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SOME ORGANOMETALLIC COMPOUNDS CONTAINING REACTIVE FUNCTIONAL GROUPS

by

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I. INTRODUCTION

Prior to the independent discovery of the halogen-metal interconversion reaction by Gilman, Langham and Jacoby[1] and by Wittig and co-workers[2], relatively few types of reactive organometallic compounds which contained a functional group were known. These compounds may be grouped into the following classes: enolates of esters and ketones, enamates, acetylenic types, metallic derivatives of pyrrole and indole, and aromatic and aliphatic types containing halogen or another carbon-metal linkage. The mode of preparation was either by the direct action of an organic halide upon metal or by the metalation reaction with other organometallic compounds or alkali amides.

The procedure, employing the direct reaction of an organic halide containing a reactive group upon the metal in a solvent, is subject to a number of well-known disadvantages. The reaction may be exceedingly slow because of the low reactivity of the halogen or because the metal becomes coated with the reaction product. In some cases, if the organometallic compound is formed, it may be as rapidly consumed in intra- and/or inter-molecular reactions. On the other hand, this method has been particularly successful with preparations of Grignard reagents

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[1] Gilman, Langham and Jacoby, _J. Am. Chem. Soc._, _61_, 106 (1939).

[2] Wittig, Pockels and Dröge, _Ber._, _71_, 1903 (1938).

from chloroaromatic bromides to give high yields of the chloroarylmagnesium bromides. Mixtures of isomeric organomagnesium halides usually result when the halogens have the same order of reactivity. A striking example of the difficulties encountered with such mixtures is the conclusion drawn by Paty and Quelet[3] that a rearrangement had taken place subsequent to carbonation of the monomagnesium derivative of 2,4-dibromoanisole. However it was shown recently by Hussey and Wilk[4] that the results of these investigators were easily interpreted when the presence of isomeric bromomagnesium derivatives was established.

The metalation reaction, generally employing *n*-butyllithium in ether, can be used with varying degrees of success with compounds containing groups which do not react beyond giving up an active hydrogen. The reaction time at ether reflux temperature is usually long, and this precludes the metalation of compounds which add the organometallic reagent or which are reduced by it. In general the yields are lower than would be obtained in a corresponding halogen-metal interconversion reaction.

The halogen-metal interconversion reaction with organolithium reagents, because of the rapidity of the reaction and the good yields obtained, was employed in the preparation of new organolithium intermediates containing one or more potentially reactive groups. This work had as its purpose the development of new organometallic compounds which

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[3] Paty, *Compt. rend.*, *214*, 910 (1942); Paty and Quelet, *Bull. soc. chim. France*, *8*, 55 (1942); *Compt. rend.*, *217*, 229 (1943); *Bull. soc. chim. France*, *11*, 505 (1944); *Compt. rend.*, *220*, 324 (1945).

[4] Hussey and Wilk, *J. Am. Chem. Soc.*, *72*, 830 (1950).

would find application in the organic chemistry of silicon, tin and lead for the introduction of water-solubilizing groups.

Of special interest, however, are those organometallic compounds which contain groups that have a high order of reactivity toward the interconverting agent and toward the newly-formed intermediate. In carrying out the objective of this work, methods for covering or protecting such groups were devised.

The halogen-metal interconversion reaction applied to polyhalogenophenols has been found to be of a complex nature, but the discovery that interconversion was followed by rapid reductive ortho-debromination made the study of such a transformation attractive. A part of this investigation was then directed toward clarification of the mechanism of this interesting side reaction.

Exploratory work on the reactions of organolithium compounds with tertiary amino- and chloro-epoxides has shown that the expected conversions to the corresponding secondary alcohols occurred in high yields. These secondary alcohols appeared to be suitable intermediates for syntheses of alkamine ethers of physiological interest, in particular, histamine antagonists.

In the last decade, considerable interest in compounds which possess antihistamine activity has been shown by the large number of papers published since Bovet and Staub[5] reported that certain basically-substituted phenolic ethers exert a protective action in histamine

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[5] Bovet and Staub, Compt. rend. soc. biol., 124, 547 (1937).

intoxication. The striking success of Benadryl[6,7] (β-dimethylaminoethyl benzohydryl ether) in giving relief from urticaria, hayfever and asthma has added impetus to investigation of what changes (isosteric and other) in this basic structure could be made in order to increase the effectiveness of this type and minimize untoward effects. Therefore, to add to the knowledge concerning the relationship of structure to physiological action, two new series of alkamine ethers were prepared for pharmacological testing as possible antihistamine agents.

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[6] Rieveschl, U. S. Patent 2,421,714, June 3, 1947 [C.A., 41, 5550 (1947)].

[7] Loew, Kaiser and Moore, J. Pharmacol. Exptl. Therap., 83, 120 (1945).

II. HISTORICAL

The purpose of the literature survey to be discussed in the following pages of this section was to consider all the organometallic compounds of magnesium, lithium, sodium and potassium which contain a reactive functional group in the molecule. As a practical limitation to the scope of this review the following types were omitted from the discussion and from Table I: acetylides, metal addition compounds from olefins, and organometallic types containing only methoxy and/or tertiary amino groups. Table I containing approximately two hundred compounds is a careful compilation classified by the functional group present.

Early attempts at the preparation of organomagnesium compounds containing functional groups were generally carried out by the action of the organic halide upon magnesium in ether. Sachs and Sachs[8] were unable by the ordinary procedures to effect a reaction between 2-bromoquinoline and magnesium. However, Grignard reagents which contained a halogen or a second -MgX were readily prepared by the action of the dihalide upon magnesium. Grignard and Vignon[9] were able to prepare pentamethylenedimagnesium bromide, and later v. Braun and Sobecki[10] extended the application of the Grignard reaction to the preparation of tetramethylene- and heptamethylene-dimagnesium bromides as well as

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[8] Sachs and Sachs, Ber., 37, 3088 (1904).

[9] Grignard and Vignon, Compt. rend., 144, 1358 (1907).

[10] v. Braun and Sobecki, Ber., 44, 1918 (1911).

decamethylenedimagnesium iodide. Hydrolysis and carbonation were used to form derivatives of the organomagnesium compounds. Later workers[11] employed decamethylenedimagnesium bromide in reaction with methyl formate to form the polymeric substance $[-(CH_2)_{10}CHOH-]_5$.

Votocek and Köhler[12] investigated the reaction between certain polyhalogenobenzenes and magnesium. These authors found that o-bromoiodobenzene, m-diiodobenzene and 2,4-dichloroiodobenzene react with magnesium and that 2,4-dichlorobromobenzene and 1,2,4-tribromobenzene do not react. The products of the reaction between p-diiodobenzene and magnesium followed by hydrolysis were found to be benzene, biphenyl and p-iodobiphenyl. Thomas[13a] and Bruhat and Thomas[13b] found that the three diiodobenzenes and 2,5-diiodothiophene would dissolve 80-85% of the theoretical amount of magnesium when treated with two gram atoms of the metal. Carbonation produced a very low yield of the meta acid and a fair yield of the para acid but with o-phenylenedimagnesium iodide only benzoic acid was formed. Benzonitrile, however, reacted in the expected fashion with o-phenylenedimagnesium iodide.

p-Dibromobenzene and excess magnesium gave a 70%[14] yield of p-bromophenylmagnesium bromide and a 12.8% yield of p-phenylenedimagnesium bromide under ordinary conditions. Grignard[15] by use of an

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[11] Carothers and Hill, J. Am. Chem. Soc., 54, 1588 (1932).

[12] Votocek and Köhler, Ber., 47, 1219 (1914).

[13] (a) Thomas, Compt. rend., 181, 218 (1925); (b) Bruhat and Thomas, ibid., 183, 297 (1926).

[14] Quelet, Bull. soc. chim. France, 41, 933 (1927).

[15] Grignard, Compt. rend., 198, 625 (1934).

entrainment technique was able to obtain a 40% yield of p-phenylenedimagnesium bromide. This procedure was found to be particularly successful with difficultly soluble halides which reacted only slightly with magnesium. However, it was found that for the preparation of 1,4-dideuterobenzene[16] the two step process involving the hydrolysis of p-bromophenylmagnesium bromide with deuterium oxide, the preparation of p-deuterophenylmagnesium bromide and the subsequent hydrolysis with deuterium oxide gave a much more pure product than was obtained by the single step procedure.

In the furan series Gilman and Hewlett[17] were able to effect the smooth conversion of 2,5-diiodofuran to 5-iodo-2-furylmagnesium iodide. In a like manner Bachman and Heisey[18] prepared in the thiophene series 5-bromo- and 5-chloro-2-thienylmagnesium bromides and 3,4,5-trichloro-2-thienylmagnesium chloride. These organic dihalides which contained like as well as unlike halogens gave good yields of the monomagnesium derivatives.

The effect of the position of the second halogen (whether in the same or different ring) is strikingly illustrated by reactions of the dibromonaphthalenes[19] with magnesium. 1,4-Dibromonaphthalene upon reaction with two gram atoms of magnesium per mole gave a mixture of 35-50% naphthalene and 25-31% of 1-bromonaphthalene subsequent to

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[16] Weldon and Wilson, J. Chem. Soc., 235 (1946).

[17] Gilman and Hewlett, Rec. trav. chim., 51, 93 (1932).

[18] Bachman and Heisey, J. Am. Chem. Soc., 70, 2378 (1948).

[19] Salkind, Ber., 67, 1031 (1934).

hydrolysis. If one gram atom were used and the mixture carbonated, a 77% yield of 4-bromo-1-naphthoic acid was obtained. However, when 1,5-dibromonaphthalene was used, reaction with two gram atoms of magnesium followed by carbonation gave a quantitative yield of 1,5-naphthalenedicarboxylic acid. With one gram atom of magnesium only the dimagnesium derivative was obtained. Introduction of a second -MgX group into the same ring was shown to be more difficult than attachment of the group to another ring in the molecule.

It is also interesting to notice that 1,6-dibromonaphthalene[20] when reacted with one gram atom of magnesium per mole gave high yields of 1-bromonaphthalene, 5-bromo-2-naphthol, and 5-bromo-2-naphthoic acid subsequent to hydrolysis, oxidation and carbonation, respectively. Later workers[21] also carrying out syntheses in the phenanthrene series reacted 5-bromo-2-naphthylmagnesium bromide with acetone to obtain 1-bromo-6-isopropenylnaphthalene.

In the biphenyl series Gibert[22] has shown that satisfactory yields of 4,4'-biphenylenedimagnesium bromide could be obtained by Grignard's entrainment procedure[15] or by use of the binary system $Mg-MgI_2$. The latter procedure was claimed to be more economical and at the same time to diminish side reactions. Other workers[23] found Gibert's application of the $Mg-MgI_2$ binary system to be satisfactory for the preparation

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[20] Fieser and Riegel, J. Am. Chem. Soc., 59, 2564 (1937).

[21] Short and Wang, J. Chem. Soc., 991 (1950).

[22] Gibert, Compt. rend., 205, 445 (1937).

[23] Champetier and Smarzewska, ibid., 220, 891 (1945).

of *p*-phenylenedimagnesium bromide as well as for *p*-biphenylenedimagnesium bromide. 3,3'-Dibromobiphenyl[24] has been converted in good yields to the mono- and di-magnesium derivatives by use of a catalytic amount of ethylmagnesium bromide. In a recent patent[25] a method was described for the preparation of dibasic acids of the benzene, biphenyl, naphthalene and polynuclear hydrocarbon series by carbonation of the respective Grignard reagents prepared by a special procedure from the aromatic dichlorides.

Reaction between 9,10-dibromoanthracene[26] and lithium in a sealed flask at 30-60° gave only the 10-bromo-9-anthracenecarboxylic acid subsequent to carbonation. This again illustrates the low reactivity of the second halogen in the same ring toward attack by the metal.

The preparation of organometallic compounds by the direct method from dihalides in which the halogens have different degrees of reactivity has been very successful in that the yields are generally high. The best examples of this type are *p*-chlorophenylmagnesium bromide[27],

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[24] Snyder, Weaver and Marshall, *J. Am. Chem. Soc.*, *71*, 289 (1949).

[25] Gluesenkamp, U. S. Patent 2,508,022, May 16, 1950 [*C.A.*, *44*, 7351 (1950)].

[26] Mikhailov, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.* (Bull. acad. sci. U.R.S.S., Classe sci. chim.) 420 (1948) [*C.A.*, *43*, 208 (1949)].

[27] (a) Gilman, Yablunky and Svigoon, *J. Am. Chem. Soc.*, *61*, 1170 (1939); (b) Burkhard, *ibid.*, *68*, 2103 (1946); (c) Bergkvist, *Kgl. Fysiograf. Sällskap. Lund. Förh.*, *18*, No. 2, 18 (1948) [*C.A.*, *44*, 1446 (1950)]; (d) British Patent 626,515, July 15, 1949 [*C.A.*, *44*, 2555 (1950)]; (e) Pepper and Kulka, *J. Am. Chem. Soc.*, *72*, 1417 (1950) and (f) Bodroux, *Compt. rend.*, *137*, 710 (1903).

p-chlorobenzylmagnesium chloride[28], m-trifluoromethylphenylmagnesium bromide[29], 6-chloro-1-naphthylmagnesium bromide[20] and 3,3,3-trifluoropropylmagnesium chloride[30]. In connection with the preparation of organometallic compounds from bromo or iodo polyfluorinated alkanes, it was found that, if halogen were on the carbon atom adjacent to the one forming the C-M linkage, decomposition to the metal salt and unsaturated molecule took place. This was the experience of Henne[31] with 2,2-difluoroethyl iodide and bromide with sodium, potassium or magnesium in ether. Gilman and Jones[32] found that 2,2,2-trifluoroethyl iodide behaved in a similar fashion with magnesium to give 1,1-difluoroethylene and magnesium salts. These previously reported difficulties in the preparation of organometallic compounds from 1,2-dihalides did not deter Brice, Pearlson and Simons[33] from reporting that they had prepared a Grignard reagent from 1-bromoheptafluoropropane. Others[30] have not been able to duplicate this result. The presence of heptafluoropropane subsequent to hydrolysis may be due to the existence of intermediate radicals which react with the solvent rather than due to

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[28] Fuson and Porter, J. Am. Chem. Soc., 70, 895 (1948).

[29] (a) Bradsher and Bond, ibid., 71, 2659 (1949); (b) Markarian, U.S. Patent 2,477,543, July 29, 1949 /C.A., 44, 3026 (1950)/; (c) Szmant, Anzenberger and Hartle, J. Am. Chem. Soc., 72, 1419 (1950) and (d) O'Donnell, Iowa State Coll. J. Sci., 20, 34 (1945) /C.A., 40, 4689 (1946)/.

[30] McBee and Truchan, J. Am. Chem. Soc., 70, 2910 (1948).

[31] Henne, ibid., 60, 2275 (1938).

[32] Gilman and Jones, ibid., 65, 2037 (1943).

[33] Brice, Pearlson and Simons, ibid., 68, 968 (1946).

hydrolysis of a Grignard reagent. This was the explanation offered by Emeléus and Haszeldine[34], for the presence of pentafluoroethane subsequent to hydrolysis of the reaction mixture from iodopentafluoroethane and magnesium. These authors found also that iodotrifluoromethane did not react with magnesium, lithium or alloys of sodium.

In connection with organometallic compounds from 1,2-dihalides, Wittig and Harborth[35] have shown that with phenyllithium and certain 1,2-dibromides bromine-lithium interconversion took place to give a compound of the type $\mathrm{Br\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}Li}$ which promptly decomposed to form an unsaturated molecule and lithium bromide. These authors pointed out that halides or ethers of the structures $\mathrm{X\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}Li}$ and $\mathrm{X\overset{|}{C}=\overset{|}{C}Li}$ were unstable toward decomposition to the salt. These facts preclude the preparation of similar types by the direct method, metalation, halogen-metal interconversion or any other procedure used for the production of organometallic compounds.

Protection of reactive functional groups, for example carbonyl, in organometallic compounds by the formation of acetals[36] has not been successful according to the available literature sources. Acetals have the particular merits, however, of being stable to basic reagents[37]

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[34] Emeléus and Haszeldine, J. Chem. Soc., 2948 (1949).

[35] Wittig and Harborth, Ber., 77, 306 (1944).

[36] Chemical Abstracts uses this name for 1,1-dialkoxyalkanes whether acetals or ketals. See C.A., 39, 5924 (1945).

[37] (a) Chichibabin and Jelgasin, Ber., 47, 1843 (1914); (b) Späth, Ber., 47, 766 (1914); Monatsh., 35, 319, 463 (1914); ibid., 36, 1 (1915); (c) Levina, Kulikov and Parshikov, J. Gen. Chem. (U.S.S.R.), 11, 567 (1941) [C.A., 35, 6931 (1941)].

under the usual conditions in Grignard reactions and easily hydrolyzed by dilute acids. This would make such a group ideal for the protection of the carbonyl function during the reaction and for the removal under mild conditions subsequent to completion of the preparation. A 50% acetic acid solution of the acetal heated several hours over a steam bath was found to effect hydrolysis in certain cases[38]. These mild conditions perhaps would permit the regeneration of an aldehyde or ketone grouping in organolead compounds which are quite sensitive toward cleavage by acids.

The reasons for the failure of these acetals to react satisfactorily with magnesium are manifold. Willfang[39] prepared a series of cyclic acetals from aldehydes and ketones by use of epichlorohydrin and epibromohydrin and an acid catalyst. He stated that benzophenone 3-chloropropylene acetal, chloral 3-bromopropylene acetal and 3-pentanone 3-bromopropylene acetal were stable toward magnesium. It is possible that in these cases the acetals contained traces of the carbonyl compounds and the magnesium became coated. Krause and Slobodin[40] claimed to have treated β-ionone and bromoacetal in ether with magnesium to obtain the expected Grignard addition. It seems unlikely that the reaction with magnesium would proceed as indicated, since other workers[41] did not obtain the expected products when

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[38] Fieser, Fields and Lieberman, J. Biol. Chem., 156, 191 (1944).

[39] Willfang, Ber., 74B, 145 (1941).

[40] Krause and Slobodin, J. Chim. gén., 10, (72) 907 (1940) [Chem. Zentr., 111, II 2898 (1940)].

[41] Heilbron, Johnson, Jones and Spinks, J. Chem. Soc., 727 (1942).

lithium was used in place of magnesium. Kuhn[42] who prepared a large number of cyclic acetals of ketones stated that pure phenacyl bromide ethylene acetal reacted readily with magnesium to form a Grignard derivative. He was more correct in a footnote in which he suggested that a cyclic acetal of p-bromoacetophenone would have application in numerous syntheses. However, acetals of this type should give a reaction with magnesium, but the normal Grignard reagent would not be expected on the basis of earlier work with which these authors were not familiar.

Freundler and Ledru[43] as early as 1905 studied the reaction between magnesium and bromoacetal and found that a violent reaction took place at 110-115° to give ethyl vinyl ether as the organic product. These authors formulated the reaction as follows:

$$2BrCH_2CH(OC_2H_5)_2 + 2Mg \xrightarrow{110-115^\circ} 2CH_2{=}CHOC_2H_5 + MgBr_2 + Mg(OC_2H_5)_2$$

Work by Wittig and Harborth[35] showed that the type reaction formulated below occurred with lithium derivatives of ethers having the general formula $RO\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}Li$.

$$RO-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-M \longrightarrow ROM + \overset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}}$$

If this formulation holds then the expected products from Kuhn's

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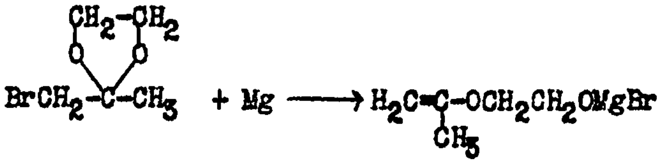
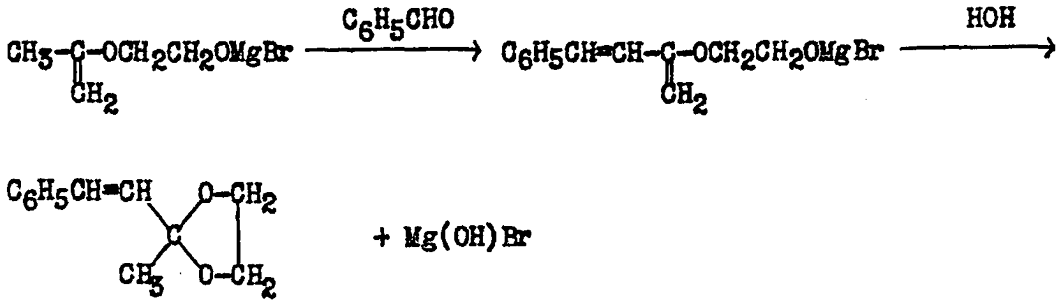
[42] Kuhn, J. prakt. Chem., 156, 103 (1940).

[43] Freundler and Ledru, Compt. rend., 140, 795 (1905).

bromoacetone ethylene acetal and magnesium would be the following:



This bromomagnesium salt of the glycol monoether of acetone enol would not be expected to give Grignard addition products to ketones. Arens and van Dorp[44] actually found this to be the case and the ketones were recovered unchanged. With benzaldehyde on the other hand, the same features as in normal Grignard condensations can be observed, and the acetal of benzalacetone and free benzalacetone can be obtained. These products were formed by condensation of the aldehyde with enolized acetone.



The Grignard reaction of the magnesium derivative of bromoacetaldehyde dimethyl acetal[40] with β-ionone could not be repeated. The observed reactions were probably due to the formation of methyl vinyl ether.

Willimann and Schinz[45] recently prepared the magnesium derivative of 1-bromo-3-butanone ethylene acetal and reacted this substance in ether with acetone. The product, however, was a complex mixture which

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[44] Arens and van Dorp, Rec. trav. chim., 65, 729 (1946).

[45] Willimann and Schinz, Helv. Chim. Acta, 32, 2151 (1949).

decomposed upon distillation. It is possible that the Grignard reagent caused enolization of part of the acetone which promptly condensed with more acetone to give products which would dehydrate during distillation.

There have been a few instances in which organometallic compounds have been prepared from organic halides containing in the molecule an active hydrogen or an azomethylene group. Spencer and Stokes[46] were able to prepare m-aminophenylmagnesium bromide (90%), p-hydroxyphenylmagnesium bromide (40-50%) and o-aminophenylmagnesium chloride (as halogenomagnesium salts) as well as organomagnesium derivatives from 1-bromonaphthalene, bromoacenaphthene, iodobenzene, bromobenzene, p-iodotoluene and o-bromotoluene by the direct action of magnesium on the hot aromatic halide. The respective Grignard reagents were identified through the hydrolysis products. A preparation of phenylmagnesium iodide was dissolved in ether and treated with Dry Ice to obtain a low yield of benzoic acid. It is interesting that halogenated aromatic acids lost carbon dioxide under the conditions of the reaction and that halogen-substituted nitro compounds were charred. In one experiment with the nitro compounds the heat of reaction caused the glass tube to soften. Tribromophenol also reacted violently with magnesium to give products which contained less bromine than the starting material. The authors were not able to moderate this latter reaction. The direct action of magnesium upon these aryl halides appeared to be a satisfactory way to remove an aromatic halogen.

The failure of 2-bromoquinoline to form a Grignard reagent has

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[46] Spencer and Stokes, J. Chem. Soc., 93, 70 (1908).

already been mentioned[8]. In more recent work Harris[47] was able to react 3-bromo-, 3,5-dibromo-, and 2-iodo-pyridines with magnesium to obtain an intermediate organometallic compound which changed to a tarry mass. By use of ethyl bromide as an auxiliary reagent in amounts equal to 0.25 - 1.00 mole per mole of 2-bromopyridine, it was possible to obtain yields of 2-pyridylmagnesium bromide up to 55%[48]. It was suggested[49] that a halogen-metal exchange reaction may account for the action of ethyl bromide in promoting the formation of the Grignard reagent. Actually such an interconversion reaction was found to take place, but only low yields were obtained. Therefore, the halogen-metal interconversion reaction can only be responsible to a very small extent for the good yields obtained. Proost and Wibaut[50] in a subsequent paper reported the preparation of 2,6-pyridinedimagnesium bromide with the aid of ethyl bromide.

The highly-substituted 3,4,6-triphenyl-2-bromopyridine reacted very slowly with lithium suspended in ether to give after several days at room temperature 20-25% of 3,4,6-triphenylpyridine subsequent to hydrolysis[51]. It was shown by Gilman and Melstrom[52] that by use of

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[47] Harris, Iowa State Coll. J. Sci., 6, 425 (1932) /̲C.A., 27, 279 (1933)̲7.

[48] Overhoff and Proost, Rec. trav. chim., 57, 179 (1938).

[49] Urion, Compt. rend., 198, 1244 (1934).

[50] Proost and Wibaut, Rec. trav. chim., 59, 971 (1940).

[51] Allen and Frame, J. Am. Chem. Soc., 62, 1301 (1940).

[52] Gilman and Melstrom, ibid., 68, 103 (1946).

n-butyllithium at -35° for ten minutes this organolithium compound could be prepared in at least 67% yield as determined by carbonation.

The metalation reaction has provided a large number of very useful synthetic intermediates containing the azomethylene linkage. This group is sometimes given the term "enamates" since each contains the grouping I which bears a formal relationship to the enolate

$-N=\overset{|}{C}-CH_2M$ [I]

$O=\overset{|}{C}-CH_2M$ [II]

structure II in which the oxygen atom is replaced by nitrogen. Metalation of 2-picoline, quinaldine and 9-methylacridine has been carried out with phenyllithium by Ziegler and Zeiser[53] who were able to employ these intermediate lithium derivatives as true organometallic compounds. Picolyllithium has become a very useful reagent as may be judged by the large numbers of synthetic applications described in numerous papers[54]. It is interesting in connection with syntheses with picolyllithium and picolylmagnesium bromide and iodide that unlike their structurally analogous compounds, benzyllithium and benzylmagnesium chloride, no rearranged products were formed during reaction with acetyl chloride and ethylene oxide[54h].

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[53] Ziegler and Zeiser, Ann., 485, 174 (1931).

[54] Some selected references are: (a) Bergmann and Rosenthal, J. prakt. Chem., 135, 267 (1932); (b) Walter, Org. Syntheses, 23, 83 (1943); (c) Kloppenburg and Wibaut, Rec. trav. chim., 65, 393 (1946); (d) Burger and Ullyot, J. Org. Chem., 12, 342 (1947); (e) Edwards and Teague, J. Am. Chem. Soc., 71, 3548 (1949); (f) Wibaut and de Jong, Rec. trav. chim., 68, 485 (1949); (g) Schofield, J. Chem. Soc., 2408 (1949) and (h) Gilman and Towle, Rec. trav. chim., 69, 428 (1950).

Picolyllithium and a large group of other enamates[55] have been prepared by metalation with alkali amides. Courtot and Tchelitcheff[55c] prepared 2-benzothiazolylmethyl-sodium and -lithium by the action of sodamide and phenyllithium, respectively, upon 2-methylbenzothiazole. These reagents were coupled with certain alkyl halides to give the expected products. Reaction of 2-benzothiazolylmethylsodium with p-nitrobenzyl chloride, however, resulted in the formation of 2-(p-nitrophenyl)-benzothiazole and 2-(p-aminophenyl)-benzothiazole in unspecified yields. This is indeed an unusual reaction because (1) a nitro-containing product was isolated and (2) two carbon atoms are missing from the combined molecules. Further studies should be carried out to confirm these observations and to determine whether the enamates may be useful synthetic intermediates in reactions with compounds containing nitro groups. More recently[55d] 2-benzothiazolylmethyllithium was used to prepare some heterocyclic fatty acids in connection with antituberculous studies.

The lithium derivatives of 4-picoline and lepidine are actually vinylogs of the enamates and properly belong to the same class. Interest in compounds affecting the growth of microorganisms led Prijs, Lutz and Erlenmeyer[56] to prepare some pyridine acetic acids. Phenyllithium was added to 4-picoline to give, subsequent to carbonation,

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[55] (a) Bergstrom, J. Am. Chem. Soc., 53, 3027, 4065 (1931); (b) Chichibabin, Bull. soc. chim. France, 3, 1607 (1936); (c) Courtot and Tchelitcheff, Compt. rend., 217, 231 (1943) and (d) Graef, Fredericksen and Burger, J. Org. Chem., 11, 257 (1946).

[56] Prijs, Lutz and Erlenmeyer, Helv. Chim. Acta, 31, 571 (1948).

2-phenyl-4-pyridylacetic acid. Gilman and Broadbent[57] carried out a similar synthesis using n-butyllithium and 4-picoline and obtained in addition to 2-n-butyl-4-methylpyridine a few milligrams of an unidentified acid subsequent to carbonation. It appears likely that this unknown acid may be 2-n-butyl-4-pyridylacetic acid.

