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Organolead compounds containing water-solubilizing groups

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NOTE TO USERS

ORGANOLEAD COMPOUNDS CONTAINING WATER-SOLUBILIZING GROUPS

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TABLE OF CONTENTS

INTRODUCTION

Lead and its compounds have shown considerable promise as therapeutic agents in the treatment of cancer.[1] Two serious difficulties have been encountered in the application of organolead compounds in this most important field: namely, the general toxicity of these compounds toward benign as well as malignant tissue, and their insolubility in water.

The present study has been concerned primarily with attempts to overcome the second of the disadvantages mentioned above--that is, with the preparation of organolead compounds containing water-solubilizing groups. Some of the common groups which tend to promote solubility in water are the carboxyl, the phenolic or alcoholic hydroxyl, the sulfonic acid, and the amino or substituted amino groups. Except for the alcoholic hydroxyl, all of the above-mentioned groups offer the possibility of further promoting solubility in water by formation of salts with acids or with bases.

Relatively few organolead compounds containing one or more of these groups have been prepared. Numerous workers have concerned themselves with the problem of synthesizing such compounds, but the work has been

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[1] For a review of the use of lead and its compounds in the treatment of cancer, see Stuckwisch, Doctoral Dissertation, Iowa State College (1943).

made especially difficult by the ease with which the carbon-lead linkage undergoes cleavage by acidic reagents. Indeed, the conditions necessary for the introduction of the groups mentioned are in many cases just those conditions which result in cleavage of carbon-lead linkages. A further difficulty is the fact that Grignard reagents, common intermediates in the preparation of organolead compounds, are in general not available from halides containing reactive functional groups.

The halogen-metal interconversion reaction[2,3,4] which has been recently extended to aromatic halides containing a wide variety of functional groups, seemed to present a means of synthesizing some organolithium compounds which might prove useful in the preparation of organolead compounds containing water-solubilising groups without subjecting the intermediate or final products to cleavage conditions. Consequently, a study of the halogen-metal interconversion reaction and its extension to different types of aromatic halides was made in connection with the work on organolead compounds.

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[2]Gilman, Langham, and Jacoby, J. Am. Chem. Soc., 61, 106 (1939); Gilman, Langham, and Willis, Ibid., 62, 346 (1940); and subsequent papers.

[3]Wittig and co-workers, Ber., 71, 1903 (1938); 72, 89 (1939); and subsequent papers.

[4]Moore, F.W., Doctoral Dissertation, Iowa State College (1941).

An organolead compound is defined as a compound of lead in which at least one organic group is joined directly to the lead atom by a carbon-lead bond. This definition excludes such compounds as salts of inorganic lead with organic acids, since in these the organic groups are separated from the lead atom by an oxygen atom.

Organolead salts, such as triphenyllead chloride, are of interest primarily as intermediates in the preparation of organolead compounds in which all four of the valences of lead are satisfied by organic groups. The emphasis in the present study has been placed on the preparation of organolead compounds containing four carbon-lead linkages.

HISTORICAL

The following discussion of the introduction of water-solubilising groups into organometallic compounds of the Group IV metals constitutes a survey of the general procedures and special methods which have been successfully applied in this section of organometallic chemistry, as well as a consideration of the less successful experiments which have also contributed to the total knowledge available in the field.

Organosilicon compounds are excluded from consideration here, since they are not strictly organometallic compounds and their preparation and properties resemble those of the analogous carbon compounds. The organogermanium compounds are intermediate in their properties between the organosilicon compounds and the organotin compounds. The organotin and organolead compounds show great similarity; their dissimilarities are differences of degree rather than of kind, as might have been predicted on the basis of the greater molecular weights of the organolead compounds compared with those of the corresponding organotin compounds.

In the discussion of organogermanium, organotin, and organolead compounds containing water-solubilising groups, only those compounds are considered in which the water-solubilising group is part of an organic radical attached to the metal directly by a carbon-metal linkage. The discussion includes some organometallic compounds containing groups which

are not of themselves water-solubilizing (for example, the nitro, bromophenyl, bromoalkyl, and carbalkoxy groups). Compounds with these groups are of interest as intermediates in the preparation of compounds containing water-solubilizing groups.

Organogermanium Compounds

Relatively little work has been done on the introduction of water-solubilizing groups into organogermanium compounds. Germanium and its inorganic compounds are comparatively rare and costly chemicals; consequently it is not surprising that the organometallic chemistry of this element has been studied to a lesser extent than that of the readily available metals, tin and lead.

Attempts to prepare water-soluble organogermanium compounds were inspired by the possibility that such compounds might be useful in the treatment of pernicious anemia.[5] Organogermanium compounds are, in general, less toxic than the corresponding compounds of tin and lead; however, it appears that germanium and its compounds are not of great importance as therapeutic agents.[6]

The first study of organogermanium compounds containing polar groups was reported by Orndorff, Tabern, and Dennis.[5] These workers were able to introduce some substituted amino groups and the sulfonic acid group into organogermanium compounds.

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[5]Orndorff, Tabern, and Dennis, J. Am. Chem. Soc., 49, 2512 (1927).

[6]Burschkies, Ber., 69, 1143 (1936).

When triphenylgermanium bromide was refluxed with an excess of dry dimethylaniline under varying conditions no reaction took place. However, when triphenylgermanium bromide and two moles of p-bromodimethylaniline were refluxed in xylene with an excess of sodium, sodium bromide was deposited and triphenyl-p-dimethylaminophenylgermanium was formed.[5] This compound easily formed a solid, crystalline hydrochloride, which was insoluble in water and in hydrochloric acid but which dissolved readily in absolute alcohol.

The anhydride of p-dimethylaminophenylgermanonic acid,[5] $[\ p\text{-}(CH_3)_2NHC_6H_4GeO\ ]_2O$, was prepared by heating germanium tetrachloride with excess dimethylaniline followed by hydrolysis of the reaction mixture with base and precipitation of the anhydride by saturating the basic solution with carbon dioxide. The product was a pearly white, fluffy powder, soluble in very dilute mineral acids and in excess alkali. It had no definite melting point. The anhydride, when kept in thin layers for some time in an atmosphere of dry hydrogen chloride, was converted into the hydrochloride of p-dimethylaminophenylgermanium trichloride. This compound was readily and completely soluble in water, and from the aqueous solution the original anhydride could be precipitated by ammonium hydroxide.

Later, Bauer and Burschkies[7] prepared the anhydrides of p-monomethylaminophenylgermanonic acid and p-diethylaminophenylgermanonic acid by procedures similar to that described above for the dimethyl compound.

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[7]Bauer and Burschkies, Ber., 65, 956 (1932).

It was shown by these workers that, contrary to the statement of Thomas and Southwood,[8] diethylaniline reacted with germanium tetrachloride; the product was the p-diethylaminophenylgermanonic acid anhydride. Bauer and Burschkies also prepared the dithio acid anhydrides, $[\,p\text{-}(CH_3)_2NC_6H_4GeS\,]_2S$ and $[\,p\text{-}(C_2H_5)_2NC_6H_4GeS\,]_2S$, by treatment of the corresponding oxygen anhydrides in dilute acetic acid solution with hydrogen sulfide. The thio compounds were colorless, amorphous substances, which lost hydrogen sulfide and turned rose-colored in moist air. They were soluble in mineral acid, alkali, and alkali sulfides.

The only organogermanium compound containing the sulfonic acid group was prepared by Orndorff, Tabern, and Dennis.[5] Tetrabenzylgermanium was sulfonated by means of twenty-five per cent fuming sulfuric acid below 35°. The sulfonic acid was isolated as the normal barium salt, which dissolved readily and completely in cold water, but was insoluble in acetone, alcohol, or ether. Analysis of the salt for barium, sulfur, and germanium established the constitution of the sulfonation product as a tetrasulfonic acid, $(HO_3SC_6H_4CH_2)_4Ge$. However, the free acid was not isolated, nor was the position occupied by the sulfonic acid groups in the benzene ring determined.

Burschkies[6] attempted to prepare water-soluble organogermanium compounds by nitration or oxidation of the R_4Ge compounds, tetraphenyl-

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[8] Thomas and Southwood, J. Chem. Soc., 2083 (1931).

germanium, tetrabenzylgermanium, and tetratolylgermanium. This work was unsuccessful, and the only reaction observed was decomposition of the organogermanium compounds with cleavage of the carbon-germanium bond. For example, when tetrabenzylgermanium was treated with fuming nitric acid in boiling acetic acid, the only product isolated was nitrobenzaldehyde. Nitration at 15-20° or at 50-60° gave only unchanged tetrabenzylgermanium.

However, the nitration and oxidation of compounds of the type $(RGeO)_2O$, in which the carbon-germanium bond is relatively stable, were effected. The anhydride of p-dimethylaminophenylgermanonic acid was nitrated by means of a mixture of sulfuric and nitric acids; the product obtained upon dilution of the reaction mixture and neutralization with ammonia was the anhydride of 3-nitro-4-dimethylaminophenylgermanonic acid.[6] This was a yellow, amorphous substance, readily soluble in alkali. The oxidation of p-tolylgermanonic acid anhydride by alkaline permanganate gave p-carboxyphenylgermanonic acid anhydride,[6] $(p\text{-}HOOCC_6H_4GeO)_2O$, an amorphous substance soluble in alkali.

By means of the reaction between pentamethylenedimagnesium bromide and germanium tetrachloride, Schwarz and Reinhardt[9] synthesized cyclopentamethylenegermanium dichloride. The action of two moles of ethylmagnesium bromide on this dichloride produced diethylcyclopentamethylenegermanium. It seems probable that cleavage of this compound

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[9]Schwarz and Reinhardt, Ber., 65, 1743 (1932).

with one mole of bromine would give diethyl-5-bromoamylgermanium bromide, which in turn could be converted to triethyl-5-bromoamylgermanium by treatment with ethylmagnesium bromide. A similar series of reactions has been carried out in the tin and lead series (these are discussed in later sections). The triethyl-5-bromoamylgermanium would offer the possibility of introducing a carboxyl group through formation and subsequent carbonation of the Grignard reagent. However, the cleavage of diethylcyclopentamethylenegermanium by bromine has not yet been studied.

The work on organogermanium compounds may be summarized by the statement that the only water-solubilizing groups which have been introduced are some substituted amino groups, the carboxyl group, and the sulfonic acid group. It will be apparent, from the following discussion of organotin and organolead compounds, that the methods of introducing water-solubilizing groups into organogermanium compounds are, in general, specific for germanium and cannot be applied to the synthesis of the analogous tin and lead compounds.

Organotin Compounds

Although organotin compounds have shown little promise as therapeutic agents,[10] several workers have studied the preparation of organotin compounds containing water-solubilizing groups. Most of the known organotin

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[10] For a discussion of the therapeutic properties of some organotin compounds, see Arntzen, Doctoral Dissertation, Iowa State College (1942).

compounds with such groups have been prepared in recent years. The first water-solubilising group to be introduced into an organotin compound of the type R_4Sn was the carboxyl group. Chambers and Scherer[11] reported the synthesis of triphenylcarboxymethyltin in 1926. Prior to this time, organotin compounds containing the carbethoxy, 5-bromoamyl, and nitro groups had been prepared. Also, some hydroxyalkylstannonic acids were reported in a patent in 1923 (discussed in a later section).

Organotin compounds containing carbalkoxy groups

In 1911 Emmert and Eller[12] reported the synthesis of two compounds which were assigned the structures of dicarbethoxymethyltin diiodide and di-o-carbethoxyphenyltin diiodide. The former compound was obtained in a yield of eighty-four per cent from the reaction of tin with ethyl iodoacetate in the presence of a small amount of iodine as catalyst.

$$Sn + 2ICH_2COOC_2H_5 \longrightarrow (C_2H_5OOCCH_2)_2SnI_2$$

The authors did not mention any attempts to hydrolyze the ester groups to carboxyl groups, but the dicarbethoxymethyltin diiodide decomposed with cleavage of the carbon-tin linkages on treatment with basic reagents or even with water. Consequently, this diiodide could not be converted to the dicarbethoxymethyltin oxide. Treatment of the diiodide with phenylmagnesium bromide gave, not the expected dicarbethoxymethyldiphenyltin, but tetraphenyltin. Similarly, treatment with

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[11] Chambers and Scherer, J. Am. Chem. Soc., 48, 1054 (1926).

[12] Emmert and Eller, Ber., 44, 2328 (1911).

ethylmagnesium bromide gave tetraethyltin almost exclusively, even at low temperatures. Di-o-carbethoxyphenyltin diiodide was prepared from tin, ethyl o-iodobenzoate, and a small amount of iodine, heated together in a bomb at 150° for five days. This diiodide decomposed above 300° without melting. It was practically insoluble in all organic solvents, and was decomposed by water in a manner similar to that described for the dicarbethoxymethyltin diiodide. The R_2SnI_2 structure of these compounds is open to some question because of their ease of cleavage with water and because of the anomalous reaction of the dicarbethoxymethyl compound with Grignard reagents.

Quite different properties were reported for the di-p-carbethoxyphenyltin dihalides which were prepared by Eskin, Nesmeyanov, and Kocheshkov.[15] The dichloride, dibromide, and diiodide were obtained by the reaction of di-p-carbethoxyphenylmercury and the corresponding stannous halide. The dichloride and dibromide were low-melting crystalline solids, and the diiodide was an oil which could not be crystallized. This oil, when treated with 8-hydroxyquinoline, gave the same dioxinate, $(p\text{-}C_2H_5OOCC_6H_4)_2Sn(OC_9H_6N)_2$, as did the dichloride and the dibromide. The dibromide was converted to the corresponding oxide in almost quantitative yield by treatment with twelve per cent ammonium hydroxide. The action of hydrogen sulfide in five per cent alcoholic potassium hydroxide on the dichloride resulted in the formation of the sulfide, $(p\text{-}C_2H_5OOCC_6H_4)_2SnS$.

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[15] Eskin, Nesmeyanov, and Kocheshkov, J. Gen. Chem. (U.S.S.R.), 8, 35 (1938) [C.A., 32, 5586 (1938); Chem. Zentr., I, 2174 (1939)].

The course of the reaction of di-p-carbethoxyphenyltin dichloride with phenylmagnesium bromide is described in a later section in connection with the preparation of organotin compounds containing the hydroxyl group.

Kocheshkov, Nesmeyanov, and Klimova[14] studied the action of powdered metals on complexes of stannic chloride with diazonium chlorides of the type $(RN_2Cl)_2 \cdot SnCl_4$, in which R represents an aryl group. The product was in most cases an organotin compound of the type R_2SnCl_2, and more rarely of the type $RSnCl_3$. When the complex between o-carbomethoxybenzenediazonium chloride and stannic chloride was treated with tin, there was obtained, after treatment of the reaction product with concentrated hydrochloric acid and extraction with benzene, o-carbomethoxyphenyltin trichloride, $o\text{-}CH_3OOCC_6H_4SnCl_3$.

The preparation of triaryltin chlorides by the reaction of arylmercury chlorides with powdered tin was reported by Nad and Kocheshkov.[15] The general formulation of the reactions involved is as follows:

$$6C_6H_5HgCl + 3\ Sn \longrightarrow 3(C_6H_5)_2SnCl_2 + 6Hg$$

$$3(C_6H_5)_2SnCl_2 \longrightarrow 2(C_6H_5)_3SnCl + SnCl_4$$

$$SnCl_4 + Sn \longrightarrow 2SnCl_2$$

The arylmercury chloride was boiled with tin in xylene for eighteen hours. From the reaction of p-carbethoxyphenylmercury chloride with tin powder there was obtained tri-p-carbethoxyphenyltin chloride, an oil, which, when dissolved in alcohol and treated with hydrogen sulfide, gave

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[14] Kocheshkov, Nesmeyanov, and Klimova, J. Gen. Chem. (U.S.S.R.), 6, 167 (1936) [C. A., 30, 4854 (1936)]; Nesmeyanov, Kocheshkov, and Klimova, Ber., 68, 1877 (1935).

[15] Nad and Kocheshkov, J. Gen. Chem. (U.S.S.R.), 8, 42 (1938), [C.A., 32, 5587 (1938)].

the solid sulfide, $[(C_2H_5OOCC_6H_4)Sn]_2S$.

