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CONVENIENT DEOXYGENATION OF PENICILLIN AND CEPHALOSPORIN SULFOXIDES

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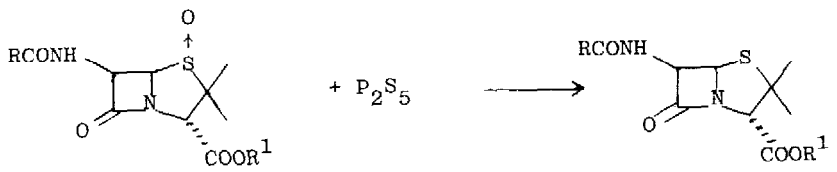
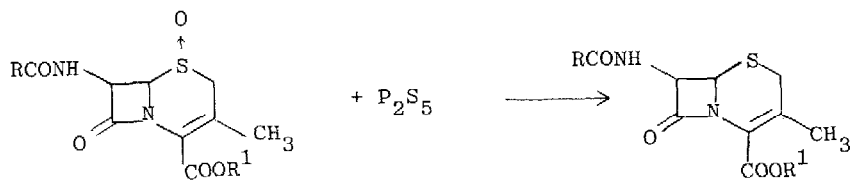
In connection with our studies on the chemistry of the 6-thioamides of penicillin sulfoxides the effect of P_2S_5 on penicillin sulfoxides was investigated. Carbonyl compounds are conveniently converted to their thiocarbonyl analogues by reaction with sulfides such as phosphorus pentasulfide,[1] boron sulfide[2] and silicon disulfide[2]. Phosphorus pentasulfide reacts with penicillins and cephalosporins to form the C_6- or C_7- thioamides respectively [3,4], while boron sulfide was recently reported to produce the β-thionolactam analogues of these compounds by substitution of the oxygen of the β-lactam ring by sulfur[5]. With the penicillin sulfoxide 1, or cephalosporin sulfoxide 3, (R = ϕOCH_2, R^1 = CH_3) however, phosphorus pentasulfide in the presence of pyridine, gave the penicillin 2, or cephalosporin 4, in high (conversion) yields.

When methyl 6-phenoxyacetamidopenicillinate sulfoxide, 1 (R = ϕOCH_2, R^1 = CH_3) was treated with P_2S_5 (½ mole equivalent), and pyridine (4 mole equivalents) in methylene chloride at ambient temperature for 16 hrs, the pmr spectrum of the reaction product showed an about 1:1 mixture of starting ester, 1, and methyl 6-phenoxyacetamidopenicillinate, 2. These compounds were separated by column chromatography on silicic acid, and their identity confirmed by comparison (ir and pmr spectra and tlc) with authentic samples. Under the same conditions methyl 7-phenoxyacetamido-3-cephem-3-methyl-4-carboxylate sulfoxide, 3 (R = ϕOCH_2, R^1 = CH_3) was converted to methyl 7-phenoxyacetamido-3-cephem-3-methyl-4-carboxylate, 4, in over 90% yield.

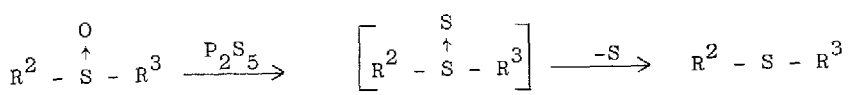
Although the deoxygenation of sulfoxides using thiols (RSH) [6-8], O,O-dialkyl dithiophosphoric acid [$(RO)_2PS_2H$][9], and carbodithioic acids (RCS_2H)[10] have been reported, this is the first time, to our knowledge that P_2S_5 has been utilised for the deoxygenation of sulfoxides. The deoxygenation of the biologically inactive sulfoxides of β-lactam antibiotics (particularly in the cephalosporin series), to the sulfides (3 → 4), is an essential step



