γ-Lactam Analogues of Carbapenicillanic Acids

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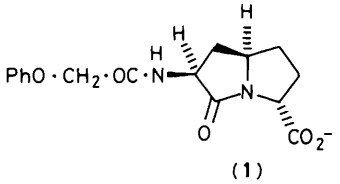
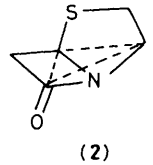
The synthesis and biological evaluation of the bicyclic-4,5-γ-lactam analogues [(**4a,b**), (**5**)] of carbapenicillanic acid are described.

In efforts to construct molecules having antibiotic properties similar to those of penicillins, we recently synthesised the β-lactam analogue (**1**) and showed it was devoid of both antibacterial and β-lactamase inhibitory activity.[1] *X*-Ray structure determination showed that the nitrogen atom of (**1**) was planar. Since it has been argued that the degree of pyramidal distortion of the N-4 nitrogen atom in penicillins, as in (**2**), is connected with antibacterial activity[2] we decided to synthesise fused γ-lactam-azetidine analogues, such as (**3**), since molecular models indicated similar pyramidal distortions at the nitrogen atom as observed in penicillins. The syntheses of these substances, (**4a,b**), and (**5**), were achieved *via* Schemes 2, 3, and 4.

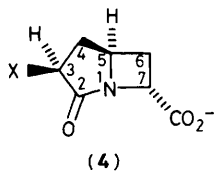


(**1**)

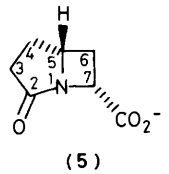


(**2**)

(**3**)



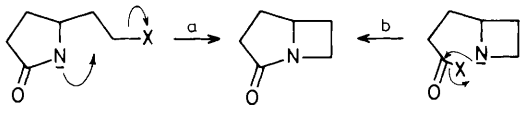
(**4**)



(**5**)

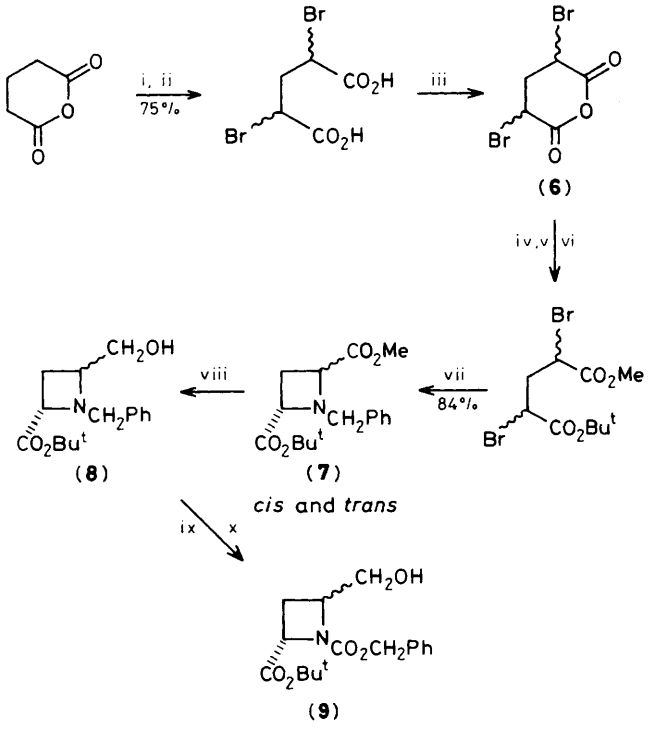
a; X = H
b; X = NHCOCH$_2$OPh

Thus glutaric anhydride was converted into α,α′-dibromoglutaric anhydride (**6**) [(±): *meso ca.* 3 : 1] and thence to diastereoisomeric azetidines *cis*-(**7**) and *trans*-(**7**) [84% from (**6**), *cis* : *trans* 2 : 3].† Reduction ($NaBH_4$) gave *cis*- and