The preparation of two dicarbalkoxyalkyltin dibromides by a procedure similar to that of Emmert and Eller[12] for the preparation of the supposed R_2SnI_2 compounds (previously described) has recently been reported by Leeper.[16] The iodine catalyst employed by the earlier workers was not used in the later work. The reaction of ethyl bromoacetate and of ethyl α-bromopropionate with tin powder gave products which were assumed to be dicarbethoxymethyltin dibromide and di-α-carbethoxyethyltin dibromide, respectively. The former dibromide was a crystalline solid, and the latter was a distillable oil. No pure organotin compound was isolated from similar reactions of tin powder with the following esters: bromomethyl acetate, β-bromoethyl acetate, diethyl α-bromosuccinate, and diethyl dibromomalonate.

It is probable that compounds such as di-p-carbethoxyphenyltin dihalides or the corresponding oxides could be hydrolyzed to a carboxylic acid like di-p-carboxyphenyltin oxide. However, no attempt to prepare a carboxyl-containing organotin compound from any of the above esters has been reported in the literature. Leeper[16] proposed a synthesis of carboxyalkyltin compounds which is illustrated below starting with dicarbethoxymethyltin dibromide.

$$(C_2H_5OOCCH_2)_2SnBr_2 + (C_2H_5)_2Zn \longrightarrow (C_2H_5OOCCH_2)_2Sn(C_2H_5)_2 + ZnBr_2$$

$$(C_2H_5OOCCH_2)_2Sn(C_2H_5)_2 + 2NaOH \longrightarrow (NaOOCCH_2)_2Sn(C_2H_5)_2 + 2C_2H_5OH$$

$$(NaOOCCH_2)_2Sn(C_2H_5)_2 + 2HCl \longrightarrow (HOOCCH_2)_2Sn(C_2H_5)_2 + 2NaCl + H_2O$$

This series of reactions has not yet been attempted.

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[16]Leeper, Doctoral Dissertation, Iowa State College (1942).

Organotin compounds containing the carboxyl group

Chambers and Scherer[11] studied the reaction of triphenyltin-sodium with a number of aromatic halides containing functional groups. Among these halides was sodium p-bromobenzoate, which appeared to react with triphenyltin-sodium, but the product was unstable, being hydrolyzed to triphenyltin hydroxide and benzoic acid. The aliphatic halide, ethyl chloroacetate, did not react with triphenyltin-sodium in ether; but sodium chloroacetate did react with triphenyltin-sodium in liquid ammonia to give the sodium salt of triphenylcarboxymethyltin. This sodium salt was very soluble in water. The free acid was soluble in most organic solvents except petroleum ether, and was practically insoluble in water. It could be recrystallized from eighty per cent acetic acid.

Triphenyl-p-carboxyphenyltin was prepared by Arntzen[17] by oxidation of triphenyl-p-hydroxymethylphenyltin (the preparation of this compound is discussed in the section on organotin compounds containing the hydroxyl group) with potassium permanganate in acetone. The triphenyl-p-carboxyphenyltin was a stable compound, and could be recrystallized from dilute alcohol. Its sodium salt was insoluble in water. Oxidation of triphenyl-o-hydroxymethylphenyltin gave an amorphous, infusible product which was tentatively identified as the inner anhydride of diphenyl-o-carboxyphenyltin hydroxide.[18]

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[17]Arntzen, Doctoral Dissertation, Iowa State College (1942). This work lists in tabular form all the known organotin compounds with their melting or boiling points.

[18]Unpublished studies by C.E. Arntzen.

Wall[19] attempted to oxidise triphenyl-p-tolyltin to triphenyl-p-carboxyphenyltin by means of alkaline permanganate, but was unable to isolate any tin-containing carboxylic acid. The tin compound apparently decomposed, but the products were not identified. The action of alkaline potassium ferricyanide on o-tolylstannonic acid was studied by Kocheshkov and Nad.[20] These authors obtained no carboxyphenyltin compound. The carbon-tin linkage was cleaved to give an almost quantitative yield of potassium stannate, and the organic products were toluene and o-tolunitrile.

Some organotin compounds containing the p-iodophenyl and p-bromophenyl groups have been prepared by the following general reactions:[21]

$$R_2Hg + SnX_2 \longrightarrow R_2SnX_2 + Hg$$

$$2R_2SnX_2 + 2SnX_4 \longrightarrow 4RSnX_3$$

The treatment of the complex between p-iodobenzenediazonium chloride and stannic chloride with powdered tin yielded no p-iodophenyltin halide.[14] No organotin compounds of the type R_4Sn (where the R groups may be the same or different) containing the iodophenyl groups are known. Triethyl-p-bromophenyltin was prepared by Wall,[19] and triphenyl-p-bromophenyltin was prepared by Krause and Weinberg.[22]

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[19] Wall, W.L., Master's Thesis, Iowa State College (1928).

[20] Kocheshkov and Nad, Ber., 67, 717 (1934); J. Gen. Chem. (U.S.S.R.), 5, 1158 (1935) [C.A., 30, 1036 (1936)].

[21] Kocheshkov and Nesmeyanov, Ber., 64, 628 (1931); J. Gen. Chem. (U.S.S.R.), 1, 219 (1931) [C.A., 26, 2182 (1932)].

[22] Krause and Weinberg, Ber., 62, 2235 (1929).

Several organotin compounds containing the p-chlorophenyl group are also known. There is no mention in the literature of attempts to convert any of these halophenyltin compounds to the Grignard reagent or to some other active organometallic derivative which might react with carbon dioxide to form a tin-containing carboxylic acid.

The interesting compounds, diethylcyclopentamethylenetin and dimethylcyclopentamethylenetin, in which the tin atom is part of a six-membered heterocyclic ring, were prepared by Grüttner, Krause, and Wiernik.[23] The following series of reactions (using the diethyl compound as an example) was carried out on these heterocycles: diethylcyclopentamethylenetin was cleaved with one mole of bromine in the cold to give diethyl-5-bromoamyltin bromide; this was treated with ethylmagnesium bromide to give triethyl-5-bromoamyltin; and the latter was converted to the Grignard reagent which reacted with water to form triethyl-n-amyltin. The investigators who performed these experiments did not report any attempt to prepare a carboxylic acid by the reaction of the above-mentioned Grignard reagent with carbon dioxide.

Organotin compounds containing the nitro group

Vorländer,[24] in 1925, reported that tetra-p-nitrophenyltin was obtained when tetraphenyltin was gradually added to a mixture of fuming

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[23] Grüttner, Krause, and Wiernik, Ber., 50, 1549 (1917).

[24] Vorländer, Ber., 58, 1893 (1925).

nitric acid and concentrated sulfuric acid. The product was soluble only in pyridine from which it could be reprecipitated by dilute acids. It was uncrystallisable and infusible, and exploded when heated above 350°. The analyses for nitrogen and tin indicated approximately the composition of tetranitrophenyltin. Cleavage with bromine gave, it was reported, only p-bromonitrobenzene, indicating that the tetraphenyltin had nitrated in the positions para to the tin atom. This result is in contradiction to the subsequently proved nitration of diphenyltin oxide chiefly in the positions meta to the tin atom.[25] In this later work, the nitration product was not shown to be a definite compound, but was cleaved with bromine to give a mixture of bromonitrobenzenes which was shown to contain seventy-nine per cent of the meta isomer.

Attempts to prepare nitrophenyltin compounds by the action of powdered tin on the p-nitrobenzenediazonium chloride-stannic chloride complex,[14] or by the reaction of triphenyltin-sodium with o-chloronitrobenzene,[11] were unsuccessful. In the latter case, a vigorous reaction took place to form colored products which could not be identified. It is possible that the reaction involved the nitro group.

Organotin compounds containing the amino or substituted amino groups

Chambers and Scherer[11] attempted to prepare triphenylaminophenyltin by the reaction of triphenyltin-sodium with p- or m-chloroaniline.

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[25]Challenger and Rothstein, J. Chem. Soc., 1258 (1934).

However, only hexaphenylditin and aniline could be found as products.

Arntzen[17] attempted to prepare triphenyl-p-aminophenyltin by means of a halogen-metal interconversion reaction between n-butyllithium and p-bromoaniline, followed by treatment of the product with magnesium bromide and reaction of the Grignard reagent thus formed with triphenyltin iodide. The product formed a hydrochloride but was difficult to purify and seemed to decompose during recrystallization. There was finally obtained a small yield of a compound which was probably somewhat impure triphenyl-p-aminophenyltin, as indicated by the analytical data.

Austin[26] prepared tetra-p-dimethylaminophenyltin by means of the reaction between p-dimethylaminophenyllithium and stannic chloride. The product was recrystallized from an alcohol-benzene mixture. It dissolved in tenth-normal nitric acid from which it could be reprecipitated unchanged by alkali after about one-half hour. Longer standing in acid solution brought about gradual decomposition of the organotin compound.

Triethyl-p-dimethylaminophenyltin[27] was obtained by means of the reaction between di-p-dimethylaminophenylmercury and hexaethylditin. The product was an oil, easily soluble in organic solvents and insoluble in water. It dissolved readily in five per cent hydrochloric acid to give a solution which separated after a short time into two layers. The

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[26]Austin, J. Am. Chem. Soc., 54, 3726 (1932).

[27]Kocheshkov, Nesmeyanov, and Puzyreva, Ber., 69, 1639 (1936); Nesmeyanov, Kocheshkov, and Puzyreva, J. Gen. Chem. (U.S.S.R.), 7, 118 (1937) [C.A., 31, 4290 (1937)].

lower of these layers consisted of triethyltin chloride; the upper contained dimethylaniline hydrochloride.

Triphenyl-o-dimethylaminophenyltin was prepared in good yield by Arntzen[17] from the reaction of either o-dimethylaminophenyllithium or o-dimethylaminophenylmagnesium bromide with triphenyltin iodide. Triphenyl-p-dimethylaminophenyltin was obtained in equally good yield by the action of p-dimethylaminophenyllithium on triphenyltin chloride.

By means of a coupling reaction between p-nitrobenzenediazonium chloride and triphenyl-p-dimethylaminophenyltin, the azo compound, triphenyl-4-dimethylamino-3-(4'-nitrophenylazo)-phenyltin,[17] was prepared in a small yield. No pure product could be isolated from a similar coupling reaction between triphenyl-o-dimethylaminophenyltin and p-nitrobenzenediazonium chloride nor from the reaction of triphenyl-p-dimethylaminophenyltin and p-carboxybenzenediazonium chloride.

Leeper[16] obtained no identifiable product from the reaction of 2-bromopyridine with tin powder.

Organotin compounds containing the hydroxyl group

Triethyl-o-hydroxyphenyltin was first prepared by the reaction of hexaethylditin and di-o-hydroxyphenylmercury.[27] A simpler method of preparation involved the halogen-metal interconversion reaction between n-butyllithium and o-bromophenol, treatment of the interconversion product with magnesium bromide to form the Grignard reagent, and reaction of the latter with triethyltin bromide.[17] Triphenyl-o-hydroxyphenyltin was

prepared in a fifty-seven per cent yield from triphenyltin chloride and o-bromophenol by a similar series of reactions. Di-o-hydroxyphenyldiphenyltin was obtained in good yield by the reaction of diphenyltin dichloride with the Grignard reagent prepared indirectly from o-bromophenol. However, when triphenyltin chloride was treated with the Grignard reagent from p-bromophenol, only a ten per cent yield of triphenyl-p-hydroxyphenyltin was produced.

No triphenyl-o-hydroxyphenyltin was formed in the reaction of triphenyltin-sodium with sodium o-chlorophenoxide; the only products were hexaphenylditin and phenol.[11]

An attempted coupling reaction between triethyl-o-hydroxyphenyltin and p-nitrobenzenediazonium chloride gave an amorphous red solid which contained no tin.[17] A similar reaction in the case of triphenyl-o-hydroxyphenyltin and p-nitrobenzenediazonium chloride yielded an amorphous red solid which contained tin but from which no pure product could be isolated.

The first tetraaryltin compound containing an alcoholic rather than a phenolic hydroxyl group was prepared by Eskin, Nesmeyanov, and Kocheshkov.[13] The compound, di-p-(α-hydroxybenzohydryl)-phenyldiphenyltin, $(C_6H_5)_2Sn\left[\ p\text{-}C_6H_4\text{-}C(C_6H_5)_2OH\ \right]_2$, was formed when di-p-carbethoxyphenyltin dichloride was treated with an excess of phenylmagnesium bromide. The reaction involved the replacement of both chlorine atoms of the dichloride by phenyl groups, and the usual action of an excess of Grignard reagent on esters in the case of each carbethoxy group of the dichloride, to form

a di-tertiary alcohol. In this connection, it should be pointed out that in the original paper and in both the American and German abstracts,[13] the structure of the product is incorrectly given: the two carbon atoms holding the hydroxyl groups are omitted and the formula is represented as $(C_6H_5)_2Sn\left[\ (C_6H_5)_2C_6H_4OH\ \right]_2$. (The theoretical values of the analyses were calculated for the correct formula.) In addition, the proportion of the reactants is incorrectly given in the American abstract, which states that the reaction of 0.15 mole of di-p-carbethoxyphenyltin dichloride with 0.16 mole of phenylmagnesium bromide gave a seventy-two per cent yield of the tertiary alcohol. This is obviously impossible, since six moles of the Grignard reagent are theoretically required for each mole of the dichloride; actually there was used 0.015 mole of the dichloride and the Grignard reagent prepared from 0.16 mole of bromobenzene and 0.15 gram atom of magnesium.

Two tetraaryltin compounds containing alcoholic hydroxyl groups were prepared recently by Artnzen.[17] These were triphenyl-o-hydroxymethylphenyltin, $(C_6H_5)_3SnC_6H_4CH_2OH$-o, and triphenyl-p-hydroxymethylphenyltin. The method of synthesis of these compounds was similar to that used in the preparation of o- or p-hydroxyphenyltriphenyltin, and involved halogen-metal interconversion of o- or p-bromobenzyl alcohol, conversion of the product to the Grignard reagent by means of magnesium bromide, and reaction of the Grignard reagent with triphenyltin chloride.-

A patent by Oechslin[28] describes a method for the synthesis of hydroxyalkylstannonic acids. The method involves the action of stannous chloride on chlorohydrins or bromohydrins in the presence of alkali hydroxides. Thus, with ethylene chlorohydrin, β-hydroxyethylstannonic acid was formed:

$$SnCl_2 + 2NaOH + HOCH_2CH_2Cl \longrightarrow HOCH_2CH_2SnOOH + 2NaCl + H_2O$$

Similarly, dihydroxypropylstannonic acid was obtained from the reaction of stannous chloride with glycerol monobromohydrin. The hydroxyalkylstannonic acids were difficult to isolate, decomposed at relatively low temperatures, and were sensitive to acids, even in the cold. They were converted to the dithio acid anhydrides by treatment with barium chloride and hydrogen sulfide. These thio anhydrides, unlike the thio anhydrides from unsubstituted alkylstannonic acids, were unstable compounds which decomposed with the loss of their organic constituents in the presence of acids or upon heating.

Organotin compounds containing miscellaneous functional groups

A number of alkylstannonic acids were prepared by Lesbre and Glots,[29] and among these acids were some containing reactive functional groups. The method of preparation involved the reaction of mono- or polyhalides on potassium stannite in strongly alkaline medium. Dichloromethylstannonic

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[28] Oechslin and Poulenc Frères, French patent, 582,412 (1923) [Chem. Zentr., I, 3361 (1926)] ; U.S. patent, 1,575,738 [C.A., 20, 1415 (1926)]; see also Krause and von Grosse, "Die Chemie der metall-organischen Verbindungen," Borntraeger, Berlin (1937), p. 332.

[29] Lesbre and Glots, Compt. rend., 198, 1426 (1934).

acid, β-bromoethylstannonic acid, and acetonylstannonic acid, CH_3COCH_2SnOOH, were obtained from the halides, chloroform, ethylene dibromide, and chloroacetone, respectively. The acids were amorphous and infusible solids, insoluble in organic solvents but soluble in acids or bases. They decomposed on heating to 50° in the moist state.

Leeper[16] studied the reaction of tin powder with the following dihalides: 1-chloro-2-iodoethane, 1-bromo-2-chloroethane, and 1-bromo-3-chloropropane. From the first he obtained a red liquid which was probably impure di-β-chloroethyltin diiodide. No pure organotin compound could be isolated from the reactions of tin powder with the other two dihalides.

A reaction occurred between tri-n-propyltin bromide and diazoethane to give, after distillation, a product which contained halogen but which decomposed before it could be analyzed.[16]

No organotin compound containing the carbonyl group was isolated from the reaction of phenacyl bromide with powdered tin.[16] The dark-colored product could not be crystallized or distilled.

