Synthesis of β-Lactams by Photolytic Wolff Rearrangement

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3-Diazo-5-methylpyrrolidine-2,4-dione (5) undergoes a Wolff rearrangement when irradiated in the presence of t-butyl carbazate to give *cis*- and *trans*-β-lactam derivatives [(6) and (7)]. The (*Z*)-adduct (8) derived from the dione (5) by the addition of acetylenedicarboxylic esters gives both the (*E*)- and the (*Z*)-*trans*-β-lactams [(10) and (11)] when irradiated for a short time in the presence of t-butyl carbazate, but on prolonged irradiation the (*E*)-*trans*-β-lactam (10) is generated exclusively. Benzyl 6-diazo-5,7-dioxohexahydropyrrolizine-3-carboxylate (16; R = CH_2Ph), when irradiated at low temperature in the presence of β-methylphenethyl carbazate gives the 7-oxo-1-azabicyclo[3.2.0]heptane derivative (17; R = CH_2Ph), which, as expected, is a highly reactive system.

ALTHOUGH many methods are now available for the synthesis of β-lactams, the search for new methods continues, mainly with a view to their use in the synthesis of penicillins and cephalosporins or their nuclear analogues. Most of the methods currently available are not very satisfactory for this purpose, however, because of the high degree of functionality the ring must bear and because of the need to generate the thermodynamically less stable *cis*-stereoisomer.

Several methods are known for ring contraction of alicyclic systems, but to our knowledge they have not been used for the synthesis of β-lactams. The most suitable method for this purpose appeared to be the photolytic Wolff rearrangement, since with diazocyclopentanones good yields of cyclobutanecarboxylic acids or their derivatives are obtained and the reaction proceeds stereoselectively with kinetic control.[1] The expectation that the photolysis of 3-diazopyrrolidine-2,4-diones would afford β-lactams has now been realised.[2]

3-Diazo-5-methylpyrrolidine-2,4-dione (5) is the simplest derivative suitable for studying the stereoselectivity of the photolytic reaction. Accordingly L-alanine ethyl ester and t-butyl hydrogen malonate were condensed using dicyclohexylcarbodi-imide, and the alanine derivative (1) was cyclised with sodium hydride in benzene solution. The product was a mixture of the keto-ester (2), the enol ester (3), and the tetramic acid (4). The presence of the tetramic acid suggested that removal of the t-butoxycarbonyl group could readily be achieved. By refluxing the product in xylene for 1·5 h, conversion into the tetramic acid (4) was completed. This method of synthesising tetramic acids is a considerable improvement over a related procedure.[3]

The tetramic acid (4) was rapidly converted into (5*R*)-3-diazo-5-methylpyrrolidine-2,4-dione (5) by methanesulphonyl azide in acetonitrile at −10° in the presence of triethylamine (*cf.* ref. 4). The diazo-ketone (5) was optically active; indeed attempts to obtain the racemic mixture by treatment with triethylamine in refluxing dioxan or sodium hydride in benzene failed, the optically active diazo-ketone being unchanged. When the reaction sequence was repeated with DL-alanine ethyl ester, potassium t-butoxide in benzene solution was found to be a better base for cyclisation and an overall yield of 52% of the racemic diazo-ketone (5) was obtained.

Irradiation of the 3-diazo-5-methylpyrrolidine-2,4-dione (5) in aqueous solution with a medium-pressure mercury lamp in a water-cooled Pyrex vessel gave intractable products which did not contain a β-lactam. When ether or benzene was used as the solvent and t-butyl carbazate was added to the reaction solution, only two products were obtained, which were both β-lactams ($\nu_{max.}$ 1760 cm^{-1}); there was no evidence of azetidin-3-one formation. The two products were readily separated by trituration with chloroform. The product which was soluble in chloroform was shown to be the *trans*-β-lactam (6) from the coupling constant of the ring protons (J 2·5 Hz).[5] The β-lactam which was insoluble in chloroform was assigned the *cis*-configuration (7) although the coupling constant of the ring protons could not be determined because of the similarity of their chemical shifts in all suitable solvents. The *cis–trans* ratio was 5 : 8 and the combined yield was 90%. Attempts to change the ratio of stereoisomers by variation of solvent and temperature did not lead to any significant improvement in the *cis–trans* ratio. The presence of pivalic acid, a relatively hindered proton source, led to a lowering of this ratio.

[1] L. Horner and E. Spietschka, *Chem. Ber.*, 1955, **88**, 934; M. P. Cava, R. L. Little, and D. R. Napier, *J. Amer. Chem. Soc.*, 1958, **80**, 2257; J. Meinwald, G. G. Curtius, and P. G. Gassman, *ibid.*, 1962, **84**, 116; P. R. Brook and B. V. Brophy, *Tetrahedron Letters*, 1969, 4187.

