[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

The Preparation and Properties of Some Substituted Benzyl Fluorides[1]

BY JACK BERNSTEIN,[2,3] JAY S. ROTH[4] AND WILLIAM T. MILLER, JR.

The substituted benzyl halides are of special importance because of their theoretical interest and because of their suitability for experimental investigation. Since a series of substituted benzyl fluorides had not been prepared previously, a general method for their preparation was sought in order to permit a study of their properties and relative reactivities. Benzyl fluoride and *p*-nitrobenzyl fluoride are the only compounds in this series which have been previously reported. They were prepared and characterized by the Ingolds[5]: benzyl fluoride itself by the thermal decomposition of benzyltrimethylammonium fluoride and *p*-nitrobenzyl fluoride by the nitration of benzyl fluoride. Swarts[6] had previously reported benzyl fluoride to be a liquid which decomposed very readily, but he did not describe his method of preparation or characterize the product. Ray and Ray[7] reported the preparation of benzyl fluoride by the action of thallous fluoride on benzyl bromide in absolute alcohol solution The product isolated by them was a yellow lachrymatory liquid which decomposed, and apparently was impure since benzyl fluoride is a colorless nonlachrymatory liquid. Attempts to prepare benzyl fluoride by the action of silver fluoride on benzyl chloride[8] and by the decomposition of phenyldiazomethane in 40% hydrofluoric acid[9] were unsuccessful.

In this research, benzyl fluoride was first prepared by thermally decomposing benzyl trimethylammonium fluoride according to Ingold's procedure. Poor yields were obtained, 22 to 29%, based on the starting benzyl chloride, due to polymerization which occurred during the decomposition of the quaternary salt. In addition, Ingold had shown that this method of preparation was not a general one, so that various other procedures had to be investigated. The reactions of benzyl halides with antimony fluoride, thallous fluoride,[7] silver fluoride and potassium fluoride were tried, but in no case could any benzyl fluoride be isolated from the reaction mixtures.

The method of synthesis finally found satisfactory as a general procedure consisted of treating mercuric fluoride[10] with benzyl bromides in chloroform solution. The replacement of the side-chain bromine by fluorine lowered the boiling point of the product sufficiently, about 40°, so that the benzyl fluorides could be easily separated from unreacted bromide by distillation. Absolutely anhydrous conditions were essential for satisfactory fluorinations since the presence of traces of water resulted in the formation of hydrogen fluoride which caused the polymerization of the benzyl fluoride. In general, the catalytic properties of hydrogen fluoride[11] greatly complicate the preparation and study of organic fluorine compounds as compared with the other halides and reactions leading to the formation of hydrogen fluoride are likely to be autocatalytic.

An attempt was made to prepare benzyl fluoride by the reaction of mercuric fluoride with benzyl chloride in benzene solution. From this reaction no benzyl fluoride was obtained, but a considerable quantity of diphenylmethane was isolated. The formation of this compound probably occurred through a Friedel–Crafts type reaction of either benzyl chloride or benzyl fluoride, catalyzed by the mercuric salts or by hydrogen fluoride. Calloway[12] has found that alkyl fluorides are the most reactive of the alkyl halides in Friedel–Crafts alkylation. The reaction of *p*-chlorobenzyl fluoride with benzene did not take place in the absence of a catalyst at moderate temperature. However, in the presence of boron trifluoride,[13] the benzyl fluorides reacted smoothly with aromatic hydrocarbons and diphenylmethane derivatives were isolated.

As indicated by Ingold, benzyl fluoride polymerizes very rapidly in the presence of catalysts. In this work the stability of the substituted benzyl fluorides was found to vary greatly with the substituent. No evidence was obtained for the polymerization of *p*-nitrobenzyl fluoride, and even *p*-bromobenzyl fluoride did not polymerize in the presence of a trace of sulfuric acid, which caused a very violent reaction when added to benzyl fluoride itself. In general, ring inactivating substituents made the benzyl fluoride more stable. This effect was consistent with a Friedel–Crafts type polymerization reaction as was the ready formation of diphenylmethane derivatives by reaction

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(2) Sage Fellow in Chemistry, 1940–1941.

