SEMISYNTHETIC β-LACTAM ANTIBIOTICS. IV[1].
SYNTHESIS OF A NEW α-HYDRAZINOBENZYL-6α-METHOXYPENICILLIN

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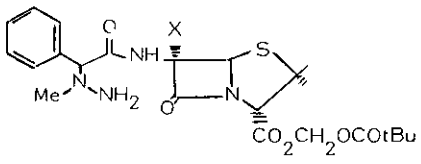
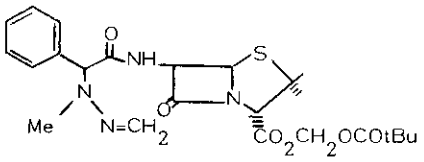
Abstract - Acylation of 6β-amino-6α-methoxypenicillanate (4b) with the α-methylene-hydrazinoacid chloride (3b) afforded the new 6α-methoxy-6β-triazinonepenicillin (5).

Within the framework of a research programme to prepare new α-hydrazinobenzylpenicillins[2,3] we became interested in the synthesis of 6α-methoxypenicillin (1b). It was previously reported that, under the conditions of synthesis employed, penicillin (1b) undergo a complete intramolecular cyclization promoted by the free hydrazino group to the corresponding spiro (1,2,4-triazino)-3,6'-penicillanate[4].
Assuming that the cyclization step of (1b) is slow enough in vivo, we thought that the problem might be circumvented by means of a hydrolitically cleavable protection of the hydrazino group. In this paper we describe the synthesis of a methylene derivative of (1b).



1a X = H
b X = OMe



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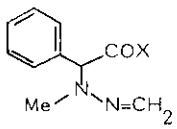
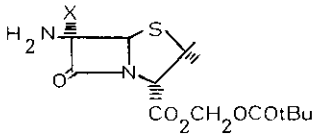
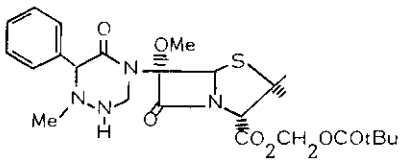


3a X = OH
b X = Cl



4a X = H
b X = OMe



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Some approaches to obtain the derivative (2), a protected form of the penicillin (1a) were initially studied. An excess of gaseous formaldehyde was bubbled into a methylene chloride solution of the penicillin (1a) at room temperature. After work up, the methylene derivative (2) (90%) was obtained as foam, mp 41-44°C: ir (neat) [1785, 1750, 1680, 1108, 980 cm^{-1}]; nmr ($CDCl_3$) [δ 7.40 c.a., Ar-H; 6.33 s, N = CH_2; 5.95 - 5.55

c.a.; O-C$\underline{H}_2$-O, $\underline{H}$-5, $\underline{H}$-6; 5.05 s, Ar-C$\underline{H}$; 4.49 s, $\underline{H}$-3; 2.67 s, N-C$\underline{H}_3$; 1.60 s and 1.51 s, gem C$\underline{H}_3$; 1.20 s, C(C$\underline{H}_3$)$_3$-] ; ms (70 eV) [504 (M^+), 345, 274, 147, 118, 85, 57 m/e].

In an alternate way, the methylenation of sodium R-α-(1-methylhydrazino)phenylacetate[2] with formaldehyde in water containing a catalytic amount of acetamide afforded the compound (3a) which was isolated in nearly quantitative yield as an oily TEA salt [$[\alpha]_D^{20}$ = -96.2° (c=1; $CHCl_3$); ir (neat) [2500, 1615, 1380 cm^{-1}]; nmr ($CDCl_3$) [δ7.55 - 7.25 c.a., Ar-$\underline{H}$; 6.33 and 6.02, AB system, J_{AB} =12Hz, N=C$\underline{H}_2$; 5.30 s, Ar-C$\underline{H}$; 2.99 q J=7.3 Hz, $\overset{\oplus}{N}$-C$\underline{H}_2$-CH$_3$; 2.70 s, N-C$\underline{H}_3$; 1.20 t J=7.3 Hz, $\overset{\oplus}{N}$-CH$_2$-C$\underline{H}_3$]. The TEA salt of (3a) was reacted with one equivalent of thionyl chloride in methylene chloride at -25°C to give the corresponding acyl chloride (3b) [ir (CH_2Cl_2) ν_{CO} = 1790 cm^{-1}] which was treated at the same temperature with an excess of propylene oxide and 0.5 equivalents of (4a). After one hour at 0°C and silica gel chromatography with hexane-ethyl acetate, (2) was obtained identical to that from the above preparation.

The same condensation was finally performed on (4b)[4,5] and, on the basis of spectral data, the triazine structure (5) was assigned to the obtained penicillin (yield 33%, mp 52 - 58°C). [$[\alpha]_D^{20}$ = +69.1° (c=1; $CHCl_3$); ir (oil mull) [ν_{CO}=1760 cm^{-1}]; nmr ($CDCl_3$ + D_2O) [δ7.48 c.a., Ar$\underline{H}$; 5.89 s, -O-C$\underline{H}_2$-O; 5.40 s, $\underline{H}$-5; 4.72 s, Ar-C$\underline{H}$; 4.50 s, $\underline{H}$-3; 4.62 and 4.42 AB system, J_{AB}= 15 Hz, N-C$\underline{H}_2$-N; 3.46 s, OC$\underline{H}_3$; 2.87 s, N-C$\underline{H}_3$; 1.51 s and 1.48 s, gem C$\underline{H}_3$; 1.22 s, C(C$\underline{H}_3$)$_3$-]; ms (70 eV) [534 (M^+), 519, 502, 373, 274, 147, 118, 85, 57 m/e]. It is worth noting the analogy of structure (5) with hetacillin, a known prodrug of ampicillin. The methylene penicillin (2) displays in vivo[6] the same antimicrobial activity already described[3] for the parent compound (1a). The activity of the penicillin (5) is about one-third and one-eighth, respectively, of that one of (1a) and ampicillin.

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References and Notes

1. Note III: M. Pinza, G. LiBassi, G. Broccali and G. Pifferi, Heterocycles, 1976, 4, 1699.
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6. Antibacterial activities were evaluated by subcutaneous administration to mice experimentally infected with Staphylococcus aureus Gray Weinstein.

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