Synthetic Studies on the Heterocyclic Nucleus of the Cytochalasans

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A synthetic route is described to a tricyclic lactone-lactam (10), the gross structure of which represents a logical type of intermediate for a synthetic approach to the cytochalasans. The required stereochemistry was built into the starting material (5) by a Diels–Alder reaction involving interaction of maleic anhydride and (*E,E*)-4-methylhexa-2,4-dienol. However, an unexpected double epimerisation took place in the elaboration process leading from (5) to (10).

THE complex structures of the large family of mould metabolites known as the cytochalasans [1] may be exemplified by two of the members, cytochalasin A (1) and zygosporin G (2). The combination of unusual cytological properties and challenging structural complexity exhibited by the cytochalasans has prompted considerable interest in their synthesis.[2] An initial target is the stereoselective synthesis of a cytochalasan-like nucleus such as (3), where the double bond in the carbocycle is strategetically situated to provide the structural variations in a range of cytochalasans and X and Y are groupings suitable for elaboration to the required macrocyclic junctions of the carbocyclic or lactonic types.

To this end tiglaldehyde [3] was treated with zinc and ethyl bromoacetate and the resulting hydroxy-ester dehydrated with phosphorus pentaoxide. Hydrolysis gave the readily purified (*E,E*)-4-methylhexa-2,4-dienoic acid, which was esterified and reduced with lithium aluminium hydride to give the required (*E,E*)-4-methylhexa-2,4-dienol (4). Reaction of this diene with maleic anhydride gave a high yield of a homogeneous lactone acid [4] (5), the stereochemistry of which could be confidently assigned as the required all-*cis*-structure † (5) formed by the familiar *endo*-addition process. This ready formation of the lactone automatically generated a free carboxy group at the position required for further elaboration. The corresponding acid chloride was condensed with the lithio-derivative of t-butyl phenylacetate to give the β-oxo-ester (6), which was hydrolysed and decarboxylated with trifluoroacetic acid to give the crystalline homogeneous ketone (7). The n.m.r. spectrum of (7) suggested that the all-*cis*-stereochemistry had been preserved in the transformation of (6) into (7), and this was confirmed by an *X*-ray crystallographic examination [5] which unequivocally established the structure of the ketone as (7).

Reductive amination of (7) was then carried out by means of sodium cyanoborohydride in the presence of ammonium acetate.[6] This process probably generated initially the expected primary amine (8), but the product isolated was an inseparable mixture of isomeric hydroxylactams (9), presumably epimeric at C-7 and generated by intramolecular nucleophilic attack of the amino-group of (8) on the γ-lactone ring. Initial attempts to functionalise (9) at C-1 in order to yield a compound of type (3) were unpromising. Thus treatment of (9) with 3 equiv. of lithium di-isopropylamide followed by treat-

† Racemates are illustrated as one enantiomer.

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[2] J. Auerbach and S. M. Weinreb, *J. Org. Chem.*, 1975, **40**, 3311; S. Masamune, J. Hayase, W. Schilling, W. K. Chan, and G. S. Bates, *J. Amer. Chem. Soc.*, 1977, **99**, 6756; R. Brettle and D. P. Cummings, *J.C.S. Perkin I*, 1977, 2385; E. Vedejs and R. C. Gadwood, *J. Org. Chem.*, 1978, **43**, 376; S. J. Bailey, E. J. Thomas, W. B. Turner, and J. A. J. Jarvis, *J.C.S. Chem. Comm.*, 1978, 474.

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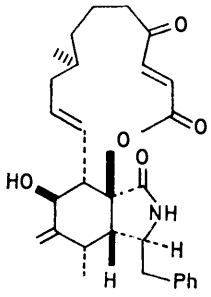
[4] *Cf.* I. M. Heilbron, E. R. Jones, J. T. McCombie, and B. C. L. Weedon, *J. Chem. Soc.*, 1945, 84.

[5] P. G. Jones and O. Kennard, *Acta Cryst.*, 1978, **B34**, 2022, 2025.