The reaction of tetraphenyltin with chlorosulfonic acid was studied by Arntzen,[17] who was interested in the preparation of an organotin compound containing an arylsulfonyl chloride or an arylsulfonamide grouping. From the reaction of tetraphenyltin with a large excess of chlorosulfonic acid at -75°, there was obtained, after the reaction mixture had been poured on ammonium hydroxide, only metastannic acid and a small amount of benzenesulfonamide. From the reaction with only two equivalents of

chlorosulfonic acid, carried out in petroleum ether and subsequently treated with liquid ammonia, the products were metastannic acid, diphenylsulfone, and unreacted tetraphenyltin.

The stability of tetraphenyltin and of triphenyl-o-hydroxyphenyltin toward strong alkali was investigated by Arntzen[17] prior to attempting a Reimer-Tiemann reaction with organotin compounds. It was found that tetraphenyltin was not affected by refluxing for three hours with alcoholic sodium hydroxide. However, similar treatment of triphenyl-o-hydroxyphenyltin resulted in decomposition of the organotin compound, so no Reimer-Tiemann reaction was attempted.

Arntzen[17] also studied the reaction of phenylboric acid with stannic chloride, in the hope that the method might subsequently be applied to the synthesis of some organotin compounds containing water-solubilizing groups. It was found that phenylboric acid did not react with stannic chloride; therefore, the action of other arylboric acids on stannic chloride was not investigated.

Summary

The known organotin compounds containing water-solubilizing groups are limited to a few representatives of the types with carboxyl, substituted amino, and phenolic and alcoholic hydroxyl groups. Nitro groups have been introduced into organotin compounds, but the products were not well-defined substances, and no studies of their behavior toward reducing agents have been reported. The sulfonation of organotin

compounds apparently has not been studied; the chlorosulfonation of tetraphenyltin did not result in the formation of any organotin compound containing the arylsulfonyl chloride group. Several carbalkoxy-substituted organotin compounds have been prepared, but their saponification to the carboxylic acids has not been reported. No attempt to prepare an organotin carboxylic acid by carbonation of a Grignard reagent obtained from any of the known halogen-substituted alkyl or aryl organotin compounds has been described in the literature.

The methods which have been applied successfully to the synthesis of organotin compounds containing functional groups are, for the most part, rather limited in their application. The general methods for the preparation of unsubstituted alkyl or aryl organotin compounds are either not applicable to the synthesis of the types containing water-solubilizing groups, or they give only poor yields of such types.

Organolead Compounds

The great interest in organolead compounds as therapeutic agents in the treatment of cancer[1] has resulted in numerous attempts, especially in recent years, to prepare organolead compounds containing water-solubilizing groups. The introduction of such groups might not only increase the solubility in water of some organolead compounds, but might also effect a "masking" of the lead atom, thereby reducing the toxicity of these compounds.

The first investigation undertaken with the express purpose of

preparing water-soluble organolead compounds was that of Robinson[30] which was reported in 1929. The first organolead compound containing a water-solubilizing group was triphenyl-2,3-dihydroxypropyllead, the preparation of which was described by Austin[31] in 1931. The earlier work of Vorländer[24] on the nitration of diphenyllead dinitrate is of interest in connection with the introduction of groups not in themselves water-solubilizing but which might serve as intermediates in the preparation of compounds containing water-solubilizing groups. Compounds containing other intermediate groups than the nitro (the bromophenyl, bromoalkyl, and carbalkoxy groups) are also discussed in this section.

The introduction of water-solubilizing groups into organolead compounds has been discussed briefly by Leeper.[32]

Organolead compounds containing carbalkoxy groups

Prior to the present study, the only organolead compounds containing ester groupings were triphenylcarbethoxymethyllead and triphenyl-α-benzyl-α-carbethoxymethyllead. These compounds were prepared by Kocheshkov and Aleksandrov[33] from the triphenyllead salts of monoethyl acid malonate

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[30]Robinson, J.D., Doctoral Dissertation, Iowa State College (1929).

[31]Austin, J. Am. Chem. Soc., 53, 3514 (1931).

[32]Leeper, Doctoral Dissertation, Iowa State College (1942). This work lists in tabular form the known organolead compounds with their melting or boiling points.

[33]Kocheshkov and Aleksandrov, Ber., 67, 527 (1934).

and monoethyl acid α-benzylmalonate, respectively. These salts, when heated under vacuum, lost carbon dioxide with the formation of a carbon-lead bond. The hydrolysis of one of the above-mentioned esters to a carboxylic acid, which was recently accomplished by Stuckwisch, is discussed in the next section.

The preparation of some carbalkoxy-substituted organolead compounds by means of a modified Reformatsky reaction[34] using magnesium[35] and other metals instead of zinc was studied by Robinson[30] and by Towne.[36] The reaction of triethyllead chloride with ethyl bromoacetate or with ethyl α-bromopropionate in the presence of magnesium gave only tetraethyllead, metallic lead, and inorganic lead salts.[30] Robinson obtained no better result from an experiment in which triphenyllead bromide was used. From the reaction of triphenyllead chloride, magnesium, and ethyl bromoacetate, Towne[36] obtained only tetraphenyllead, triphenyllead bromide, and unreacted triphenyllead chloride. Similarly, no organolead compound containing a carbethoxy group was produced in any of the following reactions: triphenyllead chloride, magnesium, and ethyl chloroacetate; triphenyllead bromide, magnesium, and ethyl bromoacetate; triethyllead bromide, zinc-copper couple, and ethyl bromoacetate; triethyllead bromide, sodium, and ethyl bromoacetate.

The malonic ester condensation betwesn triphenyllead chloride and sodium malonic ester, attempted by Robinson,[30] gave none of the expected

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[34]Reformatsky, Ber., 20, 1210 (1887).

[35]Zeltner, Ber., 41, 589 (1908).

[36]Towne, E.B., Doctoral Dissertation, Iowa State College (1932).

carbethoxy organolead compound. There was found, in addition to unchanged starting materials, a mixture which probably contained tetraethyllead and diethyl malonate.

The reaction of organolead-sodium compounds with halides containing other functional groups in addition to the halogen has been unsuccessful when applied to the synthesis of organolead compounds with functional groups. Bindschadler[37] isolated only p-bromobenzamide from the reaction of triphenyllead-sodium with methyl p-bromobenzoate in liquid ammonia. Leeper[32] treated triphenyllead-sodium with ethyl α,β-dibromosuccinate, but obtained no pure product.

The reaction of bromoesters with lead powder was unsuccessful, in contrast to the similar reaction in the tin series (previously discussed) which resulted in the formation of what are believed to be dicarbalkoxytin dihalides. Leeper[32] recovered the starting materials quantitatively from the attempted reaction of lead powder with ethyl α-bromopropionate. Likewise, no reaction took place between lead powder and bromomethyl acetate or ethyl bromoacetate.

<u>Organolead compounds containing the carboxyl group</u>

The first organolead compound containing the carboxyl group was α,β-di-(triphenyllead)-succinic acid, prepared by Leeper[32] by the

$$\begin{array}{l}(C_6H_5)_3PbCHCOOH \\ \quad\quad\quad\quad | \\ (C_6H_5)_3PbCHCOOH\end{array}$$

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[37]Bindschadler, Doctoral Dissertation, Iowa State College (1941).

reaction of hexaphenyldilead with maleic anhydride. The acid was an amorphous, infusible powder, insoluble in the common organic solvents except glacial acetic acid, and slightly soluble in hot water. It was converted to the equally insoluble sodium salt by refluxing with ten per cent sodium hydroxide solution in the presence of a small amount of dioxane.

The inner anhydride of diethyl-o-carboxyphenyllead hydroxide was obtained by Abbott[38] from the reaction between triethyllead chloride and the organolithium compound prepared by halogen-metal interconversion of o-bromobenzoic acid with n-butyllithium. The anhydride dissolved readily upon warming with base, but on acidification of the alkaline solution the anhydride was immediately formed again. Consequently, the free acid could not be isolated.

The preparation of triphenyl-p-carboxyphenyllead, which is described in the experimental part of this work, was accomplished by a method that was subsequently applied to the synthesis of the corresponding organotin compound (see page 14).

Stuckwisch[39] obtained triphenylcarboxymethyllead by alkaline hydrolysis of triphenylcarbethoxymethyllead, prepared according to the procedure of Kocheshkov and Aleksandrov.[33] The sodium salt of this carboxylic acid was not appreciably soluble in water. Triethylcarboxymethyllead was recently prepared by Stuckwisch[39] by permanganate oxidation

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[38]Unpublished studies by R.K. Abbott.

[39]Unpublished studies by C.G. Stuckwisch.

of the dimer of triethylallyllead. The acid was somewhat soluble in water, and its sodium salt was readily soluble in the same solvent. No oxidation product was formed by the ozonolysis of the triethylallyllead dimer.[39]

Robinson[30] made two attempts to oxidize triethylallyllead with aqueous permanganate, but found no carboxylic acid as product. The neutral oil from the reactions was not identified, but it was thought to be the original organolead compound.

The preparation of carboxyphenyllead compounds by permanganate oxidation in acetone was attempted by Austin.[40] From experiments with tetra-o-tolyllead, tetra-p-tolyllead, triphenyl-p-tolyllead, and tri-o-tolyllead chloride, no organolead compound other than unreacted material was isolated. The recovery averaged between sixty-four and eighty-four per cent. Oxidation of hexa-p-tolyldilead (tri-p-tolyllead) resulted in the formation of triphenyllead acetate, which was probably formed from triphenyllead hydroxide and acetic acid produced by oxidation of some of the acetone used as solvent. Treatment with hydrochloric acid of the product of oxidation of hexa-o-tolyldilead by permanganate gave tri-o-tolyllead chloride, indicating that tri-o-tolyllead hydroxide had been formed. The work of Austin on the oxidation of triphenylallyllead[40] is discussed in the section on organolead compounds containing the hydroxyl group.

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[40]Austin, J. Am. Chem. Soc., 53, 3514 (1931).

Hurd and Austin[41] found that no organolead compound was produced by the pyrolysis of lead tetrabenzoate or lead tetraacetate. Dimroth[42] had obtained organomercury compounds by a similar pyrolysis of the mercuric salts of some organic acids. Pyrolysis of lead tetrabenzoate was accompanied by a mild explosion. Benzoic acid was given off, but the only lead compound isolated from the residue was lead benzoate. Similarly, lead tetraacetate gave upon pyrolysis only acetic acid and lead acetate.

No iodophenyllead compounds are known. Robinson[30] prepared tetra-p-bromophenyllead, triphenyl-p-bromophenyllead, and diphenyldi-p-bromophenyllead, and made numerous attempts to prepare a Grignard reagent from each of these compounds. However, these halides did not appear to react with magnesium, and carbonation of the reaction mixture produced no carboxylic acid. Robinson also prepared impure triethyl-p-bromophenyllead; this compound decomposed on attempted distillation. The undistilled oil from a second preparation was refluxed with magnesium in dry ether, but no Grignard reagent was formed.

Gilman, Moore, and Jones[43] proposed the synthesis of carboxyphenyllead compounds by the carbonation of an organolithium compound prepared either by metalation of an organolead compound of the type $R_3PbC_6H_5$ by means of an alkyllithium compound, or by halogen-metal

$$R_3PbC_6H_5 + R'Li \longrightarrow R_3PbC_6H_4Li + R'H$$

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[41]Hurd and Austin, ibid., 53, 1543 (1931).

[42]Dimroth, Ber., 35, 2870 (1902).

[43]Gilman, Moore, and Jones, J. Am. Chem. Soc., 63, 2482 (1941).

interconversion of an organolead compound of the type $R_3PbC_6H_4Br$-p with an alkyllithium compound.

$$R_3PbC_6H_4Br + R'Li \longrightarrow R_3PbC_6H_4Li + R'Br$$

Both of these reactions were unsatisfactory, since it was shown that metal-metal interconversion took place more rapidly than either metalation or halogen-metal interconversion. In experiments using triphenyl-p-bromophenyllead in benzene-petroleum ether solution with t- or s-butyllithium in petroleum ether, no lead-containing acid was obtained. The recovery of triphenyl-p-bromophenyllead averaged above ninety per cent.

Grüttner and Krause[44] prepared the lead heterocycle, diethyl-cyclopentamethylenelead, and they obtained from it the compounds, diethyl-5-bromoamyllead bromide, triethyl-5-bromoamyllead, and triethyl-n-amyllead, by a series of reactions paralleling those already described for the tin analogs. The last-named compound was produced by the action of water on the Grignard reagent derived from triethyl-5-bromoamyllead. Robinson[30] prepared triethyl-5-bromoamyllead by the method of Grüttner and Krause, and found that it reacted with magnesium. However, no acidic substance was formed on carbonation of the reaction product; the only substances isolated were triethyl-n-amyllead and some unchanged starting material.

Organolead compounds containing the nitro group

The nitration of tetraphenyllead was first studied by Vorländer,[24] who obtained no definite organolead compound, and found as products of

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[44] Grüttner and Krause, Ber., 49, 2666 (1916).

treatment with a mixture of nitric and sulfuric acids only nitrobenzene, m-dinitrobenzene, and a brown, flaky substance which exploded on heating. The nitration with a similar mixture of acids at -50°, studied by Leeper,[32] yielded only nitrobenzene, lead sulfate, and unreacted tetraphenyllead.

Vorländer[24] was successful in nitrating the more stable diphenyllead dinitrate, which, upon heating in a sealed tube with fuming nitric acid, gave a product that was shown to be di-m-nitrophenyllead dinitrate by analysis and by cleavage with bromine to form m-bromonitrobenzene. Later, Challenger and Rothstein[25] nitrated diphenyllead dinitrate with a mixture of fuming nitric and concentrated sulfuric acids at -15 to -10°, and isolated from the reaction di-m-nitrophenyllead dinitrate dihydrate. Nitration was shown to have taken place to the extent of ninety-six per cent in the position meta to the lead atom by cleavage with bromine to give a mixture of bromonitrobenzenes which was analyzed by Dimroth's method[45] and by thermal analysis.

Schmidt[46] prepared dinitrophenyllead oxide (probably di-m-nitrophenyllead oxide) by nitration of diphenyllead diacetate with fuming nitric acid without external cooling. The reduction of the nitro compound is described in the next section.

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[45]Dimroth, Ann., 446, 148 (1925).

[46]Schmidt, "Medicine in its chemical aspects," Bayer, Leverkusen, Germany (1938), Vol. III, p. 400. This originally appeared in Med. u. Chem. Abhandl. med.-chem. Forschungsstatten, I. G. Farbenind., 3, 418 (1936) [C. A., 31, 5866 (1937)].

The nitration of diphenyllead dichloride with nitric and sulfuric acids was attempted by Leeper,[32] but no pure product was isolated. However, Leeper was able to prepare di-m-nitrophenyllead dichloride and di-m-nitrophenyllead diiodide by the action of aqueous sodium chloride and sodium iodide, respectively, on di-m-nitrophenyllead dinitrate, prepared by a slight modification of the procedure of Challenger and Rothstein.[25] Triphenyllead nitrate was also nitrated by this modified procedure to give tri-m-nitrophenyllead nitrate,[32] a crystalline compound which decomposed with the formation of inorganic lead salts on standing. No pure product could be isolated from the nitration of triphenyllead chloride by the same method.

Bindschadler[37] was unable to prepare nitrophenyllead compounds by the reaction of triphenyllead-sodium with halogen-substituted aromatic nitro compounds. The reaction of triphenyllead-sodium with p-iodonitrobenzene produced hexaphenyldilead, tetraphenyllead, and inorganic lead salts. When the halide used was 2,4-dinitrochlorobenzene, there was obtained only unreacted starting material and a tar from which no pure product could be isolated.

Organolead compounds containing primary amino groups

The first aminophenyllead compounds (in which the amino groups are primary) were prepared by Schmidt.[46] Reduction of di-m-nitrophenyllead oxide with titanium trichloride in alcoholic hydrochloric acid led to the formation of di-m-aminophenyllead dichloride, which was slightly soluble

in water. It was reported that the amino groups in this compound could be detected by diazotization and coupling and also by the formation of Schiff's bases. The dichloride was converted to the dihydroxide by treatment with aqueous sodium hydroxide, and the dihydroxide reacted with sodium catecholdisulfonate to give the sodium salt of diamino-diphenyllead catecholdisulfonic acid. This salt was readily soluble in water.

