Synthesis *via* a Bicyclic β-Lactam of (αS,2R/αR,2S)-α-Aminopiperidine-2-acetic Acid, an Amino-acid Related to the Anti-tumour Agent '593A' [3,6-Bis-(5-chloro-2-piperidyl)piperazine-2,5-dione]

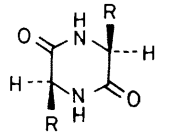
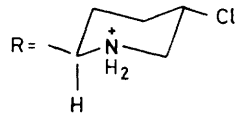
By BERNARD T GOLDING* and ANTHONY J SMITH
(*Department of Chemistry and Molecular Sciences, University of Warwick, Coventry* CV4 7AL)

Summary A stereoselective synthesis of (αS,2R/αR,2S)-α-aminopiperidine-2-acetic acid (**2a**) from ethyl 8-oxo-l-azabicyclo[4 2 0]octane-7-carboxylate (**4a**) is described

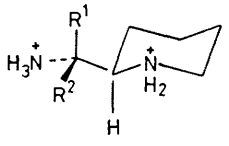
WE have undertaken the synthesis of the bifunctional alkylating agent 3,6-bis-(5-chloro-2-piperidyl)piperazine-2,5-dione ['593A' or *cyclo*-streptolutyl-streptolutyl, (**1**)] produced by *Streptomyces griseoluteus* [1] This compound is a potential anti-cancer drug[2] and its stereoisomers, homologues, and radiolabelled derivatives are required for biological evaluation We now report a straightforward synthesis of both diastereoisomers of α-aminopiperidine-2-acetic acid [(**2a**) and (**2b**)], the parent amino-acid of (**1**), thus paving the way to (**1**) and many analogues Other approaches to (**1**) have recently been reported [3,4]†

There is a correlation between the structure and stereochemistry of (**1**) and the penicillins, *e g* penicillin G (**3**) Strategies for the synthesis of β-lactam antibiotics and their nuclear analogues should therefore be adaptable to the preparation of (**1**) and analogues We have sought to extend Lowe's method[5] for preparing nuclear analogues of penicillins to the synthesis of structures related to (**1**)

Racemic ethyl 8-oxo-l-azabicyclo[4 2 0]octane-7-carboxylate[5] (**4a**) was hydrolysed (1 equiv KOH in aq dioxan left overnight at room temperature) to the acid (**4b**) ‡ Several attempts, using literature procedures,[5,6] to replace the carboxy-group of (**4b**) by an amino group failed Treating (**4a**) with NaH (1 equiv) in dimethyl sulphoxide easily generated the anion (**4c**), which was characterised by its ^{1}H n m r spectrum and by kinetic protonation (rapid addition to excess of dil acetic acid) to (**4a**) + (**4d**) (9 : 1) Reaction of the anion (**4c**) [generated by treating (**4a**) with lithium di-isopropylamide in tetrahydrofuran] with toluene-*p*-sulphonyl azide followed by chlorotrimethylsilane (procedure of ref 7) gave the azides (**4e**)‡ and (**4f**)‡ [the mixture was purified by 'flash chromatography'[8] on silica gel 60 (elution with ether)] Reduction (excess of H_2S and triethylamine[9] in CH_2Cl_2 for 15 min at room temperature) of (**4e**) + (**4f**) gave the amino–esters (**4g**)‡ and (**4h**)‡ purified by short column chromatography on silica gel (gradient elution with ether–methanol) Saponification (1·1 equiv NaOH in ethanol left overnight at room temperature) of (**4g**) + (**4h**) gave (**4i**)‡ which separated directly from the reaction mixture in 78% yield Heating (**4i**) in 5 M hydrochloric acid (5 h, 110 °C) gave a 2 : 1 mixture of the diastereoisomers [54% overall yield from (**4a**)], characterised as (**2a**)‡ and (**2b**),‡ respectively, by comparing their ^{1}H n m r spectra in 2 M DCl/D_2O with spectra[10] for *threo*- and *erythro*-2,3-diaminobutanoic acid, respectively The predominant diastereoisomer (**2a**) shows a narrow doublet (*J* 3 Hz) for α-H, as expected[10,11] for the diprotonated structure (**2a**) in the preferred conformation shown (protonated amino groups *anti*) (*cf J* 3·6 Hz for α-H of *threo*-2,3-diaminobutanoic acid under similar conditions) [10] The (αS,2R)-isomer of (**2a**) has the same chirality as at C-3 and C-2 of (**1**) The minor diastereoisomer (**2b**) shows a relatively wide doublet (*J* 7 Hz) for α-H which is consistent with the diprotonated structure (**2b**) existing in the preferred conformation shown (*cf J* 6 6 Hz for α-H of *erythro*-2,3-diaminobutanoic acid) [10]

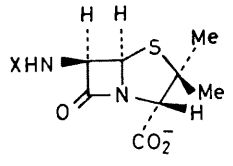



(1)



