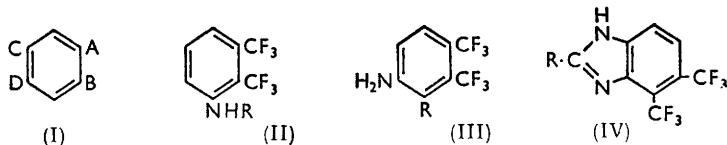


**790. The Synthesis of 4,5-Bistrifluoromethylbenzimidazole.**By J. FERNANDEZ-BOLAÑOS, W. G. OVEREND, A. SYKES,  
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The synthesis from *o*-xylene of 4,5-bistrifluoromethylbenzimidazole is described. New compounds derived from 1,2-bistrifluoromethylbenzene have been obtained as intermediates and their structures have been established. Preliminary results indicate that the benzimidazole has appreciable bacteriostatic activity against certain organisms.

RECENT publications from our laboratories have described syntheses<sup>1-4</sup> and structural studies<sup>5,6</sup> of substituted benzimidazoles, which were prepared for biological study. A number of fluorine-containing benzimidazoles have been reported by us<sup>1,2,4</sup> and other workers,<sup>7,8</sup> and we found that 4- and 5-trifluoromethylbenzimidazole have growth-inhibitory power against micro-organisms.<sup>4,9</sup> Consequently, with the object of preparing metabolite-inhibitors of vitamin B<sub>12</sub> as potential chemotherapeutic agents, we attempted to synthesise 5,6-bistrifluoromethylbenzimidazole. In the event the 4,5-isomer was obtained.



An obvious starting point for the synthesis is 1,2-bistrifluoromethylbenzene (I; A = B = CF<sub>3</sub>, C = D = H), but little is known about its derivatives. So far as we are aware, there are in the literature reports from only two groups of workers on 1,2-bistrifluoromethylbenzene or its derivatives. In the first, described in a German patent,<sup>10</sup>

<sup>1</sup> Sykes and Tatlow, *J.*, 1952, 4078.<sup>2</sup> Belcher, Sykes, and Tatlow, *J.*, 1954, 4159.<sup>3</sup> Cleaver, Foster, and Overend, *J.*, 1957, 3961.<sup>4</sup> Cleaver, Foster, and Overend, *J.*, 1959, 409.<sup>5</sup> Cleaver, Foster, Hedgley, and Overend, *J.*, 1959, 2578.<sup>6</sup> Ferrier and Overend, *J.*, 1959, 3638.<sup>7</sup> Smith and Steinle, *J. Amer. Chem. Soc.*, 1953, **75**, 1292; Fisher and Joullié, *J. Org. Chem.*, 1958, **23**, 1944.<sup>8</sup> Lane, *Chem. and Ind.*, 1953, 798; *J.*, 1955, 534; Lane and Williams, *ibid.*, 1956, 569.<sup>9</sup> Hughes, unpublished observations; Jones, unpublished observations in the Birmingham laboratories<sup>10</sup> Scherer, Schumacher, and Muller, G.P. 668,033 (*Chem. Abs.*, 1939, **33**, 2149); B.P. 465,885, 466,007 (*Chem. Abs.*, 1937, **31**, 7667).

*o*-dichloromethylbenzotrifluoride (I; A = CHCl<sub>2</sub>, B = CCl<sub>3</sub>, C = D = H) with anhydrous hydrogen fluoride gave *o*-difluoromethylbenzotrifluoride which was chlorinated to the chloropentafluoride, and then a second fluorination stage by exchange gave the hexafluoride (I; A = B = CF<sub>3</sub>, C = D = H). No reactions of this compound were reported. This multi-stage synthesis was necessary since the size of the chlorine atoms prevents the introduction of more than five into the side chains of *o*-xylene. This rather laborious synthesis, necessary only for the series derived from *o*-xylene, undoubtedly explains why 1,2-bistrifluoromethylbenzene has received less attention than the 1,3- and the 1,4-isomer. McBee and his co-workers<sup>11</sup> later described the bromination of compound (I; A = B = CF<sub>3</sub>, C = D = H) to its 4-bromo-derivative, and its conversion *via* a Grignard reaction into a bistrifluoromethylstyrene. 4-Chloro-1,2-bistrifluoromethylbenzene was mentioned also.<sup>12</sup> During our work more derivatives of compound (I; A = B = CF<sub>3</sub>, C = D = H) have been synthesised.

We prepared 1,2-bistrifluoromethylbenzene (I; A = B = CF<sub>3</sub>, C = D = H) from *o*-xylene *via* compounds (I; A = CHCl<sub>2</sub>, B = CCl<sub>3</sub>, C = D = H), (I; A = CHCl<sub>2</sub>, B = CF<sub>3</sub>, C = D = H), and (I; A = CCl<sub>3</sub>, B = CF<sub>3</sub>, C = D = H) since no method is known for the controlled direct replacement by fluorine of only the side-chain hydrogen atoms of an aromatic compound. Side-chain chlorination, followed by the exchange of fluorine for chlorine, remains the only practicable process\* for the production of compounds of this type. In an earlier investigation in the Birmingham laboratories<sup>13</sup> the fluorination of *o*-dichloromethylbenzotrifluoride<sup>14</sup> (I; A = CHCl<sub>2</sub>, B = CCl<sub>3</sub>, C = D = H) with anhydrous hydrogen fluoride under conditions which gave *o*-dichloromethylbenzotrifluoride (I; A = CHCl<sub>2</sub>, B = CF<sub>3</sub>, C = D = H) as the exclusive product was examined. A difference in reactivity towards hydrogen fluoride of a dichloro- and trichloro-methyl side chain is to be expected, but the clear-cut distinction between the two is rather surprising, particularly as the German workers<sup>10</sup> obtained only the pentafluoride from their fluorinations.

