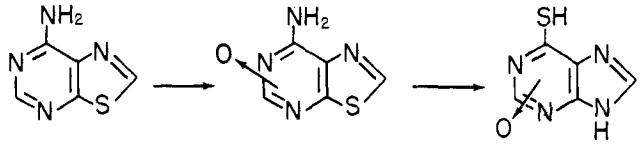
Communication to the Editor

Synthesis of a 6-Mercaptopurine N-Oxide[1]

Sir:

A theoretical advantage[2] of an N-oxide of a chemotherapeutically effective purine is based, in part, upon the possibility that it, like adenine-1-N-oxide,[3] may undergo a reduction *in vivo* to the parent purine. The greatly reduced toxicity and improved therapeutic index[4] of 6-methylpurine-1-N-oxide over the parent purine was the first supporting example.

Direct oxidation of 6-mercaptopurine to an N-oxide of it has failed because of oxidation of the mercapto group. Oxidation of 6-chloropurine has resulted in a prior hydrolysis to the nonoxidizable hypoxanthine, and attempts to introduce mercapto or halogeno groups into appropriate purine N-oxides have resulted in the reduction of the N-oxide group.



I II III

Scheme I

The synthesis of a 6-mercaptopurine N-oxide has now been accomplished by introduction of the N-oxide function while the sulfur is protected from oxidation in a thiazole.

Oxidation of 7-aminothiazolo[5,4-*d*]pyrimidine (I)[5] in acetic acid with H_2O_2 yielded 60% of the N-oxide II, m.p. 278° dec.

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.71; H, 2.37; N, 33.33; S, 19.05. Found: C, 35.94; H, 2.48; N, 33.50; S, 19.04.

Heating the N-oxide II in an equivalent of *N* NaOH results in rearrangement to a 6-mercaptopurine-N-oxide (III) in 25% yield, m.p. 230° dec.

Anal. Calcd. for $C_5H_4N_4OS \cdot H_2O$: C, 32.26; H, 3.22; N, 30.11; S, 17.20. Found: C, 32.39; H, 3.00; N, 30.26; S, 17.40.

Evidence that the purine ring is present in III derives from the fact that treatment with Raney nickel yields purine and that irradiation with ultraviolet light results in a removal of the oxygen to yield 6-mercaptopurine, a reaction characteristic of several purine N-oxides.[6] The position of the oxygen has not yet been established but, in analogy to adenine, I may undergo oxidation at N-6, resulting in a purine 3-N-oxide after the rearrangement.

Initial observations by Dr. H. C. Reilly, with Sarcoma 180 in Swiss mice,[7] indicate no toxicity at 500 mg./kg./day and a chemotherapeutic activity, including inhibitions and delayed regressions, which exceeds that obtained with toxic levels of 6-mercaptopurine.

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(6) G. Levin and G. B. Brown, *Federation Proc.*, **21**, 372 (1962), and unpublished observations.

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Book Reviews

Experimental Chemotherapy. Vol. 1. R. J. Schnitzer and Frank Hawking, Editors. Academic Press, Inc., New York, N. Y., 1963. xv + 1008 pp. $38.00.

This is the first of three projected volumes of a comprehensive treatise on all aspects of chemotherapy. If the other two volumes will follow the tradition of high quality set by the present book, this treatise may well become the standard reference work for biologists interested in all phases of the subject. Introduced fittingly by a photograph of the patron saint of chemotherapy, Paul Ehrlich, one of the editors surveys the history of the field from antiquity to the present. Like all other chapters, this first one is amply and well documented. The fact that the majority of the references concerned with the discovery of chemotherapeutic drugs come from the biological literature points to the division of labor, as well as to the teamwork of medicinal chemists and biologists in this area. Stress is laid on decisive testing procedures in laboratory animals, on statistical analyses of these procedures, on the pharmacological and toxicological aspects of the drugs, and on the development and treatment of resistant strains.

On the whole, the clinically useful drugs are discussed primarily and their biological and host–parasite relationships are illustrated. In several cases, however, the influence of the chemical structure in a series of related drugs is considered, and the effect of drug metabolites is detailed wherever it is known. This first volume treats the chemotherapy of protozoan and metazoan infections. Each chapter is written by authorities in the particular field who have had long actual experience in the area. Most authors are well known members either of British industrial research organizations or of American and British university or governmental laboratories. Specific diseases and their chemotherapy treated are trypanosomiasis, leishmaniasis, trichomoniases, histomoniasis, giardiasis, amebiasis, coccidiosis, malaria, babesiasis, theileriasis, anaplasmosis, toxoplasmosis, balantidiasis, spirochetal and miscellaneous infections, helminthiases, filariasis, and myriasis. A general author and subject index concludes the book.