Two tetraaryllead compounds containing the amino group have been prepared. These are triphenyl-o-aminophenyllead[47] and triphenyl-p-aminophenyllead,[48] obtained from the reaction of triphenyllead chloride with the organolithium compounds prepared by halogen-metal interconversion of o-bromoaniline and p-bromoaniline, respectively. It was first reported that it was necessary to convert the organolithium compound to the Grignard reagent by treatment with magnesium bromide[48] before the organometallic compound was added to the triphenyllead chloride. However, later work[47] showed that this conversion was unnecessary if the time of reaction was made very short. The hydrochloride of triphenyl-p-aminophenyllead, insoluble in water and in ether, was formed when dry hydrogen chloride was bubbled through an ethereal solution of the free amine.

Triphenyl-p-aminophenyllead was diazotized and coupled with β-naphthol in the usual manner to form the azo lead compound, triphenyl-1-(2-hydroxy-naphthyl)-azophenyl-4-lead.[47] In general, however, the diazotization

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[47]Stuckwisch, Doctoral Dissertation, Iowa State College (1943).

[48]Gilman and Stuckwisch, J. Am. Chem. Soc., 64, 1007 (1942).

of the triphenylaminophenyllead compounds was not a satisfactory reaction, probably because of the extensive cleavage of the aminophenyl groups in acid solution.

The reduction of di-m-nitrophenyllead dibromide by several reducing agents and under various conditions was studied by Kocheshkov and Borodina.[49] These workers were interested chiefly in the length of time required for complete reduction with simultaneous cleavage to form aniline, and they reported the preparation of no aminophenyllead compounds.

Towne[36] heated the double salt of aniline and lead acetate, but no rearrangement occurred to form an aminoaryllead compound.

Organolead compounds containing substituted amino groups

The only known organolead compound containing a monosubstituted amino group is triphenyl-p-N-methylaminophenyllead. This compound was prepared by Stuckwisch[47] from triphenyllead chloride and the organolithium compound obtained from p-bromo-N-methylaniline by halogen-metal interconversion.

Tetra-p-dimethylaminophenyllead was prepared by Austin[26] by the reaction of p-dimethylaminophenyllithium with lead chloride. The yields of this compound and of di-p-dimethylaminophenyldiphenyllead, which was prepared by the reaction of p-dimethylaminophenyllithium with diphenyllead dichloride, were rather low (less than twenty per cent). However, the

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[49] Kocheshkov and Borodina, Bull. acad. sci. U.R.S.S., Classe sci. math. nat., Sér. Chim., 569 (in English 576), 1937 [C. A., 32, 2095 (1938)].

action of the same organolithium compound on triphenyllead chloride produced triphenyl-p-dimethylaminophenyllead in a yield of seventy-seven per cent. Austin showed that it was necessary to use equimolecular proportions of the two reactants when organolithium compounds were used in the reaction with triphenyllead chloride or diphenyllead dichloride to prepare unsymmetrical organolead compounds. An excess of the organolithium compound brought about replacement of the aryl groups already attached to lead. It was also found that these reactions were satisfactory only when a large proportion of ether was present as solvent; when benzene was used the reaction of aryllead chlorides with p-dimethylaminophenyllithium did not give the expected products.

Bailie[50] was unable to prepare the so-called free radical, "tri-p-dimethylaminophenyllead", by the reaction of p-dimethylaminophenyllithium with an excess of lead chloride. The only organolead compound formed under the conditions of the experiment was tetra-p-dimethylaminophenyllead.

Stuckwisch[47] prepared triphenyl-o-dimethylaminophenyllead by the method of Austin, using o-dimethylaminophenyllithium instead of the para isomer. Triethyl-p-dimethylaminophenyllead, a distillable oil, was obtained from the reaction of triethyllead chloride and p-dimethylaminophenyllithium.[47]

A number of azo lead dyes were synthesized by Stuckwisch[47] by means of coupling reactions between triphenyl-o-dimethylaminophenyllead and some

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[50]Bailie, J.C., Doctoral Dissertation, Iowa State College (1938).

substituted aryldiazonium chlorides. In each case the coupling took place in the position para to the dimethylamino group and meta to the lead atom. The following groups were introduced by this means into the 5-position of triphenyl-2-dimethylaminophenyllead: p-chlorophenylazo, p-bromophenylazo, p-iodophenylazo, p-nitrophenylazo, and p-carboxyphenylazo. The sodium salt of the azo compound obtained by the coupling reaction with p-carboxybenzenediazonium chloride was somewhat soluble in water.

By the reaction of triethyllead chloride with the organolithium compound obtained from p-bromo-N-phenylphthalimide by halogen-metal interconversion, Stuckwisch[47] prepared triethyl-p-(N-phthalimido)-phenyllead. This compound could be distilled under high vacuum. No triethyl-p-aminophenyllead could be isolated from attempted hydrolysis of the phthalimide derivative; the only product isolated was phthalic acid.

Two organolead compounds containing the 2-pyridyl groups were prepared by Gregory.[51] Diphenyl-2-pyridyllead iodide was produced by the reaction of diphenyllead diiodide with 2-pyridylmagnesium bromide, formed by halogen-metal interconversion of 2-bromopyridine and subsequent treatment with magnesium bromide. The $R_2R'PbI$ compound was the only product even when an excess of the Grignard reagent was used. Triphenyl-2-pyridyllead was obtained by the reaction of diphenyl-2-pyridyllead iodide with phenylmagnesium bromide. No pyridyllead compounds were produced in the reaction of 2-pyridylmagnesium bromide with triphenyllead chloride or iodide, or in the reaction of 2-pyridyllithium with various phenyllead halides.

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[51]Gregory, W.A., Master's Thesis, Iowa State College (1942).

Organolead compounds containing hydroxyl groups

The only organolead compound containing a phenolic hydroxyl group is triphenyl-o-hydroxyphenyllead, which was prepared by Leeper[32] in a low yield by the reaction of triphenyllead chloride with the organolithium compound obtained by halogen-metal interconversion of o-bromophenol. In this preparation, the reactants were refluxed for one hour in ether-benzene solution. Stuckwisch[47] was able to improve the yield of triphenyl-o-hydroxyphenyllead by shortening the time of reaction and by using as solvent ether only. The reaction of triphenyllead chloride with the organolithium compound prepared from p-bromophenol by halogen-metal interconversion did not give the expected triphenyl-p-hydroxyphenyllead.[47]

By means of a coupling reaction similar to that employed in the preparation of azo lead dyes from triphenyl-o-dimethylaminophenyllead, Stuckwisch[47] prepared azo compounds in which the 5-position of triphenyl-2-hydroxyphenyllead was substituted with the following groups: p-chlorophenylazo, p-bromophenylazo, p-iodophenylazo, and p-carboxyphenylazo. The sodium salt of the azo compound containing the p-carboxyphenylazo group was soluble in water. The reaction of triphenyl-2-hydroxyphenyllead with p-nitrobenzenediazonium chloride produced a dye in which both the 3- and 5-positions of the hydroxyphenyl group were substituted with p-nitrophenylazo groups. p,p'-Biphenylenetetrazonium chloride reacted with two molecules of the 2-hydroxyphenyllead compound to form a coupling product in which the azo groups were attached in the 5-positions of each of the two organolead residues.

The only organolead compound containing the alcoholic hydroxyl group which was known prior to the present study was triphenyl-2,3-dihydroxypropyllead. A small amount of this compound was obtained by Austin[40] from permanganate oxidation of triphenylallyllead in acetone. The main product of the oxidation was an alkali-insoluble solid which possessed no definite melting point. It was probably triphenyllead hydroxide, since it was converted to triphenyllead acetate by treatment with acetic acid. Triphenyl-2,3-dihydroxypropyllead was a white, crystalline compound, which could be crystallised from dilute alcohol.

Ozonization of triphenylallyllead[40] resulted in the elimination of the allyl group with the formation of an amorphous product which Austin concluded was triphenyllead oxide (or hydroxide), because it was converted to triphenyllead acetate by the action of acetic acid.

Very recently, Stuckwisch[39] synthesized triethyl-β-hydroxyethyllead by the reaction of triethyllead-sodium in ether with ethylene oxide, followed by hydrolysis of the product with water. The hydroxyethyllead compound was a pale yellow oil which could be distilled under reduced pressure.

Organolead compounds containing miscellaneous functional groups

Bindschadler[37] was unable to prepare triphenyl-β-bromethyllead by the reaction of triphenyllead-sodium with ethylene dibromide. When one equivalent of the dibromide was used, hexaphenyldilead was formed in a yield of eighty per cent. When a large excess of the dibromide

was used, the products found in the non-volatile residue remaining after steam distillation of the reaction mixture were triphenyllead hydroxide, tetraphenyllead, and hexaphenyldilead.

No reaction took place between triethyllead chloride and either diazomethane or diazoethane.[32] The reaction expected was the elimination of nitrogen with the formation of triethylchloroalkyllead compounds.

Leeper[32] attempted the sulfonation of tetraphenyllead. From an experiment in which tetraphenyllead was added to fuming sulfuric acid at 0°, the only lead-containing products were inorganic lead salts.

The reaction of metals with some complexes between lead salts and aryldiazonium chlorides was studied extensively by Towne,[36] who was unable to prepare any organolead compounds by this method. Nesmeyanov, Kocheshkov, and Klimova[52] obtained a very small yield of triphenyllead chloride from the decomposition of the benzenediazonium chloride-lead tetrachloride complex in ether by zinc dust. Treatment of the benzenediazonium chloride-lead dichloride complex with copper powder gave a very small amount of diphenyllead dichloride. Similar treatment of the benzenediazonium bromide-lead dibromide complex gave no better result. Because of the low yields in these experiments, the method was not applied to the synthesis of organolead compounds containing water-solubilizing groups.

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[52] Nesmeyanov, Kocheshkov, and Klimova, Ber., 68, 1877 (1935).

Summary

The known organolead compounds containing water-solubilising groups include a few representatives of the types with carboxyl, amino and substituted amino, and phenolic and alcoholic hydroxyl groups. Nitro groups have been introduced, and in one case, these were reduced to primary amino groups. An attempt to sulfonate tetraphenyllead was unsuccessful. The general methods of preparing carbalkoxy-substituted organotin compounds have been unsuccessful when applied in the organolead series. However, two carbalkoxy-substituted organolead compounds have been prepared, and one of these has been hydrolyzed to the corresponding carboxylic acid. Attempts to prepare organolead carboxylic acids by carbonation of Grignard reagents derived from halogen-substituted alkyl or aryl organolead compounds have proved unsuccessful. The attempted preparations of organolead acids by oxidation reactions have failed in most cases. No alkylplumbonic or arylplumbonic acids containing water-solubilising or reactive functional groups are known.

It may be stated that, in general, the methods of introducing water-solubilising groups into organotin compounds fail or are less successful when applied in the organolead series. An exception to this statement is found in the coupling reaction between aryldiazonium chlorides and aryl organolead or organotin compounds containing activating groups such as the dimethylamino or hydroxyl groups. This coupling reaction has been quite satisfactory in the case of organolead compounds, but has

succeeded in the case of only one organotin compound.

The statement that was made in summarizing the work on organotin compounds applies equally well to the organolead compounds; that is, the general methods for the preparation of unsubstituted alkyl or aryl organolead compounds are not applicable to the synthesis of the types containing water-solubilizing groups, or they give only poor yields of such types.

EXPERIMENTAL

Halogen-Metal Interconversion Reactions

The halogen-metal interconversion reaction,[2,3,4] between aromatic halides and n-butyllithium has been shown to be an excellent method for the preparation of organolithium compounds from halides which react only to a slight extent or not at all with lithium metal or with magnesium to form a Grignard reagent. The present study includes some investigations of the halogen-metal interconversion reaction with: (1) compounds containing so-called "unreactive" halogen atoms, and (2) aromatic halides containing functional groups which cannot be introduced into organolead compounds by the customary procedures for the preparation of organolead compounds.

Preparation of n-butyllithium

The n-butyllithium used in these reactions was prepared by the usual method, which is rather extensively reported in the literature,[4,53,54] and is therefore discussed only briefly here. The apparatus consisted of a three-necked flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel. The entire apparatus was dried thoroughly and flushed with dry, oxygen-free nitrogen before the reagents were added.

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[53]Gilman, Zoellner, and Selby, J. Am. Chem. Soc., 54, 1957 (1932).

[54]Gilman, Langham, and Moore, ibid., 62, 2327 (1940).

During the preparation the reaction mixture was kept under a slight pressure of nitrogen.

The earlier preparations of n-butyllithium were obtained in approximately 0.5 molar solution in diethyl ether and in apparent yields of about 50 per cent, as determined by a single acid titration. The n-butyl bromide, dissolved in about one-half of the total volume of ether used, was added slowly to a slight excess of lithium suspended in the remainder of the ether. The concentrations of n-butyllithium in the product were determined by hydrolysing an aliquot portion with water and then titrating the total base with standard acid.[55] The concentrations and yields as determined by this method are about 15 per cent higher than the actual values.

The more recent preparations were obtained in concentrations of nearly 1 molar and in yields of 40 to 50 per cent. The method is discussed in more detail elsewhere.[47] A small amount of n-butyl bromide was added to the ether suspension of lithium and, after a vigorous reaction had begun, the reaction vessel was cooled in an ice bath and the rest of the halide added so rapidly that ether continued to reflux from the cooled solution. The reaction mixture was allowed to come to room temperature with continued stirring after all the halide had been added. The concentrations and yields were determined by the double titration method of Haubein,[56] and the values are much more accurate than those determined by the single titration.

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[55]Gilman, Wilkinson, Fishel, and Myers, ibid., 45, 150 (1923).

[56]Haubein, A.H., Doctoral Dissertation, Iowa State College (1942).

The n-butyllithium prepared by either method was allowed to stand for about two hours and was then decanted from any solid residue and unreacted lithium through a sintered glass plate or through glass wool into a dropping funnel or the reaction vessel to be used for the interconversion. The titrations mentioned above were carried out on aliquot portions taken from supernatant or filtered solutions.

General procedure for the interconversion reactions

The reactions were carried out in an apparatus similar to that described for the preparation of n-butyllithium. In general, the aromatic halide, dissolved in ether, was added from a dropping funnel to an ether solution of n-butyllithium of known volume and concentration. Any variations in the procedure, such as cooling or refluxing of the reaction and variation of the solvent used, are noted in the discussion of specific reactions. If it is not otherwise stated, the reaction was carried out at room temperature.

In the case of interconversions of halides containing functional groups with active hydrogen atoms (hydroxyl, sulfonamide, etc.), the n-butyllithium solution was always added to the halide. This order of addition was adopted as a result of the suggestion made by Arntzen (who applied the halogen-metal interconversion reaction to the preparation of some organotin compounds)[17] that, when the halide was added to the n-butyllithium solution, the following reactions might occur to some extent, as illustrated with p-bromobenzyl alcohol:

$$\underline{p}\text{-}BrC_6H_4CH_2OH + \underline{n}\text{-}C_4H_9Li \longrightarrow \underline{p}\text{-}BrC_6H_4CH_2OLi + \underline{n}\text{-}C_4H_{10}$$

$$\underline{p}\text{-}BrC_6H_4CH_2OLi + \underline{n}\text{-}C_4H_9Li \longrightarrow \underline{p}\text{-}LiC_6H_4CH_2OLi + \underline{n}\text{-}C_4H_9Br$$

$$\underline{p}\text{-}LiC_6H_4CH_2OLi + \underline{p}\text{-}BrC_6H_4CH_2OH \longrightarrow C_6H_5CH_2OLi + \underline{p}\text{-}BrC_6H_4CH_2OLi$$

The occurrence of the reaction shown in the last of the above equations would result in the loss of some of the desired interconversion product. Accordingly, it was decided to add the n-butyllithium to the halide in all such cases. By this means an excess of the n-butyllithium was avoided throughout the entire addition, and all the active hydrogen was replaced before any interconversion could occur.

$$\underline{p}\text{-}BrC_6H_4CH_2OH + \underline{n}\text{-}C_4H_9Li \longrightarrow \underline{p}\text{-}BrC_6H_4CH_2OLi + \underline{n}\text{-}C_4H_{10}$$

$$\underline{p}\text{-}BrC_6H_4CH_2OLi + \underline{n}\text{-}C_4H_9Li \longrightarrow \underline{p}\text{-}LiC_6H_4CH_2OLi + \underline{n}\text{-}C_4H_9Br$$

The nature and yields of the interconversion products were determined by carbonation of the reaction mixture and isolation of the resulting acid. In general, the mixtures obtained from carbonation were hydrolysed with water and extracted with 10 per cent potassium hydroxide solution. In some cases it was necessary to acidify in order to decompose lithium carbonate before making the extraction with alkali. The alkaline extract was acidified with dilute mineral acid to liberate the organic acid, which was filtered off directly or extracted with ether. The yields of crude acids were significant in most cases, since the acids obtained were solids and could usually be freed without recrystallization from the relatively volatile and water-soluble n-valeric acid resulting from the carbonation of excess n-butyllithium. In any case, yields of organolithium compounds as determined by carbonation are minimal, because of side reactions occurring during the carbonation process.