*o*-Dichloromethylbenzotrifluoride (I; A = CHCl<sub>2</sub>, B = CF<sub>3</sub>, C = D = H) was chlorinated further in the side chain, though with some difficulty, by elementary chlorine under ultraviolet irradiation, the reaction being followed by vapour-phase chromatography. The major product was *o*-trichloromethylbenzotrifluoride (I; A = CCl<sub>3</sub>, B = CF<sub>3</sub>, C = D = H), but carbon tetrachloride and *o*-chlorobenzotrifluoride were also obtained, showing that chlorinolysis of the chlorinated side chain had occurred to some extent. This effect has been observed before<sup>14</sup> in exhaustive side-chain chlorinations under drastic conditions, particularly when appreciable crowding would result if full chlorination were achieved. Replacement of only three chlorine atoms in compound (I; A = CHCl<sub>2</sub>, B = CCl<sub>3</sub>, C = D = H) by fluorine reduces sufficiently the interactions between the adjacent halogenated groups to permit the remaining hydrogen atom in the side chains to be replaced, but there must be some crowding in a compound with CCl<sub>3</sub> and CF<sub>3</sub> functions on adjacent carbon atoms of a benzene ring.

The constitution of the trichloro-trifluoro-compound (I; A = CCl<sub>3</sub>, B = CF<sub>3</sub>, C = D = H) was demonstrated by hydrolysis of the side-chain halogeno-residues with sulphuric acid, a useful method<sup>15</sup> for structural determinations on compounds of this type. According to the conditions either the known<sup>16</sup> *o*-trifluoromethylbenzoic acid or phthalic acid is produced. Anhydrous hydrogen fluoride readily converted compound (I; A = CCl<sub>3</sub>,

\* Alternatives may be based on the recent discovery of the conversion of CO<sub>2</sub>H into CF<sub>3</sub> by sulphur tetrafluoride (Smith *et al.*, *J. Amer. Chem. Soc.*, 1959, **81**, 3165).

<sup>11</sup> McBee, Sanford, and Graham, *J. Amer. Chem. Soc.*, 1950, **72**, 1651; McBee and Sanford, *ibid.*, p. 4053.

<sup>12</sup> McBee and Frederick, U.S.P. 2,601,310 (*Chem. Abs.*, 1953, **47**, 1734).

<sup>13</sup> Belcher, Sykes, and Tatlow, *Analyt. Chim. Acta*, 1954, **10**, 34.

<sup>14</sup> Harvey, Smith, Stacey, and Tatlow, *J. Appl. Chem.*, 1954, **4**, 319.

<sup>15</sup> Le Fave, *J. Amer. Chem. Soc.*, 1949, **71**, 4148.

<sup>16</sup> Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2346.

B = CF<sub>3</sub>, C = D = H) into 1,2-bistrifluoromethylbenzene (I; A = B = CF<sub>3</sub>, C = D = H) in good yield. Nitration of this substance (I; A = B = CF<sub>3</sub>, C = D = H) gave a liquid mixture of two products, which was reduced and acetylated. The mixed *N*-acetyl amines could not be separated satisfactorily in reasonable amounts by crystallisation techniques, but two pure derivatives were isolated in much improved yield after chromatography on alumina. Later, sufficient of the mixed nitro-compounds was made to permit fractional distillation at reduced pressure: two pure low-melting compounds were isolated, each as a solid. The more volatile was shown to be 4-nitro-1,2-bistrifluoromethylbenzene (I; A = B = CF<sub>3</sub>, C = H, D = NO<sub>2</sub>) by hydrolysis to 4-nitrophthalic acid. The other was converted similarly into 3-nitrophthalic acid and so was 3-nitro-1,2-bistrifluoromethylbenzene. From the amounts obtained it appeared that the nitration gave about 2 parts of the 4-nitro-derivative (I; A = B = CF<sub>3</sub>, C = H, D = NO<sub>2</sub>) to 1 part of the 3-isomer. Each compound was reduced by hydrogen in the presence of Raney nickel to the amine, and both amines readily underwent *N*-acetylation and *N*-trifluoroacetylation, the former products being identical with the derivatives obtained from the chromatographic separation referred to previously.

