cant, since both the oxazolidine and the isomeric vinyl ether have identical boiling points[9] and no fractionation could have occurred by distillation if both these compounds had been formed in the reaction. Moreover, if the reaction proceeds in two steps, then the presumed first step (vinyl transetherification) would not be appreciably hindered sterically, whereas the presumed second step (cyclization) should be seriously hindered. Thus, this example is a particularly favorable case for isolation of the vinyl ether if any had formed.

2-Methyltetrahydro-1,3-oxazine was prepared by both methods A and B: $n^{25}D$ 1.4407, d^{25}_4 0.9459. *Anal.* Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.57; H, 11.00; N, 13.59.

Preparation of 2-Methyl-3-phenyloxazolidine.—N-Phenylethanolamine (141.5 g., 1.03 moles) was dissolved in 86.3 g. (1.20 moles) of ethyl vinyl ether and 1 g. of mercuric acetate added to this solution. The solution warmed spontaneously and began to boil before all the mercuric salt had gone into solution. It was immediately placed under a reflux condenser and heated under reflux for 2 hr. During this period, the reaction temperature rose from 45 to 78°. The reaction mixture was then poured into a beaker and chilled in ice, whereupon it set to a crystalline mass. The solid was removed by filtration and recrystallized from ethyl alcohol, giving 143.8 g. of 2-methyl-3-phenyloxazolidine, m.p. 58–59°, a yield of 85.5%. This product was recrystallized again from 30–60° petroleum ether, resulting in 107.5 g. of pure product (64% yield), m.p. 58.5–59°. A final recrystallization from 85–100° petroleum ether gave an analytical sample, m.p. 59–59.5° (lit.[2e] 60.5–61°).

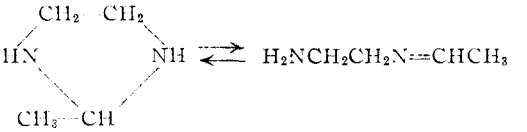
Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.62; H, 7.89; N, 8.54.

Preparation of 2-Methylimidazolidine.—Ethylenediamine (65.5 g., 1.09 moles) was dissolved in 133.5 g. (1.85 moles) of ethyl vinyl ether and 1 g. of mercuric benzoate added to this solution. The mercuric salt dissolved only partially even with vigorous shaking; there was no immediate exotherm. The mixture was then heated under reflux for 8 hr. During this period the pot temperature rose from 42 to 51°, and almost all of the mercuric salt went into solution, accompanied by the formation of some globules of mercury. The solution was cooled and left overnight at room temperature. On the following day another 1 g. of mercuric benzoate was added. This time the mercuric salt went rapidly and completely into solution. Reflux was resumed, and over a 1-hr. period the pot temperature rose from 51.5 to 60°. The solution was then cooled and flash-distilled at about 0.5 mm. pressure into a receiver cooled with Dry Ice–acetone. The first cut of this flash-distillation, 66.9 g., was obtained without heating the distilling flask; this cut was terminated when a solid material started to plug the outlet of the take-off tube. A wide-bore outlet was then utilized, and a second cut was taken by heating the distilling flask to a maximum liquid temperature of 73°. This second fraction, 107.7 g., was partly solid at room temperature, but the solid soon dissolved in the liquid portion. The residue weighed 18.1 g.

The second fraction was overlaid with about twice its volume of 100–140° petroleum ether, well shaken, and chilled in Dry Ice–acetone to induce crystallization. The crystals were filtered under nitrogen from the resultant two-phase liquid mixture. The filtrate was again chilled, and the solid which formed again filtered off under nitrogen. This procedure was repeated about six times until no further crystallization occurred. The combined solid product was dried under vacuum at room temperature. The yield of this once-crystallized product, m.p. 46–49°, was 38.4 g., 41% based on the diamine. This material was recrystallized out of 30–60° petroleum ether to obtain an analytical sample, which was a white, very volatile, hygroscopic solid, m.p. 47.5–48.5°. Potentiometric titration of this sample with standard 0.1 *N* HCl gave replicate values of 43.39 and 42.91 for the neutralization equivalent (theor. for 2-methylimidazolidine, 43.07). Elementary analysis was found to be very difficult because of the hygroscopicity and volatility of the material, and an analysis for nitrogen could not therefore be obtained.

