In the rearrangement of N,N-dimethylbenzylamine oxide, if the rates of both reactions were equal, the ratio of formaldehyde to benzaldehyde would be 3:1, from the statistical ratio of the number of available protons. The observed ratio of 2.3:1 thus indicates an effect due to the increased acidity of the benzylic hydrogen, and despite any steric hindrance of that hydrogen caused by the presence of the aromatic ring. The rearrangement of N,N-dimethyl-*p*-nitrobenzylamine oxide gave the much lower observed molecular ratio of 0.57:1 of formaldehyde to *p*-nitrobenzaldehyde. Since the steric situation is unchanged in the two cases, and the number of available protons is identical, this difference in the observed ratio must reflect the markedly greater acidity of the benzylic proton in the latter case.

The absence of either formic acid or of the appropriate benzoic acid from the products of the reaction indicated that a reduction of some N-oxide by formaldehyde or by the benzaldehyde did not occur during this rearrangement. This conclusion was further supported by the detection by thin layer chromatography of the presence of N-methylbenzylamine and of N-methyl-*p*-nitrobenzylamine, respectively, and by the absence of N,N-dimethylbenzylamine and N,N-dimethyl-*p*-nitrobenzylamine.

The above results show that the rearrangement of an unsymmetrical tertiary amine oxide may occur concurrently along several pathways, and that (in the absence of marked steric hindrance) the ratio of the possible reaction rates will be determined, *inter alia*, by the relative acidities of the available protons. In cases in which one type of proton is significantly sterically hindered, this may also be expected to influence the relative rates of rearrangement. The application of these results to the demethylation of nicotine, in which such a situation obtains, was described in a preceding communication.[16]

(16) J. C. Craig, N. Y. Mary, N. L. Goldman, and L. Wolf, *J. Am. Chem. Soc.*, **86**, 3866 (1964).

Potential Carcinolytic Agents. II. Fluoroethylamines by Reduction of Fluoroacetamides with Diborane[1]

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The reduction af aliphatic amides by diborane gives amines in good yields. This method is especially suitable for reducing fluoroacetamide and N-substituted fluoroacetamide derivatives where lithium aluminum hydride and lithium aluminum hydride–aluminum chloride cause hydrogenolysis of the C–F bond.

In our studies of new deactivated alkylating agents,[2] bis(2-fluoroethyl)amine (IIc) and 2-chloro-2′-fluorodiethylamine (IIb) were required as starting materials, but the reported[3] synthetic methods involving the reaction of 2-chlorofluoroethane, 2-bromofluoroethane, or 2-fluoroethyl benzenesulfonate with ammonia or amines appeared to be cumbersome and are known to yield mixtures of amines in rather low yields.

The preparation of IId by reduction of Id with lithium aluminum hydride has been claimed by Olah and Pavlath.[4] We attempted to extend this reaction and to prepare the desired amines II by the reduction of the corresponding amides I.

$$\underset{\text{I}}{FCH_2CONHR} \longrightarrow \underset{\text{II}}{FCH_2CH_2NHR}$$

a, R = CH_2CH_2OH
b, R = CH_2CH_2Cl
c, R = CH_2CH_2F
d, R = H

Treatment of Ia with lithium aluminum hydride in refluxing tetrahydrofuran for 1 hr. yielded mostly unreacted amide. When the reaction mixture was refluxed for 5 hr., N-ethyl-2-aminoethanol was obtained in 60% yield. Reduction of Id with lithium aluminum hydride in ether solution, in an attempt to duplicate the exact conditions described by Olah and Pavlath,[4] yielded ethylamine as the only identifiable product.

The easy hydrogenolysis of the C–F bond in these reactions is in accordance with the observation of Pattison, *et al.*,[5] who mentioned that particularly low yields of the desired fluoroalkylamines were obtained in the attempted lithium aluminum hydride reduction of ω-fluoronitriles having less than five carbon atoms.

