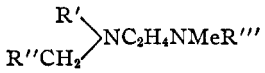
[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF LAKESIDE LABORATORIES, INC.]

Antihistaminics. I. Some Ethylene Diamines and an Aminoether

BY JOHN H. BIEL

In the course of a search for new antihistaminic agents we have investigated the effect of substituting chloro and methoxy as well as various heterocyclic groups into different moieties of compounds possessing antihistaminic activity. With one exception the compounds prepared conformed to the general formula



where R′ was a substituted or unsubstituted phenyl, 2-pyridyl or 2-pyrimidyl radical, R″ was a phenyl, substituted phenyl, 2-thienyl or 2-furyl radical and R‴ was a methyl or isopropyl group. In addition we prepared a furan analog of "Benadryl"

$C_4H_3OCH(Ph)OC_2H_4NMe_2$, $(Ph)_2CHOC_2H_4NMe_2$ (Benadryl)

The synthesis as well as the chemical and antihistaminic properties of one of these compounds, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-furfuryl)-ethylenediamine, has recently been described by Vaughan and Anderson.[1] The authors reported a 15% yield of the purified base which was described to be quite unstable even at temperatures of −80° and to polymerize in the presence of mineral acids. We prepared the pure tertiary amine in 54% yield by condensing N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine[2] with freshly distilled 2-furfuryl chloride[3] in the presence of lithium amide (procedure V). The light yellow oil could be stored in the refrigerator for a long period of time without decomposition. Its dihydrochloride salt proved to be non-hygroscopic and stable on storage at room temperature. Its 1% aqueous solution has not shown any loss in antihistaminic activity in the guinea pig ileum test after being stored in the refrigerator for a considerable length of time.

The intermediate secondary amines of the pyridine and pyrimidine series (R″ = phenyl or substituted phenyl) were prepared by condensing 2-aminopyridine, 2-aminopyrimidine or their substituted derivatives with either the appropriate araldehyde in the presence of formic acid[4] (method I) or with the corresponding chloromethyl compound in toluene using lithium amide as the condensing agent (method II).

The intermediate secondary ethylenediamines $R'NHC_2H_4NMe_2$ (R′ = 2-pyridyl, 2-pyrimidyl, phenyl or substituted phenyl) were obtained by treating the primary amine with β-dimethylaminoethyl chloride in the presence of either anhydrous potassium carbonate[5,6] or lithium amide[6] according to general methods described in the literature (method III).

I. $R'NH_2 + R''CHO \xrightarrow{HCOOH} R'NHCH_2R''$ (A)

II. $R'NH_2 + R''CH_2Cl \xrightarrow{LiNH_2} R'NHCH_2R''$ (A)

III. $R'NH_2 + ClC_2H_4NMe \xrightarrow[K_2CO_3 \text{ or } LiNH_2]{} R'NHC_2H_4NMe_2$ (B)

The tertiary amines were obtained by the alkylation of (A) by method IV or the aralkylation of (B) by method V using lithium amide in dry toluene as the condensing agent

IV. (A) + $ClC_2H_4NMe_2 \xrightarrow{LiNH_2} R'N(CH_2R'')C_2H_4NMe_2$

V. (B) + $ClCH_2R'' \xrightarrow{LiNH_2} R'N(CH_2R'')C_2H_4NMe_2$

They were then converted to water soluble salts in which form they were evaluated pharmacologically. The N-isopropyl analog of "Pyribenzamine" did not form a solid derivative. For the purpose of pharmacological testing the base was dissolved in dilute acetic acid and the *p*H of the aqueous solution adjusted to 6.8.

The furan analog of "Benadryl" was readily prepared by standard procedures.

$C_4H_3OCHO + PhMgBr \longrightarrow C_4H_3O{-}CH(Ph)OH$

$C_4H_3O{-}CH(Ph)OH \xrightarrow[\text{Ether}]{(1)\ Na;\ (2)\ ClC_2H_4NMe_2} C_4H_3OCH(Ph)OC_2H_4NMe_2$

The tertiary amino ether proved to be quite unstable in the presence of mineral acids, but in dilute acetic acid solution it was stable long enough to be tested pharmacologically.

