Pyrrolizidine Alkaloid Analogues. Synthesis of Macrocyclic Diesters of (−)-Platynecine

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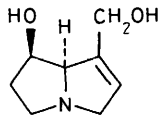
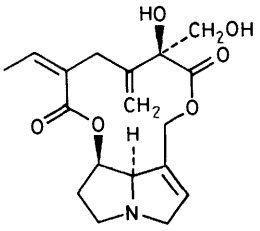
The first macrocyclic diesters of (−)-platynecine (**3**) containing 10- and 11-membered rings have been prepared. (−)-Platynecine was obtained by catalytic hydrogenation of readily available (+)-retronecine (**1**). Esterification of (+)-retronecine with different glutaric anhydride derivatives yielded mainly the 9-monoesters of (+)-retronecine. Lactonisation was carried out under high dilution conditions *via* the *S*-2-pyridyl thioesters to give the 11-membered macrocyclic diesters [(**4**)—(**7**)] of (−)-platynecine. Similar treatment of (−)-platynecine with succinic anhydride, and with *cis*- and *trans*-cyclohexane-1,2-dicarboxylic anhydride, produced the 10-membered pyrrolizidine alkaloid analogues (**8**), (**9**), and (**10**), respectively.

Pyrrolizidine alkaloids have a wide distribution in a number of unrelated plant families,[1,2] and they show a range of biological activities.[3] Many pyrrolizidine alkaloids which contain (+)-retronecine (**1**) are potent hepatotoxins. The key structural feature required for this hepatotoxic action is believed to be an allylic ester function occurring as part of a 2,5-dihydropyrrole system as in riddelliine (**2**). Dehydrogenation of the 1,2-unsaturated alkaloid (**2**) by hepatic microsomal oxidase enzymes yields the corresponding pyrrole derivative which can then act as a bifunctional alkylating agent.[3]



(**1**)

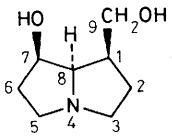


(**2**)

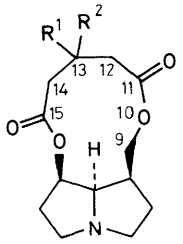
Good synthetic routes to macrocyclic pyrrolizidine alkaloids and selected analogues are clearly required for a detailed study of the structure–biological activity relationships in this area. Pyrrolizidine alkaloids have been isolated with ring sizes of 11—14 containing a range of different base portions (necines). However, synthesis of macrocyclic alkaloids has been restricted to a few 11-membered[4–8] and 12-membered examples containing (+)-retronecine (**1**).[9–11] In addition, some 11-membered[12] and 10-membered[13] analogues containing (+)-retronecine have also been prepared. Very few macrocyclic diesters of saturated necine diols occur naturally,[1,2] and none of them has yet been synthesized. In the case of (−)-platynecine (**3**), only seven examples of macrocyclic dilactones have been isolated; these contain either 12- or 13-membered rings.[1,2] In order to provide information about the effect of the absence of the double bond in the necine nucleus on the biological activity, and to find out if macrocyclic diesters of (−)-platynecine with 10- or 11-membered rings can exist, we decided to make some macrocyclic dilactones containing (−)-platynecine.

Results and Discussion

Because pyrrolizidine alkaloids which contain (−)-platynecine are comparatively rare, we looked for an alternative source of this necine as a starting material for the production of analogues. (−)-Platynecine (**3**) is available by catalytic hydrogenation of the most common necine, (+)-retronecine (**1**). The amounts of some pyrrolizidine alkaloids in plants can be extraordinarily high—at one collection site in the Western rangelands of the U.S.A., Molyneux and Johnson discovered levels of riddelliine (**2**) that were 10—18% of the dry weight of *Senecio riddellii* (family Compositae).[14] This obviously constitutes a severe hazard to grazing livestock. We are indebted to Dr Molyneux for supplying us with quantities of the mother liquors of riddelliine crystallisations. These mother liquors contained appreciable amounts of alkaloids which have (+)-retronecine as the base portion. Consequently, basic hydrolysis of these mother liquors produced (+)-retronecine, from which supplies of (−)-platynecine were obtained by catalytic hydrogenation.