[6] R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, 1971, **93**, 2897.

ment with oxygen and sodium sulphite [7] (to generate the bridgehead alcohol) or carbon dioxide (to give the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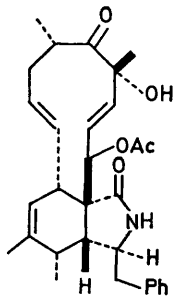
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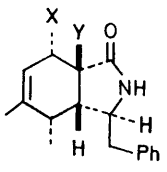
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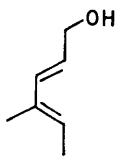
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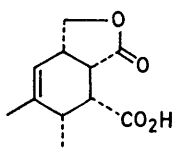
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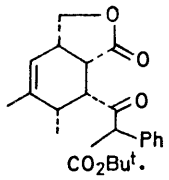
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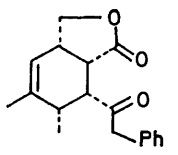
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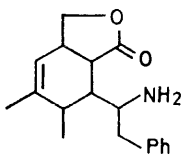
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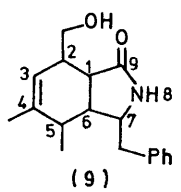
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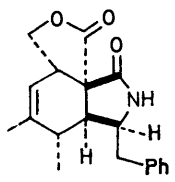
(10)

bridgehead acid) were unsuccessful. However, reaction of the tris-anion with excess of dimethyl carbonate produced two new compounds whose i.r. and mass spectra suggested that they were stereoisomers of the lactone-lactam structure (10). Presumably the formation of an initial mixed carbonate had been followed by an intramolecular attack of the C-1 carbanion to form the γ-lactone ring. As unequivocal stereochemical information could not be derived from the n.m.r. spectra, one of the products was subjected to *X*-ray crystallographic examination.[5] The result certainly confirmed the gross structure of the compound but the stereochemistry revealed was most unexpected [see (10)]. Both the lactone and lactam rings were revealed to be fused *cis* to the cyclohexene ring with the stereochemistry of the lactam ring *opposite* to that required for a cytochalasan intermediate of type (3). The close spectroscopic resemblance between the two products indicates that the isomer of (10) is probably epimeric at the C-7 benzyl attachment.

The most likely stage for the occurrence of this double epimerisation is the conversion of the ketone (7) into the lactam (9) by cyanoborohydride. A possible sequence of events involves initial epimerisation of (7) at the centre α to the ketone function, followed by reductive amination, intramolecular formation of the *trans*-lactam and finally a second epimerisation at C-1 to the *cis*-lactam. Further investigation is being undertaken to see whether rigorous pH control can obviate these unwanted epimerisations and thus yield a fruitful cytochalasan precursor.

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. T.l.c. and preparative thick-layer chromatography (p.l.c.) were carried out using Merck Kieselgel $60F_{254}$. Mass spectra were determined on A.E.I. MS 30 and MS 902 instruments. I.r. spectra were determined on a Perkin-Elmer 257 spectrometer. ^1H N.m.r. spectra were run on Perkin-Elmer R 12B and Varian HA-100D instruments with tetramethylsilane as internal standard. Extracts were dried over magnesium sulphate. Light petroleum refers to the fraction of boiling range 60—80 °C.

(E,E)-4-*Methylhexa*-2,4-*dienol* (4).—To a stirred suspension of activated zinc turnings (24 g) in dry tetrahydrofuran (200 ml), dry trimethyl borate (200 ml), and tiglaldehyde (31.9 g) under nitrogen at room temperature was added methyl bromoacetate (58 g), followed by a crystal of iodine. After 14 h stirring, glycerol (100 ml) and ammonia solution (*d* 0.880; 150 ml) were added and, after 15 min further stirring, the whole was thoroughly extracted with ether. Washing (water), drying, evaporation, and distillation gave the expected hydroxy-ester, b.p. 120—124° at 28 mmHg (39 g).

A solution of this product (16.1 g) in dry benzene (20 ml) was added dropwise over 30 min to a refluxing suspension of phosphorus pentaoxide (10 g) in benzene (200 ml). After 2 h further heating the benzene layer was decanted from the cooled mixture and the residue washed with ether. The combined extracts were evaporated and distilled to give the diene esters, b.p. 59—62° at 1 mmHg (15.3 g). Integration of the ester methyl signals in the n.m.r. spectrum showed the ratio of 2*E*,4*E*- to 2*Z*,4*E*- isomer to be 87 : 13. Hydrolysis of the ester mixture (37.5 g) with aqueous sodium hydroxide (20% w/v; 150 ml) in methanol (80 ml) for 3 h under reflux was followed by removal of methanol and acidification at 0 °C. Isolation with ether and crystallisation from cyclohexane gave pure *E*,*E*-diene acid (30 g), m.p. 93—94° (lit.,[8] 94—95°). Esterification [9] of this acid (12.6 g) gave

