Formation and Reactions of Ethyl 2,2-Dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-6-carboxylate, a Penam Analogue

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U.v. irradiation of ethyl 2-diazo-3-(4,4-dimethyloxazolidin-3-yl)-3-oxopropionate (3) gives a product whose spectroscopic properties and reactions are consistent with its formulation as ethyl 2,2-dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-6-carboxylate (1d). Nucleophilic reagents rapidly cleave the β-lactam ring of compound (1d) [*e.g.* treatment with benzylamine yields the benzylamide (4a)]. In solution in carbon tetrachloride (1d) is converted into the 14-membered ring dilactone (7). The structures of compounds (4a) and (7) are supported by independent syntheses.

SYNTHETIC analogues of natural penicillins (1a) [1] are potentially of value for gaining an understanding of the mechanism of action of this type of antibiotic. Furthermore, such compounds may be superior drugs ideally combining antibacterial efficacy with resistance to penicillinases. The theory of penicillin action due to Tipper and Strominger [2] suggests that any analogue which retains the essential shape of the natural (penam) skeleton while enhancing reactivity of the β-lactam system towards nucleophiles is an attractive target. The oxygen analogues (1b) should fulfill these criteria as the lengths of their C–O bonds [shorter than the C–S bonds of (1a)] will increase strain in the bicyclic system. Also, the greater electronegativity of O relative to S will be felt inductively at N-1, diminishing amide resonance in (1b) and so increasing the reactivity of the β-lactam system.†

An unsuccessful attempt to synthesise compounds of type (1b) *via* the combination of a Δ^2-oxazoline with a keten (or keten equivalent) has been described.[3] One reason for the failure of this approach could be the inherent instability of the 4-oxa-1-azabicyclo[3.2.0]heptan-7-one skeleton (1c) such that it spontaneously undergoes rapid ring opening to, for example, the zwitterion (2), which should also be highly reactive and undergo further degradation. It was desirable therefore to seek an alternative synthesis of a structure of the type (1c) under the mildest conditions. The photocyclisation of α-diazo-amides, as developed by Lowe [4] for the synthesis of bicyclic β-lactams (including an analogue of penicillin in which S is replaced by CH_2) was considered to be a good test for the existence of a 4-oxa-1-azabicyclo[3.2.0]-heptan-7-one. The α-diazo-amide (3), easily prepared from ethyl 3-(4,4-dimethyloxazolidin-3-yl)-3-oxopropionate, has been used as a model system for this purpose.[5]

Preparation of the Penam Analogue (1d) *and its Spectroscopic Properties.*—A dilute solution of compound (3) in carbon tetrachloride was irradiated under nitrogen with a medium-pressure mercury lamp. The diazo i.r. band (2 135 cm^{-1}) disappeared within 2 h, and new intense bands appeared at 1 790 and 1 737 cm^{-1}, replacing those of the starting ester (1 712) and amide (1 650 cm^{-1}) functions.

† *Note added in proof.* The synthesis of the oxygen analogue of (±)-cephalothin has been described recently (L. D. Cama and B. G. Christensen, *J. Amer. Chem. Soc.*, 1974, **96**, 7582).

[1] *Cf. e.g.* D. N. McGregor in *Progr. Chem. Org. Natural Products*, 1974, **31**, 1; M. J. Cook and C. D. Johnson in *Ann. Reports* (*B*), 1973, **70**, 482, for reviews of recent syntheses.

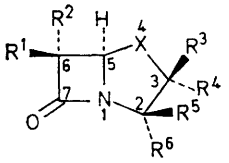
[2] P. M. Blumberg and J. L. Strominger, *Bact. Rev.*, 1974, **38**, 291, and references therein.

[3] B. T. Golding and D. R. Hall, *J.C.S. Perkin I.*, in the press.

[4] G. Lowe and M. V. J. Ramsay, *J.C.S. Perkin I*, 1973, 479 and references therein.

[5] Preliminary report, B. T. Golding and D. R. Hall, *J.C.S. Chem. Comm.*, 1973, 293.

