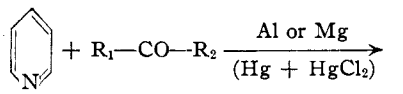
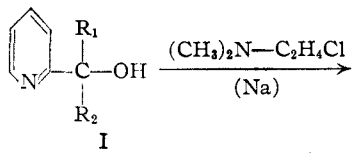
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH LABORATORIES, THE WILLIAM S. MERRELL COMPANY]

Histamine Antagonists. Basically Substituted Pyridine Derivatives

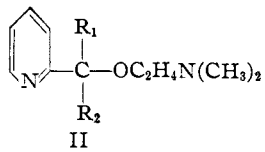
BY CHARLES H. TILFORD, ROBERT S. SHELTON AND M. G. VAN CAMPEN, JR.

In the search for new antihistaminic agents,[1] a series of β-dimethylaminoethyl ethers (II) of α-substituted-pyridinemethanols (I) was prepared. The most convenient method for the preparation of the intermediate carbinols was a modification of





I



II

R_1 = H, alkyl or substituted alkyl. R_2 = alkyl, cycloalkyl, phenyl, thienyl or substituted phenyl. R_1R_2C = cyclic structure.

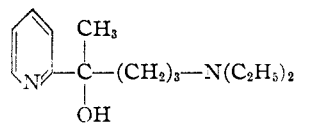
that of Emmert and Asendorf,[2] in which a ketone was condensed with pyridine in the presence of aluminum or magnesium, mercuric chloride and iodine.

In contrast to Emmert's work, it was found that very small amounts of mercuric chloride would suffice when a few drops of mercury was also used, and that the reaction proceeded smoothly using aldehydes as well as ketones. In one experiment, when pyridine, magnesium, acetophenone and a small amount of mercury were used in the regular condensation, the reaction occurred in the absence of mercuric chloride, though with more difficulty and a lower yield of desired product. When magnesium was used as the condensing agent, any variation of the ratios of the reactants from the amounts given by Emmert and Asendorf[2] usually resulted in lower yields of 2-pyridinemethanols. However, this was not the case when aluminum was used; a small amount of mercuric chloride catalyzed the reaction and increased proportions of pyridine and aluminum increased the yields, possibly by decreasing pinacol formation. Magnesium was a superior agent for condensing benzaldehyde with pyridine, whereas with substituted benzaldehydes the yields with aluminum were about the same as those with magnesium.

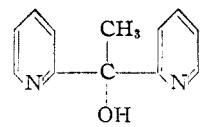
Preparation of carbinols of type I also has been reported in good yield using either pyridylmagnesium bromide[3] or picolinic acid[4] and the carbonyl compound as well as phenylmagnesium bromide and a pyridylcarbonyl derivative.[5] A 3-pyridinemethanol[6] was prepared in 30% yield from the reaction of 3-pyridylmagnesium bromide and benzaldehyde. From benzophenone and 2-pyridylmagnesium bromide a 58% yield of α,α-diphenyl-2-pyridinemethanol was obtained.

When aluminum was used in carrying out the condensation reaction, the higher boiling 4-pyridinemethanol could also be isolated. For each gram atom of aluminum used in the reaction with acetophenone, 0.44 mole of α-phenyl-α-methyl-2-pyridinemethanol[2] and 0.12 mole of α-phenyl-α-methyl-4-pyridinemethanol were obtained. The latter was identical with the product from the reaction of 4-benzoylpyridine and methylmagnesium iodide. A pinacol, 2,3-diphenyl-2,3-butanediol, was isolated in a 14% yield from a neutral fraction. Another by-product obtained in a very small yield was 4,4'-dipyridyl.[7] This suggests that the reaction might proceed through the formation of a pyridyl radical.

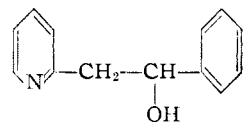
Halogen, alkoxy and alkyl substituted aromatic aldehydes and ketones were used in the preparation (Table II) of the substituted 2-pyridinemethanols in the reaction with pyridine and aluminum. Although 2-methoxybenzaldehyde and 2-methylacetophenone readily gave the desired carbinols, various 2-methoxyacetophenones failed to yield any of the desired pyridinemethanols. 1-Diethylamino-4-pentanone was used in the reaction, and



III



IV



V

the desired carbinol (III) was isolated. Aliphatic and alicyclic ketones usually gave better yields than the aromatic ones.

A dipyridinemethanol (IV) was synthesized from 2-pyridylmagnesium bromide and methyl acetate in a 10% yield. Since it is necessary to

(1) For review articles, see Feinberg, *J. Am. Med. Assoc.*, **132**, 702 (1946); Viaud, *Produits pharm.*, **2**, 53 (1947).

(2) Emmert and Asendorf, *Ber.*, **72B**, 1188 (1939); Emmert and Pirot, *ibid.*, **74**, 714 (1941); German Patent 693,415 (1940).

(3) Overhoff and Proost, *Rec. trav. chim.*, **57**, 179 (1938); Proost and Wibaut, *ibid.*, **59**, 971 (1940).

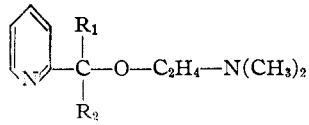
(4) Ashworth, Daffern and Hammick, *J. Chem. Soc.*, 811 (1939).

(5) Tschitschibabin and Benewolenskaja, *Ber.*, **61B**, 547 (1928).

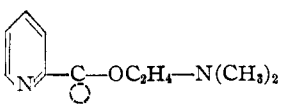
(6) LaForge, THIS JOURNAL, **50**, 2487 (1928); no properties given.

(7) Smith, *ibid.*, **53**, 279 (1931).

