[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

ANTIHISTAMINE AGENTS. III. SUBSTITUTED N,N-DIMETHYL-N'-(2-PYRIDYL)-N'-THENYLETHYLENEDIAMINES AS ANTIHISTAMINE AGENTS

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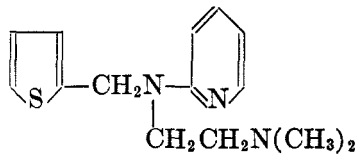
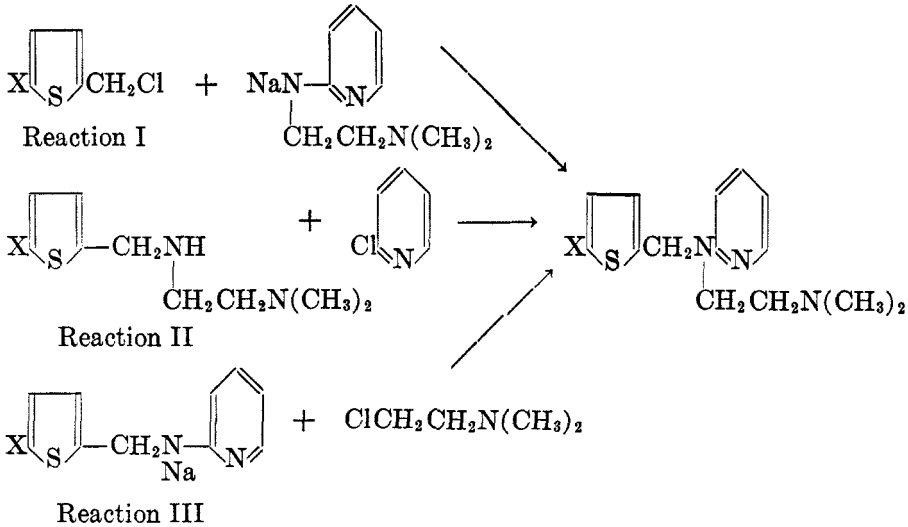
Preliminary announcement of the high antihistamine activity of thenylpyridyldimethylethylenediamines (I) incident to halogenation of the thiophene ring has been made (1). Following this observation, the effects of other substituents in the thiophene and pyridine rings of N,N-dimethyl-N'-2-pyridyl-N'-2-thenylethylenediamine (I) were determined. This paper presents the synthesis of such new compounds and reports their antihistamine activity.



I

The structure assigned to the N,N-dimethyl-N'-2-pyridyl-N'-(5-halo-2-thenyl)ethylenediamines in the earlier report has been confirmed by their synthesis in two other ways. The orientation of the intermediate 5-bromothenyl chloride was shown by its oxidation to 5-bromo-2-thiophenecarboxylic acid. Previously, the compounds had been synthesized by the reaction of the 5-halo-2-thenyl halides with the sodium salt of N,N-dimethyl-N'-2-pyridylethylenedi-



Reaction I

Reaction II

Reaction III

amine (Reaction I). Compounds identical with those prepared from the thenyl halides also resulted from the reaction of 2-chloropyridine with N,N-dimethyl-N′-(5-chloro-2-thenyl)ethylenediamine (Reaction II) and from the reaction of N,N-dimethylaminoethyl chloride and 2-(5-bromo-2-thenyl)aminopyridine (Reaction III).

The new compounds prepared are presented in Table I. They were usually prepared by reaction of a thenyl halide with the sodium or potassium salt of a pyridyldimethylethylenediamine. These salts were conveniently prepared by the reaction of the amine in liquid ammonia or toluene with sodium hydride, or sodium or potassium amide.

The thenyl halides were prepared by three general methods. In the first of these, thiophenes were chloromethylated in an α-position unless both of these were substituted, in which case the chloromethylation occurred in the β-position. Although 2,5-dichlorothiophene was successfully chloromethylated, 2,5-dibromo thiophene failed to react. Attempts to chloromethylate 2-iodothiophene were consistently unsuccessful, decomposition being the invariable result even under the mildest conditions used.

The bromination of various 2-methylthiophenes with N-bromosuccinimide was successful. In the third method, alkyl 2-thienyl carbinols were converted into alkyl 2-thenyl bromides by the action of hydrogen bromide in benzene. Yields were less satisfactory than in the first two methods, possibly because of the ready dehydrobromination of the products, although this assumption has not been proved.

In a large number of cases the instability of the thenyl halides led to their immediate use and they were not analyzed. Their properties and those of the compounds prepared from them were as expected.

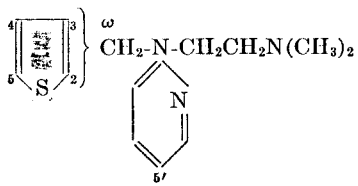
When compound I was treated with bromine, decomposition resulted. However, bromination of compound I having a halogen in the 5-position of the thiophene ring and of N,N-dimethyl-N′-2-pyridylethylenediamine gave compounds brominated in the 5-position of the pyridine ring. These compounds were identified by comparison with those prepared from 2-amino-5-bromopyridine.

