[CONTRIBUTED FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

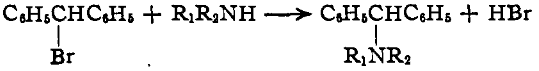
N-Substituted Benzohydrylamines

BY NORMAN H. CROMWELL AND W. E. FITZGIBBON

Numerous investigators[1] have reported the preparation of benzohydrylamines.

Sommelet[1a] found that when such compounds are prepared by condensing benzohydryl bromide with various amines the medium should not be a reactive one such as an alcohol because it is possible for the benzohydryl ether to form instead of the desired benzohydryl amine, especially at elevated temperatures.

N-Methyl-*p*-methoxybenzylamine, N-methylethanolamine and N-benzylethanolamine each was condensed with benzohydryl bromide in benzene solution using essentially the conditions reported previously[1j] to give good yields of the desired N-substituted benzohydryl amines, (I), (II) and (III). The latter two compounds were isolated as their hydrochlorides.



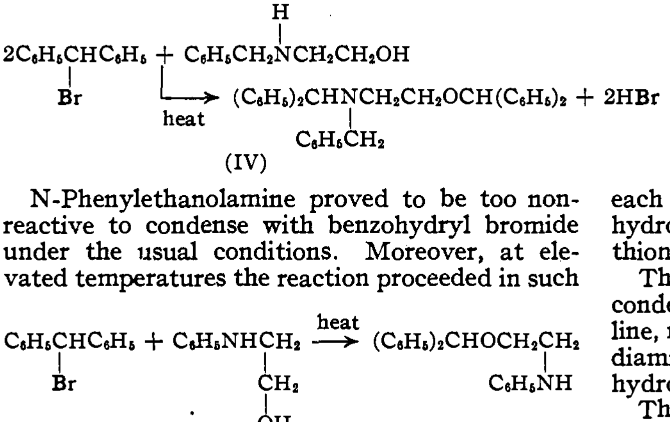
$$\underset{\displaystyle Br}{C_6H_5CHC_6H_5} + R_1R_2NH \longrightarrow \underset{\displaystyle R_1NR_2}{C_6H_5CHC_6H_5} + HBr$$

(I), $R_1 = CH_3$; $R_2 = p\text{-}CH_3OC_6H_4$

(II), $R_1 = CH_3$; $R_2 = CH_2CH_2OH$

(III), $R_1 = C_6H_5CH_2$; $R_2 = CH_2CH_2OH$

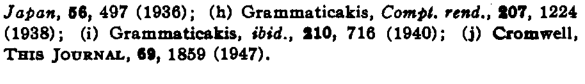
In one experiment N-benzylethanolamine was heated with benzohydryl bromide to the boiling point of the toluene solution. From this reaction mixture only the amino ether (IV) was isolated, resulting from reaction of the bromide with both the amino group and the hydroxyl group of the N-benzylethanolamine.



$$2\underset{\displaystyle Br}{C_6H_5CHC_6H_5} + C_6H_5CH_2\overset{\displaystyle H}{N}CH_2CH_2OH \xrightarrow{heat} \underset{\displaystyle C_6H_5CH_2}{(C_6H_5)_2CHNCH_2CH_2OCH(C_6H_5)_2} + 2HBr$$

(IV)

N-Phenylethanolamine proved to be too nonreactive to condense with benzohydryl bromide under the usual conditions. Moreover, at elevated temperatures the reaction proceeded in such a manner as to give the amino ether (V), resulting from reaction of the benzohydryl bromide with only the hydroxyl group of the N-phenylethanolamine.