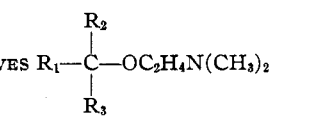
TABLE I

A. SUBSTITUTED 2-PYRIDINE DERIVATIVES 

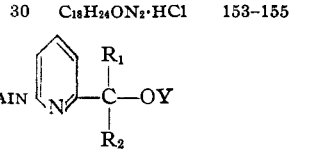
No.	R_1	R_2	Free base: Distillation range °C.	Mm.	Yield,[a] %	Hydrohalide: Formula	M. p., °C. (cor.)	% Halogen (ionizable) Calcd.	Obs.	Histamine activity,[b] γ/ml.
1	Phenyl	H	147–151	0.3	74	$C_{16}H_{20}ON_2 \cdot HCl$	103–105[c]	12.05	12.10	0.05
2	α-Methylbenzyl	H	148–152	.2	7	$C_{18}H_{24}ON_2 \cdot HCl$	144–146	11.00	11.00	1.0
3	*p*-Cumyl	H	159–163	.1	73	$C_{19}H_{26}ON_2 \cdot HCl$	122–123	10.64	10.85	0.5
4	*o*-Anisyl	H	152–154	.2	46	$C_{17}H_{22}O_2N_2 \cdot HCl$	133–135	10.85	10.90	5.0
5	3,4-Methylenedioxyphenyl	H	182–185	.1	75	$C_{17}H_{20}O_3N_2 \cdot HCl$	147–149	10.53	10.48	2.0
6	2-Chlorophenyl	H	174–176	.15	43	$C_{16}H_{19}ON_2Cl \cdot HCl$	116–118	10.85	10.90	1.0
7	Phenyl	CH_3	145–153	.4	75	$C_{17}H_{22}ON_2 \cdot HCl$	169–170	11.58	11.50	0.05
8	Benzyl	CH_3	146–155	.3	75	$C_{18}H_{24}ON_2 \cdot 2HBr$	118–120	35.8	35.0	5.0
9	*p*-Tolyl	CH_3	145–155	.2	53	$C_{18}H_{24}ON_2 \cdot HCl$	178–179	11.02	11.05	0.05
10	*o*-Tolyl	CH_3	160–162	.1	31	$C_{18}H_{24}ON_2 \cdot HCl$	172–174	11.02	11.12	5.0
11	*m*-Tolyl	CH_3	152–156	.1	44	$C_{18}H_{24}ON_2 \cdot HCl$	134–136	11.02	11.00	0.5
12	3,4-Xylyl	CH_3	162–164	.08	58	$C_{19}H_{26}ON_2 \cdot HCl$	152–154	10.64	10.50	1.0
13	Carvacryl	CH_3	160–165	.15	42	$C_{20}H_{30}ON_2 \cdot HCl$	184–186	9.78	9.73	5.0
14	α-Naphthyl	CH_3	185–195	.3	56	$C_{21}H_{24}ON_2 \cdot HCl$	229–230	9.98	10.00	5.0
15	β-Naphthyl	CH_3	185–195	.2	50	$C_{21}H_{24}ON_2 \cdot HCl$	161–162	9.98	10.00	5.0
16	*m*-Anisyl	CH_3	167–173	.2	60	$C_{18}H_{24}O_2N_2 \cdot HCl$	130–132	10.53	10.45	0.05
17	*p*-Anisyl	CH_3	173–175	.2	67	$C_{18}H_{24}O_2N_2 \cdot HCl$	152–153	10.53	10.45	0.1
18	3,4-Dimethoxyphenyl	CH_3	175–180	.2	52	$C_{19}H_{26}O_2N_2 \cdot HCl$	174–175	9.68	9.68	20.0
19	3-Chlorophenyl	CH_3	158–162	.1	58	$C_{17}H_{21}ON_2Cl \cdot HCl$	137–138	10.40	10.45	0.1
20	4-Chlorophenyl	CH_3	154–156	.2	60	$C_{17}H_{21}ON_2Cl \cdot HCl$	162–164	10.40	10.35	0.1
21	3-Bromophenyl	CH_3	180–185	.2	39	$C_{17}H_{21}ON_2Br \cdot HCl$	126–128	9.2	9.3	0.1
22	Phenyl	C_2H_5	150–153	.09	34	$C_{18}H_{24}ON_2 \cdot HCl$	201–202	11.00	10.95	0.5
23	Phenyl	$CH(CH_3)_2$	158–162	.1	34	$C_{19}H_{26}ON_2 \cdot HCl$	161–163	10.64	10.70	5.0
24	Phenyl	$CH_2CH_2N(CH_3)_2$	[d]		70	$C_{20}H_{29}ON_3 \cdot 2HBr$	244–245	32.8	33.2	1.0
25	Phenyl	Phenyl	180–188	.3	26	$C_{22}H_{24}ON_2 \cdot HCl$	186–187	9.65	9.62	1.0
26	Benzyl	Benzyl	175–180	.25	40	$C_{24}H_{28}ON_2 \cdot 2HCl$	267–268	16.35	16.25	20.0
27	1-Cyclohexenyl	CH_3	138–142	.2	32	$C_{17}H_{26}ON_2 \cdot HCl$	136–138	11.40	11.55	0.1
28	Cyclohexyl	CH_3	128–132	.2	25	$C_{17}H_{28}ON_2 \cdot HCl$	164–165	11.32	11.25	3.0
29	Cyclopropyl	CH_3	95–102	.28	35	$C_{14}H_{22}ON_2 \cdot HCl$	95–97	13.18	13.18	10.0
30	*n*-Hexyl	CH_3	138–143	.3	28	$C_{17}H_{30}ON_2 \cdot HCl$	95–96	11.28	11.30	5.0
31	$CH(CH_3)_2$	$CH(CH_3)_2$	95–103	.3	19	$C_{16}H_{28}ON_2 \cdot HCl$	187–188	11.82	11.86	10.0
32	CH_3	$CH_2CH_2CH_2N(C_2H_5)_2$	155–160	0.23	41	$C_{18}H_{33}ON_3 \cdot 3HCl$	191–192	25.6	25.5	20.0
33	2-Pyridyl	CH_3	[d]		10	$C_{16}H_{21}ON_3 \cdot 3HBr$[e]	154–156	45.4	45.2	1.0
34	2-Thienyl	CH_3	155–158	0.5	41	$C_{15}H_{20}ON_2S \cdot HCl$	119–120	11.32	11.30	10.0

B. CYCLIC 2-PYRIDINE DERIVATIVES 

No.										
35	Cyclohexylidene		139–142	1.0	14	$C_{18}H_{24}ON_2 \cdot 2HCl$	163–164	22.08	21.95	20.0
36	*dl*-Bornylidene		134–138	0.2	48	$C_{19}H_{30}ON_2 \cdot 2HCl$	146–148	18.95	19.10	5.0
37	*dl*-Fenchylidene		135–138	.2	61	$C_{19}H_{30}ON_2 \cdot HCl$	197–198	10.50	10.45	1.0
38	1-Indanylidene		162–164	.3	28	$C_{18}H_{22}ON_2 \cdot HCl$	137–139	11.12	11.15	5.0

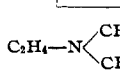
C. 2-, 3- AND 4-PYRIDINE DERIVATIVES 

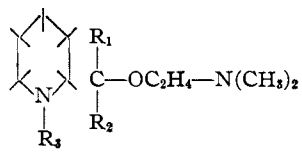
No.	R_1	R_2	R_3							
39	3-Pyridyl	Phenyl	H	160–165	0.2	55	$C_{16}H_{20}ON_2 \cdot HBr$	79–81	23.70	23.55[f] 1.0
40	4-Pyridyl	Phenyl	H	145–148	.2	32	$C_{16}H_{20}ON_2 \cdot HCl$	103–105	12.05	12.12 0.5
41	4-Pyridyl	Phenyl	CH_3	158–160	.3	51	$C_{17}H_{22}ON_2 \cdot 2HCl$	282.5–284.5	20.65	20.20 20.0
42	(2-Pyridyl)-methyl	Phenyl	H	150–160	.5	7	$C_{17}H_{22}ON_2 \cdot 2HBr$	152–154	37.05	37.15 5.0
43	2-(4-Picolyl)	Phenyl	CH_3	152–156	.1	66	$C_{18}H_{24}ON_2 \cdot HCl$	162–164	11.02	11.05 1.0
44	2-(6-Picolyl)	Phenyl	CH_3	145–150	.3	30	$C_{18}H_{24}ON_2 \cdot HCl$	153–155	11.02	11.12 0.1

D. VARIATION OF SIDE CHAIN 

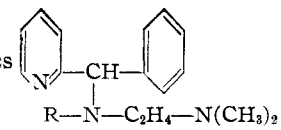
No.	R_1	R_2	Y							
45	Phenyl	CH_3	$C_2H_4N(CH_3)_2 \cdot 2CH_3I$			47	$C_{19}H_{28}ON_2I_2$	143–144	45.80	45.10 20.0
46	Phenyl	CH_3	$C_2H_4N(CH_3)_2 \cdot HO—C_2H_4Cl$			75	$C_{18}H_{27}O_2N_2Cl$	73–75	9.60	9.55 0.5
47	Phenyl	CH_3	$C_2H_4—N(C_2H_5)_2$	150–156	0.2	73	$C_{18}H_{28}ON_2 \cdot HBr$	109–111	21.18	21.18 0.5

TABLE I (*Continued*)

No.	R_1	R_2	Y	Free base: Distillation range °C.	Mm.	Yield,[a] %	Hydrohalide: Formula	M. p., °C. (cor.)	% Halogen (ionizable) Calcd.	Obs.	Histamine activity,[b] γ/ml.
48	Phenyl	CH_3	$CH_2CH(CH_3)—N(CH_3)_2$	148–151	.05	61	$C_{18}H_{24}ON_2\cdot HCl$	147–149	11.02	11.10	1.0
49	Phenyl	CH_3	$C_2H_4N(CH_2)_4CH_2$	160–166	.08	68	$C_{20}H_{26}ON_2\cdot HCl$	177–179	10.22	10.30	0.1
50	Phenyl	CH_3	$C_2H_4N(CH_2)_2O(CH_2)_2$	168–174	.1	61	$C_{18}H_{24}O_2N_2\cdot HCl$	184–186	10.17	10.20	1.0
51	Phenyl	CH_3		156–162	.1	53	$C_{18}H_{24}ON_2\cdot HCl$	145–147	10.68	10.60	1.0
52	*dl*-Fenchyl-[g]		$C_2H_4—N(C_2H_5)_2$	150–156	.2	65	$C_{21}H_{34}ON_2\cdot HCl$	192–194	9.65	9.6	5.0

E. SUBSTITUTED 2-PIPERIDINE DERIVATIVES 

	R_1	R_2	R_3								
53	Phenyl	Phenyl	H	150–155	.2	40	$C_{22}H_{30}ON_2\cdot 2HCl$	246–246.5	17.25	17.15	5.0
54	Phenyl	CH_3	CH_3	133–139	.1	30	$C_{18}H_{26}ON_2\cdot 2HCl$	222–224	19.55	19.35	50.0