The physical properties and analytical data of the secondary and tertiary amines are summarized in Tables I and II, respectively. The data on the antihistaminic activities are to be found in Table II. For the synthesis of the tertiary amines procedure IV was used except where it is otherwise indicated.

Preliminary *in vitro* studies on the isolated guinea pig ileum strip indicate the furyl isosteres of "Pyribenzamine" (PBZ), N,N-Dimethyl-N′-(2-pyridyl)-N′-benzylethylenediamine, and "Antergan," N,N-dimethyl-N′-phenyl-N′-benzyl-

(1) Vaughan and Anderson, THIS JOURNAL, **70**, 2607 (1948).

(2) Whitmore, Mosher, Goldsmith and Rytina, *ibid.*, **67**, 393 (1945).

(3) Kirner, *ibid.*, **50**, 1955 (1928).

(4) Tchitchibabin and Knunjanz, *Ber.*, **64**, 2839 (1931).

(5) Leonard and Solmssen, THIS JOURNAL, **70**, 2065 (1948).

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

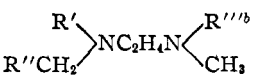
TABLE I

SECONDARY AMINES R_1—NHR_2

R_1	R_2	Procedure	B. p., °C.	B. p., Mm.	M. p., °C.	Yield, %	Formula	N Analyses, % Calcd.	N Analyses, % Found
2-(4-Methoxy)-pyrimidyl	$-CH_2C_6H_5$	II			85–87	23	$C_{12}H_{13}N_3O$	19.55	19.50
2-(5-Chloro)-pyridyl	$-CH_2C_6H_5$	I			119–119.5	54	$C_{12}H_{11}ClN_2$	12.81	12.70
2-(5-Chloro)-pyridyl	$-CH_2C_6H_4OMe$	I			158–159	36	$C_{13}H_{13}ClN_2O$	11.27	11.05
p-Isopropyl-phenyl	$-C_2H_4NMe$	III	113–115	0.2	.....	74	$C_{13}H_{22}N_2$	13.60	13.55
p-Methoxy-phenyl	$-C_2H_4NMe_2$	III	141–146	0.9–1.0	.....	79	$C_{11}H_{18}N_2O$	14.44	14.30
2-Pyridyl	$-CH_2C_6H_4OCH(CH_3)_2$	II	170–177	0.15–0.20	101–103	28	$C_{15}H_{18}N_2O$	11.57	11.41

TABLE II

TERTIARY AMINES AND THEIR HYDROCHLORIDES



		Bases							Hydrochlorides		
		B. p.			Nitrogen, %		Chlorine, %		M. p.,	Activity[h]	LD_{50}[i]
R′	R″	°C.	Mm.	Formula	Calcd.	Found	Calcd.	Found	°C.		mg./kg.
2-$C_4H_3N_2$	2-C_4H_3S[a]	131–133	0.05	$C_{18}H_{18}N_4S$	21.40	21.32	11.90	12.01	176–177	10	19.0
2-C_5H_4N	2-C_4H_3O[a,c,e]	106–108	.02	$C_{14}H_{19}N_3O$	17.15	17.09	22.30	22.08[k]	163–164	76	19.0
4-CH_3O-2-$C_4H_2N_2$	C_6H_5	141–143	.04	$C_{16}H_{22}N_4O$	19.57	19.40	11.00	10.99	164–166	36	12.5–15.0
5-Cl-2-C_5H_3N	C_6H_5	145–146	.02	$C_{18}H_{20}ClN_3$	14.51	14.42	10.90	10.73	179–180	58	12.5–15.0
C_6H_5	2-C_4H_3O[a,d]	127–129	.05	$C_{15}H_{20}N_2O$	11.49	11.45	12.65	12.56	147–148	70	30.0
5-Cl-2-C_5H_3N	*p*-$CH_3OC_6H_4$	180–185	.05	$C_{17}H_{22}ClN_3O$	13.12	13.04	9.97	10.07	141–142	34	26.0
4-$(CH_3)_2CHC_6H_4$	2-C_4H_3O[a]	130–131	.04	$C_{18}H_{26}N_2O$	9.79	9.72	11.00	10.84	137–139	29	9.4
4-$CH_3OC_6H_4$	2-C_4H_3O[a]	155–156	.075	$C_{16}H_{22}N_2O_2$	10.22	10.25	11.43	11.56	125–126	3	35.0
					6.99	7.17[g]			96–97[g]		
2-C_5H_4N	C_6H_5[f,i]	155–156	.075	$C_{18}H_{23}N_3$	14.84	14.86	...	...	.....	21	10.4
2-C_5H_4N	*p*-$(CH_3)_2CHOC_6H_4$	194–195	.20	$C_{19}H_{27}N_3O$	13.42	13.40	10.16	10.23	151–152	60	18.5
2-C_5H_4N	C_6H_5[i]	.....	...	.....	.....	...	...	...	.....	37	12.5–15.0
$(C_6H_5)(2\text{-}C_4H_3O)CHOC_2H_4NMe_2$[i]		100–101	.035	$C_{15}H_{19}NO_2$	5.71	5.70	...	...	.....	30	24.0
$(C_6H_5)_2CHOC_2H_4NMe_2$ (Benadryl)					...	...	...	...	.....	17	19.5

