

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Metalation of Phenolic and Phenol Ether Systems

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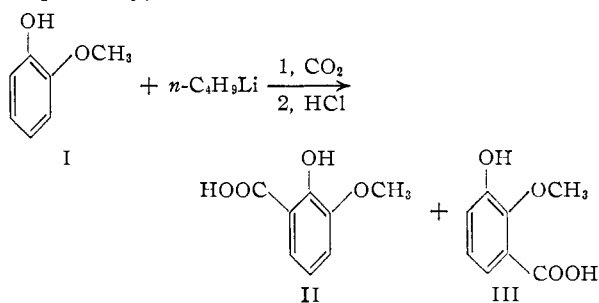
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o-Methoxyphenol and *m*-methoxyphenol were metalated with *n*-butyllithium, and, upon carbonation, were found to give a mixture of isomeric acids which were separated and identified. The directive influence of the hydroxyl *vs.* the methoxyl group is discussed. The 2-tetrahydropyranyl ethers of *m*-methoxyphenol and *p*-bromophenol were prepared and their metalation also studied.

The metalation of phenol, resorcinol and of the methyl ethers of these and other phenolic compounds¹ has been investigated under a variety of experimental conditions. The most noticeable features about these reactions are the greater activation, based on the yields of metalation products, of the ethers with respect to the corresponding phenols and, concurrently, the formation of more isomers with the metalation of free phenols. This seems to be consistent with the opinion² that in metalation reactions, which have also been termed "protophilic" substitutions,³ the substituent groups in the aromatic nuclei exert their influence through a predominantly inductive (-I) effect, resulting in an increased acidity of the ring hydrogen atoms. Consequently, a lower activation is to be expected from the negatively charged phenoxide ion, present in the reaction mixture, than from the covalent ethereal oxygen.

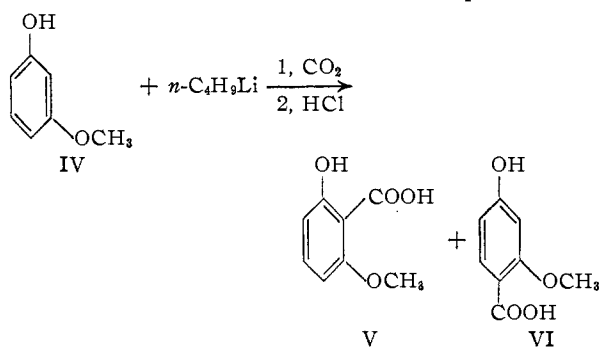
Although the metalation of substituted benzenes containing both the hydroxy and the alkoxy functions could have provided parallel information as to the relative activation of these substituents in the same molecule, apparently no such reactions have been reported. In an attempt to obtain preliminary information about such mixed systems, *o*- and *m*-methoxyphenol were allowed to react with phenyllithium and *n*-butyllithium.

When *o*-methoxyphenol was treated with phenyllithium, no metalation products were isolated. The reaction with *n*-butyllithium, followed by carbonation, produced 2-hydroxy-3-methoxy- and 2-methoxy-3-hydroxybenzoic acid (II and III, respectively) in amounts of the same order of



magnitude, but the latter predominated in a reaction run for a shorter time. *m*-Methoxyphenol (IV), treated with *n*-butyllithium under similar conditions, gave about the same over-all yield as

the *o*-isomer, but the extent of metalation in the position between the two substituents resulted in a 3:1 ratio to metalation in the other position at-



tacked, *ortho* to the methoxy group. The observed yields, however, are much lower than those reported for the corresponding methyl ethers.^{4,5} Comparison with the yields from resorcinol (catechol was not investigated) is difficult, because the pure yield was not given, but they are probably of the same order of magnitude.

These results, which may be interpreted as indicating a stronger activation toward metalation from the methoxy than the hydroxy group, are in agreement with the relative behavior of phenols and the corresponding ethers, and show that such a rule holds within the same molecule. Unfortunately, the low yields attendant on the difficulty of separation, make firm conclusions difficult.

