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STERIC AND ELECTRONIC INFLUENCES IN ORGANOLITHIUM METALATIONS

by

John West Morton, jr.

A Dissertation Submitted to the
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DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

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Dean of Graduate College

Iowa State College
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TABLE OF CONTENTS

INTRODUCTION

The earliest use of a highly reactive organometallic compound as a metalating agent was reported nearly half a century ago.[1] At that time, the preparation of organoalkali compounds was both inconvenient and hazardous; the procedure usually employed was a reaction between the alkali metal and an R_2Hg compound. For this reason, the extensive investigation of the synthetic possibilities of the organoalkali reagents, in metalations as well as in other reactions, was delayed until more convenient methods of preparation[2,3,4] became available.

During the past two decades, enough data have accumulated concerning the organoalkali metalations to enable many general conclusions to be drawn concerning orientation[5,6,7]

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[1] P. Schorigin, Ber., 41, 2723 (1908).

[2] K. Ziegler and H. Colonius, Ann., 479, 135 (1930).

[3] H. Gilman, E. A. Zoellner and W. M. Selby, J. Am. Chem. Soc., 54, 1957 (1932).

[4] A. A. Morton and I. Hechenbleikner, ibid., 58, 1697 (1936).

[5] H. Gilman, H. B. Willis, T. H. Cook, F. J. Webb and R. N. Meals, ibid., 62, 667 (1940).

[6] H. Gilman and G. E. Brown, ibid., 62, 3208 (1940).

[7] W. Langham, R. Q. Brewster and H. Gilman, ibid., 63, 545 (1941).

and the relative directing influences of various groups in such reactions. Theories dealing with the general electronic character of metalation reactions have also been presented.[8,9,10] In only a few cases, however, have stereochemical considerations been adduced to explain the outcome of such reactions,[11,12] although steric influences in other reactions of organometallic compounds have been studied.[13]

A second aspect of metalation which has received only scant attention is that of electronic influences in the metalated product in bringing about further reaction after metalation has taken place. The only systematic studies so far reported in this field have been the brilliant investigations of Wittig and co-workers on the metalation-rearrangements of certain ethers and quaternary ammonium salts.[14]

The studies described in the Experimental part of this dissertation were undertaken with a view toward exploring

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[8] J. D. Roberts and D. Y. Curtin, ibid., 68, 1658 (1946).

[9] A. A. Morton, ibid., 69, 969 (1947).

[10] S. V. Sunthankar and H. Gilman, J. Org. Chem., 16, 8 (1951).

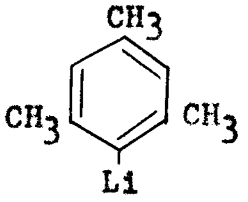
[11] S. M. Spatz, Iowa State Coll. J. Sci., 17, 129 (1942).

[12] H. Gilman and S. M. Spatz, J. Org. Chem., 17, in press (1952).

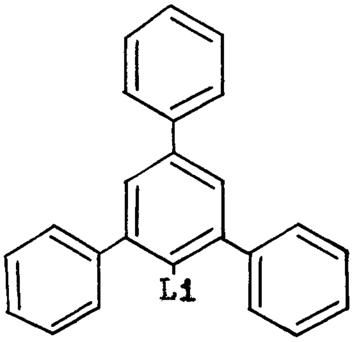
[13] R. C. Fuson, G. P. Speranza and R. Gaertner, ibid., 15, 1155 (1950).

[14] See the Section entitled "The Stevens and Sommelet Rearrangements" in the Historical part of this dissertation.

both of these little-studied fields of metalation. The metalation reactions of the sterically hindered organolithium compounds mesityllithium (I) and 2,4,6-triphenylphenyllithium (II) were compared with those of the less sterically hindered organolithium compounds, such as phenyllithium and *o*-tolyllithium. It was of interest to investigate comparative yields from the various RLi compounds in similar metalation reactions, and also to discover whether sterically hindered RLi compounds might in some cases yield metalation products different from those produced by their less hindered analogues.

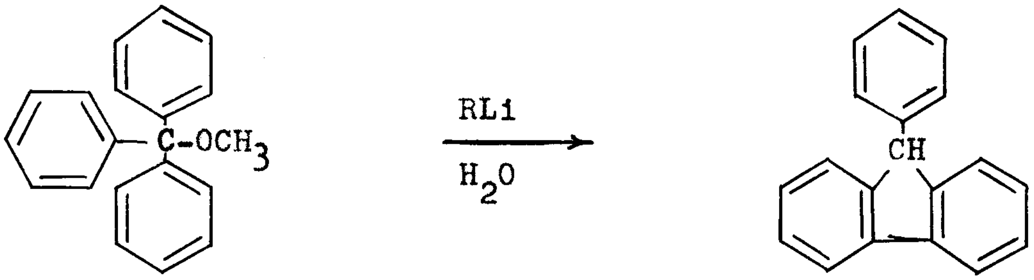


I



II

The role of electronic factors in bringing about further reactions of the metalated product was explored through investigation of the action of organolithium compounds upon ethers of the type Ar_3COCH_3. Several years ago, Mr. W. J. Meikle studied the reaction of trityl methyl ether with phenyllithium as a possible method of preparing tetraphenylmethane. It had previously been shown that tetraphenylmethane was formed in the reaction between trityl ethers and



III

phenylmagnesium bromide.[15] With phenyllithium, however, no tetraphenylmethane was produced, and the only product isolated was 9-phenylfluorene.[16] It was thought that phenyllithium (a more reactive metalating agent than phenylmagnesium bromide) had metalated the ether, and that the metalated intermediate had in some fashion undergone a ring closure to yield the final product. The studies of the above type of reaction which are described in this dissertation were undertaken with the following objectives: (1) to verify the presumed occurrence of metalation as a preliminary step in the reaction; (2) to determine the scope of the reaction; i.e., to discover which ethers and which RM compounds could serve as reactants; and (3) to explore the possible use of the reaction in the production of other ring systems, by varying the groups present in the original ether.

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[15] M. Gomberg and O. Kamm, J. Am. Chem. Soc., 39, 2009 (1917).

[16] H. Gilman, W. J. Meikle and J. W. Morton, ibid., 74, in press (1952).

It was also of interest, in connection with the study of the general electronic character of metalation, to investigate the possible use of Grignard reagents and organocalcium compounds in metalation reactions, and to compare their properties as metalating agents with those of organolithium compounds.

HISTORICAL

The purpose of the survey presented on the following pages is to provide a complete review of the literature of reactions in which organometallic compounds have been used as metalating agents. The survey is divided into several sections, the first of which deals with simple metalations, *i.e.*, those in which no other reaction occurs besides the replacement of hydrogen by metal to yield an organometallic compound.[17] Each of the later sections treats of metalation reactions which are accompanied, or followed, by some particular secondary reaction, such as coupling, dehydrogenation, reduction, or rearrangement.

Wherever possible, the original literature was consulted in the writing of this survey. Pertinent articles were located through the use of the indices of *Chemical Abstracts*. The literature has been covered completely through the year 1950, and as thoroughly as possible for the succeeding period.

Simple Metalations

Metalations with organolithium compounds

Although an early attempt to metalate thiophene with ethyllithium was reported in 1910,[18] the first successful

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[17] H. Gilman and R. V. Young, *ibid.*, *56*, 1415 (1934).

[18] P. Schorigin, *Ber.*, *43*, 1938 (1910).

use of an organolithium compound as a metalating agent was not described until almost two decades later, when Schlenk and Bergmann reported that ethyllithium reacted with fluorene to replace one of the methylene hydrogens.[19] Dimetalation was also found to occur to some extent; in a reaction between fluorene and ethyllithium in which benzoyl chloride was used to derivatize the product, a compound characterized by the authors as 9-benzoylfluorene was isolated;[20] other workers demonstrated shortly afterward that the product was actually 9,9-dibenzoylfluorene, the derivative of laterally dimetalated fluorene.[21,22] Later studies showed that the replacement of an activated hydrogen atom by a lithium atom was a general reaction; organolithium compounds have been used in the metalation of indene,[23,24] 3,3-diphenylindene,[25]

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[19] W. Schlenk and E. Bergmann, Ann., 464, 192 (1928).

[20] W. Schlenk and E. Bergmann, Ber., 62, 748 (1929).

[21] A. Kliegl, F. Weng and G. Wiest, ibid., 63, 1262 (1930).

[22] P. Pfeiffer and E. Lübbe, ibid., 63, 762 (1930).

[23] O. Blum-Bergmann, Ann., 484, 26 (1930).

[24] L. S. Miller, Doctoral Dissertation, Iowa State College, 1950.

[25] O. Blum-Bergmann, Ber., 65, 109 (1932).

phenylacetylene,[26,27] phenyl-1-naphthylmethane,[28] p-benzhydryltetraphenylmethane,[29] acenaphthene,[28] 2-picoline[30,31] and quinaldine.[30] Both the monometalation[28] and the dimetalation[32] of diphenylmethane by RLi reagents have been reported. The reaction of triphenylmethane with organolithium compounds has been found to produce the bright red triphenylmethyllithium,[24,27] and this color has been used as a qualitative test for both alkyl- and aryllithium reagents.[33] Xanthene was found to undergo metalation in the 9-position with phenyllithium, and a patent has been issued for the preparation of antispasmodic agents by the condensation of metalated xanthene with dialkylaminoalkyl halides

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[26] M. A. Plunkett, Doctoral Dissertation, Iowa State College, 1947.

[27] H. Gilman and R. V. Young, J. Org. Chem., 1, 315 (1936).

[28] H. Gilman and R. L. Bebb, J. Am. Chem. Soc., 61, 109 (1939).

[29] J. Wynstra, Doctoral Dissertation, University of Michigan, 1943 ⁄ Microfilm Abstr., 5, 15 (1943); C. A., 38, 3637 (1944) ⁄.

[30] K. Ziegler and H. Zeiser, Ann., 511, 45 (1934).

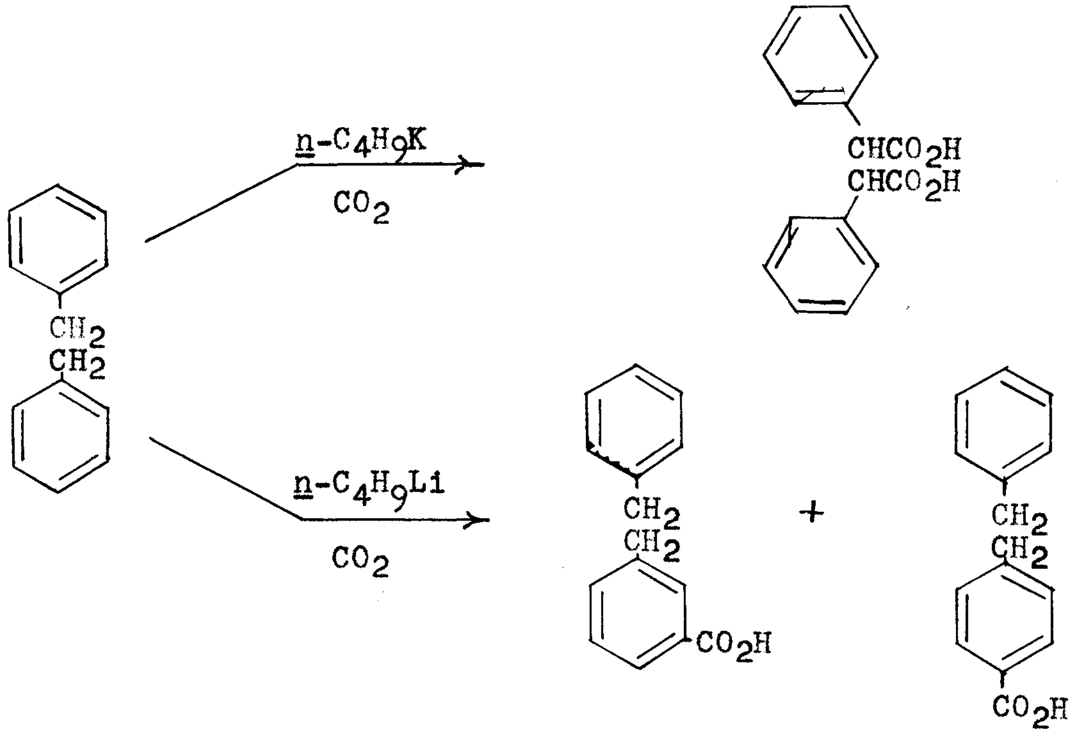
[31] L. A. Walter in L. I. Smith, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. 23, p. 83.

[32] A. Lüttringhaus, G. Wagner-von Sääf, E. Sucker and G. Borth, Ann., 557, 46 (1945).

[33] H. Gilman and J. Swiss, J. Am. Chem. Soc., 62, 1847 (1940).

to yield 9-dialkylaminoalkylxanthenes.[34]

Toluene was laterally metalated by *n*-butyllithium, although the yield of benzyllithium was very poor,[35] and mesitylene was not metalated at all by *n*-butyllithium.[36] Acetomesitylene was found to undergo replacement of an active hydrogen atom when treated with RLi compounds or with other organometallic reagents. The sterically hindered carbonyl



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[34] J. W. Cusic (to G. D. Searle & Co.), U. S. Patent 2,368,006 (1945) [*C. A.*, *39*, 3630 (1945)].

[35] H. Gilman, H. A. Pacevitz and O. Baine, *J. Am. Chem. Soc.*, *62*, 1514 (1940).

[36] R. L. Bebb, Doctoral Dissertation, Iowa State College, 1938.

group was unaffected by the reaction, and acetomesitylene was recovered on hydrolyzing the mixture.[37] Bibenzyl, which underwent normal dimetalation on the two lateral carbon atoms when treated with n-butylsodium or n-butylpotassium in hydrocarbon solvents, was metalated in the nucleus by n-butyllithium in ether, to give a mixture of meta- and para-metalated products.[28]

The polymetalation of various hydrocarbons containing activated hydrogens has been reported recently. Toluene, when heated with ethyllithium, was found to give a mixture of tetra- and pentametalated products, and diphenylmethane reacted with ethyllithium in benzene to yield a tetralithio derivative. Benzyllithium was metalated quantitatively under the same conditions to give a dilithio product.[38] The positions of substitution were not determined, but at least some nuclear metalation must have occurred in the first two cases.

Metalations of completely aromatic hydrocarbons with organolithium compounds have not been extensively studied. Benzene was metalated by n-butyllithium to give a small

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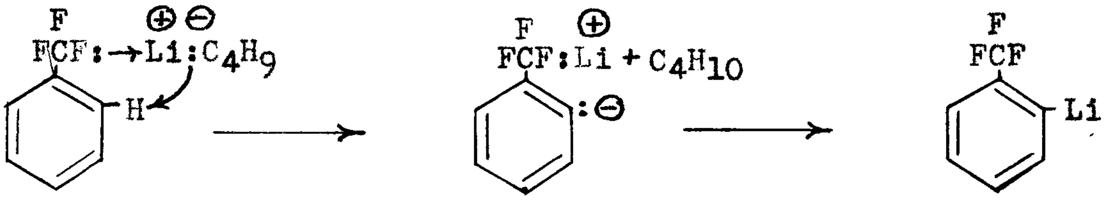
[37] H. Gilman and R. L. Jones, J. Am. Chem. Soc., 63, 1162 (1941).

[38] T. V. Talalaeva and K. A. Kocheshkov, Doklady Akad. Nauk S.S.S.R., 77, 621 (1951) /C. A., 45, 1091 (1951)/.

amount of phenyllithium,[39] and naphthalene reacted with the same RLi compound to yield a mixture of 1- and 2-naphthyllithium.[28] Biphenyl was metalated by n-butyllithium to yield, after carbonation, 15 per cent of p-phenylbenzoic acid.[28]

Certain simple halogen derivatives of aromatic hydrocarbons have been metalated by organolithium compounds. In most cases, the metalated product was found to couple immediately with excess RLi; this type of reaction will be discussed in a later section of the present review. In one instance, however, the metalation of a halogen compound has been reported to lead to a stable derivative. Roberts and Curtin described the metalation of benzotrifluoride with n-butyllithium to yield o-trifluoromethylphenyllithium, together with a small amount of the m- and p-isomers.[8] The predominating ortho orientation was interpreted by the authors



as indicating that metalation by RLi was primarily a nucleophilic process, involving, in this case, preliminary com-

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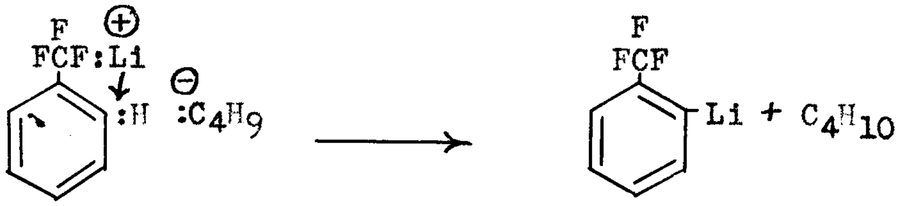
[39] R. V. Young, Doctoral Dissertation, Iowa State College, 1936.

plexation of the lithium cation with a pair of unshared electrons belonging to a fluorine atom. An alternative explanation for this orientation, and for that of other metalation reactions, was suggested by A. A. Morton,[9] who postulated that, simultaneously with the complexation of the lithium cation with fluorine, or immediately thereafter, the "anchored" cation attacked an ortho carbon atom with the



expulsion of a proton. The effect of the n-butyl carbanion in facilitating proton removal was pictured as being of secondary importance. This electrophilic interpretation of the metalation reaction was in accord with the theory[40] that organoalkali compounds generally functioned as electrophilic species.

A number of compounds containing amino nitrogen as the only hetero element have been metalated with organolithium compounds. Aniline, N-n-butylaniline, and diphenylamine were all found to be metalated by n-butyllithium in the

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[40] A. A. Morton, Chem. Revs., 35, 1 (1944).

position *ortho* to the nitrogen atom.[41] Similarly, carbazole and 9-ethylcarbazole were metalated by *n*-butyllithium in the 1-position.[42] 9-Phenylcarbazole was also metalated *ortho* to the nitrogen atom, but in this case substitution occurred in the phenyl ring rather than in the carbazole nucleus.[43] By the use of an excess of metalating agent, a second lithium atom could be introduced in the remaining *ortho* position of the phenyl group.[44] The metalation of triphenylamine by *n*-butyllithium was found to be an exception to the normal rule of *ortho*-metalation; on carbonation of the reaction mixture, only *m*-carboxytriphenylamine was produced.[6] Triphenylphosphine[45] and triphenylarsine[46] were also metalated in the *meta* position by *n*-butyllithium. It has been suggested that the *meta*-metalation of triphenylamine may have been due to steric hindrance about the *ortho* positions of the three freely rotating phenyl groups, and that in 9-phenylcarbazole, where two of the phenylene groups were fixed permanently in

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[41] H. Gilman, G. E. Brown, F. J. Webb and S. M. Spatz, *J. Am. Chem. Soc.*, *62*, 977 (1940).

[42] H. Gilman and R. H. Kirby, *J. Org. Chem.*, *1*, 146 (1936).

[43] H. Gilman, C. G. Stuckwisch and A. R. Kendall, *J. Am. Chem. Soc.*, *63*, 1758 (1941).

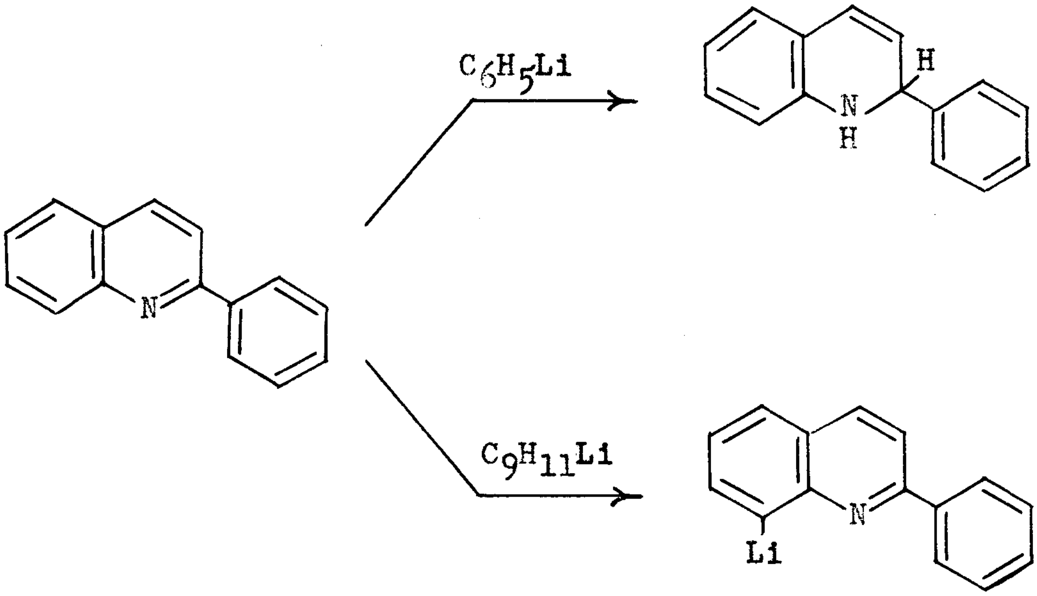
[44] H. Gilman and C. G. Stuckwisch, *ibid.*, *65*, 1729 (1943).

[45] H. Gilman and G. E. Brown, *ibid.*, *67*, 824 (1945).

[46] H. Gilman and C. G. Stuckwisch, *ibid.*, *63*, 3532 (1941).

one plane, the ortho positions of the remaining phenyl group were more accessible for attack by the RLi compound than was the case in triphenylamine.[12] Steric considerations have also been adduced to account for the fact that 9-methylcarbazole was dimetalated by n-butyllithium, whereas 9-ethylcarbazole was found to undergo only monometalation, even with an excess of n-butyllithium.[12]

Nitrogen in an azomethine linkage was found to be capable of directing metalation when there was sufficient steric hindrance to suppress the normally rapid addition of RLi to the azomethine linkage. 2-Phenylquinoline reacted



with phenyllithium in the normal fashion to produce 2,2-diphenyl-1,2-dihydroquinoline,[47] but the reaction with

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[47] H. Gilman and G. C. Gainer, ibid., 69, 877 (1947).

mesityllithium resulted in the metalation of 2-phenylquinoline in the 8-position.[48] The isolation of bis-compounds from the reaction between hindered RLi reagents and azomethine compounds such as 6-phenylphenanthridine,[49] 2-phenylquinoline, and benzo(h)quinoline, has been explained on the basis of metalation of the azomethine compound to yield a less sterically hindered RLi which could then add to unreacted azomethine compound in the normal fashion.[48] The reaction of 2-chloroquinoline with *n*-butyllithium, followed by carbonation, yielded a small amount of an acid which was tentatively identified as a 2-chloroquinoline-x-carboxylic acid, indicating the possibility that metalation had taken place.[50]

The reaction of benzylamine and of dibenzylamine with organolithium compounds was found to result in a characteristic red coloration which could be used as a qualitative test for reactive RM compounds. Although the color suggested that lateral metalation had occurred, carbonation of a mixture of *n*-butyllithium and dibenzylamine produced the nuclearly substituted product, N-benzyl-α-amino-*o*-toluic acid,[51]

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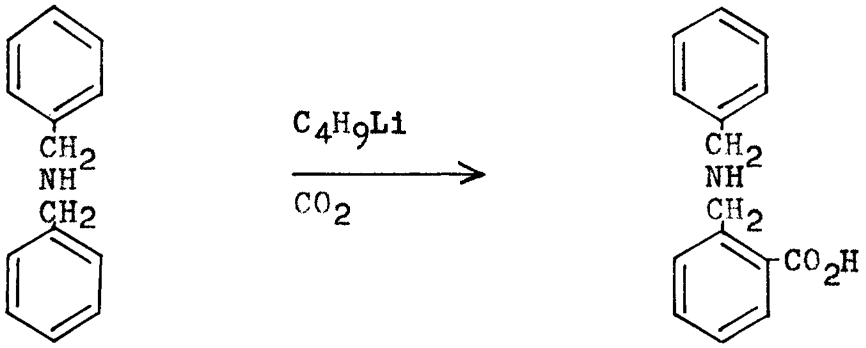
[48] D. Nelson and T. L. Reid, unpublished studies.

[49] H. Gilman and R. D. Nelson, *J. Am. Chem. Soc.*, *70*, 3316 (1948).

[50] H. Gilman and S. M. Spatz, *ibid.*, *63*, 1553 (1941).

[51] H. Gilman and L. A. Woods, *ibid.*, *65*, 33 (1943).

indicating either that some nuclear metalation had occurred or that an "*ortho*-rearrangement" of the type common to



certain benzylmetallic compounds[52,53,54,55,56] had taken place. Sodamide, a compound similar to the RLi reagents by virtue of its strong basicity, has also been reported to give a red color with benzylamine and with dibenzylamine.[57]

Quaternary ammonium salts have been shown to undergo simple metalation by RLi compounds in some cases. Wittig and Rieber found that tetramethylammonium bromide reacted with phenyllithium to yield two products which could be

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[52] H. Gilman and F. Breuer, *ibid*., *56*, 1127 (1934).

[53] H. Gilman and J. F. Nelson, *ibid*., *61*, 741 (1939).

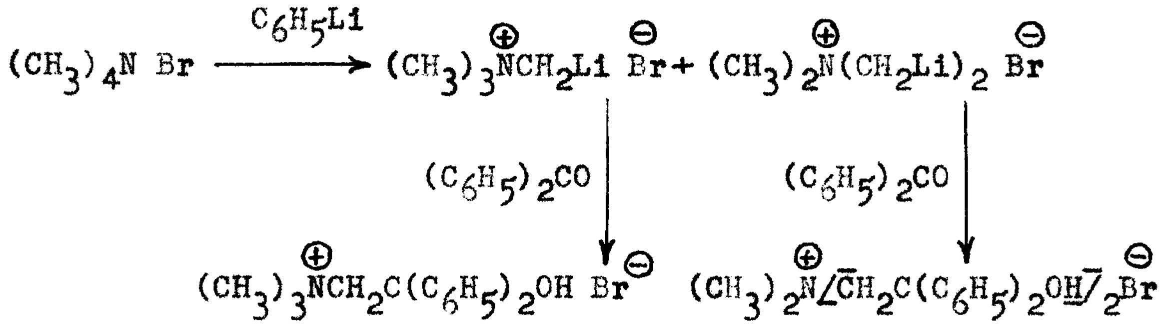
[54] H. Gilman and S. A. Harris, *ibid*., *53*, 3541 (1931).

[55] R. Gaertner, *ibid*., *73*, 3934 (1951).

[56] R. Gaertner, *ibid*., *74*, 2185 (1952).

[57] W. Krabbe, G. Grunwald, E. Olzin and W. Menzel, *Ber*., *74*, 1343 (1941).

separated on the basis of differing solubilities in ether. One of these products reacted with benzophenone to give trimethyl-β-hydroxy-β,β-diphenylethylammonium bromide, while



$$\begin{tikzcd}
(CH_3)_4N\ Br \arrow[r, "C_6H_5Li"] & (CH_3)_3\overset{\oplus}{N}CH_2Li\ \overset{\ominus}{Br} \arrow[d, "(C_6H_5)_2CO"'] & + & (CH_3)_2\overset{\oplus}{N}(CH_2Li)_2\ \overset{\ominus}{Br} \arrow[d, "(C_6H_5)_2CO"'] \\
& (CH_3)_3\overset{\oplus}{N}CH_2C(C_6H_5)_2OH\ Br^{\ominus} & & (CH_3)_2\overset{\oplus}{N}[CH_2C(C_6H_5)_2OH]_2\overset{\ominus}{Br}
\end{tikzcd}$$

the other product reacted with the same ketone to yield dimethylbis-(β-hydroxy-β,β-diphenylethyl)-ammonium bromide, indicating that mono- and dimetalation of the ammonium salt had taken place.[58] A similar monometalation of tetramethylammonium chloride was also reported.[59] Tetramethylphosphonium iodide reacted with phenyllithium to yield products whose benzophenone derivatives showed that mono- and dimetalation had occurred. With a larger excess of phenyllithium, there

$$(CH_3)_4\overset{\oplus}{P}\ \ \overset{\ominus}{I} \xrightarrow{C_6H_5Li} \overset{\oplus}{P}(CH_2Li)_4\ \ \overset{\ominus}{I} \xrightarrow{CH_3I} (C_2H_5)_4\overset{\oplus}{P}\ \ \overset{\ominus}{I}$$

resulted a product which reacted with methyl iodide to yield tetraethylphosphonium iodide, indicating that metalation had

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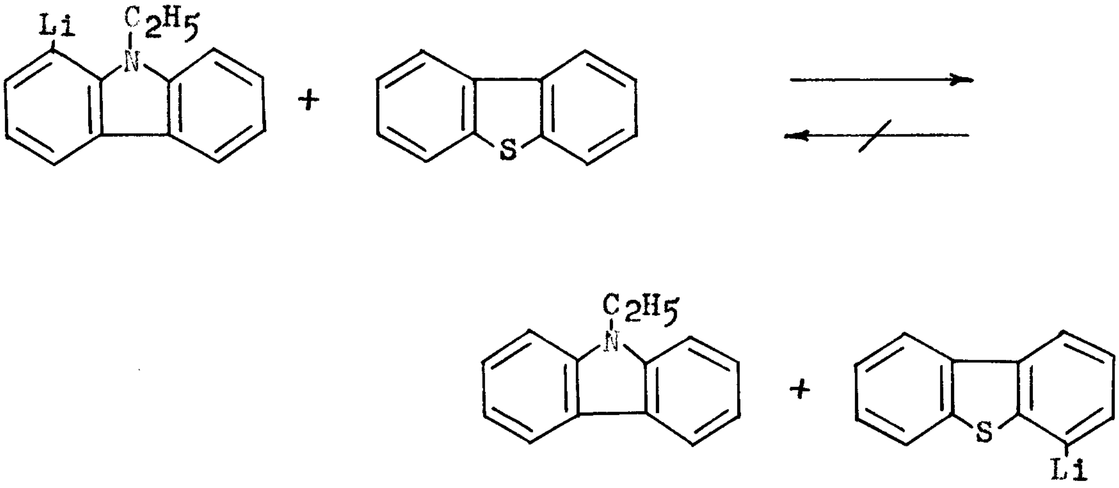
[58] G. Wittig and M. Rieber, *Ann.*, *562*, 177 (1949).

[59] G. Wittig and M. H. Wetterling, *ibid.*, *557*, 193 (1947).

occurred on each of the methyl groups of the original phosphonium salt.[58]

In certain cases, the metalation of ammonium salts has been found to lead to rearrangement. Reactions of this type will be considered in a later section of the present review.

The precedence taken by the sulfide linkage over the tertiary amino linkage in directing the orientation of metalation reactions has been demonstrated through a series of competitive metalations. When a mixture of 9-ethylcarbazole and dibenzothiophene was allowed to react with an insufficient quantity of *n*-butyllithium, only the dibenzothiophene was metalated. 1-(9-Ethylcarbazolyl)-lithium was found to metalate dibenzothiophene in the 4-position, while 4-dibenzothienyllithium had no effect upon 9-ethylcarbazole.[60]



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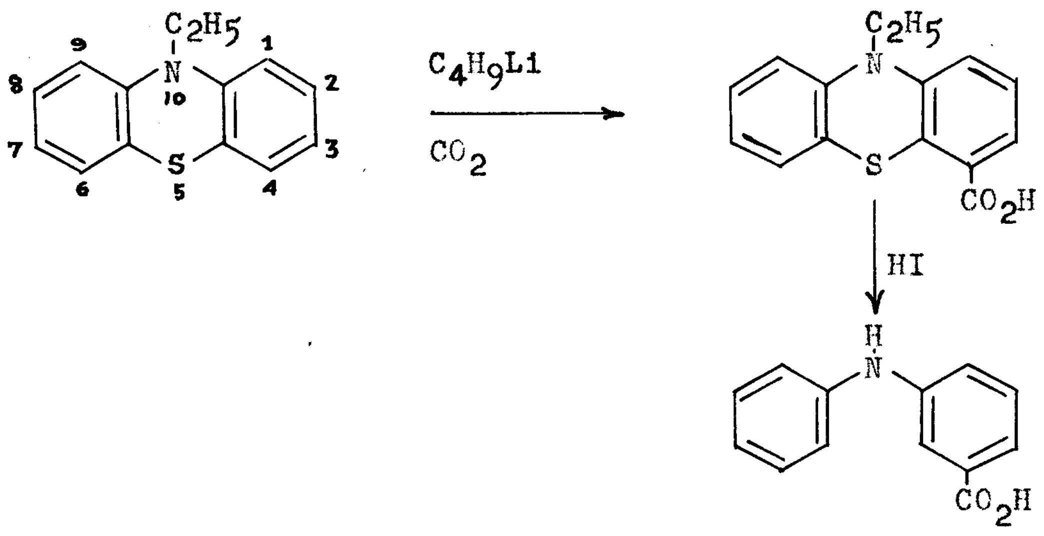
[60] H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, *67*, 877 (1945).

10-Ethylphenothiazine was metalated by n-butyllithium to produce, after carbonation, an acid which was reductively cleaved by hydrogen iodide to yield m-carboxydiphenylamine, thus indicating that the original acid was either 2- or 4-carboxy-10-ethylphenothiazine.[61] The results of the



competitive metalations mentioned above suggested that metalation had occurred ortho to the sulfur atom, and that the acid was the 4-isomer. This conjecture was indirectly confirmed several years later, when an independent

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[61] H. Gilman, P. R. Van Ess and D. A. Shirley, ibid., 66, 1214 (1944).

synthesis[62,63] of 10-ethylphenothiazine-2-carboxylic acid established that the latter compound was different from the metalation acid. The metalation[61,64,65] and dimetalation[64] of other N-substituted phenothiazines have been reported, but the positions of substitution have not been rigorously determined. Phenothiazine itself was found to undergo metalation _ortho_ to the nitrogen rather than to the sulfur atom,[66] suggesting that the rule of precedence of sulfur over nitrogen in governing the course of metalation did not hold for secondary amines.

The metalation of thianthrene in the 1-position[67] and of diphenyl sulfide[28] and thianaphthene[68,69] in the 2- or

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[62] R. Baltzly, H. Harfenist and F. J. Webb, _ibid_., _68_, 2673 (1946).

[63] The synthesis cited in Reference 62 was based on the assumption that acetylation of phenothiazine should occur in the position _para_ to sulfur. This assumption was substantiated in a later study: see J. G. Michels and E. D. Amstutz, _ibid_., _72_, 288 (1950).

[64] R. D. Nelson, Doctoral Dissertation, Iowa State College, 1951.

[65] T. Goreau, unpublished M. S. Thesis, Iowa State College, 1951.