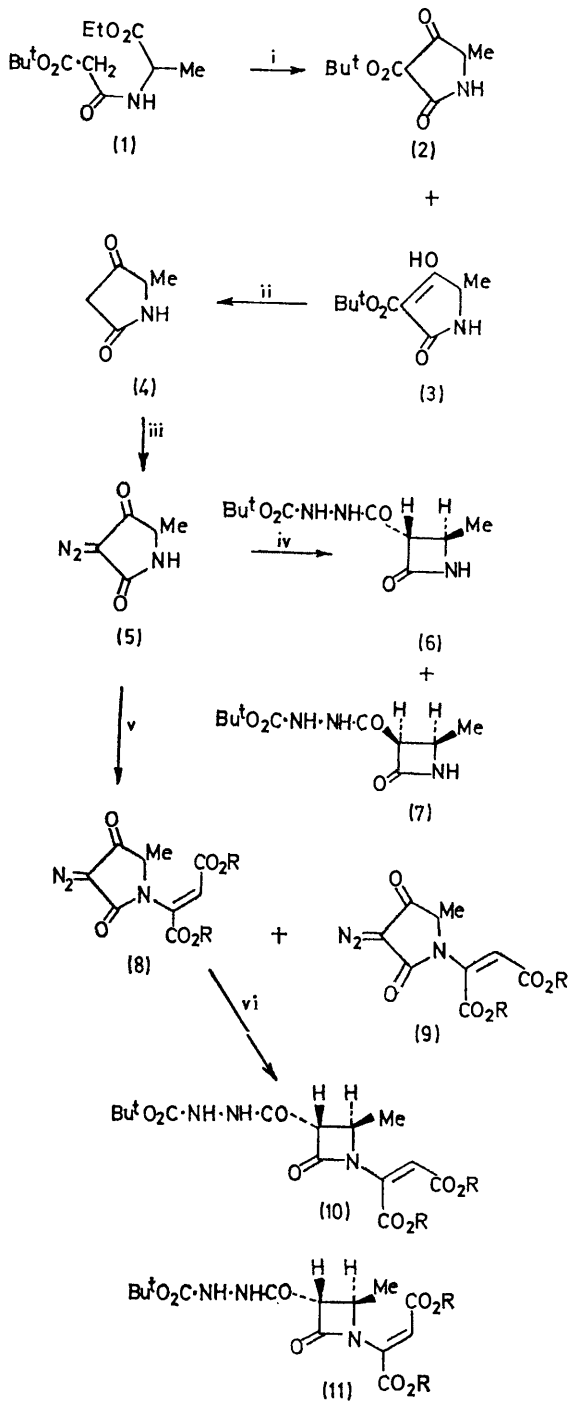
[2] Preliminary communication, G. Lowe and D. D. Ridley, *J.C.S. Chem. Comm.*, 1973, 328.

[3] Y. Isowa and M. Ohta, *Bull. Chem. Soc. Japan*, 1962, **35**, 1941.

[4] M. Regitz, *Angew. Chem. Internat. Edn.*, 1967, **6**, 733.

[5] H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Letters*, 1964, 941; K. D. Barrow and T. M. Spotswood, *ibid.*, 1965, 3325.

Protected hydrazides have been successfully exploited previously in the synthesis of nuclear analogues of the penicillins and cephalosporins,[6] but preliminary



Reagents; i, NaH or KOBu^t; ii, Heat; iii, $MeSO_2N_3$ + NEt_3; iv, $h\nu$ + $Bu^tO_2C{\cdot}NH{\cdot}NH_2$; v, NaH + $RO_2C{\cdot}C{\equiv}C{\cdot}CO_2R$; vi, $h\nu$ + $Bu^tO_2C{\cdot}NH{\cdot}NH_2$.

studies indicated that deprotection of the β-lactam (6) followed by treatment with nitrous acid led to destruction of the β-lactam ring, presumably owing to the availability of the β-lactam NH group in these molecules. Several methods for the protection of this function are available, but with a view to simultaneously activating the β-lactam ring, protection was effected in the following way.

The diazo-compound (5) in benzene solution at room temperature was treated with one equivalent of sodium hydride and dimethyl acetylenedicarboxylate. The major adduct (32%) was identified on the basis of the u.v. spectrum [$\lambda_{max.}$ 297 nm (log ε 3·7)] as the (*Z*)-isomer (8; R = Me), and the minor adduct (6%) [$\lambda_{max.}$ 282 nm (log ε 4·2)] as the (*E*)-isomer (9; R = Me).[7] These assignments were confirmed by the chemical shifts of the olefinic protons. The major adduct (8; R = Me) had τ 3·16, 1·37 p.p.m. to lower field than the chemical shift of the olefinic proton of the minor adduct (9; R = Me). The resonance of the olefinic proton in substituted or unsubstituted maleate esters appears always to be at higher field than in the corresponding fumarate ester.[8] When the diazo-compound (5) in benzene solution at room temperature was treated with sodium hydride and dibenzyl acetylenedicarboxylate again two isomeric adducts were obtained, in 50 and 7% yield, which were similarly assigned structures (8; R = CH_2Ph) and (9; R = CH_2Ph) respectively, from their u.v. and n.m.r. spectra.

When the (*Z*)-adduct (8; R = Me) was irradiated in benzene solution in the presence of t-butyl carbazate for 1·5 h essentially only one product (t.l.c.) was obtained. This was a β-lactam ($\nu_{max.}$ 1770 cm^{-1}), and from its spectroscopic properties was assigned the structure (10; R = Me), the coupling constant of the ring protons (*J* 2·0 Hz) clearly indicating the *trans*-stereochemistry.[5] Thus photoisomerisation about the double bond had occurred and only the *trans*-β-lactam was obtained. If, however, the reaction mixture was irradiated for only 0·5 h, some starting diazo-compound (8; R = Me) was recovered together with a small amount of the isomeric diazo-compound (9; R = Me). Two *trans*-β-lactams were also obtained which were assigned the structures (10; R = Me) and (11; R = Me) on the basis of spectroscopic evidence. Thus the rate of isomerisation about the double bond is comparable with that of the photolytic Wolff rearrangement and longer reaction times were required to obtain exclusively the (*E*)-stereoisomer. When the dibenzyl ester (8; R = CH_2Ph) was photolysed in ether at −5° for 3 h in the presence of t-butyl carbazate only the *trans*-β-lactam (10; R = CH_2Ph) was obtained.

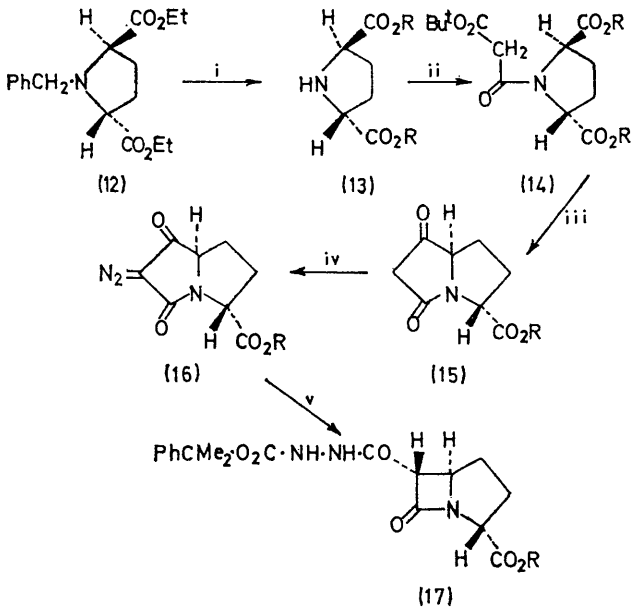
Attention was now turned to the synthesis of fused β-lactam-heterocyclic systems. To provide a critical test of this new method, the synthesis of the highly

[6] D. M. Brunwin, G. Lowe, and J. Parker, *J. Chem. Soc.* (*C*), 1971, 3756; G. Lowe and M. V. J. Ramsay, *J.C.S. Perkin I*, 1973, 479; G. Lowe and D. M. Brunwin, *ibid.*, 1973, 1321.

