7-Hydroxy-3'-methylflavanone. The above chalcone was isomerized to flavanone in the usual way. The reaction product, after the removal of alcohol under reduced pressure, on standing in contact with glacial acetic acid in a refrigerator for 12 hr. partially solidified. The adherent oily portion was centrifuged and the solid thus recovered was dissolved in ethanol and precipitated by the addition of water, filtered, and dried. The product on repeated dissolution in benzene and precipitation by light petroleum ether gave the flavanone as pinkish white microcrystalline powder, m.p. 146–147°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.74; H, 5.82.

2',4'-Dihydroxy-4-methylchalcone. A solution of resacetophenone (3.0 g.), *p*-tolualdehyde (2.36 cc., $d_4^{16.7}$ 1.0194) in ethanol (25 cc.) was treated with potassium hydroxide pellets of 85% purity (15 g. dissolved in 15 cc. water), and heated in a water bath at about 60° for 2 hr. It was worked up as before. The crude chalcone (2.6 g.) separated as a yellow oil. It was washed several times with warm water (about 70°) and dried. On nucleation with the crystals of isomeric 2',4'-dihydroxy-2-methylchalcone and cooling in a freezing mixture, with stirring, the oil suddenly solidified. An alcoholic solution of this solidified mass on standing deposited the 2',4'-dihydroxy-4-methylchalcone in needles, but the compound was not pure since the crystals occluded an appreciable quantity of resinous matter from the solution. The crystalline magma was filtered at a pump, washed with a little ethanol, and then crystallized from aqueous ethanol in yellow needles and finally from benzene in yellow, well shaped prisms, m.p. 153–154°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.41; H, 5.80.

The resulting aqueous alcoholic mother liquor deposited 7-hydroxy-4'-methylflavanone in irregular plates, m.p. 170°.

7-Hydroxy-4'-methylflavanone. The ring closure of the above chalcone (crude) by refluxing it with aqueous-alcoholic sulfuric acid gave an oily product which crystallized slowly (80 days) in contact with acetic acid. Recrystallization from alcohol (animal charcoal) furnished the flavanone in colorless rectangular plates, m.p. 170–171°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.22; H, 5.62.

The chalcones described in this paper give a yellow coloration with concentrated sulfuric acid (except 2',4,4'-trihydroxy-3-methoxychalcone-red, 2',4'-dihydroxy-2,3-dimethoxychalcone-orange), dissolve in alkali with the production of an orange color which changes to yellow, and give a dark brown coloration with ethanolic ferric chloride.

All the flavanones, described herein, on reduction with magnesium and ethanolic hydrochloric acid give a pink color, whereas 4',7-dihydroxy-3'-methoxyflavanone, gives various transitory shades of color, *viz.* bluish violet, violet, rose-violet, and finally pink.

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KANPUR, INDIA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Organometallic Compounds from Aryl Halides Containing Ether Functions[1]

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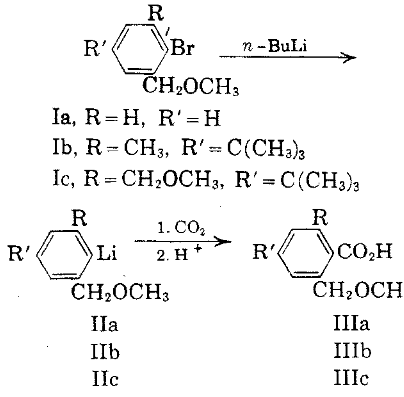
A number of *o*-methoxymethylaryl halides have been synthesized, and a study has been made of the synthesis and properties of the corresponding aryllithium and arylmagnesium compounds.

Although aryl methyl ethers which contain lithium in the nucleus have been synthesized previously, a careful study of the preparation and properties of *o*-methoxymethylphenyllithium compounds has apparently not been made. In the present study a method for the preparation of such compounds has been developed which consists of allowing an *o*-bromobenzyl methyl ether to react with *n*-butyllithium for a limited time. In this way *o*-methoxymethylbromobenzene (Ia), 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene (Ib), and 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene (Ic) were converted to the corresponding lithium derivatives, IIa, IIb, and IIc. Carbonation of these lithium compounds afforded the acids, IIIa, IIIb, and IIIc in yields of 34, 65, and 91%, respectively. In comparison, 4 - *t* - butyl - 2,6 - dimethylbromobenzene, when treated similarly, gave the corresponding acid in a 51% yield.



Ia, R = H, R' = H

Ib, R = CH_3, R' = $C(CH_3)_3$

Ic, R = CH_2OCH_3, R' = $C(CH_3)_3$

IIa IIIa

IIb IIIb

IIc IIIc

Coupling of the aryllithium with the aryl bromide may be responsible for the variation in the yields of acids; the aryllithium compound least hindered

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sterically might couple to the greatest extent and give the acid in lowest yield.