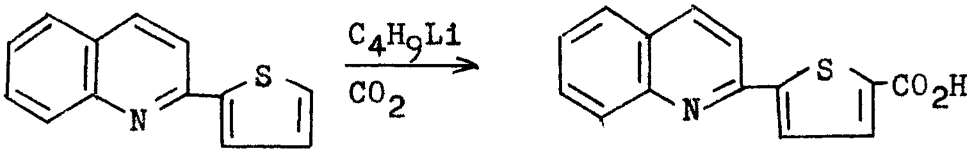
[66] H. Gilman, D. A. Shirley and P. R. Van Ess, _J_. _Am_. _Chem_. _Soc_., _66_, 625 (1944).

[67] H. Gilman and C. G. Stuckwisch, _ibid_., _65_, 1461 (1943).

[68] D. A. Shirley and M. Cameron, _ibid_., _72_, 2788 (1950).

[69] D. A. Shirley and M. Cameron, _ibid_., _74_, 664 (1952).

ortho-position by n-butyllithium has been reported. Thiophene was metalated with unusual rapidity and in good yields by n-butyllithium, to yield 2-thienyllithium.[70,71] 2-(2'-Thienyl)-quinoline underwent metalation, probably in the 5'-position, when treated with n-butyllithium. Again, as in the reaction of mesityllithium with 2-phenylquinoline, metalation was able to proceed faster than addition to the azomethine linkage. This result was not surprising in view of the great ease with which thiophene itself was found to be metalated.[71]



The metalation of dibenzothiophene in the 4-position by RLi compounds has been investigated extensively.[28,60,72,73,74,75]

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[70] H. Gilman, R. A. Benkeser and G. E. Dunn, ibid., 72, 1690 (1950).

[71] H. Gilman and D. A. Shirley, ibid., 71, 1870 (1949).

[72] S. Avakian, Doctoral Dissertation, Iowa State College, 1944.

[73] H. Gilman, F. W. Moore and O. Baine, J. Am. Chem. Soc., 63, 2479 (1941).

[74] H. Gilman and J. F. Nobis, ibid., 67, 1479 (1945).

[75] A. L. Jacoby, Doctoral Dissertation, Iowa State College, 1938.

Gilman and Jacoby reported a study in which dibenzothiophene was metalated by several different organolithium reagents under similar conditions.[76] The yields of dibenzothiophene-4-carboxylic acid obtained by carbonation of the reaction mixtures was as follows: n-butyllithium, 54 per cent; phenyllithium, 12 per cent; 1-naphthyllithium, 7.6 per cent. No metalation acid at all was isolated in the reaction with p-anisyllithium. A comparison of the effects of various solvents on the yield of metalation product from the reaction between dibenzothiophene and n-butyllithium was reported by Bebb.[36] When the reaction was carried out in di-n-butyl ether at room temperature for twenty-four hours, the yield of 4-acid was 61 per cent. From a similar reaction carried out at 80°, the yield was 90 per cent. No metalation product was isolated from reaction products using petroleum ether,[77] benzene or dioxane as the solvent.

Phenyl methyl sulfide reacted with n-butyllithium with the replacement of one of the methyl hydrogens; carbonation

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[76] H. Gilman and A. L. Jacoby, J. Org. Chem., 3, 108 1938).

[77] The reaction in two different grades of petroleum ether (b.p. 30-35° and b.p. 60-68°) was examined. The mixture was refluxed in each case. This appears to be the only study in which a comparison has been made between two different grades of petroleum ether as solvents in the same metalation reaction.

of the reaction mixture yielded phenylmercaptoacetic acid.[78,79] Other aryl methyl sulfides were also laterally metalated by _n_-butyllithium. However, the higher alkyl phenyl sulfides, such as phenyl ethyl, phenyl _n_-propyl, phenyl isopropyl, phenyl _n_-butyl, and phenyl cyclohexyl sulfides, were metalated in the nucleus _ortho_ to the sulfur atom. In the metalation of these sulfides, some tendency toward cleavage as a side reaction was noted. The reaction of phenyl methyl sulfide with butyllithium, under forcing conditions, led to the formation of a 23 per cent yield of thiophenol.[79] In this tendency to undergo cleavage concurrently with metalation, the compounds of sulfur were found to stand midway between those of oxygen and those of selenium. Anisole gave only metalation product with _n_-butyllithium, while methyl phenyl selenide[79] and diphenyl selenide[28] yielded only cleavage products.

Diphenyl disulfide was found to undergo dimetalation with _n_-butyllithium, to yield, after carbonation, 2,2'-dicarboxydiphenyl disulfide.[79] The same diacid was isolated when a mixture of thiophenol and _n_-butyllithium

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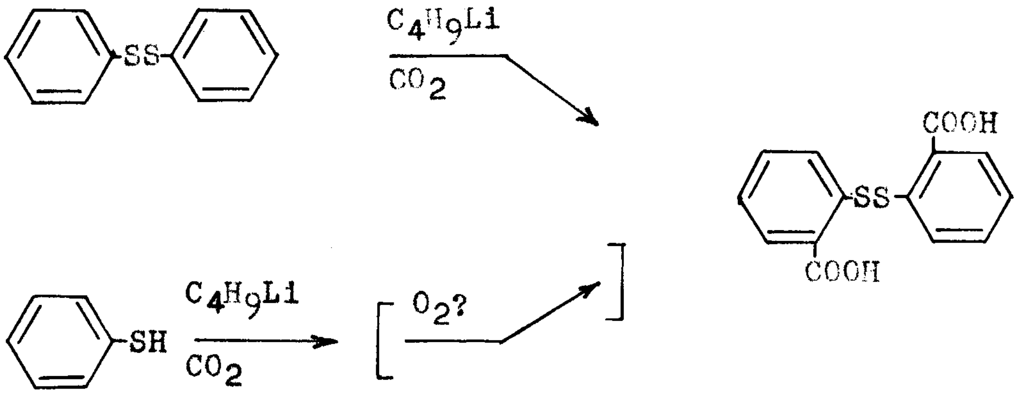
[78] H. Gilman and F. J. Webb, _J_. _Am_. _Chem_. _Soc_., _62_, 987 (1940).

[79] H. Gilman and F. J. Webb, _ibid_., _71_, 4062 (1949).

was carbonated. In the latter case, air oxidation may have occurred as an intermediate reaction while the product was



being worked up.[80]

Early attempts to effect the metalation of sulfones with RLi compounds generally led to unidentifiable products. In the case of methyl phenyl sulfone, however, carbonation of the reaction mixture led to the formation of benzenesulfonylacetic acid, indicating that lateral metalation had taken place.[79] Later investigations showed that aryl sulfones could be metalated in good yields by n-butyllithium if low temperatures were employed. Under these conditions, dibenzothiophene-5-dioxide underwent metalation in the 4-position and dimetalation in the 4- and 6-positions, depending

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[80] H. Gilman, C. E. Arntzen and F. J. Webb, J. Org. Chem., 10, 374 (1945).

on the proportion of the reactants.[81] Similarly, diphenyl sulfone could be metalated in the 2-position[81,82] and dimetalated in the 2- and 2'-positions.[81] Phenyl 2-thienyl sulfone was metalated in the thienyl rather than in the phenyl nucleus, to yield 5-benzenesulfonyl-2-thenoic acid on carbonation. m-Bromodiphenyl sulfone and p-bromodiphenyl sulfone were both metalated in the 2-position. The latter compound also underwent halogen-metal interconversion to some extent; p-benzenesulfonylbenzoic acid was found as one of the carbonation products. With o-bromodiphenyl sulfone, halogen-metal interconversion took place to the complete exclusion of metalation.[82]

Comparative studies showed that the ether linkage had a greater activating influence in metalation than the sulfide linkage. In a reaction in which dibenzofuran and dibenzothiophene were allowed to compete for an insufficient quantity of n-butyllithium, only the dibenzofuran was metalated. 4-Dibenzothienyllithium was found to metalate dibenzofuran, while 4-dibenzofuryllithium had no effect upon dibenzothio-

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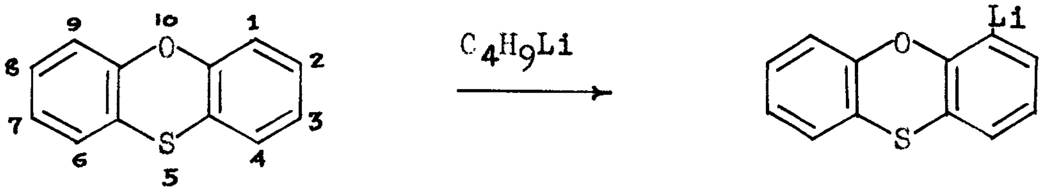
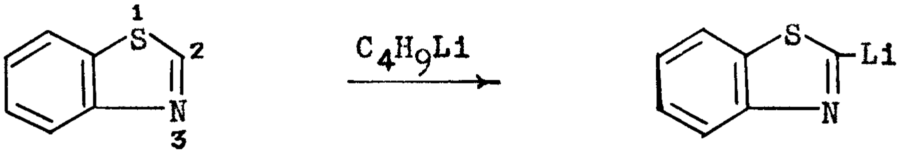
[81] D. L. Esmay, Doctoral Dissertation, Iowa State College, 1951.

[82] W. E. Truce and M. F. Amos, J. Am. Chem. Soc., 73, 3013 (1951).

phene. The metalation of phenoxathiin by n-butyllithium



occurred ortho to the oxygen atom.[83] These data, together with those of the competitive metalations of sulfur and nitrogen compounds previously mentioned, suggested that the order of decreasing influence in governing the orientation of metalation reactions should be: ethereal oxygen > sulfide > tertiary amino nitrogen. This general order was confirmed in the metalation of 2-ethoxyquinoline by n-butyllithium, in which the lithium atom entered the 3-position rather than the 8-position.[84] In one case, however, studies have been reported which might be interpreted as constituting an exception to the rule of precedence of oxygen over sulfur in directing the course of RLi metalations. Benzothiazole was metalated in



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[83] H. Gilman, P. R. Van Ess, H. B. Willis and C. G. Stuckwisch, ibid., 62, 2606 (1940).

[84] H. Gilman and J. A. Beel, ibid., 72, 32 (1951).

excellent yield, and with unprecedented rapidity, by n-butyllithium.[85,86,87] On the basis of the previously mentioned competitive metalations, it might have been expected that the oxygen analogue, benzoxazole, would undergo metalation with even greater facility. However, the reaction of benzoxazole with n-butyllithium yielded no derivatizable metalation product, and most of the benzoxazole was recovered unchanged.[86]

A competitive metalation in which anisole and benzotrifluoride were mixed with an insufficient quantity of n-butyllithium yielded, after carbonation, only 2-methoxybenzoic acid, suggesting that the ether linkage was more powerful in governing metalation than the trifluoromethyl group.[8]

Dibenzofuran was found to be metalated in the 4-position by organolithium compounds.[88,89,90] A series of reactions

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[85] H. Gilman and J. A. Beel, ibid., 71, 2328 (1949).

[86] J. A. Beel, Doctoral Dissertation, Iowa State College, 1949.

[87] The metalation of 4,5-dimethylthiazole by phenyllithium has also been reported, but no attempt was made to study the speed of the reaction. See M. Erne and H. Erlenmeyer, Helv. Chim. Acta, 31, 652 (1948).

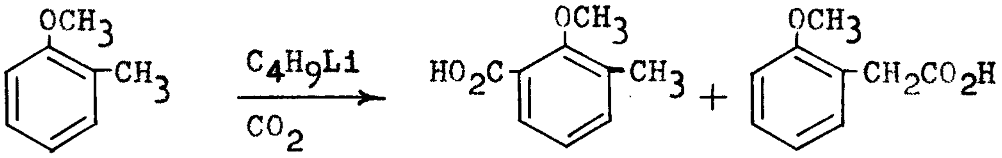
[88] W. G. Bywater, Doctoral Dissertation, Iowa State College, 1934.

[89] D. M. Hayes, unpublished M. S. Thesis, Iowa State College, 1934.

[90] H. B. Willis, Doctoral Dissertation, Iowa State College, 1943.

in which a number of different RLi reagents were allowed to react with dibenzofuran in various solvents showed that the normal alkyllithium compounds were better metalating agents for dibenzofuran than were their secondary and tertiary isomers when an ether medium was used, but that, in petroleum ether, better yields were obtained with the branched RLi reagents. In ether, the comparative efficacies of a number of RLi compounds in the metalation of dibenzofuran were found to lie in the following order: n-butyllithium ethyllithium n-amyllithium phenyllithium methyllithium. The use of n-butyllithium in di-n-butyl ether at 80° led to an unusually high (90 per cent) yield of metalation product with dibenzofuran.[73]

Anisole underwent nuclear metalation with n-butyllithium;[28,78] however, o-methylanisole reacted with n-butyl-



lithium to yield, after carbonation, not only the expected 2-methoxy-3-methylbenzoic acid, but also some 2-methoxyphenylacetic acid, indicating that lateral as well as nuclear metalation had occurred. The reaction of o-ethylanisole with n-butyllithium was found to yield only the nuclear product, 2-methoxy-3-ethylbenzoic acid, on carbonation.[91]

In the reaction of n-butyllithium with 2-methoxynaphthalene, substitution was found to occur in the 3-position rather than in the 1-position.[10,92] It was argued that this orientation supported the nucleophilic mechanism for metalation that had been proposed by Roberts and Curtin, since electrophilic substitution in 2-methoxynaphthalene would be expected to occur in the 1-position. In a similar fashion, 2,8-dimethoxynaphthalene was dimetalated in the 3- and 7-positions;[10] 2-naphthol was metalated in the 3-position;[80] 2-hydroxy- and 2-methoxyphenanthrene were metalated in the 3-position, and 3-methoxyphenanthrene in the 2-position,[93] to yield in each case a product substituted in that *ortho*-position which should be less susceptible to electrophilic attack.

Resorcinol dimethyl ether was metalated between the two methoxyl groups by n-butyllithium[5,94] and by

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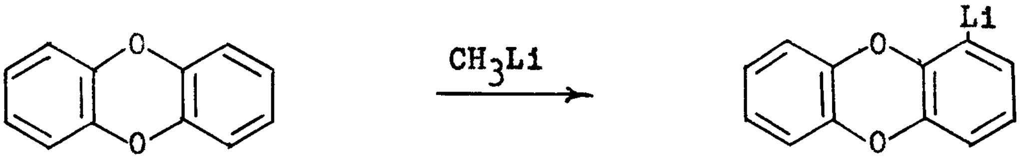
[91] R. L. Letsinger and A. W. Schnizer, *J. Org. Chem.*, *16*, 869 (1951).

[92] S. V. Sunthankar and H. Gilman, *J. Am. Chem. Soc.*, *72*, 4884 (1950).

[93] H. Gilman and T. H. Cook, *J. Am. Chem. Soc.*, *62*, 2813 (1940).

[94] R. Adams, H. Wolff, C. K. Cain and J. H. Clark, *ibid.*, *62*, 1770 (1940).

phenyllithium.[94,95] Resorcinol itself gave a mixture of metalated products with n-butyllithium; carbonation yielded 25 per cent of 2,6-dihydroxybenzoic acid and 6 per cent of 2,4-dihydroxybenzoic acid.[5] Veratrole was metalated by n-butyllithium to give 2,3-dimethoxyphenyllithium.[96] Phloroglucinol trimethyl ether with n-butyllithium yielded 2,4,6-trimethoxyphenyllithium.[80] 1,2,4-Trimethoxybenzene was metalated by n-butyllithium in the same manner as resorcinol dimethyl ether, to yield 2,3,6-trimethoxybenzoic acid on carbonation.[97] Pyrogallol trimethyl ether was metalated by n-dodecyllithium[98] and by phenyllithium[99] to yield 2,3,4-trimethoxyphenyllithium. The reaction of dibenzo-p-dioxin with methyllithium led to substitution in the 1-position.



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[95] G. Wittig in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 579.

[96] H. Gilman, J. Swiss and L. C. Cheney, J. Am. Chem. Soc., 62, 1963 (1940).

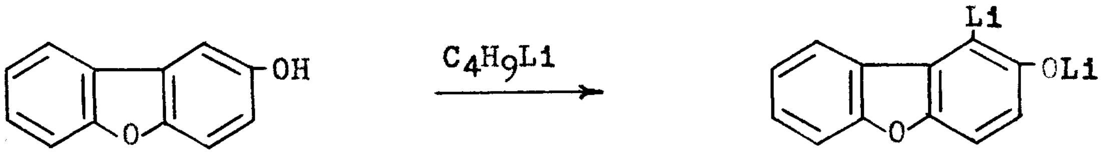
[97] H. Gilman and J. R. Thirtle, ibid., 66, 858 (1944).

[98] R. N. Meals, J. Org. Chem., 9, 211 (1944).

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

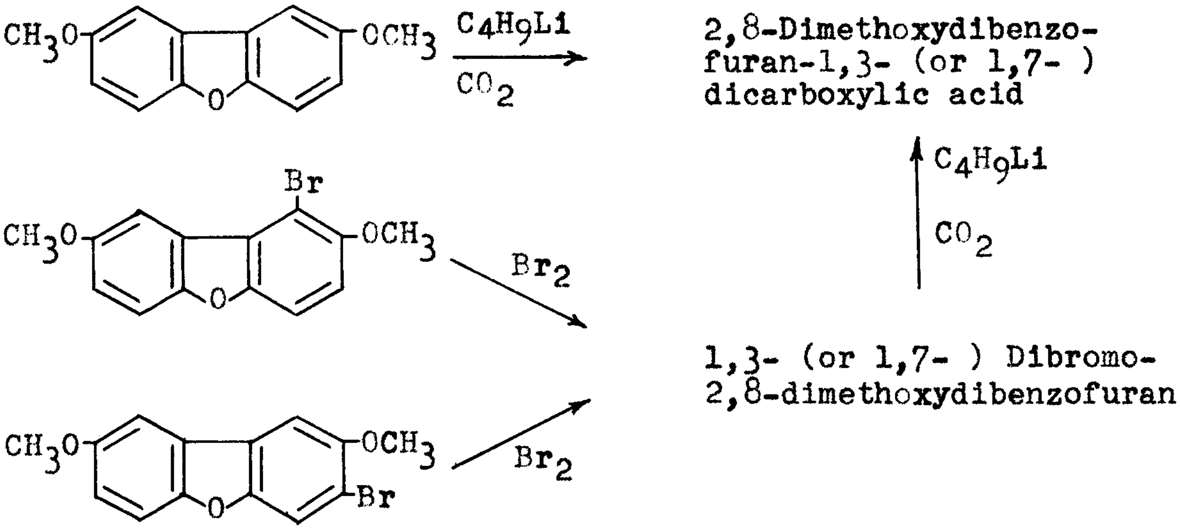
With n-butyllithium, dimetalation occurred; carbonation of the reaction mixture yielded two unidentified dibenzo-p-dioxindicarboxylic acids.[67]

The general tendency (not without some exceptions) for ethers to undergo metalation with RLi compounds more easily than phenols has been interpreted in the light of the nucleophilic theory of metalation.[10] Phenol gave only a trace of metalation product with n-butyllithium,[80] while anisole was metalated to give, on carbonation, a 19 per cent yield of 2-methoxybenzoic acid and a 40 per cent yield of bis-(2-methoxyphenyl) ketone.[28] 2-Naphthol[80] gave a smaller yield of metalation product with n-butyllithium than did its methyl ether.[10] Similarly, both 2- and 3-methoxyphenanthrene were found to be metalated in higher yields than the corresponding phenols.[93] The reaction of 4-hydroxydibenzofuran with n-butyllithium yielded a product substituted in the position ortho to the etheral rather than to the phenolic oxygen atom.[5] Exceptions to the general rule were found in 2-hydroxydibenzofuran, which was metalated ortho to the phenolic oxygen,[5] and in 9-hydroxyphenanthrene, which gave a higher yield of



metalation product with n-butyllithium than did its methyl ether.[93]

Several organolithium metalations of diaryl ethers containing alkoxyl substituents have been reported, and in each case substitution has been found to occur either totally or partially *ortho* to the alkoxyl group. *p*-Methoxydiphenyl ether was metalated in the 3-position by *n*-butyllithium;[100] 2-methoxydibenzofuran was metalated by the same reagent to yield a mixture of 1- and 3-substituted products.[28] The metalation of 2,8-dimethoxydibenzofuran by *n*-butyllithium yielded, after carbonation, a dicarboxylic acid whose structure was uncertain at the time, but which could also be



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[100] W. Langham, R. Q. Brewster and H. Gilman, *J. Am. Chem. Soc.*, *63*, 545 (1941).

prepared from the dibromination product of 2,8-dimethoxydibenzofuran through a halogen-metal interconversion followed by carbonation.[101] Later studies showed that the same dibromo compound could be prepared by the monobromination of either 1-bromo- or 3-bromo-2,8-dimethoxydibenzofuran.[102] This demonstrated that the dibromo compound was either the 1,3- or the 1,7-derivative, and therefore that the dimetalation product was either the 1,3- or the 1,7-dilithio compound.

A number of reactions of halogenated aryl ethers with RLi compounds have been studied. In such reactions, not only metalation but also halogen-metal interconversion and Wurtz-type coupling have been found to occur, and the exact course of each reaction has been found to depend on the type and position of the halogen atom, on the kind of RLi reagent used, and on the time and temperature of reaction. There has been no report of the metalation of a phenyl ether containing an *ortho* halogen substituent. *o*-Bromo- and *o*-iodoanisole have been found to undergo halogen-metal interconversion with RLi compounds, while *o*-fluoro- and *o*-chloroanisole have been reported to yield coupling products.[99] The reaction of

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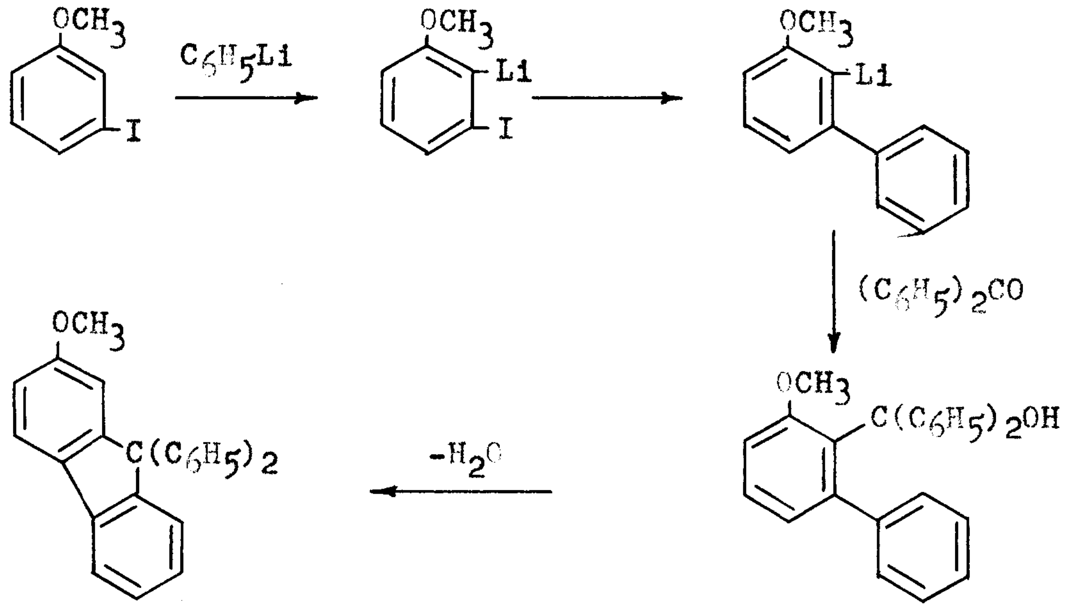
[101] J. Swislowsky, Doctoral Dissertation, Iowa State College, 1939.

[102] J. A. Hogg, Doctoral Dissertation, Iowa State College, 1944.

m-iodoanisole with phenyllithium yielded, after hydrolysis, a mixture of iodobenzene and m-phenylanisole. However, when



a similar mixture was treated with benzophenone prior to hydrolysis, there was isolated a carbinol which underwent dehydration to yield 1-methoxy-9,9-diphenylfluorene, indicating that 2-methoxy-6-phenylphenyllithium had been present in the reaction mixture. This RLi compound could not have arisen from the metalation of the simple coupling product, m-phenylanisole, for the latter compound was found to undergo metalation with phenyllithium in the position para to the phenyl group. These data suggested that the m-iodoanisole had been metalated between the two hetero atoms, and that the resulting 2-iodo-6-methoxyphenyllithium had coupled with excess phenyllithium to yield the final RLi compound.

Similar results were obtained in reactions of phenyllithium with each of the other three m-halogenoanisoles.[99] The reaction between 3-bromodibenzofuran and n-butyllithium, followed by carbonation, yielded a mixture of dibenzofuran-3-carboxylic acid and its 4-isomer.[103] The authors postulated that the latter product arose through a sequence of reactions in which 3-dibenzofuryllithium, the product of normal halogen-metal interconversion, metalated unreacted 3-bromodibenzofuran, probably in the 4-position (analogous to the metalation of m-halogenoanisoles by phenyllithium.) The dibenzofuran produced in this reaction could then in turn be metalated by any of the RLi compounds (n-butyllithium, 3-dibenzofuryllithium, or 3-bromo-4-dibenzofuryllithium) that would be present in the mixture. Since no 3-bromodibenzofuran-4-carboxylic acid was isolated, it was thought most likely that 3-bromo-4-dibenzofuryllithium had been the metalating agent.

Phenyllithium was found to metalate each of the four p-halogenoanisoles in the position ortho to the methoxyl group.[96,99,104] With n-butyllithium and p-bromo- or p-iodoanisole, however, either metalation or halogen-metal

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[103] H. Gilman, H. B. Willis and J. Swislowsky, J. Am. Chem. Soc., 61, 1371 (1939).

[104] G. Wittig, U. Pockels and H. Dröge, Ber., 71, 1903 (1938).

interconversion could be made to occur preferentially. Short periods of reaction were found to lead to interconversion, while longer reaction times and the use of an excess of the haloether favored the formation of metalation products.[105] These data could be explained on the assumption that interconversion took place initially in every case, and that if sufficient time was allowed, the newly formed RLi compound metalated unreacted haloether. p-Chloro- and p-fluoroanisole yielded only metalation products on treatment with n-butyllithium, as might have been expected from the difficulty of bringing about halogen-metal interconversions involving fluorine and chlorine.[106] p-Bromo- and p-iododiphenyl ether, like the corresponding anisoles, yielded either interconversion or metalation products with n-butyllithium, depending on the conditions of the reaction.[100] Metalation occurred ortho to oxygen in the ring containing the halogen substituent, suggesting that the presence of halogen activated that ring toward metalation. This effect was similar to that observed in the metalation of m- and p-bromodiphenyl sulfone mentioned previously.[82] p-Chlorodiphenyl ether was found to be metalated, again in the ring containing the halogen atom, by

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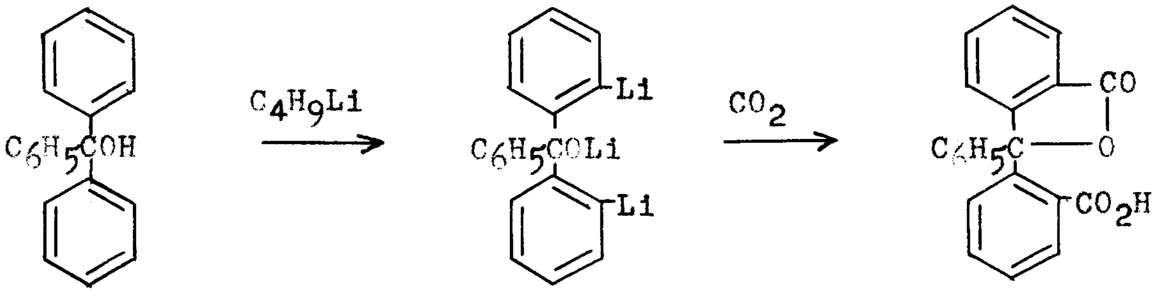
[105] H. Gilman, W. Langham and H. B. Willis, J. Am. Chem. Soc., 62, 346 (1940).

[106] H. Gilman, W. Langham and F. W. Moore, ibid., 62, 2327 (1940).

n-butyllithium, phenyllithium, and methyllithium.[100,107,108]

The reaction of certain arylcarbinols with n-butyllithium has been found to result in metalation. Benzyl alcohol was metalated in the ortho position to yield, after carbonation, o-hydroxymethylbenzoic acid; benzhydrol reacted similarly to yield 3-phenylphthalide.[41] Triphenylcarbinol underwent dimetalation; carbonation yielded 2'-carboxy-3,3-diphenylphthalide.[6,41] Diphenylmethylcarbinol underwent an analogous dimetalation to yield, after carbonation, 3-(o-carboxyphenyl)-3-methylphthalide.[41]



Metalations with organosodium and organopotassium compounds

In 1908, Schorigin reported the reaction of several

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[107] For a discussion of metalation as a side reaction in the halogen-metal interconversion of haloethers, see R. Jones and H. Gilman in R. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1951, Vol. 6, p. 339.

[108] Metalations similar to those discussed in this section have been noted in the reaction of lithium with p-halogenoanisoles: se H. Gilman, W. Langham and A. L. Jacoby, J. Am. Chem. Soc., 61, 106 (1939).

hydrocarbons with a mixture of sodium metal and diethylmercury to yield metalated derivatives which were characterized by carbonation.[1] In this manner, phenylacetic acid was obtained from toluene, m-tolylacetic acid from m-xylene, and hydratropic acid from ethylbenzene. Benzene gave a 12 per cent yield of benzoic acid under these conditions. Shortly afterward, Schorigin found that, when thiophene or benzene was treated with ethylsodium, a gas was evolved which he identified as ethane, thus establishing the metathetical nature of the metalation reaction. The carbonation of the thiophene mixture led to the formation of 2-thenoic acid. A similar metalation of thiophene could be made to occur with a mixture of potassium and diethylmercury, but an attempted reaction with lithium and diethylmercury yielded no thenoic acid on carbonation. With sodium and diethylmercury, o-xylene and p-xylene yielded the corresponding tolylacetic acids on carbonation. Mesitylene gave 3,5-dimethylphenylacetic acid, p-cymene gave p-homocuminic acid and diphenylmethane yielded diphenylacetic acid.[18] Schorigin noticed that, in each case, the acid isolated was the one having the lowest melting point of all the known positional isomers, and he formulated the rule that the orientation in metalation would always be such as to lead to the lowest-melting acid on carbonation. However, subsequent studies showed that Schorigin's rule did not have general applicability, and that his invariable isolation of lowest-melting isomers had been fortuitous. The metalation of sylvan by ethylsodium to yield 5-methyl-2-furoic acid,[109] and the previously mentioned metalations of dibenzofuran and dibenzothiophene by RLi compounds, were cases in which the final acid was not the isomer having the lowest melting point.

A later theory concerning orientation in the metalation of hydrocarbons arose from the studies of Conant and Wheland,[110] who took the view that hydrocarbons such as triphenylmethane were extremely weak acids, and that the reaction of such compounds with metalating agents was essentially a neutralization in which a stronger acid donated a proton to the anion of a weaker acid:

$$\underset{\text{(Stronger acid)}}{(C_6H_5)_3CH} + (C_6H_5)_2CHNa \longrightarrow (C_6H_5)_3CNa + \underset{\text{(Weaker acid)}}{(C_6H_5)_2CH_2}$$

On this basis, the metalation of hydrocarbons (or of other compounds) should result in the replacement of the most strongly acidic hydrogen atom. The later nucleophilic theory of Roberts and Curtin,[8] while it did not predict that the most acidic hydrogen atom would invariably be replaced in

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[109] H. Gilman and F. Breuer, *ibid.*, *56*, 1123 (1934).

[110] J. B. Conant and G. W. Wheland, *ibid.*, *54*, 1212 (1932).

metalation, was nevertheless an outgrowth of this acid-base concept of metalation, since it stressed the nucleophilic (*i.e.*, basic) properties of the metalating agent. Conant and Wheland carried out a series of reactions in which the potassium or sodium derivative of one hydrocarbon was allowed to react with another hydrocarbon. At the end of a suitable reaction period, the position of equilibrium was measured either colorimetrically or by carbonating the mixture and measuring the amount of each acid produced. In this fashion, the following order of increasing acidic strengths was determined: cumene $<$ 1,1-diphenyl-1-propene $<$ diphenylmethane $<$ diphenyl-1-naphthylmethane $<$ triphenylmethane $<$ diphenyl-*p*-xenylmethane $<$ xanthene $<$ fluorene $<$ 9-phenylfluorene $<$ indene $<$ phenylacetylene $<$ acetophenone. The use of carbonation in ascertaining the position of equilibrium in these studies had the disadvantage that the equilibrium might shift during carbonation, so that the proportion of the acid products might not be a true index of the extent of reaction. This difficulty was obviated in a later study by McEwen,[111] in which the position of equilibrium in metalation mixtures similar to those of Conant and Wheland was determined solely by optical measurements. The approximate pK values which McEwen assigned to various weakly acidic compounds are given in Table 1.

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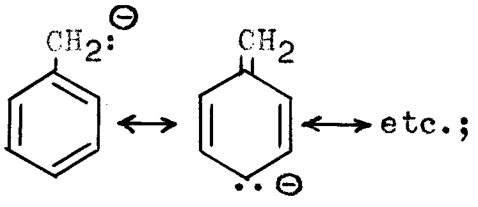
[111] W. K. McEwen, *ibid.*, *58*, 1124 (1936).