[7] N. A. Sorensen, *Annalen*, 1941, **546**, 57; M. W. Lockhart, Part II Thesis, University of Oxford, 1971.

[8] L. M. Jackman, ' Applications of Nuclear Magnetic Resonance in Organic Chemistry,' Pergamon, Oxford, 1959, p. 121; N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, ' NMR Spectra Catalog,' Varian Associates, 1962, nos. 212 and 213; J. E. Dolfini, *J. Org. Chem.*, 1965, **30**, 1298.

strained 7-oxo-1-azabicyclo[3.2.0]heptane system was undertaken. *cis*-*N*-Benzyl-2,5-bisethoxycarbonylpyrrolidine [9] was isomerised to the *trans*-stereoisomer (12) by treatment with sodium ethoxide in ethanol, and (12)



Reagents; i, Pd–C + H_2; ii, $Bu^tO_2C{\cdot}CH_2{\cdot}CO_2H$ + $C_6H_{11}{\cdot}N{:}C{:}N{\cdot}C_6H_{11}$; iii, (*a*) NaH, (*b*) heat; iv, $MeSO_2N_3$ + NEt_3; v, *hν* + $PhCMe_2{\cdot}O_2C{\cdot}NH{\cdot}NH_2$.

on hydrogenolysis gave the *trans*-ester (13; R = Et). Conversion of this ester into the *trans*-dibenzyl ester (13; R = CH_2Ph) was achieved through the *trans*-acid (13; R = H). The *trans*-benzyl ester (13; R = CH_2Ph) was then coupled to t-butyl hydrogen malonate with the aid of dicyclohexylcarbodi-imide to afford the pyrrolidine derivative (14; R = CH_2Ph). Cyclisation was achieved with sodium hydride in refluxing benzene and the t-butoxycarbonyl group was removed from the product by refluxing in toluene solution. The pyrrolizidinedione (15; R = CH_2Ph) underwent rapid diazo-exchange when treated with methanesulphonyl azide in the presence of triethylamine, to give benzyl 6-diazo-5,7-dioxohexahydropyrrolizine-3-carboxylate (16; R = CH_2-Ph), which could be conveniently purified chromatographically.

Irradiation of the ester (16; R = CH_2Ph) at room temperature in the presence of one equivalent of β-methylphenethyl carbazate gave no detectable β-lactam, but when the photoreaction was performed at −70° in ether solution it was clear from the i.r. and n.m.r. spectra of the mixture that the product was mainly the *trans*-β-lactam (17; R = CH_2Ph). Attempts to purify this product by t.l.c. on silica gel however led to rapid decomposition, and attempts to induce crystallisation were abortive. The photolytic Wolff rearrangement is thus capable of generating the highly strained 7-oxo-1-azabicyclo[3.2.0]heptane system. However, in view of the instability of the product, it seems unlikely that the subsequent synthetic manipulation required to convert it into a nuclear analogue of the penicillins could be accomplished.

EXPERIMENTAL

M.p.s were determined using a Kofler hot-stage apparatus. Refractive indices were measured using an Abbé refractometer. Optical rotations were measured using a Perkin-Elmer 141 photoelectric polarimeter at 20° in a 1 dm cell. I.r. spectra were obtained from a Perkin-Elmer 257 grating spectrometer. N.m.r. spectra were recorded on Perkin-Elmer R10 and R14 instruments (60 and 100 MHz, respectively). Tetramethylsilane (TMS) and sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) were used as internal standards for solutions in organic solvents and deuterium oxide, respectively. Mass spectra were determined using A.E.I. MS9 and Varian M.A.T. CH7 instruments. Microanalyses were carried out by Dr. Strauss in the Dyson Perrins Laboratory, Oxford.

Harrington's M60 silica gel was used for column chromatography. Adsorbents used in t.l.c. and preparative layer chromatography (p.l.c.) were $HF_{254+366}$ and $PF_{254+366}$ silica gel (Merck) respectively. Organic extracts were dried with anhydrous magnesium sulphate.

N-(*t-Butoxycarbonylacetyl*)-L-*alanine Ethyl Ester* (1).—To a rapidly stirred solution of t-butyl hydrogen malonate (2·94 g) in dichloromethane (10 ml) at −15° were added L-alanine ethyl ester (2·15 g) in dichloromethane (10 ml) and dicyclohexylcarbodi-imide (3·80 g) in dichloromethane (10 ml). The mixture was stirred at −15° for 0·5 h and then for 1 h at room temperature. The suspension was filtered and the precipitate was washed with ether. The combined filtrates were washed successively with sodium hydrogen carbonate solution, 5% citric acid, and brine. The dried extract was evaporated and the residue extracted three times with light petroleum (b.p. 40—60°). The extract was evaporated and yielded diester (1) as a yellow oil (4·11 g, 86%). This material was pure enough for use in the next step, but for analytical purposes the ester was further purified by p.l.c.; $\nu_{max.}$ ($CHCl_3$) 3400, 1725, and 1670 cm^{-1}; $[\alpha]_D^{20}$ (EtOH) −25·4°; τ (CCl_4) 2·40 (1H, d, $J_{NH,CH}$ 7 Hz. NH), 5·60 (1H, m, CH), 5·80 (2H, q, *J* 8 Hz, $CH_2{\cdot}CH_3$), 6·85 (2H, s, $CO{\cdot}CH_2{\cdot}CO$), 8·53 (9H, s, Bu^t), 8·60 (3H, d, *J* 7·5 Hz, $CH_3{\cdot}CH$), and 8·70 (3H, t, *J* 6·8 Hz, $CH_2{\cdot}CH_3$) (Found: C, 55·6; H, 8·0; N, 5·6. $C_{12}H_{21}NO_5$ requires C, 55·6; H, 8·2; N, 5·4%).

