anhydride and DBU gave an 11-membered analogue (**15**) in 65% yield. The Δδ values for the C-6 and C-7 protons in the ^{1}H n.m.r. spectrum of this new dilactone (**15**) are within the range found for the 10-membered compounds (Table).

The ten-membered [(**4**)—(**7**)] and 11-membered pyrrolizidine alkaloid analogues [(**16**)—(**20**)] containing (±)-synthanecine A were prepared using Corey–Nicolaou conditions in yields given in the Table.[8] Most of these yields were improved by use of the new procedure with DBU as base. The two exceptions are the succinate (**4**) and 2,3-dimethylsuccinate (**5**) dilactones, where lactonisation *via* the pyridine 2-thiol esters is more efficient.



(**16**) $R^1 = R^2 = H$
(**17**) $R^1 = R^2 = Me$
(**18**) $R^1, R^2 = (CH_2)_5$
(**19**) $R^1 = OH$, $R^2 = Me$



(**20**) a; $R^1 = Me$, $R^2 = H$ and
b; $R^1 = H$ $R^2 = Me$
(**21**) $R^1 = R^2 = Me$

These observations differ somewhat from those with retronecine,[4,6] where it was found that the Corey–Nicolaou conditions gave better yields of dilactones with all the saturated anhydrides. One analogue of special interest is the 3,3-dimethylglutarate dilactone (**17**), because tests have shown that this is one of the most toxic analogues, with hepatotoxic effects similar to pyrrolizidine alkaloids, and with high resistance to detoxification by esterase hydrolysis in rats.[10] The yield of this analogue (**17**) obtained by the Corey–Nicolaou method (25%) was improved using the allylic chloride (**11**) to 37% with DBN and to 53% with DBU. No cyclized product was obtained using Hunig's base.

Finally, it has been suggested that the steric hindrance present in many pyrrolizidine alkaloids at the α-positions of the diacid portion enhances the toxicity by making the alkaloids less susceptible to detoxification by hydrolysis. We had tried to make the α,α′-tetrasubstituted glutarate analogue (**21**) by the Corey–Nicolaou method without success. Treatment of 2,2,4,4-tetramethylglutaric anhydride with the allylic chloride (**11**) and DBU gave the desired analogue (**21**) in 44% yield.

It should be noted from the Table that the 11-membered pyrrolizidine alkaloid analogues [(**15**)—(**21**)] display a range of Δδ values for the protons at C-6 and C-7, possibly reflecting a range of different conformations of the macrocyles. Indeed, *X*-ray studies have shown that two of these analogues have different conformations of the dilactone.[14] In the 3,3-dimethylglutarylsynthanecine A (**17**), the ester carbonyls lie on opposite sides of the macrocycle, but the allylic ester carbonyl is on the same side of the ring as the 2-H [this is the opposite orientation to the succinate dilactone (**4**)]. On the other hand, the ester carbonyls in the analogue (**20a**) are both on the same side of the macrocycle, but pointing away from the 2-H.

Further studies are required to establish the conformations and to determine the toxicity of these new pyrrolizidine alkaloid analogues.

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-200SY spectrometer operating at 200 MHz for ^1H. Spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as internal standard, and they were subjected to first-order analysis in order to obtain *J* values. Mass spectra were obtained with A.E.I. MS 12 or 902 spectrometers. T.l.c. of the bases was carried out on Kieselgel G plates of 0.25 mm thickness developed with chloroform–methanol–conc. ammonia (85:14:1), and the unsaturated bases were located by oxidation with *o*-chloranil, followed by treatment with Ehrlich's reagent.[15] *N*,*N*-Dimethylformamide (DMF) was dried using 3Å molecular sieves as described by Burfield and Smithers.[16]