Table 1

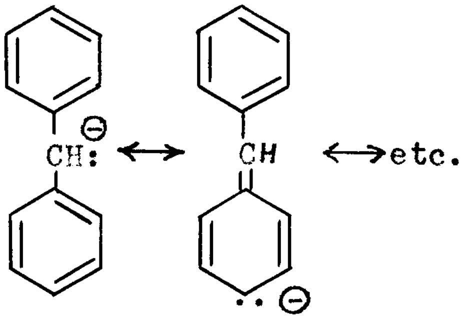
Weakly Acidic Compounds

Compound	Approximate pK
Cumene	37
Diphenylmethane	35
Phenyl-1-naphthylmethane	34
Triphenylmethane	33
Diphenyl-p-xenylmethane	31
Phenylxanthene	29
Xanthene	29
Fluorene	25
Indene	21
Phenylacetylene	21
1-Naphthylfluorene	21
Phenylfluorene	21
Acetophenone	19

During succeeding years, the development of resonance concepts and of general electronic theory made it possible to rationalize the above order of acid strengths on a theoretical basis. Wheland explained the relative acidities of methane, toluene, diphenylmethane and triphenylmethane on the basis of the possible number of resonance structures contributing to the anion of each molecule.[112] For instance,



(Four Structures)



(Seven Structures)

since more structures could be drawn for the anion of diphenylmethane than for that of toluene, the former anion should be more stable with respect to the free hydrocarbon--*i.e.*, diphenylmethane should be a stronger acid than toluene. The relative acidities of indene and fluorene were not in the order which would be indicated by this theory, however, The anion of fluorene should be stabilized by more resonance

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[112] G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 173.

structures than that of indene, but the latter was found to be the stronger acid of the two. It has been suggested that, in the anions of these and other derivatives of cyclopentadiene, stabilization was partly the result of a symmetrical distribution of charge on each carbon atom of the five-membered ring, and that this symmetry of charge distribution would be lowered by the introduction of benzo substituents, with the effect of making the mono- and dibenzo derivatives of cyclopentadiene progressively weaker acids.[113]

The fact that fluorene was a stronger acid than triphenylmethane was also inexplicable on the basis of the number of resonance structures contributing to the anions. Two separate effects have been postulated as operating to make fluorene the stronger acid. First, the rotational energy of the phenyl groups in triphenylmethane must be sacrificed to some extent to allow the anion to assume the coplanarity required to give significant resonance stabilization; no similar loss of rotation energy would be required to stabilize the planar fluorene anion. Second, the methylene carbon atom of fluorene should be able to ease the strain of the five-membered ring by losing a proton to become an anion -- *i.e.*, by passing from a tetrahedral to a planar

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[113] E. Wenkert, private communication.

trigonal configuration.[114]

The concept of weakly acidic hydrogen was useful in the interpretation of the reaction between sodium and m-chlorotoluene in petroleum ether. Under mild conditions, the carbonation of this mixture led to the formation of the expected m-toluic acid; but, if the mixture was refluxed before carbonation, only phenylacetic acid was isolated.[115] These results suggested that the initially formed m-tolylsodium underwent autometalation with the replacement of one of the methyl hydrogens to yield benzylsodium, whose anion should be more highly stabilized by resonance than the original m-tolyl anion. An autometalation of the same type has been observed with p-tolylsodium. Attempts to prepare the three tolylsodiums through reaction of sodium with the corresponding ditolylmercury in refluxing petroleum ether (b.p. 85-115°) led to autometalation in every case. The yields of phenylacetic acid obtained by carbonating the reaction mixtures were 18, 37 and 66 per cent for the <u>ortho</u>, <u>meta</u>, and <u>para</u> compounds respectively. The reaction of potassium with di-p-tolylmercury also yielded phenylacetic acid on carbonation.[35]

The metalation of toluene was found to proceed more

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[114] G. S. Hammond, private communication.

[115] H. Gilman and H. A. Pacevitz, J. Am. Chem. Soc., 62, 673 (1940).

easily with organopotassium than with organosodium compounds. Phenylsodium could be prepared from sodium and chlorobenzene in a toluene medium, but the analogous reaction with potassium led to metalation of the toluene, even at 0°. The metalation of mesitylene with phenylpotassium afforded a 79 per cent yield of 3,5-dimethylphenylacetic acid on carbonation. 2-Methylnaphthalene reacted with n-butylsodium to yield 31 per cent of 2-naphthylacetic acid after carbonation; the yield from a corresponding reaction with phenylsodium was only 4 per cent.[35]

Cumene was metalated by n-amylsodium to yield p-cuminic acid, together with a little of the ortho isomer, on carbonation.[116] With ethylpotassium[117] or with ethylsodium,[35] however, lateral metalation occurred, and the product of carbonation was dimethylphenylacetic acid.

Morton and co-workers, in studying the yields of acids obtained by the carbonation of alkylsodium compounds, noticed that varying amounts of alkylmalonic acids were formed along with the expected alkanecarboxylic acids. For instance, n-amyl chloride and sodium reacted to produce, after carbonation, both caproic and n-butylmalonic acids. n-Butyl,

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[116] A. A. Morton, J. T. Massengale and M. L. Brown, ibid., 67, 1620 (1945).

[117] H. Gilman and L. Tolman, ibid., 68, 522 (1946).

ethyl, 1-methyl-1-butyl, 3-methyl-2-butyl, n-hexyl, cetyl, and benzyl chlorides were similarly converted into mixtures of mono- and dicarboxylic acids.[118] The carbonation of a mixture of di-n-amylmercury and sodium gave as much as 50 per cent of n-butylmalonic acid.[119] These results were interpreted to mean that disodium compounds had been present before carbonation. In the case of the reaction between n-amyl chloride and sodium, for instance, it was supposed that both n-amylsodium and amylidenedisodium were formed. A mechanism was postulated involving the disproportionation of free amyl radicals, as shown in the accompanying formulation.[120]

$$2C_5H_{11}\cdot \longrightarrow C_5H_{12} + C_4H_9CH\langle$$

Somewhat later, Morton, Fallwell and Palmer advanced a different mechanism to account for the formation of phenylmalonic acid from the carbonation of a mixture of benzyl chloride and sodium.[121] They found that sodium phenylacetate could be metalated by phenylsodium to give phenylmalonic acid after carbonation. Also, the yield of phenylmalonic

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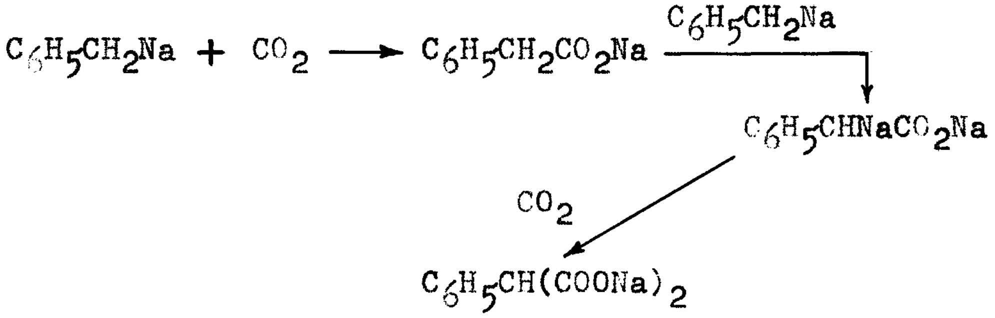
[118] A. A. Morton, W. J. Le Fevre and I. Hechenbleikner, ibid., 58, 754 (1936).

[119] A. A. Morton and I. Hechenbleikner, ibid., 58, 1024 (1936).

[120] A. A. Morton and I. Hechenbleikner, ibid., 58, 2599 (1936).

[121] A. A. Morton, F. Fallwell and L. Palmer, ibid., 60, 1426 (1938).

acid from the carbonation of a mixture of phenylsodium and toluene was found to increase when the mixture was carbonated more slowly, while the yield of phenylacetic acid



$$C_6H_5CH_2Na + CO_2 \longrightarrow C_6H_5CH_2CO_2Na \xrightarrow{C_6H_5CH_2Na} C_6H_5CHNaCO_2Na \xrightarrow{CO_2} C_6H_5CH(COONa)_2$$

decreased. These data were consistent with the hypothesis that phenylmalonic acid arose through the metalation of sodium phenylacetate during the process of carbonation, and that benzylidenedisodium had not been present. However, the authors were unable to observe any similar rate effects in the carbonation of n-amylsodium, and, in later publications, Morton and co-workers continued to express the belief that amylidenedisodium existed.[122,123] Other workers, however, showed that when a mixture of n-amyl chloride and sodium was carbonated, the proportion of the acidic products did depend on the conditions of carbonation. When gaseous carbon dioxide was used, n-butylmalonic and caproic acids were formed in approximately equal amounts; a carbonation using

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[122] A. A. Morton and J. T. Massengale, ibid., 62, 120 (1940).

[123] A. A. Morton and G. M. Richardson, ibid., 62, 129 (1940).

Dry Ice yielded 38.5 per cent of caproic acid and less than 1 per cent of _n_-butylmalonic acid.[124] These data made it appear likely that butylmalonic acid was a product of metalation occurring during carbonation, and not the product of carbonation of a disodium compound.[125]

The metalation of certain olefins by organosodium and organopotassium compounds has been reported. 1-Pentene was found to react with either _n_-amylsodium or _n_-amylpotassium to yield, after carbonation, 3-carboxy-1-pentene, together with an acid tentatively identified as 1-carboxy-1-pentene. In the same way, propene reacted with _n_-amylsodium to yield 3-butenoic acid, while isobutene with the same reagent gave a mixture of 3-methyl-3-butenoic acid and a product tentatively identified as 3-carboxymethyl-3-butenoic acid.[126] Ziegler and co-workers studied the reaction between phenylisopropylpotassium and a number of propylenes bearing methyl and phenyl substituents. In all cases, metalation was found to occur in such a way as to yield a substituted allylpotassium. With 1,4-diphenyl-2-butene and with 1,6-diphenyl-2,4-hexadiene, metalation took place at each end of the central

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[124] H. Gilman and H. A. Pacevitz, _ibid._, _62_, 1301 (1940).

[125] Morton and co-workers later acknowledged the validity of this mechanism for the formation of _n_-butylmalonic acid. See A. A. Morton, J. B. Davidson and H. A. Newey, _ibid._, _64_, 2240 (1942).

[126] A. A. Morton, M. L. Brown, M. E. T. Holden, R. L. Letsinger and E. E. Magat, _ibid._, _67_, 2224 (1945).

carbon chain, yielding dipotassio derivatives.[127]

The metalation of alkynes by the sodium or potassium salts of other alkynes has been reported.[128] Phenylacetylene was metalated by ethynylsodium in a mixture of ether and liquid ammonia to give 83 per cent of phenylethynyldiphenylcarbinol on treatment with benzophenone.[28] The yield was decreased to 61 per cent when liquid ammonia alone was used as the solvent. 1-Heptyne was not metalated by ethynylsodium or ethynylpotassium in liquid ammonia.[36]

The polymetalation of certain aromatic hydrocarbons with RK and RNa reagents has been studied. Ethylpotassium reacted with benzene to yield, after carbonation, 33-45 per cent of benzoic acid, 11-17 per cent of terephthalic acid, and a trace of phthalic acid.[129] In the reaction of n-amylsodium with benzene, however, dimetalation was found to occur in the meta and para positions only,[130,131] and the

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[127] K. Ziegler, F. Crössmann, H. Kleiner and O. Schäfer, Ann., 473, 1 (1929).

[128] T. H. Vaughn, G. F. Hennion, R. R. Vogt and J. A. Nieuwland, J. Org. Chem., 2, 1 (1937).

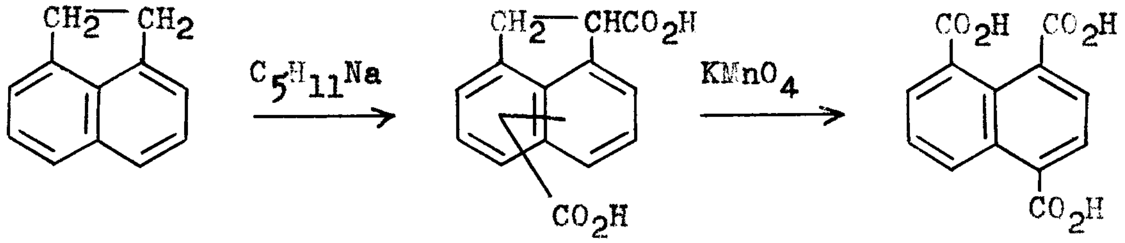
[129] H. Gilman and R. H. Kirby, J. Am. Chem. Soc., 58, 2074 (1936).

[130] A. A. Morton and F. Fallwell, ibid., 60, 1924 (1938). These authors observed that some phthalic acid was produced if sodium benzoate was added to the reaction mixture.

[131] A. A. Morton, E. Little and W. O. Strong, ibid., 65, 1339 (1943).

ratio of *meta*- to *para*-substituted product was 4:1 when a large excess of benzene was used. With smaller amounts of benzene and very vigorous stirring, all the dimetalation occurred in the *meta*-position. The dimetalation of toluene by *n*-amylsodium also yielded a *meta* derivative; a 40 per cent yield of homoisophthalic acid was obtained by carbonating the mixture. These results were interpreted in the light of the electrophilic theory of metalation on the basis that the sodium ion in monometalated benzene or toluene should have a *meta*-directing influence towards the entrance of the second sodium ion, analogous to the strong *meta*-directing influence of the positive nitrogen atom in arylammonium salts. The metalation of the three xylenes with *n*-amylsodium was found to give laterally substituted products only. The use of an excess of xylene led to monometalation followed by Wurtz-type coupling with *n*-amylsodium to yield the corresponding *n*-hexyltoluene. When smaller amounts of xylene were employed, metalation occurred on each of the two methyl groups, and carbonation produced the corresponding benzenediacetic acid. The yields were 19, 37 and 36 per cent from *o*-, *m*- and *p*-xylene, respectively.[131]

The reaction of naphthalene with *n*-butylsodium in tri-*n*-butylamine, or with phenylsodium in benzene, followed by carbonation, yielded a mixture of 1- and 2-naphthoic acids.[28] The reaction with *n*-amylsodium or with *n*-octylsodium in petroleum ether also gave a mixture of these acids on carbonation, together with small amounts of naphthalene-1,3-dicarboxylic, naphthalene-1,8-dicarboxylic, naphthalene-2,6-dicarboxylic and possibly some naphthalenetricarboxylic acids.[132] Acenaphthene was metalated by n-amylsodium to yield a mixture of mono- and dimetalated products. Carbonation gave acenaphthene-1-carboxylic acid and a dicarboxylic acid which was oxidized by potassium permanganate to yield naphthalene-1,4,8-tricarboxylic acid. The authors believed



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[132] A. A. Morton, J. B. Davidson, T. R. P. Gibb, E. Little, E. F. Clarke and A. G. Green, ibid., 64, 2250 (1942).

the original diacid to have been acenaphthene-1,5-dicarboxylic acid. The reaction of decalin with n-amylsodium, followed by carbonation, yielded a tetracarboxylic acid. This result was quite surprising, since saturated hydrocarbons generally were not known to undergo metalation, and, in fact, were commonly used as solvents for metalating agents. From the fact that the acid readily formed a dianhydride, the authors concluded that the product was probably decalin-1,4,5,8-tetracarboxylic acid.[132] This replacement of non-activated hydrogen was reminiscent of earlier studies by Carothers and Coffman on the thermal decomposition of methylsodium[133,134] and methylpotassium.[134] It was found that these RM compounds, when strongly heated, evolved methane to leave a solid residue which, on treatment with ethanol, yielded hydrogen and acetylene. The authors postulated that the organometallic compounds had undergone autometalation to yield tetrasodio- and tetrapotassiomethane, and that the tetranegative anion of the CM_4 gave up electrons to the metal cation, with the final production of free metal and metal

$$4CH_3Na \longrightarrow CNa_4 + CH_4$$

$$2C^{-4} + 8Na^{\oplus} \longrightarrow Na_2C_2 + 6Na$$

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[133] W. D. Carothers and D. D. Coffman, ibid., 51, 588 (1929).

[134] W. D. Carothers and D. D. Coffman, ibid., 52, 1254 (1930).

acetylide.

Organosodium and organopotassium reagents have been used in the metalation of compounds containing hetero elements, and the tendency toward *ortho*-metalation has been noticed here as in the organolithium metalations. Dimethylaniline was not metalated by phenylsodium in benzene, or by *n*-butylsodium in tri-*n*-butylamine,[36] but was metalated by *n*-amylsodium in petroleum ether,[28,120] to yield a small amount of N,N-dimethylanthranilic acid after carbonation. This reaction was found to proceed only if the *n*-amylsodium was formed *in situ*; a mixture of dimethylaniline and previously prepared *n*-amylsodium yielded no metalation product.[36] The reaction of 9-ethylcarbazole with ethylsodium, *n*-butylsodium, ethylpotassium, or *n*-butylpotassium, yielded a solid acid product on carbonation in each case, but the structures of the acids were not determined. It was thought that dimetalation had occurred in these reactions.[42]

2-Methylthiophene was metalated by a mixture of sodium and dibenzylmercury in heptane, to yield 21 per cent of 5-methyl-2-thenoic acid after carbonation.[109] Dibenzothiophene was metalated in the 4-position by *n*-amylsodium in petroleum ether, and by phenylsodium in benzene.[28] Attempts were made to effect the dimetalation of dibenzothiophene by the use of various organosodium and organopotassium compounds, but only monometalation resulted in each case.[81] Diphenyl sulfide was metalated by phenylsodium in benzene to yield 56 per cent of *o*-phenylmercaptobenzoic acid after carbonation. The reaction of phenyl methyl sulfide with phenylsodium resulted in lateral metalation; phenylmercaptoacetic acid was isolated after carbonation of the reaction mixture.[79,135]

Schick and Hartough studied the metalation of a large number of alkylthiophenes by organosodium compounds. Thiophene itself was metalated in excellent yields by a mixture of bromobenzene and sodium amalgam; a somewhat smaller yield was obtained when ethyl chloride was used in place of bromobenzene.[136] The metalation of 2-alkylthiophenes was found to occur in the 5-position. 3-Methylthiophene was also metalated in the 5-position, with no observable substitution on the 2-carbon. The results of these studies are summarized in Table 2.[137]

Recently, Blanchette and Brown have reported a further study of the reaction of 3-methylthiophene with RNa compounds.[138] They found that the reaction with ethylsodium or

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[135] F. J. Webb, Doctoral Dissertation, Iowa State College, 1941.

[136] J. W. Schick and H. D. Hartough, *J. Am. Chem. Soc.*, *70*, 286 (1948).

[137] J. W. Schick and H. D. Hartough, *ibid.*, *70*, 1645 (1948).

[138] J. A. Blanchette and E. V. Brown, *ibid.*, *74*, 1848 (1952).

Table 2

Substituted 2-Thenoic Acids from Alkylthiophenes and Ethylsodium

Substituted 2-Thenoic Acid	Yield, Per Cent
5-Methyl-	70
4-Methyl-	42
5-_t_-Butyl-	85
5-_t_-Amyl-	46
5-(1,1,3,3-Tetramethylbutyl)-	66
5-(1-Phenylethyl)-	60

with n-butylsodium, followed by carbonation, led to the formation of 4-methyl-2-thenoic acid in each case, substantiating the findings of Schick and Hartough, but they also found that a considerable amount of non-acidic by-product was formed. From the results of analysis, they concluded that the non-acidic material was the product of a

Wurtz-Fittig coupling between metalated 3-methylthiophene and excess alkyl halide. In the case of the reaction with ethylsodium, it was established that the neutral product was not 2-ethyl-3-methylthiophene, since the acetyl derivative gave a semicarbazone whose properties were different from that of 2-acetyl-4-methyl-5-ethylthiophene.

The monometalation of furan by ethylsodium, phenylsodium, and benzylsodium has been reported. In the reaction with benzylsodium, carbonation yielded no only 2-furoic acid but also an unidentified acid melting at 120-121°, which was shown to be different from 3-furoic acid.[109] Morton and Patterson reported the dimetalation of furan with n-amylsodium. The reaction was carried out in octane at 0°, and yielded furan-2,5-dicarboxylic acid after carbonation. On the basis of the theory that a metal substituent should exert a *meta*-directing influence on further substitution, the authors had expected that dimetalation might occur in the 2- and 4-positions, and explained their unexpected results by stating that

> absence of the powerful *meta*-directing influence of the sodium ion in the furan nucleus suggests that it is overcome by a strong *ortho*-directing influence such as ether linkage inside the ring.[139]

When triphenylmethylsodium was treated with a large excess of furan and the resulting mixture was carbonated after a suitable period, a small amount of 2-furoic acid and a large amount of triphenylacetic acid were isolated. An attempt to reverse the reaction by treating triphenylmethane with 2-furylsodium gave only 2-furoic acid on carbonation. Phenylethynylsodium did not metalate furan even after eleven days of contact.[109]

The reaction of furan with a mixture of sodium and bis-2-thienylmercury, followed by carbonation, yielded 20 per cent 2-furoic acid and no thenoic acid. This result was similar to that observed in the previously mentioned metalation of dibenzofuran with 4-dibenzothienyllithium. However, the reaction of thiophene with a mixture of sodium and bis-2-furylmercury, followed by carbonation, yielded

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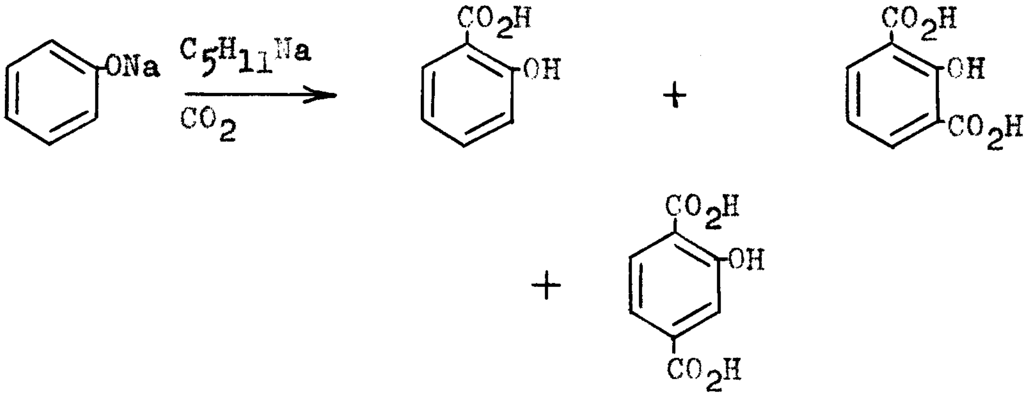
[139] A. A. Morton and G. H. Patterson, *ibid.*, *65*, 1348 (1943).

2-thenoic acid.[109] The absence of furoic acid in the crude product was not demonstrated. This appears to be the only case yet reported in which the metallic derivative of an oxygen-containing compound metalated a sulfur-containing compound.

In a comparative study of the effect of different metalating agents, dibenzofuran was allowed to react with ethyllithium, with ethylsodium, and with ethylpotassium under comparable conditions. After a fifteen-day reaction period, carbonation showed that the amount of metalation was approximately the same in all three reactions. However, if the mixtures were carbonated after only two and one-half hours, the relative amounts of metalation products from the lithium, sodium, and potassium compounds were, respectively, 1, 46 and 139. Only monometalation was observed with ethyllithium, while the other two reagents gave a mixture of mono- and dimetalation products. Ethylpotassium gave the higher proportion of dimetalation.[27,39]

Anisole reacted with n-butylsodium in petroleum ether to yield 42 per cent of o-methoxybenzoic acid on carbonation. The reaction with phenylsodium in benzene led to a 44 per cent yield of the same acid when a twenty-four-hour reaction period was employed, and a 64 per cent yield when the reaction was allowed to proceed for forty-eight hours.[28] o-Methylanisole was found to undergo only lateral metalation with n-amylsodium in petroleum ether, to yield o-methoxyphenylacetic acid on carbonation. o-Ethylanisole, under the same conditions, gave a mixture of 2-o-methoxyphenylpropionic acid and 2-methoxy-3-ethylbenzoic acid, indicating that both lateral and nuclear metalation had taken place.[91]

Sodium phenoxide was not metalated by n-butylsodium in petroleum ether even after three days of contact,[36] but was metalated by n-amylsodium to yield, after carbonation, a mixture of salicylic acid and 2-hydroxyisophthalic acid, together with a small amount of 2-hydroxyterephthalic acid.[140]



Metalations with other organometallic compounds

A few metalations with RMX and R_2M compounds of the Group II metals have been reported. Phenylcalcium iodide reacted with dibenzofuran to yield the expected

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[140] A. A. Morton and R. L. Letsinger, ibid., 67, 1537 (1945).

dibenzofuran-4-carboxylic acid on carbonation.[141] Dibenzothiophene was also metalated by this reagent, but the reaction did not lead to substitution in the 4-position. Carbonation of the reaction mixture produced a dibenzothiophenecarboxylic acid which was different from the 1-, the 2- and the 4- acids, and which was therefore characterized as the hitherto unknown dibenzothiophene-3-carboxylic acid.[142] The structure of this compound was confirmed later through studies in which a number of 3-substituted dibenzothiophene derivatives were prepared from 3-aminodibenzothiophene, which in turn was prepared by the rearrangement-amination of 4-iododibenzothiophene. 3-Bromodibenzothiophene was synthesized from the amino compound by the Sandmeyer reaction, and was converted into the corresponding RLi compound by halogen-metal interconversion.[143] The infrared absorption spectrum of 3-trimethylsilyldibenzothiophene, prepared from the lithium derivative, showed the presence of a 1,2,4-trisubstituted benzene nucleus.[144] Carbonation of the RLi compound

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[141] H. Gilman, R. H. Kirby, M. Lichtenwalter and R. V. Young, Rec. trav. chim., 55, 79 (1936).

[142] H. Gilman, A. L. Jacoby and H. A. Pacevitz, J. Org. Chem., 3, 120 (1938).

[143] G. Illuminati, J. F. Nobis and H. Gilman, J. Am. Chem. Soc., 73, 5887 (1951).

[144] M. Margoshes, unpublished studies.

produced an acid which was identical with that isolated from the phenylcalcium iodide reaction.[145] The identity of the products was established by a mixed melting point and by comparison of infrared absorption spectra. This _meta_-metalation was particularly interesting in view of the fact that diethylcalcium was found to metalate dibenzothiophene in the normal 4-position.[146]

Phenoxathiin was metalated by phenylcalcium iodide to yield, after carbonation, an acid melting at 260-262°. The acid was not further identified, but was shown to be different from the 2-acid melting at the same temperature.[83] The reaction between 9-ethylcarbazole and phenylcalcium iodide, followed by carbonation, yielded an acid mixture which could not be purified.[42] Both diethylbarium and diethylstrontium were found to metalate phenyl methyl sulfide in the nucleus, to yield very small amounts of _o_-methylmercaptobenzoic acid on carbonation. Diethylbarium metalated anisole in the _ortho_ position and dibenzofuran in the 4-position.[146] A complex of diethylstrontium with diethylzinc reacted with anisole and with dibenzofuran in the same way as diethylbarium. This complex was also found to metalate dibenzo-

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[145] G. Illuminati, unpublished studies.

[146] H. Gilman, A. H. Haubein, G. O'Donnell and L. A. Woods, _J. Am. Chem. Soc._, _67_, 922 (1945).

thiophene in the 4-position.[147]

A number of compounds containing activated hydrogen attached to carbon have been metalated with organomagnesium halides. Shortly after Grignard's discovery of this class of compounds, it was noted that, when acetylene was bubbled through a solution of ethylmagnesium bromide, the hydrocarbon was absorbed and ethane was evolved.[148] It was demonstrated that, depending on the conditions of the reaction, either one or both of the hydrogens of acetylene could be replaced by -MgBr.[149,150,151,152] 1-Heptyne was also found to undergo replacement of hydrogen with ethylmagnesium bromide.[153] Grignard and Courtot reported the reaction of RMgX compounds with cyclopentadiene, but the products of the reaction were not characterized.[154] Zerewitinoff noted the reaction of

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[147] H. Gilman, R. N. Meals, G. O'Donnell and L. A. Woods, ibid., 65, 268 (1943).

[148] I. Iotsitch, Bull. soc. chim. [3], 28, 922 (1902).

[149] G. I. Iotsitch, ibid., 30, 208, 210 (1903).

[150] J. Salkind and A. Rosenfeld, Ber., 57, 1690 (1904).

[151] B. Oddo, Atti accad. Lincei [5], 13, (II), 187 [Chem. Zentr., (II), 943 (1904)].

[152] M. Lespieau, Compt. rend., 157, 1439 (1913).

[153] A. Willemart, Ann. chim. [10], 12, 345 (1929).

[154] V. Grignard and C. Courtot, Compt. rend., 158, 1763 (1914).

9-phenylfluorene with methylmagnesium iodide, in which one mole of methane was evolved for every mole of 9-phenylfluorene.[155] Ethylmagnesium bromide has been employed as a metalating agent for indene[156] and for fluorene.[19] However, no reaction was noted when diphenylmethane was treated with ethylmagnesium bromide.[157]

In several cases, the replacement of aromatic hydrogen by -MgX has been reported. Forcing conditions were generally necessary to bring about reactions of this kind, and yields were usually low. Challenger and Miller[158] described an attempt to synthesize 2-thienylmercaptoacetic acid by a reaction between 2-thienylmagnesium bromide and sulfur, followed by treatment with chloroacetic acid. The reaction was carried out in phenetole at high temperatures. Instead of the expected product, o-phenetylmercaptoacetic acid was isolated. It was supposed that this product had arisen through the metalation of phenetole by the Grignard reagent. In order to test this hypothesis, the high-temperature reaction between

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[155] T. Zerewitinoff, Ber., 45, 2384 (1912).

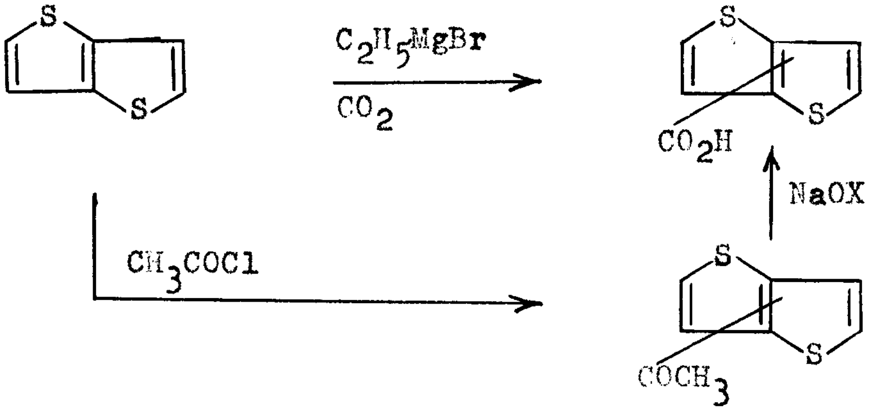
[156] V. Grignard and C. Courtot, Compt. rend., 152, 272 (1911).

[157] H. Gilman and J. M. Peterson, Rec. trav. chim., 48, 247 (1929).

[158] F. Challenger and S. A. Miller, J. Chem. Soc., 894 (1938).

RMgX and phenetole alone was studied, and it was found that ethylmagnesium bromide could function as a metalating agent for the ether under these conditions. Similarly, anisole underwent <u>ortho</u>-metalation with either ethyl- or <u>n</u>-propylmagnesium bromide under forcing conditions. Dimethylaniline was metalated by ethylmagnesium bromide to yield dimethylanthranilic acid on carbonation.

The reaction between ethylmagnesium bromide and thiophene, carried out in dimethylaniline at 160-170°, yielded a small amount of 2-thenoic acid on carbonation. A similar reaction between ethylmagnesium bromide and thiophthene led



to the formation of an acid whose structure was not determined, but which could also be prepared by acetylation of thiophthene followed by an iodoform reaction. When an excess of the Grignard reagent was used, carbonation produced a thiophthenedicarboxylic acid.[159]

n-Butylmagnesium bromide did not react with phenyl methyl sulfide when the mixture was heated to 135-140° for two hours. However, nuclear metalation occurred to a slight extent after a five-hour reaction period at 150-155°; carbonation of the mixture gave 0.2 per cent of o-methylmercaptobenzoic acid.[79] 9-Ethylcarbazole did not react with ethylmagnesium bromide when the mixture was heated to 85° for twenty hours.[42] Dibenzofuran, when heated to 165° with a large excess of ethylmagnesium bromide for six hours, was metalated to yield 5 per cent of the 4-acid on carbonation.[160] At lower temperatures, dibenzofuran has been found to react with methylmagnesium iodide, ethylmagnesium bromide, phenylmagnesium bromide, and benzylmagnesium chloride to yield stable complexes containing one molecule each of dibenzofuran and the Grignard reagent.[161]

Courtot and Tchelitcheff reported the metalation of benzothiazole by ethylmagnesium bromide. However, no experimental details or yields were given.[162]

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[159] F. Challenger and G. M. Gibson, ibid., 305 (1940).

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

[161] E. Cherbuliez and M. K. Araqui, Helv. Chim. Acta, 26, 2251 (1943).

[162] C. Courtot and S. Tchelitcheff, Compt. rend., 217, 231 (1943).

Reductive Metalations

The reaction of dibenzothiophene-5-oxide with _n_-butyllithium was found to lead to reductive metalation. Carbonation of the reaction mixture produced dibenzothiophene-4-carboxylic acid.[163] Low temperature and an excess of the RLi were found to give the best yields. The reduction of sulfoxides by RM compounds had been reported previously,[164] but the reaction of dibenzothiophene-5-oxide with _n_-butyllithium apparently did not proceed by way of reduction followed by metalation of the resulting dibenzothiophene, since dibenzothiophene itself was not metalated at all under the low-temperature conditions which were employed. This indicated that the reaction was a concerted reductive metalation, or else that metalation preceded reduction. The fate of the oxygen atom in this reaction has not been determined.

A similar reductive metalation of 10-ethylphenothiazine-5-oxide by _n_-butyllithium has been reported.[64] The acid isolated from the carbonation of the reaction mixture was identical with that obtained in the metalation of 10-ethylphenothiazine with _n_-butyllithium, followed by carbonation. On the assumption that this reductive metalation proceeded

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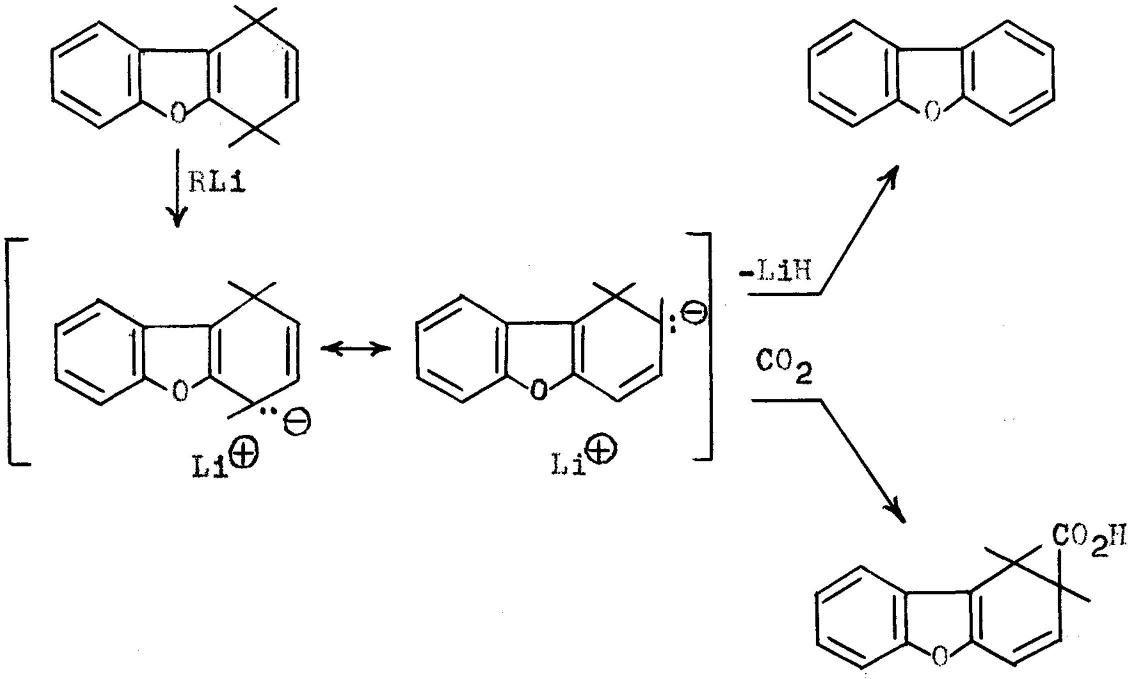
[163] H. Gilman and D. L. Esmay, _J. Am. Chem. Soc._, _74_, 266 (1952).

