The authors wish to express their thanks and gratitude to Messrs P. Sadtler and Son, Inc., Research Laboratories, Philadelphia, U.S.A., for kindly carrying out the infrared spectrograms. The infrared measurements of Ia were also carried out by Mr. Nagib Doss, Chemistry Department, Ohio State University, U.S.A., to whom we are highly indebted.

ABBASSIA, CAIRO, EGYPT

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN CORPORATION]

Aminophenylethanols and Related Compounds

BY SEYMOUR L. SHAPIRO, HAROLD SOLOWAY AND LOUIS FREEDMAN

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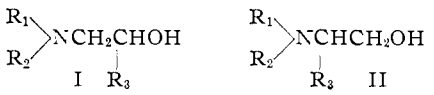
Aminophenylethanols of the types I and II, and the corresponding halides were required as synthetic intermediates. The alcohols of the type I were prepared by condensation of styrene oxide and secondary amines, while the alcohols of the type II were prepared by amination of 2-bromo-2-phenylethanol. Treatment of the alcohols I or II with thionyl chloride in ether afforded the identical chloride which in the instance of the isomeric pyrrolidino alcohols proved to be 1-(2-chloro-2-phenylethyl)-pyrrolidine hydrochloride.

In connection with the broad study of the pharmacological activity of substituted α- and β-phenylethylamines, we required a number of alcohols of the type represented by I and II.



I II

The groups R_1 and R_2 were varied as alkyl, aralkyl, aryl and cycloalkyl, and R_3 was retained principally as phenyl but was also varied as *p*-chlorophenyl, *p*-tolyl, α-naphthyl and cyclohexyl.

Reports of derivatives of the structures I and II in a variety of pharmacological categories such as methadon analogs,[1] antihistamines, antispasmodics and anesthetics[2] will be detailed in subsequent papers. Derivatives of this type have received but scant inspection.[3,4]

The synthesis of the aminoalcohols of the type I was effected by condensation of the appropriate secondary amine with styrene oxide or the related oxide; the compounds prepared are described in Table I.

It has been clearly established that with secondary amines[5,6] styrene oxide forms only secondary alcohols of the type I. From Table I it is seen that bulky groups attached to the secondary amine tend to give lower yields. When a steric effect was anticipated, the reaction was carried out at a higher temperature and for a longer heating period.

It is of interest that controlled studies[7] of the reaction of diethylamine and styrene oxide at 60° showed virtually no reaction at 6 hours and about 70% of the reactants remained after 12 hours. These workers concluded that styrene oxide reacts only sluggishly with amines, although they noted vigorous interaction of diethanolamine with styrene oxide which was attributed to the catalytic effect of the hydroxyl groups of the reactant amine. In contrast to these observations, a 92% yield (compound 14, Table I) with diethylamine was obtained after 16 hours reaction time. These data suggest that after the 6-hour induction period a catalytic effect is obtained from the formed aminoalcohol of the reaction.

The amino alcohols represented by II and described in Table II were prepared from secondary amines and 2-bromo-2-phenylethanol using the method of King, *et al.*,[8] and Golumbic and Cottle[9] with slight modification.

The amino alcohols of the type I, as well as their hydrochlorides were readily converted to the corresponding chloride hydrochlorides (Table III) by treatment with thionyl chloride in ether.

When the amino alcohol of the type II as the hydrochloride was treated similarly with thionyl chloride, the chloride obtained in 72% yield was identical with that obtained using the secondary alcohol I as the reactant.

Using the isomeric amino alcohols (compound 25, Table I, and compound 3, Table II), the series of reactions reflecting the rearrangement and the identity of the chloride formed is shown in Scheme I.

In the rearrangement of the product from the amino alcohol II, liberation from its salt[10] was not required for conversion to Ia. With no noted formation of sulfur dioxide during the thionyl chloride treatment of II, and evolution of sulfur dioxide upon subsequent handling of this initial reaction product IIb, the 2-pyrrolidino-2-phenethyl chlorosulfite hydrochloride could form Ia directly or yield Ia through the ethylenimonium chloride IIa.[10]

(1) S. L. Shapiro, H. Soloway and L. Freedman, Meeting-in-Miniature, Westchester Section, American Chemical Society, April 21, 1955.

(2) S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, THIS JOURNAL, in press.

(3) G. A. Alles and P. K. Knoefel, *Arch. intern. pharmacodynamie*, **47**, 96 (1934).

(4) C. S. Marvel and V. du Vigneaud, THIS JOURNAL, **46**, 2093 (1924).

(5) W. Emerson, *ibid.*, **67**, 516 (1945).

(6) A. Funke and G. Benoit, *Bull. soc. chim. France*, **20**, 1021 (1953).

(7) L. Shecter, J. Wynstra and R. P. Kurkjy, *Ind. Eng. Chem.*, **49**, 1107 (1957).

(8) L. C. King, N. W. Berst and F. N. Hayes, THIS JOURNAL, **71**, 3498 (1949).

(9) C. Golumbic and D. L. Cottle, *ibid.*, **61**, 996 (1939).

