Anal. Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.37; N, 4.27. Found: C, 77.30, 77.46; H, 8.46, 8.38; N, 4.36, 4.29.

1-Ethyl-2-piperidinomethyl-3-benzo(f)chromene (XIII, R is C_2H_5).—Exactly 0.01 mole of ethanolic hydrogen chloride was added gradually to a solution of 0.01 mole of the chromanol in butyl ether. A yellow oil precipitated which slowly crystallized to colorless crystals, m. p. 230–233°. Recrystallization from methanol gave pure 1-ethyl-2-piperidinomethyl-3-benzo(f)chromene hydrochloride, m. p. 244–245°. The free base, recrystallized from ethanol, melted at 89.0–89.5°.

Anal. Calcd. for $C_{21}H_{25}NO\cdot HCl$: C, 73.32; H, 7.62; Cl, 10.31. Found: C, 73.14, 73.27; H, 7.70, 7.75; Cl, 10.33, 10.22.

1-Methyl-2-piperidinomethyl-3-benzo(f)chromene.—The Grignard reagent was prepared from 17.0 g. of methyl iodide (0.12 mole) and 2.92 g. of magnesium turnings (0.12 mole). A solution of 17.8 g. of IV (0.06 mole) in 100 ml. of anhydrous ether was added during one hour to the stirred reaction mixture. It was then heated at reflux for an additional thirty minutes. An excess of saturated aqueous ammonium chloride was added carefully and the reaction mixture was extracted with four 100-ml. portions of ether. Evaporation of the dried ether extracts gave 15.5 g. of a brown oil which could not be crystallized. It was dissolved in methanol and added to a solution of hydrogen chloride in anhydrous ether. On standing a colorless crystalline material, m. p. 237–239°, was obtained. Recrystallization from methanol–water (3:1) gave 4.7 g. of the chromene hydrochloride, m. p. 249–250°; yield 22.6%.

Anal. Calcd. for $C_{20}H_{23}NO\cdot HCl$: C, 72.85; H, 7.28; N, 4.25; Cl, 10.76. Found: C, 72.78, 72.67; H, 7.35, 7.30; N, 4.11, 4.22; Cl, 10.85, 10.76.

Summary

1-Benzo(f)chromanone and 1-benzo(f)thiochromanone have been prepared by an improved method. The former has been converted into various hydroxylamino derivatives and related compounds for testing as antimalarials.

LAFAYETTE, INDIANA RECEIVED FEBRUARY 5, 1947

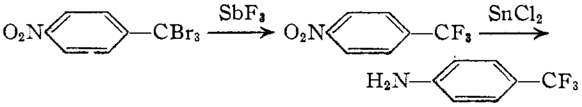
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Ortho and Para Substituted Derivatives of Benzotrifluoride

BY REUBEN G. JONES

The ordinary substitution reactions such as nitration[1] and halogenation[2,3] take place exclusively in the meta position of benzotrifluoride. Thus, the readily obtained meta-substituted derivatives have been rather extensively investigated while the ortho- and para-substituted derivatives of benzotrifluoride are relatively unknown.

In connection with an investigation of the physiological properties of compounds containing the trifluoromethyl (CF_3-) group, a need arose for a number of derivatives of benzotrifluoride with substituents in the ortho and para positions. The most convenient approach to the synthesis of a variety of ortho- and para-substituted benzotrifluorides appeared to be through the corresponding amino compounds. The known *o*-aminobenzotrifluoride was prepared by modifications of the method of Rouche.[4] *p*-Aminobenzotrifluoride was obtained by the following sequence of reactions



By the well known diazonium transformations, the amino compounds were converted to the phenols, fluorides, chlorides, bromides and iodides presented in Table I.

TABLE I

ORTHO AND PARA SUBSTITUTED BENZOTRIFLUORIDES

Substituent	Yield, %	B. p., °C.[a]	Mm.	$n^{25}D$	d^{26}_{26}	Analyses, % Calcd. C	Calcd. H	Found C	Found H
o-OH[b]	68	147 –148	760			51.86	3.11	51.65	3.28
p-OH[c]	80	71.5–72	8			51.86	3.11	51.96	3.45
o-F	83	114.5	750	1.4040	1.293	51.23	2.46	50.96	2.65
o-Cl[6]	80	148.5–149	760	1.4533	1.356	46.56	2.23	46.64	2.39
o-Br	88	167.5–168	745	1.4805	1.656	37.36	1.79	37.37	1.96
p-Br	85	160 –160.5	745	1.4710	1.614	37.36	1.79	37.25	1.76
o-I	78	197.5–198	750	1.5258	1.896	30.91	1.48	31.36	1.54
p-I[d]	90	185.5–186	745	1.5158	1.851	30.91	1.48	30.93	2.10

[a] Corrected. [b] Melting point 45.5–46°. [c] Melting point 46.5–47°. [d] Melting point 17–17.5°.

