New Reaction of Penicillins: the Formation, and Crystal and Molecular Structure of a β-Lactam-fused Heterocyclic Ylide

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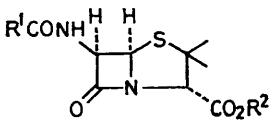
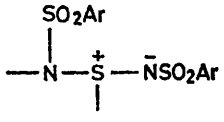
Summary The formation and *X*-ray crystallographic structure of the ylide (**3**) derived from reaction of chloramine T with methyl 6β-phenylacetamidopenicillanate are reported.

WE have investigated the reaction of chloramine T with penicillins with the objective of chemically modifying the thiazolidine ring and forming β-lactams with possible antibiotic activity. It was expected that chloramine T, which is well known to react under mild conditions with sulphides to form ylides,[1] would afford a penicillin sulphilimine[2] or products derived therefrom.

In a typical reaction a methanolic solution of (**1a**) was treated at room temperature with chloramine T (2 mol. equiv.) in methanol, to give white crystals, m.p. 151—152°, $[\alpha]_D^{20}$ + 77° (*c* 1·00,$CHCl_3$), whose elemental analysis indicated the formula $C_{31}H_{34}N_4O_8S_3$, implying incorporation of two molecules of toluene-*p*-sulphonyl 'nitrene' into the penicillin. Although no molecular ion was detected in the mass spectrum, vapour phase osmometric determination of molecular weight was in accord with the assigned empirical formula. The i.r. spectrum indicated a β-lactam ring (1790 cm^{-1}) and possibly the functional group (**2**)[3]

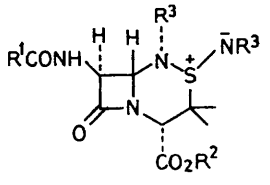


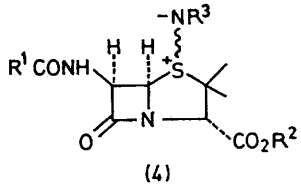
(**1**)



(**2**)

a; $R^1 = CH_2Ph$, $R^2 = Me$
b; $R^1 = CH_2OPh$, $R^2 = Me$
c; $R^1 = CH_2OPh$, $R^2 = CH_2Ph$
d; $R^1 = Me$, $R^2 = CH_2Ph$





(**4**)

(**3**); $R^1 = CH_2Ph$, $R^2 = Me$, $R^3 = p\text{-}SO_2C_6H_4Me$

(1360, 1168, 1150, and 990 cm^{-1}). The n.m.r. spectrum indicated a bicyclic system containing *gem*-dimethyl (τ 8·90 and 8·42, both 3H, s), two tosyl units (τ 7·60, 6H, s), and *trans*-β-lactam protons (τ 4·70 and 4·80, total 2H, $J < 1$ Hz). The molecule proved remarkably inert to an extensive series of chemical reactions aimed at oxidation or reduction of the ylide. On the basis of spectroscopic analysis three closely related structures were plausible, but could not unambiguously be distinguished. An *X*-ray crystallographic structure determination was therefore undertaken, and has proved the molecular structure to be (**3**).

Crystal data: $C_{31}H_{34}O_8N_4S_3$, $M = 686·8$, monoclinic, $a = 15{,}613$, $b = 7·951$, $c = 13·840$ Å, $\beta = 108·98$, $U = 1570·6$ Å^3. $D_m = 1·44$ g cm^{-3} (by flotation in aqueous KI), $Z = 2$, $D_c = 1·46$ g cm^{-3}, F (000) = 720, space group $P2_1$, $\mu = 2·94$ cm^{-1} for $\lambda = 0·7107$ Å.

3105 ($I > 2\sigma_I$) independent intensities were measured on a Hilger and Watts Y290 diffractometer with Mo-K_α radiation using the $\theta,2\theta$ scan technique in the range $0 \leqslant 2\theta \leqslant 54°$. The structure was solved by non-centrosymmetric direct methods using the *X*-ray suite of programs.[4] Refinement of positional and thermal parameters by full-matrix least-squares has reduced R to a value of 0·054.

The penicillins (**1a—d**) were shown to react readily affording the products (**3a—d**). Compounds lacking the secondary amido-function at C-6, including methyl 6β-phthalimidopenicillanate, benzyl 6β-(triphenylmethylamino)penicillanate, and methyl 6,6-dibromopenicillanate did not react under the conditions described for (**1a**). The mechanistic implications therefore include the possibility[5] that the initial step in the reaction may involve *N*-chlorination of the 6-acylamino-group followed by intra-molecular halogen transfer to sulphur, affording an *S*-chlorosulphonium species. Subsequent nucleophilic attack by a toluene-*p*-sulphonamidate anion would yield the transient sulphilimine (**4**). Ring expansion of this thiazolidine ylide followed by reaction of chloramine T on the resultant cyclic sulphenamide would afford the ylide (**3**).

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