Anal. Calcd. for $C_4H_{10}N_2$: C, 55.77; H, 11.70; N, 32.53. Found: C, 56.36; H, 11.57.

The infrared spectrum of this compound showed bands at 1670 cm.$^{-1}$ attributable to —C=N— stretching, and at 1595 cm.$^{-1}$, probably due to $-NH_2$ deformation. These results are consistent with the Schiff base form of the imidazolidine



Preparation of 2-Methyl-1,3-diphenylimidazolidine.—N,N'-Diphenylethylenediamine (100.9 g., 0.48 mole) was shaken vigorously with 72.0 g. (1.0 mole) of ethyl vinyl ether, but only a small part of the solid diamine dissolved. One gram of mercuric benzoate was dissolved in this mixture, and a strong exotherm then resulted. The mixture was immediately placed under reflux and heating applied when the initial exotherm subsided. After 21 min. of reflux almost all of the solid had gone into solution and the liquid temperature had risen from 35.5 to 49°. Almost immediately thereafter crystallization suddenly occurred, filling the flask with solid and lowering the liquid temperature to 42°. After a further 40 min. of reflux, the mixture was cooled and the solid product dried under vacuum. Part of this solid was recrystallized from methanol, m.p. 90–91.5°, and the remainder from 85–100° petroleum ether, m.p. 91.5–95°. The total yield of recrystallized product was 93.4 g., 82% based on the diamine. This product was further recrystallized out of methanol, giving 75 g. (66% yield) of pure 2-methyl-1,3-diphenylimidazolidine, m.p. 92–93.5° (lit.[3c] 98–100°), ebulliometric molecular weight, 226 (theor. 238).

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.40; H, 7.47; N, 11.76.

PHILADELPHIA 37, PENNA.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Hypotensive Agents. V. 4-(2'-Aminoethyl)-piperidine Derivatives

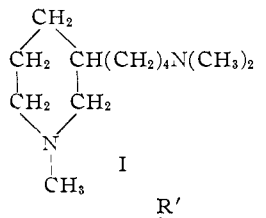
BY ARTHUR P. PHILLIPS

RECEIVED DECEMBER 19, 1956

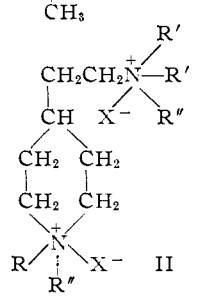
A series of 4-(2'-aminoethyl)-piperidines has been prepared for testing for hypotensive ganglionic blocking activity. The most active compound in the series was comparable in activity to hexamethonium.

Following the discovery[1,2] of ganglionic blocking activity in 1-methyl-3-(4'-dimethylaminobutyl)-piperidine (I) and its bis-quaternary ammonium salts, several series of compounds[3] modelled after I have been prepared and tested for this kind of activity. The present paper reports the preparation and properties of another series of compounds structurally related to I. These are some 4-(2'-aminoethyl)-piperidine derivatives which can be represented by the general formula II. The products were made by the sequence of reactions shown in Fig. 1.

(1) S. Norton and A. P. Phillips, *Nature*, **172**, 867 (1953).
(2) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).
(3) Paper IV of this series, A. P. Phillips, *ibid.*, **78**, 1930 (1956).



I



II

R = H or CH_3; $N\langle^{R'}_{R'}$ = $(CH_3)_2N$, $(C_2H_5)_2N$, pyrrolidine, piperidine or morpholine; R″X = HCl, CH_3I or C_2H_5I, etc.