Various reactions of the halogen of the N,N-dimethyl-N′-2-pyridyl-N′-(5-halo-2-thenyl)ethylenediamines were tried. In general, reaction with butyllithium, sodium methoxide, or sodium resulted in cleavage of the thenyl group and N,N-dimethyl-N′-2-pyridylethylenediamine resulted. Under other conditions treatment of these compounds with sodium, lithium, methyl lithium, or Grignard reagents resulted in dehalogenation and N,N-dimethyl-N′-2-pyridyl-N′-2-thenylethylenediamine was produced. In all of the above reactions the bromo compounds proved to be more reactive than the chloro. Evidence for metallation was obtained only in the case of the action of butyllithium on the bromo compound followed by carbonation to give a low yield of the corresponding 5-carboxy compound.

When the compounds of this series were tested *in vitro* against histamine (see Table I) none was as active as either N,N-dimethyl-N′-2-pyridyl-N′-(5-bromo-2-thenyl)ethylenediamine or its chloro analog.

TABLE I

N,N-DIMETHYL-N′-2-PYRIDYL-N′-THENYLETHYLENEDIAMINES



CPD.	—CH₃—	2 OR 3	5	ω	5′	METHOD[l] OF Prep'n	METHOD[l] OF Work-up	B.P. °C/MM.	CRYSTAL SOLVENT	M.P. °C[j]	SALT	YIELD %	EMP. FORMULA ANALYTICAL FORM	CALC'D % C	CALC'D % H	CALC'D % N	CALC'D Eq. Wt.	FOUND % C	FOUND % H	FOUND % N	FOUND Eq. Wt.	FOUND H Ratio[k]
1	2							123–135 / 0.1		162–165	A											1–10
2	2		Cl			II		155–156 / 1		106–108	A		$C_{14}H_{19}Cl_2N_3S$	50.6	5.8	12.6		50.9	6.1	12.3		10–100
3	2		Cl							105–106	B		$C_{14}H_{21}ClN_3O_4PS$			10.7				10.5[e]		10–100
4	2		Cl							115–118	C		$C_{20}H_{26}ClN_3O_7S$			8.6				8.5[e]		10–100
5	2		Br			III	2	173–175 / 1	Ethyl acetate	124–126	A	<19	$C_{14}H_{19}BrClN_3S$[a]	44.6	5.1	11.1		44.9	5.2	11.0		10–100
6	2	3-Br	Br			I-KNH_2	1	150–160 / 0.001	Abs. alc.	208–209	A	39	$C_{14}H_{18}Br_2ClN_3S$[b]			9.2				9.1		0.01–0.1
7	2		*t*-Bu			I-$NaNH_2$	4	185–190 / 3.5	Toluene	145–146	A	10	$C_{18}H_{28}ClN_3S$	61.1	8.0	11.9		61.2	7.8	11.7		0.01–0.1
8	3	2-Cl	Cl			I-$NaNH_2$	3	174–180 / 1	Ethyl acetate or benzene	168–170	A	25	$C_{14}H_{18}Cl_3N_3S$[c]			11.5				11.7		0.1–1.0
9	2				Br	I-KNH_2	1	175–185 / 0.6	Methyl ethyl ketone	140–141	A	11	$C_{14}H_{19}BrClN_3S$	44.6	5.1	11.2		44.6	5.4	11.3		0.1–1.0
10	2	3-Br				I-$NaNH_2$	2		Benzene	184–185	A	55	$C_{14}H_{19}BrClN_3S$[f]			11.2				10.9		0.1–1.0
11	2		Cl		Br	I-$NaNH_2$	5		Ethyl acetate or Methyl ethyl ketone	136–137	A	48	$C_{14}H_{18}BrCl_2N_3S$	40.8		10.2	411	41.0[g]		10.2	410	0.1–1.0

12	2		*t*-Bu		Br	I-NaH	5		Methyl ethyl ketone	175–176	A	<1	$C_{18}H_{27}BrClN_3S$[h]	49.9		9.7	433	49.8[g]		9.6	131	0.01–0.1
13	2		Br		Br	I-NaH	2	175–190 0.0001	"	163–166	A	15	$C_{14}H_{18}Br_2ClN_3S$	36.9	4.0	9.2		37.1	4.3	8.9		0.01–0.1
14	2			n-C_3H_7		I-NaH	2	130–135 0.5				5	$C_{17}H_{25}N_3S$	67.3	8.3	13.9		67.4	7.4	13.5		0.1–1.0
15	2			CH_3		I-$NaNH_2$	2	150–151 1	*i*-Propanol	172–173	A	23	$C_{15}H_{22}ClN_3S$[i]	57.9	7.7	13.5	311.5	58.1	7.4	13.2	307.5	0.1–1.0
16	2		COOH							198–200	D	5	$C_{27}H_{25}N_9O_{16}S$[d]	42.5	3.3	16.5		42.6	3.4	16.5		0.01–0.1