(3) Present address: Squibb Institute for Medical Research, New Brunswick, N. J.

(4) Present address: Department of Chemistry, Rutgers University, New Brunswick, N. J.

(5) Ingold and Ingold, *J. Chem. Soc.*, 2249 (1928).

(6) Swarts, *Bull. soc. chim.*, [4] **35**, 1533 (1924).

(7) Ray and Ray, *J. Indian Chem. Soc.*, **13**, 427 (1936).

(8) Tronov and Kruger, *J. Russ. Phys.-Chem. Soc.*, **58**, 1270 (1926).

(9) Tseng, Chia and Ho, *Science Reports*, National Univ. Peking, **1**, 9 (1936).

(10) Henne and Midgley, THIS JOURNAL, **58**, 884 (1936).

(11) Simons, *Ind. Eng. Chem.*, **32**, 178 (1940).

(12) Calloway, THIS JOURNAL, **59**, 1474 (1937).

(13) Compare: Burwell and Archer, *ibid.*, **64**, 1032 (1942).

with benzene.[14] The polymerization may be catalyzed by boron trifluoride or boron trifluoride etherate. Ingold had already reported that sulfuric acid, hydrogen fluoride and even soft glass catalyzed the decomposition of benzyl fluoride. When pure or in the presence of traces of bases, the benzyl fluorides were found to be stable in Pyrex glass at room temperature for long periods of time. Some samples of *p*-chlorobenzyl fluoride have remained undecomposed after seven years storage, although other samples decomposed violently after standing for several weeks. In general, the marked tendency to polymerize increased the difficulty of the preparation of the benzyl fluorides although the use of rigorously anhydrous conditions and reagents, and reasonable care to prevent thermal decomposition during distillation resulted in fairly satisfactory yields of products.

The benzyl fluorides are pleasant smelling compounds with odors similar to the parent hydrocarbons. They show typical halide reactivity in many reactions, and with the exception of the Friedel and Crafts reactions are in general considerably less reactive than the chlorides. Reaction in aqueous alcoholic sodium hydroxide led to the formation of the corresponding ether and alcohol. In dilute aqueous alcoholic hydrogen chloride, significantly, the corresponding ether was also formed. By refluxing the fluoride in a mixture of hydrochloric acid and dioxane, the fluorine could be replaced by chlorine, possibly through the alcohol. The reaction of a fluoride with sodium phenolate in excess phenol led to the formation of the phenyl ethers. These ethers are crystalline compounds, easily purified, and would be suitable as derivatives for the identification of the fluorides which are mostly liquids. The preparation of esters was attempted using the method of Reid.[15] Under conditions which give almost quantitative yields of esters from *p*-nitrobenzyl chloride in three hours, or from *p*-nitrobenzyl bromide in fifteen minutes, practically no reaction had occurred in forty-six hours with *p*-nitrobenzyl fluoride. A small yield of acetate was obtained by reaction with potassium acetate in acetic acid.

Several attempts were made to prepare a Grignard reagent from benzyl fluoride, since benzyl chloride forms a Grignard reagent with great ease. At reflux temperature with ethyl ether no reaction took place while under more vigorous conditions in di-*n*-butyl ether polymerization of the benzyl fluoride occurred. It was found possible to obtain dibenzyl by heating benzyl fluoride in ether solution with Gilman's[16] activated magnesium catalyst in a bomb tube at 100° for ten days, although using ordinary magnesium under similar conditions gave no reaction. Under these vigorous conditions, any Grignard reagent formed would be expected to enter into secondary reactions and consequently would not have been detected. A Wurtz–Fittig reaction was carried out in ether solution, using lithium metal, to form dibenzyl.

Experimental Part

Preparation of Benzyl Fluorides

Benzyl Bromides.—The substituted benzyl bromides were prepared from the corresponding toluenes by direct bromination, usually at the boiling point, in Pyrex all-glass apparatus, illuminated by a mercury vapor lamp. Their physical properties and the yields obtained, based on the starting toluenes, are summarized in Table I.