3,4-Bistrifluoromethylacetanilide (I; A = B = CF<sub>3</sub>, C = H, D = NHAc) was nitrated with a mixture of acetic anhydride and nitric acid, a reagent known to favour *ortho*-substitution and used<sup>17,18</sup> to produce *o*-nitro-amines in the benzotrifluoride series. Nitration occurred but the primary product could not be purified and so the crude mixture was treated with hot dilute aqueous alkali to remove the acetyl residue. The free nitro-amine was then isolated by steam-distillation, but only in poor yield (*ca.* 16%). Fluoride ions were detected in the mother-liquors from the alkaline hydrolysis. This result was not unexpected, since Jones<sup>16</sup> has shown that *p*-hydroxy- and *p*-amino-benzotrifluoride have fairly reactive trifluoromethyl groups which lose fluorine very much more readily than do the better-known *meta*-isomers. It was hoped that the presence of adjacent trifluoromethyl and nitro-groups in our derivative would stabilise the trifluoromethyl substituent located *para* to the amino-function, and this did seem to occur to some extent. However, it appeared to be impossible to remove the *N*-acetyl group from the primary nitration product without causing fairly extensive loss of fluorine. Despite various modifications of the isolation procedure, including attempted hydrolysis with aqueous acid, no significant improvement in the yield could be obtained. Accordingly the *N*-trifluoroacetyl derivative (I; A = B = CF<sub>3</sub>, C = H, D = NH·CO·CF<sub>3</sub>) was prepared and its nitration studied. It is known<sup>19,20</sup> that *N*-trifluoroacetyl groups can be removed very easily with quite dilute alkali. Nitration of the trifluoroacetate (I; A = B = CF<sub>3</sub>, C = H, D = NH·CO·CF<sub>3</sub>) was carried out first with acetic anhydride-nitric acid as before, and, as expected, the isolation of the nitro-amine was less difficult and improved yields (30%) were obtained. Even better results were obtained when the nitration was carried out with trifluoroacetic anhydride-nitric acid,<sup>21</sup> a rather more reactive nitrating system. The same product was obtained in yields of about 50% and further investigation would probably give even better recoveries. This affords another example of the usefulness of the trifluoroacetyl residue as a protecting group in organic synthesis.

In contrast to the results obtained with the acylated derivatives of 3,4-bistrifluoromethylaniline when *N*-acetyl- and *N*-trifluoroacetyl-2,3-bistrifluoromethylaniline (II; R = Ac or CF<sub>3</sub>·CO) were treated under comparable conditions with acetic anhydride-nitric acid, or with trifluoroacetic anhydride-nitric acid, no nitration products could be detected. The acyl compound (or the parent amine if a hydrolysis stage had been included) was recovered.

<sup>17</sup> Rouche, *Bull. Acad. roy. Belg. Classe Sci.*, 1927, **13**, 346.

<sup>18</sup> Pouterman and Girardet, *Helv. Chim. Acta*, 1947, **30**, 107.

<sup>19</sup> Bourne, Henry, Tatlow, and Tatlow, *J.*, 1952, 4014.

<sup>20</sup> Schallenberg and Calvin, *J. Amer. Chem. Soc.*, 1955, **77**, 2779.

<sup>21</sup> Bourne, Stacey, Tatlow, and Tedder, *J.*, 1952, 1695.

It was hoped that the final product from the nitration of an *N*-acyl-3,4-bistrifluoromethylaniline (I; A = B = CF<sub>3</sub>, C = H, D = NHAc and NH·CO·CF<sub>3</sub>) would be 2-nitro-4,5-bistrifluoromethylaniline (I; A = B = CF<sub>3</sub>, C = NO<sub>2</sub>, D = NH<sub>2</sub>) which could be converted *via* the diamine (I; A = B = CF<sub>3</sub>, C = D = NH<sub>2</sub>) into the required 5,6-bistrifluoromethylbenzimidazole. However, it was found to be 2-nitro-3,4-bistrifluoromethylaniline (III; R = NO<sub>2</sub>). The structure was established by diazotisation and elimination of the diazonium group with ethanol and cuprous oxide, as recommended by Hodgson and Turner.<sup>22</sup> Attempts at deamination by diazotisation and reduction with hypophosphorous acid were not successful. The product of deamination was hydrogenated and the amine so obtained was characterised as its acetate (II; R = Ac) and trifluoroacetyl derivative (II; R = CF<sub>3</sub>·CO). It was found that the amine was 2,3-bistrifluoromethylaniline (II; R = H) since these derivatives were identical with the specimens prepared directly from 2,3-bistrifluoromethylaniline (obtained from 1,2-bistrifluoromethylbenzene by nitration and reduction as described previously) whose structure had been established. Consequently, although from a steric viewpoint there might appear to be more hindrance to nitration at the 2-position in 3,4-bistrifluoromethylaniline than in the 6-position, this is not important in practice. In the nitration<sup>18</sup> of 3-acetamidobenzotrifluoride the 2- and the 4-nitro-product are formed in comparable quantities. If it is assumed that the trifluoromethyl group can deactivate a benzene nucleus by a hyperconjugative as well as an inductive effect, then the nitration of *N*-acyl-3,4-bistrifluoromethylanilines exclusively at position 2, and the low reactivity of the 2,3-bistrifluoromethyl isomers, can be accounted for by an extension of Ingold's explanation<sup>23</sup> of similar effects in other series.

Hydrogenation of the nitro-amine (III; R = NO<sub>2</sub>) afforded 3,4-bistrifluoromethyl-1,2-phenylenediamine (III; R = NH<sub>2</sub>), which was readily converted into 4,5-bistrifluoromethylbenzimidazole (IV; R = H) by formic acid and concentrated hydrochloric acid. Substitution of glacial acetic acid for formic acid resulted in the production of 2-methyl-4,5-bistrifluoromethylbenzimidazole (IV; R = Me), and trifluoroacetic acid afforded 2,4,5-tristrifluoromethylbenzimidazole (IV; R = CF<sub>3</sub>).