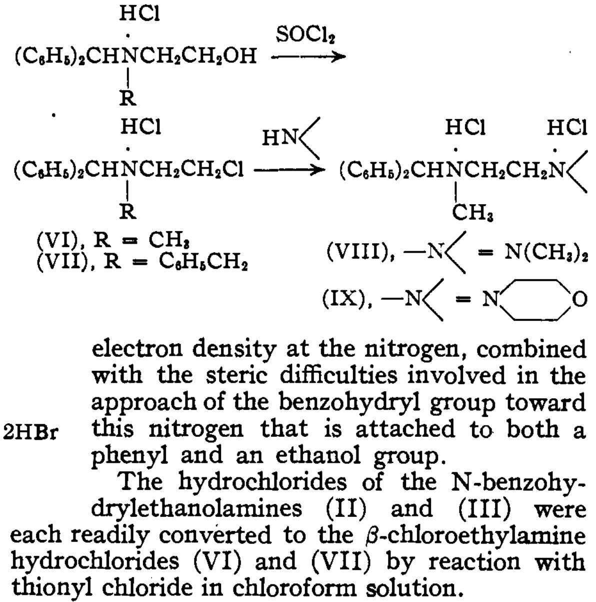


$$\underset{\displaystyle Br}{C_6H_5CHC_6H_5} + \underset{\underset{\displaystyle OH}{\displaystyle CH_2}}{C_6H_5NHCH_2} \xrightarrow{heat} \underset{\displaystyle C_6H_5NH}{(C_6H_5)_2CHOCH_2CH_2}$$

(V)

When this condensation was attempted in aqueous alcohol in the presence of potassium carbonate the benzohydryl bromide was slowly converted to benzohydrol. Using absolute alcohol and anhydrous potassium carbonate at reflux temperature for four hours, the benzohydryl bromide apparently reacted only with the ethyl alcohol to give benzohydryl ethyl ether. When (V) was treated with thionyl chloride only the hydrochloride of (V) resulted, indicating the absence of the alcohol group.

The low reactivity of the amino group in N-phenylethanolamine with the benzohydryl bromide would seem to be the result of the reduced electron density at the nitrogen, combined with the steric difficulties involved in the approach of the benzohydryl group toward this nitrogen that is attached to both a phenyl and an ethanol group.



$$\underset{\displaystyle R}{(C_6H_5)_2CH\overset{\displaystyle HCl}{\overset{\cdot}{N}}CH_2CH_2OH} \xrightarrow{SOCl_2} \underset{\displaystyle R}{(C_6H_5)_2CH\overset{\displaystyle HCl}{\overset{\cdot}{N}}CH_2CH_2Cl} \xrightarrow{HN\langle} \underset{\displaystyle CH_3}{(C_6H_5)_2CH\overset{\displaystyle HCl}{\overset{\cdot}{N}}CH_2CH_2\overset{\displaystyle HCl}{\overset{\cdot}{N}}\langle}$$

(VI), $R = CH_3$; (VII), $R = C_6H_5CH_2$

(VIII), $-N\langle = N(CH_3)_2$

(IX), $-N\langle = N\bigcirc O$

The hydrochlorides of the N-benzohydrylethanolamines (II) and (III) were each readily converted to the β-chloroethylamine hydrochlorides (VI) and (VII) by reaction with thionyl chloride in chloroform solution.

The β-chloroethylamine hydrochloride (VI) was condensed with dimethylamine and with morpholine, respectively, to give the substituted ethylenediamines (VIII) and (IX), isolated as their dihydrochlorides.

The various N-substituted benzohydrylamines resulting from this investigation have been submitted for pharmacological screen testing, the results of which will be reported elsewhere.

Experimental

Benzohydryl Bromide.—The benzohydryl bromide used in these condensations was prepared from benzohydrol in 90% yields by the method given by Courtot,[2] and purified

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[1] For examples see: (a) Sommelet, *Compt. rend.*, **175**, 1149 (1922); (b) Gilman and Hoyle, THIS JOURNAL, **44**, 2621 (1922); (c) Valette, *Bull. soc. chim.*, (4) **47**, 289 (1930); (d) Bonnard and Meyer-Oulif, *ibid.*, (4) **49**, 1303 (1931); (e) Hughes and Ingold, *J. Chem. Soc.*, 69 (1933); (f) Maxim and Mavrodineanu, *Bull. soc. chim.*, (5) **3**, 1084 (1936); (g) Ogata and Shinnobu, *J. Pharm. Soc. Japan*, **56**, 497 (1936); (h) Grammaticakis, *Compt. rend.*, **207**, 1224 (1938); (i) Grammaticakis, *ibid.*, **210**, 716 (1940); (j) Cromwell, THIS JOURNAL, **69**, 1859 (1947).

[2] Courtot, *Ann. chim.*, [9] **5**, 80 (1916).