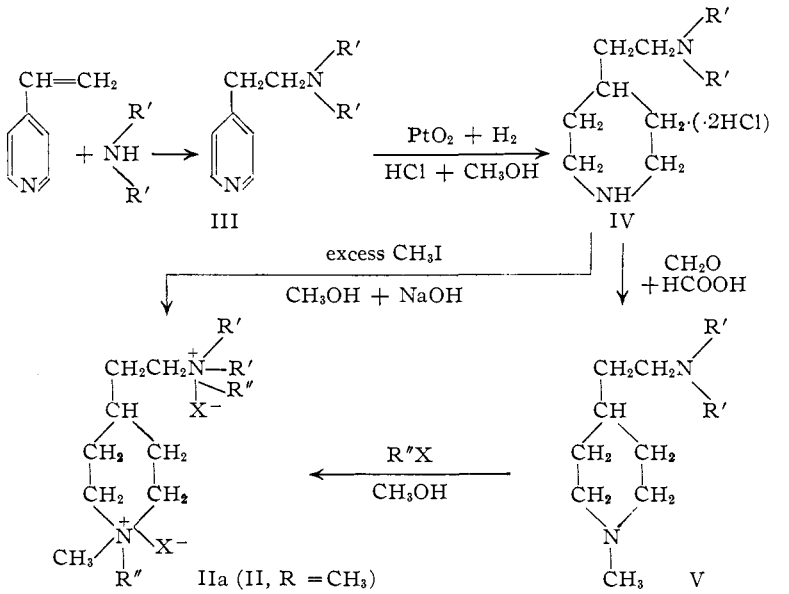


Fig. 1.

The reactions shown in Fig. 1 were carried through on the products obtained by the addition of dimethylamine, diethylamine, pyrrolidine, piperidine and morpholine to 4-vinylpyridine. The addition of amines to 4-vinylpyridine has been described in some detail earlier[4] and needs no further comment here.

The dihydrochlorides of the 4-(2′-aminoethyl)-pyridines (III) were hydrogenated in methanol solution using Adams catalyst, at about three to four atmospheres of hydrogen pressure and room temperature. Hydrogen uptake was usually slow, but high yields of the 4-(2′-aminoethyl)-piperidines (IV) were obtained.

Methylation of the 4-(2′-aminoethyl)-piperidines (IV) by the well-known Eschweiler[5]–Clarke[6] procedure gave the N-methyl-bis-tertiary amines V. The latter, V, were quaternized by refluxing with excess of the appropriate alkyl halide in methanol solution and gave the products IIa. When the products IIa were to be quaternized with methyl iodide, they could be obtained by an alternative route, the direct methylation of the compounds IV using excess methyl iodide in methanol in the presence of at least one equivalent of alkali.

The physical and analytical data for all the compounds are listed in Table I.

Pharmacology.—These 4-(2′-aminoethyl)-piperidines resemble the 3-(4′-dimethylaminobutyl)-piperidines (such as I) structurally. The new compounds differ in the point of attachment and the length of the side chain on the piperidine ring. With an inter-nitrogen chain of five carbons they are pentamethonium rather than hexamethonium analogs. Both the bis-tertiary amines and the derived bis-quaternary salts showed ganglionic blocking activity in cats; usually, however, the hypotensive effects were of a low order and of brief duration. Only the diethiodide and dimethiodide of the 4-(2′-pyrrolidinoethyl)-piperidine (compounds 12 and 11 of Table I) approached I and hexamethonium in potency. Thus the diethiodide (compound 12) at 2 mg./kg. gave a 50% lowering of blood pressure lasting for 1 hr.

The best of the bis-tertiary amines, 1-methyl-4-(2′-pyrrolidinoethyl)-piperidine (compound 10, Table I) gave a comparable blood pressure lowering but of shorter duration only at 8 mg./kg.

A more detailed report on the pharmacology of these compounds will appear elsewhere.

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included.

Experimental

Typical procedures for each of the general types of reactions are described below.

