The Synthesis of Certain Trifluoromethylquinoline Derivatives.

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Skraup reactions upon 3-amino-2-, -4-, and -5-nitrobenzotrifluoride afforded 8-nitro-7-, 8-nitro-5-, and 5-nitro-7-trifluoromethylquinoline, respectively, reduction of which gave the corresponding aminotrifluoromethylquinolines. These were deaminated *via* their diazonium salts, and the latter were coupled with β-naphthol and, though the two possessing 8-diazo-groups could not be converted into the 8-hydroxyquinolines, they gave, in the usual way, 8-iodo-7- and -5-trifluoromethylquinoline. 8-Amino-7-trifluoromethylquinoline yielded the 8-hydroxy-analogue when treated with hydrochloric acid. A Skraup reaction on 4-amino-3-hydroxybenzotrifluoride afforded 8-hydroxy-6-trifluoromethylquinoline.

There have been several reports of syntheses of trifluoromethylquinolines by Skraup reactions. Gilman and Blume (*J. Amer. Chem. Soc.*, 1943, **65**, 2467) and Pouterman and Girardet (*Experientia*, 1947, **3**, 28) made 5- and 7-trifluoromethylquinoline from 3-aminobenzotrifluoride, and the latter authors (*Helv. Chim. Acta*, 1947, **30**, 107) prepared 6- and 8-trifluoromethylquinoline from the 2- and 4-amino-isomers, whilst Gilman, Tolman, Yeoman, Woods, Shirley, and Avakian (*J. Amer. Chem. Soc.*, 1946, **68**, 426) converted 3-amino-6-nitrobenzotrifluoride into 6-nitro- and thence 6-amino-7-trifluoromethylquinoline. There are three other nitro-3-aminobenzotrifluorides, the 2- and the 4- (Rouche, *Bull. Acad. roy. Belg.*, 1927, **13**, 346; Pouterman and Girardet, *loc. cit.*), and the 5- (Finger and Reed, *J. Amer. Chem. Soc.*, 1944, **66**, 1972) nitro-isomer. This paper reports the application of the Skraup reaction to these compounds, and to 3-amino-4-hydroxybenzotrifluoride, together with investigations on the products and on related trifluoromethylquinoline derivatives, particularly the amines.

Treatment of 3-amino-2-, -4-, and -5-nitrobenzotrifluoride with glycerol, sulphuric acid, and arsenic pentoxide under the conditions recommended by Smith and Richter [" Phen anthroline and Substituted Phenanthroline Indicators," G. F. Smith Chemical Co., Columbus (Ohio), 1944, p. 8; *J. Amer. Chem. Soc.*, 1944, **66**, 396] afforded 8-nitro-7-, 8-nitro-5-, and, as was shown later, 5-nitro-7-trifluoromethylquinoline, respectively. Earlier ideas (Manske, *Chem. Reviews*, 1942, **30**, 113), about the directing effects which applied when Skraup