TABLE I
PHYSICAL AND ANALYTICAL DATA

Benzohydrylamines	No.	M. p., °C.	Yield, %	Formula	Chlorine, %[a] Calcd.	Chlorine, %[a] Found
N-Methyl-N-(*p*-methoxybenzyl)-benzohydrylamine	(I)[b]	62	83	$C_{22}H_{23}NO$		
N-Benzohydrylethanolamine hydrochlorides						
N-Methyl	(II)	159	62	$C_{16}H_{20}ClNO$	12.76	12.72
N-Benzyl	(III)	179	75	$C_{22}H_{24}ClNO$	10.02	9.94
β-Aminoethylbenzohydryl ethers						
N-Benzohydryl-N-benzyl[c]	(IV)	109	10	$C_{35}H_{33}NO$		
N-Phenyl[d]	(V)	100	17	$C_{21}H_{21}NO$		
Hydrochloride		210	90	$C_{21}H_{22}ClNO$	10.43	10.40
N-Benzohydryl-β-chloroethylamine hydrochlorides						
N-Methyl	(VI)	191	90	$C_{16}H_{19}Cl_2N$	23.93	23.93
N-Benzyl	(VII)	171	63	$C_{22}H_{23}Cl_2N$	19.05	19.01
N-Benzohydryl-N-methylethylamine dihydrochlorides						
β-Dimethylamino	(VIII)	227	67	$C_{18}H_{26}Cl_2N_2$	20.78	20.47
β-Morpholino	(IX)	236	70	$C_{20}H_{28}Cl_2N_2O$	18.50	18.46

[a] We are indebted to Dr. H. Armin Pagel of the University of Nebraska for advice in carrying out the total chlorine analyses of the β-chloroethyl amine hydrochlorides by the hydrogen jet method, reported by Winter, *Ind. Eng. Chem., Anal. Ed.*, 15, 571 (1943). [b] Calcd.: C, 83.25; H, 7.30. Found: C, 82.93; H, 7.49. [c] Calcd.: C, 86.91; H, 6.87; N, 2.90. Found: C, 86.86; H, 7.01; N, 2.99. [d] Calcd.: C, 83.32; H, 6.98. Found: C, 83.53; H, 6.84.

to a colorless crystalline product by vacuum distillation, b. p. 176–180°(17 mm.).

N-Methyl-N-(*p*-methoxylbenzyl)-benzohydrylamine (I).—This compound was prepared by the method given previously[1j] for the preparation of N-benzohydrylmorpholine, by condensing benzohydryl bromide with N-methyl-*p*-methoxybenzylamine[3] (see Table I).

N-Benzohydrylethanolamine Hydrochlorides (II) and (III).—Pure benzohydryl bromide (24.7 g., 0.10 mole) was mixed with 14.8 g. (0.21 mole) of N-methylethanolamine[4] and with 31.7 g. (0.21 mole) of N-benzylethanolamine,[5] respectively, in 30 ml. of dry benzene. After standing for twelve hours at room temperature the solutions were diluted with 300 ml. of dry ether to complete the precipitation of the by-product hydrobromides of the starting ethanol amines. The ether–benzene solutions of the products were decanted from the oily by-product and washed with ten 10-ml. portions of water and dried for twelve hours over anhydrous calcium sulfate.

The hydrochlorides (II) and (III) were precipitated by passing dry hydrogen chloride gas into the solutions. These crude products were recrystallized twice from mixtures of absolute alcohol and dry ether to give colorless granular products, (II) and (III).

N-Benzohydryl-N-benzyl-β-aminoethyl Benzohydryl Ether, (IV).—Pure benzohydryl bromide (16.05 g., 0.065 mole) was mixed with 20.8 g. (0.137 mole) of N-benzylethanolamine in 16 ml. of toluene and refluxed for one hour. After standing at room temperature for twelve hours 100 ml. of dry ether was added to complete the precipitation of the by-product hydrobromide. The ether–toluene layer was decanted from the oily hydrobromide and washed with water. Evaporation of the solvent left an oil which was dissolved in alcohol. Addition of water to this solution and cooling caused an oily solid to form (3.6 g.). Recrystallization of this product first from boiling absolute alcohol and then from boiling petroleum ether (b. p. 60–70°) gave a colorless granular product (IV).

