azonium fluoroborate was readily prepared in 73% yield by diazotization in fluoroboric acid solution.

The reaction of this diazonium fluoroborate with phosphorus trichloride, reduction, and isolation of the 10-chlorophenoxaphosphine was carried out in the same manner as described above for 5-chlorodibenzophosphole. The reaction was run on a 0.5-mole scale; the yield of the yellow crystalline solid, m.p. 62–64°, was 28.2 g., 24%.

Anal. Calcd. for $C_{12}H_8ClOP$: C, 61.43; H, 3.44; P, 13.20. Found: C, 60.81; H, 3.51; P, 12.59.

Phenoxaphosphinic Acid.—The oxidation of 10-chlorophenoxaphosphine suspended in alkaline solution with 30% hydrogen peroxide gave, after acidification of the alkaline solution, the acid in 99% yield. It was recrystallized from alcohol, m.p. 231–234°.

Anal. Calcd. for $C_{12}H_9O_3P$: C, 62.08; H, 3.91. Found: C, 61.81; H, 3.84.

***o*-Benzylphenylphosphonous Dichloride.**—*o*-Aminodiphenylmethane[22] was converted to the diazonium fluoroborate in 83% yield by diazotization in fluoroboric acid. The reaction of this salt (113 g., 0.4 mole) with phosphorus trichloride and reduction with powdered aluminum was carried out as described above for 5-chlorodibenzophosphole. The high-boiling material that was obtained was finally fractionated through a 21-in. spinning band column. The yield of *o*-benzylphenylphosphonous dichloride was 6.9 g. (6.4%), b.p. 132–137° (0.2 mm.).

Anal. Calcd. for $C_{13}H_{11}Cl_2P$: Cl, 26.35; P, 11.51. Found: Cl, 26.10; P, 11.55.

5-Chloro-5,10-dihydrodibenz[*b*,*e*]phosphorin.—*o*-Benzylphenylphosphonous dichloride (2.04 g.) and 1.1 g. of anhydrous zinc chloride were heated together in a nitrogen atmosphere for 24 hr. The liquid was then distilled at 10 μ. The compound was obtained as yellow crystals, 25% yield, m.p. 78–86°.

Anal. Calcd. for $C_{13}H_{10}ClP$: C, 67.11; H, 4.33; P, 13.31. Found: C, 66.86; H, 4.59; P, 13.49.

5-Hydroxy-5,10-dihydrodibenz[*b*,*e*]phosphorin 5-Oxide.—5-Chloro-5,10-dihydrodibenz[*b*,*e*]phosphorin suspended in alkaline solution was oxidized with 30% hydrogen peroxide. The free acid was obtained in 81% yield when the alkaline solution was acidified. It decomposed on heating above 225°.

Anal. Calcd. for $C_{13}H_{11}O_2P$: C, 67.83; H, 4.82. Found: C, 67.51; H, 4.69.

***o*-Benzylphenylphosphonic Acid.**—*o*-Benzylphenylphosphonous dichloride was suspended in aqueous alkali and oxidized with 30% hydrogen peroxide. The acid was obtained in 92% yield by acidification of the alkaline solution. It was recrystallized from aqueous alcohol, m.p. 186–188°.

Anal. Calcd. for $C_{13}H_{13}O_3P$: C, 62.91; H, 5.28. Found: C, 62.70; H, 5.34.

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[22] J. Collette, D. McGreer, R. Crawford, F. Chubb, and R. B. Sandin, *J. Am. Chem. Soc.*, **78**, 3819 (1956).

Reactions of Organometallics with Fluoroaromatic Compounds[1]

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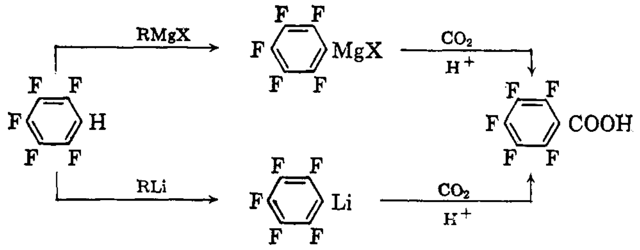
Nucleophilic displacement reactions of Grignard reagents on hexafluorobenzene in tetrahydrofuran have been studied. In general the reaction becomes more facile with the change from aryl to alkyl to allyl Grignard reagents. If the fluoroaromatic ring contains a hydrogen moiety, an acid–base reaction becomes predominant. This is true whether a Grignard or alkyllithium reagent is employed. In this manner mono- or di-Grignard and mono- or dilithio reagents of highly fluorinated benzene compounds have been prepared and converted to the corresponding acids by carbonation.