Nitration of *m*-iodobenzotrifluoride[5] produced a mixture from which the solid 2-nitro-5-iodobenzotrifluoride (57.5% yield) readily was separated. This compound was identified by comparison with a sample made from 2-nitro-5-aminobenzotrifluoride through the Sandmeyer reaction. The

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[1] Swarts, *Bull. sci. acad. roy. Belg.*, **6**, 389 (1920) [*Chem. Zentr.*, **92**, II, 32 (1921)].

[2] Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

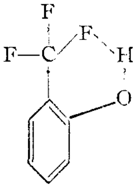
[3] Wertyporoch, *Ann.*, **493**, 153 (1932).

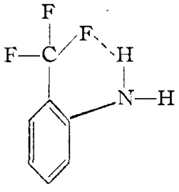
[4] Rouche, *Bull. sci. acad. roy. Belg.*, **13**, 346 (1927); [*Chem. Zentr.*, **98**, II, 1817 (1927)].

[5] Finger and Kolinowski, *Trans. Illinois State Acad. Sci.*, **37**, 66 (1944) [*C. A.*, **39**, 1146 (1945)].

nitration of *m*-bromobenzotrifluoride[2,5] gave an excellent yield of mononitro compounds, but the mixture, presumably consisting of 2-nitro- and 4-nitro-5-bromobenzotrifluorides, could not be separated by the distilling apparatus at hand.

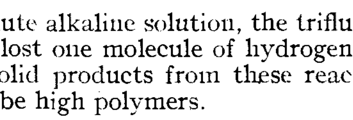
Boiling Points.—The boiling points of the ortho-halogenated benzotrifluorides averaged 10 to 20° higher than the boiling points of the corresponding meta and para isomers, and in this respect they resemble the halogenated nitrobenzenes, the ortho isomers of which boil somewhat higher than the corresponding meta isomers. Incidentally, the boiling point observed at this time for *o*-chlorobenzotrifluoride (148.5–149°, cor.) is about 5° lower than that reported by Booth, Elsey and Burchfield.[6] *o*-Trifluoromethylphenol and *o*-trifluoromethylaniline exhibit boiling points more than 30° lower than the respective meta compounds. These unusually low boiling points are probably best explained by intramolecular hydrogen bonding for which both ortho compounds appear to possess ideal configurations.



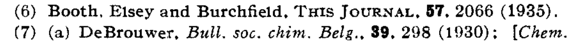


Chemical Properties.—It was not suprising to find that the bromo- and iodobenzotrifluorides reacted normally with magnesium in dry ether to form the trifluoromethylphenyl Grignard reagents in good yields. Carbonation of the appropriate Grignard reagents led to *o*-trifluoromethylbenzoic acid[7] and *p*-trifluoromethylbenzoic acid. *o*-Chlorobenzotrifluoride in dry ether solution failed to react with magnesium.

An outstanding characteristic of benzotrifluoride and most of its derivatives is the unusual resistance of the CF_3 group to chemical degradation. It has now been found, however, that both *p*- and *o*-trifluoromethylphenol are extremely labile in the presence of base. With concentrated sodium hydroxide, vigorous reactions took place, and the hydroxybenzoic acids were formed as the main products.



In cold dilute alkaline solution, the trifluoromethylphenols lost one molecule of hydrogen fluoride, and the solid products from these reactions appeared to be high polymers.

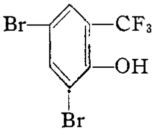


It was interesting to find that these polymeric materials were now resistant to further loss of fluorine even in the presence of boiling concentrated sodium hydroxide solution.

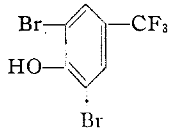
The presence of a trace of hydrogen fluoride also appeared to induce the polymerization of *p*-trifluoromethylphenol with the expulsion of hydrogen fluoride. In contrast with the ortho and para isomers, *m*-trifluoromethylphenol was completely stable in hot sodium hydroxide solution.