Cyclisation of N-(*t-Butoxycarbonylacetyl*)-L-*alanine Ethyl Ester* (1).—Sodium hydride (0·48 g, 1 mol. equiv.; 50% oil suspension) was added to the ester (2·59 g) in dry benzene (50 ml) under nitrogen and the mixture was refluxed overnight. The solution was cooled and diluted with iced water, and the aqueous layer was washed with ether. The aqueous layer was acidified with 5% citric acid solution and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried, and evaporated. The crude product (0·92 g, 43%) was a viscous oil, $\nu_{max.}$ 3500—3200 and 1750—1650 cm^{-1}. The n.m.r. spectrum of this material showed the presence of the keto-ester (2), the enol ester (3), and the ketone (4), τ ($CDCl_3$) 8·5 and 8·6 [both s, Bu^t in (2) and (3)], 8·6—8·7 [3 × d, CH_3 in (2), (3), and (4)], 6·95 [s, $CO{\cdot}CH_2{\cdot}CO$ in (4)], 5·4—6·0 [m, −CH− in (2) and (3)], 2·4, 2·2, and 1·7 [each br,s, NH in (2), (3), and (4)], and −0·9br [s, OH in (3)]. The enol ester (3) was the predominant product as judged from

[9] G. Cignarella and G. Nathansohn, *J. Org. Chem.*, 1961, **26**, 1500.

the n.m.r. spectrum; the ketone was present only in small amounts. On account of the complexity of the product, no attempt was made to obtain pure components, and the mixture was used directly in the next step.

(5R)-3-*Diazo*-5-*methylpyrrolidine*-2,4-*dione* (5).—The crude cyclisation product (4 g) [from the ester (1) (10·36 g)] was refluxed in xylene (100 ml) for 1 h. The solvent was removed under reduced pressure and the residual yellow oil (3·3 g) slowly crystallised. To this product in acetonitrile (200 ml) at 0° were added methanesulphonyl azide [10] (14 g, 5 mol. equiv.) and triethylamine (3 g, 1 mol. equiv.). (The initial suspension became homogeneous shortly after the addition of the base.) The mixture was stirred at 0° under nitrogen for 1 h. The acetonitrile was removed at room temperature under vacuum and the oily residue was subjected to p.l.c., with ethyl acetate as eluant. The dark purple band visible under light of wavelength 254 nm was collected. The total extract (1·6 g) was a pale yellow powder which on recrystallisation from acetone–ether (1 : 2) afforded pale yellow cubes of the *diazo-ketone* (5) (1·2 g), m.p. 115—116°, $\nu_{max.}$ ($CHCl_3$) 3440, 3210, 2135, and 1695 cm^{-1}; $[\alpha]_D^{20}$ (EtOH) −9·6°; τ ($CDCl_3$) 2·92br (1H, s, NH), 5·92 (1H, 8 lines, J_{H,CH_3} 7·2, $J_{H.NH}$ 1·1 Hz, CH), 8·55 (3H, d, J 7·2 Hz, CH_3) (Found: C, 42·9; H, 3·8; N, 30·2. $C_5H_5N_3O_2$ requires C, 43·1; H, 3·6; N, 30·2%).

Attempted Racemisation of (5R)-3-*Diazo*-5-*methylpyrrolidine*-2,4-*dione* (5).—(a) *With triethylamine.* A solution of the diazo-compound (30 mg) and triethylamine (5 drops) was refluxed in dichloromethane (10 ml) overnight, cooled, and extracted with water (10 ml). The pale yellow organic layer was dried and evaporated; the yellow crystalline residue (25 mg), m.p. 116°, had $[\alpha]_D^{20}$ (EtOH) −9·6°.

(b) *With sodium hydride.* A suspension of the diazo-compound (30 mg) and sodium hydride (50% oil suspension; 10 mg) was refluxed in benzene (10 ml) for 4 h. The mixture was cooled and washed with water. From the benzene extract was obtained the crystalline diazo-compound (26 mg), m.p. 115—116°, $[\alpha]_D^{20}$ (EtOH) −9·6°.

N-(*t-Butoxycarbonylacetyl*)-DL-*alanine Ethyl Ester* (1).—To a rapidly stirred solution of DL-alanine ethyl ester (11·7 g) and t-butyl hydrogen malonate [6] (16·0 g) in dichloromethane (300 ml) at −10° was added dicyclohexylcarbodi-imide (20·6 g) in dichloromethane (200 ml) and the mixture was stirred in the cold for 5 h. The suspension was filtered and the filtrate was washed with saturated sodium hydrogen carbonate solution, 5% citric acid solution, and finally brine. The dried extract was evaporated under reduced pressure and the residual oil (22·2 g) had $\nu_{max.}$ ($CHCl_3$) 3400, 1725, and 1673 cm^{-1} (Found: C, 55·4; H, 8·4. $C_{12}H_{21}NO_5$ requires: C, 55·6; H, 8·2%). The n.m.r. spectrum was identical with that obtained previously from the L-isomer.