The nucleophilic substitution reactions of alkyl- and aryllithium reagents on fluoroaromatic compounds have been previously reported.[2] The reaction proceeds to give good yields of the desired alkyl fluoroaromatic compounds. Disubstitution is also possible with the second group substituting *para* to the original

$$RLi + C_6F_6 \longrightarrow RC_6F_5 + LiF$$

alkyl group. For Grignard reagents the published information is more limited. Thus, Pummer and Wall[3a] have reported that 2,3,4,5,6-pentafluorotoluene is formed in 3% yield by the reaction of methylmagnesium iodide with hexafluorobenzene. Harper and Tamborski[3b] have reported the preparation of 1,4-dibenzyl-2,3,5,6-tetrafluorobenzene in 54% yield by the reaction of benzylmagnesium chloride with hexafluorobenzene in tetrahydrofuran.

In addition to reporting further information on the substitution of Grignard reagents on hexafluorobenzene, we wish to report a new series of metalation reactions between organometallic reagents and hydrofluoroaromatic compounds. With hydrofluoroaromatics, the nucleophilic displacement of fluoride ion frequently becomes secondary to an acid–base type reaction as illustrated by the preceding equations.



Nucleophilic Displacement of Fluorine with Grignard Reagents.—The action of Grignard reagents on hexafluorobenzene in tetrahydrofuran have been studied. The reactivity of the Grignard reagents with hexafluorobenzene decreases in the following order: allyl or benzyl > alkyl > aryl. While allylmagnesium chloride reacts vigorously with hexafluorobenzene, the yield of allylpentafluorobenzene is only 26%, as a result of secondary side reactions. The reaction of benzylmagnesium chloride with hexafluorobenzene is similarly vigorous and yields 1,4-dibenzyltetrafluorobenzene in 54% yield. The reaction of 1 equiv. of ethylmagnesium bromide with hexafluorobenzene is moderate and gives ethylpentafluorobenzene in 37% yield. When the mole ratio of Grignard reagent to hexafluorobenzene is increased to 2:1, ethylpentafluorobenzene is produced in 62% yield. Based upon gas–liquid chroma-

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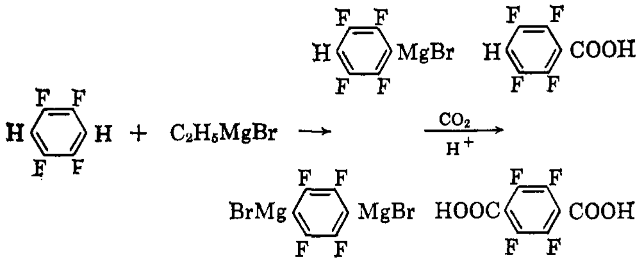
[1] This work was reported at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

[2] (a) A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 808 (1961); (b) J. M. Birchall and R. N. Haszeldine, *ibid.*, 3719 (1961); (c) J. M. Birchall, T. Clarke, and R. N. Haszeldine, *ibid.*, 4977 (1962).

[3] (a) W. J. Pummer and L. A. Wall, *Science*, **127**, 643 (1958); (b) R. J. Harper and C. Tamborski, *Chem. Ind.* (London), 1824 (1962).

tography, the amount of disubstituted material produced is approximately 2%. A similar yield (2%) of dialkyl-substituted material is noted for the reaction of ethylmagnesium bromide with 2,3,4,5,6-pentafluorotoluene. These results suggest that the presence of an alkyl substituent hinders further substitution of fluorine by nucleophilic attack of the Grignard reagent. This result is consistent with the electron-donating effect of the alkyl groups. By contrast, 2,3.5,6-tetrafluoroxylene is produced in 85% yield from the reaction of methyllithium with 2,3,4,5,6-pentafluorotoluene.[2a] The reaction of phenylmagnesium bromide with hexafluorobenzene is most sluggish. There is no apparent reaction until the solution is heated to reflux. After a reflux period of 11 hr., 2,3,4,5,6-pentafluorobiphenyl in 17% yield and 1,4-diphenyl-2,3,5,6-tetrafluorobenzene in 3% yield are obtained.

Reaction of Hydrofluoroaromatic Compounds with Grignard Reagents.—Suitably activated protons in hydrofluoroaromatics may be metalated with Grignard reagents. Thus, if ethylmagnesium bromide is treated with pentafluorobenzene in tetrahydrofuran and the resultant mixture carbonated, pentafluorobenzoic acid is obtained in 85% yield. The same reaction using methylmagnesium iodide as the Grignard reagent gives pentafluorobenzoic acid in 56% yield. However, with isopropylmagnesium chloride as the Grignard reagent and with ether as the solvent, pentafluorobenzoic acid is produced in 25% yield. The reduced yield of acid in the last case probably reflects either poor metalation or incomplete carbonation of the resultant Grignard reagent in ether. Similarly, the reaction of ethylmagnesium bromide with 1,2,4,5-tetrafluorobenzene in a 3:1 mole ratio, followed by carbonation, gives 2,3,5,6-tetrafluorobenzoic acid in 29% yield and tetrafluoroterephthalic acid in 24% yield. The replacement of both hydrogens to give tetrafluoroterephthalic acid indicates that the acidity of both hydrogens in 1,2,4,5-tetrafluorobenzene are sufficiently active to react with the Grignard reagent. By contrast the treatment of 1,2,3,4-tetrafluorobenzene with ethylmagnesium bromide followed by carbonation gives none of the desired 2,3,4,5-tetrafluorobenzoic acid. This indicates that two *ortho* fluorines are required to permit metalation of tetrafluoroaromatic moieties to occur with Grignard reagents. Such is not the case when alkyllithium reagents are used for metalation as shall be shown subsequently.



