3-Chloro-1,2,5-trifluorobenzene.—This compound was obtained as a by-product from IV. It is a colorless liquid, b.p. 121° (micro cap.), $n^{20}\mathrm{D}$ 1.4550.

Anal. Calcd. for $C_6H_2ClF_3$: C, 43.27; H, 1.21. Found: C, 43.57; H, 1.24.

4-Nitro-1,2,3,5-tetrafluorobenzene.—To a mixture of 25 g. of 1,2,3,5-tetrafluorobenzene and 30 cc. of concd. sulfuric acid, a solution of 12 cc. of concd. nitric acid in 10 cc. of concd. sulfuric acid was added at 0–10°, followed by stirring, for two hours at 10°. The yield of crude steam distilled nitro compound was 23 g. or 72%. Vacuum distilatlion gave pure 4-nitro-1,2,3,5-tetrafluorobenzene, b.p. 78.5° (20 mm.), $n^{20}\mathrm{D}$ 1.46507, f.p. *ca.* −5°.

Anal. Calcd. for $C_6HO_2NF_4$: C, 36.94; H, 0.52; N, 7.18. Found: C, 37.17; H, 0.65; N, 7.24.

4-Amino-1,2,3,5-tetrafluorobenzene.—This amine was obtained from the preceding nitro compound by the usual iron reduction[9] in an 86% crude yield. It is a steam distillable liquid, b.p. 65° (20 mm.), $n^{20}\mathrm{D}$ 1.46228.

Anal. Calcd. for $C_6H_3NF_4$: C, 43.65; H, 1.83; N, 8.49. Found: C, 43.65; H, 1.79; N, 8.35.

The acetyl derivative was obtained as white, granular crystals from ethanol, m.p. 140–141°.

Anal. Calcd. for $C_8H_5ONF_4$: N, 6.76. Found: N, 6.78.

Summary

The preparation of 1,2,3,5-tetrafluorobenzene and some of its intermediates is described.

Cuprous oxide as a catalyst was used to advantage in the hypophosphorous acid deamination method.

URBANA, ILLINOIS RECEIVED JUNE 9, 1950

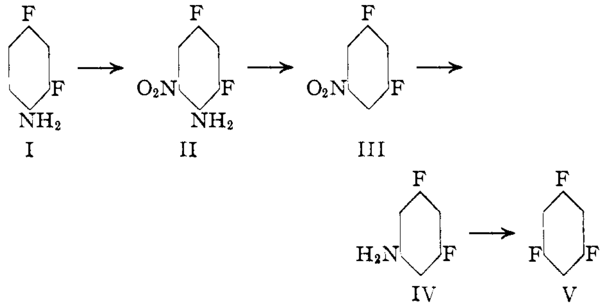
[CONTRIBUTION FROM THE GEOCHEMICAL SECTION OF THE ILLINOIS STATE GEOLOGICAL SURVEY]

Aromatic Fluorine Compounds. V. 1,3,5-Trifluorobenzene[1]

BY G. C. FINGER, F. H. REED AND J. L. FINNERTY

Among the polyfluorobenzenes there has been considerable speculation as to the probable physical and chemical properties of symmetrical trifluorobenzene. This compound has now been synthesized and some of its properties and derivatives have been studied.

The nitration of the acetyl derivative of 4-amino-1,3-difluorobenzene (I) gave 4-amino-5-nitro-1,3-difluorobenzene (II). Reduction of the nitroamine to the diamine, followed by the formation of 2,3-diphenyl-5,7-difluoroquinoxaline proved the adjacency of the nitro and amine groups. A modified hypophosphorous acid deamination procedure[2] gave an average yield of 50% of 5-nitro-1,3-difluorobenzene (III), and a subsequent iron reduction gave 5-amino-1,3-difluorobenzene (IV).



A diazotization–Schiemann transformation on the amine gave a 60% yield of 1,3,5-trifluorobenzene (V).