reactions were carried out upon anilines in which a substituent was in a position *meta* to the amino-group, were as follows: when an *ortho-para*-directing substituent was in the *meta*-position, ring closure occurred on either side of the amino-group whilst, when a *meta*-directing substituent was present, closure was effected between it and the amino-group. More recently, Bradford, Elliott, and Rowe (*J.*, 1947, 437) showed that, at least under the reaction conditions given in the I. G. Farben A.-G. Patent, B.P. 394,416, from *meta*-substituted anilines with (*a*) strongly *ortho-para*-directing groups, 7-substituted quinolines were obtained, with (*b*) weakly *ortho-para*-directing groups, mixtures of 5- and 7-substituted quinolines, the latter isomers predominating, were formed, and with (*c*) *meta*-directing groups, similar mixtures, but with the former isomers predominating, resulted. Hence, if it is assumed that the type of product obtained in a Skraup reaction is not greatly influenced by the reaction conditions, the trifluoromethyl group seems to occupy an anomalous position. Thus, 3-aminobenzotrifluoride gave 5- (6%) and 7- (32%) trifluoromethylquinoline (Gilman and Blume, *loc. cit.*; these figures were essentially confirmed in the present work); 3-amino-6-nitrobenzotrifluoride afforded 6-nitro-7-trifluoromethylquinoline (Gilman, Tolman, *et al.*, *loc. cit.*), and, in this work, from 3-amino-5-nitrobenzotrifluoride only 5-nitro-7-trifluoromethylquinoline was isolated. Thus, the formation of 7-trifluoromethylquinolines seems to be favoured. Though it is, in general, a *meta*-directing substituent, the trifluoromethyl group behaves, in the Skraup synthesis, as would be expected of an *ortho-para*-directing residue. If this effect is due only to variations in reaction conditions between different series, then the classification of directive influences in this particular process would appear to be very difficult. The reason for the discrepancies may lie in steric effects, but it seems unlikely that the trifluoromethyl group is sufficiently large for these to be the only factors involved.

8-Amino-7-trifluoromethylquinoline was obtained by reduction of the nitro-analogue. It was diazotised and the diazo-solution subjected to several standard reactions. Treatment with hypophosphorous acid gave 7-trifluoromethylquinoline, confirming the structure of the amine, and a coupling product was obtained with alkaline β-naphthol. However, the diazo-solution did not give the corresponding 8-hydroxyquinoline, though various reaction conditions were tried. In general, unidentified high-melting resins were obtained. Diazotised 8-amino-5-trifluoromethylquinoline also could not be converted into the hydroxyquinoline (see p. 3850). This failure to give phenols *via* the diazonium salts is apparently common with 8-aminoquinolines, though there are few indications of it in the literature. 8-Iodo-7-trifluoromethylquinoline was made readily from the analogous amine by using the diazo-reaction. With ethanolic or methanolic potassium hydroxide this iodo-derivative gave 7-trifluoromethylquinoline, presumably by a reductive process. This suggested again that substituents in position 8 in this quinoline have some unusual properties.

8-Amino-7-trifluoromethylquinoline would not undergo hydrolysis to the corresponding 7-carboxylic acid with concentrated sulphuric acid. With concentrated hydrochloric acid, however, which effects hydrolysis of the amino-groups of 5- and 7-aminoquinoline (Claus and Howitz, *J. pr. Chem.*, 1893, **47**, 426; Claus and Massau, *ibid.*, **48**, 170; Kochańska and Bobrański, *Ber.*, 1936, **69**, 1807), the amino-group was removed, and but little attack on the trifluoromethyl group occurred, 8-hydroxy-7-trifluoromethylquinoline being formed. The trifluoromethyl group of this compound was hydrolysed with concentrated sulphuric acid, and, after reaction with alcohol, there was obtained ethyl 8-hydroxyquinoline-7-carboxylate, identical with a specimen prepared by carboxylation, etc., of the sodium derivative of 8-hydroxyquinoline.

Diazotisation of 8-amino-5-trifluoromethylquinoline in aqueous sulphuric acid was complicated in that a precipitate was formed, and very little diazonium salt remained in the solution. The structure of this precipitate was not established. By diazotisation of the amine in a solution containing hypophosphorous acid, 5-trifluoromethylquinoline was obtained, confirming the structure of the parent compound. The diazotisation of this amine was best effected by Hodgson and Walker's method using nitrosylsulphuric acid (*J.*, 1933, 1620); dilution with water caused precipitation of the solid mentioned previously, but addition of alkaline β-naphthol gave the corresponding coupling derivative, and aqueous potassium iodide yielded 8-iodo-5-trifluoromethylquinoline. This was converted, by