(10) (a) E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948); (b) R. C. Fuson and C. L. Zirkle, *ibid.*, **70**, 2760 (1948); (c) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp. 121–124; (d) in ref. 10a, 2-dimethylamino-1-chloropropane did not rearrange immediately when liberated from its hydrochloride at room temperature, but did change to the isomeric 1-dimethylamino-2-chloropropane upon distillation, b.p. 64–67° (97–100 mm.). In turn, ref. 10b reported that when 1-ethyl-2-chloromethylpyrrolidine is liberated from its hydrochloride salt, it rearranges at room temperature to 1-ethyl-3-chloropiperidine.

TABLE I

α-PHENYLAMINOETHANOLS AND SALTS $R_3CHCH_2N(R_1)(R_2)\cdot R_4X$[a] (OH)

Compounds	R_1	R_2	R_4X	M.p., °C.,[b,c] or b.p. (mm.)	Yield,[d] %	Formula	Analyses, %[e] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	CH_3-	CH_3-		116–117 (19)	96							
2[f]	CH_3-	CH_3-	HCl	142–144[ca]	61							
3	CH_3-	CH_3-	HPic.[g]	133–135		$C_{16}H_{18}N_4O_8$	48.7	49.1	4.6	4.5	14.2	14.3
4	CH_3-	i-C_3H_7-		115–116 (4)	91	$C_{12}H_{19}NO$	74.6	74.6	9.9	10.0		
5	CH_3-	C_4H_9-[h]		104 (0.2)	84	$C_{13}H_{21}NO$	75.3	75.0	10.2	10.1	6.8	6.9
6	CH_3-	$C_6H_{11}-$[i]		117–120 (0.06)	78	$C_{15}H_{23}NO$	77.2	77.2	9.9	10.2	6.0	5.6
7	CH_3-	$C_6H_{11}-$[i]	HCl	160–162[cb]	68	$C_{15}H_{24}ClNO$	66.8	67.0	9.0	9.2	5.2	5.0
8	CH_3-	$C_6H_5CH_2-$		130–132 (0.06)	80	$C_{16}H_{19}NO$	79.6	79.5	7.9	8.1	5.8	5.8
9	CH_3-	$C_6H_5CH_2-$	HCl	132–133[cb]	70	$C_{16}H_{20}ClNO$	69.2	69.3	7.3	7.2	5.0	5.1
10	CH_3-	C_7H_8N-[j]		168–169 (0.03)	27	$C_{16}H_{20}N_2O$	75.0	74.7	7.9	7.8	10.9	11.3
11	CH_3-	C_6H_5-		146–148 (0.06)	75	$C_{15}H_{17}NO$	79.3	79.2	7.5	7.9	6.2	6.4
12	CH_3-	C_6H_5-	HCl	156–157[cb]	31	$C_{15}H_{18}ClNO$	68.3	68.3	6.9	6.8		
13	CH_3-	C_8H_9-[k]		142–143 (0.1)	47	$C_{17}H_{21}NO$	80.0	80.0	8.3	8.7	5.5	5.1
14[l]	C_2H_5-	C_2H_5-		112 (2.5)	92							
15	C_2H_5-	C_2H_5-	CH_3Br	154–156[ca]	32	$C_{13}H_{22}BrNO$	54.2	54.4	7.7	7.8	4.9	4.8
16[aa]	C_2H_5-	C_2H_5-		110–112 (0.15)	94	$C_{12}H_{18}ClNO$	63.3	63.4	8.0	8.2	6.2	5.7
17[ad]	C_2H_5-	C_2H_5-		102–104 (0.2)	80	$C_{13}H_{21}NO$	75.3	76.1	10.2	10.3	6.8	6.2
18[ac]	C_2H_5-	C_2H_5-		152–154 (0.4)	74	$C_{16}H_{21}NO$	79.0	79.2	8.7	8.6	5.8	5.9
19	n-C_3H_7-	n-C_3H_7-		104–106 (0.22)	88	$C_{14}H_{23}NO$	76.0	76.0	10.5	10.4	6.3	6.0
20	n-C_3H_7-	n-C_3H_7-	HCl	91–92[cc]	52	$C_{14}H_{24}ClNO$	65.2	65.2	9.4	8.8		
21	i-C_3H_7-	$C_6H_5CH_2-$		135–139 (0.12)	78	$C_{13}H_{23}NO$	80.3	80.6	8.6	8.7	5.2	4.8
22	i-C_3H_7-	$C_6H_5CH_2-$	HCl	142–143[ca]	79	$C_{18}H_{24}ClNO$	70.7	71.1	7.9	7.9		
23	n-C_4H_9-	n-C_4H_9-		114–115 (0.5)	86	$C_{16}H_{27}NO$	77.1	77.2	10.9	10.6	5.6	6.0
24	C_8H_9-[m]	C_8H_9-[m]		190 (0.11)	21	$C_{24}H_{27}NO$	83.4	83.2	7.9	8.2	4.1	4.1
25	$-(CH_2)_4-$			57–58[cd]	70	$C_{12}H_{17}NO$	75.4	75.3	9.0	9.2		
26	$-(CH_2)_4-$		HCl	162–164[cb]	79	$C_{12}H_{18}ClNO$					6.2	6.0
27	$-(CH_2)_4-$		HPic.[g]	150–152		$C_{18}H_{20}N_4O_8$	51.4	51.5	4.8	4.4	13.3	13.2
28	$-(CH_2)_4-$		CH_3Br	167–168[ca]	61	$C_{13}H_{20}BrNO$	54.6	54.8	7.0	7.3	4.9	4.8
29[aa]	$-(CH_2)_4-$			76–77[ce]	60	$C_{12}H_{16}ClNO$	63.9	64.2	7.2	7.1	6.2	5.7
30[ab]	$-(CH_2)_4-$			112 (2.4)	73	$C_{12}H_{23}NO$	73.0	73.0	11.8	12.2	7.1	6.8
31	$-(CH_2)_5-$			65–67[cf]	72	$C_{13}H_{19}NO$	76.1	76.0	9.3	9.3	6.8	6.7
32	$-(CH_2)_5-$		HCl	201–203 [ca]	63	$C_{13}H_{20}ClNO$					5.8	5.4
33	$-C_8H_{16}-$[n]			117–119 (0.05)	86	$C_{16}H_{25}NO$	77.7	77.9	10.2	10.2	5.7	5.7
34	$-C_8H_{16}-$[n]		HCl	148–150[cb]	40	$C_{16}H_{26}ClNO$	67.7	67.7	9.2	8.8		
35[o]	$-(CH_2)_2O(CH_2)_2-$			82–83[cf]	70							
36	$-(CH_2)_2O(CH_2)_2-$		HCl	192–193[ca]	93	$C_{12}H_{18}ClNO_2$					5.8	5.7
37	$-C_6H_{12}O-$[p]			141–143 (1.5)	95	$C_{14}H_{21}NO_2$					6.0	6.3
38	$-C_6H_{12}O-$[p]		HCl	187–188[ca]	35	$C_{14}H_{22}ClNO_2$	61.9	62.1	8.2	8.1	5.2	5.2
39	$-(CH_2)_6-$			102–103 (0.05)	65	$C_{14}H_{21}NO$	76.7	76.8	9.7	9.6	6.4	6.2
40	$-C_8H_5-$[q]			172–174 (0.2)	85	$C_{16}H_{17}NO$	80.3	80.4	7.2	6.9	5.9	5.8
41	$-C_5H_{11}N-$[r]			95–96[cf]	33	$C_{13}H_{20}N_2O$	70.9	70.9	9.2	9.1	12.7	12.8
42	$-C_5H_{11}N-$[r]		2.HCl	198–201	43	$C_{13}H_{22}Cl_2N_2O$					9.6	9.4