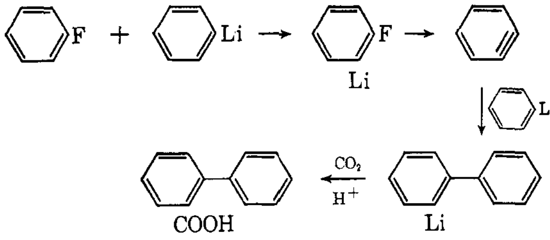
Similarly, very little metalation is observed in the reaction of ethylmagnesium bromide with 2,3,4,5,6-pentafluorotoluene. This indicates that the proton in pentafluorobenzene is more acidic than the protons in 2,3,4,5,6-pentafluorotoluene, which is the reverse of the hydrocarbon analogs. Thus, the inductive effect of the ring fluorines operates much more strongly on the ring proton than it does on the protons in the side chain of pentafluorotoluene.

The apparent change of pK_a values from benzene to pentafluorobenzene is quite significant. While benzene[4] has a pK_a value of ~50, Rochow[5] indicates that a pK_a value of 21 or less is required for substances to react with alkyl Grignard reagents. This indicates that the pK_a value of pentafluorobenzene is 21 or less and shows the marked increase in acidity from the introduction of the fluorine substituents in the ring.

Reaction of Hydrofluoroaromatic Compounds with Alkyllithiums.—Metalation is likewise observed when alkyllithium reagents are treated with hydrofluoroaromatics. The basic procedure employed in this study is that the organolithium and the fluoroaromatic are treated at −65° until Gilman color test IIA[6] indicates that the alkyllithium has been consumed. The reaction time varies from a few minutes to several hours depending upon the fluoroaromatic compound and the solvent system. At this point, the mixture is carbonated; the acid products are separated as usual.

The reaction of alkyllithium with pentafluorobenzene appears to go to completion in hexane–ether, ether, or ether–tetrahydrofuran since after carbonation crude pentafluorobenzoic acid is obtained in near quantitative yield. However, approximately 2-hr. reaction time is needed with hexane–ether as the solvent, whereas, in ether or ether–tetrahydrofuran, the reaction is complete in 5 min. The yield of pure pentafluorobenzoic acid varied between 67–83%, but the yield difference is believed due to the purification procedure employed rather than the reaction itself. No significant difference is noted whether the alkyllithium is added to the fluoroaromatic or whether inverse addition is used. It might also be noted that the perfluoroaryllithiums appear to carbonate readily in ether or tetrahydrofuran contrary to earlier published work.[7]

These results indicate that this synthesis of pentafluorophenyllithium is more facile than the earlier method reported by Coe, Stephens, and Tatlow,[7] in which metalation is accomplished by using pentafluorobromobenzene and either an alkyllithium or lithium amalgam. The metalation of a hydrogen *ortho* to a fluorine has a precedent in the classic work of Wittig, *et al.*,[8] as illustrated by the following reaction scheme.



The principal difference from Wittig's work is that benzyne formation can be forestalled by maintaining the pentafluorophenyllithium at low temperatures (−50 to −65°). A simlar procedure was employed by Gilman

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(4) A. A. Morton, *Chem. Rev.*, **35**, 1, 1944.

(5) E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 93.

(6) H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, **62**, 1847 (1940).

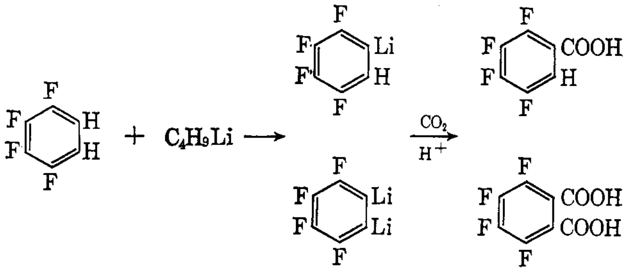
(7) P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 3227 (1962)

(8) G. Wittig, G. Pieper, and G. Fuhrmann, *Ber.*, **73**, 1193 (1940).

and Gorsich[9] in the preparation of 2-fluorobenzoic acid from 2-fluorophenyllithium. The work of Coe, Stephens, and Tatlow[7] does suggest, however, that the presence of a number of fluorine atoms in the ring renders the pentafluorophenyllithium more stable than the simpler 2-fluorophenyllithium. Thus, the aforementioned investigators[7] prepared pentafluorobenzaldehyde from pentafluorophenyllithium in 55% yield at 0°. Other workers[9,10] have found benzyne formation too pronounced with 2-fluorophenyllithium at this or lower temperatures (−25°) to permit the preparation of such nonbenzyne derivatives in good yields.