The boiling point of 1,3,5-trifluorobenzene is 75.5°, thus making it the only fluorinated benzene boiling lower than benzene, 80°. It is odorless, whereas its isomer 1,2,4-trifluorobenzene, and the next higher homolog, 1,2,4,5-tetrafluorobenzene have a faint, sweet odor.

Chlorination and bromination gave the mono, di and trihalo derivatives. The trichloro derivative was identical with 2,4,6-trichloro-1,3,5-trifluorobenzene obtained by the chlorinolysis of trifluoromesitylene.[3]

Symmetrical trifluorobenzene was readily nitrated to 2-nitro-1,3,5-trifluorobenzene, and an iron reduction gave the corresponding 2-amino-1,3,5-trifluorobenzene. The amine reacted readily with hydrochloric or sulfuric acids to form the amine salts. The hydrosulfate salt was surprisingly soluble.

Nitration of the acetyl derivative of IV gave 4-nitro-5-amino-1,3-difluorobenzene; the nitro group entered an ortho position to the amino rather than the expected para. The structure of the nitroamine was proven by deamination to the known 4-nitro-1,3-difluorobenzene.

Experimental[4,5]

4-Amino-5-nitro-1,3-difluorobenzene (II).—In a mixture of 400 cc. of concd. sulfuric acid and 140 cc. of acetic acid, 340 g. of 4-acetylamino-1,3-difluorobenzene[6,7] was dissolved with stirring. After cooling to 20°, a mixture containing equal volumes (140 cc. each) of concd. nitric and sulfuric acids was added in fifteen minutes, and the temperature allowed to rise to 40°. Stirring was continued for 90 minutes at 40–50°. The reaction mixture was poured over ice, and the crude nitroacetylamino compound after drying weighed 400 g. The crude product was hydrolyzed to the nitroamine in 350 cc. of concd. sulfuric acid by heating for two hours on a steam-bath, and then poured over ice. The yield of dry crude product was 228 g. or 65%. The nitroamine is steam distillable, but the purest product was obtained by recrystallization from ethanol followed by sublimation. No tangible evidence was obtained for the existence of other nitroamine isomers. Pure 4-amino-5-nitro-1,3-difluorobenzene is a yellow solid, m.p. 85.5–86.5°.

Anal. Calcd. for $C_6H_4O_2N_2F_2$: C, 41.39; H, 2.31; N, 16.08. Found: C, 41.48; H, 2.14; N, 15.91.

The acetyl derivative was recrystallized as cream colored

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(1) Presented before the Organic Division at the 117th Meeting of the American Chemical Society, Philadelphia, Pennsylvania, April 1950. The authors wish to acknowledge the financial assistance of the Office of Naval Research provided by coöperative research Contract N6ori-71; Task XIV. Published with the permission of the Chief of the Illinois State Geological Survey.

(2) Finger, Reed and Oesterling, THIS JOURNAL, **73**, 152 (1951).

(3) Finger, Reed, Maynert and Weiner, *ibid.*, **73**, 149 (1951).

(4) Analyses, densities and surface tension measurements by H. S. Clark, microanalyst for the Illinois Geological Survey.

(5) Melting and boiling points are uncorrected, and the freezing points were determined with a toluene thermometer.

(6) Swarts, *Rec. trav. chim.*, **35**, 154 (1915).

(7) Schiemann, *J. prakt. Chem.*, **140**, 97 (1934).

needles from an ethanol–chloroform mixture, m.p. 142–143°.

Anal. Calcd. for $C_8H_6O_3N_2F_2$: N, 12.96. Found: N, 12.66.

4,5-Diamino-1,3-difluorobenzene.—Four grams of the preceding nitroamine (II) was reduced to the diamine by addition with stirring to 24 g. of stannous chloride in 30 cc. of concd. hydrochloric acid. The reaction mixture after being made alkaline with sodium hydroxide solution, was extracted with ether, and evaporation of the ether extract gave the crude diamine. Recrystallization from an *n*-pentane–ether mixture followed by sublimation gave the 4,5-diamino-1,3-difluorobenzene as white crystals, m.p. 48.5–49.5°.

