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THE 6-THIOAMIDES AND 6-THIONCARBAMATES OF PENICILLIN SULFOXIDES

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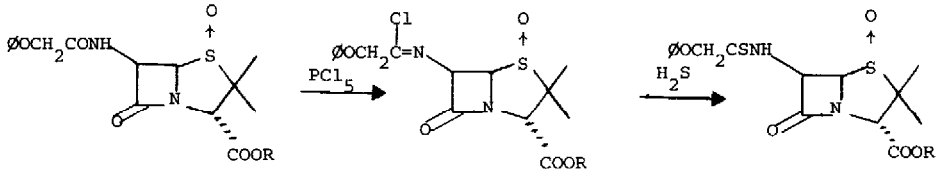
In connection with our studies on the intramolecular cyclisation reactions of azetidinone-4-sulfenic acids (see following papers), we required the 6-thioamides and 6-thioncarbamates of various penicillin sulfoxides. Although a few examples of the 6-thioamides of penicillins [3-7], and the 7-thioamides of cephalosporins [7-9] are described in the literature, the only example of a 6-thioamide of a penicillin sulfoxide reported is p-nitrobenzyl 6-phenylthioacetamidopenicillinate sulfoxide [10]. Schemes 1 and 2 summarise the reactions utilised by us for the preparation of these compounds, starting from the penicillin sulfoxides (Scheme 1), or from 6-aminopenicillanic acid sulfoxide [11] (Scheme 2).

The readily available 6-phenoxyacetamidopenicillanic acid sulfoxide, 1c [12], and its methyl ester, 1a, on treatment with phosphorous pentachloride and dimethylaniline in methylene chloride as solvent, gave the chloroimines, 2, which on reaction with hydrogen sulfide provided the thioamides, 3c and 3a, in about 70% yield (estimated conversion yield from nmr spectroscopy)[13, 14]. These compounds were purified by column chromatography on silicic acid. In the case of compound 1c, the carboxylic acid was protected by conversion *in situ* to the trimethylsilyl ester, 1b, by treatment with trimethylsilyl chloride and dimethylaniline, prior to these reactions, the free acid, 3c, being the product isolated. Compound 3a, a crystalline white solid (methanol) had m.p. 148 - 149° [15] and nmr ($CDCl_3$) δ1.25 and 1.75 (ss, 6H, gem-CH_3), 3.88 (s, 3H, $COOCH_3$), 4.78 (s, 1H, C_3-H), 4.99 (s, 2H, $-OCH_2$), 5.23 (d, J = 4 c/s, 1H, C_5-H), 6.73 to 7.52 (m, 6H, C_6H_5 and C_6-H), 9.88 (d, J = 10 c/s, 1H, NH). Compound 3c, an off-white powder had m.p. 145 - 149° dec, and nmr ($DMSOd_6$) δ1.20 and 1.53 (ss, 6H, gem-CH_3), 3.52 (s, 1H, COOH), 4.43 (s, 1H, C_3-H), 4.92 (s, 2H, $-OCH_2$), 5.58 (d, J = 4 c/s, 1H, C_5-H), 6.50 and 6.63 (q, 1H, C_6-H), 6.90 to 7.49 (m, 5H, C_6H_5), 10.16 (d, J = 9 c/s, 1H, NH).

When 6-aminopenicillanic acid sulfoxide, 4, was stirred in DMF with carbon disulfide (1 mole eq.), triethylamine (2 mole eq.), and methyl iodide (2 mole eq.) (1½ hr at 0° and then at ambient temperature for 16 hrs), a mixture of the 6-methyldithiocarbamate free acid, 5b, and its methyl ester, 5a, were among the products formed [14]. Compounds 5a and 5b were separated from the other products of the reaction by column chromatography on silicic acid, both compounds 5a and 5b being eluted together as a 1:1 mixture in about 25% yield (by weight). The methyl ester, 5a, was obtained pure by removing the acid using aqueous sodium bicarbonate, or by reacting the mixture of 5a and 5b under carefully controlled conditions with diazomethane [16]. Compound 5a, isolated as a white solid had