In the case of the reaction of an alkyllithium with 1,2,4,5-tetrafluorobenzene, the superiority of tetrahydrofuran over ether indicated previously in the literature[3b] is evident. Thus, if 2 equiv. of butyllithium are treated with 1,2,4,5-tetrafluorobenzene using tetrahydrofuran as the predominant solvent, after carbonation there is obtained tetrafluoroterephthalic acid in an 83% crude yield (68% pure) with only a 3% yield of 2,3,5,6-tetrafluorobenzoic acid. The same reaction with ether as the principal solvent gives tetrafluoroterephthalic acid in 38% yield and 2,3,5,6-tetrafluorobenzoic acid in 33% yield. By comparison, with the Grignard reagent, the yields of diacid and monoacid are 30 and 25%, respectively. That the presence of a monoorganometallic does not hinder formation of a second organometallic bond in the *para* position can be seen in the foregoing experiments. Further evidence of this effect is provided by the reaction of 1 equiv. of alkyllithium with 1,2,4,5-tetrafluorobenzene. After carbonation the monoacid, 2,3,5,6-tetrafluorobenzoic acid, is obtained in 66% yield and the disubstituted tetrafluoroterephthalic acid, is obtained in 16% yield.

The reaction of butyllithium with 1,2,3,4-tetrafluorobenzene is a case in which both the previously mentioned solvent effects and the greater metalating ability of the alkyllithium are shown. Thus, this reaction with tetrahydrofuran as the principal solvent gives 2,3,4,5-tetrafluorobenzoic acid in 36% yield and tetrafluorophthalic acid in 9% yield. In addition, there are obtained neutral and acidic products containing alkyl groups, which indicate some alkylation is also occurring. By contrast in the same reaction with ether as the predominant solvent, the yield of diacid is less than 1%. Similarly, no metalation is observed with the Grignard reagent and 1,2,3,4-tetrafluorobenzene.



Experimental[11]

Ethyl-2,3,4,5,6-pentafluorobenzene.—Hexafluorobenzene (56.0 g., 0.30 mole) was added to ethylmagnesium bromide (0.62 mole) in 380 ml. of tetrahydrofuran. The reaction was mildly exothermic. At the end of 23 hr., titration indicated 0.24 mole of unchanged Grignard reagent. The reaction was hydrolyzed with 4 *N* hydrochloric acid. The organic phase was extracted with 4*N* hydrochloric acid and the aqueous phase was back-extracted with pentane. The organic phases were combined, dried, and distilled through a 30-in. spinning band column. There was obtained 33.3 g. (56%) of ethyl-2,3,4,5,6-pentafluorobenzene, b.p. 130–132°. The vapor phase chromatograms of the other fractions indicated a total product yield of 36.5 g. (62%). The middle cut, b.p. 132°, $n^{23}\mathrm{D}$ 1.4087, was submitted for analysis. Vapor phase chromatography of the other distillation cuts also indicated 8% hexafluorobenzene, 7% pentafluorobenzene, and 10% higher aromatics (2% maximum of diethyltetrafluorobenzene).

Anal. Calcd. for $C_8H_5F_5$: C, 48.98; H, 2.57; F, 48.43. Found: C, 48.95; H, 2.56; F, 48.70.

In a similar experiment, a 1.2:1 mole ratio of Grignard reagent to hexafluorobenzene gave ethyl-2,3,4,5,6-pentafluorobenzene in 37% yield.

Allyl-2,3,4,5,6-pentafluorobenzene.—Allylmagnesium chloride (0.31 mole, 210 ml. of a tetrahydrofuran solution) was added dropwise over a 2-hr. period to an ice–water cooled solution of hexafluorobenzene (55.8 g., 0.30 mole) in 85 ml. of tetrahydrofuran. The solution turned wine red immediately and the color gradually deepened. After the reaction was stirred for an additional hour, titration indicated 85% of the Grignard had been consumed. The ice-cooled reaction mixture was hydrolyzed with 300 ml. of 4 *N* hydrochloric acid. The aqueous layer was extracted with ether–pentane (80–20), the extract was combined with the organic fraction, and the dried mixture was fractionated through a 30-in. spinning band column. There was obtained 8.60 g. (14%) of allyl-2,3,4,5,6-pentafluorobenzene, b.p. 148–149°, $n^{23}\mathrm{D}$ 1.4265. The vapor phase chromatograms of the other fractions indicated a total yield of 16.0 g. (26%) of allyl-2,3,4,5,6-pentafluorobenzene.

Anal. Calcd. for $C_9H_5F_5$: C, 51.92; H, 2.43; F, 45.63. Found: C, 51.93; H, 2.57; F, 45.38.

