Simple and Condensed β-Lactams. Part 5.† The Synthesis of some (5*RS*,6*SR*)-2-(2-Formylaminoethylthio)-6-(2-methyl-1,3-dioxolan-2-yl)carbapenem-3-carboxylic Acid Derivatives and Related Compounds

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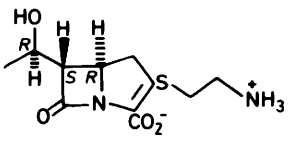
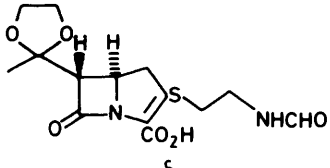
Starting with the 4-oxoazetidine-2-carboxylic acids (**3a**) and (**3b**), methods for the synthesis of derivatives of the racemic carbapenem-3-carboxylic acid (**2**), an analogue of the potent antibiotic thienamycin have been developed. The synthetic steps included chain elongations by the methods of Arndt-Eistert and Masamune, diazo group transfers, oxidative removals of *N*-protecting 2,4-dimethoxybenzyl and *p*-methoxyphenyl groups, cyclization involving a carbene insertion reaction, and conversion of the ketone moiety of the bicyclic compound (**13b**) into an enethiol moiety *via* enolphosphate activation. The target compound, the sodium salt (**14c**) did not possess any useful biological activity.

The discovery of the potent antibiotic thienamycin[2] (**1**) has prompted efforts in many laboratories throughout the world to synthesize a considerable number of its derivatives and analogues with the aim of further improving the antibiotic properties of thienamycin.[3]

Here we report the synthesis of some derivatives of (5*RS*,6*SR*)-2-(2-formylaminoethylthio)-6-(2-methyl-1,3-dioxolan-2-yl)carbapenem-3-carboxylic acid (**2**), a compound closely related to thienamycin, as well as of some other β-lactams obtained as products of model reactions studied in the course of the development of the synthesis of derivatives of compound (**2**) (Scheme).



(**1**)



(**2**)§

The 4-oxoazetidine-2-carboxylic acids (**3a**)[4] and (**3b**)[4] were selected as the starting compounds for the synthesis of derivatives of compound (**2**). Activation of their carboxylic groups by formation of their mixed anhydrides with ethyl hydrogen carbonate, followed by reaction with diazomethane led to the diazomethyl ketones (**4a**) and (**4b**), respectively, in fair to good yields. Similarly obtained were the diazomethyl ketones (**4c**) and (**4d**) starting with the acids (**3c**)[4] and (**3d**),[5] respectively. Irradiation of the diazomethyl ketones (**4a**—**d**) in aqueous THF solutions through Pyrex, furnished the 4-oxoazetidin-2-ylacetic acids (**5a**)—(**5d**), respectively, in fair to good yields. This method of chain elongation had been used in the β-lactam series before,[6a] and, while this work was in progress, some further examples of the application of the Arndt-Eistert method in the β-lactam field have been published.[6b-d]

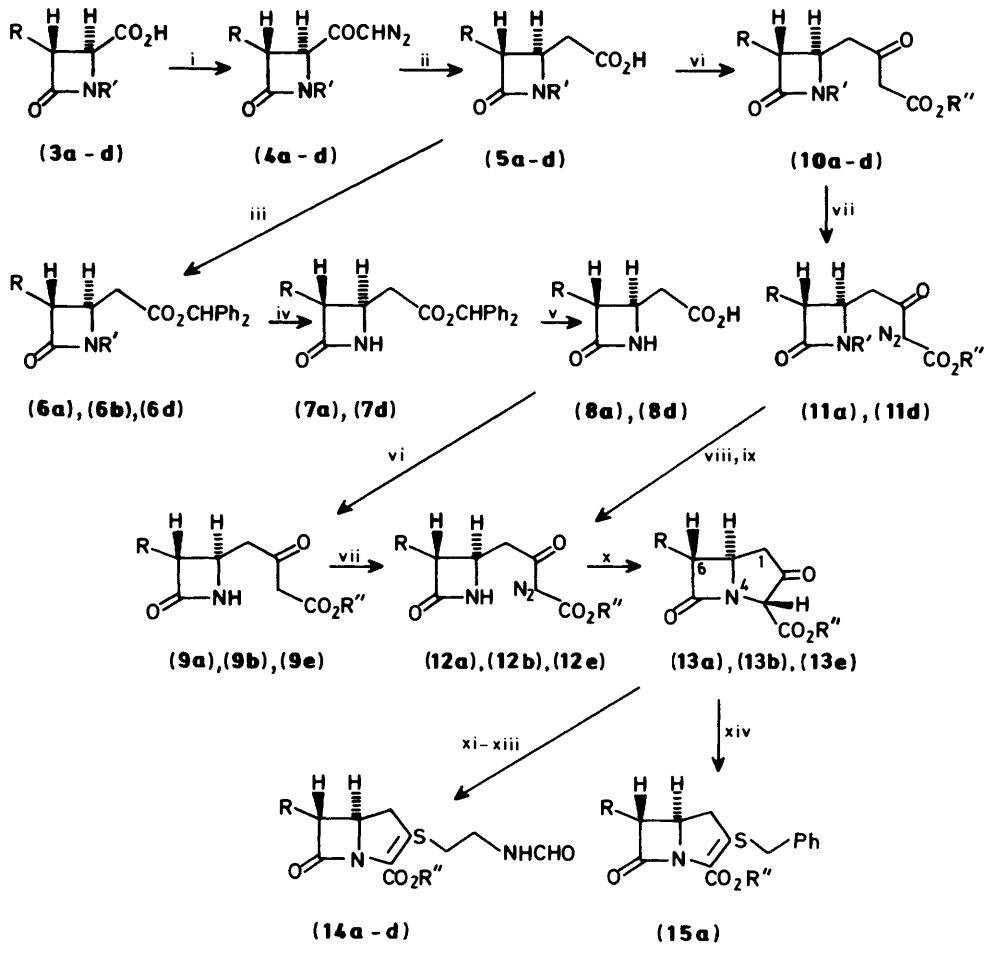
The next synthetic goal was the preparation of the *N*-unsubstituted 2-diazo-4-(4-oxoazetidin-2-yl)acetoacetates of type (**12**). Starting with the appropriate 4-oxoazetidin-2-ylacetic acids (**5**) this was achieved, *via* compounds of types (**6**)—(**9**), by removal of the *N*-substituent and subsequent elaboration of the side chain attached to C-2 of the azetidine ring or, *via* compounds (**10**) and (**11**), by reversing the order of these steps.

In order to facilitate isolation of the *N*-deprotected derivatives, the acids (**5a**), (**5b**), and (**5d**) were treated in CH_2Cl_2 solution with diazodiphenylmethane to give their benzhydryl esters (**6a**), (**6b**), and (**6d**), respectively. The *N*-(2,4-dimethoxybenzyl) protecting groups of the esters (**6a**) and (**6e**) were removed, without preliminary purification, by oxidation with $K_2S_2O_8$ in the presence of Na_2HPO_4 to give the *N*-unsubstituted esters (**7a**) and (**7d**), respectively. The ester (**7a**) could also be obtained by oxidative removal [cerium(IV) ammonium nitrate] of the *N*-(*p*-methoxyphenyl) protecting group of compound (**6b**).[7] Hydrogenolysis of the benzhydryl esters (**7a**) and (**7d**) in the presence of 8% Pd–C catalysts led to the *N*-unsubstituted 4-oxoazetidin-2-ylacetic acids (**8a**) and (**8d**), respectively.

