Tetrahedron Vol 41, No. 2, pp 479 to 484, 1985
Printed in Great Britain.

0040 4020/85 $3.00 + 00

SIMPLE AND CONDENSED β-LACTAMS—I

THE APPLICATION OF DIKETENE IN β-LACTAM SYNTHESIS. THE SYNTHESIS AND FUNCTIONAL GROUP MANIPULATIONS OF DIETHYL 3-ACETYL-4-OXOAZETIDINE-2,2-DICARBOXYLATES

GYULA SIMIG,* GÁBOR DOLESCHALL and GYULA HORNYÁK
Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, H-1521 Budapest, Hungary

JÓZSEF FETTER, KÁROLY LEMPERT, JÓZSEF NYITRAI, PÉTER HUSZTHY and TIBOR GIZUR
Department of Organic Chemistry, Technical University Budapest, H-1521 Budapest, Hungary

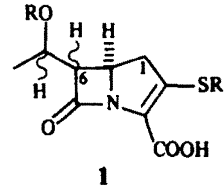
and

MÁRIA KAJTÁR-PEREDY
Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, Hungary

(*Received in UK* 22 *May* 1984)

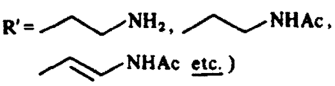
Abstract—Acylation of the N-substituted diethyl aminomalonates **3a**–**3d** with diketene furnished the ring tautomers **6a**–**6d** of the expected acetoacetyl derivatives **5**. By treatment with iodine and sodium ethoxide compounds **6a**–**6d** are smoothly converted into the β-lactam derivatives **2a**–**2d**. Deethoxycarbonylation of the ethylene ketals **7a**–**7d** of the latter furnishes mixtures of the corresponding diastereomeric monoesters **8** and **10**. The ethoxycarbonyl groups of the *trans* esters **8** are more reactive than those of the *cis* isomers **10**. This permits, under appropriate conditions, selective alkaline hydrolysis and $NaBH_4$ reduction of the *trans* esters **8** in the presence of the *cis* esters **10**. Reduction of the *cis* ester **10c** under more forceful conditions furnishes the *trans* hydroxymethyl derivative **11c**.

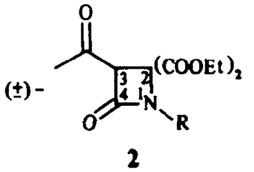
In view of the recent active interest in carbapenem antibiotics, in general, and those members of this family, in particular, which contain a simple or O-substituted 1-hydroxyethyl group attached to position 6 of the carbapenem nucleus, i.e. in compounds **1**,[1] we were interested in the elaboration of an independent method of synthesis for this class of compounds. It appeared to us that compounds of type **2**, containing an acetyl group in position 3 (which could serve as the precursor of the 1-hydroxyethyl group of the target compounds **1**) could be suitable starting compounds for this purpose. For the synthesis of the type **2** compounds a novel method, based on the reaction of diethyl (subst aminomalonates **3a**–**3d** with diketene, and ring closure of the resulting products by treatment with sodium ethoxide and iodine was developed.



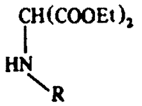
1

(R = H, NaO_3S-,





2



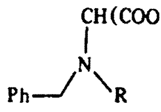
3

a R = Ph
b R = C_6H_4OMe-4
c R = CH_2Ph
d R = $CH_2C_6H_3(OMe)_2$-2,4

The arylaminomalonates **3a**[2] and **3b** were obtained by allowing diethyl bromomalonate to react with aniline and *p*-anisidine, respectively. Although compound **3c** could be similarly obtained by allowing diethyl bromomalonate and benzylamine to react in the presence of triethylamine, the method of partial debenzylation of the diethyl N,N-dibenzylaminomalonate **4a**[3] proved to be a more efficient method. Similarly, selective debenzylation of **4b** furnished **3d**. Compounds **3a**–**3d** were smoothly acylated by diketene in refluxing acetic acid. The resulting products were shown by their ^{1}H-NMR and IR spectra to exist in chloroform soln solely, and in the crystalline state at least partly as the ring isomers **6a**–**6d** of the desired acetoacetyl derivatives **5a**–**5d**.

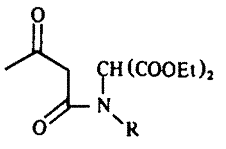
Simultaneous addition of ethanolic sodium ethoxide and ethereal iodine solns to the ethereal solns of compounds **6a**–**6d** furnished the desired β-lactam derivatives **2a**–**2d**.

All attempts at partial deethoxycarbonylation of **2** by Krapcho and Lovey's method[4] resulted in the formation of tarry products. Therefore **2a**–**2d** were converted into their ethylene ketals **7a**–**7d** which were subsequently subjected to partial deethoxycarbonylation to furnish mixtures of the *trans* (**8**) and *cis* monoesters (**10**). Although chromatographic separ-

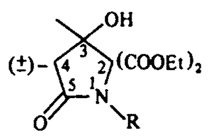


4

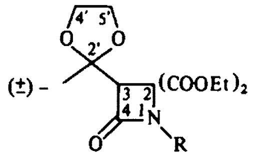
a R = CH_2Ph
b R = $C_6H_3(OMe)_2$ - 2,4



5



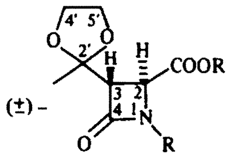
6



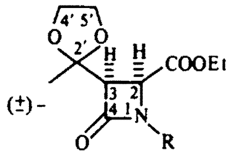
7

a R = Ph
b R = C_6H_4OMe - *p*
c R = CH_2Ph
d R = $CH_2C_6H_3(OMe)_2$ - 2,4

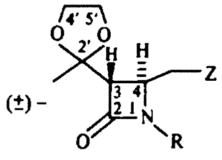
ation of the diastereomers is possible (**d** series in Experimental), their reactivities differ sufficiently so as to permit more or less selective transformations (alkaline hydrolysis and sodium borohydride reduction) of the *trans* monoesters, after which the resulting products may easily be separated from the unchanged *cis* monoesters. In this way the diastereomeric esters **8d** and **10d**, the *cis* ester **10c**, the *trans* acids **9a**, **9b** and **9d**, and the *trans* hydroxymethyl derivatives **11a**, **11c** and **11d** were obtained in pure form. Under more forceful conditions the *cis* ester **10c** was also reduced by sodium borohydride but furnished the *trans* hydroxymethyl derivative **11c**.



