Novel Ring Expansion Product of Penicillin V β-Sulphoxide: *X*-Ray Crystal Structure of 3,8-Dihydro-3,3,8,8-tetramethyl-6-phenoxyacetamido-1-oxo-oxazolo-[4,3-c][1,4]thiazinium Chloride

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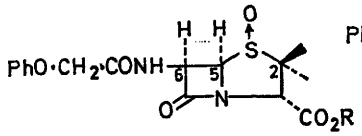
Summary Penicillin V β-sulphoxide has been converted into a novel orange product which was structurally characterised as the 2*H*-1,4-thiazinium chloride (II) following an *X*-ray crystallographic study.

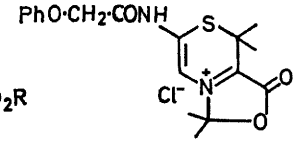
PENICILLIN β-SULPHOXIDE ESTERS [*e.g.* (Ia)] are known to undergo various rearrangements including ring expansion involving an S–C(2) cleavage to dihydro-2*H*-1,3-thiazine derivatives, as in the semi-synthetic route to various cephalosporins.[1] This communication describes a ready alternative ring expansion of the free acid (Ib) with S–C(5) cleavage leading to a novel 2*H*-1,4-thiazinium chloride (II).

In the course of studies of the metabolism of penicillin derivatives,[2] it was observed that a 3% acetone solution of the acid (Ib), when stirred with an equal weight of phenylacetyl chloride in an open flask for 2 h at room temperature, yielded (30%) an orange crystalline product (II), $C_{18}H_{21}N_2O_4S$ Cl, m.p. 192—193°, ν_{max} (KBr) 1775 cm^{-1} requiring the incorporation of one molecule of acetone and one atom of Cl. The orange crystals were not obtained on replacing (Ib) by penicillin V α-sulphoxide, m.p. 145° (prepared as the crystalline free acid by a minor modification of the ozonolysis procedure of Spry[3]). A mass spectrum showed no molecular ion nor any Cl-containing ions, indicating ionically bound chlorine, the highest mass peak appearing at *m/e* 360 (M^+ — HCl). The crystals are insoluble in water and only sparingly soluble in dry methanol, yet readily dissolve in aqueous methanol with decomposition, forming a yellow acidic solution containing acetone (recovered as its 2,4-dinitrophenylhydrazone). On heating in $CHCl_3$, (II) slowly dissolves, yielding a mixture of at least three products (t.l.c.).

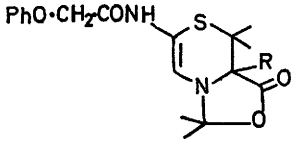
In view of this behaviour, it was decided to undertake an *X*-ray crystallographic determination of structure. The crystals occur as pleochroic plates which exhibit dispersion of the optic indicatrix. They are triclinic $P\bar{1}$, $a = 6{\cdot}936$, $b = 14{\cdot}486$, $c = 9{\cdot}742$ Å, $\alpha = 98{\cdot}23°$, $\beta = 88{\cdot}57°$, $\gamma = 100{\cdot}67°$, $Z = 2$. Intensities of 3704 reflections were



(Ia) R = Me
(Ib) R = H



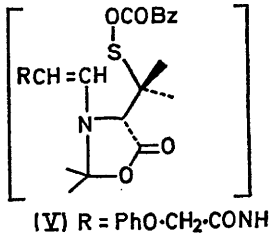
(II)



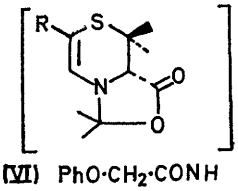
(IIIa) R = CH_2Cl
(IIIb) R = $PO(OEt)_2$

PhO·CH$_2$·CONH·CHOH·CS·NH$_2$

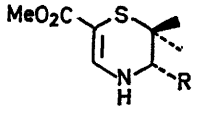
(IV)