Heating 3,4-bistrifluoromethyl-*o*-phenylenediamine with benzil in methanol yielded 2,3-diphenyl-5,6-bistrifluoromethylquinoxaline, thereby confirming the structure of the diamine (III; R = NH<sub>2</sub>).

Preliminary results obtained by our colleague Dr. A. S. Jones indicate that 4,5-bistrifluoromethylbenzimidazole has appreciable activity against certain organisms.

## EXPERIMENTAL

*o*-Dichloromethylbenzotrifluoride.—*o*-Xylene was chlorinated as described previously<sup>13</sup> to give, after one recrystallisation from aqueous ethanol, *o*-dichloromethylbenzotrifluoride<sup>14</sup> (77%), m. p. 50—51° (Belcher *et al.*<sup>13</sup> give m. p. 50°). In general, yields of 90—95% of non-recrystallised material, m. p. 46—49°, were obtained.

*o*-Dichloromethylbenzotrifluoride.—*o*-Dichloromethylbenzotrifluoride (428.6 g.) and anhydrous hydrogen fluoride (160 c.c.) were heated in a rocking autoclave (1 l.) during 2.5 hr. to 95° (pressure then 75 atm.), and after being kept for 1.25 hr. at 95—105° were cooled during 2.5 hr. to 60° (52 atm.) and then rapidly to 25° (40 atm.). The hydrogen chloride and excess of hydrogen fluoride were allowed to escape and the product was poured into ice-water (500 c.c.). The aqueous mixture was treated as before,<sup>13</sup> to yield *o*-dichloromethylbenzotrifluoride (295 g.), b. p. 188—190°,  $n_D^{23}$  1.4767 (Found: F, 24.8. Calc. for C<sub>8</sub>H<sub>5</sub>Cl<sub>2</sub>F<sub>3</sub>: F, 24.9%). Belcher *et al.*<sup>13</sup> give b. p. 187—189°, and  $n_D^{17}$  1.4790.

*Chlorination of o*-Dichloromethylbenzotrifluoride.—*o*-Dichloromethylbenzotrifluoride (551.1 g.) was irradiated at 90—110° in a quartz flask with ultraviolet light while chlorine was bubbled through it slowly. The reaction was controlled by analytical vapour-phase chromatography [Perkin-Elmer Co. (Bodenseewerk) Fraktometer, packing "C," column length 1 m., 180°, nitrogen flow setting 3.0], and chlorination was terminated after 18 hr. Excess of chlorine was swept out

<sup>22</sup> Hodgson and Turner, *J.*, 1942, 748.

<sup>23</sup> Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 268.

with nitrogen, and the crude product was distilled through a glass vacuum-jacketed Vigreux column (1 ft.) to give fractions: (i) 10.6 g., b. p. 70—150°; (ii) *o*-chlorobenzotrifluoride (92.9 g.), b. p. 154—157°,  $n_D^{18}$  1.4558 (cited values,<sup>24</sup> b. p. 152.8°,  $n_D^{22}$  1.4544) [this material gave a single peak when analysed by gas chromatography (conditions as before)]; (iii) 51.2 g., b. p. 160—189°; (iv) *o*-dichloromethylbenzotrifluoride (62.1 g.), b. p. 189—193°,  $n_D^{14}$  1.4781; (v) 122.4 g., b. p. 195—229°; and (vi) *o*-trichloromethylbenzotrifluoride (275.4 g.), b. p. 230—232°,  $n_D^{18}$  1.5082.

In another experiment, *o*-dichloromethylbenzotrifluoride (207.9 g.) and the intermediate fraction, b. p. 195—229° (53.7 g.), from an earlier run were chlorinated under the above conditions for 10 hr. at 100—110°. Distillation of the product through a column (6 in.) afforded fractions: (i) carbon tetrachloride (9.9 g.), b. p. 77°,  $n_D^{20}$  1.4600; (ii) 6.2 g., b. p. 77.5—151°; (iii) *o*-chlorobenzotrifluoride (21.7 g.), b. p. 151.5—152.5°,  $n_D^{16.5}$  1.4562 (Found: C, 46.1; H, 2.2; F, 31.9. Calc. for  $C_7H_4ClF_3$ : C, 46.6; H, 2.2; F, 31.6%) (Booth *et al.*<sup>24</sup> report b. p. 152.8°,  $n_D^{22}$  1.4544 for this substance); (iv) 19.6 g., b. p. 153—188.5°; (v) *o*-dichloromethylbenzotrifluoride (21.7 g.), b. p. 189—194°,  $n_D^{17.5}$  1.4790; (vi) 40.5 g., b. p. 195—229°; and (vii) *o*-trichloromethylbenzotrifluoride (127.5 g.), b. p. 229—230°,  $n_D^{20}$  1.5090 (Found: C, 36.5; H, 1.5; F, 21.7.  $C_8H_4Cl_3F_3$  requires C, 36.5; H, 1.5; F, 21.6%). The total overall yield of the trichloride was ca. 44%.