2,4,5-Triphenyl-3-bromofuran and n-butyllithium

The 2,4,5-triphenyl-3-bromofuran used in this experiment was kindly supplied by Dr. C.F.H. Allen. A solution of 3.75 g. (0.01 mole) of 2,4,5-triphenyl-3-bromofuran in 50 cc. of ether was added rapidly to a solution of 0.02 mole of n-butyllithium (single titration) in 50 cc. of ether. The reaction mixture was stirred for thirty minutes and then carbonated by pouring on crushed solid carbon dioxide. Acidification of the alkaline extract yielded 2.67 g. (78 per cent) of crude acid, melting at 241-244°. After crystallisation from glacial acetic acid there was obtained 2.23 g. or a 66 per cent yield of pure, white 2,4,5-triphenylfuran-3-carboxylic acid, melting at 257-258°. This acid begins to sublime at 210°.

Anal. Calcd. for $C_{23}H_{16}O_3$: neut. equiv., 340. Found: neut. equiv., 333, 347.

The structure of the acid was proved by its decarboxylation to give the known 2,3,5-triphenylfuran.[57] A 0.5 g. portion of the acid was mixed intimately with 1.0 g. of soda lime. From this mixture there was obtained by strong heating 0.3 g. (69 per cent) of an oily material which solidified on rubbing to give a product melting at 84-87°. Treatment with Norite and crystallization from alcohol gave 0.13 g. (30 per cent) of 2,3,5-triphenylfuran, melting at 93-94°, identified by a mixed melting point with an authentic specimen (kindly supplied by Dr. R.E. Lutz).

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[57]Japp and Klingemann, J. Chem. Soc., 57, 674 (1890).

Methyl 2,4,5-triphenylfuran-3-carboxylate

A suspension of 0.5 g. of 2,4,5-triphenylfuran-3-carboxylic acid in 10 cc. of ether was treated with 6 cc. of an ethereal solution containing excess diazomethane. After the solvent and unreacted diazomethane had been evaporated, the residue was crystallized from alcohol to give 0.44 g. (85 per cent) of methyl 2,4,5-triphenylfuran-3-carboxylate, white needles melting at 123.5-124°.

Anal. Calcd. for $C_{24}H_{18}O_3$: methoxyl, 8.76. Found: methoxyl, 8.84.

2,4,5-Triphenyl-3-chlorofuran and n-butyllithium

A solution of 1.0 g. (0.003 mole) of 2,4,5-triphenyl-3-chlorofuran (obtained from Dr. R.E. Lutz) in 15 cc. of ether was added rapidly to a solution of 0.005 mole of n-butyllithium in 15 cc. of ether. The mixture was stirred for one hour, and then carbonated and worked up in the usual manner. The yield of crude acid, melting at 240-245°, was 0.14 g. (14 per cent). After crystallization from glacial acetic acid, the weight of pure acid melting at 257-258° was 0.10 g. (10 per cent). This acid was shown to be identical with that obtained from 2,4,5-triphenyl-3-bromofuran by mixed melting points of the acids and of their methyl esters. From the neutral fraction, 0.58 g. (58 per cent) of unchanged 2,4,5-triphenyl-3-chlorofuran was recovered.

3,4,6-Triphenyl-2-bromopyridine and n-butyllithium

The 3,4,6-triphenyl-2-bromopyridine was prepared by the method of Kohler and Allen.[58] A solution of 3.0 g. (0.008 mole) of 3,4,6-triphenyl-2-bromopyridine in 25 cc. of ether was added during five minutes to a solution of 0.017 mole of n-butyllithium in 60 cc. of ether, cooled to -35° in a dry ice-acetone bath. The solution turned orange-red during the addition, and deposited a precipitate about one minute after addition of the halide was complete. After the reaction mixture had been stirred for ten minutes at -35° the reaction was carbonated and worked up in the usual manner. A considerable amount of white solid (probably the lithium salt of the organic acid), insoluble in dilute potassium hydroxide solution, was obtained; this was dissolved in hot water and added to the alkaline extract. Acidification of this alkaline extract precipitated 1.82 g. (67 per cent) of acid melting at 166-168° with decomposition. A portion was recrystallized from a mixture of benzene and petroleum ether (b.p. 60-68°); the melting point was not changed. The 3,4,6-triphenylpyridine-2-carboxylic acid was readily soluble in alcohol and benzene, but only slightly soluble in ether and petroleum ether.

Anal. Calcd. for $C_{24}H_{17}O_2N$: neut. equiv., 351; N, 3.99. Found: neut. equiv., 348, 349; N, 4.18.

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[58]Kohler and Allen, J. Am. Chem. Soc., 46, 1522 (1924).

The structure of the acid was proved by its decarboxylation to give the known 2,4,6-triphenylpyridine.[59] A 0.5 g. portion of the acid, crystallised from benzene-petroleum ether, was placed in a test tube and heated in an oil bath at 170-175° until the evolution of carbon dioxide had ceased, and finally for a short time at 185°. The product was cooled to a glassy solid which on crystallisation from alcohol gave 0.15 g. (86 per cent) of pure, white 2,4,6-triphenylpyridine, melting at 111-112°, identified by a mixed melting point with an authentic specimen (kindly supplied by Dr. C.F.H. Allen).

Methyl 3,4,6-triphenylpyridine-2-carboxylate

A solution of 0.5 g. (0.0014 mole) of 3,4,6-triphenylpyridine-2-carboxylic acid in dry benzene was treated with an ethereal solution of approximately 0.004 mole of diazomethane. After the initial evolution of nitrogen had ceased, the solution was warmed slightly and the solvents then allowed to evaporate. The pale yellow residue was crystallised twice from ethyl alcohol and finally from dilute methyl alcohol to give pure methyl 3,4,6-triphenylpyridine-2-carboxylate, melting at 117-118°. This ester, like the acid from which it was derived, was not appreciably soluble in ether.

Anal. Calcd. for $C_{25}H_{19}O_2N$: N, 3.84. Found: N, 3.98.

From a preliminary experiment, in which a suspension of the acid in ether was treated with ethereal diazomethane, the product melted at 99-104° and could not be purified.

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[59] Allen and Frame, ibid., 62, 1301 (1940).

2-Bromobenzofuran and n-butyllithium

The 2-bromobenzofuran was prepared from benzofuran dibromide according to the directions of E.W. Smith.[60] A solution of 2.0 g. (0.01 mole) of 2-bromobenzofuran in a few cc. of ether was added all at once to a solution of 0.014 mole of n-butyllithium in 50 cc. of ether, cooled to -70° in a dry ice-acetone bath. The yield of crude benzofuran-2-carboxylic acid, melting at 187-189°, was 1.4 g. (86 per cent). After crystallization from dilute alcohol, the yield of pure acid melting at 192.5-193° was 1.04 g. (62 per cent). The acid was identified by a mixed melting point with authentic benzofuran-2-carboxylic acid, prepared from coumarin dibromide by the method of Fittig and Ebert,[61] as modified by E.W. Smith.[60]

In experiments carried out at room temperature, the yield of crude benzofuran-2-carboxylic acid after twenty minutes was 62 per cent, and after forty minutes it was 28 per cent. The aqueous filtrates from the acid possessed an odor of o-ethinylphenol, indicating that some cleavage of the benzofuran ring had occurred.

3-Bromobenzofuran and n-butyllithium

Numerous experiments were carried out between 3-bromobenzofuran and n-butyllithium, at first in order to obtain the hitherto unavailable

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[60]Smith, E.W., Doctoral Dissertation, Iowa State College (1936).

[61]Fittig and Ebert, Ann., 216, 163 (1883).

3-benzofuryllithium, and subsequently in an attempt to correlate the anomalous results noted in the earlier studies. The time of reaction in the various experiments varied from about one-half minute to thirty minutes; the temperature from about 25° to -70°. In most cases the solvent used was diethyl ether; however, three reactions were carried out in petroleum ether (b.p. 28-38°).

The 3-bromobenzofuran was prepared as follows: Benzofuran-2-carboxylic acid was prepared as noted above from coumarin dibromide. The acid was then decarboxylated to benzofuran according to the directions of Reichstein and Baud.[62] The benzofuran was converted to the dibromide and the dibromide to 3-bromobenzofuran by the method of Stoermer and Kahlert,[63] as modified by E.W. Smith[60] and by Reichstein and Baud. The 3-bromobenzofuran was obtained as a white crystalline solid melting at 35.5-36° after crystallization from petroleum ether (b.p. 28-38°) at -20°. The compound, however, seemed to be unstable and turned black after standing about a week, even in a tightly-stoppered bottle in the ice box. This instability may be in part responsible for some of the anomalous results obtained in the interconversion studies.

Interconversion at -70° for two minutes. This was the only experiment from which benzofuran-3-carboxylic acid, the expected product, was isolated after carbonation of the reaction mixture. A solution of 2.0 g. (0.01 mole) of 3-bromobenzofuran in a few cc. of ether was added

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[62]Reichstein and Baud, Helv. Chim. Acta, 20, 892 (1937).

[63]Stoermer and Kahlert, Ber., 35, 1636 (1902).

quickly to a solution of 0.014 mole of n-butyllithium in 50 cc. of ether at -70°. The reaction was stirred for two minutes and then carbonated. From the alkaline extract there was obtained 0.23 g. (14 per cent) of crude acid melting at 154-159°. This was crystallized from a mixture of benzene and petroleum ether (b.p. 60-68°) to give 0.19 g. (12 per cent) of product melting at 160-161°. The melting point reported in the literature[64] for benzofuran-3-carboxylic acid is 162° (corr.). A portion of the above product after crystallization from dilute alcohol still melted at 160-161°. The neutral equivalent of this acid was found to be 164 and 161; the theoretical value for benzofuran-3-carboxylic acid is 162. A mixed melting point with authentic benzofuran-2-carboxylic acid, which has the same neutral equivalent as the 3-acid, was depressed. It should be noted that no odor of valeric acid could be detected when the alkaline extract from the carbonation was acidified.

Interconversions giving benzofuran-2-carboxylic acid. These experiments were performed in the same manner as the one reported above, but the time of reaction varied from one to ten minutes. In each case, the only acid isolated was benzofuran-2-carboxylic acid, identified by a mixed melting point with an authentic sample. One of the reactions was carried out at room temperature, the others at -70°. The results are summarized in the accompanying table.

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[64]Titoff, Miller, and Reichstein, Helv. Chim. Acta, 20, 883 (1937).

Table 1. Formation of Benzofuran-2-carboxylic Acid from 3-Bromobenzofuran

Moles of halide used	Moles of n-BuLi used	Total volume of ether	Temperature	Time of reaction	Yield (%) of crude acid
0.025	0.035	55 cc.	-70°	1 min.	13
0.025	0.036	55 "	-70°	2 "	10
0.04	0.042	65 "	-70°	3 "	23.5
0.025	0.034	65 "	-70°	10 "	13
0.04	0.13	175 "	25°	30 "	16

In the case of each of the experiments listed in the above table, a strong odor of o-ethinylphenol was noted when the alkaline extracts were acidified. The last experiment, in which slightly more than three equivalents of n-butyllithium were used, was run with the expectation of obtaining o-hydroxyphenylpropiolic acid from carbonation of any o-hydroxyphenylethinyllithium derived from the o-ethinylphenol.

Interconversions at -70° and with very short time of reaction. Two experiments were carried out in an attempt to derivatize, by carbonation immediately after mixing the reagents, any transitorily formed 3-benzofuryllithium. The reactions were carried out in the same manner as the previous ones, except that the time of contact of the 3-bromobenzofuran with the n-butyllithium before carbonation was between one-half and one minute. The acid, which was obtained in yields of 6 and 17 per cent (crude), melted at 140-141° after crystallization from benzene. It depressed the melting points of both the 2- and the 3-benzofurancarboxylic

acids. However, the values found for its neutral equivalent were 160 and 162; the theoretical value for either the 2- or the 3-benzofurancarboxylic acids or for o-hydroxyphenylpropiolic acid is 162. It is possible that this unidentified product was a mixture or molecular compound of the 2- and 3-benzofurancarboxylic acids, but neither of the pure components could be separated from it by crystallization or by vacuum sublimation.

Interconversions in petroleum ether. Three experiments were carried out in petroleum ether (b.p. 28-38°) in the hope that in this solvent cleavage of the benzofuran ring would be minimized and that 3-benzofuryllithium might be formed. In each of the experiments, 5 g. (0.025 mole) of 3-bromobenzofuran in 20 cc. of petroleum ether was added to a slight excess of n-butyllithium in the same solvent. In the first reaction, which was carried out at room temperature, the halide was added dropwise during fifteen minutes, and stirring was then continued for ten minutes before carbonation. A trace of unidentified acid, melting at 127-129° (possibly o-hydroxyphenylpropiolic acid), and 0.15 g. of crude o-ethinylphenol were obtained.

In the second reaction, carried out at 0°, the halide was added during one minute and the mixture immediately carbonated. A trace of very impure acidic product and 0.15 g. of crude o-ethinylphenol were obtained.

In the third reaction, carried out at -70°, the halide was added all at once and the solution immediately carbonated. Only a trace of o-ethinylphenol and no acidic fraction were obtained.

Preparation of o-ethinylphenol from 3-bromobenzofuran

Reichstein and Baud[62] obtained o-ethinylphenol in 27.6 per cent yield from the reaction between 3-bromobenzofuran and copper-magnesium alloy.

A solution of 10 g. (0.051 mole) of 3-bromobenzofuran in 30 cc. of ether was added during five minutes to a solution of 0.154 mole of n-butyllithium in 220 cc. of ether at room temperature. The solution was stirred for one hour and then hydrolyzed by pouring on iced dilute hydrochloric acid. The ether layer was extracted with dilute potassium hydroxide solution. The alkaline solution was then acidified and extracted with ether. The ether extract was dried over sodium sulfate, the ether evaporated, and the residue distilled under reduced pressure. The yield of pure o-ethinylphenol, distilling at 95-98° under 10 mm., was 4.0 g. (67 per cent).

A portion of this product was converted to the p-nitrobenzoate by treatment with p-nitrobenzoyl chloride in pyridine. The product melted at 108-109°. Reichstein and Baud[62] report that the melting point of the p-nitrobenzoate of o-ethinylphenol is 107-108° (corr.).

o-Ethinylphenol and n-butyllithium

This reaction was performed in an attempt to prepare o-hydroxyphenylpropiolic acid and to compare the properties of this acid with those of the unidentified acid obtained from the short time reaction of 3-bromobenzofuran with n-butyllithium at -70°.

The first experiment was carried out at 0°, and no solid acid was obtained. The second experiment was conducted as follows: To a solution of 1.0 g. (0.0085 mole) of o-ethinylphenol in 25 cc. of ether there was added during ten minutes a solution of 0.02 mole of n-butyllithium in 50 cc. of ether. The solution, which warmed up and refluxed slightly during the addition, became yellow in color and slightly turbid. It was refluxed for thirty minutes, and then cooled and carbonated. The carbonation product was extracted first with 10 per cent potassium hydroxide solution and then with water. The combined extracts were saturated with carbon dioxide after which a purple tar separated. This was filtered off and any additional phenolic material was removed by extraction with ether. Dissolved ether was removed by heating the bicarbonate solution which was then cooled and acidified with cold concentrated hydrochloric acid. A rather bulky precipitate formed; this was filtered off but much of it dissolved when washed on the filter with distilled water. The filtrate was extracted with ether, the ether solution dried over sodium sulfate, most of the ether distilled off, and the residue allowed to evaporate on a watch glass. A white solid remained which appeared to be purer on the outer edges, this portion melting at 127-130° with decomposition. The total yield of crude acid was 0.55 g. (40 per cent, calculated as $C_9H_6O_3$). The acid was readily soluble in alcohol, ether, and water, and practically insoluble in cold or hot benzene and petroleum ether. When added to hot water it seemed to decompose giving a turbid solution.