Hydrogenolysis of the C–F bond was also obtained in the reduction of Ib with lithium aluminum hydride–aluminum chloride reagent[6] and 2-chlorodiethylamine was obtained in 33% yield. Very recently Pettit and Smith[7] confirmed our observation that this reagent causes hydrogenolysis of the C–F bond. These authors reported that reduction of the amide group without hydrogenolysis of the C–F bond was effected when N-bis(2-fluoroethyl)-3,4,5-trimethoxybenzamide was treated with lithium aluminum hydride for 24 hr. at room temperature. We found that this method was unsuccessful for reducing fluoroacetamide (Id); all the starting material was recovered unchanged.

(1) Previous paper: O. M. Friedman, R. S. Levi, Z. B. Papanastassiou, and W. M. Whaley, *J. Med. Chem.*, **6**, 449 (1963). This work was sponsored by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-4360.

(2) Z. B. Papanastassiou and R. J. Bruni, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 42L.

(3) (a) A. F. Childs, *et al.*, *J. Chem. Soc.*, 2174 (1948); (b) E. Wilson and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3635 (1951); (c) V. G. Nemets and G. L. Epshtein, *Izv. Vysshykh Uchebn. Zavedenii Khim. i Khim. Tekhnol.*, **5**, 101 (1962); *Chem. Abstr.*, **58**, 3298 (1963); (d) V. G. Nemets and G. G. Tsybaeva, *Tr. Leningr. Tekhnol. Inst. im. Lensoveta*, **No. 60**, 49 (1960); *Chem. Abstr.*, **55**, 20,943 (1961); (e) A. P. Martinez, W. W. Lee, and L. Goodman, Abstracts of Papers, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964, p. 29M.

(4) G. Olah and A. Pavlath, *Magy. Tud. Akad. Kem. Tud. Oszt. Kozlemen.*, **6**, 411 (1955); *Chem. Abstr.*, **50**, 10,642 (1956).

(5) F. L. M. Pattison, W. C. Howell, and R. W. White, *J. Am. Chem. Soc.*, **78**, 3487 (1956).

(6) G. R. Pettit, M. F. Bauman, and K. N. Rangammal, *J. Med. Pharm. Chem.*, **5**, 800 (1962).

(7) G. R. Pettit and R. L. Smith, *Can. J. Chem.*, **42**, 572 (1964).

Diborane has been shown by Brown and his collaborators[8] to be a selective reducing agent. In contrast to sodium borohydride and lithium aluminum hydride, diborane is inert toward carbon–halogen bonds. However, the reduction of amides by diborane has not been adequately studied, although Brown[9] concluded that tertiary amides are presumably reduced to the tertiary amines and that primary amides react with diborane evolving hydrogen, but with no apparent reduction. On the other hand, sodium borohydride–boron trifluoride etherate (in which diborane is the reducing agent) reduced trifluoroacetamide and its N-substituted derivatives at 100°.[10]

When we passed diborane through a solution of the amides (I) in tetrahydrofuran or diglyme, a mildly exothermic[11] reaction occurred and a white solid was formed. Addition of absolute ethanol caused the dissolution of the solid, and acidification of the mixture with an excess of dry hydrogen chloride yielded the desired hydrochloride salts of the amines. An excess of hydrogen chloride was necessary in order to cause precipitation of the amine hydrochloride. Only in the case of IIa, the desired amine could not be freed from boron impurities, but analytically pure derivatives of the amine were obtained.

The present investigation demonstrates that diborane is an excellent reagent for reducing the functional groups of monofluorinated and, in general, monohalogenated aliphatic compounds in which loss of hydrogen halide may be faciliated by intramolecular nucleophilic attack.

Brown[8a] has reported that acid chlorides and chloral are not reduced by diborane because the inductive effect of halogen substituents decreases the basicity of the carbonyl oxygen making it less amenable to the diborane attack. The reduction of amides I, in spite of the presence of the electron-withdrawing fluorine atoms, was indicative of the applicability of the diborane reduction to all amides. This assumption was verified by reducing propionamide with diborane; propylamine was obtained in good yield.

