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PENICILLIN AND CEPHALOSPORIN SULPHOXIMINES

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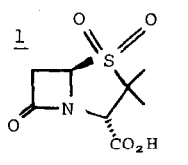
Summary Penicillin N-cyanosulphoximines are obtained by permanganate oxidation of the sulphilimines. Phthalimidosulphoximines are obtained from penicillin or cephalosporin sulphoxides and phthalimidonitrene (from N-aminophthalimide with lead tetraacetate).

We wish to report the first β-lactam sulphoximines, analogues of the novel β-lactamase inhibitor[1] penicillanic acid sulphone, CP-45,899 (1).

PENICILLIN N-CYANOSULPHOXIMINES (Scheme 1). The penicillin sulphilimine 2[2] (600 mg) was treated with potassium permanganate (450 mg) in acetone (20 ml) for 1 hr. at 20°, filtered through "Hyflo", and evaporated and partitioned between chloroform and water, yielding from the organic phase, sulphoximine 3** (220 mg, 35%), a colourless oil, IR ($CHCl_3$) 1810 cm^{-1} (β-lactam), 2170 cm^{-1} (C≡N); NMR: see Table, MS [Chemical Ionization (CH_4)] P + 1 = 393, $C_{16}H_{16}N_4O_6S$ requires M = 392. The aqueous layer yielded a secopenicillin, probably 4 (72 mg), a glass, IR (film) 1765 cm^{-1} (β-lactam), 2180 cm^{-1} (C≡N), 3440 cm^{-1} (N-H); NMR (DMSO-d_6) δ2.01 (s,3,Me), 2.19 (s,3,Me), 3.04 (ABX, 1, H3β, $J_{3\beta4\alpha}$ = 2.5 Hz), 3.28 (ABX, 1, H3α, $J_{3\alpha4\alpha}$ = 5.6 Hz), 5.87 (ABX,1,H4α), 6.40 (s,2, ar CH_2), 7.72 and 8.27 (ar AA'XX', 4, J=8.4 Hz). Satisfactory CHN or mass spectral data were not obtained. This compound presumably arose via an initial sulphinamide, akin to the sulphinic acids produced from cleavage of penicillin sulphones.[3]



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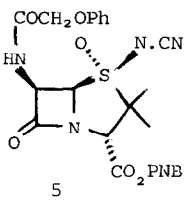

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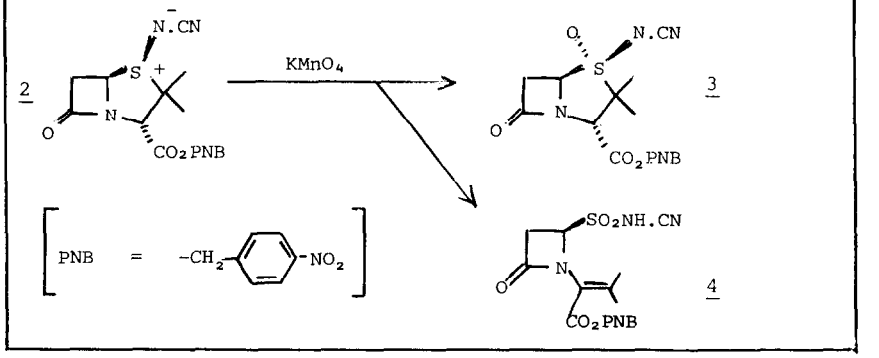
Scheme 1 Penicillanic Acid N-Cyanosulphoximine



