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ANTIHISTAMINE AGENTS. IV. HALOGENATED N,N-DIMETHYL-N′-BENZYL-N′-(2-PYRIDYL)-ETHYLENEDIAMINES

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The introduction of halogen into the thiophene group of N,N-dimethyl-N′-(2-pyridyl)-N′-(2-thenyl)ethylenediamine has been effective in some instances in enhancing the antihistamine activity of that compound (1, 2). Also, high antihistamine activity has been reported for N,N-dimethyl-N′-(4-methoxybenzyl)-N′-(2-pyridyl)ethylenediamine (Neoantergan) (3, 4) as well as for the parent compound, N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)ethylenediamine (Pyribenzamine) (4). In view of these results, it seemed of interest to determine the effect of halogenation on the antihistamine activity of N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)ethylenediamine. The compounds prepared are listed in Table I along with their relative antihistamine activities.

Compounds I to VI were prepared by the condensation of N,N-dimethyl-N′-(2-pyridyl)ethylenediamine (DPE) with the appropriate halogenated benzyl halide in the presence of alkali amide or hydride. The yields in general were about 40–60%. In most cases no further attempt was made to improve these yields, since the primary object was to obtain sufficient material for preliminary pharmacological testing.

Direct bromination of N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)ethylenediamine resulted in substitution in the 5-position of the pyridine ring to yield N,N-dimethyl-N′-benzyl-N′-(5-bromo-2-pyridyl)ethylenediamine (VIII). The orientation of the substituent was proved by the alternate synthesis of the compound, starting from N,N-dimethyl-N′-(5-bromo-2-pyridyl)ethylenediamine (2). In like manner, direct bromination of N,N-dimethyl-N′-(3-bromobenzyl)-N′-(2-pyridyl)ethylenediamine (V) gave a compound which is assigned the structure of N,N-dimethyl-N′-(3-bromobenzyl)-N′-(5-bromo-2-pyridyl)ethylenediamine (IX). The structure of N,N-dimethyl-N′-benzyl-N′-(5-chloro-2-pyridyl)ethylenediamine (VII) is based on its synthesis from 5-chloro-2-(N-benzyl)-aminopyridine and dimethylaminoethyl chloride. The intermediate 5-chloro-2-(N-benzyl)aminopyridine was prepared from 2-amino-5-chloropyridine and benzaldehyde in formic acid by the procedure of Tschitschibabin (5).

The antihistamine activities listed in Table I were obtained in guinea pigs by the histamine-aerosol technique (6), and are expressed as relative to Pyribenzamine, which has an assigned value of one. The highest activity is found in those derivatives halogenated in the 4-position of the benzyl group, and this

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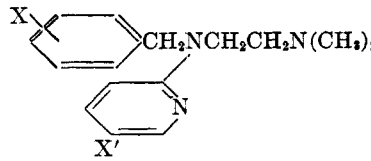
activity increases as the electronegativity of the substituent increases and its atomic weight decreases from iodo to fluoro. The 4-bromobenzyl derivative has approximately the same activity as Pyribenzamine but the 4-fluorobenzyl derivative is three to four times as active. Halogen substituents in the 2- or 3-position of the benzyl group or in the 5-position of the pyridyl group led to essentially inactive compounds. In the one example tested (compound IX), dihalogenation was also disadvantageous.

Four additional compounds structurally related to Pyribenzamine but not containing halogen were prepared and are reported here. Reaction of DPE with α-chloromethylnaphthalene and with n-hexyl bromide led, respectively, to the

TABLE I

HALOGENATED N,N-DIMETHYL-N'-BENZYL-N'-(2-PYRIDYL)ETHYLENEDIAMINES



COMPOUND	SUBSTITUENT		ACTIVITY (6)
	X	X'	
Pyribenzamine			1
I	4-F		3–4
II	4-Cl		2–3
III	2-Cl		<0.5
IV	4-Br		1
V	3-Br		<0.5
VI	4-I		0.3–0.5
VII		Cl	<0.5
VIII		Br	<0.5
IX	3-Br	Br	<0.5

formation of N,N-dimethyl-N'-(α-naphthylmethyl)-N'-(2-pyridyl)ethylenediamine (X) and N,N-dimethyl-N'-(n-hexyl)-N'-(2-pyridyl)ethylenediamine (XI). Reaction of 2-(N-benzyl)aminopyridine with chloroacetyl chloride followed by reaction with diethyl and with dimethylamine, respectively, led to the formation of N-benzyl-N-(2-pyridyl)-α-diethylaminoacetamide (XII) and N-benzyl-N-(2-pyridyl)-α-dimethylaminoacetamide (XIII) in low yield. The last two compounds are analogs of Pyribenzamine in which the dimethylaminoethyl group is replaced by a dialkylaminoacetyl group. Compounds X through XIII were inactive as histamine antagonists when tested on the isolated guinea pig ileum and, therefore, were not tested *in vivo*.