[a] R_3 = phenyl unless otherwise specified; [aa] R_3 = *p*-chlorophenyl; [ab] R_3 = cyclohexyl; [ac] R_3 = α-naphthyl; [ad] R_3 = *p*-tolyl. [b] Melting points are not corrected. [c] Recrystallization solvent is ethanol unless otherwise specified; [ca] isopropyl alcohol; [cb] methyl ethyl ketone; [cc] methyl ethyl ketone–isopropyl ether; [cd] heptane; [ce] acetonitrile; [cf] hexane; [cg] isopropyl alcohol–isopropyl ether; [ch] acetone. [d] Yields are based on distilled or recrystallized product. [e] Analyses by Weiler and Strauss, Oxford, England. [f] H. Bretschneider, *Monatsh.*, **78,** 82 (1948), reports m.p. 139–142°. [g] HPic. = picric acid derivative. [h] C_4H_9 = *sec*-butyl. [i] C_6H_{11} = cyclohexyl. [j] C_7H_8N = 2-(4-pyridineëthyl). [k] C_8H_9 = 2,6-dimethylphenyl. [l] Ref. 6 reports b.p. 143–145° at 14 mm. [m] C_8H_9 = α-phenethyl. [n] $-C_8H_{16}-$ with attached nitrogen is 2-methyl-5-ethylpiperidyl. [o] Ref. 6 reports m.p. 80–81°. [p] $-C_6H_{12}O-$ with attached nitrogen is 2,6-dimethylmorpholinyl. [q] $-C_8H_8-$ with attached nitrogen is 1-indolinyl. [r] $-C_5H_{11}N-$ with attached nitrogen is 4-methylpiperazyl.

The identity of the chloride Ia was established by conversion to 1-phenethylpyrrolidine by reductive dehalogenation with palladium-on-calcium carbonate, and the identity of the hydrochloride and picrate with these salts of authentic 1-phenethylpyrrolidine prepared from (2-bromoethyl)-benzene and pyrrolidine.

The isomeric salts prepared from 1-(α-phenylethyl)-pyrrolidine also were prepared for reference. The compounds concerned with this phase of our investigation are shown in Table IV.

