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Published on 01 January 1972. Downloaded by University of Lancaster on 24/10/2014 18:29:35.

Penicillin 6,6′-Dimer

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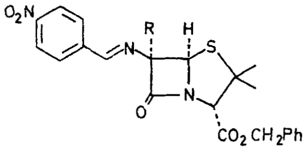
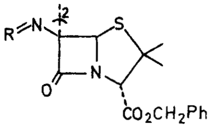
Summary Treatment of the *p*-nitrobenzaldehyde Schiff base of 6-APA benzyl ester (I) with phenyl-lithium and then with oxygen affords the 6,6′-dimer (IV) and the nitrone (X).

Schiff base (I) is readily alkylated as its lithium enolate (II) with alkyl halides to 6-alkyl derivatives (III), which after suitable transformation, afford bioactive 6-alkyl penicillins.[1]

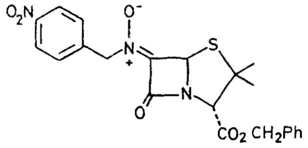
Treatment of (II) with O_2 at 0° in THF was expected to provide 6-hydroxy-Schiff base (IV).[2] However, although the inky blue colour of (II) was discharged after a few minutes exposure to pure dry O_2, the product contained little (IV), consisting instead principally of the 6,6′-dimer (VI) (22%) and the nitrone (X) (10%).† The tautomeric structure of (X) is established by the i.r. and n.m.r. spectra. Methods described previously[2] were used to convert (VI) into (VII)—(IX)† whose antimicrobial activity was markedly less than that of benzylpenicillin.



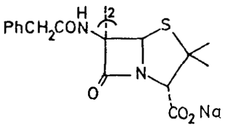
(I) R = H
(II) R = Li
(III) R = Alk
(IV) R = OH
(V) R = •



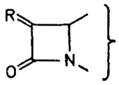
(VI) R = $CHC_6H_4NO_2$
(VII) R = H,H
(VIII) R = H, $COCH_2Ph$



(X)



(IX)



(XI) R = NNH_2
(XII) R = $\overset{+}{N}{=}\overset{-}{N}$

A variety of other oxidizing agents, such as t-butyl hydroperoxide, methyl t-butyl peroxide, and bis-trifluoromethyl peroxide‡ also reacted with (II) to give the dimer (VI), along with other products. The most likely explanation, then, is that (II) is readily oxidized by a one-electron process to the radical (V), which dimerizes.

The assignment of stereochemistry to (VI) is based on the likelihood that steric control of the approach of a bulky group to the planar radical centre of (V) should guide it into the α-configuration. A good analogy exists in the case of (II); when the lithium cation is complexed with DMF, the less bulky reagents methyl iodide and solvated proton both approach predominantly or exclusively from the α side.[1]

The nitrone (X) is unusual in that examples of preferred exocyclic conjugation with the β-lactam carbonyl are rare; thus for example, Schiff bases of type (I) are always found as that tautomer which is not conjugated with the β-lactam, a possibility open to (X) as well. We ascribe the phenomenon to the stabilization afforded by the delocalization of negative charge to the carbonyl oxygen.§ The only other functionality known to us that also exhibits preferred conjugation with the lactam is the hydrazone (XI),[3] in which the unshared electrons on the outer nitrogen are similarly delocalized.

(*Received*, 31*st July* 1972; *Com.* 1340.)

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† Products were characterized by i.r., n.m.r., and m.s. Reported yields are after chromatography.

‡ The latter experiment was performed by Dr. D. B. R. Johnston.

§ Negative charge delocalization is also indicated by the marked i.r. shift of the lactam carbonyl (5·69 μm) from the normal position (5·61 μm), a feature which (X) shares with the electronically similar diazolactams (XII).

[1] R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Letters*, **1972**, 375. See also E. H. W Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, 1971, **93**, 4324.

[2] E. Muller and T. Töpel, *Ber.*, 1939, **72**, 273.

[3] D. M. Brunwin and G. Lowe, *Chem. Comm.*, 1972, 192.