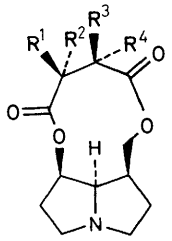


(**3**)



(**4**) $R^1 = R^2 = Me$
(**5**) $R^1 = R^2 = H$
(**6**) $R^1, R^2 = (CH_2)_4$
(**7**) $R^1, R^2 = (CH_2)_5$

Treatment of (−)-platynecine (**3**) with 3,3-dimethylglutaric anhydride in dry 1,2-dimethoxyethane (DME) gave a quantitative yield of an insoluble product. The ^1H n.m.r. spectrum of this precipitate in deuteriomethanol showed signals for the 9-monoester of (−)-platynecine at δ 4.2 (1 H, m, 7-H) and 4.65 and 4.80 (2 H, AB part of ABX system, 9-H_2), and for the 7-monoester at δ 3.8 and 3.9 (2H, AB part of ABX system, 9-H_2) and 5.41 (1 H, m, 7-H). From the integrations for these signals the ratio of 9- to 7-monoester is 6:1. Lactonisation of this mixture of monoesters was achieved *via* the *S*-2-pyridyl thioesters.[15] These were prepared by addition of di-2-pyridyl disulphide and triphenylphosphine to a suspension of the monoesters in DME. The mixture was stirred vigorously until a homogeneous solution was obtained and thioester formation was complete (t.l.c. data). Lactonisation was effected by heating



(**8**) $R^1 = R^2 = R^3 = R^4 = H$
(**9**) $R^1, R^3 = (CH_2)_4$, $R^2 = R^4 = H$
and $R^1 = R^3 = H$, $R^2, R^4 = (CH_2)_4$
(**10**) $R^1, R^4 = (CH_2)_4$, $R^2 = R^3 = H$
and $R^1 = R^4 = H$, $R^2, R^3 = (CH_2)_4$

the diluted mixture at reflux in DME for 5 days. The dilactone (**4**) was isolated and purified by column chromatography on alumina followed by preparative t.l.c. on silica gel in 11% yield. Accurate mass data gave the molecular formula as $C_{15}H_{23}NO_4$ with a fragment ion at *m/z* 122 ($C_8H_{12}N$), corresponding to loss of the diacyl portion. A base peak was observed at *m/z* 82 which is characteristic of platynecine esters.[16] An important feature in the ^1H n.m.r. spectrum of the analogue (**4**) in deuteriochloroform is an AB part of an ABX system for the diastereotopic protons at C-9 at δ 4.20 and 4.32. The chemical-shift difference between these protons is thus 0.12 p.p.m.

Separate treatment of (−)-platynecine (**3**) with glutaric anhydride, 3,3-tetramethyleneglutaric anhydride, and 3,3-pentamethyleneglutaric anhydride and lactonisation *via* the *S*-2-pyridyl thioesters produced three more 11-membered alkaloid analogues (**5**)—(**7**) in 13—16% yields. All three were obtained as oils, which gave correct accurate mass data and had major fragment peaks in their mass spectra at *m/z* 122 and 82. The chemical shift differences for the C-9 protons in dilactones (**5**)—(**7**) were 0.25, 0.08, and 0.25 p.p.m., respectively.

Attention was next directed towards formation of 10-membered macrocyclic diesters of (−)-platynecine (**3**). Treatment of (−)-platynecine with succinic anhydride and formation of the *S*-2-pyridyl thioesters proceeded normally. Lactonisation was carried out as before to afford succinylplatynecine (**8**) as an oil in 12% yield. Accurate mass data for the 10-membered analogue (**8**) established the molecular formula as $C_{12}H_{17}NO_4$, and the chemical-shift difference for the C-9 protons was 0.30 p.p.m.

Finally we prepared macrocyclic diesters of (−)-platynecine with substituents at the α-positions of the diacid portion. The additional steric hindrance around the ester groups is expected to increase the toxicity of these alkaloid analogues by reducing the extent by which they are detoxified by acidic or enzymic hydrolysis.[3] Separate treatment of (−)-platynecine (**3**) with *cis*- and *trans*-cyclohexane-1,2-dicarboxylic anhydride followed by lactonisation *via* the *S*-2-pyridyl thioesters gave the two mixtures (**9**) and (**10**) of diastereoisomeric products in 11 and 13% yields, respectively. These mixtures could not be separated by chromatography; characterisation data were therefore obtained for the two mixtures.