A. hydrochloride.
B. dihydrogen phosphate.
C. dihydrogen citrate.
D. dipicrate.

[a] S, Calc'd 8.5; found, 8.7.
[b] Cl^-, Calc'd 7.8; found (Volhard) 7.7.
[c] Cl^-, Calc'd 9.7; found (Volhard) 9.6.
[d] Picric acid, Calc'd 60.1%; found (spectrally) 58.6.
[e] Macro Kjeldahl.
[f] Cl^-, Calc'd 7.4; found 7.5.
[g] van Slyke wet carbon.
[h] S, Calc'd 7.4; found 7.5.
[i] Cl^-, Calc'd 11.4; found (Volhard) 11.3.
[j] Melting points were taken either in a bath or on a Fisher-Johns block.
[k] H ratio = μ g. histamine (to produce a given contraction)/μ g. compound (required to suppress this response), and was determined on the isolated guinea pig gut by the method of (14).
[l] For examples of the various methods, see Experimental.

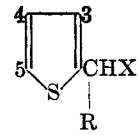
EXPERIMENTAL[1]

The thenyl halides used are described in Table II.

Method I. Workup 1. N,N-Dimethyl-N'-2-pyridyl-N'-(3,5-dibromo-2-thenyl)ethylenediamine. Thirty and eight-tenths grams (0.092 mole) of 3,5-dibromo-2-thenyl bromide was condensed with 15.5 g. (0.095 mole) of N,N-dimethyl-N'-2-pyridylethylenediamine (3) by the usual process using potassium amide in toluene. After filtration, the toluene was extracted with dilute hydrochloric acid and the acid solution made strongly basic by the addition of solid sodium hydroxide. The oil which separated was extracted with benzene. The benzene was distilled and the residue was vaporized at very low pressure in a short-path still. A forerun was collected at a bath temperature of 110–120° and a pressure

TABLE II

THENYL HALIDES



X	R	3	4	5	METHOD OF PREP'N	YIELD, %	PAPER REFS. INTERMEDIATE	B.P., °C./MM.
Br	H	Br	H	Br	A	61	(2)	104–108/1
Br	H	Br	H	H	A	86	(2)	60–125/1[c]
Cl[a]	H	Cl	H	Cl	B	10	Texaco	125–128/30
Cl	H	H	H	*t*-Bu	B	52	Socony-Vacuum	67–71/1
Br	CH_3	H	H	H	C	20	C	
Br	*n*-C_3H_7	H	H	H	C	24	C	63/3
2,5-Dichloro-3-thenylchloride[b]					B	11	Texaco	125–128/30

Methods of preparation:

A. N-Bromosuccinimide on methyl compound.

B. Chloromethylation of 2-H thiophene by method of (1).

C. see Experimental.

[a] Hydrolysable Cl^-, Calc'd: 7.6; Found: 7.3, n_D^{20} 1.5258.

[b] Hydrolysable Cl^-, Calc'd: 17.6; Found: 17.3, n_D^{25} 1.5805.

[c] Superheat.

of about 0.01 mm. This was followed by a fraction at a bath temperature of 150–160° and a pressure of 0.001 mm.; yield, 15 g. This was converted into its monohydrochloride by treatment with the theoretical amount of alcoholic hydrogen chloride. The solid was purified by recrystallization from absolute alcohol.

Method I. Workup 2. N,N-Dimethyl-N'-2-pyridyl-N'-(3-bromo-2-thenyl)ethylenediamine hydrochloride. Twenty and five-tenths grams of N,N-dimethyl-N'-2-pyridylethylenediamine was converted to its sodium salt in liquid ammonia by treatment with sodamide freshly prepared from 2.9 g. (0.126 atom) of sodium. The ammonia was displaced by 150 cc. of dry toluene and 31.8 g. (0.124 mole) of 3-bromo-2-thenyl bromide was added. The reaction was stirred and heated on the steam-bath for two hours. After standing at room temperature overnight, the reaction mixture was filtered and the toluene was distilled at

[1] All melting points are corrected. Combustion analyses were carried out in these Laboratories under the direction of Dr. J. A. Kuck. In all cases the figures presented are the average of two values not differing by more than 0.3.

reduced pressure. The residue was fractionated at about 1 mm. The forerun boiling at 50–144° was discarded; the remainder distilled at 148–153°, and weighed 24.6 g. This was redistilled to give 23 g.; n_D^{25} 1.5988; b.p. 170–180° (*ca.* 1 mm.), although this represents considerable superheating. On treating the material with an equivalent of alcoholic hydrochloric acid the salt precipitated. Crystallization from benzene containing a small proportion of alcohol does not improve the melting point.