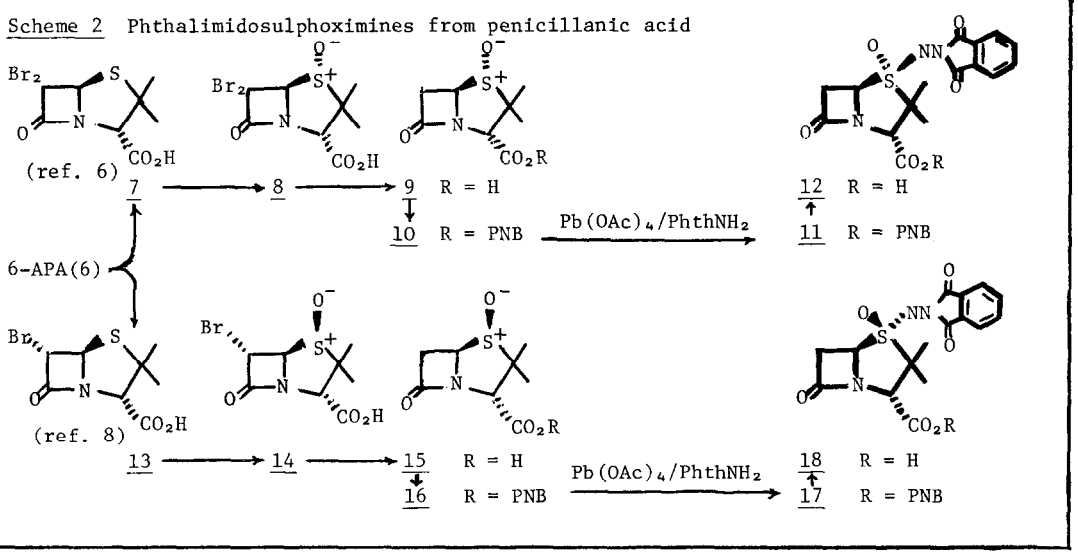
**All sulphoximine esters gave satisfactory tlc, NMR, IR, and (except for 5) CHN (or in a few cases, MS) data. Ester 5 and the sulphoximine free acids, which were less stable, were characterised by tlc, NMR, and IR only.

Similar oxidation of phenoxymethylpenicillin cyanosulphilimine PNB ester[2] yielded the sulphoximine 5 (100 mg, 32%), a pale yellow oil, (300 mg) IR (film) 1795 cm^{-1} (β-lactam), 2205 cm^{-1} (C≡N). These sulphoximines are stable indefinitely at -10°, but have a half-life of about 1 day at room temperature, and on de-esterification (H_2/Pd/C or dithionite) yielded very unstable free acids which could not be obtained pure. IR and NMR data (Table) indicate a very activated β-lactam in the penam cyanosulphoximine system, detracting from chemical stability and biological activity. We then attempted to make a second class of sulphoximines, reasoning that the nucleophilic nitrene, phthalimidonitrene[4,5] would react with the sulphoxides to give a less activated class of β-lactam phthalimidosulphoximines.

PENICILLIN (Scheme 2) AND CEPHALOSPORIN (Scheme 3) SULPHOXIDE STARTING COMPOUNDS. 6,6-Dibromopenicillanic acid[6] (8.4 g) in THF (33.6 ml) was stirred (ice cooling) and treated with m-chloroperoxybenzoic acid (m-CPBA, 85%, 4.82g) in two portions 3 min apart. The mixture was then allowed to warm to room temperature and kept 2 days; petrol bp 40-60° (100 ml) was then added, precipitating pure α-oxide 8 (6.8 g, 77%) mp 183-5° (previously reported in admixture with the β-isomer[7]). Reduction (H_2/Pd/$CaCO_3$, cf. ref 6). of 8 gave penicillanic acid α-oxide (9) mp 170-2°, isolated initially as the sodium salt (85%), from which we obtained ester 10, mp 167-9°.

6-α-Bromopenicillanic acid (13)[8] yielded (m-CPBA) the bromo-oxide 14 which with H_2/Pd/$CaCO_3$ gave the β-oxide 15 [distinct (tlc and spectra) from 9] which yielded the ester 16, mp 157°.