[7] H. H. Wasserman and B. H. Lipschutz, *Tetrahedron Letters*, 1975, 1731.
[8] K. von Auwers and J. Heyna, *Annalen*, 1923, **434**, 140.
[9] R. O. Clinton and S. G. Laskowski, *J. Amer. Chem. Soc.*, 1848, **70**, 3135.

the *methyl ester* (11.6 g), b.p. 102—103° at 25 mmHg (Found: C, 68.25; H, 8.6. $C_8H_{12}O_2$ requires C, 68.55; H, 8.65%), δ(CCl_4) 1.80 (6 H, s + d, 2 × CH_3), 3.65 (3 H, s, CO_2CH_3), 5.70 (1 H, d, *J* 16 Hz, 3-H), 5.93 (1 H, q, *J* 6 Hz, 5-H), and 7.22 (1 H, d, *J* 16 Hz, 2-H).

A solution of this ester (8.74 g) in dry ether (70 ml) was treated with lithium aluminium hydride (1.9 g) in portions with stirring and sufficient cooling to keep the temperature at 5—10 °C. After 30 min further stirring at 0 °C water (2 ml), aqueous sodium hydroxide (15%; 2 ml), and again water (6 ml) were added and the stirring was continued for 1 h at room temperature. The mixture was filtered and the filter cake well washed with ether containing 10% methanol. The combined filtrates were evaporated under reduced pressure and the residue distilled to give the *E,E*-dienol (5.8 g), b.p. 102—103° at 24 mmHg, giving a single peak on g.l.c., $\lambda_{max.}$(MeOH) 236 nm (log ε 4.34), $\nu_{max.}$(CCl_4) 3 610, 3 015, 2 920, 1 000, and 968 cm^{-1}, δ(CCl_4) 1.72 (6 H, s + d, 2 × CH_3), 2.30 (1 H, s, OH; lost on D_2O shake), 4.06 (2 H, d, *J* 8 Hz, CH_2O), 5.47—5.73 (2 H, m, 2-H and 5-H), and 6.15 (1 H, d, *J* 16 Hz, 3-H). No satisfactory analysis was obtained as the dienol was rapidly autoxidised, but the compound was characterised as its p-*nitrobenzoate*, m.p. 68—69° (from hexane) (Found: C, 64.3; H, 5.85; N, 5.3. $C_{14}H_{15}NO_4$ requires C, 64.35; H, 5.8; N, 5.35%).

3,4-*Dimethyl*-7-*oxo*-8-*oxabicyclo*[4.3.0]*non*-2-*ene*-5-*carboxylic Acid* (5).—Maleic anhydride (5.8 g) was dissolved in warm benzene containing a few crystals of hydroquinone. The 2*E*,4*E*-dienol (4) (6.03 g) was then added and the solution set aside under nitrogen for 7 days. Some of the product crystallised from solution, the remainder being obtained by evaporation. Crystallisation from toluene–light petroleum gave the *lactone-acid* (5) (7.8 g, 69%) as plates, m.p. 168—170° (Found: C, 62.7; H, 6.65. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7%). Spectra were determined on the more soluble methyl ester; $\nu_{max.}$(CCl_4) 2 950, 1 779, 1 740, and 1 210 cm^{-1}, δ($CDCl_3$) 1.13 (3 H, d, *J* 7 Hz, CH–C*H*$_3$), 1.77 (3 H, s, =C–CH_3), 2.68 (1 H, m, –C*H*Me), 2.96 (1 H, 't', *J* 6 Hz, –CH–CO_2Me), 3.20 (1 H, m, –C*H*–CH_2O–), 3.48 (dd, *J* 4 and 8 Hz, 6-H), 3.79 (3 H, s, CO_2CH_3), 4.30 (2 H, m, –CH_2–O), and 5.32 (1 H, br,s, =CH–).

In later preparations the mixture of geometrically isomeric dienols derived from the direct hydride reduction of the corresponding mixture of diene esters was used. As expected only the 2*E*,4*E*-dienol component reacted with maleic anhydride under the conditions described.