The enolates of esters and ketones have found considerable use in organic synthesis since some types act like true organometallic compounds. These enolates may be prepared by direct action of α-haloesters or α-haloketones upon the metal in ether or by metalation at the α-carbon. Ethyl bromoacetate was reacted with magnesium to form the intermediate enolate which in turn was reacted with methyl bromoacetate to give a 20% yield of ethyl 4-bromoacetoacetate[58a]. The bromomagnesium enolate from ethyl bromoacetate was reacted in a similar fashion with 2-cyclohexyl cyclohexanone[58b] to give the expected product of addition at the carbonyl group. 2-Chloromagnesium 3-butanone[59] was prepared from 3-chloro-2-butanone and magnesium, and the intermediate was reacted with citral to give a 40% yield of the corresponding carbinol.

The bromomagnesium enolate[60] of the highly-hindered ketone, acetomesitylene, unlike enolates of other ketones, combined with carbon

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[57] Gilman and Broadbent, J. Am. Chem. Soc., 70, 2809 (1948).

[58] (a) Rottinger and Wenzel, Monatsh., 34, 1867 (1914) and (b) Winternitz, Mousseron and Trebillon, Bull. soc. chim. France, 16, 715 (1949).

[59] Beets, Rec. trav. chim., 69, 307 (1950).

[60] Kohler and Baltzly, J. Am. Chem. Soc., 54, 4015 (1932).

dioxide to form a carbonate which lost carbon dioxide and regenerated acetomesitylene when it was acidified. It also reacted with acetyl chloride, benzoyl chloride and ethyl chlorocarbonate to give the diacyl derivatives. A quantitative study of the reaction between acetomesitylene and organomagnesium compounds was reported by Kohler, Fuson and Stone[61]. These authors found that acetomesitylene did not add methylmagnesium iodide because of steric hindrance but did cause the liberation of methane equivalent to one active hydrogen. Gilman and Jones[62] found that reaction with methyllithium caused the liberation of 97% of the theoretical amount of methane assuming one active hydrogen. These authors also reacted acetomesitylene with phenylmagnesium bromide, phenyllithium and phenylsodium to give good recovery of acetomesitylene subsequent to hydrolysis. Each of the enolates was found to give a color test with Michler's ketone[63].

The direct action of α-bromoacetomesitylene has been used to prepare the bromomagnesium enolate[64], but metalation[61,62] of acetomesitylene with a Grignard reagent gave higher yields. Fuson and coworkers[65] have extended the usefulness of the reagent by showing that it would react with acid chlorides, esters, carbon dioxide, aldehydes and ketones. The product in each case was that predicted

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[61] Kohler, Fuson and Stone, J. Am. Chem. Soc., 49, 3181 (1927).

[62] Gilman and Jones, ibid., 63, 1162 (1941).

[63] Gilman and Schulze, ibid., 47, 2002 (1925).

[64] Fisher, ibid., 57, 381 (1935).

[65] (a) Fuson, Fugate and Fisher, ibid., 61, 2362 (1939) and (b) Fuson and McKeever, ibid., 62, 999 (1940).

by the formula, 2,4,6-$(CH_3)_3C_6H_2COCH_2MgBr$. Other enolates[66] of hindered ketones have been studied but few were found which would give exclusively C-acylation.

Pyrrylmagnesium halides and indolylmagnesium halides are related to the enolates by virtue of the fact that the reactions of the pyrrole anion may lead to N- or C-substitution depending upon the nature of the reactants[67]. In early work by Oddo[68] it was shown that the bromomagnesium derivative of pyrrole reacted with carbon dioxide in the presence of pyridine to give pyrrole-2-carboxylic acid. Later work by other authors[69] showed that acylation in the 2-position could be carried out by reaction with esters of acetic, propionic and butyric acids. Nenitzescu[70] reported that pyrrylmagnesium halides react with Michler's ketone to give a violet color and concluded from this fact that the -MgX group was on carbon. Gilman and Heck[71] suggested that although pyrrylmagnesium halides gave Color Test I the assignment of a position in the molecule to -MgX cannot be made prior to its reaction with a miscellany of compounds.

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[66] (a) Kohler, Tishler and Potter, J. Am. Chem. Soc., 57, 2517 (1935) and (b) Fuson, Fisher, Ullyot, and Fugate, J. Org. Chem., 4, 111 (1939).

[67] Dewar, "The Electronic Theory of Organic Chemistry", Oxford University Press, London, 1949, pp. 103, 188.

[68] Oddo, Gazz., chim. ital., 39, I 649 (1911) /C.A., 5, 686 (1911)/.

[69] Chelintzev and Terentiev, Ber., 47, 2647 (1914).

[70] Nenitzescu, Bul. soc. chim. Romania, 11, 130 (1930) /C.A., 24, 2458 (1930)/.

[71] Gilman and Heck, J. Am. Chem. Soc., 52, 4949 (1930).

Metalation of compounds containing unusually acidic hydrogens has been carried out in high yields. Some examples of compounds of this type are: dibromomagnesium dimethylethinylcarbinol[72], 5-bromo-2-furylethinylmagnesium bromide[73], α-cyanobenzyllithium[74], benzothiazolylmagnesium bromide[55c], 4,5-dimethylthiazolyllithium[75] and benzothiazolyllithium[76]. The latter reagent, although it is not stable above -35°, showed a high degree of reactivity toward aldehydes, ketones, nitriles and carbon dioxide and it may be a reagent of choice for the introduction of the benzothiazole nucleus into certain physiologically active types.

The metalation reaction has an advantage over other aromatic substitution reactions with certain aromatic heterocycles because the hydrogen-metal exchange generally takes place *ortho* to the hetero atom, a position not available through electrophilic reagents. Typical examples of these highly specific reactions are the metalations of carbazole[77], phenothiazine[78] and dibenzofuran[79,80]. A second

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[72] Newman, Fones and Booth, *J. Am. Chem. Soc.*, *67*, 1053 (1945).

[73] Gilman, Hewlett and Wright, *ibid.*, *53*, 4192 (1931).

[74] Murray, Foreman and Langham, *Science*, *106*, 277 (1947).

[75] Erne and Erlenmeyer, *Helv. Chim. Acta*, *31*, 652 (1948).

[76] Gilman and Beel, *J. Am. Chem. Soc.*, *71*, 2328 (1949).

[77] Gilman and Kirby, *J. Org. Chem.*, *1*, 149 (1936).

[78] Gilman, Shirley and Van Ess, *J. Am. Chem. Soc.*, *66*, 625 (1944).

[79] Gilman and Young, *ibid.*, *57*, 1121 (1935) and U.S. Patent 2,146,730, Feb. 14, 1939 [*C.A.*, *33*, 3816 (1939)].

[80] Gilman, Moore and Baine, *J. Am. Chem. Soc.*, *63*, 2479 (1941).

characteristic of the metalation reaction is that heteronuclear[79,80] metalation generally occurs in preference to homonuclear metalation[81]. Invariably a nucleus having a negative substituent has been found to be metalated in preference to a nucleus without a substituent. Langham, Brewster and Gilman[82] employed n-butyllithium and phenyllithium to metalate p-iodo-, p-bromo- and p-chloro-diphenyl ethers and found that in each case hydrogen-metal interconversion had occurred ortho to the ether linkage in the nucleus holding the halogen. Methyllithium gave the same result when it was used on p-bromo- and p-chloro-diphenyl ethers. The metalation of 2-bromodibenzofuran with n-butyllithium, however, was shown to be a two-stage process[83,84] involving an intermediate halogen-metal interconversion reaction followed by metalation of the unreacted 2-bromodibenzofuran to give 2-bromo-4-dibenzofuryllithium. When 2,8-dibromodibenzofuran[85] was reacted with n-butyllithium only 2,8-dibenzofurandicarboxylic acid was isolated subsequent to carbonation.

It has been shown that metalation in the ortho position is a reaction not only of ethers but also of the corresponding phenols. In the dibenzofuran series where isomeric metalation products are possible, the phenols appear to form fewer isomers[86].

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[81] However see Gilman and Stuckwisch, J. Am. Chem. Soc., 65, 1729 (1943) who reported the homonuclear metalation of 9-phenylcarbazole.

[82] Langham, Brewster and Gilman, ibid., 63, 545 (1941).

[83] Gilman, Cheney and Willis, ibid., 61, 951 (1939).

[84] Gilman, Langham and Willis, ibid., 62, 346 (1940).

[85] Gilman, Willis and Swislowsky, ibid., 61, 1371 (1939).

[86] Gilman, Willis, Cook, Webb and Meals, ibid., 62, 667 (1940).

The mechanism[87] of the metalation reaction may be most satisfactorily considered a nucleophilic attack on hydrogen. In compounds having relatively acidic hydrogen, e.g. triphenylmethane, fluorene, diphenylmethane, phenylacetylene etc., the reaction may be described as a weak acid transferring proton to the more strongly basic anion of the organometallic ion-pair. The fact that β-chlorostyrene[88,89] when reacted with phenyllithium yielded phenylacetylene may be interpreted as a metalation followed by elimination of lithium chloride. The metalation reaction, however, need not be thought entirely due to the action of a carbanion upon hydrogen. Morton[90] chooses to take the opposite view that the cation is the reactive portion of the ion-pair and that electrophilic attack on carbon initiated by the metal is followed by removal of proton with the aid of the basic anion. While in the case of mercuration this mechanism may be the correct one, there are many cases where metalation does not occur at positions that would be predicted on the basis of initial electrophilic attack. Generally, by use of _n_-butyllithium on substances containing hetero atoms in a ring, or attached to a ring, hydrogen-metal exchange is effected _ortho_ to the hetero atom. Some exceptions to this observation are known but steric factors may be responsible for these seemingly

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[87] Morton, Organic Chemistry Seminar, Iowa State College, 1950.

[88] Gilman, Langham and Moore, _J. Am. Chem. Soc._, _62_, 2327 (1940).

[89] Wittig and Witt, _Ber._, _74_, 1474 (1941).

[90] Morton, _Chem. Revs._, _35_, 1 (1944).

anomalous results[91,92]. The hydrogen replaced is not necessarily the most acidic one, and in these cases it seems probable that there is an initial coordination of the metal end of the organometallic dipole with the unshared electrons on the hetero atom or on the substituent group followed by removal of an ortho hydrogen by the anion[87]. The operation of the coordination step[93] of the mechanism would be expected to aid the reaction by increasing the polarization of the carbon-metal bond of the metalating agent and by augmenting the inductive effect of the electron attracting substituent. The initial coordination may aid the reaction by counteracting the expected decrease in the acidity of the ortho and para hydrogens due to resonance of the unshared electron pairs with the aromatic ring. The relative degrees of activation of ortho hydrogen by certain substituent groups and hetero atoms in aromatic systems may be shown by the following approximate relationships: $F > Cl$; $F > -OCH_3 > -CF_3 > H$; $F > -N(CH_3)_2$ and $O > S > N$. It is of interest to observe that groups which direct ortho - para in nitration, sulfonation, halogenation, mercuration and the Friedel-Crafts reaction do the same in the metalation reaction with n-butyllithium and other reagents of this type. Roberts and Curtin[93] found

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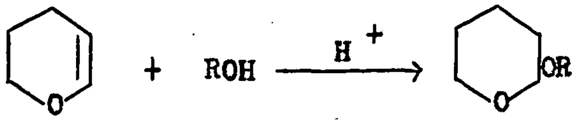
[91] Triphenyl-amine, -phosphine and -arsine were found to metalate in the meta positions. See (a) Gilman and Brown, J. Am. Chem. Soc., 62, 3208 (1940); (b) Gilman and Stuckwisch, ibid., 63, 3532 (1941) and (c) Gilman and Brown, ibid., 67, 824 (1945).

[92] 9-Hydroxy- and 9-methoxy-phenanthrene upon reaction with n-butyllithium followed by carbonation gave 9-hydroxy- and 9-methoxy-x-phenanthrenecarboxylic acids. See Gilman and Cook, ibid., 62, 2813 (1940).

[93] Roberts and Curtin, ibid., 68, 1658 (1946).

that metalation of benzotrifluoride, which contains the meta-directing group $-CF_3$, gave, subsequent to carbonation, 48% of acid which was composed of 83% o-, 16% m- and <1% p-trifluoromethylbenzoic acids. This work was interesting and significant because it did lead to the concept of initial coordination followed by nucleophilic attack on hydrogen. It also was the first metalation reaction to be carried out on a compound containing a meta-directing group. In general, reaction of such groups with the usual metalating agents occurred more rapidly than nuclear metalation.

The direct metalation of simple alcohols and amines[94] and of certain phenols[95] by n-butyllithium followed by carbonation gave yields of acids which on the whole were quite low and unsatisfactory for synthetic purposes. Parham and Anderson[96] recognized the limitations of metalation of compounds containing active hydrogens, and for their studies with phenol, catechol, resorcinol and hydroquinone they converted these substances first to the acetals. The reagent chosen was dihydropyran which had been used previously[97,98] to prepare 2-tetrahydropyranyl ethers of aliphatic alcohols and phenol. The following equation represents the formation of the acetal.



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[94] Gilman, Brown, Webb and Spatz, J. Am. Chem. Soc., 62, 977 (1940).

[95] Gilman, Arntzen, and Webb, J. Org. Chem., 10, 374 (1945).

[96] Parham and Anderson, J. Am. Chem. Soc., 70, 4187 (1948).

[97] Paul, Bull. soc. chim. France, [5] 1, 971 (1934).

[98] Woods and Kramer, J. Am. Chem. Soc., 69, 2246 (1947).

These tetrahydropyranyl ethers were found to effectively cover the phenolic groups during reaction with n-butyllithium, and following carbonation of the intermediate aryllithium the acetal was readily hydrolyzed with 2 N hydrochloric acid solution. The yields of the various hydroxybenzoic acids after cleavage of the acetal were good and compared favorably with yields obtainable by use of the halogen-metal interconversion reaction.

The scope and limitations of the halogen-metal interconversion reaction have been thoroughly reviewed by Jones and Gilman[99], in a chapter for the forthcoming volume of "Organic Reactions". However, certain aspects of the reaction which have a direct bearing on the subject matter of this literature survey will be discussed.

While use of the metalation reaction has not been a successful approach to the preparation of organometallic compounds containing a variety of functional groups, the halogen-metal interconversion reaction has found wide application for this purpose. The halogen-metal interchange, with organolithium compounds in particular, is a relatively fast reaction even at low temperatures. It has made possible the preparation of organolithium compounds of pyridine and quinoline[74,100-103]

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[99] The author is grateful to Dr. Henry Gilman for making an early draft of this chapter available. See Jones and Gilman, "Organic Reactions", John Wiley and Sons, Inc., New York, N.Y., Vol. 6, 1951.

[100] Gilman and Spatz, J. Am. Chem. Soc., 62, 446 (1940).

[101] Spatz and Gilman, Proc. Iowa Acad. Sci., 47, 262 (1940) [C.A., 35, 7405 (1941)].

[102] Gilman and Spatz, J. Am. Chem. Soc., 63, 1553 (1941).

[103] Murray, Foreman and Langham, ibid., 70, 1037 (1948).

by use of moderately low reaction temperatures and short reaction periods. Actually under conditions effective for the halogen-metal interconversion reaction in a compound like 3-bromoquinoline, the parent heterocycle itself added n-butyllithium promptly to give good yields of 2-n-butylquinoline. When the interconversion was carried out at higher temperatures, secondary reactions at the azomethylene linkage took place to give tarry products.

Of especial interest was the interconversion of aromatic halides containing groups more reactive than azomethylene. Several bromo- and iodo-benzoic acids[104], N,N-diethyl-p-iodobenzenesulfonamide[104], p-bromobenzenesulfonamide[105], p-bromobenzonitrile[105] and N-(p-iodophenyl)-phthalimide[106] have been interconverted with n-butyllithium by similar modifications of the ordinary reaction conditions that were used in the pyridine and quinoline series. It will be observed, however, that the Entemann and Johnson[107] series of relative reactivities

$$-CHO > -COCH_3 > -NCO > -COF > COC_6H_5,\ COCl,\ COBr > -CO_2C_2H_5 > -C{\equiv}N$$

of functional groups has been but barely touched with respect to the introduction of reactive groups into organometallic compounds. The reasons for this are obvious. These groups because of their high reactivity toward organolithium reagents consume the interconverting

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[104] Gilman and Arntzen, J. Am. Chem. Soc., 69, 1537 (1947).

[105] Gilman and Melstrom, ibid., 70, 4177 (1948).

[106] Gilman and Stuckwisch, ibid., 71, 2933 (1949).

[107] Entemann and Johnson, ibid., 55, 2900 (1933).

reagent more rapidly than the interconversion of a bromine or an iodine atom in the same molecule can take place. Apparently some suitable protection must be provided for the functional group before a halogen-metal interconversion reaction on such a compound can be effected.

Protection of groups containing active hydrogen in the halogen-metal interconversion reaction is unnecessary and actually may lower the yield of the intermediate organometallic compound. It appears that the presence of a phenoxide or amide ion may actually aid coordination of the lithium end of the organometallic dipole and facilitate removal of halogen by a mechanism similar to that described for metalation. It must be stated, however, that halogen-metal interconversion does not occur only at the _ortho_ position, since by use of _n_-butyllithium interconversions of _p_-bromoaniline[108,109], _p_-bromothiophenol[109], _p_-bromobenzyl alcohol[105,110], _p_-bromophenol[104] and _m_-bromophenol[111] have been effected.

With respect to the relative reactivities of the halogen atoms in positions _ortho_, _meta_ or _para_ to the hydroxyl group or methoxyl group in aromatic molecules, the following observations are pertinent.

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[108] (a) Gilman and Stuckwisch, _J. Am. Chem. Soc._, _63_, 2844 (1941); (b) _ibid._, _64_, 1007 (1942) and (c) _ibid._, _71_, 2935 (1949).

[109] Gilman and Gainer, _ibid._, _69_, 1946 (1947).

[110] Gilman and Melstrom, _ibid._, _72_, 2953 (1950).

[111] Sunthankar and Gilman, _J. Org. Chem._, _15_, 0000 (1950).

Interconversion of 2,2'-dimethoxy-3,3',5,5'-tetrabromobiphenyl[112] with two equivalents of phenyllithium gave a high yield of 2,2'-dimethoxy-5,5'-dibromo-3,3'-biphenyldicarboxylic acid. Gilman, Langham and Moore[88] reported that one or both _ortho_ bromine atoms in 2,4,6-tribromoanisole may be interconverted with _n_-butyllithium under special conditions. In this case as before no evidence for interconversion of the bromine _para_ to the methoxy group was detected. With the simpler compound, 2,4-dibromoanisole[111], and _n_-butyllithium only 2-methoxy-5-bromobenzoic acid was obtained subsequent to carbonation. Wittig and Pockels[113] found that phenyllithium would interconvert both bromine atoms in 4,6-dibromoresorcinol dimethyl ether but it will be observed that each halogen was _ortho_ to one methoxy group as well as _para_ to the other.

Sunthankar and Gilman[111] in their extensive investigation on the halogen-metal interconversion reaction in the naphthalene series showed that 2,4-dibromonaphthol and 2,4-dibromophenol reacted with three equivalents of _n_-butyllithium each, to give subsequent to carbonation exclusively 4-bromo-1-hydroxy-2-naphthoic acid and 5-bromosalicylic acid, respectively. These authors conclude that the reactivity of the halogen depends upon its position in the ring with respect to other activating groups i.e. _o_ > _p_ > _m_. Furthermore, the interconversion reaction with one _ortho_ halogen in substituted phenols and anisoles is more rapid than the interconversion reaction with the second atom if

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[112] Gilman, Swiss and Cheney, _J. Am. Chem. Soc._, _62_, 1963 (1940).

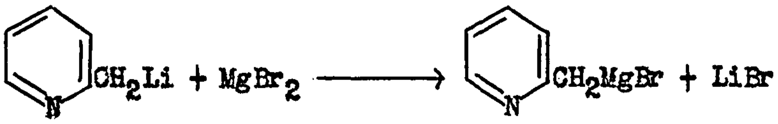
[113] Wittig and Pockels, _Ber._, _72_, 89 (1939).

the latter is not in a second *ortho* position.

Although *m*-trifluoromethylphenyl bromide reacts smoothly with magnesium to form a Grignard reagent[114], it does not react with lithium under the conventional conditions. The desired organolithium compound[115], however, can be prepared by the halogen-metal interconversion reaction with *n*-butyllithium. The use of *m*-trifluoromethylphenyllithium would appear to be a way to introduce the *m*-carboxyphenyl moiety into certain types, but the fluorine atoms can be removed only under rather drastic conditions. For products which are stable to refluxing 80% sulfuric acid[114] or to other concentrated acids, this procedure may have some synthetic value.

The metal-metal interconversion reaction may be considered an exchange of metals between two RM types or between an RM type and a salt such that an organometallic compound of lesser reactivity is formed, e.g.[116,54h],

$$(p\text{-}BrC_6H_4)_2Hg + 2n\text{-}C_4H_9Li \longrightarrow 2p\text{-}BrC_6H_4Li + (n\text{-}C_4H_9)_2Hg$$



This interconversion reaction should have wide application to the preparation of organometallic compounds bearing functional groups although it has been used only to a limited extent for this purpose.

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[114] Simons and Ramler, *J. Am. Chem. Soc.*, *65*, 389 (1943).

[115] Gilman and Woods, *ibid.*, *66*, 1981 (1944).

[116] Gilman and Jones, *ibid.*, *63*, 1443 (1941).

Arntzen[117] for the synthesis of certain organotin compounds employed Grignard reagents prepared from products of a halogen-lithium exchange reaction and magnesium bromide. This procedure offered a means of preparation of Grignard reagents hitherto unavailable by other methods.

Nesmeyanov and Pecherskaya[118] were able to convert o-chloromercuriphenol to O-bromomagnesium-o-hydroxyphenylmagnesium bromide by a metal-metal interconversion reaction with ethylmagnesium bromide. The yield, however, was only 20-25% as determined by carbonation and by reaction with benzophenone.

It may be readily seen from the limited amount of literature available that the metal-metal interconversion reaction has potentially greater possibilities for the preparation of organometallic compounds containing functional groups than have been investigated. One of the subsections of the Discussion part of this thesis contains some suggestions for future research work which are based upon the author's experience during the course of this investigation.

Table I with accompanying footnotes lists the organometallic compounds considered by this survey[119] according to the functional group present. In instances where several reference numbers are given, the first includes a suitable preparative procedure if one is

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[117] Arntzen, Iowa State Coll. J. Sci., 18, 6 (1943) [C.A., 38, 61 (1944)].

[118] Nesmeyanov and Pecherskaya, Bull. acad. sci. U.R.S.S., Classe sci. chim., 317 (1943) [C.A., 38, 5492 (1944)].

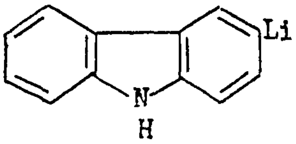
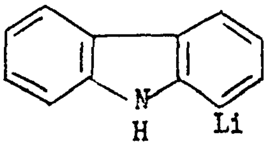
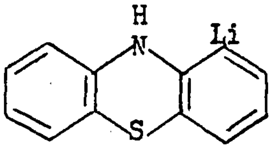
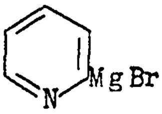
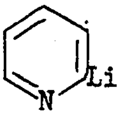
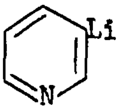
[119] See page 5.

available. In addition to exclusion of acetylides, metal addition compounds from olefins and organometallic compounds containing methoxy and/or tertiary amino groups, certain other types have also been omitted from Table I. Compounds containing the groups RCd-, RHg-, R_3Si-, R_3Ge-, R_3Sn-, R_3Pb-, R_2P-, R_2As-, R_2Sb-, R_2Bi- etc. which undergo ready metal-metal interconversion reactions or cleavage by organometallic compounds or metals have not been included.

It is to be understood that, although some of the formulas in the table contain active hydrogens, these types are actually salts. The nature of the salts in some instances was unknown and it was thought best to avoid inaccuracies and inconsistencies by not replacing the reactive hydrogens in the formulas by metallic cations.

Table I

Organometallic Compounds Classified by Functional Groups

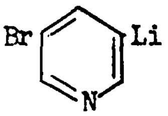
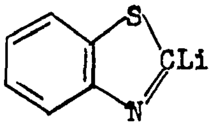
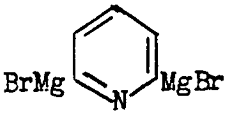
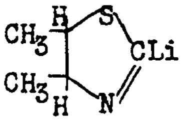
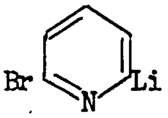
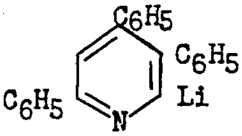
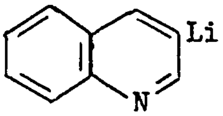
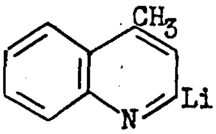
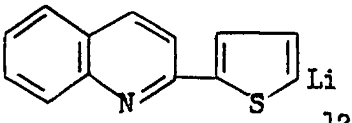
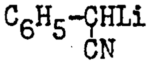
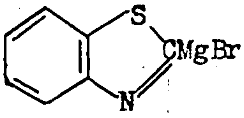
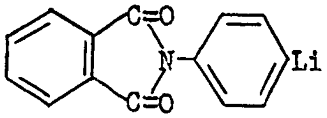
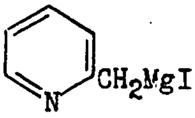
Compound	References	Compound	References
Amino Group*			
o-$H_2NC_6H_4MgCl$	46		102
o-$H_2NC_6H_4Li$	106,94		
m-$H_2NC_6H_4MgBr$	46		77
p-$H_2NC_6H_4MgBr$	108b,117		
p-$H_2NC_6H_4Li$	108c,108a 109,103,74		78
p-$CH_3NHC_6H_4Li$	108c	Azomethylene Group	
o-(n-C_4H_9NH)-C_6H_4Li	94		48,50
o-(C_6H_5NH)-C_6H_4Li	94		121
o-($C_6H_5CH_2NHCH_2$)-C_6H_4Li	120		
	68,69, 70,71		100,101, 103,74

*All reactive hydrogen atoms are replaced by appropriate metallic cations.

[120] Gilman and Woods, J. Am. Chem. Soc., 65, 33 (1943).

[121] Abbott, Iowa State Coll. J. Sci., 18, 3 (1943) [C.A., 38, 61 (1944)].

Table I (Continued)

Compound	References	Compound	References
Azomethylene Group (contd.)			
	101		76
	50		75
	122	Carboxyl*, Cyano and Imido Groups	
	52,51	*o*-$HO_2CC_6H_4Li$	104
	100,101 102	*p*-$HO_2CC_6H_4Li$	104
	102	*p*-NCC_6H_4Li	105
	123	 $C_6H_5-\underset{CN}{C}HLi$	74
	55c		106
		Enamates	
			54h

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*All reactive hydrogen atoms are replaced by appropriate metallic cations.

[122] Spatz, Iowa State Coll. J. Sci., 9, 213 (1934) /C.A., 37, 3434 (1943)/.

[123] Gilman and Shirley, J. Am. Chem. Soc., 71, 1870 (1949).

Table I (Continued)

Compound	References	Compound	References
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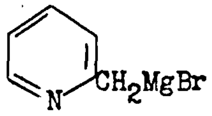
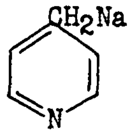
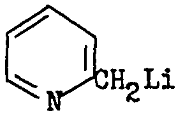
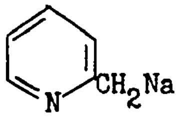
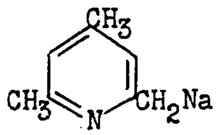
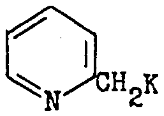
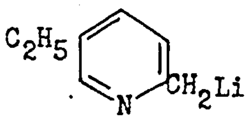
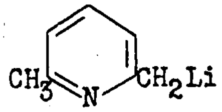
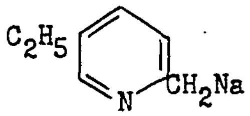
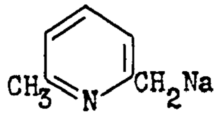
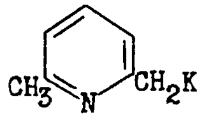
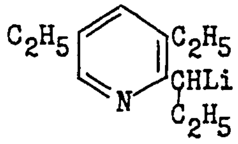
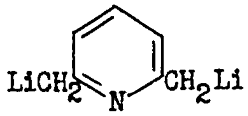
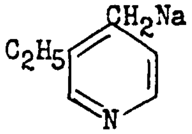
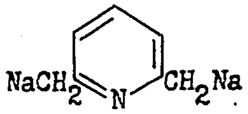
	54h		55b
	53,54a-h, 55a		55a
	55a,b		55a
	55a		54d
	54c,d		55b,124
	55b		54d
	55a		125
	54a		55b
	55b		

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[124] Prelog and Metzler, *Helv. Chim. Acta*, *29*, 1163 (1946).

[125] Haskelberg, *Chemistry* & *Industry*, *13*, 261 (1935).