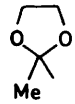
Elongation of the C-2 side chain of the former by two carbon atoms was carried out by applying Masamune's method[8] as modified by Merck's chemists.[9a,b] Thus, acid (**8a**) was treated in THF solution successively with 1,1′-carbonyldi-imidazole and the magnesium salts of ethyl hydrogen and hydrogen *p*-nitrobenzyl malonate to give the acetoacetic acid derivatives (**9a**) and (**9b**), respectively. Diazo exchange[10] with toluene-*p*-sulphonyl azide then furnished the diazo derivatives (**12a**) and (**12b**), respectively. Compound (**8d**) was similarly converted *via* compound (**9e**) into the diazo derivative (**12e**).

Alternatively, the *N*-substituted 4-oxoazetidin-2-ylacetic acids (**5a**), (**5b**), and (**5d**) were subjected to the chain elongation procedure,[8,9] and the resulting *N*-substituted 4-(4-oxoazetidin-2-yl)acetoacetic esters (**10a**—**d**) to the diazo exchange reaction[10] to give the *N*-substituted diazo derivatives (**11a**—**d**). The 2,4-dimethoxybenzyl *N*-protecting groups of compounds (**11a**), (**11b**), and (**11d**) could be oxidatively removed ($K_2S_2O_8$) to give the deprotected derivatives (**12a**), (**12b**), and (**12e**),

† For Part 4, see ref. 1.
‡ Recipient of a Gedeon Richter Chemical Works (Budapest, Hungary) scholarship, 1980—1982.
§ All compounds described in the present paper are racemic; for convenience only one enantiomer is shown.



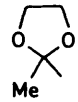
(3)-(8)

	R	R' *
a		$CH_2C_6H_3(OMe)_2$-o,p
b		C_6H_4OMe-p
c		Ph
d	H	$CH_2C_6H_3(OMe)_2$-o,p

(9), (12)-(15)

	R	R''
a		Et
b		$CH_2C_6H_4NO_2$-p
c		Na
d		$CH_2O_2CBu^t$
e	H	$CH_2C_6H_4NO_2$-p

(10),(11)

	R	R'	R''
a		$CH_2C_6H_3(OMe)_2$-o,p	Et
b		$CH_2C_6H_3(OMe)_2$-o,p	$CH_2C_6H_4NO_2$-p
c		C_6H_4OMe-p	Et
d	H	$CH_2C_6H_3(OMe)_2$-o,p	$CH_2C_6H_4NO_2$-p

Scheme. (For convenience only one enantiomer of the racemic compounds is shown). *Reagents:* i, $ClCO_2Et$–Et_3N–THF, CH_2N_2–Et_2O; ii, *hv*–Ar–THF; iii, Ph_2CN_2–CH_2Cl_2; iv, a and d series: $K_2S_2O_8$–Na_2HPO_4–aqueous MeCN; b series: CAN, aqueous H_2SO_4; v, H_2–Pd–C, EtOH; vi, carbonyldi-imidazole–THF, $Mg(O_2CCH_2CO_2R'')_2$; vii, TsN_3–Et_3N–MeCN; viii, a, b, and d series: $K_2S_2O_8$–Na_2HPO_4–aqueous MeCN; ix, c series: CAN, aqueous H_2SO_4; x, $Rh_2(OAc)_4$–benzene–reflux; xi, a and b series: $(PhO)_2P(O)Cl$–Et_3N–MeCN, $HS(CH_2)_2NHCHO$–Et_3N; xii, for (**14b**) ⟶ (**14c**): H_2–Pd–C–dioxane, $NaHCO_3$; xiii, for (**14c**) ⟶ (**14d**): $ClCH_2O_2CBu^t$–DMF; xiv, $(PhO)_2P(O)Cl$–Et_3N–MeCN, $HSCH_2Ph$–Et_3N.

respectively. The moderate to low yields in these reactions probably reflect the sensitivity of the C-2 side chains of these compounds to the oxidizing agent. The *p*-methoxyphenyl *N*-protecting group of compound (**11c**) could also be removed by oxidation with cerium(IV) ammonium nitrate but the yield of (**12a**) was rather low.

* Where applicable.

Both the *N*-unprotected and the *N*-protected 4-(4-oxoazetidin-2-yl)acetoacetates of the types (**9**) and (**10**) do exist, as shown by their ^{1}H n.m.r. spectra in chloroform solution, as mixtures of the ketonic and enolic forms, the tautomeric equilibria being shifted towards the ketonic forms [*e.g* the enol content of compounds (**9a**) and (**10d**) in chloroform solution amounted to 5—10 and *ca.* 10%, respectively].

Ring closures of the diazo esters (**12a**), (**12b**), and (**12e**) were effected by the carbene insertion reaction developed by Merck's chemists.[11] The ketonic carbonyl groups of the resulting 2-oxocarbapenam-3-carboxylates (**13a**) and (**13b**) were activated by conversion with diphenyl phosphorochloridate into the enol phosphates which were then allowed to react with *N*-formylcysteamine[12]† to give the ethyl (**14a**) and *p*-nitrobenzyl esters (**14b**), respectively, of compound (**2**) by application of the Merck method.[9a,13,14] Starting with compound (**13a**), the benzylthio derivative (**15a**) was similarly obtained, except that *N*-formylcysteamine was replaced by toluene-α-thiol.

Hydrogenolysis of the *p*-nitrobenzyl ester (**14b**) in the presence of $NaHCO_3$ furnished the sodium salt (**14c**) of the acid (**2**), from which, by reaction with chloromethyl pivalate,[15] the pivaloyloxymethyl ester (**14d**) was also obtained.

The biological screening results, performed at the Department of Chemotherapy of the Institute of Pharmacology, University Medical School Debrecen (Debrecen, Hungary) were disappointing: compound (**14c**) did not possess any antibacterial activity and its β-lactamase inhibiting effect was weak.

Experimental

Melting points are uncorrected. I.r. spectra were obtained with a Spektromom 2000 instrument (Hungarian Optical Works, Budapest). Unless otherwise stated, ^{1}H and ^{13}C n.m.r. spectra were obtained at 100 and 25.2 MHz, respectively, with a Varian XL-100 spectrometer, using $CDCl_3$ as the solvent and $SiMe_4$ as the internal reference. The mass spectrum of compound (**14a**) was obtained with an AEI MS 902 double focussing instrument at 70 eV, using the direct insertion system. For column chromatography Kieselgel 60 (0.063—0.200 mm) was used as the adsorbent. Ether refers to diethyl ether.

(3RS,4RS)-4-*Diazoacetyl*-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*azetidin*-2-*ones* (**4a**)—(**4c**) *and* (4RS)-4-*Diazoacetyl*-1-(2,4-*dimethoxybenzyl*)*azetidin*-2-*one* (**4d**).—(*a*) Triethylamine (7.3 ml, 52.5 mmol) and ethyl chloroformate (5.0 ml, 52.5 mmol) were added successively with continuous stirring and ice cooling to a solution of the (2*RS*,3*RS*)-acid (**3a**)[4] (17.6 g, 50 mmol) in anhydrous THF (150 ml). The mixture was cooled to −15 °C and stirred for 20 min at this temperature. The crystalline triethylammonium salt was filtered off under argon. A cold ethereal (230 ml) diazomethane solution (150 mmol) was added to the filtrate, and the mixture was allowed to warm up to room temperature with continuous stirring. The excess of diazomethane was decomposed by adding acetic acid, and the mixture was evaporated to dryness. The resulting thick brown paste was dissolved in benzene (20 ml) and purified by column chromatography [Kieselgel 60, 0.063—0.200 mm, 150 g; benzene–acetone, (7:2)] to give compound (**4a**) as an oil (12.0 g, 64%) (Found: C, 57.8; H, 5.4. $C_{18}H_{21}N_3O_6$ requires C, 57.59; H, 5.64%); $\nu_{max.}$(film) 2 110 and 1 760 cm^{-1}.

