SPIROPENICILLINS.
SYNTHESIS OF A NEW SPIRO (1,2,4-TRIAZINO)-3,6'-PENICILLIN

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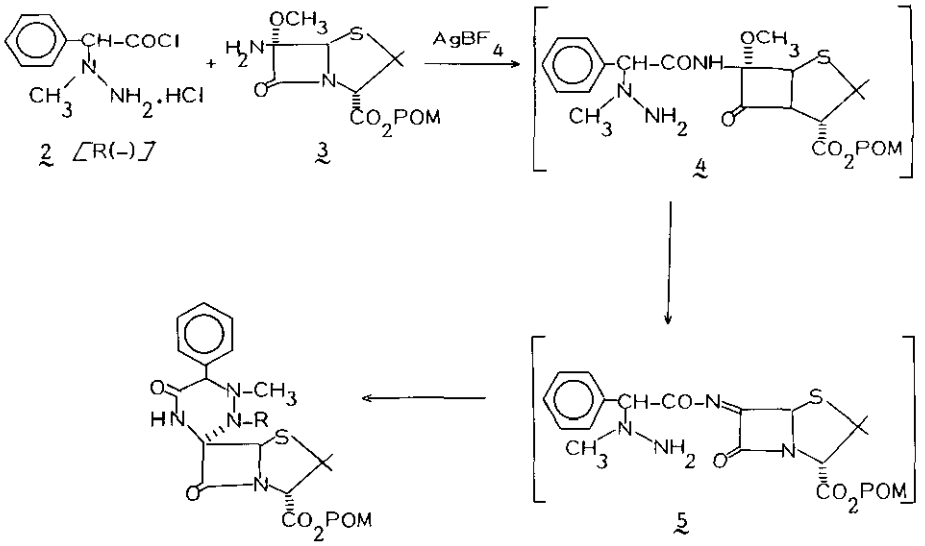
Abstract - Acylation of 6β-amino-6α-methoxypenicillanate (3) with the α-hydrazino-acid chloride (2), afforded the new spirotriazinopenicillin (1a). This unusual ring formation might proceed via an acylimino intermediate.

With the aim of increasing the penicillinase resistance of some α-hydrazinobenzylpenicillins, a new class of oral broad spectrum antibiotics[1], the introduction of 6α-methoxy group into the penam nucleus was considered worth investigating. We now report that condensation of the acid chloride (2) with the 6β-amino-6α-methoxy-penicillanate (3) led to the isolation of the spiropenicillin (1a) instead of the expected penicillin (4). Literature reports only few spiropenicillins with two heteroatoms linked to C_6[2], but (1a) is the first spirotriazinopenicillin.

The key intermediate for the preparation of (1a) was the pivaloyloxymethyl (POM) *ester* (3), which was obtained from the corresponding 6β-aminopenicillanic acid POM ester as described[3]. Compound (3) was reacted with (2) in methylene chloride at 0° in the presence of anhydrous $AgBF_4$ and an excess of propylene oxide as acid scavenger. After work up and silicagel chromatography, the spiro (1,2,4-triazino)-3,6'-penicillinate (1a) was obtained as foam in 30% yield.



1a R = H POM = $CH_2OCOC(CH_3)_3$

1b R = $COCF_3$

Structure assignment of (1a) was based on the following spectral data [4]: ir (oil mull) [1775, 1760, 1675, 1595, 1110, 980 cm^{-1}, lack amide II]; nmr ($CDCl_3$) [7.6 - 7.4 c.a., Ar - H; 5.93 s, OCH_2O; 5.75 s, H-5; 4.82s, ArCH; 4.60 s, H-3; 2.95 s, N-CH_3; 1.63 s and 1.51 s, gem CH_3; 1.24 s, $C(CH_3)_3$]; ms (70eV) [490 (M^+), 462, 274, 118, 85 m/e].

The configuration at C_6 was tentatively assigned on the basis of the preferred mode of attack at the less hindered side [5,6] of penicillin molecule, probably via the acylimino derivative (5). In addition, the derivative (1b) was easily obtained by acylation of (1a) with equimolar quantities of $(CF_3CO)_2O$ and pyridine in benzene at room temperature. This acylation would be sterically strongly hindered if the attack of the hydrazino group was beta, as seen by inspection of Dreiding models of the C_6 epimer of (1a). The compound (1b) had the following spectral data: ir (oil mull) [1760, 1670, 1195, 1155 cm^{-1}]; nmr ($CDCl_3$) [7.55 - 7.35 c.a., ArH; 6.02 s, H-5; 5.85 s, O-CH_2O; 4.78 s, Ar-CH; 4.58 s H-3; 2.90 s N-CH_3; 1.55 and 1.50 s, gem CH_3; 1.20s, $C(CH_3)_3$].

The biological assay of (1a) showed a very low antimicrobial activity.

References and Notes

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3. H. Yanagisawa, M. Fukushima, A. Ando and H. Nakao, J. Antibiotics, 1976, 29, 969; Compound 3, reported as a syrup, is a white solid with m.p. 63-65° and $[\alpha]_D^{20}$ = + 121° (C=1; $CHCl_3$).
4. Ir spectra were recorded on a Perkin Elmer spectrophotometer model 177, nmr spectra on a Perkin Elmer R12B instrument and ms spectra on a Varian spectrometer model MAT 112. The following abbreviations were here used: c.a. = complex absorption; s = singlet.
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Received, 3rd August, 1979