3,4-*Dimethyl*-5-*phenylacetyl*-7-*oxo*-8-*oxabicyclo*[4.3.0]*non*-2-*ene* (7).—The lactone-acid (5) (1 g) was stirred in benzene under nitrogen and oxalyl chloride (0.9 ml) was added at 0 °C. The mixture was warmed at 30 °C for 2 h and then evaporated under reduced pressure to give the acid chloride.

To a stirred solution of di-isopropylamine (1.25 ml) in dry tetrahydrofuran (20 ml) at 0 °C under nitrogen, n-butyl-lithium (2.4M in hexane; 3.5 ml) was added dropwise. After 10 min the solution was cooled to −78 °C and a solution of t-butyl phenylacetate (1 g) in tetrahydrofuran (20 ml) was added dropwise over 10 min; stirring was continued for 1.5 h. A solution of the above acid chloride in tetrahydrofuran (20 ml) was added over 10 min and the mixture was allowed to warm to room temperature, then poured into aqueous phosphoric acid (10%; 100 ml) and extracted with ether. Washing (water), drying, evaporation, and crystallisation from ether–light petroleum gave the β-*oxo-ester* (6) (1.5 g, 82%) as needles, m.p. 139—141°, $\nu_{max.}$($CHCl_3$) 2 980, 1 780, 1 738, 1 370, and 1 150 cm^{-1}, δ($CDCl_3$) 1.12 (3 H, d, *J* 7 Hz, –CH–C*H*$_3$), 1.46 (9 H, s, CMe_3), 1.76 (3 H, s, =C–CH_3), 2.66 (1 H, m, 4-H), 3.00 (1 H, 't', *J* 4 Hz, 5-H), 3.10 (1 H, m, 1-H), 3.50 (1 H, dd, *J* 4 and 8 Hz, 6-H), 4.20 (2 H, m, –CH_2–O–), 5.19 (1 H, s, enol H), 5.24 (1 H, s, =CH–), and 7.34 (5 H, s, Ph), *m/e* 384 (7%, M^+), 328 (34), 316 (17), 213 (24), 195 (14), and 95 (100).

This oxo-ester (6) (1 g) was added in one portion to trifluoroacetic acid (100 ml) at −15 °C and the solution set aside at −15 °C for 2 h. The solvent was removed under reduced pressure and replaced with benzene (160 ml), and the resulting solution was heated under reflux for 1 h. Removal of solvent and purification by p.l.c. (dichloromethane–methanol, 95 : 5) gave the *oxo-acetone* (7) (695 mg, 94%), crystallising from ether in prisms, m.p. 119—121° (Found: C, 76.1; H, 6.95. $C_{18}H_{20}O_3$ requires C, 76.05; H, 7.1%), $\nu_{max.}$(CCl_4) 2 910, 1 780, 1 705, and 1 180 cm^{-1}, δ($CDCl_3$) 1.10 (3 H, d, *J* 8 Hz, –CH–C*H*$_3$), 1.74 (3 H, s, =C–CH_3), 2.63 (1 H, m, 4-H), 2.84 (1 H, 't', *J* 5 Hz, 5-H), 3.18 (1 H, m, 1-H), 3.50 (1 H, dd, *J* 4 and 9 Hz, 6-H), 3.99 (2 H, d, *J* 2 Hz, PhC*H*$_2$), 4.20 (2 H, m, –CH_2–O–), 5.25 (1 H, s, =CH–), and 7.26 (5 H, s, Ph), *m/e* 284 (40%, M^+), 193 (75), 165 (28), 121 (57), 118 (84), and 91 (100).