The addition of amines to 4-vinylpyridine proceeded very well in most cases and the details of these reactions have been described fully elsewhere.[4]

Catalytic Hydrogenation of 4-(2′-Pyrrolidinoethyl)-pyridine Dihydrochloride (Compound 9, Table I).—A solution containing 5 g. (0.02 mole) of 4-(2′-pyrrolidinoethyl)-pyridine dihydrochloride (m.p. 214–216°) in 150 cc. of methanol and 0.2 g. of Adams catalyst was shaken in a Burgess–Parr type machine at 3–4 atmospheres of hydrogen pressure and room temperature. The theoretical amount of hydrogen (0.06 mole) was absorbed over 5 hr. After removal of the platinum the filtrate was concentrated by evaporation and the product was crystallized by the addition of ethyl acetate. After several recrystallizations from ethanol–ethyl acetate mixtures, 5 g. (>95%) of white crystalline product was obtained, m.p. 266–267°.

Eschweiler–Clarke Methylation of 4-(2′-Dimethylaminoethyl)-piperidine (Compound 3, Table I).—After liberation of the oily base from its dihydrochloride, 8 g. (0.05 mole) of 4-(2′-dimethylaminoethyl)-piperidine was carefully neutralized by and dissolved in 10 cc. of 98–100% formic acid with cooling. About 10 cc. of 35–37% formalin was added at once and the mixture was heated for 2 hr. on a steam-bath. Another 5 cc. each of formic acid and formaldehyde solution was added and heating was continued for 2 hr. longer. An excess (15 cc.) of concentrated hydrochloric acid was added and the solution was evaporated to dryness. The residual solid was purified by several recrystallizations from hot ethanol and then gave 10 g. (85%) of white crystals, m.p. 299–300°. This was the dihydrochloride of 1-methyl-4-(2′-dimethylaminoethyl)-piperidine.

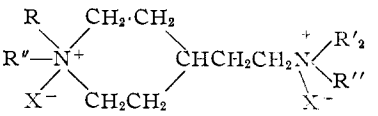
(4) A. P. Phillips. THIS JOURNAL, **78**, 4441 (1956).

(5) W. Eschweiler, *Ber.*, **38**, 880 (1905).