The chemical-shift differences for the C-9 protons in the ^1H n.m.r. spectra of the 11-membered analogues (**4**)—(**7**) containing (−)-platynecine are 0.08—0.25 p.p.m. These values are not markedly different from those for the 10-membered analogues (**8**)—(**10**) of 0.1—0.3 p.p.m. This situation is in direct contrast to that observed for retronecine dilactones. The range of chemical-shift differences for 11-membered diesters of (+)-retronecine (**1**) is 0—0.9 p.p.m., whereas for 10- and 12-membered dilactones it is 1.25—1.55 p.p.m. These values have been related to the conformations of the macrocyclic systems by *X*-ray crystal structure data. Most 11-membered macrocyclic diesters of (+)-retronecine that have been studied have ester carbonyl groups that are synperiplanar, whereas all 10- and 12-membered diesters of (+)-retronecine so far studied have ester carbonyl groups that are antiparallel. Attempts will be made to establish the conformations of some of these new 10- and 11-membered platynecine dilactones by *X*-ray crystallography. These conformations may be an important factor when considering the biological activity of these 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 for solutions in deuteriochloroform with tetramethylsilane as the internal standard on a Bruker WP-200SY spectrometer operating at 200 MHz for ^1H and 50 MHz for ^{13}C, unless otherwise stated. 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 thickness developed with chloroform–methanol–conc. ammonia (85:14:1). The location of the bases was determined by the modified Dragendorff reagent.[17] 1,2-Dimethoxyethane (DME) was dried by distillation from potassium hydroxide and then from sodium and benzophenone under argon immediately prior to use.

(−)-*Platynecine* (**3**).—(+)-Retronecine (500 mg, 3.2 mmol) was dissolved in absolute ethanol (25 ml) and hydrogenated at 1 atm for 18 h at room temperature over 10% Pd–charcoal (50 mg) as catalyst. The solution was filtered through Celite and the solvent was removed under reduced pressure to give (−)-platynecine (**3**) as a clear oil, which crystallised from acetone (383 mg, 75%), m.p. 149—151 °C (lit.,[18] 148—149 °C); $[\alpha]_D^{20}$ −58° (*c* 1, EtOH) (lit.,[18] −56.8°); $\nu_{max.}$(KBr disc) 3 350, 2 940, 2 880, and 1 480 cm^{-1}; δ_H 1.56—2.24 (4 H, complex, 2- and 6-H_2), 2.41 (1 H, m, 1-H), 2.69—3.00 (2 H, complex, 3- or 5-H_2), 3.04 (1 H, m, 8-H), 3.20 (2 H, complex, 3- or 5-H_2), 3.81 (1 H, dd, *J* 11.2 Hz and 4.2 Hz, 9-H), 3.91 (1 H, dd, *J* 11.2 Hz and 2.6 Hz, 9-H) and 4.21 (1 H, m, 7-H); δ_C(25 MHz) 28.6 (C-2), 36.5 (C-6), 43.9 (C-1), 53.7 and 55.3 (C-3 and C-5), 61.6 (C-9), 71.1 (C-8), and 73.1 (C-7); *m/z* 157 (M^+, 7%), 113, 83, 82, and 81 (Found: M^+, 157.1108; C, 61.21%; H, 9.71; N, 9.02. $C_8H_{15}NO_2$ requires *M*, 157.1103; C, 61.15; H, 9.55; N, 8.92%).

General Procedure for the Synthesis of the Dilactones (**4**)—(**10**).—The anhydride (0.76 mmol) was added to a solution of (−)-platynecine (**3**) (100 mg, 0.64 mmol) in dry DME (20 ml) at room temperature under dry N_2. The solution was stirred for 7 d to form the zwitterionic monoesters [t.l.c., MeOH–NH_3 (9:1), R_F 0.30]. Di-2-pyridyl disulphide (220 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol) were added and the mixture was stirred at room temperature under N_2 for 48 h until thioester formation was complete (R_F 0.13). The homogeneous yellow solution was added over 0.5 h by syringe to dry DME (100 ml) heated at reflux under dry N_2. The mixture was then heated for a further 5 d. The diester was partially purified by application to a basic alumina (activity 1) column and elution with $CHCl_3$. (This removed most of the pyridine-2-thione and triphenylphosphine oxide.) The fractions containing the more polar compounds (R_F *ca.* 0.0—0.4) were concentrated under reduced pressure to give crude dilactones as yellow oils. Final purification was achieved by preparative t.l.c.