F. ETHYLENEDIAMINE DERIVATIVES 

	R								
55	H	140–143	0.5	15	$C_{16}H_{21}N_3\cdot 3HCl$	170–175	29.1	28.8	5.0
56	CH_3	160–163	1.0	75	$C_{17}H_{23}N_3\cdot 2HCl$	130–140	20.8	20.9	20.0
57	2-Pyridyl	185–190	0.2	45	$C_{21}H_{24}N_4\cdot 3HCl$	177–178	24.0	23.8	5.0

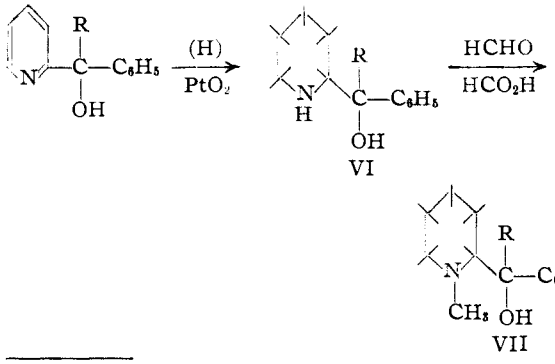
G. STANDARDS FOR COMPARISON

58	β-Dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl Hydrochloride)	0.05
59	N′-Pyridyl-N′-benzyl-N-dimethylethylenediamine monohydrochloride (Pyribenzamine Hydrochloride)	0.01

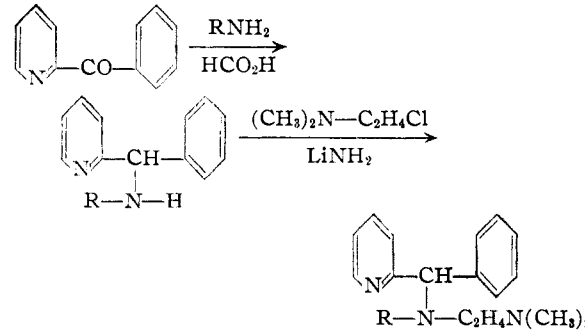
[a] These yields are based on recovered unchanged pyridinemethanol, which usually amounted to about 10–15%; [b] minimal dose of test compound necessary to antagonize 0.1 γ/cc. of histamine diphosphate on isolated guinea pig intestine; [c] hygroscopic; [d] not distilled but hydrohalide isolated by fractional recrystallization; [e] analyzed for monohydrate; [f] benzene was always necessary as a solvent for the crystallization of this aminoether; drying at 80° (1 mm.) removed the benzene from the crystalline material leaving the product as a viscous oil. [g] same structure as no. 37 except that the dimethylamino group has been replaced by the diethylamino group.

have ethylmagnesium bromide present[3] during the preparation of the pyridyl Grignard reagent and since the latter should be in at least a 2:1 molar ratio to the methyl acetate, a low yield would be expected. A pyridineëthanol (V) was obtained from benzaldehyde and α-picoline.[8]

Several of the pyridinemethanol hydrochlorides were reduced catalytically[9] in good yields to the corresponding piperidinemethanols (VI). The compound in which R is methyl was treated with formalin and formic acid, and the N-methyl derivative (VII) was obtained.



Another series of compounds was prepared in which an –NR– group replaced the ether oxygen. These were obtained from 2-benzoylpyridine and the substituted amine using formic acid as the reducing medium.[10]



R = hydrogen, methyl, 2-pyridyl, or 2-pyrimidyl

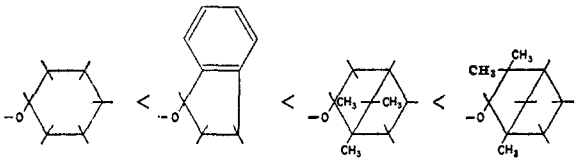
Pharmacological Results[11]

The antihistaminic activities of the compounds of this study are given in Table I. Compounds 1

(8) Loeffler and Grunert, *Ber.*, **40**, 1343 (1907).
(9) Crook and McElvain, THIS JOURNAL, **52**, 4009 (1930).
(10) Forsee and Pollard, *ibid.*, **57**, 1789 (1935).
(11) See Brown, Weiss and Maher, *Ann. Allergy*, **6**, 1 (1948).

and 7 are two of the most active of these tested. Substitution on the phenyl group of either of these compounds with alkyl, alkoxy or halogen groups does not increase the activity, although nos. 7, 9, 16, 17, 19, 20 and 21 have about equal potency. When a naphthyl (nos. 14 and 15), pyridyl (no. 33), thienyl (no. 34) or cyclohexyl (no. 28) group replaced the phenyl group of no. 7, the activity is diminished considerably. The greater the degree of hydrogenation of the R_1 group of no. 7, the lower the activity (no. 28 < no. 27 < no. 7). Replacement of the pyridine ring with a piperidine group has no apparent beneficial antihistaminic effect, as shown by the low order of activity of nos. 53 and 54.

As the length of the carbon chain of group R_2 increases beyond one carbon atom, the potency decreases; thus no. 23 < no. 22 < no. 7. Substitution on the chain with basic groups (nos. 24 and 32) also lowers the activity. The antihistaminic effect of cyclic compounds (group B) seems to increase with branching on the carbon atoms near the ether linkage



Compounds of group C, in which the point of attachment to the pyridine ring is at the 3- or 4-position, are not within the range of potency of nos. 1 and 7. An additional methylene group separating the phenyl or the pyridyl ring from the ether linkage is detrimental to the antihistaminic activity as shown by nos. 8 and 42. Any variation of the dimethylaminoethyl side chain of no. 7 decreases the potency.

None of the diamine compounds (group G) analogous to the aminoethers was an active histamine antagonist.

The most active compounds, nos. 1, 7 and 9, when administered intravenously to guinea pigs at levels of 4 to 32 mg./kg. gave complete protection against 50–300 fatal doses of histamine injected intravenously.

Acknowledgments.—The pharmacological data were furnished by Dr. H. W. Werner, Miss B. B. Brown and Mr. E. Peters.

Thanks are also due Mr. Lewis Doerle for the preparation of some of the intermediate ketones and to Mr. Donald F. Meisner for his suggestions concerning 3-substituted pyridine derivatives. We also wish to acknowledge the assistance of Dr. J. L. Farmer in many phases of this work.

We are grateful to Parke, Davis and Company and Ciba Pharmaceutical Products, Inc., for the supply of Benadryl and Pyribenzamine, respectively.

Papa, *et al.*, reported on the antihistaminic activity of nos. 1, 3, 5 and 7 of Table I at the Chicago Meeting of the American Chemical Society in April, 1948.

Experimental[11a]

Intermediate Aldehydes and Ketones.—All of the aldehydes and most of the ketones were available from commercial sources.[12] *o*-Methylacetophenone[13] and *m*-methylacetophenone[14] were obtained in 66–87% yields from the reaction of the appropriate tolunitrile with methylmagnesium iodide by the method of Blicke and Powers.[15] The rearrangement of fenchone in concd. sulfuric acid gave a 30% yield of 3,4-dimethylacetophenone.[16] Isobutyrophenone[17] was prepared in a 74% yield from the reaction of benzene and isobutyryl chloride with aluminum chloride. *o*-Methoxyacetophenone[18] was prepared from the *o*-hydroxyacetophenone by methylation with dimethyl sulfate in a 79% yield. *m*-Methoxyacetophenone[18] was prepared by methylation in a similar manner in a 60% yield. 3,4-Dimethoxyacetophenone[19] was obtained in an 81% yield by the acetylation of veratrole. 2-Chloroacetophenone[20] was prepared in an 88% yield from *o*-chlorobenzoyl chloride. 3-Chloroacetophenone[21] was formed in an 85% yield and 3-bromoacetophenone[22] in a 53% yield from the diazotization of 3-aminoacetophenone. ω-Methoxyacetophenone[23] was obtained in a 95% yield from methoxyacetonitrile. 2,3,4,5-Tetrahydroacetophenone[24] was prepared in a 40% yield from cyclohexene. Good yields of 2-bromo and 2-chloro-5-acetylthiophene were obtained from the 2-halothiophenes (Michigan Chemical Corp.) using the method of Hartough and Conley.[25]

α-Phenyl-2-pyridinemethanol (Method A).—The method of Emmert and Asendorf[2] was used with some modifications. To a refluxing mixture of 20 g. (0.83 gram atom) of magnesium turnings, 30 g. (0.11 mole) of mercuric chloride and 200 g. (2.5 moles) of pyridine previously dried over anhydrous magnesium sulfate was slowly added 234 g. (2.2 mole) of redistilled benzaldehyde[26] with stirring. Usually a vigorous reaction began after about a fourth of the benzaldehyde had been added, and it was necessary to remove the heat source to prevent the reaction from becoming too violent. In case the reaction had not started at this point it was found advisable to reflux the mixture; a crystal of iodine was sometimes found to be a catalyst for starting the reaction. After the addition of the benzaldehyde was complete (two to three hours), the mixture was refluxed four to six hours longer or until most of the magnesium had reacted. About 500 ml. of toluene was added to the hot (80–90°) reaction mixture followed by addition of a saturated aqueous solution of 95 g. (1.75 moles) of ammonium chloride with cooling. An emulsion usually formed at this point and it was necessary to filter it through Celite to remove insoluble mercury salts and a small amount of polymer. The toluene layer was separated and extracted with an excess of dilute hydrochloric acid in order to separate the basic components (the toluene layer was

(11a) All melting points are corrected.