Method I. Workup 3. N,N-Dimethyl-N'-2-pyridyl-N'-(2,5-dichloro-3-thenyl)ethylenediamine. Nine and two-tenths grams of 2,5-dichloro-3-thenyl chloride reacted with the sodium salt of N,N-dimethyl-N'-2-pyridylethylenediamine prepared from 7.8 g. (0.047 mole) of the amine and the sodamide from 1.06 g. (0.046 mole) of sodium in liquid ammonia. The reaction was carried out in 250 cc. of toluene which had displaced the ammonia in which the sodium salt was formed. After heating for four hours on the steam-bath, the mixture was allowed to stand overnight and then hydrolyzed and filtered. The toluene layer was separated, dried over sodium sulfate, and the toluene distilled. The concentrate was extracted with 50 cc. of anhydrous ether and the ether-soluble material fractionated to give 3.86 g. of product boiling at 174–180° (1 mm.), n_D^{25} 1.5866. The material was converted to its monohydrochloride by treatment with an equivalent of absolute alcoholic hydrogen chloride and precipitation with ether. Two and three-tenths grams of a white solid melting at 158–163° was obtained. After crystallization from ethyl acetate and alcohol, followed by benzene, 1.28 g. of white plates was obtained.

Method I. Workup 4. N,N-Dimethyl-N'-2-pyridyl-N'-(5-t-butyl-2-thenyl)ethylenediamine hydrochloride. Sodamide from 4.6 g. (0.2 mole) of sodium was treated with 33 g. (0.2 mole) of N,N-dimethyl-N'-2-pyridylethylenediamine in toluene and this product in 500 cc. of toluene was treated with 37.3 g. (0.2 mole) of 5-*t*-butyl-2-thenyl chloride at room temperature with cooling. After stirring for two hours at room temperature, 300 cc. of water was added cautiously, and the layers were separated. The toluene layer was dried over potassium carbonate and the toluene was distilled at about 30 mm. pressure. The residue was fractionated at 3.5 mm. pressure. A forerun of 7.5 g. boiling at 70–78° was discarded and 7.7 g. of a fraction of b.p. 185–190° was obtained. The material was converted to its monohydrochloride by treatment with an equivalent of alcoholic hydrogen chloride and precipitation with ether. The crystals were hygroscopic and the hydrochloride was reconverted to the free base by solution in water, treatment with sodium hydroxide, and extraction with ether. The ether was distilled and the residue was again treated with an equivalent of alcoholic hydrogen chloride. The crystals obtained in this fashion were non-hygroscopic and were crystallized from toluene four times to a constant m.p. of 145–146°, using Norit the first two times.

1-(2-Thienyl)ethanol [for another method of preparation see (4)] was prepared by the addition of 0.56 mole of 2-thiophenaldehyde (Arapahoe) to a Grignard reagent prepared from 0.75 mole of methyl iodide and 0.5 g. of magnesium in ether. The reaction mixture was stirred for ten minutes after the addition of the aldehyde was complete and then poured onto cracked ice. After the addition of sulfuric acid, the ether layer was separated and the aqueous layer extracted six times with ether. The ether layers were combined, dried, and the ether distilled. The product was obtained in 79.4% yield, b.p. 89–92° (11 mm.).

1-(2-Thienyl)ethyl bromide. A solution of 30 g. of the carbinol and 150 cc. of benzene was slowly saturated with anhydrous hydrogen bromide and then treated with hydrogen bromide for forty minutes longer (5). The solution was dried over sodium sulfate, the benzene was distilled, and the residue fractionated. The product was unstable even in the refrigerator.

1-(2-Thienyl)butanol was prepared in 84.1% yield by the addition of 0.7 mole of 2-thiophenaldehyde to a Grignard reagent prepared from 1 mole of propyl bromide and 1 mole of magnesium in ether (dried with calcium hydride). The product weighed 90 g. and boiled at 84–86° (3 mm.).

1-(2-Thienyl)butyl bromide. The 90 g. (0.58 mole) of 1-(2-thienyl)butanol was treated with anhydrous hydrogen bromide in 400 cc. of benzene. An orange water layer separated

as the reaction proceeded and the reaction was stopped after two hours. The benzene was washed with sodium bisulfite solution, evaporated, and the black residue was fractionally distilled.

N,N-Dimethyl-N'-(5-bromo-2-pyridyl)ethylenediamine dihydrochloride. A. *From N,N-dimethyl-N'-2-pyridylethylenediamine.* One hundred grams (0.61 mole) of this compound in 500 cc. of chloroform was cooled in an ice-bath and treated with 105 g. (0.65 mole) of bromine in thirty minutes. The chloroform was then extracted with several 150-cc. portions of water and these extracts combined. The aqueous solution was made strongly alkaline and extracted with ether to remove the separated oil. The ether was distilled and the product was fractionated at 0.1 mm. pressure; 89 g. (60%) was collected at 102–106°, n_D^{30} 1.5745. A sample of this was converted to the dihydrochloride by treatment with alcoholic hydrogen chloride and recrystallized from 95% alcohol. The melting point was 224–227° (dec.) and was not depressed by mixture with the material prepared by Method B. When carried out in aqueous solution the bromination gave a 76% yield. Some dibromo product was formed, however, which complicated the purification.

