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PENICILLIN N-CYANOSULPHILIMINES; CYANAMIDE/IODOBENZENE DIACETATE, A CONVENIENT CYANONITRENE REAGENT FOR N-CYANO SULPHILIMINES, SULPHOXIMINES, PHOSPHINIMINES AND AZIRIDINES

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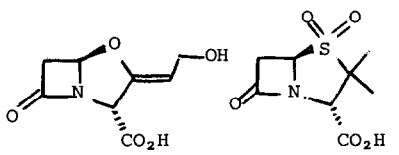
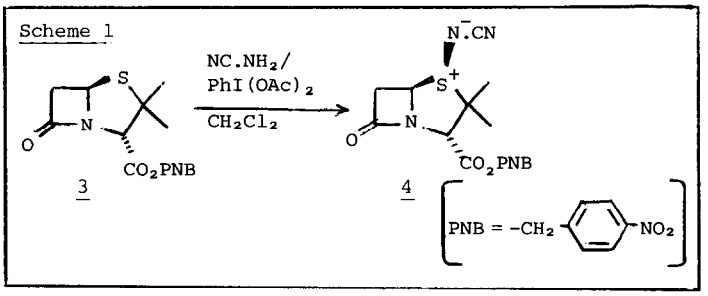
Summary Cyanamide with iodobenzene diacetate give cyanonitrene adducts of sulphides, sulphoxides, phosphines, and olefins. Penicillins give N-cyanosulphilimines, shown by intramolecular N-H...N hydrogen bonding or NMR ASIS to have β(S) stereochemistry.

New types of clinically useful β-lactam drugs have emerged with the discovery of potent β-lactamase inhibitors such as clavulanic acid[1] (1) and penicillanic acid sulphone (CP-45,899, 2). The latter compound[2] is the first penicillin sulphone with useful biological activity, and we now report the first isolable β-lactam sulphilimines, precursors of some related sulphoximines.[3]



1 2

Scheme 1

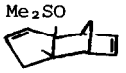
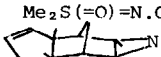


3 4

Penicillanic acid[4] was esterified (PNB-Br/$NaHCO_3$/DMF, 20°, 4hr) to give 3. Many conventional reagents, including mesitylenesulphonylhydroxylamine[5] (MSH) failed to convert 3 (or its sulphoxides) to sulphilimines or sulphoximines, presumably due to steric hindrance. We therefore turned to cyanamide/iodobenzene diacetate, a new mild reagent with low steric demands which we developed specifically for this work.

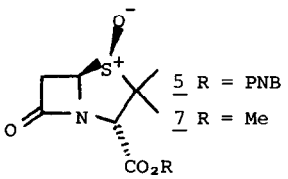
Our new reagent added the elements of cyanonitrene to dimethylsulphide, to DMSO, to alkenes, and to phosphorus compounds (Table 1). It also reacted analogously with penicillins but not with penicillin sulphoxides, nor, curiously, with cephalosporins.[6]

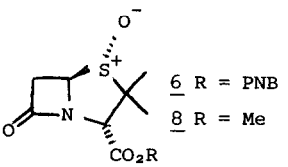
Table 1 FORMAL ADDITION PRODUCTS OF CYANONITRENE VIA $NC.NH_2/PhI(OAc)_2$

Starting Compound	Solvent	Duration	Product	Yield	Ref.
Me_2S	excess Me_2S+Et_2O	16 hr	$Me_2\overset{+}{S}-\overset{-}{N}.CN$	75%	7
Me_2SO	excess Me_2SO	45 min	$Me_2S(=O)=N.CN$	36%	8 (new)
	Et_2O	1½ hr		61%	9
Ph_3P	Et_2O	1½ hr	$Ph_3\overset{+}{P}-\overset{-}{N}.CN$	16%	10
			Ph_3P-O	not isolated	