*Hydrolysis of o-Trichloromethylbenzotrifluoride.*—(i) The trichloro-compound (3.3 g.) was heated at 130—145° for 1.5 hr. with concentrated sulphuric acid (6 c.c.) and water (3 c.c.). The precipitate formed when the mixture was poured into water (10 c.c.) was collected and dried. Recrystallisation from water gave *o*-trifluoromethylbenzoic acid (1.6 g.), m. p. 108—109° (Found: C, 50.7; H, 2.7; F, 29.9. Calc. for  $C_8H_5O_2F_3$ : C, 50.5; H, 2.6; F, 30.0%), for which m. p. 107.5° has been reported.<sup>18</sup>

(ii) When the trichloro-derivative (2.3 g.) was heated at 150—160° for 15 min. with concentrated sulphuric acid (8 c.c.) and water (4 c.c.) the product was *o*-phthalic acid (0.8 g.), m. p. and mixed m. p. 196°.

*1,2-Bistrifluoromethylbenzene.*—*o*-Trichloromethylbenzotrifluoride (197 g.) and anhydrous hydrogen fluoride (110 c.c.) were heated together in a rocking autoclave (1 l.) for 3 hr. during which a temperature of 115° was reached. After 2 hr. at 115—120° and slow cooling to 30° the hydrogen chloride and excess of hydrogen fluoride were released and the product was poured into ice-water (1 l.). The mixture was neutralised with sodium hydroxide and steam-distilled. The distillate was extracted with ether, and the extract was dried ( $MgSO_4$ ) and distilled to afford 1,2-bistrifluoromethylbenzene (132.7 g.), b. p. 141—142°,  $n_D^{16}$  1.3942 (Found: C, 44.8; H, 1.7; F, 53.2. Calc. for  $C_8H_4F_6$ : C, 44.9; H, 1.9; F, 53.2%). Scherer *et al.*<sup>10</sup> give b. p. 140—142°.

*Nitration of 1,2-Bistrifluoromethylbenzene.*—1,2-Bistrifluoromethylbenzene (50.0 g.) was added slowly to fuming nitric acid (275 g.; *d* 1.5) and concentrated sulphuric acid (450 g., *d* 1.84), and the mixture was heated at 100° for 4.5 hr. under two reflux condensers (one cooled by water and the other by solid carbon dioxide-ethanol). The product was poured on ice (1.5 kg.), and the aqueous phase was extracted with ether. The extract was washed successively with water (thrice), saturated sodium carbonate solution (thrice), and again with water (thrice) and dried ( $MgSO_4$ ). Concentration of the ethereal solution and distillation of the residue gave a mixture of 3- and 4-nitro-1,2-bistrifluoromethylbenzene (36.7 g.), b. p. 206—226° (Found: C, 37.1; H, 1.0; F, 43.9. Calc. for  $C_8H_3O_2NF_6$ : C, 37.1; H, 1.2; F, 44.0%).

The mixed nitro-compounds (137.5 g.) from several nitration experiments were distilled under diminished pressure [column 1 ft. long packed with Dixon gauzes ( $\frac{1}{16}$ "  $\times$   $\frac{1}{16}$ " ); the pressure was controlled by means of a Model 6 Cartesian Manostat (W. Edwards and Co., Ltd.)]. The distillation was controlled by analytical gas chromatography [Perkin-Elmer Co. (Bodensee-werk) Fraktometer, packing "C," 1 m., 190°, nitrogen flow setting 5.0]. Fractionation yielded: (i) 4-nitro-1,2-bistrifluoromethylbenzene (56.6 g.), b. p. 98.5—99.5°/20 mm., m. p. 23—25°,  $n_D^{38}$  1.4322,  $n_D^{22}$  1.4382 (Found: C, 37.3; H, 1.3; F, 43.9%); (ii) an intermediate fraction (20.5 g.), b. p. 100—105.5°/20 mm.; and (iii) 3-nitro-1,2-bistrifluoromethylbenzene (41.8 g.), b. p. 105.5—106.5°/20 mm., m. p. 27—29°,  $n_D^{38}$  1.4293,  $n_D^{23}$  1.4361 (Found: C, 36.7; H, 1.4; F, 43.7%). At atmospheric pressure the 4-isomer had b. p. 208—209° and the 3-isomer had b. p. 223.5—225°.

*4-Nitrophthalic Acid from 4-Nitro-1,2-bistrifluoromethylbenzene.*—The nitro-compound (1.2 g.) was stirred with concentrated sulphuric acid (3 c.c.) at 195—205° for 1.75 hr. The solution was

<sup>24</sup> Booth, Elsey, and Burchfield, *J. Amer. Chem. Soc.*, 1935, **57**, 2066.

poured into water (5 c.c.), and the precipitate was collected and recrystallised from water to give a product (0.75 g.) with m. p. 148—152° undepressed on admixture with 4-nitrophthalic acid. This product (0.55 g.) was heated with acetic anhydride (0.6 g.) for 3 min. and then evaporation under diminished pressure afforded a solid. Recrystallisation from chloroform-light petroleum (b. p. 40—60°) yielded 4-nitrophthalic anhydride (0.37 g.), m. p. 117—119° undepressed on admixture with a specimen prepared<sup>25</sup> from authentic 4-nitrophthalic acid,<sup>26</sup> but depressed on admixture with 3-nitrophthalic anhydride similarly prepared from authentic 3-nitrophthalic acid.