(*b*) Compound (**4b**) [m.p. 95—96 °C (from benzene–ether)] was similarly obtained in 90% yield starting with the acid (**3b**)[4] (10 mmol), except that the oily crude product gradually solidified with time in benzene–ether (Found: C, 58.4; H, 5.8; N, 4.65. $C_{15}H_{17}NO_5$ requires C, 58.63; H, 5.57; N, 4.56%); $\nu_{max.}$(KBr) 2 160 and 1 755 cm^{-1}; δ_H (60 MHz) 1.50 (s, Me), 3.50 (d, *J* 2.7 Hz, 3-H), 3.75 (s, OMe), 3.9—4.1 (m, OCH_2CH_2O), 4.30 (d, *J* 2.7 Hz, 4-H), 5.45 (s, CHN_2), and 6.85 and 7.25 (AA'BB' system, *J* 9 Hz, 4 × ArH).

(*c*) Compound (**4c**) [m.p. 96—97 °C (from benzene–ether)] was similarly obtained in 77% yield starting with the acid (**3c**)[4] (50 mmol), except that the oily crude product crystallized when triturated with ether (Found: C, 60.65; H, 5.7; N, 5.0. $C_{14}H_{15}NO_5$ requires C, 60.64; H, 5.45; N, 5.05%); $\nu_{max.}$(KBr) 2 140 and 1 750 cm^{-1}; δ_H (60 MHz) 1.50 (s, Me), 3.50 (d, *J* 2.7 Hz, 3-H), 4.0—4.1 (m, OCH_2CH_2O), 4.35 (d, *J* 2.7 Hz, 4-H), 5.45 (s, CHN_2), and 7.2—7.3 (m, Ph).

(*d*) Compound (**4d**) (m.p. 90—91 °C) was obtained in 73% yield starting with the acid (**3d**)[5] (50 mmol) as described in (*a*). The oily product obtained by chromatography crystallized when triturated with ether (Found: C, 58.25; H, 5.45; N, 14.6. $C_{14}H_{15}N_3O_4$ requires C, 58.12; H, 5.23; N, 14.5%); $\nu_{max.}$(KBr) 2 100, 1 740, and 1 625 cm^{-1}; δ_H (60 MHz) 2.85—3.15 and 3.3—3.5 (2 × m, 3-H_2), 3.73 and 3.75 (2 × s, 2 × MeO), *ca.* 3.85 (m, 4-H), 4.1 and 4.55 (AB system, *J* 15 Hz, NCH_2Ar), 5.37 (s, CHN_2), 6.3—6.6 (m; 2 × ArH), and 7.1 (d, J 9 Hz, ArH).

(2RS,3SR)-3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-yl-*acetic Acids* (**5a**)—(**5c**), (**8a**) *and* (2RS)-4-*Oxoazetidin*-2-*ylacetic Acids* (**5d**), (**8d**).—(*a*) A solution of compound (**4a**) (2.25 g, 6 mmol) in a mixture of peroxide-free THF (100 ml) and water (50 ml) was irradiated with a high-pressure mercury immersion lamp (HPK 125) through Pyrex under argon until the starting compound was consumed (*ca.* 4 h). The solution was concentrated to *ca.* 50 ml under reduced pressure. Water (130 ml) and aqueous NaOH (10%; 2.4 ml) were added, and the alkaline solution was extracted with CH_2Cl_2 (3 × 20 ml). The aqueous phase was acidified (pH 2) with concentrated HCl, and extracted with CH_2Cl_2 (3 × 20 ml) to give, after work-up of the CH_2Cl_2 solution, compound (**5a**) (1.82 g, 82%), m.p. 124 °C (from ether) (Found: 59.2; H, 6.5; N, 4.05. $C_{18}H_{23}NO_7$ requires C, 59.17; H, 6.34; N, 3.87%); $\nu_{max.}$(KBr) 3 500—2 500, 1 730 and 1 700 cm^{-1}.

(*b*) The oily compound (**5b**) was similarly obtained in 50% yield starting with compound (**4b**) (10 mmol); the progress of the reaction was conveniently followed by t.l.c. [Kieselgel G; benzene–acetone, (7:1)] (Found: C, 59.6; H, 5.75; N, 4.1. $C_{16}H_{19}NO_6$ requires C, 59.80; H, 5.96; N, 4.36%); $\nu_{max.}$(film) 3 500—2 750 and 1 730br cm^{-1}; δ_H 1.47 (s, Me), 2.67 and 3.02 (*ABX* system, J_{gem} 15, J_{vic} 8.2 and 4.4 Hz, respectively, CH_2CO_2H), 3.44 (d, *J* 2.3 Hz, 3-H), 3.79 (s, OMe), 3.85—4.2 (m, OCH_2CH_2O), 4.35 (ddd, *J* 8.2, 4.4, and 2.3 Hz, 2-H), 6.88 and 7.31 (AA'BB' system, *J* 8.6 Hz, 4 × ArH), and 7.2 (br s, CO_2H). This product was converted into the ester (**6b**) without further purification, see below.

(*c*) Compound (**5c**), m.p. 128—129 °C (from ethanol), was similarly obtained in 50% yield, starting with compound (**4c**) (12.6 mmol), the reaction being monitored as described in (*b*) (Found: C, 61.75; H, 5.85; N, 5.1. $C_{15}H_{17}NO_5$ requires C, 62.00; H, 5.88; N, 4.82%); $\nu_{max.}$(KBr) 3 300—2 250, 1 720, and 1 680 cm^{-1}; δ_H (60 MHz) 1.50 (s, Me), 2.65 and 3.10 (AB part of an ABX system, J_{gem} 14.7, J_{vic} 8.7 and 4.0 Hz, respectively, $CHCH_2CO_2H$), 3.48 (d, *J* 2.5 Hz, 3-H), 3.9—4.1 (m, OCH_2CH_2O), 4.2—4.5 (m, 2-H), 7.2—7.45 (m, Ph), and 9.35 (br s, CO_2H).

(*d*) Compound (**5d**), m.p. 112 °C (from benzene) was obtained in 84% yield as described in (*a*), except that the starting material was compound (**4d**) (7 mmol). This product was converted into compound (**10d**) without further purification, as described below.