Treatment of the 2-pyrrolidino-2-phenylethanol with 48% hydrobromic acid[11] in an attempt to ob-

(11) W. Pearlman, THIS JOURNAL, **70,** 871 (1948), converted N-phenylethanolamine to N-β-bromoethylaniline hydrobromide in 85% yield.

TABLE II

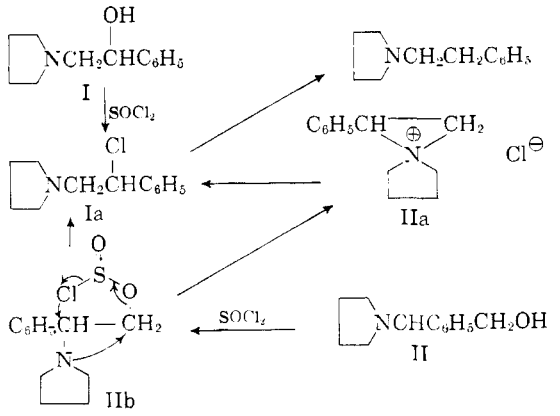
β-PHENYLAMINOETHANOLS AND SALTS $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!NCHCH_2OH\cdot R_4N^a$ (with R_3)

Compounds	R_1	R_2	R_4N	M.p., °C., b.c or b.p. (mm.)	Yield,d %	Formula	Analyses, %e Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	C_2H_5–	C_2H_5–		128–132 (21)	55	$C_{12}H_{19}NO$	74.6	74.5	9.9	9.9	7.3	7.0
2	C_2H_5–	C_2H_5–	CH_3Br	152–154[eg]	15	$C_{13}H_{22}BrNO$	54.2	54.3	7.7	7.7	4.9	4.7
3	–$(CH_2)_4$–			99–102 (2)	39	$C_{12}H_{17}NO$					7.3	6.9
4	–$(CH_2)_4$–		HCl	174–177	39	$C_{12}H_{18}ClNO$	63.4	63.4	8.0	8.0		
5	–$(CH_2)_4$–		HPic.g	103–105		$C_{18}H_{20}N_4O_8$	51.4	51.7	4.8	4.8	13.3	12.9
6	–$(CH_2)_5$–			127–136 (2)	44	$C_{13}H_{19}NO$	76.1	76.4	9.3	9.1	6.8	6.9
7	–$(CH_2)_2O(CH_2)_2$–		HCl	154–156[ch]	40	$C_{12}H_{18}ClNO_2$	59.1	59.2	7.4	7.3	5.8	5.8

Footnotes have same significance as in Table I.

tain the primary bromide resulted only in isolation of the reactant alcohol recovered in 75% yield as the hydrobromide.

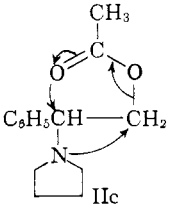
SCHEME I



When 2-pyrrolidino-2-phenylethanol was treated with acetyl chloride, two products were isolated, the expected 2-pyrrolidino-2-phenylethyl acetate in 58% yield and 15% of the acetate which was identical with that obtained in quantitative yield from the 2-pyrrolidino-1-phenylethanol.[12]

The isomeric acetates (compounds 7 and 9, Table IV) were next considered as reactants for conversion to the bromides following the procedure of Stempel and Buzzi.[13] In the instance of 2-pyrrolidino-1-phenylethyl acetate (compound 7, Table IV), the only isolable product obtained was a hydrocarbon, m.p. 99–102°, in 28% yield, which proved to be 2-phenylnaphthalene.[14-16]

Treatment of the isomeric acetate (compound 9, Table IV) under comparable conditions indicated initial hydrolysis of the acetate, and ultimate isolation of 2-pyrrolidino-2-phenylethanol hydrobromide in 94% yield.



Experimental[17]

Materials.—Unless otherwise specified all materials were commercially available. We are grateful to the American Cyanamid Co. for a sample of *p*-methylstyrene oxide. The other oxides were synthesized as described below.

***p*-Chlorostyrene oxide** was prepared by the method of Bergkvist[18] in 84% yield, b.p. 82–86° (4.1 mm.).

1-(1,2-Epoxyethyl)-naphthalene.—Using the same reaction sequence,[18] 2-chloro-1-(α-naphthyl)-ethanol was prepared in 36% yield, b.p. 132–135° (0.15 mm.), and converted in 68% yield to the product, b.p. 90–96° (0.10–0.13 mm.).

1,2-Epoxyethylcyclohexane.—The same procedure as directly above was used, cyclohexylmagnesium bromide being prepared by the technique of Gilman and Zoellner.[19] A 36% yield of 2-chloro-1-cyclohexylethanol was obtained, b.p. 83–86° (3.3 mm.), and was converted (70%) to (1,2-epoxyethyl)-cyclohexane, b.p. 116–119° (151 mm.).

Anal. Calcd. for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 76.3; H, 11.1.

Compounds of Table I. General Procedures.—A mixture of 1.0 equivalent of styrene oxide (or equivalent oxide) and 1.5 equivalents of the secondary amine was maintained under reflux. When steric effects were anticipated the heating period was prolonged. The product was then isolated by distillation.