One gram of the diamine was condensed with 1.4 g. of benzil in 70 cc. of water by heating and stirring for one hour. The insoluble crude product was purified by recrystallizations from ethanol and methanol and also sublimations to give pure 2,3-diphenyl-5,7-difluoroquinoxaline as a white solid, m.p. 137–138°.

Anal. Calcd. for $C_{20}H_{12}N_2F_2$: C, 75.46; H, 3.80; N, 8.80. Found: C, 75.56; H, 3.73; N, 8.87.

5-Nitro-1,3-difluorobenzene (III).—The 4-amino-5-nitro-1,3-difluorobenzene was diazotized by the nitrosylsulfuric-phosphoric acid procedure[8,9] for weakly basic amines. The final deamination step with hypophosphorous acid[10] was successful only when cuprous oxide was used as a catalyst.

A solution of 67 g. of pure 4-amino-5-nitro-1,3-difluorobenzene (II) in 150 cc. of concd. sulfuric acid was stirred for three hours to form the amine salt. Nitrosylsulfuric acid was prepared by dissolving 28 g. of sodium nitrite in 150 cc. of concd. sulfuric acid (precooled to 0°) with stirring, and the mixture cooled to 20°. To the amine hydrosulfate at 0°, the nitrosylsulfuric acid was added and the reaction temperature allowed to rise to 10°. In order to complete the diazotization, 300 cc. of 85% phosphoric acid was added slowly in two hours while the temperature was maintained at 10–15°.

To the rapidly stirred diazonium solution at 0°, a slurry of 250 g. of sodium hypophosphite, 35 g. of cuprous oxide and 150 cc. of water was added slowly and the exothermic reaction kept below 35°. Nitrogen evolution was practically complete after 80% of the slurry had been added. The reaction mixture, after dilution with an equal volume of water and transference to a large flask (12-l.) was cautiously steam distilled. A large flask is essential as the hypophosphorous acid, near the end of the steam distillation, reduces the copper salts by an almost uncontrollable exotherma reaction causing the entire mixture to superheat and foam suddenly. The yield of pure 5-nitro-1,3-difluorobenzene was 37 g. or 60%, f.p. *ca.* 17.5°, b.p. 78–79° (20 mm.) or 176–177° (atm.).

Anal. Calcd. for $C_6H_3O_2NF_2$: C, 45.30; H, 1.90; N 8.80. Found: C, 45.50; H, 1.70; N, 8.92.

5-Amino-1,3-difluorobenzene (IV).—To a stirred, refluxing mixture of 140 g. of iron filings in 200 cc. of ammonium chloride solution (0.78 *N*), 100 g. of 5-nitro-1,3-difluorobenzene was added slowly. The reduction was complete in two hours. Removal of the amine by steam distillation gave a yield of 75 g. or 92%. Vacuum distillation gave the pure amine as a white solid, m.p. 39–40°, b.p. 81–82° (20 mm.).

Anal. Calcd. for $C_6H_5NF_2$: C, 55.82; H, 3.90; N, 10.84. Found: C, 55.89; H, 4.03; N, 11.11.

The acetyl derivative was obtained as a white solid by successive recrystallizations from ethanol and benzene followed by sublimation, m.p. 129–129.5°.

Anal. Calcd. for $C_8H_7ONF_2$: C, 56.14; H, 4.13; N, 8.18. Found: C, 55.93; H, 4.09; N, 8.40.

4-Nitro-5-amino-1,3-difluorobenzene.—To a solution of 7 g. of the acetyl derivative of IV in 20 cc. of concd. sulfuric and 10 cc. of acetic acids, a mixture of concd. nitric–sulfuric acids (3.5 cc. of each acid) was added, and the reaction temperature maintained at 30–40°. Stirring was continued for 90 minutes after addition. After isolation of the crude reaction product, it was hydrolyzed to the nitroamine by warming with 10 cc. of concd. sulfuric acid. Recrystallization from ethanol and *m*-fluorobenzotrifluoride,[11] and a final sublimation gave pure 4-nitro-5-amino-1,3-difluorobenzene as orange crystals, m.p. 107–108°. No evidence was found for the formation of other isomers, although this compound is isomeric with II.