(12) Dow, Paragon, Eastman, Farchan, du Pont, George Fries, General Drug Co., U. S. Industrial Chemicals and Socony Vacuum.

(13) Auwers, *Ann.*, **408**, 242–246 (1915).

(14) Mauthner, *J. prakt. Chem.*, **103**, 394 (1922).

(15) Blicke and Powers, THIS JOURNAL, **51**, 3378 (1929).

(16) Zaugg, *ibid.*, **67**, 1861 (1945).

(17) Braun and Schattner, *Ber.*, **74B**, 23 (1941).

(18) Jaegle, Besthorn and Banzhok, *ibid.*, **27**, 3042 (1894).

(19) Ross, Percy, Brandt, Gebhard, Mitchell and Yolles, *Ind. Eng. Chem.*, **34**, 924 (1942).

(20) Walker and Hauser, THIS JOURNAL, **68**, 1386 (1946).

(21) Simpson, Atkinson, Schofield and Stephenson, *J. Chem. Soc.*, 646 (1945).

(22) Elson, Gibson and Johnson, *ibid.*, 1131 (1930).

(23) Moffett and Shriner, "Organic Syntheses," **21**, 79 (1941).

(24) Wallach and Evans, *Ann.*, **360**, 46 (1908); Johnson and Offenhauer, THIS JOURNAL, **67**, 1045 (1945).

(25) Hartough and Conley, *ibid.*, **69**, 3097 (1947).

(26) Slightly lower yields were obtained using U. S. P. benzaldehyde. In several experiments the mercuric chloride was dissolved in the carbonyl compound as reported in ref. 2.

discarded) from neutral material, and the aqueous extract was made strongly alkaline. The insoluble oil was extracted with toluene and fractionally distilled through a 20–40 cm. Vigreux column. The desired product was collected at 127–129° (0.3 mm.) and usually solidified; m. p. 76–78°; yield, 60 g. (39% based on magnesium). A sample was dissolved in ether, and a slight excess of alcoholic hydrochloric acid was added. The precipitated salt was recrystallized from 2-propanol; m. p. 182–184°.

When the ratio of reactants was varied in the above procedure, decreased yields of the pyridinemethanol were obtained as determined by five different experiments using increased proportions of pyridine and decreased amounts of mercuric chloride. Reactions using increased proportions of acetophenone and mercuric chloride were not carried out. In one experiment using one gram atom of magnesium, one mole of acetophenone, three moles of pyridine, one drop of mercury but with no mercuric chloride or iodine, 0.12 mole of desired product was obtained; however, the initial reaction was difficult to start.

On the other hand, the ratio could be varied without decrease in yield when benzaldehyde was used in place of acetophenone. Using the proportions of the above procedure, 0.39 mole of α-phenyl-2-pyridinemethanol was obtained. When the amount of benzaldehyde was decreased by 20% and the mercuric chloride by 80%, the yield was still 0.35 mole.

α-(2-Chlorophenyl)-2-pyridinemethanol (Method B).—The above procedure was followed using 23 g. (1 gram atom) of magnesium, 5 g. (0.018 mole) of mercuric chloride, 5 drops of mercury, 300 g. (3.7 moles) of pyridine and 260 g. (1.85 moles) of *o*-chlorobenzaldehyde. It was found convenient to start the reaction by heating the first three above named reactants with about 25 g. each of pyridine and aldehyde until the reaction started; this was followed by addition of the remainder of the pyridine in one portion and finally the dropwise addition of the chlorobenzaldehyde.

α-Phenyl-α-methyl-2-pyridinemethanol (Method C).—The above procedure (Method B), in which magnesium turnings were replaced with granular aluminum, was carried out using the following amounts of reactants: 27 g. (1 gram atom) of 30-mesh granular aluminum, 0.5 g. (0.0018 mole) of mercuric chloride, 5 drops of mercury, a crystal of iodine, 280 g. (3.5 moles) to 360 g. (4.5 moles) of pyridine and 210 g. (1.75 moles) of acetophenone. The aluminum, mercuric chloride and mercury were initially stirred together at about 100° to assure dryness and possibly promote amalgamation of the aluminum. The reaction mixture was decomposed at the end of the refluxing period with 120 g. of potassium hydroxide in a liter of water instead of a saturated ammonium chloride solution as in Method B. The yield of product distilling at 115–120° (0.1 mm.) was 46–53%. The pure carbinol has a boiling point of 130° (0.8 mm.) and 165° (12 mm.); $n^{20}D$ 1.5814. The yields were slightly better when 4.5 moles of pyridine was used as compared to 3.5 moles of pyridine. Further distillation gave 10–20% of the 4-pyridinemethanol distilling at 165–168° (0.5 mm.).

From the toluene layer that had been previously extracted with 10% hydrochloric acid, there was isolated by distillation 18 g. of unchanged acetophenone, b. p. 93–97° (15 mm.); and 32 g. of 2,3-diphenyl-2,3-butanediol, b. p. 192–196° (15 mm.), which melted at 123–124°[27] after one recrystallization from petroleum ether.

In one experiment, the above pyridinemethanol was converted to the hydrochloride, which was recrystallized from 2-propanol. A small amount of another less soluble material melting with sublimation at 302–306° was isolated.

Anal. Calcd. for $C_{10}H_8N_2 \cdot 2HCl$: Cl, 30.9. Found: Cl, 31.0.

This insoluble hydrochloride was converted to the free base, which was recrystallized from petroleum ether; m. p. 113–114°. 4,4′-Dipyridyl has been reported[28] to melt at 114°.

α,α-Diphenyl-2-pyridinemethanol (Method D).—The procedure of Overhoff and Proost[8] was followed with some modification. To 60 g. (2.5 gram atom) of a 1 to 1 mixture of magnesium turnings and magnesium powder in 200 ml. of dry ether was added a solution of 37 g. (0.34 mole) of ethyl bromide and 120 g. (0.75 mole) of 2-bromopyridine (Dow Chemical Co.) in 400 ml. of dry ether over a period of one and a half hours with stirring under reflux. The 2-pyridylmagnesium bromide began to separate out as an oil during the first part of the addition, and finally solidified near the end, causing considerable difficulty in stirring the mixture. Next a solution of 186 g. (1.02 moles) of benzophenone in 400 ml. of dry ether was added during a thirty-minute period. The ether was removed by distillation and dry toluene was added to maintain the original volume. The mixture was refluxed an hour, cooled and decomposed with about 75 ml. of water. The toluene layer was decanted and the residue stirred with 200 ml. of toluene and again decanted. The combined toluene solution was extracted with an excess of dilute hydrochloric acid. The aqueous extract was made strongly alkaline and the oil formed was then extracted once with 300 ml. of benzene. The benzene extract was fractionally distilled. At 165–172° (0.3 mm.), 110 g. (58%) of desired product melting at 104–105° (reported m. p. 104°) was obtained.

In another preparation of the Grignard reagent from 2-bromopyridine, this same procedure using about two-thirds the above amounts of ether proved to be more satisfactory in that the 2-pyridylmagnesium bromide did not solidify. A higher boiling solvent such as diethyl cellosolve or dibutyl ether might be more satisfactory than diethyl ether.

α-Phenyl-2-pyridineëthanol (Method E).—The procedure of Loeffler and Grunert[8] was followed in which 60 g. (0.57 mole) of benzaldehyde, 40 g. (0.43 mole) of α-picoline and 30 ml. of water were heated together in the autoclave at 135° for eight hours. A yield of 10 g. (12%) of product melting at 108–110° was obtained (reported m. p. 107–108°).