Synthesis of (±)-3-*Chloromethyl*-2-*hydroxymethyl*-1-*methyl*-2,5-*dihydropyrrolium Chloride* (**11**).—Thionyl chloride (2 ml, 2.8 mmol), cooled to 0 °C, was added to synthanecine A[8,12] (**3**) (0.5 g, 3.5 mmol) at −5 °C. The mixture was stirred for 45 min at 0 °C after which the excess thionyl chloride was removed under reduced pressure (0 °C, *ca.* 2 mmHg). The purple residue was dissolved in ethanol and treated with activated charcoal until the colouration was removed. The solution was then filtered through Celite and concentrated under reduced pressure to give a pale brown oil (0.59 g, 85%). Crystallisation using ethanol–acetone afforded the title compound (**11**) (0.38 g, 55%) as prisms, m.p. 135 °C; R_F 0.28; $\nu_{max.}$(KBr) 3 340 (OH), 2 920 (CH), 2 640 (R_3N^+H), 1 090 (CO), 835 [$R_2C{=}C(R)H$], and 695 cm^{-1} (CCl); δ_H(D_2O; 200 MHz) 2.95 (3 H, s, NMe), 3.85 (1 H, m, 5-H), 3.92 (2 H, m, 6-H_2), 4.20 (2 H, m, 7-H_2), 4.35 (1 H, m, 5-H), 4.40 (1 H, m, 2-H), and 5.99 (1 H, br s, 4-H); δ_C(D_2O; 50 MHz) 39.1 (C-7), 42.2 (NMe), 58.0 (C-6), 62.2 (C-5), 76.0 (C-2), 125.8 (C-4), and 135.2 (C-3); *m*/*z* 132 (M^+ − MeOH), 112, 94, 81, 67, and 53 (Found: C, 42.3; H, 6.6; N, 7.0. $C_7H_{13}Cl_2NO$ requires C, 42.44; H, 6.62; N, 7.07%).

General Procedure for the Synthesis of Synthanecine A Dilactones [(**4**)—(**10**) *and* (**12**)—(**21**)].[13]—The anhydride (1 mmol) and base (2.1 mmol) were added to a solution of (±)-3-chloromethyl-2-hydroxymethyl-1-methyl-2,5-dihydropyrrolium chloride (**11**) (1 mmol) in dry DMF (18 ml) under argon, and the mixture was stirred at room temperature, generally for 24 h. The solvent (DMF) was removed under reduced pressure (*ca.* 40 °C, 3 mmHg) to give the crude product as an oily or crystalline residue, which was purified by column chromatography on basic alumina (5% v/v chloroform in dichloromethane as the eluant). The polarity of the eluant was steadily increased by increasing the proportion of chloroform. The yields of the dilactones [(**4**)—(**10**) and (**12**)—(**21**)] are given in the Table.

(±)-6,7-O,O-(4,5-*Dichlorophthaloyl*)*synthanecine A* (**8**) was obtained as needles, m.p. 177—178 °C (ethanol;) R_F 0.76; $\nu_{max.}$(KBr) 2 960, 2 855, 2 790, 1 730, 1 590, 1 550, 1 375, 1 300, 1 127, 833, and 775 cm^{-1}; $\lambda_{max.}$(EtOH) 252 (ε 5 550), 286 (843), and 269 nm (630); δ_H(200 MHz) 2.49 (3 H, s, NMe), 3.20 (1 H, m, 5-H), 3.71 (1 H, m, 2-H), 3.85 (1 H, m, 5-H), 4.23 (1 H, dd, J_{gem} 12, J_{vic} 6 Hz, 6-H), 4.57 (1 H, dd, J_{gem} 12, J_{vic} 4 Hz, 6-H), 4.77 (1 H, d, J_{gem} 13 Hz, 7-H), 5.24 (1 H, d, J_{gem} 13 Hz, 7-H), 6.02 (1 H, m, 4-H), 7.61 (1 H, s, 14- or 17-H), and 7.64 (1 H, s, 17- or 14-H); δ_C(50 MHz) 41.6 (NMe), 60.5 and 62.6 (C-5 and -6), 66.3 (C-7), 71.3 (C-2), 131.3, 131.5, 131.9, and 132.0 (C-4, -10, -11, -14, and -17), 136.2, 136.3, and 136.5 (C-3, -15, and -16), and 166.0 and 166.8 (C-9 and -12); *m*/*z* 343 and 341 (M^+), 265, 144, 124, 110, 94, 82, and 74 (Found: M^+, 341.0199; C, 52.5; H, 3.7; N, 4.0%. $C_{15}H_{13}{}^{35}Cl_2NO_4$ requires *M*, 341.0222; C, 52.76; H, 3.84; N, 4.10%).