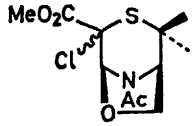
(V) R = PhO·CH$_2$·CONH



(VI) PhO·CH$_2$·CONH

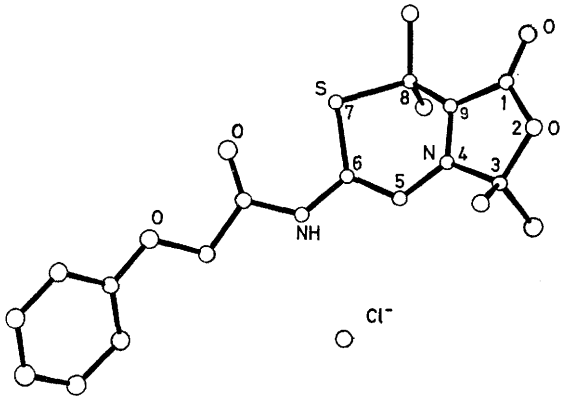


(VII) R = CO_2Me
(VIII) R = CH_2OH



(IX)

measured on a Siemens diffractometer with Cu-K_α radiation ($\theta \leqslant 71°$), and of these 291 were reckoned unobserved. The structure, which was solved by the symbolic-addition procedure and refined to a current R value of 0·049, is illustrated in the Figure. A comparatively short S–C(6) bond [1·728(3) Å] when compared with S–C(8) [1·854(4) Å], indicates a significant degree of π bonding between S and C(6).



FIGURE

This compound exhibits unusual reactivity. Thus, with ethereal diazomethane it forms a colourless crystalline derivative, $C_{19}H_{23}N_2O_4S$ Cl, m.p. 135°, $\nu_{max.}$ 1775 cm^{-1}, the mass spectrum showing molecular ions at m/e 410 and 412 (indicative of covalently bound ^{35}Cl and ^{37}Cl respectively) with prominent peaks at m/e 361 ($M^+ - CH_2Cl$), 303 (361 − Me_2CO), and 275 (361 − $Me_2C{\cdot}O{\cdot}CO$). Its n.m.r. spectrum ($CDCl_3$) showed, in addition to the characteristic phenoxyacetamido-signals, 4 tertiary methyl signals at τ 8·21 (3H,s), 8·36 (6H,s), 8·63 (3H,s), one olefinic signal at 3·41 (1H,s), and two doublets at 6·00 and 6·37 (each 1H, J 11·5 Hz) consistent with the expected AB spin system of a diazomethane-derived methylene group. C.d. measurements (in MeOH) failed to detect any optical activity. These data are satisfied by the structure (IIIa) although alternative possibilities cannot at present be excluded.

A colourless crystalline phosphorus-containing but chlorine-free product, $C_{22}H_{31}N_2O_7PS$, m.p. 111—113°, $\nu_{max.}$ 1775 cm^{-1}, is obtained on refluxing (II) with triethyl phosphite. Its mass spectrum also exhibits prominent peaks at m/e 361 [$M^+ - (Et_2O)_2PO$], 303(361 − Me_2CO), and 275, which, together with n.m.r. ($CDCl_3$) data, support its formulation as the diethyl phosphonate (IIIb) corresponding to the chloromethyl derivative (IIIa). The decomposition of (II) in aqueous acetone at pH 7 yields, as a minor component, a colourless crystalline product, m.p. 137°, with a probable structure (IV), necessitating a migration of the S from C(6) to C(5).

This latter migration is in effect the reverse of that which takes place in the initial conversion of (Ib) into (II), *via* an oxidative process (the product not forming in the absence of air) which is also accompanied by loss of the β-lactam carbonyl. Feasible intermediates could include a sulphenic anhydride [*e.g.* (V)] and a dihydro-2*H*-1,4-thiazine such as (VI). The related dihydro-2*H*-1,4-thiazine derivative (VII) has been prepared from esters of 6-chloro-[4] and 6-bromo-penicillanic acid.[5] Furthermore, the sulphoxide of the dihydrothiazine (VIII) has recently been reported[6] to form compound (IX) on treatment with acetyl chloride and acetonitrile, and this novel reaction may be relevant to the required oxidative derivation of (II) *via* the hypothetical enamine intermediate (VI) in the presence of phenylacetyl chloride.

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[1] R. B. Morin and B. G. Jackson, *Fort. Org. Chem. Natur.*, 1970, **28**, 343; D. H. R. Barton and P. G. Sammes, *Proc. Roy. Soc.*, 1971, *B*, **179**, 345.
[2] R. Thomas, *J.C.S. Chem. Comm.*, 1972, 478.
[3] O. Spry, *J. Org. Chem.*, 1972, **37**, 795.
[4] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.
[5] N. Maggi and G. Cignarella, *Chimica e Industria*, 1970, **52**, 164.
[6] J. Kitchin and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1972, 959.