The heating period varied: 1 hour, compound 25; 2–3 hours, compounds 1, 29, 30, 31, 35, 39, 41; 12–16 hours, compounds 14, 16, 18; 20–24 hours, compounds 5, 6, 17, 19, 33; 30 hours, compound 4.

In certain instances, a solvent (about 4 vol. solvent:1 vol. reactant) was used to modify the reaction. Compounds 11, 13, 23, 34 and 37 (ethanol) and compound 24 (butanol) were prepared in this manner using a 3-hour reflux period.

For the synthesis of compounds 8, 10 and 21, the external temperature was controlled for 2 hours by use of an oil-bath maintained at 125–135°. The preparation of compound 40 utilized heating on a steam-bath for 15 hours.

Exothermic reactions were noted in mixing the reactants which involved the less hindered secondary amines yielding compounds 1, 8, 11, 25, 29, 39 and 41. The influence of steric factors is also manifest in comparable yields obtained with the pyrrolidino products (compounds 25, 29, 30) with a

(12) (a) W. H. Saunders, Jr., S. Asperger and D. H. Edison, THIS JOURNAL, **80**, 2421 (1958), in a study of rates of solvolysis of deuterated 2-phenylethyl *p*-toluenesulfonates have shown that about 10% phenyl migration occurs in acetolysis, and in contrast about 45% phenyl migration had occurred in formolysis, and concluded that phenyl participation predominates in formolysis but is unimportant in acetolysis; (b) in the rearrangement we have noted it is not likely that phenyl participation occurs as shown in ref. 12a, since under these conditions the anticipated rearranged product would be 2-phenyl-1-(1-pyrrolidino)-ethyl acetate. The fact that acetylation of 2-pyrrolidino-2-phenylethanol is associated with isolation of 15% rearranged product in contrast to isolation of 72% rearranged product upon reaction with thionyl chloride, would indicate difference in susceptibility of the formed onium intermediate IIa to nucleophilic attack by acetoxy as compared to chloride ion.[12c] In the instance of acetylation a cyclic transition state similar to IIb, shown as IIc, may be operative; (c) C. G. Swain and C. B. Scott, *ibid.*, **75**, 141 (1953), report nucleophilic constants for chloride ion and acetate ion in polar systems.

(13) E. Stempel and E. C. Buzzi, *ibid.*, **71**, 2969 (1949).

(14) T. Zincke and A. Breuer, *Ann.*, **226**, 24 (1884).

(15) The authors are grateful to the Referee of this manuscript for his perceptive suggestion that the hydrocarbon obtained might be 2-phenylnaphthalene.

(16) F. Bettzieche, *Z. physiol. Chem., Hoppe-Seyler's*, **150**, 177 (1925), reports the conversion of phenylserine with acid to 2-phenylnaphthalene and proposes a possible mechanism [*C. A.*, **20**, 593 (1926)].

(17) Data shown in the tables are not reproduced in the Experimental section.

(18) T. Bergkvist, *C. A.*, **44**, 1446 (1950).

(19) H. Gilman and E. A. Zoellner, THIS JOURNAL, **53**, 1945 (1931).

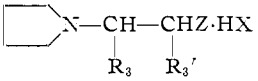
TABLE III

α-PHENYLAMINOETHYL CHLORIDES AND SALTS $R_3CHCH_2N(R_1)(R_2)\cdot R_4X$[a] (Cl)

Compounds	R_1	R_2	R_4X	M.p., °C.[b,c]	Yield,[d] %	Formula	Analyses, %[e] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[g]	CH_3-	CH_3-	HCl	202–203	38	$C_{10}H_{15}Cl_2N$	54.6	54.5	6.9	6.8	6.4	6.3
2	-$(CH_2)_4$-		HCl	183–185	67	$C_{12}H_{17}Cl_2N$					5.7	5.9
3	-$(CH_2)_4$-		HPic.[g]	132–135 d.		$C_{18}H_{19}ClN_4O_7$	49.3	49.1	4.4	4.3	12.8	12.9
4	-$(CH_2)_5$-		HCl	180–182	79	$C_{13}H_{19}Cl_2N$					5.4	5.3
5	-$(CH_2)_2O(CH_2)_2$-		HCl	192–194	49	$C_{12}H_{17}Cl_2NO$	55.0	55.2	6.5	6.6	5.3	5.1
6	-$(CH_2)_2O(CH_2)_2$-		HPic.[g]	131–134 d.		$C_{18}H_{19}ClN_4O_8$	47.5	47.9	4.2	4.4	12.3	12.4

Footnotes have same significance as in Table I. [s] H. Bretschneider, *Monatsh.*, **78**, 82 (1948), reported m.p. 203°.

