the hydrogen absorption had ceased. Another solution of 1.00 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid was added and the reduction resumed. After six additional hours, the hydrogen uptake had again ceased. The catalyst and support were filtered, washed well with absolute alcohol and then water. The aqueous solution was taken to dryness on a steam cone and contained no organic material. The alcohol layer was evaporated to 2 cc. and 50 cc. of absolute alcohol added, causing the precipitation of 3.7 g. (58%) of product as voluminous white crystals, m. p. 204–207°. This material was very hygroscopic. Recrystallization from alcohol–ether gave small white needles. After drying at 100° and 1 mm. for six hours the m. p. was 216–218°.

Anal. Calcd. for $C_8H_{14}Cl_2N_2$: N, 13.4. Found: N, 13.3.

2,3-Dimethyl-5-hydroxymethylpyridine and Hydrochloride (VII).—To a solution of 2.3 g. of 5-aminoethyl-2,3-dimethylpyridine dihydrochloride (VI) in 10 cc. of water was added a solution of 40 cc. of concentrated hydrochloric acid in 80 cc. of water, and the resulting solution heated to 95°. A solution of 4.5 g. of sodium nitrite in 10 cc. of water was then added all at once, with vigorous shaking. The temperature was maintained at 85–90° until the gas evolution had ceased. The solution was then evaporated until a semi-crystalline mass remained. Attempts to obtain the crystalline hydrochloride by the method described for its isomer failed, as a liquid was always obtained. This liquid hydrochloride was then added to 10 cc. of water containing 1 g. of sodium bicarbonate. The water was removed *in vacuo*, and the residue extracted with three 15-cc. portions of boiling absolute alcohol. After filtering off the inorganic salts, the combined alcoholic extracts were concentrated until an oil remained. This was distilled and a colorless liquid, 0.45 g. (30%), b. p. 108° at 0.5 mm., was obtained.

Anal. Calcd. for $C_8H_{11}NO$: N, 10.2. Found: N, 9.9.

The hydrochloride was finally prepared by dissolving this free base in 100 cc. of dry ether and passing in dry hydrogen chloride gas as a voluminous white solid separated out. This was very hygroscopic. A sample dried at 40° and 1 mm. for seventy-two hours had a m. p. 103–106°.

Summary

2,3-Dimethyl-5-hydroxymethylpyridine and 2,4-dimethyl-5-hydroxymethylpyridine (3,4-didesoxypyridoxin) have been synthesized. The former compound exhibited neither vitamin nor anti-vitamin activity, while the latter compound proved to be a weak antagonist for pyridoxin.

EVANSTON, ILL. RECEIVED JULY 30, 1948

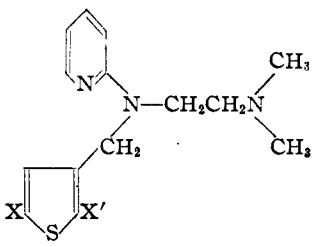
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

3-Substituted Thiophenes. III. Antihistaminics of the N-(3-Thenyl)-ethylenediamine Series[1]

BY E. CAMPAIGNE AND WILLIAM M. LESUER[2]

Recently it has been discovered that incorporation of the thiophene nucleus in antihistaminic compounds leads to desirable properties.[3–6] The work of Clapp, *et al.*,[5] indicates that the inclusion of a halogen atom on the thiophene ring improves the therapeutic ratio. Continuing a study of the properties of 3-thienyl analogs of physiologically active compounds,[7–9] attention was turned to the antihistaminic series. The preparation of four N-substituted dimethylaminoethylaminopyridines, containing the 3-thenyl and halogen-substituted 3-thenyl nucleus are described in this paper. The compounds prepared were: I, N,N-dimethyl-N′-(2-pyridyl)-N′-(3-thenyl)-ethylenediamine; II, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-chloro-3-thenyl)-ethylenediamine; III, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-bromo-3-thenyl)-ethylenediamine; and IV, N,N-dimethyl-N′-(2-pyridyl)-N′-(2,5-dichloro-3-thenyl)-ethylenediamine.