The F^{19} nuclear magnetic resonance of a solution in carbon tetrachloride showed a quartet centered at 66.7, a triplet centered at 80.1, and a multiplet centered at 85.6 p.p.m. from trifluoroacetic acid. These were assigned as due to *ortho*, *para*, and *meta* fluorine, respectively. The proton nuclear magnetic resonance showed three multiplets in area ratio of 1:2:2 at 5.89, 5.10, and 3.45 p.p.m. from tetramethylsilane.

2,3,4,5,6-Pentafluorotoluene.—Methyl iodide (47 g., 0.33 mole) dissolved in 20 ml. of tetrahydrofuran was added to a tetrahydrofuran solution of pentafluorophenylmagnesium bromide prepared from 47 g. (0.33 mole) of pentafluorobromobenzene and 7.29 g. (0.30 g.-atom) of magnesium. The reaction was stirred overnight and then was hydrolyzed with 6 *N* hydrochloric acid. The aqueous layer was extracted with pentane and combined with the organic layer. The organic layer was extracted with water several times and then dried. Vapor phase chromatography indicated 2,3,4,5,6-pentafluorotoluene was produced in a 56% yield and pentafluorobenzene in 21% yield. A good separation of these two materials by fractionation was not possible since only 15.1 g. (27%) of 2,3,4,5,6-pentafluorotoluene was obtained, b.p. 115–116°, $n^{22}\mathrm{D}$ 1.4021 (lit.[2b] $n^{20}\mathrm{D}$ 1.4023).

2,3,4,5,6-Pentafluorotoluene.—Methylmagnesium iodide (0.132 mole, 120 ml. of a tetrahydrofuran solution) was added to an ice bath-cooled solution of hexafluorobenzene (11.2 g., 0.060 mole) in 55 ml. of tetrahydrofuran. The temperature was raised in 5° increments from 5 to 50°. No noticeable reaction occurred so the reaction was stirred overnight at room temperature. Titration of an aliquot indicated little reaction had occurred. A 5-ml. aliquot was removed, hydrolyzed, extracted with pentane, and washed with dilute hydrochloric acid. Examination of the vapor phase chromatogram of this mixture indicated that 2,3,4,5,6-pentafluorotoluene was formed in approximately 2% yield.

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(9) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **78**, 2217 (1956).

(10) H. Gilman and R. D. Gorsich, *ibid.*, **79**, 2625 (1957); **77**, 3919 (1955).

(11) All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen. All melting points are uncorrected. Alumina column separations were carried out on Woelm neutral grade alumina. Vapor phase chromatographic analyses were carried out on an F and M Model 500 gas chromatogram. A 2-ft. silicone gum rubber (20%) on Chromasorb P (60–80 mesh) using helium carrier gas at about 60 ml./min. was used. The temperature for most analyses was programmed at 7.9°/min.

1,4-Dibenzyl-2,3,5,6-tetrafluorobenzene.—Ether was removed by distillation from 300 ml. of an ether–tetrahydrofuran (5:1) solution containing benzylmagnesium chloride (0.42 mole) until the vapor temperature reached 58°. Then 50 ml. of tetrahydrofuran was added followed by hexafluorobenzene (34.5 g., 0.185 mole) in increments of 7.0, 14.0, 5.8, and 1.9 g. The hexafluorobenzene was added over a 2.5-hr. period and vigorous refluxing was noted except with the final increment. The mixture was stirred for 30 min. and then hydrolyzed with 5 ml. of water. A mixture of ligroin and ether (1:1) was added and the inorganic salts were removed by filtration. Removal of the ether–tetrahydrofuran led to crystallization of the product. There was collected 32.94 g. (54%) of a white solid, m.p. 117–121°. A sample was recrystallized from hexane to give 1,4-dibenzyl-2,3,5,6-tetrafluorobenzene, m.p. 120–121.5°.

Anal. Calcd. for $C_{20}H_{14}F_4$: C, 72.72; H, 4.27; F, 23.00. Found: C, 72.62; H, 4.10; F, 23.30.

The F^{19} nuclear magnetic resonance of a solution in carbon tetrachloride showed a single sharp resonance with a chemical shift of 65.9 p.p.m. from trifluoroacetic acid. This is consistent with a *para* orientation of the benzyl groups. The proton nuclear magnetic resonance showed two peaks in area ratio of 5:2 at 7.42 and 4.08 p.p.m. from tetramethylsilane. The larger peak was assigned to the aromatic protons while the smaller peak was assigned to the methylene protons.

Ethyltetrafluorotoluene.—Ethylmagnesium bromide (0.079 mole, 50 ml. of a tetrahydrofuran solution) was added to 2,3,4,5,6-pentafluorotoluene (11.8 g., 0.065 mole) in 40 ml. of tetrahydrofuran. The reaction was stirred overnight. A 5-ml. aliquot was removed, hydrolyzed, extracted with pentane, and washed with dilute hydrochloric acid. Analysis of the vapor phase chromatogram indicated that alkylation to ethyltetrafluorotoluene had occurred to a maximum of 2%. The remaining mixture was carbonated and did not give any 2,3,4,5,6-pentafluorophenylacetic acid after work-up.