Table I (Continued)

Compound	References	Compound	References
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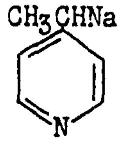
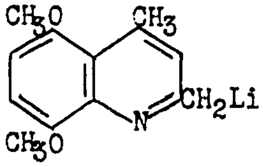
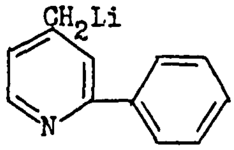
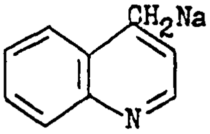
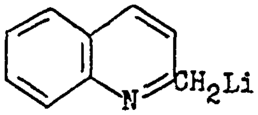
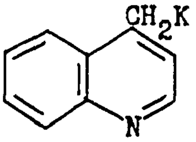
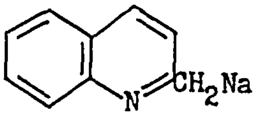
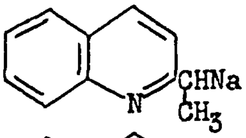
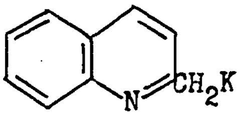
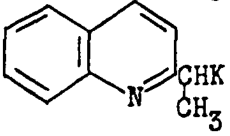
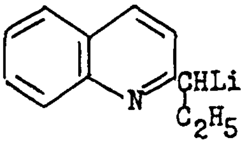
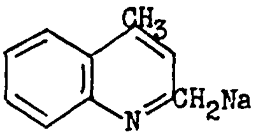
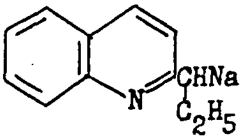
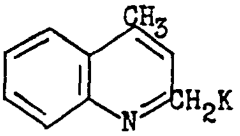
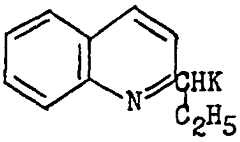
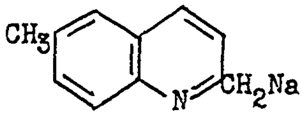
	55b		55d
	56		55a,b
	53,54g, 55d,55a		55a
	55a,b		55a
	55a		55a
	55a		55a
	55a		55a
	55a		55a
	55a		55a

Table I (Continued)

Compound	References	Compound	References
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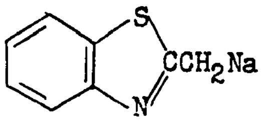
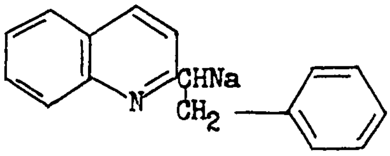
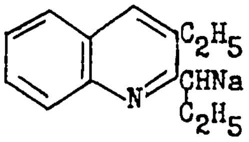
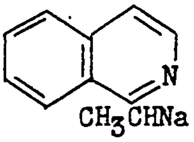
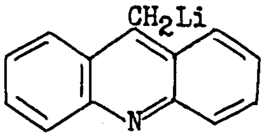
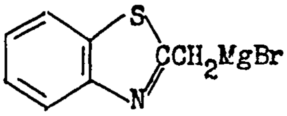
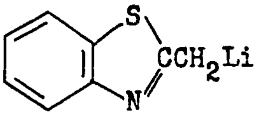
	55a		55c,d
		Enolates*	
	55a	$BrMgCH_2CO_2C_2H_5$	58a,b
	55a	$CH_3COCH(MgCl)CH_3$	59
		2,4,6-$(CH_3)_3C_6H_2COCH_2MgBr$	60,62,65, 64,66
	55a	2,4,6-$(CH_3)_3C_6H_2COCH_2Li$	62
	53	2,4,6-$(CH_3)_3C_6H_2COCH_2Na$	62
		Halogen	
	126	o-BrC_6H_4MgBr	127
		m-BrC_6H_4MgBr	127
	55c	m-ClC_6H_4Li	88,128

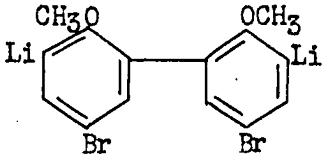
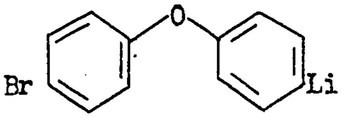
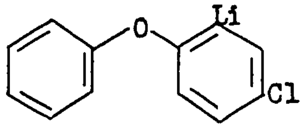
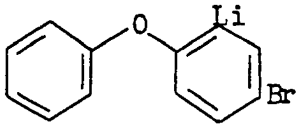
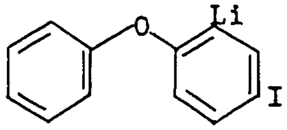
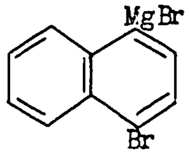
*The enolates are ionic compounds giving O- or C-acylation depending upon the nature of the reactants.

[126] Courtot and Tchelitcheff, Compt. rend., 217, 201 (1943).

[127] Beaber, Iowa State Coll. J. Sci., 5, 317 (1931) [C.A., 26, 379 (1932)].

[128] (a) Gilman, Christian and Spatz, J. Am. Chem. Soc., 68, 979 (1946) and (b) Gilman and Spatz, ibid., 66, 621 (1944).

Table I (Continued)

Compound	References	Compound	References
Halogen (contd.)		*m*-$F_3CC_6H_4Li$	115
p-ClC_6H_4MgBr	27,129a	3-(3'-BrC_6H_4)-C_6H_4MgBr	24
p-ClC_6H_4MgCl	27d	4-(4'-BrC_6H_4)-C_6H_4Li	88
p-ClC_6H_4Li	88,128		
p-BrC_6H_4MgBr	27b,d,f,14 129a,127,16		112
p-BrC_6H_4Li	88,116		88
p-$ClC_6H_4CH_2MgCl$	28		
p-$BrC_6H_4CH_2MgBr$	15		82
2,4-$CH_3(Br)C_6H_3Li$	88		
3,4-$CH_3(Br)C_6H_3Li$	88		82
2,4,6-$Cl_3C_6H_2MgI$	129b		82
$F_3CCH_2CH_2MgCl$	30		
o-$F_3CC_6H_4Li$	93		19,130
m-$F_3CC_6H_4MgBr$	29	3,5-$Br_2C_6H_3Li$	88

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[129] (a) Zoellner, *Iowa State Coll. J. Sci.*, *9*, 213 (1934) [*C.A.*, *29*, 5413 (1935)], and (b) Peak and Watkins, *J. Chem. Soc.*, 445 (1950).

[130] Bodroux, *Bull. soc. chim. France*, [3] *31*, 33 (1904).

Table I (Continued)

Compound	References	Compound	References
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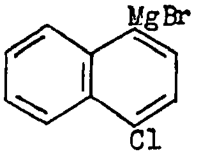
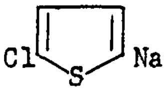
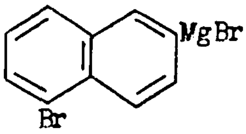
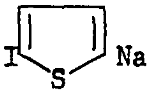
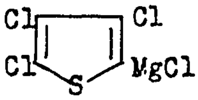
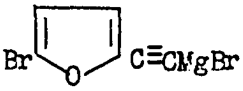
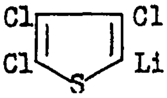
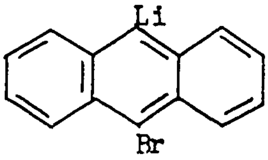
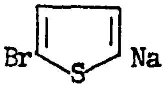
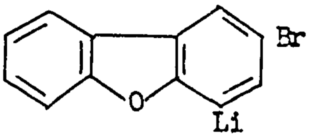
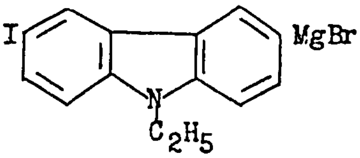
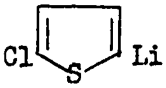
	130		132
	20,21		132a
	17		18
	73,131		18
	18		26
	132a		83,84
	18		102
	18		

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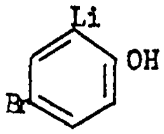
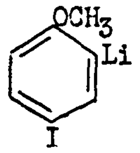
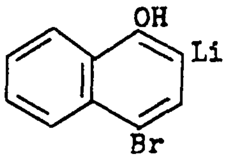
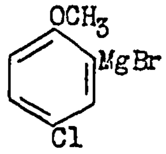
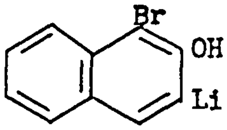
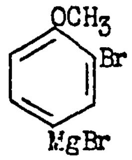
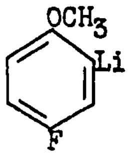
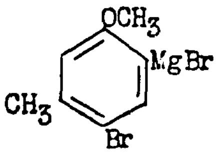
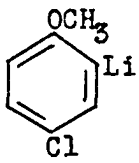
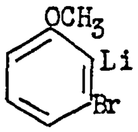
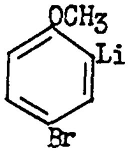
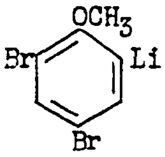
[131] Hewlett, Iowa State Coll. J. Sci., 6, 439 (1932) [C.A., 27, 979 (1933)].

[132] (a) Schick and Hartough, J. Am. Chem. Soc., 70, 286 (1948) and (b) ibid., 70, 1646 (1948).

Table I (Continued)

Compound	References	Compound	References
Halogen and Hydroxyl* Groups			
	111		133
	111		4
	111		4
Halogen and Methoxyl Groups			
	88,82, 133		134
	88,82, 133		133
	111,112,1, 2,133,82		88

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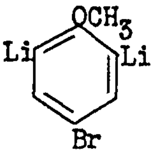
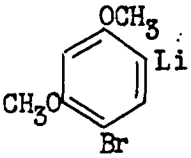
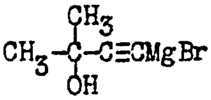
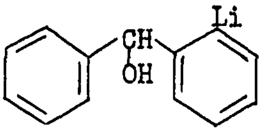
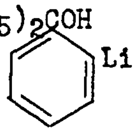
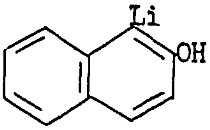
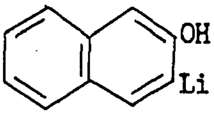
[*] All reactive hydrogen atoms are replaced by appropriate metallic cations.

[133] Wittig and Fuhrmann, Ber., 73, 1197 (1940).

[134] Quelet and Paty, Procès verbaux soc. sci. phys. et nat. Bordeux, 19 (1944-1945) [C.A., 44, 6829 (1950)].

Table I (Continued)

Compound	References	Compound	References
Halogen and Methoxyl Groups (contd.)		p-$HOCH_2C_6H_4Li$	105,110
	88	p-$HOCH_2C_6H_4MgBr$	117
	113,2	p-$CH_3CHOHC_6H_4Li$	105
Hydroxyl or Thiol Group*		p-$HOCH_2CH_2C_6H_4Li$	105,110
 $CH_3-\overset{CH_3}{\underset{OH}{C}}-C\equiv CMgBr$	72	2,6-$(HO)_2C_6H_3Li$	86
o-HOC_6H_4Li	95,104		94
o-HOC_6H_4MgBr	117,135,118	$(C_6H_5)_2COH$ 	94
p-HOC_6H_4Li	95,104		111
p-HOC_6H_4MgBr	117,46		95
o-$HOCH_2C_6H_4Li$	105,110,94		
o-$HOCH_2C_6H_4MgBr$	117		
m-$HOCH_2C_6H_4Li$	105,110		

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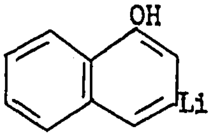
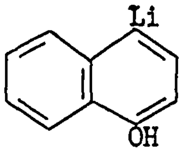
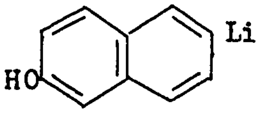
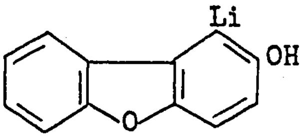
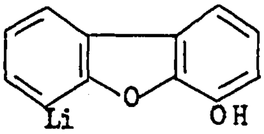
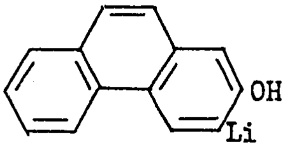
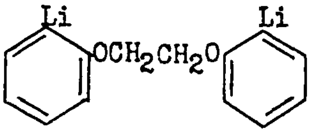
*All reactive hydrogen atoms are replaced by appropriate metallic cations.

[135] Gilman and Haubein, J. Am. Chem. Soc., 67, 1033 (1945).

Table I (Continued)

Compound	References	Compound	References
Hydroxyl or Thiol Groups*(contd.)		o-HSC_6H_4Li	95
	111	p-HSC_6H_4Li	109
		Metal (Mg,Li,Na,K)	
	111	$CH_3CH_2CH_2CH_2CHNa_2$	136,137
		$BrMgCH_2(CH_2)_2CH_2MgBr$	10
	111	$BrMgCH_2(CH_2)_3CH_2MgBr$	10,9
		$BrMgCH_2(CH_2)_5CH_2MgBr$	10
	86	$BrMgCH_2(CH_2)_8CH_2MgBr$	11
		$IMgCH_2(CH_2)_8CH_2MgI$	10
	86	p-(p'-$BrMgC_6H_4CH_2CH_2$)-C_6H_4MgBr	15
	92		35

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*All reactive hydrogen atoms are replaced by appropriate metallic cations.

[136] (a) Morton and Fallwell, J. Am. Chem. Soc., 59, 2387 (1937) and (b) Morton and Massengale, ibid., 62, 120 (1940).

[137] Gilman and Pacevitz, ibid., 62, 1301 (1940).

[138] Gilman, Moore and Jones, ibid., 63, 2482 (1941).

Table I (Continued)

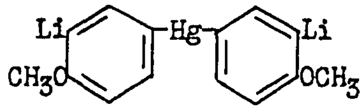
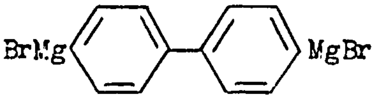
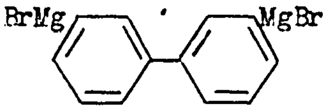
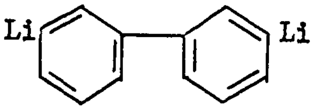
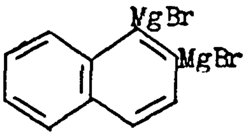
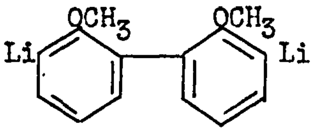
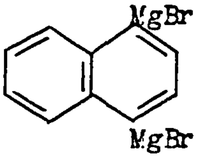
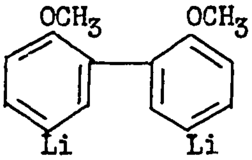
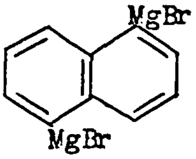
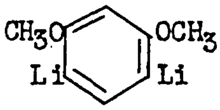
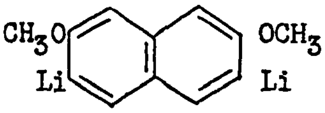
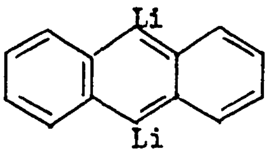
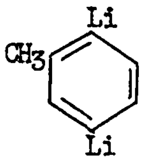
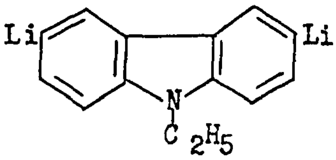
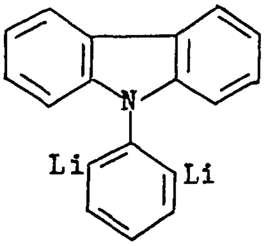
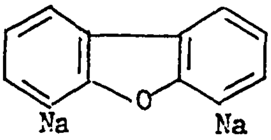
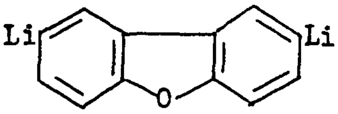
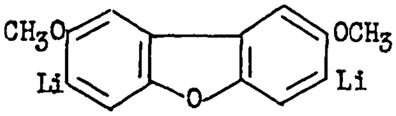
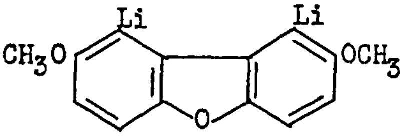
Compound	References	Compound	References
Metal (Mg,Li,Na,K) (contd.)		o-$IMgC_6H_4MgI$	13
	138	m-$IMgC_6H_4MgI$	13,127
	22,23	p-$IMgC_6H_4MgI$	13,12,127
	24	p-$BrMgC_6H_4MgBr$	15,23
	24		19
	112		19
	112		19
	113		111
p-LiC_6H_4Li	88		26
	88		

Table I (Continued)

Compound	References	Compound	References
Metal (Mg,Li,Na,K) (contd.)			
	13a		102,101
	139		81
	79,80	Sulfonamido Group*	
	85	p-$H_2NO_2SC_6H_4Li$	105
	140	p-$(C_2H_5)_2NO_2SC_6H_4Li$	104
	140a		

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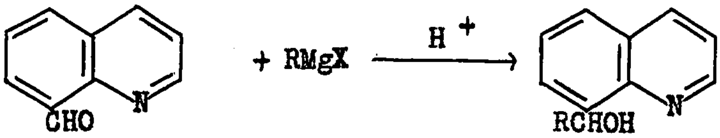
*All reactive hydrogen atoms are replaced by appropriate metallic cations.

[139] Campaigne and Foye, J. Am. Chem. Soc., 70, 3941 (1948).

[140] (a) Gilman, Swislowsky and Brown, ibid., 62, 348 (1940) and (b) Gilman, Swiss, Willis and Yeoman, ibid., 66, 798 (1944).

Certain selective reactions have been carried out with organometallic reagents upon polyfunctional compounds. These in some cases have been between a Grignard reagent and a compound containing a very reactive group and one which has low reactivity. Howitz and Kopke[141] treated 8-quinolinealdehyde with several Grignard reagents and in each instance obtained good yields of the expected secondary alcohols. The following equation represents the reaction involved:



More striking examples of the selectivity of reaction with certain groups are instances in which reaction occurs exclusively with one of a pair of functional groups which are both highly reactive toward the same organometallic compound. Phenylmagnesium bromide was found to react readily with *t*-butyl benzoate to give triphenylmethanol, but 1,4-addition took place with *t*-butyl cinnamate to give *t*-butyl β,β-diphenylpropionate[142]. The three mononitrobenzaldehydes reacted in the cold with phenyl- and 1-naphthyl-magnesium bromides to give the corresponding nitromethanols which were not isolated but were oxidized to the nitroketones[143]. Later workers[144] found also that a preferential

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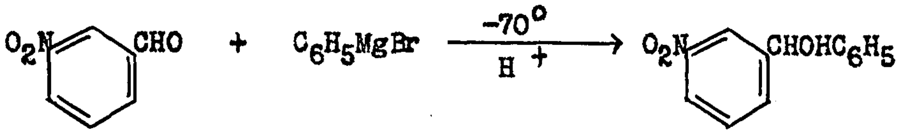
[141] Howitz and Kopke, Ann., 396, 38 (1913).

[142] Frostick, Baumgarten and Hauser, J. Am. Chem. Soc., 66, 305 (1944).

[143] Berlingozzi, Atti. accad. Lincei, 19, 332 (1934) [C.A., 28, 5055 (1934)].

[144] Newman and Smith, J. Org. Chem., 13, 592 (1948).

reaction between phenylmagnesium bromide and m-nitrobenzaldehyde could be carried out to obtain a 77% yield of phenyl m-nitrophenylmethanol.



The fact that the Grignard reagent reacted with the aldehyde group instead of having been oxidized[145] by the nitro group is astonishing and rather pointedly illustrates the degree to which selectivity of reaction may be accomplished with proper choice of organometallic compound and with suitable reaction conditions.

It has been possible by introduction of methoxy groups ortho to bromine atoms in the molecule to carry out a halogen-metal interconversion reaction on an organomercurial[138]. The latter ordinarily undergoes a more rapid metal-metal interconversion (the order of decreasing rates of interconversion generally being M-M > X-M) but the presence of groups capable of coordination with the interconverting agent may reverse the relative rates of the two competitive reactions.

Carter[146] has reviewed the literature to 1939 concerned with the preferential reactions of organometallic compounds with polyfunctional types. An extensive discussion of reactions of organometallic compounds with ketonic esters, cyano esters, aldehydic acids and esters, acid

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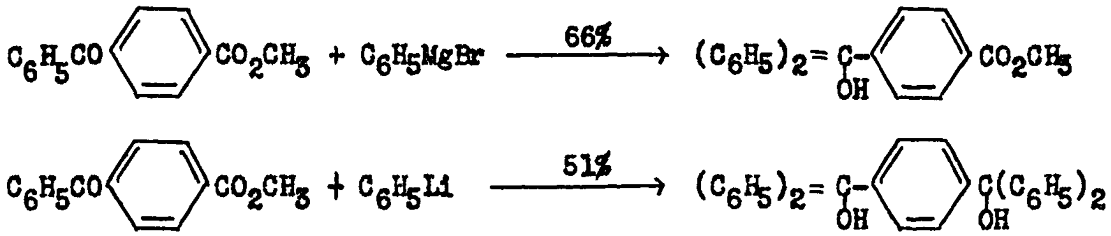
[145] Gilman and McCracken, J. Am. Chem. Soc., 51, 821 (1929).

[146] (a) Carter, Doctoral Dissertation, Iowa State College, 1939 and (b) Carter, Iowa State Coll. J. Sci., 15, 63 (1940) /C.A., 35, 3225 (1941)/.

chloride esters, amidic esters, diesters, diamides and imides, acid anhydrides, diacid chlorides, diketones and quinones, dinitriles and miscellaneous polyfunctional compounds has been included. Each group of compounds has been tabulated for easy reference. It has been found[146] that the Grignard reagents and methyllithium gave preferential reactions with cyano esters, ketonic esters and ketonic nitriles but phenyllithium reacted predominantly with both groups, e.g.,



The work of Gooch[147] has extended the Entemann and Johnson[107] series of relative reactivities of functional groups by his investigations employing benzalacetophenone, azobenzene, benzalaniline and diethylbenzamide. The extended series that follows includes in parenthesis the groups placed by Entemann and Johnson.

$$(\text{-CHO}) \geqq \text{-CH=CHCOC}_6\text{H}_5 > (\text{-COCH}_3) > (\text{-NCO}) > (\text{-COF}) > (\text{-COC}_6\text{H}_5, \text{-COCl}, \text{-COBr}) > \text{-COI} > (\text{-CO}_2\text{C}_2\text{H}_5) > (\text{-CN}) > \text{-N=N-} > \text{-CH=NC}_6\text{H}_5, \text{-CON(C}_2\text{H}_5)_2.$$

A similar series worked out with phenyllithium[147] placed benzophenone equally reactive if not more reactive than acetophenone. This series differs slightly from the Entemann and Johnson series determined with phenylmagnesium bromide. The order of reactivities with

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[147] Gooch, Master Thesis, Iowa State College, 1939.

phenyllithium is as follows:

$$-CHO > -COC_6H_5 \geq -COCH_3 > -CO_2C_2H_5 > -CN > -N{=}N-$$

The same groups when reacted with other organometallic compounds may give a different order of reactivities. This situation in most cases may be explained by the assumption of a different mechanism of reaction. However, Carter's work has shown that the Grignard reagent does react preferentially with one of the groups in the disubstituted benzene derivatives studied, and that the group which reacts is the one which would be predicted on the basis of the series of relative reactivities of functional groups.

III EXPERIMENTAL

A. General Procedure

n-Propyllithium was used almost exclusively as the reagent for effecting the halogen-metal interconversion reaction. There were several reasons for the choice of this organolithium compound. These were: (1) with 1-bromonaphthalene in ether n-propyllithium was found to be a more effective interconverting agent than ethyllithium which in turn was more effective than n-butyllithium[148]; (2) n-butyric acid is easier to remove from the carbonation products because it is miscible with water whereas n-valeric acid is only partially soluble in water and contaminates the desired acids; and (3) n-propyllithium, prepared by the same procedure described for n-butyllithium[149], was formed in higher yields than has heretofore been obtained for this reagent. The average yield attained in twenty-six preparations was 70.5% as determined in each case by the Haubein titration procedure[150]. The solution was found to be reasonably stable since at room temperature for ten and twenty-four hours, the decreases in concentration of a solution of n-propyllithium were 2% and 6%, respectively. Table II and footnote give additional information concerning the stability of n-propyllithium during storage in a refrigerator.

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[148] Gilman and Moore, J. Am. Chem. Soc., 62, 1843 (1940).

[149] Gilman, Beel, Brannen, Bullock, Dunn and Miller, ibid., 71, 1499 (1949).

[150] Gilman and Haubein, ibid., 66, 1515 (1944).

Table II

Stability of n-Propyllithium Solutions at 10°

Initial normality[a]	Final normality[a]	Storage time days	% Decrease
1.087	1.018	3	6.4
1.087	0.977	7	10.1
1.317	1.12	12	15.0
1.317	1.00	28	24.1

[a] Determined by the Haubein double titration. The solution was stored in a 300 ml. three-necked flask which was sealed by ground glass stoppers. Two ml. aliquots were taken.

Mr. Cecil Brannen has carefully collected information concerning the stability of n-butyllithium solutions and these unpublished data are listed in Table III for purposes of comparison.

Actually the data on the stability of n-propyllithium and n-butyllithium are not strictly comparable since the latter may have been stored in a tighter container. Any appreciable ether loss would increase the titer of the solution and cause an incorrect evaluation of the stability. It seems fair to say, however, that n-propyllithium can be obtained in consistently satisfactory yields and is reasonably stable even at room temperature. If the data obtained on each organometallic compound can be duplicated by a single individual, n-propyllithium may be the reagent of choice for the halogen-metal

Table III

Stability of n-Butyllithium Solutions at 10°

Initial normality[a]	Final normality[a]	Storage time days	% Decrease
1.205	1.11	2	7.9
1.205	1.04	5	13.7
1.205	1.02	9	15.4
1.205	0.997	10	17.3
1.205	0.81	21	32.8
1.205	0.76	31	37.0
1.205	0.55	62	54.3

[a] Determined by the Haubein double titration. The solution was stored in a Schlenk tube sealed by a piece of Tygon tubing and screw clamp. Five ml. aliquots were taken.

interconversion reaction.

It would be interesting in connection with the stability of alkyllithium reagents to set aside in the dark a sample of methyllithium solution for a long period of time[151]. This information would have particular significance in the application of methyllithium to the Zerewitinoff determination of active hydrogen. Careful examinations

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[151] Haubein, Iowa State Coll. J. Sci., 18, 48 (1943) [C.A., 38, 716 (1944)] found that the normality of a methyllithium solution dropped from 0.54 N to 0.14 N in one year.

of the products of reaction between these reactive organolithium reagents and ether have been made. Wittig and Witt[89] in an attempt to metalate cyclohexyl fluoride in ether with phenyllithium found that the ether was cleaved to form lithium ethoxide and ethylene according to the following equation.

$$CH_3CH_2OCH_2CH_3 + C_6H_5Li \longrightarrow CH_3CH_2OLi + C_6H_6 + CH_2=CH_2$$

Some very recent work concerned with ether cleavage by organometallic compounds has been reported by Ziegler and Gellert[152]. These authors found that ethyl ether was metalated by n-butyllithium to give butane and ethylene in a molar ratio of one to one.

In every case the n-propyllithium solution was added to an ether solution of the organic halide. This has the particular advantage that the extent of secondary reactions involving functional groups is minimized. The side reactions possible when the halogen compound contains a group with active hydrogen have been discussed by Gilman and Arntzen[104].

In instances where a rapid transfer of the organolithium compound at low temperatures was desired, the reagent was filtered into a dropping funnel and after titration was transferred to a two- or three-necked flask. The flask was immersed in a Dry Ice-acetone bath and allowed to remain there until the contents were thoroughly cooled.

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[152] Ziegler and Gellert, Ann., 567, 185 (1950).

A gas inlet tube with a relatively large bore (10 mm.) was inserted into one neck of the flask and by proper manipulation complete transfer was made within five seconds.

Only crude filtrations of the n-propyllithium solutions were carried out by use of glass wool plugs inserted in gas inlet tubes unless a note has been made to the contrary. A Hormann pressure filter has been extremely useful in instances where the organometallic solutions must be free of foreign material e.g. lithium nitride.

For filtrations of small preparations of n-propyllithium the following procedure gave results every bit as satisfactory as use of the expensive pressure filter. A loose plug of glass wool was pushed into a gas inlet tube of 10 mm. bore. This was followed by a thin but carefully made mat of asbestos fiber. Following this mat was placed a longer and tighter section of glass wool. The glass wool both effects a rough filtration and serves as a support for the asbestos fiber which removes the very fine particles. Pressure from a nitrogen train having a mercury trap is usually sufficient to give a reasonably fast filtration.

The carbonation reaction was found to be the most convenient way to form derivatives of the organometallic compounds. The use of a slurry of ether and powdered Dry Ice[76,137] gave little or no ketone formation and/or hydrolysis.