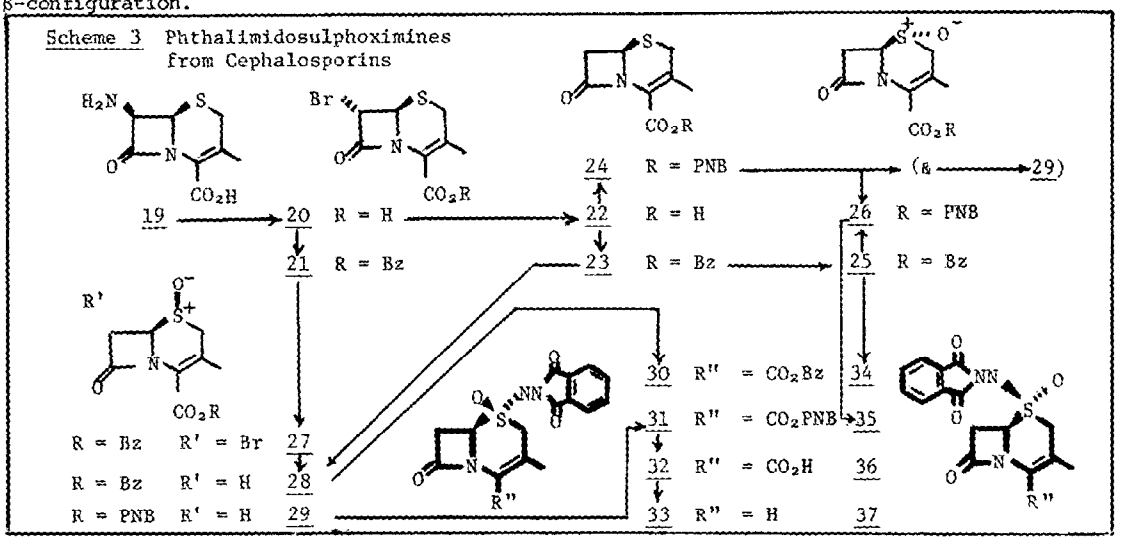
Scheme 2 Phthalimidosulphoximines from penicillanic acid



7-ADCA (19) was converted (as for 13) to the 7-α-bromo-compound 20, which was debrominated (Zn/HOAc/20°/3 hr) to desacetoxy cephalosporanic acid,[9] (22) mp 162-5°, which gave the esters 23 and 24. Ester 23 gave (m-CPBA) a 1:1 mixture of two sulphoxides, 25 and 28, separated by rapid short path chromatography on silica, with gradient elution EtOAc to Me_2CO. We identified the isomers on the basis of three observations: (a) Oxidation of the new bromo ester 21 gave an isomerically pure sulphoxide 27, presumed β on steric grounds, which on

debromination gave a reference sample of 28. (b) 28, but not 25, showed the 2α6α coupling of 1.9 Hz in the NMR, characteristic of cephalosporin β-oxides.[10] (c) The cephalosporin α-oxides resembled the penicillin α-oxides in their tlc properties, being less polar (higher Rf) than their β-isomers.

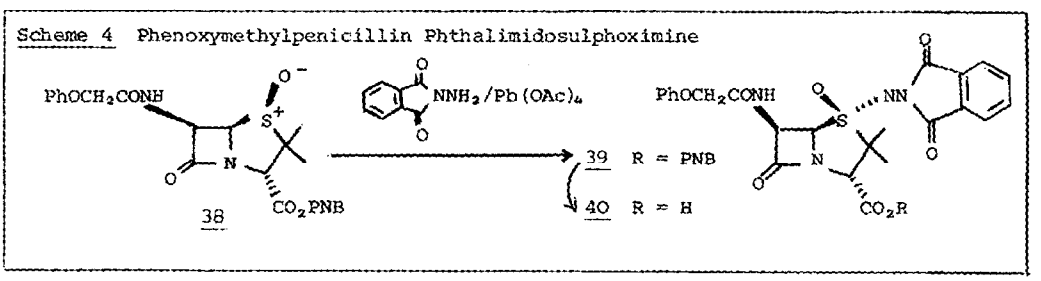
The PNB esters 26 (mp 152-4°) and 29 [m(dec) 215°] were prepared analogously to 23 and 28, by oxidation of 24. The final starting material,[11] 38, was of a class known to have the β-configuration.[12]



PENICILLIN AND CEPHALOSPORIN PHTHALIMIDOSULPHOXIMINES (Schemes 2 to 4). We treated each of the sulphoxides 10, 16, 25, 26, 28, 29 and 38 with N-aminophthalimide and lead tetra-acetate, the following preparation being typical (cf. Rees' group;[4,5] such reactions occur with retention of configuration at sulphur).[13]

Compound 10 (80 mg) in dichloromethane (5 ml), stirred at 0°, was treated with N-aminophthalimide (37 mg) and lead tetra-acetate (85%, 120 mg) and stirred for 15 min. at 0°. Short path chromatography on silica eluting with hexane/ethyl acetate (1:1) gave the sulphoximine 11 (89 mg, 76%), analysis: found: C54.04, H 4.06, N 10.72%; calc. for $C_{23}H_{20}N_4O_8S$: C 53.91, H 3.93, N 10.93% (other data: see Table). Isomer 17: prepared analogously, yield 62%.

