Total Synthesis of Nuclear Analogues of 7-Methyl-cephalosporin

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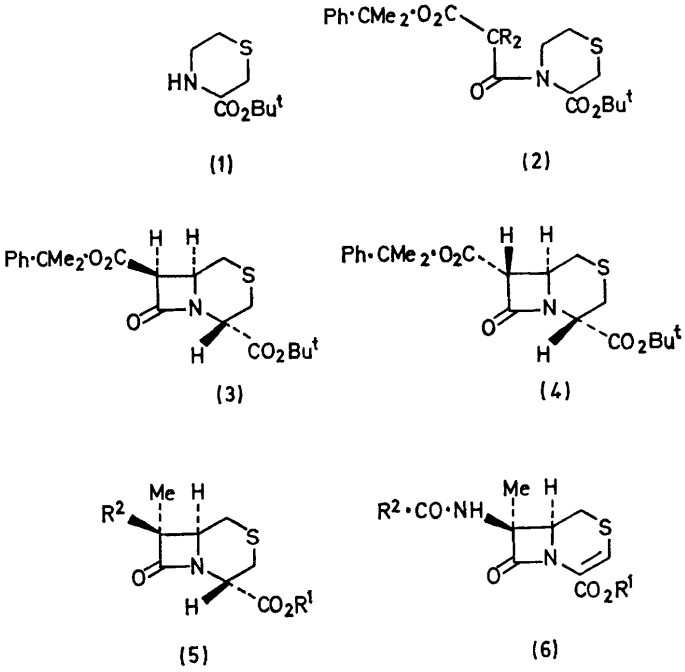
Summary The synthesis of (±)-8-oxo-7β-phenylacetamido-7α-methyl-6α*H*-1-aza-4-thiabicyclo[4,2,0]octane-2α-carboxylic acid (**5**; R^1 = H, R^2 = Ph·CH_2·CONH) and (±)-8-oxo-7β-phenylacetamido-7α-methyl-6α*H*-1-aza-4-thiabicyclo[4,2,0]oct-2-ene-2-carboxylic acid (**6**; R^1 = H, R^2 = Ph·CH_2) are described.

THE prediction that 6-methyl-penicillins and 7-methyl-cephalosporins 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 7α-methyl-β-lactam (**5**; R^1 = Bu^t, R^2 = Ph·CMe_2·O_2C). Similar stereoselective alkylations leading to 6α-methyl-penicillanic acid and 7α-methyl-cephalosporanic acid derivatives have been observed.[3]

The 7α-methyl-derivative (**5**; R^1 = Bu^t, R^2 = Ph·CMe_2·O_2C) was selectively deprotected by treatment with anhydrous HCl in CH_2Cl_2 for 3 min at 0°, and the acid coupled with phenylisopropylcarbazate. The protected hydrazide (**5**; R^1 = Bu^t, R^2 = Ph·CMe_2·O_2C·NH·NHCO) was selectively deprotected by treatment with anhydrous HCl in CH_2Cl_2 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-butyl-urethane (**5**; R^1 = Bu^t, R^2 = Bu^tO_2C·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} ($CHCl_3$) 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·NH) with trifluoroacetic acid, followed by acylation with phenylacetyl chloride gave the phenylacetamido-derivative (**5**; R^1 = H, R^2 = Ph·CH_2·CONH). Esterification of this acid with ββ-trichloroethyl chloroformate in the presence of triethylamine gave the trichloroethyl ester (**5**; R^1 = CH_2·CCl_3, R^2 = Ph·CH_2·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·CCl_3, R^2 = Ph·CH_2) as the only isolable product [λ_{max} (EtOH) 306 (ε 5100), 264 nm (ε 5600); ν_{max} ($CHCl_3$) 1790 cm^{-1} (β-lactam)]. Removal of the ββ-trichloroethyl ester was effected with zinc in 90%

aqueous acetic acid to give the β-lactam-dihydrothiazine-carboxylic acid (**6**; $R^1 = H$, $R^2 = Ph{\cdot}CH_2$) [λ_{max} (EtOH) 296 nm (ε 4300); ν_{max} ($CHCl_3$) 1775 cm^{-1} (β-lactam)]. The (±)-7α-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.

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