[164] C. Courtot and C. Pomonis, _Compt. rend._, _182_, 893 (1926).

in the same way as that of dibenzothiophene-5-oxide, these results further substantiated the belief that the metalation of 10-ethylphenothiazine had occurred in the 4-position.

Metalations Accompanied by Dehydrogenation

Gilman and Bradley reported a number of reactions of RLi reagents with dihydroaromatic compounds.[165] They found that, when 1,4-dihydrodibenzofuran reacted with phenyllithium in refluxing ether, lithium hydride was deposited from the solution. When the supernatant liquor was decanted off and



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[165] H. Gilman and C. W. Bradley, J. Am. Chem. Soc., 60, 2333 (1938).

analyzed, it was found to contain benzene and dibenzofuran. When a similar reaction was carried out at -15°, and the mixture was carbonated, 1,2-dihydrodibenzofuran-2-carboxylic acid could be isolated. These data indicated that replacement of one of the activated 4-hydrogens had occurred, to yield a lithium derivative which tended to eliminate lithium hydride under forcing conditions, but which was stable enough to be carbonated under milder conditions. The appearance of the carboxyl group in the 2-position of the carbonation product was compared with similar "allylic rearrangements" of RM compounds that had been reported by Schlenk and Bergmann[166] and by others.[52] n-Butyllithium was also found to effect the dehydrogenation of 1,4-dihydrodibenzofuran. The reaction of 1,4-dihydrodibenzofuran with n-butylsodium in petroleum ether, followed by carbonation, led to the formation of dibenzofuran-4-carboxylic acid. This product presumably arose through dehydrogenation of 1,4-dihydrodibenzofuran followed by metalation of the resulting dibenzofuran.

1,4-Dihydronaphthalene reacted with phenyllithium in refluxing ether to yield naphthalene and lithium hydride; the reaction with n-butyllithium at -15°, followed by carbonation, yielded 1,2-dihydro-2-naphthoic acid. The reaction of 1,4-diphenyl-2-butene with n-butyllithium yielded, on

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[166] W. Schlenk and E. Bergmann, Ann., 479, 78 (1930).

carbonation, 1,4-diphenyl-2-butene-1,4-dicarboxylic acid. from the neutral fraction was isolated 1,4-diphenyl-1,3-butadiene. Seemingly both monometalation and dimetalation had taken place, and the monometalated derivative had undergone elimination of lithium hydride.

1,2,3,4-Tetrahydrodibenzofuran reacted with phenyllithium in refluxing ether to yield, after carbonation, 1,2,3,4-tetrahydrodibenzofuran-6-carboxylic acid.[167] The reaction with p-tolyllithium and with n-butylsodium gave similar results. Apparently the hydrogens in the reduced ring of this dibenzofuran derivative were not strongly enough activated to undergo replacement, and the only reaction was metalation in the aromatic ring.

The reaction between 1,4-dihydrodibenzothiophene and phenyllithium in refluxing ether led to dehydrogenation; only benzoic acid and dibenzothiophene were found as products when the mixture was carbonated. A similar reaction with phenylisopropylpotassium, followed by carbonation, yielded dibenzothiophene together with an acidic product which could not be purified.[76]

Gilman and Bebb reported the metalation of 9,10-dihydroanthracene with n-butyllithium. No dehydrogenation was observed; carbonation yielded a mixture of 9,10-dihydro-

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[167] H. Gilman, E. W. Smith and L. C. Cheney, J. Am. Chem. Soc., 57, 2095 (1935).

anthracene-9-carboxylic acid and the corresponding 9,10-dicarboxylic acid.[28] More recently, Mikhailov and Blokhina confirmed these observations. They also found that a similar mixture of mono- and dimetalation products could be obtained from 9,10-dihydroanthracene by using an adduct of lithium with anthracene as the metalating agent. Phenyllithium could also be used, with the same results. The reaction of n-butyllithium with 9,10-dihydro-1,2-benzanthracene, followed by treatment with methyl chloride, yielded cis- (or trans-)9,10-dimethyl-9,10-dihydro-1,2-benzanthracene, together with other products which, on being heated with sulfur, yielded a mixture of 9-methyl- and 10-methyl-1,2-benzanthracene. The authors assumed that dehydrogenation had occurred during the sulfur treatment rather than during the reaction with n-butyllithium.[168]

Metalation and the Wurtz-Fittig Reaction

In 1927, Bachmann and Clarke suggested a mechanism for the Wurtz-Fittig reaction involving organosodium intermediates, and postulated in particular that the appearance of high-molecular-weight products in such reactions might be

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[168] B. M. Mikhailov and A. N. Blokhina, Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk, 1949, 279 /_ C. A., 44, 2963 (1950)_7.

due to metalation followed by coupling.[169] For instance, the formation of diphenylbenzene as a by-product in the reaction of sodium with chlorobenzene was pictured as involving metalation of biphenyl by phenylsodium, followed by coupling of the metalated product with chlorobenzene:

$$C_6H_5C_6H_5 + C_6H_5Na \longrightarrow C_6H_5C_6H_4Na + C_6H_6$$

$$C_6H_5C_6H_4Na + C_6H_5Cl \longrightarrow C_6H_5C_6H_4C_6H_5 + NaCl$$

The presence of phenylsodium as an intermediate was demonstrated by conducting the reaction in the presence of toluene. Under these conditions, no biphenyl was formed, but diphenylmethane and p-methylbiphenyl were isolated.

A later investigation of this reaction by Morton, Massengale, and Richardson[170] made it appear less likely that metalation played a part in the reaction. It was found that biphenyl was metalated to a small extent in the *para*-position by n-amylsodium, but that no such reaction occurred with phenylsodium. These authors also examined the possibility that the occurrence of tri-o-phenylene as a by-product in the sodiumchlorobenzene reaction might be due to metalation of o-terphenyl by phenylsodium, followed by the elimination of sodium hydride. It was found that o-terphenyl could be

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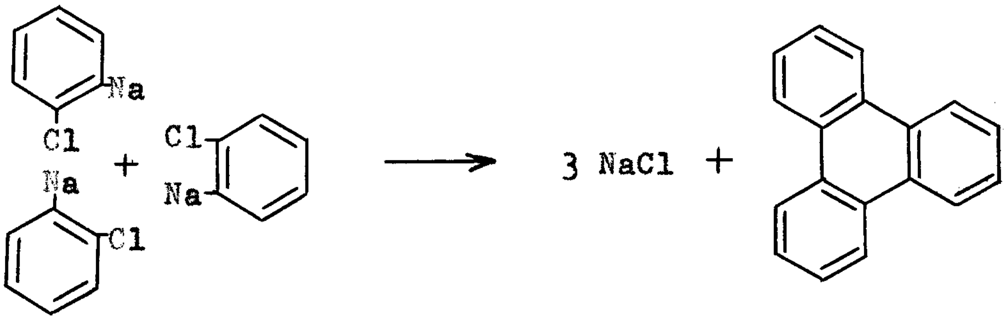
[169] W. E. Bachmann and H. T. Clarke, *J. Am. Chem. Soc.*, *49*, 2089 (1927).

[170] A. A. Morton, J. T. Massengale and G. M. Richardson, *ibid.*, *62*, 126 (1940).

metalated by n-amylsodium, but not by phenylsodium, thus ruling out the metalation-elimination mechanism. The possibility that tri-o-phenylene might arise through the ortho-metalation of chlorobenzene, followed by the condensation of three molecules of the resulting o-chlorophenylsodium, was also considered. However, attempts to isolate o-chlorobenzoic acid by carbonating a mixture of phenylsodium and benzene were unsuccessful. The acid mixtures obtained by this method were found to be free of chlorine. At the time of this investigation, it was assumed that metalated chlorobenzene would be stable enough to be detectable through carbonation.



Later studies by Wittig and co-workers, however, made it appear more likely that the metalation of aryl halides played a part in the Wurtz-Fittig couplings. It was found that phenyllithium reacted with all four halobenzenes to produce biphenyl.[171] Surprisingly, the highest yield (70 per cent)

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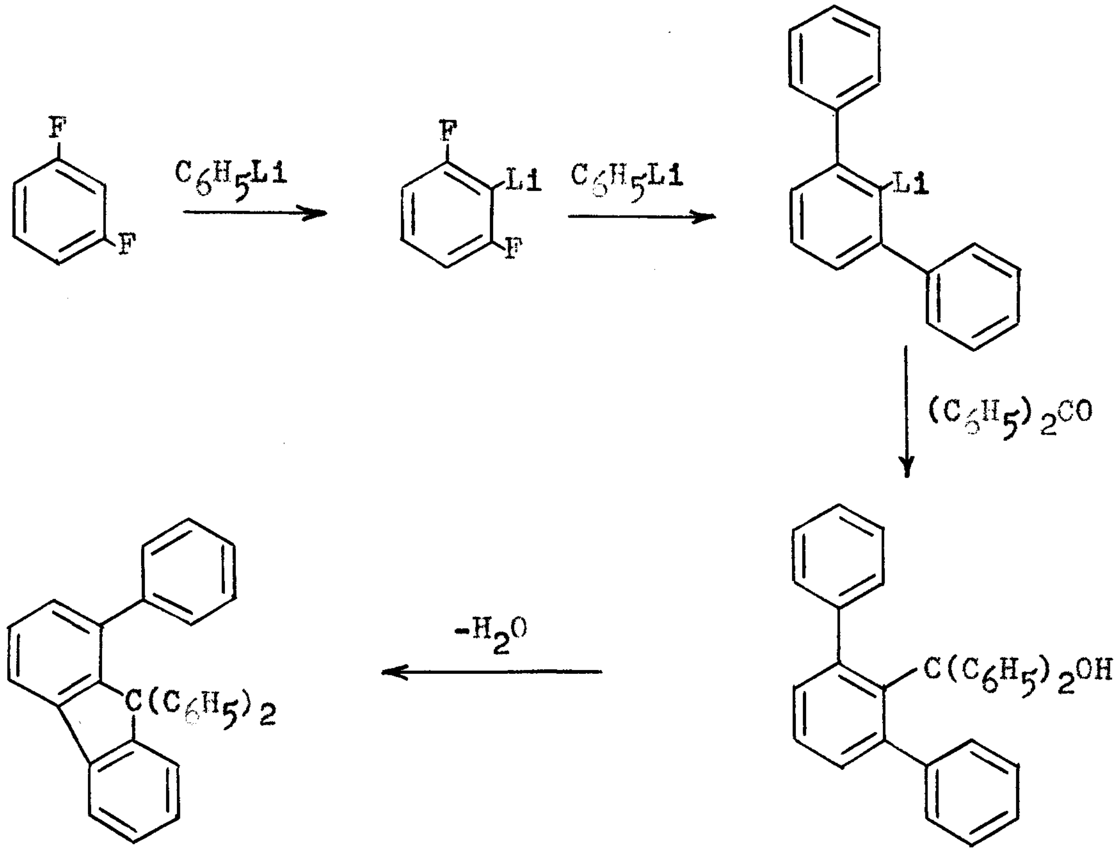
[171] G. Wittig, G. Pieper and G. Fuhrmann, Ber., 73, 1193 (1940).

was obtained from fluorobenzene; the other three halobenzenes gave yields of 10 per cent or less. The occurrence of metalation as a preliminary process in these reactions was suggested by the fact that when the reaction mixtures were treated with benzophenone prior to hydrolysis, diphenyl-o-xenylcarbinol was isolated, thus demonstrating that o-xenyllithium had been present in the mixture. Wittig postulated that the halobenzene had been metalated in an ortho-position by phenyllithium, and that the resulting o-halogenophenyllithium immediately coupled with excess phenyllithium to yield the final RLi. m-Difluorobenzene reacted with phenyllithium to yield m-terphenyl. When the reaction mixture was treated with benzophenone, there was isolated a carbinol which could be dehydrated to yield

1,9,9-triphenylfluorene.[172] This indicated that 2,6-diphenylphenyllithium had been present, and again suggested that metalation followed by coupling had occurred.



It was found that, in the reaction between phenyllithium and chlorobenzene, yields of the by-product, tri-o-phenylene, were as high as 13 per cent. Wittig and Merkle suggested that this product arose through the condensation of three molecules of metalated chlorobenzene. It will be recalled that a similar mechanism had been considered and rejected

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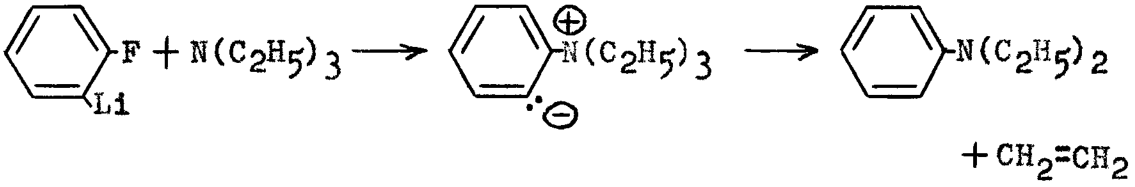
[172] G. Wittig and W. Merkle, ibid., 75, 1491 (1942).

by Morton and co-workers for the reaction of chlorobenzene with sodium to produce tri-o-phenylene. Morton's conclusions were based on the fact that carbonation of the reaction mixture yielded no chlorine-containing acids. However, Wittig's investigations showed that metalated halobenzenes were unstable with respect to the metalating agent. This suggested that Morton's failure to isolate chloroacids might have been due to the occurrence of rapid coupling of the metalated product.

A study of the reaction between halobenzenes and phenyllithium in the presence of tertiary amines provided further evidence of the reactive character of halogen atoms ortho to a metal substituent.[173] A mixture of fluorobenzene, phenyllithium, and triethylamine reacted to yield ethylene,



diethylaniline, and lithium fluoride. Some o-ethyldiethylaniline was also isolated. Phenyllithium alone did not react with triethylamine, nor did fluorobenzene. It was concluded

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[173] G. Wittig and W. Merkle, ibid., 76, 109 (1943).

that metalation first occurred, and that the resulting *o*-fluorophenyllithium added to the amine to yield an internal quaternary ammonium salt which could decompose in a manner analogous to the Hofmann degradation to yield ethylene and diethylaniline. A similar reaction was found to occur when iodobenzene was used in place of fluorobenzene, although the yield of diethylaniline was smaller. That the mechanism of decomposition of the internal quaternary salt was not strictly analogous to the Hofmann degradation was indicated by the fact that N-methylpiperidine reacted with phenyllithium and fluorobenzene to yield N-phenylpiperidine. If degradation had followed the Hofmann mechanism, ring opening would have occurred and the final product would have been an alkenylamine. It was suggested that excess phenyllithium might have participated in the degradation by removing a proton (in the case of the reaction with triethylamine) or a carbonium ion (in the case of the N-methylpiperidine reaction.)

Metalation-Elimination Reactions of Vinyl Halides and Ethers

In 1927, Marvel, Hager and Coffman[174] reported the reaction of *n*-butyllithium with -bromostyrene in petroleum ether, to yield 1-phenyl-1-hexene and 1,4-diphenylbutadiene.

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[174] C. S. Marvel, F. D. Hager and D. D. Coffman, *J. Am. Chem. Soc.*, *49*, 2323 (1927).

Some years later, Gilman, Langham and Moore investigated the influence of temperature and solvent on the course of this reaction.[175] They found that, when a higher temperature was employed in the reaction, carbonation of the mixture led to the formation of trans-cinnamic acid, indicating that halogen-metal interconversion had taken place; it was suggested that the hydrocarbons isolated by Marvel and co-workers might have arisen through this route. However, when the same reaction was carried out in diethyl ether, the product of carbonation

$$C_6H_5CH{=}CHBr \xrightarrow{RLi} C_6H_5CLi{=}CHBr \xrightarrow{-LiBr} C_6H_5C{\equiv}CH$$

was phenylpropiolic acid. One mechanism postulated for this reaction was the metalation of the bromostyrene on the α-carbon atom, followed by elimination of lithium bromide to yield phenylacetylene. Metalation of the phenylacetylene by unreacted n-butyllithium would account for the final product.

Shortly afterward, Wittig and Witt reported a similar reaction of β-chlorostyrene with phenyllithium, to yield phenylacetylene on hydrolysis.[176] Attempts to "trap" the intermediate halogen-containing RLi compound by adding benzophenone to the reaction mixture were unsuccessful, and the authors concluded that, if the metalation-elimination

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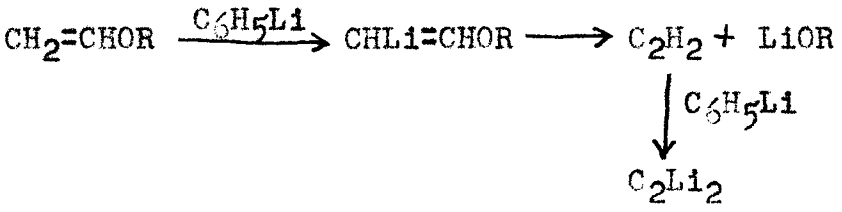
[175] H. Gilman, W. Langham and F. W. Moore, ibid., 62, 2327 (1940).

[176] G. Wittig and H. Witt, Ber., 74, 1474 (1941).

mechanism was correct, the elimination step occurred immediately after metalation.

Vinyl bromide was found to behave in a similar fashion. A reaction with n-butyllithium in diethyl ether, followed by carbonation, yielded acetylenedicarboxylic acid. From a similar reaction in petroleum ether, the same product, together with a small amount of propiolic acid, was isolated.[177]

Wittig and Harborth[178] studied the reaction of RLi compounds with vinyl ethers, and found that reactions analogous to those of the vinyl halides occurred. Phenyl vinyl ether and isobutyl vinyl ether both reacted with phenyllithium



$$\begin{tikzcd}
CH_2{=}CHOR \arrow[r, "C_6H_5Li"] & CHLi{=}CHOR \arrow[r] & C_2H_2 + LiOR \arrow[d, "C_6H_5Li"] \\
 & & C_2Li_2
\end{tikzcd}$$

to yield lithium acetylide, benzene, and the lithium salt of the corresponding hydroxyl compound. By analogy with the metalation of aromatic ethers and halides, the authors reasoned that the intermediate metalation product of a vinyl ether might be more stable than that of a vinyl halide, just as metalated anisole had been found to be more stable than

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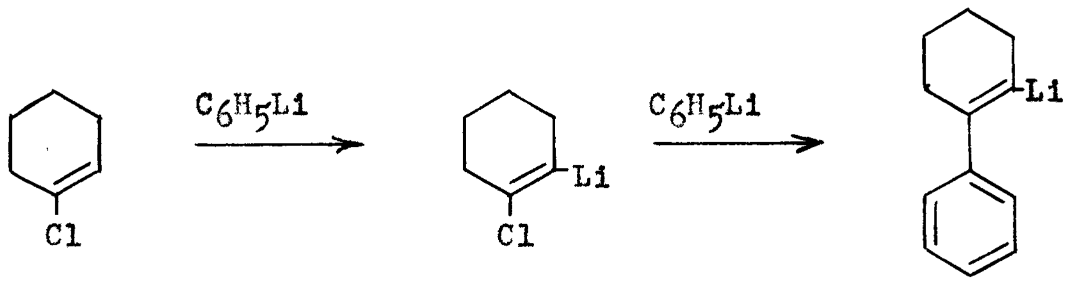
[177] H. Gilman and A. H. Haubein, J. Am. Chem. Soc., 67, 1420 (1945).

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

metalated chlorobenzene. However, it was not possible to "trap" any intermediate metalated product of the vinyl ethers by the use of benzophenone, benzoyl chloride, or benzyl chloride. It was noted that the overall reaction was slower with vinyl ethers than with halides. Vinyl bromide reacted completely with phenyllithium within a few minutes, while phenyl vinyl ether took several hours for complete reaction, and isobutyl vinyl ether required several days.

In a further attempt to isolate an intermediate metalation product, the reaction of 1-chlorocyclohexene with phenyllithium was studied. In this case, it was reasoned, lithium chloride could not be eliminated from the metalated product, because such a reaction would lead to the highly strained compound cyclohexyne. It was found that the products of reaction were 1-phenylcyclohexene and biphenyl. The authors explained the formation of the former compound on the basis of metalation followed by Wurtz coupling, and suggested that the formation of biphenyl might have been due to successive



metalation-elimination reactions of 1-phenylcyclohexene.

Generally, metalation-elimination was not observed in monohalogen derivatives of alkanes. With ethylene dihalides, however, two distinct types of elimination were found to occur, depending on the kind of halogen present. Ethylene chloride reacted with phenyllithium to yield acetylene after

$$\begin{tikzcd}
(ClCH_2)_2 \arrow[r, "C_6H_5Li"] & ClCHLi\text{-}CH_2Cl \arrow[r] & ClCH{=}CH_2 + LiCl \arrow[d, "C_6H_5Li"] \\
 & LiCl + C_2H_2 & ClCH{=}CHLi \arrow[l]
\end{tikzcd}$$

hydrolysis. In the reaction of phenyllithium with ethylene bromide, ethylene chlorobromide, or ethylene iodide, however, the products formed were ethylene and the corresponding

$$(ICH_2)_2 \xrightarrow{C_6H_5Li} ICH_2\text{-}CH_2Li \longrightarrow C_2H_4 + LiI$$

halobenzenes. This suggested that, when only chlorine was present, metalation-elimination occurred, but that, in the case of the bromo and iodo compounds, elimination had been preceded by halogen-metal interconversion rather than by metalation. A similar reaction between phenyllithium and 1-iodo-2-methoxyethane yielded ethylene, iodobenzene, and lithium methoxide. No reaction took place between phenyllithium and ethylene glycol dimethyl ether at room temperature, but when the mixture was heated to 100°, ethylene was very slowly evolved. Ethylene glycol diphenyl ether reacted with phenyllithium to give a nuclear metalation product instead of ethylene; treatment of the mixture with benzophenone yielded ethylene glycol bis-2-(diphenylhydroxymethyl)-phenyl ether.

A kinetic investigation[179] of the reaction between β-chlorostyrene and phenyllithium showed that the rate-determining step required two molecules of phenyllithium.

$$C_6H_5CH{=}CHCl \xrightarrow{2C_6H_5Li} C_6H_5CLi{=}CLiCl \xrightarrow{-LiCl} C_6H_5C{\equiv}CLi$$

It was suggested that, instead of the originally postulated monometalation process, a dimetalation might be involved, as shown in the accompanying formulation. Elimination of lithium chloride from the dilithio compound would yield phenylethynyllithium directly. These kinetic data were later challenged on the grounds that it was not specifically stated which, if either, pure stereoisomer of β-chlorostyrene had been used in the rate studies.[180] More recently, Grummitt and Lucier repeated the work of Wittig, using a pure stereoisomer of chlorostyrene, and have substantiated the earlier measurements.[181] However, they have offered a different

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[179] G. Wittig, G. Harborth and W. Merkle, ibid., 77, 315 (1944).

[180] S. J. Cristol, J. W. Ragsdale and J. S. Meek, J. Am. Chem. Soc., 73, 810 (1951).

[181] O. Grummitt and J. J. Lucier, Abstracts Papers Am. Chem. Soc., 121, 49K (1952).

interpretation of the data, involving a monometalation process similar to the earlier mechanism of Gilman, Langham and Moore.[175]

The Stevens and Sommelet Rearrangements[182]

In 1942, Wittig and Löhmann reported the reaction of benzyl methyl ether with phenyllithium to yield phenylmethylcarbinol. They postulated that metalation had occurred on

$$C_6H_5CH_2OCH_3 \xrightarrow{C_6H_5Li} C_6H_5CHLiOCH_3 \longrightarrow C_6H_5CH(CH_3)OLi$$

the methylene carbon atom, and that the metalated derivative had undergone a cationotropic rearrangement to yield the lithium salt of the carbinol. Dibenzyl ether was found to rearrange under similar conditions, yielding phenylbenzylcarbinol.[183]

Later studies by Wittig and Happe[184] substantiated the above mechanism, and indicated that the reaction was of wide scope. 9-Fluorenyl methyl ether, when treated with phenyllithium, yielded 9-methyl-9-fluorenol on hydrolysis; however, if the mixture was treated with benzophenone after the reac-

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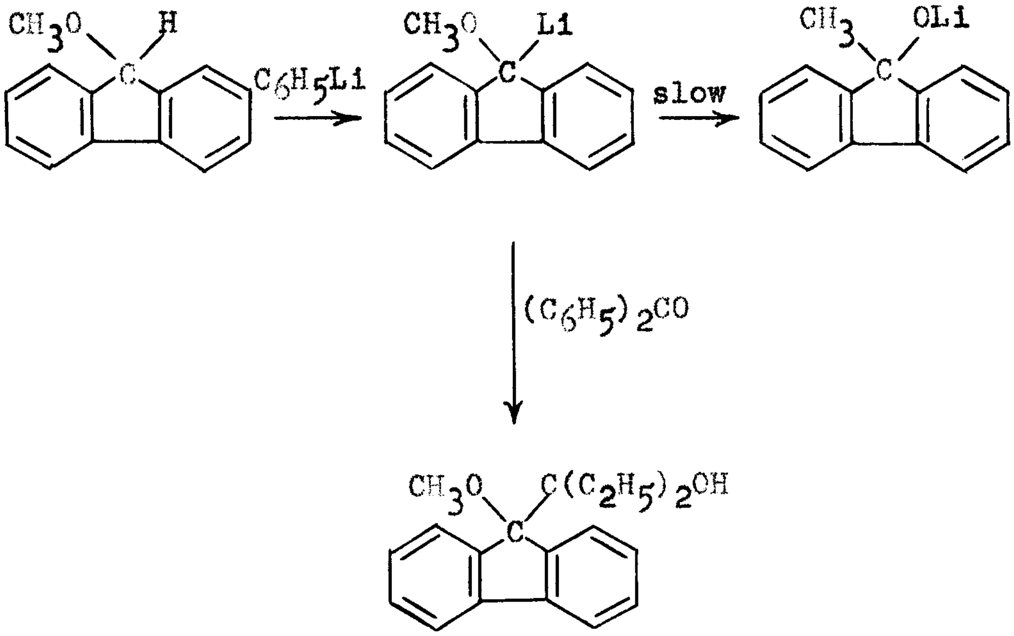
[182] For an extensive review of the Sommelet and Stevens rearrangements, see G. Wittig, Angew. Chem., 63, 15 (1951).

[183] G. Wittig and L. Löhmann, Ann., 550, 260 (1942).

[184] G. Wittig and W. Happe, ibid., 557, 205 (1947).

tion was allowed to proceed for a shorter period, (9-methoxy-9-fluorenyl)-diphenylcarbinol was isolated, thus indicating



that metalation preceded rearrangement. Benzhydryl methyl ether was found to rearrange to diphenylmethylcarbinol on treatment with phenyllithium, while benzhydryl phenyl ether yielded triphenylcarbinol under similar conditions. By ingenious modifications of technique, Wittig and Happe were able to prepare the potassium, rubidium, cesium, chloromagnesium, and chlorozinc derivatives of benzhydryl phenyl ether, and to study the influence of the type of metal upon the speed of isomerization. The potassium, rubidium, and cesium derivatives were prepared by the action of the free metal on benzopinacol diphenyl ether, while the chloro-

$$[(C_6H_5)_2C(OC_6H_5)]_2 + 4K \longrightarrow 2(C_6H_5)_2CKOC_6H_5 + 2KOC_6H_5$$

magnesium and chlorozinc compounds were obtained from the reaction between the lithium derivative of benzhydryl phenyl

$$(C_6H_5)_2CLiOC_6H_5 + MgCl_2 \longrightarrow (C_6H_5)_2C(MgCl)OC_6H_5 + LiCl$$

ether and the halide of the divalent metal. It was found that the following orders obtained in the speed of isomerization of the metalated derivatives: $Li > MgCl > ZnCl$ and $Li > Na > K > Rb, Cs$. It was also found that the rearrangement of the lithium derivative took place with greater speed in tetrahydrofuran than in pyridine.

The reaction of phenyllithium or methyllithium with various ethers of 9-fluorenol generally led to rearrangement, yielding the corresponding 9-substituted-9-fluorenol, but the speed and extent of reaction varied widely with different groups.[185] The methyl and ethyl ethers gave moderate yields, and the rearrangement was slow. The allyl and benzyl ethers rearranged instantaneously on treatment with the RLi compound, to give yields of 80 per cent and 98 per cent, respectively. With the phenyl ether, however, no 9-phenyl-9-fluorenol was

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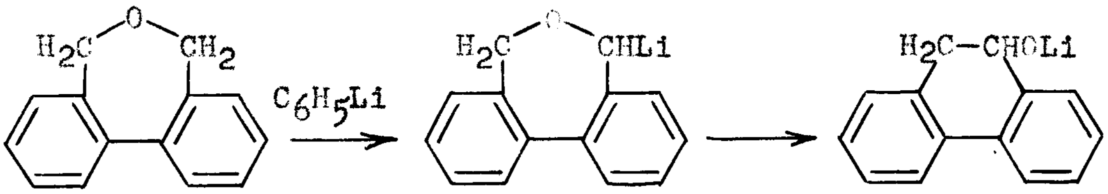
[185] G. Wittig, H. Doser and I. Lorenz, ibid., 562, 192 (1949).

formed; instead, dibiphenyleneethylene was isolated. Similar results were obtained with the p-tolyl, p-chlorophenyl and p-iodophenyl ethers, although normal rearrangement occurred with the p-nitrophenyl ether.[186] The authors postulated that the dibiphenyleneethylene was formed through the coupling of two molecules of metalated ether, involving the successive elimination of two molecules of lithium phenoxide. The failure to observe rearrangement in the case of the phenyl, p-tolyl, p-chlorophenyl, and p-iodophenyl ethers was attributed to the relative inability of these groups to migrate as cations.

In only one case has a rearrangement of the above type been carried out with a cyclic ether. 3,4,5,6-Dibenzo-1-oxa-3,5-cycloheptadiene reacted with phenyllithium to yield 9-hydroxy-9,10-dihydrophenanthrene.[187]



The studies of Wittig and co-workers on the

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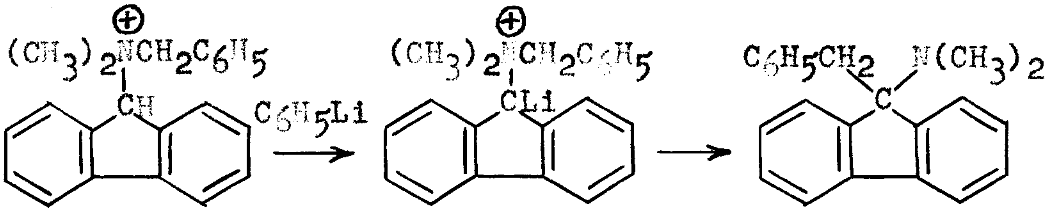
[186] Lithium methoxide was used as the metalating agent in the case of the p-nitrophenyl ether.

[187] G. Wittig, P. Davis and G. Koenig, Chem. Ber., 84, 627 (1951).

isomerization of metalated ethers recalled the earlier work of Späth, who reported in 1914 that diphenyl ether, when strongly heated with ethylmagnesium bromide, rearranged to yield o-hydroxybiphenyl.[188] Gilman and Bebb observed a similar rearrangement of diphenyl ether with ethynylsodium in liquid ammonia.[28] Lüttringhaus and Wagner-von Säaf have reported analogous isomerizations of aryl ethers with phenylsodium. Phenyl 1-naphthyl ether rearranged to 2-phenyl-1-naphthol, and phenyl 2-naphthyl ether yielded 2-(o-hydroxyphenyl)-naphthalene.[189] It has not been established whether these reactions involved metalation as a preliminary process.

Wittig and Felletschin found that dimethylbenzyl-9-fluorenylammonium bromide reacted with phenyllithium to yield



9-dimethylamino-9-benzylfluorene.[190] They postulated for this reaction a mechanism analogous to that put forward for

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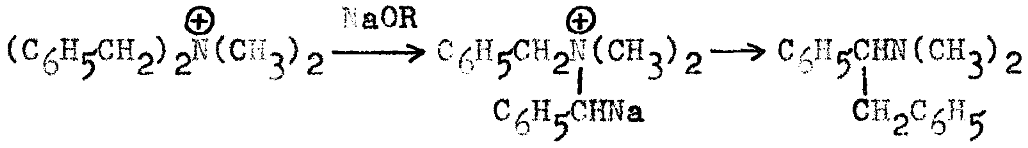
[188] E. Späth, Monatsh., 35, 319 (1914).

[189] A. Lüttringhaus and G. Wagner-von Säaf, Ann., 557, 25 (1945).

[190] G. Wittig and G. Felletschin, ibid., 555, 133 (1944).

the ether rearrangements. Wittig called attention to the resemblance between these reactions and the alkali-induced isomerization of dimethyldibenzylammonium chloride previously



$$(C_6H_5CH_2)_2\overset{\oplus}{N}(CH_3)_2 \xrightarrow{NaOR} C_6H_5CH_2\underset{C_6H_5CHNa}{\overset{\oplus}{N}}(CH_3)_2 \longrightarrow C_6H_5\underset{CH_2C_6H_5}{CH}N(CH_3)_2$$

reported by Thomson and Stevens,[191] and suggested that all reactions of this type might be conveniently termed "Stevens rearrangements." They all appeared to involve (1) the removal of an activated hydrogen atom from an α-carbon and (2) the subsequent migration of a cation within the deprotonated species.[192]

In a further study of the scope of the Stevens rearrangement of quaternary ammonium salts,[193] it was found that trimethylbenzylammonium bromide reacted with phenyllithium to yield dimethyl-α-phenylethylamine. A similar reaction between trimethylbenzhydrylammonium bromide yielded not only the expected product, dimethyl-α,α-diphenylethylamine, but also a second amine having the formula $C_{29}H_{29}N$, which could

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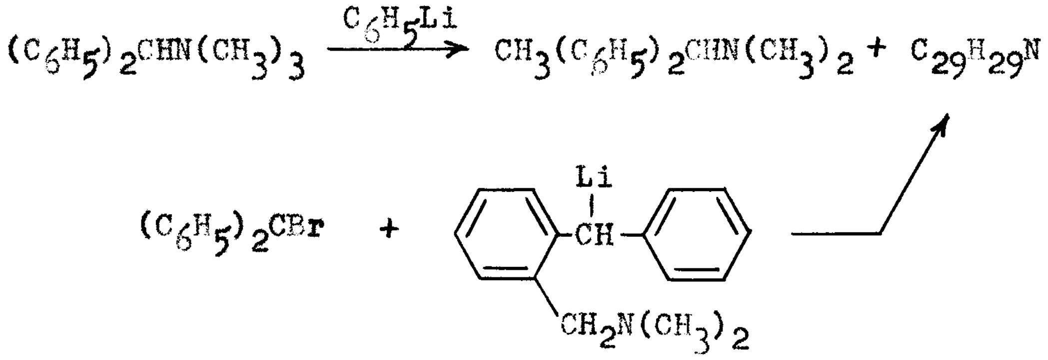
[191] T. Thomson and T. S. Stevens, J. Chem. Soc., 55 (1932).