8 R' = Et
9 R' = H



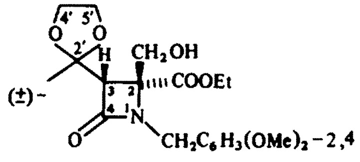
10



11 Z = OH
12 Z = O - SO_2Me
13 Z = I
14 Z = CN

a, R = Ph; **b**, R = C_6H_4OMe - *p*;
c, R = CH_2Ph; **d**, R = $CH_2C_6H_3(OMe)_2$ - 2,4;
e (for **12** and **13**), R = H

In some cases the crude deethoxycarbonylation product of **7d** was subjected to sodium borohydride reduction. Small amounts of **15** were obtained in addition to the *trans*-hydroxymethyl derivative **11d**.



15

The relative configurations of C-2 and C-3 in **15** (which is obviously the partial reduction product of unchanged **7d** present in the crude deethoxycarbonylation mixture) are inferred from the observation that the ethoxycarbonyl groups of **8** which are *trans* to the substituent in position 3 are much more easily reduced than those of **10** which are *cis* relative to the substituent in position 3.

The hydroxymethyl derivatives **11c** and **11d** were converted *via* the methanesulphonates **12c** and **12d** and the iodomethyl derivatives **13c** and **13d** into the cyanomethyl derivatives **14c** and **14d**, respectively. Oxidative removal of the 2,4-dimethoxybenzyl group of the methanesulphonate **12d** furnished the N-*un*substituted lactam **12e** which was converted into the corresponding iodide **13e**.

EXPERIMENTAL

100 MHz ^1H- and 25.2 MHz ^{13}C-NMR spectra were obtained with a Varian XL-100 spectrometer, 60 MHz ^1H-NMR spectra with a Perkin–Elmer R-12 spectrometer and, unless otherwise stated, in $CDCl_3$ solns and using Me_4Si as the internal reference.

In the descriptions of the NMR spectra primed and doubly primed locants, where included, refer to the 1,3-dioxolane ring and the 2,4-dimethoxybenzyl group, respectively; multiplicities listed in the descriptions of the ^{13}C-NMR spectra refer to the off-resonance spectra. IR spectra were obtained with a Spektromom 2000 instrument (Hungarian Optical Works, Budapest).

Benzyl-(2,4-dimethoxybenzyl)ammonium chloride

A mixture of 2,4-dimethoxybenzaldehyde (50 g, 0.30 mol), benzylamine (33.6 g, 0.31 mol), dry toluene (300 ml) and *p*-toluenesulphonic acid (1 g) was refluxed for 8 hr, continuously removing the water formed with the aid of a water-separator. The solvent was distilled off under reduced pressure and the oily residue was dissolved in dioxane (120 ml). $NaBH_4$ (3.2 g) was added with external ice-cooling and continuous stirring. The mixture was stirred for 2 hr and then another portion of $NaBH_4$ (3.2 g) was added as above. The mixture was kept for 3 days at ambient temp and diluted with water. The resulting oil was taken up in ether, the ethereal soln was dried ($MgSO_4$). Part of the solvent was distilled off, and anhyd ethanolic HCl was added with ice-cooling and continuous stirring to obtain 59 g (67%) of the title compound, m.p. 156–157° (from EtOAc). (Found: C, 65.63; H, 7.30; Cl, 11.69; N, 4.72. Calc for $C_{16}H_{20}ClNO_2$ (293.78): C, 65.41; H, 6.86; Cl, 12.07; N, 4.77%.)

Diethyl (subst. amino)malonates **3b–3d**

(a) A mixture of diethyl bromomalonate (23.9 g, 0.1 mol), and *p*-anisidine (24.6 g, 0.2 mol) was stirred for 2 days at ambient temp. The resulting mixture was triturated with ether (100 ml), and the anisidine hydrobromide was filtered off and washed with a small amount of ether. The combined ethereal filtrate and washings were evaporated to dryness, and the residue was triturated with dil AcOH to give 13.2 g (47%) of diethyl (*p*-methoxyanilino)malonate (**3b**), m.p. 64–65° from EtOH. (Found: C, 59.99; H, 6.97; N, 5.25. Calc for $C_{14}H_{19}NO_5$ (281.31); C, 59.77; H, 6.81; N, 4.99%.) ^{1}H-NMR (60 MHz): δ 1.23t + 4.20q (J = 7.2 Hz, 2 × OEt), 3.67s (MeO), 4.1–4.5 br (NH), 4.62s (>C—H), 6.55 + 6.70 (AA′BB′, J = 9 Hz, ArH′s).

(b) Benzylamine (24 g, 0.21 mol) was added by drops to a mixture of diethyl bromomalonate (59.2 g, 0.25 mol) and Et_3N (23.3 g, 0.23 mol) with continuous stirring and efficient external ice-cooling to give a thick paste which was stirred for 1.5 hr and triturated with ether. The crystalline product was filtered off and washed with ether. To the combined filtrate and washings anhyd ethanolic HCl was added by drops to obtain 23 g (37%) of **3c**·HCl, m.p. 146–148° (dec), identical with an authentic sample of the salt, obtained by partial debenzylation of **4a** hydrochloride.[3]

(c) A mixture of benzyl-(2,4-dimethoxybenzyl)amine (175 g, 0.68 mol) (liberated from its hydrochloride which was obtained as described above) and diethyl bromomalonate (89.6 g, 0.38 mol) was stirred at ambient temp until a very thick paste formed and further stirring became impossible. The mixture was triturated with ether and the hydrobromide of the excess starting amine was filtered off and washed with ether (95% recovery). The combined filtrate and washings were evaporated to dryness, and the oily residue was triturated with EtOH to obtain 114.5 g (81%) of **4b**, m.p. 62–63° from EtOH. (Found: C, 66.58; H, 7.09; N, 3.43. Calc for $C_{23}H_{29}NO_6$ (415.47): C, 66.49; H, 7.04; N, 3.37%.) IR (KBr): 1750, 1725 cm^{-1}.

(d) A mixture of 2,4-dimethoxybenzaldehyde (109.7 g, 0.66 mol), benzylamine (70.5 g, 0.66 mol) and MeOH (660 ml) was stirred for 20 min at ambient temp. $NaBH_4$ (13.2 g, 0.33 mol) was added in small portions to the resulting clear soln with continuous stirring and external ice-cooling. When the Schiff's base produced in the first step was completely reduced (TLC; Kieselgel G; benzene–acetone, 9:1), the mixture was evaporated to dryness at reduced pressure. The residue was taken up in water (200 ml) and ether (500 ml), and the aqueous phase was extracted with ether (2 × 200 ml). The combined ethereal solns were dried ($MgSO_4$), diethyl bromomalonate (156 g, 0.66 mol) and Et_3N (67 g, 0.66 mol) were added, and the mixture was stirred at ambient temp for 2–3 days. The resulting $Et_3N \cdot HBr$ was filtered off and washed with ether. The combined ethereal filtrate and washings were worked up as described in (c) to obtain 197 g (72%) of recrystallized **4b**, m.p. 62–63° from EtOH.