N-Phenyl-β-aminoethyl Benzohydryl Ether, (V).—When 10 g. of benzohydryl bromide was mixed with 11.1 g. (2.1 equiv.) of N-phenylethanolamine in 25 ml. of dry benzene and refluxed for two hours no precipitate of an amine hydrobromide appeared. The benzene was removed by distillation and the residual dark oil heated on an oil-bath for two hours at 130–140°. Dry ether and benzene were added to the cooled, dark mass to cause precipitation of a grey powder which was removed by filtration (10.8 g. as compared with the expected theoretical weight of 8.9 g. of N-phenylethanolamine hydrobromide). The filtrate was washed with water, dried and evaporated to leave a brown oil. Crystallization from benzene and petroleum ether followed by recrystallization from alcohol and water gave a colorless, flaky product (V).

When a sample of (V) was treated with thionyl chloride according to the procedure given below for the preparation of β-chloroethylamines only the hydrochloride of (V) resulted, identical with a sample prepared by treating (V) with dry hydrogen chloride gas in dry ether. When a sample of (V) was treated with a solution of nitrous acid in an alcohol–water mixture a pale yellow oil precipitated which could not be crystallized, but which gave the Liebermann test[6] for a nitrosamine.

N-Benzohydryl-β-chloroethylamine Hydrochlorides (VI) and (VII).—Cold solutions of the N-benzohydrylethanolamines (II) and (III)(0.10 mole) in 100 ml. of chloroform were treated dropwise over a period of one-half hour with an ice-cold solution of 0.20 mole of thionyl chloride in 15 ml. of chloroform. The solutions were allowed to come to room temperature and then refluxed for two hours. The solvent and excess thionyl chloride were removed under reduced pressure on a steam-bath. The resulting white powders were recrystallized three times from absolute alcohol and ether to give colorless granular products (VI) and (VII).

N-Benzohydryl-N-methyl-β-dimethylaminoethylamine Dihydrochloride, (VIII).—Anhydrous dimethylamine (5.41 g., 0.12 mole) was added to a solution of 8.9 g. (0.030 mole) of (VI) in 100 ml. of absolute alcohol at room temperature and allowed to stand in a tightly stoppered flask for ninety-six hours. The solution was refluxed for an hour and the solvent removed by distillation. The solid residue was extracted with four 20-ml. portions of ether but this extract left no residue on evaporation.

The ether-insoluble residue was mixed with 10 ml. of 6 *N* sodium hydroxide and the resulting oil extracted with

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[3] Cromwell and Hoeksema, THIS JOURNAL, **67**, 1658 (1945).

[4] Supplied by the Carbide and Carbon Chemicals Corporation, New York, N. Y.

[5] N-Benzylethanolamine for this experiment was prepared by condensing benzaldehyde with ethanolamine in absolute alcohol solution, followed by reduction of the crude imine with hydrogen under 40 lb. pressure in the presence of platinum oxide catalyst; b. p. 153° (14.5 mm.); yield, 69%. See Schotte, Priewe and Roescheisen, *Z. physiol. Chem.*, **174**, 119 (1928); Rumpf and Kwass, *Bull. soc. chim.*, **10**, 342 (1943); West, *J. Soc. Chem. Ind.*, **61**, 158 (1942).

[6] S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1946, p. 120.

ether. The ether extract was washed with four 10-ml. portions of 6 *N* sodium hydroxide. The ether solution was dried and evaporated to leave a yellow oil which was dissolved in 15 ml. of absolute alcohol and treated with dry hydrogen chloride gas. Addition of dry ether precipitated a colorless solid which was recrystallized from absolute alcohol and dry ether to give (VIII).

N-Benzohydryl-N-methyl-β-morpholinoethylamine Dihydrochloride (IX).—A solution of 7.0 g. (0.08 mole) of morpholine and 7.41 g. (0.025 mole) of (VI) in 25 ml. of 70% ethyl alcohol was placed in a closed flask and allowed to stand at room temperature for twenty-four hours. The solvent was removed by distillation from a steam-bath under reduced pressure. The residue was extracted with dry ether and the ether solution washed with water, dried and evaporated to leave a colorless oil that could not be crystallized from petroleum ether or alcohol–water mixtures. The oily product was dissolved in 30 ml. of absolute alcohol and dry hydrogen chloride gas added. After addition of 200 ml. of dry ether a colorless crystalline precipitate formed which was recrystallized from absolute alcohol and dry ether to give (IX).

Summary

1. The synthesis of certain N-benzohydrylethanolamines by reaction of benzohydryl bromide with ethanolamines of the type $RNHCH_2CH_2OH$ has been studied. When R was methyl or benzyl the desired N-benzohydrylethanolamines were obtained, but when R was phenyl only ether formation resulted.