Anal. Calcd. for $C_6H_4N_2O_2F_2$: C, 41.39; H, 2.31; N, 16.08. Found: C, 41.46; H, 2.12; N, 16.17.

Recrystallization of the acetyl derivative from *m*-fluorobenzotrifluoride gave white needles, m.p. 137–138°.

The structure of the nitroamine was established by deamination to 4-nitro-1,3-difluorobenzene[6] using the special procedure applied to II.

1,3,5-Trifluorobenzene (V).—To 200 cc. of concd. hydrochloric acid with rapid stirring, 75 g. of melted 5-amino-1,3-difluorobenzene was added slowly, and the amine hydrochloride paste was diluted with 80 cc. of water. Diazotization was effected at 0° by the addition of 42 g. of sodium nitrite as a 40% solution. To the clear diazonium solution, 160 g. of sodium fluoborate was added as a 40% solution, and the white diazonium fluoborate precipitate was filtered at −10°. The yield of dried fluoborate salt was 132 g. or 98%. The salt was thermally decomposed[12] by continuous heating, and steam distillation of the crude product gave a yield of 44 g. or 62.8% of trifluorobenzene based on the amine. A further treatment with cold concd. sulfuric acid followed by distillation through a packed 5-ft. vacuum-jacketed column gave pure 1,3,5-trifluorobenzene as a colorless, odorless liquid, f.p. *ca.* −5.5°, b.p. 75.5°, d^{20}_4 1.277, n^{20}_{D} 1.41403, γ^{20} 27.16 dynes/cm.

Anal. Calcd. for $C_6H_3F_3$: C, 54.56; H, 2.29; F, 43.15. Found: C, 54.59; H, 2.19; F, 42.90.

1-Chloro-3,5-difluorobenzene.—This compound was obtained as a by-product from the synthesis of V. The pure compound is a colorless liquid, b.p. 118.5°, n^{20}_{D} 1.4683.

Anal. Calcd. for $C_6H_3ClF_2$: C, 48.51; H, 2.03. Found: C, 48.59; H, 2.16.

Chlorination of 1,3,5-Trifluorobenzene.—A sample of 1,3,5-trifluorobenzene was chlorinated for six hours by bubbling chlorine through it in the presence of an iron catalyst. The chief product was 2-chloro-1,3,5-trifluorobenzene, f.p. *ca.* −2 to −3°, b.p. 124°, d^{20}_4 1.463, n^{20}_{D} 1.45505, γ^{20} 28.59 dynes/cm.

Anal. Calcd. for $C_6H_2ClF_3$: C, 43.27; H, 1.21. Found: C, 43.52; H, 1.26.

Chlorination by the sulfuryl chloride–sulfur monochloride method[13] in the presence of aluminum chloride gave chiefly the dichloro compound along with a small amount of the trichloro derivative. The reaction product was steam distilled, and purified by fractional distillation. Pure 2,4-dichloro-1,3,5-trifluorobenzene is a colorless liquid, f.p. *ca.* −10 to −11°, b.p. 161.5–162°, d^{20}_4 1.599, n^{20}_{D} 1.48637, γ^{20} 30.41 dynes/cm.

Anal. Calcd. for $C_6HCl_2F_3$: C, 35.85; H, 0.50; F, 28.36. Found: C, 35.91; H, 0.70; F, 28.41.

The trichloro derivative was isolated as a white solid by freezing the preceding high boiling fraction. Vacuum sublimation gave pure 2,4,6-trichloro-1,3,5-trifluorobenzene, m.p. 60–62°. A mixed melting point with a pure sample (m.p. 62–63°) obtained by the chlorinolysis of trifluoromesitylene[3] showed no depression.