(*e*) The benzhydryl ester (**7a**) (see below) (3.8 g, 10 mmol) was catalytically hydrogenolysed in anhydrous ethanolic (50 ml) solution in the presence of a Pd–C catalyst (8%; 0.4 g) at ambient temperature and normal pressure (*ca.* 2 h) to give, after work-up, compound (**8a**) (2.0 g, 94%), m.p. 126—129 °C (by

† *N*-Formylcysteamine = 2-formylaminoethanethiol.

trituration with ether; non-recrystallized material); $\nu_{max.}$(KBr) 3 500—2 500, 1 730, and 1 700 cm^{-1}; δ_H (^2H_2O; reference dioxane, δ 3.70) 1.42 (s, Me), 2.77 and 2.81 (*ABX* system, J_{gem} 16, J_{vic} 7.5 and 5.8 Hz respectively, CH_2CO_2H), 3.37 (d, *J* 2.3 Hz, 3-H), 3.92 (ddd, *J* 7.5, 5.8, and 2.3 Hz, 2-H), and 3.95—4.15 (m, OCH_2CH_2O). This product was converted without further purfication into compound (**9a**) (see below).

(*f*) The benzhydryl ester (**7d**) (see below) (1.48 g, 5 mmol) was similarly hydrogenolysed to yield the acid (**8d**), m.p. 215 °C (decomp.; by trituration with ether; non-recrystallized material), in quantitative yield (lit.,[16,17] 116—117 °C and 120—126 °C) (Found: N, 10.7. $C_5H_7NO_3$ requires N, 10.85%); $\nu_{max.}$(KBr) 3 500—2 500, 1 750, and 1 695 cm^{-1}; δ_H (^2H_2O; reference dioxane, δ 3.70) 2.4—2.85 (m, 3-H_2 and CH_2CO_2H) and 3.85 (m, 2-H).

Benzhydryl (2RS,3SR)-3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*ylacetates* (**6a**), (**6b**), (**7a**) *and Benzhydryl* (2RS)-4-*Oxoazetidin*-2-*ylacetates* [**6d**) *and* (**7d**).—(*a*) Diazodiphenylmethane (3.05 g, 15.8 mmol) was added in portions to a solution of the acid (**5a**) (5.5 g, 15 mmol) in CH_2Cl_2 (50 ml) at room temperature. When the evolution of nitrogen had ceased, the excess of diazo compound was decomposed by adding a few drops of acetic acid. The solution was evaporated to dryness, and the crude ester (**6a**) (6.8 g) was dissolved in acetonitrile (84 ml). An aqueous solution (54 ml) of $K_2S_2O_8$ (16.2 g, 60 mmol) and $Na_2HPO_4{\cdot}2\,H_2O$ (21.6 g, 120 mmol) was added, and the mixture was refluxed for 4 h with continuous stirring; it was then allowed to cool. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 30 ml), the combined organic solutions were dried and evaporated to dryness. The residue was taken up in benzene and purified by column chromatography [benzene–acetone (7:2)] to obtain compound (**7a**) (2.7 g, 47%), m.p. 130 °C (from ethanol) (Found: C, 69.15; H, 6.2; N, 3.55. $C_{22}H_{23}NO_5$ requires C, 69.27; H, 6.08; N, 3.67%); $\nu_{max.}$(KBr): 3 250, 1 760, and 1 740 cm^{-1}; δ_H 1.38 (s, Me), 2.65 and 2.89 (*ABX* system, J_{gem} 16.3, J_{vic} 9.1 and 4.4 Hz, respectively, CH_2CO_2), 3.12 (d, *J* 2.5 Hz, 3-H), 3.89 (ddd, *J* 9.1, 4.4, and 2.5 Hz, 2-H), 3.9—4.15 (m, OCH_2CH_2O), 6.1 (br s, exchangeable, NH), 6.91 (s, Ph_2CH), and 7.28 (s, 2 × Ph).

(*b*) The oily compound (**6b**) was obtained in quantitative yield as described for compound (**6a**), except that the starting material was the acid (**5b**) (5 mmol) (Found: C, 71.15; H, 6.2; N, 2.95. $C_{29}H_{29}NO_6$ requires C, 71.44; H, 5.99; N, 2.87%); $\nu_{max.}$(film) 1 740br, 820, 740, and 690 cm^{-1}; δ_H 1.37 (s, Me), 2.80 and 3.03 (*ABX* system, J_{gem} 15.2, J_{vic} 7.3 and 4.7, respectively, CH_2CO_2), 3.37 (d, *J* 2.4 Hz, 3-H), 3.73 (s, OMe), 3.8—4.1 (m, OCH_2CH_2O), 4.34 (ddd, *J* 7.3, 4.7, and 2.4 Hz, 2-H), 6.81 and 7.26 (AA′BB′ system, *J* 8.6 Hz, 4 × ArH), and 6.89 (s, Ph_2CH).

(*c*) A solution of $[Ce(NH_4)_2](NO_3)_6$ (0.9 g, 1.6 mmol) in aqueous H_2SO_4 (5%; 2 ml) was added dropwise to a solution of compound (**6b**) (0.28 g, 0.65 mmol) in acetone (2 ml) with continuous stirring at room temperature. After addition of the oxidising agent, the mixture was stirred for a further 2 min and was then neutralized by the addition of 5% aqueous $NaHCO_3$. Extraction with ethyl acetate (3 × 4 ml) and chromatographic work-up as described in (*a*) furnished compound (**7a**) (60 mg, 30%), identical with the product obtained in (*a*).

(*d*) Compound (**7d**), m.p. 89 °C (from ether), was obtained from compound (**6d**) in 58% yield as described in (*a*), except that compound (**5d**) was used as the starting material (Found: C, 73.35; H, 5.85; N, 4.7. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%); $\nu_{max.}$(KBr) 3 250, 1 760, and 1 730 cm^{-1}; δ_H 2.64 and 3.08 (*ABX* system, J_{gem} 14.8, J_{vic} 2.5 and 5.0, $^4J_{3H,NH}$ 1.1 and 2.2 Hz, respectively, 3-H_2), 2.70 and 2.77 (*ABX* system, J_{gem} 16.5, J_{vic} 8.0 and 5.6 Hz, respectively, CH_2CO_2), 3.92 (dddd, *J* 2.5, 5.0, 8.0, and 5.6 Hz, 2-H), 6.2 (br s, NH), 6.92 (s, Ph_2CH), and 7.1—7.5 (m, 2 × Ph).

Ethyl and p-*Nitrobenzyl* (2RS,3SR)-4-[3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*yl*]*acetoacetates* (**9a**), (**9b**), (**10a**), (**10b**), *and* (**10c**), *and* p-*Nitrobenzyl* (2RS)-4-(4-*Oxoazetidin*-2-*yl*)*acetoacetates* (**9e**) *and* (**10d**).—(*a*) A solution of compound (**8a**) (2.15 g, 10 mmol) in dry THF (60 ml) was stirred for 30 min with 1,1′-carbonyldi-imidazole (98% pure; 1.8 g, 11 mmol) at room temperature. Diethyl magnesium dimalonate (1.58 g, 5.6 mmol) was added, and the mixture was stirred for 2 h and evaporated to dryness at reduced pressure. The residue was stirred for a few minutes with CH_2Cl_2 (180 ml) and aqueous HCl (0.5M; 180 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 ml) and the combined organic solutions were washed with 5% aqueous Na_2CO_3 (2 × 20 ml), dried ($MgSO_4$), and evaporated to dryness to yield compound (**9a**), (2.0 g, 71%) m.p. 65—68 °C (from ether) (Found: C, 54.65; H, 6.9; N, 4.9. $C_{13}H_{19}NO_6$ requires C, 54.73; H, 6.71; N, 4.91%); $\nu_{max.}$(KBr) 3 220, 1 770, 1 735, and 1 720 cm^{-1}; δ_H 1.29 and 4.22 (t and q, *J* 7.1 Hz, CO_2Et), 1.43 (s, Me), 2.81 and 3.06 (*ABX* system, J_{gem} 17.8, J_{vic} 9.4 and 3.7 Hz, respectively, CH_2CO), 3.11 (d, *J* 2.6 Hz, 3-H), 3.46 (s, $COCH_2CO_2$), 3.91 (ddd, *J* 9.4, 3.7, and 2.6 Hz, 2-H), 3.95—4.1 (m, OCH_2CH_2O), 5.05 (s, =CH, enol form), 6.1 (br s, NH), and 12.1 (br s, enolic OH).