Penicillin 3 (1 g) and cyanamide (250 mg) in CH_2Cl_2 (8 ml) were treated with iodobenzene diacetate (1.92 g) portionwise over 15 min, and the mixture stirred at room temp. for a further 30 min. (Scheme 1). The product was isolated by rapid short path pressure chromatography on silica gel, eluting with ethyl acetate, yielding 380 mg (34%) of the sulphilimine 4 as a cream foam, stable for 1 day at 20° and several days at -10°, IR ($CHCl_3$) 1795 cm^{-1} (β-lactam)*, 2160 cm^{-1} (C≡N), NMR ($CDCl_3$)δ 1.41 (s, 3,α—Me), 1.83 (s, 3, β—Me, assigned by NOE), 3.56 [d, 2, H6α + H6β, ½($J_{5\alpha6\beta}$+ $J_{5\alpha6\beta}$= 2.9 Hz)], 4.70 (s, 1, H3β), 5.36 (s, 2, $arCH_2O$), 5.41 (t, 1, H5α), 7.57 and 8.27 (ar AA'XX', 4, J = 8.6 Hz); Mass spectrum: Electron Impact gave m/e = 334 (P - $NC.NH_2$ and/or P - CH_2=C=O), Chemical Ionisation (CH_4) gave m/e = 377 (P + 1); Calc. for $C_{16}H_{16}N_4O_5S$: M = 376. Analysis, found: C 49.85, H 4.39, N 14.06%; calc. for $C_{16}H_{16}N_4O_5S$; $\frac{1}{2}H_2O$: C 49.91, H 4.41, N 14.53.

The β-sulphilimine structure was strongly indicated by the overall similarity of the proton NMR spectrum to that[9] of the sulphoxide 5 rather than 6. The spectrum showed aromatic solvent induced shifts[11] (ASIS) (Table 2, and Figure) exactly paralleling those observed with the β-sulphoxide 5, the large ASIS observed with the 5α proton being especially diagnostic of a β-substituent on the sulphur. The ^{13}C NMR (in CD_3COCD_3) showed the two C2 methyl carbons almost coincident at -20.24 ppm and -20.71 ppm downfield from Me_4Si: compare the sulphoxide[12] 7 (-18.4 ppm, 2αMe, -20.0 ppm, 2βMe) and 8 (-15.7 ppm 2αMe, -24.0 ppm, 2βMe), again suggestive of the stereochemistry at sulphur.





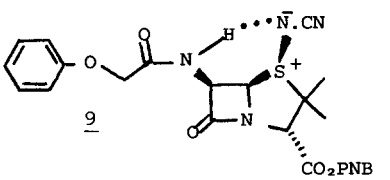
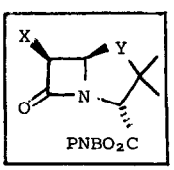
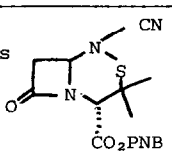


Table 2 NMR ASIS (Downfield shifts induced in spectrum in $CDCl_3$ by C_6D_6 (to 17% v/v)



X	Y	Comp. No.	-[ASIS (X) - ASIS (X = S), ppm] 2α	2β	3β	5α	6α	6β
H	S^+—$N.CN^-$	4	0.17	0.11	0.10	0.38	0.11	0.17
H	S^+—O^-	5	0.16	0.07	0.06	0.33	0.17	0.09
H	S^+....O^-	6	0.05	0.12	0.10	0.13	0.17	0.20
$PhOCH_2CONH$	S^+—$N.CN^-$	9	0.21	0.12	0.00	0.38	0.11	-
$PhOCH_2CONH$	S^+—O^-	10	0.06	0.01	0.01	0.17	0.04	-

*This carbonyl frequency excludes ring expanded structures such as



Phenoxymethylpenicillin (as K salt) was esterified (PNB-Br, KI, aq. Me_2CO, reflux 6 hr) giving the p-nitrobenzyl ester,[13] which on treatment as above with $NC.NH_2/PhI(OAc)_2$ yielded the sulphilimine 9 isolated (63%) as a cream foam m(dec)~126°, IR (nujol) 1808 cm^{-1} (β-lactam), 2183 cm^{-1} (C≡N), 3420 cm^{-1} (N-H); NMR ($CDCl_3$) 1.39 (s, 3, αMe), 1.89 (s, 3, βMe, assigned by analogy with 4), 4.03 (s, 2, $PhOCH_2$), 4.73 (s, 1, H3), 5.38 (d, 1, H5, $J_{5\alpha6\alpha}$ = 4.4 Hz), 5.38 (s, 2, $arCH_2O$), 6.18 (dd, 1, H6α, $J_{6\alpha NH}$ = 9.2 Hz), 7~7.5 (m, 5, Ph), 7.60 & 8.32 (ar AA'XX', 4, J = 8.6 Hz), 8.26 (d, 1, exchanges with D_2O, NH). Analysis: found: C 54.33, H4.40, N 13.86%; M^+ = 525.12705; calc. for $C_{24}H_{23}N_5O_7S$: C 54.85, H 4.41, N 13.33%; M = 525.13168.

