

SPIROPENICILLINS.

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

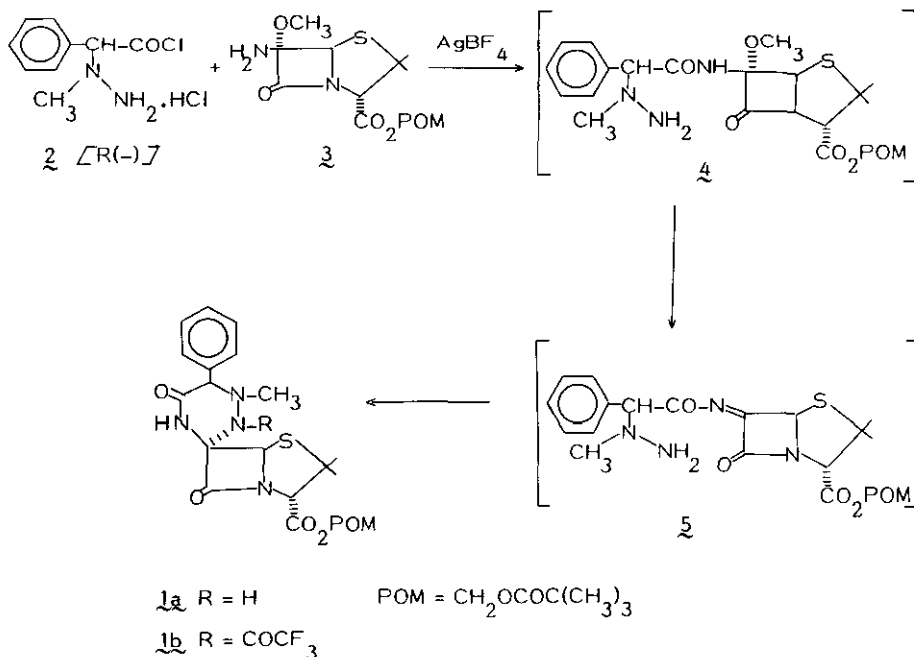
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Abstract - Acylation of 6 β -amino-6 α -methoxypenicillanate (**3**) with the α -hydrazinobenzoyl acid chloride (**2**), afforded the new spirotriazinopenicillin (**1a**). This unusual ring formation might proceed via an acylimino intermediate.

With the aim of increasing the penicillinase resistance of some α -hydrazinobenzylpenicillins, a new class of oral broad spectrum antibiotics¹, the introduction of 6 α -methoxy group into the penam nucleus was considered worth investigating. We now report that condensation of the acid chloride (**2**) with the 6 β -amino-6 α -methoxypenicillanate (**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 C₆², 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 6 β -aminopenicillanic acid POM ester as described³. Compound (**3**) was reacted with (**2**) in methylene chloride at 0° in the presence of anhydrous AgBF₄ 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.



Structure assignment of (1a) was based on the following spectral data⁴: ir (oil mull) $\bar{\nu}$ 1775, 1760, 1675, 1595, 1110, 980 cm^{-1} , lack amide II $\bar{\nu}$; nmr (CDCl_3) δ 7.6 – 7.4 c.a., Ar-H; 5.93 s, OCH_2O ; 5.75 s, H-5; 4.82 s, 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, $\text{C}(\text{CH}_3)_3$; ms (70eV) m/z 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 $(\text{CF}_3\text{CO})_2\text{O}$ 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) $\bar{\nu}$ 1760, 1670, 1195, 1155 cm^{-1} ; nmr (CDCl_3) δ 7.55 – 7.35 c.a., ArH; 6.02 s, H-5; 5.85 s, $\text{O}-\text{CH}_2\text{O}$; 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 ; 1.20 s, $\text{C}(\text{CH}_3)_3$.

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

References and Notes

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2. K. Hirai, Y. Iwano, T. Saito, T. Hiraoka and Y. Kishida, *Tetrahedron Lett.*, 1976, 1303; D.H. Bremner, M.M. Campbell and G. Johnson, *J. Chem. Soc. Perkin I*, 1976, 1918; D.H. Bremner, M.M. Campbell and G. Johnson, *Chem. Comm.*, 1976, 293; M.M. Campbell and R.G. Marcus, *Tetrahedron Lett.*, 1979, 1441.
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 $[\alpha]_D^{20} = +121^\circ$ ($\text{C}=1$; 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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