The inert atmosphere employed during the preparation and use of organometallic compounds was dry nitrogen. The train for the purification of the nitrogen was changed slightly from the conventional series of traps containing alkaline pyrogallol, sulfuric acid and calcium chloride. The gas wash bottles containing alkaline pyrogallol were replaced by two traps, each containing 100 g. of zinc amalgam and a solution of 4.0 g. of vanadyl sulfate dissolved in 200 ml. of water[153]. The stem of a dropping funnel containing concentrated sulfuric acid was inserted through the stopper of each bottle and the solution was made slightly acid. This arrangement should be followed by an alkaline solution to remove the small amount of hydrogen sulfide given off from the reduction of sulfuric acid. Regeneration of the solution is carried out by acidification of the vanadyl sulfate solutions without the usual inconvenience of taking the train apart.

All new compounds have been analyzed for a single element. The melting points and boiling points reported in the following sections are uncorrected.

B. Protection of Reactive Functional Groups

_p_-Nitrobromobenzene and Phenyllithium.- A solution of phenyllithium (0.022 mole in 80 ml. of ether) cooled to -78° was added rapidly ($<$ 10 seconds) to a stirred suspension of 5 g. of _p_-nitrobromobenzene in 75 ml. of ether at the same temperature. The deep red reaction mixture was stirred for one-half minute and at the end of one minute was transferred rapidly into a slurry of Dry Ice and ether.

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[153] Meites and Meites, _Anal. Chem._, _20_, 984 (1948).

The ether layer was washed with water and dried over anhydrous sodium sulfate. Dilute hydrochloric acid was added to the aqueous portion but no acid precipitated.

The ether was removed by distillation and the black residue was subjected to a steam distillation. A total of 2.45 g. (49%) of p-nitrobromobenzene was recovered. From the aqueous portion of the distillate after addition of bromine water, a 28% yield of crude 2,4,6-tribromophenol was obtained.

In a second attempt 60 ml. (0.019 mole) of phenyllithium solution cooled to -78° were added quickly to 4.04 g. (0.02 mole) of p-nitrobromobenzene in 150 ml. of ether at -78°. The reaction time was 67 seconds and then the mixture was carbonated.

The ether layer was extracted twice with 100 ml. portions of 10% NaOH and then twice with water. The aqueous solution was acidified and treated with bromine water. A 47% yield of crude tribromophenol (m.p. 85-89°) was obtained.

The ether layer was dried over anhydrous sodium sulfate and subsequently the ether was removed by distillation. From the residue a 57% recovery of p-nitrobromobenzene (m.p. 125-127°) was obtained. Table IV lists other attempts to prepare p-nitrophenyllithium.

n-Propyllithium and Bromomesitylene.- n-Propyllithium (0.069 mole in 98 ml. of ether) was added over a period of fifteen minutes to 13.75 g. (0.069 mole) of bromomesitylene in 100 ml. of ether at room temperature (26°). Very little heat was liberated but the solution slowly became cloudy with the precipitated mesityllithium

Table IV

Organolithium Reagents and Some Nitroiodobenzenes at -78°

RLi	RNO_2	Mole RLi	Mole RNO_2	Total Vol. Ether ml.	Time, min.	Yield crude acid, g.	Recovered RNO_2 %
p-$(CH_3)_2NC_6H_4Li$	*p*-$IC_6H_4NO_2$	0.019	0.02	223	1.17	trace[a]	63
C_6H_5Li	*p*-$IC_6H_4NO_2$	0.019	0.02	219	1.08	trace[b]	52
C_6H_5Li	*p*-$IC_6H_4NO_2$	0.0193	0.02	227	1.33	—[c]	64
C_6H_5Li	*p*-$IC_6H_4NO_2$	0.0156	0.02	202	2.17	—[d]	—
n-C_4H_9Li	*p*-$IC_6H_4NO_2$	0.069	0.023	300	1.33	0.05[e]	—
n-C_4H_9Li	*p*-$IC_6H_4NO_2$	0.078	0.078	300	10	—[f]	—
C_2H_5Li	*p*-$IC_6H_4NO_2$	0.074	0.074	300	10	0.72[g]	—
n-C_3H_7Li	*p*-$IC_6H_4NO_2$	0.054	0.056	300	10	3.30[h]	—
n-C_3H_7Li	*o*-$IC_6H_4NO_2$	0.062	0.062	294	10	2.0[i]	—

[a] A mixed m.p. with *p*-nitrobenzoic acid (m.p. 239-240°) was depressed to 215-222°.

[b] M.p. 233-243°. A 23.5% yield of phenol was obtained as the tribromo derivative.

[c] By sublimation 0.2 g. benzoic acid (mixed m.p.) was obtained. M.p. of crude acid was 227-237° but chromatography on a column of diatomaceous earth using chloroform and acetone as solvents gave only oils. A *p*-nitrobenzyl ester could not be prepared.

[d] Black impure acids were obtained as in previous runs.

[e] The m.p. was 200°+. By ether extraction 2.3 g. (32.5%) of valeric acid (n_D^{19} = 1.4090) was obtained.

[f] An attempt was made to prepare the *p*-bromophenacyl ester but no pure substance was obtained.

C_6H_5Li	p-$IC_6H_4NO_2$	0.019	0.02	219	1.08	trace[b]	52
C_6H_5Li	p-$IC_6H_4NO_2$	0.0195	0.02	227	1.35	—[c]	64
C_6H_5Li	p-$IC_6H_4NO_2$	0.0156	0.02	202	2.17	—[d]	—
n-C_4H_9Li	p-$IC_6H_4NO_2$	0.069	0.025	300	1.33	0.05[e]	—
n-C_4H_9Li	p-$IC_6H_4NO_2$	0.078	0.078	300	10	—[f]	—
C_2H_5Li	p-$IC_6H_4NO_2$	0.074	0.074	300	10	0.72[g]	—
n-C_3H_7Li	p-$IC_6H_4NO_2$	0.054	0.056	300	10	3.30[h]	—
n-C_3H_7Li	o-$IC_6H_4NO_2$	0.062	0.062	294	10	2.0[i]	—

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[a] A mixed m.p. with p-nitrobenzoic acid (m.p. 239-240°) was depressed to 215-222°.

[b] M.p. 233-243°. A 23.5% yield of phenol was obtained as the tribromo derivative.

[c] By sublimation 0.2 g. benzoic acid (mixed m.p.) was obtained. M.p. of crude acid was 227-237° but chromatography on a column of diatomaceous earth using chloroform and acetone as solvents gave only oils. A p-nitrobenzyl ester could not be prepared.

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[f] An attempt was made to prepare the p-bromophenacyl ester but no pure substance was obtained.

[g] M.p. > 360°. No pure p-nitrobenzyl ester could be isolated.

[h] The p-nitrobenzyl ester could not be purified.

[i] The Craig counter-current distribution method of purification was suggested but the insolubility of the acid precluded using this procedure. Digestion with cyclohexane yielded a light yellow acid of m.p. ca. 162°. Both procedures were suggested by Mr. C. G. Brannen.

which gave the characteristically unpleasant odor associated with preparations of mesityllithium either by direct reaction[154] with the metal or by halogen-metal interconversion. Color Test II-A[155] was negative after two hours and ten minutes and Color Test I[63] was very strong. Since no Dry Ice was available the suspension was stirred for the remainder of twelve hours and then carbonated.

The ether suspension of the salts was extracted with water, and the aqueous solution was freed of ether on the steamplate. After acidification 5.20 g. (45.8%) of crude mesitoic acid m.p. 143-149° were obtained. A single crystallization from an ethanol-water mixture gave 4.50 g. (39.7%) of pure acid m.p. 151-152°.

The ether soluble material was distilled at 12 mm. to give 4.5 g. of material which probably was a mixture of bromomesitylene and n-propylmesitylene.

In a similar run at -78° for a reaction time of fifty-one minutes, the only acid obtained was butyric. From the ether solution an 85% recovery of the bromomesitylene (b.p. 96-100°/12 mm., n_D^{20} 1.5507) was obtained.

n-Propyllithium and bromomesitylene were reacted at room temperature for varying periods of time and subsequently carbonated in order to find the optimum conditions for the halogen-metal interconversion reaction. Table V and accompanying footnotes give the results of these experiments.

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[154] Gilman and Nelson, J. Am. Chem. Soc., 70, 3316 (1948).

[155] Gilman and Swiss, ibid., 62, 1847 (1940).

Table V

n-Propyllithium and Bromomesitylene at 26°

	Mole RLi	Mole RBr	Vol. ether, ml.	Time, min.	Yield of Mesitoic Acid g.	%
1.	0.0216[a]	0.0216	50.5	1	0.05	1.4
2.	0.0216[a]	0.0216	50.5	3	0.22	6.2
3.	0.0216[a]	0.0216	50.5	6	0.42	11.8
4.	0.0216[a]	0.0216	50.5	12	0.90	25.3
5.	0.0234[b]	0.0234	50	20	1.25	32.6
6.	0.0234[b]	0.0234	50	40	1.70	44.2
7.	0.0234[b]	0.0234	50	80	0.92	24.0
8.	0.0234[b]	0.0234	50	120	0.90	23.5

[a] Reactions 1-4 were carried out individually by the addition of 25.5 ml. of *n*-propyllithium solution to 3.26 ml. of bromomesitylene dissolved in 25 ml. of ether. This procedure was facilitated by use of a three-necked flask having a stopcock sealed at the bottom.

[b] Reactions 5-8 were carried out by removing 50 ml. aliquots from the mixture resulting from the addition of 99 ml. (0.0935 mole) of *n*-propyllithium to 18.6 g. (0.0935 mole) of bromomesitylene in 100 ml. of ether. The results from reactions 7 and 8 must be in error since the yield of crude acid after twelve hours is 45.8%.

Preparation of Nitrobromomesitylene.- An attempt was made to nitrate bromomesitylene according to the directions of Fittig and Storer[156] but no reaction could be effected. After six more attempts to nitrate the compound in which the variables time, temperature,

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[156] Fittig and Storer, *Ann.*, *147*, 7 (1868).

concentration and solvent were changed, the following procedure was developed.

Twenty grams of bromomesitylene in 100 ml. of glacial acetic acid were mixed at 0° with 50 ml. of fuming nitric acid (d. 1.49) in 50 ml. of glacial acetic acid. The reaction mixture was heated over a steam bath for thirty minutes and then poured over ice. The product after being washed with water was subjected to fractional crystallization from ethanol. The crystals obtained melted at 100-120° and appeared to be a mixture of the mono- and di-nitrated bromomesitylenes. After removal of the ethanol the residue from the filtrate was distilled at 12 mm. The material distilling between 137-145° was crystallized, and after being pressed on a porous plate 7.37 g. (30%) m.p. 47-53° were obtained. Crystallization from ethanol raised the m.p. of 4.2 g. to 54-55°. An additional 1.5 g., m.p. 50-52°, were obtained to give a total yield of 5.7 g. (23%). The reported m.p. was 54° but the yield was not given[156].

n-Propyllithium and Nitrobromomesitylene.- Fourteen milliliters (0.0105 mole) of *n*-propyllithium solution were added rapidly to 2.44 g. (0.01 mole) of nitrobromomesitylene in 25 ml. of anhydrous ether. The reaction was very vigorous and the solution turned to a dark green. The total reaction time was three minutes and then the solution was carbonated. No organic acid was obtained when the carbonation mixture was washed with water and the aqueous extract acidified.

Preparation of 4-Bromo-m-xylene.- The bromination of *m*-xylene was carried out by a procedure similar to that used by Buu-Hoi and

Cagniant[157]. To a cooled suspension of a small amount of iron powder in 53 g. (0.5 mole) of m-xylene were added slowly 26 ml. of bromine with stirring. An ice-salt mixture was used as the cooling medium. The reaction mixture was then allowed to stand at room temperature for ten hours.

The reaction product was washed with an aqueous solution of sodium bisulfite and then with water. The last traces of product were extracted from the aqueous layer with ether. The ether solution was added to the separated bromo-m-xylene and the solution was dried over sodium sulfate.

The ether was removed by distillation and the product was distilled[158] at 78-80°/11 mm. The yield was 80 g. (86.5%) having n_D^{20} 1.5510.

n-Propyllithium and 4-Bromo-m-xylene.- Forty-eight milliliters (0.033 mole) of n-propyllithium solution were added rapidly to 0.033 mole of 4-bromo-m-xylene in 60 ml. of ether at room temperature. The reaction time before carbonation was twenty minutes.

The yield of crude acid was 3.90 g. (78.7%) m.p. 116-118°. After crystallization from an ethanol-water mixture the yield was 3.40 g. (68.7%), m.p. 121-122°. The reported[159] m.p. of 2,4-dimethylbenzoic acid was 125-126°.

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[157] Buu-Hoi and Cagniant, Bull. soc. chim. France, 10, 151 (1943).

[158] Grignard, Bellet and Courtot, Ann. chim., 4, 45 (1915) reported b.p. 84°/13 mm.

[159] Jacobsen, Ber., 11, 18 (1878).

In another run 71 ml. (0.053 mole) of n-propyllithium solution were added rapidly to 0.053 mole of 4-bromo-m-xylene dissolved in 60 ml. of anhydrous ether cooled to -78°. After a reaction time of two minutes followed by carbonation, a halogen-containing acid (0.07 g.) m.p. 164-8° was obtained. This substance was not investigated.

Table VI gives the results of a series of four experiments in which n-propyllithium was used to interconvert 4-bromo-m-xylene in order to obtain the optimum conditions at room temperature.

Table VI

n-Propyllithium and 4-Bromo-m-xylene at 27°

Mole RLi	Mole RBr	Vol. ether, ml.	Time, min.	Yield 2,4-Dimethylbenzoic acid g.	Yield 2,4-Dimethylbenzoic acid %
0.027	0.027	49	1	1.07	26.4
0.027	0.027	49	3	2.40	59.2
0.027	0.027	49	6	2.85	70.2
0.027	0.027	49	12	2.60	64.0

Preparation of 2-Nitro-4-bromo-1,3-dimethylbenzene.- The bromination of 2-nitro-1,3-dimethylbenzene was carried out by a method similar to that of Auwers and Markovits[160]. A pinch of iron powder was stirred with 0.5 mole of 2-nitro-1,3-dimethylbenzene in a 200 ml. three-necked flask fitted with a reflux condenser, mechanical stirrer

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[160] Auwers and Markovits, Ber., 41, 2337 (1908).

and a dropping funnel. The mixture was cooled in an ice bath and about half the bromine was added slowly. No reaction occurred until the mixture was allowed to warm to room temperature. The remainder of the bromine was added slowly as the flask was cooled in an ice bath. When the reaction was essentially complete, the solid product was melted to a homogeneous mass over a water bath, and it was then allowed to remain for 24 hours at room temperature.

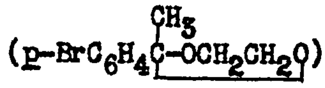
The solid was broken up and washed with dilute sodium carbonate solution. A single crystallization from ethanol gave 87.5 g., m.p. 69-70°, and 3.5 g. of additional material m.p. 66-69° were obtained from the mother liquor. The total yield was 91 g. (79.3%). The reported melting point was 70-71°.

n-Propyllithium and 2-Nitro-4-bromo-1,3-dimethylbenzene.- Forty-four milliliters (0.03 mole) of n-propyllithium solution were cooled to -78° and added rapidly to 0.05 mole of 2-nitro-4-bromo-1,3-dimethylbenzene in 100 ml. of ether at -78°. The color changed to a greenish-brown and at the end of two minutes the mixture was carbonated. When the carbonation mixture was worked up, no organic acid was obtained.

In a second run the same quantities of reagents were used but the reaction was carried out at room temperature for three minutes. The solution turned a dark green and the ether refluxed vigorously. The mixture was carbonated but no acid was obtained from the carbonation mixture.

n-Propyllithium and N-(β-Bromoethyl)-phthalimide.- The *n*-propyllithium solution (0.064 mole in 70 ml. of ether) was cooled to -78° at which temperature it solidified. The solid was allowed to warm until melted and the solution was added rapidly to a suspension of 16.5 g. (0.064 mole) of N-(β-bromoethyl)-phthalimide in 200 ml. of ether cooled to -78°. The reaction mixture was stirred for ten minutes and then it was carbonated.

The carbonation mixture was extracted with water and the aqueous layer was acidified. No precipitate formed and a strong odor of butyric acid was detected. From the ether solution 15.8 g. (97%) of N-(β-bromoethyl)-phthalimide m.p. 78-80° were recovered. A mixed m.p. with an authentic specimen was 78-80°.



Ethylene Acetal of p-Bromoacetophenone ($p\text{-BrC}_6\text{H}_4\overset{\text{CH}_3}{\text{C}}\text{-OCH}_2\text{CH}_2\text{O}$).- This compound was prepared by the method described by Salmi[161] for formation of cyclic acetals. Into a 125 ml. pear-shaped flask were placed 0.1 mole of *p*-bromoacetophenone, 0.1 mole of ethylene glycol, 0.05 g. of *p*-toluenesulfonic acid and 70 ml. of anhydrous thiophene-free benzene. The flask was connected to a Dean-Stark distilling tube, and the azeotropic distillation was carried out for six hours after which 2.0 ml. of water was measured in the calibrated tip.

The benzene solution was washed with dilute sodium carbonate solution and then dried over anhydrous sodium sulfate. The benzene was removed and the product was distilled at 134-135°/12 mm. The

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[161] Salmi, *Ber.*, *71*, 1803 (1938).

yield was 19.1 g. (78.5%) of the ethylene acetal; n_D^{20} 1.5560, $d^{20/20}$ 1.455, MR_D 53.71 (calcd. 53.53).

Anal. Calcd. for $C_{10}H_{11}O_2Br$: Br, 32.9. Found: Br, 33.3.

Ethylene Acetal of p-Bromoacetophenone and Lithium.- A solution of 3.35 ml. (0.02 mole) of the ethylene acetal of p-bromoacetophenone in 50 ml. of ether was dropped into a suspension of 0.06 g. atom of lithium wire suspended in 50 ml. of ether. The reaction did not start; therefore, a crystal of iodine was added to the reaction mixture. Since the iodine color persisted, a few drops of methyl iodide were added to polish the surfaces of the metal and initiate the reaction. After two hours of refluxing, there seemed to be no change in the amount of suspended lithium.

An additional 0.06 g. atom of the wire was added to the reaction mixture and this was followed by another 3.35 ml. of the acetal added dropwise. After one hour more of stirring at reflux temperature, Color Test I was negative.

n-Propyllithium and the Ethylene Acetal of p-Bromoacetophenone.- To 3.35 ml. (0.02 mole) of the ethylene acetal of p-bromoacetophenone in 50 ml. of ether were added 34 ml. (0.03 mole) of n-propyllithium solution. The mixture was stirred for thirty minutes and then carbonated.

The carbonation mixture was acidified and the ether layer was extracted with a dilute solution of sodium carbonate. The aqueous solution was warmed on the steamplate to remove the dissolved ether and it was then cooled and acidified. The crude acid was a yellow, sticky solid (2.4 g.) which was taken up in an ethanol-water mixture and allowed to crystallize. After a week a white solid m.p. 194-200° precipitated, and after a single crystallization 0.3 g. of yellow solid melting at 207-208° was obtained[162]. Since the acetal of *p*-acetylbenzoic acid was already partially cleaved during the workup, no further attempt was made to isolate it. To the filtrate containing the remainder of the acid was added some glacial acetic acid and several milliliters of hydriodic acid. The solution was heated on the steamplate for approximately one-half hour and then cooled. The precipitated acid was recrystallized from boiling water to give 0.70 g. of white acid, m.p. 205-206°. A mixed m.p. with the yellow acid (m.p. 207-208°) was 205-208°. The total yield of *p*-acetylbenzoic acid was 1.0 g. (30.5%)

Anal. Calcd. for $C_9H_8O_3$: neut. equiv., 164. Found: neut. equiv., 170.

The methyl ester was prepared by the action of diazomethane in ether solution. After a single crystallization from hot water the m.p. was 95-96°[162].

n-Propyllithium and Methyl p-Bromobenzoate at -78°.- Ninety-eight milliliters (0.0593 mole) of *n*-propyllithium solution cooled to -78° were added rapidly to 12.8 g. (0.0593 mole) of methyl *p*-bromobenzoate

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[162] Meyer, *Ann.*, *219*, 263 (1883) reported the m.p. of *p*-acetylbenzoic acid 200° dec. and the m.p. of the methyl ester 92°, each obtained from hot water. Later workers Rupe and Steinbach, *Ber.*, *43*, 3466 (1910) and Pfeiffer, Kollbach and Haack, *Ann.*, *460*, 147 (1928) reported the m.p. of the acid 205° and 210°, respectively. All m.p.'s were uncorrected.

in 200 ml. of ether at -78°. Color Test II-A was negative at the end of seven minutes and the reaction mixture was carbonated at the end of twelve minutes.

By extraction of the carbonation mixture with water and subsequent acidification of the aqueous layer, 0.2 g. (1.9%) of acid, m.p. 190-220°, was obtained. After a single crystallization from an ethanol-water mixture the m.p. was raised to 200-215°. Sublimation of the latter material gave a trace of acid m.p. ca. 232°. The m.p. reported[163] for p-carbomethoxybenzoic acid was ca. 230°. This acid was converted to the methyl ester with diazomethane in ether but the amount was too small for adequate purification.

The ether soluble material was distilled to give fraction I b.p. 130-160°, a solid, and fraction II b.p. 160-165°, n_D^{20} 1.5377, $d^{20/20}$ 1.255.

Fraction I yielded 1.6 g. of methyl p-bromobenzoate m.p. 79-80°. A mixed m.p. with an authentic specimen was not depressed.

The molar refraction of fraction II was 56.7 which is high for p-bromobutyrophenone (calcd. 52.46). A 2,4-dinitrophenylhydrazone of this material has been prepared (m.p. 200-201°).

n-Propyllithium and Methyl p-Iodobenzoate at -78°.- To a well agitated suspension of 10 g. (0.0382 mole) of methyl p-iodobenzoate in 200 ml. of ether cooled to -78° were added 52.5 ml. (0.0382 mole) of n-propyllithium solution at -78°. The reaction was allowed to

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[163] Kattwinkel and Wolffenstein, Ber., 37, 3222 (1904).

proceed for five minutes and then the mixture was carbonated.

The carbonation mixture yielded only 0.07 g. (1%) of crude acid m.p. 180-205°. Purification through the preparation of the methyl ester with diazomethane was attempted. The ester was recrystallized to m.p. 122-128° but the amount was too small to carry this through more crystallizations. Pure dimethyl terephthalate melts at 141°.

t-Butyl *p*-Bromobenzoate.- This sterically-hindered ester was prepared in essential accordance with the directions given by Norris and Rigby[164] for the preparation of *t*-butyl benzoate. *p*-Bromobenzoyl chloride was reacted with *t*-butyl alcohol in the presence of pyridine to give the desired product.

p-Bromobenzoyl chloride was prepared by the action of thionyl chloride upon 20.1 g. (0.1 mole) of *p*-bromobenzoic acid[165]. The product distilled at 118°/14 mm. giving long needles, m.p. 37-38°, after crystallization. The reported boiling point[165] was 117-120°/15 mm. and the reported melting point[166] was 42°.

The *p*-bromobenzoyl chloride was mixed with 0.14 mole of *t*-butyl alcohol and 0.2 mole of pyridine, and the mixture was allowed to stand overnight. The product was distilled at 107°/0.1 mm. to give 5.5 g. (21.4%), which after redistillation at 138-139°/12 mm. had n_D^{20} 1.5240, $d^{20/20}$ 1.309, MR_D 60.11 (calcd. 58.72).

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[164] Norris and Rigby, *J. Am. Chem. Soc.*, *54*, 2088 (1932).

[165] Müller, *J. prakt. Chem.*, *121*, 109 (1929).

[166] Schotten, *Ber.*, *21*, 2249 (1888).

Anal. Calcd. for $C_{11}H_{13}O_2Br$: Br, 31.1. Found: Br, 30.5.

In a second preparation 0.174 mole of p-bromobenzoic acid was converted to the acid chloride and after two distillations at 12 mm., 32.4 g. (85%) of p-bromobenzoyl chloride, m.p. 36-37°, were obtained.

Using t-butyl alcohol which had been dried over barium oxide and pyridine which had been dried by azeotropic distillation with benzene, 0.146 mole of p-bromobenzoyl chloride was converted in ether solution to 14.9 g. (39.2%) of the ester, n_D^{20} 1.5240, and 10.8 g. (38.6%) of p-bromobenzoic anhydride[167], m.p. 214-216°. From the sodium carbonate extract 3.1 g. (10.6%) of p-bromobenzoic acid was obtained.

The physical constants on the ester from the second preparation were determined and found to agree well with those reported.

n-Propyllithium and t-Butyl p-Bromobenzoate.- To a solution of 3.92 ml. (0.02 mole) of t-butyl p-bromobenzoate in 50 ml. of ether at -35 to -40° were added rapidly 35 ml. (0.03 mole) of n-propyllithium solution. The reaction time before carbonation was ten minutes.

The carbonation mixture was acidified, and the ether layer was separated and extracted with sodium carbonate solution. The aqueous layer was freed of ether on the steamplate, cooled and acidified. The oil obtained was taken up in ether and a milliliter of concentrated sulfuric acid was added. After evaporation of the ether, dilution with

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[167] Robertson and Neish, Can. J. Research, 26B, 737 (1948) gave m.p. 219-219.5°. The action of wet pyridine on p-chlorobenzoyl chloride was given as method of preparation of this aromatic acid anhydride. See Allen, Kibler, McLachlin and Wilson, Org. Syntheses, 26, 1 (1946).

water and partial neutralization, no terephthalic acid was obtained.

The neutral substance from the ether solution was distilled at 168-172°/12 mm. The distillate did not give a test with 2,4-dinitrophenylhydrazine reagent but did give a test for active hydrogen with lithium aluminum hydride. The yield of p-bromophenyl-di-n-propylmethanol was 3.25 g. (60%) having n_D^{20} 1.5340, $d^{20/20}$ 1.248, MR_D 67.53 (calcd. 67.83).

Anal. Calcd. for $C_{13}H_{19}OBr$: Br, 29.5. Found: Br, 29.3. It is possible that a small amount of p-bromobutyrophenone may have been formed, but this is inconsistent with a negative 2,4-dinitrophenylhydrazine test and the fact that t-butyl esters react promptly with Grignard reagents to give tertiary alcohols[142].

Preparation of 4-Bromophenyl 2-Tetrahydropyranyl Ether.- As an orienting preparation, the 2-tetrahydropyranyl ether of p-bromophenol was prepared by the method of Parham and Anderson[96]. One-quarter mole of p-bromophenol was added to 0.5 mole of dihydropyran containing four drops of concentrated hydrochloric acid. The crude yield was 65.5 g. and after crystallization from ethanol the yield was 59.5 g. (92.5%) of product, m.p. 56-57°. The reported m.p. was 57-57.5° and the reported yield was 83%.

2,4,6-Tribromophenyl 2-Tetrahydropyranyl Ether (Attempted).- 2,4,6-Tribromophenol (0.05 mole) was added to 10 ml. of dihydropyran containing two drops of concentrated hydrochloric acid. The phenol went into solution with slight warming. After twenty-one hours at room temperature, the reaction mixture was taken up in ether and washed with 10% sodium hydroxide solution. The ether solution was dried over anhydrous sodium sulfate. After removal of the ether the 4.0 g. of residue were shown to be the sodium salt of 2,4,6-tribromophenol by the following procedure. The solid from the distillation flask gave a large residue and a characteristic sodium flame upon ignition. It was also water-soluble and gave a colored silver salt upon addition of an aqueous silver nitrate solution. A solution of the sodium salt in water upon treatment with dilute hydrochloric acid gave 2,4,6-tribromophenol, m.p. 94-95°.

In a second preparation the reactants were heated over the steam bath for 2 hours. No acetal was obtained and 74.5% of the 2,4,6-tribromophenol was recovered.

A third preparation was also unsuccessful. The reactants in this case were refluxed for 4.25 hours at 150-155°. An 82% recovery of 2,4,6-tribromophenol was obtained.

<u>2,4-Dibromo-1-naphthyl 2-Tetrahydropyranyl Ether</u> (Attempted).- 2,4-Dibromo-1-naphthol (0.07 mole) was added to 12 ml. of dihydropyran containing one drop of concentrated hydrochloric acid. The phenol went into solution and the mixture was allowed to stand seventeen hours at room temperature.

As soon as alkali was added to an ether solution of the reaction mixture, a heavy, blue, indigo-like precipitate formed immediately[168]. Since this colored precipitate was due to the oxidized salt of 2,4-dibromo-1-naphthol, the mixture was not further investigated.

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[168] Dahmer, Ann., 333, 367 (1904).

<u>2-Tetrahydropyranyl p-Bromobenzoate</u> (Attempted)[169].- One-tenth mole (20.1 g.) of p-bromobenzoic acid was added to 34 ml. of dihydropyran which had been warmed on the steamplate. The acid did not go into solution with the addition of one drop of concentrated hydrochloric acid and heating at 110° for four hours. The reaction mixture was worked up in the usual way to give 18.5 g. (92%) of p-bromobenzoic acid.