The resulting spectrum was that expected for the penam analogue (1d). An alternative possibility [6] that carbene insertion had occurred principally into the methylene group of the ethoxycarbonyl group to give a β-lactone could be ruled out since a carbonyl group in that entity

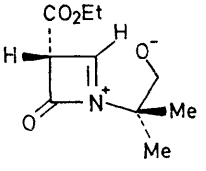


(1) a; X = S, R^1 = various RCONH, R^2 = R^5 = H, R^3 = R^4 = Me, R^6 = CO_2H

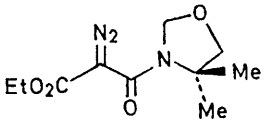
b; X = O, R^{1-6} as for (1a)

c; X = O, R^{1-6} = H

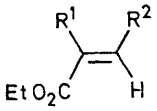
d; X = O, R^1 = R^3 = R^4 = H, R^2 = CO_2Et, R^5 = R^6 = Me



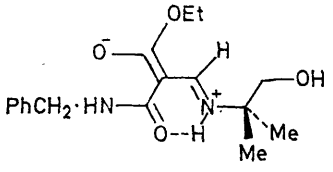
(2)



(3)



	R^1	R^2
(4) a;	$PhCH_2·NH·CO$,	$NH·CMe_2·CH_2·OH$
b;	$PhCH_2·NH·CO$	OEt
c;	MeO_2C	$NH·CMe_2·CH_2·OH$
d;	HO_2C	$NH·CMe_2·CH_2·OH$
e;	MeO_2C	OEt
f;	EtO_2C	$NH·CMe_2·CH_2·OH$
g;	EtO_2C	NH_2



(5)

absorbs at *ca.* 1 810 cm^{-1} (there was actually a weak shoulder at 1 820 cm^{-1} in the i.r. spectrum of the reaction mixture which could arise from a small amount of a β-lactone). The ^1H n.m.r. spectrum of the reaction mixture, after evaporation *in vacuo* to 0.5 ml, showed the following features consistent with structure (1d): a two-proton AB quartet (J 8 Hz, component doublets at δ 3.62 and 3.81) due to the ring methylene protons (the low geminal coupling constant is typical of such protons in *N*-acyloxazolidines [3,7]); a one-proton doublet ($J_{5,6}$ 1.0 Hz, δ 5.31) assigned to H-5 (*cf.* δ *ca.* 5.0 for the chemical shift of H-2 in 2-unsubstituted *N*-acyloxazolidines [7]), the low coupling constant signifying [8] a *trans* relationship between H-5 and H-6; a one-proton doublet (J 1.0 Hz, δ 3.71) assigned to H-6 since it collapses to a singlet on irradiation of the signal at δ 5.31; three-proton singlets at δ 1.20 and 1.53 belonging to the *gem*-dimethyl group; and a triplet (3H) and quartet (2H) at δ 1.30 and 4.18, respectively, due to the ethyl group. The substantial difference in chemical shift between the CMe_2 signals is probably due to one of them lying above the plane of the β-lactam carbonyl group and hence being shielded. The signal due to H-6 is a sharp doublet, whereas the doublet splitting of H-5 is barely discernible at 60 MHz. This is probably the result of W-coupling of H-5 with the *cis* ring methylene proton at C-3; consistent with this interpretation the higher field doublet of the AB quartet is appreciably broader than the other. A similar effect is seen in the spectra of 2-substituted *N*-acyl-4,4-dimethyloxazolidines.[7] The signal due to H-5 integrates for 55% of the total and this figure therefore provides an estimate of the yield of (1d).

Attempts to obtain an analytical sample of (1d) by crystallisation or chromatography (see below) failed. Mass spectral examination of the crude product gave inconclusive results. However, we submit that the above spectroscopic data, taken with the degradative results discussed below, establish that the penam analogue (1d) is formed.

Degradations of the Penam Analogue (1d).—Addition of 1 mol. equiv. of benzylamine to the cold dilute solution from a complete photoreaction of the diazo-amide (3) resulted in a rapid reaction as evidenced by the disappearance of the β-lactam carbonyl band in the i.r. spectrum, and compound (4a) was isolated in 60% yield [*cf.* the value of 55% derived above from the n.m.r. spectrum for the yield of (1d)]. This structure was confirmed by analytical and spectroscopic data (see Experimental section) and by independent synthesis from the ethoxymethylenemalonate (4b) and 2-amino-2-methylpropan-1-ol.