(e) Catalytic hydrogenation of **4b** (61.7 g, 0.15 mol) in EtOH (500 ml) in the presence of an 8% Pd/C catalyst (20 g) at room temp furnished, after conventional work-up 47.1 g (97%) of **3d** as an oil which was used without further purification in the reaction with diketene. IR (film): 3250, 1730, 1720 cm^{-1}. HCl salt, m.p. 122–124° from EtOAc. (Found: C, 52.51; H, 6.77; Cl, 10.30; N, 4.09. Calc for $C_{16}H_{24}ClNO_6$ (361.82): C, 53.11; H, 6.69; Cl, 9.80; N, 3.87%.)

N-*Substituted diethyl* 3-*hydroxy*-3-*methyl*-5-*oxopyrrolidine*-2,2-*dicarboxylates* (6)

(a) A mixture of **3a**[2] (38 g, 0.15 mol), freshly distilled diketene (15.3 g, 0.18 mol) and AcOH (38 ml) was refluxed for 30 min and evaporated to dryness at reduced pressure. The oily residue was triturated with ether to give 36.5 g (72%) of **6a**, m.p. 98–99° from EtOAc–light petroleum. (Found: C, 60.83; H, 6.15; N, 4.43. Calc for $C_{17}H_{21}NO_6$ (335.35): C, 60.88; H, 6.31; N, 4.18%.) IR (KBr): 3350, 1760, 1750, 1700 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.02t + 1.30t (J = 7.2 Hz, both) + 4.00–4.45 m (2 × OEt), 1.60s ($\underline{C}$—Me), 2.80s (CH_2CO), 3.6 br (OH), 7.20s (Ph).

(b) Compound **6b**, m.p. 136–137° from EtOAc, was similarly obtained in 72% yield from **3b** (11.2 g, 40 mmol) and diketene (4.0 g, 48 mmol) in AcOH (15 ml). (Found: 58.98; H, 6.90; N, 4.04. Calc for $C_{18}H_{23}NO_7$ (365.38): C, 59.17; H, 6.39; N, 3.83%.) IR (KBr): 3600–3000, 1760, 1740, 1685 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.07t + 1.28t + 4.10q + 4.27q (J = 7.2 Hz; 2 × OEt), 1.58s (C—Me), 2.76s (CH_2CO), 3.64 br (OH), 3.76s (MeO), 6.70 + 7.00 (AA′BB′, J = 9 Hz, 4 × ArH).

(c) Compound **6c**, m.p. 85–86° from EtOAc–light petroleum, was similarly obtained in 63% yield from **3c** (33.3 g, 0.125 mol) and diketene (12.8 g, 0.15 mol) in AcOH (40 ml). (Found: C, 61.74; H, 6.78; N, 4.30. Calc for $C_{18}H_{23}NO_6$ (349.37): C, 61.88; H, 6.63; N, 4.01%.) IR (KBr): 3400 br, 1755, 1725, 1685 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.12t (J = 7.2 Hz) + 3.65–4.25m (5H; 2 × OEt + OH), 1.51s (C—Me), 2.68s (CH_2CO), 4.70 + 4.82 (AB, J = 14.5 Hz) + 7.20s (Ph).

(d) Compound **6d**, m.p. 106–107° from EtOAc–light petroleum was similarly obtained in 60% yield from **3d** (39.6 g, 0.12 mol) and diketene (12.3 g, 0.15 mol) in AcOH (80 ml). (Found: C, 58.79; H, 6.33; N, 3.34. Calc for $C_{20}H_{27}NO_8$ (409.43): C, 58.67; H, 6.65; N, 3.42%.) IR (KBr): 3400, 1740sh, 1730, 1710 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.10 + 1.17 (2 × t, J = 7.2 Hz, both) + 3.80–4.15m (2 × OEt), 1.52s (C—Me), 2.65 br s (4-CH_2) 3.75s (2 × OMe), 4.7 br s (N—CH_2—Ar), 6.25–6.45m (3″-H + 5″-H), 7.1 m (6″-H).

N-*Substituted diethyl* 3-*acetyl*-4-*oxoazetidine*-2,2-*dicarboxylates* **2**

(a) An anhyd ethanolic (250 ml) soln of metallic Na (10.2 g, 447 mmol) was successively treated with **6a** (50 g, 149 mmol) and an anhyd ethereal (200 ml) soln of I_2 (37.9 g, 149 mmol). When **6a** was completely consumed (TLC), AcOH (8.5 ml), water (200 ml) and ether (100 ml) were added. The aqueous phase was extracted with ether (100 ml). Conventional work-up of the combined ethereal solns furnished an oily product which was crystallized from i-PrOH (50 ml) to obtain 31 g (62%) of **2a**, m.p. 55–56°. (Found: C, 61.38; H. 5.89; N, 4.24. Calc for $C_{17}H_{19}NO_6$ (333.33) C, 61.25; H, 5.75; N, 4.20%.) IR (KBr): 1770, 1740, 1720 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.12t + 4.25q (J = 7 Hz; 2 × OEt), 2.30s (Ac), 4.75s (3-H), 7.0–7.6 m (Ph).

(b) To an anhyd ethereal (50 ml) suspension of **6b** (9.1 g, 25 mmol) solns of metallic Na (1.72 g, 75 mmol) in anhyd EtOH (30 ml), and of I (6.35 g, 25 mmol) in anhyd ether (50 ml) were rapidly and simultaneously added with continuous stirring and external ice-cooling. The mixture was poured into sat NaCl aq (100 ml). $NaHSO_3$ (2 g) and AcOH (2 ml) were added.

Conventional work-up by extraction with ether furnished an oily product which crystallized when triturated with i-PrOH to yield 6.2 g (68%) of **2b**, m.p. 70–71° from EtOH. (Found: C, 59.04; H, 5.84; N, 4.08. Calc for $C_{18}H_{21}NO_7$ (363.38): C, 59.50; H, 5.82; N, 3.85%.) IR (KBr) 1760, 1735, 1720 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.20t + 1.22t + 4.17q + 4.19q (J = 7.2 Hz, 2 × OEt), 2.33s (Ac), 3.70s (MeO), 4.70s (3-H), 6.70 + 7.30 (AA′BB′, J = 9 Hz; 4 × ArH).

(c) Starting with **6c** (10 g, 28.6 mmol), metallic Na (1.97 g, 85.8 mmol) and I (7.26 g, 28.6 mmol), **2c** was obtained as an oil which crystallized from i-PrOH–light petroleum to give 8 g (80%) of **2c**, m.p. 55–56°. (Found: C, 62.27; H, 5.70; N, 4.08. Calc for $C_{18}H_{21}NO_6$ (347.36): C, 62.24; H, 6.09; N, 4.03%.) IR (KBr): 1745, 1720, 1705 cm^{-1}. ^{1}H-NMR (100 MHz): δ 1.09t + 1.23t (J = 7 Hz) + 3.6–4.4 m (2 × OEt), 2.32s (Ac), 4.48 + 4.80 (AB, J = 15.5 Hz; N—CH$_2$—Ph) 4.80s (3-H), 7.28s (Ph). ^{13}C-NMR: δ 13.61q + 13.75q + 62.47t + 62.68t + 166.18s + 166.31s (2 × COOEt), 30.08q + 197.42s (Ac), 46.13t (N—CH$_2$—Ar), 65.74s (C-2), 68.68d (C-3), 127.74d + 128.37d + 128.54d + 135.54s (aromatic C atoms), 162.57s (C-4).