The activating influence on the CF_3 group of electron donor groups in the para position was again illustrated in the case of *p*-aminobenzotrifluoride. When this compound was heated to about 200°, in an attempt to distil it at atmospheric pressure, a vigorous polymerization took place with the evolution of large quantities of hydrogen fluoride and the formation of a hard glassy resin. Even the heat evolved during catalytic hydrogenation of *p*-nitrobenzotrifluoride was enough to cause extensive decomposition of the resulting amino compound. On the other hand, *o*-aminobenzotrifluoride appeared to be much more stable and could be distilled at atmospheric pressure with no decomposition.

Both *o*- and *p*-trifluoromethylphenol readily reacted with two moles of bromine to yield the crystalline dibromotrifluoromethylphenols [A] and [B]. These were identified by conversion with hot sodium hydroxide solution to the known dibromohydroxybenzoic acids.



[A]



[B]

Experimental

2-Nitro-5-aminobenzotrifluoride.[4]—In a 2-liter, three-necked flask was placed 1 liter of concentrated sulfuric acid. This was cooled to −5°, 190 g. (0.94 mole) of *m*-trifluoromethylacetanilide[8] was added, and the mixture was stirred until a clear solution formed. From a dropping funnel was added a solution of 76 g. of fuming nitric acid in 95 cc. of concentrated sulfuric acid during forty-five minutes while the temperature was maintained at −5 to 0°. The solution was allowed to warm up to room temperature and stand for three hours then warmed to 40° for one hour, and poured onto 4 kg. of crushed ice. The yellow gummy precipitate gradually crystallized. It was collected and washed well with water.

The crude 2-nitro-5-acetaminobenzotrifluoride from two such runs was combined and added to a solution of 350 cc. of 12.5 *N* sodium hydroxide in 1 liter of alcohol. The resulting dark solution was refluxed gently for six to ten hours, evaporated under vacuum to about two-thirds its original volume, and poured into 6 liters of water. The yellow precipitate of 2-nitro-5-aminobenzotrifluoride was collected, washed with water and air dried. It melted at 118–120°. A sample upon recrystallization from dilute aqueous alcohol melted at 126–127° (lit.,[4] 129°). None of the expected 4-nitro-5-aminobenzotrifluoride[4,7a] was found when a portion of the crude nitroaminobenzotrifluoride was subjected to steam distillation. The yield

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[6] Booth, Elsey and Burchfield, THIS JOURNAL, **57**, 2066 (1935).

[7] (a) DeBrouwer, *Bull. soc. chim. Belg.*, **39**, 298 (1930); [*Chem. Zentr.*, **101**, II, 2373 (1930). (b) Roberts and Curtin, THIS JOURNAL, **68**, 1658 (1946).

[8] Swarts, *Bull. sci. acad. roy. Belg.*, **35**, 375 (1898); [*Chem. Zentr.*, **69**, II, 26 (1898).

of crude product was 263 g. which is 69% based on the *m*-trifluoromethylacetanilide.

2-Nitro-5-iodobenzotrifluoride.—A solution of 2.0 g. (0.01 mole) of 2-nitro-5-aminobenzotrifluoride (m. p. 126–127°) in 50 cc. of 6 *N* sulfuric acid was cooled to 5° and diazotized. The diazonium solution was poured into a solution of 5 g. of potassium iodide in 20 cc. of water. The resulting solid product was collected and recrystallized from alcohol. The yield was 3.0 g. (95%); m. p. 61–62°.

Anal. Calcd. for $C_7H_3F_3INO_2$: C, 26.52; H, 0.95. Found: C, 26.59; H, 1.09.