(±)-6,7-O,O-(3,4,5,6-*Tetrachlorophthaloyl*)*synthanecine A* (**9**) was obtained as needles, m.p. 139—141 °C (ethyl acetate); R_F 0.77; $\nu_{max.}$(KBr) 2 955, 2 890, 2 845, 2 770, 1 735, 1 525, 1 452, 1 232, 1 169, 1 095, 1 082, 689, and 578 cm^{-1}; $\nu_{max.}$($CHCl_3$) 2 945, 2 850, 2 785, 1 740, 1 450, 1 355, 1 270, 1 175, and 1 100 cm^{-1}; $\lambda_{max.}$(EtOH) 225 (ε 39 810), 298 (1 053), and 308 nm (1 100); δ_H(200 MHz) 2.49 (3 H, s, NMe), 3.19 (1 H, m, 5-H), 3.77 (1 H, m, 2-H), 3.87 (1 H, m, 5-H), 4.31 (1 H, dd, J_{gem} 11.5, J_{vic} 7 Hz, 6-H), 4.54 (1 H, dd, J_{gem} 11.5, J_{vic} 4 Hz, 6-H), 4.95 (1 H, d, J_{gem} 13 Hz, 7-H), 5.18 (1 H, d, J_{gem} 13 Hz, 7-H), and 6.06 (1 H, br s, 4-H); δ_C(50 MHz) 42.2 (NMe), 60.3 and 62.6 (C-5 and -6), 65.9 (C-7), 71.0 (C-2), 131.2, 131.4, 131.5, 131.8, 136.9, and 137.0 (C-10, -11, -14, -15, -16, and -17), 132.5 (C-4), 136.1 (C-3), and 162.8 and 163.2 (C-9 and -12); *m*/*z* 414, 412, 410, and 408 (M^+), 241, 213, 142, 110, 94, and 82 (Found: M^+, 410.9404; C, 52.5; H, 3.7; N, 4.0%. $C_{15}H_{11}{}^{35}Cl_3{}^{37}ClNO_4$ requires *M*, 410.9413; C, 52.76; H, 3.84; N, 4.10%).

(±)-6,7-O,O-(3,4,5,6-*Tetrabromophthaloyl*)*synthanecine A* (**10**) was obtained as needles, m.p. 160—161 °C (ethanol); R_F 0.77; $\nu_{max.}$(KBr) 2 955, 2 850, 2 785, 1 738, 1 385, 1 245, 1 220, 1 150, 1 070, and 989 cm^{-1}; $\lambda_{max.}$(EtOH) 230 (ε 4 326) and 310 nm (127); δ_H(200 MHz) 2.48 (3 H, s, NMe), 3.19 (1 H, m, 5-H), 3.78 (1 H, m, 2-H), 3.87 (1 H, m, 5-H), 4.35 (1 H, dd, J_{gem} 11, J_{vic} 8 Hz, 6-H), 4.48 (1 H, dd, J_{gem} 11 J_{vic} 4 Hz, 6-H), 4.98 (1 H, d, J_{gem} 13 Hz, 7-H), 5.13 (1 H, d, J_{gem} 13 Hz, 7-H), and 6.05 (1 H, br s, 4-H); δ_C(50 MHz) 42.3 (NMe), 60.2 and 62.7 (C-5 and -6), 65.8 (C-7), 70.9 (C-2), 123.7, 123.8, 2 × 133.7, 134.4, and 134.7 (C-10, -11, -14, -15, -16, and -17), 132.2 (C-4), 136.4 (C-3), and 163.9 and 164.1 (C-9 and -12); *m*/*z* 588 (M^+), with a cluster of isotope peaks, 419, 231, 124, 110, 107, 94, and 82 (Found: M^+, 588.7364; C, 30.8; H, 2.0; N, 24%. $C_{15}H_{11}{}^{79}Br_2{}^{81}Br_2NO_4$ requires *M*, 588.7380; C, 30.59; H, 1.88; N, 2.38%).