(d) Starting with **6d** (20.5 g, 50 mmol), metallic Na (3.45 g, 150 mmol) and I (12.7 g, 50 mmol), **2d** was obtained as an oil which was crystallized from i-PrOH (30 ml) to give 10.9 g (54%) of **2d**, m.p. 84–85°. (Found: C, 58.99; H, 6.04; N, 3.57. Calc for $C_{20}H_{25}NO_8$ (407.41): C, 58.96; H, 6.19; N, 3.44%.) IR (KBr): 1780, 1740, 1710 cm^{-1}. ^{1}H-NMR (100 MHz): δ 1.12t + 1.21t (J = 7 Hz) + 3.8–4.2 m (2 × OEt), 2.31s (Ac), 3.76s (2 × OMe), 4.53 + 4.63 (AB, J = 16 Hz; N—CH$_2$—Ar), 4.69s (3-H), 6.3–6.4 m (3″-H + 5″-H), 7.07d (J = 8 Hz; 6″-H). ^{13}C-NMR: δ 13.7 + 62.2 + 62.6 + 166.2 (2 × COOEt), 30.7 + 197.9 (Ac), 40.7 (N—CH$_2$—Ar), 55.3 (2 × OMe), 65.2 (C-2), 68.4 (C-3), 98.1 (C-3″), 103.7 (C-5″), 115.2 (C-1″), 130.7 (C-6″), 158.4 + 160.7 (C-2″ + C-4″), 162.1 (C-4).

Preparation of the ethylene ketals **7a**–**7d**

(a) BF_3-diethyl etherate (36.5 g, 255 mmol) was added dropwise with continuous stirring and external ice-cooling to a mixture of **2a** (28.5 g, 85 mmol), dry dioxane (90 ml) and dry 1,2-ethandiol (21 g, 340 mmol). The mixture was stirred for 2 hr at ambient temp, neutralized with sat Na_2CO_3 aq, diluted with water (100 ml), and worked up by extraction with ether to obtain an oily product which crystallized when triturated with ether to furnish 28.5 g (90%) of **7a**, m.p. 59–61° from gasoline. (Found: C, 60.74; H, 6.21; N, 3.79. Calc for $C_{19}H_{23}NO_7$ (377.38): C, 60.47; H, 6.14; N, 3.71%.) IR (KBr): 1770, 1740 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.18t + 1.24t (J = 7.2 Hz) + 4.1–4.4 m (5H; 2 × COOEt + 3-H), 1.51s (2′-Me), 3.92 m (4′-H$_2$ + 5′-H$_2$), 7.2 m (Ph).

(b) Similarly obtained was, starting with **2b** (6.0 g, 17 mmol) and **7b** (6.0 g, 89%), m.p. 82–83° from EtOH. (Found: C, 58.70; H, 5.68; N, 3.63. Calc for $C_{20}H_{25}NO_8$ (407.43): C, 58.96; H, 6.18; N, 3.44%.) IR (KBr): 1740 cm^{-1}, broad. ^{1}H-NMR (60 MHz): δ 1.17t + 1.25t (J = 7.2 Hz) + 4.0–4.2 m (5H; 2 × COOEt + 3-H), 1.50s (2′-Me), 3.7s (MeO), 3.9 m (4′-H$_2$ + 5′-H$_2$), 6.67 + 7.34 (AA′BB′, J = 9 Hz; 4 × ArH).

(c) **7c** and **7d** were obtained similarly but no attempts were made at their isolation in pure form. Instead, the crude products were used for the subsequent conversions. The preparation of the crude **7c** and **7d** is described below in conjunction with the preparation of the *trans* **11c** and of the diastereomeric monoesters **8d** and **10d**, respectively.

trans *and* cis *Ethyl 1-(2,4-dimethoxybenzyl)-3-(2-methyl-1,3-dioxolan-2-yl)-4-oxoazetidinecarboxylates* **8d** *and* **10d**

(a) BF_3-diethyl etherate (206 g, 1.45 mol) was added dropwise with vigorous stirring and external ice-cooling to a mixture of **2d** (179 g, 484 mmol), 1,2-ethanediol (120 g, 1.94 mol) and anhyd dioxane (500 ml). The mixture was kept for 1 day with occasional stirring at ambient temp. 10% of Na_2CO_3 aq (154 g, 1.45 mol) was slowly added with continuous stirring and ice cooling, and the mixture was stirred for 15 min. Ether and water (1 l of each) were added, the layers were separated, and the aqueous phase was extracted with ether (500 ml). The combined ethereal solns furnished crude **7d** in quantitative yield as an oil.

(b) A mixture of the above crude **7d**, NaCl (33.9 g, 0.58 mol), water (17 ml) and DMSO (220 ml) was stirred at 180° until **7d** was completely consumed (TLC; Kieselgel G; benzene–EtOAc, 6:4; about 15 hr), and poured into sat NaCl aq (1100 ml). Extraction with ether (1 × 1000 + 2 × 500 ml), treatment with charcoal, drying ($MgSO_4$), concentration of the ethereal soln to about 200 ml and chilling to 0° of the concentrate furnished 59 g (35%, overall) of *trans* **8d**, m.p. 91° from heptane. (Found: C, 60.37; H, 6.74; N, 3.83. Calc for $C_{19}H_{25}NO_7$: C, 60.14; H, 6.64; N, 3.69%.) ^{1}H-NMR (100 MHz): δ 1.25t + 4.15q (J = 7.0 Hz; COOEt): 1.40s (2′-Me), 3.40d (J = 2.4 Hz; 3-H), 3.78 + 3.80 (2 × s, 2 × OMe), 3.80d (J = 2.4 Hz; 2-H), 3.9–4.05m (4′-H$_2$ + 5′-H$_2$), 4.22 + 4.62 (AB, J = 14.8 Hz; N—CH$_2$—Ar), 6.35–6.5m (3″-H + 5″-H), 7.15d (J = 9 Hz; 6″-H).