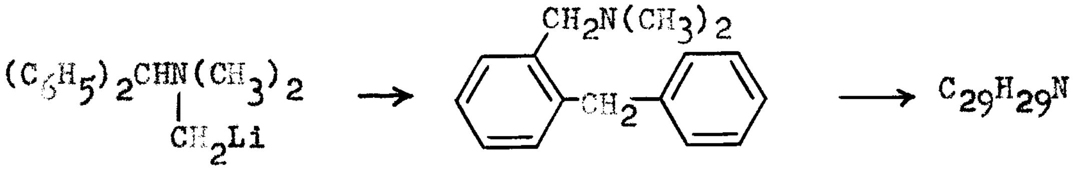
[192] For a similar rearrangement of a sulfonium salt, see T. Thomson and T. S. Stevens, ibid., 69 (1932).

[193] G. Wittig, R. Mangold and G. Felletschin, Ann., 560, 116 (1948).

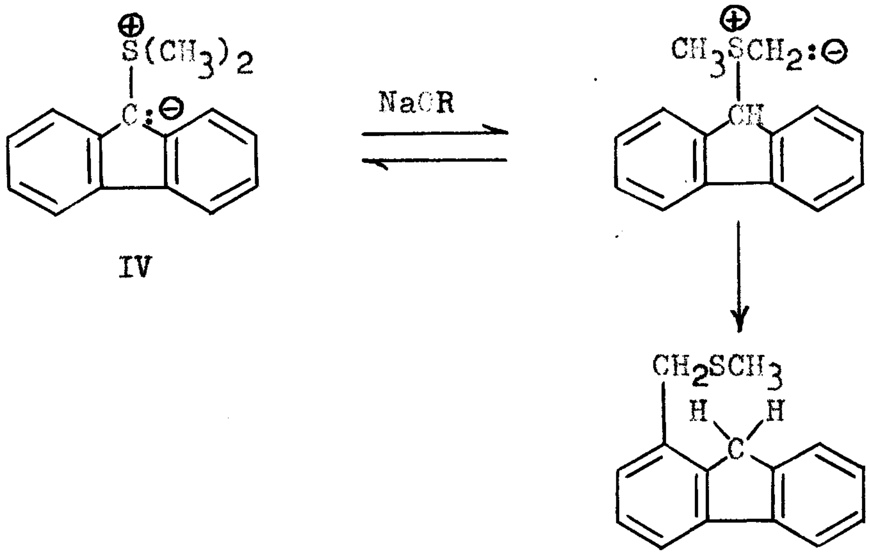
also be synthesized by adding diphenylbromomethane to a mixture of phenyl-(o-dimethylaminomethylphenyl)-methane and phenyllithium. The authors concluded that the unknown amine



was either 1-dimethylamino-1-(o-benzylphenyl)-2,2-diphenylethane or 1-(o-dimethylaminomethylphenyl)-1,2,2-triphenylethane, and that, in either case, it had arisen through the



preliminary formation of phenyl-(o-dimethylaminomethylphenyl)-methane, as indicated in the accompanying figure. They called attention to the fact that this reaction scheme implied a mechanism different from that of the Stevens rearrangement, since it would appear that a proton had been removed from one of the methyl groups of the ammonium salt, rather than from the methylene carbon of the benzhydryl group. Sommelet[194] had previously described the decomposition of trimethylbenzhydrylammonium hydroxide to yield phenyl-(o-dimethylaminomethylphenyl)-methane, and it was suggested by Wittig and co-workers that the name "Sommelet rearrangement" be attached to reactions of this kind. As another early example of this type of isomerization, they recalled the work of Hilbert and Pinck, who had reported the rearrangement of the internal sulfonium salt IV to yield 1-methylmercaptomethylfluorene.[195] Hilbert and Pinck had suggested the mechanism illustrated in the accompanying formulation, involving an equilibrium



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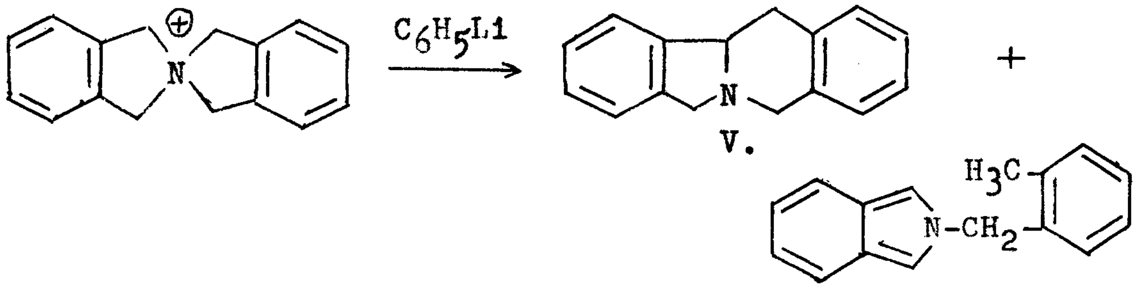
[194] M. Sommelet, Compt. rend., 205, 56 (1937).

[195] G. E. Hilbert and L. A. Pinck, J. Am. Chem. Soc., 60, 494 (1938).

between fluorenylide and methylide structures. All of the above reactions had in common the fact that they seemed to involve the replacement of an unactivated hydrogen atom.

In discussing the relationship between the Stevens and the Sommelet rearrangements, Wittig, Mangold and Felletshin[193] noted that the ability of a metalated ether or ammonium salt to undergo the Stevens rearrangement seemed to depend on the polarity of the metal-to-carbon bond. Up to a certain threshold value, the speed of the rearrangement increased with increasing polarity of the carbon-to-metal bond; but after this threshold value was reached, a further increase in polarity made the rearrangement slower. This was demonstrated (1) by the previously mentioned studies with benzhydryl phenyl ether, using different metals; (2) by the fact that the Stevens rearrangement of the lithium derivative of benzhydryl phenyl ether was slower when a more highly "ionizing" solvent was used; and (3) by the fact that trimethylbenzhydrylammonium bromide underwent metalation followed by rearrangement, whereas trimethyl-9-fluorenylammonium bromide was metalated without rearrangement. The C-Li bond should be more polar in the metalated fluorenyl salt than in the metalated benzhydryl salt, and it was held that the threshold value of polarity had been passed in the former case. The corollary implied by this theory was that, in an ether or ammonium salt containing a very strongly acidic α-hydrogen atom, together with other α-hydrogen atoms of weaker acidity, the Stevens reaction might be suppressed in favor of the Sommelet rearrangement; for the replacement of the most strongly acidic hydrogen would yield a carbon-to-metal bond too polar to favor the Stevens rearrangement, whereas the replacement of one of the less activated hydrogens would yield a less polar carbon-to-metal bond, thus permitting a Sommelet rearrangement to take place. This corollary was substantiated in the reaction between phenyllithium and phenacyltrimethylammonium bromide, a compound containing very strongly activated methylene hydrogen atoms. The only rearranged product isolated from this reaction was 3-dimethylamino-1,1-diphenyl-1-propanol, presumably the product of a Sommelet reaction followed by addition of phenyllithium to the carbonyl group of the rearranged amine.

In a study of the synthetic possibilities of the Stevens and Sommelet rearrangements,[196] Wittig and co-workers found



V.

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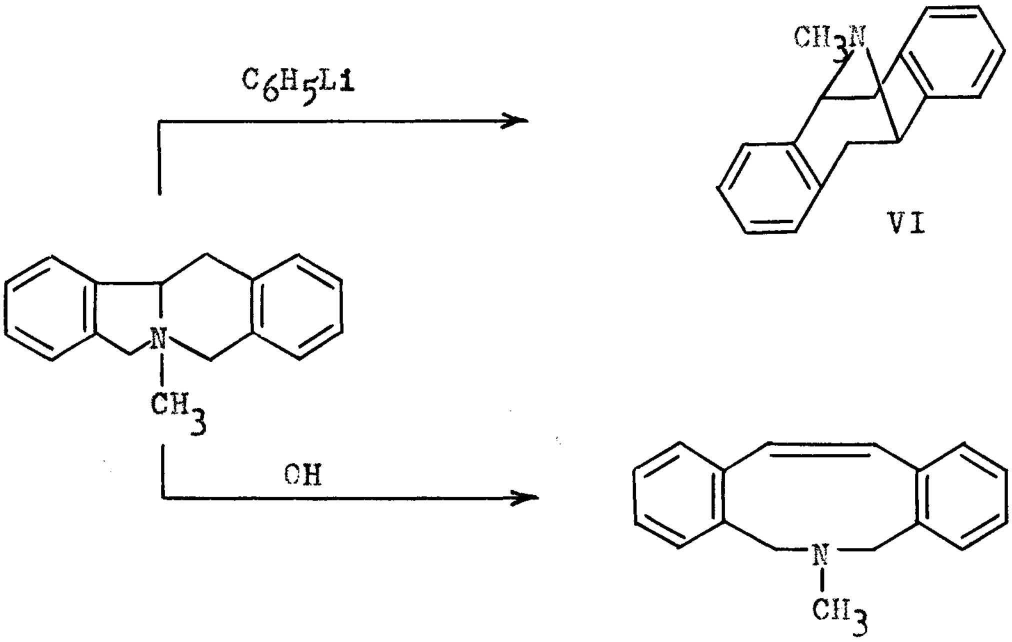
[196] G. Wittig, H. Tenhaeff, W. Schoch and G. Koenig, Ann., 372, 1 (1951).

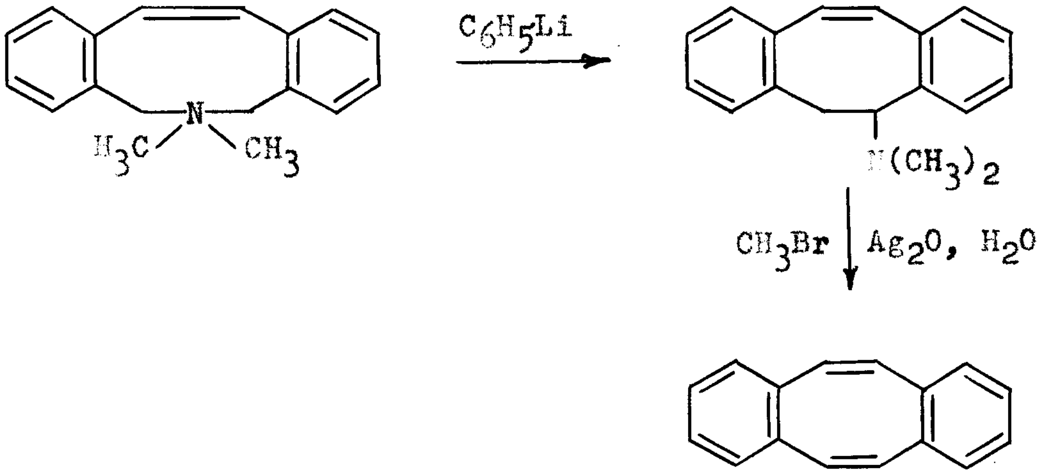
that the reaction of phenyllithium with di-*o*-xylyleneammonium bromide resulted in the formation of the dihydroisoindole derivative V, a product of Stevens rearrangement. N- -*o*-xylylisoindole was also isolated. The same two products were formed in the thermal decomposition of di-*o*-xylyleneammonium hydroxide. The methobromide of V, when treated with phenyllithium, underwent a Stevens rearrangement to yield the tetrahydroisoquinoline derivative VI. The corresponding ammonium hydroxide, however, decomposed in the regular



VI

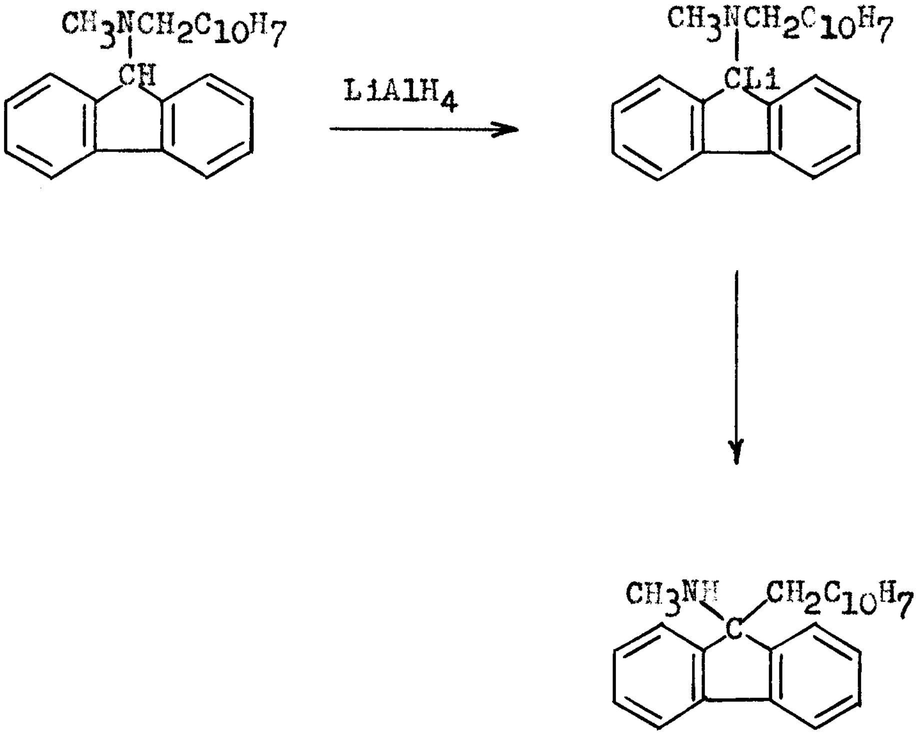
VII

Hofmann fashion to yield N-methyl-3,4,7,8-dibenzo-1-aza-3,5,7-cyclononatriene (VII). The methobromide of VII reacted in turn with phenyllithium to yield the Stevens product, 1-dimethylamino-2,6-dibenzo-2,4,6-cyclooctatriene. This



amine could be converted into 1,2,5,6-dibenzo-1,3,5,7-cyclooctatetraene through the action of silver oxide on its methobromide.

Only one report of a metalation-rearrangement of a tertiary amine has appeared. Dahn and Solms described the reaction of methyl-9-fluorenyl-1-naphthylamine with lithium aluminium hydride to yield an amine which they believed to be 9-methylamino-9-(1-naphthylmethyl)-fluorene. The product



was characterized by hydrogenolysis to yield 9-(1-naphthylmethyl)-fluorene.[197] The 2-naphthyl analogue underwent a similar series of reactions. It has been pointed out[113] that

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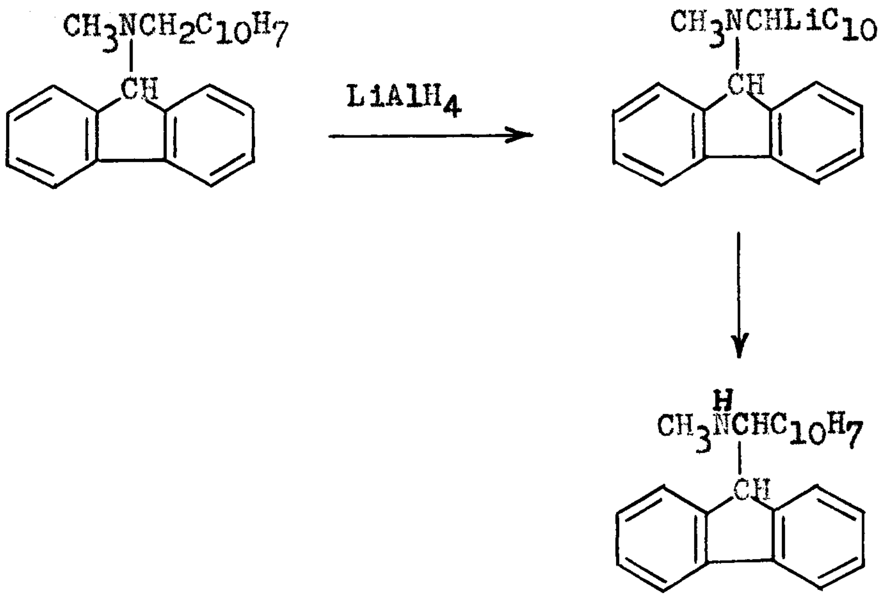
[197] H. Dahn and U. Solms, Helv. Chim. Acta, 34, 907 (1951).

the characterization of these products by hydrogenolysis was ambiguous, and that, in each case, the rearranged amine could have been a methyl-(9-fluorenylnaphthylmethyl)-amine. In either event, however, a Stevens rearrangement had evidently taken place. The use of lithium aluminum hydride as a metalating agent in these reactions was of particular interest. According to the nucleophilic theory, this strongly basic compound might be expected to effect metalation as well as the RLi reagents. In one other case this expectation has been realized, for Trevoy and Brown reported the metalation of fluorene by lithium aluminum hydride in refluxing tetrahydrofuran.[198]



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[198] L. W. Trevoy and W. G. Brown, J. Am. Chem. Soc., 71, 1675 (1949).

EXPERIMENTAL

Organometallic Compounds

General remarks concerning preparation and use

The usual precautions were observed in the preparation and reactions of the organometallic compounds of lithium, calcium and magnesium. All glassware was rinsed with acetone and dried in an oven at 100° prior to use. The nitrogen with which all apparatus was swept out was freed of oxygen and moisture by passage through a train containing vanadous sulfate, concentrated sulfuric acid and calcium chloride, in the order named.[199] All solvents were dried either with sodium wire or with calcium hydride. n-Butyllithium was prepared by the low-temperature procedure.[200] The method of Miller[201] was used in the preparation of phenyllithium and of o-tolyllithium.

Unless otherwise noted, all carbonations were effected by pouring the organometallic solution jetwise over a slurry of Dry Ice and ether. The procedures used in working up

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[199] L. Meites and T. Meites, Anal. Chem., 20, 984 (1948).

[200] H. Gilman, J. A. Beel, M. W. Bullock, G. E. Dunn and L. S. Miller, J. Am. Chem. Soc., 71, 1499 (1949).

[201] See Reference 107, p. 353.

carbonation mixtures varied according to the expected products, and are described in detail in each section.

2,4,6-Triphenylphenyllithium

Preparation from 2,4,6-triphenylbromobenzene and lithium. A 500-ml. three-necked flask equipped with a stirrer, a reflux condenser and a solids funnel was swept with dry nitrogen, and 2.0 g. (0.28 gram-atom) of finely-cut lithium was introduced. Anhydrous ether (100 ml.) was run into the flask. The solids funnel was then replaced by a dropping funnel containing a solution of 10.0 g. (0.026 mole) of 2,4,6-triphenylbromobenzene in 100 ml. of anhydrous benzene. A few drops of this solution were run into the flask, and the stirrer was started. After a few minutes, a pink color had developed in the flask. The remainder of the halide solution was dropped into the flask over a period of between forty minutes and one hour. The mixture was further stirred for five hours and then filtered through glass wool into a nitrogen-swept, graduated dropping funnel. The yield was determined by hydrolyzing a 1-ml. aliquot of the solution with distilled water, and titrating the hydrolyzate with 0.01 N sulfuric acid, using phenolphthalein as an indicator. Yields were in the range 82-100 per cent; the average yield of ten preparations was 92 per cent.

In order to check the accuracy of the alkalimetric method for determining the yield of 2,4,6-triphenylphenyllithium, a sample (0.02 mole) of the RLi compound, prepared as described above, was hydrolyzed with water, and the aqueous layer (combined with two water washings of the organic layer) was diluted to 1.00 liter. A 100-ml. aliquot of the resulting solution was treated with an excess of standard silver nitrate solution, and the excess silver was titrated with standard potassium thiocyanate solution, using ferric alum as an indicator. The original molarity of the RLi compound, as determined by this method, was 0.131; an alkalimetric titration of another sample of the same RLi solution indicated a molarity of 0.136.

During the preparation of 2,4,6-triphenylphenyllithium, the development of an intense blood-red color was noted. In some cases, this color disappeared before all the halide had been added, but in other cases the color persisted in the final solution even after several days. The color is apparently not due to the organolithium compound; both the colored and the colorless solutions were found to give a positive Color Test I,[202] and to undergo other reactions characteristic of RLi compounds.

On exposure to the atmosphere, 2,4,6-triphenylphenyllithium was found to show a strong lavender chemiluminescence, presumably a concomitant of the oxidation of the RLi compound.

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[202] H. Gilman and F. Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

The lavender glow was visible even in daylight, and was reminiscent of the chemiluminescence observed in the reactions of certain Grignard reagents.[203,204,205]

Preparation from 2,4,6-triphenylbromobenzene and n-butyllithium. To a solution of 0.0265 mole of n-butyllithium in 25 ml. of ether was added a solution of 10 g. (0.026 mole) of 2,4,6-triphenylbromobenzene in 120 ml. of dry benzene over the course of one minute, with stirring. An orange color developed during the addition, and the evolution of heat was noticed. The clear orange solution was stirred for one additional minute after all the halide had been added, and was then carbonated. After evaporation of the Dry Ice, the carbonation mixture was hydrolyzed with water. The organic layer was separated and washed twice with water. The combined aqueous solutions were acidified with hydrochloric acid, and the resulting solid was filtered off, washed with water and dried to yield 0.970 g. (11.0 per cent crude yield) of material melting over the range 229-250°. Purification was effected by dissolving the solid in boiling glacial acetic acid and adding water to the resulting solution until

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[203] H. Gilman, J. McGlumphy and R. E. Fothergill, Rec. trav. chim., 49, 526 (1930).

[204] H. Gilman, R. E. Fothergill and J. McGlumphy, ibid., 49, 726 (1930).

[205] C. D. Thomas and R. T. Dufford, J. Optical Soc. Am., 23, 251 (1933) /C. A., 27, 4737 (1933)/.

crystals began to appear. The cooled mixture was filtered, and the residue was washed with water and dried to yield 0.590 g. (6.7 per cent) of 2,4,6-triphenylbenzoic acid, m.p. 251-253°. A mixed melting point with an authentic specimen was not depressed.

Mesityllithium

Preparation in ether-benzene. The procedure and molar amounts in this preparation were exactly the same as those used in the preparation of 2,4,6-triphenylphenyllithium from 2,4,6-triphenylbromobenzene and lithium, except that the halide used was bromomesitylene. The highly odoriferous product was insoluble in the ether-benzene medium, and, in order to secure a representative sample for titration, the mixture was stirred vigorously during the withdrawal of the aliquot. The yield, as determined by alkalimetric titration, was 100 per cent.

Preparation in ether. Into a nitrogen-swept flask containing 5.0 g. (0.71 gram-atom) of finely cut lithium and 100 ml. of ether was run dropwise, and with stirring, a solution of 19.9 g. (0.10 mole) of bromomesitylene in 35 ml. of ether. Reaction began almost immediately, and spontaneous refluxing occurred throughout the addition. The mixture was stirred at room temperature for three hours after addition was complete. The final product was a white suspension. The yield, as determined by alkalimetric titration, was 96 per cent.

Phenylcalcium iodide

Preparation. Two different grades of calcium metal were used in these preparations. In some cases, redistilled calcium (purity at least 99.9 per cent)[206] was employed; in others, crystalline calcium containing about 5 per cent of oxide and halide contaminants was used.[207] Yields of phenylcalcium iodide did not vary significantly with the grade of calcium used. A 2-l., three-necked flask equipped with a stirrer, a reflux condenser and a wide-throated solids funnel was thoroughly swept with dry nitrogen, and 80 g. (2.0 gram-atoms) of calcium was introduced. Two hundred ml. of ether and a small crystal of iodine were added, and the solids funnel was replaced by a dropping funnel containing a solution of 204 g. (1.0 mole) of iodobenzene in 800 ml. of ether. About 20 ml. of this solution was run into the flask, and the stirrer was started. The iodine color disappeared within a few minutes, and after about fifteen minutes the mixture began to reflux spontaneously. The remainder of the iodobenzene solution was run into the flask at such a rate as

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[206] Kindly furnished by Dr. A. A. Daane.

[207] Kindly furnished by Dr. Harold Soroos of the Ethyl Corporation.

to maintain constant, gentle refluxing. The addition required three hours. The mixture was further stirred for one hour and then allowed to settle overnight. The clear red solution was then siphoned from the copious brown precipitate into a nitrogen-swept dropping funnel. The yield, as determined by alkalimetric titration, was 60-66 per cent.

Analysis. A comparison of three different methods of determining the concentration of phenylcalcium iodide was made, using aliquots of a solution prepared as above.

In the alkalimetric method,[208] a 2-ml. aliquot of the phenylcalcium iodide solution was run into a measured excess of standard hydrochloric acid, and the excess acid was titrated with standard sodium hydroxide, using phenolphthalein as an indicator.

In the iodometric method,[209] a 2-ml. aliquot of the phenylcalcium iodide solution was run into a measured excess of a standard solution of iodine in benzene. The mixture was allowed to stand for a few minutes, and the excess of iodine was then titrated with standard sodium thiosulfate solution.

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[208] M. N. Katz, unpublished M. S. Thesis, Iowa State College, 1942.

[209] Modeled after the iodometric method for determination of the concentration of RMgX solutions. See H. Gilman and C. H. Meyers, Rec. trav. chim., 45, 314 (1926).

In the Versenate method, a 2-ml. aliquot of the phenylcalcium iodide solution was hydrolyzed in water. The pH of the hydrolyzate was adjusted to 10 by addition of a concentrated solution of ammonium chloride in ammonium hydroxide, and titrated with a 0.1 N solution of disodium Versenate (disodium dihydrogen ethylenediaminetetraacetate), using Eriochrome black T as an indicator.

The molarity of the same phenylcalcium iodide solution, as determined by the methods given above, had the following values: alkalimetric method, 0.402, 0.399; iodometric method, 0.295, 0.296; Versenate method, 0.544, 0.553. The strength of the phenylcalcium iodide solutions whose reactions are described on the following pages was determined by the alkalimetric method.[211]

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[210] See H. Diehl, C. A. Goetz and C. C. Hach, J. Am. Water Works Assoc., 42, 40 (1950), where a procedure is given for the determination of small amounts of calcium and magnesium in water. The present procedure is essentially that of Diehl and co-workers, adapted to the determination of larger amounts of calcium.

[211] The low results obtained by the iodometric method were possibly due to secondary reactions such as

$$C_6H_5I + C_6H_5CaI \longrightarrow (C_6H_5)_2 + CaI_2,$$

leading to a lower consumption of iodine than would be expected. The high results shown by the Versenate method probably indicated the presence of calcium iodide in the organometallic solution. The production of calcium iodide in the synthesis of RCaI reagents has been noted: see H. Gilman and F. Schulze, J. Am. Chem. Soc., 48, 2463 (1926).

Metalations with Sterically Hindered Organometallic Compounds

Metalation of thiophene with 2,4,6-triphenylphenyllithium

To a solution of 0.024 mole of 2,4,6-triphenylphenyllithium in 180 ml. of 1:1 ether-benzene was added 20 g. (0.24 mole) of thiophene. There was no noticeable evolution of heat on mixing the reactants. The solution was refluxed under nitrogen for twenty-five hours and then carbonated in the usual manner. After the Dry Ice had evaporated, the mixture was hydrolyzed with hydrochloric acid, and the organic layer was separated and extracted with four 25-ml. portions of 10 per cent sodium hydroxide solution. The combined alkaline extracts were chilled with ice and acidified with hydrochloric acid. When the acidified mixture had stood for several hours at room temperature, fine needles had formed. These were filtered off, washed with water, and dried to yield 0.885 g. of 2-thenoic acid, m.p. 129-130°. The acidic filtrate was extracted with two 30-ml. portions of benzene, and the combined extracts were evaporated to yield an additional 0.535 g. of 2-thenoic acid, m.p. 128-130°, bringing the total yield to 45.7 per cent. Both crops of the acid were identified by mixed melting points with an authentic specimen.

Metalation of p-bromoanisole with 2,4,6-triphenylphenyllithium

A solution of 0.024 mole of 2,4,6-triphenylphenyllithium in 200 ml. of 1:1 ether-benzene was run into a flask containing 10.5 g. (0.056 mole) of p-bromoanisole. There was some lightening of color, but no noticeable evolution of heat, when the reagents were mixed. The solution was refluxed for twenty-two hours. A bright orange color had developed by the end of the reaction period. About half of the solvent was then removed by distillation, and the remaining solution was further refluxed for seventeen hours. Carbonation was effected in the usual manner. After the Dry Ice had evaporated, the mixture was hydrolyzed with dilute hydrochloric acid. The organic layer was separated and washed with three 30-ml. portions of 10 per cent sodium hydroxide solution to yield an aqueous suspension containing a considerable amount of undissolved material. The suspended matter dissolved completely when 150 ml. of water was added to the combined alkaline extracts. The resulting solution was acidified with hydrochloric acid and filtered, and the residue was washed with water and dried to yield 1.40 g. (25 per cent) of 5-bromo-2-methoxybenzoic acid, m.p. 119-121°. A mixed melting point with an authentic specimen showed no depression.

The organic layer from the hydrolysis of the carbonation mixture was freed of solvent by evaporation. The residue was a dark tar containing large, colorless crystals. These were separated by hand, washed with methanol and dried to yield 5.69 g. (71.5 per cent), of 1,3,5-triphenylbenzene, identified by a mixed melting point with an authentic specimen.

Resorcinol dimethyl ether

Metalation with mesityllithium. A mixture of 13.8 g. (0.1 mole) of resorcinol dimethyl ether and 0.098 mole of mesityllithium in 127 ml. of ether was refluxed for forty-six hours. The mixture did not become homogeneous during this period. Carbonation was effected in the usual manner. The carbonation mixture was hydrolyzed with dilute hydrochloric acid. A white solid appeared which failed to dissolve in either layer. This material was separated and dissolved in 5 per cent sodium hydroxide, and the solution was acidified to yield 4.51 g. of 2,6-dimethoxybenzoic acid, m.p. 184-187°d. A mixed melting point with an authentic specimen was undepressed. When the original ether layer from the carbonation mixture was extracted with 5 per cent sodium hydroxide and the extract was acidified, an additional crop of crude acid (2.12 g., m.p. 174-179°d) was isolated. Recrystallization from aqueous ethanol yielded 1.70 g. of pure acid, m.p. 186-187°d, bringing the total yield to 6.21 g. (34.9 per cent.)

Metalation with 2,4,6-triphenylphenyllithium. A solution of 3.3 g. (0.024 mole) of resorcinol dimethyl ether and 0.024 mole of 2,4,6-triphenylphenyllithium in 196 ml. of 1:1 ether-benzene was refluxed for fifty-four hours. At the end of the reaction period, a light precipitate had appeared.

The mixture was carbonated in the usual manner. After the Dry Ice had evaporated, the mixture was hydrolyzed with hydrochloric acid, and the organic layer was separated and extracted with three 30-ml. portions of 5 per cent sodium hydroxide solution. Only a faint turbidity developed when the alkaline extracts were acidified. The resulting suspension was extracted with three portions of ether. Evaporation of the combined extracts left a slight residue of reddish solid. This was refluxed with water, and the hot suspension was filtered to remove a little undissolved material. The filtrate was evaporated to give 0.15 g. (3.4 per cent crude yield) of a colorless crystalline product, m.p. 183-184°. The solid was refluxed with 2 ml. of petroleum ether (b.p. 80-115°), and chloroform was added to the boiling mixture until only a small amount of solid remained undissolved. The mixture was filtered, and the filtrate was evaporated to yield 0.060 g. (1.4 per cent) of 2,6-dimethoxybenzoic acid, m.p. 185-187°d. A mixed melting point with an authentic specimen was not depressed.

Metalation of dibenzofuran with 2,4,6-triphenylphenyllithium

A solution of 4.27 g. (0.025 mole) of dibenzofuran and 0.025 mole of 2,4,6-triphenylphenyllithium in 200 ml. of 1:1 ether-benzene was stirred at 30-35° for twenty-two hours. At the end of this period, the solution had become cloudy and a yellow coloration had developed. The mixture was carbonated in the usual fashion, and, after the Dry Ice had evaporated, was hydrolyzed with iced concentrated hydrochloric acid. The organic layer was separated and extracted with three 30-ml. portions of 5 per cent sodium hydroxide. A heavy white precipitate which appeared during the extraction was retained with the alkaline extract. The combined extracts were chilled and acidified with hydrochloric acid, and the precipitated product was filtered off, washed with cold water, and dried to yield 3.41 g. of white powder melting over the range 216-270°. The crude acidic material was repeatedly extracted with boiling water. The combined extracts, when chilled, deposited light-yellow crystals, which were filtered off, washed with water, and dried to yield 0.18 g. (3.6 per cent) of dibenzofuran-4-carboxylic acid, m.p. 208-210°. A mixed melting point with an authentic specimen was not depressed.

Reaction of 6-phenylphenanthridine with 2,4,6-triphenylphenyllithium

To a solution of 5.1 g. (0.02 mole) of 6-phenylphenanthridine in 50 ml. of ether was added 0.021 mole of 2,4,6-triphenylphenyllithium in 130 ml. of 1:1 ether-benzene. The mixture was refluxed for forty-eight hours. A dark brownish-green color had developed by the end of this period. After hydrolysis with water, the red organic layer was separated, washed twice with water, and evaporated to dryness. The residue was shaken with 70 ml. of 2:3 chloroform-methanol, and the extract so obtained was evaporated to leave a red tar. This material was ground in a mortar with petroleum ether (b.p. 60-70°), and the resulting solution was filtered. The filtrate was evaporated to yield 1.20 g. (11.9 per cent crude yield) of a light yellow residue melting over the range 158-185°. Purification was effected by dissolving the solid in the minimum amount of boiling chloroform, and adding methanol to the resulting solution to the point of incipient turbidity. Three successive recrystallizations carried out in this manner yielded 0.215 g. (2.1 per cent) of yellow crystalline material, m.p. 284-286°d. A mixed melting point with a specimen of the bis-6-phenylphenanthridine obtained from a reaction between 6-phenylphenanthridine and mesityllithium was not depressed.