These compounds were readily synthesized by the reaction of the sodio-derivative of 2-dimethylaminoethylaminopyridine with the appropriate 3-thenyl bromide, obtained when the proper 3-methylthiophene reacted with N-bromosuccinimide.[7] In order to produce the corresponding halogenated compounds, it was necessary to extend the N-bromosuccinimide reaction to the halogenated 3-methylthiophenes, and characterize the halogenated thenyl bromides. As was expected, it was found that blocking the active 2-position with a halogen greatly improved the yield of side-chain bromination with N-bromosuccinimide. The reactions carried out in the preparation of the four antihistaminics and intermediates are outlined in the accompanying diagram. In each case the thenyl bromide was converted to the hexamethylenetetramine salt, the salt steam distilled to obtain the aldehyde, which was then oxidized to the acid with silver oxide.



I, X = H, X′ = H
II, X = H, X′ = Cl
III, X = H, X′ = Br
IV, X = Cl, X′ = Cl

The chlorination of 3-methylthiophene with sulfuryl chloride[10] was extended to the preparation

(1) Taken from part of the thesis submitted by William M. LeSuer in partial fulfilment of the requirements for the degree Doctor of Philosophy at Indiana University, June, 1948.

(2) Sterling-Winthrop Fellow in Chemistry, 1947. Present address: Lubrizol Corporation, Cleveland, Ohio.

(3) Weston, THIS JOURNAL, **69**, 980 (1947).

(4) Lee, Dinwiddie and Chen, *J. Pharm.*, **90**, 83 (1947).

(5) Clapp, *et al.*, THIS JOURNAL, **69**, 1549 (1947).

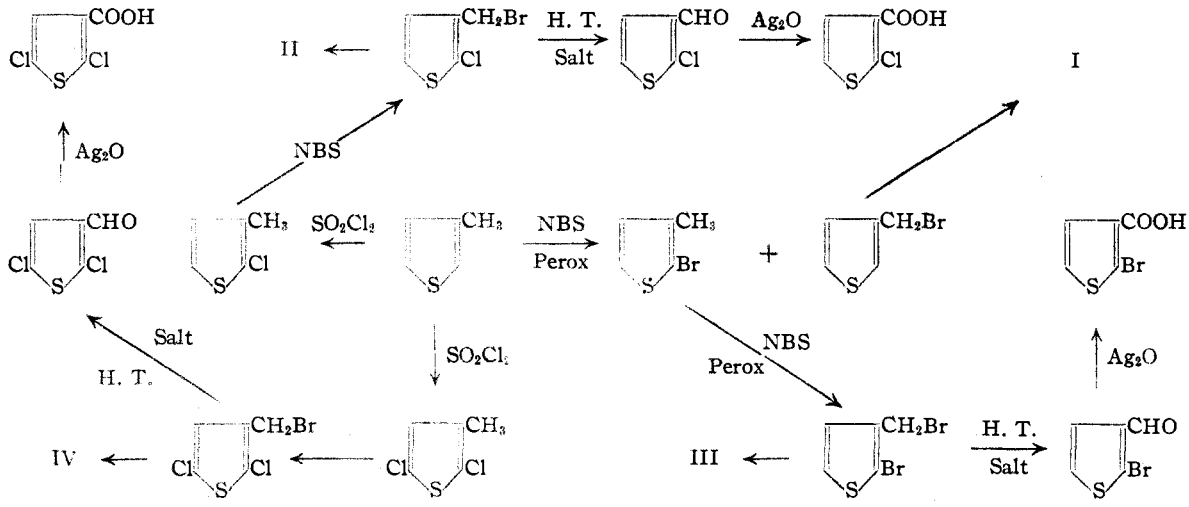
(6) Kyrides, Meyer and Zienty, *ibid.*, **69**, 2239 (1947).

(7) Campaigne and LeSuer, *ibid.*, **70**, 1555 (1948).

(8) Campaigne, *et al.*, *ibid.*, **70**, 2611 (1948).

(9) Campaigne and LeSuer, *ibid.*, **70**, 3498 (1948).

(10) Campaigne and LeSuer, *ibid.*, **70**, 415 (1948).



of 2,5-dichloro-3-methylthiophene, which was found to be produced in good yield by this reaction.