As an alternative approach to the metalation of compounds containing free hydroxy groups, it was proposed^{6a} to resort to their etherification by means of a labile agent, easily removable after metalation had taken place, as has been attempted in the case of Grignard reactions.⁷ Some work in this direction has been done,^{6a,b} using dihydropyran as the etherifying agent, and it was found that phenols so protected give yields of metalation comparable to those obtained from the corresponding methyl ethers.

(4) H. Gilman, H. B. Willis, T. H. Cook, F. J. Webb and R. N. Meals, *THIS JOURNAL*, **62**, 667 (1940).

(5) H. Gilman, J. Swiss and L. C. Cheney, *ibid.*, **62**, 1963 (1940).

(6) (a) W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948); (b) B. Hofferth, *Iowa State Coll. J. Sci.*, **26**, 219 (1952); (c) W. E. Parham and D. M. DeLaitich, *THIS JOURNAL*, **76**, 4962 (1954); see also R. R. Whetstone, U. S. Patent 2,574,444 (1951) [*C. A.*, **46**, 5090 (1952)].

(7) (a) G. Willfang, *Ber.*, **74B**, 145 (1941); (b) M. W. Krause and J. W. Slobodin, *J. Chem. gen.*, **10** [72] 907 (1940) [*Chem. Zentr.*, **111**, II, 2898 (1940)]; (c) I. M. Heilbron, A. W. Johnson, E. R. H. Jones and A. Spinks, *J. Chem. Soc.*, 727 (1942); (d) M. Kuhn, *J. prakt. Chem.*, **156**, 103 (1940); (e) J. F. Arens and D. A. Van Dorp, *Rec. trav. chim.*, **65**, 729 (1946); (f) L. Willmann and H. Schinz, *Helv. Chim. Acta*, **32**, 2151 (1949).

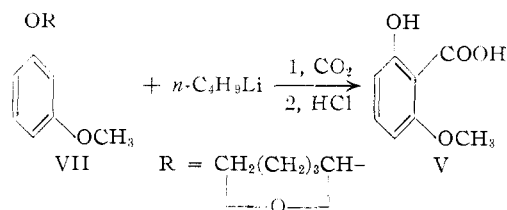
(1) H. Gilman and J. W. Morton, Jr., in Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1954, Vol. 8, p. 258.

(2) See for example L. A. Wiles, *Chem. Revs.*, **56**, 329 (1956); p. 363.

(3) D. Bryce-Smith, *J. Chem. Soc.*, 1086 (1954).

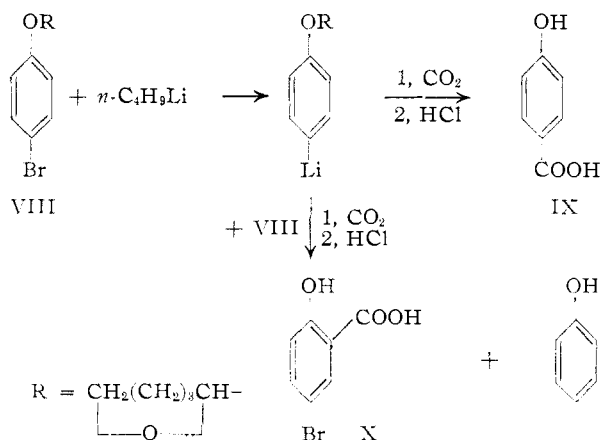
We are now reporting the reactions of two such acetals, whereby not only the position *ortho* to oxygen is much more activated than in the case of the free phenol, but also, in one case, the course of the reaction is radically changed.

