chloroacetal was added at a fairly rapid rate to the stirred mixture. Refluxing was continued eight hours longer. The reaction mixture was then filtered and the insoluble material washed with ether. After removal of the solvents from the filtrate, the liquid which remained was distilled *in vacuo*. The orange-yellow oil, distilling at 151–154° (20 mm.), weighed 261.4 g. (58%). On redistillation the fraction distilling at 147° (18 mm.) was collected.

Anal. Calcd. for $C_{10}H_{15}NO_2$: N, 7.73. Found: N, 7.75.

The hydrochloride precipitated as an oil when an ether solution of the base was treated with ethereal hydrogen chloride. The oil crystallized immediately on rubbing and was recrystallized from methanol–ether, m.p. 111–112°.

Anal. Calcd. for $C_{10}H_{15}NO_2 \cdot HCl$: N, 6.44. Found: N, 6.56.

Dimethyl N-(2-Pyridyl)-aminoacetal.—Prepared by the same procedure and using the same molar amounts, there was recovered 106 g. of unreacted 2-aminopyridine. The product, a light yellow liquid, distilled at 168–171° (28 mm.) and weighed 194.2 g. (78%, correcting for the 2-aminopyridine recovered). On redistillation, the fraction distilling at 146–147° (14 mm.) was collected.

Anal. Calcd. for $C_9H_{14}N_2O_2$: N, 15.38. Found: N, 15.33.

The picrate melted at 133–134° after recrystallization from methanol.

Anal. Calcd. for $C_9H_{14}N_2O_2 \cdot C_6H_3N_3O_7$: N, 16.62. Found: N, 16.41.

Dimethyl N-Benzyl-N-(2-pyridyl)-aminoacetal.—Using the same procedure this compound, b.p. 113.5° (0.03 mm.), was prepared in 93% yield (81.7 g.) from 54.6 g. (0.3 mole) of dimethyl N-(2-pyridyl)-aminoacetal, 11.4 g. of lithium amide and 75.9 g. (0.6 mole) of benzyl chloride in 150 ml. of toluene.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: N, 10.29. Found: N, 10.26.

The hydrochloride precipitated as an oil when prepared in ether. The oil crystallized in acetone and was recrystallized from acetone–isopropyl alcohol, m.p. 215.5–216.5°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2 \cdot HCl$: N, 9.07. Found: N, 9.06.

Dimethyl N-(3-Phenylpropyl)-aminoacetal.—The method of Kaye and Minsky[1] was followed. From 135.2 g. (1.0 mole) of 3-phenylpropylamine and 62.3 g. (0.5 mole) of dimethyl chloroacetal, heated at a bath temperature of 155° for 15.5 hours, there was obtained 111.7 g. (43%) of product, b.p. 149–153° (12 mm.).

Anal. Calcd. for $C_{13}H_{21}NO_2$: N, 6.27. Found: N, 6.19.

The hydrochloride melted at 109–111° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{13}H_{21}NO_2 \cdot HCl$: Cl, 13.65. Found: Cl, 13.75.

Acknowledgment.—The author wishes to thank Endo Products, Inc., and Research Corporation, each of which supported this project in part.

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BROOKLYN 10, N. Y.

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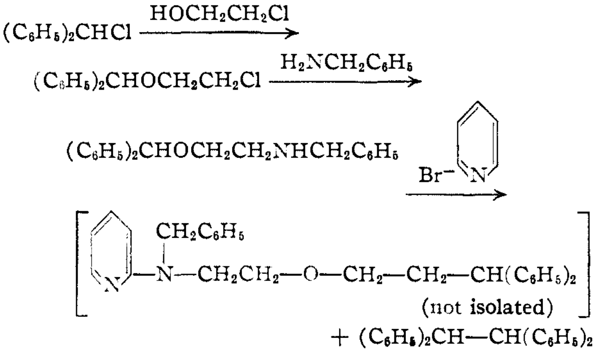
Benzohydryl Ethers of 2-Benzylaminoethanol and 2-(2-Pyridyl)-aminoethanol

