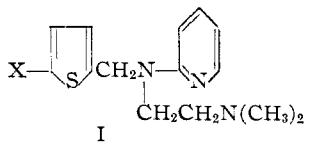
HALOGENATED THIOPHENE DERIVATIVES AS ANTIHISTAMINE AGENTS

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.



I

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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(1) A. W. Weston, THIS JOURNAL, **69**, 980 (1947).

(2) Huttrer, Djerassi, Beears, Mayer and Scholz, *ibid.*, **68**, 1999 (1946).

(3) Litchfield, Goddard, Adams and Jaeger, *Bull. Johns Hopkins Hosp.*, in press.

(4) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(5) Blicke and Leonard, *ibid.*, **68**, 1934 (1946).

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).

(2) N. G. Brink, F. A. Kuehl, Jr., and K. Folkers, *Science*, **102**, 506 (1945).

(3) I. R. Hooper, L. H. Klemm, W. J. Polglase and M. L. Wolfrom, THIS JOURNAL, **68**, 2120 (1946).

a similar procedure and shown to be identical with the higher-melting isomer B from streptomycin B by melting point (161–162°, no depression on admixture of isomer B), rotation ($[\alpha]^{25}D$ −65° (*c*, 1.1 in chloroform)), and analysis (C, 49.19; H, 5.98; S, 8.41; CH_3CO, 44.7). The dextrorotatory isomer A from streptomycin B presumably represents the previously unknown anomeric α-thioethyl-tetracetyl-D-mannoside.

Dihydrostreptomycin B trihydrochloride[1], m. p. 194–5° (cor. dec.), $[\alpha]^{25}D$ −55° (*c*, 0.9 in water), on treatment with 3% methanolic hydrogen chloride for forty hours at room temperature and subsequent acetylation yielded α-methyl pentaacetyl dihydrostreptobiosaminide[4,5] m. p. 192–3° (cor.), $[\alpha]^{25}D$ −119° (*c*, 0.49 in chloroform) and β-methyl tetraacetyl D-mannopyranoside, $[\alpha]^{25}D$ −50° (*c*, 0.69 in chloroform), m. p. 160–161° (cor.), unchanged on admixture of an authentic specimen.

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, 49.61; H, 6.08; OCH_3, 8.35; CH_3CO, 48.5.

These results together with analytical data previously reported[1] for the reineckate[1] and hydrochloride of streptomycin B indicate that streptomycin B is made up of streptidine, streptobiosamine and D-mannose joined glycosidically to form a triacidic base of the composition $C_{27}H_{49}O_{17}N_7$.

Anal. Calcd. for $C_{27}H_{49}O_{17}N_7 \cdot 3HCr[(NH_3)_2(SCN)_4] \cdot 2H_2O$: C, 26.97; H, 4.29; N, 20.15; S, 22.11; Cr, 8.98. Found[1] (after drying *in vacuo* at 80° for two hours): C, 26.89; H, 4.24; N, 20.1; S, 22.2; Cr, 8.70. Calcd. for $C_{27}H_{49}O_{17}N_7 \cdot 3HCl \cdot H_2O$: C, 37.26; H, 6.24; N, 11.25; Cl, 12.23. Found (after drying *in vacuo* at 140° for two hours): C, 36.85; H, 6.11; N, 11.3; Cl, 12.83.

(4) J. Fried and O. Wintersteiner, THIS JOURNAL, **69**, 79 (1947).

(5) Q. R. Bartz, J. Controulis, H. M. Crooks, Jr., and M. C. Rebstock, *ibid.*, **68**, 2163 (1946).

DIVISION OF ORGANIC CHEMISTRY JOSEF FRIED
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RECEIVED MAY 19, 1947

THE REACTION OF IODONIUM SALTS WITH THIOL COMPOUNDS

Sir:

In the interesting paper by Freedlander and French[1] on the chemotherapy of certain iodonium compounds, they have suggested tentatively that the activity of the iodonium compounds may, in some cases, be due to a reaction with certain thiol groups essential to the microörganisms.

For some time we have been engaged in the study of the reactions which occur between iodonium salts and sulfhydryl compounds. We have found, for example, that diphenyliodonium chloride reacts in an aqueous solution with thioglycolic acid (kept neutral with sodium carbonate) to produce phenyl iodide and S-phenylthioglycolic acid (21% yield), m. p. 58–60° (lit. 61–63°[2]); sparingly soluble in water, soluble in benzene. This reaction is a rapid one at the boiling point of the solution. It also proceeds at room temperature but at a reduced rate. When thioglycolic acid dissolved in water is shaken with diphenyliodonium chloride, sodium carbonate, tellurium and ether at room temperature, diphenyltellurium is formed. The latter compound can be isolated from the ether layer as the yellow dibromide, m. p. 199–200°. The reaction with tellurium is an interesting one because of the possibility of a free radical mechanism, although other interpretations are possible.[3]

It has also been found that diphenyliodonium chloride reacts with other thiol compounds, such as thiophenol and cysteine. In the latter case the product is S-phenylcysteine, m. p. 200° (lit. 201–202°)[4]; calcd. for $C_9H_{11}O_2SN$: S, 16.3. Found: S, 16.2. All the iodonium reactions show a characteristic transient yellow color or precipitate.

The above reactions should be of interest from the standpoint of enzyme studies. Further work is in progress and we hope to communicate full details at a later date. We are very grateful to the Alberta Branch of the Canadian Cancer Society for financial aid in support of this work.

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RECEIVED MAY 14, 1947

(1) Freedlander and French, *Proc. Soc. Exptl. Biol. Med.*, **63**, 319 (1946); *C. A.*, **41**, 2115 (1947).

(2) Gilman and Webb, THIS JOURNAL, **62**, 987 (1940).

(3) Sandin, McClure and Irwin, THIS JOURNAL, **61**, 2944 (1939); Sandin and Brown, unpublished work.

(4) Clarke and Inouye, *J. Biol. Chem.*, **94**, 541 (1931).

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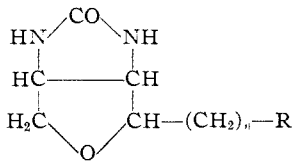
FURAN AND TETRAHYDROFURAN DERIVATIVES. VIII. THE SYNTHESIS OF THE SULFONIC ACID ANALOGS OF OXYBIOTIN AND HOMOOXYBIOTIN

Sir:

In connection with our studies on the relationships of chemical structure and biological activity in the biotin and oxybiotin series,[1] we became interested in *dl*-oxybiotin sulfonic acid (I) and *dl*-homoöxybiotin sulfonic acid (II), the sulfonic acid analogs of *dl*-oxybiotin (III) and *dl*-homoöxybiotin (IV), respectively. In this communication we wish to record the synthesis of these two compounds.



	n	R
(I)	4	SO_3H
(II)	5	SO_3H
(III)	4	COOH
(IV)	5	COOH

(1) Hofmann, Chen, Bridgwater and Axelrod, THIS JOURNAL, **69**, 191 (1947).