*3-Nitrophthalic Acid from 3-Nitro-1,2-bistrifluoromethylbenzene.*—3-Nitro-1,2-bistrifluoromethylbenzene (6.0 g.) and fuming sulphuric acid (24 c.c.; 20% of SO<sub>3</sub>) were heated at 100° for 4 hr. and then at 150° for a further hour. After cooling, the mixture was poured slowly into water (25 c.c.). The solid which separated was filtered off, dissolved in ether, and treated with charcoal. Evaporation of the solution and recrystallisation of the residue from water gave 3-nitrophthalic acid (0.96 g.), m. p. 214—216°. The m. p. was undepressed when the compound was mixed with authentic 3-nitrophthalic acid,<sup>25,26</sup> but was depressed when authentic 4-nitrophthalic acid was substituted in the mixture. The infrared spectrum of the sample was that of 3-nitrophthalic acid.

*3,4-Bistrifluoromethylaniline.*—The 4-nitro-compound (5.4 g.), ethanol (80 c.c.), and Raney nickel (*ca* 1 g.) were shaken together in hydrogen in a low-pressure hydrogenator. When the uptake of hydrogen ceased the solution was filtered and concentrated under reduced pressure to leave a liquid which was distilled to give 3,4-bistrifluoromethylaniline (1.45 g.), b. p. 74°/0.9 mm. (Found: C, 42.3; H, 2.3. C<sub>8</sub>H<sub>5</sub>NF<sub>6</sub> requires C, 41.9; H, 2.2%).

The amine (0.75 g.) was treated in dry ether (5 c.c.) with trifluoroacetic anhydride (1 c.c.). After 16 hr. at 15° the solution was evaporated under diminished pressure and the residue was treated twice with carbon tetrachloride which was evaporated under diminished pressure. The solid product, recrystallised from light petroleum (b. p. 60—80°), gave *N*-trifluoroacetyl-3,4-bistrifluoromethylaniline (0.79 g.), m. p. 62—63° (Found: C, 36.9; H, 1.2. C<sub>10</sub>H<sub>4</sub>ONF<sub>9</sub> requires C, 36.9; H, 1.2%).

The nitro-compound (8.35 g.) was reduced as described above and the residue remaining after distilling off the alcohol was taken up in dry ether. The solution was dried (MgSO<sub>4</sub>), filtered, and treated with trifluoroacetic anhydride (8.25 g.). After 3 hr. the solution was treated as described previously and the solid recrystallised, to yield the same trifluoroacetanilide (7.25 g.), m. p. and mixed m. p. 62—63°.

The nitro-compound (1.81 g.) was reduced as before and the product was acetylated [acetic acid (2 c.c.) and acetic anhydride (2 c.c.)] at 100° for 30 min. 3,4-bistrifluoromethylacetanilide (1.51 g.) was obtained, having m. p. 105—106.5° (from aqueous ethanol or carbon tetrachloride) (Found: C, 44.2; H, 2.5. C<sub>10</sub>H<sub>7</sub>ONF<sub>6</sub> requires C, 44.3; H, 2.6%).

*2,3-Bistrifluoromethylaniline.*—The 3-nitro-compound (13.0 g.) in ethanol (35 c.c.) was reduced at room temperature and atmospheric pressure with hydrogen in the presence of Raney nickel (*ca* 0.5 g.). The solution was boiled with charcoal, filtered, and evaporated to dryness to leave a solid product (10.8 g.). A sample was distilled at 15 mm. to give 2,3-bistrifluoromethylaniline, m. p. 30—32° (Found: C, 42.1; H, 2.2%). The amine (5.0 g.) was trifluoroacetylated and the *product* recrystallised from light petroleum (b. p. 60—80°); this (6.4 g.) had m. p. 115—117° (Found: C, 36.7; H, 1.3%). Similarly 2,3-bistrifluoromethylacetanilide was prepared; recrystallised from aqueous ethanol, it had m. p. 160—162° (Found: C, 44.6; H, 2.4; F, 41.7. C<sub>10</sub>H<sub>7</sub>ONF<sub>6</sub> requires C, 44.3; H, 2.6; F, 42.0%).

*Separation of Mixed Acetamido-compounds by (i) Chromatography and (ii) Fractional Crystallisation.*—(i) The mixed nitro-compounds from the nitration of 1,2-bistrifluoromethylbenzene were reduced and acetylated as described above for the 4-nitro-isomer. The mixed acetamido-derivatives in carbon tetrachloride were passed through a column of aluminium oxide which had been previously neutralised by warming it with ethyl formate in light petroleum (b. p. 60—80°) for about 0.5 hr. The 3-isomer was eluted first with carbon tetrachloride. After evaporation the residue recrystallised from either aqueous ethanol or carbon tetrachloride and had m. p. (alone or in admixture with an authentic sample) 158—160° (Found: C, 44.4; H, 3.0%). The 4-isomer was then eluted, isolated, and recrystallised from either of the above solvents; it had m. p. and mixed m. p. 106—107° (Found: C, 44.7; H, 2.6%). Overall,

<sup>25</sup> Cohen, Woodroffe, and Anderson, *J.*, 1916, **109**, 222.

<sup>26</sup> Crossley and Renouf, *J.*, 1909, **95**, 208.

recoveries based on the original mixed nitro-compounds were about 35% of the 4-isomer and about 20% of the 3-isomer.

(ii) Repeated fractional crystallisation from carbon tetrachloride of the acetamido-derivatives obtained from the mixed nitro-compounds (2.1 g.) afforded two products, m. p. 107—108° and 154—156° (0.01 g. and 0.02 g. respectively).