[a] Prepared according to procedure V. [b] R‴ = methyl, except where otherwise indicated. [c] Vaughan and Anderson, THIS JOURNAL, 70, 2607 (1948). [d] Viaud, *Produits Pharmaceutiques*, 2, 53 (1947). [e] $n^{30}D$ 1.5485. [f] R‴ = isopropyl. [g] Bisuccinate. [h] Average per cent. by which a bath concentration of 0.00009375 micrograms/cc. of antihistaminic reduced guinea pig ileum response to a histamine base concentration of 0.024 microgram/cc. [i] Acute toxicity, intravenous to rats. [j] For the purpose of pharmacological testing the base was dissolved in dilute acetic acid and the *p*H of the aqueous solution adjusted to 6.8. [k] Dihydrochloride. [l] Pyribenzamine.

ethylenediamine, to be the most potent histamine antagonists of this series. They proved to be approximately twice as active as PBZ. The acute toxicities were comparable to those of the parent compounds.[7] The antihistaminic activity of these two compounds has been described previously by other authors. Viaud[8] reported the furyl analog (2803 R.P.) of PBZ (2750 R.P.) to be less active than "Antergan" (2339 R.P.) or less than one-half as active as PBZ in the ileum test, but equal in activity to PBZ in the histamine aerosol test. Vaughan and Anderson[1] found its activity to be "comparable to PBZ when tested in guinea pigs by the histamine aerosol technique or the intravenous injection of histamine." Viaud[8] described the antihistaminic activity of the furyl analog (2349 R.P.) of "Antergan" to be equal to that of the parent compound in the ileum test.

Methoxyl or isopropyl substitution in the para-position of the phenyl ring of the furyl isostere of "Antergan" resulted in an appreciable lowering of activity, coupled with an increase of acute toxicity in the case of the isopropyl derivative.

The furyl isostere of "Benadryl," β-dimethylaminoethyl benzhydryl ether, proved to be about 80% as active as PBZ, and less than twice as "Benadryl," however, the true evaluation of this drug was hampered by deterioration in aqueous solution.

Winter[9] reported the antihistaminic activity of "Benadryl" to be about sixty per cent. that of PBZ in the ileum test. Other investigators[10] described it to be only 20% that of PBZ in the same test.

The introduction of chlorine in the pyridine ring almost doubled the activity of the unsubstituted analog (PBZ), while the toxicity was only slightly elevated. A similar observation was made by Clapp and associates[11] who reported that the introduction of chlorine in the thiophene ring (Chlorothen) of "Thenylene," N,N-dimethyl-N′-(2-pyridyl-N′-(2-thienylmethyl)-ethylenediamine, doubled the activity of that compound and decreased its acute toxicity by one-half.

A simultaneous introduction of chlorine and methoxyl in the pyridine and phenyl ring, respectively, resulted in decreased activity, but also

(7) Loew, *Physiol. Rev.*, **27**, 542 (1947).

(8) Viaud, *Produits Pharmaceutiques*, **2**, 53 (1947). We are indebted to Dr. C. P. Huttrer of the Warner Institute for Therapeutic Research, New York City, for a copy of this article.