In another experiment the same reactants plus 20 g. of sodium *p*-toluenesulfonate were refluxed (104°) for one hundred hours and 12 g. (14%) of desired product melting at 108–110° was obtained.

α-Phenyl-α-methyl-2-piperidinemethanol (Method F).[9]—A solution of 30 g. (0.13 mole) of α-phenyl-α-methyl-2-pyridinemethanol hydrochloride in 100 ml. of ethanol was shaken at 70–80° at an initial hydrogen pressure of 50 pounds in the presence of 0.4 g. of Adams platinum catalyst. The theoretical amount of hydrogen was absorbed in one hour. The mixture was filtered, and the filtrate was evaporated on the steam-bath. The residue was recrystallized from butanone. The yield of white crystalline hydrochloride was 24 g. (80%); m. p. 182–184°.

In another run, the residue obtained after the alcohol had been removed was treated with an excess of dilute sodium hydroxide, extracted with benzene and the benzene extract distilled. The base was collected at 104–108° (0.2 mm.) and had a melting point of 93–95°.

α-Phenyl-α-methyl-1-methyl-2-piperidinemethanol (Method G).[10]—A mixture of 20 g. (0.1 mole) of the above 2-piperidinemethanol, 32 g. (0.65 mole) of 90% formic acid and 16 g. (0.195 mole) of formalin was refluxed forty-eight hours. The reaction mixture was made alkaline with 30% sodium hydroxide, extracted with benzene, and the benzene extract fractionally distilled through a 20 cm. Vigreux column. The product distilling at 125–129° (0.4 mm.) amounted to 20 g. (91%). A sample was converted to the white crystalline hydrochloride; m. p. 220–221°.

α-Phenyl-α-methyl-4-pyridinemethanol.—An ether solution of methylmagnesium iodide (prepared from 5 g. of magnesium turnings, 24 g. of methyl iodide and 200 ml. of anhydrous ether) was treated with 3.5 g. (0.018 mole) of 4-benzoylpyridine,[29] and the reaction mixture was decomposed with a saturated ammonium chloride solution. The ether layer was separated and evaporated on the steam-bath to a volume of about 100 ml., at which point

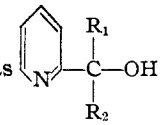
(27) Ciamician and Silber, *Ber.*, **47**, 1808 (1914); reported m. p. 122°.

(28) Smith, THIS JOURNAL, **46**, 416 (1924).

(29) Crook and McElvain, *ibid.*, **52**, 4006 (1930).

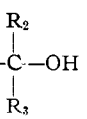
TABLE II

A. α-SUBSTITUTED 2-PYRIDINEMETHANOLS



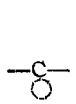
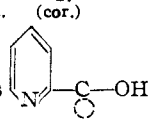
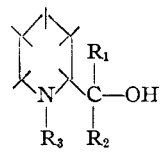
No.	R_1	R_2	Free base: Method	Yield,[a] %	Distillation range °C.	Mm.	M. p., °C. (cor.)	Hydrohalide: Formula	M. p., °C. (cor.)	% Halogen (ionizable) Calcd.	Obs.
1	Phenyl[b]	H	A	39	127–129	0.3	76–78	$C_{12}H_{11}ON\cdot HCl$	182–184	16.05	16.10
2	α-Methylbenzyl	H	B	6	131–133	.3	46–48	$C_{14}H_{15}ON\cdot HCl$	196–198	14.22	14.60
3	*p*-Cumyl	H	B	14	142–145	.15		$C_{16}H_{17}ON\cdot HCl$	151–153	13.50	13.45
4	*o*-Anisyl	H	C	18	144–148	.3		$C_{13}H_{13}O_2N\cdot HCl$	170–171	14.10	14.15
5	*p*-Anisyl[c]	H	A	51	180–185	1.0	130–132	$C_{13}H_{15}O_2N\cdot HBr$	132–134	26.78	26.80
6	3,4-Methylenedioxyphenyl	H	B	37	178–181	0.3		$C_{13}H_{11}O_3N\cdot HCl$	182–184	13.38	13.30
7	2,3-Dimethoxyphenyl	H	B	12	152–156	.15	138–139	$C_{14}H_{15}O_2N\cdot HCl$	166–168	12.60	12.65
8	2-Chlorophenyl	H	B	23	145–148	.2		$C_{12}H_{10}ONCl\cdot HCl$	174–175	13.83	13.95
9	Phenyl[d]	CH_3	A	44	175–180	13.0	53–54	$C_{13}H_{13}ON\cdot HCl$	199–200	15.08	15.05
10	Phenyl	CH_3	C	53	129–134	0.5		$C_{13}H_{13}ON\cdot HCl$			
11	Benzyl	CH_3	A	36	129–134	.3	68–72	$C_{14}H_{15}ON\cdot HCl$	183–185	14.20	14.15
12	*o*-Tolyl	CH_3	C	21	130–132	.2	86–88	$C_{14}H_{15}ON\cdot HCl$	217–219	14.20	14.18
13	*m*-Tolyl	CH_3	C	38	132–135	.18		$C_{14}H_{15}ON\cdot HCl$	162–164	14.20	14.20
14	*p*-Tolyl	CH_3	C	51	134–138	.3	67–68	$C_{14}H_{15}ON\cdot HCl$	166–167	14.20	14.20
15	3,4-Xylyl	CH_3	C	31	148–152	.3	55–57	$C_{15}H_{17}ON\cdot HCl$	185–187	13.48	13.48
16	Carvacryl	CH_3	C	40	145–150	.5	92–95	$C_{17}H_{21}ON\cdot HCl$	168–169	12.15	12.10
17	α-Naphthyl	CH_3	C	25	185–198	.4	130–131	$C_{17}H_{15}ON\cdot HCl$	194–196	11.75[e]	11.75
18	β-Naphthyl	CH_3	C	14	175–210	.4		$C_{17}H_{15}ON\cdot HCl$	177–178	12.42	12.4
19	*o*-Anisyl	CH_3	C	0							
20	*m*-Anisyl	CH_3	C	28	145–152	.4		$C_{14}H_{15}O_2N\cdot HCl$	166–168	13.35	13.42
21	*p*-Anisyl	CH_3	A	62	165–168	.4	54–55	$C_{14}H_{15}O_2N\cdot HCl$	171–172	13.35	13.25
22	3,4-Dimethoxyphenyl	CH_3	C	39	160–165	.3		$C_{15}H_{17}O_2N\cdot HCl$	156–157	12.00	12.00
23	2-Chlorophenyl	CH_3	B	0							
24	3-Chlorophenyl	CH_3	C	26	145–148	.3		$C_{13}H_{12}ONCl\cdot HCl$	155–157	13.15	13.05
25	4-Chlorophenyl	CH_3	C	15	145–148	1.0		$C_{13}H_{12}ONCl\cdot HCl$	202–204	13.15	13.3
26	3-Bromophenyl	CH_3	C	31	165–172	0.7		$C_{13}H_{12}ONBr\cdot HCl$	162–165	11.28	11.30
27	4-Methyl-2-methoxyphenyl	CH_3	C	0							
28	5-Methyl-2-methoxyphenyl	CH_3	C	0							
29	Phenyl	C_2H_5	C	50	134–140	0.4	79–82	$C_{14}H_{15}ON\cdot HCl$	142–145	14.20	14.20
30	Phenyl	$CH(CH_3)_2$	C	44	138–142	0.15	66–68	$C_{15}H_{17}ON\cdot HCl$	156–158	13.50	13.60
31	Phenyl	CH_2OCH_3	C	16	145–148	0.5		$C_{14}H_{15}O_2N\cdot HCl$	198–199	13.38	13.45
32	Phenyl	$CH_2CH_2N(CH_3)_2$	D	4	150–160	1.0		$C_{16}H_{20}ON_2\cdot 2HCl$	168–170	24.3	24.2
33	Methyl	$(CH_2)_2N(C_2H_5)_2$	C	35	130–134	0.2		$C_{14}H_{24}ON_2$[g]			
34	Phenyl	$CH_2CO_2C_2H_5$	C	0							
35	Phenyl[f]	Phenyl	D	58	165–172	.3	104–105	$C_{18}H_{15}ON\cdot HCl$	178–179	12.3	12.18
36	Benzyl	Benzyl	C	33	165–170	.4		$C_{20}H_{19}ON\cdot HCl$	220–223	11.0	10.80
37	1-Cyclohexenyl	CH_3	C	16	83–87	.2		$C_{12}H_{17}ON$[h]			
38	Cyclohexyl	CH_3	C	56	118–122	.1		$C_{13}H_{19}ON\cdot HCl$	230	14.70	14.65
39	Cyclopropyl	CH_3	C	16	83–87	.2		$C_{10}H_{13}ON\cdot HCl$	172–174	16.95	17.05
40	*n*-Hexyl	CH_3	C	69	120–124	.2		$C_{13}H_{21}ON$		6.78[i]	6.95
41	Isopropyl	$CH(CH_3)_2$	C	26	85–88	.2		$C_{12}H_{19}ON\cdot HCl$	300	15.50	15.60
42	2-Thienyl	CH_3	A	17	130–136	.5		$C_{11}H_{11}ONS\cdot HCl$	155–157	14.70	14.62
43	2-Thienyl	CH_3	C	16	130–138	.5					
44	5-Chlorothienyl	CH_3	D	6	138–142	.2		$C_{11}H_{10}ONSCl\cdot HCl$	173–174	12.80	12.65
45	5-Bromothienyl	CH_3	C	0							