The acetal of *m*-methoxyphenol (VII) was prepared and, when treated with *n*-butyllithium using



the same conditions as for the free phenol, the yield of 2-hydroxy-6-methoxybenzoic acid from carbonation and hydrolysis of the reaction mixture showed a twofold increase. Furthermore, no other isomer was isolated, in agreement with the case of resorcinol dimethyl ether.⁴

p-Bromophenol was the other etherified compound^{5a,b} studied. The reaction of this acetal (VIII) with *n*-butyllithium bore a striking resemblance to that of *p*-bromoanisole, for a comparatively high yield of 5-bromosalicylic acid (X) and none or little *p*-hydroxybenzoic acid (IX) was



obtained. The free phenol, instead, gives *p*-hydroxybenzoic acid⁸ only, by halogen-metal interconversion. In the case of *p*-bromoanisole, this unexpected reaction was proved⁹ to follow from metalation of unreacted *p*-bromoanisole by *p*-anisyllithium, produced in the halogen-metal interconversion between *n*-butyllithium and *p*-bromoanisole. Similarly we have found that, by carbonation after a short period of reaction, a greater amount of IX can be isolated, while the yield of X is very much decreased. Further proof for this mechanism was obtained when a reaction which employed one-half equivalent of *n*-butyllithium gave the same yield of X as when equimolar mixtures reacted. An increase in yield was

(8) H. Gilman, C. E. Arntzen and F. J. Webb, *J. Org. Chem.*, **10**, 374 (1945).

(9) (a) H. Gilman, W. Langham and F. W. Moore, *THIS JOURNAL*, **62**, 2327 (1940); (b) H. Gilman, W. Langham and A. L. Jacoby, *ibid.*, **61**, 106 (1939); (c) H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938); (d) G. Wittig, U. Pockels and H. Dröge, *Ber.*, **71**, 1903 (1938).

expected by the use of phenyllithium, but this was not observed to any significant degree.

All the evidence concerning metalation of tetrahydropyranyl acetals of phenols, then, shows that the so-called "protection" of hydroxy groups in metalation reactions may be interpreted in terms of an activation of the same kind that is attributed to the true etherification of hydroxyls.

Experimental¹⁰

2-Tetrahydropyranyl Ethers.—The 2-tetrahydropyranyl ethers of *m*-methoxyphenol and *p*-bromophenol were prepared essentially by the method of Parham and co-workers,^{6a,c} but with the following modifications: (1) as catalyst, a 2% aliquot of dihydropyran saturated with hydrogen chloride was used, (2) the reactions were run for 3–4 hours in a dry, oxygen-free nitrogen atmosphere and (3) the products were distilled over sodium hydroxide pellets.

p-Bromophenyl 2-tetrahydropyranyl ether was obtained in yields of 89.5–91%, m.p. 58–59° (reported m.p. 57–57.5°^{6a} and 56–57°^{6b}).

m-Methoxyphenyl 2-tetrahydropyranyl ether was obtained in 74–75% yields, b.p. 108–110° (0.02 mm.), *n*_D²⁰ 1.5247, *d*₄²⁰ 1.108. The infrared analysis gave supporting information in favor of the expected structure.

Anal. Calcd. for C₁₂H₁₆O₃: C, 69.22; H, 7.76; MRD, 57.45. Found: C, 69.63; H, 7.94; MRD, 57.42.

General Metalation Procedure.—Unless otherwise stated, all metalations were carried out by adding the organolithium reagent to a stirred ethereal solution (anhydrous) of phenol or acetal, in an atmosphere of dry, oxygen-free nitrogen. At the end of the reaction, the mixture was carbonated by pouring it jet-wise into a slurry of Dry Ice and ether, and after evaporation of all the solid carbon dioxide, hydrolyzed with 10% hydrochloric acid. The ether layer was then separated from the aqueous layer, and extracted with 8% sodium bicarbonate and 5–10% sodium hydroxide. The alkaline extracts were acidified, usually stepwise, with 10% hydrochloric acid and the acidic material collected by filtration or ether extraction, preceded by concentration, when necessary. The ethereal extracts were evaporated and the residue identified by melting point or refractive index.

***o*-Methoxyphenol. (a) Reaction with Phenyllithium.**—Three-hundredths mole (3.73 g.) of *o*-methoxyphenol (I) and 0.06 mole of phenyllithium in 90 ml. of anhydrous ether were stirred at room temperature for 28 hours. Following carbonation, 2.45 g. (33%) of benzoic acid, m.p. 123–123.5° (mixture melting point with authentic specimen not depressed), and 3.0 g. (80%) of unreacted I, *n*_D²⁰ 1.54, were obtained.