(6) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

TABLE I

4-(2′-AMINOETHYL)-PIPERIDINES



Compd.	R	R′₂N	R″X	Yield, %	M.p., °C.	Crystn. solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1[b]	H	CH_3NH	HCl	100	185-186	A·Æ	$C_8H_{20}N_2Cl_2$	44.6	44.2	9.4	9.1
2[b]	H	$(CH_3)_2N$	HCl	95	240–241	A	$C_9H_{22}N_2Cl_2$	47.1	47.0	9.7	9.6
3[c]	CH_3	$(CH_3)_2N$	HCl	85–90	299–300	A	$C_{10}H_{24}N_2Cl_2$	49.4	49.8	10.0	10.3
4[d,e]	CH_3	$(CH_3)_2N$	CH_3I	100	307–308	M	$C_{12}H_{28}N_2I_2$	31.7	32.0	6.2	5.9
5[c]	CH_3	$(CH_3)_2N$	C_2H_5I	100	275–276	M·Æ	$C_{14}H_{32}N_2I_2$	34.8	35.0	6.7	6.7
6[c]	CH_3	$(CH_3)_2N$	nC_3H_7I	100	214–215	M·Æ	$C_{16}H_{36}N_2I_2$	37.6	37.6	7.1	7.4
7[c]	CH_3	$(CH_3)_2N$	$C_6H_5CH_2Cl$	100	Hygr. oil	A·E	$C_{24}H_{36}N_2Cl_2\cdot 4H_2O$	58.1	59.0	8.9	8.7
8[b]	H	$(C_2H_5)_2N$	HCl	100	186–187	A·Æ	$C_{11}H_{26}N_2Cl_2$	51.4	51.4	10.2	10.2
9[b]	H	$(CH_2)_4N$[f]	HCl	100	266–267	A·Æ	$C_{11}H_{24}N_2Cl_2$	51.8	51.5	9.5	9.1
10[c]	CH_3	$(CH_2)_4N$[f]	HCl	95	310–312	A	$C_{12}H_{26}N_2Cl_2$	53.5	53.8	9.7	9.8
11[d]	CH_3	$(CH_2)_4N$[f]	CH_3I	95	291–292	M·Æ	$C_{14}H_{30}N_2I_2$	35.0	35.0	6.3	6.2
12[e]	CH_3	$(CH_2)_4N$[f]	C_2H_5I	100	264–265	M·E	$C_{16}H_{34}N_2I_2$	37.8	37.6	6.8	7.0
13[b]	H	$(CH_2)_5N$[g]	HCl	95	301-302	A	$C_{12}H_{26}N_2Cl_2$	53.5	53.5	9.7	9.7
14[c]	CH_3	$(CH_2)_5N$[g]	HCl	90	>334	M·Æ	$C_{13}H_{28}N_2Cl_2$	55.1	55.4	10.0	9.7
15[d]	CH_3	$(CH_2)_5N$[g]	CH_3I	100	290–291	M	$C_{15}H_{32}N_2I_2$	36.4	36.4	6.5	6.3
16[b]	H	$O(C_2H_4)_2N$[h]	HCl	80	290–293	M·A	$C_{11}H_{24}N_2OCl_2$	48.7	48.6	8.9	8.5
17[c]	CH_3	$O(C_2H_4)_2N$[h]	HCl	100	>330	M	$C_{12}H_{26}N_2OCl_2$	50.6	50.7	9.2	8.8
18[d]	CH_3	$O(C_2H_4)_2N$[h]	CH_3I	80	298–300	Aq·Ac	$C_{14}H_{30}N_2OI_2$	33.9	33.9	6.1	6.1

[a] A = ethanol; Ac = acetone; Aq = water; Æ = ethyl acetate; E = ether; M = methanol. [b] Made by catalytic hydrogenation of the 4-(2′-aminoethyl)-pyridine dihydrochloride. [c] From the secondary amine with formic acid and formalin. [d] From the secondary amine, excess methyl iodide and sodium hydroxide. [e] From the ditertiary amine and alkyl halide. [f] $(CH_2)_4N$ is the pyrrolidino group. [g] $(CH_2)_5N$ is the piperidino group. [h] $O(C_2H_4)_2N$ is the morpholino group.

1-Methyl-4-(2′-dimethylaminoethyl)-piperidine Bis-*n*-propiodide (Compound 6, Table I).—The oily base was liberated from the dihydrochloride described above. A solution of 1.7 g. (0.01 mole) of this base was refluxed with 5 cc. of *n*-propyl iodide in 50 cc. of methanol for 18 hr. (overnight). Evaporation of part of the methanol and addition of acetone gave 5.1 g. (100%) of white crystalline product. After recrystallization from ethanol the purified product melted at 214–215°.

1-Methyl-4-(2′-piperidinoethyl)-piperidine Bis-methiodide (Compound 15, Table I). By Alkylation of the Secondary Amine with Excess Methyl Iodide.—A solution of 2 g. (0.01 mole) of the base, 4-(2′-piperidinoethyl)-piperidine, in 50 cc. of methanol with 5 cc. of methyl iodide was refluxed for 2 hr. Another 5 cc. of methyl iodide and a solution of 1 g. of sodium hydroxide in 50 cc. of methanol were added and refluxing was continued for 3 hr. The reaction mixture was evaporated to dryness *in vacuo* and sodium iodide was removed by washing the solid residue with several 25-cc. portions of acetone. This procedure left 5 g. (100%) of white crystals. These were purified by crystallization from methanol and melted at 290–291°.

TUCKAHOE 7, N. Y.