Fluorene

General procedure. A solution of 3.82 g. (0.0228 mole) of fluorene and 0.023 mole of the metalating agent in 200 ml. of a 1:1 ether-benzene mixture was stirred at room temperature for twenty-four hours and then carbonated in the usual fashion. After evaporation of the Dry Ice, the mixture was hydrolyzed with iced hydrochloric acid, and the organic layer was separated and extracted with two 30-ml. portions of 5 per cent sodium hydroxide and then with two 30-ml. portions of water. The alkali extractions produced a white precipitate which was retained with the aqueous layer. This solid dissolved when the alkali extracts were combined with the water extracts. The resulting solution was chilled with ice and acidified with hydrochloric acid, and the precipitated fluorene-9-carboxylic acid was filtered off, washed with water, and dried. All samples of the acid were identified by mixed melting points with an authentic specimen.[212]

Metalation with phenyllithium. A yellow color developed immediately on treating fluorene with phenyllithium. The yield of fluorene-9-carboxylic acid, m.p. 214-219°, was 3.60 g. (78 per cent).

Metalation with o-tolyllithium. The evolution of heat and the immediate appearance of a yellow color were noted when the reactants were mixed. The yield of fluorene-9-carboxylic acid, m.p. 217-221°, was 3.91 g. (84.5 per cent).

Metalation with mesityllithium. A yellow color resulted when the reactants were mixed, but the precipitate of mesityllithium did not disappear for ten hours. The yield of fluorene-9-carboxylic acid, m.p. 214.5-218°, was 2.44 g.

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[212] Fluorene-9-carboxylic acid has a rather diffuse melting point, and the range of melting depends on the rate of heating. Values for the melting point found in the literature range from 209° [213] to 225°.[214]

[213] Delacre, Bull. soc. chim., [3], 27, 875 (1902).

[214] H. Staudinger, Ber., 39, 3062 (1906).

(53.5 per cent).

Metalation with 2,4,6-triphenylphenyllithium. The yield of fluorene-9-carboxylic acid, m.p. 218-221°, from this reaction was 3.0 g. (65.2 per cent).

Triphenylmethane

General procedure. A solution of 5.6 g. (0.023 mole) of triphenylmethane and 0.023 mole of the metalating agent in 200 ml. of a 1:1 ether-benzene mixture was stirred at room temperature for twenty-four hours (unless otherwise noted) and then carbonated as usual. The methods of working up the carbonation product were varied, as described below, according to the acid present in each case.

Metalation with phenyllithium. There was immediate yellow coloration on mixing the reactants. The carbonation mixture was acidified with iced hydrochloric acid, and the organic layer was separated and extracted with three 30-ml. portions of 5 per cent sodium hydroxide solution. The combined extracts were chilled and acidified with hydrochloric acid to yield 0.745 g. (11.3 per cent crude yield) of white powder, m.p. 237-249°d. Recrystallization from glacial acetic acid yielded 0.390 g. (5.9 per cent) of triphenylacetic acid, m.p. 265-267°d. A mixed melting point with an authentic specimen was not depressed.

Metalation with o-tolyllithium. There was very little color change, and no perceptible evolution of heat, on mixing the reactants. By the end of the reaction period, however, the solution was cherry-red. The carbonation mixture was hydrolyzed with iced hydrochloric acid, and the organic layer was separated and extracted with three 30-ml. portions of 5 per cent sodium hydroxide solution. The combined extracts were iced and acidified with hydrochloric acid, and the precipitated product was filtered off, washed with water, and dried to yield 2.35 g. of a product that melted over the range 95-250°. The crude product was refluxed for twenty-four hours with water. During this time, white crystals sublimed on the cold finger of the reflux condenser. The mixture was filtered while still hot, to yield a residue weighing 0.77 g. (11.6 per cent crude yield), m.p. 253-255°. This material was washed with benzene and recrystallized from glacial acetic acid to yield 0.51 g. (7.7 per cent) of triphenylacetic acid, m.p. 265-267°d. A mixed melting point with an authentic specimen was not depressed.

When the hot aqueous filtrate was cooled, crystals deposited. These, combined with the material that had sublimed on the reflux condenser, weighed 0.94 g. (30 per cent) and melted at 103-104°. A mixed melting point with an authentic sample of _o_-toluic acid was not depressed.

Metalation with mesityllithium (attempted). There was no color change when the reactants were mixed, but by the end of the reaction period a very slight yellow color had developed. The carbonation mixture was hydrolyzed with iced hydrochloric acid, and the organic layer was separated and extracted with three 30-ml. portions of 5 per cent sodium hydroxide solution. The combined extracts were chilled and acidified with hydrochloric acid, and the precipitated product was filtered off, washed with water, and dried to yield 0.87 g. (22 per cent) of mesitoic acid, m.p. 146-149°. A mixed melting point with an authentic specimen was not depressed.

Metalation with 2,4,6-triphenylphenyllithium (attempted.) There was no color change on mixing the reagents, and the appearance of the metalation mixture was unchanged after sixty-eight hours of stirring. The carbonation mixture was acidified with dilute hydrochloric acid, and the organic layer was extracted with 60 ml. of 5 per cent sodium hydroxide solution. A white precipitate which developed during the extraction was retained in the aqueous phase. The organic layer was further extracted with two 30-ml. portions of water, and the combined extracts were chilled and acidified with hydrochloric acid. The resulting precipitate was filtered off, washed with water and dried to yield 2.91 g. (36.8 per cent) of 2,4,6-triphenylbenzoic acid, m.p. 251-252°. A mixed melting point with an authentic specimen was not depressed.

Ring Closure Reactions of Ethers

Trityl methyl ether

Reaction with phenyllithium followed by hydrolysis. A solution of 10 g. (0.036 mole) of trityl methyl ether and 0.073 mole of phenyllithium in 60 ml. of ether was distilled under nitrogen until the residue was syrupy. Sixty ml. of toluene was added, and the resulting brown suspension was refluxed for twenty-four hours. A scarlet color and precipitate appeared shortly after refluxing began. The mixture was hydrolyzed with iced, dilute sulfuric acid. The organic layer was separated and freed of solvent by distillation. The residual brown syrup was refluxed with 35 ml. of 95 per cent ethanol. Not all of the material dissolved, and the portion that did not dissolve became crystalline. The mixture was cooled, and the yellow solid was filtered off, washed with a large volume of cold 95 per cent ethanol, and dried to give 6.28 g. (71 per cent crude yield) of crystalline product, m.p. 120-130°. The filtrate and washings from the ethanol treatment were used as a recrystallization solvent for the crude product. This operation yielded 4.50 g. of somewhat lighter-colored material, m.p. 146-147°). A mixed melting point with an authentic specimen was not depressed. The filtrate from the second ethanol treatment, on partial evaporation, deposited an additional 0.72 g., bringing the total yield of pure material to 3.02 g. (34 per cent).

Reaction with phenyllithium followed by carbonation. The amounts and procedure in this reaction were the same as those used in the reaction followed by hydrolysis, except that the scarlet mixture was carbonated by pouring over a slurry of Dry Ice and ether. The carbonation mixture was hydrolyzed with ice water, and the water layer was separated and carefully acidified with iced hydrochloric acid to yield a gummy precipitate which solidified on standing. The solid acid was filtered off, washed with water, and dried to give 6.0 g. of white powder, m.p. 170-179° with sintering at 160°. The crude product was refluxed for two hours with 10 ml. of ether to yield, after cooling and filtration, 2.48 g. (23.7 per cent crude yield) of solid, m.p. 189-193°d. Final purification was effected by dissolving the product in the minimum amount of benzene at room temperature, filtering to remove a trace of suspended material, and diluting the filtrate with a twofold volume of petroleum ether (b.p. 60-70°). The resulting solution deposited well-formed crystals after standing for several hours at room temperature. These were filtered off, washed with petroleum ether (b.p. 60-70°) and dried to yield 1.36 g. (13.0 per cent) of 9-phenylfluorene-9-carboxylic acid, m.p. 192-193°. A mixed melting point with an authentic specimen was not depressed.

When boiling water was used instead of ether in the purification of the crude carbonation product, only

9-phenylfluorene was isolated. The thermal decarboxylation of this acid on being heated in the dry state has been noted by others.[19]

Reaction with n-butyllithium followed by hydrolysis. Run I. A solution of 13 g. (0.0475 mole) of trityl methyl ether and 0.14 mole of n-butyllithium in 150 ml. of ether was refluxed for twenty-four hours. The resulting scarlet mixture was hydrolyzed with ice water, and the ether layer was separated and evaporated to yield tarry yellow crystals, m.p. 76-125°. The crude product was dissolved in petroleum ether (b.p. 60-70°) and chromatographed on alumina, using benzene to elute the column. Of the twenty-four fractions collected, only the twelfth and the thirteenth showed any appreciable crystalline residue on removal of the solvent. These fractions were combined and digested with 95 per cent ethanol to yield 1.96 g. (20 per cent) of 9-phenylfluorene, m.p. 145-147°, identified by a mixed melting point with an authentic specimen.

Run II. A solution of 12.3 g. (0.045 mole) of trityl methyl ether and 0.91 mole of n-butyllithium in 100 ml. of ether was distilled under nitrogen until most of the solvent had been removed. A red color and precipitate developed during this operation. Ninety ml. of toluene was added to the residue, and the resulting mixture was refluxed for twenty-four hours and then hydrolyzed with iced dilute sulfuric acid. The organic layer was separated, and the solvent was removed by distillation to leave a dark-brown syrupy residue. This material, and the fractions subsequently obtained from it, were exceptionally difficult to purify. The crude product yielded tarry crystals on treatment with benzene; an additional crop was obtained by evaporating the benzene filtrate and triturating the residual material with a mixture of acetone and chloroform. The combined crystals (3.1 g., m.p. 123-131°) were dissolved in benzene and chromatographed on alumina, using benzene as an eluent. Of the ten fractions so obtained, only the second, third, fourth, fifth and sixth gave solid residues when the solvent was removed. These fractions were combined and recrystallized from a mixture of benzene and 95 per cent ethanol to yield 1.91 g. (17.5 per cent crude yield) of yellow solid, m.p. 128-139°. This material was dissolved in methanol, and the solution was refluxed with Norit A and filtered. The filtrate was evaporated to leave a yellow residue, which was dissolved in benzene and chromatographed on alumina, using petroleum ether (b.p. 60-70°) to elute the column. Several fractions from the earlier part of the elution gave semicrystalline residues on removal of the solvent. These were combined and extracted with 10 ml. of boiling methanol. The undissolved material was filtered off, washed with a little cold methanol, and dried to yield 0.40 g. (3.98 per cent) of 9-phenylfluorene, m.p. 145-147°. A mixed melting point with an authentic specimen was not depressed.

Reaction with n-butyllithium followed by carbonation. A solution of 10 g. (0.036 mole) of trityl methyl ether and 0.036 mole of n-butyllithium in 60 ml. of ether was refluxed for twenty-four hours and then carbonated in the usual manner. A deep purple color appeared immediately when the reaction mixture was poured into the Dry-Ice-ether slurry. After evaporation of the Dry Ice, the mixture was hydrolyzed with water, and the aqueous layer was separated and acidified to produce a tarry orange precipitate. This was extracted by shaking the acidified mixture with ether, and the ether extract was evaporated to leave a tarry residue which, on standing for several days at room temperature, changed into a purple semicrystalline solid. The crude product was dissolved in benzene and the resulting solution was treated with approximately an equal volume of petroleum ether (b.p. 60-70°). The mixture was filtered to remove a small amount of tarry solid which precipitated when the petroleum ether was added, and the filtrate was evaporated to yield a dark-colored syrup which, on being triturated with 95 per cent ethanol, deposited colorless crystals. These were filtered off, washed with cold 95 per cent ethanol, and dried to yield 1.77 g. (18.2 per cent) of 3,3-diphenylphthalide, m.p. 117.5°-118.5°. A mixed melting point with an authentic specimen showed no depression, and the infrared absorption spectrum of a carbon disulfide solution of the product was identical with that of an authentic specimen.[215]

Reaction with benzylmagnesium chloride. Ten g. (0.036 mole) of trityl methyl ether was treated with 0.072 mole of benzylmagnesium chloride in 50 ml. of ether. The solvent was removed by distillation, and 60 ml. of toluene was added to the syrupy residue. The resulting mixture was refluxed for twenty-four hours. There was no color change from the time of mixing the reactants to the end of the reaction period. The mixture was hydrolyzed with iced dilute hydrochloric acid, and the organic layer was separated and evaporated to yield a semisolid yellow mass. The cryde product was triturated with petroleum ether (b.p. 60-70°) to yield colorless crystals. After being filtered off, washed with cold petroleum ether (b.p. 60-70°) and dried, the product weighed 2.65 g. (21.8 per cent crude yield), and melted over the range 130-139°. Purification was effected by dissolving the product in the minimum amount of warm benzene and adding a twofold volume of petroleum ether (b.p. 60-70°). The resulting solution, after standing for several hours at room temperature, deposited well-formed crystals which were freed

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[215] The author is grateful to Dr. V. A. Fassel and to Messrs. Marvin Margoshes and Richard Hedges for the infrared absorption studies reported in this dissertation.

from the supernatant liquors by decantation. The yield of pure 1,1,1,2-tetraphenylethane, m.p. 141.5-143°, was 14.3 per cent. A mixed melting point with an authentic specimen was not depressed.

Reaction with t-butylmagnesium chloride. The method of Whitmore and Badertscher[216] was employed for the preparation of t-butylmagnesium chloride. Thirty-seven g. (0.40 mole) of t-butyl chloride was used, and the yield of Grignard reagent was 67 per cent.

Ten g. (0.036 mole) of trityl methyl ether was dissolved in a solution of 0.072 mole of the Grignard reagent, and the solvent was distilled from the mixture until the residue was syrupy. Sixty ml. of toluene was added, and the resulting suspension was refluxed for twenty-four hours. No color change was noticed during the reaction period. The mixture was hydrolyzed with iced dilute hydrochloric acid, and the organic layer was separated and evaporated to leave a pasty residue. This was triturated with petroleum ether (b.p. 60-70°) to yield colorless crystals, which were filtered off, washed with petroleum ether and dried. The crude product weighed 0.875 g. (7.4 per cent) and melted over the range 133-151°. The crystals were dissolved in the minimum amount of warm benzene, and the resulting solution was diluted with

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[216] F. C. Whitmore and D. E. Badertscher, J. Am. Chem. Soc., 55, 1550 (1933).

a twofold volume of petroleum ether (b.p. 60-70°). The crystals which deposited on chilling the solution were filtered off, washed with cold petroleum ether (b.p. 60-70°) and dried to yield 0.41 g. of material melting over the range 145-177°. Final purification was effected by refluxing the product with 10 ml. of methanol. The hot solution was decanted from a small amount of undissolved material and chilled to yield crystals which, after being filtered, washed with cold methanol and dried, weighed 0.060 g. (0.50 per cent) and melted at 190-191°. A mixed melting point with an authentic specimen of 1,1,1-triphenyl-2,2,2-trimethylethane was undepressed.

By concentration of the recrystallization liquors there was obtained 0.15 g. of impure crystalline material melting over the range 151-160°. This material was not further purified. Its infrared absorption spectrum indicated the absence of 9-phenylfluorene; the absorption maxima at 13.2μ and 13.4μ, characteristic of 9-phenylfluorene, were missing from the spectrum.

Reaction with phenylcalcium iodide (attempted). The procedure and molar amounts were identical with those used in the reaction of trityl methyl ether with *t*-butylmagnesium chloride described above.[217] The dark-colored organic layer

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[217] The phenylcalcium iodide used in this experiment was obtained in a preparation using half the quantities indicated on p. 101. The yield of phenylcalcium iodide was 20 per cent.

from the hydrolysis was heated with Norit A, filtered, and evaporated to yield a dark tar. No crystals could be obtained from the crude product by treatment with petroleum ether (b.p. 60-70°), 95 per cent ethanol, or methanol. When the tarry material was dissolved in glacial acetic acid and the solution was allowed to evaporate slowly, some semi-crystalline material was deposited. The mixture was filtered, and the residue (a tar containing some crystalline product) was repeatedly pressed between pieces of filter paper to remove as much of the tar as possible. This treatment yielded sticky brown crystals. The product was dissolved in boiling methanol, and the solution was refluxed with Norit A and filtered while hot. The cooled filtrate deposited only a tar. When the solvent was removed from the filtrate and the residue was triturated with a little benzene, a very small amount of crystalline material deposited. The benzene was decanted off, and the solid was recrystallized from methanol to yield a trace (about 5 mg.) of impure triphenylcarbinol, m.p. 156-159°. A mixed melting point with an authentic specimen had the value of 157-160°.

The recrystallization liquors were evaporated to leave a brown semisolid whose infrared absorption spectrum suggested that 9-phenylfluorene was present. The spectrum showed the characteristic absorption maxima at 13.2 and 13.4μ. However, attempts to purify the material by recrystallization from methanol yielded only tars.

Reaction of trityl phenyl ether with *n*-butyllithium

Six and fifty-three hundredths g. (0.02 mole) of trityl phenyl ether was treated with a solution of 0.04 mole of *n*-butyllithium in 40 ml. of ether. A yellow color developed immediately when the reagents were mixed. After fifteen minutes of refluxing, the mixture had become red. The trityl phenyl ether did not all dissolve at once, but after eight hours of refluxing the system had become homogeneous. Refluxing was continued for twenty-four hours, and the mixture was then hydrolyzed with dilute hydrochloric acid. Both layers from this treatment were nearly colorless. The ethereal phase was separated, extracted with dilute sodium hydroxide solution and then with water, and finally dried over sodium sulfate. The dry solution was evaporated to yield a yellow tar which had a faint odor of phenol, and which yielded no crystalline product when triturated with methanol or with 95 per cent ethanol. The tar was dissolved in benzene, and petroleum ether (b.p. 60-70°) was added to the solution. No solid was deposited. The solution was chromatographed on alumina; petroleum ether (b.p. 60-70°) was used to elute the column. All of the fractions so obtained yielded only tarry products on removal of the solvent. Treatment of the tars with methanol yielded no crystals.

9-Phenyl-9-fluorenyl methyl ether

Reaction with phenyllithium. Two g. (0.0074 mole) of 9-phenyl-9-fluorenyl methyl ether was dissolved in a solution of 0.05 mole of phenyllithium in 50 ml. of ether. The solvent was distilled off and 50 ml. of toluene was added to the orange residue. The resulting mixture was refluxed for twelve hours, at the end of which time a dark-red color and precipitate had appeared. The mixture was hydrolyzed with iced dilute sulfuric acid, and the organic layer was separated and freed of solvent to leave a dark, semisolid residue. The crude product was refluxed with 150 ml. of 95 per cent ethanol, and the solution was decanted from undissolved material. No solid deposited when the ethanolic extract was cooled. The extract was evaporated, and the residue was dissolved in a mixture of benzene and petroleum ether (b.p. 60-70°). The solution was filtered to remove a little undissolved material, and the filtrate was evaporated to yield a mixture of tar and crystals. The crystals were separated by hand, washed with a small amount of benzene, and dried to yield 0.180 g. (10.2 per cent) of 9-phenylfluorene, m.p. 144.5°. The product was identified by a mixed melting point with an authentic specimen, and by comparison of the infrared absorption spectrum with that of an authentic specimen.

The material which was left undissolved by the treatment with 95 per cent ethanol was taken up in 15 ml. of warm glacial acetic acid, and 30 ml. of 95 per cent ethanol was added to the solution. A very small amount of brown solid precipitated. This was filtered off and dried to yield 8 mg. of sandy material. The product charred over the range 380-400°, but exhibited no further change on being heated to 450°. The infrared absorption spectrum of this material was somewhat similar to that of 9-phenylfluorene; both compounds showed absorption maxima in the vicinity of 13.2μ, 13.4μ, and 14.3μ.

Reaction with n-butyllithium. Thirteen and six-tenths g. (0.05 mole) of 9-phenyl-9-fluorenyl methyl ether was mixed with a solution of 0.10 mole of n-butyllithium in 100 ml. of ether. An orange color developed immediately on mixing the reagents. The mixture was refluxed for twenty-four hours, during which time a brick-red color and precipitate had appeared. The mixture was hydrolyzed with iced hydrochloric acid, and the brown ethereal layer was separated and evaporated. The brown solid residue was refluxed with 150 ml. of 95 per cent ethanol, and the hot solution was filtered to remove a small amount of undissolved material. The residue weighed 20 mg. and melted at 272-273° with decomposition. This product was not examined further. The ethanolic filtrate was chilled in an ice-salt bath, and the solid material which deposited was filtered off and washed with cold methanol to yield 6.75 g. (49.6 per cent recovery) of 9-phenyl-9-

fluorenyl methyl ether, m.p. (and mixed m.p.) 92-93°. The filtrate from this treatment was decanted from a small amount of sandy material which had deposited on standing, and the decantate was evaporated. The tarry residue was dissolved in benzene, and petroleum ether (b.p. 60-70°) was added to the solution. The chilled mixture deposited clusters of needles which were separated and washed with cold petroleum ether (b.p. 60-70°) to yield 0.950 g. (8.3 per cent) of 9-phenylfluorene, m.p. 144-145°. A mixed melting point with an authentic specimen was not depressed.

Reaction of benzopinacol diphenyl ether with phenyllithium

To a suspension of 1.0 g. (0.0019 mole) of benzopinacol diphenyl ether in 10 ml. of toluene was added 3.3 ml. (0.004 mole) of a 1.2 molar solution of phenyllithium in ether. The mixture was refluxed for twenty-four hours, at the end of which time a red-orange color had developed. The mixture was hydrolyzed with water, and the layers were separated. The odor of phenol was noticed in the aqueous layer. By concentration of the organic phase there was obtained 0.450 g. of crystalline orange material which melted over the range 205-215°, with sintering at 190°. Recrystallization from benzene did not change the melting range of the orange material; however, the benzene filtrate deposited 0.18 g. of white powder which melted at 173-175° with yellowing at 150° and sintering at 170°. This product was quite insoluble in boiling absolute ethanol. Neither of the products was identified. Infrared absorption spectra showed that both of the products were different from the starting material, and also from ditrityl peroxide. The spectrum of the orange product was different from that of dibiphenyleneethylene.

Miscellaneous Metalations

Metalation of benzothiazole with *n*-butylmagnesium bromide

At -60° (attempted). A solution of 0.1 mole of *n*-butylmagnesium bromide in 65 ml. of ether was stirred at -60° while a solution of 13.5 g. (0.10 mole) of benzothiazole in 50 ml. of ether was added over a period of ten minutes. The mixture was then stirred at -60° for one-half hour and then carbonated in the usual manner. After the Dry Ice had evaporated, the carbonation mixture was hydrolyzed with dilute hydrochloric acid. The ethereal phase was separated and extracted with two portions of dilute potassium hydroxide solution, and then with water. The combined extracts were acidified with hydrochloric acid. A liquid having the odor of valeric acid separated at this point. Evaporation of the liquid acid left no solid residue.

The same results were obtained from a reaction carried out under conditions similar to the one above except that the Grignard reagent was added to the benzothiazole.

At 0°. The amounts of reagents were the same as those used in the reaction at -60°. The system was cooled to 0° in an ice-salt bath, and the benzothiazole solution was added over a period of fifty minutes. The mixture was further stirred for ten minutes, and then carbonated and worked up as described above. Again, only a liquid acidic product having the odor of valeric acid was isolated. However, when the acidic liquors from the hydrolysis of the carbonation mixture were allowed to stand at room temperature for four days, a precipitate was formed. This was filtered off, washed with water and dried to yield 0.450 g. (3.4 per cent crude yield) of brown powder, m.p. 306° with preliminary sintering at 160°. Recrystallization from toluene yielded 0.220 g. (1.6 per cent) of bis-2-benzothiazolyl, m.p. 309-310°. A mixed melting point with an authentic specimen was not depressed.

At 20-25°. A flask containing 0.1 mole of *n*-butylmagnesium bromide in 60 ml. of ether was cooled to 20° in a water bath. The contents were stirred while a solution of 13.5 g. (0.1 mole) of benzothiazole in 50 ml. of ether was added over a period of twenty minutes. A blue Color Test I was obtained ten minutes after complete addition of the benzothiazole solution. After 40 minutes of continued stirring at 20-25°, the mixture showed a green Color Test I. Carbonation was effected in the usual manner, and the carbonation mixture was worked up as in the reactions described above. Acidification of the alkaline extract produced a yellow precipitate which was filtered off, washed with water and dried to yield 0.45 g. (2.5 per cent) of solid melting at 98-99° with decomposition. This product was probably benzothiazole-2-carboxylic acid. It decomposed after standing at room temperature for several weeks, yielding a liquid having the odor of benzothiazole.[218]

Metalation of triphenylamine with phenylcalcium iodide (attempted). A solution of 12.2 g. (0.05 mole) of triphenylamine and 0.10 mole of phenylcalcium iodide[219] in 120 ml. of ether was stirred at room temperature for fifty-six hours and then carbonated in the usual manner. After the Dry Ice had evaporated, the mixture was hydrolyzed with water. The mixture was filtered to remove a considerable amount of solid which did not dissolve in either layer. The ethereal phase was separated and evaporated to give a semisolid residue which, when shaken with ether, yielded 5.87 g. of triphenylamine, m.p. and mixed m.p., 124-127°. By partial evaporation of the ether extract there was obtained an additional 1.26 g.

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[218] Decomposition of this type was observed in an authentic sample of benzothiazole-2-carboxylic acid which had been stored in a closed container at room temperature.

[219] The procedure for the preparation of the phenylcalcium iodide used in this experiment was essentially that given on p. 101, except that only three-tenths of the specified amount of each reagent was used. The yield was 55 per cent.

of triphenylamine, bringing the total recovery to 7.13 g. (58.5 per cent).

The solid material which had been filtered from the carbonation hydrolyzate was allowed to stand in contact with a mixture of 1:1 hydrochloric acid and benzene until all of the solid had dissolved. The benzene layer was extracted with sodium hydroxide solution. A brown precipitate which appeared during the extraction was retained with the benzene layer. The alkaline extract was acidified, and the resulting green precipitate was filtered off. The crude product, without further drying, was recrystallized from glacial acetic acid to yield about 10 mg. of dark-green powder melting over the range 130-160°, with apparent decomposition. A second recrystallization from acetic acid did not alter the melting range.

The brown precipitate which had been retained with the benzene layer was filtered off and shaken with a mixture of hydrochloric acid and benzene. All the precipitate dissolved, and the benzene layer became green. Separation of the benzene layer and evaporation of the solvent left 0.10 g. of a greenish black residue which sintered at 170° and was apparently completely melted by 195° (the upper end of the melting range was difficult to determine). The infrared absorption spectrum of this material showed the expected carbonyl absorption maximum at 5.9μ, but there were no other strong maxima, and it was not possible to determine from the spectrum whether diphenyl-3-carboxyphenylamine was present in the mixture. The solid was refluxed with 6 ml. of glacial acetic acid, and the mixture was filtered hot to remove a considerable amount of suspended material. The cooled filtrate deposited a green solid which was filtered off and dried. It weighed 2 mg. and melted over the range 220-260°. The amount isolated was not sufficient for further purification.

Dibenzothiophene-5-dioxide

Metalation with phenylcalcium iodide (attempted). This reaction was modeled after the metalation of the dioxide with n-butyllithium described by Esmay. A suspension of 10.8 g. (0.05 mole) of dibenzothiophene-5-dioxide in 400 ml. of ether was stirred at -30°, and a solution of 0.1 mole of phenylcalcium iodide[220] in 120 ml. of ether was run into the suspension over a period of forty-five minutes. Stirring at -30° was continued for six hours after all the phenylcalcium iodide had been added, and the mixture was then carbonated in the usual manner. After evaporation of the Dry Ice, the carbonation mixture was hydrolyzed with iced dilute hydrochloric acid. The layers were separated, and a white solid which did not dissolve was retained with the aqueous layer. The ethereal solution was extracted with two 25-ml., portions of 10 per cent

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[220] Prepared in 66 per cent yield by the procedure given on p. 101.

potassium hydroxide solution and then with 30 ml. of water. The combined extracts were chilled and acidified with hydrochloric acid, and the resulting brown precipitate was filtered off and washed with water. It was a tarry semisolid. The crude product was extracted with boiling water to remove benzoic acid. This treatment left a small amount of dark-colored tarry residue undissolved. The residue was extracted in a Sohxlet apparatus with petroleum ether (b.p. 60-70°). The yellow extract so obtained was shaken with a 10 per cent solution of potassium hydroxide and then with water. The combined aqueous extracts were acidified with hydrochloric acid. Only a slight turbidity was observed on acidification.

The material which was retained with the aqueous layer from the hydrolysis of the carbonation mixture was filtered off, washed with water and dried to yield 9.1 g. of recovered dibenzothiophene-5-dioxide, identified by a mixed melting point with an authentic specimen. Evaporation of the ethereal layer yielded an additional 0.90 g. of the dioxide, bringing the total yield of recovered starting material to 10.0 g. (93 per cent).

<u>Metalation with n-butylmagnesium bromide (attempted)</u>. <u>Run I</u>. To a suspension of 5.8 g. (0.025 mole) of dibenzothiophene-5-dioxide in 200 ml. of ether was slowly added a solution of 0.05 mole of <u>n</u>-butylmagnesium bromide in ether. The mixture was stirred at room temperature for eleven hours

after the Grignard reagent had been added, and was then carbonated in the usual fashion. After evaporation of the Dry Ice, the carbonation mixture was hydrolyzed with iced dilute hydrochloric acid. The layers were separated, and a white solid insoluble in either layer was retained with the aqueous phase. The ethereal layer was extracted with two portions of a 10 per cent solution of sodium hydroxide and then with water. The combined extracts were chilled and acidified with hydrochloric acid. A liquid having the odor of valeric acid separated from the solution. When the acidic liquid product was evaporated, only a very slight, tarry residue remained. This residue was not further identified. The white solid which was retained with the aqueous phase from the hydrolysis of the carbonation mixture was filtered off, washed with water and dried to yield 3.35 g. of dibenzothiophene-5-dioxide, m.p. 232-234°. A mixed melting point with an authentic specimen was not depressed. Evaporation of the ethereal solution left a residue of crystalline material which melted diffusely around 220°, with preliminary sintering at 100°. This material was recrystallized from 95 per cent ethanol to yield an additional 0.45 g. of dibenzothiophene-5-dioxide, bringing the total yield of recovered material to 3.80 g. (66 per cent). The filtrate from the ethanol recrystallization was evaporated, and the residue was thrice recrystallized from watered methanol to yield 0.075 g. (1.6 per cent) of dibenzothiophene, m.p. 96-97°. A mixed melting point with an authentic specimen was not depressed.

Run II. To a suspension of 5.8 g. (0.025 mole) of dibenzothiophene-5-dioxide in 200 ml. of di-n-butyl ether was added a solution of 0.075 mole of n-butylmagnesium bromide in ether. The mixture became warm during the addition, and a flocculent precipitate developed. A deep-blue Color Test I was obtained after complete addition of the Grignard reagent. The mixture was stirred at 100° for twelve hours. At the end of this time, a faint green Color Test I was obtained. The mixture was carbonated and worked up exactly as in Run I. No precipitate or turbidity resulted when the alkaline extracts were acidified. The recovery of dibenzothiophene-5-dioxide was 3.30 g. (57 per cent). Evaporation of the di-n-butyl ether left a light-brown residue which was recrystallized from watered methanol to yield 0.70 g. (15.2 per cent) of dibenzothiophene, m.p. 95-96°, identified by a mixed melting point with an authentic specimen.

Metalation of fluorene with lithium aluminum hydride (attempted)

In ether. A solution of 4.15 g. (0.025 mole) of fluorene and 0.95 g. (0.025 mole) of lithium aluminum hydride in 150 ml. of ether was stirred at room temperature for seventy-two hours. A light orange color had developed at the end of this period. The mixture was carbonated in the usual manner. After evaporation of the Dry Ice, wet ether was cautiously added to destroy unreacted lithium aluminum hydride. The mixture was then treated with hydrochloric acid. The ethereal layer was separated and extracted with a 5 per cent solution of sodium hydroxide. Acidification of the alkaline extract resulted only in the appearance of a slight turbidity. Evaporation of the ethereal solution led to a 99 per cent recovery of fluorene, identified by mixed melting point with an authentic specimen.

In ether-benzene. The amounts of fluorene and of lithium aluminum hydride were the same as those used in the previous experiment. One hundred ml. of a 1:1 ether-benzene solution was used as the solvent, and the mixture was refluxed for forty-eight hours. Carbonation was effected in the usual manner, and the mixture was worked up as in the previous experiment. Again, no acid was obtained. The recovery of fluorene was 97 per cent.

Metalation of 9-phenylfluorene with *n*-butyllithium[221]

A solution of 1.0 g. (0.0041 mole) of 9-phenylfluorene in 20 ml. of ether was treated with a solution of 0.01 mole of *n*-butyllithium in 10 ml. of ether. An orange color developed immediately, and heat was evolved. The solution was refluxed for five hours and then carbonated in the usual manner. After evaporation of the Dry Ice, the mixture was hydrolyzed with

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[221] For an analogous preparation of 9-phenylfluorene-9-carboxylic acid by the carbonation of 9-phenyl-9-fluorenylsodium, see reference 19, p. 98.

ice water, and the aqueous layer was separated and acidified with hydrochloric acid. The resulting suspension was allowed to stand for several hours at room temperature until the precipitated acid had coagulated. The mixture was filtered, and the residue was washed repeatedly with water and dried to yield 0.940 g. (79.6 per cent) of 9-phenylfluorene-9-carboxylic acid, m.p. 189-190.5°d. The melting points given for this acid in the literature range between 183°d[222] and 193°d.[19]

Mercuration of 2-methoxynaphthalene

With mercuric nitrate at room temperature. Two hundred ml. of 5 M sodium nitrate solution was saturated with mercuric nitrate, and 10 g. (0.063 mole) of 2-methoxynaphthalene was added. The solution was stirred at room temperature. Samples were withdrawn at frequent intervals and tested for mercuric ion by treatment with alkali. After three days, the alkali test became weak. The mixture was filtered, and the residue was washed with four portions of water and dried to yield 18.4 g. (65 per cent crude yield) of a brown powder containing some lighter-colored crystals. The product was shaken with 100 ml. of ether, filtered, washed with two portions of ether, and dried to yield 12.4 g. (48 per cent) of buff-colored powder, m.p. 143-146°d.

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[222] D. Vorländer and A. Pritsche, *Ber.*, *46*, 1793 (1913).

Anal.[223] Calcd. for $C_{11}H_9HgNO_4$: Hg, 48.0. Found, Hg, 47.9, 47.6.

With mercuric nitrate at 100° (attempted). The same amounts of reactants were used as in the room-temperature reaction, but the mixture was stirred on a steam bath. After one-half hour, the mixture had become black, and gave a very weak response in the test for mercuric ion. The mixture was cooled and filtered to give a black tar and a yellow filtrate. The filtrate, on treatment with sodium chloride, yielded a copious white precipitate of inorganic material which blackened when treated with ammonium hydroxide, indicating the presence of mercurous ion in the original filtrate. No attempt was made to work up the black tar, which was presumably the product of oxidation of 2-methoxynaphthalene by mercuric nitrate.