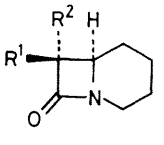
(2)

a, R^1 = CO_2H, R^2 = H
b, R^1 = H, R^2 = CO_2H



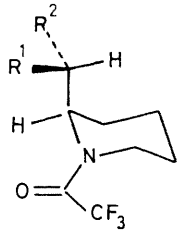
(3)

X = $PhCH_2C(:O)$



(4)

a, R^1 = H, R^2 = CO_2Et
b, R^1 = H, R^2 = CO_2H
c, R^1,R^2 = CO_2Et,–
d, R^1 = CO_2Et, R^2 = H
e,f, R^1,R^2 = CO_2Et, N_3
g,h, R^1,R^2 = CO_2Et, NH_2
i, R^1,R^2 = $CO_2^-Na^+$, NH_2



(5)

a, R^1 = $NHCOCF_3$, R^2 = CO_2Me
b, R^1 = CO_2Me, R^2 = $NHCOCF_3$

† Since submission of this manuscript, the synthesis of racemic (**1**) has been reported (T Fukuyama, R K Frank, and C F Jewell, *J Am Chem Soc*, 1980, **102**, 2122) *via* a monocyclic β-lactam

‡ New compounds had spectroscopic characteristics in accord with their assigned structure.

The mixture of amino-acids (**2a**) and (**2b**) was converted into their bis-*N*-trifluoroacetyl methyl esters (**5a**)‡ and (**5b**),‡ respectively, which were easily separated [60% recovery based on (**2a**) and (**2b**)] by 'flash chromatography'[8] on silica gel 60 (elution with ether–petrol, 1 : 1). The predominant diastereoisomer shows R_f 0·27 (t.l.c. Kieselgel GF_{254}, elution with ether–petrol, 1 : 1); m.p. 122·5—123·5 °C; δ ($CDCl_3$) 1·4—1·9 (m, $CH_2CH_2CH_2$), 3·31 (sextuplet, H-6_{ax}), 3·83 (m, H-6_{eq}), 3·83 (s, OCH_3), 4·88 (d of t, *J* 11, 3, and 3 Hz, *H*-2_{eq}), 5·15 (dd, *J* 10 and 11 Hz, α-H), and 7·13 (d, *J* 10 Hz, NH). As expected[12] for a 2-substituted *N*-acylpiperidine the preferred conformation of (**5a**) is a chair with the substituent at C-2 axial. Saponification (4 equiv. NaOH in 1 : 1 aq. methanol for 1 h at room temperature) of (**5a**) gave pure (**2a**). Similar treatment of (**5b**) [m.p. 122·5—123·5 °C, R_f 0·37 (t.l.c. as above)] gave (**2b**).

Conversion of (**5a**) into de-chloro-(**1**) and extension of the described route to (**1**) and a variety of analogues is in progress.

We thank the Cancer Research Campaign for financial support.

(*Received, 16th April* 1980; *Com.* 394.)

[1] B. H. Arison and J. L. Beck, *Tetrahedron*, 1973, **29**, 2743; G. R. Pettit, R. B. Von Dreele, D. L. Herald, M. T. Edgar, and H. B. Wood, *J. Am. Chem. Soc.*, 1976, **98**, 6742.
[2] J. A. Gottlieb, E. J. Freireich, G. P. Bodey, V. Rodriguez, K. B, McCredie, and J. U. Gutterman, *Proc. Am. Assoc. Cancer Res.*, 1975, **16**, 86; S. E. Jones, W. G. Tucker, A. Haut, B. L. Tranum, C. Vaughn, E. M. Chase, and B. G. M. Durie, *Cancer Treatment Reports*, 1977, **61**, 1617.
[3] G. R. Krow and C. Johnson, *Synthesis*, 1979, 50.
[4] M. T. Edgar, G. R. Pettit, and T. S. Krupa, *J. Org. Chem.*, 1979, **44**, 396.
[5] G. Lowe and J. Parker, *Chem. Commun.*, 1971, 577; D. M. Brunwin, G. Lowe, and J. Parker, *J. Chem. Soc.* (*C*), 1971, 3756.
[6] K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 1398.
[7] K. Kuhlein and H. Jensen, *Justus Liebigs Ann. Chem.*, 1974, 369.
[8] W. Clark Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
[9] *cf* T. Adachi, Y. Yamada, I. Inoue, and M. Saneyoshi, *Synthesis*, 1977, 45.
[10] E. Atherton and J. Meienhofer, *Z. Physiol. Chem.*, 1973, **354**, 689; W. K. Hausmann, D. B. Borders, and J. E. Lancaster, *J. Antibiot., Ser. A*, 1969, **22**, 207.
[11] Concerning the application of the Karplus relationship to amino-acids see R. B. Martin, *J. Phys. Chem.*, 1979, **83**, 2404.
[12] D. J. Hart, *J. Am. Chem. Soc.*, 1980, **102**, 397, and references cited therein.