tracted with two 100-ml. portions of ether. After the evaporation of the solvent from the combined organic layer, the residue (crude diethylthiophosphinic acid) was taken up in 100 ml. of water and was cautiously treated with 30 ml. of 30% hydrogen peroxide. The precipitated sulfur was filtered off and the filtrate was stirred with an excess of freshly precipitated silver oxide, according to Collie's directions.[4]

The filtrate was concentrated to approximately 35 ml. and was mixed with two volumes of 95% ethanol, resulting in precipitation of the previously described silver diethylphosphinate; yield 28.5 g. (41.5%). The silver salt was converted to the free acid by treatment with 1:1 hydrochloric acid, filtration, evaporation to dryness and azeotropic drying with toluene. The free acid was an oil, whose freezing point was in the vicinity of −20°.

Treatment of the diethylphosphinic acid, in benzene, with the theoretical amount of phosphorus pentachloride (see the dimethyl analog, above) gave 47.5% (based on the silver salt) of diethylphosphinyl chloride, a colorless liquid, b.p. 102–104° at 15 mm. Plets[5] gives b.p. 79–81° at 15 mm., which appears to be much too low.

Treatment of diethylphosphinyl chloride (8.5 g.) with sodium ethoxide, prepared from 1.3 g. of sodium and 40 ml. of absolute ethanol, in benzene, as described above, gave 6 g. (67%) of ethyl diethylphosphinate, a colorless liquid, b.p. 93–95° at 14 mm., d^{25}_4 1.0022, $n^{25}D$ 1.4375.

Anal. Calcd. for $Et_2P(O)OEt$: P, 20.63; *MR*, 39.6. Found: P, 20.49; *MR*, 39.3.

Heating 5 g. of diethylphosphinyl chloride with 5.35 g. of ethyl diethylphosphinate for 45 minutes to 145–160° gave 5.6 g. (69%) of diethylphosphinic anhydride, a viscous liquid, b.p. 186–188° at 14 mm., d^{23}_4 1.1053, $n^{23}D$ 1.4720; found, *MR* 57.2; calcd. *MR*, 57.0. The product hydrolyzed rapidly in water and titration of such a solution gave the molecular weight of 227.0, against the theoretical value of 226.2. Calcd. for $Et_2P(O)OP(O)Et_2$: P, 27.31. Found: P, 27.23. Like the dimethyl analog, the anhydride reacts rapidly with alcohols at moderately elevated temperatures.

Attempted Preparation of Dimethyl-di-*n*-butylphosphinic Anhydride.—When 13 g. of ethyl di-*n*-butylphosphinate and 7.1 g. of dimethylphosphinyl chloride were heated for 45 minutes to 145–160°, normal evolution of ethyl chloride took place. Application of reduced pressure to the liquid residuum led to rapid crystallization of the material and on distillation two fractions were obtained, which corresponded to the two symmetric anhydrides: dimethylphosphinic anhydride and di-*n*-butylphosphinic anhydride, respectively. The sublimation of the former made a sharp separation of the fractions impossible, but no evidence for the unsymmetric anhydride could be detected in the boiling points or the physical constants of the products. Apparently, the unsymmetric anhydride disproportionates into the two symmetric forms very readily.

(4) Collie, *J. Chem. Soc.*, **127**, 964 (1925).

(5) Plets, Dissertation, Kazan, 1938.

THE ROSS CHEMICAL LABORATORY
ALABAMA POLYTECHNIC INSTITUTE
AUBURN, ALABAMA

RECEIVED JULY 25, 1951

Dimethyl N-(Phenyl-, 2-Pyridyl-, and 3-Phenylpropyl)-aminoacetals

BY IRVING ALLAN KAYE

The method previously described[1] could not be used for the preparation of compounds of structure, $R'RNCH_2CH(OCH_3)_2$ (I), where R is phenyl or 2-pyridyl and R′ is hydrogen.

Though a vigorous reaction developed when dimethyl chloroacetal was heated to reflux with two equivalents of aniline in the absence of a solvent, only a tarry mass could be isolated. When repeated in toluene, or in cumene in the presence of potassium carbonate,[2] there was no evidence that any reaction had occurred.