2. The N-benzohydrylethanolamines were converted to N-benzohydryl-β-chloroethylamines, one of which was condensed with dimethylamine and morpholine, respectively, to give substituted ethylenediamines.

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[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Isomeric Unsaturated Esters. II. The Dehydration of Ethyl 3-Hydroxy-2-ethyl-3-methylbutanoate

BY RALPH C. HUSTON, GORDON L. GOERNER AND HANS H. GYÖRGY

In a previous communication[1] the dehydration of ethyl 3-hydroxy-2,3-dimethylbutanoate was shown to yield a mixture of α,β and β,γ unsaturated esters which were readily separated because of their large difference in boiling points. The β,γ unsaturated ester, contrary to the report in the literature, was found to possess the lower boiling point. It appeared that other unsaturated esters might be recorded erroneously.

Blaise and Maire[2] dehydrated ethyl 3-hydroxy-2-ethyl-3-methylbutanoate (I) and obtained an unsaturated ester boiling at 167°. To this they assigned formula III. They also obtained a small quantity of an ester boiling at 175°.

$$(CH_3)_2C(OH)CH(C_2H_5)COOC_2H_5 \longrightarrow$$

I

$$CH_2{=}C(CH_3)CH(C_2H_5)COOC_2H_5,\ \text{and}$$

II

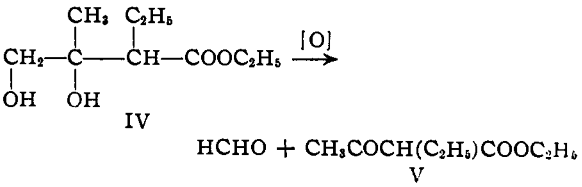
$$(CH_3)_2C{=}C(C_2H_5)COOC_2H_5$$

III

This was assumed to be an isomer of the low boiling ester. Hydrolysis of the ester boiling at 167° yielded an acid distilling at 100° (10 mm.). If esters II and III are analogous to those obtained by Huston and Goerner,[1] ester II should boil at 167° and ester III at the higher temperature. Further evidence that Blaise and Maire had probably assigned the incorrect formula to their low boiling ester was found in the fact that Crossley and LeSueur[3] report a boiling point of 175–180° (748 mm.) for a mixture of ester III and ethyl 2-(1-methylethyl)-2-butenoate obtained by dehydrobromination of ethyl 2-bromo-2-ethyl-3-methylbutanoate by diethylaniline.

Ester I was prepared from propanone and ethyl 2-bromobutanoate by the Reformatsky reaction. It proved to be more stable than expected. An attempt to dehydrate it with dry hydrogen chloride[4] was unsuccessful. Phosphorus pentoxide[2,5] in benzene gave the unsaturated esters in good yield. Esters II and III could be separated readily in approximately equal quantities by fractionation under diminished pressure.

The proof of structure consisted of hydroxylating the esters to the glycols[6] IV and VI and splitting these into aldehydes and ketones by means



$$\underset{\text{OH}}{CH_2}-\overset{CH_3}{\underset{\text{OH}}{C}}-\overset{C_2H_5}{CH}-COOC_2H_5 \xrightarrow{[O]}$$

IV

$$HCHO + CH_3COCH(C_2H_5)COOC_2H_5$$

V

of "ceric perchlorate"[1,7] or by thermal decomposition. The low boiling ester gave glycol IV. This was split into methanal (which is oxidized to carbon dioxide and water) and ethyl 3-keto-2-ethylbutanoate (V). The solution containing compound V gave 2-pentanone upon alkaline hydrolysis. The high boiling ester gave glycol VI. On distillation this decomposed into propanone and 2-ketobutanoic acid.

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[1] Huston and Goerner, THIS JOURNAL, **68**, 2504 (1946).

[2] Blaise and Maire, *Ann. chim.*, [8] **15**, 573 (1908).

[3] Crossley and LeSueur, *J. Chem. Soc.*, **77**, 95 (1900).

[4] Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

[5] Kon and Nargund, *J. Chem. Soc.*, 2461 (1932).

[6] Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936).

[7] Smith and Duke, *Ind. Eng. Chem.*, *Anal. Ed.*, **13**, 558 (1941); **15**, 120 (1943).