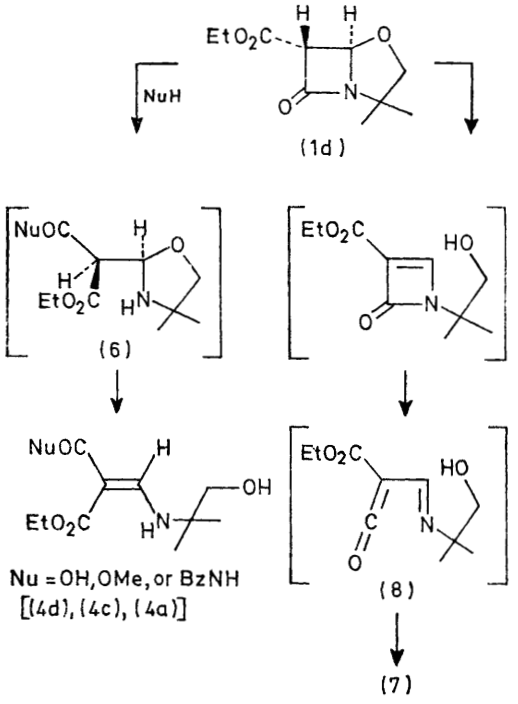
A dilute solution of methanol in deuteriochloroform slowly converted the β-lactam (1d) into the diester (4c), and attempted chromatography on silica gel hydrolysed (1d) to the acid (4d). These structures are supported by analytical and spectral data as well as independent synthesis for (4c), and by spectral data in the case of the acid (4d).

The large coupling constant between vinylic CH and NH was characteristic of the ^1H n.m.r. spectra of these degradation products. The possibility of resonance interaction of the nitrogen lone-pair of electrons with the electron-deficient olefinic portion favours a planar molecule with appreciable contribution from dipolar resonance structures such as (5). Restricted rotation about the C–N bond and a reduced barrier to rotation about

[6] G. Lowe and J. Parker, *Chem. Comm.*, 1971, 577.
[7] D. R. Hall, Ph.D. Thesis, Warwick, 1972.
[8] K. D. Barrow and T. M. Spotswood, *Tetrahedron Letters*, 1965, 3325.

the C=C bond would be predicted, and has been verified in related compounds.[9] The presence of the quaternary carbon atom adjacent to nitrogen in compounds (4a, c, and d) would be expected to favour greatly the *trans*-configuration about the C–N bond, giving rise to the large ·CH,NH coupling constant.[10] Also, only this configuration permits formation of the intramolecular hydrogen bond denoted in (5), which is indicated by i.r. data (bonded NH stretch at 3 320 cm^{-1}).

The formation of compounds (4a, c, and d) can only be readily interpreted on the basis of structure (1d) for



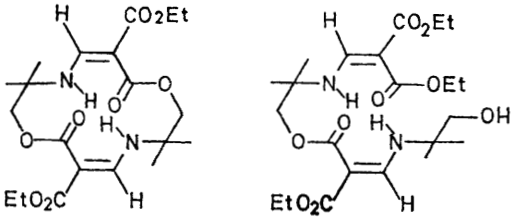
SCHEME Pathways for degradation of the β-lactam (1d) [leading to (4a, c, or d) or (7)]

the product from irradiation of (3). Nucleophilic opening of the β-lactam ring of (1d) would give an oxazolidine (6), which should undergo ready eliminative fragmentation to the observed products (see Scheme). The proton on the carbon atom in structure (6) derived from C-6 in (1d) is flanked by two carbonyl functions and its consequent acidity should facilitate the elimination. In the natural penicillins (1a) the corresponding proton is not so acidic and the thiazolidine ring is more stable, so that nucleophilic opening of the β-lactam ring is not normally followed by an analogous fragmentation. However, under certain acidic conditions intramolecular attack on the β-lactam by the acylamino side-chain may be followed by eliminative fragmentation of the thiazolidine ring.[11]

Even if the pure penam analogue (1d) (*trans*-H-5–H-6) were available, it is unlikely that the overall reaction [to (4a, c, or d)] would be stereospecific. Epimerisation of the acidic proton on the carbon atom of (6) derived from C-6 of structure (1d) could occur prior to elimination, and equilibration of geometrical isomers about the C=C bond in the products (4a, c, and d) may be possible (see before). Thus, the n.m.r. spectra of compounds (4a and d) suggest they are single isomers, but the spectrum of (4c) shows it to be a mixture of geometrical isomers (ratio 45 : 55). An identical spectrum was obtained for (4c) synthesised by a different route from the ethoxymethylenemalonate (4e) and 2-amino-2-methylpropan-1-ol. Since an amide carbonyl group is more basic than an ester carbonyl, intramolecular hydrogen bonding [*see* (5)] may favour the configuration drawn for (4a) (*i.e.* amide group *cis* to $NH{\cdot}CMe_2{\cdot}CH_2{\cdot}OH$).

