8-Hydroxy-5-trifluoromethylquinoline.

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4-Chloro-3-nitrobenzotrifluoride gave, with ammonia, the 4-amino-analogue, from which 4-hydroxy-3-nitro- and thence 3-amino-4-hydroxybenzotrifluoride were made. A Skraup reaction on the latter afforded 8-hydroxy-5-trifluoromethylquinoline. Methylation of this gave the 8-methoxy-derivative, prepared also from 3-amino-4-methoxybenzotrifluoride.

This work is part of an investigation upon the organic and analytical chemistry of trifluoromethylquinoline derivatives (see also Belcher, Stacey, Sykes, and Tatlow, preceding paper; Belcher, Sykes, and Tatlow, *J.*, 1954, in the press), and was directed particularly towards the synthesis of 8-hydroxy-5-trifluoromethylquinoline. 4-Chloro-3-nitrobenzotrifluoride (I.G. Farben. A.-G., F.P. 745,293; *Chem. Abs.*, 1933, **27**, 4414) was used as starting material since it possesses a reactive chlorine atom. A complication which arises, however, is that, when, by exchange of this atom an activating substituent has been introduced into the position *para* to the trifluoromethyl group, the reactivity of the latter may be enhanced considerably, so that its fluorine may be subsequently lost. Thus, when treated with aqueous-alcoholic potassium hydroxide, the 4-chloro-compound afforded 4-hydroxy-3-nitrobenzoic acid, also formed in small yield by the action of sodium carbonate or nitrite, reagents which give the phenol from 1-chloro-2 : 4-dinitrobenzene (Clemm, *J. prakt. Chem.*, 1870, **1**, 145; Kym, *Ber.*, 1901, **34**, 3311). However, with alcoholic ammonia at 120°, the trifluoromethyl group was unattacked and 4-amino-3-nitrobenzotrifluoride was formed (cf. Hoffa and Müller, U.S.P. 2,056,899). With aqueous-alcoholic ammonia at higher temperatures, the yield of amine was greatly reduced, there being obtained also a high-melting solid, formed apparently by intermolecular elimination of hydrogen fluoride.

Diazotisation of the nitro-amine, followed by heating, gave 4-hydroxy-3-nitrobenzotrifluoride which was stable when pure, but was hydrolysed readily by dilute alkali to 4-hydroxy-3-nitrobenzoic acid, and on catalytic hydrogenation afforded 3-amino-4-hydroxybenzotrifluoride. This compound, by a Skraup reaction, afforded 8-hydroxy-5-trifluoromethylquinoline, which, as expected, was unstable in an alkaline medium, the fluorine being liberated readily as fluoride ion. Loss of fluorine occurred even in the cold under the mild conditions (N/20-alkali) used in analytical tests (Belcher, Sykes, and Tatlow, *loc. cit.*). Methylation of the hydroxyquinoline by diazomethane gave 8-methoxy-5-trifluoromethylquinoline, identical with the compound made independently from 8-amino-5-trifluoromethylquinoline (Belcher, Stacey, Sykes, and Tatlow, *loc. cit.*). This 8-methoxy-derivative was prepared also by a Skraup reaction upon 3-amino-4-methoxybenzotrifluoride, which had been made from 4-chloro-3-nitrobenzotrifluoride by Benkeser and Buting's method (*J. Amer. Chem. Soc.*, 1952, **74**, 3011). Catalytic reduction of 4-methoxy-3-nitrobenzotrifluoride afforded not only the amine but in one case also the corresponding azo- and azoxy-compounds.

In contrast to the hydroxy-compound, 8-methoxy-5-trifluoromethylquinoline was not attacked by boiling aqueous-alcoholic alkali. Boiling hydriodic acid demethylated it but, in a Zeisel determination, a reaction time of 8 hr. or so was apparently needed for a quantitative methoxyl recovery. On a larger scale, etching in the reflux condenser suggested that the trifluoromethyl group also had been hydrolysed, presumably after the demethylation. The only material isolated, however, was 8-hydroxyquinoline, the process having gone still further, in that the expected 5-carboxylic acid had suffered decarboxylation. A similar effect was found with the corresponding 8-amino-compound (Belcher, Stacey, Sykes, and Tatlow, *loc. cit.*).

EXPERIMENTAL

Amination of 4-Chloro-3-nitrobenzotrifluoride.—The chloronitro-compound (50·0 g.) and saturated ammoniacal ethyl alcohol (250 c.c.) were heated at 120° in an autoclave under autogenous pressure for 5 hr. The solution was concentrated and the residue was recrystallised from aqueous ethyl alcohol to give 4-amino-3-nitrobenzotrifluoride (35·5 g.), m. p. 106—107° (Found : C, 41·0; H, 2·5; F, 27·4. Calc. for $C_7H_5O_2N_2F_3$: C, 40·8; H, 2·4; F, 27·7%) (F.P. 745,293 gives m. p. 109—110°). Treatment of the product in ether with trifluoroacetic anhydride yielded the N-*trifluoroacetyl* derivative, m. p. 65—66° (Found: C, 35·7; H, 1·5. $C_9H_4O_3N_2F_6$ requires C, 35·8; H, 1·3%).