TABLE I

Substituent	% Yield	Physical properties
m-CH_3[a]	50	B. p. 96–98° at 11 mm.
p-CH_3[a]	51	B. p. 96° at 12 mm., m. p. 36–37°
m-F[b]	54	B. p. 80° at 13 mm.
p-F[b]	57	B. p. 75–76° at 11 mm.
o-Cl[c]	52	B. p. 107° at 12 mm.
m-Cl[d]	57	B. p. 103–104° at 10 mm.
p-Cl[d]	71	B. p. 108° at 12 mm.; m. p. 49.0–49.5°
o-Br[b]	56	B. p. 118–120° at 9 mm.; m. p. 31–32°
m-Br[b]	60	B. p. 122–124° at 12 mm.; m. p. 41.5–42.5°
p-Br[b]	65	B. p. 117–119° at 10 mm.; m. p. 62–63°
m-I[e,g]	28	M. p. 49–50°
p-I[e,g]	28	M. p. 77–79°
m-NO_2[f,h]	30	B. p. 130° at 3 mm.; m. p. 56.5–57.0°
p-NO_2[f,i]	55	M. p. 97.5–99°

[a] Atkinson and Thorpe, *J. Chem. Soc.*, **91**, 1687 (1907). [b] Shoesmith and Slater, *ibid.*, 214 (1926). [c] Leonard, *ibid.*, **109**, 570 (1916). [d] Jackson, *Am. Chem. J.*, **1**, 93 (1879). [e] Shoppee, *J. Chem. Soc.*, 696 (1932). [f] *Org. Syntheses*, **16**, 54 (1936). [g] Bromination temperature 170–180°. [h] Bromination temperature 160°. [i] Bromination temperature 150°.

Mercuric Fluoride.—Mercuric fluoride was prepared by the fluorination of anhydrous mercuric chloride (powder) in a rotating brass reaction vessel according to the general method of Henne.[10] An improved reaction vessel was designed to permit more complete utilization of the fluorine. This consisted of a brass tube 52 cm. long and 5 cm. in diameter which was fitted with interchangeable screw caps. The tube was divided in the middle by a diaphragm with a center opening of 1.5 cm. Mercuric chloride, 0.3 mole and a nickel rod the length of the chamber, to prevent caking of the solid, were placed in each side. The tube was rotated at 30 r. p. m. and fluoride from a closed type nickel electrolysis cell[17] was passed in until the charge in the side into which the fluorine entered was completely converted to mercuric fluoride, as shown by a negative test for chloride ion. This chamber was then emptied and refilled with mercuric chloride. The reaction vessel was then reversed so that the fluorine passed first into the chamber containing partially converted mercuric chloride and the process repeated. The mercuric fluoride was either used directly or stored in a tightly closed copper container fitted with a metal cap and a lead gasket.

Benzyl Fluorides.—The fluorination reactions were carried out in 1-liter three-necked flasks which were fitted with a mercury-sealed stirrer, a reflux condenser and a section of 1.25" rubber tubing which was closed just above the neck of the flask by a screw clamp. The reflux condenser was fitted with a drying tube and contained a thermometer suspended inside so that its bulb dipped into the chloroform solution. The apparatus was all carefully dried. Chloroform, usually 650 cc., and from 0.2

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[14] Compare: Henne and Leicester, THIS JOURNAL, **60**, 864 (1938).

[15] Reid, *ibid.*, **39**, 124 (1917).

[16] Gilman, Peterson and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

[17] Miller, unpublished work.