methanolic sodium methoxide, into 8-methoxy-5-trifluoromethylquinoline, identical with that prepared from 4-chloro-3-nitrobenzotrifluoride (Pettit and Tatlow, following paper). 8-Amino-5-trifluoromethylquinoline was attacked by concentrated sulphuric acid to give what was probably the corresponding amino-carboxylic acid, but which decomposed at the melting point with the formation of 8-aminoquinoline. 8-Amino-5-trifluoromethylquinoline did not give the hydroxy-analogue with concentrated hydrochloric acid, because of preferential attack on the trifluoromethyl group with liberation of fluoride ion; it appeared that this occurred at temperatures below those necessary to remove the amino-group. Application of the Skraup reaction to 8-amino-5-trifluoromethylquinoline did not give a trifluoromethylphenanthroline, again because of attack on the fluoroalkyl group. The only product isolated was 1 : 10-phenanthroline, the trifluoromethyl group being lost, presumably, by hydrolysis to the carboxylic acid, followed by decarboxylation.

3-Amino-4-nitrobenzotrifluoride, by a diazo-reaction gave 3-hydroxy-4-nitrobenzotrifluoride, obtained by De Brouwer (*Bull. Soc. chim. Belg.*, 1930, **39**, 298) by alkaline hydrolysis of the nitro-amine. This nitro-phenol was reduced catalytically to the corresponding amino-phenol, which was stable to dilute acids but lost fluoride ion in warm dilute alkali and gave an amorphous solid product. This effect is similar to that observed with 4-aminobenzotrifluoride itself (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2346). 4-Amino-3-hydroxybenzotrifluoride in the Skraup reaction afforded 8-hydroxy-6-trifluoromethylquinoline, which was hydrolysed to the known 8-hydroxyquinoline-6-carboxylic acid.

From 3-amino-5-nitrobenzotrifluoride, a Skraup reaction gave only 5-nitro-7-trifluoromethylquinoline, identified by reduction and deamination to 7-trifluoromethylquinoline, in good yield.

Experimental

3-Amino-5-nitrobenzotrifluoride.—This was made by a slight modification of Finger and Reed's method (*loc. cit.*) by nitration of 3-nitrobenzotrifluoride (114 g.) with nitric acid (200 c.c.) and sulphuric acid (600 c.c.), at 90—100° for 2 hr. and at 120° for 4½ hr., followed by isolation of 3 : 5-dinitrobenzotrifluoride (yield 45%), and partial reduction as described by these authors.

Skraup Reaction on 3-Aminobenzotrifluoride.—The amine (32·2 g.), glycerol (73·6 g.), and arsenic pentoxide (34·5 g.) were stirred mechanically, whilst concentrated sulphuric acid (40·0 g.) was added slowly. The mixture was heated to 135° and after 1 hr. it was refluxed for a further 3 hr. After isolation by Gilman and Blume's method (*loc. cit.*), there were obtained 7- (12·4 g.), m. p. 67°, and 5-trifluoromethylquinoline (3·5 g.), b. p. 214—217°. The only product obtained from the reaction of 7-trifluoromethylquinoline with fuming nitric acid–sulphuric acid was *7-trifluoromethylquinolinium nitrate*, m. p. 171° (Found: C, 46·2; H, 2·6; F, 21·4. $C_{10}H_7O_3N_2F_3$ requires C, 46·15; H, 2·7; F, 21·9%), from which, by treatment with aqueous ammonia, the original quinoline was regenerated.

From attempts to nitrate 5-trifluoromethylquinoline only the starting material was obtained.

8-Nitro-7-trifluoromethylquinoline.—3-Amino-2-nitrobenzotrifluoride (20·6 g.), glycerol (36·8 g.; dried at 180° for 2 hr.), and arsenic pentoxide (17·2 g.) were stirred, and sulphuric acid (17 g.) was added slowly. The mixture was heated cautiously for 1 hr. (at *ca.* 135°) so that the ensuing reaction never became vigorous, and finally it was refluxed for a further 3 hr., stirring being continued throughout. The mixture was poured into water and neutralised with aqueous sodium hydroxide (2N); the precipitate was removed and treated with charcoal in boiling ethyl alcohol, and the solution filtered and concentrated. The deposited solid afforded *8-nitro-7-trifluoromethylquinoline* (3·4 g.), m. p. 167° (from ethyl alcohol) (Found: C, 49·5; H, 1·9; F, 23·3. $C_{10}H_5O_2N_2F_3$ requires C, 49·6; H, 2·1; F, 23·5%).