B. *From 2-amino-5-bromopyridine.* The potassium salt of 86 g. (0.5 mole) of 2-amino-5-bromopyridine (6) was made in liquid ammonia from freshly prepared potassium amide. After stirring for one-half hour the ammonia was replaced by toluene and 53.8 g. (0.5 mole) of dimethylaminoethyl chloride (7) was added. The reaction mixture was heated with stirring on a steam-bath for eighteen hours, cooled, and filtered. The filtrate was concentrated by distillation and the residue was distilled *in vacuo*. The fraction of b.p. 120–130° (1 mm.) weighed 51 g. (42%). This was converted into its dihydrochloride by treatment with alcoholic hydrogen chloride; 60 g. of material of m.p. 175–190° was obtained. After two recrystallizations from 95% alcohol the colorless material melted at 226–228° with decomposition.

Anal. Calc'd for $C_9H_{16}BrCl_2N_3$: N, 13.3. Found: N, 13.0, 13.1.

N,N-Dimethyl-N'-(5-bromo-2-pyridyl)-N'-(5-chloro-2-thenyl)ethylenediamine monohydrochloride. The material was prepared more satisfactorily than is shown in the Table by the treatment of a solution of 7.5 g. (0.023 mole) of N,N-dimethyl-N'-2-pyridyl-N'-(5-chloro-2-thenyl)ethylenediamine monohydrochloride (1) in 50 cc. of chloroform with a solution of 4 g. (0.025 mole) of bromine in 25 cc. of chloroform at room temperature over a forty-five minute period. At the end of the addition the reaction mixture was extracted with 50–75 cc. of a 2% sodium hydroxide solution and the chloroform layer was separated and concentrated. The dark residue was dissolved in dilute hydrochloric acid and decolorized with Darco. The solution was made alkaline and the separated oil extracted with ether. Concentration of the ether gave 6.1 g. (65%) of light red oil. After treatment with an equivalent of alcoholic hydrogen chloride the monohydrochloride was precipitated by ether; yield, 4.3 g. (45%), melting at 127–129°. When mixed with material prepared by Method A, the melting point was not depressed.

N,N-Dimethyl-N'-(5-bromo-2-pyridyl)-N'-(5-bromo-2-thenyl)ethylenediamine monohydrochloride. The material was obtained more satisfactorily than is shown in the Table by the bromination at room temperature of 1.0 g. (0.003 mole) of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine monohydrochloride (1) in 25 cc. of chloroform, with a solution of 0.43 g. (0.0027 mole) of bromine in 20 cc. of chloroform. The chloroform solution was extracted with 100 cc. of water containing 1 cc. of concentrated hydrochloric acid. The product thus extracted could not be converted to a suitable derivative. The chloroform solution was treated with anhydrous potassium carbonate and concentrated to give 0.9 g. of a light red oil. This was converted to a monohydrochloride by treatment with one equivalent of alcoholic hydrogen chloride. After three crystallizations from 10-cc. portions of methyl ethyl ketone, 0.35 g. of product melting constantly at 164–164.5° was obtained. This melting point was not depressed by the material prepared by Method A.

An attempt to brominate N,N-dimethyl-N'-2-pyridyl-N'-2-thenylethylenediamine gave only intractable tars in addition to more than a 50% recovery of the starting material in an impure form.

2-(5-Chloro-2-thenyl)aminopyridine. One mole of the sodium salt of 2-aminopyridine was prepared by adding 94 g. (1.0 mole) of 2-aminopyridine to 24 g. (1.0 mole) of sodium hydride (du Pont) in 400 cc. of dry toluene in forty-five minutes and heating on a steam-bath for one and three-quarter hours. After cooling the mixture to room temperature, 83.5 g. (0.5 mole) of 5-chloro-2-thenyl chloride was added dropwise with ice cooling. The mixture was then heated on the steam-bath for four hours and hydrolyzed by the addition of 30 cc. of alcohol, then 300 cc. of water. After standing overnight, the black toluene layer was separated and the aqueous portion extracted with three 500-cc. portions of ether and the extracts combined with the toluene. Following drying over sodium carbonate and distillation of solvents, the product was fractionated at 1 mm. to yield 10 g. of aminopyridine, 36 g. of material boiling at 170–192°, and 53 g. of residual tar. The 36 g. of distillate solidified and was recrystallized from methyl ethyl ketone to give 23 g. of the desired product (20% yield), m.p. 71–74°. A further crystallization from this solvent gave 17 g., m.p. 84–86°.

A 1-g. sample was converted to the hydrochloride by treatment with an equivalent of alcoholic hydrogen chloride and precipitation of the product with ether; m.p. 110–115°, neutral equivalent 275 (theoretical 261). Recrystallization from methyl ethyl ketone raised the m.p. to 125–127°.

Anal. Calc'd for $C_{10}H_{10}Cl_2N_2S$: N, 10.7. Found: N, 10.6.