TABLE II

PHYSICAL PROPERTIES OF SUBSTITUTED BENZYL FLUORIDES

Substituent	M. p., °C.	B. p.		d^{20}_4	n^{20}_D	Fluorine, %		MR_D	
		°C.	Mm.			Calcd.	Found	Calcd.	Found
None[a]		50	27						
m-CH_3		48.5	8.5	1.0089	1.4952	15.31	15.3	35.55[b]	35.91
p-CH_3	19.5–20.0	46.5–47	8	1.0037	1.4918	15.31	15.2	35.55	35.89
m-F		41	15	1.1592	1.4660	29.66	29.9[c]	30.92	30.61
p-F		54	28	1.1573	1.4667	29.66	29.8[c]	30.92	30.69
o-Cl		58.5	9	1.2224	1.5159	13.15	13.2	35.80	35.72
m-Cl		65	11	1.2157	1.5158	13.15	13.0	35.80	35.83
p-Cl	3–4	72–73	16	1.2127	1.5149	13.15	13.1	35.80	35.95
		64	10.5						
o-Br		84–85	18	1.5557	1.5470	10.05	10.0	38.70	38.53
m-Br		83	13	1.5450	1.5448	10.05	10.1	38.70	38.67
p-Br	32.9–33.2	80.0–81.5	10–11			10.05	10.1		
m-I		68.0–68.5	2.5	1.8052	1.5933	8.05	7.98	43.73	44.32
p-I	51.5–52[d]	75	4			8.05	8.00		
m-NO_2		91	3.5	1.3019	1.5381	12.25	12.2	37.13	37.27
p-NO_2	38.2–38.5[e]					12.25	12.2[f]		

[a] First prepared by Ingold, who reported the b. p. as 55° at 30 mm. [b] See Gilman, "Organic Chemistry," Vol. II, 1938, p. 1737. The value of 1.09 used for the atomic refraction of fluorine was determined by Ingold. [c] Sodium peroxide decompositions were run on these samples to determine total fluorine. [d] Recrystallized from petroleum ether (b. p. 30–60°). [e] First prepared by Ingold, who reported the m. p. 38.5°. Sample was recrystallized from ether–petroleum ether mixture (1:1). [f] Treatment of *p*-nitrobenzyl fluoride with sodium ethoxide solution caused the formation of a dark brown solution. Upon steam distillation, a solid precipitated out, which was filtered off. The filtrate was treated with decolorizing carbon and then analyzed for F^-.

to 0.6 mole of the benzyl bromide were poured into the flask and about 50 cc. of chloroform distilled out, with the reflux condenser temporarily replaced by a condenser arranged for distillation, to assure removal of traces of water. The reflux condenser was then replaced. Freshly prepared mercuric fluoride, usually 0.3 mole, was placed in the rubber addition tube attached to the reaction flask and the open end stoppered. The solution was stirred vigorously and the mercuric fluoride added slowly by opening the screw clamp on the rubber tubing. The first portions of mercuric fluoride turned red-orange in color, but upon continued stirring the color changed to pale yellow and the temperature of the reaction mixture started to rise. When the temperature reached about 35°, the flask was cooled in water to prevent a more vigorous reaction. The addition of the mercuric fluoride was continued at 35° with occasional cooling of the reaction flask in a cold water-bath. About forty minutes were ordinarily required for the addition of the mercuric fluoride.

The reaction mixture was then stirred for from one-half to seventy hours. The longer times of reaction did not result in improved yields. The usual time of stirring was from two to four hours. The reaction mixture was then filtered and the residue washed with chloroform. The chloroform solutions were combined and washed once with saturated sodium carbonate solution, once with dilute nitric acid (1:10), again with saturated sodium carbonate solution, and finally with water. Two drops of pyridine or other tertiary amine were added to prevent polymerization of the fluoride and the chloroform solution dried over calcium chloride. After drying overnight, the chloroform was removed by distillation through an efficient column. The residue was then distilled under reduced pressure from a modified Claisen flask and then either redistilled or crystallized for further purification. In this redistillation, no pyridine was added.

