Summary

1. Procedures have been developed for the synthesis of 5,6-diamino-2,4-dihydroxypyrimidine and 4-hydroxy-2,5,6-triaminopyrimidine bisulfite in appreciably better yields and involving fewer isolations of intermediate products than previously reported.

2. These compounds have been condensed with several dicarbonyl compounds to yield pyrimido[4,5-b]pyrazines symmetrically substituted in the 6- and 7- positions.

3. Ultraviolet absorption spectra of alkaline solutions of the compounds have been measured.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND MICROBIOLOGY, RESEARCH DIVISION, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Heterocyclic Amines with Antihistaminic Activity[1]

BY CHARLES P. HUTTRER,[1a] CARL DJERASSI, WARREN L. BEEARS,[1b] RUDOLF L. MAYER AND CAESAR R. SCHOLZ

Extensive work from Fourneau's Laboratory[2] has indicated that some relatively simple aminoethers (type F929, F1379, F1464)[3] and diamines (type F1571, F1691, F1709, R. P. 2339, R. P. 2325)[4] possessed antihistaminic activity. Since tertiary amines of this group containing heterocyclic radicals had so far not been studied, we have synthesized a number of asymmetrically-substituted ethylenediamines of the general type $R'—N(R''')—CH_2—CH_2—N<$, in which at least one, and sometimes two, substituents were of an heterocyclic nature (pyridine or pyrimdine series). One member of this series, R. P. 2786, N,N-dimethyl-N′-(*p*-methoxybenzyl)-N′-(α-pyridyl)-ethylenediamine, has since been described.[4a]

The work reported here was not published earlier pending extensive pharmacological and clinical investigation.[5] In recent articles, Whitmore and co-workers[6] have described secondary amines of similar structure as part of their work on antimalarials.

The secondary amines (Table I) were prepared by condensing the primary amines with a dialkylaminoethyl halide in toluene solution in the presence of sodium or lithium amide (procedure A). This method, first introduced by Tschitschibabin,[7] has been used recently by Eisleb[8] and by Whitmore.[6] We usually preferred this method to that of condensing the asymmetrically-substituted diamine with an halogen-substituted heterocyclic compound (procedure B), because of the latter's lower degree of reactivity and higher cost.

A $R'NH + XCH_2CH_2N<$ → $R'NHCH_2CH_2N<$

B $R'X + H_2NCH_2CH_2N<$ → $R'NHCH_2CH_2N<$

R′ = heterocyclic

In procedure A, the best yields were obtained with a substantial excess of the primary amine and a slight excess of sodamide. In the cases where the alkyl side chain was a dimethyl or diethylaminoethyl group, we employed the hydrochloride or hydrobromide salts. These salts were much easier to handle than the free halides, but necessitated the use of double quantities of sodamide or lithium amide. Whitmore, *et al.*,[6] employed the free halides, but that method is applicable to dimethylaminoethyl halides only if special precautions are taken. Knorr[9] reported that the dimethyl derivative polymerized very rapidly to the cyclic dimer. Recent kinetic studies from our laboratories have indicated that this compound can be stored for prolonged periods of time under proper conditions. These results will be reported in the near future.

Tertiary amines (Table II) were prepared either by condensing the dialkylaminoethyl substituted amino heterocyclic compound with an alkyl-, or aralkyl halide (procedure C); by condensing the halogenated heterocyclic substance with an asymmetrically tri-substituted alkylenediamine (procedure D); or by condensing the alkyl or aralkyl substituted amino heterocyclic derivative

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(2) For key references and pharmacological results, *cf.* Staub, *Ann. Inst. Pasteur*, **63**, 400 (1939), and Halpern, *Arch. Intern. Pharmacodynamie*, **68**, 339 (1942).

(3) F929, 2-isopropyl-5-methylphenoxyethyldiethylamine; F1379, 2-methyl-5-isopropylphenoxyethyldiethylamine; F1464, 2-isopropyl-5-methylphenoxyethylpiperidine.

(4) F1571, N,N-Diethyl-N′-phenyl-N′-ethylethylenediamine; F-1691, N,N-diethyl-N′-(2-methyl-5-isopropylphenyl)-ethylenediamine; F1709, N,N-diethyl-N′-phenyl-N′-isopropylethylenediamine; R. P. 2339, N,N-dimethyl-N′-benzyl-N′-phenyl ethylenediamine; R. P. 2325, N,N-dimethyl-N′-ethyl-N′-phenylethylenediamine.