TABLE IV

DERIVATIVES OF PHENYLETHYLPYRROLIDINES 

Compounds	R_3	R_3'	Z	HX	M.p., °C.,[b,c] or b.p. (mm.)	Formula	Analyses, %[e] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[t]	H	C_6H_5-	H		122–124 (12)	$C_{12}H_{17}N$	82.2	82.3	9.8	9.7	8.0	7.9
2[u]	H	C_6H_5-	H	HCl	168–170[cb]	$C_{12}H_{18}ClN$	68.1	68.2	8.6	8.6	6.9	6.9
3	H	C_6H_5-	H	HPic.[g]	142–144	$C_{18}H_{20}N_4O_7$	53.5	53.1	5.0	5.1	13.9	14.0
4	C_6H_5-	H	H		111 (13)	$C_{12}H_{17}N$	82.2	82.4	9.8	9.8	8.0	8.0
5	C_6H_5-	H	H	HCl	156–157[cb]	$C_{12}H_{18}ClN$	68.1	67.7	8.6	8.7	6.6	6.8
6	C_6H_5-	H	H	HPic.[g]	127–129	$C_{18}H_{20}N_4O_7$	53.5	53.5	5.0	5.2	13.9	14.1
7	H	C_6H_5-	CH_3COO-	HCl	210–212[cb]	$C_{14}H_{20}ClNO_2$	62.3	62.1	7.5	7.3	5.2	4.7
8	H	C_6H_5-	CH_3COO-	HPic.[g]	118–120	$C_{20}H_{22}N_4O_9$	52.0	52.5	4.8	4.9	12.1	11.8
9	C_6H_5-	H	CH_3COO-	HCl	122–124[cg]	$C_{14}H_{20}ClNO_2$	62.3	61.8	7.5	7.6	5.2	5.2
10	C_6H_5-	H	CH_3COO-	HPic.[g]	145–147	$C_{20}H_{22}N_4O_9$	52.0	52.1	4.8	4.9	12.1	12.4
11	H	C_6H_5-	$C_7H_4NO_4$-[v]	HCl	201–203[cv]	$C_{19}H_{21}ClN_2O_4$	60.6	60.1	5.6	5.4	7.4	7.3
12	C_6H_5-	H	$C_7H_4NO_4$-[v]	HCl	222–225	$C_{19}H_{21}ClN_2O_4$	60.6	60.7	5.6	5.8	7.4	7.4

Footnotes have same significance as shown in Table I. [t] B. Wojcik and H. Adkins, THIS JOURNAL, **56**, 2419 (1934), report b.p. 113–115° at 9 mm. [u] *Ibid.*, report m.p. 162–164°. [v] $C_7H_4NO_4$- is *p*-nitrobenzoyloxy-.

1–3 hour reaction time and the diethylamino products (compounds 14, 16, 17, 18) which required a 16–24 hour reaction time for the noted conversions.

In the few syntheses wherein the substituent on the oxide ring was other than phenyl, *i.e.*, *p*-chlorophenyl (compounds 16, 29), *p*-tolyl (compound 17), cyclohexyl (compound 30) and α-naphthyl (compound 18), no critical influence upon yields was noted (see Table I).

Typical syntheses reflecting these procedures are given below.

2-(N-Cyclohexyl-N-methylamino)-1-phenylethanol (Compound 6, Table I).—A mixture of 48 g. (0.4 mole) of styrene oxide and 67.8 g. (0.6 mole) of N-methylcyclohexylamine was heated under reflux for 21 hours. Distillation gave 12 g. of N-methylcyclohexylamine, b.p. 56° (26 mm.), then 73 g. (78%) of product, b.p. 117–120° (0.06 mm.).

2-(N-Benzyl-N-methylamino)-1-phenylethanol (Compound 8, Table I).—N-Benzylmethylamine (72.6 g., 0.6 mole) was heated to 125° and 48 g. (0.4 mole) of styrene oxide added over 1 hour with stirring and maintenance of internal temperature by external cooling. Heating was continued for 2 hours at 125–135° after addition was complete. The reaction mixture distilled to give 56 g. of forerun, followed by 77.1 g. (80%) of product, b.p. 130–132° (0.06 mm.).

2-(N-Methylanilino)-1-phenylethanol (Compound 11, Table I).—To a boiling solution of 48 g. (0.45 mole) of N-methylaniline in 400 ml. of ethanol, 36 g. (0.3 mole) of styrene oxide was added over 30 minutes. Heating under reflux was continued for 3 hours. Upon distillation there was obtained 51 g. (75%) of product, b.p. 146–148° (0.06 mm.).

2-Piperidino-2-phenylethanol (Compound 6, Table II).—The following preparation is typical of the preparation of the compounds of Table II. To a stirred mixture of 120 g. (1.0 mole) of styrene oxide and 200 ml. of hexane, 114 ml. of 48% hydrobromic acid was added over 1 hour. The reaction temperature was maintained below 20° by external cooling. The liquid product, insoluble in both the hexane and aqueous phases, was separated, washed with water, dilute aqueous sodium bisulfite and hexane, and dried (magnesium sulfate). Filtration yielded 140 g. (70%) of crude 2-bromo-2-phenylethanol which was used without further purification. This was dissolved in 1000 ml. of benzene and 120 g. (1.4 moles) of piperidine added with stirring, at a rate sufficient to maintain reflux. After addition was complete, reflux and stirring were continued for 1.5 hours. When cool, 67 g. of piperidine hydrobromide was separated and the benzene filtrate was dried (magnesium sulfate), filtered, the solvent removed and the residue distilled to yield 63.5 g. (44%), b.p. 127–136° (1.5–2.0 mm.).