The N-*acetyl* derivative, prepared by use of acetic acid–acetic anhydride, had m. p. 112—113° (Found : C, 43·4; H, 2·7. $C_9H_7O_3N_2F_3$ requires C, 43·6; H, 2·8%).

4-*Hydroxy*-3-*nitrobenzotrifluoride*.—4-Amino-3-nitrobenzotrifluoride (15·0 g.) was dissolved in concentrated sulphuric acid (40 c.c.) and water (10 c.c.), and diazotised with a saturated solution of sodium nitrite. The resulting solution was added gradually to a boiling solution of copper sulphate pentahydrate (70 g.) in water (200 c.c.), volatile matter being continuously removed in steam. The distillate was extracted with ether, and the extracts were dried ($MgSO_4$) and evaporated. Distillation of the residue afforded 4-*hydroxy*-3-*nitrobenzotrifluoride* (7·1 g.), a pale yellow oil, b. p. 92—94°/12 mm. (Found : C, 40·6; H, 1·8; F, 27·3. $C_7H_4O_3NF_3$ requires C, 40·6; H, 1·95; F, 27·5%). Its *toluene*-p-*sulphonyl* ester had m. p. 58—59° (Found: C, 46·6; H, 2·5. $C_{14}H_{10}O_5NSF_3$ requires C, 46·5; H, 2·8%).

Hydrolysis of 4-*Hydroxy*-3-*nitrobenzotrifluoride*.—A solution of the nitrophenol (0·42 g.) in ethyl alcohol (2·0 c.c.) was added slowly to an excess of hot aqueous sodium hydroxide (10%). The mixture was heated under gentle reflux for 20 min., cooled, and acidified with concentrated hydrochloric acid. Recrystallisation of the precipitate from water gave 4-hydroxy-3-nitrobenzoic acid (0·28 g.), m. p. 181—182° (Found : C, 45·7; H, 2·7. Calc. for $C_7H_5O_5N$: C, 45·9; H, 2·75%). Biehringer and Borsum (*Ber.*, 1915, **48**, 1314) recorded m. p. 182—183° for this acid.

Action of Potassium Hydroxide on 4-*Chloro*-3-*nitrobenzotrifluoride*.—To a solution of 4-chloro-3-nitrobenzotrifluoride (2·15 g.) in ethyl alcohol (11 c.c.) a solution of potassium hydroxide (3·3 g.) in water (11 c.c.) was added. The mixture was refluxed for 15 hr., filtered, and extracted with ether. The dried extract was evaporated to give an orange liquid (0·11 g.). The yellow aqueous phase was acidified with concentrated hydrochloric acid, a second ether extraction was carried out, and the residue obtained after evaporation of the ether was recrystallised from water to give 4-hydroxy-3-nitrobenzoic acid (1·40 g.), m. p., and mixed m. p. with the material reported above, 181—182°.

Reduction of 4-*Hydroxy*-3-*nitrobenzotrifluoride*.—4-Hydroxy-3-nitrobenzotrifluoride (6·32 g.) in ethyl alcohol (50 c.c.) was reduced by hydrogen–Raney nickel at atmospheric pressure. When the theoretical amount of hydrogen had been absorbed, the dark solution was evaporated to dryness under diminished pressure. The residue was recrystallised from benzene, giving needles of 3-*amino*-4-*hydroxybenzotrifluoride* (4·92 g.), m. p. 121—122° (Found: C, 47·7; H, 3·2. $C_7H_6ONF_3$ requires C, 47·5; H, 3·4%); the *acetyl* derivative had m. p. 157—158° (Found: C, 49·5; H, 3·7. $C_9H_8O_2NF_3$ requires C, 49·3; H, 3·7%).

Skraup Reaction upon 3-*Amino*-4-*hydroxybenzotrifluoride*.—3-Amino-4-hydroxybenzotrifluoride (2·19 g.), arsenic oxide (2·4 g.), glycerol (4·9 g.), and concentrated sulphuric acid (2·9 g.) were stirred and heated at 160—175° for 3½ hr. When cool, the mixture was stirred with water (200 c.c.), and the pH of the solution was brought to 4 by addition of saturated sodium acetate solution. After exhaustive extraction with ether, the extracts were dried (Na_2SO_4) and evaporated, and the residue was recrystallised from ethyl alcohol to give 8-*hydroxy*-5-*trifluoromethylquinoline* (0·70 g.), m. p. 92—96°, which was sublimed *in vacuo* to give a very pale yellow solid, m. p. 96—97°, depressed by the 6-trifluoromethyl isomer (m. p. 95°; Belcher, Stacey, Sykes, and Tatlow, *loc. cit.*) (Found: C, 56·6; H, 2·6; F, 26·7. $C_{10}H_6ONF_3$ requires C, 56·3; H, 2·8; F, 26·7%). The *toluene*-p-*sulphonate* had m. p. 156·5—157·5° (Found: C, 55·8; H, 3·4. $C_{17}H_{12}O_3NSF_3$ requires C, 55·6; H, 3·3%).