We are indebted to Dr. J. T. Litchfield, Jr., Mrs. Maxine Adams Peluso, and Miss Marion S. Jaeger of these Laboratories for the pharmacological data reported here.

EXPERIMENTAL[4]

4-Fluorobenzyl bromide. A solution of 110 g. (1.0 mole) of 4-fluorotoluene in 150 cc. of dry benzene was heated to reflux (90°) under an efficient condenser and irradiated with a 150-watt ultraviolet lamp. Liquid bromine (128 g.; 0.8 mole) was then added dropwise as rapidly as it was decolorized over a six-hour period. The reaction mixture was distilled at atmospheric pressure to yield 18.0 g. (80% recovery) of the excess 4-fluorotoluene used, b.p. 110–120°, n_D^{22} 1.4857, and 98.0 g. (65%) of 4-fluorobenzyl bromide, b.p. 195–202°, n_D^{22} 1.5480. The b.p. at 20 mm. was 93–95° which agrees with the literature value of 85° (15 mm.) (7). The product was stored over anhydrous potassium carbonate to remove traces of hydrogen bromide.

N,N-Dimethyl-N′-(4-fluorobenzyl)-N′-(2-pyridyl)ethylenediamine monohydrochloride. A suspension of 120 g. (5 moles) of sodium hydride in 2.5 liters of dry toluene was heated with stirring to 105° and maintained at this temperature while 830 g. (5 moles) of N,N-dimethyl-N′-(2-pyridyl)ethylenediamine (DPE) (4, 8) was added dropwise over a three-hour period. The reaction mixture was then heated at reflux for an additional three hours and cooled to 50°. At this temperature, 850 g. (4.5 moles) of 4-fluorobenzyl bromide was added dropwise at a rate sufficient to allow the resulting exothermic reaction to maintain the temperature of the mixture at 50–60°. The addition required three hours. The reaction mixture was stirred overnight at room temperature and then hydrolyzed cautiously with 750 cc. of water. The toluene layer was separated and concentrated. The residue was distilled *in vacuo* to yield 305 g. (excess used plus 27%) of DPE, b.p. 85–130° (0.15 mm.), n_D^{23} 1.5412, and 821 g. (67%) of N,N-dimethyl-N′-(4-fluorobenzyl)-N′-(2-pyridyl)ethylenediamine, b.p. 130–145° (0.25 mm.), n_D^{23} 1.5635. On standing for a short time at room temperature, the product crystallizes as long yellow needles. Recrystallization of these from hexane yielded colorless needles melting at 52–53°. The base was converted to its monohydrochloride in 86% yield by dissolving it in six parts by volume of toluene and adding 0.7 parts by volume of absolute ethanol containing one equivalent of hydrogen chloride. Recrystallization of the salt from toluene-alcohol (7:1) yielded colorless plates melting at 169.5–170.5°.

Anal. Calc'd for $C_{16}H_{20}FN_3 \cdot HCl$: C, 62.0; H, 6.8; N, 13.6; neutral equivalent, 310.
Found: C, 62.1; H, 6.8; N, 13.4; neutral equivalent, 305.

2-(4-Chlorobenzyl)aminopyridine. A solution of 30 g. (0.32 mole) of 2-aminopyridine and 46.8 g. (0.33 mole) of 4-chlorobenzaldehyde in 60 g. (1.3 moles) of 98–100% formic acid was heated at its reflux temperature for six hours. The reaction mixture was then worked up as described below for 5-chloro-2-benzylaminopyridine. The crude product weighed 73 g. (theory 70 g.) and melted at 93–95°. After recrystallization from dilute (1:1) aqueous alcohol the pure material melted at 100–102°.