Nitration of *m*-Iodobenzotrifluoride and *m*-Bromobenzotrifluoride.—To a solution of 105 g. of concentrated nitric acid in 300 g. of concentrated sulfuric acid maintained at 35–40° and well stirred was added 237 g. (0.87 mole) of *m*-iodobenzotrifluoride[5] during one-half hour. After the addition was complete and the reaction was no longer exothermic, the mixture was heated at 60° for one-half hour, cooled, and poured into ice water. The mixture was extracted with chloroform. The chloroform solution was dried, the chloroform was removed and the residual liquid was distilled in vacuum. It boiled at 117–127° (7 mm.). The yield was 257 g. (93%). The distillate, which partially crystallized upon cooling, was mixed with an equal volume of petroleum ether and chilled to −20°. The crystalline material was collected on a filter and recrystallized from a little petroleum ether (b. p. 60–68°). The yield of crystalline solid was 158 g. (57.5%); m. p. 58–60°. A sample recrystallized from alcohol, melted at 60–61°, and mixed with authentic 2-nitro-5-iodobenzotrifluoride, it melted at 61–62°.

m-Bromobenzotrifluoride[2] was nitrated as described above for *m*-iodobenzotrifluoride to give a 94% yield of pale yellow liquid boiling at 78–84° (3 mm.).

Anal. Calcd. for $C_7H_3BrF_3NO_2$: C, 31.13; H, 1.12. Found: C, 30.99; H, 1.12.

***o*-Nitrobenzotrifluoride.**[4]—A solution of 385 g. (1.85 mole) of crude 2-nitro-5-aminobenzotrifluoride (m. p. 118–120°) in 1500 cc. of absolute alcohol in a 5-liter three-necked flask was cooled to 0°, and with stirring 370 g. (3.7 mole) of concentrated sulfuric acid was added slowly. The solution was maintained at 0 to 5° while 280 g. (3.70 mole) of ethyl nitrite (precooled to −70°) was added with stirring from a dropping funnel over a period of one hour. The solution was kept at 5 to 10° for one additional hour, and then it was allowed to warm up while stirring continuously. When the temperature had reached 15°, 3 g. of copper-bronze powder was added. Evolution of nitrogen began immediately, and as the smooth, mildly exothermic reaction proceeded, the temperature was allowed to gradually rise until it reached 40° where it was held until the evolution of nitrogen had almost stopped (two hours). The solution was finally boiled on the steam-bath for fifteen minutes, cooled, and diluted with 2 liters of water. The dark oily layer which separated to the bottom was drawn off, and the aqueous-alcohol solution was extracted with five 200-cc. portions of chloroform. The combined oily layer and chloroform extracts were dried over magnesium sulfate. After removing the chloroform through a short packed column, the residual liquid was distilled in vacuum to yield 295 g. (83.5%) of *o*-nitrobenzotrifluoride, b. p. 106–108° (20 mm.); m. p. 31–31.5° (lit.[4] 32.5°).

***o*-Aminobenzotrifluoride.**[4]—A mixture of 144 g. (0.75 mole) of *o*-nitrobenzotrifluoride and 0.20 g. of platinum oxide catalyst or 2.0 g. of 5% palladium–charcoal catalyst was shaken with hydrogen at three to four atmospheres until no more hydrogen was absorbed (three to four hours). The water and catalyst were separated and the *o*-trifluoromethylaniline was distilled; b. p. 72–74° (21 mm.), 174–175° (cor.) (753 mm.); $n^{25}D$ 1.4785; d^{25}_{25} 1.290. The yields in duplicate runs were 95.5 and 96%.

The acetyl compound melted at 94.5–95° (lit.[4] 94°), and the benzoyl compound melted at 140–141°.

Anal. Calcd. for $C_{14}H_{10}F_3NO$: N, 5.28. Found: N, 5.10.

***p*-Nitrobenzotribromide.**—This compound was prepared according to Fisher[9] from *p*-nitrobenzal bromide except that only a two-fold excess of sodium hypobromite was used. For the preparation of larger quantities a method was developed starting from *p*-nitrotoluene.

In a 500-cc. three-necked flask provided with a stirrer, dropping funnel and reflux condenser was placed 96 g. (0.70 mole) of *p*-nitrotoluene. The flask was about one-half immersed in a wax-bath heated to 195–200°, and the contents were rapidly stirred while 280 g. (1.75 mole) of bromine was added during a period of two hours. At this rate of addition, little bromine passed through unreacted until near the end of the reaction. The melt was poured into a dish, and, after it had cooled, it was dissolved in 1 liter of hot petroleum ether (b. p. 60–68°) leaving a little semi-solid, insoluble material. The petroleum ether solution was evaporated to a volume of 500 cc. and then chilled to 0°. The crystalline product was collected on a filter and dried. It weighed 180 g. In order to obtain this material (a mixture of *p*-nitrobenzal bromide and *p*-nitrobenzyl bromide) in a state of fine subdivision for the next step, it was dissolved in 500 cc. of warm methanol. The solution was treated with carbon, filtered, and the filtrate poured with stirring into 2 liters of ice-water. The finely divided precipitate was collected on a filter and washed well with water, care being taken not to let the filter cake suck dry and become compressed. The material was carefully removed from the funnel and suspended in a cold sodium hypobromite solution made by adding 180 g. of bromine to a solution of 180 g. of sodium hydroxide in 1500 cc. of water. The suspension was occasionally shaken and allowed to stand at room temperature for two days. The solid was collected on a funnel, washed with water and then dissolved in 800 cc. of boiling methanol. The methanol solution was chilled to 0° and the crystalline precipitate was collected and recrystallized from a minimum quantity of methanol to yield 151 g. (58%) of *p*-nitrobenzotribromide, m. p. 86–87°.