When lithium metal was used in place of *n*-butyllithium with the above bromobenzenes, the results were much more involved. It was known, of course, that nuclear metalation of benzyl ethers by organoalkali compounds could be complicated since ethers of the type had been shown to react with these reagents in a number of ways. Among these are cleavage[2] and reactions involving metalation of the side-chain followed by elimination,[3] displacement,[4] and rearrangement.[5]

When the simplest of the aryl bromides (Ia) was treated with lithium, and the resulting mixture poured on solid carbon dioxide the only product that could be identified, in fact, was bibenzyl and that in small amount. Similar treatment of Ib produced the debrominated derivative, 3-*t*-butyl-5-methoxymethyltoluene, in a yield of 25%. The formation of this compound is best explained perhaps by hydrogen-metal interchange between IIb and the α-hydrogen atom of a benzyl methyl ether, most probably the coupling product formed from Ib. This reaction would then be analogous to similar metalations observed by interaction of benzyl ethers with phenyllithium.[4,5]

The bibenzyl could have originated in the following way. Benzyl methyl ether might first be produced in a manner analogous to the formation of 3-*t*-butyl-5-methoxymethyltoluene just indicated. Cleavage of benzyl methyl ether by lithium would give benzyllithium, which could then displace a methoxyl group from another molecule of the ether to yield bibenzyl. Although benzyl ethers are not normally cleaved by metals at the temperature of refluxing ether, it has been shown that a slow cleavage of benzyl phenyl ether by sodium begins at 39°.[2] The occurrence of bibenzyl as a product in the cleavage of benzyl ethers has been ascribed to nucleophilic displacement rather than free radical combination.[6]

It is noteworthy that when 4-*t*-butyl-2,6-dimethylbromobenzene was allowed to react with lithium under the conditions employed for Ia and Ib, the corresponding acid was obtained in a 30% yield. This experiment supports the hypothesis that the disappearance of the aryllithium compounds IIa and IIb is associated with attack of the ether function. Similar reaction of Ic with lithium followed by treatment with carbon dioxide failed to produce any acid; only starting material was recovered.

Although it was expected that the major products formed by the reaction between Ia and Ib with lithium might be coupling products, attempts to isolate these compounds by distillation, recrystallization, and chromatography were unsuccessful. It seemed possible that oxidation would convert the coupled ethers to carboxylic acids which could then be identified more easily. Accordingly the benzyl methyl ethers Ia and Ib were subjected to the action of potassium permanganate. Compound Ia afforded *o*-bromobenzoic acid in an 86% yield, but Ib yielded the dicarboxylic acid, 2-bromo-5-*t*-butylisophthalic acid (71%), rather than the monocarboxylic acid. Apparently the methyl group is oxidized about as easily as the methoxymethyl group. When the oxidation was carried out on the complex mixtures obtained from the reaction of Ia and Ib with lithium, no acids were formed.

Organometallic compounds which contain suitably placed ether groups offer the possibility of internal coordination between an electron pair of the ether oxygen atom and the metal atom. Such coordination has been used by Holmberg to explain the behavior of certain *o*-methoxyphenyl Grignard reagents toward carbonation.[7] Of the organomagnesium compounds studied, those which could form four- and five-membered rings gave both ketones and acids, while those which could form six-membered rings gave only acids. He ascribed the enhanced reactivity of the former Grignard reagents to strain in the rings. Investigation of *o*-bromobenzyl methyl ether revealed that the entrainment method was required for adequate conversion of this bromide to the Grignard reagent; the latter compound when carbonated afforded the corresponding acid in only a 13% yield. The apparent sluggishness of the reaction was attributed to stability of the five-membered ring formed by internal coordination.[8]

The Grignard reagent of Ib was prepared only by the use of the entrainment method. 4-*t*-Butyl-2-(β-methoxy)ethyl-6-methylbenzyl chloride, in contrast, formed the Grignard reagent in the normal manner. Although these two organomagnesium compounds are capable of internal coordination, no unusual behavior was observed; they were converted to the corresponding acids in yields of 26 and 28%, respectively. The diether bromide (Ic) failed to react with magnesium even though conditions were varied over a wide range. The diether iodide, prepared by action of iodine on the diether lithium intermediate (IIIc), was also unreactive toward magnesium.

Several interesting effects were uncovered in the synthesis of the diether bromide (Ic). Treatment of 4-*t*-butyl-2,6-dimethylbromobenzene with two equivalents of *N*-bromosuccinimide yielded a mixture of 2-bromomethyl-4-*t*-butyl-6-methylbromobenzene and 4-*t*-butyl-2,6-di(bromomethyl)-bromobenzene. Although these compounds are solids, they

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(3) C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

(4) A. Lüttringhaus, G. Wagner-v. Sääf, E. Sucker, and G. Borth, *Ann.*, **557**, 46 (1945).

(5) G. Wittig and L. Löhmann, *Ann.*, **550**, 260 (1942).