Experimental[12]

N-(2-Hydroxyethyl)fluoroacetamide (Ia).—This amide was prepared according to the method of Buckle, *et al.*,[13] except that we started with ethyl fluoroacetate. The product was purified by distillation: b.p. 110–115° (0.1–0.2 mm.), m.p. 25°, ν_{max}^{NaCl} 1665 and 1555 cm.$^{-1}$ (amide); lit.[13] b.p. 114° (0.1 mm.), m.p. *ca.* 21°.

Anal. Calcd. for $C_4H_8FNO_2$: C, 39.67; H, 6.66. Found: C, 39.59; H, 7.04.

N-(2-Chloroethyl)fluoroacetamide (Ib). A.—A solution of 14.4 g. (0.18 mole) of 2-chloroethylamine (freshly prepared by neutralizing a cold aqueous solution of its hydrochloride, extracting the free amine with ether, drying, and concentrating the ether extract) in 21 g. (0.20 mole) of ethyl fluoroacetate was allowed to stand overnight at room temperature. The ethyl alcohol formed was distilled slowly from the reaction mixture; the residue was distilled[14] under reduced pressure giving 6.1 g. (24%) of a colorless liquid (Ib) which solidified: m.p. 62–64°, lit.[13] m.p. 65°.

B.—A solution of 36 g. (0.3 mole) of thionyl chloride in 50 ml. of chloroform was added dropwise to 36.3 g. (0.3 mole) of Ia in 50 ml. of chloroform. The rate of addition was regulated to allow the chloroform to reflux gently. After the addition was completed (about 0.5 hr.), the mixture was stirred for 1 hr. and then heated under reflux for 1 hr. more. The solution was cooled and evaporated to dryness in a rotary evaporator. The solid residue was recrystallized from 200 ml. of carbon tetrachloride (decolorizing charcoal) to give 32 g. (76%) of Ib, $\nu_{max}^{CHCl_3}$ 1680 and 1530 cm.$^{-1}$ (amide), m.p. 63–65°, lit.[13] m.p. 65°.

N-(2-Fluoroethyl)fluoroacetamide (Ic).—A solution of 8 g. (0.127 mole) of 2-fluoroethylamine in 20 ml. of ethyl fluoroacetate was heated under reflux for 1 hr. The ethyl alcohol formed was removed by slow distillation (quantitative recovery) and then the excess of ethyl fluoroacetate was removed at *ca.* 15-mm. pressure. The residue was distilled yielding 9.5 g. (61%) of Ic, b.p. 58–59° (0.3 mm.), $n^{25}D$ 1.4187, ν_{max}^{NaCl} 1675 and 1550 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_4H_7F_2NO$: C, 39.02; H, 5.73. Found: C, 39.45; H, 6.13.

Reduction of N-(2-Hydroxyethyl)fluoroacetamide (Ia) by Lithium Aluminum Hydride. Preparation of N-Ethyl-2-aminoethanol.—A solution of 60.5 g. (0.50 mole) of Ia in 60 ml. of dry tetrahydrofuran was added during 30 min. to a well-stirred suspension of 30 g. (0.75 mole) of lithium aluminum hydride in 200 ml. of dry tetrahydrofuran. The mixture was refluxed for 5 hr. and then cooled in ice. The excess of lithium aluminum hydride was decomposed by the slow addition of 2-propanol (228 ml., 3.0 moles) followed by 54 ml. (3.0 moles) of water. A solid was obtained, which was separated by filtration, washed with 2-propanol, and continuously extracted (in a Soxhlet extractor) with 2-propanol. The filtrate, washings, and extract were combined and evaporated to dryness. Distillation of the residue gave N-ethyl-2-aminoethanol in 60% yield: b.p. 75–76° (15 mm.), $n^{25}D$ 1.4410, lit.[15] $n^{20}D$ 1.4411.

Anal. Calcd. for $C_4H_{11}NO$: C, 53.89; H, 12.44; neut. equiv., 89. Found: C, 53.66; H, 12.62; neut. equiv., 89 (potentiometric titration with 0.1 *N* HCl).