Bromination of 2-methoxy-1-naphthylmercuric nitrate

Four and two-tenths grams (0.01 mole) of the product of

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[223] The sample was decomposed by the method of Schulek and Floderer,[224] and titrated by the method of Kolthoff and Stenger.[225]

[224] E. Schulek and S. Floderer, Z. anal. Chem., 96, 388 (1934).

[225] I.M. Kolthoff and V. A. Stenger, "Volumetric Analysis," Interscience Publishers, Inc., New York, N. Y., 1947, Vol. 2, p. 337.

the room-temperature reaction between 2-methoxynaphthalene and mercuric nitrate was suspended in carbon tetrachloride, and a solution of 1.8 g. (0.011 mole) of bromine in carbon tetrachloride was slowly dropped into the suspension, with stirring. The mixture was stirred for one-half hour after all the bromine solution had been added. At the end of this time, a test for bromine made with starch-potassium-iodide paper was very weak. The mixture was filtered, and the filtrate was washed with acidified sodium sulfite solution and then with water. Evaporation of the carbon tetrachloride left a light-brown residue which weighed 1.41 g. (59.4 per cent crude yield) and melted over the range 58-61°. The product was successively recrystallized from 95 per cent ethanol, aqueous methanol, and petroleum ether (b.p. 80-115°) to yield 0.20 g. (8.4 per cent) of 1-bromo-2-methoxynaphthalene, m.p. 78-81°. A mixed melting point with an authentic specimen showed no depression.

Iodination of 2-methoxy-1-naphthylmercuric nitrate

To a suspension of 4.2 g. (0.01 mole) of 2-methoxy-1-naphthylmercuric nitrate in carbon tetrachloride was slowly added a solution of 2.54 g. (0.01 mole) of iodine in carbon tetrachloride. The mixture was stirred during the addition. The iodine was taken up quite rapidly; immediately after complete addition of the iodine solution, the mixture was colorless. Stirring was continued for fifteen minutes more; then the mixture was filtered and the residue was washed with carbon tetrachloride. The combined filtrate and washings were freed of solvent to yield 2.7 g. (94 per cent) of light yellow crystals, m.p. 84-88°. The melting point of 1-iodo-2-methoxynaphthalene is given in the literature as 88°.[226]

Mercuration of 2-methoxynaphthalene by mercuric bisulfate (attempted)

In a one-liter flask equipped with a stirrer was placed 39.5 g. (0.1 mole) of mercuric bisulfate and a solution of 108 ml. of concentrated sulfuric acid in 430 ml. of water. Most of the mercuric salt dissolved after a few minutes of stirring. 2-methoxynaphthalene (15.8 g., 0.1 mole) was added and the mixture was stirred for twenty-one days, at the end of which time a purple precipitate had formed. The mixture was filtered and the residue was washed with water. By titrating the filtrate with standard potassium thiocyanate solution, it was found that 92.8 per cent of the mercury originally present had disappeared from the solution. The solid product was washed twice with ether and dried to yield 58.1 g. of crystals. This material decomposed without melting when heated to redness. It was organic (flame test). Analysis showed a mercury content of 61.1 per cent, indicating a polymercurated product or mixture. When a suspension of the material in carbon tetrachloride was treated with iodine and stirred for sixteen hours, no

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[226] F. E. Ray and W. A. Moomaw, *J. Am. Chem. Soc.*, *55*, 3833 (1933).

fading of the iodine was observed, and evaporation of the filtered carbon tetrachloride left a negligible residue.

Mercuration of dibenzothiophene (attempted)

With mercuric nitrate at room temperature. In a solution made from 56 ml. (0.05 mole) of 0.89 M mercuric nitrate and 135 ml. of 7.4 M sodium nitrate was suspended 9.21 g. (0.05 mole) of dibenzothiophene. The mixture was stirred for twenty-one days and then filtered. The residue was washed with water and dried to yield 9.04 g. (98 per cent recovery) of dibenzothiophene. Titration of the filtrate with standard potassium thiocyanate showed that 98.3 per cent of the original amount of mercuric ion was still present.

With mercuric nitrate at 100°. A mixture of 56 ml. (0.05 mole) of 0.89 M mercuric nitrate, 100 ml. of water, and 100 g. of potassium nitrate was stirred on the steam bath until the system was homogeneous, and 18.4 g. (0.10 mole) of dibenzothiophene was added. Heating and stirring were continued for two and three-quarters days; at the end of this time, a thiocyanate titration of an aliquot showed that the concentration of mercuric ion in solution had fallen to one-fifth of its original value. The mixture was filtered, and the residue was washed with a large amount of water, dried, and extracted with boiling 95 per cent ethanol and then with ether to yield 8.75 g. of brown powder which decomposed without melting when heated to redness. A flame test indicated that the product was organic, but an infrared absorption spectrum showed no recognizable carbon-hydrogen bonds. The high mercury content of the product (59.6 per cent) indicated a polymercurated compound or mixture.

With mercuric bisulfate. A suspension of 9.21 g. (0.05 mole) of dibenzothiophene in 238 ml. of an aqueous solution containing 19.7 g. (0.05 mole) of mercuric bisulfate and 50 ml. of concentrated sulfuric acid was stirred for seven days at room temperature. Titration of an aliquot with potassium thiocyanate showed that only a negligible amount of mercuric ion had been consumed. The mixture was placed on a steam bath, and stirring was continued. After three days at the elevated temperature, the mercuric-ion content of the solution had fallen to one-fifth of its original value. The mixture was filtered, and the residue was washed with a large volume of water, dried, and extracted with three 100-ml. portions of ether. The resulting light-yellow powder weighed 19.9 g., and decomposed without melting when heated to redness. The infrared absorption spectrum of this material showed all the absorption maxima of dibenzothiophene, but no band corresponding to a carbon-mercury bond. The product may have been a complex of dibenzothiophene with mercuric bisulfate.

Metalation of thiophene with indium chloride (attempted)

Into a 125-ml. nitrogen-swept Erlenmeyer flask was weighed 4.06 g. (0.018 mole) of anhydrous indium chloride and 10.6 g.

(0.127 mole) of thiophene. The mixture was refluxed under nitrogen for ten hours. There was no evidence of reaction during this time; both the liquid and the solid phase remained unchanged in appearance. The mixture was then distilled under nitrogen from a steam bath. The thiophene was quantitatively recovered, and the weight of the solid was unchanged.

Miscellaneous Preparations and Reactions

Carbonation of 2,4,6-triphenylphenyllithium[227]

Using Dry Ice. One hundred ml. of a solution of 0.012 mole of 2,4,6-triphenylphenyllithium in 1:1 ether-benzene was poured over a slurry of Dry Ice and ether. After the Dry Ice had evaporated, the mixture was treated with dilute hydrochloric acid, and the organic layer was separated and extracted with two 70-ml. portions of 10 per cent sodium hydroxide solution. A heavy white precipitate which developed during the extraction was retained with the organic layer. This precipitate disappeared when the organic layer was extracted with water, but reappeared when the water extract was combined with the alkaline extracts. Acidification of the resulting mixture yielded a white solid, which was filtered off, washed with water, and

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[227] For an analogous preparation of 2,4,6-triphenylbenzoic acid by carbonation of the corresponding Grignard reagent, see E. P. Kohler and L. W. Blanchard, J. Am. Chem. Soc., 57, 367 (1935).

dried to yield 2.15 g. (53 per cent) of 2,4,6-triphenylbenzoic acid, m.p. 251-252° with preliminary sintering at 248°.

Using gaseous carbon dioxide. A carbon dioxide generator was made by introducing 850 g. of finely powdered Dry Ice into a 1-l. Erlenmeyer flask, which was then closed with a stopper carrying an outlet tube and allowed to stand for several hours in order to sweep out residual air. Into a second 1-l. Erlenmeyer flask which had been swept with nitrogen was introduced 100 ml. of a solution of 0.012 mole of 2,4,6-triphenylphenyllithium in 1:1 ether-benzene. One hundred ml. of ether was added, and the resulting solution was stirred for six and one-half hours while carbon dioxide from the generator was bubbled into the solution. From time to time during the carbonation, ether was added to replace solvent which had been swept out by the stream of carbon dioxide. The mixture was hydrolyzed and worked up exactly as in the low-temperature carbonation, to yield 2.55 g. (63 per cent) of 2,4,6-triphenylbenzoic acid, m.p. 252°.

Preparation of 1,3,5-triphenylbenzene[228]

A 2-l. flask containing 1130 g. (9.38 moles) of acetophenone was equipped with a condenser for downward distillation,

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[228] This preparation was essentially that of C. Engler and L. Dengler, Ber., 26, 1444 (1893). The authors reported a 45 per cent yield of 1,3,5-triphenylbenzene, but the temperature of reaction was not specified.

and heat was applied to the flask until the internal temperature reached 160°. Heating was continued for seventeen days. During this time the contents of the flask became dark brown, and a considerable amount of water was evolved. The mixture was distilled at the water pump until no more acetophenone came over. The syrupy residue was shaken with 600 ml. of 95 per cent ethanol, whereupon a yellow solid deposited. This was filtered and washed with cold 95 per cent ethanol to give 171 g. (17.8 per cent crude yield) of material melting at 169-171°. Purification was effected by refluxing the product with 1 l. of 95 per cent ethanol, cooling, and filtering to yield 156 g. (16.2 per cent) of almost-white powder, m.p. 171-174°.

Preparation of 2,4,6-triphenylbromobenzene[229]

A solution of 191 g. (0.623 mole) of 1,3,5-triphenylbenzene in 1400 ml. of carbon disulfide was treated with 210 g. (1.3 moles) of bromine. The solution was allowed to stand at room temperature for twenty hours and was then poured into 2700 ml. of methanol. The solvent was removed by

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[229] This preparation followed the procedure of Kohler and Blanchard,[227] who reported a 91 per cent yield. They used methanol alone as the recrystallization solvent. It was found in the present study that the bromo compound was not appreciably soluble in boiling methanol, and that a benzene-methanol mixture was more convenient for recrystallization because of the smaller volume of solvent required.

careful distillation, and the residue was washed with methanol to give 211 g. (87.7 per cent crude yield) of almost colorless material, m.p. 131-134°. Recrystallization from a mixture of benzene and methanol gave 193 g. (80.5 per cent) of white crystals, m.p. 133-134.5°.

Preparation of resorcinol dimethyl ether[230]

A solution of 154 g. (3.85 moles) of sodium hydroxide in 675 ml. of water was placed in a two-liter flask equipped with a stirrer, a nitrogen inlet, and a wide-throated solids funnel. After the flask had been thoroughly swept with nitrogen, 192 g. (1.74 moles) of resorcinol was introduced through the funnel, and the stirrer was started. The resorcinol dissolved almost immediately, with little coloration. The solids funnel was replaced by a dropping funnel containing 530 g. (4.20 moles) of freshly distilled dimethyl sulfate. The flask was cooled by immersion in cold water, and the dimethyl sulfate was added slowly, with stirring. The mixture was stirred at room temperature for three hours after addition was complete. The organic layer was separated and distilled under reduced pressure to yield 167 g. (69.5 per cent) of colorless product, b.p. 104-107° (13 mm.).

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[230] See K. H. Slotta and H. Heller, Ber., 63, 3029 (1930). These authors reported a 90 per cent yield of the ether in a preparation starting with 400 g. of resorcinol. For stirring the reaction mixture, they employed a stream of nitrogen rather than mechanical agitation.

Preparation of dibenzothiophene-5-dioxide

The procedure followed in this preparation was essentially that of Esmay,[81] with slight simplifications in the apparatus. A 1-l. Erlenmeyer flask containing 40.0 g. (0.218 mole) of dibenzothiophene, 150 ml. of glacial acetic acid, and 124 ml. (1.20 moles) of 30 per cent hydrogen peroxide was equipped with a reflux condenser. The mixture was refluxed for one and one-half hours. The dibenzothiophene went into solution quickly, and a copious white precipitate deposited quite suddenly after eight minutes of refluxing. The mixture was cooled and filtered, and the residue was washed with glacial acetic acid and then with a large quantity of water, and dried in an oven at 100°. The yield of dibenzothiophene-5-dioxide was 45.5 g. (95.8 per cent), m.p. 233-234°.

Preparation of 9-phenyl-9-fluorenol[231]

To a solution of 0.73 mole of phenylmagnesium bromide in 300 ml. of ether was added portionwise, and with stirring, 100 g. (0.56 mole) of fluorenone. By the end of the addition, the mixture was almost solid, and consisted largely of white precipitate. The mixture was refluxed for one hour and allowed to stand overnight. Iced, dilute sulfuric acid was then added. The organic layer was separated, and the solvent was removed by distillation until the residue was viscous.

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[231] W. E. Bachmann, J. Am. Chem. Soc., 52, 3287 (1930).

Then 250 ml. of petroleum ether (b.p. 80-115°) was added, and the mixture was chilled in an ice bath. The white crystals which precipitated were filtered off, washed with a large amount of petroleum ether (b.p. 80-115°), and dried to yield 112.5 g. (77 per cent) of 9-phenyl-9-fluorenol, m.p. 106-107.5°.

In a preparation similar to the one described above, a lighter grade of petroleum ether (b.p. 28-39°) was used in working up the crude mixture. The product so obtained melted at 68-70°, with marked evolution of a gas which had the odor of this grade of petroleum ether. The product was not biphenyl; a mixed melting point with this material showed a large depression. When a weighed sample of the product was maintained at 100° for ten hours, it showed a 4.85 per cent loss of weight. That this material contained 9-phenyl-9-fluorenol was demonstrated by dissolving a sample in 100 per cent sulfuric acid and adding the resulting red solution slowly to cold methanol to precipitate 9-phenyl-9-fluorenyl methyl ether (identified by mixed melting point with an authentic specimen). The crystalline material melting at 68-70° was probably 9-phenyl-9-fluorenol containing petroleum ether of crystallization. The tendency of 9-phenyl-9-fluorenol to form solvated crystals with carbon tetrachloride and with benzene has been noted elsewhere.[232]

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[232] A. Kliegl, <u>Ber.</u>, <u>38</u>, 284 (1905).

Preparation of 9-chloro-9-phenylfluorene[19]

To a solution of 100 g. (0.388 mole) of 9-phenyl-9-fluorenol in 200 ml. of benzene was added 50 g. (0.64 mole) of acetyl chloride. The solution was saturated with hydrogen chloride gas, whereupon there was a darkening of color and marked evolution of heat. The mixture was then distilled at 100° under a pressure of 20 mm. until as much solvent as possible had been removed. The syrupy yellow residue was treated with 300 ml. of petroleum ether (b.p. 80-115°) and chilled in an ice-salt bath. The resulting precipitate was filtered off, washed with petroleum ether (b.p. 60-70°), and dried to yield 63.0 g. (59 per cent) of 9-chloro-9-phenylfluorene, m.p. 78-79°.

Preparation of 1,1,1,2-tetraphenylethane[233]

A solution of 5.6 g. (0.02 mole) of trityl chloride in 15 ml. of benzene was dropped slowly, and with stirring, into 20 ml. (0.025 mole) of a 1.3 M solution of benzylmagnesium chloride in ether. There was vigorous refluxing during the addition, and a yellow precipitate appeared. The mixture was refluxed for thirty minutes after all the trityl chloride had been added, and was then hydrolyzed with dilute hydrochloric

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[233] See M. Gomberg and L. H. Cone, *ibid.*, *39*, 1463 (1906). These authors reported a quantitative yield of crude product in a preparation starting from 1.33 moles of benzyl chloride.

acid. The organic layer was separated and evaporated to leave a residue of yellow crystals, which, after washing with petroleum ether (b.p. 60-70°), weighed 4.25 g. (64 per cent crude yield) and melted at 138-143°. The crude product was dissolved in warm benzene, and the solution was diluted with twofold volume of petroleum ether (b.p. 60-70°) and chilled in an ice bath. The resulting well-formed crystals were freed of solvent by decantation. The yield of pure material was 3.32 g. (49.7 per cent), m.p. 141.5-143°.

Preparation of 1,1,1-triphenyl-2,2,2-trimethylethane

The procedure of Hantzch and Meyer[234] was followed, except that trityl chloride was employed in place of the less readily accessible trityl bromide. A solution of 5.6 g. (0.02 mole) of trityl chloride in 40 ml. of ether was run fairly rapidly into a solution of 0.05 mole of *t*-butylmagnesium chloride in 30 ml. of ether. Vigorous heat evolution and the development of a precipitate were noticed during the addition. The mixture was refluxed for ten hours and then hydrolyzed with iced dilute hydrochloric acid. The organic layer was separated and freed of solvent, and the syrupy residue was triturated with petroleum ether (b.p. 60-70°) to yield 0.60 g. (10 per cent crude yield) of white crystals, m.p. 180-182° with preliminary sintering at 150°. The product

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[234] A. Hantzch and K. H. Meyer, *ibid.*, *43*, 336 (1910). These authors did not specify the yield of product.

was dissolved in the minimum amount of warm benzene, and the solution was diluted with a twofold volume of petroleum ether (b.p. 60-70°). Crystals were deposited when the solution was chilled to 10°. The product was filtered off, washed with cold petroleum ether (b.p. 60-70°) and dried to yield 0.27 g. (4.8 per cent) of 1,1,1-triphenyl-2,2,2-trimethylethane, m.p. 189-190°.

Preparation of trityl methyl ether

Using 100 per cent sulfuric acid.[235] Twenty grams (0.0768 mole) of triphenylcarbinol was dissolved in 60-120 g. of 100 per cent sulfuric acid (prepared by mixing sulfur trioxide with the calculated amount of 96 per cent sulfuric acid). The resulting orange solution was dropped slowly, and with stirring, into 300 ml. of methanol kept at 0° to -10° in an ice-salt bath. During the latter part of the addition, a white precipitate began to appear. Immediately after all of the triphenylcarbinol solution had been added, the mixture was poured into 1 l. of ice water and the resulting suspension was allowed to stand until the precipitate had coagulated. The mixture was filtered and the residue was washed with a large quantity of water and dried. The resulting crude material

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[235] H. A. Smith and R. J. Smith, J. Am. Chem. Soc., 70, 2400 (1948). These authors reported a 92 per cent yield of the ether in a preparation starting with 2 g. of triphenylcarbinol.

weighed 20-21 g. (95-100 per cent) and melted at 75-80°. The fresh crude product was white, but developed a yellow color on standing in the air for several hours. Recrystallization from methanol gave 16.5-18.5 g. (78.3-88 per cent) of colorless crystals, m.p. 83-84°.[236]

When the above procedure was modified by running the triphenylcarbinol solution fairly rapidly into stirred methanol kept at -30° in a Dry-Ice-acetone bath, the yield of recrystallized material (m.p. 81-83°) was 18.2 g. (86.0 per cent).

Using 96 per cent sulfuric acid. A solution of 50 g. (0.192 mole) of triphenylcarbinol in 100 ml. of concentrated sulfuric acid was dropped slowly, with stirring, into 750 ml. of methanol chilled in an ice-salt bath. After addition was complete, the mixture was poured into 2 l. of ice water and allowed to stand overnight. The precipitate was filtered off, washed with water, and dried to yield 52 g. (99 per cent) of crude product, m.p. 75-80° This material was refluxed with 150 ml. of methanol, and the mixture was cooled and filtered to yield 48 g. (91.3 per cent) of white crystals, m.p. 82.5-83.5°.

Preparation of 9-phenyl-9-fluorenyl methyl ether

From 9-phenyl-9-chlorofluorene.[237] Fifty g. (0.18 mole)

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[236] This was the lower-melting modification of the ether. See H. H. Hatt, J. Chem. Soc., 483 (1938).

[237] Reference 19, p. 202.

of 9-chloro-9-phenylfluorene was refluxed with 250 ml. of methanol for one and one-quarter hours. Most of the solid went into solution at once, and shortly afterward a heavy crystalline precipitate appeared. The mixture was chilled in an ice-salt bath, then filtered. The residue was washed with a little cold methanol and dried to yield 45.4 g. (92.3 per cent) of crystalline product, m.p. 93-94°.

From 9-phenyl-9-fluorenol. Twenty g. (0.078 mole) of 9-phenyl-9-fluorenol was treated with 110 g. of 100 per cent sulfuric acid. Most of the solid dissolved, with evidence of some charring. The resulting red solution was run fairly rapidly into 300 ml. of stirred methanol chilled in a Dry-Ice-acetone bath, at such a rate that the temperature never rose above -10°. After complete addition, the reddish solution was filtered through glass wool to remove lumps of dark-blue material, and the filtrate was poured into 100 ml. of ice water. The resulting mixture was stored overnight at -10° and then filtered. The filtration was sluggish, and required three hours. The residue was washed with water and dried to yield 10.1 g. (46 per cent crude yield) of dirty-gray material. This was refluxed with methanol, and the hot solution was decanted from a small amount of undissolved syrup and cooled to yield a dull-gray crystalline mass. Without drying, this material was refluxed with Norit A in 50 ml. of methanol, and the mixture filtered while hot. The filtrate was evaporated to a volume of about 10 ml. When this solution was chilled, crystals were deposited. Filtration and air-drying yielded 2.87 g. (13.1 per cent) of white product, m.p. 92-93.5°. A mixed melting point with an authentic specimen of 9-phenyl-9-fluorenyl methyl ether was not depressed.

Preparation of trityl phenyl ether[238]

A suspension of 4.0 g. (0.17 mole) of sodium hydride in 200 ml. of anhydrous ether was slowly treated with 20 g. (0.21 mole) of phenol. After the evolution of hydrogen had ceased, 25 g. (0.090 mole) of trityl chloride was added to the solution. Spontaneous refluxing occurred during the addition. The mixture was further refluxed for five hours, and then extracted with water and with dilute sodium hydroxide. Finally, it was shaken with a little 40 per cent potassium hydroxide to precipitate the insoluble potassium salt of the by-product, *p*-hydroxytetraphenylmethane. The mixture was filtered, and the filtrate was evaporated to yield a glass which, on being triturated with absolute ethanol, crystallized to a white solid. The solid was refluxed with 100 ml. of absolute ethanol, and the mixture was chilled and filtered. The residue was washed with 95 per cent ethanol and dried to yield 19.4 g. (64 per cent) of colorless crystals, m.p.

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[238] See the procedure given in reference 15. A 90 per cent yield of the ether was reported, but the proportion of reactants was not specified.

102-103°.

Preparation of benzopinacol diphenyl ether[239]

Five g. (0.0095 mole) of ditrityl peroxide was refluxed under nitrogen with 15 ml. of dry xylene. After ten minutes, all of the solid had dissolved. The solution was further refluxed for fifteen minutes and then cooled and filtered. The residue was washed with cold toluene and twice recrystallized from benzene to yield 1.20 g. (24 per cent) of white powder which sintered at 143° and gradually softened until it was completely melted at 210°. An infrared absorption spectrum showed the absence of unrearranged peroxide in the final product.

Preparation of methyl o-iodobenzoate

The preparation of this ester from the corresponding acid and methanol has been described.[240] The present synthesis was modeled after the procedure of Gomberg and Van Slyke for the preparation of methyl o-bromobenzoate.[241] One hundred g. (0.40 mole) of o-iodobenzoic acid was neutralized with concentrated aqueous sodium hydroxide, and the resulting

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[239] This preparation followed the procedure of H. Wieland, Ber., 44, 2550 (1911). The author did not report the yield of purified product.

[240] A. M. Kellas, Zeitschr. phys. Chem., 24, 244 (1897).

[241] M. Gomberg and D. D. Van Slyke, J. Am. Chem. Soc., 33, 531 (1911).

solution was evaporated to dryness. The residue was powdered in a mortar and mixed with 56 g. (0.45 mole) of freshly distilled dimethyl sulfate. The mixture was refluxed for three hours by means of a glass mantle set at 50-60 v., and then cooled and partitioned between water and ether. A little dark solid which failed to dissolve was retained with the aqueous phase. The ethereal layer was dried over sodium sulfate and then freed of solvent. The sweet-smelling residue was distilled at a pressure of 1 mm. After a small forerun, 74 g. (70.5 per cent) of product boiling at 103-107°/1 mm. was collected.

Preparation of 2-iodophenyldiphenylcarbinol (attempted)

The procedure devised by Gomberg and Van Slyke[241] for the synthesis of the corresponding bromo compound was employed. To a stirred solution of 0.60 mole of phenylmagnesium bromide in 300 ml. of ether was slowly added 74 g. (0.282 mole) of methyl o-iodobenzoate. The mixture was refluxed for twelve hours and then cooled and hydrolyzed by the slow addition of iced dilute sulfuric acid. The ethereal layer was separated and washed with sodium thiosulfate solution to remove traces of iodine. The solvent was then distilled off, and the orange liquid residue was steam-distilled to remove biphenyl. The residue from the steam distillation was dissolved in benzene, and petroleum ether (b.p. 60-70°) was added to the solution. Only tar was precipitated by this treatment. All the solvent was removed, and the residue was dissolved in hot petroleum ether (b.p. 80-115°) and refluxed for several hours with Norit A. The filtered solution again deposited tar on cooling. The crude product was dissolved in benzene and chromatographed on alumina, using benzene to elute the column. Except for a very small forerun of crystalline material, m.p. 183-185°, the fractions obtained from the chromatogram were tarry, and did not yield crystals on treatment with any of the common solvents. The crystalline product was apparently not 2-iodophenyldiphenylcarbinol. Its infrared absorption spectrum indicated the presence of ortho-disubstitution, but the absence of the hydroxyl group.

DISCUSSION

Metalations with Sterically Hindered Organolithium Compounds

In the studies with 2,4,6-triphenylphenyllithium, it was of interest to determine, first of all, whether this RLi was too sterically hindered to effect any metalation reactions. The reaction with thiophene was studied in this connection for two reasons. First, thiophene has been found to undergo metalation with unusual rapidity and in good yields with n-butyllithium.[71] Second, thiophene should exhibit no steric impediments on its own part toward a metalating agent. It was found that 2,4,6-triphenylphenyllithium metalated thiophene to yield, after carbonation, 46 per cent of 2-thenoic acid, thus indicating that the RLi could function as a metalating agent under favorable conditions. The reaction with 6-phenylphenanthridine was next investigated. Gilman and Nelson[49] had found that the reaction of this heterocycle with mesityllithium led to the formation of a compound whose nitrogen content and molecular weight indicated a bis-6-phenylphenanthridine. It was believed that the hindered mesityllithium had metalated 6-phenylphenanthridine, probably in the 5-position, and that the newly formed RLi, being less sterically hindered than mesityllithium itself, had added to the azomethine linkage of unreacted 6-phenylphenanthridine. It was found in the present investigation that the same bis-compound was produced from 6-phenylphenanthridine and 2,4,6-triphenylphenyllithium, but that the yield was considerably lower than in the reaction with mesityllithium. This supported the hypothesis that the bis-compound should be produced from the reaction of 6-phenylphenanthridine with a sterically hindered RLi, and suggested that, possibly for steric reasons, 2,4,6-triphenylphenyllithium acted more slowly upon the heterocycle than did mesityllithium.

The reaction of 2,4,6-triphenylphenyllithium with dibenzofuran led to substitution in the expected 4-position, but the yield of dibenzofuran-4-carboxylic acid was quite low.

In connection with the possible influence of steric hindrance on the position of substitution in metalation reactions, it was of particular interest to study the reaction of resorcinol dimethyl ether with mesityllithium and with 2,4,6-triphenylphenyllithium. The metalation of this ether by n-butyllithium[5,94] or by phenyllithium[94,95] has been found to take place in the rather hindered position between the two methoxyl groups. It was conceivable that a more sterically hindered RLi might not be able to remove a proton from this relatively inaccessible position, and that metalation in the 4-position might occur instead. However, it was found that both mesityllithium and 2,4,6-triphenylphenyllithium effected the metalation of the ether in the normal 2-position. The yield from the reaction with mesityllithium was moderately large (39.4 per cent), while that from the reaction with 2,4,6-triphenylphenyllithium was almost negligible (1.4 per cent). Seemingly the effect of steric hindrance in these reactions was simply to slow the normal metalation, without encouraging substitution in the less hindered 4-position of the ether.

The four organolithium compounds, phenyllithium, o-tolyllithium, mesityllithium and 2,4,6-triphenylphenyllithium, exhibit differing degrees of steric hindrance in the vicinity of the lithium atom, and it was of interest to study the possible effect of this hindrance on the speed of metalation of the weakly acidic hydrocarbons, fluorene and triphenylmethane. Although no attempts have been made to determine relative pK values for the four hydrocarbons, benzene, toluene, mesitylene and 1,3,5-triphenylbenzene, it may be safely estimated that all four hydrocarbons are considerably weaker acids than either fluorene or triphenylmethane. Neither the phenyl, the o-tolyl, the mesityl nor the 2,4,6-triphenylphenyl anion is stablized by any mode of resonance not present in the parent hydrocarbon, whereas the 9-fluorenyl and the trityl anion are highly stabilized. Accordingly, it was to be expected that, if the reaction between fluorene (or triphenylmethane) and the RLi derivative of any of the less strongly acidic hydrocarbons were allowed to proceed to equilibrium, almost complete metalation would result. Under these circumstances, any significant difference in the extent of reaction might be an index of steric hindrance.

Table 3 shows the data collected in the studies with fluorene and triphenylmethane. In the case of fluorene, all four RLi reagents effected metalation in yields exceeding 50 per cent, as estimated by the amount of fluorene-9-carboxylic acid isolated on carbonation of the reaction mixtures. However, the relative amounts of acid were not inversely proportional to the degree of steric hindrance present in the metalating agent. o-Tolyllithium gave a higher yield than phenyllithium, and 2,4,6-triphenylphenyllithium a higher yield than mesityllithium. In the case of the reaction with triphenylmethane, however, steric influences appeared to play a part. Both phenyllithium and o-tolyllithium reacted with this hydrocarbon to produce small amounts of triphenylacetic acid on carbonation. With mesityllithium, the development of a yellow color during the reaction suggested that metalation had occurred to some extent, but only mesitoic acid was isolated when the mixture was carbonated. With 2,4,6-triphenylphenyllithium, no color developed even when the reaction period was extended to almost three times the length employed with the other RLi reagents, and the only product of carbonation was 2,4,6-triphenylbenzoic acid. It was reasonable to expect that triphenylmethane, being more sterically hindered

Table 3

Metalation of Weakly Acidic Hydrocarbons by Various RLi Compounds

Hydrocarbon	Li Compound	Reaction Time, Hours	Yield of Metalation Product, Per Cent
Fluorene	Phenyl	24	78
Fluorene	o-Tolyl	24	84
Fluorene	Mesityl	24	53
Fluorene	2,4,6-Triphenylphenyl	24	65
Triphenylmethane	Phenyl	24	6
Triphenylmethane	o-Tolyl	24	8[a]
Triphenylmethane	Mesityl	24	0[b]
Triphenylmethane	2,4,6-Triphenylphenyl	68	0[c]

[a] A 30 per cent yield of o-toluic acid was also obtained.

[b] Only mesitoic acid (22 per cent yield) was isolated.

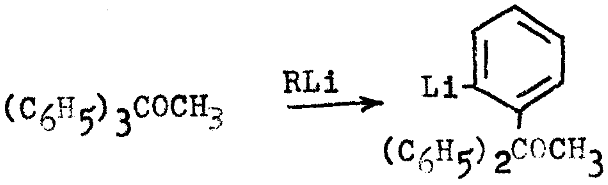
[c] Only 2,4,6-triphenylbenzoic acid was isolated.

in the vicinity of the active hydrogen, should be more sensitive toward differences in steric hindrance of the metalating agent than fluorene.

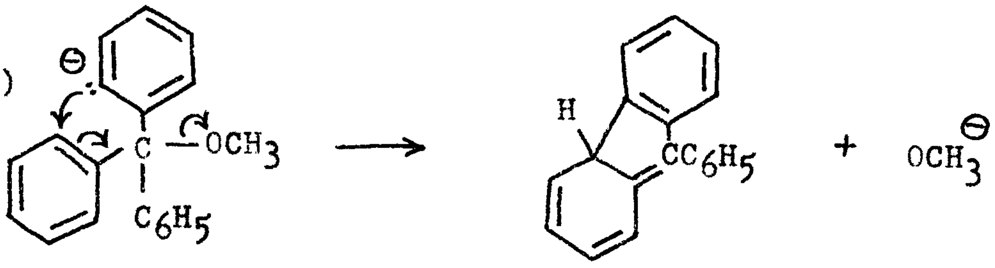
Ring Closure Reactions of Ethers

It was found in the present studies that the conversion of trityl methyl ether into 9-phenylfluorene could be made to occur not only under the conditions originally employed by Meikle (*i.e.*, using phenyllithium at elevated temperatures),[16] but also under milder conditions, using *n*-butyllithium. The highest pure yield (34 per cent) of 9-phenylfluorene was obtained in a reaction using two equivalents of phenyllithium with extended refluxing in toluene. An attractive mechanism for the reaction involves the following processes: (1) metalation of trityl methyl ether in one of the *ortho* positions; (2) nucleophilic attack by the resulting carbanion on an *ortho*-position of another phenyl group, with concomitant expulsion of a methoxide ion, to yield a quinoid intermediate; (3) removal of a proton from the quinoid intermediate, yielding the 9-phenyl-9-fluorenyl anion. Investigation of

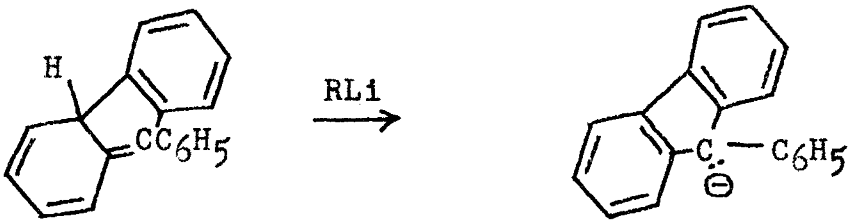
(1)


(C6H5)3COCH3
RLi
Li
(C6H5)2COCH3

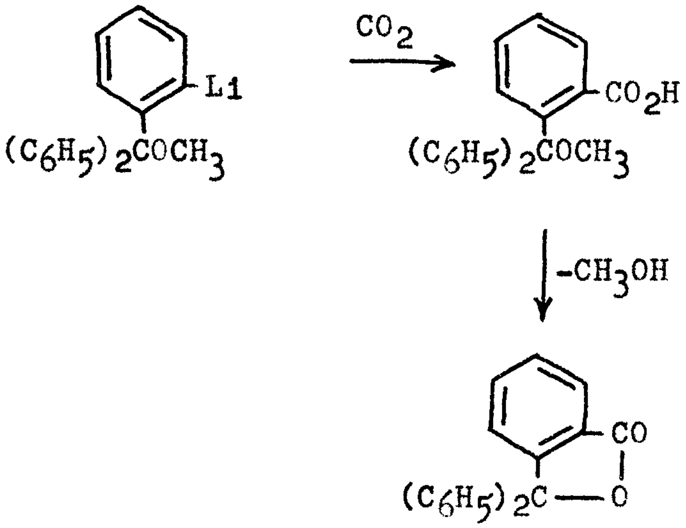
(2)


⊖
C
OCH3
C6H5
H
CC6H5
+
OCH3⊖

(3)


H
CC6H5
RLi
C
⊖
C6H5

the acids produced by carbonation of mixtures of the ether and phenyl- or n-butyllithium provided evidence that metalation did indeed occur. When a mixture of the ether with phenyllithium was carbonated after refluxing in toluene, the expected 9-phenylfluorene-9-carboxylic acid was isolated; but in the carbonation of a mixture of the ether with n-butyllithium which had been allowed to react under mild conditions, only 3,3-diphenylphthalide was produced. This lactone presumably arose through the loss of methanol from the initially formed 2-carboxyphenyldiphenylcarbinyl methyl ether, the derivative of ortho-metalated trityl methyl ether.[242]



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[242] The spontaneous loss of methanol from the analogous acid, o-carboxybenzyl methyl ether, has been reported. See S. N. McGeoch and T. S. Stevens, J. Chem. Soc., 1465 (1934).