(9) Winter, *J. Pharmacol.*, **90**, 224 (1947).

(10) Lee, Dinwiddie and Chen, *ibid.*, **90**, 83 (1947).

(11) Clapp, Clark, Vaughan, English and Anderson, THIS JOURNAL, **69**, 1548 (1948).

an appreciable lowering of acute toxicity. A *p*-isopropoxy substituent in the benzyl moiety of PBZ markedly enhanced the antihistaminic activity and lowered the acute toxicity of the parent compound. A similar effect was obtained following the introduction of a para-methoxy group in the same position (Neo-Antergan) as reported by Viaud[8] (2786 R.P.) and Winter.[9] An ethoxy group[8] (2843 R.P.), however, did not seem to bring about any change in activity.

The thienyl isostere of "Hetramine," N,N-dimethyl-N'-(2-pyrimidyl)-N'-benzylethylenediamine, produced a compound of very low activity. Thienyl isosteres of PBZ[10,12] and "Antergan[8,13,14] were reported to be less potent antihistaminics than their corresponding parent compounds.

Introduction of a methoxyl group in the pyrimidine ring of "Hetramine" afforded a compound with an activity and acute toxicity comparable to PBZ. Substitution of N-methyl by N-isopropyl in PBZ resulted in a decrease in activity and increase in acute toxicity. A similar observation was made by Viaud[8] concerning the activity of the N,N-diethyl analog (2323 R.P.) of PBZ.

Of the compounds tested the furyl analogs of "Pyribenzamine" and "Antergan" deserve particular attention: the first, because of its high activity and fair toxicity, the second, because of its high activity and particularly low toxicity.

Experimental

2-Thienyl chloride,[15] 2-(β-dimethylaminoethyl)-aminopyrimidine,[16] 2-(β-dimethylaminoethyl)-aminopyridine,[2] 2-furfuryl chloride,[3] 2-amino-4-methoxypyrimidine,[16] 2-amino-5-chloropyridine,[17], *p*-nitrocumene,[18] β-dimethylaminoethyl chloride hydrochloride[19] and phenyl isopropyl ether[20] were obtained by methods described in the literature.

Substituted Aniline Derivatives.—These compounds were readily prepared by the catalytic reduction of their respective nitro compounds. In a typical experiment 36.0 g. (0.22 mole) of *p*-nitrocumene was dissolved in 75 cc. of absolute alcohol and hydrogenated over 0.15 g. of Adams platinum oxide catalyst at four atmospheres of hydrogen. The catalyst was filtered off, the filtrate concentrated *in vacuo* and 26.8 g. (91%) of primary amine collected, b. p. 60–61° (0.3 mm.).[21]

β-Isopropylaminoethanol.—To a mixture of 307 g. (5.20 mole) of isopropylamine,[22] 18.0 g. (1.0 mole) of water and 8.6 g. (approximately 0.1 mole) of concentrated hydrochloric acid there was added with stirring from a Dry Ice–acetone jacketed dropping funnel 76.8 g. (1.74 mole) of ethylene oxide over a period of three and a half hours. The temperature of the reaction mixture gradually rose to 51° during the course of the addition. After all the ethylene oxide had been added the mixture was refluxed for another twelve hours, fractionated and 137 g. (76%) of product collected, b. p. 169–171°.[23]

β-(N-Methyl-N-isopropyl)-aminoethanol.—Method A: To a mixture of 113 g. (1.10 mole) of isopropylaminoethanol, 152 g. (1.10 mole) of anhydrous potassium carbonate and 200 cc. of benzene was added 156 g. (1.10 mole) of methyl iodide with vigorous mechanical stirring over a period of six hours. Stirring and refluxing was continued for another three hours, the reaction mixture filtered and the precipitate dissolved in water. The aqueous solution was then made strongly alkaline with solid sodium hydroxide, extracted with benzene and the benzene extracts combined with the filtrate. The benzene was removed and the residual liquid distilled at 67–70° (13–14 mm.); yield, 46.0 g. (36%).

Anal. Calcd. for $C_6H_{15}NO$: N, 11.97. Found: N, 12.19.