8-Amino-7-trifluoromethylquinoline.—The nitro-compound (4·75 g.), concentrated hydrochloric acid (50 c.c.), and stannous chloride dihydrate (30 g.) were heated under reflux for 30 min. and then cooled. The precipitate was filtered off and treated with aqueous sodium hydroxide until the solution was strongly alkaline, and the suspension extracted with ether. The extracts were washed, dried ($MgSO_4$), filtered, and evaporated, and the residue was crystallised from aqueous ethyl alcohol to give *8-amino-7-trifluoromethylquinoline* (3·40 g.), m. p. 156° (Found: C, 56·6; H, 3·1; F, 26·4. $C_{10}H_7N_2F_3$ requires C, 56·6; H, 3·3; F, 26·9%). This amine was unattacked after 3 hr. with concentrated sulphuric acid at 200°; after 3 hr. at 220° charring had occurred and no product could be isolated.

The N-*acetyl* derivative (from ethyl alcohol) had m. p. 200·5—201° (Found : C, 56·6; H, 3·2; F, 22·2. $C_{12}H_9ON_2F_3$ requires C, 56·7; H, 3·6; F, 22·4%).

Diazotisation of 8-*Amino*-7-*trifluoromethylquinoline*.—This amine (0·50 g.), in water (20 c.c.) and concentrated hydrochloric acid (1·25 c.c.) at 0°, was diazotised by addition of sodium nitrite (0·17 g.) in water (2·5 c.c.), and, after 15 min., urea was added. The solution was divided into two equal parts; to one was added hypophosphorous acid (3·0 c.c. of 30%), and after 16 hr. at 15°, the solution was made alkaline with sodium hydroxide; the resultant precipitate gave 7-trifluoromethylquinoline (0·15 g.), m. p. and mixed m. p. 67° (from aqueous ethyl alcohol) (Found : C, 60·7; H, 3·3. Calc. for $C_{10}H_6NF_3$: C, 60·9; H, 3·1%).

To the second portion of the diazo-solution β-naphthol in alkali was added. Recrystallisation of the red precipitate from acetic acid afforded 7-*trifluoromethyl*-8-*quinolylazo*-β-*naphthol* (0·41 g.), m. p. 233° (Found : C, 65·4; H, 3·3; F, 15·6. $C_{20}H_{12}ON_3F_3$ requires C, 65·4; H, 3·3; F, 15·5%).

8-*Iodo*-7-*trifluoromethylquinoline*.—8-Amino-7-trifluoromethylquinoline (1·00 g.) was diazotised at 5° by means of sulphuric acid (6 c.c.; 6N) and sodium nitrite (0·36 g.) in water (5 c.c.). A little urea was added, and then the solution was added to water (5 c.c.) containing potassium iodide (1·0 g.). After 2 hr. at 15° the precipitate was filtered off and recrystallised from aqueous ethyl alcohol to give 8-*iodo*-7-*trifluoromethylquinoline* (0·67 g.), m. p. 112° (Found : C, 37·5; H, 1·6; I, 39·2; F, 17·3. $C_{10}H_5NIF_3$ requires C, 37·2; H, 1·6; I, 39·3; F, 17·6%).