(c) In another experiment the ethereal soln, obtained as described in (b), was evaporated to dryness to give an oily mixture of the title compounds (75% yield). 11.7 g of this mixture was separated into its components by column chromatography (Kieselgel 60, 0.063–0.200 mm; benzene → benzene–acetone, 9:1). The first fraction consisted of the *trans* **8d** (6.4 g), identical (^{1}H-NMR) with the product obtained as described in (b), the second of a mixture of the two diastereomers (3 g), and the last of the oily *cis* **10d** (0.85 g). **10d**, ^{1}H-NMR (100 MHz): δ 1.31t + 4.25q (J = 7.1 Hz; COOEt), 1.43s (2′-Me), 3.64d (J = 6 Hz; 3-H), 3.76 + 3.79 (2 × s, 2 × OMe), 3.85–4.1m (4′-H$_2$ + 5′-H$_2$), 3.92d (J = 6.0 Hz; 2-H), 4.22 + 4.70 (AB, J = 14.4 Hz; N—CH$_2$—Ar), 6.35–6.5m (3″-H + 5″-H), 7.11d (J = 9 Hz; 6″-H).

1-*Substituted* trans-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidine-2-carboxylic acids* **9**

(a) A mixture of **7a** (28.5 g, 75 mmol), DMSO (44 ml), NaCl (5.6 g) and water (3 ml) was stirred at 175° until the starting compound was completely consumed (TLC; Kieselgel G; benzene–EtOAc, 6:4). The resulting soln was poured into sat NaCl aq (200 ml). After conventional work-up by extraction with ether, a mixture of the diastereomeric esters **8a** and **10a** (16.4 g) was obtained as an oil.

(b) An aqueous (30 ml) soln of NaOH (2.15 g, 54 mmol) was added with continuous stirring and external ice-cooling to the ethanolic (100 ml) soln of the above crude ester mixture. The mixture was stirred for 30 min, diluted with water (150 ml), and extracted with ether (3 × 20 ml). The aqueous phase was acidified (pH 1) with conc HCl. Conventional work-up by CH_2Cl_2 extraction furnished **9a** as an oil which was crystallized from benzene to obtain 12 g (56%, overall) of **9a**, m.p. 165°. (Found: C, 60.64; H, 5.72; N, 4.99. Calc for $C_{14}H_{15}NO_5$ (277.27): C, 60.64; H, 5.45; N, 5.05%.) IR (KBr): 3500–2700, 1770, 1730 cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.50s (2′-Me), 3.69d (J = 3 Hz; 3-H), 4.0m (4′-H$_2$ + 5′-H$_2$), 4.42d (J = 3 Hz; 2-H), 7.3m (Ph), 7.55 (br s; COOH).

(c) Starting with **7b** (11 g, 25 mmol), a mixture of **8b** and **10b** (6.0 g) was similarly obtained.

(d) Hydrolysis of this ester mixture with aqueous ethanolic NaOH and similar work-up as described in (b) furnished 4 g (54%, overall) of **9b**, m.p. 131–132° from benzene. (Found: C, 58.40; H, 5.80; N, 4.66. Calc for $C_{15}H_{17}NO_6$ (307.32): C, 58.63; H, 5.57; N, 4.56%.) IR (KBr): 3400–2700, 1750 cm^{-1} (br). ^{1}H-NMR (100 MHz): δ 1.50s (2′-Me), 3.67d (J = 2.7 Hz; 3-H), 3.76s (MeO), 3.8–4.2m (4′-H$_2$ + 5′-H$_2$), 4.39d (J = 2.7 Hz; 2-H), 6.87 + 7.29 (AA′BB′, J = 9 Hz; 4 × ArH), 8.75 br s (COOH).

(e) An aqueous (60 ml) soln of NaOH (5.2 g, 130 mmol) was added with continuous stirring and external ice cooling to a suspension of the *trans* **8d** (41.2 g, 109 mmol) in EtOH (50 ml). Stirring was continued until a clear soln was formed (about 20 min). Water (100 ml) was added and the soln was extracted with ether (100 ml). The aqueous phase was acidified (pH 1) with conc HCl and rapidly extracted with CH_2Cl_2 (1 × 100 + 2 × 50 ml). Conventional work-up of the combined CH_2Cl_2 solns furnished an oil which was crystallized from toluene–light petroleum to obtain 35 g (92%) of the *trans* **9d**, m.p. 117–118° from toluene. (Found: C, 58.17; H, 6.30; N, 4.24. Calc for

$C_{17}H_{21}NO_7$ (351.35): C, 58.11; H, 6.03; N, 3.99%.) IR (KBr): 3500–2500, 1760, 1720 cm^{-1}. ^{1}H-NMR (100 MHz): δ 1.41s (2′-Me), 3.50d (J = 2.4 Hz; 3-H), 3.78 + 3.80 (2 × s; 2 × OMe), 3.85d (J = 2.4 Hz, 2-H), 3.9–4.1m (4′-H_2 + 5′-H_2), 4.22 + 4.65 (AB, J = 15 Hz; N—CH_2—Ar), 6.35–6.5m (3″-H + 5″-H), 7.17d (J = 9 Hz; 6″-H), 7.58 br s (COOH).

(f) An aqueous (5 ml) soln of NaOH (0.37 g, 9.3 mmol) was added with continuous stirring and external ice cooling to the ethanolic (20 ml) soln of a mixture (3.0 g, 7.9 mmol) of **8d** and **10d** (obtained as described above). The mixture was stirred for 30 min and poured into water (30 ml). Extraction of the alkaline soln furnished 0.57 g (19%) of unchanged *cis* **10d**, identical with the product described in (c).

Acidification (pH 1) of the aqueous soln with conc HCl, and extraction with CH_2Cl_2 furnished 1.35 g (49%) of the *trans* **9d**, m.p. 117–118° from toluene, identical with the product described in (e).

trans-4-*Hydroxymethyl-3-(2-methyl-1,3-dioxolan-2-yl)-azetidin-2-ones* **11**

(a) Partial deethoxycarbonylation of **7a** (36.5 g, 97 mmol) as described above furnished a mixture (24.9 g, 82 mmol) of *trans* and *cis* **8a** and **10a**. $NaBH_4$ (12.5 g, 250 mmol) was added to the methanolic (220 ml) soln of this mixture with continuous stirring and external ice-cooling. Stirring was continued for 1 hr at ambient temp. The mixture was poured into water (750 ml) and extracted with CH_2Cl_2 (2 × 300 + 1 × 150 ml) to obtain an oily product (13.9 g). This was dissolved in i-PrOH (35 ml) and kept in a freezer to give 8.65 g (34%, overall) of **11a**, m.p. 104–105°. (Found: C, 64.17; H, 6.80; N, 5.22. Calc for $C_{14}H_{17}NO_4$ (263.29): C, 63.86; H, 6.51; N, 5.32%.) ^{1}H-NMR (100 MHz): δ 1.47s (2′-Me), 2.00t (J ≈ 5.5 Hz; OH), 3.48d (J = 2.4 Hz; 3-H), 3.8–4.25m (4-H + CH_2OH + 4′-H_2 + 5′-H_2), 7.0–7.55m (Ph).