(4a) Bovet Horclois and Walthert, *Compt. rend. soc. biol.*, **138**, 99 (1944); C. A., **39**, 3070 (1945).

(5) (a) Mayer, Huttrer and Scholz, *Science*, **102**, 93 (1945); *Feder. Proc.*, **4**, 129 (1945); (b) Rennick, Chess, Hays, Mathieson, Mayer and Yonkman, *ibid.*, **4**, 133 (1945); (c) Yonkman, Chess, Mathieson and Hansen, *ibid.*, **4**, 143–144 (1945); (d) Mayer, *J. Allergy*, **17**, 153 (1946); (e) Koepf, Arbesman and Lenzner, *Feder. Proc.*, **5**, 56 (1946).

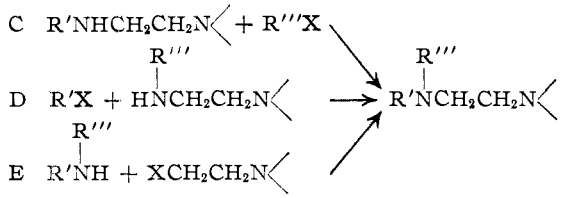
(6) *Cf.* (a) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945); (b) D. P. J. Goldsmith, Ph.D. Thesis, Penn State College, 1942; (c) Adams and Whitmore, THIS JOURNAL, **67**, 735 (1945).

(7) Tschitschibabin, Konowalowa and Konowalowa, *Ber.*, **54**, 814 (1921).

(8) Eisleb, *ibid.*, **74**, 1433 (1941).

(9) Knorr, *Ber.*, **37**, 3507 (1904).

with a dialkylaminoethyl halide (procedure E).



R′ = heterocyclic
C, R‴ = alkyl or aralkyl
D, R‴ = alkyl, aralkyl, aryl or heterocyclic
E, R‴ = aralkyl or alkyl

In the preparation of both the secondary and tertiary amines, the yields varied over a wide range, depending upon the character of the reactants, as well as on changes in procedure. The secondary and tertiary amines were usually yellow oils of rather high boiling points and slight solubility in water. The bases were characterized by means of their mono- or dihydrochlorides, depending on the amount of hydrogen chloride used. In the case of hygroscopic hydrochlorides, picrates were prepared. These derivatives are given in Tables I and II.

TABLE I

BASICALLY-SUBSTITUTED PYRIDINE AND PYRIMIDINE COMPOUNDS (SECONDARY AMINES) R′—NH—R″

R′	R″	Procedure	B. p., °C.	B. p., mm.	Yield, %	M. p., °C., hydrochloride	Formula		Analyses, % Calcd.	Found
α-Pyridyl	—$CH_2CH_2NMe_2$[a]	A (B)	100-106	0.1	67 (50)	224 (229)	$C_9H_{15}N_3 \cdot 2HCl$	HCl	30.67	30.70
α-Pyridyl	—$CH_2CH_2NEt_2$[a,b]	A (B)	140-150	13	53 (85)	184-186 (picrate)	$C_{22}H_{23}O_{14}N_9$	N	19.35	19.38
α-Pyridyl	—$CH_2CH_2NC_5H_{10}$	A	135	0.03	80	164	$C_{12}H_{19}N_3 \cdot HCl$	HCl	15.11	15.14
α-Pyridyl	—$CH_2CH_2NC_4H_8O$	A	136-138	0.01	43	184.5-186 (picrate)	$C_{17}H_{20}O_8N_8$	N	19.26	19.32
α-Pyridyl	—$CH_2C_6H_5$[c]	A	137-144	0.02	52		$C_{12}H_{12}N_2$	N	15.22	15.25
α′-Picolyl	—$CH_2CH_2NMe_2$	A	134-140	15	53	228-229	$C_{10}H_{17}N_3 \cdot 2HCl$	HCl	28.97	28.91
α′-Picolyl	—$CH_2CH_2NC_5H_{10}$	A	110-112	0.01	83	154-156	$C_{13}H_{21}N_3 \cdot HCl$	HCl	14.29	14.50
α′-Picolyl	—$CH_2C_6H_5$	A	m. p. 66		50		$C_{13}H_{14}N_2$	N	14.14	14.17
β-Picolyl	—$CH_2CH_2NMe_2$	A	88- 91	0.05	88	231	$C_{10}H_{17}N_3 \cdot HC$	HCl	16.94	17.10
β-Picolyl	—$CH_2CH_2NC_5H_{10}$	A	112-120	0.02	31	234	$C_{13}H_{21}N_3 \cdot HCl$	HCl	14.29	14.26
γ-Picolyl	—$CH_2CH_2NMe_2$	A	96-121	0.03	35	220-222	$C_{10}H_{17}N_3 \cdot 2HCl$	HCl	28.97	28.97
2-Pyrimidyl	—$CH_2CH_2NMe_2$[d]	A	85- 90	0.02	24	174	$C_8H_{14}N_4 \cdot HCl$	HCl	18.03	18.02
2-Pyrimidyl	—$CH_2CH_2NC_4H_8O$	A	128-135	0.02	25	184	$C_{10}H_{16}N_4O \cdot HCl$	HCl	14.93	14.90
2-Pyrimidyl-4-methyl	—$CH_2CH_2NC_5H_{10}$	A	168-171	0.08	32	151	$C_{12}H_{20}N_4 \cdot HCl$	HCl	14.23	14.12