*Nitration of 3,4-Bistrifluoromethylacetanilide.*—The acetanilide (1.5 g.; m. p. 106°) was added slowly to a stirred mixture of acetic anhydride (1.5 c.c.) and fuming nitric acid (1.5 c.c.; *d* 1.5) which was maintained at 0—10°. The solution was stirred continuously, while the temperature increased during 1.5 hr. to 10—15°. After a further 16 hr. the solution was poured into water (50 c.c.), and the aqueous solution was decanted from the oily product. After addition to the latter of 2*N*-sodium hydroxide (30 c.c.) the mixture was steam-distilled. The distillate was extracted with ether, and the extract was dried (MgSO<sub>4</sub>) and concentrated. The residue recrystallised from carbon tetrachloride, to yield 2-nitro-3,4-bistrifluoromethylaniline (0.25 g.), m. p. 88—89° (Found: C, 35.0; H, 1.6; F, 41.6. C<sub>8</sub>H<sub>4</sub>O<sub>2</sub>N<sub>2</sub>F<sub>6</sub> requires C, 35.0; H, 1.5; F, 41.6%).

A part of the alkaline solution remaining after the hydrolysis and steam-distillation was acidified with glacial acetic acid and treated with cerous nitrate solution. A copious precipitate of cerous fluoride indicated that appreciable hydrolysis of the trifluoromethyl groups had occurred.

In attempts to increase the yield in this reaction the nitration product was hydrolysed with 2*N*-sulphuric acid but no tractable product was obtained. The nitro-amine was not very volatile in steam, but attempts to isolate it by other methods after the hydrolysis with alkali failed because it could not be separated from a dark material formed simultaneously. When the solution was neutralised immediately before the steam-distillation no significant improvement in yield resulted.

*Nitration of N-Trifluoroacetyl-3,4-bistrifluoromethylaniline.*—(i) The trifluoroacetyl compound (1.6 g.; m. p. 62°) was added slowly to a stirred mixture of fuming nitric acid (2.0 c.c.) and trifluoroacetic anhydride (2 c.c.) at 0—5°. The solution was stirred for 2 hr. (temperature increased to 10—15°) and after a further 16 hr. at 10—15° was poured into water (50 c.c.). The gummy solid which separated was filtered off and added to 0.5*N*-sodium hydroxide (40 c.c.), and the mixture was steam-distilled. The distillate was extracted with ether, and concentration of the dried (MgSO<sub>4</sub>) extract and recrystallisation of the residue from carbon tetrachloride yielded 2-nitro-3,4-bistrifluoromethylaniline (0.24 g.), m. p. and mixed m. p. 88—89°.

(ii) After nitration as described, the solid obtained when the mixture was poured into water was hydrolysed with 0.5*N*-sodium hydroxide (40 c.c.) at 100° for 0.5 hr. The solution was cooled, and the precipitate collected and recrystallised from carbon tetrachloride to give the nitro-amine (0.67 g.), m. p. 86—88°.

(iii) *N*-Trifluoroacetyl-3,4-bistrifluoromethylaniline (15.6 g.) was added slowly with stirring at 0° to a mixture of fuming nitric acid (20 c.c.) and trifluoroacetic anhydride (20 c.c.). After 2 hr. at 0°, stirring was continued for 17 hr. at 15° and then the mixture was poured into water (300 c.c.). After neutralisation with 4*N*-sodium hydroxide, additional sodium hydroxide (0.5*N*; 200 c.c.) was added and the solution was boiled under reflux for 15 min. The cooled solution was neutralised with 4*N*-nitric acid, made just alkaline with sodium carbonate, and steam-distilled. The distillate was extracted continuously for 16 hr. with ether. The dried (MgSO<sub>4</sub>) ethereal solution was evaporated to a solid which recrystallised from chloroform to yield 2-nitro-3,4-bistrifluoromethylaniline (7.7 g.), m. p. 87—88°.

(iv) The trifluoroacetanilide (1.65 g.) was added slowly to a stirred mixture of acetic anhydride (2.5 c.c.) and fuming nitric acid (2.5 c.c.; *d* 1.5) which was maintained at 0—5°. The solution was stirred for 2 hr. (temperature allowed to rise to 10—15°) and then set aside for 16 hr. Working-up as described in (ii) above yielded 2-nitro-3,4-bistrifluoromethylaniline (0.37 g.), m. p. 88—89°. This product was darker than that obtained as in (ii) but two further recrystallisations removed the contaminants.

*Attempted Nitration of N-Acetyl- and N-Trifluoroacetyl-2,3-bistrifluoromethylaniline.*—The derivatives were separately treated with acetic anhydride-fuming nitric acid, and with trifluoroacetic anhydride-fuming nitric acid under conditions similar to those used for the isomers. In no case was a nitro-amine obtained and the free amine or the appropriate acyl derivative was recovered.