(*b*) The oily *p*-nitrobenzyl ester (**9b**) was similarly obtained in 62% yield from acid (**8a**), except that the magnesium salt of the ethyl hydrogen malonate was replaced by that of hydrogen *p*-nitrobenzyl malonate: $\nu_{max.}$(film) 3 250, 1 760, 1 740, 1 720, 1 510, and 1 340 cm^{-1}. This product was converted without further purification into the diazo derivative (**12b**), see below.

(*c*) The oily compound (**10a**) was obtained in 47% yield by the method described in (*a*), except that compound (**5a**) (2 mmol) was used as the starting material. $\nu_{max.}$(film) 1 750, 1 740, and 1 720 cm^{-1}; δ_H (60 MHz) 1.27 (t, *J* 7.1 Hz, OCH_2Me), 1.40 (s, Me), 2.74—3.20 (m, CH_2CO_2 and 3-H), 3.28 (s, $COCH_2CO$), 3.80 (2 × s, 2 × MeO), 3.95—4.40 (m, OCH_2Me, 2-H, NCH_2Ar, and OCH_2CH_2O), 6.35—6.5 (m, 2 × ArH), and 7.2 (d, *J* 9 Hz, ArH). This product was converted without further purification into the diazo derivative (**11a**), see below.

(*d*) When the magnesium salt of ethyl hydrogen malonate was replaced by that of hydrogen *p*-nitrobenzyl malonate, the analogous oily *p*-nitrobenzyl ester (**10b**) was obtained in 78% yield from the acid (**5a**) (8 mmol), $\nu_{max.}$(film) 1 760br cm^{-1}. This product was converted without further purification into the diazo derivative (**11b**), see below.

(*e*) The oily ethyl ester (**10c**) was obtained in 62% yield by applying the method described in (*a*) to acid (**5b**) (1.25 mmol) (Found: C, 61.2; H, 6.6; N, 3.7. $C_{20}H_{25}NO_7$ requires C, 61.37; H, 6.44; N, 3.58%); $\nu_{max.}$(film) 1 750br and 1 730sh cm^{-1}; δ_H 1.27 and 4.19 (t and q, *J* 7.1 Hz, CO_2Et), 1.48 (s, Me), 2.92 and 3.22 (*ABX* system, J_{gem} 16.6, J_{vic} 7.6 and 4.3 Hz, respectively, CH_2CO), 3.32 (d, *J* 2.3 Hz, 3-H), 3.45 (s, $COCH_2CO_2$), 3.79 (s, OMe), 3.85—4.2 (m, OCH_2CH_2O), 4.40 (ddd, *J* 7.6, 4.3, and 2.3 Hz, 2-H), and 6.88 and 7.29 (AA′BB′ system, *J* 8.6 Hz, 4 × ArH).

(*f*) The oily *p*-nitrobenzyl ester (**9e**) was obtained in 64% yield by applying the method described in (*b*) to the acid (**8d**): $\nu_{max.}$(film) 3 250, 1 760, 1 740br, 1 530, and 1 360 cm^{-1}; δ_H 2.61 and 3.16 (*ABX* system, J_{gem} 14.8, J_{vic} 2.5 and 5.1, $^4J_{3H.NH}$ 1.1 and 2.4 Hz, respectively, 3-H_2), 2.86 and 3.00 (*ABX* system, J_{gem} 18, J_{vic} 8 and 5 Hz, respectively, CH_2CO), 3.57 (s, $COCH_2CO_2$), 3.97 (dddd, *J* 2.5, 5.1, 8 and 5 Hz; 2-H), 5.29 (s, OCH_2Ar), 6.1 (br s, NH), and 7.54 and 8.24 (AA′BB′ system, *J* 8.6 Hz, 4 × ArH). This compound was converted without further purification into the diazo derivative (**12e**), see below. Compound (**9e**) has been previously mentioned in the patent literature.[18,20]

(*g*) The oily *p*-nitrobenzyl ester (**10d**) was similarly obtained in 80% yield from compound (**5e**) (8.0 mmol) and the magnesium salt of hydrogen *p*-nitrobenzyl malonate: $\nu_{max.}$(film) 1 750, 1 740, 1 720, 1 510, 1 345, and 830 cm^{-1}; δ_H 2.55 and 3.10

(*ABX* system, J_{gem} 14.7, J_{vic} 2.5 and 5.0, respectively; 3-H_2), 2.66 and 2.97 (*ABX* system, J_{gem} 17.5, J_{vic} 8.1 and 4.8 Hz, respectively, CH_2CO), 3.41 (s, $COCH_2CO$), 3.79 (s, 2 × MeO), 3.84 (dddd, *J* 2.5, 5.0, 8.1, and 4.8 Hz, 2-H), 4.19 and 4.39 (AB system, *J* 14.8 Hz, NCH_2Ar), 5.03 (s, =CH, enol form), 5.25 (s, OCH_2Ar), 6.40—6.55 (m, 2 × ArH, NCH_2Ar group), 7.13 (d, *J* 8.8 Hz, ArH, NCH_2Ar group), 7.51 and 8.23 (AA'BB' system, *J* 8.6 Hz, 4 × ArH, OCH_2Ar group), and 11.7 (br s, enolic OH). This is in good agreement with the spectrum of the related *N*-dimethyl-t-butylsilyl) derivative obtained (by a different method) by Japanese scientists.[19]

Ethyl and p-*Nitrobenzyl* (2RS,3SR)-2-*Diazo*-4-[3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*yl*]*acetoacetates* (**11a**), (**11b**), (**11c**), (**12a**), *and* (**12b**), *and* p-*Nitrobenzyl* (2RS)-2-*Diazo*-4-(4-*oxoazetidin*-2-*yl*)*acetoacetates* (**11d**) *and* (**12e**).—(*a*) A solution of the ester (**10a**) (2.77 g, 5.0 mmol) in anhydrous acetonitrile (15 ml) was treated dropwise with continuous stirring and ice cooling, successively with triethylamine (0.69 ml, 5.0 mmol) and toluene-*p*-sulphonyl azide (0.99 g, 5 mmol). The temperature of the mixture was allowed to rise to 20 °C, and stirring was maintained throughout (*ca.* 3 h). The mixture was evaporated to dryness under reduced pressure and the residue was worked up by column chromatography [benzene–acetone, (7:3)] to give compound (**11a**) (1.41 g, 61%) as an oil: $\nu_{max.}$(film) 2 160, 1 750, 1 720, and 1 640 cm^{-1}; δ_H 1.31 and 4.27 (t and q, *J* 7.1 Hz, CO_2Et), 1.39 (s, Me), 3.06 and 3.15 (*ABX* system, J_{gem} 15.6, J_{vic} 6.6 and 6.4 Hz, respectively, CH_2CO), 3.21 (d, *J* 2.4 Hz, 3-H), 3.79 and 3.81 (2 × s, 2 × MeO), 3.93 (ddd, *J* 6.6, 6.4, and 2.4 Hz, 2-H), 3.85—4.1 (m, OCH_2CH_2O), 4.30 and 4.37 (AB system, *J* 15 Hz, NCH_2Ar), 6.4—6.5 (m, 2 × ArH), and 7.18 (d, *J* 9 Hz, ArH). This product was deprotected without further purification to give compound (**12a**), see below.