[a] Whitmore[6a] in the text of his paper reported the b. p. 112–115° at 4 mm., $n^{20}D$ 1.5320 for the diethyl compound. In his table, however, he reported the b. p. 112–134° and no refractive index, while in the same table the corresponding dimethyl compound was reported as having b. p. 105° at 4 mm., n_D 1.5320. Evidently, a printing error in the table caused the erroneous refractive index and b. p. values. [b] Also reported by German Patent 602,049. [c] M. p. of base, 95–96°; Tschitschibabin,[20] found m. p. 94°; Dr. Mull of these Laboratories, using a modification of Tschitschibabin's method, obtained a 98% yield. [d] Reported by Adams and Whitmore.[6a]

TABLE II

BASICALLY-SUBSTITUTED PYRIDINE COMPOUNDS (TERTIARY AMINES) R′—N(R‴)—R″

R′	R″	R‴	Procedure	B. p., °C.	B. p., mm.	Yield, %	M. p., °C. HCl	Formula		Analyses, % Calcd.	Found	Antihistaminic activity[a]
α-Pyridyl	—$CH_2CH_2NMe_2$	—C_6H_5	C (E)	99-104	0.04	39 (78)	112	$C_{11}H_{19}N_3 \cdot HCl$	HCl	15.91	15.90	1γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—$CH_2CH_2NMe_2$	C	103-107	0.0	67	224	$C_{13}H_{34}N_4 \cdot 3HCl$	HCl	31.69	31.68	>10γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—C_6H_5	D	185-187	14	35	217	$C_{15}H_{19}N_3 \cdot HCl$	HCl	13.15	13.10	>5γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—$CH_2C_6H_5$	C (E)	138-142	0.01	72 (89)	193	$C_{18}H_{21}N_3 \cdot HCl$	HCl	15.52	15.51	0.02γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—$CH_2C_6H_4OCH_3(p)$[b]	C (E)	168-172	0.06	63 (81)	143-143.5	$C_{17}H_{23}N_3O \cdot HCl$	HCl	11.35	11.32	0.02γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—COC_6H_5	C	150-152	0.01	45	154	$C_{16}H_{19}N_3O \cdot HCl$	HCl	11.95	11.97	>5γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—$CH_2CH_2C_6H_5$	C	131-141	0.02	21	162	$C_{17}H_{23}N_3 \cdot HCl$	HCl	11.95	12.10	>10γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—$CH(CH_3)_2$	C	120-124	1	27	226	$C_{12}H_{21}N_3 \cdot HCl$	HCl	14.99	14.86	>10γ
α-Pyridyl	—$CH_2CH_2NMe_2$	—α-pyridyl	D	126-130	0.01	18	180-181	$C_{14}H_{18}N_4 \cdot 2HCl$	HCl	23.18	23.20	[c]
α-Pyridyl	—$CH_2CH_2NMe_2$	—β-pyridyl	D	138-143	0.03	19	hygrosc.	$C_{14}H_{18}N_4 \cdot 2HCl$	HCl	23.18	23.30	>10γ
β-Pyridyl	—$CH_2CH_2NMe_2$	—C_6H_5	D	161-165	0.08	39	202-204	$C_{15}H_{19}N_3 \cdot 2HCl$	HCl	23.25	23.15	>10γ
α-Picolyl	—$CH_2CH_2NMe_2$	—$CH_2C_6H_5$	C	150-160	0.02	51	169-170	$C_{17}H_{23}N_3 \cdot HCl$	HCl	11.95	11.81	1γ