The pharmacological data on these compounds will be published elsewhere by Dr. A. M. Lands, of the Sterling–Winthrop Research Institute.

Experimental

2-Chloro-3-thenyl Bromide.—A solution of 66 g. (0.5 mole) of 2-chloro-3-methylthiophene[10] in 150 ml. of carbon tetrachloride was mixed with 88.5 g. (0.5 mole) of N-bromosuccinimide and 1.0 g. of benzoyl peroxide was added. After refluxing for eight hours, the mixture was cooled and filtered to remove succinimide. The succinimide was washed with 50 ml. of carbon tetrachloride, and the combined filtrates fractionated under reduced pressure. A highly lachrymatory oil was collected at 85–92° (1–2 mm.), and amounted to 81 g. (0.37 mole, 75%). The main portion distilled at 88° (1 mm.), and a sample of this fraction ($n^{22}D$ 1.6119), was used for analyses.

Anal. Calcd. for C_5H_4BrClS: S, 15.16. Found: S, 15.19.

Hexamethylenetetramine Salt of 2-Chloro-3-thenyl Bromide.—To 37.2 g. (0.18 mole) of 2-chloro-3-thenyl bromide in 50 ml. of chloroform was added 25 g. (0.18 mole) of hexamethylenetetramine, and the mixture was shaken. Separation of the salt began immediately, but the mixture was refluxed for one hour to ensure complete reaction. After cooling the salt was filtered, washed with ether, and air dried; yield, 52 g. (84%). Recrystallization of the salt from ethanol yielded beautiful white needles which melted at 165°.

Anal. Calcd. for $C_{11}H_{16}N_4BrClS$: S, 9.12. Found: S, 8.80.

2-Chloro-3-thenaldehyde.—A solution of 40 g. (0.14 mole) of the hexamethylenetetramine salt of 2-chloro-3-thenyl bromide in 150 ml. of hot water was rapidly steam distilled until 750 ml. of distillate was collected. The distillate was acidified with hydrochloric acid, extracted with three 75-ml. portions of ether, and the extract dried over Drierite. After removing the ether, the residue solidified on cooling. It was dissolved in high-boiling petroleum ether, and crystallized at Dry Ice temperature. After filtering, the crystalline material was transferred to a small flask and distilled in vacuum. The product was a colorless oil, b. p. 100–102° (1–2 mm.), and weighed 4.2 g. (0.029 mole, 25%). It crystallized on standing at room temperature, m. p. 25°, $n^{20}D$ 1.5908.

Anal. Calcd. for C_5H_3OClS: S, 21.87. Found: S, 21.58.

The 2,4-dinitrophenylhydrazone of 2-chloro-3-thenaldehyde was formed readily by the usual procedure, giving orange needles from chloroform, which melted at 214°.

Anal. Calcd. for $C_{11}H_7O_4N_4ClS$: S, 9.81. Found: S, 9.98.

2-Chloro-3-thenoic Acid.—A solution of 0.5 g. (0.0034 mole) of 2-chloro-3-thenaldehyde in 5 ml. of ethanol was added to a thoroughly shaken suspension of silver oxide, produced by adding 0.35 g. of sodium hydroxide to 1.0 g. of silver nitrate in 25 ml. of water, and the mixture shaken for thirty minutes. The free silver was removed by filtering, washed with water, and the filtrate acidified with concentrated hydrochloric acid. The white precipitate was recrystallized from water, yielding 0.42 g. (0.0025 mole, 75%) of 2-chloro-3-thenoic acid, which melted at 163°.

Anal. Calcd. for $C_5H_3O_2ClS$: S, 19.72. Found: S, 19.84.

2-Bromo-3-thenyl Bromide.—The 2-bromo-3-methylthiophene used for this preparation was obtained as a by-product in the bromination 3-methylthiophene with N-bromosuccinimide.[7] The compound was separated by treating the mixture produced in the bromination reaction with hexamethylenetetramine in chloroform, thus removing the 3-thenyl bromide salt. The unreacted 2-bromo-3-methylthiophene and chloroform was accumulated from a number of such preparations and fractionated. The 2-bromo-3-methylthiophene was collected from 172–174°[11] and redistilled in vacuum, b. p. 52° (3 mm.). A solution of 88.5 g. (0.5 mole) of 2-bromo-3-methylthiophene in carbon tetrachloride was treated with 0.5 mole of N-bromosuccinimide and 1.0 g. of benzoyl peroxide, as described above. The product was collected at 105–120° (7 mm.), the main portion coming over at 113° (7 mm.) ($n^{20}D$ 1.6241) and weighed 84.2 g. (0.328 mole, 65%).