All other sulphoxides yielded pure sulphoximines except the cephalosporin oxides 25 and 26. There is evidence (see below) that the products from their reactions did contain the desired compounds 34 and 35, but they could not be obtained pure.



DEPROTECTION STUDIES ON PHTHALIMIDOSULPHOXIMINES. Sulphoximine 17 (100 mg) in THF (11 ml) was hydrogenated over 5% Pd/C (200 mg) for 30 min at 15°, filtered, and the filtrate evaporated to dryness, yielding 18 as the p-toluidine salt (100 mg), a viscous yellow oil stable for several hours at room temperature. Penicillins 11 and 39 were similarly converted to the acids 12 and 40 respectively. The cephalosporin sulphoximine 31 on catalytic or chemical (dithionite)[14] deprotection gave a product of low Rf on tlc, presumably 32, which decomposed (at all pH's) over about 1 hr to yield the decarboxylated product 33 (of much higher Rf on tlc) which was completely characterized. The crude presumed sulphoximine 35 showed similar tlc behaviour on deprotection, thus giving indirect evidence for the presence of authentic 35. Penicillins 12, 18, and 40 and their esters, and the cephalosporins 30, 31, and 33 showed no useful antibacterial properties, perhaps due to the bulky phthalimido group.

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Table IR and NMR SPECTRA OF REPRESENTATIVE COMPOUNDS

No.	Mp (°C)	IR phase	β-lact(cm^{-1})	NMR solvent										
			(Penicillins)		Me2α[a]	Me2β[a]	H3α	H5α	H6α	H6β	NH	J56α	J56β	J6α6β	J6NH
3	gum	$CHCl_3$	1810	$CDCl_3$	1.39	1.69	4.47	4.92	5.65	5.65	-	[aver. 5.0]		?	-
5	gum	KBr	1795	$CDCl_3$	1.48	1.88	4.67	~5.1	~6.2	(poorly resolved spectrum)				?	
10	167-9	KBr	1788	$CDCl_3$	1.35	1.58	4.54	4.72	5.65	5.43	-	4.4	2.2	16.8	-
11	174-5	KBr	1798	CD_3COCD_3	1.53	1.84	4.81	5.24	5.78	4.36	-	4.8	2.0	17.0	-
16	157	KBr	1785	$CDCl_3$	1.20	1.71	4.63	4.99	5.39	5.39	-	[aver. 3.2]		?	-
17	120-1	KBr	1795	CD_3COCD_3	1.73	1.98	4.68	5.42	5.86	5.36	-	4.6	2.2	16.7	10.8
39	100-2	KBr	1812	$CDCl_3$	1.67	1.82	4.72	5.37	6.32	-	8.03	4.4	-	-	?
			(Cephalosporins)		H2α[a]	H2β[a]	Me3	H6α	H7α	H7β	H4	J67α	J67β	J7α7β	J2α2β
25	149-51	KBr	1778	CD_3COCD_3	3.65	3.91	2.08	4.51	5.72	5.37	-	4.6	2.4	16.8	16.6
28	149-51	KBr	1775	CD_3COCD_3	3.63	3.63	2.03	4.71	5.44	5.14	-	4.7	2.7	15.8	?
31	166-7	KBr	1778	CD_3COCD_3	4.67[b]	4.27[b]	2.19	5.53	5.77	5.77	-	?	?	?	17.6
33	183-4	KBr	1778	CD_3COCD_3	4.50[c]	3.94[c]	2.09	5.36	5.45	5.45	6.61	5.4	2.7	16.6	18.2

(a) Assigned by analogy: see refs. 10 and 15. (b) Assigned by analogy with 33. (c) Assigned[10] via $J_{2\alpha 6\alpha} \approx 1.9$Hz

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