

SEMISYNTHETIC  $\beta$ -LACTAM ANTIBIOTICS. IV<sup>1</sup>.

 SYNTHESIS OF A NEW  $\alpha$ -HYDRAZINO BENZYL-6 $\alpha$ -METHOXYPENICILLIN

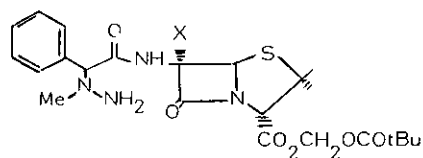
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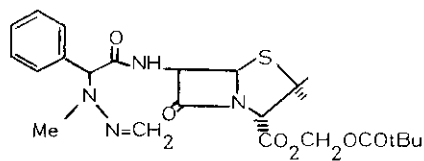
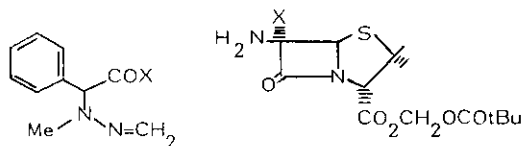
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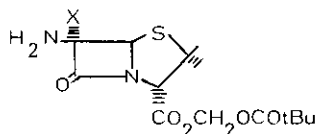
**Abstract** - Acylation of 6 $\beta$ -amino-6 $\alpha$ -methoxypenicillanate (**4b**) with the  $\alpha$ -methylene-hydrazinoacid chloride (**3b**) afforded the new 6 $\alpha$ -methoxy-6 $\beta$ -triazinonepenicillin (**5**).

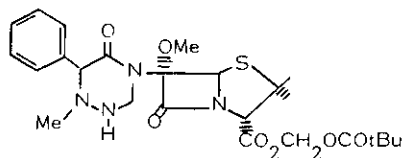
Within the framework of a research programme to prepare new  $\alpha$ -hydrazinobenzylpenicillins<sup>2,3</sup> we became interested in the synthesis of 6 $\alpha$ -methoxypenicillin (**1b**). It was previously reported that, under the conditions of synthesis employed, penicillin (**1b**) undergo a complete intramolecular cyclization promoted by the free hydrazino group to the corresponding spiro (1,2,4-triazino)-3,6'-penicillanate<sup>4</sup>.

Assuming that the cyclization step of (**1b**) is slow enough *in vivo*, we thought that the problem might be circumvented by means of a hydrolytically cleavable protection of the hydrazino group. In this paper we describe the synthesis of a methylene derivative of (**1b**).


**1a** X = H

**1b** X = OMe

**2**

**3a** X = OH

**3b** X = Cl

**4a** X = H

**4b** X = OMe

**5**

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)  $\bar{\nu}$  1785, 1750, 1680, 1108, 980  $\text{cm}^{-1}$ ; nmr (CDCl<sub>3</sub>)  $\delta$  7.40 c.a., Ar-H; 6.33 s, N = CH<sub>2</sub>; 5.95 - 5.55

c.a.; O-CH<sub>2</sub>-O, H-5, H-6; 5.05 s, Ar-CH; 4.49 s, H-3; 2.67 s, N-CH<sub>3</sub>; 1.60 s and 1.51 s, gem CH<sub>3</sub>; 1.20 s, C(CH<sub>3</sub>)<sub>3</sub>; ms (70 eV)  $\mathcal{L}^{504} (M^+)$ , 345, 274, 147, 118, 85, 57 m/e.

In an alternate way, the methylenation of sodium R- $\alpha$ -(1-methylhydrazino)phenylacetate<sup>2</sup> 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  $\mathcal{L}^{\alpha} \mathcal{J}_D^{20} = -96.2^\circ$  (c=1; CHCl<sub>3</sub>); ir (neat)  $\mathcal{L}^{2500, 1615, 1380} \text{ cm}^{-1}$ ; nmr (CDCl<sub>3</sub>)  $\mathcal{L}^{\delta} 7.55 - 7.25$  c.a., Ar-H; 6.33 and 6.02, AB system, J<sub>AB</sub> = 12 Hz, N=CH<sub>2</sub>; 5.30 s, Ar-CH; 2.99 s J=7.3 Hz, N-CH<sub>2</sub>-CH<sub>3</sub>; 2.70 s, N-CH<sub>3</sub>; 1.20 t J=7.3 Hz, N-CH<sub>2</sub>-CH<sub>3</sub>. 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)  $\mathcal{L}^{\text{ir}} (\text{CH}_2\text{Cl}_2) \nu_{\text{CO}} = 1790 \text{ cm}^{-1}$  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)<sup>4,5</sup> and, on the basis of spectral data, the triazine structure (5) was assigned to the obtained penicillin (yield 33%, mp 52 - 58°C).  $\mathcal{L}^{\alpha} \mathcal{J}_D^{20} = +69.1^\circ$  (c=1; CHCl<sub>3</sub>); ir (oil mull)  $\mathcal{L}^{\nu_{\text{CO}}} = 1760 \text{ cm}^{-1}$ ; nmr (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\mathcal{L}^{\delta} 7.48$  c.a., Ar-H; 5.89 s, -O-CH<sub>2</sub>-O; 5.40 s, H-5; 4.72 s, Ar-CH; 4.50 s, H-3; 4.62 and 4.42 AB system, J<sub>AB</sub> = 15 Hz, N-CH<sub>2</sub>-N; 3.46 s, OCH<sub>3</sub>; 2.87 s, N-CH<sub>3</sub>; 1.51 s and 1.48 s, gem CH<sub>3</sub>; 1.22 s, C(CH<sub>3</sub>)<sub>3</sub>; ms (70 eV)  $\mathcal{L}^{534} (M^+)$ , 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*<sup>6</sup> the same antimicrobial activity already described<sup>3</sup> 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. Broccoli and G. Pifferi, *Heterocycles*, 1976, 4, 1699.
2. R. Monguzzi, G. LiBassi, M. Pinza and G. Pifferi, *Farmaco, Ed. Sci.*, 1976, 31, 549; G. LiBassi, R. Monguzzi, R. Broggi, G. Broccoli, C. Carpi and G. Pifferi, *J. Antibiotics*, 1977, 30, 376
3. G. Pifferi, F. Nasi, R. Monguzzi, M. Pinza and G. Broccoli, Proceedings 10th International Congress of Chemotherapy, Zürich, 18-23 Sept. 1977, Am. Soc. Microbiol. Publ., 1978, Vol. 1, p. 609.
4. P. Bellani, P. Ventura and G. Pifferi, *Heterocycles*, 1980, 14, 1.
5. H. Yanagisawa, M. Fukushima, A. Ando and H. Nakao, *J. Antibiotics*, 1976, 29, 969.
6. Antibacterial activities were evaluated by subcutaneous administration to mice experimentally infected with *Staphylococcus aureus* Gray Weinstein.

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