[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BOSTON COLLEGE]

Derivatives of *o*-, *m*- and *p*-Aminobenzotrifluoride[1]

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o-, *m*- and *p*-aminobenzotrifluoride have been converted into 7-, 4- and 5-trifluoromethylisatin, respectively, through the corresponding isonitrosoacetanilides, by reactions analogous to those of unsubstituted aniline. Derivatives of the isatins were prepared. Two additional trifluoromethyl compounds, 5,7-bis-(trifluoromethyl)-quinoline and *m*-trifluoromethyl-N-phenylglycine were prepared from 3,5-bis-(trifluoromethyl)-aniline and *m*-aminobenzotrifluoride, respectively.

Aromatic and heterocyclic trifluoromethyl compounds, particularly those related to ortho and para substituted benzotrifluorides, have not been extensively studied. Normal methods of introducing the trifluoromethyl group into a heterocyclic compound could be expected to decompose all but the most stable rings.

Among the heterocyclic compounds of this type may be mentioned the quinoline derivatives prepared by Andersag, Breitner and Jung[2] and by Gilman and co-workers,[3] as well as 5-, 6-, 7- and 8-trifluoromethylquinolines and derivatives reported by Gilman and Blume,[4] Pouterman and Girardet[5] and Mooradian and Suter.[6]

In this paper, the preparation of additional heterocyclic compounds containing the trifluoromethyl groups is described. The three isomeric aminobenzotrifluorides have been converted into the corresponding isonitrosoacetanilides and from these were prepared the 4-, 5- and 7-trifluoromethylisatins.

Hydrolysis of the trifluoromethyl group in the 4-isomer was accomplished with hydrobromic acid in a sealed tube, the identification of the resulting compound as isatin-4-carboxylic acid indicating the position of the trifluoromethyl group. None of the isomeric 6-trifluoromethylisatin apparently was formed in the reaction.

In addition, two further compounds were prepared from *m*-aminobenzotrifluoride and 3,5-bis-(trifluoromethyl)-aniline, namely, *m*-trifluoromethyl-N-phenylglycine and 5,7-bis-(trifluoromethyl)-quinoline, both reactions indicating that the usual reactions of aniline may be expected to take place with the trifluoromethyl substituted analogs.

Experimental

2-Nitro-5-aminobenzotrifluoride.—*m*-Acetaminobenzotrifluoride[7] (196 g.) was nitrated at −2° with a fuming nitric–sulfuric acid mixture according to the directions of Jones,[8] the yield of the purified product being 180 g. (76%); m.p. 108–109° (cor.). The purified acetyl derivative was hydrolyzed by boiling with sodium hydroxide according to Jones' procedure. One hundred twenty grams (80%) of light yellow crystals was obtained; m.p. 126.5–127° (cor.).

***o*-Nitrobenzotrifluoride.**—To a stirred solution of 64 ml. of cold, concentrated sulfuric acid in 500 ml. of water was added 120 g. of 2-nitro-5-aminobenzotrifluoride in small portions. Holding the temperature at −5–0°, a precooled solution of 126 g. of sodium nitrite in 225 ml. of water was run in slowly through a dropping funnel dipping beneath the surface of the solution. Maintaining a temperature of 0°, a 15-fold excess (700 ml.) of 50% hypophosphorous acid was run in slowly through a dropping funnel with vigorous stirring. At the end of the addition, the mixture was stirred an additional three hours at 0°, and allowed to remain in the freezing-bath overnight without stoppering. The mixture was then poured into an ice–water mixture, the brownish-yellow solution extracted with chloroform, and the extracts dried over anhydrous magnesium sulfate. Evaporation of the solvent through a packed column and fractionation of the residue yielded 78 g. (69%) of a liquid boiling at 121–124° at 35 mm.; m.p. 32° (cor.).

***o*-Aminobenzotrifluoride.**—*o*-Nitrobenzotrifluoride (26 g.) was reduced with stannous chloride according to the procedure of Jones.[8] Thirteen grams (59%) of *o*-aminobenzotrifluoride was obtained; b.p. 56–57° at 5 mm.

***m*-Trifluoromethylisonitroacetanilide.**—*m*-Aminobenzotrifluoride (16.5 g.) in dilute hydrochloric acid was added to a mixture of chloral hydrate and sodium sulfate in water, and hydroxylamine hydrochloride added, according to the method of Sandmeyer as described by Marvel and Hiers.[9] On cooling the reaction mixture, white needles were formed and a brown sludge caked in the bottom of the flask. The sludge was dissolved in hot methanol and the solution poured into cold water. The resulting white precipitate was combined with the white needles from the aqueous portion and the whole purified by recrystallization from hot chloroform (300 ml. of solvent for 50 g. of isonitroso compound). The compound crystallized in white needles, which were separated and washed with cold chloroform; yield 21 g. (89%); m.p. 143° (cor.).

Anal. Calcd. for $C_9H_7O_2N_2F_3$: N, 12.07. Found: N, 12.15, 12.27.