Anal. Calc'd for $C_{12}H_{11}ClN_2$: C, 65.9; H, 5.1; N, 12.8; Cl, 16.2.
Found: C, 65.9; H, 5.2; N, 12.8; Cl, 16.4.

N,N-Dimethyl-N′-(4-chlorobenzyl)-N′-(2-pyridyl)ethylenediamine monohydrochloride. (a) In a single experiment in which the lithium derivative of 2-(4-chlorobenzyl)aminopyridine was treated with dimethylaminoethyl chloride (9), using the procedure described below for N,N-dimethyl-N′-benzyl-N′-(5-chloro-2-pyridyl)ethylenediamine, none of the desired compound was isolated.

(b) A solution of 40 g. (0.25 mole) of 2-bromopyridine and 100 g. (0.47 mole) of N,N-dimethyl-N′-(4-chlorobenzyl)ethylenediamine (10) in 106 g. of quinoline was heated at 140–145° for five hours. The reaction product was washed with 30% sodium hydroxide solution and distilled. That fraction, 9.5 g. (13%), which boiled at 145–170° (1.0 mm.), was separated and converted to the monohydrochloride by treating it with the theoretical quantity of alcoholic hydrogen chloride. After fractional crystallization from amyl alcohol (pentasol), the pure compound melted at 172–173.6°.

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[4] All melting points are corrected. The microanalyses were carried out in these Laboratories under the direction of Dr. J. A. Kuck, to whom we are indebted for these data. The values reported represent the average of two values not differing by more than 0.3.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: C, 58.9; H, 6.5; N, 12.9; Cl, 21.7.
Found: C, 58.5; H, 6.7; N, 12.7; Cl, 22.4.

(c) A mixture of 52.5 g. (0.317 mole) of N,N-dimethyl-N'-(2-pyridyl)ethylenediamine and 7.6 g. (0.33 mole) of lithium amide in 150 cc. of toluene was heated at reflux temperature with stirring for three hours. A solution of 48.3 g. (0.30 mole) of 4-chlorobenzyl chloride in 100 cc. of toluene was then added dropwise and heating continued for one hour. The reaction mixture was cooled, filtered, and distilled and that fraction which boiled at 178–185° (1.5 mm.) separated, 23.5 g. (27.1%). The light yellow oil was converted to the colorless monohydrochloride by the addition of one equivalent of alcoholic hydrogen chloride and recrystallization of the product from alcohol; 16.0 g., m.p. 172–173.6°.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: Cl^-, 10.7. Found: Cl^-, 10.9.

N,N-Dimethyl-N'-(2-chlorobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. To a solution of 0.055 mole of potassium amide in liquid ammonia was added 8.65 g. (0.053 mole) of DPE and then 50 cc. of toluene. The mixture was stirred and heated for ten minutes after all of the ammonia had been driven off. An 8.80-g. (0.053 mole) sample of 2-chlorobenzyl chloride was then added and the reaction mixture heated for an hour on a steam-bath. A second 50 cc. of toluene was then added and the reaction mixture was filtered. Distillation of the filtrate yielded 7.40 g. (49%) of N,N-dimethyl-N'-(2-chlorobenzyl)-N'-(2-pyridyl)ethylenediamine, b.p. 161–164° (1 mm.). This was converted to the monohydrochloride by dissolving it in ether and adding one equivalent of alcoholic hydrogen chloride. Two recrystallizations from isopropyl alcohol yielded colorless crystals, m.p. 203–204.5°, in 71% yield.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: C, 58.9; H, 6.5; N, 12.9; N.E. 326.
Found: C, 58.5; H, 6.5; N, 12.7; N.E. 325.

N,N-Dimethyl-N'-(4-bromobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A suspension of the potassium salt of DPE in toluene was prepared by adding 0.78 g. (0.02 gram atom) of potassium to 100 cc. of liquid ammonia containing 80 mg. of black iron oxide, adding 3.3 g. (0.02 mole) of DPE when the potassium had all reacted, and removing the ammonia on the steam-bath after adding 75 cc. of dry toluene. To the cooled and stirred mixture was added 4.26 g. (0.021 mole) of 4-bromobenzyl chloride (11), and the reaction mixture was heated with stirring on the steam-bath for eleven hours. The mixture was filtered and concentrated to an oil. This concentrate was taken up in ether, and the etheral solution washed with water, dried over sodium sulfate, and concentrated. Distillation gave 2.96 g. (43%) of a yellow liquid boiling at 184–190° (1.0–0.5 mm.). Treatment of 2.42 g. of this distillate with an equivalent quantity of hydrogen chloride in absolute alcohol and precipitation with anhydrous ether gave 2.33 g. of the monohydrochloride which melted at 184–186° after crystallization from ethyl acetate.