Action of Alcoholic Potassium Hydroxide on 8-*Iodo*-7-*trifluoromethylquinoline*.—The iodo-compound (2·0 g.) was refluxed in ethanolic potassium hydroxide (35%; 10 c.c.) for 6 hr. The solution was diluted with an excess of water and the precipitate was filtered off and distilled (at 15 mm.) on to a cold finger to give 7-trifluoromethylquinoline (0·65 g.), m. p. and mixed m. p. 66—67° (Found : C, 61·1; H, 3·0%). A similar experiment in which the iodo-compound (1·00 g.) was refluxed for 5 hr. with potassium hydroxide (4·0 g.) in methyl alcohol (7·0 c.c.) and water (3·0 c.c.) gave the same product (0·36 g.), m. p. and mixed m. p. 66—67°.

8-*Hydroxy*-7-*trifluoromethylquinoline*.—8-Amino-7-trifluoromethylquinoline (1·00 g.) and concentrated hydrochloric acid (20·0 c.c.) were heated in a sealed tube at 220° ± 5° for 4 hr. The solution was filtered, made alkaline with ammonia solution (*d* 0·88), and then neutralised with glacial acetic acid. The precipitate was filtered off, and recrystallised from ethyl alcohol to give 8-*hydroxy*-7-*trifluoromethylquinoline* (0·341 g.), m. p. 252° (Found : C, 56·2; H, 2·7; F, 26·8%; *M*, 225. $C_{10}H_6ONF_3$ requires C, 56·3; H, 2·8; F, 26·7%; *M*, 213). The O-*toluene*-p-*sulphonate* (52%; from aqueous ethyl alcohol) had m. p. 114° (Found : C, 55·9; H, 3·2; F, 15·2. $C_{17}H_{12}O_3NSF_3$ requires C, 55·6; H, 3·3; F, 15·5%), and the O-p-*nitrobenzoate* (49%; from aqueous ethyl alcohol), m. p. 157—158° (Found : C, 56·7; H, 2·7. $C_{17}H_9O_4N_2F_3$ requires C, 56·4; H, 2·5%).

Treatment of the hydroxy-compound for 3 hr. at 15° with ethereal diazomethane afforded 8-*methoxy*-7-*trifluoromethylquinoline* (60%), m. p. 79° (from aqueous ethyl alcohol) (Found : C, 58·5; H, 3·6. $C_{11}H_8ONF_3$ requires C, 58·15; H, 3·55%).

Ethyl 8-*Hydroxyquinoline*-7-*carboxylate*.—8-Hydroxy-7-trifluoromethylquinoline (0·050 g.) was heated with concentrated sulphuric acid (1·0 c.c.) for 90 min. at 180—190°. The solution was cooled, ethyl alcohol (3·0 c.c.) was added, and after 4 hours' refluxing the whole was neutralised carefully with sodium hydrogen carbonate. After 16 hr., crystals had separated; recrystallisation from benzene–light petroleum (b. p. 60—80°) afforded ethyl 8-hydroxyquinoline-7-carboxylate (0·034 g.), m. p. 88° (Found : C, 66·3; H, 5·3. Calc. for $C_{12}H_{11}O_3N$: C, 66·3; H, 5·1%) undepressed on admixture with a specimen prepared by Einhorn and Pfyl's method (*Annalen*, 1900, **311**, 26).

8-*Nitro*-5-*trifluoromethylquinoline*.—3-Amino-4-nitrobenzotrifluoride, when treated with glycerol, arsenic pentoxide, and sulphuric acid as described for its isomer, the mixture being refluxed for 4 hours, afforded 8-*nitro*-5-*trifluoromethylquinoline* (26%), m. p. 74—75° (Found : C, 49·4; H, 1·8; F, 23·7%).

Reduction of 8-*Nitro*-5-*trifluoromethylquinoline*.—Carried out as described for the 7-trifluoromethyl isomer, this reaction gave 8-*amino*-5-*trifluoromethylquinoline* (56%), m. p. 89° (after recrystallisation from ethyl alcohol, unchanged by sublimation *in vacuo*) (Found : C, 56·9; H, 3·3; F, 26·6%). Its *acetyl* derivative had m. p. 114° (from aqueous ethyl alcohol) (Found : C, 56·5; H, 3·4%).