2-(5-Bromo-2-thenyl)aminopyridine. One mole of the sodium salt of 2-aminopyridine and 0.75 mole of 5-bromo-2-thenyl chloride were reacted as above. Twenty-five grams of 2-aminopyridine (27%) was recovered at 89–150° (9 mm.). Fractional distillation of the residue at 1 mm. gave 66 g. of material boiling at 145–170°, 28 g. boiling at 170–202°, and 70.4 g. of dark residue. The first fraction was crystallized from about 300 cc. of heptane to give 53 g. of product of m.p. 80–82°. The second fraction was extracted with 100 cc. of hot heptane and yielded, in two extractions, 16.8 g., m.p. 74–80°. This was recrystallized from 150 cc. of heptane to give 15.6 g. of material melting at 81–83°. The total yield of pure material was 68.6 g. (33%). The material was converted to its hydrochloride by treatment with an equivalent of alcoholic hydrogen chloride followed by precipitation by ether. After crystallization from isopropanol it melted at 151–153.5°.

Anal. Calc'd for $C_{10}H_9BrN_2S \cdot HCl$; N, 9.2; Neutral equivalent, 305.6.
Found: N, 9.2; Neutral equivalent, 313.

Method III. N,N-Dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine. Five and four-tenths grams (0.02 mole) of 2-(5-bromo-2-thenyl)aminopyridine was added to a suspension of sodamide which had been freshly prepared from 0.69 g. (0.03 mole) of sodium in 200 cc. of liquid ammonia. The mixture was stirred for five minutes and 3.22 g. (0.03 mole) of β-dimethylaminoethyl chloride (7) was added. Dry toluene (100 cc.) was added and the mixture was heated three hours at 90° with stirring. It was cooled, 20 cc. of water was added, the toluene layer was separated and the aqueous layer was extracted with two 20-cc. portions of toluene. The toluene was distilled in vacuum and the residue was fractionated at about 1 mm. The fraction boiling at 170–187° was treated with an equivalent of alcoholic hydrogen chloride and the hydrochloride was precipitated with ether. This was recrystallized from ethyl acetate to give a low yield (the crude yield was 19%) of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine hydrochloride, m.p. 126–129°. The m.p. was not depressed by material prepared in another way (1).

N,N-Dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)propylenediamine. 1-Dimethyla-mino-2-propanol (8) was converted into 2-chloro-N,N-dimethylpropylamine hydrochloride in 32% yield by reaction with thionyl chloride; this was converted to the free base in 63% yield immediately prior to use.

The potassium salt of 2-(5-bromo-2-thenyl)aminopyridine was prepared by adding 26.9 g. (0.10 mole) of the amine to potassamide (0.10 mole) in liquid ammonia. After fifteen minutes, 13.5 g. (0.11 mole) of the above chloride was added, stirred five minutes, and then 150 cc. of dry toluene was added. The reaction was carried out and worked up as in the preceding example. The toluene was concentrated by distillation on the steam-bath at water-

pump pressure and the residue was distilled at about 0.1 mm. to give a forerun of 5 g. of material boiling at 140–164° (discarded), and 18.8 g. boiling at 164–175°. The latter was refractionated, yielding 12 g. at 135–164° and 5 g. at 164–168°. The first fraction was partially unreacted 2-(5-bromo-2-thenyl)aminopyridine which crystallized out on treatment with petroleum ether. The residual oil from evaporation of the petroleum ether gave an oily hydrochloride, as did the second fraction. These were combined, reconverted to the base, and redistilled to give a main fraction boiling at 170–174° (0.5–1 mm.). No satisfactory salt was obtained from samples of this.

Anal. Calc'd for $C_{15}H_{20}BrN_3S$: C, 50.8; H, 5.7; N, 11.9.
Found: C, 51.1; H, 5.5; N, 11.3.

No attempt was made to prove whether the product was one of the isomers, $R_1R_2NCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HN(CH_3)_2$ or $R_1R_2N\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2N(CH_3)_2$, or a mixture of the two. The last possibility might be expected, since it has been shown that 2-chloro-N,N-dimethylpropylamine gives analogous isomers in the preparation of Amidone (9).

N,N-Dimethyl-N'-(5-chloro-2-thenyl)ethylenediamine. During thirty minutes 133.6 g. (0.80 mole) of 5-chloro-2-thenyl chloride (1) was added with stirring to 282 g. (3.2 moles) of N,N-dimethylethylenediamine while cooling in an ice-bath. The temperature of the reaction mixture slowly rose to 70° and the mixture was stirred for thirty minutes without heating and was then heated on a steam-bath for two hours. The cooled mixture was treated with aqueous alkali and extracted with five portions of ether. The extract was dried with sodium sulfate, the ether distilled, and the residue distilled in vacuum. Some unreacted diamine was collected in the forerun and discarded. The product, b.p. 105–107° (2 mm.), n_D^{28} 1.5250, weighed 93 g. (53%). The material was converted to a hydrochloride by solution in alcoholic hydrochloric acid and precipitation with ether. After three crystallizations from aqueous alcohol it melted at 199–201° with some sintering at 189°.

Anal. Calc'd for $C_9H_{15}ClN_2S \cdot 2HCl \cdot 1/2\ H_2O$: C, 36.0; H, 6.0; N, 9.3.
Found: C, 36.0; H, 6.5; N, 9.1.