(6) R. L. Burwell, *Chem. Revs.*, **54**, 615 (1954).

(7) G. A. Holmberg, *Acta Chem. Scand.*, **9**, 555 (1955).

(8) F. G. Mann and F. H. Stewart, *J. Chem. Soc.*, 2819 (1954).

were separated from each other more easily by fractional distillation than by recrystallization. Treatment of the tribromide with sodium methoxide afforded the diether bromide in an 85% yield. The other bromoethers were prepared by similar procedures.

The first step in the synthesis of 4-*t*-butyl-2-(β - methoxy)ethyl - 6 - methylbenzyl chloride was treatment of 5-*t*-butyl-*m*-xylene with 1.75 equivalents of N-bromosuccinimide. This bromination yielded 3-bromo-methyl-5-*t*-butyltoluene (42%) and 3,5-di(bromomethyl)-*t*-butylbenzene (13%).

The Grignard reagent from 3-bromomethyl-5-*t*-butyltoluene reacted with chloromethyl ether to give the desired 3-*t*-butyl-5-(β-methoxy) ethyltoluene (34%); products arising from hydrolysis, coupling, and rearrangement were also isolated. Although benzyl Grignard reagents undergo rearrangement when treated with chloromethyl ether,[9,10] they yield only the normal products with carbon dioxide.[8,9] In keeping with this observation, we found that carbonation of *o*-bromobenzylmagnesium bromide gave *o*-bromophenylacetic acid as the major product with smaller amounts of *o*-bromobenzyl alcohol and *bis*-(2-carboxyphenyl) ethane. Similarly, no rearrangement products were reported in the reaction between *o*-bromobenzylmagnesium bromide and ethylene oxide.[11] Chloromethylation of 3-*t*-butyl-5-(β-methoxy)ethyltoluene afforded the benzyl chloride in a 72% yield.

EXPERIMENTAL[12]

Bromination of 4-t-butyl-2,6-dimethylbromobenzene. A mixture of 65 g. (0.27 mole) of 4-*t*-butyl-2,6-dimethylbromobenzene,[13] 96.1 g. (0.54 mole) of *N*-bromosuccinimide, 0.1 g. of benzoyl peroxide, and 300 ml. of carbon tetrachloride was heated on a steam bath, with stirring. At the end of 5 min. the color changed from cream to pink; within 30 min. the color was discharged. The mixture was heated under reflux for an additional 1.5 hr., cooled to room temperature, and filtered. The amount of succinimide (52.5 g.) recovered was quantitative. The carbon tetrachloride was removed from the filtrate, and the residual yellow liquid distilled. The first fraction (b.p. 122–123°/1.2 mm.) was the crude 2-bromomethyl-4-*t*-butyl-6-methylbromobenzene, which crystallized when cooled. After two recrystallizations from 95% ethanol it melted at 38–39.5°, yield 11.4 g. (13%).

Anal. Calcd. for $C_{12}H_{16}Br_2$: C, 45.02; H, 5.04. Found: C, 45.24; H, 5.22.

The second fraction (b.p. 165–168°/1.4 mm.), which also crystallized when cooled, melted at 75–78°, yield 76.5 g. (71%). The pure 4-*t*-butyl-2,6-di(bromomethyl)bromobenzene, m.p. 89–90°, was obtained only after repeated recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_{15}Br_3$: C, 36.12; H, 3.79. Found: C, 36.26; H, 3.86.

In another experiment a mixture of 149.5 g. (0.62 mole) of 4-*t*-butyl-2,6-dimethylbromobenzene, 165.7 g. (0.92 mole) of *N*-bromosuccinimide, 750 ml. of carbon tetrachloride, and 1 g. of benzoyl peroxide was heated with stirring for 3 hr. The succinimide was collected on a filter, and the solvent removed from the filtrate. The residual liquid when distilled yielded 90.0 g. (45%) of the dibromide, b.p. 136–138°/2.5 mm. and 40.7 g. (17%) of the tribromide, b.p. 169–174°/2.5 mm.

4-t-Butyl-2,6-di(methoxymethyl)bromobenzene. To 170 ml. of reagent grade methanol, cooled by an ice bath, was added slowly 9.4 g. (0.41 g.-atom) of sodium. When the sodium had dissolved, the solution was brought to reflux and a solution of 54 g. (0.14 mole) of 4-*t*-butyl-2,6-di-(bromomethyl)bromobenzene in 170 ml. of anhydrous benzene was added dropwise during 2 hr. After the addition was complete, stirring was continued for 0.5 hr. under reflux. The mixture was then filtered to get rid of the insoluble salts, and the filtrate was distilled azeotropically to remove the methanol. The benzene solution was washed with water and dried over calcium chloride. A yellow solid formed when the benzene was evaporated under water-aspirator pressure. After one recrystallization from 95% ethanol the dimethoxy bromide melted at 80.5–81.0°, yield 34.9 g. (85%).