Anal. Calc'd for $C_{16}H_{20}BrN_3 \cdot HCl$: C, 51.8; H, 5.7; N, 11.3.
Found: C, 51.7; H, 5.9; N, 11.3.

N,N-Dimethyl-N'-(3-bromobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A solution of 14.1 g. (0.086 mole) of DPE in 20 cc. of dry toluene was added to a solution of 0.086 mole of sodium amide in 50 cc. of liquid ammonia. The mixture was slowly heated to 100° to remove the ammonia. After cooling, 21.4 g. (0.086 mole) of 3-bromobenzyl bromide (12) in 50–60 cc. of toluene was added with stirring. After standing several hours at room temperature, the mixture was filtered and concentrated. Distillation of the residue yielded 3.5 g. (25% recovery) of DPE, b.p. 80–100° (1 mm.), and 16.3 g. (57%) of product, b.p. 176–178° (1 mm.). This was converted to the monohydrochloride in 80% yield by treatment with one equivalent of alcoholic hydrogen chloride. Addition of benzene to the alcohol solution and concentration gave the salt as a white solid. It melted at 169–170° after recrystallization from ethyl acetate containing a small amount of alcohol.

Anal. Calc'd for $C_{16}H_{20}BrN_3 \cdot HCl$: N, 11.3; N.E. 371.
Found: N, 11.3; N.E. 376.

N,N-Dimethyl-N'-(4-iodobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. The preparation of 4-iodobenzyl bromide by the bromination of 4-iodotoluene in the absence of

solvent has been reported (13). It was found more convenient to carry out the reaction in refluxing carbon tetrachloride under irradiation with ultraviolet light. A stirred mixture of 2.29 g. (0.095 mole) of sodium hydride and 16.5 g. (0.1 mole) of DPE in 300 cc. of dry toluene was heated slowly to reflux for twenty to thirty minutes until reaction was complete. After the mixture had been cooled, 28.3 g. (0.095 mole) of 4-iodobenzyl bromide was added, and the resulting mixture was heated with stirring on the steam-bath for two hours. The cooled and filtered solution was washed three times with water and concentrated under reduced pressure. Distillation gave 23.61 g. (65%) of a viscous, yellow fraction boiling at 194–207° (1 mm.), n_D^{25} 1.6144. Treatment of 20.2 g. of this liquid with one equivalent of hydrogen chloride in alcohol and precipitation by the addition of ether gave 20.96 g. of the monohydrochloride melting at 191–195°. Crystallization from methyl ethyl ketone or from ethyl acetate and absolute alcohol gave fine white needles, m.p. 200–202°.

Anal. Calc'd for $C_{16}H_{20}IN_3 \cdot HCl$: N, 10.1; Cl, 8.5.

Found: N, 9.9; Cl, 8.4.

5-Chloro-2-benzylaminopyridine. To 40 g. (0.31 mole) of 2-amino-5-chloropyridine (14) was added 60 g. (1.3 moles) of anhydrous formic acid and 34 g. (0.32 mole) of redistilled benzaldehyde. The reaction mixture was heated at reflux temperature for sixteen hours, cooled, and poured into 100 g. of 50% sodium hydroxide and 200 g. of ice. The solid product was filtered and dried in the air; yield, 60.6 g. (89%). After treatment with Darco and recrystallization from a commercial naphtha, a colorless product was obtained which softened at 94° and melted at 114–115.2°.

Anal. Calc'd for $C_{12}H_{11}ClN_2$: C, 65.9; H, 5.1; N, 12.8.

Found: C, 65.7; H, 4.8; N, 12.5.