Since all attempts to crystallize this compound failed, the crude product was dried in a vacuum desiccator and the neutral equivalent determined, using phenolphthalein as indicator. The values found were 125 and 128, compared with the theoretical value of 162 for o-hydroxyphenylpropiolic acid. It is probable that the sample was contaminated with hydrochloric acid and also that the presence of the phenolic hydroxyl group interfered with the titration of the carboxyl group. Although the identity of this product has not been established, it is probably impure o-hydroxyphenylpropiolic acid formed by carbonation of o-hydroxyphenylethinyllithium.

Preparation of p-bromobenzyl alcohol

From p-bromophenylmagnesium bromide and formaldehyde. The preparation of p-bromobenzyl alcohol by means of the reaction between p-bromophenylmagnesium bromide and formaldehyde has been reported by Ziegler and Tiemann.[65] These authors obtained a 61 per cent yield of a product which distilled at 125-140° under a pressure of 11 mm., but their yield of pure compound crystallized from alcohol is not reported. In connection with the present work this method was employed in attempts to prepare p-bromobenzyl alcohol in rather large quantities. The procedure was patterned after that given in Organic Syntheses for the preparation

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[65]Ziegler and Tiemann, Ber., 55, 3406 (1922).

of cyclohexylcarbinol.[66] The yields were unsatisfactory, since, from the Grignard reagent prepared from 1 mole of p-dibromobenzene and 1 gram atom of magnesium and treated with excess formaldehyde, the total amount of p-bromobenzyl alcohol, purified by steam distillation followed by crystallization from petroleum ether and melting at 76-77°, was 34 g. or 18 per cent.

From p-bromobenzyl chloride. Several preparations of p-bromobenzyl alcohol were carried out according to the method of Bodroux,[67] which involves the conversion of a p-bromobenzyl halide to the acetate and the saponification of the acetate with alcoholic potassium hydroxide solution. When p-bromobenzyl chloride (Eastman) was used as the starting material the product was difficult to purify and the yields were low, varying from 6 to 28 per cent. Since it appeared that the commercially available p-bromobenzyl chloride was not sufficiently pure for use in this synthesis, the method described below, starting with p-bromotoluene, was worked out.

From p-bromotoluene. The procedure which was finally adopted as the most convenient method of obtaining fairly large quantities of pure p-bromobenzyl alcohol was a modification of the method of Bodroux[67] applied to p-bromobenzyl bromide prepared by the lateral bromination of p-bromotoluene. p-Bromotoluene was brominated according to the directions of

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[66] Gilman and Catlin, Organic Syntheses, Coll. Vol. I, 2nd ed. (1941), p. 188.

[67] Bodroux, Bull. soc. chim., [3] 21, 289 (1899).

Coleman and Honeywell[68] for the preparation of p-bromobenzal bromide (intermediate in the preparation of p-bromobenzaldehyde), except that only half of the specified amount of bromine was used, and the conditions of time and temperature necessary to the addition of only the first half of the bromine were observed. The crude product was distilled under vacuum and then crystallized from alcohol. (The crystallization is not essential; when the main fraction of the distillate was used directly for the next step the final yields were somewhat lower but some time was saved.)

The detailed procedure for the conversion of the bromide to the alcohol was as follows: To a solution of 135 g. (0.54 mole) of pure, crystalline p-bromobenzyl bromide in 375 g. (355 cc.) of glacial acetic acid was added 132 g. (0.6 mole) of lead oxide (PbO). The mixture was heated gently, while the reaction flask was swirled at intervals to prevent local over-heating, until all the lead oxide had gone into solution. The solution was then heated at reflux for twenty-five minutes, during which time a white, crystalline precipitate of lead bromide was deposited. The reaction mixture was then cooled and filtered. The filtrate was first diluted with 100 cc. of water and then treated with a cold solution of 225 g. of sodium hydroxide in 600 cc. of water in order to neutralize most of the acetic acid. (If too much sodium hydroxide is used a precipitate of lead hydroxide is formed and enough acetic acid must be added to redissolve the precipitate.) The oily layer

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[68]Coleman and Honeywell, Organic Syntheses, 17, 20 (1937).

was then taken up in 200 cc. of ether, the ether layer separated, and the aqueous layer extracted with an additional 50 cc. of ether. The ether was distilled off from the combined extracts (which need not be dried), leaving the crude acetate. This was treated, without further purification, with 55 g. of potassium hydroxide dissolved (as far as possible) in 275 cc. of methyl alcohol. The solution of alcoholic alkali should be cooled before it is added to the acetate, in order to moderate the violent reaction which sometimes occurs on mixing. After the spontaneous reaction had ceased (slight heating may be necessary to start the reaction if the solutions are very cool), refluxing was continued for twenty minutes. As much of the methyl alcohol was then distilled off as was possible before foaming became so pronounced that the distillation had to be stopped. Enough water was then added to the residual mixture to dissolve the inorganic material, and the oily layer was separated and the aqueous solution extracted twice with ether. The ether solution was dried over sodium sulfate, boiled with Norite, filtered, and the ether and most of the methyl alcohol still present evaporated. The residual oil was crystallized from petroleum ether (b.p. 60-68°) containing a few cc. of benzene to give 61 g. (61 per cent) of p-bromobenzyl alcohol melting at 77-78°.

p-Bromobenzyl alcohol and n-butyllithium

A solution of 0.036 mole of n-butyllithium (determined by double titration) in 240 cc. of ether was added during ten minutes to a solution

of 3.25 g. (0.018 mole) of p-bromobenzyl alcohol in 30 cc. of ether. Gas was evolved during the addition of the first half of the organometallic solution, but no appreciable heating was noted. The reaction mixture was stirred for one hour and then carbonated. When the alkaline extract of the carbonation product was acidified, no solid acid was precipitated, so the acidic aqueous solution was extracted with three 30-cc. portions of ether. The dried ether extracts on evaporation of the ether left a sticky solid smelling strongly of valeric acid. This solid was suspended in a small amount of water and the suspension filtered with suction; most of the oily droplets of valeric acid were drawn through the filter along with the water and thus a partial separation was effected. The solid residue, after it had been dried, weighed 0.5 g. (18 per cent) and melted at 160-173°. The melting point recorded in the literature for p-carboxybenzyl alcohol[69] is 181°. Several recrystallizations from water and very dilute alcohol brought the melting point of this product up to 169-175°; further recrystallization led to the formation of a small amount of a new substance melting at about 100°. This was probably an ester formed by cross-esterification between two molecules of p-carboxybenzyl alcohol.

The neutral ether layer from the carbonation product was dried and the ether distilled. From the residue there was isolated 0.47 g. (15 per cent recovery) of p-bromobenzyl alcohol.

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[69] Löw, Ann., 231, 373 (1885).

Although only an 18 per cent yield of very crude p-carboxybenzyl alcohol was obtained upon carbonation of the product of interconversion between p-bromobenzyl alcohol and n-butyllithium, it is probable that the actual yield of the interconversion product lies somewhere between 18 and 85 per cent, since only 15 per cent of the starting material was recovered unchanged. Two possible explanations of the low yield of acid are as follows: (1) p-carboxybenzyl alcohol is relatively soluble in water, and is, therefore, difficult to separate in quantitative yield from the valeric acid produced by carbonation of unreacted n-butyllithium; and (2) during the carbonation of this reaction a large amount of a solid, probably $LiOCH_2C_6H_4COOLi$-p, was formed, and the presence of this bulky solid might interfere with the effective carbonation of all the interconversion product, $LiOCH_2C_6H_4Li$-p, by covering or occluding the latter. Conclusive evidence for the occurrence of a halogen-metal interconversion reaction between p-bromobenzyl alcohol and n-butyllithium to the extent of about 60 per cent is found in the formation of triphenyl-p-hydroxymethylphenyllead in yields of 57 to 63 per cent from reactions (described in a later section) between triphenyllead chloride and the product of this interconversion.

m-Bromobenzyl alcohol and n-butyllithium

m-Bromobenzyl alcohol was prepared from m-bromotoluene by a series of reactions exactly similar to those found most satisfactory for the preparation of p-bromobenzyl alcohol.

A solution of 0.054 mole of n-butyllithium in 70 cc. of ether was added during two minutes to a solution of 5.0 g. (0.0267 mole) of m-bromobenzyl alcohol in 20 cc. of ether. During the addition of slightly less than the first half of the n-butyllithium there was a vigorous evolution of gas; as soon as gas ceased to be evolved the solution turned yellow. By the time all the organometallic solution had been added the color of the reaction mixture had become light brown. The reaction was stirred for thirty minutes and then carbonated. The carbonation product was hydrolyzed with a little water followed by 10 per cent hydrochloric acid. The ether layer was separated and the aqueous layer extracted once with a fresh portion of ether. The combined ether solutions were then extracted with 10 per cent potassium hydroxide solution. The alkaline extract was heated to remove ether, cooled, filtered from a small amount of lithium carbonate, and acidified with hydrochloric acid. A turbidity appeared in the solution, but after the acidified mixture had stood in the ice box for a week the only product was a small amount of brown semi-solid oil. The clear aqueous solution was decanted from the oil and extracted with three 50-cc. portions of ether. The combined ether extracts were dried over sodium sulfate and the ether evaporated, leaving an oil which smelled strongly of valeric acid but which solidified on cooling. The solid was washed thoroughly with petroleum ether (b.p. 60-68°) containing a small amount of benzene. The undissolved material weighed 1.3 g. (32 per cent) and melted at 101-110°. This product, which did not

crystallize well from dilute alcohol, was purified by crystallization from benzene containing a few drops of absolute alcohol. The pure compound melted at 114.5-115°; its neutral equivalent was found to be 153. The melting point previously reported for m-carboxybenzyl alcohol[70] is 111°, and the theoretical value of the neutral equivalent is 152.

Preparation of p-bromophenethyl alcohol

Mixtures of o-, m-, and p-bromophenethyl alcohol, in which the p-isomer predominates, have been obtained from the corresponding mixtures of bromophenethyl bromides prepared by nuclear bromination of phenethyl bromide.[71]

p-Bromophenethyl alcohol has been prepared by Baddeley and Bennett,[72] and by Taylor and Hobson,[73] by diazotizing p-aminophenethyl alcohol and treating the diazonium compound with cuprous bromide. The former authors report a melting point of 20° for their product; the latter authors report 36-38°.

The following preparation, involving the reaction of ethylene oxide with a Grignard reagent, makes use of readily available starting materials.

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[70] Langguth, Ber., 38, 2063 (1905).

[71] Palfray, Sabetay, and Sontag, Compt. rend., 196, 622 (1933); Sontag, Ann. chim., [11] 1, 359 (1934).

[72] Baddeley and Bennett, J. Chem. Soc., 1819 (1935).

[73] Taylor and Hobson, ibid., 184 (1936).

It was patterned after the procedure given in Organic Syntheses for the preparation of n-hexyl alcohol.[74]

p-Bromophenylmagnesium bromide was prepared from 236 g. (1 mole) of p-dibromobenzene in 1 liter of ether and 28.4 g. (1.17 g. atom) of magnesium turnings. An excess of magnesium was used because 42 g. (0.17 mole) of p-dibromobenzene had been recovered from an earlier preparation in which only one gram atom of magnesium was used. The Grignard solution was cooled to 0° in an ice-salt bath, and then there was added to it dropwise a solution of 60 g. (1.35 mole) of ethylene oxide (practical) in 200 cc. of ether from a dropping funnel cooled by means of a jacket containing a mixture of acetone and dry ice. Color test I was still positive after the addition had been completed. About 500 cc. of the ether was then distilled off and 500 cc. of sodium-dried benzene added. Distillation was continued until no more condensate was obtained by heating over the steam bath. At this time the color test was negative. The cooled reaction product was hydrolyzed by addition of ice water followed by 400 cc. of iced 30 per cent sulfuric acid. The entire reaction mixture was then subjected to steam distillation in order to remove benzene, bromobenzene, and unreacted p-dibromobenzene. When all the p-dibromobenzene had been distilled off, as indicated by the fact that the distillate no longer solidified in the

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[74]Dreger, Organic Syntheses, Coll. Vol. I, 2nd ed. (1941), p. 306.

condenser, the steam distillation was discontinued. The mixture of oil and water which remained was extracted with ether, the ether solution dried over sodium sulfate, and the ether distilled. The residual oil was distilled under vacuum through a column. The main fraction, which distilled at 115-121° under a pressure of slightly less than 1 mm., weighed 62.0 g. Two other fractions, one of which (17.5 g.) distilled at 98-114° under less than 1 mm., and the other (17.7 g.) at 122-125°, were also retained. None of these fractions solidified in an ice bath, nor could they be crystallized from methyl or ethyl alcohol, petroleum ether, or mixtures of these solvents. Since it seemed likely that the chief impurity was p-bromostyrene formed by dehydration of the expected alcohol, the combined fractions were treated with 80 g. of anhydrous calcium chloride in order to form the calcium chloride alcoholate. The mixture warmed up somewhat on shaking. It was allowed to stand with occasional shaking for six hours; then 100 cc. of anhydrous ether was added and the mixture allowed to stand for thirty-six hours. After this time the whole mass appeared to be solid, so 100 cc. of ether was added and the solid filtered off and washed thoroughly with ether. From the ether filtrate and washings there was obtained by evaporation of the solvent 11 g. of oily liquid, probably p-bromostyrene. The solid (calcium chloride and calcium chloride alcoholate) was stirred with a liter of ice water until all the calcium chloride had dissolved. The oily layer was extracted with ether, the

ether solution dried over sodium sulfate, and the ether evaporated at room temperature under vacuum. There remained 80 g. (40 per cent) of a viscous oil which solidified in a dry ice-acetone bath but became liquid again at room temperature. The identity of the product as p-bromophenethyl alcohol was established by its conversion to the phenylurethane,[73] melting at 126°, by treatment with phenyl isocyanate.

p-Bromophenethyl alcohol and n-butyllithium

To a solution of 10.0 g. (0.05 mole) of p-bromophenethyl alcohol in 30 cc. of ether there was added during ten minutes a solution of 0.1 mole of n-butyllithium in 120 cc. of ether. A white precipitate was deposited at the beginning of the addition, and gas was evolved while the first half of the organometallic solution was added. After the reaction mixture had been stirred for one hour, carbonation was effected and the organic acid isolated in the usual manner. The yield of crude p-carboxyphenethyl alcohol, melting at 118-122°, was 4.4 g. (52 per cent). The crude product was treated with Norite and crystallized from very dilute alcohol to give 2.6 g. (31 per cent) of lustrous, white crystals, melting at 127-128°.

Anal. Calcd. for $C_9H_{10}O_3$: neut. equiv., 166. Found: neut. equiv., 163, 164.

p-Bromo-α-methylbenzyl alcohol and n-butyllithium

p-Bromo-α-methylbenzyl alcohol was prepared from p-bromobenzaldehyde and methylmagnesium iodide according to the procedure of Ziegler and Tiemann.[65]

To a solution of 10.0 g. (0.05 mole) of p-bromo-α-methylbenzyl alcohol in 30 cc. of ether there was added during ten minutes a solution of 0.1 mole of n-butyllithium in 195 cc. of ether. Gas was evolved during the addition of the first half of the n-butyllithium. The solution, which remained clear and almost colorless, was stirred for thirty minutes and then carbonated. The crude acid, isolated in the usual way, weighed 3.8 g. (45 per cent). Pure p-carboxy-α-methylbenzyl alcohol was obtained by recrystallization of the crude acid, first from dilute alcohol and finally twice from benzene containing a small amount of absolute alcohol. The pure compound melted at 138-139°.

Anal. Calcd. for $C_9H_{10}O_3$: neut. equiv., 166. Found: neut. equiv., 168, 169.

p-Bromobenzenesulfonamide and n-butyllithium

To a suspension of 4.25 g. (0.018 mole) of p-bromobenzenesulfonamide in 20 cc. of ether there was added during five minutes a solution of 0.036 mole of n-butyllithium in 70 cc. of ether. Gas was evolved during the addition of only the first half of the n-butyllithium solution. The reaction mixture was stirred for fifteen minutes and then carbonated. The product was hydrolyzed with a little water and acidified to decompose lithium carbonate. It was then made basic with potassium hydroxide solution and the alkaline layer was separated. Carbon dioxide was bubbled through the alkaline solution until no more precipitate formed. The precipitate was filtered off and stirred with hydrochloric acid to remove lithium carbonate. The insoluble part was filtered off and dried.

