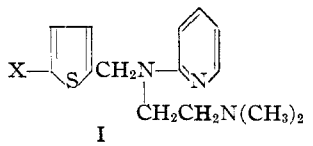
HALOGENATED THIOPHENE DERIVATIVES AS ANTIHISTAMINE AGENTS

Sir:

The preparation of N,N-dimethyl-N′-(2-pyridyl)-N′-(2-thenyl)-ethylenediamine (I, X = H) and its antihistamine activity have been reported recently.[1] This compound is the thiophene analog of N,N-dimethyl-N′-(2-pyridyl)-N′-benzylethylenediamine (Pyribenzamine).[2]

Prior to the publication of these results,[1] we had also prepared this compound and pharmacological tests had been carried out in these Laboratories.[3] The results obtained confirm those reported earlier,[1] in that the compound is of the same order of activity as is Pyribenzamine *in vivo* and of the same order of acute toxicity.



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In addition, however, we have prepared N,N-dimethyl - N′ - (2 - pyridyl) - N′ - (5 - bromo - 2-thenyl)-ethylenediamine (I, X = Br) and N,N-dimethyl - N′ - (2 - pyridyl) - N′ - (5 - chloro - 2-thenyl)-ethylenediamine (I, X = Cl). In tests using the isolated guinea pig ileum, these halogenated compounds were more active than Pyribenzamine. Preliminary tests in animals indicate that they have at least twice the antihistamine activity, twice the duration of action, and one-half the acute toxicity of Pyribenzamine.

These compounds were prepared by the reaction of 5-bromo-2-thenyl chloride and 5-chloro-2-thenyl chloride with N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine.[2,4] 5-Bromo-2-thenyl chloride, b. p. 82–83° at 1 mm., was obtained in 70–80% yield from the chloromethylation of 2-bromothiophene by the method used previously with thiophene.[5] *Anal.* Calcd. for C_5H_4BrClS: Cl, 16.8. Found: Cl (by hydrolysis), 16.9%. 5-Chloro-2-thenyl chloride, b. p. 67–68° at 1 mm., was prepared similarly by the chloromethylation of 2-chlorothiophene. *Anal.* Calcd. for $C_5H_4Cl_2S$: Cl (by hydrolysis), 21.2%. Found: Cl, 21.1.

The condensation of 5-bromo-2-thenyl chloride and N,N - dimethyl - N′ - (2-pyridyl) - ethylenediamine using sodium[2] or potassium amide gave N,N - dimethyl - N′ - (2 - pyridyl) - N′ - (5-bromo - 2 - thenyl) - ethylenediamine (I, X = Br), b. p. 173–175° at 1 mm., in 54% yield. The monohydrochloride melted at 124–126°. *Anal.* Calcd. for $C_{14}H_{19}BrClN_3S$: C, 44.6; H, 5.1; N, 11.1; S, 8.5. Found: C, 44.9, 44.8; H, 5.3, 5.1; N, 11.0, 11.0: S, 8.7, 8.6. N,N-Dimethyl-N′-(2 - pyridyl) - N′ - (5 - chloro - 2 - thenyl) - ethylenediamine (I, X = Cl), b. p. 155–156° at 1 mm., was obtained similarly in 62% yield. The monohydrochloride of this compound melted at 106–108°. *Anal.* Calcd. for $C_{14}H_{19}Cl_2N_3S$: C, 50.6; H, 5.8; N, 12.6. Found: C, 50.8, 50.9; H, 6.0, 6.2; N, 12.3, 12.3.

These compounds will be described more fully in a further publication along with other compounds prepared in the course of this study.

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STREPTOMYCIN. V.[1] DEGRADATION OF STREPTOMYCIN B TO STREPTIDINE, STREPTOBIOSAMINE AND D-MANNOSE

Sir:

Streptomycin B[1] has been degraded to derivatives of streptidine, streptobiosamine and D-mannose. It appears to be a triacidic base of the formula $C_{27}H_{49}O_{17}N_7$.

Methanolysis of streptomycin B with 1.3 *N* methanolic hydrogen chloride for five days at room temperature followed by acetylation afforded methyl tetraacetyl streptobiosaminide dimethyl acetal,[2] m. p. 124–125° (cor.); $[\alpha]^{25}D$ −122° (*c*, 0.56 in chloroform) and α-methyl tetraacetyl D-mannopyranoside, m. p. 65–66° (cor.) unchanged on admixture of an authentic specimen; $[\alpha]^{25}D$ +49° (*c*, 1.1 in chloroform).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; OCH_3, 8.56; CH_3CO, 47.5. Found: C, 50.01; H, 6.08; OCH_3, 8.98; CH_3CO, 47.7.

Treatment of streptomycin B with ethylmercaptan and concentrated hydrochloric acid for eighteen hours at room temperature and subsequent acetylation of the vacuum-dried residue afforded streptidine octaacetate, m. p. 255–257° (cor. dec.), β-thioethyl tetraacetyl streptobiosaminide diethyl mercaptal,[3] m. p. 112–113° (cor.); $[\alpha]^{25}D$ −30° (*c*, 0.95 in chloroform), and two isomeric thioethyl tetraacetyl hexosides: A, m. p. 107–108° (cor.), $[\alpha]^{25}D$ +94° (*c*, 1.06 in chloroform); and B, m. p. 161–162° (cor.), $[\alpha]^{25}D$ −67° (*c*, 0.51 in chloroform).

Anal. Calcd. for $C_{16}H_{24}O_9S$: C, 48.98; H, 6.17; S, 8.16; CH_3CO, 43.84; mol. wt., 392.4. Found for A: C, 48.91; H, 6.04; S, 8.17; CH_3CO, 44.2; mol. wt. (Rast), 378. Found for B: C, 49.16; H, 6.28; S, 8.41; CH_3CO, 43.3.

The hitherto undescribed β-thioethyl tetraacetyl D-mannoside was prepared from D-mannose by

(1) Paper IV of this series: J. Fried and E. Titus, *J. Biol. Chem.*, **168**, 391 (1947).

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