1-(2-Chloro-2-phenylethyl)-pyrrolidine Hydrochloride (Compound 2, Table III).[20]—A solution of 19.2 g. (0.1 mole) of 2-pyrrolidino-1-phenylethanol (compound 25, Table I) in 50 ml. of ether was added over 30 minutes, with cooling and stirring, to a solution of 14.3 g. (0.12 mole) of thionyl chloride in 50 ml. of ether. After addition was complete, stirring was continued at 20° for 2 hours with continuous evolution of sulfur dioxide and formation of a precipitate of the product which was separated and gave 24 g. (98%), m.p. 161–164°, of crude product.

Using compound 26, the hydrochloride of the amino alcohol as the initial reactant, the product was obtained in 94% yield, m.p. 158–161°.

When the isomeric amino alcohol, 2-pyrrolidino-2-phenylethanol hydrochloride (compound 4, Table II), was the initial reactant the same chloride (compound 2, Table III) was obtained.

A suspension of 15.4 g. (0.07 mole) of compound 4 (Table II) in a solution of 11.7 g. (0.09 mole) of thionyl chloride in 125 ml. of ether was stirred for 6 hours. No evolution of sulfur dioxide was noted, and 18.8 g. of an unstable solid, m.p. about 93°, which smelled strongly of sulfur dioxide (80% calculated as 2-pyrrolidino-2-phenethyl chlorosulfite hydrochloride) was obtained. Recrystallization (acetonitrile) gave 8.0 g., m.p. 181–183°, and a second crop of 3.0 g. (72%), m.p. 175–178°. It did not depress the melting

(20) The procedure was adapted from H. L. Goering, T. D. Nevitt and E. F. Silversmith, THIS JOURNAL, **77**, 4042 (1955).

point of compound 2 (Table III), (m.p. 183–185°), mixed m.p. 181–184°.

In a similar manner, it was shown that 2-(4-morpholino)-1-phenylethanol (compound 35, Table I) and 2-(4-morpholino)-2-phenylethanol hydrochloride afforded the same chloride (compound 5, Table III).

1-Phenethylpyrrolidine (Compound 1, Table IV).—A mixture of 10.0 g. (0.14 mole) of pyrrolidine and 13.0 g. (0.07 mole) of (2-bromoethyl)-benzene in 150 ml. of ethanol was heated under reflux for 3 hours. After removal of the ethanol, the residue was suspended in 50 ml. of water and rendered alkaline with 40% sodium hydroxide, excess potassium carbonate added, and the mixture extracted with three 100-ml. portions of ether. The combined ether extracts were dried (potassium carbonate), filtered, the ether removed and the residue distilled, yielding 6.4 g. (52%).

The hydrochloride (compound 2, Table IV) and the picrate (compound 3, Table IV) were prepared by the usual methods.

1-Phenethylpyrrolidine (from Reductive Dehalogenation of 1-(2-Chloro-2-phenylethyl)-pyrrolidine Hydrochloride.)—A 0.02-mole charge of the hydrochloride hydrogenated over palladium–calcium carbonate[21] absorbed 97% of the theoretical hydrogen within 5 minutes and was processed to yield 3.4 g. (80%) of the hydrochloride of 1-phenethylpyrrolidine, recrystallized (methyl ethyl ketone) m.p. 168–170°.

The picrate was prepared and melted at 140–142° (ethanol), and showed no depression on admixture with compound 3, Table IV.

1-(α-Phenylethyl)-pyrrolidine (Compound 4, Table IV).—Following the procedure shown for compound 1, Table IV, and substituting (1-bromoethyl)-benzene, this base was prepared in 43% yield.

It was converted to the hydrochloride (compound 5, Table IV) and the picrate (compound 6, Table IV). The melting point of the mixed picrates (compounds 3 and 6, Table IV) was 103–107°.

Attempted Bromination of 2-Pyrrolidino-2-phenylethanol (Compound 4, Table II).—Following Pearlman,[11] the compound above was treated with 48% hydrobromic acid. There was recovered 17.0 g. (75%) of product, m.p. 163–164°, which did not depress when mixed with authentic hydrobromide of 2-pyrrolidino-2-phenylethanol (m.p. 162–165°), mixed m.p. 161–164°.

Anal. Calcd. for $C_{12}H_{18}BrNO$: N, 5.2. Found: N, 5.2.

The picrate prepared from the product melted at 103–107° (see compound 5, Table II).