β-Picolyl	—$CH_2CH_2NMe_2$	—$CH_2C_6H_5$	C	185-188	14	36	241	$C_{17}H_{23}N_3 \cdot 2HCl$	HCl	21.34	21.44	2γ
γ-Picolyl	—$CH_2CH_2NMe_2$	—$CH_2C_6H_5$	C	156-161	0.18	51	176	$C_{17}H_{23}N_3 \cdot HCl$	HCl	11.95	11.94	0.2γ
γ-Picolyl	—$CH_2CH_2NMe_2$	—β-pyridyl	D	98-100	0.04	52	137	$C_{16}H_{20}N_4 \cdot HCl$	HCl	12.48	12.40	>5γ
α-Pyridyl	—$CH_2CH_2NEt_2$	—C_6H_5	D	145-150	0.08	21	136	$C_{17}H_{22}N_3 \cdot HCl$	HCl	11.95	12.2	>10γ
α-Pyridyl	—$CH_2CH_2NEt_2$	—$CH_2C_6H_5$	C	142-150	0.02	65	204-206	$C_{18}H_{25}N_3 \cdot 2HCl$	HCl	20.50	19.98	>5γ
α-Pyridyl	—$CH_2CH_2NEt_2$	—$CH_2CH_2CH_3$	C	151-155	13	35	hygrosc.	$C_{14}H_{23}N_3 \cdot HCl$	HCl	13.44	13.65	>10γ
α-Pyridyl	—$CH_2CH_2NEt_2$	—α-pyridyl	D	136-140	0.04	66	189-192	$C_{16}H_{23}N_4 \cdot 2HCl$	HCl	21.28	21.43	>10γ
β-Pyridyl	—$CH_2CH_2NEt_2$	—$CH_2C_6H_5$	D	112-113	0.03	15	hygrosc.	$C_{18}H_{25}N_3 \cdot HCl$	HCl	11.43	11.77	>10γ
α-Pyridyl	—$CH_2CH_2NC_5H_{10}$	—C_6H_5	C	122-126	0.01	25	186-187	$C_{14}H_{23}N_3 \cdot HCl$	HCl	13.54	13.56	[c]
α-Pyridyl	—$CH_2CH_2NC_5H_{10}$	—$CH_2C_6H_5$	C	170-180	0.02	66	176	$C_{19}H_{25}N_3 \cdot HCl$	HCl	11.01	11.01	>2γ
α-Pyridyl	—$CH_2CH_2NC_4H_8O$	—$CH_2C_6H_5$	C	174-180	0.03	87	206	$C_{18}H_{23}N_3O \cdot 2HCl$	HCl	19.73	19.67	[c]

[a] The activity is expressed in γ of compound per ml. of bath liquid, capable of neutralizing the contraction of an isolated guinea pig gut, caused by 1γ per ml. of histamine diphosphate (*cf.* ref. 5). [b] Bovet, *et al.*,[4a] reported some of the pharmacological but none of the chemical properties of this compound. [c] Pharmacological results not yet available.

The antihistaminic activity of these compounds is listed in Table II. Several of the tertiary amines reported here exhibited a specific protective action against histamine and anaphylactic shock.[5] One of the compounds, N,N-dimethyl-N'-benzyl-N'-(α-pyridyl)-ethylenediamine (Pyribenzamine), is now under clinical investigation, reports of which have appeared in another journal.[5e]

Experimental[10,11]

Alkyl Halides.—These were obtained in good yield (78–98%) as their hydrogen halide salts according to methods described in the literature. The melting points agreed with those previously reported, with the exception of that of dimethylaminoethyl bromide hydrobromide, which was found to be 189°.[12]