B. α-SUBSTITUTED 2-, 3- AND 4-PYRIDINEMETHANOLS



	R_1	R_2	R_3	Method	Yield,[j] %							
46	2-(6-Picolyl)	Phenyl	CH_3	C	13	134–136	0.2		$C_{14}H_{15}ON\cdot HCl$	125–127	14.20	14.30
47	2-(4-Picolyl)	Phenyl	CH_3	C	58	138–142	.1	70–71	$C_{14}H_{15}ON\cdot HCl$	185–187	14.20	14.20
48	(2-Pyridylmethyl)[k]	Phenyl	H	E	12			108–110	$C_{13}H_{13}ON\cdot HCl$	100–104	15.08	15.05
49	3-Pyridyl[l]	Phenyl	H	D	32	120–122	.25	56–58	$C_{12}H_{11}ON\cdot HCl$	156–158	16.05	16.05
50	4-Pyridyl[m]	Phenyl	H	C	19	140–150	.5	124–126	$C_{12}H_{11}ON\cdot HCl$	166–167	16.05	16.00
51	4-Pyridyl	Phenyl	CH_3	C	12	165–169	.5	140–142	$C_{13}H_{13}ON\cdot HCl$	186–189	15.05	15.00
52	4-Pyridyl	*p*-Tolyl	CH_3	C	8	162–168	.3	165–167	$C_{14}H_{15}ON\cdot HCl$	173–175	14.20	14.30
53	4-Pyridyl	*p*-Anisyl	CH_3	C	4	185–188	.4	130	$C_{14}H_{15}O_2N\cdot HCl$	198–199	13.35	13.25
54	4-Pyridyl	*p*-Chlorophenyl	CH_3	C	7	165–168	1.0	140	$C_{13}H_{12}ONCl\cdot HCl$	224–226	13.3	13.15
55	5-(or 3-)[n] Bromo-2-pyridyl	Phenyl	CH_3	C	13	148–152	0.2		$C_{13}H_{12}ONBr\cdot HCl$	192–195	11.28	11.38
56	5-(or 3-)[n] Chloro-2-pyridyl	Phenyl	CH_3	C	0							
57	2-Pyridyl[o]	2-Pyridyl	CH_3	D	10	118–125	1.0		$C_{12}H_{12}ON_2\cdot 2HCl$	200–202	25.9	25.4

TABLE II (*Continued*)

No.	R_1	R_2	Free base: Method	Yield,[j] %	Distillation range °C.	Mm.	M. p., °C. (cor.)	Hydrohalide: Formula	M. p., °C. (cor.)	% Halogen (ionizable) Calcd.	Obs.
			C. CYCLIC-2-PYRIDINEMETHANOLS 								
58	Cyclohexylidene[p]		A	55	140–145	12.0		$C_{11}H_{15}ON\cdot HCl$	157–159	16.65	16.70
59	*dl*-Bornylidene[q]		C	35	130–132	1.0	71–73	$C_{15}H_{21}ON\cdot HCl$	209–210	12.80	12.90
60	*dl*-Fenchylidene		C	52	105–110	0.2	54–56	$C_{15}H_{21}ON\cdot HCl$	200–202	12.80	12.90
61	1-Indanylidene		C	35	140–144	0.3		$C_{14}H_{13}ON\cdot HCl$	154–156	14.38	14.45
62	1-(1,2,3,4-Tetrahydronaphthylidene)		A	23	160–165	1.0		$C_{15}H_{15}ON\cdot HBr$	171–172	26.10	25.80
63	2-Cyclohexylidenecylcohexylidene		C	24	154–159	0.5	59–51	$C_{17}H_{23}ON\cdot HCl$	166–169	12.05	11.95
			D. α-SUBSTITUTED 2-PIPERIDINEMETHANOLS 								
	R_1	R_2	R_3								
64	Phenyl	Methyl	H	F	80	104–108	0.2	93–95	$C_{13}H_{19}ON\cdot HCl$	182–184	14.68	14.55
65	Phenyl	Phenyl	H	F	80				$C_{18}H_{21}ON\cdot HCl$[e]	308–309	11.45	11.50
66	Phenyl	Methyl	Methyl	G	91	125–129	0.4		$C_{14}H_{21}ON\cdot HCl$	220–221	13.85	13.75

[a] The per cent. yield is based on the magnesium or aluminum used just as the per cent. yield of pinacol ("Organic Syntheses," **5**, 88 (1925)) is based on magnesium. Based on the ketone used in the reaction, the % yield would be about half of that reported here. [b] Ref. 4; m. p. free base 78°. [c] Ref. 4; m. p. free base 131.5. [d] Ref. 2; m. p. free base 32°. [e] Monohydrate, [f] Ref. 2, m. p. free base 104°. [g] Dipicrate, m. p. 150–152°. *Anal.* Calcd. for $C_{26}H_{30}O_{15}N_8$: N, 16.14. Found: N, 16.08. [h] For solid derivative, see no. 27 of Table I. [i] Nitrogen analysis of free base. The picrate melted at 68–71°. *Anal.* Calcd. for $C_{19}H_{24}O_8H_4$: N, 12.88. Found: N, 12.80. [j] The per cent. yields reported here for 4-pyridinemethanols are the high boiling fractions that were collected after all the 2-pyridinemethanols had distilled. [k] Ref. 8; m. p. 107–108°. [l] Ref. 6. [m] Tschitschibabin, *Ber.*, **37**, 1372 (1904); m. p. free base 126°. [n] In these reactions the halogen of the 3-halopyridine was removed at some point in the reaction since α-phenyl-α-methyl-2-pyridinemethanol was also isolated as its hydrochloride. [o] Prepared from the reaction of 2-pyridylmagnesium bromide and methyl acetate. [p] Ref. 2; m. p. free base 43°. [q] Ref. 2.

the product began to crystallize. The mixture was cooled and filtered; a yield of 3.5 g. (92%) of a white crystalline product melting at 142–143° was obtained. Mixture of this product with an equal amount of the one obtained from the high boiling fraction of the acetophenone–pyridine condensation (m. p. 140–142°) melted at 141–143°. A melting point of a mixture of the hydrochlorides from both of the above products was unchanged, 186–189°.

Substituted Aminoalkyl Chlorides.—1-Dimethylamino-2-chloropropane hydrochloride[30] was obtained in a 91% yield from the aminoalcohol (Carbide and Carbon Chemicals Corp.) and thionyl chloride with chloroform as the solvent; m. p. 194–196°. This same procedure was used in preparing the following: β-(N-piperidino)-ethyl chloride hydrochloride,[31] m. p. 231–232°, 77% yield; β-(N-morpholino)-ethyl chloride hydrochloride,[32] m. p. 182–184°, 85% yield; β-(N-pyrrolidino)-ethyl chloride hydrochloride, m. p. 171–172°, 85% yield.

Anal. Calcd. for $C_6H_{12}NCl\cdot HCl$: Cl (ionizable), 21.0. Found: Cl, 20.9.

β-(N-Pyrrolidino)-ethyl alcohol, for which no reference could be found in the literature, was prepared according to the procedure of Hartman,[33] b. p. 78–81° (15 mm.), 53% yield. The hydrochloride was obtained as hygroscopic white needles melting at 88–90° when recrystallized from 2-propanol.