Anal. Calcd. for $C_{14}H_{21}BrO_2$: C, 55.81; H, 6.98. Found: C, 55.87; H, 7.24.

4-t-Butyl-2-methoxymethyl-6-methylbromobenzene. This procedure is similar to that employed for the diether bromide. A solution of sodium methoxide, prepared by the addition of 5.8 g. (0.25 g.-atom) of sodium to 100 ml. of methanol, was heated to reflux while 40.0 g. (0.125 mole) of 2-bromomethyl-4-*t*-butyl-6-methylbromobenzene in 100 ml. of benzene was added dropwise to it during 1 hr. The methanol was removed by azeotropic distillation, and the residue extracted with water. The benzene layer was dried, and the solvent evaporated. The remaining liquid afforded 29.3 g. (87%) of the monomethoxy bromide, b.p. 93.0–93.5°/0.3 mm.

Anal. Calcd. for $C_{13}H_{19}BrO$: C, 57.60; H, 7.01. Found: C, 57.67; H, 6.91.

o-Bromobenzyl methyl ether. A mixture of 158.5 g. (0.927 mole) of *o*-bromotoluene, 165 g. (0.927 mole) of *N*-bromosuccinimide, and 0.2 g. of benzoyl peroxide in 300 ml. of carbon tetrachloride was heated on the steam bath for 18 hr. Distillation of the residue left by removal of the succinimide and evaporation of the solvent gave 181.6 g. (78%) of *o*-bromobenzyl bromide, b.p. 133–134°/18.5 mm. The literature records a boiling point of 129°/19 mm.[14]

The bromide was converted to the ether by a modification of the method of Holliman and Mann.[15] To a solution of 19.0 g. (0.825 g.-atom) of sodium in 500 ml. of methanol, cooled in an ice bath, was added 181 g. (0.725 mole) of the bromide. The mixture was heated 1.5 hr., and the solvent removed by distillation. The residue was added to water in a separatory funnel, and the organic layer extracted with ether. The residual liquid left by distillation of the ether afforded 119.5 g. (82%) of the bromo ether, b.p. 111–112°/17 mm. The reported boiling point is 106–107°/16 mm.[15]

3-Bromomethyl-5-t-butyltoluene. To a mixture of 592 g. (3.33 moles) of *N*-bromosuccinimide and 308 g. (1.90 moles) of 5-*t*-butyl-*m*-xylene was added 0.5 g. of benzoyl peroxide and 1 l. of carbon tetrachloride. The mixture was stirred under reflux for 19 hr. after which the succinimide was collected on a filter and the filtrate concentrated. Distillation of the residue yielded 19.23 g. (42%) of 3-bromomethyl-5-*t*-butyltoluene, which boiled at 104–109°/2.5 mm.

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Anal. Calcd. for $C_{12}H_{17}Br$: C, 59.75; H, 7.05. Found: C, 59.73; H, 7.17.

The infrared spectrum of the second fraction (b.p. 128–130°/2.7 mm. has a band at 675 cm.$^{-1}$, which is consistent with a $—CHBr_2$ function.

From the remaining material, after three recrystallizations from 95% ethanol was obtained 78.8 g. (13%) of 3,5-di(bromomethyl)-*t*-butylbenzene, m.p. 115–118°.

Anal. Calcd. for $C_{12}H_{16}Br_2$: C, 45.02; H, 5.04. Found: C, 45.16; H, 4.91.

From the mother liquors was obtained a fraction which boiled at 99–101°/0.3 mm. The infrared spectrum of this liquid exhibits bands at 2720 cm.$^{-1}$ and 1705 cm.$^{-1}$ characteristic of an aromatic aldehyde, as well as a band at 115 cm.$^{-1}$ assignable to an aliphatic ether.

Reaction of 3-t-butyl-5-methylbenzylmagnesium bromide with chloromethyl ether. The benzyl Grignard reagent was prepared by adding a solution of 50 g. (0.21 mole) of 3-bromomethyl-5-*t*-butyltoluene in 400 ml. of ether to 12.6 g. (0.518 g.-atom) of magnesium. The addition, which required 6 hr., was followed by stirring for 1.5 hr. After the Grignard reagent had been allowed to stand overnight it was filtered under nitrogen and added during 3 hr. to a flask containing 16.7 g. (0.207 mole) of chloromethyl ether in 50 ml. of ethyl ether. The reaction mixture was cooled by an ice bath during the addition, then heated gently under reflux for 1 hr. Decomposition was effected with hydrochloric acid. The ether layer was washed, dried, and freed of solvent. Distillation of the residue yielded four fractions, the first of which (b.p. 65–68°/2.9 mm.) was shown to be 5-*t*-butyl-*m*-xylene by comparing its infrared spectrum and refractive index with those of a known sample, yield 6.1 g. (18%). The second fraction (b.p. 106–111°/3 mm.) was 3-*t*-butyl-5-(β-methoxy)ethyltoluene, yield 14.5 g. (34%).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.13; H, 10.60.