(*b*) The corresponding *p*-nitrobenzyl ester (**11b**), m.p. 44—46 °C (from CH_2Cl_2), was similarly obtained in 80% yield starting with the ester (**10b**) (5.0 mmol) (Found: C, 56.95; H, 4.75; N, 10.2. $C_{27}H_{28}N_4O_{10}$ requires C, 57.04; H, 4.96; N, 9.86%); $\nu_{max.}$(KBr) 2 250, 1 750—1 720, and 1 660 cm^{-1}; δ_H (60 MHz) 1.39 (s, Me), 3.0—3.25 (m, CH_2CO and 3-H), 3.76 and 3.78 (2 × s, 2 × MeO), 3.85—4.05 (m, OCH_2CH_2O and 2-H), 4.32 (s, NCH_2Ar), 5.32 (s, OCH_2Ar), 6.35—6.50 (m, 2 × ArH, NCH_2Ar), 7.15 (d, *J* 9 Hz, ArH, NCH_2Ar), and 7.55 and 8.31 (AA'BB' system, *J* 9 Hz, 4 × ArH, OCH_2Ar).

(*c*) Starting with the ester (**10c**) (1.45 mmol) the diazo derivative (**11c**), m.p. 131—132 °C (from ether), was similarly obtained in 36% yield (Found: C, 57.55; H, 5.8; N, 10.1. $C_{20}H_{23}N_3O_7$ requires C, 57.65; H, 5.55; N, 10.07%); $\nu_{max.}$(KBr) 2 180, 1 740, 1 710, and 1 640 cm^{-1}; δ_H 1.32 and 4.31 (t and q, *J* 7.0 Hz, CO_2Et), 1.44 (s, Me), 3.10 and 3.64 (*ABX* system, J_{gem} 14.6, J_{vic} 8.5 and 4.4 Hz, respectively, CH_2CO), 3.41 (d, *J* 2.3 Hz, 3-H), 3.78 (s, OMe), 3.9—4.15 (m, OCH_2CH_2O), 4.41 (ddd, *J* 8.5, 4.4, and 2.3 Hz, 2-H), and 6.88 and 7.38 (AA'BB' system, *J* 8.7 Hz, 4 × ArH).

(*d*) Starting with the ester (**9a**) (5.0 mmol) the oily, *N*-unsubstituted diazo derivative (**12a**) was similarly obtained in 72% yield; $\nu_{max.}$(film) 3 250, 2 170, 1 750br, 1 710, 1 640 cm^{-1}; δ_H 1.34 and 4.32 (t and q, *J* 7.1 Hz, CO_2Et), 1.42 (s, Me), 3.01 and 3.44 (*ABX* system, J_{gem} 17.4, J_{vic} 9.5 and 3.6 Hz, respectively, CH_2CO), 3.20 (d, *J* 2.5 Hz, 3-H), 3.94 (ddd, *J* 9.5, 3.6, and 2.5 Hz, 2-H), 3.95—4.15 (m, OCH_2CH_2O), and 6.1 (br s, exchangeable, NH). This product was cyclized without purification into compound (**13a**), see below.

(*e*) The corresponding *p*-nitrobenzyl ester (**12b**), m.p. 163—164 °C (from ether), was similarly obtained in 63% yield, starting with the ester (**9b**) (5.0 mmol) (Found: C, 51.4; H, 4.15; N, 13.25. $C_{18}H_{18}N_4O_8$ requires C, 51.67; H, 4.34; N, 13.39%); $\nu_{max.}$(KBr) 3 320, 2 180, 1 750, 1 710, and 1 630 cm^{-1}; δ_H 1.41 (s; Me), 3.00 and 3.42 (*ABX* system, J_{gem} 17.5, J_{vic} 9.5 and 3.6 Hz, respectively, CH_2CO), 3.18 (d, *J* 2.4 Hz, 3-H), 3.94 (ddd, *J* 9.5, 3.6, and 2.4 Hz, 2-H), 3.95—4.15 (m, OCH_2CH_3O), 5.37 (s, OCH_2Ar), 6.0 (br s, exchangeable, NH), and 7.54 and 8.26 (AA'BB' system *J* 8.8 Hz, 4 × ArH).

(*f*) Starting with compound (**10d**) (5 mmol) the oily *N*-protected diazo derivative (**11d**) was similarly obtained in 88% yield; $\nu_{max.}$(film) 2 200, 1 740br, and 1 650 cm^{-1}; δ_H 2.63 and 3.09 (*ABX* system, J_{gem} 14.6, J_{vic} 2.4 and 4.9 Hz, respectively, 3-H_2), 2.96 and 3.30 (*ABX*, J_{gem} 17.1, J_{vic} 7.5 and 5.5 Hz, respectively, CH_2CO), 3.77 and 3.79 (2 × s, 2 × MeO), 3.93 (dddd, *J* 2.4, 4.9, 7.5, and 5.5 Hz, 2-H), 4.25 and 4.38 (AB system, *J* 15.2 Hz, NCH_2Ar), 5.35 (s, OCH_2Ar), 6.40—6.55 (m, 2 × ArH, NCH_2Ar), 7.13 (d, *J* 8.8 Hz, ArH, NCH_2Ar), 7.55 and 8.27 (AA'BB' system, *J* 8.9 Hz, 4 × ArH, OCH_2Ar). This is in good agreement with the published spectra of the *N*-unprotected benzyl[11] and methyl esters.[16] This product was deprotected without further purification to compound (**12e**), see below.

(*g*) A mixture of compound (**11a**) (2.35 g, 5 mmol), $K_2S_2O_8$ (5.4 g, 20 mmol), $Na_2HPO_4{\cdot}2H_2O$ (7.2 g, 40 mmol), acetonitrile (30 ml) and water (18 ml) was refluxed for 10 h and allowed to cool. The insoluble salts were filtered off and the two layers of the filtrate were separated. The aqueous layer was extracted with EtOAc (3 × 10 ml), and the combined organic solutions were dried ($MgSO_4$) and evaporated to dryness. The residue was column chromatographed [benzene–acetone, (7:3)] to give compound (**12a**) (0.56 g, 36%) which proved to be identical (i.r., ^1H n.m.r.) with the sample obtained in (*d*).

(*h*) The corresponding *p*-nitrobenzyl ester (**12b**), m.p. 163—164 °C (from ether), was similarly obtained in 32% yield by deprotecting (**11b**) (5.0 mmol). The resulting product proved to be identical (mixed m.p., i.r., ^1H n.m.r.) with the sample obtained in (*e*).

(*i*) A solution of $[Ce(NH_4)_2](NO_3)_6$ (1.5 g, 2.7 mmol) in aqueous H_2SO_4 (5%; 4.5 ml) was added dropwise with continuous stirring to a solution of the *N*-protected ester (**11c**) (0.45 g, 0.11 mmol) in acetone (4.5 ml). The resulting yellow mixture was stirred for a further 5 min, and was then neutralized by the addition of 5% aqueous $NaHCO_3$. Extraction with EtOAc (3 × 10 ml) and t.l.c. [Kieselgel 60 $PF_{254+366}$; benzene–acetone, (7:3)] yielded compound (**12a**) (0.10 g, 27%), identical (i.r.) with samples obtained according to (*d*) or (*g*).