(±)-6,7-O,O-(*Maleoyl*)*synthanecine A* (**12**) was obtained as prisms, m.p. 82—83 °C (ethyl acetate–hexane); R_F 0.69; $\nu_{max.}$(CCl$_4$) 2 955, 2 790, 1 735, 1 290, and 1 151 cm^{-1}; $\lambda_{max.}$(EtOH) 248 nm (ε 924); δ_H(200 MHz) 2.47 (3 H, s, NMe), 3.18 (1 H, m, 5-H), 3.62 (1 H, m, 2-H), 3.83 (1 H, m, 5-H), 4.10 (1 H, dd, J_{gem} 12, J_{vic} 6 Hz, 6-H), 4.46 (1 H, dd, J_{gem} 12, J_{vic} 3.5 Hz, 6-H), 4.60 (1 H, d, J_{gem} 13 Hz, 7-H), 5.13 (1 H, d, J_{gem} 13 Hz, 7-H), 5.95 (1 H, br s, 4-H), and 6.27 and 6.35 (2 H, AB system, *J* 12 Hz, 10- and 11-H); δ_C(25 MHz) 41.4 (NMe), 60.5 and 61.8 (C-5 and -6), 65.5 (C-7), 71.4 (C-2), 130.6, 131.1, and 131.6 (C-4, -10, and -11) 136.2 (C-3), and 166.2 and 165.4 (C-9 and -12); *m/z* 223 (M^+) 110, 94, 82, and 67 (Found: M^+, 223.0842; C, 59.5; H, 5.9; N, 6.0%. $C_{11}H_{13}NO_4$ requires *M*, 223.0844; C, 59.18; H, 5.87; N, 6.27%).

(±)-6,7-O,O-(2,3-*Dimethylmaleoyl*)*synthanecine A* (**13**) was obtained as needles, m.p. 96—97 °C (hexane); R_F 0.72; $\nu_{max.}$(CCl$_4$) 2 940, 2 850, 2 785, 1 720, 1 650, 1 267, and 1 105 cm^{-1}; $\lambda_{max.}$(EtOH) 238 nm (ε 2 854); δ_H(200 MHz), 1.89 (6 H, m, 14- and 15-H$_3$), 2.41 (3 H, s, NMe), 3.11 (1 H, m, 5-H), 3.55 (1 H, m, 2-H), 3.77 (1 H, m, 5-H), 4.00 (1 H, dd, J_{gem} 12, J_{vic} 6 Hz, 6-H), 4.44 (1 H, dd, J_{gem} 12, J_{vic} 3.5 Hz, 6-H), 4.53 (1 H, d, J_{gem} 13 Hz, 7-H), 5.06 (1 H, d, J_{gem} 13 Hz, 7-H), and 5.88 (1 H, br s, 4-H); δ_C(50 MHz) 15.3 and 15.7 (C-14 and -15), 41.3 (NMe), 60.3 and 61.2 (C-5 and -6), 64.7 (C-7), 71.4 (C-2), 131.2 (C-4), 133.7 and 135.0 (C-10 and -11), 136.36 (C-3), and 168.6 and 169.8 (C-9 and 12); *m/z* 251 (M^+), 148, 124, 107, 94, 82, and 70 (Found: M^+, 251.1169; C, 62.0; H, 6.9; N, 5.3%. $C_{13}H_{17}NO_4$ requires *M*, 251.1158; C, 62.13; H, 6.82; N, 5.5%).