The stereochemistry at sulphur was established by ASIS (Table 2 and Figure) and by an NMR proof of an internal N-H...N hydrogen bond (Table 3 and Figure), giving a low-field N-H which persisted on changing the solvent from DMSO to $CDCl_3$. Similar NMR observations have been used to characterize penicillin sulphoxides as β.[11(a)]

Figure
ASIS and Hydrogen Bonding in Phenoxymethylpenicillin β-Sulphoxide [adapted from ref. 11 (b)] and β-Cyano-sulphilimine (this work)

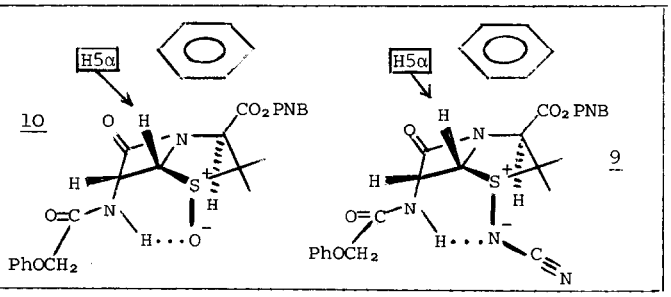
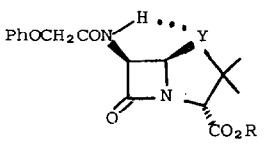


Table 3 NMR Solvent Shifts in Penicillin Amide Protons



R	Y	Comp. No.	in $DMSOd_6$ δ	in $CDCl_3$ δ	Ref
Me	S	11	8.63	7.42	11 (a)
H	$S^+ \cdots O^-$	12	9.21	7.34	14
Me	$S^+ — O^-$	13	8.25	8.25	11 (a)
PNB	$S^+ — N.CN$	9	8.55	8.26	this work

We showed that penicillins are inert to iodobenzene diacetate (and to cyanamide alone) excluding a sulphide diacetate[15] intermediate, whereas cyanamide and iodobenzene diacetate reacted quickly with each other giving iodobenzene (90%) as sole isolable product. Iodobenzene was again produced in an attempt to synthesize the iodinane 14, analogous to $ArSO_2N^- — {}^+IPh$ (an isolable precursor of sulphonylsulphilimines[17]):

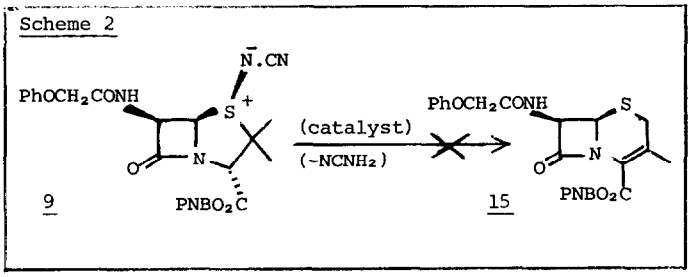
$$14\ NC.N^- — {}^+IPh \xleftarrow{\times} PhI(OAc)_2 + NC.NH_2 + 2KOH \longrightarrow 2PhI\ (88\%).$$

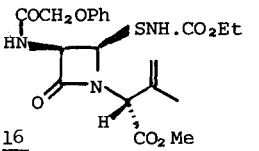
We thus favour a mechanism involving cyanonitrene (but a free radical process could occur). The intermediacy of cyanonitrene would readily account for all the products of Table 1, and our new reagent thus provides a convenient, apparently safe, source of compounds previously derived from cyanogen azide. (Penicillin sulphilimines could not be made using cyanogen azide,[6] but this reagent is not a cyanonitrene source at temperatures compatible

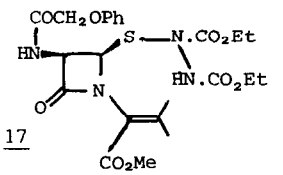
with the desired products).

We attempted to convert the cyanosulphilimine 9 to a cephalosporin 15, using two procedures used to convert secopenicillins 16 ($Et_2NH_2^+Cl^-$/DMA, Δ)[18] or 17 (iPr_2NLi/THF, -78°)[19] to cephalosporins, plus a standard procedure used for sulphoxides ($MeSO_3H$/PhH,Δ).[20] In each case we started at or below the recommended temperature and warmed the mixture until reaction occurred, at 50°, -50°, and 60° respectively. Each reaction gave intractable non-bicyclic products, and no cephalosporin 15 (Scheme 2) could be detected on tlc.

Scheme 2







Isolable penicillin sulphilimines have not been reported previously, though their transient formation is implicit in certain earlier work.[18,19,21] Compounds reported herein, related pivaloxymethyl esters, and unstable free acids were microbiologically uninteresting.

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