Procedure A. 2-(β-Dimethylaminoethyl)-aminopyridine.[13]—Method I of Whitmore, *et al.*,[6a] was employed with the following modifications: Sodamide could readily be replaced by lithium amide, and since the hydrobromide[12] or hydrochloride salts[14] of the aminohalides were employed, double quantities of the condensing agents were used. The reaction time was increased to twenty-two hours. Using this method, we obtained a 67% yield of the secondary amine, b. p. 100–106° at 0.1 mm., or 150–157° at 25 mm., $n^{25}D$ 1.5418–1.5428.[15]

The **dihydrochloride** was prepared by adding 86.5 cc. of 7.4 *N* methanolic hydrogen chloride solution to 48 g. of the base, concentrating in a current of air and chilling; m. p. 220–222°. After two recrystallizations from ethyl acetate–methanol, the analytical sample was obtained as colorless dimorphic crystals, m. p. 224 or 229°. Both forms gave a correct analysis.

Anal. Calcd. for $C_9H_{15}N_3 \cdot 2HCl$: C, 45.38; H, 7.14; HCl,[16] 30.67. Found: C, 45.37; H, 7.38; HCl, 30.70 (compound of m. p. 229°), 30.61 (compound of m. p. 224°).

Procedure B.—This procedure was adapted from Method II of Whitmore and co-workers[6a] using 2-bromopyridine and unsymmetrical dimethylethylenediamine. 2-(β-Dimethylaminoethyl)-aminopyridine, b. p. 93–106° at 0.08 mm., $n^{25}D$ 1.5424, was obtained in 50% yield. The corresponding diethyl derivative, b. p. 110–115° at 0.05 mm., $n^{25}D$ 1.5301–1.5303,[15] was obtained in 85% yield.

Procedure C. N,N-Dimethyl-N'-benzyl-N'-(α-pyridyl)-ethylenediamine.—A stirred suspension of 12 g. (0.31 mole) of dry, pulverized sodamide and 46 g. (0.28 mole) of 2-(β-dimethylaminoethyl)-aminopyridine was refluxed for two hours, the mixture cooled to about 50° and 57.2 g. (0.53 mole) of benzyl bromide was added dropwise. At the end of the addition, the orange colored solution was cooled to room temperature[17] and worked up as in procedure A. The tertiary amine (51 g., 72% yield) thus obtained was a yellow oil, b. p. 138–142° at 0.01 mm., $n^{25}D$ 1.5759–1.5765. The amine was converted into the monohydrochloride by the above method and crystallized from ethyl acetate–methanol as colorless prisms, m. p. 192–193°.

Anal. Calcd. for $C_{16}H_{21}N_3 \cdot HCl$: C, 65.87; H, 7.54; N, 14.41; HCl, 15.52. Found: C, 65.91; H, 7.50; N, 14.23; HCl, 15.51.

Procedure D. N,N-Diethyl-N',N'-*bis*-(α-pyridyl)-ethylenediamine.—This method is similar to Eisleb's[8] alkylation of secondary cyclic amines. A suspension of 1.12 g. (0.03 mole) of sodamide and 5 g. (0.026 mole) of 2-(β-diethylaminoethyl)-aminopyridine in 100 cc. of dry toluene was refluxed with stirring for two hours, 4.93 g. (0.031 mole) of α-bromopyridine was then added dropwise and the mixture refluxed for twenty-two hours. Four and one-half grams (66%) of the tertiary base was collected as a yellow oil boiling at 136–140° and 0.04 mm. The crude dihydrochloride was very hygroscopic. After recrystallization from methyl ethyl ketone, the analytical sample melted at 189–192° and was fairly stable.

Anal. Calcd. for $C_{16}H_{22}N_4 \cdot 2HCl$: C, 55.98; H, 6.99; HCl, 21.28. Found: C, 55.95; H, 6.84; HCl, 21.43.

N,N-Dimethyl-N'-phenyl-N'-(β-pyridyl)-ethylenediamine.—A mixture of 5 g. (0.032 mole) of redistilled 3-bromopyridine, 1.2 g. (0.032 mole) of sodamide, 5.2 g. (0.032 mole) of N,N-dimethyl-N'-phenylethylenediamine[18] and 40 cc. of dry toluene was refluxed for four hours. After working up as before, the yield of dark yellow oil, b. p. 161–165° at 0.08 mm., was 3 g. (39%). The dihydrochloride melted at 202–204° after recrystallization from methanol–methyl ethyl ketone.