To a solution of potassium t-butoxide [from potassium (0·9 g) and t-butyl alcohol (25 ml)] was added a solution of *N*-(t-butoxycarbonylacetyl)-DL-alanine ethyl ester (5·9 g, 1 mol. equiv.) in dry benzene (200 ml) and the mixture was refluxed for 18 h under nitrogen. The solvent was evaporated off and the residual white semicrystalline solid was dissolved in ice–water (50 ml). This solution was acidified with cold 5% citric acid solution and immediately extracted six times with dichloromethane. The combined organic layers were dried and evaporated. The residual pale yellow oil (4·6 g, 90%) was shown by n.m.r. spectroscopy to consist of a mixture of the keto and enol forms of (5*RS*)-3-(t-butoxycarbonyl)-5-methylpyrrolidine-2,4-dione. The oil was dissolved in the minimum amount of chloroform and the solution was added to boiling xylene (200 ml) and refluxed for 1·5 h. The hot xylene solution was filtered and the filtrate was evaporated. The residual semi-crystalline solid was recrystallised from acetone–ether to give (5*RS*)-5-methylpyrrolidine-2,4-dione as prisms (1·5 g, 60% overall yield), m.p. 111—114°. A further recrystallisation from acetone afforded *prisms*, m.p. 114—115·5°, $\nu_{max.}$ ($CHCl_3$) 3420, 3220, 1760, 1720, and 1695 cm^{-1}; τ ($CDCl_3$) 2·56br (1H, s, NH), 5·88 (1H, q, J 7·0 Hz, CH), 6·96 (2H, s, CH_2), and 8·62 (3H, d, J 7·0 Hz, CH_3) (Found: C, 53·2; H, 6·4; N, 12·2. $C_5H_7NO_2$ requires C, 53·1; H, 6·2; N, 12·4%).

(5RS)-3-*Diazo*-5-*methylpyrrolidine*-2,4-*dione* (5).—To a rapidly stirred suspension of finely powdered (5*RS*)-5-methylpyrrolidine-2,4-dione (1·0 g) and methanesulphonyl azide (2·2 g, 2 mol. equiv.) in acetonitrile (50 ml) under nitrogen at −10° was added a solution of triethylamine (1·0 g, 1 mol. equiv.) in acetonitrile (10 ml). The mixture was stirred at −10° for a further 0·5 h and the solvent was removed at room temperature under high vacuum. The residue was dissolved in water (10 ml) and extracted six times with chloroform. The combined chloroform extracts were dried and evaporated. The residue was treated with ether and the diazo-compound (5) immediately crystallised as pale yellow cubes (1·17 g, 95%). Recrystallisation from acetone–ether afforded *plates*, m.p. 115—115·5° [the m.p. of a 1 : 1 mixture of this derivative and the (5*R*)-diazo-compound prepared previously was 95—110°], $\nu_{max.}$ ($CHCl_3$) 3430, 3210, 2130, and 1695 cm^{-1}; τ ($CDCl_3$) 2·93br (1H, s, NH), 5·92 (1H, 8 lines, $J_{H.CH_3}$ 7, $J_{H.NH}$ 1 Hz, CH), 8·55 (3H, d, $J_{H.CH_3}$ 7 Hz, CH_3) (Found: C, 43·0; H, 3·8; N, 30·4. $C_5H_5N_3O_2$ requires C, 43·1; H, 3·6; N, 30·2%).

Irradiation of (5RS)-3-*Diazo*-5-*methylpyrrolidine*-2,4-*dione* (5).—The diazo-compound (5) (86 mg) and t-butyl carbazate (86 mg) were irradiated in benzene (170 ml) for 1 h with a medium-pressure mercury lamp in a water cooled Pyrex vessel. The solvent was evaporated off and the residue triturated with chloroform (5 ml). The suspension was filtered and the residue was washed with chloroform. The residual solid (56 mg) was the cis-β-*lactam* (7) [*cis*-3-(3-t-butoxycarbonylcarbazoyl)-4-methylazetidin-2-one], m.p. 130—140°, $\nu_{max.}$ (Nujol) 3320, 3200, 1755, 1708, and 1675 cm^{-1}, *m/e* 243 (M^+), τ [$(CD_3)_2CO$] 5·96 (2H, s and q, C*H*·C*H*·CH_3), 8·57 (9H, s, Bu^t), and 8·73 (3H, d, J 6 Hz, CH_3) (Found: C, 49·2; H, 7·0; N, 17·4. $C_{10}H_{17}N_3O_4$ requires C, 49·4; H, 7·0; N, 17·3%).

Evaporation of the combined filtrates afforded the trans-β-*lactam* (6) as an oil (88 mg), $\nu_{max.}$ ($CHCl_3$) 3400, 3250, 1760, 1730, and 1695 cm^{-1}; τ ($CDCl_3$) 5·87 (1H, dq, J 2·5 and 6 Hz, C*H*·CH_3), 6·38 (1H, d, J 2·5 Hz, CO·CH), 8·52 (9H, s, Bu^t), and 8·57 (3H, d, J 6 Hz, CH_3) (Found: C, 49·0; H, 6·8; N, 17·0%).

Addition of (5RS)-3-*Diazo*-5-*methylpyrrolidine*-2,4-*dione* (5) *to Dimethyl Acetylenedicarboxylate.*—To a rapidly stirred suspension of sodium hydride (0·7 g; 50% oil suspension) in benzene (50 ml) under nitrogen at room temperature were added the diazo-compound (5) (2·02 g, 1 mol. equiv.) and dimethyl acetylenedicarboxylate (10 g, 5 mol. equiv.) in benzene (50 ml). The mixture was stirred at room temperature for 24 h, then poured on 1% sulphuric acid at 0° and extracted three times with chloroform. The combined chloroform extracts were washed with brine, dried,

[10] M. T. Reagan and A. Nickon, *J. Amer. Chem. Soc.*, 1968, **90**, 4096.

and evaporated. The excess of dimethyl acetylenedicarboxylate was removed under high vacuum. P.l.c. of the residual oil with 30% acetone–light petroleum (b.p. 40—60°) gave three bands (seen under light of 254 nm wavelength), which were collected. The least polar fraction was a yellow oil (1·1 g, 32%). The middle fraction (0·2 g, 6%) crystallised in yellow cubes from acetone–ether, m.p. 142°, and the most polar fraction (0·4 g) was unchanged diazo-compound (5).

The yellow oil was the (Z)-*ester* (8; R = Me) [dimethyl (3-diazo-5-methyl-2,4-dioxopyrrolidin-1-yl)fumarate], $\nu_{max.}$ ($CHCl_3$) 2145, 1730, 1705, 1695, and 1650 cm^{-1}; $\lambda_{max.}$ (EtOH) 240 and 297 nm (log ε 4·8 and 3·7); τ ($CDCl_3$) 3·16 (1H, s, =CH), 5·29 (1H, q, J_{H,CH_3} 7 Hz, CH), 6·16 (3H, s, $-CO_2{\cdot}CH_3$), 6·24 (3H, s, $-CO_2{\cdot}CH_3$), and 8·64 (3H, J_{H,CH_3} 7 Hz, CH_3) (Found: C, 47·1; H, 3·9; N, 14·9. $C_{11}H_{11}N_3O_6$ requires C, 47·0; H, 3·9; N, 14·9%).