(−)-7,9-O,O-(3,3-*Dimethylglutaryl*)*platynecine* (**4**) was obtained as a non-crystalline solid (11% yield), m.p. 92–94 °C (benzene–hexane); R_F 0.15; $[\alpha]_D^{24}$ −24.0° (*c* 2, $CHCl_3$); $\nu_{max.}$(CCl_4) 2 960, 1 740, 1 230, and 1 180 cm^{-1}; δ_H 1.11 (3 H, s, 17-H_3 or 18-H_3), 1.30 (3 H, s, 17-H_3 or 18-H_3), 1.94 (2

H, m, 2-H_2), 2.08 (2 H, m, 6-H_2), 2.17 and 2.30 (2 H, AB system, J 13.5 Hz, 12-H_2 or 14-H_2), 2.20 and 2.32 (2 H, AB system, J 13.0 Hz, 12-H_2 or 14-H_2), 2.50—2.70 (1 H, m, 1-H), 2.83 (2 H, m, 3-H_2 or 5-H_2), 3.15 and 3.35 (2 H, m, 3-H_2 or 5-H_2), 3.64 (1 H, m, 8-H), 4.20 (1 H, dd, J 12.4 Hz and 2.3 Hz, 9-H), 4.32 (1 H, dd, J 12.4 Hz and 6.1 Hz, 9-H), and 5.35 (1 H, t, J 4.0 Hz, 7-H); δ_C 27.6 (C-17 or C-18), 27.9 (C-2), 31.9 (C-17 or C-18), 33.7 (C-13), 34.6 (C-6), 39.3 (C-1), 45.3 and 45.7 (C-12 and C-14), 52.6 and 53.5 (C-3 and C-5), 60.6 (C-9), 70.8 (C-8), 73.4 (C-7), 170.5 and 171.1 (C-11 and C-15); m/z 281 (M^+, 12%), 277, 181, 154, 140, 138, 122, 121, 120, 82 (100%), 81, and 80 (Found: M^+, 281.1629; C, 63.81; H, 8.45; N, 4.91. $C_{15}H_{23}NO_4$ requires M, 281.1627; C, 64.06; H, 8.18; N, 4.98%).

(−)-7,9-O,O-(*Glutaryl*)*platynecine* (**5**) was obtained as an oil (16% yield); R_F 0.18; $[\alpha]_D^{20}$ −15.0° (c 1.4, $CHCl_3$); $\nu_{max.}$(CCl_4) 2 980, 2 930, 2 870, 1 735, and 1 285 cm^{-1}; δ_H 1.22 (2 H, m, 13-H_2), 1.90—2.1 (4 H, m, 2-H_2 and 6-H_2), 2.35 (4 H, m, 12-H_2 and 14-H_2), 2.58 (1 H, m, 1-H), 2.77—3.10 (2 H, m, 3-H_2 or 5-H_2), 3.39—3.51 (2 H, m, 3-H_2 or 5-H_2), 3.65 (1 H, m, 8-H), 4.15 (1 H, dd, J 12.2 Hz and 6.6 Hz, 9-H), 4.40 (1 H, br d, J 12.2 Hz, 9-H), and 5.37 (1 H, m, 7-H); δ_C 20.8 (C-13), 26.4 (C-2), 29.6 (C-6), 34.4 and 34.6 (C-12 and C-14), 39.6 (C-1), 53.6 and 54.4 (C-3 and C-5), 60.4 (C-9), 71.2 (C-8), 74.1 (C-7), and 172.0 and 173.4 (C-11 and C-15); m/z 253 (M^+, 10%) 140, 138, 122, 121, 96, 95, and 82 (100%) (Found: M^+, 253.1314. $C_{13}H_{19}NO_4$ requires M, 253.1314).