Action of Acids on 8-*Amino*-5-*trifluoromethylquinoline*.—(a) *Sulphuric acid*. The amine (0·20 g.) and concentrated sulphuric acid (2·0 c.c.) were heated for 90 min. at 160°. Partial neutralisation with ammonia solution (2N) caused precipitation from the solution (*A*) of a yellow solid. This was filtered off and dissolved in aqueous sodium hydroxide; addition of hydrochloric acid (to pH 7) precipitated (probably) the 8-amino-5-carboxylic acid, m. p. 242° (decomp.). At

this temperature it gave 8-aminoquinoline (0·027 g.), m. p. and mixed m. p. 63—64°. Complete neutralisation of solution (*A*) with ammonia solution gave 8-amino-5-trifluoromethylquinoline (0·05 g.), m. p. and mixed m. p. 89°.

(b) *Hydrochloric acid.* The amine was unattacked by concentrated hydrochloric acid at 75° for 6 hr. At 90° and at 110° a compound, m. p. 62—63°, probably 8-aminoquinoline, was isolated in very small yield (*ca.* 1%), fluoride ion being present in the aqueous phase. At 200°, fluoride ion was removed and no identifiable product was found.

5-Trifluoromethylquinoline.—8-Amino-5-trifluoromethylquinoline (0·75 g.) in sulphuric acid (18 c.c.; 6N) was diazotised at 5° with sodium nitrite (0·30 g.) in water (5 c.c.). A precipitate was formed immediately, and was filtered off, washed, and recrystallised from ethyl alcohol to give a substance (0·60 g.), m. p. 161° [Found: C, 49·0; H, 2·3; F, 23·7%; *M* (Rast), 225].

In a second experiment, sodium nitrite (0·18 g.), in water (2·5 c.c.), was added to a mixture of the amine (0·50 g.), water (10 c.c.), concentrated sulphuric acid (1·0 c.c.), and hypophosphorous acid (3·0 c.c.; 30%), at 0°. After 16 hr. at 15°, the solution was filtered, made alkaline with sodium hydroxide, and extracted with ether. The extracts were washed, dried ($MgSO_4$), filtered, and evaporated. The liquid residue, in ethyl alcohol, was treated with saturated alcoholic picric acid. The yellow precipitate, after recrystallisation from ethyl alcohol, gave *5-trifluoromethylquinolinium picrate* (10%), m. p. and mixed m. p. 185° (Found: C, 45·2; H, 1·8. $C_{16}H_9O_7N_4F_3$ requires C, 45·1; H, 2·1%).

Diazotisation of 8-Amino-5-trifluoromethylquinoline by Means of Nitrosylsulphuric Acid.—Sodium nitrite (0·48 g.) was added slowly to concentrated sulphuric acid (4·8 c.c.) at 70°. The solution was cooled, and the amine (0·65 g.), in glacial acetic acid (2·3 c.c.), was added so that the temperature did not rise above 30°. The solution was divided into two portions. To one was added an excess of ice–water; the precipitated substance, after recrystallisation from ethyl alcohol, had m. p. and mixed m. p. with above product 161°. Alkaline β-naphthol was added to the second portion of the diazo-solution, and the red precipitate was recrystallised from acetone to give *5-trifluoromethyl-8-quinolylazo-β-naphthol* (64%), m. p. 240° (Found: C, 65·0; H, 3·1. $C_{20}H_{12}ON_3F_3$ requires C, 65·4; H, 3·3%).

8-Iodo-5-trifluoromethylquinoline.—The amine (0·65 g.) was diazotised with nitrosylsulphuric acid, as above, and the solution was added at 0° to water (5 c.c.) containing potassium iodide (0·7 g.). After 2 hr. at 15° the precipitate was filtered off, recrystallised from ethyl alcohol, and then sublimed, to give *8-iodo-5-trifluoromethylquinoline* (0·29 g.), m. p. 62—63° (Found: C, 37·0; H, 1·3. $C_{10}H_5NIF_3$ requires C, 37·2; H, 1·6%).