(b) BF_3-diethyl etherate (30.4 g, 213 mmol) was added dropwise to a vigorously stirred mixture of **2c** (24.8 g, 71 mmol), anhyd 1,2-ethanediol (17.7 g, 284 mmol) and dry dioxane (75 ml) with external ice-cooling. The mixture was kept, with occasional stirring, for 1 day at ambient temp. Subsequently a 10% Na_2CO_3 aq (60.9 g, 123 mmol) was added slowly by drops with continuous stirring and external ice-cooling. The resulting mixture was stirred for 15 min, diluted with water (150 ml) and extracted with ether (1 × 150 + 2 × 50 ml) to obtain crude **7c** in essentially quantitative yield as an oil.

A mixture of crude **7c**, NaCl (5 g), DMSO (30 ml) and water (2.6 ml) was stirred in an oil bath, kept at 180°, until the starting diester was completely consumed (TLC; Kieselgel G; benzene–aceteone, 8 : 2; about 15 hr). The mixture was poured into a sat NaCl aq (100 ml) and extracted with ether (3 × 50 ml) to obtain a mixture of the diastereomeric esters **8c** and **10c** as an oil (17 g).

$NaBH_4$ (3.8 g, 100 mmol) was added slowly to the dry methanolic (80 ml) soln of the above ester mixture with stirring and external ice-cooling. The mixture was stirred for 1 hr at ambient temp, poured into sat NaCl aq (200 ml) and extracted with ether (1 × 100 + 2 × 50 ml) to obtain an oil which crystallized when triturated with ether, to give 7.4 g (37%) of *trans* **11c**, m.p. 87–88° from EtOAc–light petroleum. (Found: C, 64.93; H, 6.62; N, 5.12. Calc for $C_{15}H_{19}NO_4$ (277.31); C, 64.97; H, 6.91; N, 5.05%.) IR (KBr): 3350, 1740 cm^{-1}. ^{1}H-NMR (100 MHz): δ 1.40s (2′-Me), 2.0 br s (OH), 3.31d (J = 2.5 Hz; 3-H), 3.45–3.8m (4-H + $C\underline{H}_2OH$), 3.9–4.1m (4′-H_2 + 5′-CH_2), 4.29 + 4.60 (AB, J = 15 Hz; N—$C\underline{H}_2$—Ph), 7.33s (Ph).

The ethereal mother liquor was evaporated to dryness, and the oily residue was worked-up by column chromatography (Kieselgel 60, 0.063–0.200 mm; benzene → benzene–acetone, 9 : 1) to give 2.95 g (13%) of the oily *cis* ester **10c**. ^{1}H-NMR (100 MHz): δ 1.29t + 4.24q (J = 7.2 Hz; COOEt), 1.45s (2′-Me), 3.74d (J = 6 Hz; 3-H), 3.85–4.05m (4′-H_2 + 5′-H_2), 3.97d (J = 6 Hz, 2-H), 4.22 + 4.90 (AB, J = 14.8 Hz, N—$C\underline{H}_2$—Ph), 7.15–7.4m (Ph).

(c) A mixture of the above *cis* ester **10c** (2.6 g, 8.2 mmol), MeOH (20 ml) and $NaBH_4$ (0.62 g, 16.5 mmol) was refluxed for 1 hr; another portion of $NaBH_4$ (0.62 g) was added, and refluxing was continued for 1 hr. The mixture was poured into sat NaCl aq (100 ml). Extraction with ether (3 × 40 ml) furnished 0.8 g (35%) of the *trans* **11c**, identical with the product obtained as described in (b).

(d) $NaBH_4$ (4.0 g, 105 mmol) was added to the methanolic (50 ml) soln of the *trans* ester **8d** (10 g, 26.4 mmol) with stirring and external ice-cooling. The mixture was stirred at ambient temp until the ester was completely reduced (TLC; Kieselgel 60, benzene–acetone, 8 : 2). The mixture was poured into water (200 ml). Extraction with EtOAc (3 × 50 ml) furnished 6.1 g (69%) of the *trans* **11d**, m.p. 106–107° from i-PrOH. (Found: C, 60.27; H, 6.57; N, 4.22. Calc for $C_{17}H_{23}NO_6$ (337.36): C, 60.52; H, 6.87; N, 4.15%.) IR (KBr): 3350, 1725 cm^{-1}. ^{1}H-NMR (100 MHz): δ 1.39s (2′-Me), 1.79 br s (OH), 3.28d (J = 2.3 Hz; 3-H), 3.4–3.7m (4-H + $C\underline{H}_2OH$), 3.80 + 3.82 (2 × s; 2 × MeO), 3.9–4.1m (4′-H_2 + 5′-H_2), 4.35 + 4.40 (AB, J = 15 Hz; N—CH_2—Ar), 6.4–6.55m (3″-H + 5″-H), 7.24d (J = 9 Hz, 6″-H).

^{13}C-NMR: δ 23.37q (2′-Me), 39.43t (N—CH_2), 55.41 + 55.47 (2 × q; 2 × MeO), 55.58d (C-4), 59.24d (C-3), 61.42t (CH_2OH), 65.07 + 65.22 (2 × t; C-4′ + C-5′), 98.71d (C-3″), 104.74d (C-5″), 107.67s (C-2′), 116.58s (C-1″), 131.01d (C-6″), 158.41s (C-4″), 160.87s (C-2″), 166.58s (C-2).

(e) A crude mixture of the *trans* and *cis* monoesters **8d** and **10d** (14.6 g, 38.5 mmol) [obtained by partial deethoxycarbonylation of the diester **7d** (21.9, 48 mmol) as described] was dissolved in MeOH (30 ml). $NaBH_4$ (2.93 g, 77 mmol) was added with continuous stirring and external ice-cooling. The mixture was stirred for 1 hr at 0°, poured into water (100 ml) and extracted with EtOAc (2 × 50 ml) to obtain an oily product which was taken up in ether (30 ml). When the soln was kept in a freezer, 6.7 g (41%) of crystalline **11d**, m.p. 99–100°, but otherwise identical with the product obtained as described in (d), were obtained.