An absorption band (875 cm.$^{-1}$) attributed to a 1,2,3,5-tetrasubstituted benzene is present in the infrared spectrum of the third fraction (b.p. 129–132°/3.4 mm.). This spectrum also contains bands at 1120 and 1100 cm.$^{-1}$, which are assignable to a hindered aliphatic ether. This compound, tentatively identified as 5-*t*-butyl-2-methoxymethyl-*m*-xylene, weighed 5.8 g. (14%). The last fraction (b.p. 188–193°/3.6 mm.) proved to be the coupling product, 3,3′-di-*t*-butyl-5,5′-dimethylbibenzyl, yield 4.0 g. (12%).

Anal. Calcd. for $C_{24}H_{34}$: C, 89.37; H, 10.63. Found: C, 89.50; H, 10.82.

Chloromethylation of 3-t-butyl-5-(β-methoxy)ethyltoluene. A mixture of 4.2 g. (0.02 mole) of 3-*t*-butyl-5-(β-methoxy)-ethyltoluene, 1.76 g. (0.0585 mole) of paraformaldehyde, and 40 ml. of concentrated hydrochloric acid was stirred while dry hydrogen chloride was bubbled into it. The temperature was kept at 35° during the reaction, which was allowed to proceed for 3 hr. The mixture was extracted with ether, the extracts were washed and dried, and the ether was removed. Distillation of the residue afforded 3.6 g. (72%) of the chloromethyl compound, b.p. 108–110°/0.45 mm.

Anal. Calcd. for $C_{15}H_{23}OCl$: C, 70.73; H, 9.04. Found: C, 70.64; H, 8.95.

Carbonation of o-bromobenzylmagnesium bromide. To a flask containing 11.7 g. (0.48 g.-atom) of magnesium was added 30 g. (0.12 mole) of *o*-bromobenzyl bromide in 250 ml. of ether during 3.5 hr. A nitrogen atmosphere was maintained during the addition. Stirring was continued for 2 hr. after which the mixture was filtered under nitrogen on solid carbon dioxide. The carbonated mixture was decomposed with iced hydrochloric acid. The ether layer was extracted with two 100-ml. portions of 10% sodium hydroxide solution. Acidification of the extracts produced crystals, which were collected on a funnel, washed, and dried. The solid was treated with hot carbon tetrachloride, which caused part of the crystals to dissolve. The undissolved bis(2-carboxyphenyl)ethane was isolated by filtration of the hot solution. After several recrystallizations from 95% ethanol-benzene this acid melted at 233–234°, yield 0.8 g. (5%).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.27; H, 5.02.

The literature records a melting point of 231° for this compound.[16]

After the dicarboxylic acid had been removed from the mixture of acids by filtration, the carbon tetrachloride was evaporated from the resulting mother liquor. The solid residue was recrystallized several times from hot water in the presence of carbon black. The pure *o*-bromophenylacetic acid melted at 105°, yield 10.0 g. (39%). The reported melting point is 103–104°.[17]

From the ether layer which remained after basic extraction crude *o*-bromobenzyl alcohol was obtained; after two recrystallizations from high-boiling petroleum ether it melted at 79.5–80.0°, yield 0.4 g. (2%). This compound is reported to melt at 80°.[18]

Reaction of o-bromobenzyl methyl ether with n-butyllithium. In a dry flask which had been flushed with nitrogen, a mixture of 4.7 g. (0.023 mole) of *o*-bromobenzyl methyl ether in 75 ml. of ether and 114 ml. (0.093 mole) of 0.81*N* *n*-butyllithium[19] was heated, with stirring, under gentle reflux for 45 min. After the mixture had cooled, it was poured on an excess of solid carbon dioxide. The carbonated mixture, upon reaching room temperature, was extracted with two 90-ml. portions of 10% sodium hydroxide solution. Acidification of the basic extracts with concentrated hydrochloric acid precipitated 2-methoxymethylbenzoic acid, yield 1.3 g. (34%), m.p. 91–94°. The literature records a melting point of 93–94°.[20]

Reaction of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene with n-butyllithium. To a dry flask containing 100 ml. (0.035 mole) of 0.35*N* *n*-butyllithium was added all at once a solution of 3.0 g. (0.011 mole) of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene in 50 ml. of ether. The mixture was stirred under reflux for 0.5 hr. and poured on solid carbon dioxide. The carbonated material was extracted with dilute sodium hydroxide solution, and the extracts were boiled for a few minutes, filtered hot, and cooled in an ice-salt bath. Acidification of the solution with concentrated hydrochloric acid produced an oil which crystallized when allowed to stand overnight in the refrigerator. The crude 4-*t*-butyl-2-methoxymethyl-6-methylbenzoic acid was collected on a filter, washed with water, and dried, yield 2.1 g. (80%), m.p. 76–80°. After several recrystallizations from low-boiling petroleum ether–methylcyclohexane the acid melted at 80–81°, yield 1.7 g. (65%).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.19; H, 8.48. Found: C, 70.93; H, 8.43.