8-Methoxy-5-trifluoromethylquinoline.—The 8-iodo-compound (0·30 g.) was refluxed for 6 hr. in dry methyl alcohol (2·0 c.c.) containing sodium methoxide [from sodium (0·2 g.)]. The solution was cooled, excess of water added, and the precipitate filtered off, washed, dried, and recrystallised from light petroleum (b. p. 60—80°) to give 8-methoxy-5-trifluoromethylquinoline (0·09 g.), m. p. 80—81°, not depressed on admixture with the specimen described by Pettit and Tatlow (*loc. cit.*) (Found: C, 58·4; H, 3·6. Calc. for $C_{11}H_8ONF_3$: C, 58·15; H, 3·55%).

Skraup Reaction on 8-Amino-5-trifluoromethylquinoline.—The quinoline (2·12 g.), glycerol (3·68 g.), arsenic pentoxide (1·79 g.), and concentrated sulphuric acid (1·9 g.) were stirred and heated at 135° for 1 hr. and then refluxed (bath temp. 160—170°) for 1½ hr. After being poured into water the mixture was made alkaline with ammonia solution, and the resultant precipitate filtered off and extracted with hot benzene. The extracts were concentrated; the solid which was deposited was recrystallised from benzene–light petroleum (b. p. 60—80°) to give 1 : 10-phenanthroline monohydrate (0·51 g.), m. p. and mixed m. p. 93—94° (Found: C, 72·0; H, 5·2. Calc. for $C_{12}H_8N_2,H_2O$: C, 72·7; H, 5·1%). After 3 hr. at 50°/15 mm. over phosphoric oxide, the product, then anhydrous, had m. p. 117°. Smith and Richter (*op. cit.*) gave m. p. 117° (anhydrous) and m. p. 99—100° (monohydrate).

From a similar reaction at 135° for 2 hr. the same product was isolated.

3-Hydroxy-4-nitrobenzotrifluoride—3-Amino-4-nitrobenzotrifluoride was diazotised and the product treated with copper sulphate as described by Whalley (*J.*, 1949, 3016) for the 3-amino-5-nitro-isomer (the product was steam-distilled from the mixture). 3-Hydroxy-4-nitrobenzotrifluoride (73%), b. p. 108—111°/34 mm., was obtained. It gave a *p*-nitrobenzoate, m. p. 106° (from ethyl alcohol) (Found: C, 47·2; H, 2·3. Calc. for $C_{14}H_7O_6N_2F_3$: C, 47·2; H, 2·0%). Whalley (*J.*, 1950, 2792) gave m. p. 103° for this ester.

4-Amino-3-hydroxybenzotrifluoride.—3-Hydroxy-4-nitrobenzotrifluoride (14·0 g.), ethyl alcohol (150 c.c.), and Raney nickel (*ca.* 1·5 g.) were shaken at *ca.* 20°/1 atm. in hydrogen until absorption was complete. The solution was filtered and evaporated *in vacuo*. The residue was recrystallised from benzene to give *4-amino-3-hydroxybenzotrifluoride* (8·8 g.), m. p. 114—115°

(Found: C, 47·4; H, 3·4; F, 32·5. $C_7H_6ONF_3$ requires C, 47·5; H, 3·4; F, 32·2%). When the hydroxy-amine was heated to 117°, or over, the liquid re-solidified, apparently with evolution of hydrogen fluoride. The *diacetyl* derivative (acetic anhydride–acetic acid) (58%, from aqueous ethyl alcohol), m. p. 113° (Found: C, 50·7; H, 3·6; F, 21·4. $C_{11}H_{10}O_3NF_3$ requires C, 50·6; H, 3·9; F, 21·8%), was soluble in dilute aqueous sodium hydroxide and was recovered by acidification. Use of less acetic anhydride afforded a *monoacetyl* derivative (57%; from aqueous ethyl alcohol), m. p. 199° (Found: C, 49·6; H, 3·8; F, 25·8. $C_9H_8O_2NF_3$ requires C, 49·3; H, 3·7; F, 26·0%).