Method B: A solution of 10.0 g. (0.10 mole) of β-isopropylaminoethanol, 13.1 g. (0.25 mole) of 88% formic acid and 8.9 g. (0.11 mole) of 37% formaldehyde was refluxed for twenty-four hours. The reaction mixture was cooled, 5.0 g. of concentrated hydrochloric acid added to it and the resulting solution distilled until the temperature of the distillation had reached 110°. To the residual liquid was added 10 cc. of water, the aqueous solution made strongly alkaline with potassium hydroxide pellets and subjected to vacuum distillation. After saturation of the distillate with solid sodium hydroxide it was extracted repeatedly with ether, the ether extracts dried over potassium carbonate and distilled. The product was collected at 161–162°; yield, 8.0 g. (68%).

Anal. Calcd. for $C_6H_{15}NO$: N, 11.97. Found: N, 11.70.

β-(N-Methyl-N-isopropyl)-aminoethyl Chloride.—To a solution of 46.1 g. (0.40 mole) of methylisopropylaminoethanol in 225 cc. of chloroform at 0° was added 47.0 g. (0.40 mole) of thionyl chloride with stirring at room temperature for thirty minutes and it was then allowed to reflux for three hours. Chloroform was removed, the residue taken up in 100 cc. of water, the aqueous solution made strongly alkaline with 40% sodium hydroxide and then quickly extracted with ether. The ether extract was dried over potassium carbonate, the ether distilled and 34.0 g. (63%) of the chloro-amine collected at 72–74° (40 mm.). On standing at room temperature the free base quickly changed to a white, crystalline solid—presumably its dimerized quaternary salt—and, therefore, had to be used immediately for any subsequent reaction.

***p*-Chloromethylphenyl Isopropyl Ether.**—The compound was prepared according to the directions described by Sommelet and Marszak[24] for the chloromethylation of anisole. From 50.0 g. (0.37 mole) of phenyl isopropyl ether there was obtained 35.0 g. (51%) of the desired product, b. p. 85–87° (0.3–0.4 mm.) and 16.0 g. of unreacted starting material. The yield based on the amount of starting material reacted was 76%.

Anal. Calcd. for $C_{10}H_{13}ClO$: Cl, 19.24. Found: Cl, 18.80.

Procedure I. N-(*p*-Methoxybenzyl)-2-amino-5-chloropyridine.—From 24.0 g. (0.19 mole) of 2-amino-5-chloropyridine, 25.4 g. (0.19 mole) of *p*-anisaldehyde (Eastman Kodak Co.) and 47 cc. of 90% formic acid there was obtained 17.0 g. (36%) of the desired product, m. p. 154–156°. This material was pure enough to be used in any subsequent reactions. A small amount recrystallized from isopropyl alcohol melted at 158–159°.

Procedure II. N-(*p*-Isopropoxybenzyl)-2-aminopyridine.—To 20.0 g. (0.19 mole) of 2-aminopyridine in 100 cc. of dry toluene was added 4.4 g (0.19 mole) of lithium amide and the resulting mixture slowly heated to reflux with stirring. Refluxing and stirring was continued for three hours. The reaction mixture was then allowed to

(12) Feinberg and Bernstein, *J. Lab. Clin. Med.*, **32**, 1370 (1947).

(13) Kyrides, Meyer and Zienty, THIS JOURNAL, **69**, 2240 (1947).

(14) Ercoli, Schachter, Hueper and Lewis, *J. Pharmacol.*, **93**, 216 (1948).

(15) Blicke and Leonard, *ibid.*, **68**, 1936 (1946).

(16) Adams and Whitmore, *ibid.*, **67**, 736 (1945).

(17) Tchitchibabin and Jegorow, *Chem. Zentr.*, **99**, II, 1670 (1928).

(18) Sterling and Bogert, *J. Org. Chem.*, **4**, 20 (1939).

(19) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(20) Waser, *Helv. Chim. Acta*, **12**, 435 (1929).

(21a) Constam and Goldschmidt, *Ber.*, **21**, 1157 (1888), reduced the nitro compound with zinc and hydrochloric acid; b. p. 217–220°.

