[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Thieno[3,2-b]pyridine. II. The Preparation of Some Dialkylaminoalkyl Derivatives of an S-Isosteric 8-Aminoquinoline[1]

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To develop the hypothesis that the antimalarials derived from 8-aminoquinoline owe their activity to a product formed by oxidation at carbon atom five, a number of dialkylaminoalkyl derivatives of S-isosteric 8-aminoquinoline wherein the carbon atoms 5 and 6 of the parent base are replaced by sulfur, have been prepared from 3-hydroxythieno[3,2-b]pyridine and tested for antimalarial activity. These compounds and related compounds have also been tested *in vitro* against bacterial organisms and the results tabulated.

While the actual metabolism of the antimalarials derived from 8-aminoquinoline derivatives is not known, evidence exists,[2] which indicates that the therapeutic activity and also the toxicity of these substances may be due to a metabolite formed by oxidation at carbon atom five. To develop this hypothesis a number of 3-dialkylaminoalkylamino derivatives of thieno(3,2-b)pyridine were prepared. These compounds, as seen in Fig. 1, are isosteric with the corresponding derivatives of 8-aminoquinoline, the carbon atoms of the quinoline ring at positions five and six having been replaced by a sulfur atom to form a thiophene ring in place of the benzenoid moiety.

R = $-(CH_2)_2N(C_2H_5)_2$
$-(CH_2)_3N(C_2H_5)_2$
$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$

Fig. 1.

When it became apparent that a sufficient quantity of 3-chlorothieno(3,2-b)pyridine[3] could not be easily obtained for conversion into 3-aminothieno-(3,2-b)pyridine, the synthesis of the amino compound directly from 3-hydroxythieno(3,2-b)pyridine was undertaken. This approach had to be abandoned when it was found that the yield of amino compound, though better than that of the chloro compound, was still inadequate. In addition, the amino compound was accompanied by the formation of the bis-(3-thieno(3,2-b)pyridyl)-amine. Finally, since the work of Bennett, Crofts and Hey[4] and others[5] indicated that 3-hydroxythieno(3,2-b)pyridine might react with an excess of the side chain dialkylaminoalkylamines at temperatures of 170–180° to furnish directly the desired products, these reactions were tried. Good yields of the 3-dialkylaminoalkylaminothieno(3,2-b)pyridines were obtained by this method, comparable to those obtained when 8-aminoquinolines reacted with the side-chain dialkylaminoalkylhalides.[6] These compounds like their quinoline isosters are oils which can be distilled and which form crystalline citrates (Table I).

The compounds described here and in the preceding paper,[3] because of their relationship to 8-hydroxyquinoline, have been screened for antibacterial activity *in vitro* against three organisms. The results are summarized in Table II. In addition, the three dialkylaminoalkylaminothieno(3,2-b)pyridines have been examined[7] as antimalarials against *Plasmodium gallinaceum* in the chick and have been found completely inactive and non-toxic even when administered twice daily at 100 mg./kg.[8] When tested[7] against *E. histolytica* in the guinea pig at 100 mg./kg. twice daily for seven days they were also non-toxic and ineffective.

Experimental[9]

3-Aminothieno(3,2-b)pyridine.—This base was prepared by the method described by Diepolder.[10] A mixture of 2 g. of 3-hydroxythieno(3,2-b)pyridine, 5 g. of ammonium chloride and 15 ml. of 28% aqueous ammonia solution was heated in a sealed tube at 150° for 20 hours. The tube was opened and the contents washed out with 100 ml. of water. The solid material was suspended in ether and the insoluble material filtered off. The ether extract was extracted with dilute hydrochloric acid and the acid extract made alkaline and extracted again with ether. From the final ether extract on evaporation a product was obtained which crystallized from hexane, m.p. 88°. A sublimed sample melted at 92°.

Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.02; N, 18.65; S, 21.34. Found: C, 55.79; H, 4.23; N, 18.23; S, 21.21.

Bis-(3-thieno(3,2-b)pyridyl)-amine.[11]—A mixture of 3 g. (0.02 mole) of 3-hydroxythieno(3,2-b)pyridine and 39 ml. of ethanol saturated with ammonia at 0° was heated in a sealed tube for 10 hours at 190°. On cooling, the insoluble material, which showed no depression in melting point when mixed with bis-(3-hydroxythieno(3,2-b)pyridyl) oxide,[3] was filtered off and the filtrate concentrated *in vacuo*. The solid residue crystallized from ethanol, and recrystallized from benzene melted at 188–190°.

Anal. Calcd. for $C_{14}H_9N_3S_2$: C, 59.40; H, 3.14; N, 14.88; S, 22.58. Found: C, 59.47; H, 3.30; N, 15.13; S, 22.32.

(1) Presented in part before the Medicinal Section of the XIIth International Congress, New York, N. Y., September 10–13, 1951.

(2) (a) K. C. Blanchard, in Wiselogle, "A Survey of Antimalarial Drugs 1941–1946," J. W. Edwards, Ann Arbor, Michigan, 1946, Vol. I, page 129 ff.; (b) E. S. Josephson, D. J. Taylor, J. Greenberg and A. P. Ray, *Proc. Soc. Exptl. Biol. Med.*, **76**, 700 (1951); (c) N. L. Drake and Y. T. Pratt, THIS JOURNAL, **73**, 544 (1951).

(3) J. T. Sheehan and G. J. Leitner, *ibid.*, **74**, 5501 (1952).

(4) G. M. Bennett, P. C. Crofts and D. H. Hey, *J. Chem. Soc.*, 227 (1949).

(5) German Patent 486,079, Dec. 2, 1929.