2,3,4,5,6-Pentafluorobiphenyl.—Hexafluorobenzene (37.6 g., 0.202 mole) in 60 ml. of tetrahydrofuran was added to phenylmagnesium bromide (0.50 mole in 300 ml. of tetrahydrofuran). No reaction was indicated either initially or after intermittent heating. The reaction was then refluxed for 11 hr. The mixture was hydrolyzed by pouring it into dilute hydrochloric acid. The aqueous layer was extracted with ether; the ether and tetrahydrofuran were removed by distillation and replaced with hexane. The hexane solution was then placed on a large alumina column. First, the column was eluted with petroleum ether (b.p. 60–90°), then with ether and acetone. From the petroleum ether extracts there was obtained a white solid product. This was recrystallized several times from hexane and once from ethanol. There was obtained 3.40 g. of 2,3,4,5,6-pentafluorobiphenyl, m.p. 109–110° (lit.[12] m.p. 110.5–112°). The other fractions were 1.45 g., m.p. 107.5–109° (94% $C_{12}H_5F_5$ and 6% $C_{12}H_{10}$); 4.80 g., m.p. 69–80° (50% $C_{12}H_5F_5$ and 40% $C_{12}H_{10}$); 4.90 g., m.p. 50° (20% $C_{12}H_5F_5$ and 77% $C_{12}H_{10}$). The product composition was determined by vapor phase chromatography. The yield of crude 2,3,4,5,6-pentafluorobiphenyl was 17% (7% pure yield).

From the ether and acetone fraction there was obtained 2.0 g. of a white solid, m.p. 230–245°. Repeated recrystallization from benzene gave a white solid, 0.86 g., m.p. 251–254°, which was shown to be 1,4-diphenyl-2,3,5,6-tetrafluorobenzene by a mixture melting point and comparison of infrared spectrum with that of a known material.[13]

Reaction of Pentafluorobenzene with Ethyl Grignard Reagent.—Ethylmagnesium bromide (0.128 mole in 80 ml. of tetrahydrofuran) was added to a stirred and water-cooled solution of pentafluorobenzene (16.8 g., 0.10 mole) in 50 ml. of tetrahydrofuran. The first 40 ml. was added initially, the remaining 40 ml. was added dropwise in 2 hr. During the 5-hr. total reaction period 86% of the theoretical amount of gas (C_2H_6) was evolved. The mixture was cooled in an ice bath and was carbonated by the addition of solid carbon dioxide. The mixture was hydrolyzed with 6 *N* hydrochloric acid. The aqueous layer was ether extracted. The organic layer was placed in 4 *N* hydrochloric acid and distilled. The fraction boiling between 40–98° contained 0.7 g. (4%) of unchanged pentafluorobenzene (based on v.p.c.). The perfluorobenzoic acid steam distilled with the hydrochloric acid above 100°. The acidic distillate was ether extracted, the ether replaced with hexane, and the acid recrystallized from hexane. There was obtained 17.93 g. (85%) of pentafluorobenzoic acid, m.p. 102.5–104° (lit.[14] m.p. 103–104°).

In a parallel reaction, methylmagnesium iodide (0.115 mole) was treated with pentafluorobenzene (0.100 mole) for 1 day. Gas evolution (CH_4) was 75%. The mixture was carbonated and pentafluorobenzoic acid was obtained in 56% yield after a similar work-up. Vapor phase chromatographic analysis of the low-boiling distillate showed 39% recovery of pentafluorobenzene.

Reaction of 1,2,4,5-Tetrafluorobenzene with Ethyl Grignard Reagent.—Ethylmagnesium bromide (0.30 mole in 170 ml. of tetrahydrofuran) was added to 1,2,4,5-tetrafluorobenzene (14.7 g., 0.098 mole) in 70 ml. of tetrahydrofuran. The reaction mixture was stirred for an additional 3.5 hr. until gas evolution (C_2H_6) seemed to stop. The mixture was cooled in an ice bath and carbonated by the addition of solid carbon dioxide.

The reaction mixture was hydrolyzed with 6 *N* hydrochloric acid. The mixture was added to a large volume of 4 *N* hydrochloric acid and distilled. The fraction boiling to 104° was collected, extracted with pentane, and washed repeatedly with dilute hydrochloric acid. The vapor phase chromatogram of this showed it contained 6.26 g. (43% recovery) of unchanged 1,2,4,5-tetrafluorobenzene. The distillate, b.p. 104–108°, was extracted with ether. The ether was replaced with hexane and all hexane extracts combined. From the hexane was obtained 5.60 g. (29%) of 2,3,5,6-tetrafluorobenzoic acid, m.p. 150.5–152° (lit.[15] m.p. 154°). The nondistilled aqueous acid layer was extracted with ether. The crude acid, obtained after removal of ether, was extracted with boiling hexane. The hexane-insoluble white solid was recrystallized from water to give 5.61 g. (24%) of tetrafluoroterephthalic acid, m.p. 281.5–282.5° (lit.[16] m.p. 283–284°).