Reaction of 4-t-butyl-2,6-di(methoxymethyl)bromobenzene with n-butyllithium. A solution of 1.5 g. (0.0050 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene in 25 ml. of ether was added all at once to 50 ml. (0.020 mole) of 0.40*N* *n*-butyllithium in 50 ml. of ether. The mixture was heated at reflux, with stirring, for 45 min. and poured on solid carbon dioxide. After being allowed to come to room temperature the carbonated material was treated as in the preceding experiment. 4-*t*-Butyl-2,6-di(methoxymethyl)benzoic acid was isolated, m.p. 77–80°, yield 1.2 g. (91%). The pure acid melts at 79.0–79.5°.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.82; H, 8.22.

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(20) J. v. Braun, E. Anton, and K. Weissbach, *Ber.*, **63**, 2847 (1930).

Reaction of 4-t-butyl-2,6-dimethylbromobenzene with n-butyllithium. A solution of 5.0 g. (0.021 mole) of 4-*t*-butyl-2,6-dimethylbromobenzene in 100 ml. of ether was added dropwise to a flash containing 150 ml. (0.083 mole) of 0.55*N* *n*-butyllithium during 0.5 hr. After the mixture had been heated for 0.5 hr., with stirring, it was poured on excess solid carbon dioxide. By the usual procedure was isolated 2.1 g. (48%) of 4-*t*-butyl-2,6-dimethylbenzoic acid, m.p. 164–168°. This acid has been reported to melt at 167–168°.[13]

Reaction of o-bromobenzyl methyl ether with lithium. To a flask containing 2.08 g. (0.30 g.-atom) of lithium metal cut in small pieces and 100 ml. of ether was added all at once 5 g. of *o*-bromobenzyl methyl ether in 25 ml. of ethyl ether. A stream of nitrogen was passed through the mixture, which was stirred mechanically. While the mixture was heated sufficiently to maintain gentle refluxing, 25 g. of *o*-bromobenzyl methyl ether, which made a total of 30 g. (0.15 mole), dissolved in 100 ml. of ether was added during 1 hr. Stirring was continued for 20 hr. at the end of which time most of the lithium had disappeared. The solution was filtered under nitrogen on solid carbon dioxide. The mixture was extracted with base; acidification of these extracts, however, failed to give an acid. The ether layer was washed and dried. The residual liquid left by evaporation of the solvent was distilled under vacuum. The first fraction (b.p. 46–48°/0.1 mm.) solidified when allowed to stand and melted at 45–51°. This melting point, the odor, and the infrared spectrum, which exhibits a band (695 cm.$^{-1}$) assignable to a monosubstituted benzene, suggested that the compound was bibenzyl. The melting point for bibenzyl is reported at 52°.[21]

Later fractions boiled at 52–74°/0.1 mm. and 72–75°/0.1 mm. The infrared spectra of these fractions show bands assignable to a monosubstituted benzene (698 cm.$^{-1}$), an *o*-disubstituted benzene (758 cm.$^{-1}$) and an aliphatic ether (1100 cm.$^{-1}$). An undistillable residue remained which could not be purified by chromatography or crystallization.

Reaction of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene with lithium. The reaction was initiated by the addition of a solution of 5 g. of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene in 15 ml. of ether to 0.85 g. (0.12 g.-atom) of lithium in 50 ml. of ether. When heat was applied, with stirring under nitrogen, fairly vigorous refluxing began. At this point an additional 10 g. of the ether bromide, making a total of 15 g. (0.055 mole), in 50 ml. of ether was added dropwise in 0.5 hr. The mixture was stirred under reflux overnight. Treatment with carbon dioxide gave no acid. The ether layer remaining after the basic extraction was dried. Distillation of the residue obtained by evaporation of the solvent yielded a liquid which boiled at 67–68°/0.5 mm. The yield was 2.7 g. or 25%, based on the assumption that the compound is 3-*t*-butyl-5-methoxymethyltoluene.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.34; H, 10.69.

The infrared spectrum of this compound exhibits bands assignable to an aliphatic ether (1108 cm.$^{-1}$) and a 1,3,5-trisubstituted benzene (855, 708 cm.$^{-1}$). Attempts to purify the nondistillable residue were unsuccessful.

Treatment of 4-t-butyl-2,6-di(methoxymethyl)bromobenzene with lithium. A mixture of 1.5 g. (0.005 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene and 0.076 g. (0.011 g.-atom) of lithium in 50 ml. of ether was heated to reflux, with stirring. Although the stirring was allowed to continue for 20 hr., little sign of reaction was noticed and no acid was obtained by treatment of the mixture with carbon dioxide. Only starting material was recovered from the ether layer.