7-*Benzyl*-2-*hydroxymethyl*-4,5-*dimethyl*-8-*azabicyclo*[4.3.0]-*non*-3-*en*-9-*one* (9).—To a solution of the oxo-lactone (7) (584 mg) in dry methanol (40 ml), molecular sieve (3 Å; 5 g predried at 150° and 0.1 mmHg) and ammonium acetate (7.7 g) were added, and the stirred suspension was cooled to 0 °C. Sodium cyanoborohydride (910 mg) was added in portions over 30 min. After 40 h the mixture was acidified to pH 1 with conc. hydrochloric acid and water (10 ml) was added. The methanol was removed under reduced pressure and the residue extracted with ether. P.l.c. (dichloromethane–methanol, 95 : 5) gave unchanged oxo-lactone (75 mg) and the *lactam* (9) (366 mg, 63%), crystallising in needles, m.p. 151—153° (from ether–dichloromethane). The n.m.r. spectrum showed the product to be a mixture of two diastereoisomers (Found: C, 75.5; H, 8.1; N, 5.25. $C_{18}H_{23}NO_2$ requires C, 75.75; H, 8.1; N, 4.9%), $\nu_{max.}$($CHCl_3$) 3 420, 3 000, 1 690, and 1 030 cm^{-1}, δ($CDCl_3$) 1.12 and 1.24 (3 H, 2 × d, *J* 7 Hz, –CH–C*H*$_3$), 1.75 (3 H, s, =C–CH_3), 2.10—3.00 (5 H, m), 3.52 (4 H, m), 3.98 (1 H, br,s, –OH; lost on D_2O shake), 5.30 (1 H, s, =CH–), and 5.86 and 6.12 (1 H, 2 × s, NH; not lost on D_2O shake but lost on CF_3CO_2H–H_2O shake), *m/e* 285 (4%, M^+), 284, (14), 268 (6), 195 (50), 121 (28), and 91 (100).

Lactones of 7-*Benzyl*-2-*hydroxymethyl*-4,5-*dimethyl*-9-*oxo*-8-*azabicyclo*[4.3.0]*non*-3-*ene*-1-*carboxylic Acid* (10).—A solution of lithium di-isopropylamide [5 ml of a solution made from di-isopropylamine (0.875 ml), n-butyl-lithium (3.0 ml of a 2.1M-solution in hexane), and dry tetrahydrofuran (21.2 ml)] was cooled to −70 °C under nitrogen and a solution of the lactam (9) (100 mg) in tetrahydrofuran (4 ml) was added. Stirring was continued at −70 °C for 30 min, then at room temperature for 10 min, and the solution was then re-cooled to −70 °C. Dimethyl carbonate (2 ml) was then added and the solution allowed to attain room temperature overnight. It was then poured into hydrochloric acid (10%; 20 ml); extraction with ether, drying, and evaporation gave a brown oil (123 mg) which was subjected to p.l.c. (ether–light petroleum, 95 : 5) to yield two isomeric products. The first, *lactam-lactone A* (10) (19 mg) (R_F 0.55) crystallised from ether–dichloromethane; m.p. 175—177° (Found: M^+, 311.150. $C_{19}H_{21}NO_3$ requires *M*, 311.152), $\nu_{max.}$($CHCl_3$) 3 425, 1 769, and 1 702 cm^{-1}, δ($CHCl_3$) 1.16

(3 H, d, J 8 Hz, $-CH-CH_3$), 1.84 (3 H, s, $=C-CH_3$), 2.10—2.96 (m), 3.28 (1 H, d, J 7 Hz), 4.16 (1 H, dd, J 3 and 8 Hz, 7-H), 4.75 (1 H, ' t ', J 8 Hz), 5.44 (1 H, br,s, =CH–), 5.72 (1 H, br,s, NH; lost on $CF_3CO_2H-D_2O$ shake) and 7.20 (5 H, m, Ph), *m/e* 311 (9%, M^+), 252 (25), 220 (100), 176 (96), 161 (24), and 133 (89). The second product, *lactam-lactone B* (56 mg) (R_F 0.38), crystallised from ether–light petroleum; m.p. 151—153° (Found: M^+, 311.153), $\nu_{max.}(CHCl_3)$ 3 425, 1 775, and 1 703 cm^{-1}, $\delta(CDCl_3)$ 0.98 (3 H, d, J 7 Hz, $-CH-CH_3$), 1.71 (3 H, s, $=C-CH_3$), 2.58 (2 H, dd, J 2 and 8 Hz), 2.80—3.44 (m), 3.99 (1 H, dd, J 2 and 7 Hz, H-7), 4.64 (1 H, ' t ', J 8 Hz), 5.38 (1 H, br,s, =CH–), 6.52 (1 H, br,s, NH, lost on $CF_3CO_2H-D_2O$ shake), and 7.21 (5 H, m, Ph), *m/e* 311 (7%, M^+), 252 (28), 220 (100), 176 (90), 161 (30), and 133 (81).

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