<u>2-Bromophenyl 2-Tetrahydropyranyl Ether</u>.- One-tenth mole (17.3 g.) of o-bromophenol was added in 5 cc. portions to 20 ml. of dihydropyran containing one drop of concentrated hydrochloric acid. The reaction was exothermic and quite rapid. The flask was allowed to stand at room temperature for four hours.

Ether was added to the reaction mixture and the solution was immediately extracted with two 30 ml. portions of 10% sodium hydroxide and one 30 ml. portion of water. The ether layer was dried over anhydrous sodium sulfate. After removal of the ether the product distilled at 111-114°/0.08 mm. yielding 22.7 g. (88.4%) of distillate; n_D^{20} 1.5490, $d^{20/20}$ 1.392, MR_D 58.77 (calcd. 59.48).

Since the MR_D did not agree well with the calculated value, the alkali extraction was repeated and the purified material was distilled at 116-117°/0.05 mm. The yield was 19.2 g. (74.7%), n_D^{20} 1.5473, $d^{20/20}$ 1.384, MR_D 58.95 (calcd. 59.48).

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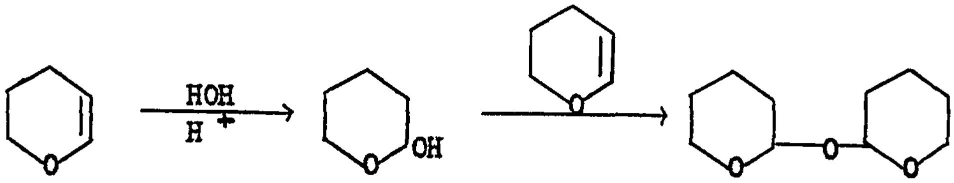
[169] This procedure is the same as that used by Woods and Kramer[98] who were able to prepare 2-tetrahydropyanyl 3,5-dinitrobenzoate in quantitative yield from dihydropyran and 3,5-dinitrobenzoic acid.

Anal. Calcd for $C_{11}H_{13}O_2Br$: Br, 31.1. Found: Br, 29.7, 29.9. It is possible that the low bromine analysis may be due to contamination of the product by some other condensation reaction of dihydropyran in the presence of moisture, e.g.,



2,4-Dibromophenyl 2-Tetrahydropyranyl Ether.- 2,4-Dibromophenol (0.07 mole) was added to 12 ml. of dihydropyran containing one drop of concentrated hydrochloric acid. A gentle warming of the flask was observed. The mixture was swirled and warmed on the steamplate for about five minutes and then allowed to stand at room temperature for 4.5 hours.

The reaction mixture was worked up in the usual way. The product distilled at 160-162°/0.2 mm. yielding 18.0 g. (76.5%) of distillate having n_D^{20} 1.5774, $d^{20/20}$ 1.662, MR_D 67.03 (calcd. 67.25).

Anal. Calcd. for $C_{11}H_{12}O_2Br_2$: Br, 47.5. Found: Br, 46.7.

n-Propyllithium and 2,4,-Dibromophenyl 2-Tetrahydropyranyl Ether.- Seventy-two milliliters (0.0785 mole) of n-propyllithium were added rapidly to 8.0 ml. (13.2 g., 0.0393 mole) of 2,4-dibromophenyl 2-tetrahydropyranyl ether dissolved in 25 ml. of anhydrous ether. A rather vigorous refluxing of the ether was maintained throughout the addition. A white precipitate formed before the addition of the n-propyllithium was complete. The mixture was allowed to stir for seventy minutes and then a 50 ml. aliquot was carbonated in the usual fashion. The remainder of the reaction mixture was refluxed for two hours and then carbonated. Color Test II-A was negative and Color Test I was positive before carbonation of this second aliquot.

The carbonation mixtures were worked up in the usual way. The tetrahydropyranyl ether obtained from each fraction was hydrolyzed by hot dilute hydriodic acid solution containing sufficient ethanol to effect solution of the acid. The yield from the seventy-minute reaction was 0.70 g. (16.4%) of 5-bromosalicylic acid. From the three-hour reaction 1.35 g. (31.7%) of 5-bromosalicylic acid were obtained. A mixed m.p. determination with an authentic specimen[170] of 5-bromosalicylic acid (m.p. 167-168°) showed no depression.

n-Propyllithium and 4,6-Dibromo-o-cresol.- After titration, 93 ml. (0.105 mole) of n-propyllithium solution were added over a period of seven minutes to 9.3 g. (0.035 mole) of 4,6-dibromo-o-cresol in 15 ml. of anhydrous ether. The reaction mixture was stirred for one hour and a 50 ml. aliquot was removed and carbonated. The remainder of the solution was refluxed for two hours and then carbonated.

The carbonation mixtures were worked up separately by water extraction and acidification. From the one-hour reaction 2.75 g. (68%) of 2-hydroxy-3-methyl-5-bromobenzoic acid m.p. 226-231° were obtained. From the three-hour reaction 3.20 g. (79%) of the same acid m.p. 226-231° were obtained. After a single crystallization from an ethanol-water mixture the m.p. was 236-237° with

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[170] Kindly furnished by Dr. S. V. Sunthankar.

decomposition[171]. A portion of the recrystallized acid was acetylated with acetic anhydride to give an acetyl derivative[171] of m.p. 154-156°.

C. Reduction. A Side Reaction in the Phenol Series

n-Propyllithium and 2,6-Dibromophenol.- Fifty-five milliliters (0.09 mole) of n-propyllithium solution were added over a ten-minute period to 7.6 g. (0.03 mole) of 2,6-dibromophenol dissolved in 50 ml. of anhydrous ether. At first the lithium salt appeared to be very insoluble in the ether, but as the addition continued it went into solution. The reaction mixture was stirred for one hour at room temperature and then carbonated.

In a second run 35 ml. (0.058 mole) of n-propyllithium solution were added over a period of five minutes to 4.9 g. (0.0195 mole) of 2,6-dibromophenol dissolved in 50 ml. of ether. The reaction mixture was refluxed for three hours and then carbonated in the usual fashion.

The two carbonation mixtures were worked up concurrently by water extraction and acidification of the aqueous layer with hydrochloric acid. The acids were filtered and the filtrates were concentrated.

The water-insoluble acids (high m.p.) were dissolved in sodium bicarbonate solution and the insoluble material was extracted with ether. The acids were recovered, extracted with boiling water, combined, dissolved in 10% sodium hydroxide solution, treated with bone black, filtered and acidified. The acid obtained had a m.p. ca. 250°

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[171] Fortner, Monatsh., 22, 950 (1901) reported m.p. 236° for 2-hydroxy-3-methyl-5-bromobenzoic acid and m.p. 155° for the acetyl derivative.

with decomposition and a neutral equivalent of 234. Upon ignition, a carbonaceous residue formed which was burned only with difficulty. In spite of the low equivalent weight as determined by titration, this dark high melting material was thought to be of a polymeric nature[172].

The material which crystallized from the filtrate after extraction of the high melting acids with boiling water was sublimed by heating over a steam bath. The sublimate (0.38 g.) consisted of long needle-like crystals of an acid, m.p. 89-90°. The compound gave no halogen test upon fusion with sodium. The ferric chloride test was blue to blue-violet compared with a similar test on salicylic acid which was a wine or red-violet color. The neutral equivalent was found to be 173. Since this substance is a hydroxy carboxylic acid, the value for the neutral equivalent may not be a reliable measure of the equivalent weight.

Salicylic acid was obtained from the concentrated filtrates. It was purified by crystallization from water and then sublimed.
Table VII and accompanying footnotes give the details.

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[172] Hunter, Olson and Daniels, _J. Am. Chem. Soc._, _38_, 1761 (1916).

Table VII

n-Propyllithium and 2,6-Dibromophenol

Time	Water-insoluble Acid				Salicylic Acid		
	Crude		Bicarbonate soluble		From hot water		
hrs.	m.p., °C.	g.	m.p., °C.	g.	m.p., °C.	g.	%
1	235	3.0	paste	—	ca. 150[a]	0.45	17
3	ca. 219	1.57	ca. 235-245	1.35	148-154[b]	0.70	17

[a] After sublimation the m.p. was 155-156° and a mixed m.p. with salicylic acid (m.p. 157-158°) was 156-158°.

[b] The crude acid was dissolved in water, treated with bone char, filtered and crystallized to give 0.25 g. (9%) m.p. 155-157°, mixed m.p. with salicylic acid 156-157°.

Purification of 2,4,6-Tribromophenol.- Eastman "practical" grade 2,4,6-tribromophenol (120 g.) was taken up in ethanol, treated with Norit A, filtered and diluted with water. The recovery of pure 2,4,6-tribromophenol, m.p. 95-96°, was 111 g. (92.5%). The reported melting point[173] is 95-96°.

Preparation of 5-Bromosalicylic Acid.- Salicylic acid was brominated in essential accordance with the procedure of Hewitt et al[174,4]. To 13.8 g. (0.1 mole) of salicylic acid dissolved in 100 ml. of glacial acetic acid were added 20 g. (11.8 ml.) of concentrated sulfuric acid. Fifty ml. of a solution of 16 g. of bromine in glacial

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[173] Lassar-Cohn and Schultze, Ber., 38, 3297 (1905).

[174] Hewitt, Kenner and Silk, J. Chem. Soc., 85, 1228 (1904).

acetic acid were added slowly to the solution of salicylic acid at 30-40°. The mixture was gently warmed on the steamplate and then allowed to remain overnight at room temperature.

The mixture was refluxed gently for thirty minutes, and then the acetic acid was removed under vacuum from a water pump. The solid residue was filtered after dilution with water. The crude acid melted at 150-160°, and after treatment with Norit A in ethanol solution followed by crystallization from dilute ethanol the m.p. was 153-165°.

The recrystallized acid was then crystallized from an ethanol-petroleum ether (b.p. 60-70°) mixture to give 7.5 g. (34.5%) of 5-bromosalicylic acid, m.p. 167-168°. A mixed m.p. between this sample and the one used earlier showed no depression[175]. An additional 6.2 g. of acid, m.p. below 160°, were also obtained but this was not purified.

n-Propyllithium and 2,4,6-Tribromophenol.- In a typical experiment, 45.5 ml. (0.072 mole) of n-propyllithium solution were added to 7.95 g. (0.024 mole) of 2,4,6-tribromophenol in 50 ml. of ether over a period of six minutes. The reaction mixture was stirred at room temperature for one hour and then carbonated in the usual fashion.

In a second run 45.5 ml. (0.072 mole) of n-propyllithium were added over a three-minute period to 0.024 mole of 2,4,6-tribromophenol in 50 ml. of ether. The reaction mixture was refluxed for three hours and then carbonated.

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[175] See Page 74.

Each carbonation mixture was worked up by water extraction and acidification with hydrochloric acid. The oil obtained in this manner was extracted with ether and the ether extract was washed with a sodium bicarbonate solution. The sodium bicarbonate solution was warmed on the steamplate to remove the dissolved ether. The solution was filtered, cooled and acidified. The yields of crude acids from the one-hour and three-hour runs were 2.72 g. and 2.60 g., respectively.

These rather dark acids were extracted with boiling water containing a small amount of ethanol. The black insoluble tar was discarded and the acid from the filtrate was recrystallized from an ethanol-water mixture. The yield of 5-bromosalicylic acid from the one-hour run was 1.50 g. (29%) m.p. 159-161°, and the yield from the three-hour run was 1.35 g. (26%) m.p. 163-164°. A mixed m.p. with 5-bromosalicylic acid (m.p. 165-166°) and the acid from the three-hour run was 163-164°. See Table VIII and accompanying footnotes for details of reactions carried out under other conditions.

Great difficulty was experienced in the purification of 5-bromosalicylic acid by ordinary procedures. Recrystallization from hot water has been found most satisfactory, but in some cases several successive crystallizations did not effect appreciable purification. Literature values for the melting point (uncor.) varied between 161° and 168°, the latter value apparently being the correct one.

Table VIII

Interconversion and Reductive *ortho*-Debromination of 2,4,6-Tribromophenol

n-C_3H_7Li[a] in ether		$Br_3C_6H_2OH$[b] in ether		Addition Time	Reaction Time(27°)	From Carbonation Mixture: 5-Bromosalicylic Acid[c] (crude)			p-Bromophenol[d] (as benzoate)		
mole	ml.	mole	ml.	min.	min.	g.	%	m.p., °C.	g.	%	m.p., °C.
0.142	106	0.0355	50	10	67	2.60[e]	33.8	160-163	—	—	—
0.145	109	0.0725	100	15	60	0.70[f]	17.8	150-160	—[g]	—	—
0.137	81	0.0685	250	27	60	3.30[h]	22	165-166	2.10[i]	11	104.5-105.5
0.145	88	0.0483	200	17	(20 (43 reflux	4.30[j]	41	157-162	—[k]	—	—
0.100[l]	98	0.033	100	20	65	1.80[m]	25	160-163	0.30[n]	3.3	105-106
0.0945[l]	97	0.0473	130	27	60	3.75[o]	36.5	164-167	0.40[p]	3.0	104-105
0.0658[l]	43	0.0329	115	3	0.5	2.55[q]	35.8	150-160	—[r]	—	—
0.0535[l,s]	39	0.0535	250	8	60[t]	—	—	—	—	—	—

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[a] In each case the *n*-propyllithium solution was added to an ether solution of 2,4,6-tribromophenol. See Gilman and Arntzen, *J. Am. Chem. Soc.*, *69*, 1537 (1947) for a discussion of side reactions possible in reversed addition.

[b] Tribromophenol was not recovered from any of the experiments employing more than an equivalent amount of *n*-propyllithium.

[c] Identified by mixed m.p. with an authentic specimen, m.p. 167-168°.

[d] *p*-Bromophenol apparently is formed as a result of hydrolysis of the intermediate O-lithio-2-hydroxy-5-bromophenyllithium during carbonation. Subsequent to removal of the carboxylic acids from ether solution with sodium bicarbonate, the phenols were removed by extraction with 5-10% sodium hydroxide solution. Benzoylation of the phenols recovered from the alkaline solution was carried out in 10% sodium hydroxide solution with an excess of benzoyl chloride. Identity was established by mixed m.p. with authentic *p*-bromophenyl benzoate m.p. 105-106°.

[e] The salts were extracted from the carbonation mixture with water and the solution was filtered acidified. The crude acid was treated with Norit A in an ethanol-water solution. After filtration

[e] The salts were extracted from the carbonation mixture with water and the solution was filtered and acidified. The crude acid was treated with Norit A in an ethanol-water solution. After filtration and dilution, the solution was boiled and filtered while hot. The acid crystallized from the filtrate, mixed m.p. with 5-bromosalicylic acid 163-164°.

[f] One fourth (50 ml.) of the reaction mixture was carbonated and acidified. The separated ether layer was extracted with sodium bicarbonate solution and after acidification the crude acids were extracted with boiling water and filtered. Recrystallization raised the m.p. to 153-160°. A mixed m.p. with salicylic acid (m.p. 157-158°) was 122-148° and with 5-bromosalicylic acid was 159-162°.

[g] Benzoylation of the phenolic material did not give a pure derivative. The remaining three-fourths of the reaction mixture was treated with 0.06 mole methyl iodide and after 5.25 hours Color Test I was negative. The reaction mixture was acidified and the separated ether layer was extracted with 5% sodium hydroxide solution. The phenol was recovered from the alkaline solution and distilled at 123-124°/12 mm. to give 3.7 g. (39%) of oil which was identified as *p*-bromophenol through the benzoate, m.p. 104-105°. A mixed m.p. with *p*-bromophenyl benzoate was 104-105°. It is uncertain whether the *p*-bromophenol was formed by reduction or hydrolysis of the intermediate O-lithio-2-hydroxy-5-bromophenyllithium.

[h] See note "f" above for separation of 5-bromosalicylic acid, mixed m.p. with authentic sample 165-167°. The crude acid before extraction with boiling water weighed 8.7 g., m.p. 157-205°, neut. equiv. 238. Attempted purification of the amorphous water-insoluble acid by decolorization in ethanol solution followed by filtration and dilution with water gave an amorphous gray-green acid which burned with a smoky flame depositing a large carbonaceous residue.

[i] The phenolic material was recovered from the basic extract by acidification, ether extraction and distillation at 116-118°/12 mm. to give 2.2 g. of oil. The oil was benzoylated and a mixed m.p. with *p*-bromophenyl benzoate was 104.5-105.5°. By use of a closed system arranged so that the gases from the reaction were passed through bromine traps, a drop of propylene bromide n_D^{20} 1.5200, b.p. 137° was obtained. Kharasch and Mayo, *J. Am. Chem. Soc.*, *55*, 2468 (1933) reported n_D^{20} 1.5194 and Linnemann, *Ann.*, *161*, 42 (1872) gave b.p. 141.6° (cor.).

[j] See note "f" for the separation of 5-bromosalicylic acid. A small sample was recrystallized from water containing a small amount of ethanol. The m.p. was 164-167° and a mixed m.p. with 5-bromosalicylic acid was 165-167°. The dark, amorphous, water-insoluble acid (2.05 g.) was not investigated.

[k] The phenolic material was not extracted and identified. By use of the closed system and suitable bromine traps to absorb unsaturated hydrocarbons, 1.2 ml. (21.6%) of propylene bromide (n_D^{20} 1.5197, b.p. 137°, $d^{20/20}$ 1.757) were obtained. The reported density of this halide is 1.933 at 20° [Dahlbaum, *Z. physik. Chem.*, *26*, 626 (1898)].

[l] Clarified by filtration under pressure through an asbestos pad.

[m] See note "f" for separation of 5-bromosalicylic acid. A small sample was recrystallized from water containing a small amount of ethanol after decolorization with Norit A in the same solvent. The m.p. was 163-165° and a mixed m.p. with 5-bromosalicylic acid was 165-168°. The amorphous water-insoluble acid (1.3 g.) was not investigated.

[i] The phenolic material was recovered from the basic extract by acidification, ether extraction and distillation at 116-118°/12 mm. to give 2.2 g. of oil. The oil was benzoylated and a mixed m.p. with *p*-bromophenyl benzoate was 104.5-105.5°. By use of a closed system arranged so that the gases from the reaction were passed through bromine traps, a drop of propylene bromide n_D^{20} 1.5200, b.p. 137° was obtained. Kharasch and Mayo, *J. Am. Chem. Soc.*, *55*, 2468 (1933) reported n_D^{20} 1.5194 and Linnemann, *Ann.*, *161*, 42 (1872) gave b.p. 141.6° (cor.).

[j] See note "f" for the separation of 5-bromosalicylic acid. A small sample was recrystallized from water containing a small amount of ethanol. The m.p. was 164-167° and a mixed m.p. with 5-bromosalicylic acid was 165-167°. The dark, amorphous, water-insoluble acid (2.05 g.) was not investigated.

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[m] See note "f" for separation of 5-bromosalicylic acid. A small sample was recrystallized from water containing a small amount of ethanol after decolorization with Norit A in the same solvent. The m.p. was 163-165° and a mixed m.p. with 5-bromosalicylic acid was 165-168°. The amorphous water-insoluble acid (1.3 g.) was not investigated.

[n] See note "d" for separation and derivatization of the phenolic material. Mixed m.p. with *p*-bromophenyl benzoate 105-106°. By use of a closed system and passing the gases from the reaction through bromine, 1.0 ml. of organic halide was obtained. After drying and neutralization of the acid only a few drops of a pungent liquid having n_D^{20} 1.5325 were obtained.

[o] See note "f" for separation of 5-bromosalicylic acid, mixed m.p. with an authentic specimen, 165-168°. Three grams of amorphous acid were obtained.

[p] See note "d". A mixed m.p. with *p*-bromophenyl benzoate was 105-106°.

[q] See note "f" for separation of 5-bromosalicylic acid. Two recrystallizations from water containing a trace of ethanol raised the m.p. to 152-158° and a mixed m.p. with an authentic sample of 5-bromosalicylic acid was 158-164°. The amorphous acid (3.3 g.) was not investigated.

[r] See note "d". The derivative was an oil and was not further investigated.

[s] Determined by simple acid titration.

[t] The mixture was hydrolyzed and the phenol was extracted with 5% sodium hydroxide. No ethanol-insoluble polymer was obtained from ether solution. See Hunter and Dahlen, *J. Am. Chem. Soc.*, *54*, 2456 (1932) and Raiford and Le Rosen, *ibid.*, *68*, 397 (1946) for information on the catalytic conversion of metal salts of polyhalogenophenols to amorphous polymers.

Preparation of 4-Bromo-2-methylphenol[176].- An authentic specimen of 4-bromo-2-methylphenol was prepared by the introduction of 8.0 g. (0.05 mole) of bromine in chloroform solution into a cooled solution of 9.35 g. (0.05 mole) of o-cresol in chloroform containing 0.5 g. of iron wire. After removal of the chloroform the product was distilled at 124-127°/12 mm. to give 7.2 g. (77%) of distillate, m.p. 52-56°. Recrystallization from petroleum ether (b.p. 60-70°) yielded 4.8 g. (51.3%) of pure 4-bromo-2-methylphenol, m.p. 64-65°.

A sample of this phenol was treated with benzoyl chloride in 10% sodium hydroxide and the derivative was crystallized from an ethanol-water mixture. The m.p. was 67-68° compared with the reported value[177] 63-64°.

Methylation of Interconverted 2,4,6-Tribromophenol.- Since the observed reduction in the halogen-metal interconversion of 2,4,6-tribromophenol with n-propyllithium may have been due to some peculiarity of the carbonation reaction, methylation of the intermediate organometallic compound with methyl iodide[148] was carried out. n-Propyllithium (0.137 mole) was added over a ten-minute period to 14.9 g. (0.045 mole) of 2,4,6-tribromophenol in 100 ml. of ether. The reaction mixture was stirred for one hour, and then 5.92 ml. (0.095 mole) of methyl iodide in 50 ml. of ether were added over a period of five minutes. At the end of fifteen minutes Color Test I was strongly positive.

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[176] Claus and Jackson, J. prakt. Chem., [2] 38, 324 (1888).

[177] Jadhav and Rangwala, J. Univ. Bombay, 3, 161 (1934) [C.A., 29, 4748 (1935)].

After 2.75 hours of stirring Color Test I was negative. The reaction mixture was hydrolyzed and acidified. The aqueous layer was extracted five times with small portions of ether and the combined ether extracts were in turn washed with 5% sodium hydroxide solution. (During the latter extraction a considerable amount of the aqueous layer was inadvertently spilled.) The aqueous layer was acidified and the phenol was taken up in ether. The ether was removed by distillation and the product was distilled at 125-127°/12 mm. The distillate was a brown oil which solidified upon seeding with crystals which formed in the condenser.

The solid was taken up in petroleum ether (b.p. 60-70°) containing some ethanol, and the solution was treated with Norit A, filtered and concentrated under a stream of air. A few small pieces of Dry Ice were added to initiate the crystallization. The product rapidly solidified in needle-like crystals which after being pressed on a porous plate melted at 58-63°. After recrystallization from petroleum ether (b.p. 60-70°), 0.70 g. (8.3%) of 4-bromo-2-methylphenol, m.p. 64-65° was obtained. A mixed m.p. with an authentic specimen (m.p. 64-65°) showed no depression.

The ether-soluble material remaining after alkali extraction was found to consist of only a few drops of oily substance which was not investigated. This indicated that a negligible amount of O-methylation had occurred.

n-Propyllithium and 2,4-Dibromophenol.- The apparatus employed in this experiment was the conventional 500 ml. three-necked flask fitted with a dropping funnel, mercury seal stirrer and condenser. The nitrogen train was connected to the side arm of the dropping funnel. The gases from the reaction were taken from the condenser and passed through a trap arrangement whereby the unsaturated hydrocarbons were absorbed into bromine. The sequence of traps (22 x 175 mm. test tubes) was as follows: empty trap, soda lime tube, two bromine traps each containing 3 ml. of bromine covered by several ml. of water, soda lime tube and oil bottles. The three traps were immersed in ice during the reaction.

One-half (47.5 ml., 0.0745 mole) of the n-propyllithium solution was added to 0.0745 mole of 2,4-dibromophenol in 110 ml. of anhydrous ether over a period of twenty minutes. The remaining 47.5 ml. of n-propyllithium solution were then added during three minutes. The mixture was refluxed for an hour and then 100 ml. of the solution was carbonated.

Four ml. (0.064 mole) of methyl iodide were added to methylate the remaining interconversion product. Color Test I was negative at the end of 4.5 hours. The reaction mixture was acidified with dilute hydrochloric acid and then allowed to stand overnight.

The carbonation mixture was acidified and the carboxylic acid was extracted from the ether with sodium bicarbonate solution. The phenolic substances were extracted with 5% sodium hydroxide solution. The ether solution of the neutral substances was not investigated.

From the sodium bicarbonate solution by acidification, 7.0 g. (87%) of 5-bromosalicylic acid, m.p. 167-168°, were obtained. A mixed m.p. with an authentic specimen (m.p. 167-168°) showed no depression.

The phenolic substances were recovered from the alkaline extract by acidification and ether extraction. This oil was benzoylated in 10% sodium hydroxide solution to give 0.95 g. (4.6%) of p-bromophenyl benzoate, m.p. 105-106°, after a single crystallization from an ethanol-water mixture. A mixed m.p. with p-bromophenyl benzoate (m.p. 105-106°) was not depressed.

The phenol from the methylation reaction was extracted from the ether solution with 5% sodium hydroxide. The basic solution was acidified and extracted with ether. The ether layer was dried over sodium sulfate and then the ether was removed by distillation over a water bath. The residue was distilled at 120-125°/12 mm. The liquid distillate (3.0 g.) was benzoylated and the derivative was recrystallized from an ethanol-water mixture to give 1.70 g. (15.7%) of 4-bromo-2-methylphenyl benzoate, m.p. 58-60°. A mixed m.p. with 4-bromo-2-methylphenyl benzoate (m.p. 67-68°) was 58-63°. Two more recrystallizations from the same solvent pair did not raise the melting point. Crystallization from 95% ethanol raised the m.p. to 61-63° and a mixed m.p. with the authentic specimen was 63-65°.

The neutral material from the methylation reaction was obtained as a small dark oily residue after evaporation of the ether. This material was not investigated.

The bromine in the traps was destroyed with sodium bisulfite solution. The droplet of propylene bromide from the first trap was washed with water and dried over anhydrous calcium sulfate. Two physical constants[178] were determined; n_D^{20} 1.5212, b.p. 140°.

n-Propyllithium and 2,4,6-Tribromoanisole.- n-Propyllithium solution (0.145 mole in 102 ml. of ether) was added over a period of fifteen minutes to 0.0485 mole of 2,4,6-tribromoanisole in 140 ml. of ether. The reaction mixture turned brown and a precipitate formed. After one hour of stirring the mixture was carbonated.

The salts were extracted from the ether with water and the dissolved ether was removed from the aqueous solution by gentle warming on the steamplate. The solution was cooled in an ice bath and then acidified with hydrochloric acid. A considerable amount of butyric acid seemed to be present as determined by the odor.

The acid was removed by filtration, but as it warmed to room temperature it became very sticky. Several attempts were made to crystallize the substance but all failed.

In a second experiment, 46 ml. (0.06 mole) of n-propyllithium solution were added to 0.02 mole of 2,4,6-tribromoanisole in 50 ml. of ether cooled to -20°. The time of addition was five minutes and the time of reaction before carbonation was one hour.

The acid was obtained as a heavy white precipitate and the odor of butyric acid was observed. The yield of crude acid softening over a wide range and melting at 184° was 4.70 g. or 85.5% calculated as 2-methoxy-5-bromo-1,3-dicarboxybenzene. The equivalent weight of this crude acid was 156 compared with a calculated value of 137.5. After

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[178] See note i, Table VIII, page 80.

several crystallizations from petroleum ether (b.p. 60-70°) containing some absolute ethanol, the m.p.[179] on 2.0 g. (36.4%) was 195-198° but the neutral equivalent was still high (152).

Preparation of 2,6-Dibromoanisole[180].- Nine grams of anhydrous potassium carbonate and 3.7 ml. (0.0393 mole) of dimethyl sulfate were added to 6.60 g. (0.0262 mole) of 2,6-dibromophenol dissolved in 50 ml. of acetone. The reaction mixture was refluxed for eight hours after which the potassium carbonate was removed by filtration. The acetone was removed and the product was distilled at 120-123°/12 mm. The yield was 5.5 g. (79%), m.p. 12-13°[181].

n-Propyllithium and 1,3,5-Tribromobenzene.- An attempt was made in this case to interconvert each of the three bromine atoms in the molecule, although an example of such an interconversion has never been observed. Forty-four milliliters (0.06 mole) of *n*-propyllithium solution were added over a period of six minutes to 0.02 mole of 1,3,5-tribromobenzene dissolved in 130 ml. of ether. The solution turned brown and then a solid precipitated. The reaction mixture was carbonated after one hour of stirring at room temperature.

The acid was obtained from the carbonation mixture by the usual

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[179] Gilman, Langham and Moore[88] carried out a similar reaction in petroleum ether (b.p. 35-50°) and obtained 75% of 2-methoxy-5-bromo-1,3-dicarboxybenzene, m.p. 192-196°.

[180] This procedure was obtained from Dr. S. V. Sunthankar.