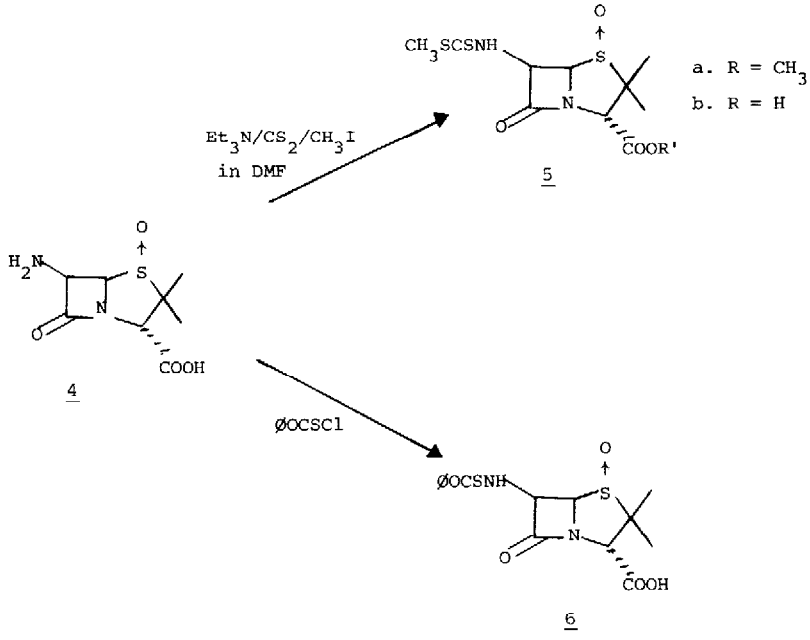
SCHEME 1



1 2 3

a. R = CH_3, b. R = $Si(CH_3)_3$, c. R = H

SCHEME 2



5 4 6

m.p. 140 - 142° dec, and nmr ($CDCl_3$), δ1.22 and 1.70 (ss, 6H, gem-CH_3), 2.63 (s, 3H, -S-CH_3), 3.85 (s, 3H, $COOCH_3$), 4.75 (s, 1H, C_3-H), 5.21 (d, J = 4 c/s, 1H, C_5-H), 6.68 and 6.82 (q, 1H, C_6-H), 8.68 (d, J = 9 c/s, 1H, NH).

Crude compound 6 was obtained in about 92% yield by the Schotten-Baumann acylation of 4 with phenyl chlorothionformate in aqueous THF as solvent. Recrystallisation from ether gave pure 6 (about 50% recovery) as a white solid, m.p. 152 - 153° (dec.) and nmr ($DMSOd_6$) δ1.29 and 1.60 (ss, 6H, gem-CH_3), 4.47 (s, 1H, C_3-H), 5.58 (d, J = 4 c/s, 1H, C_5-H), 5.98 and 6.09 (q, 1H, C_6-H), 7.10 to 7.55 (m, 5H, C_6H_5), 9.90 (d, J = 7 c/s, 1H, NH). The methyl ester of 6 was obtained by the carefully controlled reaction of 6 with diazomethane [16]. It was a crystalline white solid (methanol), m.p. 148 - 150° and nmr ($CDCl_3$), δ1.22 and 1.78 (ss, 6H, gem-CH_3), 3.88 (s, 3H, $COOCH_3$), 4.8 (s, 1H, C_3-H), 5.27 (d, J = 4 c/s, 1H, C_5-H), 6.48 and 6.63 (q, 1H, C_6-H), 7.10 to 7.51 (m, 5H, C_6H_5), 8.22 (d, J = 10 c/s, 1H, NH).

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REFERENCES AND FOOTNOTES

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3. Y.G. Perron, W.F. Minor, L.B. Crast, and L.C. Cheney, J.Org.Chem., 26, 3365 (1961).

4. A. Winther and A. Senning, Acta Chem. Scand., 27, 1456 (1973).

5. J.A. Farrington, R. Hull and W.A. Sexton, (ICI Ltd), Brit. 916,205, 23 Jan. 1965; Chem. Abstr., 58, 11367C (1963).

6. R.H. Hall, H.D. Hollingworth, D.P. Young, and R. Sherlock, (Distillers Co. Ltd.), Brit. 952,519, 18 Mar. 1964; Chem. Abstr., 60, 15877g (1964).

7. R.R. Chauvette (Eli Lilly and Co.), U.S. 3,632,578, 4 Jan. 1972; Chem. Abstr., 76, 127004d (1972).

8. S. Terao, T. Matsuo, S. Tsushima, T. Miyawaki, and N. Matsumoto, (Takeda Chem. Ind., Ltd.), Ger. Offen., 2,244,620, 22 Mar. 1973; Chem. Abstr., 78, 159635t (1973).

9. S. Tsushima, N. Matsumoto, S. Terao, T. Matsuo, and T. Miyawaki, (Takeda Chem. Ind., Ltd.), Japan. Kokai 7,413,196, 05 Feb. 1974; Chem. Abstr., 80, 95994r (1974).

10. H. Tanida, R. Muneyuki, and T. Tsushima, Tetra.Letters, 3063 (1975). This compound (no data given) was made by the DCCIcondensation of phenyldithioacetic acid with 6-aminopenicillanic acid sulfoxide p-nitrobenzyl ester.

11. A convenient method for the preparation of this compound is described in a paper by R.G. Micetich submitted to Synthesis for publication.

12. Cephalosporins and Penicillins, editor E.H. Flynn, Academic Press, New York, p.667 (1972).

13. Illustrative of this process is the preparation of 3a. A mixture of 1a, dimethylaniline (2.5 mole eq.), and PCl_5 (1.1 mole eq.) in CH_2Cl_2, was stirred (2½ hrs at -50°C) to form 2a. A slow stream of H_2S was passed through the stirred reaction mixture (1½ hr at -50° and 1 hr at 0°) and the mixture washed with aq.$NaHCO_3$, then water, then dil.HCl, then water and the organic layer dried ($MgSO_4$ with charcoal), filtered and concentrated to a yellow foam, whose weight and nmr spectrum indicated the presence of about 70% of 3a with about 25% of the starting amide, 1a. Chromatography on silicic acid, followed by crystallisation from methanol gave an about 40% overall yield of pure 3a.

14. The process has not been optimised.

15. The analysis (elemental or high resolution mass spectral) of all new compounds described were within acceptable limits.

16. The action of diazomethane on compounds such as 3, 5, and 6, will be discussed in a separate publication.