Method II. N,N-Dimethyl-N'-2-pyridyl-N'-(5-chloro-2-thenyl)ethylenediamine. A solution of 20.7 g. (0.095 mole) of N,N-dimethyl-N'-(5-chloro-2-thenyl)ethylenediamine and 21.4 g. (0.189 mole) of 2-chloropyridine in 15.0 cc. of 2,6-lutidine was refluxed for forty-eight hours. At twenty-four hours a Volhard titration (10) of an aliquot showed the formation of 11% of the theoretical chloride ion. The mixture was diluted with aqueous alkali and extracted five times with ether. The ether extract was dried over sodium sulfate and concentrated. The residue was distilled in a vacuum and the lower-boiling fraction discarded. Three fractions were collected: (a) b.p. 115–162° (0.6 mm.); (b) 162–165° (0.6 mm.); (c) 165–167° (0.6 mm.). Fraction 2 had n_D^{29} 1.5812 and weighed 4.95 g. It was dissolved in an equivalent amount of alcoholic hydrochloric acid and the product precipitated with ether. The gummy precipitate was dissolved in water, basified, and the base extracted with ether. The ether solution was dried, concentrated, and the residue distilled in a vacuum. Two fractions were collected: 127–152° (0.3 mm.), n_D^{25} 1.565, and 148–153° (0.3 mm.), n_D^{25} 1.585; weight, 2.8 g. The second fraction was again converted to a salt with hydrogen chloride and ether. Crystals and a gum separated. The crystals were collected and crystallized from benzene, m.p. 105–107°. They did not depress the m.p. of a sample of the compound prepared in a different manner (1). The non-crystalline gum gave a picrate identical with that from N,N-dimethyl-N'-2-pyridyl-N'-(5-chloro-2-thenyl)ethylenediamine. This picrate is best prepared in and recrystallized from glacial acetic acid; m.p. 145–148°.

Anal. Calc'd for $C_{14}H_{18}ClN_3S \cdot 2C_6H_3N_3O_7$: N, 16.7. Found: N, 16.7.

N,N-Dimethyl-N'-(5-bromo-2-thenyl)ethylenediamine. A solution of 17.6 g. (0.20 mole) of N,N-dimethylethylenediamine in 25 cc. of benzene was refluxed with stirring and a solution of 21.1 g. (0.10 mole) of 5-bromo-2-thenyl chloride in 25 cc. of benzene added dropwise in the course of forty-five minutes. A white crystalline precipitate formed. The reaction mixture was refluxed for an additional four hours, cooled, and worked up as for the chloro compound. The product, b.p. 93–96° (0.2–0.3 mm.), n_D^{29} 1.5395, weighed 7.47 g.

For analytical purposes, 0.47 g. of the product was treated with 2.5 cc. of 1.59 *N* alcoholic hydrochloric acid. The resultant white precipitate was dissolved by the addition of 25 cc. of boiling absolute ethanol, the minimum amount required for complete solution. After cooling, 0.42 g. of the hydrochloride, m.p. 191–217° (d) was obtained. After two recrystallizations from absolute alcohol, the dihydrochloride melted at 189–220° (d).

Anal. Calc'd for $C_9H_{15}BrN_2S \cdot 2HCl$: N, 8.3. Found: N, 8.2.

5-Bromo-2-thiophenecarboxylic acid from 5-bromo-2-thenyl chloride. To a solution of 17.5 g. of potassium permanganate and 26 g. of sodium hydroxide in 700 cc. of water was added 12.7 g. of 5-bromo-2-thenyl chloride (1), and the mixture was stirred at room temperature for sixteen hours. Sodium bisulfite was added until the green color had been destroyed. After the mixture had been filtered, the oil was removed by extraction with ether, and acidification of the aqueous solution gave 0.65 g. of white needles, m.p. 139–141°. The ethereal solution was concentrated, and the resulting oil was stirred with a solution of 17.5 g. of potassium permanganate and 26 g. of sodium hydroxide in 700 cc. of water for an additional forty-four hours at room temperature. Filtration and acidification yielded 2.1 g. of the acid, m.p. 139–141°. Concentration of the filtrate afforded an additional 0.34 g., m.p. 138–140° (total yield, 3.09 g.; 25%). This material did not depress the melting point of 5-bromo-2-thiophenecarboxylic acid prepared from thiophene-2-carboxylic acid (11) and had an identical infrared spectrum.[2]