(21b) Sterling and Bogert, *J. Org. Chem.*, **4**, 20 (1939), reduced the nitro compound with tin and hydrochloric acid; b. p. 222.5°.

(22) Generously supplied by Sharples and Company.

(23) Mathes, *Ann.*, **315**, 117 (1901); b. p. 171°.

(24) Sommelet and Marszak, *Compt. rend.*, **198**, 2256 (1934).

cool to 60° and 35.0 g. (0.19 mole) of *p*-chloromethylphenyl isopropyl ether in 50 cc. of toluene added dropwise. The temperature of the reaction mixture rose to 87° during the addition. Stirring and heating at 80–90° was continued for three hours. The cooled reaction mixture was then shaken repeatedly with 100-cc. portions of a dilute hydrochloric acid solution (60 cc. of concd. acid and 250 cc. of water). Three layers appeared; the two lower layers were separated and made alkaline with solid potassium hydroxide. The water insoluble oil was extracted with ether and the ether dried over potassium carbonate. After removal of the ether the residue was distilled *in vacuo* through a modified, vacuum-jacketed Claisen head. The product was collected at 194–202° (0.3–0.4 mm.) and 26.0 g. of a viscous, yellow oil obtained which soon solidified to a white semisolid mass. This was recrystallized from 80 cc. of Skelly B and 6 cc. of isopropyl alcohol and 13.1 g. (28.5%) of a white, crystalline precipitate obtained; m. p. 101–102°. A small amount was again recrystallized from a mixture of Skelly B and isopropyl alcohol; m. p. 101–102°.

Procedure III. N-β-Dimethylaminoethyl-*p*-isopropylaniline.—A mixture of 53.0 g. (0.39 mole) of *p*-isopropylaniline, 29.0 g. (0.21 mole) of β-dimethylaminoethyl chloride hydrochloride, 54.0 g. (0.39 mole) of anhydrous potassium carbonate and 200 cc. of dry toluene was refluxed with stirring for twenty-one hours, and worked up in the usual manner. The residual liquid was fractionated through a 10″ vacuum-jacketed Vigreux column and two fractions were collected, one at 96–97° (6 mm.), 23.0 g. of recovered *p*-isopropylaniline and the other at 113–115° (0.2 mm.); 32.5 g. (a 74% yield, based on recovered material, of the desired product).

Procedure IV. N,N-Dimethyl-N′-(2-pyridyl)-N′-(*p*-isopropoxybenzyl)-ethylenediamine Monohydrochloride.—To 2.1 g. (0.09 mole) of lithium amide in 100 cc. of dry toluene was added 22.0 g. (0.09 mole) of N-(*p*-isopropoxybenzyl)-2-aminopyridine. The mixture was stirred and refluxed for three hours, cooled and 10.8 g. (0.10 mole) of β-dimethylaminoethyl chloride in 50 cc. of dry toluene added. Stirring and refluxing were continued for eighteen hours. The mixture was allowed to cool and was then extracted several times with dilute hydrochloric acid solution. The *p*H of the aqueous phase was adjusted to 6.8 with concentrated ammonium hydroxide solution and a small amount of unreacted starting material filtered off. The filtrate was made strongly alkaline with solid potassium hydroxide and extracted several times with ether. The combined ether extracts were dried over potassium carbonate, the ether removed, the residual oil distilled through a modified, vacuum jacketed Claisen head and 18.0 g. (64%) of desired product collected, b. p. 192–193° (0.190 mm.). The yield based on actual starting material reacted was 77%.

The **monohydrochloride** was obtained by adding an equivalent amount of 3.3 *N* ethereal hydrochloric acid to the base in dry isopropyl alcohol. The white, crystalline solid melted at 151–152°.

Procedure V. N,N-Dimethyl-N′-(*p*-methoxyphenyl)-N′-(2-furfuryl)-ethylenediamine Monohydrochloride.—A mixture of 33.0 g. (0.17 mole) N,N-dimethyl-N′-(*p*-methoxyphenyl)-ethylenediamine, 3.9 g. (0.17 mole) of lithium amide and 100 cc. of dry toluene was stirred and refluxed for two hours, cooled to room temperature and 19.8 g. (0.17 mole) freshly distilled furfuryl chloride in an equal weight of dry toluene added with stirring at such a rate as to keep the temperature of the reaction mixture at 60–70°. Stirring was then continued for three hours at 50–60°, the reaction mixture cooled, washed with water and the toluene removed by distillation *in vacuo*. The residue was fractionated through a 2″ Vigreux column and 24.0 g. (63%) of product collected, b. p. 137–139° (0.030 mm.).