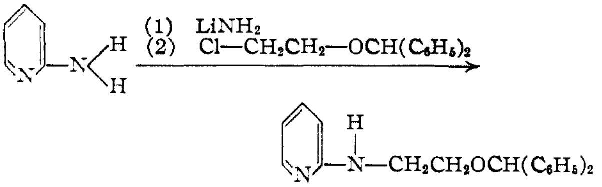
BY IRVING ALLAN KAYE

Since attempts to prepare the benzohydryl ethers of the N-pyridylalkanolamines described in a previous publication,[1] from the aminoalcohols and benzohydryl chloride in the presence of various condensing agents, were unsuccessful, other methods of preparation were investigated. It appeared possible to prepare these compounds by heating a mixture of 2-bromopyridine and an N-substituted benzohydryl ether of ethanolamine in a manner analogous to that used in the preparation of the N-pyridylalkanolamines.[1] A model reaction, wherein equivalent amounts of 2-benzylaminoethyl benzohydryl ether and 2-bromopyridine were refluxed in *n*-butanol in the presence of anhydrous potassium carbonate, gave no evidence of reaction (no carbon dioxide was evolved). In the absence of solvent and at a bath temperature of 150–160°, only a small amount of tetraphenylethane could be isolated. This is reminiscent of the recent work of Hall and Burckhalter,[2] who obtained the hydrocarbon in a reaction between 2-(benzohydrylamino)-pyridine and 2-dimethylaminoethyl chloride, and of Fox and Wenner[3] who also isolated it in an attempt to prepare 2-(benzohydrylaminomethyl)-imidazoline by treating N-benzohydryl glycine ethyl ester with ethylene diamine.

The 2-benzylaminoethyl benzohydryl ether was prepared by heating benzylamine with 2-chloroethyl benzohydryl ether. The latter was prepared in high yield from benzophenone. Without isolating intermediates, the ketone was reduced to benzohydrol which was converted to benzohydryl chloride with hydrogen chloride. Refluxing the halide in an excess of ethylene chlorohydrin gave the benzohydryl ether.



Since this approach did not appear to be promising, an attempt was made to prepare 2-(2-pyridyl)-aminoethyl benzohydryl ether by treating 2-aminopyridine with 2-chloroethyl benzhydryl ether in the presence of lithium amide. This method did yield the expected compound but in such poor yield that no attempt was made to prepare other homologs, as anticipated, by the alkylation of the secondary amine.



In tests conducted under the supervision of Dr. C. Chester Stock at the Sloan-Kettering Institute for Cancer Research, 2-benzylaminoethyl benzohydryl ether was found to be ineffective in retarding the growth of sarcoma 180.

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[1] N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949).

[2] L. A. R. Hall and J. H. Burckhalter, THIS JOURNAL, **73**, 473 (1951).

[3] H. H. Fox and W. Wenner, *J. Org. Chem.*, **16**, 225 (1951).

Experimental[4]

2-Chloroethyl Benzohydryl Ether.—The crude, moist benzohydrol, obtained by following the procedure in "Organic Synthesis"[5] but using four times the amounts described therein, was dissolved in two liters of warm benzene. After separating the water layer, the solution was filtered, and dried by distillation until its volume was reduced to *ca.* one liter. Keeping the temperature of the solution at about 20°, it was saturated with dry hydrogen chloride. The aqueous layer was separated and the benzene removed by distillation from a steam-bath. To the residue, still containing a little benzene, was added 2116 g. (26.9 moles) of ethylene chlorohydrin. The solution was refluxed for six hours, using a reflux condenser with a take-off tube to remove the benzene which remained. A copious evolution of hydrogen chloride occurred during this period of reflux. About 800–900 ml. of ethylene chlorohydrin was then removed by distillation at atmospheric pressure. The remaining liquid was distilled *in vacuo*. The colorless product was collected at 184–189° (12 mm.) and weighed 941 g. This represents an over-all yield of 87%, based on the weight of benzophenone used in the initial reduction reaction.

Anal. Calcd. for $C_{15}H_{15}ClO$: Cl, 14.38. Found: Cl, 14.31.

2-Benzylaminoethyl Benzohydryl Ether.—A mixture of 50.7 g. (0.206 mole) of 2-chloroethyl benzohydryl ether and 220.4 g. (2.06 moles) of benzylamine was heated at a bath temperature of 160–165° for 117 hours. The cooled reaction mixture was suspended in a liter of ether and the benzylamine hydrochloride removed by filtration. After washing with ether and air-drying, the salt weighed 27.3 g., corresponding to a 92.5% conversion. The ether and excess benzylamine were removed from the filtrate by distillation and the residual liquid distilled *in vacuo*. The viscous yellow oil weighed 60.0 g. (92%), b.p. 169–172°.

Anal. Calcd. for $C_{22}H_{23}NO$: N, 4.41. Found: N, 4.33, 4.31.

The ratio of the reactants, the length of the heating period and the size of the run seem to be critical factors affecting the yield. Results of experiments where these were varied are summarized in Table I.

TABLE I

FACTORS AFFECTING THE YIELD OF 2-BENZYLAMINOETHYL BENZOHYDRYL ETHER

Benzylamine, moles	2-Chloroethyl ether, mole	Heating period, hours	Bath temp., °C.	Yield, %
0.2	0.1	25	105	48
0.800	.100	23	177–182	74
1.00	.100	68	160–165	87
2.06	.206	117	160–165	92
3.73	.3730	216	160–165	68
10.0	1.00	51	160–165	66

After this work had been completed, a publication appeared describing the preparation of this compound in 25% yield by the catalytic hydrogenation of a mixture of benzaldehyde and 2-aminoethyl benzohydryl ether.[6]

The hydrochloride was prepared by adding an ethereal hydrogen chloride solution to an ether solution of the base. On standing overnight at room temperature the oily base turned to a pink solid which melted at 146.5–147.5° (cor.) after recrystallization from acetone.