(*k*) Compound (**11d**) (5.4 g, 20 mmol) was *N*-deprotected using the method described in (*g*), except that benzene–acetone (7:2) was used as the eluant for the t.l.c. Compound (**12e**) was obtained (0.32 g, 10%), m.p. 115 °C (from ether) (Found: C, 50.45; H, 3.85; N, 16.7. $C_{14}H_{12}N_4O_6$ requires C, 50.60; H, 3.64; N, 16.86%); $\nu_{max.}$(KBr) 3 250, 2 220, 1 780, 1 710, and 1 655 cm^{-1}; δ_H 2.69 and 3.15 (2 × ddd which collapsed into 2 × dd on addition of ^2H_2O, J_{gem} 14.9, J_{vic} 2.6 and 5.1 Hz, respectively, $^4J_{HCCNH}$ 1.2 and 2.3 Hz, respectively, 3-H_2), 3.09 and 3.34 (*ABX* system, J_{gem} 17.7, J_{vic} 8.4 and 4.7 Hz, respectively, CH_2CO), 4.01 (m, 2-H), 5.39 (s, OCH_2Ar), 6.2 (br s, exchangeable, NH), 7.56 and 8.25 (AA'BB' system, *J* 8.8 Hz, 4 × ArH). This was in good agreement with the published spectra of the benzyl[11] and methyl esters.[16]

(*l*) The same compound (**12e**) was obtained in 88% yield, except that compound (**9e**) was used as the starting material, by diazo exchange as described in (*d*). Compound (**12e**) has been mentioned previously in the patent literature.[20,21]

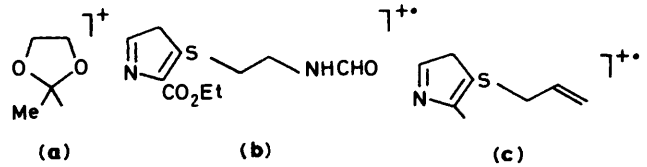
Ethyl and p-*Nitrobenzyl* (3RS,5RS,6SR)-6-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)-2-*oxocarbapenam*-3-*carboxylates* (**13a**), (**13b**) *and* p-*Nitrobenzyl* (3RS,5RS)-2-*Oxocarbapenam*-3-*carboxylate* (**13e**).—(*a*) $Rh_2(OAc)_4{\cdot}2$ THF (0.03 g) was slowly added in small portions to a refluxing benzene solution (10 ml) of compound (**12a**) (1.25 g, 4.0 mmol) in benzene (10 ml), until the latter was consumed. The mixture was filtered through Celite and evaporated to dryness to give compound (**13a**), m.p. 109 °C

(from ether), in quantitative yield (Found: C, 54.85; H, 6.2; N, 4.8. $C_{13}H_{17}NO_6$ requires C, 55.11; H, 6.05; N, 4.95%); $\nu_{max.}$(KBr) 1 770 and 1 735 cm^{-1}; δ_H 1.31 and 4.24 (t and q, J 7.1 Hz, CO_2Et), 1.49 (s, Me), 2.45 and 2.87 (*ABX* system, J_{AB} 18.8, J_{AX} 7.5, J_{BX} 7.0, $^4J_{A,3H}$ *ca.* 0.5, $^4J_{A,6H}$ *ca.* 0.5, $^4J_{B,3H}$ *ca.* 0.8 Hz, 1-H_2), 3.43 (d, J 2.4 Hz, 6-H), 3.95—4.15 (m, OCH_2CH_2O), 4.20 (ddd, J 7.5, 7.0, 2.4 Hz; 5-H), and 4.63 (t, J *ca.* 0.6 Hz, 3-H).

(*b*) Compound (**13b**), m.p. 167 °C (from benzene), was obtained in 84% yield by similar treatment of compound (**12b**) (4.0 mmol), except that the starting material required 10 h for complete consumption (Found: C, 55.6; H, 4.75; N, 7.4. $C_{18}H_{18}N_2O_8$ requires C, 55.38; H, 4.65; N, 7.18%); $\nu_{max.}$(KBr) 1 760 and 1 735 cm^{-1}; δ_H 1.48 (s, Me), 2.47 and 2.89 (2 × ddd which collapsed into 2 × dd on addition of ^2H_2O, J_{gem} 19, J_{vic} 7.6 and 7.0 Hz, respectively, with further very weak splitting which disappeared upon treatment with ^2H_2O, because of coupling with 3-H, 1-H_2), 3.46 (d, J 2.4 Hz, 6-H), 3.95—4.15 (m, OCH_2CH_2O), 4.09 (m, 5-H), 4.75 (t, ^4J *ca.* 0.5 Hz, slowly exchangeable, 3-H), 5.28 and 5.36 (AB, J 13 Hz, OCH_2Ar), and 7.53 and 8.23 (AA'BB' system, J 8.6 Hz, 4 × ArH).

(*c*) The oily compound (**13e**) was obtained in 84% yield by similar treatment of compound (**12e**). $\nu_{max.}$(film) 1 770br cm^{-1}; δ_H ($CDCl_3$ + [$^2H_6$] DMSO) 2.58 and 2.87 (*ABX* system, J_{gem} 18.5, J_{vic} 5.3 and 6.5 Hz, respectively, 1-H_2), 3.03 and 3.62 (*ABX* system, J_{gem} 16.0, J_{vic} 2.2 and 5.0 Hz, 6-H_2), 4.15 (dddd, J 5.3, 6.5, 2.2, and 5.0 Hz, 5-H), 4.77 (s, 3-H), 5.2—5.5 (m, OCH_2Ar), and 7.57 and 8.23 (AA'BB' system, J 8.6 Hz, 4 × ArH). Compound (**13e**) has been mentioned previously in the patent literature.[21]

Ethyl and p-*Nitrobenzyl* (5RS,6SR)-6-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)-2-(*substituted thio*)*carbapen*-2-*em*-3-*carboxylates* (**14a**), (**14b**), *and* (**15a**).—(*a*) Triethylamine (0.61 ml, 4.4 mmol) and diphenyl phosphorochloridate (0.91 ml, 4.4 mmol) were successively added over *ca.* 10 min with continuous stirring at 0 °C to a solution of compound (**13a**) (1.13 g, 4.0 mmol) in anhydrous acetonitrile (10 ml). A further portion of triethylamine (0.61 ml, 4.4 mmol) and *N*-formylcysteamine[12] (0.46 g, 4.4 mmol) were then added as above. Stirring at 0 °C was continued for 1 h. The mixture was evaporated to dryness at reduced pressure, and the residue was taken up in CH_2Cl_2 (20 ml). The solution was washed with aqueous $NaHCO_3$ (3%; 10 ml) and water (2 × 10 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by column chromatography [benzene–acetone, (7:3)] to give *ethyl* (5RS,6SR)-2-(2-*formylaminoethylthio*)-6-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*carbapen*-2-*em*-3-*carboxylate* (**14a**) (0.51 g, 36%), m.p. 152—153 °C (from methanol–ether) (Found: C, 51.65; H, 5.95; N, 7.4; S, 8.9. $C_{16}H_{22}N_2O_6S$ requires C, 51.87; H, 5.99; N, 7.56; S, 8.66%); $\nu_{max.}$(KBr) 3 400, 1 790, and 1 700—1 690br cm^{-1}; δ_H 1.34, 4.30, and 4.32 (t, q and q, J 7.0 Hz, CO_2Et), 1.45 (s, Me), 2.8—3.65 (m, 1-H_2, 6-H, and SCH_2CH_2N), 3.95—4.3 (m, OCH_2CH_2O and 5-H), 6.1 (br s, NH), and 8.21 (d, J *ca.* 2 Hz, CHO); δ_C 14.29 (CO_2CH_2Me), 23.39 (*C*Me), 31.64 (SCH_2), 38.59 (NCH_2), 40.06 (C-1), 51.99 (C-5), 61.32 ($CO_2CH_2CH_3$), 65.21 and 65.37 (OCH_2CH_2O), 67.20 (C-6), 106.85 (OCO), 125.40 (C-3), 144.84 (C-2), 161.44 (CO_2Et), 161.72 (NCHO), and 174.07 (C-7); *m/z*



(a) (b) (c)

* Or the aromatic tautomer.