Methylation of 8-*Hydroxy*-5-*trifluoromethylquinoline*.—To the trifluoromethylquinolinol (0·073 g.) in dry ether (30 c.c.) was added a solution of diazomethane (*ca.* 0·1 g.) in dry ether (30 c.c.), and the mixture was set aside for 48 hr. It was then filtered and evaporated at 20°/15 mm. The residual solid was taken up in ether, and the solution washed with aqueous sodium hydroxide, dried ($MgSO_4$), and evaporated. Recrystallisation afforded pale yellow prisms of 8-methoxy-5-trifluoromethylquinoline (0·045 g.), m. p. and mixed m. p. 80°, identical with that reported below.

Preparation of 3-*Amino*-4-*methoxybenzotrifluoride*.—4-Methoxy-3-nitrobenzotrifluoride (Benkeser and Buting, *loc. cit.*) (25·0 g.), ethyl alcohol (50 c.c.), and concentrated hydrochloric acid (80 c.c.) were stirred, and stannous chloride dihydrate (100 g.) added portion-wise. The mixture was refluxed for 30 min. and then poured on an excess of aqueous sodium hydroxide and crushed ice. Extraction as usual, followed by recrystallisation from light petroleum (b. p. 60—80°), afforded 3-amino-4-methoxybenzotrifluoride (15·0 g.), m. p. 58—59°. Brown, Suckling, and

Whalley (*J.*, 1949, S 95) recorded m. p. 59°; see also Whalley (*J.*, 1949, 3016). The *trifluoroacetyl* derivative, prepared by the action of trifluoroacetic anhydride on an ethereal solution, had m. p. 99—101° (Found: C, 41·9; H, 2·8. $C_{10}H_7O_2NF_6$ requires C, 41·8; H, 2·5%).

Catalytic reduction of the parent nitro-compound by Benkeser and Buting's method (*loc. cit.*) also gave the amine; from a reduction which was incomplete there were also obtained, by fractional crystallisation from ethyl alcohol, red needles of 2 : 2'-*dimethoxy*-5 : 5'-*bistrifluoromethylazobenzene*, m. p. 215—216° (Found: C, 51·0; N, 2·9. $C_{16}H_{12}O_2N_2F_6$ requires C, 50·8; H, 3·2%), and pale yellow prisms of 2 : 2'-*dimethoxy*-5 : 5'-*bistrifluoromethylazoxybenzene*, m. p. 133° (Found: C, 48·7; H, 3·2. $C_{16}H_{12}O_3N_2F_6$ requires C, 48·7; H, 3·1%).

Preparation of 8-*Methoxy*-5-*trifluoromethylquinoline*.—3-Amino-4-methoxybenzotrifluoride (4·85 g.), glycerol (8·2 g.), arsenic oxide (4·3 g.), and concentrated sulphuric acid (5·0 g.) were stirred and heated at 135° for 1 hr., and then at 160—170° for a further 3 hr. Excess of alkali was added to the product, which was subsequently exhaustively extracted with ether. The extracts were dried ($MgSO_4$) and evaporated. Recrystallisation of the residue first from aqueous ethyl alcohol and then from light petroleum (b. p. 60—80°) yielded 8-*methoxy*-5-*trifluoromethylquinoline* (1·71 g.), m. p. 81—82° undepressed in admixture with the material described by Belcher, Stacey, Sykes, and Tatlow (*loc. cit.*) (Found: C, 57·8; H, 3·9; F, 24·7. $C_{11}H_8ONF_3$ requires C, 58·1; H, 3·55; F, 25·1%). This compound was unattacked when boiled with aqueous-alcoholic potassium hydroxide (5N) for 5 hr. No fluoride ion was detected, the starting material (77%), m. p. and mixed m. p. 80°, being obtained.

Action of Hydriodic Acid on 8-*Methoxy*-5-*trifluoromethylquinoline*.—The quinoline (0·455 g.) was heated under reflux with hydriodic acid (20 c.c.; *d* 1·7) for 25 hr. Etching in the condenser indicated that hydrolysis of the trifluoromethyl group had occurred. The residual liquid was diluted with water (80 c.c.), and the liquid was extracted with ether. A saturated solution of sodium acetate was added (pH then *ca.* 4) and a second extraction with ether was carried out. After being dried (Na_2SO_4), this extract was evaporated, and the residue recrystallised from light petroleum (b. p. 60—80°) to give 8-hydroxyquinoline (0·094 g.), m. p. and mixed m. p. 74—75° (Found: C, 74·0; H, 4·7. Calc. for C_9H_7ON: C, 74·45; H, 4·9%).

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