Step 1 of the proposed mechanism is analogous to the previously reported reaction of triphenylcarbinol with n-butyllithium.[6,41] In the latter case, however, no ring closure was observed; i.e., the metalated product was stable, and showed no tendency to undergo a reaction analogous to Step 2. A possible explanation of the difference between the behavior of the metalated ether and the metalated carbinol lies in the fact that, in order to undergo ring closure, the metalated triphenylcarbinol molecule must expel the unstable lithoxide ion-pair.[243] Such an elimination is energetically much less favorable than the expulsion of methoxide in the case of the metalated ether molecule.

Reactions analogous to Step 2 of the postulated mechanism have also been reported. Fuson and co-workers have studied the reaction of sterically hindered diaryl ketones with RLi reagents, and reported in several cases the isolation of stable dihydro products, presumably from the ketonization of intermediate quinoidal enols.[13] The nucleophilic attack of the RLi compound on an ortho position of the ketone, accompanied by a shift of electrons from the phenyl group toward the carbonyl group, is quite similar to the nucleo-

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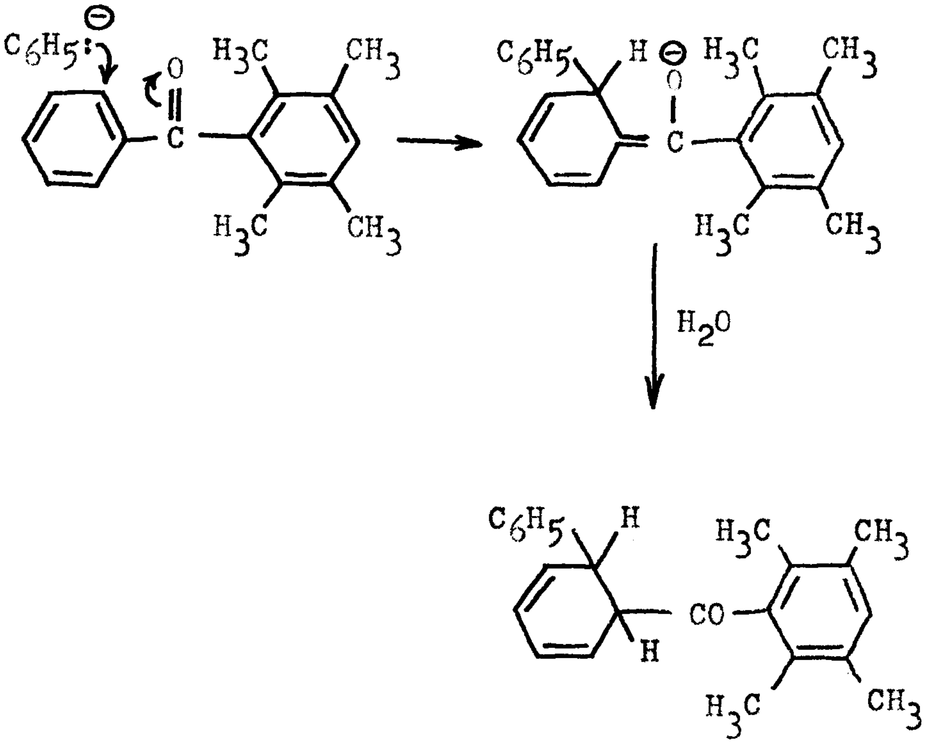
[243] For a discussion of the difficulty of elimination of metal-oxygen anions, and its implication in the reactions of silanediols, see G. E. Dunn, Doctoral Dissertation, Iowa State College, 1951.

philic attack, with its accompanying electron shift, which is postulated as constituting the second stage of the reaction of trityl methyl ether with RLi reagents.



It may be noted that the reaction of phenyllithium with triphenylmethoxysilane has been found to lead only to the normal displacement product, tetraphenylsilane, rather than to 9-phenyl-9-silicofluorene.[244] Several possible explanations for this difference between the behavior of trityl methyl

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[244] T. C. Wu, unpublished studies.

ether and that of its silicon analogue may be advanced. First, the covalent radius of silicon is larger than that of carbon, so that there should be fewer steric impediments against the production of tetraphenylsilane than against that of tetraphenylmethane. Second, it has been suggested that, in nucleophilic displacements on silicon, the Si atom may be able to expand its valence shell to accomodate ten electrons in the transition state, thus making possible an S_N2 reaction of a type which is forbidden in the carbon analogue.[245] Finally, even if triphenylmethoxysilane were to undergo ortho-metalation, the ring closure reaction would be unlikely to occur because it would require the creation of a silicon-to-carbon double bond. No compound containing a bond of this type has been prepared, and spectrophotometric studies on triarylsilyl compounds[246] have indicated that the triarylsiliconium ion, if it exists at all in solution, is not stabilized by structures involving such bonds.

In the light of Step 2 of the proposed mechanism for the ring closure of trityl methyl ether, it is possible to interpret certain earlier studies concerning the reaction of phenylmagnesium bromide with trityl chloride. Gilman and Jones reported the formation of diphenyl-p-xenylmethane,

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[245] C. G. Swain, R. M. Esteve and R. H. Jones, J. Am. Chem. Soc., 71, 965 (1949).

[246] H. Gilman and G. E. Dunn, ibid., 72, 2178 (1950).

triphenylmethane, and tetraphenylmethane in this reaction.[247] Somewhat later, Schoepfle and Trepp[248] found that various higher-molecular-weight hydrocarbons were also formed in the reaction, though in much smaller amounts. The data obtained by Schoepfle and Trepp are summarized in Table 4. These

Table 4

Products from the Reaction of Phenylmagnesium Bromide with Trityl Chloride

Compound	Yield, Per Cent
Diphenyl-*p*-xenylmethane	21-29
Tetraphenylmethane	13-35
Triphenylmethane	5
Phenyldi-*p*-xenylmethane	3
Triphenyl-*p*-xenylmethane	0.6
Tri-*p*-xenylmethane	Trace

authors were interested in the possibility that trityl chloride might exist in equilibrium with a *p*-quinoidal tautomer, and they interpreted their findings in terms of coupling of the Grignard reagent with such hypothetical tautomers.

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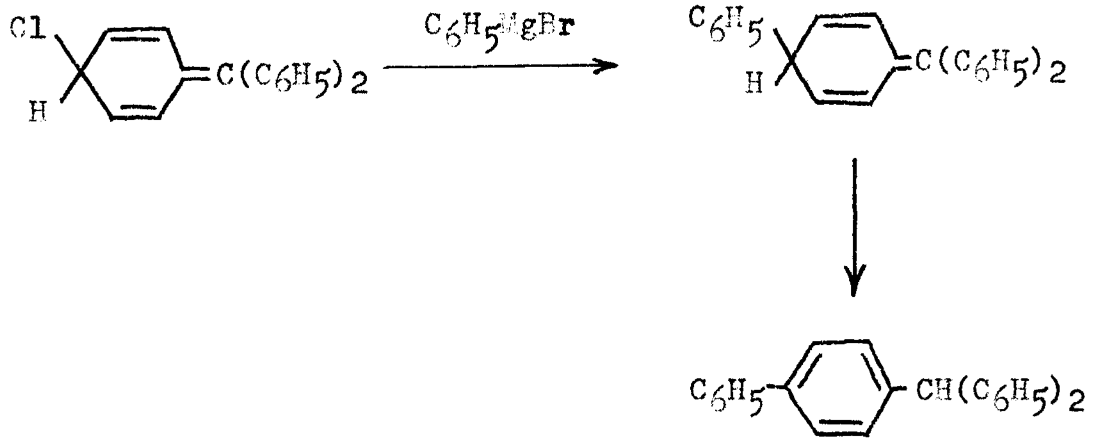
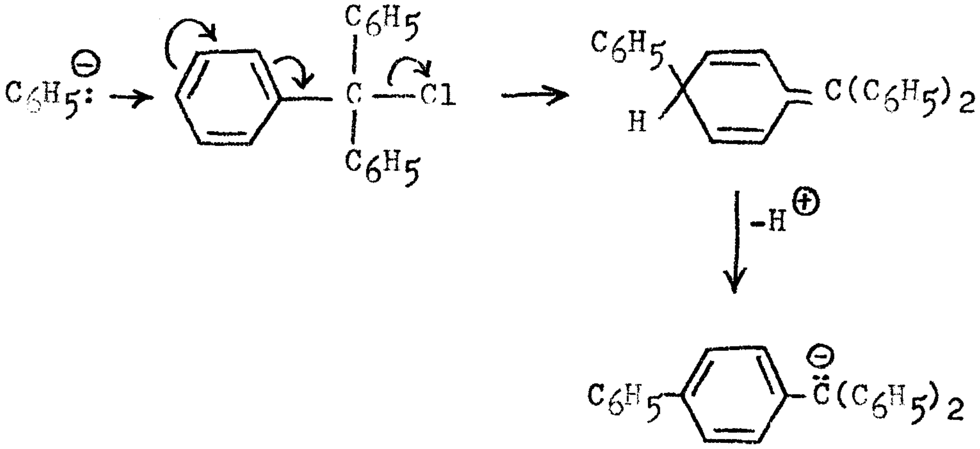
[247] H. Gilman and H. L. Jones, *ibid.*, *51*, 2840 (1929).

[248] C. S. Schoepfle and S. G. Trepp, *ibid.*, *58*, 791 (1936).

For instance, it was supposed that diphenyl-p-xenylmethane arose through the displacement of chloride from the tautomer, followed by rearrangement of the resulting 1-phenyl-4-benzhydrylidene-1,4-dihydrobenzene, as indicated in the accompanying formulation. However, no direct evidence of the existence of tautomerism in trityl chloride has been forthcoming, and it is possible to explain the formation of each of the products described by Schoepfle and Trepp on the basis of reaction with trityl chloride itself. Two facts concerning the yields of these compounds may be noted. (1) Diphenyl-p-xenylmethane was the chief product; none of the other compounds containing p-xenyl groups was isolated except in very small amounts. (2) The yield of triphenylmethane exceeded the combined yields of phenyldi-p-xenylmethane, triphenyl-p-xenylmethane and tri-p-xenylmethane. Accordingly, the following mechanisms are suggested.



Diphenyl-p-xenylmethane could have arisen through the nucleophilic attack of the Grignard reagent on a para position of trityl chloride, with expulsion of a chloride ion, to yield a quinoidal intermediate which should lose a proton by



reaction with excess Grignard reagent, giving the diphenyl-p-xenylmethyl carbanion. This sequence is strictly analogous to Steps 2 and 3 of the proposed mechanism for the reaction of trityl methyl ether with organolithium compounds.

Tetraphenylmethane, of course, could arise through simple displacement of chloride from trityl chloride. This reaction takes place at a more highly hindered site than does the para-coupling mentioned above, and tetraphenylmethane is formed in smaller amounts than diphenyl-p-xenylmethane.

The formation of triphenylmethane is explicable on the basis of a halogen-metal interconversion between phenylmagnesium bromide and trityl chloride. It should be noted that chlorobenzene would be formed in this reaction.

The other three products can be explained as having arisen through the reaction of chlorobenzene with the anion of diphenyl-p-xenylmethane. Coupling at the para position of this anion would produce an intermediate which could lose a proton to yield the anion of phenyldi-p-xenylmethane; further coupling at the para position of the latter anion would in turn lead to the anion of tri-p-xenylmethane. Coupling of chlorobenzene at the central carbon atom of the diphenyl-p-xenylmethane anion would account for the formation of triphenyl-p-xenylmethane. The fact that the combined yields of the higher-molecular-weight hydrocarbons did not exceed the yield of chlorobenzene that should be formed in the halogen-metal interconversion reaction is in agreement with the mechanism here suggested.

The reaction of trityl methyl ether with RM compounds other than those of lithium was investigated, in an effort to determine the scope of the ring closure reaction. When the ether was treated with phenylcalcium iodide, there resulted a tarry product which was quite difficult to purify. The infrared absorption spectrum of this crude product suggested that 9-phenylfluorene was present, but the only product actually isolated was triphenylcarbinol. This compound presumably arose through cleavage of the ether, either during the reaction with phenylcalcium iodide or during the working-up of the crude mixture.

Gomberg and Kamm had previously reported the reaction of trityl methyl ether with phenylmagnesium bromide to yield the normal displacement product, tetraphenylmethane. Trityl ethyl ether and trityl phenyl ether were also found to yield this hydrocarbon when treated with phenylmagnesium bromide.[15] However, it was thought possible that, with RMgX compounds more reactive than phenylmagnesium bromide, trityl methyl ether might show some tendency to undergo ring closure. To explore this possibility, the reaction of the ether with benzylmagnesium chloride and with t-butylmagnesium chloride was studied. These two Grignard reagents had been found by Fuson and Porter[249] to be more reactive than phenylmagnesium bromide toward the ethylenic linkage of dibiphenyleneethylene, and it was reasoned that they might, under forcing conditions, function as metalating agents with trityl methyl ether. However, the only compounds isolated from these reactions were the normal displacement products. Benzylmagnesium chloride with trityl methyl ether yielded 14.3 per cent of 1,1,1,2-tetraphenylethane, and the reaction with t-butylmagnesium chloride produced 0.4 per cent of 1,1,1-triphenyl-2,2,2-trimethylethane. In the latter reaction, a considerable amount of impure material was obtained by concentration of the recrystallization liquors. The constituents of this mixture

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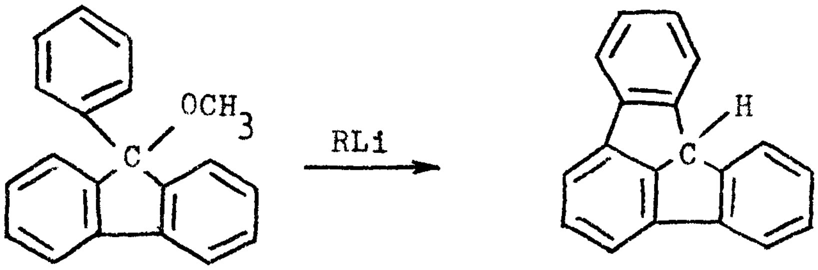
[249] R. C. Fuson and H. D. Porter, ibid., 70, 895 (1948).

were not identified, but an infrared absorption spectrum showed that 9-phenylfluorene was not present in significant amounts. The well-defined absorption maxima exhibited by 9-phenylfluorene at 13.2μ and at 13.4μ were completely absent from the spectrum of the impure material.

It was of interest to study the reaction of 9-phenyl-9-fluorenyl methyl ether with RLi reagents. If this ether reacted in the same fashion as trityl methyl ether, the final



product should be the hitherto unknown hydrocarbon, 1,9-o-phenylenefluorene. Hurd and Mold[250] have described two unsuccessful attempts to prepare this compound. First, they studied the pyrolysis of 9-phenyl-9-chlorofluorene. Since trityl chloride decomposes on heating to yield 9-phenylfluorene, it was reasoned that the analogous reaction of the fluorenyl halide should produce 1,9-o-phenylenefluorene. However, the only identifiable product of the thermal decomposition

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[250] C. D. Hurd and H. D. Mold, *J. Org. Chem.*, **13**, 339 (1948).

of 9-phenyl-9-chlorofluorene was a high-melting hydrocarbon which was identified as a dimer of 9-phenylfluorene. The second attempt made by these authors to prepare 1,9-o-phenylenefluorene consisted in the dehydrogenation of 1,9-cyclohexylenefluorene, using palladium. The product which they actually obtained, however, was 9-phenylfluorene. These results suggested that the sought-for 1,9-o-phenylenefluorene was so highly strained as to make its preparation difficult or impossible.

In the present study, 9-phenyl-9-fluorenyl methyl ether was allowed to react with phenyllithium under forcing conditions, and with n-butyllithium under mild conditions. In each case, the only product identified was 9-phenylfluorene. Seemingly, instead of undergoing metalation, the ether reacted with the RLi compound to exchange a lithium atom for a methoxyl group. This mode of ether cleavage is reminiscent of the reaction of bis-2-chloroethyl ether with benzylsodium, reported by Morton and co-workers.[251] The product which they isolated after carbonating the reaction mixture was succinic acid, suggesting that the replacement of oxygen by sodium had occurred together with halogen-metal interconversion. In the reaction of 9-phenyl-9-fluorenyl methyl ether with phenyllithium there was isolated, along with 9-phenylfluorene, a

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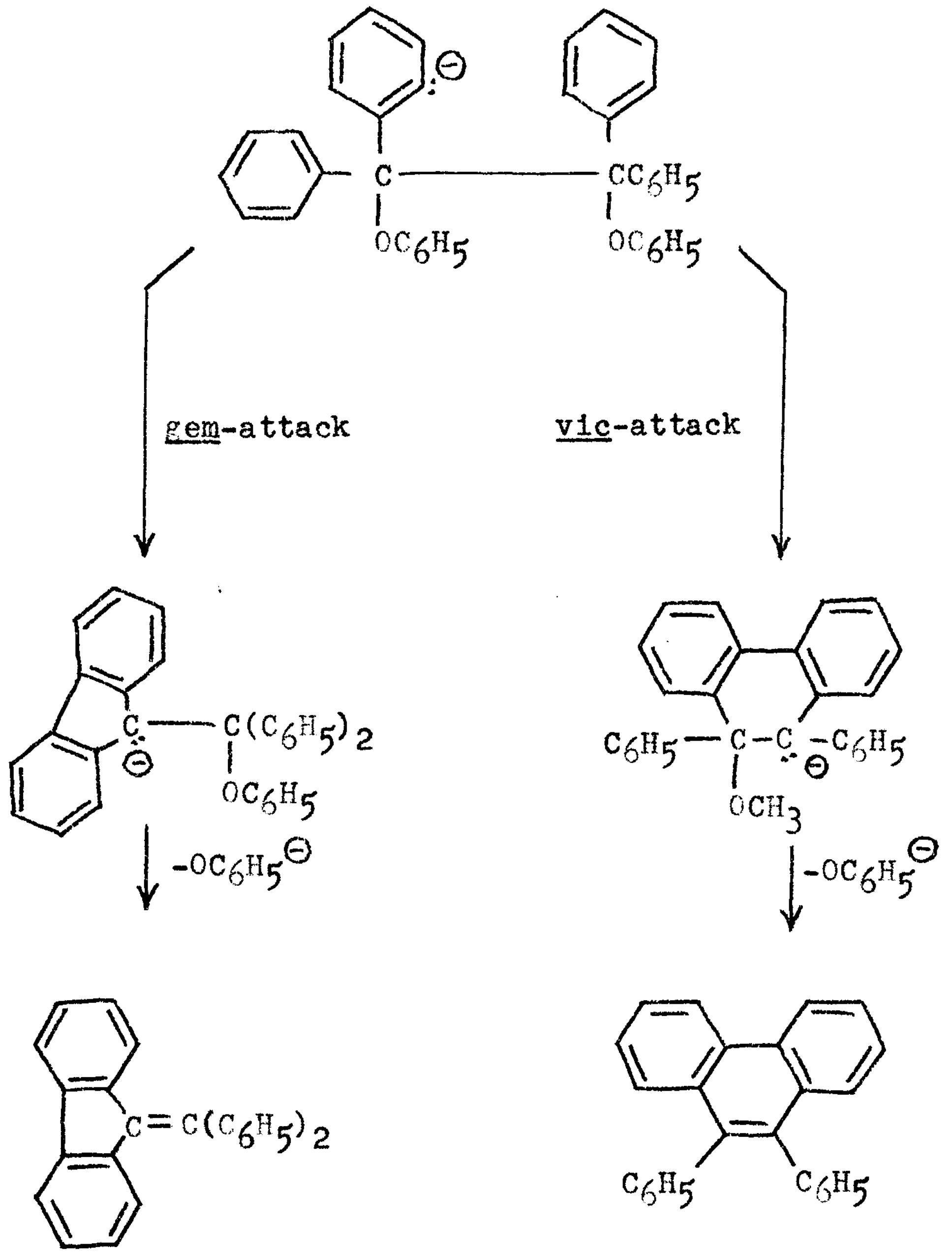
[251] A. A. Morton, J. T. Massengale and T. R. P. Gibb, J. Am. Chem. Soc., 63, 324 (1941).

small amount of unidentified material which charred without melting at 380-400°. The infrared absorption spectrum of this material was similar to that of 9-phenylfluorene, and it appears possible that this product was the same dimer of 9-phenylfluorene which Hurd and Mold obtained from the pyrolysis of 9-phenyl-9-chlorofluorene.

The reaction of benzopinacol diphenyl ether with phenyllithium was studied because it appeared to offer particularly attractive possibilities in the ring closure reaction. If this ether were to undergo normal metalation, analogous to that of trityl methyl ether, the resulting carbanion could conceivably institute nucleophilic attack either on the ortho position of the gem-phenyl group or on that of the vic-phenyl group. In either event, expulsion of a phenoxide ion, followed by removal of a second proton and elimination of a second phenoxide ion, should occur, and the final product should be either 1,1-diphenyl-2,2-biphenyleneethylene or 9,10-diphenylphenanthrene. Actually, neither of these compounds was


C
CC6H5
OC6H5
OC6H5
gem-attack
vic-attack
C
C(C6H5)2
OC6H5
-OC6H5
C6H5—C—C—C6H5
OCH3
-OC6H5
C=C(C6H5)2
C6H5
C6H5

isolated from the reaction mixture. The products which were obtained were not identified, but their physical properties showed them to be different from the two possible ring closure products. It is possible that the reaction with phenyllithium was complicated by the tendency of benzopinacol diphenyl ether to dissociate into free radicals when heated in hydrocarbon solvents.[239]

Miscellaneous Metalations

The data obtained in orienting experiments on the possible use of RMgX compounds as metalating agents substantiated the findings of other workers to the effect that Grignard reagents are much less active than RLi compounds in the metalation reaction. Benzothiazole, which is metalated very rapidly and in good yields by n-butyllithium at very low temperatures,[85] gave no metalation product at all with n-butylmagnesium bromide under corresponding conditions. When the reaction was conducted at a somewhat higher temperature (0°), a small amount of bis-2-benzothiazolyl was isolated. This compound presumably arose through metalation of benzothiazole followed by addition of the resulting RMgX compound to the azomethine linkage of unreacted benzothiazole, yielding on hydrolysis 2-(2'-benzothiazolyl)-2,3-dihydrobenzothiazole, which was converted by air oxidation to the bis compound. The isolation of bis-2-benzothiazolyl from a reaction between benzothiazole and n-butyllithium was reported by Gilman and Beel.[85]

When the reaction of benzothiazole with the Grignard reagent was carried out at room temperature and the mixture was carbonated, there was isolated a small amount of solid tentatively identified as benzothiazole-2-carboxylic acid.

Esmay has reported the mono- and dimetalation of dibenzothiophene-5-dioxide with n-butyllithium,[81] and it was of interest to determine whether n-butylmagnesium bromide could also be used to effect this metalation. The reaction between the dioxide and n-butylmagnesium bromide was carried out in diethyl ether at room temperature, and also in di-n-butyl ether at 100°. In neither case was any solid acid produced on carbonation of the reaction mixture. However, some reduction of the dioxide was noticed; a 1.6 per cent yield of dibenzothiophene was obtained from the room-temperature reaction, and a 15.2 per cent yield from the reaction carried out at 100°. A somewhat similar reduction of phenyl methyl sulfone by methylmagnesium iodide under forcing conditions has been reported by Gibson.[252] In the latter case, however, cleavage as well as reduction took place, and thiophenol was isolated. In view of the simple reduction, without cleavage, of dibenzothiophene-5-dioxide found in the present study, and in view also of the fact that phenyl methyl sulfide is known to

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[252] D. T. Gibson, J. prakt. Chem., [2], 142, 218 (1935).

undergo cleavage to thiophenol when treated with RM compounds under forcing conditions, it appears probable that the reaction reported by Gibson took place by way of preliminary reduction of phenyl methyl sulfone, followed by cleavage of the resulting phenyl methyl sulfide.

The reaction of fluorene with lithium aluminum hydride was examined in order to determine the generality of the metalation reported by Trevoy and Brown.[198] These authors had found that, when fluorene and lithium aluminum hydride were heated together in tetrahydrofuran and the mixture was carbonated, a small amount of fluorene-9-carboxylic acid was produced. In the present study, the same reaction was carried out in ether and in a mixture of ether and benzene. Although in each case the development of a yellow color was noticed during the reaction, carbonation of the mixtures failed to produce any acid, and the recovery of fluorene was almost quantitative.

It was found that the mercuration of 2-methoxynaphthalene by mercuric nitrate took place in the 1-position. The studies of Westheimer and co-workers[253] have firmly established the electrophilic nature of mercuric nitrate in reactions with aromatic nuclei, and the occurrence of substitution in the

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[253] F. H. Westheimer, W. Klapproth and R. M. Schramm, <u>Eleventh National Organic Chemistry Symposium</u>, 13 (1949). See also W. J. Klapproth and F. H. Westheimer, <u>J. Am. Chem. Soc.</u>, <u>72</u>, 4461 (1950).

1-position of 2-methoxynaphthalene was to be expected in view of the fact that other electrophilic substitutions[254,255] have been shown to effect replacement of the 1-hydrogen in this ether. From the point of view of the conflict between the electrophilic and nucleophilic theories of metalation, this mercuration reaction was of particular interest. Sunthankar and Gilman had previously pointed out that the metalation of 2-methoxynaphthalene in the 3-position by <u>n</u>-butyllithium was a strong argument against the electrophilic theory of metalation, since other electrophilic substitutions of this ether occurred in the 1-position.[10] Somewhat later, A. A. Morton and Cluff[256] took exception to this reasoning on the basis that substitutions in the naphthalene nucleus are apt to be erratic and to depend on the conditions of the reaction. The fact that naphthalene can be sulfonated either in the 1- or in the 2-position, depending on the temperature of reaction, was adduced in support of this statement. It may be pointed out, however, that substitution in naphthalene itself is not at all comparable electronically to substitution in 2-methoxynaphthalene.

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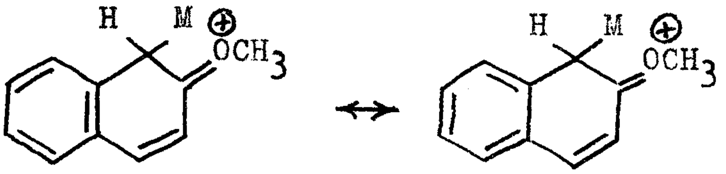
[254] O. Witt and O. Braun, <u>Ber</u>., <u>47</u>, 3216 (1914).

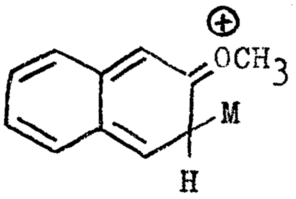
[255] C. R. Noller and R. Adams, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>46</u>, 1889 (1924).

[256] A. A. Morton and E. Cluff, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>. (in press).

The presence of the alkoxyl group in 2-methoxynaphthalene should lead to the stabilization of the transition state in electrophilic substitution by means of structures which have no analogues in the case of naphthalene itself. Oxonium structures of this type account for the observed fact that the alkoxyl group has an activating effect in electrophilic substitutions; further, it may be seen that more oxonium structures contribute to the transition state in the case of electrophilic attack on the 1-position of 2-methoxynaphthalene than in the case of attack on the 3-position. The interesting aspect of the mercuration of this ether by mercuric nitrate is that the mechanism of mercuration, as established by Westheimer's studies, parallels quite closely the supposed



(Two Oxonium Structures)



(One Oxonium Structure)

mechanism of metalation by RM compounds as set forth by A. A. Morton. First, complexation of the metal ion with the hetero atom (in this case, oxygen) occurs; second, the metal ion attacks an adjacent ortho-carbon atom; and finally, a proton is expelled.[257] The removal of this proton from the transition state is easily accomplished, and does not depend on the presence of a strongly basic anion. In this sense, the mercuration of 2-methoxynaphthalene may be taken as constituting a "model" electrophilic metalation, and the fact that substitution occurred in a different position from that involved in the metalation of the ether by n-butyllithium may legitimately be urged as an argument against the theory that RM compounds function primarily as electrophilic species in metalation reactions.

The previously cited studies by Westheimer and co-workers indicated that not only mercuric nitrate, but also mercuric

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[257] For the purpose of convenience, these three processes are considered separately. The possibility that any two, or all three, of these steps may proceed in concert does not affect the arguments concerning position of substitution. In the case of metalations with RM compounds, it should be particularly borne in mind that concerted reactions are favored by the low-dielectric-constant solvents employed. The discussions of the theory of metalation which are to be found in the literature have not generally emphasized this point. Dr. A. A. Morton, in a private communication to Dr. Henry Gilman, has commented on the fact that the possibility of a concerted reaction in metalation has always been implicit in his (Morton's) discussions of the mechanism of this reaction.

bisulfate, could function as electrophilic mercurating agents, and that both of these salts should be more selective in their orientation than the more commonly employed mercuric acetate. However, an attempt, in the present study, to mercurate 2-methoxynaphthalene with mercuric bisulfate produced an amorphous solid having no definite melting point, and whose high mercury content suggested that polymercuration had occurred. Neither mercuric nitrate nor mercuric bisulfate yielded a well-defined mercuration product with dibenzothiophene. The nitrate did not react with dibenzothiophene at all at room temperature, while at 100° there resulted a mercury-containing product which appeared to be organic, but whose infrared absorption spectrum failed to show the presence of carbon-to-hydrogen bonds. Mercuric bisulfate reacted with dibenzothiophene at room temperature to yield a mercury-containing product whose infrared absorption spectrum showed all the absorption maxima of dibenzothiophene, but failed to indicate the presence of a carbon-to-mercury bond. This product was presumably a complex between dibenzothiophene and mercuric bisulfate.

Mercury is not the only metal whose inorganic compounds have been used as metalating agents. The chlorides of gold,[258,259] thallium,[260] germanium[261] and tellurium[262] have been found to effect the metalation of certain aromatic nuclei. However, no such reaction appears to have been attempted with indium chloride. In the present study, indium chloride was refluxed with an excess of thiophene in an effort to bring about "indiation" of the heterocycle. Thiophene was chosen for use in this case because of the great ease with which it has been found to undergo mercuration. However, no reaction was observed with indium chloride, and the thiophene was quantitatively recovered from the reaction mixture.

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[258] M. S. Kharasch and T. M. Beck, *ibid.*, *56*, 2057 (1934).

[259] M. S. Kharasch and H. S. Isbell, *ibid.*, *53*, 3053 (1931).

[260] H. Gilman and R. K. Abbott, *ibid.*, *65*, 122 (1943).

[261] R. Schwartz and W. Reinhardy, *Ber.*, *65*, 1743 (1932).

[262] G. T. Morgan and H. Burgess, *J. Chem. Soc.*, 1103 (1929).

SUMMARY

A review of the literature dealing with the use of organometallic compounds as metalating agents has been presented.

Two methods for the preparation of 2,4,6-triphenylphenyllithium have been described.

It was found that 2,4,6-triphenylphenyllithium metalated thiophene and *p*-bromoanisole in the normal fashion. The same RLi compound reacted with 6-phenylphenanthridine to produce a bis-6-phenylphenanthridine. Both 2,4,6-triphenylphenyllithium and mesityllithium were found to metalate resorcinol dimethyl ether in the 2-position.

The metalation of the two weakly acidic hydrocarbons, fluorene and triphenylmethane, by a series of organolithium compounds exhibiting varying degrees of steric hindrance has been examined.

The reaction of trityl methyl ether with a number of organometallic compounds has been studied. The reaction with *n*-butyllithium or with phenyllithium, followed by hydrolysis, led to the production of 9-phenylfluorene. Carbonation of the reaction mixtures yielded either 9-phenylfluorene-9-carboxylic acid or 3,3-diphenylphthalide, depending on the conditions of reaction. A mechanism has been advanced to account for these transformations. Trityl methyl ether reacted with benzylmagnesium chloride and with t-butylmagnesium chloride to yield the normal displacement products, without evidence of any ring closure. Phenylcalcium iodide reacted with trityl methyl ether to produce a mixture which was not resolved into its components, but whose infrared absorption spectrum indicated the possible presence of 9-phenylfluorene.

The reaction of 9-phenyl-9-fluorenyl methyl ether with n-butyllithium and with phenyllithium yielded 9-phenylfluorene as the only identifiable product. Benzopinacol diphenyl ether reacted with phenyllithium to produce a mixture of two products which were not identified.

n-Butylmagnesium bromide was found to metalate benzothiazole to a very slight extent at 0° and at room temperature, but not at -60°.

The reaction between phenylcalcium iodide and triphenylamine, followed by carbonation, was found to yield a small amount of impure acidic material which was not identified.

Phenylcalcium iodide was without effect on dibenzothiophene-5-dioxide under conditions which had previously been found to lead to metalation when n-butyllithium was employed. The same dioxide reacted with n-butylmagnesium bromide to give dibenzothiophene. Metalation was apparently not involved in this reduction. The yield of dibenzothiophene was greater when the reaction was carried out at a higher temperature.

It was found that no reaction occurred between fluorene and lithium aluminum hydride in ether or in a mixture of ether and benzene.

2-Methoxynaphthalene was found to undergo mercuration in the 1-position when treated with mercuric nitrate at room temperature. At higher temperatures, the ether was oxidized by the mercuric salt, yielding an amorphous tar. The reaction of 2-methoxynaphthalene with mercuric bisulfate failed to yield a well-defined mercuration product. Similar failures resulted in the reaction of dibenzothiophene with mercuric nitrate and with mercuric bisulfate.

It was found that no reaction occurred when indium chloride was refluxed with an excess of thiophene.