(f) Experiment (e) was repeated with the crude deethoxycarbonylation mixture (30.1 g) obtained from **7d** (40.2 g), to obtain 13.4 g (45%, overall) of the *trans* **11d**. The dry residue of the ethereal mother liquor was taken up in 2-propanol (20 ml) and kept in a freezer to obtain 1.77 g (5%, overall) of **15**, m.p.: 135–136° from 2-propanol. (Found: C, 58.95; H, 6.54; N, 3.69. Calc for $C_{20}H_{27}NO_8$ (409.43): C, 58.66; H, 6.65; N. 3.42%.) IR (KBr): 3400, 1730/1720 (d) cm^{-1}. ^{1}H-NMR (100 MHz): δ 1.34t + 4.28q (J = 7.1 Hz; COOEt), 1.43s (2′-Me), 2.08dd (J = 8.4 and 6.2 Hz; exchangeable; OH), 3.51 dd (J = 12.3 and 6.2 Hz) + 3.73 dd (J = 12.3 and 8.4 Hz; both collapsing to doublets, J = 12.3, on addition of D_2O; $C\underline{H}_2OH$), 3.68s (3-H), 3.81 + 3.83 (2 × OMe), 3.9–4.15m (4′-H_2 + 5′-H_2), 4.30 + 4.75 (AB spectrum, J = 14.5 Hz; N—$C\underline{H}_2$—Ar), 6.4–6.55m (3″-H + 5″-H), 7.27d (J = 9 Hz; 6″-H).

trans-4-*Methylsulphonyloxymethyl-3-(2-methyl-1,3-dioxolan-2-yl)azetidin-2-ones* **12c–12e**

(a) Methanesulphonyl chloride (2.5 ml, 32 mmol) was added dropwise to a soln of the *trans* **11c** (7.4 g, 27 mmol) in dry pyridine (20 ml) with continuous stirring and external ice-cooling within 10 min. The mixture was stirred for 1 hr at 0° and diluted with water (100 ml) to obtain 7.7 g (81%) of **12c**, m.p. 87–88° from EtOAc–light petroleum, as a crystalline ppt. (Found: C, 53.86; H, 6.02; N, 3.99. Calc for $C_{16}H_{21}NO_6S$ (355.40): C, 54.07; H, 5.96; N, 3.94%.) IR (KBr): 1740, 1355, 1165 cm^{-1}. ^{1}H-NMR (100 MHz): δ 1.43s (2′-Me), 2.90s (mesyl), 3.31d (J = 2.5 Hz; 3-H), 3.68ddd (J = 5.5, 3.6, 2.5 Hz; 4-H), 3.9–4.05m (4′-H_2 + 5′-H_2), 4.16 + 4.33 (ABX, J_{gem} = 11 Hz, J_{vic} = 5.5 and 3.6 Hz, respectively; CH—$C\underline{H}_2O$), 4.22 + 4.70 (AB, J = 15.2 Hz, N—$C\underline{H}_2$—Ph), 7.33s (Ph).

(b) Methanesulphonyl chloride (0.5 g, 3.9 mmol) was added dropwise to a soln of the *trans* **11d** (1.0 g, 3 mmol) in dry pyridine (3 ml) with continuous stirring and external cooling. The mixture was stirred for 15 min and poured into water (15 ml). Extraction with $CHCl_3$ (3 × 6 ml) furnished an oil which crystallized when triturated with EtOH, to give 0.76 g (62%) of **12d**, m.p. 83–84° from EtOH. (Found: C, 52.33; H, 6.35; N, 3.06. Calc for $C_{18}H_{25}NO_8S$ (415.45): C, 52.04; H, 6.06; N, 3.37%.) IR (KBr): 1740, 1340, 1160 cm^{-1}. ^1H-NMR (100 MHz): δ 1.39s (2′-Me), 2.94s (mesyl), 3.28d (J = 2.4 Hz), 3.60td (J = 4.2, 4.2, 2.4 Hz; 4-H), 3.80 + 3.82 (2 × s; 2 × MeO), 3.95m ($4'-H_2 + 5'-H_2$), 4.2–4.35m (CH_2O), 4.22 + 4.54 (AB, J = 15 Hz; N—C$\underline{H}_2$—Ar), 6.4–6.55m (3″-H + 5″-H), 7.23d (J = 9 Hz; 6″-H).

^{13}C-NMR: δ 23.26 (2′-Me), 37.50 (mesyl), 39.45 (N—CH_2), 52.12 (C-4), 55.43 (2 × MeO), 60.05 (C-3), 65.06 + 65.26 (C-4′ + C-5′), 67.54 (CH_2O), 98.61 (C-3″), 104.72 (C-5″), 107.33 (C-2′), 116.08 (C-1″), 131.10 (C-6″), 158.58 (C-4″), 161.02 (C-2″), 165.32 (C-2).

(c) A mixture of **12d** (2.0 g, 4.8 mmol), $K_2S_2O_8$ (2.6 g, 9.6 mmol), $Na_2HPO_4 \cdot 2\,H_2O$ (3.4 g, 19.2 mmol), acetonitrile (25 ml) and water (15 ml) was refluxed for 7 hr. The mixture remained heterogeneous throughout. After separation of the two phases, the aqueous phase was extracted with ether (3 × 30 ml). The combined organic solns were evaporated to dryness, and the residue was taken up in $CHCl_3$ and water (30 ml each). The oily residue of the $CHCl_3$ soln crystallized, when triturated with ether (20 ml), to give 0.6 g (47%) of **12e**, m.p. 110°. IR (KBr): 3200, 1750, 1730, 1345, 1165 cm^{-1}. ^1H-NMR (100 MHz): δ 1.44s (2′-Me), 3.06s (mesyl), 3.27d (J = 2.5 Hz; 3-H), 3.88ddd (J = 6.5, 3.9, 2.5 Hz; 4-H), 4.0m ($4'-H_2 + 5'-H_2$), 4.27 + 4.42 (**ABX**, J_{gem} = 11 Hz, J_{vic} = 6.5 and 3.9 Hz, respectively; CH—C$\underline{H}_2$—O), 6.22 br s (NH).

^{13}C-NMR: ∂ 23.26 (2′-Me), 37.67 (mesyl), 48.98 (C-4), 61.22 (C-3), 65.12 + 65.36 (C-4′ + C-5′), 70.06 (CH_2O), 106.99 (C-2′), 165.94 (C-2).

trans - 4 - *Iodomethyl* - 3 - (2 - *methyl* - 1,3 - *dioxolan* - 2 - *yl*) - *azetidin -2-ones* **13c–13e**

(a) A mixture of **12c** (7.5 g, 21 mmol), NaI (12.6 g, 84 mmol) and dry acetone (50 ml) was refluxed for 4 hr with continuous stirring, and evaporated to dryness. Water (50 ml) was added to the residue. Extraction with CH_2Cl_2 (3 × 30 ml) furnished 7.7 g (94%) of **13c** as an oil. IR (KBr): 1750 cm^{-1}. ^1H-NMR (100 MHz): δ 1.45s (2′-Me), 3.20d (J = 2.2 Hz; 3-H), 3.19 + 3.29 (**ABX**, J_{gem} = 10.5, J_{vic} = 5.8 and 4.0 Hz, respectively; CHC$\underline{H}_2$I), 3.45ddd (J = 5.8, 4.0, 2.2 Hz; 4-H), 3.95–4.1m ($4'-H_2 + 5'-H_2$), 4.14 + 4.77 (AB, J_{gem} = 15.5 Hz; N—C$\underline{H}_2$—Ph), 7.33s (Ph).

