6α-Substituted Penicillins

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Summary Benzyl 6-isocyanopenicillanate (**2a**), has been utilised in the preparation of 6α-substituted penicillins.

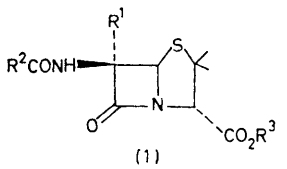
RECENT publications have described the preparation of 6(7)α-substituted penicillins and cephalosporins which are of considerable biological interest.[1] We report our approach to these substances based on the activating influence of an isocyanide group.

Treatment of benzyl 6β-formylaminopenicillanate (**1a**) with phosgene at −40° in the presence of tertiary base provided, after chromatography, benzyl 6-isocyanopenicillanate (52%) as a mixture of its 6β (**2a**) (45%) and 6α (55%) epimers. The 6α-epimer was isolated by fractional crystallisation, m.p. 87—89°, ν_{max} ($CHCl_3$) 2140, 1795, and 1745 cm^{-1}, $J_{5,6}$ ($CDCl_3$) 1·5 Hz.† The same 55:45 ratio of 6α:6β epimers was rapidly obtained when pure 6α-epimer was equilibrated with base.

When the isocyanide (**2a**) as its epimeric mixture was treated at room temperature with reactive alkyl halides in dimethylformamide and potassium carbonate as base, substitution occurred readily to give predominantly one epimer assigned the structures (**2b—2d**). Under the same conditions benzyl acrylate provided the Michael addition product (**2e**) and acetone gave (**2f**).

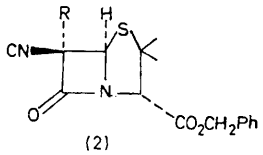
† Satisfactory analytical and spectral data were obtained for all new compounds.

The 6α-methylthio-substituent as in (**2g**) was introduced by carrying out the reaction (54%) in the presence of methyl methoxycarbonyl disulphide.



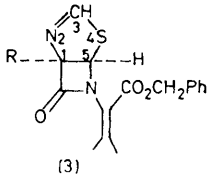
(1)

a; $R^1 = R^2 = H$, $R^3 = CH_2Ph$
b; $R^1 = R^3 = CH_2Ph$, $R^2 = H$
c; $R^1 = C(OH)Me_2$, $R^2 = H$, $R^3 = CH_2Ph$
d; $R^1 = OMe$, $R^2 = R^3 = CH_2Ph$
e; $R^1 = OMe$, $R^2 = CH_2Ph$, $R^3 = H$
f; $R^1 = OMe$, $R^2 = $ D-PhCH(NH_2), $R^3 = H$



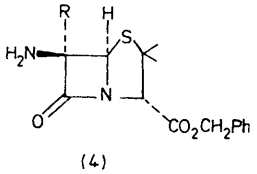
(2)

a; R = H
b; $R = CH_2Ph$
c; $R = CH_2CO_2Me$
d; $R = CH_2COPh$
e; $R = CH_2CH_2CO_2CH_2Ph$
f; $R = C(OH)Me_2$
g; R = SMe



(3)

a; $R = CH_2Ph$
b; $R = CH_2CH_2CO_2CH_2Ph$
c; R = SMe



(4)

a; $R = CH_2Ph$
b; R = SMe

The evidence for assigning the 6α-configuration to the ingoing substituents (R) in (**2b**—**2g**) was as follows. Firstly (**2g**) was converted as described below into (**4b**) and thence into benzyl 6α-methoxyphenylacetamidopenicillanate (**1d**) by phenylacetylation of (**4b**) followed by the chlorine-triethylamine–methanol procedure of Spitzer and Goodson.[2] The physical data for (**1d**) were in complete accord with those reported for (**1d**) prepared by the 6-diazo-route.[3] Hydrogenation of (**1d**) afforded 6α-methoxybenzylpenicillin (**1e**). Secondly it was observed that if the reactions leading to (**2e**) and (**2g**) were extended in time or, if (**2b**), (**2e**), or (**2g**) were subsequently treated with base, either potassium carbonate or sodium thiophenoxide in dimethylformamide, there resulted a ready rearrangement to the thiazoline azetidinones (**3a**)—(**3c**). The structure of (**3c**), m.p. 85°, M^+ 362, follows from its spectral properties, ν_{max} ($CHCl_3$) 1775, 1720, 1622 cm^{-1}; δ ($CDCl_3$) 1·88, 2·21 (2s, 3H each, CH_3), 2·29 (s, 3H, SCH_3), 5·23 (s, 2H, CH_2), 5·68 (1H, d, *J* 1·4 Hz, C_5-H), 7·41 (s, 5H, Ph-H), and 8·02 (1H, d, *J* 1·4 Hz, C_3-H).

This rearrangement, which is assumed to involve base abstraction of the thiazolidine C_3 proton from the isocyanides (**2b**), (**2e**), and (**2g**), followed by trapping of the developing thiolate by the electrophilic isocyanide carbon, defines unambiguously their stereochemistry at C-6.

Conversion of isocyanide into acylamino was initially carried out by treatment with formic acid in chloroform. In this way, isocyanides (**2b**) and (**2f**) led directly to the formyl penicillin esters (**1b**) and (**1c**) respectively. More conveniently however, it was found that treatment of the isocyanides, *e.g.* (**2b**) and (**2g**) with one equivalent of toluene-*p*-sulphonic acid resulted in the amines (**4a**) m.p. 163—164°, and (**4b**)‡ m.p. 136—138° respectively as their crystalline toluene-*p*-sulphonates.

The 6α-methoxy-derivative (**1f**) of D-α-aminobenzylpenicillin (ampicillin) was prepared in a manner similar to that described for (**1e**). The MIC values for (**1e**) and (**1f**) against *Staph. aureus* Oxford were 125 μg/ml compared with the benzyl penicillin value of 0·05 μg/ml.

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‡ (**4b**) has recently been described (ref. 4).

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[2] W. A. Spitzer and T. Goodson, *Tetrahedron Letters*, 1973, 273.
[3] L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, 1972, **94**, 1408. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, 1973, **38**, 2857.