Reduction of N-(2-Chloroethyl)fluoroacetamide (Ib) with Lithium Aluminum Hydride–Aluminum Chloride. Preparation of 2-Chlorodiethylamine Hydrochloride.—Anhydrous aluminum chloride (6.7 g., 0.05 mole) was gradually added to a well-stirred cold suspension of 1.9 g. (0.05 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran. Then a solution of 6.1 g. (0.043 mole) of Ib in 50 ml. of tetrahydrofuran was added over a period of 1 hr. at 5 to 10°. Stirring was continued for 4 hr. and the mixture was allowed to stand for 14 hr. during which time the temperature gradually rose to 12°. Stirring and cooling were resumed and 100 ml. of acetone, 100 ml. of ether, and 3.6 ml. (0.20 mole) of water were successively added. The mixture was evaporated under reduced pressure to a red solid which was partially dissolved in 220 ml. of 20% aqueous sodium hydroxide. The mixture was extracted with six 75-ml. portions of ether and the combined extracts were washed with two 50-ml. portions of saturated aqueous sodium chloride and dried over magnesium sulfate. The drying agent was removed and dry hydrogen chloride was passed into the ethereal extract. An oil precipitated, which partially crystallized to give 2.0 g. (33%) of a sticky solid. After two recrystallizations from acetone, the crystalline 2-chlorodiethylamine hydrochloride had m.p. 222–224°, lit.[16] m.p. 223°.

(8) (a) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960); (b) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(9) Ref. 8b, pp. 249 and 262. NOTE ADDED IN PROOF.—Dr. H. C. Brown has informed us that diborane has been used in his laboratory to reduce amides and a communication is forthcoming.

(10) E. R. Bissell and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959).

(11) In no case did the temperature of the mixture reach the boiling point of the solvent. Maintaining the reaction mixture at high temperature (*ca.* 80°) over long periods may decompose the desired 2-fluoroethylamines II through the formation of ethyleneimonium salts, in a manner similar to that of the 2-chloroethylamines (see W. C. J. Ross, "Biological Alkylating Agents," Butterworths and Co. (Publishers) Ltd. London, 1962, p. 11). The stability of the 2-fluoroethylamines, examined by n.m.r. spectroscopy, will be the subject of another communication with Dr. Philip L. Levins.

(12) All starting materials and solvents were carefully purified before use. Melting points were obtained with a calibrated Mel-Temp apparatus and are corrected. The infrared and n.m.r. spectra of the products were consistent with the structures given. The microanalyses were performed by Dr. S. M. Nagy of the Massachusetts Institute of Technology and by the Schwarzkopf Microanalytical Laboratory.

(13) E. J. Buckle, R. Heap, and B. C. Saunders, *J. Chem. Soc.*, 912 (1949).

(14) The infrared spectrum of the distillation residue exhibited an ester carbonyl absorption peak attributed to the rearrangement product described by W. C. J. Ross and J. G. Wilson [*ibid.*, 3616 (1959)].

(15) P. A. DiGiorgio, L. H. Sommer, and F. C. Whitemore, *J. Am. Chem. Soc.*, **71**, 3255 (1949).

(16) A. Lasselle and S. A. Sandet, *ibid.*, **63**, 2375 (1941).

Anal. Calcd. for $C_4H_{11}Cl_2N$: Cl^-, 24.6. Found: Cl^-, 24.5.[17]

N-(2-Fluoroethyl)-2-aminoethanol (IIa).—The conditions of Brown and Subba Rao[3a] were used. Diborane was generated over a period of 3 hr. by the slow addition of 26 g. (0.7 mole) of sodium borohydride in 600 ml. of dry diglyme to a solution of freshly distilled boron trifluoride etherate (141 g., 1.0 mole) in 200 ml. of diglyme. A slow stream of dry nitrogen carried the diborane (*ca.* 0.47 mole) into a solution of 36.3 g. (0.30 mole) of Ia in 250 ml. of tetrahydrofuran. (A cylindrical vessel equipped with a gas inlet dispersion tube near the bottom was used; the mixture was stirred by a magnetic stirrer.) The exit gases were passed through 400 ml. of acetone to decompose the excess diborane.