The i.r. spectrum of a dilute solution of the β-lactam (1d) in carbon tetrachloride was unchanged after 12 h at 0 °C, but after 22 h at room temperature complete disappearance of the β-lactam band had occurred. T.l.c. showed a number of compounds to have arisen, but the only one isolated in significant amount (20%) was highly crystalline with spectroscopic properties and analytical data consistent with structure (7). In particular, its n.m.r. spectrum shows a coupling constant of 14.5 Hz between each NH and vinylic CH proving their *trans*-relationship (see before), and an i.r. spectrum indicates that each NH is intramolecularly hydrogen bonded to a carbonyl group [comparison with spectra for (4a) and the reference compound diethyl aminomethylenemalonate (4 g)]. Compound (7) was also produced by heating the diester (4f) with a catalytic amount of sulphuric acid in benzene.

One possible mode of formation of (7) from (1d) could proceed *via* the keten (8) (see Scheme), then dimerisation (2 steps) might proceed faster than inversion at nitrogen which is a prerequisite for intramolecular cyclisation.



Starting from (4f), acid-catalysed transesterifications could provide compound (7) *via* structure (9). Appreciable electrostatic interaction between the enamino-systems [*cf.* dipolar resonance structure (5)] in the intermediate (9) might hold the reactive groups in close proximity for ring closure to occur.

EXPERIMENTAL

Solvents and reagents were purified where necessary in the usual manner.[3,12] Petroleum was the fraction of b.p.

[9] Y. Shvo and H. Shanan-Atidi, *J. Amer. Chem. Soc.*, 1969, **91**, 6683, 6689.

[10] *Cf.* R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, 1966, **99**, 2526.

[11] 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, 1949.

[12] N. W. Alcock, B. T. Golding, D. R. Hall, U. Horn, and W. P. Watson, *J.C.S. Perkin I*, 1975, 386.

60—80°. Unless stated otherwise n.m.r., i.r., and u.v. spectra were run as previously described.[3]

Ethyl 2-Diazo-3-(4,4-dimethyloxazolidin-3-yl)-3-oxopropionate (3).—A solution of ethyl chloroformylacetate [3] (3.74 g, 24.8 mmol) in dichloromethane (25 ml) was added dropwise to a stirred, ice-cooled mixture of 4,4-dimethyloxazolidine (2.1 g, 21 mmol) and anhydrous sodium carbonate (3.0 g, 29 mmol) in dichloromethane (20 ml). The mixture was stirred at room temperature for 1 h, refluxed for 15 min, and then filtered. The filtrate was washed with 5% citric acid solution and water, dried, and evaporated to give ethyl 3-(4,4-dimethyloxazolidin-3-yl)-3-oxopropionate (3.70 g, 85%) as an oil, which was pure enough (t.l.c. and n.m.r. analysis) for the preparation of compound (3).

To the crude product (2.15 g, 10 mmol assuming 100% purity) in acetonitrile (15 ml) were added triethylamine (1.1 g, 11 mmol) and toluene-*p*-sulphonyl azide [13] (2.0 g, 11 mmol). The mixture was left at room temperature for 24 h and was then evaporated. The residue was treated with aqueous 5M-sodium hydroxide (4 ml) and extracted with ether. The combined extracts, dried and evaporated, gave a yellow oil (2.5 g) which was chromatographed on silica gel. Elution with 5% ethyl acetate–benzene gave toluene-*p*-sulphonyl azide followed by the *diazo-amide* (3) as a golden yellow oil (1.54 g, 64%) that crystallised at 0 °C; m.p. 30°; δ 1.29 (t, *J* 7 Hz, *Me*CH_2O), 1.53 (s, Me_2), 3.77 (s, O$CH_2$$CMe_2$), 4.27 (q, *J* 7 Hz, Me$CH_2$O), and 5.02 (s, O$CH_2$N); $\nu_{max.}$ (CCl_4) 2 135s, 1 710s, and 1 630s cm^{-1}; $\lambda_{max.}$ 255 (ε 10 200 and 366 nm (627); *m/e* 226 (1.8%, $M^+ - 15$), 213 (2.3), and 100 (100) (Found: C, 50.4; H, 6.25. $C_{10}H_{15}N_3O_4$ requires C, 49.8; H, 6.25%).