Reaction of 4-t-butyl-2,6-dimethylbromobenzene with lithium. To a flask containing 0.633 g. (0.091 g.-atom) of lithium and 100 ml. of ether was added 1.0 g. of 4-*t*-butyl-2,6-dimethylbromobenzene. The flask was warmed and in a few minutes the ether became turbid, which indicated that the reaction had begun. A solution containing 9.0 g. (which made a total of 10.0 g. or 0.041 mole) of the bromide in 50 ml. of ether was then added dropwise during 0.5 hr. The mixture was heated, under gentle reflux, with stirring, for about 20 hr. After unchanged lithium had been removed by filtration through glass wool, the solution was poured on solid carbon dioxide. The carbonated material was extracted with three 50-ml. portions of 10% sodium hydroxide solution. When the basic extracts were acidified, 4-*t*-butyl-2,6-dimethylbenzoic acid precipitated as a cream colored solid. After several recrystallizations from low-boiling petroleum ether–methylcyclohexane, the acid weighed 2.6 g. (30%), m.p. 166–168°. The reported melting point is 167–168°.[13]

Oxidation of o-bromobenzyl methyl ether. A mixture of 5.0 g. (0.025 mole) of *o*-bromobenzyl methyl ether and 50 ml. of water was heated with stirring on a steam bath until the water began refluxing. A solution of 14.5 g. of potassium permanganate in 250 ml. of water was then added dropwise to the emulsion during 0.5 hr. The mixture was stirred under reflux for 3 hr. Manganese dioxide was removed by filtering the hot alkaline mixture on a Büchner funnel. The manganese dioxide was washed with two 50-ml. portions of hot water, and the resulting clear, yellow filtrate was concentrated to a volume of about 200 ml. When concentrated hydrochloric acid was added to this hot solution, a white precipitate formed immediately. After the solution had cooled, the solid was collected on a filter and washed with water until the filtrate was free of chloride ion. The dried *o*-bromobenzoic acid weighed 4.3 g. (86%), m.p. 146–147°. The literature records a melting point of 150°.[22]

Oxidation of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene. The procedure was nearly the same as that described in the preceding experiment. A mixture of 3.5 g. (0.013 mole) of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene and 30 ml. of water was heated, with stirring; to it was added a solution of 6.7 g. (0.043 mole) of potassium permanganate in 140 ml. of water during 15 min. Since permanganate ion was still present at the end of 8 hr., stirring was continued overnight. The next morning the purple color had disappeared, and the solution was alkaline. The mixture was filtered, the manganese dioxide washed, and the filtrate concentrated to a volume of about 100 ml. Acidification caused precipitation of the crude 2-bromo-5-*t*-butylisophthalic acid as a colorless solid. It was collected by filtration, washed, and air dried, m.p. 243–257°, yield 1.7 g. On the basis of the potassium permanganate used this is a yield of 71%. After one recrystallization from dioxane-benzene, the acid melted at 255–256°. An analytical sample of the acid was prepared by sublimation.

Anal. Calcd. for $C_{12}H_{13}O_4Br$: C, 47.84; H, 4.32. Found: C, 47.95; H, 4.43.

Reaction of 4-t-butyl-2-methoxymethyl-6-methylbromobenzene with magnesium. To a flask containing 1.6 g. (0.068 g.-atom) of magnesium and a crystal of iodine was added several drops of a solution containing 8.8 g. (0.032 mole) of 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene and 3.5 g. (0.032 mole) of ethyl bromide in 60 ml. of ether. The flask was warmed and, after the Grignard reaction had begun, the remaining solution was added dropwise over 1.5 hr. The mixture was then stirred under gentle reflux for 15 min. during which time almost all the magnesium was consumed. The dark brown mixture was poured on solid carbon dioxide, and the carbonated material allowed to reach room temperature. The crude 4-*t*-butyl-2-methoxymethyl-6-methylbenzoic acid, isolated by usual procedures, melted at 70–76°, yield 3.0 g. Its purification was effected by recrystallization from low-boiling petroleum ether–methylcyclohexane. The pure acid weighed 2.0 g. (26%), m.p. 80–81°.

Reaction of 4-t-butyl-2-(β-methoxy)ethyl-6-methylbenzyl chloride with magnesium. A solution containing 3.5 g. (0.014

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[21] R. A. Smith and S. Natelson, *J. Am. Chem. Soc.*, **53**, 3476 (1931).

[22] M. Rhalis, *Ann.*, **198**, 103 (1879).

mole) of 4-*t*-butyl-2-(β-methoxy)ethyl-6-methylbenzyl chloride in 100 ml. of ether was allowed to drop upon 0.7 g. (0.03 g.-atom) of magnesium over a period of 2 hr. The 4-*t*-butyl-2-(β-methoxy)ethyl-6-methylphenylacetic acid, isolated in the usual way, melted at 81–83°, yield 1.0 g. (28%). Further recrystallization of this compound from low-boiling petroleum ether–methylcyclohexane raised the melting point to 83–84°.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69: H, 9.15. Found: C, 73.01; H, 9.36.