The reaction of diborane with the amide was initially exothermic. No external cooling was necessary. The reaction mixture was allowed to stand overnight while being swept with a slow nitrogen flow. Absolute ethanol (100 ml.) was added and the solution was made acidic with dry hydrogen chloride. Gas evolved during these additions. The solution was evaporated under vacuum in a rotary evaporator. A second portion of ethanol was added to the residue and the solution was evaporated again. The residue, 46 g. of a clear sirup, still contained boron (green flame).

A portion was used to form the picrate of IIa, m.p. 120–122.5°.

Anal. Calcd. for $C_{10}H_{13}FN_4O_8$: C, 35.72; H, 3.90 F, 5.65; N, 16.66. Found: C, 35.70; H, 4.24; F, 5.83; N, 16.22.

Another portion was used to form the *p*-toluenesulfonamide–*p*-toluenesulfonate derivative of IIa, m.p. 70.5–71.5°.

Anal. Calcd. for $C_{18}H_{22}FNO_5S_2$: C, 52.03; H, 5.34; F, 4.57. Found: C, 52.50; H, 5.33; F, 4.58.

2-Chloro-2′-fluorodiethylamine (IIb).—Diborane (from 0.8 mole of sodium borohydride and 1.48 moles of boron trifluoride etherate) was bubbled into a solution of 32 g. (0.23 mole) of Ib in 300 ml. of tetrahydrofuran. The reaction mixture was treated as in the preceding experiment and then was poured from the reaction vessel into 150 ml. of absolute ethanol and made acidic with an excess of dry hydrogen chloride. The solvents were removed in a rotary evaporator; the residue was redissolved in 100 ml. of ethanol (95%) and evaporated again. The sticky residue was recrystallized from 300 ml. of dry acetone, giving 83% of crystalline hydrochloride of IIb, m.p. 193–194°.

Anal. Calcd. for $C_4H_{10}Cl_2FN$: C, 29.65; H, 6.22; Cl (total), 43.76; Cl^-, 21.9; F, 11.72; N, 8.65. Found: C, 29.52; H, 6.42; Cl (total), 43.74; Cl^-, 21.8[17]; F, 11.68; N, 8.54.

The picrate of IIb was prepared and recrystallized twice from ethanol; it had m.p. 100–101.5°.

Anal. Calcd. for $C_{10}H_{12}ClFN_4O_7$: C, 33.86; H, 3.39; F, 5.36. Found: C, 34.13; H, 3.68; F, 5.12.

Bis(2-fluoroethyl)amine (IIc).—Diborane[18] (from 1.42 moles of sodium borohydride and 2.0 moles of boron trifluoride etherate) was bubbled with a slow stream of nitrogen into a solution of 47 g. (0.38 mole) of Ic in 650 ml. of dry tetrahydrofuran. After the system had been swept with dry nitrogen and 100 ml. of absolute alcohol had been added as described before, the solution was acidified with an excess of dry hydrogen chloride and allowed to stand at 0° for 60 hr. A crystalline product, 42.6 g. (65.5%), m.p. 187–189°, was obtained. Additional solid, 6.3 g. (11%), m.p. 180–183°, was obtained by concentrating the filtrate. Recrystallization of these solids from a 1:1 acetone–ethanol mixture yielded the hydrochloride of IIc, m.p. 190–193°, lit.[7] m.p. 202°.

Anal. Calcd. for $C_4H_{10}ClF_2N$: Cl^-, 24.4. Found: Cl^-, 24.4.[17]

The free amine (IIc) was liberated by heating 15 g. of the hydrochloride with 20 g. of dry pulverized sodium hydroxide. Redistillation yielded 7.6 g. (70%) of pure IIc,[19] b.p. 120–122°, $n^{25}D$ 1.3823, lit.[3a] b.p. 123–126° (764 mm.).