1 + P_2S_5 → 2



3 + P_2S_5 → 4



1 and 3 → 5 → 2 and 4

in certain transformation schemes leading to biologically active compounds [11-19]. All these publications utilise procedures based on the publication of the Eli Lilly Group [18], who found that several reducing agents were effective in the presence of an added acid halide, and that reagents such as PCl_3, PBr_3, $SiHCl_3$, and chloromethylene dimethyliminium chloride were also effective. The reagent of choice in the case of the cephalosporin sulfoxides appears to be stannous chloride in the presence of acetyl chloride. P_2S_5 in the presence of pyridine is an equally effective reagent for the deoxygenation of penicillin and cephalosporin sulfoxides.

The mechanism of this reduction has not been established. Since no particular care was taken to exclude moisture, it is possible that the thiophosphoric acids formed by the action of moisture on the P_2S_5 may in fact be the real reducing agents, and function by a mechanism similar to that evoked for the O,O-dialkyldithiophosphoric acids[9]. Alternatively the P_2S_5 may possible react by converting the sulfoxides 1 or 3, to the thiosulfoxides 5, which spontaneously extrude sulfur (a reaction noted by Höfle and Baldwin[20]) to form the sulfides 2 or 4.

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REFERENCES

1. J.W. Scheeren, P.H.J. Ooms, and R.J.F. Nivard, Synthesis, 149 (1973).

2. F.M. Dean, J. Goodchild, and A.W. Hill, J.Chem.Soc.C., 2192 (1969).

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

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

5. P.W. Wojtkowski, J.E. Dolfini, O. Kocy, and C.M. Cimarusti, J.Amer.Chem.Soc., 97, 5628 (1975).

6. C.N. Yiannios and J.V. Karabinos, J.Org.Chem., 28, 3246 (1963).

7. T.J. Wallace, J.Amer.Chem.Soc., 86, 2018 (1964).

8. T.J. Wallace and J.J. Mahon, J.Amer.Chem.Soc., 86, 4099 (1964).

9. S. Oae, A. Nakanishi, and N. Tsujimoto, Tetra., 28, 2981 (1972).

10. S. Oae, T. Yagihara, and T. Okabe, Tetra., 28, 3203 (1972).

11. J.A. Webber, E.M. Van Heyningen, and R.T. Vasileff, J.Amer.Chem.Soc., 91, 5674 (1969).

12. a. C.F. Murphy (Eli Lilly & Co.), Ger.Offen. 2,209,019, 30 Aug. 1973; Chem.Abstr., 80, 3539v (1974); b. Idem, Ger.Offen. 2,145,946, 25 May, 1972; Chem.Abstr., 77, 75213v (1972); c. C.F. Murphy and J.A. Webber, Ger.Offen. 2,052,531, 17 Feb. 1972; Chem.Abstr., 76, 140848b (1972).

13. J.C. Clark, J. Kennedy, A.G. Long, and N.G. Weir, Ger.Offen. 2,103,014, 29 July, 1971; Chem.Abstr., 75, 118328g (1971).

14. S. Kukolja, J.Med.Chem., 13, 1114 (1970).

15. D.O. Spry, Chem.Comm., 671 (1973).

16. I.G. Wright and G. Kaiser, Ger.Offen. 2,110,387, 16 Sept. 1971; Chem. Abstr., 76, 25302g (1972).

17. I.G. Wright, C.W. Ashbrook, T. Goodson, G.V. Kaiser, and E.M. Van Heyningen, J.Med.Chem., 14 , 420, 426 (1971).

18. G.V. Kaiser, R.D.G. Cooper, R.E. Koehler, C.F. Murphy, J.A. Webber, I.G. Wright, and E.M. Van Heyningen, J.Org.Chem., 35, 2430 (1970).

19. P. Claes, A. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, J.Chem.Soc. Perkin 1, 932 (1973).

20. G. Höfle, and J.E. Baldwin, J.Amer.Chem.Soc., 93, 6307 (1971).