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Total Synthesis of Nuclear Analogues of 7-Methyl-cephalosporin

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Summary The synthesis of (\pm) -8-oxo-7 β -phenylacetamido-7 α -methyl- 6α H-1-aza-4-thiabicyclo[4,2,0]octane-2 α carboxylic acid (5; R¹ = H, R² = Ph·CH₂·CONH) and (\pm) -8-oxo-7 β -phenylacetamido-7 α -methyl- 6α H-1-aza-4thiabicyclo[4,2,0]oct-2-ene-2-carboxylic acid (6; R¹ = H, R² = Ph·CH₂) are described.

THE prediction that 6-methyl-penicillins and 7-methylcephalosporins may possess enhanced antibacterial activity compared with the corresponding penicillins and cephalosporins was made by Strominger and Tipper on the basis of their hypothesis concerning the mode of action of these antibiotics.¹ The observation that 7-methoxy-cephalosporin C, isolated from a strain of Streptomyces lipmanii, exhibited greater activity than cephalosporin C against gram-negative organisms,² provided a further stimulus to synthesise the methyl analogues of the β -lactam antibiotics. Although the recently reported syntheses of 6α methyl-penicillin G and 7α -methyl-cephalosporins appear to have disproved this prediction, their antibacterial spectra are narrower and different from those of the parent antibiotics and may therefore provide certain clinical advantages.³

The route which we have developed for the synthesis of nuclear analogues of the penicillins and cephalosporins,⁴ appeared to provide access to their methyl analogues with the correct stereochemistry. This expectation has now been realised.

t-Butyl thiamorpholine-3-carboxylate (1) was prepared from mercaptoethylamine and t-butyl 1,2-dibromopropionate in the presence of triethylamine (cf. ref. 5), and on treatment with phenyl isocyanate gave a phenylhydantoin, thus confirming that it was an α -imino-ester. Coupling of phenylisopropyl hydrogen malonate to the thiamorpholine ester (1) was effected with dicyclohexylcarbodi-imide to give the amide (2; R = H). Diazo-exchange with methanesulphonyl azide was catalysed with triethylamine (cf. ref. 6) and the diazo-compound (2; $R = N_2$) isolated by partitioning the reaction mixture between water and light petroleum. The diazo-compound (2; $R = N_2$) in benzene was photolysed in a Pyrex vessel for 2 h at room temperature with a medium pressure mercury lamp. The reaction mixture contained the cis- and trans- β -lactams (3) and (4) in the ratio 7:3. The n.m.r. spectrum of both isomers contained a signal with the characteristic shape and in the expected position for a 2β -proton,⁴ thus establishing their stereochemistry across the thiamorpholine ring. Chromatography of the reaction mixture on neutral alumina epimerised the *cis*- to the *trans*-isomer (40%). Treatment of the trans- β -lactam (4) with one equivalent of potassium t-butoxide followed by methyl iodide gave only one isolable 7-methyl- β -lactam (85%). As anticipated the methylation of the carbanion had occurred stereoselectively, presumably from the least hindered face of the molecule to give the 7 α -methyl- β -lactam (5; $R^1 = Bu^t$, $R^2 = Ph \cdot CMe_2 \cdot O_2C$). Similar stereoselective alkylations leading to 6a-methylpenicillanic acid and 7a-methyl-cephalosporanic acid derivatives have been observed.3