(−)-7,9-O,O-(3,3-*Tetramethyleneglutaryl*)*platynecine* (**6**) was obtained as an oil (13% yield); R_F 0.13; $[\alpha]_D^{20}$ −30.0° (c 1, $CHCl_3$); $\nu_{max.}$(CCl_4) 2 960, 2 930, 1 745, 1 100, and 1 030 cm^{-1}; δ_H 1.70 (8 H, m, 17-, 18-, 19-, and 20-H_2), 1.90—2.30 (4 H, complex, 2-H_2 and 6-H_2), 2.24 and 2.39 (2 H, AB system, J 12.9 Hz, 12-H_2 or 14-H_2), 2.28 and 2.40 (2 H, AB system, J 14.0 Hz, 12-H_2 or 14-H_2), 2.58 (1 H, m, 1-H), 2.85 (2 H, m, 3-H_2 or 5-H_2), 3.07 and 3.24 (2 H, m, 3-H_2 or 5-H_2), 3.56 (1 H, m, 8-H), 4.16 (1 H, br d, J 4.5 Hz, 9-H), 4.24 (1 H, br d, J 4.5 Hz, 9-H), and 5.49 (1 H, t, J 4.0 Hz, 7-H); δ_C 23.0 and 23.7 (C-18 and C-19), 28.1 (C-2), 29.8 (C-6), 34.9 and 36.8 (C-17 and C-20), 39.1 (C-1), 43.6 and 43.8 (C-12 and C-14), 44.5 (C-13), 52.6 and 53.5 (C-3 and C-5), 61.1 (C-9), 71.4 (C-8), 73.3 (C-7), and 171.1 and 171.6 (C-11 and C-15); m/z 307 (M^+, 32%), 148, 181, 140, 139, 138, 122 (100%), 121, 108, 96, 95, and 82; (Found: M^+, 307.1790. $C_{17}H_{25}NO_4$ requires M, 307.1783).

(−)-7,9-O,O-(3,3-*Pentamethyleneglutaryl*)*platynecine* (**7**) was obtained as an oil (14%); R_F 0.14; $[\alpha]_D^{20}$ −26.9° (c 1, $CHCl_3$); $\nu_{max.}$(CCl_4) 2 940, 2 860, 1 740, 1 440, 1 225, 1 160, and 1 120 cm^{-1}; δ_H 1.48 (10 H, br m, 17-, 18-, 19-, 20-, and 21-H_2), 1.90—2.09 (2 H, m, 2-H_2), 2.15—2.20 (2 H, m, 6-H_2), 2.10 and 2.57 (2 H, AB system, J 14.0 Hz, 12-H_2 or 14-H_2), 2.26 and 2.38 (2 H, AB system, J 13.4 Hz, 12-H_2 or 14-H_2), 2.62 (1 H, m, 1-H), 2.95 (2 H, m, 3-H_2 or 5-H_2), 3.36 and 3.57 (2 H, m, 3-H_2 or 5-H_2), 3.79 (1 H, m, 8-H), 4.18 (1 H, dd, J 6.2 Hz and 1.1 Hz, 9-H), 4.43 (1 H, dd, J 6.2 Hz and 2.8 Hz, 9-H), and 5.40 (1 H, t, J 3.8 Hz, 7-H); δ_C 21.5 and 21.6 (C-18 and C-20), 25.7 (C-19), 28.2 (C-2), 29.7 (C-6), 34.6 and 35.4 (C-17 and C-21), 36.5 (C-13), 39.1 and 39.6 (C-12 and C-14), 42.4 (C-1), 52.9 and 53.9 (C-3 and C-5), 60.1 (C-9), 71.2 (C-8), 73.3 (C-7), and 170.5 and 171.4 (C-11 and C-15); m/z 321 (M^+, 12%), 181, 122 (100%), 121, 120, 96, 95, and 82 (Found: M^+, 321.1923. $C_{18}H_{27}NO_4$ requires 321.1935).