2-Pyrrolidino-1-phenylethyl Acetate Hydrochloride (Compound 7, Table IV).—A solution of 15.4 g. (0.08 mole) of 2-pyrrolidino-1-phenylethanol, in 150 ml. of benzene was treated over 30 minutes, with stirring and cooling, with a solution of 9.4 g. (0.12 mole) of acetyl chloride in 50 ml. of benzene. The reaction mixture was heated under reflux for 2 hours and after standing 20 hours the copious precipitate of product was separated, 22 g. (100%), m.p. 202–204°.

The picrate was prepared (compound 8, Table IV).

Hydrolysis of 2-Pyrrolidino-1-phenylethyl Acetate Hydrochloride.—A suspension of 0.67 g. (0.0025 mole) of 2-pyrrolidino-1-phenylethyl acetate in 5 ml. of ethanol and 0.5 ml. (0.005 mole) of 40% aqueous sodium hydroxide was heated under reflux for 3 hours. The ethanol was removed at diminished pressure, 3 ml. of water was added to the semi-solid residue and the resulting white solid was removed by filtration to give 0.45 g. (98%), m.p. 44–46°. Recrystallization from pentane yielded 0.28 g. (59%), m.p. 57–58°. A mixed melting point with an authentic sample of 2-pyrrolidino-1-phenylethanol was not depressed.

2-Pyrrolidino-2-phenylethyl Acetate Hydrochloride (Compound 9, Table IV).—A mixture of 11.8 g. (0.15 mole) of acetyl chloride, 19.2 g. (0.1 mole) of 2-pyrrolidino-2-phenylethanol in 300 ml. of benzene treated as above, showed a small precipitate after standing 20 hours. Upon storage for 3 hours at 10° and filtration, 4.0 g. (15%) of crystals, m.p. 198–200°, recrystallized (methyl ethyl ketone) m.p. 210–212°, were obtained and proved to be the secondary acetate (compound 7, Table IV), mixed m.p. 210–212°.

The picrate of this product melted at 116–118° (ethanol) and did not depress the melting point of compound 8, Table IV, mixed m.p. 116–119°.

The benzene filtrate was concentrated to a residue, which after trituration with ether, afforded 15.5 g. (58%) of the unrearranged product, m.p. 104–112° (compound 9, Table IV).

The picrate was prepared (compound 10, Table IV). The melting point of the mixed picrates (compounds 8 and 10, Table IV) was depressed, mixed m.p. 102–104°.

Reaction of 2-Pyrrolidino-2-phenylethyl Acetate with Hydrobromic Acid.[13]—2-Pyrrolidino-2-phenylethyl acetate hydrochloride (8.1 g., 0.03 mole) and 35 ml. of 48% hydrobromic acid were heated under reflux for 1 hour. After removal of 2.5 ml. of the hydrobromic acid–water azeotrope, the remainder of the 48% hydrobromic acid was removed at 15 mm., then three 10-ml. portions of ethanol, and two 25-ml. portions of benzene were successively added and removed. The solid residue was washed with ether and separated; 7.2 g. (94%) m.p., 153–157°. Recrystallization from isopropyl alcohol–isopropyl ether yielded 5.1 g., m.p. 163–165°. When mixed with the hydrobromide of 2-pyrrolidino-2-phenylethanol, no depression in melting point was obtained, mixed m.p. 163–165°.

Reaction of 2-Pyrrolidino-1-phenylethyl Acetate with Hydrobromic Acid. (Isolation of 2-Phenylnaphthalene).—In a similar manner[13] a mixture of 9.5 g. (0.035 mole) of 2-pyrrolidino-1-phenylethyl acetate hydrochloride and 40 ml. of 48% hydrobromic acid was heated under reflux for 30 minutes. At the end of this period, 30 ml. of azeotrope were removed by distillation and the residue when cool yielded 1.0 g. of brown solid. Further concentration of the filtrate yielded 5.0 g. of tar. The solid on recrystallization (ethanol) yielded 0.33 g. of product, m.p. 99–102°, which contained no nitrogen or halogen; λ_{max}, 248 mμ (ε 5.05 × 10⁴), λ_{max}, 285–286 mμ (ε 1.5 × 10⁴) (methanol). A mixed melting point with authentic 2-phenylnaphthalene,[14] m.p. 101–102° (reported 101–102°) was not depressed, mixed m.p. 101–102°. The ultraviolet absorption spectrum curve reported for the authentic 2-phenylnaphthalene[22] (absolute ethanol) is virtually identical.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.2; H, 6.8; mol. wt., 206.3. Found: C, 93.0; H, 6.4; mol. wt., 181.

2-Pyrrolidino-1-phenylethyl *p*-Nitrobenzoate Hydrochloride (Compound 11, Table IV).—A solution of 19.2 g. (0.1 mole) of 2-pyrrolidino-1-phenylethanol in 150 ml. of benzene was added to a refluxing solution of 18.6 g. (0.1 mole) of *p*-nitrobenzoyl chloride in 100 ml. of benzene over a period of 30 minutes with stirring. Reflux and stirring were continued for 2 hours, a precipitate forming almost immediately. When cool, 37.6 g. (100%) was separated, m.p. 199–201°.

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(22) L. F. Fieser and E. B. Hershberg, *ibid.*, **60**, 940 (1938).