The 7 α -methyl-derivative (5; $R^1 = Bu^t$, $R^2 = Ph \cdot CMe_2$ -O₂C) was selectively deprotected by treatment with anhydrous HCl in CH₂Cl₂ for 3 min at 0°, and the acid coupled with phenylisopropylcarbazate. The protected hydrazide (5; $R^1 = Bu^t$, $R^2 = Ph \cdot CMe_2 \cdot O_2C \cdot NH \cdot NHCO$) was selectively deprotected by treatment with anhydrous HCl in CH₂Cl₂ for 10 min at -5° , and the resulting acid hydrazide converted into the acid azide with nitrous acid at 0° . Curtius rearrangement of the acid azide was effected in refluxing benzene and the product, without isolation, was refluxed with t-butanol for a further 3 h to give the t-butylurethane (5; $R^1 = Bu^t$, $R^2 = Bu^tO_2C\cdot NH$). When the urethane was treated with chlorine at -60° followed by pyridine at 20°, the dihydrothiazine (6; $R^1 = Bu^t$, $R^2 =$ Bu^tO) [λ_{max} (EtOH) 305 (ϵ 3700), 262 nm (ϵ 4000); ν_{max} (CHCl₃) 1800 cm⁻¹ (β -lactam)] was obtained. Attempts to remove the t-butyl groups with trifluoroacetic acid however led to destruction of the nucleus.



Deprotection of the t-butyl-urethane (5; $R^1 = Bu^t$, $R^2 = Bu^tO_2C\cdot NH$) with trifluoroacetic acid, followed by acylation with phenylacetyl chloride gave the phenylacetamido-derivative (5; $R^1 = H$, $R^2 = Ph\cdot CH_2\cdot CONH$). Esterification of this acid with $\beta\beta\beta$ -trichloroethyl chloroformate in the presence of triethylamine gave the trichloroethyl ester (5; $R^1 = CH_2\cdot CCl_3$, $R^2 = Ph\cdot CH_2\cdot CONH$), which with 1·1 equiv. of chlorine at 0°, followed by dehydrochlorination with pyridine for 2 h at 20°, gave the unsaturated ester (6; $R^1 = CH_2\cdot CCl_3$, $R^2 = Ph\cdot CH_2$) as the only isolable product $[\lambda_{max} (EtOH) 306 (\epsilon 5100), 264 \text{ nm}$ ($\epsilon 5600$); $\nu_{max} (CHCl_3) 1790 \text{ cm}^{-1} (\beta\text{-lactam})]$. Removal of the $\beta\beta\beta$ -trichloroethyl ester was effected with zinc in 90%

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aqueous acetic acid to give the β -lactam-dihydrothiazinecarboxylic acid (6; $R^1 = H$, $R^2 = Ph \cdot CH_2$) [λ_{max} (EtOH) 296 nm (ϵ 4300); ν_{max} (CHCl₃) 1775 cm⁻¹ (β -lactam)]. The (\pm) -7 α -methyl-cephalosporin analogues (5; $R^1 = H$, $R^2 =$ $Ph \cdot CH_2 \cdot CONH$) and (6; $R^1 = H$, $R^2 = Ph \cdot CH_2$) were tested at 1 mg ml⁻¹ against Staphalococcus aureus (Oxford strain), Salmonella typhi (Felix and Pitt), and Alcaligines faecalis (Bristol), but no antibacterial activity was observed.

We gratefully acknowledge the award of an S.R.C. studentship (to D.M.B.) and financial support from the National Research Development Corporation. We thank Miss Janet Hamilton and Mrs. Sandra V. Goodyear for experimental assistance and Dr. P. B. Loder for the antibacterial testing.

(Received, 8th March 1972; Com. 388.)

¹ J. L. Strominger and D. J. Tipper, Amer. J. Med., 1965, 39, 708; D. J. Tipper and J. L. Strominger, Proc. Nat. Acad. Sci., U.S.A., 1965, 54, 1133.

¹ R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehn, W. M. Stark, and J. G. Witney, J. Amer. Chem. Soc., 1971, 93, 2308.
³ E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, J. Amer. Chem. Soc., 1971, 93, 4324; R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, Tetrahedron Letters, 1972, 375.
⁴ D. M. Brunwin, G. Lowe, and J. Parker, J. Chem. Soc. (C), 1971, 3756; Chem. Comm., 1971, 865.

- ⁵ B. Belleau, J. Med. Pharm. Soc., 1960, 2, 553.
- ⁶ M. Regitz, Angew. Chem. Internat. Edn., 1967, 6, 733.