The hydroxy-amine was soluble in dilute hydrochloric acid and could be recovered, even after the solution had been heated, by neutralisation with ammonia solution. A solution of the compound in dilute aqueous sodium hydroxide, however, when warmed, deposited a white amorphous organic precipitate, m. p. >350°. Fluoride ion appeared in the solution.

8-*Hydroxy*-6-*trifluoromethylquinoline*.—4-Amino-3-hydroxybenzotrifluoride (6·6 g.), glycerol (13·8 g.), arsenic pentoxide (6·4 g.), and concentrated sulphuric acid (6·9 g.) were stirred and heated at 135° for 1 hr. and then under reflux for 1½ hr. The mixture was poured into water, the solution made alkaline with ammonia solution, and the pH adjusted to 6—7 with acetic acid. The resultant precipitate was filtered off, washed, recrystallised from aqueous ethyl alcohol (charcoal), and sublimed at 15 mm. to give 8-*hydroxy*-6-*trifluoromethylquinoline* (2·8 g.), m. p. 95° (Found: C, 56·6; H, 3·1; F, 27·2%; *M*, 215. $C_{10}H_6ONF_3$ requires C, 56·3; H, 2·8; F, 26·7%; *M*, 213). The *toluene*-p-*sulphonyl* ester (61%) had m. p. 179·5° (Found: C, 55·8; H, 3·3; F, 15·6%), and the p-*nitrobenzyl ester* (53%; from aqueous acetone) m. p. 150° (Found: C, 56·3; H, 2·6; F, 15·5. $C_{17}H_9O_4N_2F_3$ requires C, 56·4; H, 2·5; F, 15·7%).

8-*Hydroxyquinoline*-6-*carboxylic Acid*.—8-Hydroxy-6-trifluoromethylquinoline (0·150 g.) and concentrated sulphuric acid (1·0 c.c.) were stirred at 160—170° for 30 min. After being made alkaline with dilute aqueous sodium hydroxide, the solution was neutralised with dilute hydrochloric acid. The resultant precipitate was crystallised from ethyl alcohol to give 8-hydroxyquinoline-6-carboxylic acid (0·097 g.), m. p. 286—288° (Found: C, 63·7; H, 3·9; N, 7·5. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%), for which Niementowski and Sucharda (*Ber.*, 1916, **49**, 12) gave m. p. 284°.

5-*Nitro- and* 5-*Amino*-7-*trifluoromethylquinoline*.—3-Amino-5-nitrobenzotrifluoride, treated as for the 3-amino-2-nitro-isomer gave, after recrystallisation from carbon tetrachloride, 5-*nitro*-7-*trifluoromethylquinoline* (15%), m. p. 99° (Found: C, 49·6; H, 2·2; F, 23·3%). Reduction of this product, by the method previously described, afforded 5-*amino*-7-*trifluoromethylquinoline* (91%), m. p. 145—145·5° (Found: C, 56·7; H, 3·0%).

This amine (0·30 g.) was diazotised in the usual way. To two-thirds of the resulting solution was added hypophosphorous acid (3·0 c.c.; 30%), and after 16 hr. at 15° and isolation as before there was obtained 7-trifluoromethylquinoline (0·14 g.), m. p. and mixed m. p. 67°. The remaining one-third of the diazo-solution was treated with alkaline β-naphthol, giving 7-*trifluoromethyl*-5-*quinolylazo*-β-*naphthol* (86%; from glacial acetic acid), m. p. 240° (Found: C, 65·1; H, 3·1%).

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