In a similar run, where the mixture was stirred at room temperature for 40 hours and then refluxed for an additional 24 hours, the only isolated product was 1.66 g. (22.7%) of benzoic acid, m.p. 122–123°. The second alkaline extract was not investigated.

(b) Reaction with *n*-Butyllithium.—Three-hundredths mole of I and 0.06 mole of *n*-butyllithium in 70 ml. of ether was stirred at room temperature for 72 hours until Color Test II¹¹ was only slightly positive, and then was hydrolyzed with 10% hydrochloric acid. From further acidification of the acid layer from the hydrolysis, there was obtained a solid melting at 146–235°, which, after recrystallization from water, gave 0.1 g. of crystals melting at 149.5–150°. This gave a blue color when treated with ferric chloride and was identified as 2-hydroxy-3-methoxybenzoic acid (II) by preparing its 5-nitro derivative,¹² m.p. 223.5–224°, and by demethylating it to 2,3-dihydroxybenzoic acid,¹³ m.p. 204–205°. Infrared analysis confirmed the structure. More precipitate was obtained by concentration of the acid mother liquor, which after recrystallization from benzene weighed 0.1 g. and melted at 150–150.2°. No color was obtained with ferric chloride, and there was a depression in the mixture melting point with II. This was identified as 2-methoxy-3-hydroxybenzoic acid (III) by demethylation to the same 2,3-dihydroxybenzoic acid, which gave no depression

(10) All melting points are uncorrected.

(11) H. Gilman and J. Swiss, *THIS JOURNAL*, **62**, 1847 (1940).

(12) P. Fritsch, *Ann.*, **301**, 354 (1898).

(13) Bayer & Co., German Patent 281,214 (Oct. 25, 1913) [*Chem. Zentr.*, **87**, I, 180 (1916)].

in the mixture melting point with the product obtained in the previous case. Infrared analysis also confirmed such a formulation.

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.79; neut. equiv., 168.14. Found: C, 56.72; H, 4.98; neut. equiv., 165.5.

The first alkaline extraction yielded 0.88 g. of material melting at 114–135°. After four recrystallizations from benzene, there was obtained 0.16 g. melting at 147.5–149.5°, which was proved to be identical to II by mixture melting point. The second alkaline extraction yielded 2.45 g. (65%) of unreacted I.

To summarize, this experiment yielded from the aqueous layer of the hydrolysis 2% of both II and III. Furthermore, after one recrystallization of the material obtained from the first alkaline extraction, there was obtained a mixture amounting to 13% of the theoretical yield (m.p. 115–130°) which, as stated above, ultimately yielded another 3.2% of fairly pure II (m.p. 147.5–149.5°); but certainly the mixture contained a considerable amount of III which escaped isolation.

A second run, where the mixture was refluxed for 22 hours, yielded 3.5% of III, m.p. 149.2–149.8°, and 54% of unreacted I. In this case, no II was isolated.

In a third experiment, run under the same conditions as the second, there was obtained an 11% yield of crude III, m.p. 130–135°, and 3.5% of a mixture of the isomers. These materials ultimately yielded 3.7% of pure III and a very small amount of II.

m-Methoxyphenol.—Three-hundredths mole of *m*-methoxyphenol (IV) and 0.06 mole of *n*-butyllithium in 65 ml. of ether were stirred at room temperature for 22 hours and then refluxed for another 48 hours. The first alkaline extraction yielded 0.66 g. (13%) of product melting at 132–134°. After recrystallization from 50% ethanol, there was obtained 0.34 g. (6.7%) of a product which gave no color with ferric chloride and melted at 134–135°. The melting point reported in the literature for 2-methoxy-6-hydroxybenzoic acid is 135^{14a} or 136–136.3^{14b}. The infrared spectrum indicated a 1,2,3-trisubstituted benzene derivative containing carboxy-, hydroxy- and methoxy- groups. The mother liquor was concentrated and further acidified, giving 0.27 g. (5.3%) of solid melting at 180° dec. After recrystallization from water, this material melted at 183.8° dec. and weighed 0.11 g. (2.2%). The reported melting point for 2-methoxy-4-hydroxybenzoic acid is 186^{15a} or 187–189^{15b}. No color was obtained with ferric chloride. The infrared spectrum indicated those three substituents to be in the 1-, 2- and 4-positions. The second alkaline extract yielded 2.2 g. (60%) of unreacted IV.