(±)-6,7-O,O-(3,4,5,6-*Tetrahydrophthaloyl*)*synthanecine A* (**14**) was obtained as needles, m.p. 112—113 °C (hexane); R_F 0.74; $\nu_{max.}$(CCl$_4$) 2 950, 2 870, 2 785, 1 725, 1 450, 1 270, 1 140, 1 095, and 1 035 cm^{-1}; $\lambda_{max.}$(EtOH) 254 nm (ε 2 013); δ_H(200 MHz) 1.65 (4 H, m, 15- and 16-H$_2$), 2.40 (4 H, m, 14- and 17-H$_2$), 2.47 (3 H, s, NMe), 3.17 (1 H, m, 5-H), 3.60 (1 H, m, 2-H), 3.83 (1 H, m, 5-H), 4.06 (1 H, dd, J_{gem} 12, J_{vic} 6 Hz, 6-H), 4.52 (1 H, dd, J_{gem} 12, J_{vic} 3.5 Hz, 6-H), 4.55 (1 H, d, J_{gem} 13 Hz, 7-H), 5.15 (1 H, d, J_{gem} 13 Hz, 7-H), and 5.94 (1 H, br s, 4-H); δ_C(25 MHz) 21.1 and 21.2 (C-15 and -16), 25.7 and 26.1 (C-14 and -17), 41.3 (NMe), 60.4 and 61.2 (C-5 and -6), 64.7 (C-7), 71.6 (C-2), 131.5 (C-4), 135.8 and 136.4 (C-9 and -10), 137.6 (C-3), and 168.3 and 169.7 (C-9 and -12); *m/z* 277 (M^+), 123, 110, 107, 94, 82, 53, and 42 (Found: M^+, 277.1315; C, 64.8; H, 7.0; N, 5.0%. $C_{15}H_{19}NO_4$ requires M, 277.1315; C, 64.96; H, 6.91; N, 5.05%).

(±)-6,7-O,O-(*Naphthalene*-1,8-*dicarbonyl*)*synthanecine A* (**15**) was obtained, m.p. 178—179 °C (ethanol); R_F 0.70; $\nu_{max.}$(KBr) 3 300, 2 950, 2 790, 1 715, 1 578, 1 505, 1 465, 1 390, 1 285, 1 200, 1 150, and 770 cm^{-1}; $\lambda_{max.}$(EtOH) 226 (ε 4 307) and 296 nm (875); δ_H(200 MHz) 2.50 (3 H, s, NMe), 3.22 (1 H, m, 5-H), 3.73 (1 H, m, 2-H), 3.81 (1 H, m, 5-H), 4.23 1 H, dd, J_{gem} 12, J_{vic} 6 Hz, 6-H), 4.79 (1 H, dd, J_{gem} 12, J_{vic} 3 Hz, 6-H), 4.85 (1 H, d, J_{gem} 13 Hz, 7-H), 5.19 (1 H, d, J_{gem} 13 Hz, 7-H), 5.92 (1 H, br s, 4-H), 7.52 (2 H, t, *J* 8 Hz, 15- and 21-H), and 7.89—8.01 (4 H, m, 16-, 17-, 19-, and 20-H); δ_C(50 MHz), 41.2 (NMe), 60.4 and 60.7 (C-5 and -6), 64.1 (C-7), 71.7 (C-2), 125.2, 125.3, 127.2, 129.4, 2 × 129.6, 2 × 129.9, 132.2, 132.3, 134.1, and 137.5 (C-3, -4, -10, -11, -12, -16, -17, -18, -19, -20, and -21), and 2 × 169.0 (C-9 and -13); *m/z* 323 (M^+) 220, 198, 154, 126, 107, 94, and 82 (Found: M^+, 323.1169; C, 70.5; H, 5.3; N, 4.3%. $C_{19}H_{17}NO_4$ requires *M*, 323.1157; C, 70.58; H, 5.26; N, 9.33%).