The **monohydrochloride** was prepared in the manner described under procedure IV, m. p. 125–126°.

The **bisuccinate** was prepared by the addition of 1.18 g. (0.01 mole) of succinic acid dissolved in 10 cc. of hot isopropyl alcohol to 2.75 g. (0.01 mole) of the base in 10 cc. of anhydrous ether. After scratching and cooling for several minutes crystallization finally started. The white, crystalline material was filtered, washed with 1:1 dry ether:dry isopropyl alcohol; yield, 3.6 g. (92%), m. p. 96–97°.

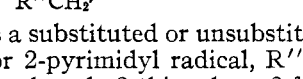
Phenyl-2-furylmethyl β-Dimethylaminoethyl Ether.—To a suspension of phenylmagnesium bromide freshly prepared from 2.5 g. (0.10 mole) of magnesium and 20.0 g. (0.10 mole) of bromobenzene in 50 cc. of anhydrous ether was added 9.1 g. (0.10 mole) of freshly distilled furfural[25] in 50 cc. of anhydrous ether with cooling and stirring over a period of fifteen minutes. Refluxing and stirring were continued for another two hours. A saturated solution of ammonium chloride (17 g.) was then added slowly with stirring. At the completion of the addition the finely divided solid had set to a stiff mass. The ethereal solution was readily decanted, the precipitate washed twice with fresh ether and the combined ether layers were dried over Drierite. The ethereal solution was then concentrated to a volume of 50 cc. and added to 2.0 g. (0.087 mole) of birdshot sodium suspended in 100 cc. of dry toluene. The mixture was stirred at 60° for three hours, when no more hydrogen was evolved. A solution of 10.8 g. (0.10 mole) of β-dimethylaminoethyl chloride in 100 cc. of dry toluene was then added and the resulting mixture stirred and refluxed for sixteen hours in such a manner as to allow the ether to distil off, in order to raise the temperature of the reaction mixture. The reaction mixture was cooled, washed with water and the toluene distilled *in vacuo*. The oily residue was poured into 50 cc. of water and the *p*H of the aqueous solution adjusted to 6.0 by the addition of 22 cc. of 2.4 *N* hydrochloric acid. The aqueous mixture was extracted with ether to remove any water insoluble material and was then made strongly alkaline with potassium hydroxide solution, extracted with ether and the ether layer dried over potassium carbonate. After removal of the ether 9.5 g. (39%) of a clear, yellow oil were obtained, b. p. 100–102° (0.035 mm.). The oil could be stored in the refrigerator over many months, but was quite unstable in the presence of mineral acids. Any attempts to form a solid salt with either organic or inorganic acids failed. For the purpose of testing the compound pharmacologically it was dissolved in dilute acetic acid solution and the *p*H adjusted to 6.8. However, this solution deteriorated on standing.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.40; H, 7.75. Found: C, 73.52; H, 7.58.

Acknowledgment.—We are indebted to Messrs. P. Nuhfer and O. Torstveit of the Biology Division for supplying the pharmacological data, to Mr. E. Schwarz for preparing some of the intermediates, and to Mr. E. Curschmann for the analytical data. We wish to thank Dr. H. L. Daiell for his continued interest throughout the course of this project.

Summary

Eight new and two previously reported ethylenediamine derivatives have been synthesized in



which R′ is a substituted or unsubstituted phenyl, 2-pyridyl or 2-pyrimidyl radical, R″ is a phenyl, substituted phenyl, 2-thienyl or 2-furyl radical, and R‴ is a methyl or isopropyl group. A furan analog of "Benadryl" also has been prepared. Some of these compounds were found to be potent antihistaminic agents. The relationship between chemical structure and antihistaminic activity has been discussed briefly.

MILWAUKEE 1, WISCONSIN

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