N,N-Dimethyl-N'-benzyl-N'-(5-chloro-2-pyridyl)ethylenediamine monohydrochloride. To 21.8 g. (0.1 mole) of 5-chloro-2-benzylaminopyridine in 100 cc. of boiling toluene was added 2.5 g. (0.11 mole) of lithium amide, and the reaction mixture was heated at reflux with stirring for two hours. A solution of 11.8 g. (0.11 mole) of dimethylaminoethyl chloride in 50 cc. of toluene was then added dropwise over fifteen minutes and the stirred suspension heated at reflux for an additional two hours. After cooling, the mixture was filtered and concentrated by distillation. The residue was then distilled and that fraction boiling between 163° (20 microns) and 185° (50 microns) collected. After standing overnight the oil was filtered to remove some solid impurity; yield, 19.8 g. (68%). Treatment of this material with one equivalent of alcoholic hydrogen chloride gave 21.2 g. of the monohydrochloride which melted at 179–180° after recrystallization from acetone.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: C, 58.9; H, 6.5; N, 12.9; Cl (total), 21.7; Cl (ion), 10.9.

Found: C, 58.9; H, 6.4; N, 12.8; Cl (total), 21.6; Cl (ion), 10.9.

N,N-Dimethyl-N'-benzyl-N'-(5-bromo-2-pyridyl)ethylenediamine monohydrochloride. To a solution of 10.8 g. (0.037 mole) of N,N-dimethyl-N'-benzyl-N'-2-pyridylethylenediamine hydrochloride (4) and 3.1 cc. (0.037 mole) of hydrochloric acid (*d.* 1.19) in 50 cc. of water was added, all at once, 5.9 g. (0.037 mole) of bromine. A reaction occurred, resulting in the formation of an orange gum. After brief heating on the steam-bath and vigorous shaking the gum dissolved and a clear solution resulted. The solution was made alkaline with solid sodium hydroxide and the resulting base extracted with 200 cc. of benzene in three portions. The extracts were concentrated and the residue (12.4 g.) treated with one equivalent of alcoholic hydrogen chloride. The resulting solution was diluted with 150 cc. of benzene and concentrated until crystallization occurred; yield, 8.4 g. (61%), m.p. 180–182°.

Anal. Calc'd for $C_{16}H_{20}BrN_3 \cdot HCl$: N, 11.3. Found: N, 11.6.

The product prepared from benzyl chloride and N,N-dimethyl-N'-(5-bromo-2-pyridyl)-ethylenediamine (2) in low yield was identical by mixed melting point with that prepared above.

N,N-Dimethyl-N'-(3-bromobenzyl)-N'-(5-bromopyridyl)ethylenediamine monohydrochloride. An 8.14-g. (0.022 mole) sample of N,N-dimethyl-N'-(3-bromobenzyl)-N'-(2-pyridyl)-ethylenediamine was dissolved in 30 cc. of 0.75 *N* hydrochloric acid (0.022 mole) and treated with 3.5 g. (0.022 mole) of bromine as in the preparation of N,N-dimethyl-N'-benzyl-N'-

(5-bromo-2-pyridyl)ethylenediamine above. The product (7.8 g.; 86%) was isolated as in the previous example and converted to its monohydrochloride. After recrystallization from ethyl acetate and methyl ethyl ketone the pure salt melted at 146.5–147.5°.

Anal. Calc'd for $C_{16}H_{19}Br_2N_3 \cdot HCl$: N, 9.3; Cl, 7.9.
Found: N, 9.6; Cl, 8.0.

N,N-Dimethyl-N'-(α-naphthylmethyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A solution of 10.0 g. (0.06 mole) of DPE in 50 cc. of toluene was added to a solution of 0.09 mole of sodium amide in liquid ammonia. The excess ammonia was then removed by heating and a solution of 11.0 g. of α-chloromethylnaphthalene (15) in 100 cc. of toluene was added. The reaction mixture was heated with stirring on the steam-bath for four hours, cooled, hydrolyzed with water, and the toluene layer separated. This was concentrated and distilled through a wide-bore head to give 2.0 g. (20%) of recovered DPE and 4.95 g. (27%) of the product, b.p. 200° (1 mm.). The material solidified on standing and after crystallization from ether-petroleum ether melted at 95°. Treatment with one equivalent of alcoholic hydrogen chloride and precipitation of the salt with ether gave a monohydrochloride which melted at 224–226° after four crystallizations from isopropanol.

Anal. Calc'd for $C_{20}H_{23}N_3 \cdot HCl$: C, 70.3; H, 6.8; N, 12.1; N.E., 342.
Found: C, 69.7; H, 7.3; N, 11.7; N.E., 342.