In a similar experiment, a 2:1 mole ratio of Grignard reagent to 1,2,4,5-tetrafluorobenzene was treated overnight. Carbonation and a similar work-up gave 2,3,5,6-tetrafluorobenzoic acid in 25% yield and tetrafluoroterephthalic acid in 30% yield.

Reaction of 1,2,3,4-Tetrafluorobenzene with Ethyl Grignard Reagent.—Ethylmagnesium bromide (0.180 mole in 100 ml. of tetrahydrofuran) was added to 1,2,3,4-tetrafluorobenzene (15 g., 0.10 mole) in 70 ml. of tetrahydrofuran. The reaction mixture was heated at 40° for 7 hr. and stirred at room temperature for 3 days. A 5-ml. aliquot was removed, hydrolyzed, and extracted with pentane for (v.p.c.) analysis. The remainder of the reaction was carbonated by the addition of solid carbon dioxide, acidified, and worked up in the usual manner. No fluorinated benzoic acid could be isolated. Analysis of the aliquot by vapor phase chromatography indicated that alkylation occurred at most to a maximum of 10%.

Reaction of Pentafluorobenzene with Butyllithium. A.—Pentafluorobenzene (16.8 g., 0.10 mole) in 50 ml. of diethyl ether was added to a cooled (−70°) stirred solution of *n*-butyllithium[17] (0.1 mole in 80 ml. of hexane solution) over a period of 14 min. The temperature was not allowed to rise over −55° during the addition. Gilman color test IIA[6] was negative only after 2 hr. indicating absence of *n*-butyllithium. The reaction was then carbonated by bubbling carbon dioxide into the solution. The mixture was allowed to warm to room temperature with continued carbonation. The reaction was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid and then extracted with diethyl ether. The dried ether extracts were distilled, leaving 21.0 g. (99%) of crude pentafluorobenzoic acid, m.p. 100–105°. One recrystallization from hexane yielded 14.3 g. (68%) of pure pentafluorobenzoic acid as the first crop, m.p. 106° (lit.[14] m.p. 103–104°).

B.—The above experiment was repeated except that freshly prepared butyllithium in diethyl ether was used. Gilman color test IIA was negative within 5 min. indicating a faster reaction. The yield of pentafluorobenzoic acid, m.p. 106°, was 80.9%.

C.—Repeating the experiment as in B except that an equal volume of tetrahydrofuran was added to the prepared butyllithium ether solution gave pentafluorobenzoic acid, m.p. 106.5–107.5°, in 82% yield. Gilman color test IIA again was negative within 5 min. indicating a faster reaction in this solvent pair.

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[13] D. Holland, G. Moore, and C. Tamborski, unpublished work, gave m.p. 253–256°.

[14] E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 166 (1959).

[15] D. J. Alsop, J. Burdon, and J. C. Tatlow, *ibid.*, 1801 (1962).

[16] B. Gething, C. R. Patrick, and J. C. Tatlow, *ibid.*, 1574 (1961).

[17] Commercially prepared in hexane solution, Foote Mineral Co., Exton, Pa.

Reaction of 1,2,4,5-Tetrafluorobenzene with Butyllithium. Method A. Tetrahydrofuran Solvent.—1,2,4,5-Tetrafluorobenzene (15.0 g., 0.10 mole) in 20 ml. of tetrahydrofuran was added to a cooled (−70°), stirred solution of *n*-butyllithium[17] (0.20 mole, in 135 ml. of hexane) dissolved in 270 ml. of tetrahydrofuran. The addition took 10 min. and the temperature was not allowed to rise over −55°. After 20 min. Gilman color test IIA was negative. The mixture was then carbonated by bubbling carbon dioxide into the reaction. The mixture was allowed to warm to room temperature with continued carbonation. The reaction was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid. This two-phase mixture was then placed in a flask equipped with a short-path Vigreux column and distilled. The aqueous distillate, boiling between 100 and 108°, was extracted with diethyl ether, dried over magnesium sulfate, and aspirated on a water bath. The residue of 0.62 g. (3.2%) had m.p. 149–152° and was identified by mixture melting point and infrared analysis as 2,3,5,6-tetrafluorobenzoic acid. The solid pot residue from the above distillation, 19.9 g. (84%), m.p. 261–276°, was recrystallized from water to yield as the first crop 16.1 g. (67%), m.p. 283° (lit.[16] m.p. 283–285°), of tetrafluoroterephthalic acid. This material was characterized by infrared analysis and a mixture melting point with an authentic sample.