Bromination of 1,3,5-Trifluorobenzene.—Liquid bromine was added dropwise to 1,3,5-trifluorobenzene in the presence of iron with stirring at room temperature. A molar ratio of reactants gave the monobromo compound as the chief product and a small amount of the dibromo derivative. After steam distillation, the reaction mixture was fractionally distilled. 2-Bromo-1,3,5-trifluorobenzene is a colorless liquid with an unpleasant odor, f.p. *ca.* 3.5°, b.p. 140.5°, n^{20}_{D} 1.48385.

Anal. Calcd. for $C_6H_2BrF_3$: C, 34.15; H, 0.96. Found: C, 34.16; H, 0.96.

2,4-Dibromo-1,3,5-trifluorobenzene was obtained from the higher boiling fraction in the preceding experiment.

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(8) Schoutissen, This Journal, **55**, 4531 (1933).

(9) C. Weygand, "Organic Preparations," Interscience Publishers, Inc., New York, N. Y., 1945, Ch. 2, p. 110.

(10) "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Ch. 7, p. 277.

(11) This compound has been found to be an excellent recrystallization solvent for many polyfluoronitroamines and their derivatives.

(12) Finger and Reed, This Journal, **66**, 1972 (1944).

(13) Cutter and Brown, *J. Chem. Ed.*, **21**, 443 (1944).

The data on the pure compound are m.p. 28–29°, b.p. 196–198°.

Anal. Calcd. for $C_6HBr_2F_3$: C, 24.86; H, 0.35; F, 19.66. Found: C, 25.02; H, 0.40, F, 19.44.

A large excess of bromine along with heating converted the monobromo compound to the tribromo derivative. Alternate vacuum sublimation and recrystallization from ethanol gave pure 2,4,6-tribromo-1,3,5-trifluorobenzene, m.p. 98–98.5°.

Anal. Calcd. for $C_6Br_3F_3$: C, 19.54. Found: C, 19.55.

2-Nitro-1,3,5-trifluorobenzene.—To a well-stirred mixture of 36 g. of 1,3,5-trifluorobenzene in 50 cc. of concd. sulfuric acid, a nitrating solution of 19 cc. of concd. nitric and 17 cc. of concd. sulfuric acids was added at such a rate that the temperature was controlled at 50°. At the end, the temperature was raised to 70° for sixty minutes. The reaction mixture was poured over ice, and the yield of crude nitro compound was 41 g. or 85%. Pure 2-nitro-1,3,5-trifluorobenzene is a heavy, pale yellow liquid, f.p. *ca.* 3.5°, b.p. 81° (20 mm.) or 172° (atm.), $n^{20}D$ 1.47833.

Anal. Calcd. for $C_6H_2O_2NF_3$: C, 40.69; H, 1.14; N, 7.91. Found: C, 40.76; H, 1.16; N, 8.17.

2-Amino-1,3,5-trifluorobenzene.—This amine was prepared from the preceding nitro compound by the same general method as indicated for IV. A 90% yield of crude amine was obtained. Vacuum distillation gave pure 2-amino-1,3,5-trifluorobenzene as a white solid, m.p. 33–34°, b.p. 57° (22 mm.).

Anal. Calcd. for $C_6H_4NF_3$: C, 48.99; H, 2.74; N, 9.52. Found: C, 48.99; H, 2.69; N, 9.58.

The amine forms a very soluble hydrochloride and hydrosulfate in contrast to most other fluorinated anilines.

The acetyl derivative was sublimed after preliminary recrystallizations from ethanol and benzene, m.p. 152–153°.

Anal. Calcd. for $C_8H_6ONF_3$: C, 50.80; H, 3.20; N, 7.41. Found: C, 50.70; H, 3.11; N, 7.58.

Summary

The synthesis and properties of 1,3,5-trifluorobenzene, its intermediates and some of its derivatives have been described.