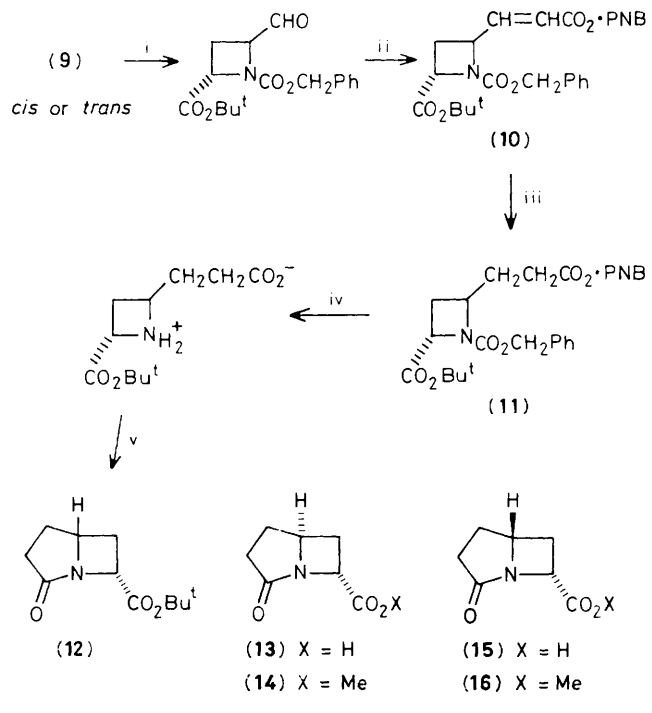


Scheme 1

† All new compounds gave satisfactory spectroscopic and analytical data.



Scheme 2. *Reagents*: i, Br_2, 100 °C; ii, HCO_2H; iii, MeCOCl, reflux; iv, MeOH, Na_2CO_3, CH_2Cl_2; v, $(COCl)_2$, C_5H_5N, CH_2Cl_2; vi, Bu^tOH, C_5H_5N, −30 °C; vii, $PhCH_2NH_2$ (3 equiv.), dimethylformamide, 80 °C (ref. 3); viii, $NaBH_4$, MeOH, 0 °C; ix, H_2, Pd, C, MeOH, 50 °C; x, $PhCH_2O{\cdot}CO{\cdot}Cl$, C_5H_5N, CH_2Cl_2.



Scheme 3. *Reagents*: i, dicyclohexylcarbodi-imide, Me_2SO, C_5H_5N, trifluoroacetic acid, C_6H_6, 0—25 °C; ii, $Ph_3P{=}CH{\cdot}CO_2PNB$, CH_2Cl_2, 25 °C; iii, $(PPh_3)_3RhCl$, C_6H_6, H_2, 50 °C; iv, H_2, 10% palladium on charcoal, MeOH, 0 °C; v, 2,2′-dipyridyl disulphide (ref. 5), PPh_3; PNB = p-$O_2NC_6H_4CH_2$.

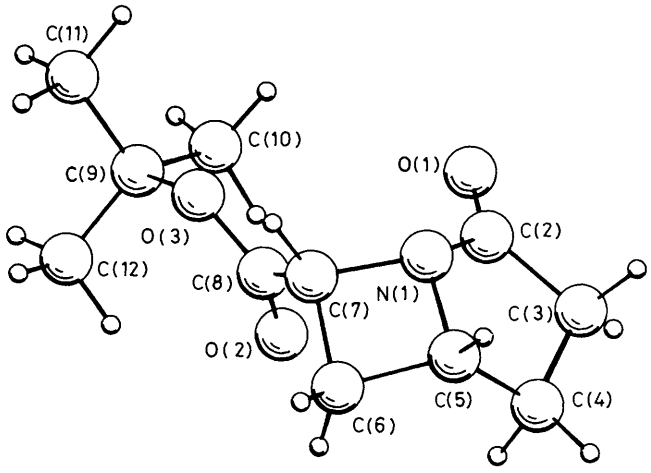


Figure 1. Structure of *cis*-(**12**).

trans-(**8**) (80%) from which *cis*-(**8**),‡ m.p. 93—95 °C, could be fractionally crystallised from light petroleum (b.p. 40—60 °C). Hydrogenation of the mother liquors [containing almost pure *trans*-(**8**)] followed by reprotection of the azetidine gave the *N*-benzyloxycarbonylazetidine *trans*-(**9**) (86%) m.p. 51–53 °C [from diethyl ether and light petroleum (b.p. 40—60 °C)]. A similar sequence applied to pure *cis*-(**8**) gave *cis*-(**9**) (93%) as an oil (Scheme 2).

The individual alcohols *trans*-(**9**) and *cis*-(**9**) were converted into the bicyclic-γ-lactam *trans*-(**12**)‡ [58% from *trans*-(**9**)], m.p. 73.5—4.5 °C (from diethyl ether and hexane), $\nu_{max.}$ ($CHCl_3$) 1740s, 1694s cm^{-1}, and bicyclic-γ-lactam *cis*-(**12**) [55% from *cis*-(**9**)], m.p. 75.0—75.5 °C (from diethyl ether), $\nu_{max.}$ ($CHCl_3$) 1736s, 1704s cm^{-1}, respectively by standard methods§ (Scheme 3). The structure¶ as *cis*-(**12**) was unequivocally established by *X*-ray crystallography (Figure 1).