This fraction, which weighed 2.5 g. and melted at 159-162°, was shown to be crude p-bromobenzenesulfonamide by means of a mixed melting point. The recovery of this material was 59 per cent. The filtrate (bicarbonate solution) was acidified and cooled to give 0.5 g. (14 per cent) of white, crystalline solid which softened in the range 200-280°, and began to melt at 284° but sublimed away as fast as it melted. All of it disappeared in the range 282-286°. It has been reported that p-carboxybenzenesulfonamide[75] decomposes at about 280° without melting. The 0.5 g. of product was crystallized from very dilute alcohol to give 0.3 g. of material which melted and sublimed in the range 284-286°. The values found for the neutral equivalent of this material were 183, 210, 225, and 226; the theoretical value for p-carboxybenzenesulfonamide is 201. In order to convert the acid to the ethyl ester,[76] a portion of the product was dissolved in absolute alcohol and dry hydrogen chloride was bubbled through the solution for twenty minutes. The residue after evaporation of the alcohol melted at 97-110°, and after crystallization from very dilute alcohol it melted at 100-104°. Further treatment did not alter the melting point. The melting point reported for p-carbethoxybenzenesulfonamide[76] is 110-111°. From these results it appears that the product of interconversion is largely p-carboxybenzenesulfonamide together with a small amount of impurity probably resulting from reduction of the sulfonamide group by n-butyllithium.

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[75]Palmer, Am. Chem. J., 4, 164 (1882).

[76]Remsen, Ann., 178, 301 (1875).

From another experiment in which the unreacted p-bromobenzenesulfonamide and the p-carboxybenzenesulfonamide were not separated by treatment of their solution in aqueous potassium hydroxide with carbon dioxide, there was obtained after a similar esterification with ethyl alcohol and hydrogen chloride, in addition to impure material, a small amount of ester melting at 108-109°. The results were no better in experiments in which three equivalents of n-butyllithium were used. Only unchanged starting material was obtained from a reaction carried out at -70°.

p-Bromobenzonitrile and n-butyllithium

To a solution of 0.05 mole of n-butyllithium in 65 cc. of ether, cooled to -70°, there was added quickly a suspension of 9.1 g. (0.05 mole) of p-bromobenzonitrile in 35 cc. of ether. The reaction mixture, which immediately turned reddish brown, was stirred for five minutes at -70° and then carbonated. The carbonated ether suspension was extracted with dilute potassium hydroxide solution, and the basic extract was heated on the steam plate for about an hour to remove dissolved ether. The solution was then cooled and acidified to give 1.4 g. (17 per cent, calculated as terephthalic acid) of acid which did not melt but sublimed at about 300°. This product was at least 60 per cent terephthalic acid, since treatment with diazomethane gave a 60 per cent yield of dimethyl terephthalate, which melted at 140-141° after crystallization from

alcohol and was identified by a mixed melting point with an authentic sample. From the neutral ether layer there was obtained a mixture which appeared to contain p-bromobenzonitrile and p-bromo-n-valerophenone.

No p-cyanobenzoic acid and no terephthalic acid were obtained from a second experiment in which the p-bromobenzonitrile, dissolved in a mixture of benzene and ether, was added to a solution of n-butyllithium in ether at -70°.

Gregory[77] obtained no acidic fraction from an attempted interconversion in which p-bromobenzonitrile, dissolved in a mixture of toluene and ether, was added to a solution of n-butyllithium in ether at 0°.

Organolead Compounds

The preparation of some new organolead compounds, several of them containing water-solubilizing groups, is reported in the following pages. Some reactions of these new compounds, several new or modified procedures for the preparation of known compounds, and some unsuccessful attempts to introduce water-solubilizing groups into organolead compounds are also described.

Preparation of starting materials

Tetraphenyllead. Tetraphenyllead was prepared from phenylmagnesium

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[77]Unpublished studies by W.A. Gregory.

bromide and lead chloride according to the directions of Setzer, Leeper, and Gilman.[78] In runs of the same size as that described by these authors, the yields of tetraphenyllead obtained by working up all the fractions approached the reported yield (82-83 per cent). However, in runs two or three times as large as that described, the yields varied from 50 to 65 per cent. It was found that the best yields of tetraphenyllead from large-scale preparations were obtained when extremely efficient stirring was provided during and immediately after the addition of the lead chloride to the Grignard reagent.

Triphenyllead chloride. A large-scale modification of the method of Gilman and Robinson[79] was used for the preparation of triphenyllead chloride. The following is a typical preparation. Dry hydrogen chloride was bubbled through a solution of 245 g. (0.52 mole) of tetraphenyllead in 2600 cc. of boiling chloroform for fifty-five minutes. The hot solution was filtered from 30 g. (15 per cent) of diphenyllead dichloride. The filtrate was distilled to dryness over the steam bath, the last traces of chloroform and benzene being removed under the vacuum of a water pump. The solid residue (195 g.) was pulverized in a mortar and then extracted nine times by boiling successively with two one-liter portions of absolute alcohol, using the filtrate from the first extraction for the third, that from the second for the fourth, etc.

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[78]Setzer, Leeper, and Gilman, J. Am. Chem. Soc., 61, 1609 (1939).

[79]Gilman and Robinson, ibid., 51, 3112 (1929).

The combined crops of triphenyllead chloride, obtained by cooling the extraction solutions, weighed 169 g. (75 per cent) and melted at 204-206°. A further portion, (12 g., 5 per cent) of less pure product was obtained by concentration of the mother liquors. The small amount of residue from the extractions consisted of impure tetraphenyllead. This was saved for use in subsequent preparations of triphenyllead chloride.

In preparations in which the amount of diphenyllead dichloride formed was smaller, the yield of triphenyllead chloride was lower and the amount of unchanged tetraphenyllead was correspondingly higher. The optimum time of treatment with hydrogen chloride varies with the rate of flow of the gas. The best indication of the progress of the cleavage is provided by the appearance of the insoluble diphenyllead dichloride and by the gradually increasing opacity of the resulting suspension.

Tetraethyllead and triethyllead chloride. Tetraethyllead was kindly supplied by Dr. G. Calingaert of the Ethyl Corporation. Triethyllead chloride was prepared by cleavage of tetraethyllead in ether with hydrogen chloride, according to the procedure of Gilman and Robinson.[80] The preparation was carried out on a six-fold scale, and the time of treatment with hydrogen chloride was considerably greater than that described for the smaller run.

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[80]Gilman and Robinson, ibid., 52, 1975 (1930).

Triphenyl-p-hydroxymethylphenyllead, $(C_6H_5)_3PbC_6H_4CH_2OH$-p

A solution of 0.16 mole of n-butyllithium in 225 cc. of ether was added during ten minutes to a solution of 15 g. (0.08 mole) of p-bromobenzyl alcohol in 50 cc. of ether. The resulting solution was stirred for one hour, and then 37.9 g. (0.08 mole) of solid triphenyllead chloride was added, with vigorous stirring, during two minutes or as rapidly as the boiling of the ether permitted. The reaction mixture was hydrolyzed at once by pouring on iced ammonium chloride solution. The hydrolysis product was filtered from 2.6 g. of insoluble material which consisted of tetraphenyllead containing a trace of triphenyllead chloride. The ether layer was separated, dried over sodium sulfate, and the ether distilled. The oily residue, which solidified on cooling, was washed with petroleum ether to give 38 g. of solid melting at 80-90°. This solid was dissolved in 250 cc. of hot (not boiling) alcohol and the solution was filtered from a small amount of undissolved solid. The filtrate was heated to boiling and diluted with 75 cc. of hot water; on cooling there was obtained 27.5 g. (63 per cent) of white solid, melting at 97-100°. This product was shown not to contain halogen by a qualitative test. On further crystallization from various solvents or mixtures of solvents, this product gave fractions of variable melting points in the range 90 to 110°. The melting point also varied with the method of determination, but no consistency could be noted in this behavior. The melting point most frequently observed was 98-100°. A portion of the above product,

melting at 97-100°, was recrystallized first from benzene-petroleum ether and then from petroleum ether (b.p. 60-68°) containing a little chloroform to give an analytically pure sample, melting at 98-100°. Triphenyl-p-hydroxymethylphenyllead was readily soluble in ethyl or methyl alcohol, benzene, and chloroform, moderately soluble in ether, and insoluble in petroleum ether.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 38.00. Found: Pb, 37.46, 37.66.

In a check run, the yield of triphenyl-p-hydroxymethylphenyllead was 57 per cent, and in an experiment in which the quantities were doubled the yield was 60 per cent.

Cleavage of triphenyl-p-hydroxymethylphenyllead with bromine

The cleavage of triphenyl-p-hydroxymethylphenyllead with bromine was carried out according to the procedure of Grüttner[81] for the preparation of triphenyllead bromide from tetraphenyllead. To a well-stirred solution of 10 g. (0.0183 mole) of the organolead compound in 100 cc. of pure pyridine at -15° there was added dropwise a solution of 2.94 g. (0.0183 mole) of bromine in 30 cc. of pyridine. After addition was complete, the solution was allowed to warm up to room temperature with continued stirring. The pyridine was then distilled off over the water bath under vacuum. The oily residue was dissolved

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[81]Grüttner, Ber., 51, 1298 (1918).

in alcohol and the solution then subjected to steam distillation to give, in the distillate, 0.69 g. (20 per cent) of p-bromobenzyl alcohol, identified by a mixed melting point with an authentic specimen. The residue from the steam distillation was crystallized from alcohol to give 4.6 g. (48 per cent) of triphenyllead bromide, melting at 163-164°. The identity of this product was established by lead analysis, and by a mixed melting point with authentic triphenyllead bromide, prepared from tetraphenyllead by the method of Grüttner.[81]

Cleavage of triphenyl-p-hydroxymethylphenyllead with hydrogen chloride

Dry hydrogen chloride was bubbled through a solution of 10 g. (0.018 mole) of triphenyl-p-hydroxymethylphenyllead in 100 cc. of boiling chloroform for twelve minutes. At the end of this time an appreciable amount of precipitate had formed. The suspension was cooled and filtered from 0.4 g. (5 per cent) of diphenyllead dichloride. The filtrate was distilled over the steam bath until all the chloroform was removed. The residue was fractionally crystallized from absolute alcohol and from dilute alcohol to give 2.4 g. (28 per cent) of triphenyllead chloride, identified by a mixed melting point with an authentic specimen, and 5.55 g. or a 55 per cent recovery of crude starting material.

From a preliminary experiment in which dry hydrogen chloride was passed through a chloroform solution of the organolead compound at room

temperature for twelve minutes, there was obtained a trace of diphenyllead dichloride, a small amount of pure triphenyllead chloride, 30 per cent of unreacted triphenyl-p-hydroxymethylphenyllead, and a mixture which appeared to contain triphenyllead chloride and starting material.

Triphenyl-p-carboxyphenyllead

To a stirred solution of 10 g. (0.018 mole) of triphenyl-p-hydroxymethylphenyllead in 100 cc. of acetone there was added in small portions during five hours 4.2 g. (0.027 mole; theoretical is 0.024 mole) of potassium permanganate. The acetone used as solvent had been refluxed with and distilled from potassium permanganate. The permanganate color disappeared one-half hour after the last portion was added, but 1 cc. of absolute alcohol was then added to insure complete decomposition of all the permanganate. The dark brown precipitate which had formed was filtered off and washed with acetone. The filtrate and washings, after evaporation of the acetone, left 1.5 g. of slightly sticky solid residue melting at 80-105°. This appeared to be impure starting material. The dark brown precipitate, which contained manganese dioxide, was dried, pulverized, and extracted by boiling with two 100-cc. portions of absolute alcohol. The combined extracts were treated with 10 cc. of 3 N hydrochloric acid (a slight excess). The acidified solution was heated (not to boiling), diluted with water, and cooled to give 2.6 g. (25 per cent) of crystalline solid which melted at 254-256°.

The filtrate from this product was slowly evaporated at 50° to give 2.6 g. of white, fluffy residue which had no definite melting point. This amorphous material, which was insoluble in hot alcohol or benzene, was not identified. A portion of the solid which melted at 254-256° was crystallized from alcohol to give a product which seemed to change crystalline form when heated to 145-150°, and which melted to a viscous liquid at 256-258°. This material was shown by analysis to be pure triphenyl-p-carboxyphenyllead. The sodium and potassium salts of this acid were moderately soluble in alcohol but insoluble in cold or hot water.

Anal. Calcd. for $C_{25}H_{20}O_2Pb$: neut. equiv., 559; Pb, 37.05. Found: neut. equiv., 568, 569; Pb, 36.73, 36.84.

Triphenyl-p-carbomethoxyphenyllead

An ethereal solution containing an excess of diazomethane was added to 1.6 g. (0.00287 mole) of triphenyl-p-carboxyphenyllead. Most of the acid went into solution. A small amount of insoluble material was filtered off, and the filtrate was evaporated to dryness. The residue weighed 1.3 g. and melted at 123-126°. It was crystallized from alcohol to give white, crystalline triphenyl-p-carbomethoxyphenyllead, melting at 125-127°.

Anal. Calcd. for $C_{26}H_{22}O_2Pb$: Pb, 36.15. Found: Pb, 36.50.

Triphenyl-o-hydroxymethylphenyllead

The o-bromobenzyl alcohol used in this experiment was prepared from o-bromotoluene by a procedure exactly similar to that found most satisfactory for the preparation of p-bromobenzyl alcohol (described in the section on halogen-metal interconversion reactions). The product melted at 80-81°.

A solution of 0.30 mole of n-butyllithium in 415 cc. of ether was added during fifteen minutes to a solution of 28.1 g. (0.15 mole) of o-bromobenzyl alcohol in 75 cc. of ether. After the resulting solution had been stirred for one-half hour, 56.9 g. (0.12 mole) of solid triphenyllead chloride was added as rapidly as possible, with vigorous stirring. The reaction mixture was immediately hydrolyzed by pouring on iced ammonium chloride solution. The solutions were then filtered from 2.5 g. of impure tetraphenyllead. The ether layer of the filtrate was separated, dried over sodium sulfate, and the ether distilled. The last traces of ether and some octane (formed by coupling during preparation of the n-butyllithium) were removed by distillation over the steam bath under the vacuum of a water pump. The partially solidified residue was boiled with 200 cc. of absolute alcohol and the solution filtered from 2 g. of insoluble material (impure triphenyllead chloride). The filtrate was cooled to give 26.2 g. (40 per cent) of triphenyl-o-hydroxymethylphenyllead, melting at 133-136°. A further 20.6 g. (31 per cent) of less pure product was obtained by distilling off some of the alcohol from the mother liquor and diluting the remainder

with water. The melting point of the pure product, obtained by crystallization of some of the 26.2 g. fraction from a mixture of benzene and petroleum ether (b.p. 60-68°), was 134-136°.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 38.00. Found: Pb, 38.49.

In a check experiment on a slightly smaller scale (using 0.08 mole of triphenyllead chloride) the yield of pure product was 45 per cent. In addition there were obtained less pure fractions in a yield of 25 per cent.

Permanganate oxidation of triphenyl-o-hydroxymethylphenyllead

The preparation of triphenyl-o-carboxyphenyllead from the corresponding hydroxymethyl compound was attempted by the same procedure as that described previously for the synthesis of triphenyl-p-carboxyphenyllead.

To a solution of 10 g. (0.018 mole) of pure triphenyl-o-hydroxymethylphenyllead in 100 cc. of permanganate-stabilized acetone there was added gradually with stirring during five hours 4 g. (a slight excess) of potassium permanganate in small portions. The reaction mixture was then allowed to stand overnight. A faint color of permanganate persisted after this time, so 1 cc. of alcohol was added to decompose the excess oxidizing agent. The dark brown precipitate was then filtered off and washed well with acetone. The precipitate was extracted by boiling with alcohol. The alcohol extract was carefully acidified to methyl red, and the solvent was then allowed to evaporate. The residue weighed 0.5 g. and melted at 288-295° with

evolution of gas. This material did not dissolve in the usual organic solvents and could not be crystallized. The acetone filtrate and washings were allowed to evaporate. The residue of solid and oil was extracted with hot alcohol, leaving 3.2 g. of insoluble white solid which melted at 300-305° to a turbid, viscous liquid. The alcohol extract was carefully acidified to methyl red, diluted with water, and cooled to give 1.2 g. of solid, which melted at 288-292° to a turbid, viscous liquid with evolution of gas. Both this fraction and the 3.2 g. mentioned above were insoluble in the common organic solvents and could not be crystallized. They did not react with diazomethane. A portion of the 3.2 g. fraction was converted to a carboxyl-containing organolead chloride (described below) by treatment with hydrochloric acid. This result together with a lead analysis indicated that the oxidation product was the anhydride of diphenyl-o-carboxyphenyllead hydroxide. The lead content was higher than that of triphenyl-o-carboxyphenyllead (37.05 per cent) or of the original triphenyl-o-hydroxymethylphenyllead (38.00 per cent).