(−)-7,9-O,O-(*Succinyl*)*platynecine* (**8**) was prepared as an oil (12% yield); R_F 0.37; $[\alpha]_D^{23}$ −16.0° (c 1.5, $CHCl_3$); $\nu_{max.}$ 2 960, 2 925, 1 760, 1 420, 1 220, and 1 140 cm^{-1}; δ_H 1.23 (5 H, complex, 1-H, 2-H_2 and 6-H_2), 2.00 (4 H, m, 12-H_2 and 13-H_2), 2.51 (1 H, m, 8-H), 2.62 (2 H, m, 3-H_2 or 5-H_2), 3.08 (2 H, br t, 3-H_2 or 5-H_2), 3.65 (1 H, d, J 7 Hz, 9-H), 3.95 (1 H, br s, 9-H), and 4.49 (1 H, br s, 7-H); δ_C 26.6 (C-2), 29.7 (C-12 and C-13), 35.4 (C-6), 41.6 (C-1), 53.8 and 54.6 (C-3 and C-5), 58.8 (C-9), 71.3 and 72.7 (C-7 and C-8), and 173.0 and 173.5 (C-11 and C-14); m/z 239 (M^+, 2%), 135, 83, 82 (100%), 81, 69, 67, and 55 (Found: M^+, 239.1163. $C_{12}H_{17}NO_4$ requires M, 239.1158).

(−)-7,9-O,O-(cis-*Cyclohexane*-1,2-*dicarbonyl*)*platynecine* (**9**) was obtained as an inseparable mixture of two diastereoisomers (11% yield) as an oil; R_F 0.43; $[\alpha]_D^{20}$ −33.5° (c 2, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 2 960, 2 930, 1 730, 1 420, 1 225 and 1 120 cm^{-1}; δ_H 1.18 (4 H, br m, 2- and 6-H_2), 1.5—2.1 (8 H, complex, 16-, 17-, 18-, and 19-H_2), 2.69 (3 H, m, 1-, 12-, and 13-H), 3.13 (1 H, m, 3- or 5-H), 3.37 (1 H, m, 3- or 5-H), 3.61 (1 H, m, 8-H), 3.88 (2 H, m, 3- or 5-H_2), 4.93 (1 H, dd, J 12.1 and 3.0 Hz, 9-H), 5.03 (1 H, d, J 12.4 Hz, 9-H), and 5.36 (1 H, br t, 7-H); m/z 293 (M^+, 31%), 156, 138, 123, 121, 96, 95, 82 (100%), 81, 80, and 55 (Found: M^+, 293.1632. $C_{16}H_{23}NO_4$ requires M, 293.1686).

(−)-7,9-O,O-(trans-*Cyclohexane*-1,2-*dicarbonyl*)*platynecine* (**10**) was obtained as a mixture of two diastereoisomers which could not be separated (13% yield); R_F 0.32; $[\alpha]_D^{20}$ −24.5° (c 1.1, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 2 960, 2 930, 2 855, 1 730, 1 450, 1 420, 1 225, and 1 120 cm^{-1}; δ_H 1.23 (4 H, br m, 2-H_2 and 6-H_2), 1.80—2.3 (8 H, complex, 16-, 17-, 18-, and 19-H_2), 2.40 (2 H, m, 12- and 13-H), 2.65 (1 H, m, 1-H), 2.78 (2 H, m, 3- or 5-H), 3.30 (1 H, m, 3- or 5-H), 3.51 (1 H, m, 3- or 5-H), 3.79 (1 H, m, 8-H), 4.17 (1 H, d, J 12.6 Hz, 9-H), 4.42 (1 H, br d, J 12.6 Hz, 9-H), and 5.50 (1 H, br s, 7-H); m/z 293 (M^+, 8%), 156, 155, 123, 122, 121, 111, 110, 108, 96, 95, 83, 82 (100%), and 55 (Found: M^+, 293.1620. $C_{16}H_{23}NO_4$ requires M, 293.1642).

Acknowledgements

We are very grateful to Dr. R. J. Molyneux, U.S.D.A. Agricultural Service, Western Regional Research Center, Berkeley, California, U.S.A., for supplying us with a generous quantity of mother liquors from crystallisations of riddelliine. We thank the S.E.R.C. for a studentship (to M. R.) and Dr. D. S. Rycroft for running the 200 MHz n.m.r. spectra.

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Received 25th *May* 1989; *Paper* 9/02212K