[181] Pope and Wood, *J. Chem. Soc.*, *101*, 1828 (1912) gave the m.p. *ca.* 13°, b.p. 143-145°/34 mm.

procedure of water extraction and acidification. The yield of crude acid was 2.40 g. having a neutral equivalent of 164. After reprecipitation of the acid from aqueous sodium bicarbonate the m.p. was 167-177°. The neutral equivalent was not in agreement with any calculated for the several possible interconversion products[182]. An investigation of the composition of this mixture by means of an ion-exchange resin is in progress.

n-Propyllithium and Pentabromophenol.- *n*-Propyllithium (0.08 mole) was added over a period of ten minutes to 13.05 g. (0.0267 mole) of pentabromophenol dissolved and suspended in 200 ml. of anhydrous ether. The reaction mixture turned to a deep brown color, and after being stirred for an hour at room temperature it was carbonated.

The carbonation mixture was extracted with water and the aqueous solution was acidified. The dark precipitate was extracted with ether and the ether solution in turn was extracted with sodium bicarbonate solution. No acid was obtained from the sodium bicarbonate extraction.

In a second run 4.9 g. (0.01 mole) of pentabromophenol suspended in 125 ml. of ether cooled to -20° were treated with 27 ml. (0.0358 mole) of *n*-propyllithium solution. As soon as one-third of the organometallic solution had been added, the reaction mixture turned to a

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[182] These are: 1,3,5-$C_6H_3(COOH)_3$ 70, 5,1,3-$BrC_6H_3(COOH)_2$ 122.5,

3,5,1-$Br_2C_6H_3COOH$ 280, 1,3-$C_6H_4(COOH)_2$ 83.

Gilman, Langham and Moore[88] were able to interconvert one bromine atom by a special titration technique.

chocolate-brown color. The mixture was carbonated after ten minutes at -20°.

The carbonation mixture was acidified and the ether layer was extracted with sodium bicarbonate solution. The acid obtained from the aqueous solution was a dark, brown, amorphous solid which gave a large carbonaceous residue upon ignition. This material was not further investigated.

D. Preparation of Some Alkamine Ethers

Preparation of 2-Diethylamino-1-phenylethanol.- This synthetic intermediate was prepared by the action of diethylamine upon styrene oxide at reflux temperature.

Styrene oxide (1.0 mole) was added slowly to 1.64 moles of diethylamine brought to reflux in a 500 ml. three-necked flask equipped with a reflux condenser, mechanical stirrer, and dropping funnel. No apparent reaction took place and the mixture was refluxed for thirteen hours.

A total of 56 ml. of diethylamine was recovered by distillation over a water bath. The residue was placed in a 500 ml. Claisen flask and distilled at 135-140°/13 mm. The yield of product was 103 g. (53%) having n_D^{25} 1.5058. Emerson[183] reported 1.5101 and Marvel and du Vigneaud[184] gave 1.507.

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[183] Emerson, *J. Am. Chem. Soc.*, *67*, 516 (1945).

[184] Marvel and du Vigneaud, *ibid.*, *46*, 2093 (1924).

In a second experiment 0.1 mole of styrene oxide was added to 0.2 mole of diethylamine in a Carius tube (vol. 150 ml.). The mixture was cooled in a Dry Ice-acetone bath, and the air was swept out by a stream of dry nitrogen. The tube was sealed and placed in a Carius oven at 70-80° for eight hours.

The excess diethylamine was removed and the product was distilled at 150-151° under vacuum from a water pump. The yield was 10.2 g. (53%) of material having n_D^{25} 1.5041.

The yield was much improved in a later preparation by the addition of a catalytic amount of water. One mole (120 g.) of styrene oxide was added slowly to a well stirred solution of 3 ml. of water in 168 ml. (1.64 moles) of diethylamine. No apparent reaction took place and the solution was then warmed over a hotplate for two hours. The reaction mixture was refluxed over a steam bath for 24 hours and then it was allowed to remain 24 hours at room temperature.

After removal of the excess diethylamine, the product was distilled at 135-140°/13 mm. to give 178.2 g. (92.2%) of 2-diethylamino-1-phenylethanol n_D^{20} 1.5077.

Preparation of 1-Chloroisoquinoline.- The following procedure for the preparation of 1-hydroxyisoquinoline and its conversion to 1-chloroisoquinoline was developed from the sketchy directions given in the literature[185]. Isoquinoline (4.0 g.) and 9.4 g. of fused and

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[185] (a) Chichibabin and Kursanova, J. Russ. Phys.-Chem. Soc., 62, 1211 (1930) [C.A., 25, 2727 (1931); Chem. Zentr., 102, I 86 (1931)]. (b) Chichibabin, Ber., 56, 1879 (1923) and (c) Gabriel and Colman, Ber., 33, 985 (1900).

pulverized potassium hydroxide were heated at 210-235° for 4.5 hours under an atmosphere of dry nitrogen. After the mixture had cooled, the solid was chipped out of the flask into 200 ml. of water and the suspension was acidified. The yield of crude 1-hydroxyisoquinoline obtained by filtration was 3.85 g. (85.5%), m.p. 204-210°. This dark material was taken up in 95% ethanol, treated with Norit A, filtered and crystallized to give 2.70 g. (60%) of colorless needles, m.p. 210-213°. The reported yield and m.p.[185a] were 62.2% and 209-210°, respectively.

One and one-half grams of pure 1-hydroxyisoquinoline were heated with 6 ml. of phosphorus oxychloride for one-half hour. The reaction mixture was poured into ice water and the solution was saturated with sodium carbonate. The suspension of crystals was filtered and washed with cold water. The yield of air-dried 1-chloroisoquinoline was 1.58 g. (93.5%), m.p. 34-35°. The reported m.p.[185c] was 37-38°.

In a subsequent experiment 500 g. of potassium hydroxide in 100 g. portions were fused in a porcelain casserole over a Bunsen flame for fifteen minutes. When the melt began to turn dark it was poured into approximately two liters of white mineral oil contained in a steel dish. After the mass had cooled, it was pulverized under the oil with a steel pestle. The oil was decanted and the crushed potassium hydroxide was transferred to a flask containing a liter of petroleum ether (b.p. 60-70°).

To 200 g. (1.55 moles) of isoquinoline in one-liter three-necked flask were added 470 g. (8.4 moles) of potassium hydroxide which was still wet with petroleum ether. A nitrogen inlet tube, thermometer and condenser for removal of the petroleum ether were attached to the flask. A hotplate was placed under the reaction flask (but not touching it) and the two were surrounded by a sheet of asbestos to conserve heat.

A steady evolution of hydrogen took place between 210-230°. The temperature of the reaction mixture began to rise rapidly and the hotplate was removed. An air jet served to cool the flask and bring the temperature down to 220°. When the hotplate was again put in place, the temperature was inadvertently allowed to go above 250° but fortunately no great amount of gas was given off rapidly at this high temperature. An air jet was again used to cool the flask and the temperature was kept at 220-235° for the remainder of the 4.5 hour heating period.

After the mixture had cooled[186], the alkaline melt was dissolved in water contained in an earthenware crock. The solution and solid were ladled into a four-liter beaker containing cracked ice and neutralized with hydrochloric acid. This operation was carried out in the hood since more than just trace amounts of gas having a cyanide-like odor were liberated. The solid was filtered to give 173 g. (77%) of crude 1-hydroxyisoquinoline which was purified by recrystallization from ethanol.

1-Hydroxyisoquinoline (60 g., 0.413 mole) and 225 ml. (2.46 moles) of phosphorus oxychloride were heated in a one-liter round bottom

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[186] The thermometer should be removed from the mixture before it cools. The flask is almost invariably broken during the cooling and a container should be placed below it.

flask fitted with an air condenser for one-half hour over a hotplate. The reaction mixture was cooled under a water tap and then it was poured into a four-liter beaker half filled with crushed ice. The hydrolysis was vigorous and all the ice was melted. The solution was neutralized by the introduction of solid sodium carbonate, but no solid precipitated. The oil was taken up in ether, dried, and distilled at 145-148°/14 mm. The yield of pale yellow liquid which later crystallized was 57.4 g. (85%).

<u>2-(2-Diethylamino-1-phenylethoxy)-benzothiazole</u>.- This procedure is a typical one used for the preparation of the series of ethers from 2-diethylamino-1-phenylethanol. Table IX and accompanying footnotes give the details for other similar preparations.

One-tenth g. atom of sodium was dissolved in 50 ml. of 2-diethylamino-1-phenylethanol by vigorous stirring with a Hershberg stirrer and heating over a hotplate. The reaction was carried out under an atmosphere of dry nitrogen. One-tenth mole (17.0 g.) of 2-chlorobenzothiazole was added rapidly to the cooled sodium alcoholate solution with stirring. The reaction mixture became extremely hot and salt precipitated from solution. The suspension was then stirred over a steam bath for 21 hours.

The reaction mixture was extracted with water and ether. The ether layer was washed with water and the aqueous layers were extracted with ether. The combined ether extracts were dried over sodium sulfate, and the ether was removed by distillation. After removal of the excess amino alcohol under vacuum from a water pump, the product was

Table IX

Ethers[a] of 2-Diethylamino-1-phenylethanol

		Vol. amino alcohol	Time hrs.	Yield		B.p., °C				Nitrogen[b], %	
Starting Compound	Mole	ml.	(100°)	g.	%	(uncor.)	Mm.	n_D^{20}	$d^{20/20}$	Calcd.	Found
2-Bromopyridine	0.10	35	18	14.4	53.3	190-192	13	1.5405	1.031[c]	10.36	10.43
2-Chloroquinoline	0.10	46	41.5	28.4	88.7[d]	190-192	0.05	1.5849	1.063	8.75	9.12
2-Chlorobenzoxazole	0.10[e]	65	15	2.35[f]	7.6	m.p. 92-93°	—	—	—	9.05	—
1-Chloroisoquinoline	0.10[g]	36	12.5	26.5	83.0	179-182	0.05	1.5820	1.074[h]	8.75	8.80
Benzyl chloride	0.10	41	18.5	14.4[i]	50.8	158-162	0.20	1.5360	0.991[j]	4.94	5.06
p-Nitrobromobenzene	0.10[k]	100	24	4.8[l]	15.3	m.p. 101-103°		—	—	8.90	9.20

[a] Prepared in each case by the action of an equivalent amount of sodium 2-diethylamino-1-phenylethoxide in excess amino alcohol upon a reactive organic halide dissolved in the same solvent. The inert atmosphere was dry nitrogen. Ethanol (95%) was the solvent for preparation and recrystallization of all picrates.

[b] Determined by the micro Dumas method.

[c] MR_D 82.37 (calcd. 81.93). The m.p. of the picrate was 133.5-134.5°.

[d] This was the crude yield of product, b.p. 181-186°/0.05 mm., n_D^{20} 1.5828, $d^{20/20}$ 1.069, MR_D 100.14 (calcd. 100.62). M.p. of picrate 144-147° after recrystallization. Anal. Calcd. for $C_{21}H_{24}ON_2$: N, 8.75. Found: N, 9.42, 9.44, 9.23. This impure product was fractionated through a Vigreaux column. On the purified material the MR_D was 100.98.

[e] The 2-chlorobenzoxazole should be added slowly since the reaction with the sodium alcoholate is very vigorous.

[f] After removal of the excess amino alcohol, the product was distilled at 178-185°/0.05 mm. The yield of viscous liquid which slowly solidified was 15.3 g. (49.3%). The solid was taken up in petroleum ether (b.p. 60-70°), treated with Norit A and allowed to crystallize. The hydrobromide (m.p. 217-218° dec.) was analyzed for bromine by the Volhard procedure. Calcd. for $C_{19}H_{23}O_2N_2Br$:

atmosphere was dry nitrogen. Ethanol (95%) was the solvent for preparation and recrystallization of all picrates.

[b] Determined by the micro Dumas method.

[c] MR_D 82.37 (calcd. 81.93). The m.p. of the picrate was 133.5-134.5°.

[d] This was the crude yield of product, b.p. 181-186°/0.05 mm., n_D^{20} 1.5828, $d^{20/20}$ 1.069, MR_D 100.14 (calcd. 100.62). M.p. of picrate 144-147° after recrystallization. Anal. Calcd. for $C_{21}H_{24}ON_2$: N, 8.75. Found: N, 9.42, 9.44, 9.23. This impure product was fractionated through a Vigreaux column. On the purified material the MR_D was 100.98.

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[g] A considerable amount of heat was liberated when the 1-chloroisoquinoline was added rapidly to the solution of sodium alcoholate.

[h] MR_D 99.60 (calcd. 98.93). M.p. on picrate was 161-164°.

[i] After the excess amino alcohol had been removed, the product was distilled at 105-145°/0.05 mm. The latter material was then fractionated in a Vigreaux-modified Claisen distilling flask to give an impure product, b.p. 127-130°/0.02 mm., n_D^{20} 1.5358, $d^{20/20}$ 0.999, MR_D 88.47 (calcd. 88.29). No picrate was obtained by the usual procedure. Anal. Calcd. for $C_{19}H_{25}ON$: N, 4.94. Found: N, 5.60, 5.52. This impure material was refractionated through a Vigreaux column.

[j] MR_D 89.17 (calcd. 88.29).

[k] The reaction mixture became very hot after the reactants had stirred for several minutes. The flask was cooled in an ice bath until the reaction had subsided.

[l] An insoluble orange solid was isolated from the aqueous layer following extraction of the reaction mixture with ether and water. The yield was 2.4 g., m.p. 172-174°. The ether solution was dried over sodium sulfate, and the ether was removed by distillation over a water bath. The excess amino alcohol was removed at 0.1 mm., and the residue was taken up in petroleum ether (b.p. 60-70°) to give upon concentration 5.4 g. of a yellow compound. Recrystallization from an ethanol-ethyl acetate mixture yielded 4.8 g. of orange needles, m.p. 173-175°. This 7.2 g. represents a 23% total yield of p,p'-dibromoazoxybenzene. See note "s" Table XI. From the petroleum ether filtrate after treatment with Norit A, were obtained 5.4 g. of a yellow compound m.p. 99-103°. Recrystallization from ethanol raised the m.p. of this acid-soluble product.

distilled at 192-198°/0.05 mm. to give 19.3 g. (59%) of liquid n_D^{20} 1.5878 which later solidified. The crude solid when recrystallized from petroleum ether (b.p. 60-70°) gave 13.0 g. (40%) of pure material, m.p. 76-77°. The picrate obtained from 95% ethanol melted at 185-187° after recrystallization.

Anal. Calcd. for $C_{19}H_{22}ON_2S$: N, 8.58; S, 9.82. Found: N, 9.0; S, 9.86.

Preparation of 3-Diethylamino-1,2-epoxypropane.- The procedure employed in this preparation was essentially that reported by Gilman and Fullhart[187]. Two moles (185 g.) of epichlorohydrin were placed in a one-liter three-necked flask fitted with a dropping funnel, mechanical stirrer and thermometer. A mixture of 202 ml. (1.97 moles) of diethylamine and 6 ml. of water was added rapidly to the epichlorohydrin with stirring. The reaction mixture was kept at 30° ± 5° for five hours and then it was allowed to stir overnight at room temperature.

A solution of 93 g. (2.33 moles) of sodium hydroxide in 150 ml. of water was added slowly to the reaction mixture which had been immersed in an ice bath to keep the temperature between 20-25°. The mixture was stirred for forty minutes and the oily layer was decanted. The remainder of the product was extracted with ether and the ether extract was added to the oily layer. After the solution had dried over potassium hydroxide pellets, the ether was removed by distillation over a steam bath and the product was distilled at 57-60°/15 mm. The

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[187] Gilman and Fullhart, J. Am. Chem. Soc., 71, 1478 (1949).

yield was 140 g. (55%) of 3-diethylamino-1,2-epoxypropane n_D^{20} 1.4320. The reported physical constants[187] were n_D^{20} 1.4362, b.p. 69°/32 mm. Fractionation of the product through a Vigreaux-modified Claisen distilling flask raised the n_D^{20} to 1.4332.

In another experiment, 556 g. of epichlorohydrin, 432 g. of diethylamine and 18 g. of water were placed in a five-liter three-necked flask equipped with a dropping funnel, thermometer and mechanical stirrer. The solution was stirred for six hours at 27-30°, and it was then allowed to stir at room temperature overnight. A solution of 280 g. of sodium hydroxide in 456 ml. of water was slowly added to the flask at such a rate that the temperature did not rise above 25°. Cooling was effected by immersing the flask in a large ice bath. The addition of base was carried out for 20 minutes and the mixture was stirred for forty minutes. From the reaction mixture 363 g. (47.5%) of 3-diethylamino-1,2-epoxypropane, n_D^{20} 1.4333, were obtained by extraction and distillation.

1-Diethylamino-3-phenyl-2-propanol.- An equivalent amount of phenyllithium solution (155 ml.) was added to 0.181 mole of 3-diethylamino-1,2-epoxypropane in approximately 50 ml. of ether. The organometallic compound was added at such a rate that a vigorous refluxing of the ether was maintained. When the refluxing ceased, excess water was added cautiously to the reaction mixture. The layers were separated and the aqueous layer was extracted with several portions of ether. The extracts were combined and dried over sodium sulfate. The ether was removed by distillation over a water bath and the product was distilled at 140-145°/14 mm. The yield of product was 21.6 g. (57.8%) having n_D^{20} 1.5040, $d^{20/25}$ 0.959, MR_D 64.03 (calcd. 64.16).

Anal.[188] Calcd. for $C_{13}H_{21}ON$: N, 6.76. Found: N, 6.44, 6.70.

The methiodide was prepared but it could not be crystallized from absolute ethanol or an ethanol-ethyl acetate mixture. Attempts were also made to prepare the benzyl chloride quaternary salt, the hydrochloride, and the 3-nitrophthalic acid half ester but no crystalline substances were obtained. The picrate obtained from ethanol melted at 106-106.5°.

In a larger preparation 1.4 moles (1090 ml.) of phenyllithium solution were added to a two-liter three-necked flask fitted with a reflux condenser, mechanical stirrer and a 500 ml. dropping funnel. The flask was immersed in an ice bath and 174.5 g. (1.35 moles) of 3-diethylamino-1,2-epoxypropane were added from the dropping funnel over a period of 1.5 hours. After the addition was complete and the vigorous reaction had subsided, the reaction mixture was refluxed over a steam bath for 1.5 hours. Color Test I was negative and the mixture was hydrolyzed with excess water.

The ether layer was decanted and the water layer was extracted several times with ether. The extracts were combined and dried over sodium sulfate. The ether was removed by distillation and the product was distilled at 133-160°/14 mm. to give 234 g. (83.5%) of distillate having n_D^{20} 1.5040.

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[188] Determined by the micro Kjeldahl procedure.

The distillate was fractionated through a Vigreaux-modified Claisen distilling flask under variable pressure (13 - 19 mm.) using a water pump. The boiling point of the product at 14 mm. was 151-153° and the yield was 205.2 g. (73.5%) having n_D^{20} 1.5047, $d^{20/20}$ 0.957, MR_D 64.20 (calcd. 64.16), neut. equiv. 203 (calcd. 207).

<u>1-Diethylamino-3-phenyl-2-propanol</u> <u>Picrate</u>.- The picrate of 1-diethylamino-3-phenyl-2-propanol was prepared to show whether this substance was seriously contaminated with the possible isomer, 3-diethylamino-2-phenyl-1-propanol. 1-Diethylamino-3-phenyl-2-propanol (1.45 g., 0.007 mole) was treated in 95% ethanol solution with 30 ml. of a saturated solution of picric acid in 95% ethanol. Four separate fractions of pure picrate, m.p. 106-107°, were obtained by crystallization. The yield was 2.71 g. (89%) of a picrate of a single isomer shown later to be the secondary alcohol.

<u>Preparation</u> <u>of</u> <u>Diethylaminoacetonitrile</u>.- This intermediate in the synthesis of 1-diethylamino-3-phenyl-2-propanol was prepared by the method described by Luten[189]. A concentrated aqueous solution of formaldehyde bisulfite was prepared by the addition of a 5% excess of solid sodium metabisulfite to 24.3 ml. of a 37% solution of formaldehyde in a one-liter beaker. After the reaction appeared to be complete, 0.3 mole of diethylamine was added with stirring to the solid bisulfite addition product at room temperature. The reaction mixture was stirred until all the lumps of formaldehyde bisulfite had reacted with the

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[189] Luten, <u>J</u>. <u>Org</u>. <u>Chem</u>., <u>3</u>, 588 (1939).

amine. The addition of a saturated solution of 19.5 g. of potassium cyanide in water caused the separation of the product as an oily layer. The latter was separated, dried over potassium carbonate and distilled at 60-61°/14 mm. The yield was 25.0 g. (68.2%) of product having n_D^{20} 1.4260. The reported b.p. was 60-60.5°/14 mm. and the reported yield was 81%[190].

Benzylmagnesium Chloride and Diethylaminoacetonitrile.- This reaction is the first step in a synthesis involving the preparation of 1-diethylamino-3-phenyl-2-propanone with subsequent reduction to 1-diethylamino-3-phenyl-2-propanol. Benzylmagnesium chloride was prepared in 95% yield from 20.2 g. (0.16 mole) of benzyl chloride and 3.89 g. (0.16 g. atom) of magnesium in 90 ml. of ether. The solution of benzylmagnesium chloride (0.152 mole) was added to 15 g. (0.134 mole) of diethylaminoacetonitrile dissolved in 100 ml. of anhydrous ether at such a rate that a gentle reflux was maintained. A solid precipitated during the addition of the Grignard reagent, and after one-half hour of reflux over a steam bath the precipitate coagulated and adhered to the sides of the flask.

An attempt was made to hydrolyze the reaction intermediate, but the stirrer was stopped by one of the lumps and a hole was punched in the flask. All the material that could be recovered was hydrolyzed and extracted with ether. The ether extract was dried over potassium carbonate and the ether was removed by distillation over a water bath.

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[190] Bloom, Breslow and Hauser, J. Am. Chem. Soc., 67, 539 (1945).

The product was fractionated through a Vigreaux column to give 5.2 g. (18.9%) of distillate having the following physical constants: b.p. 144-151°/14 mm., n_D^{20} 1.5051, $d^{20/20}$ 0.968. The molecular refraction was 62.93 compared with a calculated value of 62.65 for 1-diethylamino-3-phenyl-2-propanone which has not been previously reported. The neutral equivalent obtained by titration to a methyl red endpoint (not sharp) was 224 (calcd. 205). The picrate was prepared and the m.p. was 148-150° with decomposition. It was not possible to obtain a carbonyl derivative e.g. 2,4-dinitrophenylhydrazone or semicarbazone.

A considerable amount of residue remained in the distilling flask and an attempt was made to distill it under vacuum from an oil pump. Only a small amount of material which solidified in the condenser was obtained. The residue had the character of a varnish. The solid from the condenser was washed with petroleum ether (b.p. 60-70°) and the m.p. was 154-155°. This material was not investigated.

Reduction of 1-Diethylamino-3-phenyl-2-propanone.- 1-Diethylamino-3-phenyl-2-propanone was reduced to the secondary alcohol with lithium aluminum hydride according to the general procedure of Nystrom and Brown[191]. Lithium aluminum hydride (0.55 g.) was added to approximately 100 ml. of anhydrous ether in a 500 ml. three-necked flask fitted with a reflux condenser, dropping funnel and mechanical stirrer. The inert atmosphere was dry nitrogen. Three grams (0.0146 mole) of 1-diethylamino-3-phenyl-2-propanone were dissolved in approximately 30 ml. of ether and this solution was added to the stirred solution of lithium

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[191] Nystrom and Brown, J. Am. Chem. Soc., 69, 1197 (1947).

aluminum hydride. A gentle reflux was maintained during addition of the ketone and the mixture was stirred one-half hour at room temperature.

The intermediate was hydrolyzed with a solution of Rochelle salt and the ether was separated. The aqueous layer was extracted twice with ether, and the combined extracts were dried over sodium sulfate. After removal of the ether by distillation, the product was distilled at 145-148°/13 mm. to give 2.10 g. (69.5%) of a clear pale-yellow liquid having the following physical constants: n_D^{20} 1.5045, $d^{20/20}$ 0.955, MR_D 64.33 (calcd. 64.16). The m.p. of the picrate was 148-150° with decomposition. A mixed m.p. with the picrate (m.p. 106-106.5°) of the secondary alcohol obtained from 3-diethylamino-1,2-epoxypropane and phenyllithium was depressed (100° +). A mixed melting point with the picrate (m.p. 148-150°) of the ketone intermediate showed a depression (138-141°).

The physical constants for the reduction product agree closely with the same constants for the secondary alcohol obtained from 3-diethylamino-1,2-epoxypropane. It is not understood why the picrates are not identical.

Oxidation of 1-Diethylamino-3-phenyl-2-propanol.- The method of Duke and Witman[192] was used in an attempt to oxidize each of the secondary alcohols obtained by the two different syntheses and show their identity through the 2,4-dinitrophenylhydrazones of the

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[192] Duke and Witman, Anal. Chem., 20, 490 (1948).

corresponding ketones. The compounds were vigorously oxidized by the potassium permanganate reagent but the only material isolated after addition of the 2,4-dinitrophenylhydrazine reagent was an orange amorphous powder melting between 108-179°. The latter mixture could not be recrystallized from ethanol. When a larger amount (5 ml.) of the amino alcohol obtained from 3-diethylamino-1,2-epoxypropane and phenyllithium was oxidized and treated with 2,4-dinitrophenylhydrazine reagent, only 2,4-dinitrophenylhydrazine was isolated (mixed m.p.).

2-Diethylaminoethanol was similarly treated in order to determine whether this known compound would give a carbonyl derivative. A material m.p. 167-170° was obtained, but attempted recrystallization converted this material to a black tar. The solid material obtained by neutralizing the filtrate was chiefly inorganic in nature.

2-Diethylamino-1-phenylethanol after treatment by this oxidation procedure also gave a derivative which was largely inorganic. The alcohol-soluble substances fused at 200° and above. Apparently under the drastic conditions of oxidation the molecule is broken down into smaller fragments.

Oppenauer Oxidation of 1-Diethylamino-3-phenyl-2-propanol (Attempted).- Five grams (0.025 mole) of aluminum isopropoxide dissolved in 50 ml. of anhydrous thiophene-free benzene were added to a solution of 5.18 g. (0.025 mole) of 1-diethylamino-3-phenyl-2-propanol in 8 ml. of dry acetone. The reaction was carried out at reflux temperature for 26 hours. The inert atmosphere was dry nitrogen.

The benzene solution was then extracted four times with dilute hydrochloric acid. A solution of Rochelle salt was added to the acid solution of the product and an excess of potassium hydroxide solution was added. The product was taken up in ether and the solution was dried over sodium sulfate. After removal of the ether the product was distilled at 151-152°/14 mm. to give 5.0 g. (97.5%) of distillate having n_D^{20} 1.4988, $d^{20/20}$ 0.958, MR_D 62.90 (calcd. for ketone 62.65). Neither 2,4-dinitrophenylhydrazone nor picrate could be prepared. A vigorous evolution of gas took place when the product was treated with sodium. From this it was concluded that impure amino alcohol had been recovered.

A similar attempt was made to oxidize the known 2-diethylaminoethanol. Ten grams (0.05 mole) of aluminum isopropoxide dissolved in 100 ml. of anhydrous thiophene-free benzene were added to a solution of 5.86 g. (0.05 mole) of 2-diethylaminoethanol in 16 ml. of dry acetone. The reaction time at reflux temperature was 18 hours and the inert gas was dry nitrogen.

The product distilled at 60-70°/12 mm. to give 2.5 g. (43.5%) of distillate having n_D^{20} 1.4398. The distillate neither reduced Tollens reagent nor formed a 2,4-dinitrophenylhydrazone. The n_D^{20} on the starting material was 1.4411 and it appeared from this data that oxidation did not occur.

<u>Preparation of 1-Chloro-3-phenyl-2-propanol</u>.- This is the first reaction in a synthesis of 1-diethylamino-3-phenyl-2-propanol, the initial steps being the preparation of 1-chloro-3-phenyl-2-propanol

and 3-phenyl-1,2-epoxypropane. The procedure described here has been found to give the optimum yield of the desired chlorohydrin. Table X and accompanying footnotes give details of other preparations. Epichlorohydrin (0.44 mole) in 60 ml. of anhydrous ether was placed in a 500 ml. three-necked flask fitted with a nitrogen inlet tube, mechanical stirrer and a dropping funnel of 500 ml. capacity. The flask and contents were cooled to -78° in a Dry Ice-trichloroethylene bath and 290 ml. (0.44 mole) of phenyllithium solution were added in a steady stream over a period of one-half hour. The reaction mixture was stirred at -78° for 1.5 hours and then it was allowed to warm slowly to 0°.

Hydrolysis was carried out by pouring the mixture into a dilute solution of sulfuric acid containing crushed ice. The ether layer was decanted and washed with water, dilute sodium carbonate solution and then water. The aqueous layer was extracted twice with ether and the extracts were washed as indicated above. The combined extracts were dried over sodium sulfate, and the ether was removed by distillation over a water bath. The product was distilled between 132-142°/13-17 mm. to yield 50.5 g. (67.4%) of distillate having n_D^{20} 1.5426. The reported[193] n_D^{25} is 1.5470, but in other preparations no product having a refractive index this high was obtained. See Table X for molecular refraction data.