Anal. Calcd. for $C_{15}H_{19}N_3 \cdot 2HCl$: C, 57.32; H, 6.69; HCl, 23.25. Found: C, 57.22; H, 6.64; HCl, 23.15.

Procedure E.[19] **N,N-Dimethyl-N'-(*p*-methoxybenzyl)-N'-(α-pyridyl)-ethylenediamine.**—To a stirred suspension of 13.8 g. (0.6 mole) of lithium amide and 107 g. (0.5 mole) of *p*-methoxybenzylaminopyridine[20] in 750 cc. of benzene, which had been kept under reflux for two hours, was added a solution of 64.5 g. (0.6 mole) of dimethylaminoethyl chloride in 125 cc. of benzene and the mixture refluxed for six and one-half hours. The mixture was cooled, filtered and the filtrate fractionated under reduced pressure. The tertiary amine[21] was obtained as a light yellow oil, b. p. 165–173° at 0.07 mm., $n^{25}D$ 1.5750, yield, 115.3 g. (81%). The monohydrochloride melted at 143–143.5°.

Anal. Calcd. for $C_{17}H_{24}ON_3Cl$: C, 63.45; H, 7.47; N, 13.06; HCl, 11.35. Found: C, 63.54; H, 7.26; N, 12.81; HCl, 11.36.

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(10) All melting points are corrected.

(11) Microanalyses by Dr. G. Oppenheimer, California Institute of Technology, Pasadena, and Dr. W. Saschek, Columbia Presbyterian Medical Center, New York City.

(12) Gabriel, *Ber.*, **50**, 826 (1917); 172.5–173.5°; Cortese, THIS JOURNAL, **58**, 191 (1936); 174–175°.

(13) The synthesis of this compound was completed before we became acquainted with Goldsmith's thesis[5b] reporting a 51% yield.

(14) Slotta and Behnisch, *Ber.*, **68**, 754 (1938).

(15) *Cf.* Table I, notes a and b.

(16) The hydrogen chloride determinations were carried out according to the method of Dubsky and Trtilek, *Mikrochemie*, **12**, 315 (1933), using standardized mercuric nitrate and symmetrical diphenylcarbazone.

(17) To obtain similar yields with benzyl chloride, it was necessary to reflux for an additional two hours after all the halide had been added.

(18) This compound was prepared in 72–77% yield by refluxing an alcoholic solution of aniline and dimethylaminoethyl bromide hydrobromide for three and one-half hours in the presence of anhydrous potassium carbonate; b. p. 103–107° at 0.2 mm., $n^{25}D$ 1.5380. The monopicrate was obtained as orange prisms from ethanol, m. p. 120.5–121.5°.

Anal. Calcd. for $C_{15}H_{19}O_7N_5$: C, 48.83; H, 4.87; N, 17.82. Found: C, 48.57; H, 4.78; N, 17.91.

The dipicrate crystallized as yellow needles from ethanol, m. p. 176–177°.

Anal. Calcd. for $C_{22}H_{22}O_{14}N_8$: C, 42.43; H, 3.56; N, 18.01. Found: C, 42.40; H, 3.54; N, 17.93.

The dihydrochloride melted at 176–177°.

Anal. Calcd. for $C_{10}H_{15}N_2 \cdot 2HCl$: HCl, 30.80. Found: HCl, 30.79.

The corresponding diethyl compound was prepared by a similar method, using diethylaminoethyl chloride hydrochloride, aniline and sodium carbonate and refluxing for twenty-two hours in toluene solution. A 73% yield of N,N-diethyl-N'-phenylethylenediamine boiling at 154–158° and 17 mm. was obtained. Schulemann, Schoenhoefer and Wingler (U. S. Patent 1,752,617; *C. A.*, **24**, 2469 (1930)) reported b. p. 121–122° at 5 mm.

(19) Preliminary experiments were carried out by Dr. E. Urech of the Ciba laboratories.

(20) Tschitschibabin and Knunjanz, *Ber.*, **64**, 2839 (1931).

(21) *Cf.* Table II, note b.

Acknowledgment.—The authors wish to express their thanks to Mrs. Margaret Petroski for technical assistance.