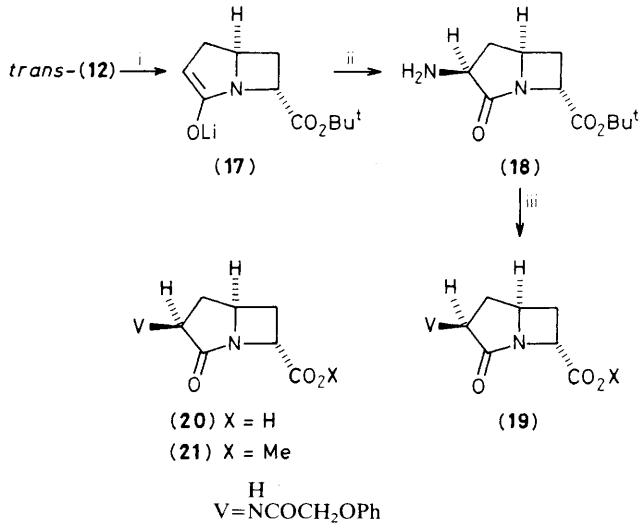
‡ The structures as *cis*-(**8**) and *trans*-(**12**) were confirmed by *X*-ray crystallographic methods (to be published).

§ Reduction using 10% palladium on charcoal as catalyst [H_2 (1 atm.), MeOH, 0 °C] of (**10**) led to ring opening of the azetidine ring (ref. 4) and thus a two stage reduction using Wilkinson's catalyst [$(PPh_3)_3RhCl,C_6H_6,H_2$ (1 atm.), 50 °C] for the initial conversion of (**10**) into (**11**) was employed to avoid this problem.

¶*Crystal data* for *cis*-(**12**): $C_{11}H_{17}NO_3$, M = 211.16, orthorhombic, space group *Pbca*, a = 10.775(3), b = 11.164(2), c = 18.807(3) Å, U = 2262.3 Å^3, Z = 8, D_c = 1.24 g cm^{-3}. 1985 Independent reflections were measured by four circle (CAD-4) diffractometry using Mo-K_α radiation (λ = 0.71069 Å). The structure was solved by direct methods (ref. 6). 1387 Reflections [$I \geq 3\sigma(I)$] uncorrected for absorption [μ(Mo-K_α) = 0.98 cm^{-1}] were used in a full matrix least squares (ref. 7) refinement for all atomic parameters including one overall temperature factor for the hydrogen atoms. Restraints (ref. 8) were applied to the C–H bonds, and to the methyl H–C–H bond angles. The final R value is 0.072 (R_w = 0.074).

Crystal data for (**19**): $C_{19}H_{24}N_2O_5$, M = 360.41, monoclinic, space group $P2_1/c$, a = 15.487(2), b = 11.093(2), c = 11.931(1) Å, β = 112.42(1)°, U = 1894.7 Å^3, Z = 4, D_c = 1.26 g cm^{-3}. 4669 Independent reflections were measured with an Enraf-Nonius CAD-4 diffractometer using Cu-K_α radiation (λ = 1.5418 Å). The structure was solved by direct methods (ref. 6). 3296 Reflections [$I \geq 3\sigma(I)$] uncorrected for absorption [μ(Cu-K_α) = 7.68 cm^{-1}] were used in a blocked matrix least squares (ref. 7) refinement. All atomic parameters were included in the refinement, including positional parameters for the hydrogen atoms and one overall temperature factor for the hydrogen atoms. The final R value is 0.057 (R_w = 0.081).

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



Scheme 4. *Reagents*: i, $LiN(SiMe_3)_2$ (1.1 equiv.), −78 °C, tetrahydrofuran; ii, $Ph_2PO{\cdot}O{\cdot}NH_2$ (ref. 9); iii, $PhOCH_2CO_2H$, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), CH_2Cl_2.

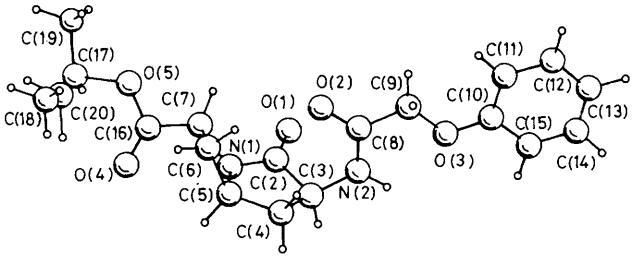
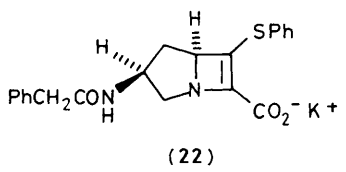


Figure 2. Structure of (**19**).