(120—160 °C) 370 (0.5, M^+), 284 (11, $M^{+\bullet}$ − **a** + H), 242 (2; **b**), 197 (4; **c**), 87 (100; **a**), 43 (22; HNCO).

(*b*) The corresponding *p*-nitrobenzyl ester (**14b**), m.p. 183 °C (from ether), was similarly obtained in 64% yield, starting with compound (**13b**) (4.0 mmol) (Found: N, 8.85; S, 6.95. $C_{21}H_{23}N_3O_8S$ requires N, 8.80; S, 6.72%); $\nu_{max.}$(KBr) 3 350, 1 740, 1 680sh, and 1 670 cm^{-1}; δ_H ($CDCl_3$ and [$^2H_6$] DMSO) 1.42 (s, Me), 2.8—3.5 (m, 1-H_2 and SCH_2CH_2N), 3.58 (d, J 2.8 Hz, 6-H), 3.95—4.1 (m, OCH_2CH_2O), 4.18 (td, J 9.1 and 2.8 Hz, 5-H), 5.26 and 5.50 (AB system, J 14 Hz, OCH_2Ar), 7.70 and 8.21 (AA'BB' system, J 8.6 Hz, 4 × ArH), and 8.13 (s, NCHO).

(*c*) The benzylthio derivative (**15a**), m.p. 109 °C (from ether), was similarly obtained in 58% yield by the conversion of compound (**13a**) (4.0 mmol) into the enol phosphate and subjecting the latter to toluene-α-thiolysis (Found: N, 3.85; S, 7.9. $C_{20}H_{23}NO_5S$ requires N, 3.60; S, 8.23%); $\nu_{max.}$(KBr) 1 780 and 1 700 cm^{-1}; δ_H 1.32, 4.29, and 4.31 (t, q and q, J 7.0 Hz, CO_2Et), 1.42 (s, Me), 2.97 and 3.19 (*ABX* system, J_{gem} 18, J_{vic} 9.0 and 9.6 Hz, respectively, 1-H_2), 3.37 (d, J 3.0 Hz, 6-H), 3.95—4.2 (m, OCH_2CH_2O, SCH_2Ph and 5-H), and 7.33 (m, Ph); δ_C 14.30 (CO_2CH_2Me), 23.35 (*C*Me), 36.85 (SCH_2Ph), 40.28 (C-1), 51.94 (C-5), 61.15 (CO_2CH_2Me), 65.18 and 65.33 (OCH_2CH_2O), 67.15 (C-6), 106.85 (OCO), 124.47 (C-3), 127.70 (C-4'), 128.69 (C-3' and C-5'), 128.88 (C-2' + C −6'), 136.42 (C-1'), 145.93 (C-2), 161.32 (CO_2Et), and 173.91 (C-7) (primed locants refer to the phenyl group).

Sodium (5RS,6SR)-2-(2-*Formylaminoethylthio*)-6-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*carbapen*-2-*em*-3-*carboxylate* (**14c**).—A suspension of Pd–C catalyst (10%; 0.25 g) in dioxane–water (2:1, v/v; 70 ml) was stirred at room temperature for 20 min under hydrogen (1 atm). A warm solution of compound (**14b**) (0.48 g, 1 mmol) in peroxide-free dioxane (30 ml) was added, and the mixture was stirred for 3 h under hydrogen. Sodium hydrogen carbonate (84 mg, 1 mmol), dissolved in the minimum possible volume of water, was added, and the mixture was filtered through Celite. The filtrate was evaporated to dryness under reduced pressure at room temperature. The residue crystallized when chilled. It was suspended in ethanol (6 ml) and filtered off to give the title compound (0.25 g, 73%), m.p. 201 °C (decomp.) (Found: C, 45.85; H, 4.8; N, 7.55; S, 8.2. $C_{14}H_{17}N_2NaO_6S$ (364.37) requires C, 46.14; H, 4.70; N, 7.69; S, 8.80%); $\nu_{max.}$(KBr) 3 450, 1 770sh, 1 760, 1 695, and 1 610 cm^{-1}; δ_H (^2H_2O; reference: dioxane, δ 3.70) 1.41 (s, Me), 2.92 (m, SCH_2), 3.0—3.2 (m, 1-H_2), 3.40 (t, J 6.5 Hz, CH_2N), 3.65 (d, J 2.6 Hz, 6-H), 3.95—4.1 (m, OCH_2CH_2O), 4.12 (td, J 9.0 and 2.6 Hz, 5-H), and 8.04 (s, CHO); δ_C (^2H_2O; reference: dioxane, δ 67.6) 23.36 (Me), 31.66 (SCH_2), 39.07 (NCH_2), 39.66 (C-1), 53.24 (C-5), 65.79 (C-6), 66.11 and 66.14 (OCH_2CH_2O), 108.12 (OCO), 125.20 (C-3), 139.63 (C-2), 165.39 (NCHO), and 178.04 (C-2).

Pivaloyloxymethyl (5RS,6SR)-2(-2-*Formylaminoethylthio*)-6-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*carbapen*-2-*em*-3-*carboxylate* (**14d**).—The aqueous solution of compound (**14c**), prepared from compound (**14b**) (1 mmol) as described above, was evaporated to dryness at room temperature and under reduced pressure. The residue was dissolved in DMF (2 ml). Chloromethyl pivalate[15] (0.23 g, 1.5 mmol) was added, and after 1 h the mixture was evaporated to dryness under reduced pressure. Work-up by extraction of the residue with CH_2Cl_2 furnished the title compound (0.18 g, 41%) which was further purified by recrystallization from dioxane to give a sample of m.p. 140 °C (Found: C, 52.9; H, 6.25; N, 5.9; S, 6.75. $C_{20}H_{28}N_2O_8S$ (456.51) requires C, 52.62; H, 6.18; N, 6.14; S, 7.02%); $\nu_{max.}$(KBr) 3 400, 1 770, 1 745, and 1 675 cm^{-1}; δ_H 1.22 (s, Bu^t), 1.44 (s, Me), 2.85—3.65 (m, SCH_2CH_2N, 1-H_2 and 6-H), 3.95—4.1 (m, OCH_2CH_2O), 4.17 (td, J 9 and 2.7 Hz, 5-H), 5.85 and 5.96 (AB system, J 5.4 Hz, OCH_2O), 6.3 (br s, NH), and 8.21 (br s, CHO).

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