Summary

2-Aminopyridine and 2-aminopyrimidine and several of their methyl derivatives were alkylated with alkyl halides using sodamide or lithium amide as the condensing agent. Further alkylation of the secondary amines with alkyl or aralkyl halides led to the corresponding tertiary amines, which could be obtained also by condensing halogenated heterocyclic compounds with the corresponding asymmetrically tri-substituted ethylenediamines. Several of these compounds possess strong antihistaminic activity.

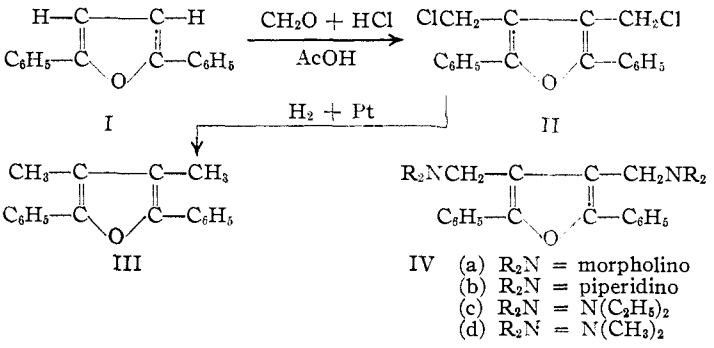
SUMMIT, NEW JERSEY RECEIVED FEBRUARY 13, 1946

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Use of the Bromo- and Chloromethylation Reactions in the Synthesis of Some Dialkylaminomethyl-2,5-diphenylfurans[1]

BY ROBERT E. LUTZ AND PHILIP S. BAILEY[2]

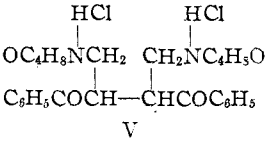
The bromomethylation and chloromethylation reactions[3] have been carried out successfully with 2,5-diphenylfuran (I), 2,5-diphenyl-3-(morpholinomethyl)-furan (VI) and 3-chloro-2,5-diphenylfuran (X), and the resulting halogenomethyl compounds have been condensed with a number of secondary amines to give 3-dialkylaminomethyl and 3,4-di-(dialkylaminomethyl)-2,5-diphenylfurans. Many of the products were made as a part of an exploratory program in the search for new types of antimalarial drugs. The work was carried to the extent herein reported because of indication of activity in some of the first members prepared.[4]



Chloromethylation of 2,5-diphenylfuran (I) yielded only the disubstitution product, 3,4-di-(chloromethyl)-2,5-diphenylfuran (II). Attempts to obtain the mono-(chloromethyl) product failed. The structure of the di-(chloromethyl) compound was proved by catalytic hydrogenolysis which yielded the known 3,4-dimethyl-2,5-diphenylfuran (III).[5]

The reactions between 3,4-di-(chloromethyl)-2,5-diphenylfuran (II) and secondary amines proceeded smoothly to yield the corresponding 3,4-di-(dialkylaminomethyl)-2,5-diphenylfurans (IV). The amines used were morpholine, piperidine, diethylamine, and dimethylamine.

It is interesting to note that analyses of the dihydrochloride of the di-(morpholinomethyl)-furan (IVa) indicated it to be either a monohydrate of extraordinary stability or the open chain saturated diketone (V), whereas the free base analyzed unmistakably for the furan. The molecule of water was not removed by heating at 140° under 1 mm. pressure. This compound is to be contrasted with the salts of the other three of the type, IVb-d, which analyzed correctly for the furans. It is a possibility that hydrolysis of the one of these furans (IVa) to the saturated diketone (V) occurs during the formation of the salt under the conditions employed, namely, precipitation from acetone by means of ethereal hydrogen chloride, and



that spontaneous furanization occurs upon liberation of the free base by treatment with aqueous sodium carbonate; however, this would be surprising because the conditions involved would not be expected to bring about facile furan ring cleavage and closure and do not do so in the other analogous cases in hand.

The relationship between the previously prepared 2,5-diphenyl-3-(morpholinomethyl)-furan[4] (VI) and 3,4-di-(morpholinomethyl)-2,5-diphenylfuran (IVa) was established by conversion of the one into the other (VI to IVa) in two steps,

(1) The greater part of this work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia. The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

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(3) Fuson and McKeever in Adams, "Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., Vol. I, 1942, p. 63.

(4) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945).

(5) Lutz and Taylor, *ibid.*, **55**, 1593 (1933).