Attempts to brominate quantities greater than about one mole of *p*-nitrotoluene resulted in much lower yields of the final product.

***p*-Nitrobenzotrifluoride.**—A mixture of 85 g. (0.23 mole) of *p*-nitrobenzotribromide and 50 g. (0.275 mole) of powdered antimony fluoride in a small round-bottom flask carrying a condenser set for distillation was cautiously heated with a flame until the mixture was entirely melted. A mild exothermic reaction took place. Heating with the flame was continued and the mixture was distilled, first at atmospheric pressure and finally under reduced pressure until nothing more came over. The distillate, which partially solidified in the condenser, was dissolved in a mixture of 100 cc. of ether and excess 6 *N* hydrochloric acid. The water layer was separated, and the ether layer was shaken with a large excess (300 cc.) of 6 *N* sodium hydroxide solution. The ether layer was separated, dried over magnesium sulfate, the ether removed, and the *p*-nitrobenzotrifluoride distilled; b. p. 81–82° (10 mm.); 198° (uncor.) (736 mm.); m. p. 40–40.5° (lit.[4] 41°). The yield was 39.5 g. (90.0%), and this was duplicated in a number of runs.

When the reaction was carried out under a pressure of 10 mm. of mercury so that the product distilled during the reaction, a large fraction was obtained which boiled at 112–113° (10 mm.). This appeared to consist largely of α-bromo-α,α-difluoro-*p*-nitrotoluene.

***p*-Aminobenzotrifluoride.**—To a solution of 100 cc. of alcohol and 150 cc. of concentrated hydrochloric acid was added 39.0 g. (0.24 mole) of *p*-nitrobenzotrifluoride. The mixture was stirred and 200 g. of stannous chloride dihydrate was added in portions during thirty minutes while the temperature was maintained at about 60°. When the exothermic reaction had subsided, the orange-yellow solution was warmed on the steam-bath to 60° for fifteen minutes, then cooled and poured into a mixture of 700 g. of ice and 500 cc. of 36% sodium hydroxide solution. The mixture was extracted with three 100-cc. por-

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[9] Fisher, This Journal, **56**, 2469 (1934).

tions of ether. The ether solution was dried over magnesium sulfate, the ether was removed, and the amine was distilled under reduced pressure. It boiled at 83° (12 mm.), 91° (19 mm.), 107° (39 mm.) and 117.5° (60 mm.). The compound readily crystallized in the ice-bath; m. p. 8.0°; $n^{25}D$ 1.4815; $d^{27}{}_{27}$ 1.283. The yield was 29.5 g. (90%).

Anal. Calcd. for $C_7H_6F_3N$: N, 8.69. Found: N, 8.99.

p-Acetaminobenzotrifluoride obtained from the amine and acetic anhydride in pyridine melted at 150–151°.

Anal. Calcd. for $C_9H_8F_3NO$: N, 6.90. Found: N, 6.92.

Halogenated Benzotrifluorides and Trifluoromethylphenols (Table I).—*o*-Fluorobenzotrifluoride was prepared by the standard Schiemann method.[10] The intermediate *o*-trifluoromethylbenzenediazonium fluoroborate obtained in 91% yield melted at 146–147°.