A modified procedure was evolved for the preparation of benzyl and methyl-, fluoro- and *o*-chlorobenzyl fluorides which showed a great tendency to polymerize during the preparative reaction. One cc. of dry pyridine was added to the chloroform solution of the bromide before the addition of the mercuric fluoride. The addition of the mercuric fluoride then produced no immediate temperature rise and the solid in the reaction became red-orange in color. Continued stirring did not change this color, but upon gentle warming to about 40° the color changed to light yellow, and the reaction mixture had to be cooled in ice-water to prevent a rapid rise in temperature. When the temperature of the reaction mixture fell to 35°, the addition of the mercuric fluoride was continued. Stirring was continued for thirty minutes after all the mercuric fluoride had been added, 1 cc. of pyridine was added and the stirring continued for three hours. The remainder of the procedure was the same as indicated above.

The yields of benzyl fluorides isolated ranged from 40 to 60% but no attempt was made to secure maximum yields since higher still pot temperatures near the end of the distillations tended to cause thermal decomposition of the fluoride and result in polymerization of the distillate. The physical properties of the benzyl fluorides are given in Table II.

The purity of the benzyl fluorides was checked by analyses for fluorine and molecular refractivity determinations. The absence of any unreacted benzyl bromides in the products was shown by a completely negative test for bromide with boiling alcoholic silver nitrate solution.

Fluorine was determined by refluxing 1-g. samples of the fluorides with sodium ethoxide solution, prepared by dissolving 2.3 g. of sodium in 30 cc. of absolute alcohol, for forty-eight hours. Water, 100 cc., was added and the solution steam distilled to remove organic matter. Fluoride ion was then titrated in an aliquot with standard cerous nitrate solution using a divided titration vessel.[18] In the case of the fluorobenzyl fluorides sodium peroxide decompositions were run to determine total fluorine. A value of 17.5% F was found for *p*-fluorobenzyl fluoride using the sodium ethoxide decomposition indicating partial removal of ring as well as side chain fluorine.

Reactions of Benzyl Fluorides.—The observed reactions of the benzyl fluorides are listed below under reactants.

Aromatic Hydrocarbons.—*p*-Chlorobenzyl fluoride, 5.8 g., was refluxed for four hours in the absence of added catalyst with 40 cc. of dry benzene while a slow stream of

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[18] Batchelder and Meloche, THIS JOURNAL, **53**, 2131 (1931); Hubbard and Henne, *ibid.*, **56**, 1078 (1934); Miller, unpublished work. This titration has recently been carefully investigated by Nichols and Olsen in this laboratory and an improved procedure described; *Ind. and Eng. Chem., Anal. Ed.*, **15**, 342 (1943).

nitrogen was passed through the reaction vessel. About 0.1% of the theoretical quantity of hydrogen fluoride was evolved. *m*-Bromobenzyl fluoride, 10.0 g., in 56.0 g. of *p*-xylene was refluxed for seven hours as above. About 1% of the theoretical amount of hydrogen fluoride was formed. The mixture was distilled. When about 75% of the *p*-xylene had been removed a vigorous reaction occurred with the copious evolution of hydrogen fluoride. Separation of the resulting mixture yielded 1.0 g. of starting fluoride, b. p. 82° at 10 mm., and 8.1 g. of viscous liquid, b. p. 185–186° at 10–12 mm. The latter material was indicated as 2,5-dimethyl-3-bromodiphenylmethane by analysis after redistillation at 0.5 mm. Calcd. for $C_{15}H_{15}Br$: Br, 29.1. Found: Br, 28.4.

p-Chlorobenzyl fluoride, 5.8 g., dissolved in 100 cc. of benzene was treated with gaseous boron trifluoride. Reaction was observed after two minutes and the boron trifluoride flow was stopped after four minutes. The solution was refluxed for an additional hour. Five grams of *p*-chlorobenzyl fluoride in 40 cc. of benzene was caused to react as above. The combined products yielded 11.4 g. of main fraction, b. p. 147–148° at 8 mm. This product, 4-chlorodiphenylmethane, on oxidation yielded *p*-chlorobenzophenone, m. p. 76–77°; reported m. p. 77–78°.[19]