Anal. Calcd. for $C_5H_4Br_2S$: S, 12.82. Found: S, 12.79.

Hexamethylenetetramine Salt of 2-Bromo-3-thenyl Bromide.—This salt was formed in the usual manner from 0.32 mole of 2-bromo-3-thenyl bromide in 75% yield (94 g.). When recrystallized from ethanol, the salt melted at 171–172°.

Anal. Calcd. for $C_{11}H_{16}N_4Br_2S$: S, 8.09. Found: S, 7.77.

2-Bromo-3-thenaldehyde.—Produced by the steam distillation of 50 g. of the hexamethylenetetramine salt, the aldehyde solidified on standing, after the ether used to extract it was removed. Two recrystallizations from high-boiling petroleum ether yielded 3.7 g. (15%) of white needles, which melted at 34°.

(11) Steinkopf, *Ann.*, **515**, 273 (1935), reported the boiling point of this compound to be 175° (729 mm.).

Anal. Calcd. for C_6H_3OBrS: S, 16.78. Found: S, 17.00.

The 2,4-dinitrophenylhydrazone of 2-bromo-3-thenaldehyde crystallized from chloroform in orange needles, which melted at 230.5°.

Anal. Calcd. for $C_{11}H_7O_4N_4BrS$: S, 8.64. Found: S, 8.65.

2-Bromo-3-thenoic Acid.—One gram (0.005 mole) of 2-bromo-3-thenaldehyde was shaken with silver oxide, and the acid worked up in the usual manner. Recrystallization from a 4:1 water–ethanol mixture yielded 0.84 g. (78%) of slender white needles, which melted at 178–179°.

Anal. Calcd. for $C_5H_3O_2BrS$: S, 15.49. Found: S, 15.54.

2,5-Dichloro-3-methylthiophene.—To 296 g. (3.0 moles) of 3-methylthiophene was added dropwise 810 g. (6.0 moles) of sulfuryl chloride over a period of three hours. Spontaneous refluxing soon began and continued throughout the addition. When spontaneous refluxing subsided, heat was applied and the mixture refluxed two hours longer, and then fractionally distilled. The yield of 2-chloro-3-methylthiophene, b. p. 50° (16 mm.), $n^{20}D$ 1.5408, was 31 g. (0.235 mole, 8%). The main product, 2,5-dichloro-3-methylthiophene, distilled at 44° (1 mm.), 65° (11 mm.), $n^{20}D$ 1.5560, and weighed 316 g. (1.89 moles, 63%). The higher boiling products were not identified.

Anal. Calcd. for $C_5H_4Cl_2S$: S, 19.2. Found: S, 19.6.

2,5-Dichloro-3-thenyl Bromide.—A solution of 83.5 g. (0.5 mole) of 2,5-dichloro-3-methylthiophene was treated, as previously described, with an equivalent portion of N-bromosuccinimide and 1.0 g. of benzoyl peroxide. A violent reaction occurred when heating was begun, and it was necessary to cool externally at first to control the reaction. After refluxing ten hours, the yellow filtrate was concentrated and the product fractionated in vacuum. The yield of 2,5-dichloro-3-thenyl bromide, b. p. 104.5–106° (4 mm.), $n^{20}D$ 1.6177, was 84.7 g. (0.345 mole, 69%).

Anal. Calcd. for $C_5H_3BrCl_2S$: S, 13.03. Found: S, 12.92.

The hexamethylenetetramine salt of 2,5-dichloro-3-thenyl bromide was obtained in 90% yield; recrystallized from methanol, m. p. 178–80° (dec.).

Anal. Calcd. from $C_{11}H_{15}N_4BrCl_2S$: S, 8.30. Found: S, 8.56.