The ortho and para-chloro-, bromo- and iodo- derivatives and the phenols were prepared by the ordinary diazonium methods in quantities of about 0.1 to 0.3 mole.

o- and p-Trifluoromethylbenzoic Acids.—In a dry 500-cc. three-necked flask provided with a condenser and calcium chloride tube, stirrer and dropping funnel was placed 5.0 g. (0.208 g. atom) of magnesium turnings, 100 cc. of anhydrous ether and 0.5 g. of iodine. When all of the iodine had reacted, a solution of 22.5 g. (0.10 mole) of *o*-bromobenzotrifluoride in 100 cc. of anhydrous ether was added during forty-five minutes. The red-brown solution was stirred for an additional fifteen minutes. Titration of a 5-cc. aliquot indicated a 98% yield of Grignard reagent.

The solution was poured onto crushed, solid carbon dioxide and worked up in the usual manner to yield 16.3 g. (85.7%) of *o*-trifluoromethylbenzoic acid. Upon crystallization from petroleum ether, the acid melted at 107–107.5° (lit.[7] 108.5°).

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found: C, 50.49; H, 2.64.

When *o*-iodobenzotrifluoride was used in place of *o*-bromobenzotrifluoride, the yield of *o*-trifluoromethylbenzoic acid was 73.4%.

p-Trifluoromethylphenylmagnesium bromide was prepared as described above for the ortho isomer. It was carbonated to yield *p*-trifluoromethylbenzoic acid (90%) which melted at 212–213° after vacuum sublimation.

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found: C, 50.74; H, 2.82.

To 8.0 g. (0.042 mole) of *o*-trifluoromethylbenzoic acid was added 10 cc. of thionyl chloride. A vigorous reaction took place. After standing for several hours at room temperature, the excess thionyl chloride was removed and the *o*-trifluoromethylbenzoyl chloride was distilled through a short column; b. p. 199–200° (uncor.) (750 mm.). The acid chloride in aqueous ammonia gave *o*-trifluoromethylbenzamide; m. p. 159° (lit.[7] 161°).

A solution of 18.1 g. (0.10 mole) of *o*-chlorobenzotrifluoride in 100 cc. of dry ether was added to 5 g. of magnesium turnings (activated with iodine) in 50 cc. of ether. There appeared to be no reaction. The mixture was stirred and refluxed for three hours and then poured onto crushed solid carbon dioxide. No acid was obtained, and when the ether layer was worked up 16.9 g. (93.4%) of unchanged *o*-chlorobenzotrifluoride (b. p., 144–145° uncor.) was recovered.

Bromination of o- and p-Trifluoromethylphenols.—A mixture of 2.0 g. of *o*-trifluoromethylphenol and 25 cc. of water in a small flask was shaken while bromine was added until the bromine color persisted. The oily product crystallized upon scratching. It weighed 4.0 g. (100%) and melted at 56–57°. A sample was recrystallized from petroleum ether; m. p. 57.5–58°.

Anal. Calcd. for $C_7H_3Br_2F_3O$: C, 26.28; H, 0.95. Found: C, 26.26; H, 0.96.

One-half gram of the 3,5-dibromo-2-trifluoromethylphenol was heated to boiling with 1 cc. of 36% aqueous sodium hydroxide. A precipitate formed which all dissolved when the mixture was diluted with 10 cc. of water. The filtered solution was acidified with hydrochloric acid and the resulting white precipitate was collected and dried. It melted at 217–218° and when mixed with an authentic sample of 3,5-dibromosalicylic acid,[11] the melting point was 218–219°.

2,6-Dibromo-4-trifluoromethylphenol obtained by brominating *p*-trifluoromethylphenol melted at 50–50.5°.

Anal. Calcd. for $C_7H_3Br_2F_3O$: C, 26.28; H, 0.95. Found: C, 26.26; H, 1.05.

With hot sodium hydroxide solution this phenol was converted to 3,5-dibromo-4-hydroxybenzoic acid,[11] identified by mixed m. p. with an authentic sample.

A suspension of *m*-trifluoromethylphenol[12] in water decolorized bromine only slowly and no pure compound was obtained from the resulting oily product.

Reaction of the o- and p-Trifluoromethylphenols with Base.—To 5 cc. of cold 12 *N* sodium hydroxide solution was added 3.2 g. (0.02 mole) of *o*-trifluoromethylphenol. First, a clear solution was formed and then after about twenty seconds a vigorous exothermic reaction took place and a white resinous precipitate separated. The mixture was diluted with 25 cc. of water, warmed, filtered, and the filtrate acidified with hydrochloric acid. The crystalline precipitate was collected, dissolved in dilute sodium bicarbonate solution, and the solution was filtered and again acidified. The product melted at 154.5–155° and was identified as salicylic acid, mixed m. p., 155–156°. The yield was 1.5 g. (54%).