m-Bromobenzyl fluoride, 11 g., dissolved in 100 g. of toluene was treated with gaseous boron trifluoride at Dry Ice temperature for six minutes. An immediate cloudiness was observed. On warming to room temperature without further addition of boron trifluoride the cloudiness disappeared and gas was evolved. The mixture was heated to reflux for thirty minutes. Distillation yielded a main fraction of 8.5 g., b. p. 170–173° at 7–8 mm. This product was characterized as 3-bromo-4′-methyldiphenylmethane by oxidation, with 10 g. of sodium dichromate in 15 cc. water and 10 cc. concentrated sulfuric acid at reflux temperature, to yield 3-bromo-4′-carboxybenzophenone. The purified acid had a neutral equivalent of 304.5; calcd. 305.

Sodium Hydroxide in Aqueous Alcohol.—Nine grams of *p*-chlorobenzyl fluoride dissolved in 200 cc. of 95% alcohol was mixed with 100 cc. of 0.99 *N* sodium hydroxide and heated at reflux on a steam-bath for one hundred hours. Extraction with petroleum ether and distillation yielded 7.5 g. of liquid, b. p. 104° at 15 mm., and 0.8 g. of solid residue. The residue after recrystallization from petroleum ether melted 69–70° and was shown to be *p*-chlorobenzyl alcohol. The redistilled liquid fraction, b. p. 220–223° at 746 mm., d^{14}_4 1.101, as compared with b. p. 225°, d^{14}_4 1.121 reported for ethyl *p*-chlorobenzyl ether, was cleaved with 48% hydrobromic acid to form ethyl bromide, converted to propionanilide m. p. 101–103°,[20] and *p*-chlorobenzyl bromide m. p. 48.5–49.5°, no depression in m. p. with authentic sample.

Hydrochloric Acid in Aqueous Alcohol.—Eleven grams of *m*-xylyl fluoride dissolved in 250 cc. of 95% alcohol was mixed with 125 cc. of 0.93 *N* hydrochloric acid and heated at reflux for seventy hours. Extraction with petroleum ether and distillation yielded 8.0 g. of liquid, b. p. 91–93° at 14 mm., without appreciable forerun or residue. The redistilled liquid had a b. p. 204–205° at 749 mm., d^{20}_4 0.939 as compared with b. p. 202° at 740 mm., d^{17}_4 0.930 reported for ethyl *m*-xylyl ether. Cleavage of the ether with 48% hydrobromic acid yielded ethyl bromide, b. p. 37–40°, which was converted into ethyl mercuric bromide,[21] m. p. 192–193°, and *m*-xylyl bromide, b. p. 215–217° at 747 mm., which was converted through the Grignard reagent into *m*-methylphenylacetic acid of m. p. 59.5–60.5°; reported m. p. 61°.

Hydrochloric Acid in Dioxane.—*p*-Nitrobenzyl fluoride, 2.0 g., dissolved in 20 cc. of dioxane was mixed with 5 cc. concentrated hydrochloric acid, and heated to reflux for sixteen hours. The mixture turned light brown and separated into two layers during this time. Distillation of the dioxane and extraction of the residue with hot 75% alcohol yielded 1.5 g. of crystals m. p. 64–67°. Two recrystallizations yielded m. p. 71–72° as compared with m. p. 71° reported for *p*-nitrobenzyl chloride.

m-Bromobenzyl fluoride was treated similarly to yield *m*-bromobenzyl chloride, m. p. 22°, as compared with reported m. p. 22.4°.

Sodium Phenolate.—Two grams of *p*-chlorobenzyl fluoride was heated for two hours in an oil-bath at 140° with a solution of sodium phenolate prepared by dissolving 0.5 g. of sodium in 5.0 g. of phenol. The reaction mixture was poured into 200 cc. of dilute sodium hydroxide and 3.0 g. of brown crystalline material separated. The solid was recrystallized from alcohol and melted at 86°; reported for *p*-chlorobenzylphenyl ether, m. p. 85.5–86.5°.

m-Bromobenzyl fluoride by a similar procedure yielded phenyl *m*-bromobenzyl ether, m. p. 37.5–38.0°, as compared with a reported m. p. of 36–37°. *p*-Chlorobenzyl fluoride yielded phenyl *p*-chlorobenzyl ether, m. p. 81°; reported m. p. 81°. *p*-Nitrobenzyl fluoride yielded phenyl *p*-nitrobenzyl ether, m. p. 91–92°; reported m. p. 91°.