(6) R. C. Elderfield, *et al.*, *ibid.*, **68**, 1524 (1946).

(7) These studies were carried out by the Laboratory of Tropical Diseases, National Microbiological Institute, Bethesda, Maryland.

(8) The antimalarial activity of SN 13,457 and SN 11,531, the isosters of compounds 2 and 3 (Table I) have been reported as 8-10Q and 6Q, respectively, *cf.* ref. 2c.

(9) All melting points are uncorrected. Microanalyses were carried out by Mr. J. F. Alicino of these Laboratories.

(10) E. Diepolder, *Ber.*, **42**, 2916 (1909).

(11) G. T. Morgan and E. D. Evens [*J. Chem. Soc.*, 1126 (1919)] used this procedure to prepare naphthylamines from α-naphthols.

TABLE I

DERIVATIVES OF 3-AMINOTHIENO(3,2-b)PYRIDINE

No.		1	2	3
R		$-(CH_2)_2N(C_2H_5)_2$[a]	$-(CH_2)_3N(C_2H_5)_2$[b,d]	$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$[c,d]
B.p. of base	°C.	166–169	171–174	176–180
	Mm.	1.8	2.0	1.0
Yield, %		58.5	54.0	38.0
Analyses of base, %	Carbon	Calcd. 62.61	63.83	65.98
		Found 62.29	63.30	65.85
	Hydrogen	Calcd. 7.67	8.03	8.64
		Found 7.66	7.60	8.66
	Nitrogen	Calcd. 16.85	15.95	14.41
		Found 16.73	15.43	14.31
	Sulfur	Calcd. 12.85	12.17	11.00
		Found 12.16	11.86	10.88
Salt		Citrate	Citrate	Citrate
M.p. of salt, °C.		153 dec.	110 dec.	82 dec.
Analyses of salt, %	Carbon	Calcd. 51.68	52.73	54.64
		Found 51.66	52.70	54.24
	Hydrogen	Calcd. 6.16	6.41	6.87
		Found 6.01	6.47	6.98

[a] Isoster prepared by K. Campbell, *et al.*, THIS JOURNAL, **68**, 1559 (1946). [b] Isoster of SN 13,457 (The designation SN refers to numbers assigned the drugs by the Survey of Antimalarial Drugs, *cf.* ref. 2a). [c] Isoster of SN 11,531. [d] Isoster prepared by E. B. Hartshorn and S. L. Baird, Jr., THIS JOURNAL, **68**, 1562 (1946).

TABLE II

THE *In Vitro* ANTIBACTERIAL ACTIVITIES[a]

	Minimal inhibiting concentration microgram./ml.		
	Staphylococcus aureus P209[b]	*Klebsiella pneumoniae*[b]	Bacillus of Calmette and Guerin[c]
8-Hydroxyquinoline	0.8	30	0.2
3-Hydroxythieno(3,2-b)pyridine	30	100	0.3
3-Hydroxythieno(3,2-b)pyridine methiodide	>300	>300	40
3-Hydroxyiodothieno(3,2-b)pyridine	>100	>100	2
3-Thieno(3,2-b)pyridyl acetate	20	200	0.2
3-Methoxythieno(3,2-b)pyridine	100	>100	30
3-Chlorothieno(3,2-b)pyridine	30	60	0.8
3-Aminothieno(3,2-b)pyridine	>100	>100	1.5
Bis-(3-thieno(3,2-b)pyridyl)-oxide	100	100	100
Bis-(3-thieno(3,2-b)pyridyl)-amine	100	>100	60
3-(2'-Diethylaminoethylamino)-thieno(3,2-b)pyridine[d]	600	>600	30
3-(3'-Diethylaminopropylamino)-thieno(3,2-b)pyridine[d]	>600	>600	150
3-(4'-Diethylamino-1'-methylbutylamino)-thieno(3,2-b)pyridine[d]	600	>600	8
8-Aminoquinoline	100	100	3

[a] Activities determined by Mr. F. Pansy in the Division of Microbiology, Research and Development Laboratories, E. R. Squibb and Sons, New Brunswick, N. J. [b] Tested in beef broth. [c] Tested in modified Kirchner's medium; G. Rake, W. Jambor, C. McKee, F. Pansy, F. Wiselogle and R. Donovick, *Am. Rev. Tuber.*, **60**, 121 (1949). [d] Tested as the citrate.

3-Dialkylaminoalkylaminothieno(3,2-b)pyridines.—The following method was used for the preparation of the three compounds shown in Table I. A mixture of 10 g. of 3-hydroxythieno(3,2-b)pyridine, 50 ml. of the dialkylaminoalkylamine and 0.1 g. of potassium iodide was heated in a sealed tube for 72 hours at 170–180°. On cooling the tube was opened and the contents washed out with ether. The insoluble material was filtered off and the filtrate concentrated at 10–20 mm. on the steam-bath. The residue was dissolved in 50 ml. of benzene and a small additional amount of insoluble material filtered off. The combined insoluble material was crystalized from benzene and identified as the **bis-(3-thieno(3,2-b)pyridyl) oxide.**[3] The filtered benzene solution was extracted three times with 40 ml. of 20% acetic acid. The combined acid extract was washed with ether and then made strongly alkaline with 20% sodium hydroxide solution and the free base extracted with ether. The ether extract, after washing and drying over potassium carbonate, was evaporated and the residue fractionated and the main fraction redistilled.

The citrate salts of these bases were formed by adding an equivalent amount of citric acid dissolved in ethanol to an ether solution of the base. The insoluble citrates precipitated immediately. Numbers 1 and 2 could be recrystallized from ethanol but no. 3 because of its great solubility in ethanol was crystallized from acetone.

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