The gummy material which was insoluble in sodium hydroxide solution appeared to be polymeric. It partially dissolved in ether leaving a granular white residue.

A 15-g. sample of crude *p*-trifluoromethylphenol containing a trace of free hydrofluoric acid was stored in a stoppered bottle. After three days, the material had liquefied and extensive decomposition appeared to have taken place. The material was extracted with five 50-cc. portions of petroleum ether (b. p. 28–38°) leaving 1.7 g. of buff-colored insoluble powder. The petroleum ether solution was dried with magnesium sulfate, filtered and evaporated to give pure *p*-trifluoromethylphenol which has been kept in a closed bottle for a long period of time without undergoing any further decomposition.

The petroleum ether-insoluble powder (1.7 g.) was easily soluble in ether. It was recrystallized from 100 cc. of 50% alcohol using carbon to decolorize the solution and 0.5 g. of colorless crystals was obtained, m. p. 161–163°.

Anal. Calcd. for $C_{14}H_9F_5O_2$: C, 55.30; H, 2.98; mol. wt., 304.20. Found: C, 59.80; H, 3.43; mol. wt., 271.00.

This compound was insoluble in hot sodium bicarbonate solution but readily soluble in dilute sodium hydroxide solution from which it was precipitated with acid; m. p. 159–160°. A 100-mg. sample of the compound was heated to boiling with 10 drops of 12 *N* sodium hydroxide solution. The solution was diluted to 2 cc., filtered and acidified to yield *p*-hydroxybenzoic acid; m. p. 209–210°, and, with an authentic sample of *p*-hydroxybenzoic acid, mixed m. p. 209–210°.

To 15 cc. of 1.00 *N* sodium hydroxide solution (0.015 mole) was added 2.0 g. (0.012 mole) of *p*-trifluoromethylphenol and the mixture was shaken. The resulting solution immediately became cloudy and soon began to deposit finely divided yellow precipitate. After one hour the solid product was collected on a filter and washed with water. The filtrate gave a strongly positive test for fluoride ion. The solid was dissolved in ether, and the cloudy solution was dried over magnesium sulfate. When the ether was evaporated, a light colored sirup remained which changed to a white granular powder when it was rubbed

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[10] Balz and Schiemann, *Ber.*, **60**, 1186 (1927).

[11] Robertson, *J. Chem. Soc.*, **81**, 1475 (1902).

[12] Swarts, *Bull. sci. acad. roy. Belg.*, **113**, 241 (1913); [*Chem. Zentr.*, **84**, II, 760 (1913)].

under petroleum ether. This material (1.8 g. yield) appeared to be completely amorphous under the polarizing microscope. A 100-mg. sample was heated to boiling for about five minutes with 1 cc. of 12 *N* sodium hydroxide solution, but the material remained unchanged. In a capillary tube the product softened and liquefied between 130 and 160°.

Anal. Calcd. for $C_7H_4F_2O$: C, 59.16; H, 2.82. Found: C, 59.28; H, 2.97.

A solution of 1.0 g. of *m*-trifluoromethylphenol[12] in 5 cc. of 50% aqueous sodium hydroxide was heated at 100° for fifteen minutes. There was no evidence of reaction. When the solution was diluted and acidified, it gave a negative test for fluoride ion.

Summary

Improved methods for the preparation of *o*- and *p*-nitrobenzotrifluorides have been described.

p-Aminobenzotrifluoride; *o*-fluorobenzotrifluoride, *o*- and *p*-bromobenzotrifluorides, *o*- and *p*-iodobenzotrifluorides and *o*- and *p*-trifluoromethylphenols have been prepared and characterized.

o-Bromo, *o*-iodo and *p*-bromobenzotrifluorides have been found to form Grignard reagents which have been carbonated to yield *o*- and *p*-trifluoromethylbenzoic acids.

o- and *p*-trifluoromethylphenols have been found to be decomposed readily by aqueous alkali.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Synthesis of Some Long-chain Primary Alcohols and Related Compounds[1]

BY REUBEN G. JONES

During an investigation of naturally-occurring waxy materials, it became necessary to have pure authentic samples of a number of long, straight-chain primary alcohols for purposes of comparison. This paper describes the synthesis of all of the straight-chain, primary alcohols and the ethyl esters of all of the straight-chain carboxylic acids containing twenty-eight to thirty-five carbon atoms. Greatly improved methods have been developed for the preparation of these compounds in comparatively large quantities from the readily available starting materials, octadecyl bromide, sebacic acid and undecylenic acid.