Anal. Calcd. for $C_{22}H_{23}NO \cdot HCl$: Cl, 10.02. Found: Cl, 9.87.

Reaction between 2-Bromopyridine and 2-Benzylaminoethyl Benzohydryl Ether.—A mixture of 15.8 g. (0.1 mole) of 2-bromopyridine and 63.5 g. (0.2 mole) of 2-benzylaminoethyl benzohydryl ether was heated at a bath temperature of 150–160° for 134 hours. The reaction mixture, while still warm, was dissolved in 100 ml. of chloroform. The solution was mixed well with 10 ml. of saturated aqueous potassium carbonate solution. Solid anhydrous potassium carbonate was added and, after standing overnight, the mixture was filtered. The filtrate was freed of chloroform and excess 2-benzylaminoethyl benzohydryl ether by distillation. Further distillation *in vacuo* yielded a small fraction distilling at 205–220° (1 mm.) which deposited a solid on standing. The mixture, after the addition of cold methanol, was filtered and the precipitate washed with the cold solvent. The product, melting at 196–202°, weighed 3.1 g. Recrystallized from ethanol, the white needles melted at 211–212°. Analysis revealed no nitrogen. Fox and Wenner[3] reported that their 1,1,2,2-tetraphenylethane melted at 211–212°. Mixed with an authentic sample,[3] the product showed no depression in melting point.

2-(2-Pyridyl)-aminoethyl Benzohydryl Ether.—A mixture of 14.1 g. (0.15 mole) of 2-aminopyridine, 3.5 g. of lithium amide and 100 ml. of dry toluene was refluxed for five hours. After adding a solution of 37 g. (0.15 mole) of 2-chloroethyl benzohydryl ether in 50 ml. of toluene, refluxing was continued 19 hours longer. The hot suspension was filtered and the insoluble material washed with ether. The solvents were removed from the filtrate *in vacuo* and the semisolid residue vacuum distilled. Five and one-half grams of 2-aminopyridine was recovered (39% of the starting compound). A dark brown viscous oil, weighing 8.8 g. (32%, corrected for the amount of 2-aminopyridine recovered), was collected at 167–188° (0.10–0.15 mm.). The large amount of tarry residue in the still-pot was not investigated. Redistillation yielded 5.8 g. (21% corrected) of a viscous yellow-orange oil, b.p. 152° (0.06 mm.).

Anal. Calcd. for $C_{20}H_{20}N_2O$: N, 9.20. Found: N, 9.07.

The picrate, prepared in ether and recrystallized from ethanol, melted at 141.5–142.5°.

Anal. Calcd. for $C_{20}H_{20}N_2O \cdot C_6H_3N_3O_7$: N, 16.53· Found: N, 16.42.

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[4] All melting points are corrected; boiling points are not.

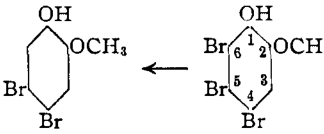
[5] H. Gilman and A. H. Blatt, "Organic Syntheses," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 90.

[6] L. H. Sutherland, S. L. Eberlin, J. D. Forsythe, I. F. Halverstadt, J. R. Vaughan, Jr., and R. C. Clapp, *J. Org. Chem.*, **14**, 235 (1949).

Bromination of Guaiacol and Debromination of Tribromoguaiacol

BY MORITZ KOHN AND SELMA KREISKY

It has been shown by Robinson and his coworkers[1] and by Raiford and Silker,[2] that Cousin's[3] dibromoguaiacol is the 4,5-dibromoisomer (I).



I II

This has now received further support by the reduction of 4,5,6-tribromoguaiacol[4] (II) with zinc dust and acetic acid. According to our earlier investigations on brominated phenols[5] it was to be expected that the bromine ortho to the hydroxyl group would be substituted by hydrogen. This reaction does take place and 4,5-dibromoguaiacol (I) results.

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[1] Hindmarsh, Knight and Robinson, *J. Chem. Soc.*, **111**, 942 (1917); Jones and Robinson, *ibid.*, 111, 913 (1917).

[2] Raiford and Silker, *J. Org. Chem.*, **2**, 346 (1937–1938).

[3] Cousin, *Ann. chim. phys.*, [7] **29**, 63 (1903).

[4] The structure II has been established by Zangirolami, *Gazz. chim. ital.*, **62**, 570 (1932).

[5] M. Kohn and J. Sussmann, *Monatsh.*, **48**, 193 (1927); M. Kohn and J. Pfeifer, *ibid.*, **48**, 212 (1927); M. Kohn and L. Steiner, *ibid.*, **58**, 92 (1931).