Formation and Reactions of Ethyl 2,2-Dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]*heptane-6-carboxylate* (1d).—The diazo-amide (3) (100 mg) was irradiated under nitrogen in carbon tetrachloride (12 ml) in a Pyrex tube strapped to the water-cooled probe of a medium pressure mercury lamp. Reactions were monitored as described in the main text. Spectral data for the β-lactam (1d) and details of its reactions leading to compounds (4a, c, and d) are also given in the main text. These products were isolated by preparative t.l.c. (multiple development) with ethyl acetate–benzene (1 : 1): *ethyl N-benzyl-2-(2-hydroxy-1,1-dimethylethylaminomethylene)malonamate* (4a), m.p. 90° (from petroleum); δ 1.27 (t, *J* 7 Hz, OCH_2*Me*), 1.28 (s, Me_2), 2.73br (OH), 3.44 (s, CH_2OH), 4.18 (q, *J* 7 Hz, OCH_2Me), 4.51 (d, *J* 6 Hz, PhCH_2), 7.32 (s, Ph), 8.13 (d, *J* 14.0 Hz, HC=), 9.22br (CONH), and 10.66br (d, *J* 14.0 Hz, NH); $\nu_{max.}$ 3 605w, 3 420w, 3 320m (bonded NH), 1 660vs, 1 640vs, 1 590s, and 1 530s cm^{-1}; $\lambda_{max.}$ 231 (ε 14 925) and 285 nm (29 850); M^+ 320 (19%) (Found: C, 64.1; H, 7.55; N, 8.55. $C_{17}H_{24}N_2O_4$ requires C, 63.75; H, 7.55; N, 8.75%), *ethyl methyl 2-(2-hydroxy-1,1-dimethylethylaminomethylene)malonate* (4c), m.p. 92° (from petroleum); δ 1.25 and 1.31 (total 3H, 2 × t, *Me*CH_2O), 1.31 (6H, s, Me_2), 3.17br (OH), 3.50br (s, CH_2OH), 3.65 and 3.73 (total 3H, 2 × s ratio 45 : 55, OMe), 4.13 and 4.21 (total 2H, 2 × q, MeCH_2O), 8.12 (d, *J* 14.7 Hz, HC=), and 9.55br (d, *J* 14.7 Hz, NH); $\lambda_{max.}$ 255(ε 12 600) and 281 nm (26 600); M^+ 245 (17%) (Found: C, 54.15; H, 7.75; N, 5.8. $C_{11}H_{19}NO_5$ requires C, 53.85; H, 7.8; N, 5.7%); *ethyl hydrogen 2-(2-hydroxy-1,1-dimethylethylaminomethylene)malonate* (4d), m.p. 104° (from petroleum); δ 1.32 (t, *J* 7 Hz, *Me*CH_2O), 1.35 (s, Me_2), 3.55br (s, CH_2OH), 4.26 (q, *J* 7 Hz, MeCH_2O), 8.11 (d, *J* 15.0 Hz, HC=), and 10.11br (NH); $\nu_{max.}$ 3 610m, 3 500—3 000w, 1 688s, and 1 603s cm^{-1}.

Diethyl 3,3,10,10-Tetramethyl-7,14-dioxo-1,8-dioxa-4,11-diazacyclotetradeca-5,12-diene-6,13-dicarboxylate (7).—The diazo-amide (3) (128 mg, 0.53 mmol) in carbon tetrachloride (15 ml) was irradiated for 2 h at room temperature. The resulting solution was kept for 22 h at room temperature, after which the i.r. spectrum showed absence of the β-lactam carbonyl absorption (1 790 cm^{-1}). Evaporation left a crystalline residue containing *ca.* 25% of the dilactone (7) (n.m.r. analysis). This residue was chromatographed on silica gel (6 g). Elution with 10% ethyl acetate–benzene gave the crystalline *dilactone* (7) (28 mg, 24%). Recrystallisation from hot ethyl acetate containing a little hexane gave a sample of m.p. 205°; $\lambda_{max.}$ 221 (ε 11 600) and 273 nm (19 900); *M* (osmometric in CH_2Cl_2) 428 (calc. 426) (Found: C, 56.4; H, 7.1; N, 6.55. $C_{20}H_{30}N_2O_8$ requires C, 56.3; H, 7.1; N, 6.55%). Other spectral data given below [for dilactone (7) obtained from compound (4f)].