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[193] Koelsch and McElvain, J. Am. Chem. Soc., 52, 1164 (1930).

Table X

Organometallic Compounds and Epichlorohydrin

RM type	Mole[a]	Total vol. ether ml.	Temp., °C	Time hrs.	1-Chloro-3-phenyl-2-propanol n_D^{20}	g.	%
C_6H_5Li	0.239	340	35	0.5	1.5463[b]	4.0[c]	9.8
C_6H_5Li	0.221	280	-30[d]	0.5	1.5420[e]	16.2[f]	43.0
C_6H_5CdCl[g]	0.30	290	35	1.0			
			25	12	—[h]	—	—

[a] An equivalent amount of epichlorohydrin was employed in each case.

[b] n_D^{25} 1.5450.

[c] B.p. 125-135°/15 mm.

[d] A Dry Ice-trichloroethylene bath was used to control the reaction temperature. The bath was then allowed to warm slowly to 0° and the mixture was hydrolyzed.

[e] The $d^{20/20}$ was 1.155 and the MR_D was 46.48 (calcd. 46.46). The m.p. on the 3,5-dinitrobenzoate was 119.5-120.5°. Koelsch and McElvain, J. Am. Chem. Soc., 52, 1164 (1930) reported 120-121°.

[f] The crude yield was 23.5 g. distilling at 132-140°/15 mm. This material was fractionated through a Vigreaux column to give pure material b.p. 133-135°/13 mm.

[g] Prepared by the addition of 210 ml. (0.305 mole) of phenylmagnesium bromide solution to a suspension of 55 g. (0.3 mole) of fused and pulverized cadmium chloride in 50 ml. of anhydrous ether. Color Test I was negative after one hour of reflux.

[h] The product had a b.p. 82-86°/15 mm. and n_D^{20} 1.5051. This material was very probably a mixture of glycerol chlorobromohydrin and glycerol dichlorohydrin. None of the desired product was obtained.

Preparation of 3-Phenyl-1,2-epoxypropane.- A solution of 2.5 g. of sodium hydroxide in approximately 10 ml. of water was added dropwise to 8.53 g. (0.05 mole) of 1-chloro-3-phenyl-2-propanol in a 100 ml. flask equipped with a mechanical stirrer. The reaction mixture was stirred for forty minutes and then it was diluted and extracted with ether. The extracts were combined and dried over sodium sulfate.

After the ether had been removed by distillation, the product was distilled at 93-100°/13 mm. to yield 3.45 g. (51.5%) of distillate having n_D^{20} 1.5238, $d^{20/20}$ 1.028, MR_D 39.92 (calcd. 39.50). The reported[194] b.p. was 94-98°/15 mm.

In another experiment 42 g. (0.246 mole) of 1-chloro-3-phenyl-2-propanol were stirred with a solution of 11.5 g. (0.287 mole) of sodium hydroxide in 20 ml. of water at room temperature for forty minutes. The product was worked up as described above to give 19.0 g. (57.5%) of 3-phenyl-1,2-epoxypropane, b.p. 98-103°/13-15 mm., n_D^{20} 1.5239.

1-Diethylamino-3-phenyl-2-propanol.- A mixture of 1.34 g. (0.01 mole) of 3-phenyl-1,2-epoxypropane, 0.73 g. (0.01 mole) of diethylamine and one drop of water was placed in a 22 x 175 mm. test tubes. The tube was stoppered and allowed to stand at room temperature for 48 hours.

The excess diethylamine which was used to transfer the small amount of reaction mixture to a 10 cc. Vigreaux-modified Claisen

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[194] Fourneau and Tiffeneau, *Bull. soc. chim. France*, [4] *1*, 1230 (1907).

flask was removed by distillation. The residue was distilled at 147°/13 mm. to yield 1.20 g. (58%) of distillate having n_D^{20} 1.5057, $d^{20/20}$ 0.966, MR_D 63.72 (calcd. 64.16). The m.p. of the picrate was 105-107°.

In a second experiment, 9 g. (0.067 mole) of 3-phenyl-1,2-epoxypropane, 4 drops of water and 15 ml. of diethylamine were placed in a 100 ml. round bottom flask and were allowed to stand at room temperature for six days. After removal of the excess diethylamine, the product was distilled at 147-152°/14 mm. The yield was 11.0 g. (79%) of product having n_D^{20} 1.5058. The m.p. on the picrate was 105-107° and a mixed m.p. with the picrate of the alcohol obtained from 3-diethylamino-1,2-epoxypropane and phenyllithium showed no depression.

Preparation of Dibenzylmethanol (Attempted).- In order to prepare an alcohol derivative of 3-phenyl-1,2-epoxypropane, 10.0 g. (0.0745 mole) of the latter in 50 ml. of anhydrous ether were cooled to -78°, and 75 ml. (0.077 mole) of phenyllithium solution were added over a period of twenty minutes. The reaction mixture was then stirred for one hour at -78° and hydrolyzed by pouring the solution over crushed ice and dilute sulfuric acid.

The ether layer was decanted and the aqueous fraction was extracted with two small portions of ether. The combined ether extracts were washed with water, dilute sodium carbonate solution and water. The ether solution was dried over sodium sulfate, and the ether was removed by distillation. The residue was distilled at 93-97°/13 mm. to give 8.0 g. (80%) of recovered 3-phenyl-1,2-epoxypropane. The n_D^{20} was 1.5255 compared with 1.5238 on the starting material. It is evident that little reaction took place at -78°.

Preparation of Dibenzylmethanol.- Dibenzylmethanol was prepared from 3-phenyl-1,2-epoxypropane to show by the preparation of a known compound the mode of addition of a nucleophilic agent to this unsymmetrical epoxide. To 7.7 g. (0.0573 mole) of 3-phenyl-1,2-epoxypropane in 60 ml. of anhydrous ether cooled to -78°, 0.0573 mole (86 ml.) of phenyllithium solution was added over a period of fifteen minutes. At the end of one hour of stirring at -78° Color Test I was strongly positive. The reaction mixture was allowed to warm to 0° over one-half hour and after one hour at 0° the color test was negative.

The reaction mixture was then poured into dilute sulfuric acid containing crushed ice. The ether layer was separated and washed with water, dilute sodium carbonate solution and then water. The ether solution was dried over sodium sulfate and the ether was removed by distillation. The product was distilled at 185-189°/13 mm.[195] to give 4.5 g. (37%) of distillate having n_D^{20} 1.5718. The p-nitrobenzoate[196] melted at 77-78° after three recrystallizations. The $d^{20/20}$ was 1.062[197] and the MR_D was 65.73 (calcd. 65.60).

Identification of dibenzylmethanol from this reaction gave

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[195] Dieckmann and Kämmerer, Ber., 39, 3050 (1906) reported the b.p. 187-189°/12 mm.

[196] Papa, Schwenk and Whitman, J. Org. Chem., 7, 587 (1942) obtained the m.p. 80-81°.

[197] Bogdanowska, Ber., 25, 1272 (1892) reported the $d^{16.5}$ 1.0619.

additional proof that attack on the epoxide occurred at the terminal carbon atom. It is interesting to notice that after three attempts dibenzylmethanol did not yield a derivative by the procedure of Duke and Witman[192].

2-(1-Diethylamino-3-phenyl-2-propoxy)-benzothiazole.- In a typical experiment, 50 ml. of 1-diethylamino-3-phenyl-2-propanol were added to a 200 ml. three-necked flask equipped with a reflux condenser, mechanical stirrer and dropping funnel. Sodium (0.05 g. atom) in the form of small pieces was added to the amino alcohol and the mixture was stirred vigorously over a steam bath for 2.5 hours. During this time the sodium dissolved. 2-Chlorobenzothiazole (0.05 mole) in 25 ml. of the amino alcohol was added to the hot solution of the alcoholate. A precipitate formed immediately and the reaction mixture was then heated over a steam bath for twelve hours.

The amino alcohol was removed by distillation under vacuum from an oil pump. An ebullator was used to prevent violent bumping in the distilling flask. The mixture of salt and product was treated with ether and water. The water layer was separated and extracted several times with ether. The combined extracts were dried over sodium sulfate and the ether was removed by distillation over a water bath. The product distilled at 228-231°/0.05 mm. to give 11.7 g. of distillate having n_D^{20} 1.5840. The distillate then slowly solidified and the solid was washed with petroleum ether (b.p. 60-70°) to yield 6.9 g. (40.7%) of almost pure product. After a single crystallization from petroleum ether (b.p. 60-70°) the m.p. was 74-75°. The compound was soluble in dilute hydrochloric acid, insoluble in water and did not give the Beilstein test.

Anal. Calcd. for $C_{20}H_{24}ON_2S$: S, 9.41. Found: S, 9.53, 9.52.

Table XI and accompanying footnotes give the details of other similar preparations.

Preparation of Benzhydryl Chloride.- The procedure employed in this preparation was essentially that of Gilman and Kirby[198]. Benzhydrol (0.282 mole) and 140 ml. of dry toluene were placed in a 500 ml. three-necked flask fitted with a mechanical stirrer, dropping funnel and reflux condenser with attached calcium chloride tube. To this well agitated solution was added dropwise 0.292 mole of thionyl chloride. After the addition was complete, the reaction mixture was refluxed for three hours.

The toluene was removed from the product by distillation and the residue was distilled at 156-159°/13 mm. to yield 48.5 g. (85%) of distillate having n_D^{20} 1.5956. The reported b.p.[198] was 161-162°/13 mm. and the reported $n_D^{19.5}$ was 1.5959[199].

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[198] Gilman and Kirby, J. Am. Chem. Soc., 48, 1735 (1926).

[199] Montagne, Rec. trav. chim., 25, 403 (1907).

Table XI

Ethers[a] of 1-Diethylamino-3-phenyl-2-propanol

Starting Compound	Mole	Vol. amino alcohol ml.	Time hrs. (100°)	Yield g.	Yield %	B.p., °C (uncor.)	Mm.	n_D^{20}	$d^{20/20}$	Nitrogen[b], % Calcd.	Nitrogen[b], % Found
2-Bromopyridine	0.07	75	23	10.5	52.7	165	0.2	1.5344	1.015[c]	9.85	10.0, 9.88
2-Chloroquinoline	0.05	75	21	12.7	76	187-190	0.04	1.5746	1.053[d]	8.38	8.44
2-Chlorobenzoxazole	0.07[e]	35	17	11.5	50.6	—[f]	—	m.p. 88-89°		8.64	9.33, 9.15
1-Chloroisoquinoline	0.05	50	21	12.7[g]	76	200-205	0.1	1.5722	1.052[h]	8.38	8.55
Benzyl chloride	0.10	70	13	12.5	42	173 [i]	1.3	1.5353	0.995[j]	4.72	4.67
Benzyl chloride[k]	0.10	35	17	13.3	45	150-160	0.1-0.3	1.5303	0.992[l]	4.72	4.97
Benzhydryl chloride	0.10	35	11.5	—[m]	—	—	—	—	—	—	—
Cyanuric chloride[n]	0.10	22[o]	—[p]	—[q]	—	—	—	—	—	—	—
p-Nitrobromobenzene	0.10	80[r]	17	—[s]	—	—	—	—	—	—	—

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[a] Prepared in each case by the action of an equivalent amount of sodium 1-diethylamino-3-phenyl-2-propoxide in excess of the amino alcohol upon a reactive organic halide dissolved in the same solvent. The inert gas was dry nitrogen. Ethanol (95%) was used as the solvent for the preparation and recrystallization of all picrates.

[b] Determined by the micro Dumas method.

[c] The MR_D was 87.12 (calcd. 86.13). The picrate melted at 129-130°.

[d] MR_D 104.9 (calcd. 105.2). The m.p. of picrate was 144-145°.

[e] The sodium alcoholate was cooled in an ice bath during addition of the 2-chlorobenzoxazole. This was followed by four hours of stirring at room temperature.

[f] After the amino alcohol had been removed, the residue was cooled and crystallized from 95% ethanol. Petroleum ether (b.p. 60-70°) was used to recrystallize the product. The m.p. of the picrate

[d] MR_D 104.9 (calcd. 105.2). The m.p. of picrate was 144-145°.

[e] The sodium alcoholate was cooled in an ice bath during addition of the 2-chlorobenzoxazole. This was followed by four hours of stirring at room temperature.

[f] After the amino alcohol had been removed, the residue was cooled and crystallized from 95% ethanol. Petroleum ether (b.p. 60-70°) was used to recrystallize the product. The m.p. of the picrate was 154-155°. This alkamine ether was soluble in dilute acid but was insoluble in water. The m.p.'s of the hydrochloride, hydrobromide and hydroiodide were 229-234°, 221-222° and 210-211°, respectively. Titration with 0.1 *N* hydrochloric acid gave neutral equivalents 315, 341 (calcd. 324.4). The large discrepancy was due to a poor endpoint with methyl red modified with methylene blue. The compound was found to be resistant to concentrated hydrochloric acid at 100° for four hours and to hydriodic acid in acetic acid for 4 hours at reflux temperature. The hydrobromide was analyzed for bromine by the Volhard procedure. Calcd. for $C_{20}H_{25}O_2N_2Br$: Br, 19.75. Found: Br, 19.8.

[g] The yield of crude product was 13.5 g., b.p. 203-209°/0.2 mm. From this semi-solid distillate 0.25 g. of 1-hydroxyisoquinoline was obtained by extraction with petroleum ether (b.p. 60-70°). The m.p. was 210-213° and a mixed m.p. with an authentic specimen (m.p. 210-213°) was not depressed. The petroleum ether-soluble material was then distilled.

[h] MR_D 104.6 (calcd. 103.55).

[i] At 13-14 mm. the b.p. was 210-216°.

[j] MR_D 93.10 (calcd. 92.91).

[k] This preparation was repeated because the molecular refraction had been miscalculated in the previous experiment and the product was thought to be impure.

[l] M.p. on picrate was 107-108° and MR_D was 92.67 (calcd. 92.91).

[m] The reaction mixture was extracted with water and ether and the insoluble solid was removed by filtration. The ether solution was dried over sodium sulfate, and the ether was removed by distillation. After removal of the excess amino alcohol, the dark tarry residue was taken up in acetone and petroleum ether (b.p. 60-70°). Upon concentration, more of the same insoluble solid was obtained. The filtrate upon further concentration contained only intractable black tars. The solid weighed 8.0 g. (48%), m.p. 208-211°, and was shown to be *sym*.-tetraphenylethane by mixed m.p. with an authentic specimen.

[n] Kindly furnished by the American Cyanamid Co.

[o] The sodium (0.1 g. atom) was dissolved in a solution of 0.1 mole (22 ml.) of the amino alcohol in 100 ml. of dry toluene. The sodium alcoholate suspension was transferred to a dropping funnel and then added to 0.1 mole of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) dissolved in 100 ml. of dry toluene. A considerable heat of reaction was observed.

[p] The mixture was heated over the hotplate for seven hours during which time a copious precipitate formed.

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[p] The mixture was heated over the hotplate for seven hours during which time a copious precipitate formed.

[q] The salts were removed by filtration and the toluene was removed by distillation under vacuum. The dark polymer-like residue decomposed before the boiling point at 0.2 mm. was reached and the material was not further investigated.

[r] One-tenth mole of <u>p</u>-nitrobromobenzene was added to 0.1 mole of the sodium alcoholate in 50 ml. of the amino alcohol. A strongly exothermic reaction was initiated by gentle warming of the reaction mixture. Thirty ml. of the amino alcohol were added to moderate the reaction.

[s] The mixture was taken up in ether and water, and 1.85 g. of yellow solid m.p. 171° were removed by filtration. This substance was identical by mixed m.p. with the substance m.p. 172-174° obtained from a reaction of <u>p</u>-nitrobromobenzene with sodium 2-diethylamino-1-phenylethoxide. This compound was thought to be <u>p</u>,<u>p</u>'-dibromoazoxybenzene. Reduction with lithium aluminum hydride, according to a procedure described by Nystrom and Brown, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>70</u>, 3738 (1948), gave a gold-colored compound, m.p. 201-203°. Werigo, <u>Ann</u>., <u>165</u>, 198 (1873) reported the m.p.'s of <u>p</u>,<u>p</u>'-dibromoazoxybenzene and <u>p</u>,<u>p</u>'-dibromoazobenzene as 175° and 204-205°, respectively. After the ether and the excess amino alcohol had been removed, additional amounts of the azoxy compound were obtained. The yield was 6.95 g. (39%).

IV. DISCUSSION

A. Protection of Reactive Functional Groups

It has been pointed out in the Historical part of this thesis that not a great amount of progress has been made in the preparation of organometallic compounds containing some of the very reactive functional groups. Attempts to prepare compounds containing a reactive C-M linkage and a reactive group by the direct method or by metalation are almost surely doomed to failure. The halogen-metal interconversion reaction and the metal-metal interconversion reaction are the most promising procedures for the preparation of these types. The remainder of the discussion will be confined to the applications of the halogen-metal interconversion reaction, the metal-metal interconversion reaction being discussed under the heading "Suggestions for Further Research".

The reactions of bromo- or iodo-nitrobenzenes with organolithium reagents have been carried out in an attempt to effect a halogen-lithium exchange reaction in the presence of a reactive nitro group. Such reactions resulted in rapid oxidation of the organolithium compound with concomitant reduction of the nitro group. Gilman and McCracken[145], after a careful study of the reactions between Grignard reagents and nitro compounds, have formulated the transformations with aromatic (ArMgX) and aliphatic (RMgX) Grignard reagents and nitrobenzene as follows:

$$4\ ArMgX + C_6H_5NO_2 \xrightarrow{(HOH)} C_6H_5NHAr + ArOH + Ar.Ar$$

$$4\ RMgX + C_6H_5NO_2 \xrightarrow{(HOH)} (C_6H_5)(R)NN(R)(C_6H_5)$$

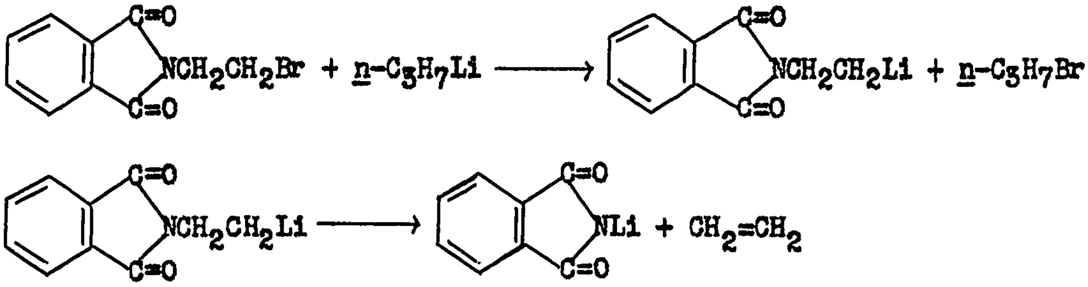
It is assumed that similar products resulted when halogenated nitrobenzenes were treated with aromatic and aliphatic organolithium compounds. Actually, when phenyllithium was employed, phenol was isolated as the tribromo derivative.

The reactions of the p-nitroiodobenzene with p-dimethylaminophenyllithium, phenyllithium, ethyllithium, n-propyllithium and n-butyllithium did not reveal any gradation of properties of sufficient magnitude to prevent the oxidation-reduction reaction and at the same time interconvert the iodine. If the reactions were carried out at low temperatures for short reaction periods prior to carbonation, only traces of dark, mixed acids were obtained. If, on the other hand, the reaction times were increased, the amounts of dark, highly-impure acids also increased. In no instance was a pure acid obtained by direct or indirect procedure for isolation of carboxylic acids.

The attempted interconversion of p-iodonitrobenzene is clearly a case of a preferential reaction with the highly reactive nitro group. In the Gooch extension of the Entemann and Johnson series of reactivities[147], the nitro group is believed to be somewhere between -CHO and $-CO_2C_2H_5$. For convenience in prediction, the nitro group should be definitely placed in the series of relative reactivities. It is apparent that the iodine-lithium exchange reaction is slow by comparison, since organolithium compounds because of their greater reactivity, generally do not show such selectivity.

An attempt was made to decrease the reactivity of the nitro group by placing bulky groups in both ortho positions. For these experiments nitrobromomesitylene and 2-nitro-4-bromo-1,3-dimethylbenzene were chosen. A series of reactions was carried out with n-propyllithium and each parent halide (bromomesitylene and 4-bromo-1,3-dimethylbenzene) to determine the optimum conditions of reaction. The hindered nitro compounds were then treated with n-propyllithium under the optimum conditions for interconversion, but no acid was obtained subsequent to carbonation. This result may have been predicted on the basis of the nitrogen-oxygen bond distances and the supposition that the group was forced out of the plane of the ring by the ortho methyl groups. Perhaps the reaction could take no other course because of the strong coordination of the lithium end of the n-propyllithium dipole at the oxygen atoms of the nitro group. It is conceivable that the reaction center may be changed by introduction of another group into the molecule which could coordinate more strongly than the nitro group with n-propyllithium.

An attempt was made to determine whether at low temperature N-(β-bromoethyl)-phthalimide could be interconverted to form N-(β-lithioethyl)-phthalimide. Actually no reaction occurred at -78°; however, the expected reaction if the findings of Wittig and Harborth[35] may be applied to an organolithium compound of the structure $\rangle N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-Li$ would be formulated as follows:



The carbonyl groups in aldehydes and ketones may be protected by acetalization. The preparation of cyclic acetals was conveniently carried out in high yield by azeotropic distillation with benzene, a procedure not readily adapted to the preparation of acetals from low-boiling alcohols. Cleavage of the acetals at ether reflux temperature does not appear to be an important side reaction since the carbonation product was readily purified after acid hydrolysis. If cleavage of these ether linkages had occurred, other acidic products would have contaminated the p-acetylbenzoic acid obtained by halogen-metal interconversion of the ethylene acetal of p-bromoacetophenone followed by carbonation and acid hydrolysis. This is a typical example of the utility of the halogen-metal exchange reaction in cases not amenable to preparation by the direct method. No attempt was made to react this carbonyl-protected p-bromoacetophenone with magnesium. However, if the usual complementary characteristics of lithium and magnesium hold in this case, a Grignard reagent should form readily by the direct procedure.

The carboalkoxy group is above the cyano group[105] in the series of relative reactivities of functional groups, and it was anticipated that little or no interconversion of methyl p-bromo- and p-iodobenzoates would take place in preference to reaction at the carbonyl group. Actually this was the case and only traces of acid believed to be p-carbomethoxybenzoic acid were obtained from each reaction at -78°.

The methyl group in methyl p-bromobenzoate was replaced by the bulky t-butyl group in order to decrease the activity of the carbonyl group toward the interconversion agent. It has been reported that the order of reactivity of the butyl benzoates was primary > secondary > tertiary (400:40:1) with ethylmagnesium bromide[200]. It was found, however, in the Experimental part of this thesis that at -35 to-40° t-butyl p-bromobenzoate reacted with n-propyllithium to give a high yield of p-bromophenyl di-n-propylmethanol. It seems reasonable to believe that this hindered ester may be interconverted by a hindered organolithium compound which could not add to the carbonyl group because of steric considerations.

The procedure of Parham and Anderson[96] for protection of phenolic hydroxyl groups during metalation with n-butyllithium has been employed for a similar purpose in the halogen-metal interconversion reaction. Dihydropyran was reacted with 2-bromo-, 4-bromo- and 2,4-dibromophenols to give the corresponding 2-tetrahydropyranyl ethers in good yield. It was observed that with compounds having both ortho positions filled no acetal formation took place. This was found to be true with 2,4,6-tribromophenol and 2,4-dibromo-1-naphthol.

Bromine-lithium interconversion of 2,4-dibromophenyl 2-tetrahydropyranyl ether with n-propyllithium gave a 16.4% yield of 5-bromosalicylic acid subsequent to carbonation and hydrolysis. A similar

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[200] Vavon, Barbier and Thiébaut, Bull. soc. chim. France, [5] 1, 806 (1934).

interconversion employing the free phenol[111] yielded 55.3% of 5-bromosalicylic acid[201]. It may be concluded, from this data and from the facts that o-bromophenol[95] and 4,6-dibromo-o-cresol gave high yields of acids subsequent to interconversion and carbonation, that protection of the hydroxyl group is unnecessary. Actually indications are that the yield of the interconversion product may be lower because of possible steric effects decreasing the tendency toward initial coordination by the organometallic compound.

The work described in the Experimental part concerning the halogen-metal interconversion of 2,4-dibromophenol, 2,4-dibromophenyl 2-tetrahydropyranyl ether, 4,6-dibromo-o-cresol and 2,4,6-tribromophenol showed that the bromine atom ortho to the oxygen was exclusively interconverted. No evidence was found for interconversion of the bromine atom para to the oxygen. This confirms the statement of Sunthankar and Gilman[111] that

> "In polyhalogen-compounds, the interconversion reaction with one ortho halogen atom is much more rapid than the interconversion with the second atom if the latter is not in the second ortho position."

B. Reduction. A Side Reaction in the Phenol Series

In connection with the investigation of the effects of changes in placement of the halogen atoms in polyhalogenophenols, it was discovered that interconversion of 2,6-dibromophenol with three

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[201] However, see page 82 of this thesis concerning the interconversion of 2,4-dibromophenol under slightly different conditions.

equivalents of n-propyllithium gave salicylic acid (17%) as the only identifiable product subsequent to carbonation. This transformation was of extreme interest because a reductive *ortho* debromination had occurred at some stage in this complex reaction. Since there was only a limited quantity of this expensive 2,6-dibromophenol, the investigation of the nature of the reaction was carried out with 2,4,6-tribromophenol which was available in considerable amounts as a "practical" grade chemical.

Reaction of 2,4,6-tribromophenol with two or more equivalents of n-propyllithium in ether gave, subsequent to carbonation, the expected product, 5-bromosalicylic acid. The yield of 5-bromosalicylic acid was approximately the same whether two, three, or four equivalents of n-propyllithium were used for every mole of 2,4,6-tribromophenol. The reaction was also a fast one since the yield was nearly the same whether the reaction time was one-half minute or sixty minutes.

These results were unusual and required further investigation to throw some light upon the possible mechanism of reaction. By analogy with the work of Gilman, Langham and Moore[88] on 2,4,6-tribromoanisole, the acid formed would be 2-hydroxy-5-bromo-1,3-dicarboxybenzene. Since it was conceivable that this substituted isophthalic acid may have decarboxylated during the workup, the interconversion product was methylated to give not 4-bromo-2,6-dimethylphenol but 4-bromo-2-methylphenol. Evidently, no decarboxylation of a dicarboxylic acid was involved in the formation of 5-bromosalicylic acid, and the intermediate organometallic compound was O-lithio-5-bromo-2-hydroxyphenyllithium. In order to show that this intermediate coupled in the normal fashion with methyl iodide, 2,4-dibromophenol was interconverted with n-propyllithium and the resultant product was methylated to form 4-bromo-2-methylphenol in low yield.

In order to eliminate the possibility that either sufficient finely-divided lithium metal or lithium nitride may be responsible for the reduction, some of the n-propyllithium solutions were filtered through an asbestos pad under pressure. The n-propyllithium which was clarified in this fashion gave results like those obtained with similar preparations filtered only through glass wool.

There were several conceivable sources for the hydrogen which replaced a bromine ortho to the oxygen. (1) Both ortho bromine atoms may have been replaced by lithium, and the resultant O-lithio-5-bromo-2-hydroxy-1,3-dilithiobenzene may have caused elimination of HBr from the unreacted n-propyl bromide to form propylene. (2) The diinterconversion product may have metalated the ether to form ethylene and lithium ethoxide. (3) One bromine atom may have been interconverted, and another molecule of n-propyllithium may have coordinated with the second ortho bromine atom. Then, by means of a possible cyclic intermediate, lithium bromide was removed, hydrogen was transferred as hydride to the same ortho carbon atom which held the bromine, and propylene was formed. Each of these possibilities together with other data will be discussed in the following paragraphs.

As mentioned in the footnotes to Table VIII several attempts were made to collect unsaturated hydrocarbon gases evolved from the reactions by use of traps containing bromine. The physical constants for the organic halide obtained agree well with literature values for propylene bromide, and although the data are not as complete as desired the identification of propylene as a product of the reaction is undoubtedly correct. Propylene was not only obtained from reaction of n-propyllithium with 2,4,6-tribromophenol but also with 2,4-dibromophenol. Perhaps it is possible that a small percentage of each of these compounds may have all the ortho bromine removed by reduction. This would give rise to p-bromophenol which has been isolated from carbonation mixtures and purified as the benzoate ester. Another explanation for the presence of p-bromophenol in the carbonation mixtures would be that a small amount of hydrolysis had taken place due to moisture present in the Dry Ice. Actually, neither explanation alone will account for all the data.

Even though diinterconversion of 2,4,6-tribromophenol occurred, an elimination reaction involving n-propyl bromide would probably not take place. It is well known that primary aliphatic halides undergo coupling with organometallic compounds to give high yields of alkylated products[148,202]. Phenyllithium and 2,4,6-tribromophenol in a molar ration of 2:1 neither yielded 5-bromosalicylic acid subsequent to carbonation nor formed the reduction product (5-bromosalicylic acid) when the interconversion reaction was carried out in the presence of n-propyl bromide. It is evident that this proposed mechanism is not in accord with the data.