URBANA, ILLINOIS RECEIVED JUNE 9, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BARNARD COLLEGE, COLUMBIA UNIVERSITY, AND THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Ionization Constants of Glycine and the Effect of Sodium Chloride upon its Second Ionization

BY EDWARD J. KING

In a previous contribution[1] the electromotive forces of cells without liquid junction containing glycine ($Z^{\pm}$), glycine hydrochloride (HZCl), and sodium chloride buffers were used to determine the effect of sodium chloride on the first ionization of glycine, $k_1 = m_H m_Z/m_{HZ}$. Extrapolation of these results to zero ionic strength gave values for the first thermodynamic ionization constant of glycine, $K_1 = a_H a_Z/a_{HZ}$, which were in good agreement with those of Owen[2] at 25° but not at higher and lower temperatures. Since these extrapolations were from ionic strengths no lower than 0.1 molal, the ionization constants were subject to considerable uncertainty. The desirability of accurate knowledge of the ionization of so important an amino acid as glycine has led to a redetermination of its ionization constants using the methods of Owen.[2] The electromotive forces of the cells

$$H_2 \mid Z^{\pm} (m_1), \text{HZCl} (m_2) \mid \text{AgCl–Ag} \qquad \text{I}$$

and

$$H_2 \mid Z^{\pm} (m_1), \text{NaG} (m_2), \text{NaCl} (m_3) \mid \text{AgCl–Ag} \qquad \text{II}$$

have been redetermined at 5° intervals from 10 to 50°. The first ionization constant, K_1, has been calculated from the measurements of Cell I and the second ionization constant,[3]

$$K_2 = \frac{a_H a_G}{a_Z} = \frac{m_H m_G}{m_Z}\,\frac{\gamma_H \gamma_G}{\gamma_Z} = k_2 \gamma_2 \qquad (1)$$

from the measurements of Cell II. In the above expressions NaG represents sodium glycinate and the concentrations m_1, m_2 and m_3 are in moles per kilogram of solvent.

The investigation of the effect of sodium chloride on the second ionization, $k_2 = m_H m_G/m_Z$, has also been carried out. The electromotive forces of cells of the type

$$H_2 \mid Z^{\pm} (m_1), \text{NaG} (m_2), \text{NaCl} (M - m_2) \mid \text{AgCl–Ag} \qquad \text{III}$$

were measured from 5 to 55° and at constant ionic strengths (M) of 0.1 and 0.3. From these, the second ionization of glycine at infinite dilution in a sodium chloride solution of concentration M could be calculated by the method of Owen and King.[4]

Experimental

Apparatus.—The investigation of the effect of sodium chloride upon the second ionization of glycine was carried out at Yale University with the same apparatus and the same samples of glycine and sodium chloride previously described.[1] The redetermination of the ionization constants was done at Barnard College with somewhat different equipment. A Rubicon Type B high precision potentiometer was used in conjunction with a Rubicon No. 3415 spotlight galvanometer. One of the two Eppley standard cells employed was certified by the National Bureau of Standards in October, 1949. A Deoxo catalytic purifier (Baker and Co.) was used to remove traces of oxygen from the hydrogen. Temperatures were measured with a thermometer certified by the National Bureau of Standards. The temperature of the water-bath in which the cells were immersed was controlled within ±0.01° except at 10 and 15° where the fluctuations were somewhat larger. The cells were those used previously[1] except that the stopcock in the connecting tube between the two electrode chambers was replaced by a short length of capillary tubing for most of the measurements. The electrode compartments were closed with HR-108 rubber stoppers (A. H. Thomas Co.), a grade of stopper which in some work with acetic acid–sodium acetate buffers was found to absorb practically no acetic acid.[5]

Materials.—The glycine was the same as that previously described.[1] Its purity as determined by formol titration[6]

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[1] King, THIS JOURNAL, **67**, 2178 (1945).

[2] Owen, *ibid.*, **56**, 24 (1934).

[3] The ionization constant K_2 is related to K_B calculated by Owen by $K_2 = K_w/K_B$.

[4] Owen and King, THIS JOURNAL, **65**, 1612 (1943). According to the conventions of that paper, the second ionization would be represented by the symbols $[k_2]_{0,M}$ or K_2^*.

[5] The use of these stoppers was suggested by Dr. Roger G. Bates.

[6] Dunn and Loshakoff, *J. Biol. Chem.*, **113**, 359 (1936).