(b) A mixture of **12d** (5 g, 12 mmol), NaI (7.5 g, 50 mmol) and dry acetone (20 ml) was refluxed for 4 hr with continuous stirring, and evaporated to dryness. The residue was triturated with water, and the insoluble crystalline product was recrystallized from EtOH to obtain 4.5 g (84%) of **13d**, m.p. 84–85°. (Found: I, 28.33; N, 3.27. Calc for $C_{17}H_{22}INO_5$ (447.27): I, 28.37; N, 3.13%.) IR (KBr): 1745 cm^{-1}. ^1H-NMR (100 MHz, acetone-d_6): δ 1.36s (2′-Me), 3.12d (J = 2 Hz; 3-H), 3.30–3.65m ($CHCH_2I$), 3.81 + 3.87 (2 × s; 2 × OMe), 3.9–4.0m ($4'-H_2 + 5'-H_2$), 4.13 + 4.45 (AB, J = 15 Hz; N—C$\underline{H}_2$—Ar), 6.45–6.6m (3″-H + 5″-H), 7.24d (J = 8 Hz; 6″-H).

^{13}C-NMR: δ 6.53t (CH_2I), 23.71q (2′-Me), 38.97t (N—CH_2), 53.56d (C-4), 55.37q (2 × OMe), 64.18d (C-3), 65.06 + 65.17 (2 × t; C-4′ + C-5′), 98.45d (C-3″), 104.46d (C-5″), 107.33s (C-2′), 115.91s (C-1″), 130.89d (C-6″), 158.43s (C-4″), 160.84s (C-2″), 165.05s (C-2).

(c) A mixture of **12e** (1.0 g, 3.8 mmol), NaI (2.0 g, 13.5 mmol) and dry acetone (10 ml) was refluxed for 4 hr, and evaporated to dryness. Water (30 ml) was added to the residue. Extraction with $CHCl_3$ (3 × 30 ml) furnished an oily product which was purified by TLC (Kieselgel $PF_{254+366}$; benzene–acetone, 7:3) to obtain 0.67 g (60%) of **13e**, m.p. 85–86° from EtOAc–light petroleum. (Found: I, 42.45; N, 5.00. Calc for $C_8H_{12}INO_3$ (297.10): I, 42.72; N, 4.71%.) ^1H-NMR (100 MHz): δ 1.45s (2′-Me), 3.17d (J = 2.4 Hz; 3-H), 3.30 + 3.42 (**ABX**, J_{gem} = 10.5 Hz, J_{vic} = 8 and 4.6 Hz, respectively; CHC$\underline{H}_2$I), 3.81 ddd (J = 8.0, 4.6 and 2.4 Hz; 4-H), 3.95–4.15m ($4'-H_2 + 5'-H_2$), 6.2 br s (NH).

trans - 4 - *Cyanomethyl* - 3 - (2 - *methyl* - 1,3 - *dioxolan* - 2 - *yl*) - *azetidinones* **14c** *and* **14d**

(a) A mixture of **13c** (4.3 g, 11 mmol), NaCN (2.15 g, 44 mmol) and anhyd DMF (10 ml) was kept, with occasional stirring, for some days at 0–5° until the iodomethyl derivative was completely consumed (TLC; Kieselgel G, benzene–acetone, 8:2). The mixture was poured into sat NaCl aq (60 ml). Extraction with ether (3 × 40 ml) furnished 2.9 g (90%) of **14c**, m.p. 64–65° from EtOAc–light petroleum. (Found: C, 67.39; H, 6.40; N, 9.99. Calc for $C_{16}H_{18}N_2O_3$ (286.32): C, 67.11; H, 6.34; N, 9.79%.) IR (KBr): 1760 cm^{-1}. ^1H-NMR (100 MHz): δ 1.43s (2′-Me), 2.51d (J = 5.6 Hz; CH_2CN), 3.29d (J = 2.4 Hz, 3-H), 3.63 td (J = 5.6 and 2.4 Hz; 4-H), 3.9–4.05m ($4'-H_2 + 5'-H_2$), 4.23 + 4.71 (AB, J = 15.2 Hz; N—C$\underline{H}_2$—Ph), 7.35s (Ph).

(b) A mixture of **13d** (1.0 g, 2.2 mmol), NaCN (0.25 g, 5.1 mmol), and anhyd DMF (5 ml) was stirred for 24 hr at ambient temp. Work-up was identical with that described in (a), except that the oily residue of the ethereal extract was purified by preparative TLC (Kieselgel $PF_{254+366}$; benzene–acetone, 8:2) to obtain 0.46 g (59%) of **14d** as an oil which slowly crystallized from an ether–EtOAc–pentane soln, m.p. 69–70°. (Found: C, 62.33; H, 6.74; N, 8.39. Calc for $C_{18}H_{22}N_2O_5$ (346.38): C, 62.41; H, 6.40; N, 8.09%.) IR (KBr): 2270 (very weak) and 1755 cm^{-1}. ^1H-NMR (100 MHz): δ 1.39s (2′-Me), 2.52 + 2.58 (**ABX**, J_{gem} = 17 Hz, J_{vic} = 5.8 and 4.7 Hz, respectively; CHC$\underline{H}_2$CN), 3.24d (J = 2.3 Hz; 3-H), 3.55ddd (J = 5.8, 4.7 and 2.3 Hz; 4-H), 3.80 + 3.82 (2 × s; 2 × OMe), 3.9–4.0m ($4'-H_2 + 5'-H_2$), 4.22 + 4.52 (AB, J = 15 Hz; N—C$\underline{H}_2$—Ar), 6.4–6.55m (3″-H + 5″-H), 7.21d (J = 9 Hz, 6″-H).

Acknowledgements—The authors are grateful to Dr. I. Balogh-Batta and staff for the microanalyses, to Mrs L. Székely for the IR spectra and to Mrs Cs. Szücs for the 60 MHz NMR spectra. Financial assistance from the Gedeon Richter Chemical Works (Budapest) and Biogal Pharmaceutical Works (Debrecen, Hungary) is gratefully acknowledged.

REFERENCES

[1] For a recent review, see R. W. Ratcliffe and G. Albers-Schönberg, *Chemistry and Biology of β-Lactam Antibiotics* (Edited by R. B. Morin and M. Gorman), Vol. 2, p. 227. Academic, New York (1982).

[2] R. Blank, *Ber. Dtsch. Chem. Ges.* **31**, 1815 (1898).

[3] J. P. Li, *J. Org. Chem.* **40**, 3414 (1975).

[4a] A. P. Krapcho and A. J. Lovey, *Tetrahedron Letters* 957 (1973); [b]A. P. Krapcho, E. G. E. Jahngen, Jr., A. J. Lovey and F. W. Short, *Ibid.* 1091 (1974); [c]A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey and W. P. Stephens, *J. Org. Chem.* **43**, 138 (1978); [d]A. P. Krapcho, *Synthesis* 805, 893 (1982).