The synthesis of the long-chain aliphatic acids and their derivatives containing more than twenty-five carbon atoms has usually been accomplished by the conventional methods of lengthening the chain by successive increments of one[1a] or two[2] carbon atoms starting from stearic or behenic acid. These methods become exceedingly tedious when derivatives containing thirty or more carbon atoms are desired. Robinson has devised a method[3] for adding long chains in one operation. The intermediate ketonic acids [A] are obtained through acetoacetic ester condensations and can be readily reduced by the Clemmensen method to the unsubstituted long-chain acid.

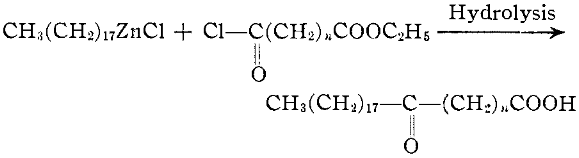
$$CH_3(CH_2)_nCO(CH_2)_{n_1}COOH$$

[A]

Over-all yields by the Robinson procedure, however, leave much to be desired.[3b]

It has now been found that the long-chain ketonic acids such as [A] can be prepared in excellent yields by the reaction of alkyl zinc or cadmium compounds with ω-carbalkoxyacyl halides. Indeed, reactions of this type have been used for the preparation of lower members of the ketonic acid series by a number of investigators.[4]

In the present work octadecylzinc chloride was treated with a series of ω-carbethoxyacyl chlorides to produce the ketonic acids (Table IV) in 75 to 90% yields.



$$CH_3(CH_2)_{17}ZnCl + Cl-\underset{\underset{O}{\|}}{C}(CH_2)_nCOOC_2H_5 \xrightarrow{\text{Hydrolysis}} CH_3(CH_2)_{17}-\underset{\underset{O}{\|}}{C}-(CH_2)_nCOOH$$

The ω-carbethoxyacyl chlorides, $C_2H_5OOC(CH_2)_nCOCl$, were made by the reaction of thionyl chloride with the acidic esters (Table III), which, in turn, were made from the straight-chain dicarboxylic acids by a modification of the "Organic Syntheses" method[5] for ethyl hydrogen sebacate (see experimental). Undecylenic acid served as the starting material for the preparation of 1,9-nonanedicarboxylic acid, 1,10-decanedicarboxylic acid, and brassylic acid according to the methods of Walker and Lumsden.[6] 1,12-Dodecanedicarboxylic acid, 1,13-tridecanedicarboxylic acid, 1,14-tetradecanedicarboxylic acid and 1,15-penta-

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(1) Presented at the 111th meeting of the American Chemical Society, Division of Organic Chemistry, April 14, 1947.

(1a) Levene and Taylor, *J. Biol. Chem.*, **59**, 905 (1924).

(2) (a) Francis, Collins and Piper, *Proc. Roy. Soc. (London)*, **A158**, 691 (1937); (b) Bleyberg and Ulrich, *Ber.*, **64**, 2504 (1931); Schuette and Vogel, *Oil & Soap*, **20**, 263 (1943).

(3) (a) Robinson, *J. Chem. Soc.*, 745 (1930); 1543 (1934); (b) Francis and King, *ibid.*, 999 (1937).

(4) (a) Blaise and Koehler, *Bull. soc. chim.*, **7**, 215(1910); (b) Ruzicka and Stoll, *Helv. Chim. Acta*, **10**, 691 (1927); (c) Späth and Darling, *Ber.*, **63**, 737 (1930); (d) Spielman, *J. Biol. Chem.*, **106**, 87 (1934); (e) Schneider and Spielman, *ibid.*, **142**, 345 (1942); (f) Cason, *Chem. Rev.*, **40**, 15 (1947); (g) the author's attention has been called to a recent publication by Schuette, Roth and Christenson, *Oil & Soap*, **22**, 107 (1945), which describes the preparation of 10-ketohentriacontanoic acid from docosylzinc chloride and ω-carbethoxynonoyl chloride.

(5) Swann, Oehler and Buswell, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 276.

(6) Walker and Lumsden, *J. Chem. Soc.*, **79**, 1191 (1901).