The yellow cubes, m.p. 142°, were the (E)-*ester* (9; R = Me) [dimethyl (3-diazo-5-methyl-2,4-dioxopyrrolidin-1-yl)maleate], $\nu_{max.}$ ($CHCl_3$) 2145, 1745, 1710, and 1625 cm^{-1}; $\lambda_{max.}$ (EtOH) 251 and 282 nm (log ε 4·0 and 4·2); τ ($CDCl_3$) 4·53 (1H, s, =CH), 5·74 (1H, q, J_{H,CH_3} 7 Hz, CH), 6·06 (3H, s, $-CO_2{\cdot}CH_3$), 6·26 (3H, s, $-CO_2{\cdot}CH_3$), and 8·47 (3H, d, J_{H,CH_3} 7 Hz, CH_3) (Found: C, 46·9; H, 4·2; N, 14·9. $C_{11}H_{11}N_3O_6$ requires C, 47·0; H, 3·9; N, 14·9%).

Dibenzyl Acetylenedicarboxylate.—A mixture of acetylenedicarboxylic acid (15 g), benzyl alcohol (200 ml), toluene-*p*-sulphonic acid (1·5 g), and hydroquinone (0·2 g) was slowly distilled at 9 mmHg (temperature of bath 100—120°). When no further benzyl alcohol (b.p. 85—90° at 9 mmHg) distilled (*ca.* 2 h), the solution was cooled and ice–water and ether were added. The ethereal extract was washed twice with saturated sodium hydrogen carbonate and with brine. The dried extract was evaporated to give an oil (42·6 g). On attempted fractional distillation at 0·5 mmHg the oil rapidly decomposed.

A sample (5 g) of the oil was chromatographed on silica gel (150 g). Ether–light petroleum (b.p. 40—60°) (1 : 19) eluted dibenzyl ether (1·5 g) and ether–light petroleum (b.p. 40—60°) (3 : 17) gave *dibenzyl acetylenedicarboxylate* (2·9 g), $\nu_{max.}$ (film) 1740 cm^{-1}; τ (CCl_4) 2·71 (10H, s, 2 × Ph) and 4·85 (4H, s, CH_2) (Found: C, 73·4; H, 4·8. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

Preparation of the Diazo-compounds (8; R = CH_2Ph) *and* (9; R = CH_2Ph).—To a suspension of sodium hydride (78 mg, 1 mol. equiv.; 50% oil suspension) and dibenzyl acetylenedicarboxylate (1·1 g, 2·5 mol. equiv.) in benzene (10 ml) was added the diazo-compound (5) (0·22 g) and the suspension was stirred under nitrogen for 24 h at room temperature. The mixture was poured on 1% sulphuric acid and chloroform at 0°, and the aqueous layer was re-extracted twice with chloroform. The combined organic layers were dried and evaporated and the residual oil was subjected to p.l.c., with 20% acetone–light petroleum (b.p. 40—60°) as eluant. After three elutions, three dark blue bands were evident on examination of the plate under light of wavelength 254 nm. The most polar fraction was unchanged diazo-compound (5) (50 mg). The least polar fraction (260 mg) crystallised from acetone–ether in yellow cubes, m.p. 109—110°, and was identified as the (Z)-*ester* (8; R = $CH_2{\cdot}$Ph) [dibenzyl (3-diazo-5-methyl-2,4-dioxopyrrolidin-1-yl)fumarate], $\nu_{max.}$ ($CHCl_3$) 2140, 1725, 1695, and 1640 cm^{-1}; $\lambda_{max.}$ (EtOH) 240 and 292 nm (log ε 4·08 and 3·64); τ (CCl_4) 2·70 (10H, s, 2 × Ph), 3·22 (1H, s, =CH), 4·81, 4·90 (4H, 2s, 2 × CH_2Ph), 5·40 (1H, q, J_{H,CH_3} 7·5 Hz, CH), and 8·83 (3H, d, J_{H,CH_3} 7·5 Hz, CH_3) (Found: C, 63·6; H, 4·3; N, 9·7. $C_{23}H_{19}N_3O_6$ requires C, 63·7; H, 4·4; N, 9·3%). The middle fraction (40 mg) was a pale yellow oil, which was identified as the (E)-*ester* (9; R = CH_2Ph) [dibenzyl (3-diazo-5-methyl-2,4-dioxopyrrolidin-1-yl)maleate], $\nu_{max.}$ ($CHCl_3$) 2130, 1740, 1710, and 1615 cm^{-1}; $\lambda_{max.}$ (EtOH) 255 and 285 nm (log ε 4·00 and 4·15); τ ($CDCl_3$) 2·70 (10H, s, 2 × Ph), 4·55 (1H, s, =CH), 4·74, 4·86 (2H, ABq, *J* 12 Hz, CH_2Ph), 4·88 (2H, s, CH_2Ph), 5·86 (1H, q, J_{H,CH_3} 7 Hz, CH), and 8·55 (3H, d, J_{H,CH_3} 7 Hz, CH_3) (Found: C, 63·8; H, 4·8; N, 9·7. $C_{23}H_{19}N_3O_6$ requires C, 63·7; H, 4·4; N, 9·7%).

