Penicillin Analogues with Modified Nucleus[1]

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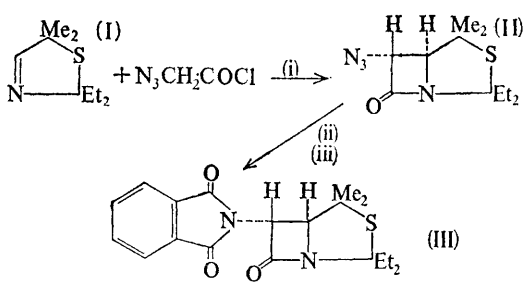
ALTHOUGH many 'semisynthetic' penicillins have been reported, few instances are known where the penicillin nucleus' has been modified.[2] We report here the synthesis of a few penicillin analogues of the latter type.

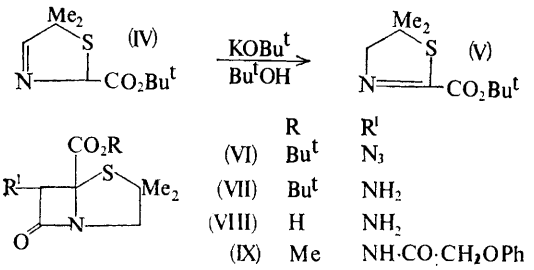
Previously[3] we described a synthesis of α-azido-β-lactams from α-azido-acid chlorides and a variety of Schiff bases. Similarly triethylamine was added under high-dilution conditions to a methylene chloride solution of azido-acetyl chloride and 2,2-diethyl-5,5-dimethyl-Δ^3-thiazoline (I) prepared from α-bromo-isobutyraldehyde, hydrogen sulphide, pentan-3-one and ammonia.[4] This reaction led to a non-crystalline α-azido-β-lactam (II) which was hydrogenated in the presence of Adams catalyst. The resulting amino-compound was heated under reflux with phthalic anhydride and triethylamine.[5] The product showed properties consistent with the expected structure (III) (β-lactam of 2,2-diethyl-5,5-dimethyl-α-phthalimido-4-thiazolidineacetic acid). The 4,6-*trans* stereochemistry of the β-lactam ring was apparent from the coupling constant $J_{4,6}$ 1·7 c./sec.[6]



Reagents: (i) NEt_3, (ii) H_2–PtO_2, (iii) phthalic anhydride, NEt_3.

In the hope of synthesizing an isomer of penicillin-V with the rearranged penam nucleus [as in (III)], 2-t-butoxycarbonyl-5,5-dimethyl-Δ^3-thiazoline (IV) was prepared by a modified Asinger

reaction[4] using t-butyl glyoxalate hydrate.[7] When (IV) was allowed to react with azido-acetyl chloride and triethylamine, only traces of a β-lactam were formed. Brief treatment of (IV) with potassium t-butoxide in t-butanol led to an isomer, 2-t-butoxycarbonyl-5,5-dimethyl-Δ^2-thiazoline (V) which with azido-acetyl chloride and triethylamine readily afforded in good yield the same product as was obtained earlier from (IV). This compound was identified as the β-lactam of 2-t-butoxycarbonyl-5,5-dimethyl-α-azido-2-thiazolidine acetic acid (VI). Catalytic reduction of (VI) to (VII) followed by treatment with trifluoroacetic acid produced the amino-acid (VIII) which was difficult to purify. Acylation of crude (VIII) with phenoxy-acetyl chloride and subsequent treatment with diazomethane gave (IX)—a structural isomer of penicillin-(V) methyl ester.



	R	R¹
(VI)	But	N_3
(VII)	But	NH_2
(VIII)	H	NH_2
(IX)	Me	NH·CO·CH_2OPh

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[1] For the previous paper in this series, see: M. S. Manhas, S. Jeng, and A. K. Bose, *Tetrahedron*, 1968, **3**, 1237.
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[3] A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.
[4] M. Thiel, F. Asinger, and K. Schmeidel, *Annalen*, 1958, **611**, 121.
[5] *cf.* A. K. Bose, *Org. Synth.*, 1960, **40**, 82.
[6] H. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Letters*, 1964, 941.
[7] Synthesized by the method of N. Kornblum and H. W. Frazier, *J. Amer. Chem. Soc.*, 1966, **88**, 865.