N,N-Dimethyl-N'-2-pyridyl-N'-(5-carboxy-2-thenyl)ethylenediamine dipicrate. A solution of 14.5 g. (0.042 mole) of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine in 50 cc. of ether was added rapidly to a solution of 0.05 mole of butyllithium and 35 cc. of ether (12) with vigorous stirring. The reaction mixture was maintained at −35° for fifteen minutes. Solid, ground, carbon dioxide was then added in large excess and the reaction mixture was stirred for forty minutes. At the end of this time the mixture was hydrolyzed with 75–100 cc. of water and filtered to remove lithium carbonate and break the emulsion. The ether layer was extracted with 75 cc. of dilute sodium hydroxide in two portions. These were combined, acidified with acetic acid, and concentrated to leave a viscous tar. The tar was dissolved in alcohol, filtered, and diluted with several volumes of ether to precipitate a brown solid. The brown solid was dissolved in alcohol and treated with an alcoholic solution of 7 g. of citric acid, which precipitated a sodium or lithium salt of citric acid. The alcohol filtrate was dissolved in dilute sodium hydroxide and extracted with ether. The solution was then acidified with hydrochloric acid and extracted with ether, the extracts discarded, and the aqueous solution concentrated to an oily solid mixture on the steam-bath. This was extracted with alcohol to leave an insoluble inorganic solid and give 5.7 g. of a light red oil, insoluble in ether but soluble in water. An attempt to form a hydrochloride of this material gave only hygroscopic solids which were combined, dissolved in water, neutralized with ammonia, evaporated to dryness, and dissolved in alcohol. The alcoholic solution was treated with an equal volume of 50 cc. of saturated alcoholic picric acid and cooled to precipitate a picrate. After two crystallizations from 300-cc. portions of absolute alcohol the picrate was obtained as yellow needles melting constantly at 198–200°, yield 1.45 g.

Anal. Calc'd picric acid, 60.1%. Found: 58.6%. This was found by ultraviolet spectral determination. For other analyses see the table.

In addition to this material, there was obtained from the original ether layer of the reaction some of the debrominated compound which was identified by distillation, conversion to its monohydrochloride and comparison with an authentic sample.

Reactions of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine.

1. When the compound and sodium methoxide were heated in methanol in a bomb tube at 150° for six hours and the basic product was fractionated, a 21% recovery of the starting material and a 28% yield of N,N-dimethyl-N'-2-pyridylethylenediamine was obtained.

2. When the bromo compound was treated with sodium sand and propyl iodide, both

[2] We are indebted to Dr. R. C. Gore of the Physics Division of these Laboratories for this measurement.

N,N-dimethyl-N′-2-pyridyl-N′-2-thenylethylenediamine and N,N-dimethyl-N′-2-pyridylethylenediamine were isolated.

3. When the bromo compound was treated with sodium sand in hot benzene for twenty-four hours, a 20–30% yield of the debrominated compound was obtained. When the corresponding chloro compound was used, however, the starting material was recovered unchanged.

4. When the bromo compound was treated with finely divided lithium, both the debrominated compound and N,N-dimethyl-N′-2-pyridylethylenediamine were recovered. If lithium sand was used, an increased reaction rate resulted and none of the debrominated compound was recovered. The compound was also debrominated by the action of propyllithium. No alkylated product was isolated; *cf.* (13).

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine dihydrogen phosphate. Three grams (0.01 mole) of the base (1) was dissolved in 10 cc. of absolute alcohol containing 1.16 g. (0.01 mole) of 85% phosphoric acid. The salt was precipitated by the addition of ether (crystallization could be induced directly with the aid of seeds) and solidified by trituration with acetone. After crystallization from alcohol it melted at 105–106°. The compound was not as hygroscopic as the hydrochloride but was markedly more so than the dihydrogen citrate.

Attempts to make the monohydrogen and neutral phosphates by the same method led only to the dihydrogen phosphate.

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine dihydrogen citrate. A solution of 118 g. (0.398 mole) of the base and 83.5 g. (0.397 mole) of citric acid hydrate in 425 cc. of warm absolute alcohol was crystallized by the addition of seeds obtained from a smaller preparation by precipitation with ether. The yield was 174.6 g. (90%); m.p. 102–106°. Crystallization from 500 cc. of absolute alcohol gave 156 g. melting at 115–118°, and this was not changed by further crystallization.

Attempts to prepare the monohydrogen and neutral citrates led only to the dihydrogen citrate. The dihydrogen citrate is non-hygroscopic, gaining less than 0.5% in weight when exposed in a closed vessel to an atmosphere saturated with water vapor for twenty-four hours.

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine methiodide. Ten grams (0.034 mole) of N,N-dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine was dissolved in ether and treated with 4.78 g. (0.034 mole) of methyl iodide. Crystals formed quickly and were filtered off after twenty-four hours. These (12.96 g., 88%) were crystallized from 50 cc. of water and from 150 cc. of acetone to give material of m.p. 159–160° (unchanged from the water crystallization).

Anal. Calc'd for $C_{15}H_{21}ClIN_3S$; N, 9.6. Found: N, 9.7.

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine benzochloride. The above preparation was repeated using 4.26 g. of benzyl chloride in place of the methyl iodide. It was necessary to reflux the solution to cause the reaction to take place and the ether was finally displaced with benzene to complete the reaction. The gummy precipitate was washed with acetone and crystallized from the same solvent, using Darco. Material of m.p. 94–96° was obtained. The m.p. was not raised by further recrystallization.

Anal. Calc'd for $C_{21}H_{25}Cl_2N_3S$; N, 10.0. Found: N, 10.2.

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SUMMARY

Twelve new thenylated N,N-dimethyl-N′-pyridylethylenediamines have been prepared.

The structure of some previously prepared compounds of this class has been proved.

The *in vitro* antihistamine activities of these compounds have been reported.

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