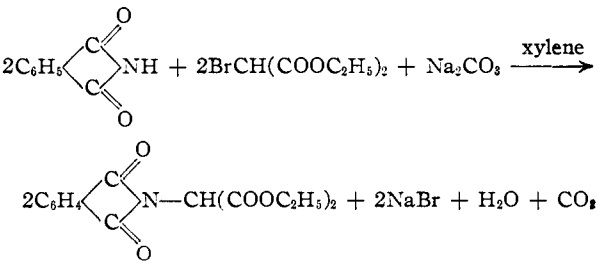
Diethyl N-phenylaminoacetal has been prepared[3] in good yield from aniline and diethyl chloroacetal in the presence of sodium amide. Using a similar procedure, but substituting lithium amide for sodium amide and toluene for ether, both dimethyl N-phenylaminoacetal and dimethyl N-(2-pyridyl)-aminoacetal, were readily prepared.

Dimethyl N-benzyl-N-(2-pyridyl)-aminoacetal was synthesized by the aralkylation of dimethyl N-(2-pyridyl)-aminoacetal with benzyl chloride, using lithium amide as a condensing agent. An attempt to prepare the tertiary amine from 2-bromopyridine and dimethyl N-benzylaminoacetal in pyridine gave only tars; in toluene, in the presence of potassium carbonate,[2] no reaction was observed. From a reaction mixture of 2-benzylaminopyridine, dimethyl chloroacetal, lithium amide and toluene, there were obtained only unreacted starting materials.

Molar equivalents of dimethyl chloroacetal and 3-phenylpropylamine[4] in tri-*n*-propylamine gave only a 25% yield of dimethyl-N-(3-phenylpropyl)-aminoacetal; in the absence of solvent and using two moles of amine to one of acetal there was obtained a 43% yield. The hydrochloride of the product shows powerful, though transient, topical anesthetic properties. The other three acetals (I; R′ is H and R is phenyl or 2-pyridyl; R′ is 2-pyridyl and R is benzyl) were inactive in retarding the growth of sarcoma 180.[5]

Experimental[6]

Dimethyl N-Phenylaminoacetal.—To a stirred suspension of 64 g. of lithium amide in one liter of dry toluene there was added slowly 232.5 g. (2.5 moles) of aniline. When addition was complete, the reaction mixture was refluxed for 3.5 hours. During this time, the suspension changed into a purple-colored solution which soon deposited a tan solid with the simultaneous evolution of ammonia. Without interrupting the refluxing, 311.3 g. (2.5 moles) of dimethyl



(1) I. A. Kaye and I. Minsky, THIS JOURNAL, **71**, 2272 (1949).

(2) A moisture trap was included in the set-up and the progress of the reaction was conveniently observed by noting the amount of water collected in this trap. When carbonates are used in reactions where acids are formed as by-products, yields are usually improved somewhat when the water which has formed in the reaction is removed from the reaction mixture in this fashion. For example, the yield of ethyl phthalimidomalonate, prepared by the following method, was 86% by this technique, while E. Booth, V. C. E. Burnop and W. E. Jones, *J. Chem. Soc.*, 666 (1944), reported an 80% yield using the same procedure without removing the water.

(3) A. Wohl and M. Lange, *Ber.*, **40**, 4727 (1907). The same compound and diethyl N-(2-pyridyl)-aminoacetal were described by R. G. Jones, E. C. Kornfeld, K. C. McLaughlin and R. C. Anderson, THIS JOURNAL, **71**, 4000 (1949), but there is some ambiguity as to which method of preparation they employed.

(4) A sample generously donated by Sharples Chemicals, Inc.

(5) These compounds were tested at The Sloan-Kettering Institute for Cancer Research, under the supervision of Dr. C. Chester Stock.

(6) All melting points are corrected; boiling points are not.

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.

DEPARTMENT OF CHEMISTRY
BROOKLYN COLLEGE
BROOKLYN 10, N. Y. RECEIVED MAY 14, 1951

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.

$$(C_6H_5)_2CHCl \xrightarrow{HOCH_2CH_2Cl} (C_6H_5)_2CHOCH_2CH_2Cl \xrightarrow{H_2NCH_2C_6H_5} (C_6H_5)_2CHOCH_2CH_2NHCH_2C_6H_5$$

$$\xrightarrow{Br^-\text{(2-pyridyl)}} \left[\text{(2-pyridyl)}\text{-}N(CH_2C_6H_5)\text{-}CH_2CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH(C_6H_5)_2\right]_{\text{(not isolated)}} + (C_6H_5)_2CH\text{-}CH(C_6H_5)_2$$

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.

$$\text{(2-pyridyl)}\text{-}NH_2 \xrightarrow[(2)\ Cl\text{-}CH_2CH_2\text{-}OCH(C_6H_5)_2]{(1)\ LiNH_2} \text{(2-pyridyl)}\text{-}N(H)\text{-}CH_2CH_2OCH(C_6H_5)_2$$

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.

(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).