4-Trifluoromethylisatin.—To 90 ml. of concentrated sulfuric acid held at 75–80°, *m*-trifluoromethylisonitrosoacetanilide (26.5 g.) was added with stirring over a period of 30 minutes. At the end of this time, the temperature was raised to 85–90° for 15 minutes. (Some decomposition and evolution of hydrogen fluoride was noted.) The deep red solution was cooled to room temperature and poured into a liter of cracked ice. The resulting crude isatin was dissolved in ten times its weight of glacial acetic acid and crystallized by chilling. Further recrystallization from hot methanol yielded 12 g. (47%) of 4-trifluoromethylisatin; m.p. 212–212.5° (cor.). The compound gave a positive indophenin test. 0.1 g. of the 4-trifluoromethylisatin was heated with 1 ml. of 48% hydrobromic acid in a sealed tube for two hours at 190°. The brownish-yellow crystals of isatin-4-carboxylic acid thus obtained were successively recrystallized from hot ligroin and petroleum ether; m.p. 261° (cor.).[10]

Anal. Calcd. for $C_9H_4O_2NF_3$: N, 6.51. Found: N, 6.51, 6.54.

4-Trifluoromethylisatin-3-phenylhydrazone was prepared by the action of phenylhydrazine on the isatin, and was recrystallized from ethanol; m.p. 201–202° (cor.).

Anal. Calcd. for $C_{15}H_{10}ON_3F_3$: N, 13.75. Found: N, 13.63, 13.51.

4-Trifluoromethylisatin-3-(2,4-dinitro)-phenylhydrazone was made from the isatin and 2,4-dinitrophenylhydrazine,

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[1] Taken from a thesis submitted by Camille A. Gaulin to the Boston College Graduate School in partial fulfillment of the requirements for the degree of Master of Science.

[2] H. Andersag, S. Breitner and H. Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

[3] H. Gilman and co-workers, THIS JOURNAL, **68**, 426 (1946).

[4] H. Gilman and D. Blume, *ibid.*, **65**, 2467 (1943).

[5] E. Pouterman and A. Girardet, *Experientia*, **3**, 28 (1947); *Helv. Chim. Acta*, **30**, 107 (1947).

[6] A. Mooradian and C. M. Suter, THIS JOURNAL, **71**, 3507 (1949).

[7] Prepared from *m*-aminobenzotrifluoride, kindly supplied by the Hooker Electrochemical Co., Niagara Falls, N. Y.

[8] R. G. Jones, THIS JOURNAL, **69**, 2346 (1947).

[9] T. Sandmeyer, *Helv. Chim. Acta*, **2**, 237, 239 (1919); C. S. Marvel and G. S. Hiers, "Organic Syntheses," Coll. Vol. I, 1941, p. 327.

[10] P. Friedlaender and J. Weisberg, *Ber.*, **28**, 1641 (1895), reported 260° as the m.p. of isatin-4-carboxylic acid.

and purified by recrystallization from ethanol; m.p. 137° (cor.).

Anal. Calcd. for $C_{15}H_8O_5N_5F_3$: N, 17.70. Found: N, 17.49, 17.35.

p-Trifluoromethylisonitrosoacetanilide.—This compound was prepared from 5.5 g. of p-aminobenzotrifluoride (from p-nitrobenzotrifluoride and stannous chloride as reported by Jones[8]) as described for the preceding isomer, except that a smaller amount (13 g.) of hydrated sodium sulfate was used without decreasing the yield. A much larger amount of brown sludge was formed than in the previous case. This was treated as described above, and 6 g. (76%) of p-trifluoromethylisonitroacetanilide was obtained as white needles; m.p. 148.5° (cor.).

Anal. Calcd. for $C_9H_7O_2N_2F_3$: N, 12.07. Found: N, 11.97, 12.24.

5-Trifluoromethylisatin.—p-Trifluoromethylisonitrosoacetanilide (6 g.) was treated as described above for the preparation of 4-trifluoromethylisatin. Recrystallization from acetic acid and from methanol yielded 2.5 g. (45%) of light brown crystals; m.p. 246° (cor.). The compound gave a positive indophenin test.

Anal. Calcd. for $C_9H_4O_2NF_3$: N, 6.51. Found: N, 6.47, 6.77.

Sealed tube hydrolysis with hydrobromic acid gave the corresponding isatin-5-carboxylic acid; m.p. 293.5 (cor.).[11]

5-Trifluoromethylisatin-3-phenylhydrazone was prepared and purified as described for the preceding isomer; m.p. 181° (cor.).

Anal. Calcd. for $C_{15}H_{10}ON_3F_3$: N, 13.75. Found: N, 13.47, 13.66.

5-Trifluoromethylisatin-3-(2,4-dinitro)-phenylhydrazone was prepared from the isatin and 2,4-dinitrophenylhydrazine; m.p. 273° (cor.).