Independent Syntheses of Compounds (4a *and* c) *and* (7).—*Compound* (4a). Potassium ethyl malonate [14] (11.7 g, 69 mmol) in water (10 ml) was neutralised with 10M-hydrochloric acid (7 ml), while keeping the mixture cold. Ethyl hydrogen malonate was extracted into ether and the extract was dried and evaporated. The residue (9.1 g, 100%) was refluxed with thionyl chloride (7.5 ml, 100 mmol) for 2 h. The excess of thionyl chloride was removed and the residue was dissolved in benzene (20 ml). Evaporation gave crude acid chloride which was used directly.

Ethyl chloroformylacetate (5.1 g) in benzene (40 ml) was added dropwise over 30 min to a stirred, ice-cooled mixture of benzylamine (3.75 g, 35 mmol) and triethylamine (3.54 g, 35 mmol) in benzene (50 ml). The suspension was stirred overnight at room temperature, triethylamine hydrochloride was filtered off, and the filtrate was washed with dilute hydrochloric acid, saturated sodium carbonate solution, and brine. The organic phase was dried and evaporated and the residue distilled (kugelrohr) at 169° and 0.6 mmHg to give the ethyl *N*-benzylmalonate (3.35 g, 43%).

The product was refluxed for 22 h with ethyl orthoformate, acetic anhydride, and zinc chloride (after ref. 15) to give ethyl *N*-benzyl-2-ethoxymethylenemalonamate (4b), b.p. 200° at 0.04 mmHg (distillation in a kugelrohr). This compound was treated with 2-amino-2-methylpropan-1-ol essentially as described below for the preparation of (4f) to give a crude product which was chromatographed on silica gel. Elution with 20% ethyl acetate–benzene gave several fairly pure fractions. These were combined and recrystallised from ether–pentane and then hexane to yield compound (4a) (46%), m.p. 90.5° [mixed m.p. with (4a) from β-lactam (1d) 90°]; its n.m.r., i.r., u.v., and mass spectra were almost identical with those of compound (4a) from the β-lactam (1d) (see above).

Compound (4c). Ethyl hydrogen malonate was converted into ethyl methyl malonate by ethereal diazomethane. The crude diester (3.7 g, 25 mm) was refluxed for 10 h with ethyl orthoformate, acetic anhydride, and zinc chloride (after ref. 15) to yield after distillation a fraction of b.p. 100—101° at 0.2 mmHg which, according to n.m.r. data, consisted of *ca.* 70% ethyl methyl 2-ethoxymethylenemalonate (4e) and 30% starting diester. A portion of this product [0.51 g, containing *ca.* 2 mmol of (4e)] in dichloromethane (8 ml) was treated with 2-amino-2-methylpropan-1-ol (0.178 g, 2

[13] W. von E. Doering and C. H. DePuy, *J. Amer. Chem. Soc.*, 1953, **75**, 5955.

[14] M. Freund, *Ber.*, 1884, **17**, 780.

[15] L. Claisen, *Annalen*, 1897, **297**, 1.

mmol) as described below [preparation of (4f)] to give a residue which was pumped at 0.01 mmHg until (*ca.* 48 h) it reached constant weight. Recrystallisation of the resulting crystals from ether and then hexane gave a compound (4c) [0.17 g; m.p. 92—94°; mixed m.p. 93° with (4c) derived from β-lactam (1d)] and a second crop (0.22 g; m.p. 93°) (total 79%); n.m.r., i.r., and mass spectra very similar to those of (4c) from (1d); $\lambda_{max.}$ 225 (ε 9 800) and 281 nm (20 500) (Found: C, 53.95; H, 7.8; N, 5.6. Calc. for $C_{11}H_{19}NO_5$: C, 53.85; H, 7.8; N, 5.7%).