2,5-Dichloro-3-thenoic Acid.—Steam distillation of a solution of 42 g. (0.109 mole) of the hexamethylenetetramine salt of 2,5-dichloro-3-thenyl bromide yielded a small amount of oil having an almond odor. The crude aldehyde was oxidized with silver oxide, and the crude acid crystallized from a 50:50 water–ethanol mixture, yielding 2.3 g. (0.0125 mole, 11.4%) of 2,5-dichloro-3-thenoic acid, which melted at 146.5–147.5°.[12]

Dimethylaminoethylaminopyridine Derivatives.—The syntheses of all of the antihistaminic compounds were conducted in essentially the same manner. The procedure for the preparation of the 3-thenyl derivative is described, and the physical constants and yields of all are tabulated in Table I. To a stirred suspension of 3.12 g. (0.08 mole) of sodamide in 50 ml. of dry tolene was added dropwise 12 g. (0.073 mole) of 2-dimethylaminoethylaminopyridine.[13] The mixture was refluxed for two hours, cooled to 50°, and 21 g. (0.12 mole) of 3-thenyl bromide was added dropwise. When the reaction subsided, the brownish-orange mixture was refluxed one-half hour longer, cooled, and poured into 150 ml. of water. Three layers formed, water, toluene and a black oil which contained none of the desired product, but was probably the quaternary salt resulting from the reaction of 3-thenyl bromide with the dimethylamine group. The toluene layer was separated, extracted with 5% hydrochloric acid, and the hydrochloric acid layer saturated with potassium carbonate. The free base was extracted with ether, dried and fractionated. In this way, 6 g. (0.023 mole, 31.4%) of a yellow oil boiling at 169–172° (1 mm.) was obtained.

TABLE I

PROPERTIES OF THE 3-THENYL-DIMETHYLAMINOETHYLAMINOPYRIDINES

Compounds	Yield, %	B. p., °C. (1 mm.)	$n^{20}D$	Formula	Anal. S, % Calcd.	Found
I	31.4	169–172	1.5915	$C_{14}H_{19}N_3S$	12.27	12.24
II	28	156–158	1.5950	$C_{14}H_{18}N_3ClS$	10.84	11.33
III	20	177–179	1.6590	$C_{14}H_{18}N_3BrS$	9.42	9.14
IV	38	179–181	1.5968	$C_{14}H_{17}N_3Cl_2S$	9.71	10.01

The monohydrochloride of N,N-dimethyl-N′-(3-thenyl-)-N′-(2-pyridyl)-ethylenediamine was prepared in the following manner from a larger quantity of the base.[14] 106 g. of the free base was dissolved in 500 ml. of isopropyl alcohol and 34 ml. of concentrated hydrochloric acid was added. After shaking, the reaction mixture was allowed to crystallize. After thorough cooling in an ice–methanol mixture, the salt was collected and washed on the filter with low-boiling petroleum ether. The salt was dried in an oven at 70°, giving 91 g. of a white solid, m. p. 169.5–170°. A second crop of 13 g. was obtained by concentrating the filtrate, making the total yield 86%.

Anal. Calcd. for $C_{14}H_{20}N_3SCl$: Cl, 11.93; S, 10.76; N, 14.12. Found: Cl, 11.80; S, 10.79; N, 13.97.

Acknowledgment.—The authors gratefully acknowledge the coöperation and financial support of this research by the Sterling–Winthrop Research Institute.

Summary

Four new compounds containing the 3-thenyl and halogen-substituted 3-thenyl radical, have been synthesized for testing for antihistaminic activity.

The peroxide-catalyzed reaction of N-bromosuccinimide with halogen substituted 3-methylthiophenes has been shown to give good yields of the corresponding 3-thenyl bromides.

Several new 3-substituted thiophene derivatives, containing the methyl, bromomethyl, aldo and carboxyl group in the 3-position, have been synthesized and characterized.

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(12) Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947), reported 147–148° for the acid prepared by oxidation of 2,5-dichloro-3-acetylthiophene.

(13) Generously supplied by Dr. C. M. Suter of the Sterling-Winthrop Research Institute.

(14) We are indebted to Mr. B. F. Tullar of the Sterling-Winthrop Research Institute for the preparation of this salt.