Treatment of *trans*-(**12**) with lithium hexamethyldisilazide (1.1 equiv.) gave the monoanion (**17**) which was quenched with *O*-(diphenylphosphinoyl)hydroxylamine[9] to the 3-aminobicyclic-γ-lactam (**18**)‖ (47%), δ_H(300 MHz, C^2HCl_3) 1.49 (9H, s, Bu^t), 1.69—1.89 (1H, m, 4-H), 2.10—2.42 (2H, br. m, NH_2), 2.56—2.73 (2H, m, 6-H), 2.77—2.87 (1H, m, 4-H), 3.78—3.85 (1H, m, 3-H), 4.42—4.51 (1H, m, 5-H), and 4.59 (1H, dd, *J* 5, 9.5 Hz, 7-H), which was then coupled to the phenoxymethylamido moiety to give (**19**) [40% from *trans*-(**12**)], m.p. 104—105 °C (from diethyl ether and hexane), $\nu_{max.}$ ($CHCl_3$) 1740s, 1705s, 1700 cm^{-1} (Scheme 4). The structure as (**19**) was established by *X*-ray crystallography (Figure 2).¶

The analogues *trans*-(**12**), *cis*-(**12**), and (**19**) were deprotected (trifluoroacetic acid) to (**13**), (**15**), and (**20**) respectively, then dissolved in pH 7.6 50 mM KH_2PO_4–K_2HPO_4–KCl buffer to give (**4a**), δ_H (300 MHz) 1.90—2.04 (1H, m, CH_2), 2.05—2.13 (1H, m, CH_2), 2.21—2.46 (4H, m, 2 × CH_2), 4.50—4.54 (1H, m, 5-H), and 4.93—5.04 (1H, m, 7-H); (**5**), δ_H(300 MHz) 2.06—2.49 (5H, m, CH_2), 2.67—2.76 (1H, m, 6-H), 4.27—4.32 (1H, m, 5-H), 4.64—4.71 (1H, m, 7-H, partially obscured by HOD); and (**4b**), δ_H(300 MHz) 2.08—2.22 (1H, m, 4-H), 2.54—2.83 (3H, m, 4-H, 6-H), 4.37—4.49 (1H, m, 5-H), 4.56 (2H, s, CH_2O), 4.59—4.70 (1H, m, 3-H), 4.75 (1H, dd, *J*8, 14 Hz, 7-H), and 6.83—7.28 (5H, m, aryl-*H*), respectively.

‖ The amine function was introduced *trans*- to the carboxylate ester function (*trans* : *cis* addition *ca.* > 10 : 1).



(**22**)

The analogues (**4a**), (**4b**), and (**5**) could be re-esterified (dimethylformamide, MeI) to the corresponding methyl ester derivatives (**14**), (**21**), and (**16**) respectively.

In common with antibacterial bicyclic-β-lactams, compounds *cis*-(**12**), *trans*-(**12**), and (**19**) have pyramidal lactam nitrogen atoms. The pyramidality was of a similar order to penicillin, the sum of the angles[10] around nitrogen for *cis*-(**12**), *trans*-(**12**), (**19**), and penicillin G being 334, 330, 326, and 337° respectively. However Cohen[11] has recently pointed out that a more significant parameter for antibacterial activity is the interatomic distance between the β-lactam oxygen atom and the carboxylate carbon, values of 3.0 and 3.9 Å being found for active compounds. In the crystal structures the analogous distances for *trans*-(**12**) and (**19**) were both 4.1 Å.

The bicyclic analogues (**4a**), (**4b**), and (**5**) were tested (Pfizer, Sandwich) against a representative panel of Gram positive and Gram negative organisms, including strains highly sensitive to penicillins. No significant antibacterial activity was detected. In separate experiments (**4a**), (**4b**), and (**5**) were tested for β-lactamase inhibitory effect against β-lactamase 1 (from *Bacillus cereus*). Again no significant activity was detected. Recently the preparation of an analogous compound, as (**22**), has appeared in a patent.[12] This substance was claimed to possess antibacterial activity against a wide range of bacterial pathogens.

We thank Dr. H-H. Ting, Dysons Perrins Laboratory for the β-lactamase inhibitory tests, Pfizer Central Research, Sandwich, Kent for support (to C. Z.) and the S.E.R.C. and Pfizer for C.A.S.E. support (to C. J. S.).

Received, 16th October 1984; Com. 1458

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