Anal. Calcd. for $C_{15}H_8O_5N_5F_3$: N, 17.70. Found: N, 17.55, 17.38.

o-Trifluoromethylisonitrosoacetanilide.—The compound was prepared from o-aminobenzotrifluoride (13 g.) essentially as described above. A viscous brown sludge, but no crystals, separated when the reaction mixture was cooled. The mixture was then extracted with chloroform, and the dried extracts allowed to evaporate. Light brown crystals separated, which were taken up in chloroform. The solution was partially evaporated and cooled in an ice-bath, whereupon 12 g. (64%) of o-trifluoromethylisonitrosoacetanilide separated as pale brown needles; m.p. 79–80° (cor.).

Anal. Calcd. for $C_9H_7O_2N_2F_3$: N, 12.07. Found: N, 11.92, 12.32.

7-Trifluoromethylisatin.—o-Trifluoromethylisonitrosoacetanilide (6 g.) was treated as previously described for the preparation of the 4-trifluoromethyl-isomer. Recrystallization from acetic acid and from methanol yielded 3.5 g. (60%) of reddish-brown crystals; m.p. 189–190° (cor.). The indophenin test was positive.

Anal. Calcd. for $C_9H_4O_2NF_3$: N, 6.51. Found: N, 6.73, 6.48.

7-Trifluoromethylisatin-3-phenylhydrazone was prepared from the isatin and phenylhydrazine and recrystallized from glacial acetic acid; m.p. 209.5–210° (cor.).

Anal. Calcd. for $C_{15}H_{10}ON_3F_3$: N, 13.75. Found: N, 13.84, 13.97.

7-Trifluoromethylisatin-3-(2,4-dinitro)-phenylhydrazone was prepared as described above and recrystallized from glacial acetic acid; m.p. *ca.* 330° with dec.

Anal. Calcd. for $C_{15}H_8O_6N_5F_3$: N, 17.70. Found: N, 17.79, 17.60.

3,5-Bis-(trifluoromethyl)-aniline.—Hexafluoro-m-xylene was nitrated by a fuming nitric–sulfuric acid mixture as described by Swarts[12] for the nitration of benzotrifluoride. The 3,5-bis-(trifluoromethyl)-nitrobenzene (b.p. 92–93° at 20 mm.) thus obtained was reduced with tin and hydrochloric acid following the method of Aelony[13] to the 3,5-bis-(trifluoromethyl)-aniline; b.p. 85° at 15 mm.

5,7-Bis-(trifluoromethyl)-quinoline.—The conventional Skraup synthesis[14] was used in this preparation, employing 6.9 g. of 3,5-bis-(trifluoromethyl)-aniline, 3 g. of ferrous sulfate, 30 g. of glycerol, 6 g. of nitrobenzene and 12 ml. of concentrated sulfuric acid. The yield after distillation and fractionation was 2.5 g. (33%); b.p. 97–98° at 17 mm.

Anal. Calcd. for $C_{11}H_5NF_6$: N, 5.28. Found: N, 5.57, 5.29.

m-Trifluoromethyl-N-phenylglycine.—The glycine was prepared by a modification of the method of Hausdörfer.[15] Fifty grams of chloroacetic acid was added to a stirred solution of 90 g. of m-aminobenzotrifluoride in 100 ml. of dioxane in a 500-ml. flask. A solution of 35 g. of sodium acetate in 100 ml. of water was run in and the reaction mixture refluxed for 12 hours with stirring. The mixture was then neutralized with dilute sodium hydroxide solution and steam distilled. Forty grams of m-aminobenzotrifluoride was recovered unchanged. The dark brown gum remaining in the flask was taken up in ethanol, from which solution a small amount of fine light brown crystals of m-trifluoromethyl-N-phenylglycine was obtained upon the addition of finely chopped ice. This result, however, could not be reproduced on a larger scale. To crystallize the mass it was necessary to dissolve it in a dilute solution of water in pyridine and crystallize by chilling. Final purification was accomplished by recrystallization from ether; m.p. 117.5 (cor.).

Anal. Calcd. for $C_9H_8O_2NF_3$: N, 6.39. Found: N, 7.02, 6.80.

Acknowledgment.—The authors wish to express their indebtedness to the late Dr. Wilfred A. Grapes, Jr., under whose direction this investigation was begun.

CHESTNUT HILL, MASS. RECEIVED AUGUST 16, 1950

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(11) E. Giovanni and C. Portmann, *Helv. Chim. Acta*, **31**, 1392 (1948), gave as the m.p. 295°.

(12) F. Swarts, *Bull. sci. acad. roy. Belg.*, [3] **35**, 375 (1898)· *Chem. Zentr.*, **69**, II, 26 (1898).

(13) D. Aelony, THIS JOURNAL, **56**, 2063 (1934).

(14) H. T. Clarke and A. W. Davis, "Organic Syntheses," Coll. Vol. I, 1941, p. 478.

(15) A. Hausdörfer, *Ber.*, **22**, 1795 (1889); *cf.* also J. Mai, R. Kahn and W. Heiman, *ibid.*, **35**, 576 (1902).