N,N-Dimethyl-N'-(n-hexyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A stirred mixture of 6.0 g. (0.25 mole) of sodium hydride and 41.0 g. (0.25 mole) of DPE in 250 cc. of dry toluene was heated at 95° for forty minutes, then cooled to 57° and 33 g. (0.20 mole) of *n*-hexyl bromide added. The reaction mixture was further heated at 95° for eighteen to twenty hours, cooled, and hydrolyzed with 100 cc. of water. The organic layer was separated, concentrated, and distilled to give 34 g. (68%) of crude product boiling at 110–150° (2 mm.). This was refractionated to yield 18.9 g. (38%) of product boiling at 136–146° (1 mm.), $n_D^{31.5}$ 1.5090. This was converted to the monohydrochloride by treatment with one equivalent of alcoholic hydrogen chloride and evaporation of the solution to dryness. After two crystallizations from benzene, the colorless salt melted at 104–105°. A satisfactory analysis for carbon was not obtained for this compound.

Anal. Calc'd for $C_{15}H_{27}N_3 \cdot HCl$: C, 63.0; H, 9.9; N, 14.7; N.E., 286.
Found: C, 61.8; H, 9.6; N, 14.5; N.E., 288.

N-Benzyl-N-(2-pyridyl)-α-diethylaminoacetamide hydrochloride (16). A mixture of 24.6 g. (0.133 mole) of 2-benzylaminopyridine (5) and 13.2 g. (0.133 mole) of triethylamine in 250 cc. of anhydrous ether was stirred and chilled in an ice-bath while a solution of 14.9 g. (0.133 mole) of chloroacetyl chloride in 250 cc. of ether was added dropwise in about ninety minutes. After stirring one hour longer, the mixture was filtered and 177 cc. (1.7 mole) of diethylamine added to the filtrate with stirring under anhydrous conditions. The solution darkened and diethylamine hydrochloride slowly precipitated. This was removed after forty-eight hours and the filtrate evaporated in a water-bath at aspirator pressure. The residue was redissolved in 100 cc. of absolute alcohol and treated with a solution of 29 g. of 90% picric acid in 500 cc. of absolute alcohol to precipitate slowly unreacted 2-benzylaminopyridine as a crystalline monopicrate. After standing six days at room temperature, the solution was decanted and the 2-(N-benzyl)aminopyridine picrate recrystallized from methanol, m.p. 115–116°.

Anal. Calc'd for $C_{18}H_{23}N_3O \cdot C_6H_3N_3O_7$: picric acid, 43.5. Found: picric acid, 43.4.

On addition of more picric acid to the decantate and scratching, the picrate of the desired product precipitated slowly. This was separated after several hours, suspended in a mixture of water and chloroform and treated with an excess of sodium hydroxide. The chloroform layer was concentrated, and the residue was converted to a hydrochloride salt by solution in ether and treatment with one equivalent of dry hydrogen chloride in ether. The salt was purified by digestion with ether, concentration of a methanol-benzene solution, and crystallization from acetone; yield, 4.1 g. (10%), m.p. 147–148.5°.

Anal. Calc'd for $C_{18}H_{23}N_3O \cdot HCl$: C, 64.7; H, 7.2; N, 12.6.
Found: C, 64.9; H, 7.4; N, 12.8.

N-Benzyl-N-(2-pyridyl)-α-dimethylaminoacetamide hydrochloride. This compound was

prepared as described for the diethyl derivative on a 0.133-mole scale using a solution of 154 g. (3.4 moles) of dimethylamine in 500 cc. of dry ether. The picrate prepared from the reaction product was an uncrystallizable oil. Conversion to the free base and subsequently to a monohydrochloride salt gave a solid which was purified by thorough drying and repeated crystallization from acetone; yield, 4.0 g. (10%), m.p. 181–184°.

Anal. Calc'd for $C_{16}H_{19}N_3O \cdot HCl$: C, 62.8; H, 6.6; N, 13.7.
Found: C, 62.6; H, 6.8; N, 13.4.

SUMMARY

The preparation of one dihalogenated and eight monohalogenated derivatives of N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)ethylenediamine (Pyribenzamine) and four other compounds structurally related to it are reported.

The physiological activities as histamine antagonists of all compounds are given.

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