*Deamination of 2-Nitro-3,4-bistrifluoromethylaniline.*—The nitro-amine (5.3 g.) in glacial

acetic acid (25 c.c.), cooled to 15°, was added slowly to a solution of sodium nitrite (2.0 g.) in concentrated sulphuric acid (12 c.c.): the mixture was kept below 20°. After 20 min. the mixture was poured slowly into a vigorously stirred suspension of cuprous oxide (5.7 g.) in ethanol (150 c.c.). The temperature rose rapidly to 60° and nitrogen was evolved. After 17 hr. at 15° the mixture was poured into water (50 c.c.) and steam-distilled. Concentration of the dried ethereal extract of the distillate afforded a liquid which was reduced in ethanol (150 c.c.) with hydrogen (uptake *ca.* 450 c.c.) and Raney nickel (*ca.* 2.0 g.). Evaporation under diminished pressure of the filtered solution gave a residue which was divided into two equal portions. One portion was heated with glacial acetic acid (5 c.c.) and acetic anhydride (5 c.c.) at 100° for 0.5 hr. The mixture was poured into water, and the solid obtained was recrystallised from aqueous ethanol, to give 2,3-bistrifluoromethylacetanilide (0.7 g.), m. p. and mixed m. p. 160—162°. The other portion was trifluoroacetylated (5 c.c. of anhydride in 15 c.c. of ether). After 15 hr. at 15° the solution was evaporated to dryness and the residue recrystallised from light petroleum (b. p. 60—80°) to afford *N*-trifluoroacetyl-2,3-bistrifluoromethylaniline (0.9 g.), m. p. and mixed m. p. 116°. The infrared spectra of the derivatives were identical with those of authentic samples.

**3,4-Bistrifluoromethyl-*o*-phenylenediamine.**—2-Nitro-3,4-bistrifluoromethylaniline (1.88 g.) in ethanol (20 c.c.) was reduced at 15° and atmospheric pressure with hydrogen and Raney nickel (*ca.* 0.2 g.). The resulting diamine (1.38 g.), recrystallised from benzene–light petroleum (b. p. 100—120°), had m. p. 64—65° (Found: C, 39.0; H, 2.3.  $C_8H_6N_2F_6$  requires C, 39.3; H, 2.5%).

**4,5-Bistrifluoromethylbenzimidazole.**—The preceding diamine (0.3 g.), 90% formic acid (1 c.c.), and concentrated hydrochloric acid (3 drops) were kept at 100° for 3 hr. The solution was neutralised carefully with concentrated ammonia solution and the precipitate formed was collected and recrystallised from water. 4,5-Bistrifluoromethylbenzimidazole (0.21 g.) has m. p. 189—190° (Found: C, 42.8; H, 1.7; F, 44.5.  $C_9H_4N_2F_6$  requires C, 42.5; H, 1.6; F, 44.9%),  $\lambda_{max}$  2470, 2520, 2700, and 2800 Å [ $\epsilon$  ~3500, 3600, 2560, and 1350 respectively; *c* 0.10 in ethanol–water (3 : 7)]. It formed a *picrate*, m. p. 184—186° (from benzene) (Found: C, 37.6; H, 1.8.  $C_{15}H_9O_7N_5F_6$  requires C, 37.3; H, 1.5%).

**2-Methyl-4,5-bistrifluoromethylbenzimidazole.**—The diamine (0.5 g.), acetic acid (2 c.c.), and concentrated hydrochloric acid (10 drops) were kept at 100° for 4 hr. Working-up as before yielded 2-methyl-4,5-bistrifluoromethylbenzimidazole (0.41 g.), m. p. 227—228° (from aqueous ethanol),  $\lambda_{max}$  2520, 2550, 2710, and 2810 Å [ $\epsilon$  ~4200, 4400, 3250, and 2280 respectively; *c* 0.056 in ethanol–water (3 : 7)] (Found: C, 44.4; H, 2.59.  $C_{10}H_6N_2F_6$  requires C, 44.8; H, 2.2%) [*picrate*, m. p. 130—132° (from ethanol) (Found: C, 38.8; H, 2.3; F, 22.5.  $C_{16}H_9O_7N_5F_6$  requires C, 38.6; H, 1.8; F, 22.9%)].

**2,4,5-Tristrifluoromethylbenzimidazole.**—Trifluoroacetic acid (2 c.c.) was added to a mixture of the diamine (0.5 g.) and concentrated hydrochloric acid (10 drops). The mixture solidified almost immediately and was heated at 100° for 2 hr. 2,4,5-Tristrifluoromethylbenzimidazole (0.37 g.), m. p. 222—223°,  $\lambda_{max}$  2550, 2720, and 2810 Å [ $\epsilon$  ~4400, 3570, and 2800 respectively; *c* 0.067 in ethanol–water (3 : 7)] (Found: C, 37.6; H, 1.2.  $C_{10}H_3N_2F_9$  requires C, 37.3; H, 0.9%) was obtained by distillation at 180° (bath-temp.) on to a cold finger; it recrystallised from chloroform containing a trace of acetone but with low recovery.

**2,3-Diphenyl-5,6-bistrifluoromethylquinoxaline.**—3,4-Bistrifluoromethyl-*o*-phenylene-diamine (0.24 g.) and benzil (0.21 g.) were heated under reflux in methanol (10 c.c.) for 1 hr. Removal of the solvent and recrystallisation of the residue from aqueous ethanol afforded 2,3-diphenyl-5,6-bistrifluoromethylquinoxaline (0.20 g.), m. p. 124—126° (Found: C, 62.8; H, 2.9.  $C_{22}H_{12}N_2F_6$  requires C, 63.2; H, 2.9%).

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