Potassium Acetate.—Appreciable reaction did not occur when *p*-nitrobenzyl fluoride was refluxed in 67% aqueous alcohol solution with potassium or magnesium acetates for periods up to forty-six hours. Partial conversion to the acetate occurred when a solution of 2.0 g. of *p*-nitrobenzyl fluoride and 4 g. of potassium acetate in 30 cc. of glacial acetic acid was refluxed for twenty-four hours. Unreacted fluoride was slowly sublimed from the water insoluble product and a 0.3-g. residue obtained, m. p. 76°; m. p. with authentic *p*-nitrobenzyl acetate 77°.

Lithium and Magnesium Metals.—Lithium metal, 0.4 g. scraped and cut into small pieces under xylene, was added to 20 cc. of dry ether with nitrogen blanketing. Benzyl fluoride, 3.0 g., was added and the mixture warmed to reflux. A white deposit formed on the surface of the metal but after one and one-half hours the solution gave a negative test for benzyl lithium with Michler ketone.[22] After twelve hours, evaporation of the ether solution yielded 1.5 g. of dibenzyl, m. p. 51–52° after recrystallization from alcohol.

Thirteen grams of benzyl fluoride dissolved in 80 cc. of sodium dry ether was placed in the dropping funnel of a thoroughly dried Grignard set-up provided with nitrogen blanket. Freshly turned magnesium metal, 3.7 g., was introduced into the conical three-necked reaction flask and 20 cc. of the ether solution added. The mixture was stirred for several hours and warmed with no apparent reaction. Addition of iodine crystals or of Gilman activated magnesium catalyst[15] failed to produce any signs of reaction. Addition of phenylmagnesium bromide also failed to initiate reaction. Three cc. samples of the ethereal solution of benzyl fluoride were heated in glass bomb tubes with freshly turned magnesium and with the activated magnesium alloy at 100° for ten days. At the end of this period negative tests were obtained for the presence of Grignard reagent but the solution from the tube containing activated magnesium yielded crystals of dibenzyl, m. p. 51°. No dibenzyl could be obtained from the tube containing ordinary magnesium.

Summary

A general procedure for the preparation of benzyl fluorides by the reaction of mercuric fluoride with the corresponding benzyl bromide has been developed.

The benzyl fluorides underwent the typical Friedel–Crafts type reaction with aromatic hydrocarbons in many cases with great ease. They underwent typical halide replacement type reactions but at much slower rates than the corresponding chlorides.

The Grignard reagent could not be prepared

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(19) Montagne, *Rec. trav. chim.*, **26**, 263 (1907).

(20) Underwood and Gale, THIS JOURNAL, **56**, 2117 (1934).

(21) Marvel, Gauerke and Hill, *ibid.*, **47**, 3009 (1925).

(22) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

from benzyl fluoride. Attempts to prepare it under vigorous conditions led to the formation of dibenzyl.

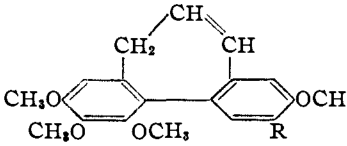
ITHACA, NEW YORK RECEIVED APRIL 1, 1948

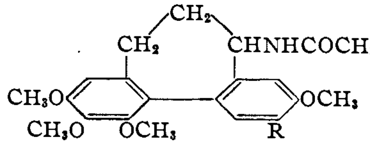
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Studies on the Structure of Colchicine.[1] Syntheses in the Biphenyl Series

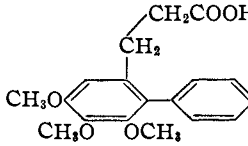
BY H. RICHARD FRANK,[2a] PAUL E. FANTA[2b] AND D. STANLEY TARBELL