Anal. Calcd. for $C_4H_9F_2N$: C, 44.02; H, 8.31; N, 12.84. Found: C, 44.33; H, 8.56; N, 13.00.

2-Fluoroethylamine (IId).—Diborane[18] (from 1 mole of sodium borohydride and 1.4 mole of boron trifluoride etherate) was bubbled during 3 hr. with a slow nitrogen stream into a solution of 23 g. (0.3 mole) of Id in 250 ml. of diglyme. The reaction mixture was decomposed with 100 ml. of absolute ethanol, and the resulting solution was acidified with an excess of dry hydrogen chloride. A precipitate formed, and, after the mixture had stood at 0° overnight, 20 g. (67%) of white crystalline hydrochloride of IId was obtained: m.p. 95° dec., lit.[3c] m.p. 92–93°.

One gram of the hygroscopic hydrochloride was converted to the *p*-toluenesulfonamide by stirring a mixture of the amine hydrochloride overnight with a solution of 1 g. of *p*-toluenesulfonyl chloride in 10 ml. of ether and 1.5 g. of sodium hydroxide in 18 ml. of water. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The crude N-(2-fluoroethyl)-*p*-toluenesulfonamide, m.p. 97–102°, was purified by recrystallization from a 1:1 ethanol–water mixture: m.p. 102–104°, lit.[3a] m.p. 104°.

The free amine (IId) was obtained by heating 17 g. of its hydrochloride with 12 g. of dry pulverized sodium hydroxide: b.p. 60–62°, $n^{25}D$ 1.3690. Redistillation through a 10-cm. vacuum-jacketed, silvered Vigreux column gave 8 g. (75%) of pure IId,[20] b.p. 63.5–64.5°, $n^{25}D$ 1.3705, lit. b.p. 35–42°,[3a,c] 39–42°.[4]

Anal. Calcd. for C_2H_6FN: C, 38.08; H, 9.59. Found: C, 37.81; H, 9.80.

A portion of IId was reconverted to the amine hydrochloride in ether, dried, and titrated with 0.1 *N* aqueous silver nitrate.

Anal. Calcd. for C_2H_7ClFN: Cl^-, 35.6. Found: Cl^-, 35.5.[17]

***n*-Propylamine.**—Diborane (from 0.4 mole of sodium borohydride and 0.73 mole of boron trifluoride etherate) was bubbled into a solution of 7.3 g. (0.1 mole) of propionamide in 200 ml. of tetrahydrofuran. Absolute ethanol (70 ml.) was then added; the solution was acidified with an excess of dry hydrogen chloride and cooled to 0° for 2 hr. A crop of hygroscopic propylamine hydrochloride was collected by suction filtration and vacuum-dried: yield 4.9 g. (51.5%), m.p. 142–145°. Recrystallization from ethanol–ether raised the melting point to 148–155°. This value was not depressed when the product was mixed with authentic propylamine hydrochloride (m.p. 157–158°, obtained from commercial sources). The infrared spectrum of the product was identical with the authentic sample. A portion of the product was converted to the picrate, m.p. 133–135°, lit.[21] m.p. 138°.

Concentration of the mother liquor from the first crop of product gave a second crop (*ca.* 5 g.) as a sticky gum. The infrared spectrum of this crop indicated that it was mostly propylamine hydrochloride.

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(17) Determined by titration with aqueous silver nitrate solution using dichlorofluorescein as the indicator.

(18) Commercial diborane purchased from Callery Chemical Co. was used when this reduction was scaled up to 1 mole of amide. A small quantity (0.1% by volume) of boron trifluoride etherate was added in the reaction vessel, and the diborane was introduced at *ca.* 0.6 l./hr.

(19) Gas chromatography indicated that the product was at least 99.9% pure.

(20) Gas chromatography indicated that the product was at least 98% pure.

(21) J. Mitchell, Jr., and W. M. D. Bryant, *J. Am. Chem. Soc.*, **65**, 128 (1943).