In another run where the reaction mixture was stirred at room temperature for two hours, there was isolated only 3.2 g. (85.5%) of unreacted IV.

m-Methoxyphenyl 2-Tetrahydropyranyl Ether.—The compound VII (0.03 mole) was treated with *n*-butyllithium under the same conditions as the free phenol, and from the first alkaline extract there was obtained 0.98 g. (26%) of 2-

methoxy-6-hydroxybenzoic acid (V) melting at 133–134.5°. The melting point was raised to 134–135° after one recrystallization from 50% ethanol (which yielded 0.83 g.), and gave no depression in the mixture melting point with the corresponding product from the reaction of the free phenol. No other carboxylic acid was isolated in this experiment.

p-Bromophenyl 2-Tetrahydropyranyl Ether.—A mixture of 3.10 g. (0.012 mole) of the acetal VIII and 0.015 mole of *n*-butyllithium in 23 ml. of ether was stirred at room temperature for 24 hours and then carbonated. The first alkaline extraction yielded 0.97 g. (37%) of a product melting at 165.5–167°. Recrystallization from benzene yielded 0.92 g. (35%) of pure 5-bromosalicylic acid¹⁶ which melted at 166.5–167.5°, and was identified by mixture melting point with an authentic specimen and comparison of their infrared spectra. No acidic material was obtained from the second alkaline extraction. The neutral fraction was not investigated.

Another run, where one-half equivalent of *n*-butyllithium was used under the same conditions, gave a crude yield of 38% and a pure yield of 34.7% of X.

When the reaction mixture employing 0.03 mole of both reactants was carbonated after 4 hours at room temperature and hydrolyzed with water, there was obtained 1.94 g. of material melting over the range 136–160°. Upon fractional recrystallization, this ultimately yielded 0.99 g. (15.3%) of pure 5-bromosalicylic acid and a small amount of a product melting at 203.5–207°. The latter was identified as *p*-hydroxybenzoic acid by mixture melting point with an authentic specimen and comparison of their infrared spectra. A ferric chloride test also was positive.

When a mixture containing 0.02 mole of the acetal and 0.06 mole of *n*-butyllithium was carbonated after 15 minutes of stirring at room temperature, there was obtained 1.09 g. of a two-fraction mixture, 0.86 g. of which melted over the range 95–182° and the rest over 151–159°. After repeated recrystallizations, there was obtained a final 3.6% of *p*-hydroxybenzoic acid, m.p. 207.5–211°, and 3.7% of 5-bromosalicylic acid, m.p. 157–162.5°. Furthermore, upon additional acidification of the original aqueous mother liquor from the hydrolysis, 0.38 g. of a solid melting over the range 207–218° was collected, which, after repeated recrystallizations, melted at 239–242°. Its final small amount was not identified.

In a run where an equimolar amount of phenyllithium was used, and carbonation was effected after 25 hours at room temperature, a 42.2% yield of 5-bromosalicylic acid melting at 166.5–167.5° was obtained. Recrystallization from benzene yielded 36.8% of product melting at 167.3–168°. There was no depression in the mixture melting point with an authentic specimen, and their spectra were identical.

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(14) (a) H. W. B. Clewer, S. J. Green and F. Tutin, *J. Chem. Soc.*, **107**, 837 (1915); (b) D. B. Limaye and G. R. Kelkar, *Rasayanami*, **1**, 24 (1936).

(15) (a) M. Bergmann and P. Dangschat, *Ber.*, **52**, 383 (1919); (b) M. Nierenstein, *This Journal*, **52**, 4012 (1930).

(16) It should be noted that, according to the proposed mechanism, the theoretical yield would be 50%, based on the molar amount of starting material.