Irradiation of the Diazo-compound (8; R = Me).—(a) *With t-butyl carbazate* (1 *mol. equiv.*) *in benzene for* 1·5 *h*. The diazo-compound (8; R = Me) and t-butyl carbazate (0·105 g, 1 mol. equiv.) were irradiated in benzene at room temperature for 1·5 h. The solvent was evaporated off under reduced pressure. The residual oil (0·30 g) was purified by p.l.c., the major fraction (0·28 g) being the *trans*-β-lactam (10; R = Me) {dimethyl [*cis*-3-(3-t-butoxycarbonylcarbazoyl)-2-methyl-4-oxoazetidin-1-yl]maleate}, $\nu_{max.}$ ($CHCl_3$) 2600—3300, 1770, 1730, 1708, 1695, and 1630 cm^{-1}; τ ($CDCl_3$) 8·55 (9H, s, Bu^t), 8·56 (3H, d, J_{H,CH_3} 6·5 Hz, CH–CH_3), 6·08 and 6·28 (each 3H, s, $-CO_2{\cdot}CH_3$), 6·21 (1H, d, *J* 2·0 Hz, CO·CH·CO), 5·55 (1H, dq, *J* 2·5 and 6 Hz, C*H*–CH_3), 4·38 (1H, s, =CH), 3·05br (1H, s, NH), and 1·5br (1H, s, NH).

(b) *With t-butyl carbazate* (1 *mol. equiv.*) *in benzene for* 0·5 *h*. A solution of the diazo-compound (58 mg) and t-butyl carbazate (30 mg, 1 mol. equiv.) in benzene was irradiated at room temperature for 0·5 h. T.l.c. of the crude product indicated the presence of the starting diazo-compound, a trace of the isomeric diazo-compound (9), and two other polar compounds which were of very similar polarity. The mixture was subjected to p.l.c. and these two compounds were collected in one fraction (20 mg), $\nu_{max.}$ 3500—3300, 1780, 1730, 1710—1690, and 1630 cm^{-1}. The n.m.r. spectrum of this fraction contained all the signals found in the spectrum of the *trans*-β-lactam (10), together with signals at τ 3·44 (1H, s, =CH), 5·1 (1H, m, C*H*–CH_3), 6·13 (3H, s, $-CO_2{\cdot}CH_3$), and 6·22 (3H, s, $-CO_2{\cdot}CH_3$), which were assigned to the stereoisomer (11; R = Me). From the intensities, the ratio of (10; R = Me) to (11; R = Me) was estimated to be 1 : 2.

Irradiation of the Diazo-compound (8; R = $CH_2{\cdot}$Ph).—A solution of the diazo-compound (8) (235 mg) and t-butyl carbazate (79 mg) (1·1 mol. equiv.) in ether (700 ml) was irradiated under nitrogen. The vessel was cooled in an ice–salt bath which maintained the solution at about −5°. After 2 h no diazo-compound remained. The solvent was evaporated under reduced pressure at room temperature and the residual oil (300 mg) was shown by t.l.c. (eluting with ethyl acetate) to contain essentially only one product (R_F 0·5), which was the *trans*-β-lactam (10; R = CH_2Ph) {dibenzyl [*cis*-3-(3-butoxycarbonylcarbazoyl)-2-methyl-4-oxoazetidin-1-yl]maleate}, $\nu_{max.}$ ($CHCl_3$) 1770, 1740, 1730, 1700, and 1615 cm^{-1}; τ (CCl_4) 2·75 (10H, s, 2 × Ph), 2·82br (1H, s, NH), 4·85br (1H, s, NH), 4·42 (1H, s, =CH), 4·90 (2H, s, CH_2Ph), 5·00 (2H, s, CH_2), 5·70 (1H, dq, *J* 2 and 6 Hz, –C*H*·CH_3), 6·45 (1H, d, *J* 2 Hz, CO·CH·CO), 8·61 (9H, s, Bu^t), and 8·64 (3H, d, *J* 6 Hz, CH·CH_3) (Found: C, 62·8; H, 5·4. $C_{28}H_3N_3O_8$ requires C, 62·6; H, 5·8%).

trans-N-*Benzyl*-2,5-*bisethoxycarbonylpyrrolidine* (12).—A solution of the *cis*-isomer of (12) [9] (350 g) and sodium ethoxide [from sodium (27 g)] in ethanol (2 l) was stirred at

room temperature for 4 days. The solvent was evaporated and the residue taken up in ether and water. The organic extract was washed with water, dried, and evaporated. The residual *trans*-diester (12) (165 g) had b.p. 146° at 0·1 mmHg; $\nu_{max.}$ ($CHCl_3$) 1740 cm^{-1}; τ (CCl_4), 2·75 (5H, m, Ph), 5·94 (4H, q, *J* 7·2 Hz, 2 × CO_2·C$H_2$$CH_3$), 6·0—6·35 (4H, m, 2 × N–CH and CH_2Ph), 7·60—8·20 (4H, m, 2 × CH_2), 8·80 (6H, t, *J* 7·2 Hz, 2 × CO_2·CH_2·CH_3) (Found: C, 66·7; H, 8·0; N, 5·0. $C_{17}H_{23}NO_4$ requires C, 66·9; H, 7·6; N, 4·6%).

trans-2,5-*Bisethoxycarbonylpyrrolidine* (13; R = Et).—A solution of the *trans*-ester (12) (60 g) in absolute ethanol (600 ml) was hydrogenated at 40° and 40 atm over 10% palladium–charcoal (10 g) for 24 h. The solution was filtered and evaporated. The residual *ester* (13; R = Et) (33 g, 77%) had b.p. 94° at 0·1 mmHg, $\nu_{max.}$ ($CHCl_3$) 3500—3300 and 1740 cm^{-1}; τ (CCl_4) 5·85 (4H, q, *J* 7·2 Hz, 2 × CO_2·CH_2·CH_3), 6·0—6·4 (2H, m, 2 × N–CH), 7·35 (1H, s, NH), and 7·90—8·10 (4H, m, 2 × CH_2) (Found: C, 55·9; H, 8·2; N, 6·0. $C_{10}H_{17}NO_4$ requires C, 55·8; H, 8·0; N, 6·5%).

trans-*Pyrrolidine*-2,5-*dicarboxylic Acid* (13; R = H).—*trans*-2,5-Bisethoxycarbonylpyrrolidine (90 g) was refluxed in water (3 l) for 24 h. The solution was concentrated to *ca.* 200 ml and left at 0° for 24 h. The product was collected and crystallised from water as needles (23 g), m.p. 275—280° (decomp.).