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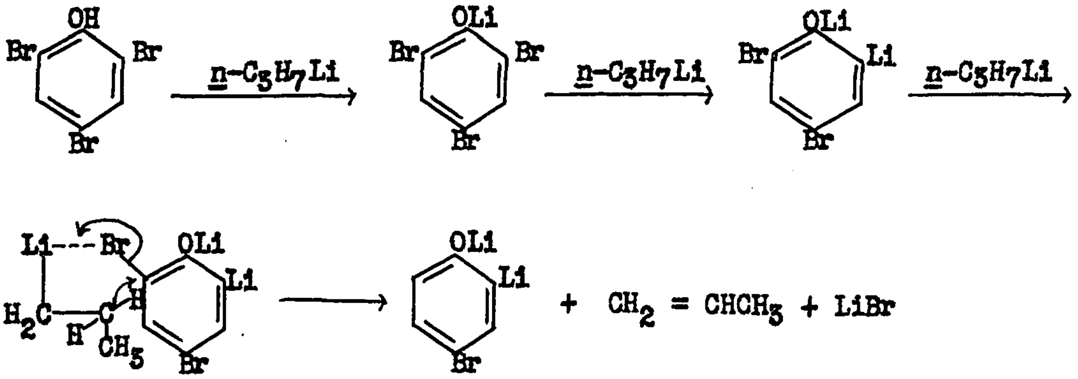
[202] Unpublished studies of Mr. C. G. Brannen and Mr. C. C. Wanser showed that 1-naphthyllithium coupled with n-butyl bromide to give a 90% yield of 1-(n-butyl)-naphthalene. Kharasch, Lewis and Reynolds, J. Am. Chem. Soc., 65, 498 (1943) obtained a 55% yield of n-butylbenzene from the reaction of phenyllithium and n-butyl bromide.

The second mechanism which was proposed may also be discarded since propylene bromide and not ethylene bromide was obtained from the bromine traps. It is also believed unlikely that both <u>ortho</u> bromine atoms could be interconverted and the ether cleaved to give a 36% yield of 5-bromosalicylic acid within a period of one-half minute.

The third mechanism that has been proposed is the one which most closely fits the data obtained and incorporates known properties of the reactants. The following sequence of reactions represents this mechanism[203].



This formulation agrees with the experimental data in the following ways.

1. The active hydrogen is removed preferentially before other reactions occur. When 2,4,6-tribromophenol was treated with one equivalent of n-propyllithium and the reaction mixture worked up, only 2,4,6-tribromophenol was recovered and no polymer formation was observed.

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[203] The author wishes to thank Dr. G. S. Hammond and Mr. W. J. Meikle for their valuable suggestions concerning the possible mechanism of reaction.

2. A rapid halogen-metal interconversion reaction takes place followed immediately by reduction. It is believed that only one atom of bromine is exchanged for lithium since the interconversion of a second atom should be considerably slower. In the reactions with phenyllithium discussed above no reduced product was obtained. There is some evidence to show that phenyllithium may have interconverted both atoms of bromine _ortho_ to oxygen without metalating the ether and/or _n_-propyl bromide.
3. Reduction is a common side reaction of organometallic compounds. Work carried out with Grignard reagents showed that with benzophenone and certain other ketones _n_-propylmagnesium bromide gave high yields of the reduction products[204]. Noller, Grebe and Knox[205] state that the type of reduction most frequently encountered with Grignard reagents occurs only when a hydrogen-bearing carbon atom is adjacent to the carbon atom that is combined with magnesium. This conclusion was borne out by the work of Gilman and Abbott[206]. The analogous organolithium reagents may be expected to act similarly to give reduced products.
4. The presence of relatively large percentages of polymer-like acids in the carbonation product may perhaps be due to the

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[204] Blicke and Powers, _J. Am. Chem. Soc._, _51_, 3378 (1929).

[205] Noller, Grebe and Knox, _ibid._, _54_, 4690 (1932).

[206] Gilman and Abbott, _J. Org. Chem._, _8_, 224 (1943).

multiplicity of other side reactions characteristic of salts of polyhalogenated phenols.

The formulation of the reduction step in the reaction as an initial coordination of the organometallic dipole with the *ortho* bromine and formation of a transient six-membered ring avoids the difficulties involved with free hydride ions and Nef carbon atoms as intermediates.

In connection with the isolation of dark, impure polymer-like acids from the carbonations of interconverted 2,6-dibromophenol and 2,4,6-tribromophenol, the observations of Hunter and coworkers[172,207] and Raiford and LeRosen[208] concerning the decomposition of salts of halogenated phenols may be pertinent. During investigation of the red and white chromoisomeric silver salts of 2,4,6-tribromophenol, it was found[207a] that methyl and ethyl iodides would catalytically convert these substances to polymers. Later work[207b] showed that the polymers contained neither silver, iodine nor an alkyl group. The molecular formula was shown to be $(C_6H_2OBr_2)_n$[207c,172], the value for "n" being variable but the percentage of bromine remaining almost constant. The reaction was assumed to be intramolecular and general for trihalogenated phenols. Tribromoresorcinol monomethyl ether[172],

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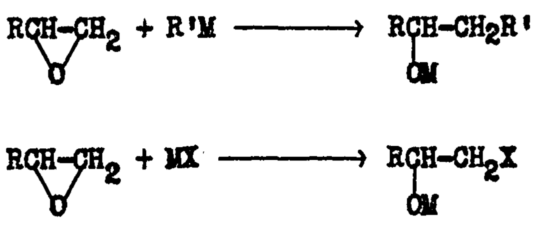
[207] (a) Torrey and Hunter, *Ber.*, *40*, 4335 (1907); (b) *J. Am. Chem. Soc.*, *33*, 196 (1911); (c) Hunter, Daniells, Olsen and Karatz, *Orig.* Comm. 8th Intern. Congr. Appl. Chem. (Appendix), *25*, 393 (1913) /*C.A.*, *7*, 2189 (1913)/; (d) Wollett, *J. Am. Chem. Soc.*, *38*, 2474 (1916); (e) Hunter and Joyce, *ibid.*, *39*, 2640 (1917); (f) Hunter and Woollett, *ibid.*, *43*, 131,135 (1921); (g) Hunter and Seyfried, *ibid.*, *43*, 151 (1921); (h) Hunter and Morse, *ibid.*, *48*, 1618 (1926); (i) Hunter and Whitney, *ibid.*, *54*, 1167 (1932) and (j) Hunter and Dahlen, *ibid.*, *54*, 2456 (1932).

[208] Raiford and LeRosen, *ibid.*, *68*, 397 (1946).

trichlorophenol[172], triiodophenol[207d], 4-chloro-2,6-dibromophenol[207e], 4-bromo-2,6-dichlorophenol[207e], 4-chloro-2,6-diiodophenol[207e], 4-(4-chloro-2,6-diiodophenoxy)-2,6-dibromophenol[207j] and 2,4,6-tribromo-3-fluorophenol[208] under suitable conditions as metallic salts could be converted to similar polymeric substances. It seems possible that under the conditions of the halogen-metal interconversion reaction lithium 2,4,6-tribromophenoxide may undergo similar transformations to polymers which in turn are interconverted by n-propyllithium.

C. Preparation of Some Alkamine Ethers

In connection with investigations concerning the reactions of organolithium reagents with dialkylamino- and chloro-epoxides, it was found that good yields of the secondary alcohols could be obtained. This is in contrast to the generally unsatisfactory results obtained with Grignard reagents[193]. Lithium and magnesium halides are good reagents themselves for opening the epoxide linkage, and if the organometallic compound is of a low order of reactivity this latter reaction may predominate. The following equations represent the two competing reactions:



where M = metal and X = halogen. Actually, an attempted reaction between epichlorohydrin and phenylcadmium chloride yielded only glycerol dichlorohydrin and glycerol bromochlorohydrin. Lithium bromide at ether reflux temperature offered very serious competition to phenyllithium in reaction with epichlorohydrin. It was found, however, that at lower temperatures higher yields of the desired chlorohydrin were obtained.

Since the organolithium reagents made 1-diethylamino-3-phenyl-2-propanol readily accessible from epichlorohydrin, a series of heterocyclic ethers was prepared for physiological testing as possible antihistamine agents. A similar series was also prepared from 2-diethylamino-1-phenylethanol which was easily obtained from styrene oxide and diethylamine. The general formulas for the two series of ethers are:

$(C_2H_5)_2NCH_2CH(OR)C_6H_5$ [I]

$(C_2H_5)_2NCH_2CH(OR)CH_2C_6H_5$ [II]

Prior to the initiation of this work the most active known alkamine ether as an antihistamine agent was β-dimethylaminoethyl benzhydryl ether (Benadryl). Consequently, the structures of the compounds prepared show varying degrees of resemblance to this established agent. More recent work[209] has included the preparation of 2-(2-dimethylaminoethoxy)-pyridine and 2-(2-dimethylaminoethoxy)-benzothiazole in addition to certain other heterocyclic alkamine ethers. None of the latter compounds was found to be more active than

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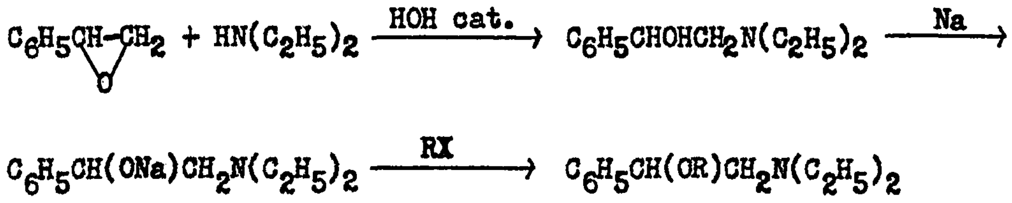
[209] Sutherland, Eberlin, Forsythe, Halverstadt, Vaughan and Clapp, J. Org. Chem., 14, 235 (1949).

Benadryl.

Type I was prepared by reactions represented by the following equations:

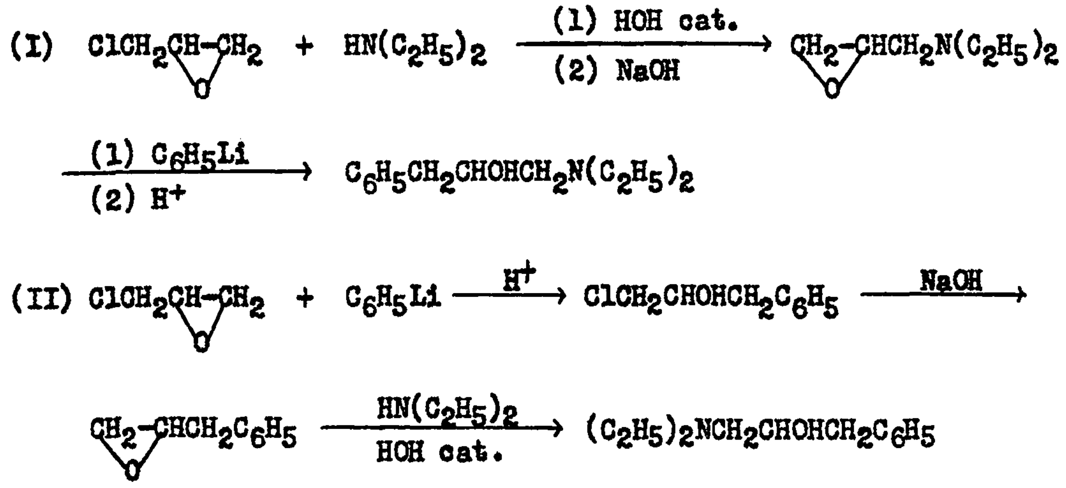


$$C_6H_5\underbrace{CH-CH_2}_{O} + HN(C_2H_5)_2 \xrightarrow{\text{HOH cat.}} C_6H_5CHOHCH_2N(C_2H_5)_2 \xrightarrow{Na}$$

$$C_6H_5CH(ONa)CH_2N(C_2H_5)_2 \xrightarrow{RX} C_6H_5CH(OR)CH_2N(C_2H_5)_2$$

The reaction was carried out in excess 2-diethylamino-1-phenylethanol to give in most cases very satisfactory yields of products. Compounds of Type II were also prepared by the action of a reactive halide upon the corresponding sodium alcoholate in excess amino alcohol. It was found, however, that with p-nitrobromobenzene p,p'-dibromoazoxybenzene was formed in appreciable amounts. The reduction of nitro compounds to azoxy compounds appears to be a general reaction for primary and secondary sodium alcoholates.

The synthesis of 1-diethylamino-3-phenyl-2-propanol was carried out by two different procedures which are outlined by the following equations:



$$\text{(I)}\quad ClCH_2\underbrace{CH-CH_2}_{O} + HN(C_2H_5)_2 \xrightarrow[\text{(2) NaOH}]{\text{(1) HOH cat.}} \underbrace{CH_2-CH}_{O}CH_2N(C_2H_5)_2$$

$$\xrightarrow[\text{(2) }H^+]{\text{(1) }C_6H_5Li} C_6H_5CH_2CHOHCH_2N(C_2H_5)_2$$

$$\text{(II)}\quad ClCH_2\underbrace{CH-CH_2}_{O} + C_6H_5Li \xrightarrow{H^+} ClCH_2CHOHCH_2C_6H_5 \xrightarrow{NaOH}$$

$$\underbrace{CH_2-CH}_{O}CH_2C_6H_5 \xrightarrow[\text{HOH cat.}]{HN(C_2H_5)_2} (C_2H_5)_2NCH_2CHOHCH_2C_6H_5$$

The products from reaction sequences I and II were identical as determined by a mixed melting point of the two picrates. Although a mixture of primary and secondary alcohols is possible, the yield of the picrate from the product of I showed that at least 89% of a single isomer was present. Additional evidence for the opening of the epoxide linkage from the least hindered side is the formation and identification of dibenzylmethanol from reaction of phenyllithium and 3-phenyl-1,2-epoxypropane.

An attempt was made to prepare 1-diethylamino-3-phenyl-2-propanol from diethylaminoacetonitrile by the following series of reactions:

$$\text{(III)}\ (C_2H_5)_2NCH_2CN \xrightarrow[\text{(2) } H^+]{\text{(1) } C_6H_5CH_2MgCl} (C_2H_5)_2NCH_2COCH_2C_6H_5$$

$$\xrightarrow{LiAlH_4} (C_2H_5)_2NCH_2CHOHCH_2C_6H_5 \quad (?)$$

The physical constants of the intermediate ketone were those which would be predicted for the compound. However, the reactions of Grignard reagents with basically-substituted nitriles may give predominately side products[210]. On the basis of the work of Thomson and Stevens[210b] the principal product should be the ketone regardless of the nature of the Grignard reagent. These authors found that benzylmagnesium chloride gave greater than a 50% yield of the expected ketone from dimethylaminoacetonitrile.

The reduction of the intermediate amino ketone should have

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[210] (a) Stevens, Cowan and MacKinnon, *J. Chem. Soc.*, 2568 (1931) and (b) Thomson and Stevens, *ibid.*, 2607 (1932).

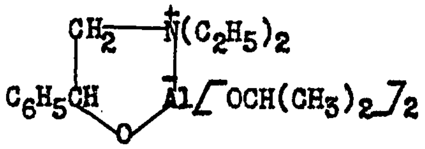
proceeded smoothly without side reactions, but the melting point of the mixed picrates of the products from reaction series I and III was depressed. However, when the physical constants of the products from reaction series I and III are compared the agreement is good. See Table XII. No explanation involving the unreliability of the reactions seems tenable.

Table XII

Physical Properties of 1-Diethylamino-3-phenyl-2-propanol

Reaction sequence	n_D^{20}	Dispersion (z value)	$d^{20/20}$	MR_D calcd.	MR_D found
I	1.5040	30.0	0.959	64.16	64.03
	1.5047	29.7	0.957	64.16	64.20
II	1.5057	29.7	0.966	64.16	63.72
	1.5058	29.7	—	64.16	—
III	1.5045	29.8	0.955	64.16	64.33

Attempts to oxidize the amino alcohols from sequences I and III with a saturated solution of potassium permanganate in 2 M sulfuric acid followed by treatment with oxalic acid and 2,4-dinitrophenylhydrazine reagent[192] failed to yield a derivative of the corresponding ketone. The known compounds, 2-diethylaminoethanol and 2-diethylamino-1-phenylethanol under similar conditions gave no derivative. The material obtained upon neutralization of the acid solution was inorganic in nature. The use of aluminum isopropoxide and acetone in benzene solution did not effect the oxidation of 1-diethylamino-3-phenyl-2-propanol and 2-diethylamino-1-phenylethanol. In a very recent paper by Lutz, Jordan and Truett[211], the interference with the Oppenauer oxidation of aliphatic 1,2-amino alcohols was explained in terms of the formation of five-membered chelate complexes involving aluminum, alcoholic hydroxyl and amine nitrogen, e.g.,



which would form from the action of aluminum isopropoxide upon 2-diethylamino-1-phenylethanol.

It is interesting in connection with the failure to derivatize the alcohols containing diethylamino groups by the procedure of Duke and Witman[192], that dibenzylmethanol after three attempts did not form a derivative. Perhaps in this case the conditions of oxidation were not vigorous enough to convert a sufficient amount of the alcohol to the corresponding ketone.

D. Suggestions for Further Research

The metal-metal interconversion reaction has not been widely applied to the preparation of synthetically-useful intermediate

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[211] Lutz, Jordan and Truett, J. Am. Chem. Soc., 72, 4085 (1950).

organometallic compounds containing reactive functional groups. Broadening the scope of this reaction would appear to be a fruitful field for the investigator, since it is generally true that the rates of the interconversion reactions decrease in the order M-M > X-M > H-M. The halogen-metal interconversion reaction is quite rapid, this fact accounting for its unusually great utility for interconversion of compounds containing reactive groups. By use of a faster preparative procedure, it should be possible to go further up the series of relative reactivities of functional groups without resorting to protection of these groups.

In order to carry out the preparation of organolithium compounds containing such groups as nitro, carboalkoxy, isothiocyanato, acid halide, epoxy, etc., it would be necessary to prepare symmetrical or unsymmetrical organomercurials[212] containing these groups. It may be readily understood that for the preparation of an organolithium compound containing, for example, a carbomethoxy group, the interconversion reaction must be carried out for a very brief period of time and must be quenched almost immediately by another compound containing a group more reactive than the carbomethoxy group. The quenching agent for purposes of identification in this case may be phenyl isocyanate or benzaldehyde. The reactants in the interconversion reaction may be methyl p-chloromercuribenzoate and n-propyllithium, and the sequence

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[212] For a discussion of the preparation and reactions of organomercurials see Gilman "Organic Chemistry", John Wiley and Sons, Inc., New York, 1943, p. 549ff. and Whitmore, "Organic Compounds of Mercury", Chemical Catalog Co., New York, 1921.

of reactions would be as follows:

$$p\text{-}CH_3O_2CC_6H_4HgCl + n\text{-}C_3H_7Li \xrightarrow{-50^{\circ}} p\text{-}CH_3O_2CC_6H_4Li + n\text{-}C_3H_7HgCl$$

$$p\text{-}CH_3O_2CC_6H_4Li + C_6H_5NCO \xrightarrow{H^+} p\text{-}CH_3O_2CC_6H_4CONHC_6H_5$$

In connection with the extension of the uses of the halogen-metal interconversion reaction, the following experiments should be tried.

1. Interconvert p-bromostyrene oxide ($p\text{-}BrC_6H_4\underline{CHCH_2O}$) with n-propyllithium at -78° for approximately ten minutes. It was found that the epoxy linkage was resistant to attack by phenyllithium for an hour at this low temperature. See page 106 for a description of the experiment upon which this suggestion is based.
2. Interconvert p-bromobenzalaniline ($p\text{-}BrC_6H_4CH = NC_6H_5$) with n-propyllithium at -50°. This reaction should proceed satisfactorily since the azomethylene linkage is low in the Gooch extension of the Entemann and Johnson series of relative reactivities of functional groups[147]. See page 48 of this thesis. Cleavage of the anil subsequent to reaction may provide an easy method for introduction of the aldehydophenyl group into organo-silicon, tin and lead compounds.
3. It is possible that p-bromobenzalaniline may react with magnesium by employing Grignard's entrainment procedure[15]. The procedure used for the preparation of 2-pyridylmagnesium bromide and 2,6-pyridinedimagnesium bromide may also be effective[48,50]. It should be pointed out, however, that open

chain azomethylene groups are more reactive than those present in heterocycles such as pyridine or quinoline.

4. *t*-Butyl *p*-bromobenzoate should be treated with *t*-butyllithium in petroleum ether to effect a halogen-metal interconversion reaction. It is assumed here that an organolithium reagent with a bulky alkyl group will not add readily to the carbonyl group as *n*-propyllithium did in ether solution. See pages 69 and 115 of this thesis.
5. Halogen-metal interconversion reactions may be carried out upon organo-tin, lead or mercury compounds if a bromine or iodine atom is *ortho* to a hydroxyl or methoxyl group. The purpose of the oxygen-containing group is to aid initial coordination of the organolithium reagent which in turn will increase the rate of the halogen-metal interconversion reaction. See pages 29 and 47.
6. *p*-Bromoacetophenone ethylene acetal may react with magnesium under the influence of a catalyst like ethyl bromide. It has been reported (page 65) that this halide does not react with metallic lithium; however, it has been found that in a large number of cases halogen compounds which do not react with lithium will react with magnesium and *vice versa*.
7. 3,4-Dibromophenol and 3,4-dibromoanisole should be interconverted to confirm preference of reaction at the *para* halogen. Reactions with the three monobromophenols and with 2,4-dibromophenol show that the rates of reaction and yields of carbonation products decrease in the order *o* > *p* > *m*[111].

See pages 29, 30 and 116.

8. 2-Bromo-4-iodophenol should be reacted with at least three equivalents of n-propyllithium to determine whether a more positive halogen in the para position may be replaced with lithium. In the case of the halogen-metal interconversion of 2,4-dibromophenol there is no evidence for reaction at the para bromine. With iodine in the para position perhaps both halogens would be replaced by lithium or perhaps one may react preferentially.

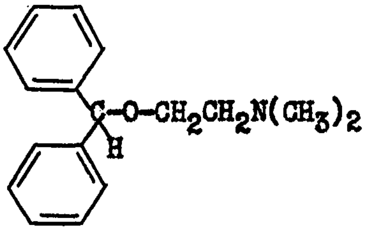
9. A two-stage metalation in the naphthalene series should take place with 4-bromo-1-methoxynaphthalene and n-propyllithium. Such a reaction has been shown to take place with p-bromoanisole[1,2] and 2-bromodibenzofuran[83,84].

10. 2,4,6-Tribromo-N-methylaniline, by analogy with the reactions of 2,4,6-tribromophenol, should give 5-bromo-2-methylaminobenzoic acid subsequent to reaction with excess n-propyllithium and carbonation. 2,4,6-Tribromophenol under these conditions is interconverted in one ortho position and bromine is replaced by hydrogen in the second position ortho to the hydroxyl group. 5-Bromosalicylic acid was obtained subsequent to carbonation of the intermediate O-lithio-5-bromo-2-hydroxyphenyllithium.

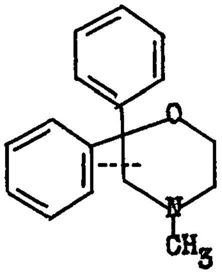
11. It would be interesting in connection with syntheses in the naphthalene series to show whether there is a positional selectivity in the reaction of 1,6-dibromonaphthalene with n-propyllithium. If one atom may be preferentially

interconverted, determine whether appropriate placement of a hydroxyl group may not change the reaction center. Though the reaction mechanisms are different, it was found that formation of the Grignard reagent by the direct procedure gave exclusively 5-bromo-2-naphthylmagnesium bromide[20].

In extension of the work of Gilman and Wanser[213] who successfully prepared the cyclic analog of Benadryl,

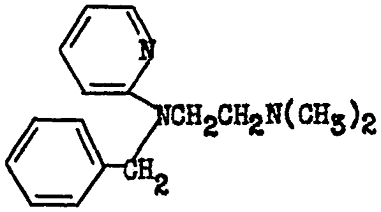


Benadryl

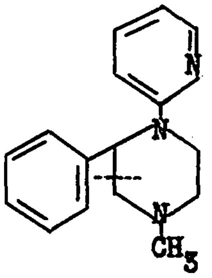


2,2-diphenyl-4-methylmorpholine

the cyclic form of Pyribenzamine should also be prepared.



Pyribenzamine



4-methyl-2-phenyl-1-(2-pyridyl)-piperazine

It will be observed that hydrogenolysis of both cyclic structures at the bonds crossed by the dotted lines would produce Benadryl and Pyribenzamine, respectively. The following sequence of reactions

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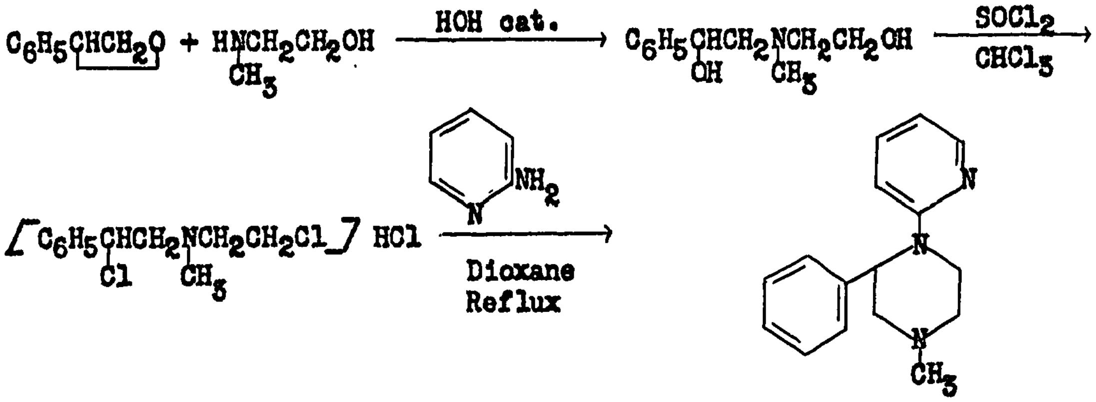
[213] Gilman and Wanser, *J. Am. Chem. Soc.*, *73*, 000 (1951).

represents the proposed synthesis.



$$C_6H_5\underset{\lfloor}{C}HCH_2\underset{\rfloor}{O} + H\underset{CH_3}{N}CH_2CH_2OH \xrightarrow{HOH\ cat.} C_6H_5\underset{OH}{C}HCH_2\underset{CH_3}{N}CH_2CH_2OH \xrightarrow[CHCl_3]{SOCl_2}$$

$$[C_6H_5\underset{Cl}{C}HCH_2\underset{CH_3}{N}CH_2CH_2Cl]\ HCl \xrightarrow[\text{Dioxane Reflux}]{}$$

The β-chloroethylamines are powerful vesicants; therefore, no attempt should be made to isolate the free base from the intermediate salt.

Although the use of a morpholine derivative as an antihistamine agent has not been reported, the 1,4-disubstituted piperazine derivatives[214] were shown to be very effective in protection against histamine intoxication.

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[214] (a) Hamlin, Weston, Fischer and Michaels, J. Am. Chem. Soc., 71, 2731, 2734 (1949). (b) Albro, Baltzly and Phillips, J. Org. Chem., 14, 771 (1949). (c) Baltzly, DuBreuil, Ide and Lorz, ibid., 14, 775 (1949).

V. SUMMARY

A survey of the literature concerned with the preparation of organo-magnesium, lithium, sodium, and potassium compounds which contain a reactive functional group in the molecule has been presented. A table of almost two hundred compounds has been prepared.

Bromo- and iodo- nitrobenzenes could not be interconverted with a variety of organolithium compounds. The nitro group was not protected from the reducing action of the organometallic compounds by the steric effects of two ortho methyl groups.

The conversion of a ketone to the ethylene acetal proved to be an effective procedure for protection of the carbonyl group during the halogen-metal interconversion reaction.

t-Butyl esters were not sterically protected at the carbonyl group toward n-propyllithium.

Protection of phenolic hydroxyl by acetalization with dihydropyran appeared to have an adverse effect upon the halogen-metal interconversion reaction. Interconversion of di- and tri-brominated phenols gave bromine-lithium exchange exclusively in the ortho positions.

Reaction of phenols having two bromine atoms ortho to the hydroxyl group with n-propyllithium gave interconversion at one ortho position and reductive debromination at the other. A mechanism of reaction has been proposed.

Seven new ethers of 2-diethylamino-1-phenylethanol and six ethers of heretofore unreported 1-diethylamino-3-phenyl-2-propanol were prepared for pharmacological testing. Two syntheses of 1-diethylamino-3-phenyl-2-propanol were presented.

Reaction of phenyllithium with epichlorohydrin was found to be a suitable procedure for the preparation of 1-chloro-3-phenyl-2-propanol.