Anal. Calcd. for $C_6H_{13}ON\cdot HCl$: Cl, 23.42. Found: Cl, 23.25.

β-Dimethylaminoethyl chloride and β-diethylaminoethyl chloride hydrochlorides were purchased from Michigan Chemical Corp.

(30) Brode and Hill, THIS JOURNAL, **69**, 724 (1947); reported m. p. 191–191.5°.

(31) Blicke and Maxwell, *ibid.*, **64**, 429 (1942); reported m. p. 229–231°.

(32) Mason and Block, *ibid.*, **62**, 1445 (1940); reported m. p. 182°.

(33) Hartman, "Organic Syntheses," **14**, 28 (1934).

Aminoethers.—All of the aminoethers listed in Table I were prepared by the genera procedure given below except nos. 2 and 34. The method for these two aminoethers did not include separation of the substituted pyridinemethanol from the aminoether by fractional extraction of the mixture with aqueous hydrochloric acid, and this might account for the low yields.

2-[α-(2-Dimethylaminoethoxy)-α-methylbenzyl]-pyridine (General Procedure).—A solution of 84 g. (0.42 mole) of α-phenyl-α-methyl-2-pyridinemethanol in 400 ml. of toluene was distilled until 50 ml. of distillate had been collected; this step removed a small amount of water present. The reaction mixture was stirred vigorously under reflux and 9.7 g. (0.42 gram atom) of freshly cut sodium was added over a period of fifteen minutes, with refluxing and stirring being continued an additional one to two hours or until practically all of the sodium had reacted.

During this period, a toluene solution of β-dimethylaminoethyl chloride was prepared. To a solution of 80 g. (0.55 mole) of β-dimethylaminoethyl chloride hydrochloride in about 100 ml. of water was added 350 ml. of toluene. The mixture was cooled at 0 to 5° during the addition (twenty minutes) of 33 g. of potassium hydroxide in 35 ml. of water. The temperature was then lowered to −15° and the toluene layer was decanted from the frozen aqueous layer. The aqueous layer was again extracted with toluene (200 ml.) in a similar manner, and the combined toluene extracts were dried by stirring for twenty to thirty minutes with about 20 g. of anhydrous magnesium sulfate.

This toluene solution of β-dimethylaminoethyl chloride was then added over a period of one to two hours to the above sodium alkoxide in toluene with stirring under mild refluxing.[34] The mixture was refluxed twelve to sixteen hours, cooled, and 200 ml. of water added. The toluene layer was separated and treated with sufficient 10% hydrochloric acid (100–130 ml.) to render the well-stirred mix-

(34) When α-phenyl-α-methyl-4-pyridinemethanol was used, the sodium derivative precipitated from the toluene.

ture acid to congo red paper. Then enough of a saturated sodium bicarbonate solution was added to make the stirred mixture alkaline to congo red. This operation resulted in most of the unchanged pyridinemethanol remaining in the toluene layer and the aminoether being extracted into the aqueous layer. The toluene layer was distilled and 18 g. of α-phenyl-α-methyl-2-pyridinemethanol was recovered (b. p. 125–128° (0.45 mm.)).

The aqueous layer was made strongly alkaline with 20% potassium hydroxide, and extracted once with 500 ml. of 40–60° petroleum ether.[35] The extract was fractionally distilled through a 20–30 cm. Vigreux column; the desired amino ether was collected at 145–153° (0.4 mm.) and amounted to 54 g. (61% based on recovered pyridinemethanol). The pure amino ether had a boiling point of 126° (0.04 mm.), 135° (0.26 mm.), 145° (0.8 mm.) and 172° (4.5 mm.); $n^{20}D$ 1.5804.

The neutral succinate was prepared by dissolving 22.4 g. (0.083 mole) of the above base and 9.7 g. (0.082 mole) of succinic acid in 30–40 ml. of 2-propanol. About 3 vols. of ethyl acetate was added and the mixture was cooled to −20° and filtered; yield, 20 g. (64%); m. p. 102–103°. Acetone alone was also a satisfactory solvent. An analytical sample melted at 103–104°.

Anal. Calcd. for $C_{21}H_{28}O_5N_2$: N, 7.22. Found: N, 7.26, 7.30.

The monohydrochloride was prepared by the addition of 8 ml. (0.1 mole) of 46% alcoholic hydrochloric acid to 27 g. (0.1 mole) of the above amino ether in 250 ml. of a 1 to 1 mixture of 2-propanol and ethyl acetate and cooling to −20°. The first crop amounted to 17 g. (55%); m. p. 166–168°.

2-[α-(2-Dimethylaminoethoxy)-α-methylbenzyl]-pyridine β-Hydroxyethochloride.—A mixture of 1.6 g. (0.02 mole) of ethylene chlorohydrin and 4.1 g. (0.015 mole) of the above base was heated at 70° for sixteen hours, and the product thus formed was recrystallized from 2-propanol–butanone mixture; yield 4 g. (75%); m. p. 73–75°.

2-[α-(2-Dimethylaminoethoxy)-α-methylbenzyl]-pyridine Dimethiodide.—A cooled solution of 10 g. (0.37 mole) of the above base in 20 ml. of methanol was mixed with 30 g. (0.21 mole) of methyl iodide and then heated for thirty-six hours at 70° in a closed container. The cooled reaction mixture was diluted with 3 volumes of ether and the precipitated solid was recrystallized from ethyl alcohol; yield 10 g. (47%) of a white crystalline product; m. p. 143–144°.

β-Dimethylaminoethyl Ether of 2,3-Diphenyl-2,3-butanediol.—The above etherification procedure was carried out using 18 g. (0.074 mole) of 2,3-diphenyl-2,3-butanediol that had been obtained as a by-product. The monoaminoether distilled at 155–162° (0.3 mm.) and amounted to 14 g. (61%). The hydrochloride was prepared and recrystallized from a 1 to 3 mixture of methanol and 2-propanol (yield, 15 g.); m. p. 252°.

Anal. Calcd. for $C_{20}H_{27}O_2N\cdot HCl$: Cl, 10.15. Found: Cl, 10.22.

2-Benzoylpyridine (2-Pyridyl Phenyl Ketone).—The procedure of Crook and McElvain[29,36] was carried out. The product was isolated by crystallization from petroleum ether rather than distillation; m. p. 43–44°. The hydrochloride melted at 124–126° (reported[29] m. p. 126°). The above method using α-phenyl-2-pyridinemethanol instead of 2-benzylpyridine was found more convenient. The oxidation of 250 g. (1.35 moles) of the pyridinemethanol with 163 g. (1.03 moles) of potassium permanganate in 2 l. of water gave 188 g. (77%) of ketone melting at 48–50°. The hydrochloride had a melting point of 126–127°.

2-[α-Methylaminobenzyl]-pyridine.—The procedure of Crossley and Moore,[37] for the conversion of ketones to amines was followed using 18 g. (0.1 mole) of 2-benzoylpyridine, 60 g. (1 mole) of methyl formamide and 13 g. (0.25 mole) of 90% formic acid. The desired product distilled at 120–122° (0.5 mm.) and amounted to 12 g. (60%). The dihydrochloride salt melted at 214–216° and analysis before and after a second recrystallization indicated a molecule of water of crystallization.

Anal. Calcd. for $C_{13}H_{14}N_2\cdot 2HCl\cdot H_2O$: Cl, 24.6. Found: Cl, 24.6.

2-[α-(2-Dimethylaminoethylamino)-benzyl]-pyridine.—A mixture of 18.3 g. (0.1 mole) of 2-benzoylpyridine, 14 g. (0.16 mole) of β-dimethylaminoethylamine,[38] 100 ml. of ethanol and 0.5 g. of Adams platinum oxide catalyst was hydrogenated at an initial pressure of fifty pounds. After fifteen minutes, 97% of the theoretical amount of hydrogen was absorbed. The mixture was filtered, and the filtrate was fractionally distilled. At 120–130° (0.3 mm.), 17.5 g. (92%) of α-phenyl-2-pyridinemethanol (m. p. 76–78°) was obtained and identified by the melting point and analysis of its hydrochloride salt. No higher boiling component was present.

The above procedure was repeated except that a mixture of the ketone and amine was initially refluxed one and one-half hours previous to the hydrogenation. At 120–123° (0.5 mm.), 10 g. of the α-phenyl-2-pyridinemethanol was obtained. At 140–143° (0.5 mm.), 9 g. (82% based on recovery of the above pyridinemethanol) of product was isolated; its trihydrochloride (no. 55 of Table I) melted at 170–175°.