Method B. Diethyl Ether Solvent.—The above experiment was repeated except that diethyl ether was used in place of the tetrahydrofuran. Gilman color test IIA, however, was negative only after 2 hr. Carbonation and work-up as above yielded 6.5 g. (33%) of crude 2,3,5,6-tetrafluorobenzoic acid, m.p. 147–151°, 9.0 g. (37.7%) of crude tetrafluoroterephthalic acid, m.p. 276–278° (after one recrystallization from water), and 1.4 g. of an unidentified acidic material, m.p. 337.5–340°.

Reaction of 1,2,3,4-Tetrafluorobenzene with Butyllithium in Tetrahydrofuran.—1,2,3,4-Tetrafluorobenzene (15.0 g., 0.10 mole) in 20 ml. of tetrahydrofuran was added to a cooled (−70°), stirred solution of *n*-butyllithium[17] (0.20 mole in 135 ml. of hexane) dissolved in 270 ml. of tetrahydrofuran. The addition took 13 min. and the temperature was not allowed to rise over −55°. After 18 min. Gilman color test IIA was negative. The mixture was then carbonated by bubbling carbon dioxide into the reaction. The mixture was allowed to warm to room temperature with continued carbonation. The reaction was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid. This two-phase mixture was then placed into a flask equipped with short-path Vigreux column and distilled. The aqueous distillate boiling between 100 and 108° was extracted with diethyl ether. The diethyl ether was extracted with 5% sodium hydroxide solution. The extracted ether layer was dried and the ether was removed by distillation leaving 2.51 g. of a nonacidic liquid. Infrared analysis of this material suggested that it was an alkylated fluorobenzene. Vapor phase chromatographic analysis indicated that this material was a three- or four-component mixture.

The sodium hydroxide extract of the ether layer was acidified with 6 *N* hydrochloric acid and extracted with diethyl ether. The ether layer was dried and the solvent ether was removed by distillation to yield 6.04 g. of a semisolid material. This material was recrystallized from petroleum ether (b.p. 60–90°) and produced 4.14 g. of 2,3,4,5-tetrafluorobenzoic acid, m.p. 92–92.5°.

Anal. Calcd. for $C_7H_2F_4O_2$: C, 43.32; H, 1.04; F, 39.15. Found: C, 43.44; H, 1.19; F, 39.26.

The pot residue from the original distillation through the Vigreux column was extracted with diethyl ether. The ether was extracted with 5% sodium hydroxide solution. The basic solution was acidified with 6 *N* hydrochloric acid and again extracted with diethyl ether. The ether solution was dried over magnesium sulfate and distilled to remove the solvent leaving 8.96 g. of a dark brown semisolid material. This material was recrystallized from petroleum ether (b.p. 90–120°) several times to yield 2.23 g. of tetrafluorophthalic acid, m.p. 151–152° (lit.[16] m.p. 153–154°). In addition 4.25 g. of an unidentified material was obtained whose infrared spectrum showed both alkyl substitution as well as a carboxylic acid function.

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Isomerization of the Ascorbic Acids

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The rare L-araboascorbic and D-xyloascorbic acids are herein shown to be formed from their well-known epimers, L-xyloascorbic and D-araboascorbic acids, respectively, when they are heated with excess base in aqueous methanol. Their formation is shown to proceed *via* racemization of the asymmetric ring carbon (C-4), resulting in an approximately equal mixture of C-4 epimers at equilibrium in each case. Methods are described for the separation and purification of isomers, thus providing a new, convenient route to these uncommon ascorbic acids.

It has been known for a long time that esters of L-*xylo*-hexulosonic (2-keto-L-gulonic) and D-*arabino*-hexulosonic (2-keto-D-gluconic) acids are converted by bases *via* internal alcoholysis to the corresponding ascorbic acids, L-xyloascorbic and D-araboascorbic acid, respectively.[1] We wish to report the previously unrecorded fact that these reactions, when conducted with excess base, lead to racemization at C-4 of the product and that the rare ascorbic acids, L-araboascorbic and D-xyloascorbic acid, are formed in each case in about equal amount with the common epimer, L-ascorbic and D-isoascorbic acid, respectively.

Surprisingly little degradation is involved, and our initial, chance chromatographic detection of the phenomenon has led to the development of a convenient synthetic method for the preparation of these uncommon ascorbic acids, heretofore obtainable only *via* rare sugars or cumbersome fragment condensation methods.[2] The racemizations involved present rather interesting and novel carbohydrate behavior and so will be discussed in some detail.

Reducing sugars are relatively stable in weakly acid solutions, but in alkaline solution they are subject to isomerizations, cleavages, and condensations. In fact, the classic Lobry de Bruyn–Alberda van Ekenstein transformation of aldoses by base to mixtures of C-2

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[2] B. Helferich and O. Peters, *Ber.*, **70**, 464 (1937); "The Vitamins," Vol. I, Sebrell and Harris, Ed., Academic Press, New York, N. Y., 1954, pp. 198-202.