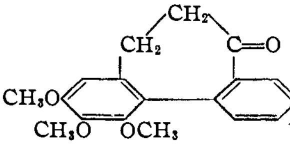
Degradation studies on deaminocolchinol methyl ether[3] I and its iodine derivative[1] II have provided evidence for the presence of the central seven-membered ring. Assuming that no rearrangement of the carbon skeleton occurred during the formation of I or II from N-acetyl-(iodo)-colchinol methyl ether the latter compounds must have structures III and IV. It is obviously necessary, in order to establish the constitution of colchicine, to provide synthetic evidence for structures I–IV. Furthermore, the importance which colchicine and its derivatives have assumed in research on the cancer problem as a result of their antimitotic properties makes it highly desirable to explore possible methods of synthesizing compounds of this type.[4]


I, R = H
II, R = I


III, R = H
IV, R = I

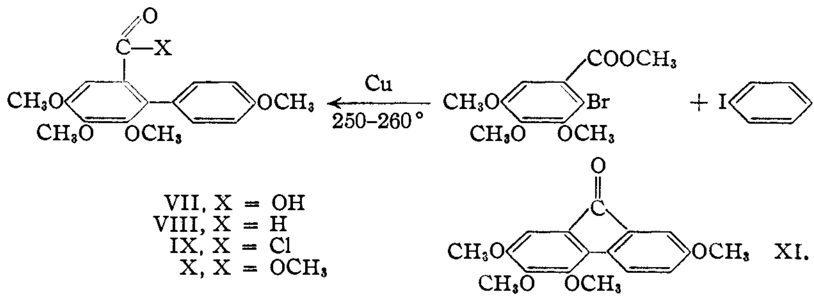
Our work was designed to lead to structures I and III through the synthesis of the biphenylpropionic acid V and its ring closure to the ketone VI, which could be converted by obvious methods to compounds I and III.


V

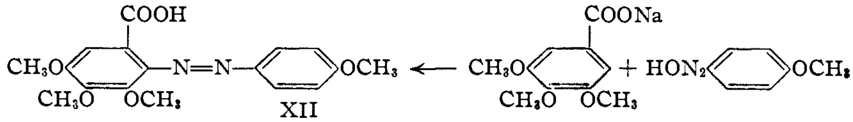

VI

The biphenyl aldehyde VIII seemed to offer a feasible approach to the acid V, since the propionic acid side chain could be readily built up from the aldehyde by condensation with malonic acid followed by decarboxylation and reduction.

The acid VII was therefore prepared in 25–35% yield by the crossed Ullmann[5] reaction from p-iodoanisole and methyl 2-bromo-3,4,5-trimethoxybenzoate. The Ullmann synthesis using the iodo ester, methyl 2-iodo-3,4,5-trimethoxybenzoate and iodoanisole, yielded the two symmetrical products to the exclusion of the desired unsymmetrical compound VII.



VII, X = OH
VIII, X = H
IX, X = Cl
X, X = OCH_3
XI.


XII

Some preliminary experiments on the preparation of the acid VII by the Gomberg reaction from diazotized p-anisidine and sodium 3,4,5-trimeth-

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[1] In memory of H. Richard Frank, died March 21, 1948; for the preceding paper see Tarbell, Frank and Fanta, THIS JOURNAL, **68**, 502 (1946).

[2] (a) Abbott Laboratories Fellow, 1946–1947. (b) Present address, Department of Chemistry, Harvard University, Cambridge, Massachusetts.

[3] (a) Buchanan, Cook and Loudon, *J. Chem. Soc.*, 325 (1944); (b) Barton, Cook and Loudon, *ibid.*, 176 (1945).

[4] For a discussion of colchicine and other compounds as chemotherapeutic agents for cancer, see Greenstein, "The Biochemistry of Cancer," Academic Press, New York, N. Y., 1947, pp. 170–172.

[5] For a review of the Ullmann reaction see Fanta, *Chem. Rev.*, **38**, 139 (1946).