trans-2,5-*Bisbenzyloxycarbonylpyrrolidinium Toluene*-p-*sulphonate*.—A solution of the *trans*-diacid (13; R = H) (2 g), toluene-*p*-sulphonic acid (2·6 g), and benzyl alcohol (20 ml) in benzene (80 ml) was refluxed for 3 h, the water generated being removed in a water separator. The solvent was removed under reduced pressure and the residual oil triturated with ether at 0°. The *salt* formed white needles (4·0 g), m.p. 152—154° (from water), $\nu_{max.}$ ($CHCl_3$) 1740 cm^{-1}; τ ($CDCl_3$) 1·15br (2H, s, $\overset{+}{N}H_2$), 2·24 and 2·90 (4H, m, SO_3Ar), 2·70 (10H, s, 2 × CH_2*Ph*), 4·86 (4H, s, 2 × CH_2Ph), 4·90—5·35 (2H, m, $\overset{+}{N}H_2$–CH_2), 7·70 (3H, s, Ar·CH_3), and 7·60—7·90 (4H, m, 2 × CH_2) (Found: C, 63·2; H, 5·7; N, 3·0. $C_{27}H_{29}NO_7S$ requires C, 63·4; H, 5·7; N, 2·7%).

The free amine was obtained by suspending the salt in saturated sodium hydrogen carbonate and extracting the solution with ether. The ethereal extract was dried and evaporated. The residual oil decomposed on attempted distillation at 0·1 mmHg; $\nu_{max.}$ ($CHCl_3$) 3450 and 1730 cm^{-1}; τ (CCl_4) 2·70 (10H, s, 2 × Ph), 4·91 (4H, s, 2 × CH_2Ph), 5·97—6·20 (2H, m, NH–C*H*), 7·50 (1H, s, NH), and 7·92—8·08 (4H, m, 2 × CH_2).

Dibenzyl trans-N-(*t-Butoxycarbonylacetyl*)*pyrrolidine*-2,5-*dicarboxylate* (14; R = CH_2Ph).—A solution of *trans*-dibenzyl pyrrolidine-2,5-dicarboxylate (3 g), t-butyl hydrogen malonate (1·6 g), and dicyclohexylcarbodi-imide (2 g) in methylene chloride (100 ml) was stirred at 0° for 48 h. The precipitate was collected and washed with methylene chloride. The combined organic washings were washed with 5% sulphuric acid, water, saturated sodium hydrogen carbonate solution, and finally brine. The solution was dried and evaporated and the residue was extracted with ether. The ethereal solution was evaporated; the residual oil (4·1 g) was pure enough for use in the next step. For analytical purposes, a fraction (0·2 g) was subjected to p.l.c., which gave the *ester* as an oil, $\nu_{max.}$ ($CHCl_3$) 1730 and 1660 cm^{-1}; τ (CCl_4) 2·73 (10H, s, 2 × Ph), 4·92, 4·95 (each 2H, s, CH_2Ph), 5·40 (2H, m, N–CH), 6·92 (2H, s, CO·CH_2·CO), 7·60—8·25 (4H, m, $2CH_2$), and 8·60 (9H, s, Bu^t) (Found: C, 67·3; H, 6·8; N, 3·0. $C_{27}H_{31}NO_7$ requires C, 67·3; H, 6·5; N, 2·9%).

Benzyl 6-*Diazo*-5,7-*dioxohexahydropyrrolizine*-3-*carboxylate* (16; R = CH_2Ph).—A solution of the ester (14; R = CH_2Ph) (2 g) in benzene (40 ml) was refluxed under nitrogen with sodium hydride (50% oil suspension; 0·2 g, 1 mol. equiv.) for 15 h. The solution was diluted with ice–water and ether, and the aqueous layer was acidified with cold 5% sulphuric acid and extracted several times with chloroform. The combined extracts were dried and evaporated and the residue (0·8 g) was refluxed in toluene (50 ml) for 2 h. Removal of the solvent gave the dione (15) (0·46 g), which was treated with methanesulphonyl azide (1 g) and triethylamine (0·17 g) in acetonitrile (10 ml) under nitrogen at 0° for 3 h. The solvent was evaporated off under reduced pressure and the residue was subjected to p.l.c., with 40% ethyl acetate–light petroleum (b.p. 40—60°) as eluant. The band which was dark blue when viewed under light of wavelength 254 nm was collected and gave the *diazo-compound* (16; R = CH_2Ph) (0·20 g), $\nu_{max.}$ ($CHCl_3$) 2150, 1740, and 1700—1690 cm^{-1}; τ ($CDCl_3$) 5·72 (1H, dd, *J* 7 and 10 Hz, CO·CH), 7·3—8·7 (4H, m, CH_2·CH_2), 5·34 (1H, t, *J* 8 Hz, ·C*H*·CO_2·CH_2Ph), 4·80 (2H, s, CH_2Ph), and 2·64 (5H, s, Ph) (Found: C, 60·4; H, 4·4; N, 14·3. $C_{15}H_{13}N_3O_4$ requires C, 60·2; H, 4·4; N, 14·0%).

Irradiation of the Diazo-compound (16; R = CH_2Ph).—A solution of the diazo-compound (16; R = CH_2·Ph) (50 mg) and β-methylphenethyl carbazate (30 mg, 1 mol. equiv.) in ether (10 ml) was irradiated at −70° for 3 h. The solvent was evaporated off; the residual gum had $\nu_{max.}$ ($CHCl_3$) 1770, 1750, 1730, and 1700 cm^{-1}; τ ($CDCl_3$) 2·68br (10H, s, 2 × Ph), 2·4br, 4·9br (each 1H, s, NH), 4·90 (2H, s, CH_2Ph), 5·60 (1H, m, 5-H), 5·87 (1H, m, 2-H), 6·28 (1H, d, *J* 2 Hz, 6-H), 7·4—8·0 (4H, m, 3·4-H), 8·24 (6H, s, CMe_2). Further purification was not possible since the product rapidly decomposed on attempted chromatography, and only oils were obtained on attempted crystallisation. The product was however essentially one substance, *viz.* the *trans*-β-lactam {benzyl 7-oxo-6α-[3-(2-phenyl-2-propyloxycarbonyl)-carbazoyl]-5αH-1-azabicyclo[3.2.0]hexane-2α-carboxylate} (17; R = CH_2Ph).

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