(±)-6,7,-O,O-(2,2,4,4-*Tetramethylglutaryl*)*synthanecine A* (**21**) was obtained as a colourless oil which crystallised when allowed to stand, m.p. 83—84 °C; R_F 0.68; $\nu_{max.}$(CCl$_4$) 2 975, 2 780, 1 740, 1 280, and 1 160 cm^{-1}; δ_H(200 MHz) 2 × 1.19, 1.20, and 1.21 (each 3 H, s, 15-, 16-, 17-, and 18-H$_3$), 1.73 (1 H, d, J_{gem} 14.5 Hz, 11-H), 2.05 (1 H, d, J_{gem} 14.5 Hz, 11-H), 2.48 (3 H, s, NMe), 3.23 (1 H, m, 5-H), 3.53 (1 H, m, 2-H), 3.76 (1 H, m, 5-H), 3.81 (1 H, dd, J_{gem} 12, J_{vic} 2.5 Hz, 6-H), 3.86 (1 H, dd, J_{gem} 12, J_{vic} 7.5 Hz, 6-H), 4.63 (2 H, br s, 7-H$_2$), and 5.77 (1 H, br s, 4-H); δ_C(25 MHz) 26.0, 27.4, 28.3, and 28.9 (C-15, -16, -17, and -18), 41.0 (NMe), 41.7 and 42.0 (C-10 and -12), 51.7 (C-11), 60.3 and 60.9 (C-5 and -6), 63.7 (C-7), 71.3 (C-2), 127.3 (C-4), 137.9 (C-3), and 176.2 and 176.4 (C-9 and -13); *m/z* 295 (M^+), 123, 108, 107, 94, 83, and 70 (Found: M^+, 295.1767. $C_{16}H_{25}NO_4$ requires *M*, 295.1783). The *picrolonate* had m.p. 191—192 °C (from ethanol). (Found: C, 55.8; H, 6.0; N, 12.5. $C_{26}H_{33}N_5O_9$ requires C, 55.80; H, 5.94; N, 12.52%).

Acknowledgements

We thank the S.E.R.C. and the M.R.C. for a CASE studentship (to R. H. B.), and we are grateful to Dr. A. R. Mattocks, M.R.C. Toxicology Unit, Carshalton, Surrey, for helpful discussions. We thank Dr. D. S. Rycroft for running the 200 MHz n.m.r. spectra.

References

1 D. J. Robins, *Fortschr. Chem. Org. Naturst.*, 1982, **41**, 115; *Nat. Prod. Rep.*, 1984, **1**, 235; 1985, **2**, 213; 1986, **3**, 297.
2 A. R. Mattocks, 'Chemistry and Toxicology of Pyrrolizidine Alkaloids,' Academic Press, London, 1986.
3 J. A. Devlin and D. J. Robins, *J. Chem. Soc., Chem. Commun.*, 1981, 1272; K. Brown, J. A. Devlin, and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1819.
4 D. J. Robins and S. Sakdarat, *J. Chem. Soc., Chem. Commun.*, 1980, 282; J. A. Devlin, D. J. Robins, and S. Sakdarat, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1117.
5 K. Brown, M. Burton, D. J. Robins, and G. A. Sim, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1261.
6 M. Burton and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1985, 611.
7 E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1974, **96**, 5614.
8 R. H. Barbour and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2475.
9 R. H. Barbour, A. A. Freer, and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2067.
10 A. R. Mattocks, H. E. Driver, R. H. Barbour, and D. J. Robins, *Chem. Biol. Interact.*, 1986, **58**, 95.
11 M. Burton and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 585.
12 A. R. Mattocks, *J. Chem. Soc., Perkin Trans. 1*, 1974, 707; 1978, 896.
13 H. Stoeckli-Evans and D. H. G. Crout, *Helv. Chim. Acta*, 1976, **59**, 2168.
14 D. J. Robins and G. A. Sim, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1379.
15 H. J. Huizing, F. DeBoer, and T. M. Malingré, *J. Chromatogr.*, 1980, **195**, 407; R. J. Molyneux and J. N. Roitman, *ibid.*, p. 412.
16 D. R. Burfield and R. H. Smithers, *J. Org. Chem.*, 1978, **43**, 3966.

Received 9th June 1987; *Paper* 7/1014