Compound (7). To diethyl 2-ethoxymethylenemalonate[15] (4.38 g, 20.3 mmol) in dichloromethane (30 ml) cooled in an ice-bath, was added dropwise, over 5 min, 2-amino-2-methylpropan-1-ol (1.81 g, 20.3 mmol). The mixture was then left for 30 min at room temperature. Solvent was removed and the residue was pumped in high vacuum. The product was recrystallised twice from ether (with cooling to −20 °C) to give *diethyl* 2-(2-*hydroxy*-1,1-*dimethylethylaminomethylene*)*malonate* (4f) (4.31 g, 82%), m.p. 95—96°; δ 1.29 and 1.35 (ester triplets), 3.05 (t, *J* 6 Hz, OH, disappears on addition of D_2O), 3.54 (d, *J* 6 Hz, CH_2OH), 4.19 and 4.15 (ester quartets), 8.15 (d, *J* 14.5 Hz, HC=), and 9.53br (d, *J* 14.5 Hz, NH) [addition of D_2O with subsequent daily shaking converted the signal at 8.15 into a singlet whilst that at 9.53 vanished (75% conversion after 16 days)]; $\nu_{max.}$ ($CHCl_3$) 3 630w, 3 440br, 3 260w, 3 180vw, 1 678s, 1 650s, and 1 608s cm^{-1}; $\lambda_{max.}$ 225 (ε 11 750) and 281 nm (23 100); *m/e* 259 (7%, M^+) and 182 (100) (Found: C, 55.6; H, 8.15; N, 5.4. $C_{12}H_{21}NO_5$ requires C, 55.6; H, 8.15; N, 5.35%). Compound (4f) (0.182 g, 0.7 mmol) in benzene (20 ml) containing a trace of concentrated sulphuric acid was refluxed for 48 h. (*N.B.* Best results were obtained from such incomplete small-scale reactions.) The resulting yellow solution was washed with saturated aqueous sodium carbonate and back-extracted with dichloromethane. The combined extracts were dried and evaporated and the residue was chromatographed on alumina (activity IV; 7.5 g). Elution with 50% chloroform–hexane gave the crystalline dilactone (7) (26 mg, 18%). [75% Chloroform–hexane eluted starting material (60 mg, 33%).] Recrystallisation (ethyl acetate) gave a sample of m.p. 205° [mixed m.p. 205.5° with dilactone (7) derived from (1d) (see above)]; δ 1.38 (t, *J* 7.0 Hz, 2 × *Me*CH_2O), 1.44 (s, 2 × Me_2), 4.12 (s, 2 × OCH_2CMe_2), 4.29 (q, *J* 7.0 Hz, 2 × $MeCH_2O$), 8.54 (d, *J* 14.5 Hz, 2 × HC=), and 9.29br (d, *J* 14.5 Hz, 2 × NH) [there was no change in this n.m.r. spectrum on addition of D_2O and daily shaking for 20 days at room temperature; *cf.* behaviour of (4f)]; $\nu_{max.}$ ($CHCl_3$) 3 375vw, 3 270m, 3 195w, 3 002m, 2 980m, 2 940w, 2 900vw, 2 880vw,sh, 1 708s, 1 655s, and 1 605s cm^{-1}; $\lambda_{max.}$ 221 (ε 11 100) and 273 nm (18 900); *m/e* 426 (33%, M^+), 396 (32), 382 (10, *M* − 44), 381 (12), 380 (10), 214 (100), 200 (14, 396 −196), 184 (19), 183 (69), 182 (97), and 168 (34, 214 − EtOH); *M* (osmometric in CH_2Cl_2) 421; calc. for $C_{20}H_{30}N_2O_8$: *M*, 426 (Found: C, 56.3; H, 7.1; N, 6.65. Calc. for $C_{20}H_{30}N_2O_8$: C, 56.3; H, 7.1; N, 6.55%).

Diethyl 2-*Aminomethylenemalonate*.—This was prepared in the manner of ref. 15; m.p. 64.5° (from ether–hexane) (lit.,[15] 65—67°); δ 1.28 and 1.33 (ester triplets), 4.12 and 4.20 (ester quartets), 6.8—7.2br (*cis-HN*, HC=), 8.02 (dd, *J* 15.5 and 8.5 Hz, =CH), and 8.66br (d, *J* 15.5 Hz, *trans*-N*H*,HC=) [on addition of D_2O the NH resonances disappeared and the signal at 8.02 collapsed to a singlet (60% conversion after 1 min at 20 °C)]; $\nu_{max.}$ ($CHCl_3$) 3 500s and 3 390m (free NH), and 3 320m and 3 230w cm^{-1} (bonded NH); $\lambda_{max.}$ 219 (ε 24 000) and 268 nm (35 500) (Found: C, 51.3; H, 6.95; N, 7.5. Calc. for $C_8H_{13}NO_4$: C, 51.35; H, 7.0; N, 7.5%).

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