Treatment of 4-t-butyl-2,6-di(methoxymethyl)bromobenzene with magnesium. Various attempts to effect a reaction between 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene and magnesium were made. Such solvents as ether, benzene, toluene, and tetrahydrofuran as well as ether-benzene and ether-toluene solvent pairs were used. Catalysts employed were iodine, ethyl bromide, mercuric chloride, and aluminum chloride. In all cases only starting material was recovered.

4-t-Butyl-2,6-di(methoxymethyl)iodobenzene. To a flask containing a solution of 6.0 g. (0.02 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene in 100 ml. of ether was added 60 ml. of 0.68*N* (0.04 mole) *n*-butyllithium. The orange-brown mixture was heated, with stirring, for 1 hr. and then cooled in an ice bath. The addition of a solution of 15.2 g. (0.060 mole) of iodine in 75 ml. of ether to the cold mixture was begun. The mixture was stirred for an additional hour in the cold and decomposed with crushed ice. The ether layer, after separation from the water layer, was washed successively with 50 ml. of a 5% sodium sulfite solution and water and dried over magnesium sulfate. After the ether had been removed the residue crystallized readily. The iodide, recrystallized from 95% ethanol, melted at 76–77°, yield 4.8 g. (69%).

Anal. Calcd. for $C_{14}H_{21}O_2I$: C, 48.28; H, 6.03. Found: C, 48.34; H, 5.98.

Treatment of 4-t-butyl-2,6-di(methoxymethyl)iodobenzene with magnesium. A mixture of 1.5 g. (0.0043 mole) of 4-*t*-butyl-2,6-di(methoxymethyl)iodobenzene and 0.94 g. (0.0086 mole) of ethyl bromide in 50 ml. of ether was added dropwise during 0.5 hr. to a flask containing 0.42 g. (0.017 g.-atom) of magnesium. After the addition, the mixture was stirred under reflux for 7 hr. and filtered through glass wool on solid carbon dioxide. The mixture failed to yield any acidic product.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Applicability of the Arndt-Eistert Reaction to Fluorinated Acids and Their Derivatives[1]

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Perfluorinated acids containing three or more carbon atoms failed to undergo the Arndt-Eistert reaction in a normal fashion. At least two methylene groups must be present in order to obtain satisfactory yields from this reaction. In all cases, it appears that the intermediate diazo ketone is formed and that it is the second stage of the reaction, the Wolff rearrangement, that fails to take place normally, resulting in the formation of α-halo ketones.

The following ketones, $C_2F_5COCH_2Cl$, $C_3F_7COCH_2Cl$, and $C_3F_7COCH_2Br$ were prepared and characterized, and the physical properties of a number of new compounds were determined and tabulated.

This investigation reports on the applicability of the Arndt-Eistert reaction[2] to perfluorinated acids and their homologs and to the preparation of ketones of the type R_FCOCH_2X (where X is any halogen and R_F is a perfluorinated group) from perfluorinated acids and diazomethane. Since perfluorinated acids are now commercially available, it seemed the easiest and most direct way of preparing the higher acids and ketones containing the perfluorinated group.

The acids, C_2F_5COOH, C_3F_7COOH, $C_3F_7CH_2COOH$, $C_3F_7CH_2CH_2COOH$, and C_4F_9COOH, were converted to their respective acid chlorides, and added to an excess of cold ethereal diazomethane to form the corresponding diazo ketone. In each case, the diazo ketone was isolated but not purified, before the attempted rearrangement. The presence of the —$COCHN_2$ group was shown by the evolution of nitrogen when the compound was treated with concentrated hydrochloric acid.

The diazo ketones derived from C_2F_5COOH, C_3F_7COOH and C_4F_9COOH failed to undergo the Wolff rearrangement and the diazo ketone from $C_3F_7CH_2COOH$ appeared to give only negligible amounts of $C_3F_7(CH_2)_2COOCH_3$. The diazo ketone derived from $C_3F_7(CH_2)_2COOH$ underwent the rearrangement in a normal fashion in good yield.

The acids, *n*-$C_3F_7CH_2COOH$ and $C_3F_7CH_2CH_2COOH$ were prepared from C_3F_7COOH through the following sequence of previously known reactions.

$$R_FCOOH \xrightarrow{AgOH} R_FCO_2Ag^3 \xrightarrow{I_2} R_FI^4 \xrightarrow{CH_2{=}CH_2}$$

$$R_FCH_2CH_2I^5 \xrightarrow{Mg} R_FCH_2CH_2MgI \xrightarrow{O_2}$$

$$R_FCH_2CH_2OH^6 \xrightarrow{[O]} R_FCH_2COOH^6$$

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