2-[α-(2-N-Dimethylaminoethyl-N-methylamino)-benzyl]-pyridine.—A mixture of 9 g. (0.035 mole) of the above benzylpyridine, 16 g. (0.35 mole) of 98–100% formic acid and 8 g. (0.1 mole) of formalin was refluxed for forty-eight hours, made alkaline with 120 ml. of 20% potassium hydroxide and extracted with benzene. The benzene extract was fractionally distilled in a modified Claisen flask, and the product was collected at 160–163° (1 mm.); yield, 7 g. (75%). A sample was converted to the very hygroscopic dihydrochloride, which was recrystallized from 2-propanol–butanone mixture; m. p. 130–140° with sintering at 100° (no. 56 of Table I).

2-[α-(2-Pyridylamino)-benzyl]-pyridine.—A mixture of 45 g. (0.3 mole) of 2-benzoylpyridine, 28.5 g. (0.3 mole) of 2-aminopyridine and 100 ml. (2.1 moles) of 98–100% formic acid were refluxed forty-eight hours and the desired product isolated as above; b. p. 145–147° (0.2 mm.); yield: 12 g. (30% based on the recovery of 16 g. of α-phenyl-2-pyridinemethanol, b. p. 120–125° at 0.2 mm.) of an oil that solidified on standing. The dihydrochloride melted at 200–202°.

Anal. Calcd. for $C_{17}H_{15}N_3\cdot 2HCl$: Cl, 21.20. Found: Cl, 21.18.

2-[α-(2-Pyrimidylamino)-benzyl]-pyridine.—The above procedure was carried out using 28.8 g. (0.3 mole) of 2-aminopyrimidine. At 170–175° (0.2 mm.), 8 g. (20% based on recovery of 18 g. of α-phenyl-2-pyridinemethanol) of product melting at 102–103° was collected. The dihydrochloride had a melting point of 220–223°.

Anal. Calcd. for $C_{16}H_{14}N_4\cdot 2HCl$: Cl, 21.20. Found: 21.25.

2-[α-(N-2-Dimethylaminoethyl-N-2-pyridylamino)-benzyl]-pyridine.—The method of Huttrer, *et al.*,[39] was carried out using 7.8 g. (0.03 mole) of 2-[α-(2-pyridylamino)-benzyl]-pyridine, 1.4 g. (0.06 mole) of lithium amide, 100 ml. of dry toluene, and a toluene solution of β-dimethylaminoethyl chloride (as prepared in the above etherification procedure) from 7.2 g. (0.05 mole) of the hydrochloride. A yield of 4 g. (45%) of desired product distilling at 185–190° (0.2 mm.) was obtained (no. 57 of Table I).

Summary

A series of forty-eight new α-substituted-

(35) All of the aminoethers prepared were fairly soluble in petroleum ether whereas all of the pyridinemethanols having an aryl group were slightly soluble, which may constitute an additional favorable step in removing unchanged starting material.

(36) Crook, THIS JOURNAL, **70**, 416 (1948).

(37) Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944).

(38) Turner, THIS JOURNAL, **68**, 1607 (1946).

(39) Huttrer, Djerassi, Beears, Meyer and Scholz, *ibid.*, **68**, 2001 (1946).

pyridinemethanols have been prepared. The antihistaminic activity of their dimethylaminoethyl ethers has been evaluated.

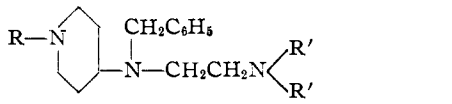
CINCINNATI, OHIO RECEIVED APRIL 23, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

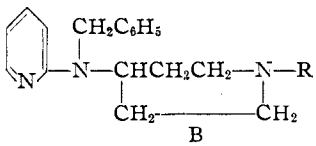
Histamine Antagonists. III. Derivatives of 4-Aminopiperidine

BY ROBERT H. REITSEMA AND JAMES H. HUNTER

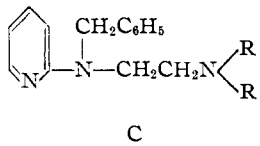
Certain 4-aminopiperidines have been prepared as potential antihistaminic agents based on their structural analogy to N,N-dialkyl-N'-benzyl-N'-(α-pyridyl)-ethylenediamines (C) which are known to have antihistaminic activity.[1] The 4-aminopiperidine group has been substituted for the α-aminopyridine group in type A and for the ethylenediamine group in type B.



A



B

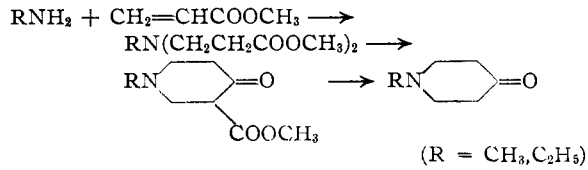


C

All of these new piperidine derivatives were shown to exhibit some activity against histamine-induced spasms in the isolated gut. The most effective member of this series, 1-ethyl-4-(N-benzyl-N-α-pyridylamino)-piperidine (VII), was three-fourths as active as β-dimethylaminoethyl benzohydryl ether hydrochloride.[2]

The majority of 4-aminopiperidines reported in the literature had been made from chelidonic acid derivatives.[3,4] Utilizing 1-ethyl-4-piperidone, Fuson, Parham and Reed[5] were able to prepare 1-ethyl-4-aminopiperidine by reductive amination. This latter method now has been extended to indicate its generality in the synthesis of secondary aminopiperidines.

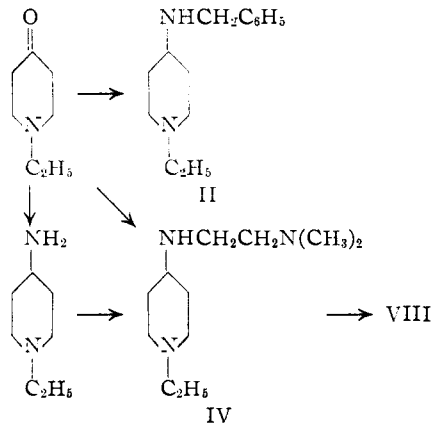
The condensation of methyl- and ethylamine with the methyl acrylate proceeded smoothly. Subsequent cyclization gave 1-methyl- and 1-ethyl-4-piperidone hydrochloride in high yields.



(R = CH_3,C_2H_5)

Reductive alkylation of primary amines with the piperidones yielded the substituted 4-aminopiperidines indicated in Table I.

These secondary amines were alkylated with benzyl bromide or α-bromopyridine to give tertiary amines of types A and B. Unsuccessful attempts were made to prepare 1-ethyl-4-(N-benzyl - N - dimethylaminoethylamino) - piperidine (VIII) by alkylation of the sodium salt or the Grignard derivative of II with β-dimethylaminoethyl chloride. Apparently the alkylation of the secondary amine proceeded so slowly that the halide was decomposed first. Condensation of IV with benzyl bromide proceeded satisfactorily. It was also possible to alkylate 1-ethyl-4-aminopiperidine with dimethylaminoethyl chloride to provide an alternate, though inferior, synthesis of the secondary amine, IV.



II

IV

The pyrrolidylethylamine required in the synthesis of V was obtained by reduction of pyrrolidylacetonitrile. It had been found that higher yields of N,N-dimethylethylenediamine were obtained by rapid reduction of the nitrile without solvent than were possible in the presence of methanolic ammonia. Consequently this method was also used for pyrrolidylacetonitrile although the use of ammonia with this more stable amine probably would have reduced the amount of the secondary amine and improved the yield.

Experimental[6]

bis-(β-Carbomethoxyethyl)-ethylamine.—By a procedure analogous to that used earlier,[5,7] from 135 g. (3.0

(1) Huttrer, *et al.*, THIS JOURNAL, **68**, 1999 (1946).

(2) We are indebted to Dr. Milton J. VanderBrook of our Pharmacology Department for carrying out these preliminary assays.

(3) Hahn, Cerkovnikov and Prelog, *Helv. Chim. Acta*, **26**, 1132 (1943).

(4) Cerkovnikov and Prelog, *Ber.*, **74B**, 1648, 1658 (1941).

(5) Fuson, Parham and Reed, THIS JOURNAL, **68**, 1239 (1946).

(6) Microanalyses by Mr. Harold Emerson and staff of these Laboratories.

(7) Mozingo and McCracken, "Organic Syntheses," **20**, 35 (1940).