Anal. Calcd. for $C_{19}H_{14}O_2Pb$: Pb, 42.08. Found: Pb, 41.72.

Diphenyl-o-carboxyphenyllead chloride

The conversion of the above anhydride to the organolead chloride was carried out by the procedure of Arntzen[18] for the preparation of the analogous organotin chloride from the product of oxidation of triphenyl-o-hydroxymethylphenyltin.

A 1 g. portion of the anhydride was suspended in 25 cc. of absolute alcohol and treated with a few cc. of concentrated hydrochloric acid. Most of the solid dissolved. A small amount of undissolved material was removed by filtration, and the filtrate was diluted with 6 N hydrochloric acid to give, after cooling, 0.9 g. of white crystalline solid. This compound, diphenyl-o-carboxyphenyllead chloride, seemed to change crystalline form at 145°, and melted to a viscous, turbid liquid at 210-220°. The presence of the carboxyl group was shown by the reaction with diazomethane (described below). The compound gave off hydrogen chloride when treated with cold concentrated sulfuric acid.

Anal. Calcd. for $C_{19}H_{15}O_2ClPb$: Pb, 40.02. Found: Pb, 40.69.

Diphenyl-o-carbomethoxyphenyllead chloride

A solution of 0.5 g. of diphenyl-o-carboxyphenyllead chloride in ether was treated with a solution of excess diazomethane in ether. The solvent was evaporated and the product was crystallized from methanol. There was obtained 0.45 g. (72 per cent) of white, crystalline diphenyl-o-carbomethoxyphenyllead chloride, melting at 170-171°. This compound dissolved in cold concentrated sulfuric acid, with evolution of hydrogen chloride, to give a clear, colorless solution.

Anal. Calcd. for $C_{20}H_{17}O_2ClPb$: Pb, 38.97. Found: Pb, 39.08.

Triphenyl-m-hydroxymethylphenyllead

To a solution of 18.7 g. (0.1 mole) of m-bromobenzyl alcohol in 45 cc. of ether there was added during ten minutes a solution of 0.20 mole of n-butyllithium in 210 cc. of ether. After the resulting solution had been stirred for one-half hour, 38 g. (0.08 mole) of solid triphenyllead chloride was added during two minutes. The reaction mixture was stirred for three minutes and then hydrolyzed by pouring on iced ammonium chloride solution. A small amount (1.8 g.) of crude tetraphenyllead was removed by filtration. The ether layer was separated, dried over sodium sulfate, and the solvent and other low-boiling materials removed by distillation. The residue, which weighed 46 g., was heated almost to boiling with 200 cc. of alcohol and filtered while hot from 4.8 g. of white solid (largely triphenyllead chloride). The filtrate was cooled to give 18.4 g. (41 per cent) of crude triphenyl-m-hydroxymethylphenyllead. A portion of this product was crystallized twice from a mixture of benzene and petroleum ether, and finally from methyl alcohol to give a pure sample, which melted at 113-114° with slight turbidity.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 38.00. Found: Pb, 38.46.

Permanganate oxidation of triphenyl-m-hydroxymethylphenyllead

To a solution of 10 g. (0.018 mole) of triphenyl-m-hydroxymethylphenyllead in 100 cc. of permanganate-stabilized acetone there was added gradually with stirring during two hours 4 g. (a slight excess)

of potassium permanganate. The permanganate color had almost entirely disappeared three hours after the last portion was added. At this point one-half cc. of alcohol was added to decompose excess permanganate, and stirring was continued for one-half hour longer. The dark brown precipitate was then filtered off and washed well with acetone. The acetone filtrate and washings were allowed to evaporate to dryness. Only a trace of residue remained. The dark brown precipitate, which weighed 12.3 g. (the theoretical weight of manganese dioxide from 4 g. of potassium permanganate is 2.2 g.) was extracted successively with hot absolute alcohol and cold and hot alcohol containing dilute hydrochloric acid. The filtrates were cooled and the mother liquors concentrated to give a small amount of material which melted at 208-215° and several fractions which melted in the range 130-140° or 140-155°. None of these products could be purified to give a substance with a sharp melting point. Some of the fractions were treated with diazomethane, and a reaction occurred but no definite products could be isolated.

Triphenyl-*p*-β-hydroxyethylphenyllead, $(C_6H_5)_3PbC_6H_4CH_2CH_2OH$-*p*

A solution of 0.145 mole of *n*-butyllithium in 250 cc. of ether was added during ten minutes to a solution of 14.1 g. (0.07 mole) of *p*-bromophenethyl alcohol in 30 cc. of ether. After the resulting suspension had been stirred for one hour, 28.5 g. (0.06 mole) of solid triphenyllead chloride was quickly added with vigorous stirring. The reaction mixture was immediately hydrolyzed by pouring on iced ammonium

chloride solution. The solutions were filtered from 1.8 g. of a mixture of tetraphenyllead with a small amount of triphenyllead chloride. The ether layer in the filtrate was separated, dried, and most of the solvent evaporated to leave an oil which was cooled to give a solid from which some octane was decanted. The solid weighed 27 g. and melted at 83-95°. This material was crystallized from absolute alcohol and the mother liquors concentrated to give a total of 19 g. (57 per cent) of fairly pure triphenyl-p-β-hydroxyethylphenyllead, melting at 83-85°. The pure compound, obtained by recrystallizing this product twice from a mixture of benzene and petroleum ether, melted at 87-88°.

Anal. Calcd. for $C_{26}H_{24}OPb$: Pb, 37.05. Found: Pb, 37.03, 37.06.

Triphenyl-p-α-hydroxyethylphenyllead, $(C_6H_5)_3PbC_6H_4CHOHCH_3$-p

A solution of 0.30 mole of n-butyllithium in 350 cc. of ether was added during fifteen minutes to a solution of 30.1 g. (0.15 mole) of p-bromo-α-methylbenzyl alcohol in 40 cc. of ether. The resulting solution was stirred for one-half hour, and then 56.9 g. (0.12 mole) of solid triphenyllead chloride was added during two minutes with vigorous stirring. The reaction mixture was stirred for three minutes more, and then hydrolyzed by pouring on iced ammonium chloride solution. A small amount (2.5 g.) of crude tetraphenyllead was filtered off. The ether layer was separated, dried over sodium sulfate, and the solvent removed by distillation. The very viscous residual oil, which did not crystallize

on cooling, was dissolved in absolute alcohol. On cooling, there was deposited 5 g. of impure triphenyllead chloride. The filtrate was heated and diluted with water, but on cooling the first part of the product came down as an oil. After many attempts, a crystalline product was finally obtained by the following procedure: a portion of the oil was dissolved in methyl alcohol at room temperature. The solution was diluted with water until a turbidity just appeared, then heated until it became clear, and allowed to cool slowly. When it had cooled almost to room temperature, a slight turbidity appeared again, so just enough methyl alcohol was added to clear the solution, which was then cooled in the ice box to give well-formed crystals. After another crystallization from dilute methyl alcohol, the pure triphenyl-p-α-hydroxyethylphenyllead melted at 68-70°. The total yield of fairly pure product was 35 g. (52 per cent).

Anal. Calcd. for $C_{26}H_{24}OPb$: Pb, 37.05. Found: Pb, 37.22.

Attempted preparation of triphenyl-o-methoxymethylphenyllead

A solution of 12.1 g. (0.06 mole) of o-bromobenzyl methyl ether in 50 cc. of ether was added gradually to 1.46 g. (0.06 g. atom) of magnesium. After the first small portion of the halide had been added the reaction mixture was heated intermittently during twenty minutes to reflux the ether. At the end of this time a considerable turbidity appeared and the reaction seemed to start, but proceeded spontaneously only for one minute. The rest of the halide was then introduced during thirty minutes,

and the reaction was stirred at reflux for five hours. Most of the magnesium still remained unchanged, so 50 cc. of benzene and 100 cc. of ether were added and the reaction was refluxed for four hours. Although most of the magnesium had not reacted at this time, color test I was positive. To the reaction mixture there was added 3 g. (0.0064 mole) of triphenyllead chloride. After ten minutes the color test was still faintly positive, but after the reaction mixture had stood overnight the color test was negative. The reaction was hydrolyzed by pouring on iced ammonium chloride solution. The organic layer was separated and dried, the solvents evaporated, and the residual oil, which it was thought consisted of a mixture of the desired product and unreacted o-bromobenzyl methyl ether, was cooled and treated with petroleum ether. The only solid isolated, however, was triphenyllead chloride (0.5 g.).

Triphenyllead chloride and the lithium salt of p-carboxyphenyllithium

It has been shown by Arntzen[17] that p-iodobenzoic acid undergoes halogen-metal interconversion (to give the lithium salt of p-carboxyphenyllithium) to the extent of 62 per cent when treated with n-butyllithium at -75° for four minutes.

A solution of 0.043 mole of n-butyllithium in 225 cc. of ether, cooled to approximately -70° in a jacketed dropping funnel, was added quickly to a suspension of 5.33 g. (0.0215 mole) of p-iodobenzoic acid in ether, also cooled to -70°. One minute after the n-butyllithium had been added, 10.2 g. (0.0215 mole) of solid triphenyllead chloride was quickly introduced. Color test I was strongly positive five minutes

and also thirty minutes later. After a total time of two hours the reaction mixture had warmed up to -5° and the color test was negative. The reaction was then hydrolyzed with dilute potassium hydroxide solution. The alkaline layer was separated, and the ether layer was again extracted with base. The combined extracts were carefully acidified in the cold to give 1 g. (19 per cent recovery) of a product which was shown to be crude p-iodobenzoic acid. The alkali-insoluble products were not investigated.

Triphenyllead chloride and p-phenylenedilithium

A solution of 15.8 g. (0.067 mole) of p-dibromobenzene in 100 cc. of ether was added during five minutes to a solution of 0.20 mole of n-butyllithium in 400 cc. of ether. The reaction was stirred for one hour and then allowed to stand for eighteen hours. A double titration on aliquot portions at this time indicated that practically no n-butyllithium remained at this time and that approximately 0.07 mole of phenylenedilithium was present. To the solution there was added during five minutes 31.8 g. (0.067 mole) of solid triphenyllead chloride. The reaction mixture was stirred for forty-five minutes and then carbonated by pouring on an ether slush of dry ice. The resulting ether suspension was hydrolyzed with 10 per cent potassium hydroxide solution, and 18 g. of insoluble white solid was removed by filtration. The alkaline layer was separated, and the ether layer was extracted with another portion of potassium hydroxide solution. The combined extracts were

cooled in an ice bath and carefully acidified with iced 10 per cent hydrochloric acid. There was obtained only 1.45 g. of a powder which did not contain lead, and which sublimed at about 300°. This was probably terephthalic acid, formed by carbonation of phenylenedilithium. The 18 g. of solid, mentioned above, had no definite melting point and seemed to be a mixture. It was boiled with 450 cc. of absolute alcohol. The filtrate, on cooling, deposited 0.6 g. of triphenyllead chloride. The alcohol-insoluble residue, which weighed 15 g., was boiled with 400 cc. of chloroform. Most of the solid dissolved. The chloroform solution, on cooling, deposited 2.9 g. of white crystalline solid, melting at 285-288°. This product analyzed for p-phenylenedi-(triphenyllead), $p\text{-}(C_6H_5)_3PbC_6H_4Pb(C_6H_5)_3$. The theoretical lead content of triphenyl-p-carboxyphenyllead is 37.05 per cent.

Anal. Calcd. for $C_{42}H_{34}Pb_2$: Pb, 43.51. Found: Pb, 43.91, 42.92.

Triphenyllead chloride and sodium malonic ester

A solution of 0.025 mole of sodium ethoxide in alcohol was prepared by dissolving 0.575 g. (0.025 g. atom) of sodium in 50 cc. of absolute alcohol (distilled over sodium). To the cooled solution there was added with stirring 4.12 g. (0.0257 mole) of diethyl malonate. Then 11.85 g. (0.025 mole) of triphenyllead chloride and 125 cc. of dry benzene were added. The stirred mixture was heated to reflux, allowed to cool with continued stirring, and let stand for thirty-six hours.

The ether and benzene were distilled under vacuum at a temperature which was not permitted to exceed 50°. Water was added to the residual liquid, which then turned solid. This solid was shown to be triphenyllead chloride, recovered in quantitative yield.

Sandmeyer reactions with triphenyl-p-aminophenyllead

Two attempts were made to prepare triphenyl-p-cyanophenyllead by the reaction of cuprous cyanide with the diazonium salt derived from triphenyl-p-aminophenyllead. Both attempts, described in detail below, were unsuccessful.

Preparation of triphenyl-p-aminophenyllead. Triphenyl-p-aminophenyllead was prepared by a modification of the method of Gilman and Stuckwisch.[48] A solution of 0.3 mole of n-butyllithium in 350 cc. of ether was added to 17.2 g. (0.1 mole) of p-bromoaniline in 50 cc. of ether. The resulting solution was stirred for forty minutes, and then 38 g. (0.008 mole) of solid triphenyllead chloride was added as quickly as possible. The reaction mixture was stirred for three minutes and hydrolyzed by pouring on iced ammonium chloride solution. A small amount (2.3 g.) of crude tetraphenyllead was removed by filtration, after which the ether layer was separated and dried over sodium sulfate. Dry hydrogen chloride was passed into the dried ether solution for ten minutes. There was deposited a dark-colored, tarry precipitate weighing 12 g. This was discarded, since it was almost entirely soluble

in water. Hydrogen chloride was again passed into the ether filtrate, this time for twenty minutes or until no more precipitate formed. The light tan precipitate, which weighed 30.5 g., was triturated with water. The insoluble material weighed 22.5 g. This represents a 42 per cent yield of the hydrochloride of triphenyl-p-aminophenyllead. The product was used without further purification for the diazotizations described below.

Sandmeyer reaction no. 1. This reaction was carried out according to the directions of Gattermann[82] for the preparation of p-tolunitrile from p-toluidine.

A suspension of 5.3 g. (0.0095 mole) of triphenyl-p-aminophenyllead hydrochloride in a solution of 2.5 cc. of concentrated hydrochloric acid in 25 cc. of water was cooled in an ice bath, and then treated with sodium nitrite solution (0.76 g. or 0.011 mole of sodium nitrite in 10 cc. of water) until the reaction mixture gave a test for nitrite ion with potassium iodide-starch paper. The diazonium suspension was then added to a cuprous cyanide solution (at 60-70°), which had been prepared by adding 4.3 g. (0.088 mole) of sodium cyanide in 10 cc. of water to a warm solution of 5.5 g. (0.072 mole) of copper sulfate pentahydrate in 20 cc. of water. After the initial vigorous evolution of gas had ceased, the reaction mixture was heated on the steam plate for a few minutes and then cooled and filtered. The dark brown solid which was

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[82]Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," Macmillan, New York (1937), p. 291.

obtained weighed 5.6 g. and had no definite melting point. This product was extracted successively with ether, chloroform, and absolute alcohol. The undissolved residue was discarded. The ether and alcohol extracts on evaporation left only traces of residue. The chloroform extract was decolorized with Norite and allowed to evaporate. The residue was a tan solid, weighing 0.52 g. and melting at 135-150° with turbidity. A few crystals which sublimed out melted at 210-220°; these were probably tetraphenyllead. The 0.52 g. of product was crystallized from alcohol to give three fractions all of which sintered and melted in part at 155-200° but resolidified and did not melt again below 300°. These fractions were so small in amount that they were not further investigated.

Sandmeyer reaction no. 2. This reaction was carried out according to the directions of Clarke and Read[83] for the preparation of o- or p-tolunitrile from o- or p-toluidine.

A solution of cuprous chloride was prepared as follows: to a solution of 6.25 g. (0.025 mole) of copper sulfate pentahydrate and 1.63 g. (0.028 mole) of sodium chloride in 20 cc. of hot water there was added an alkaline solution of sodium sulfite (1.21 g. of sodium metabisulfite and 0.88 g. of sodium hydroxide in 10 cc. of water). The mixture was cooled and the white precipitate of cuprous chloride was washed with water by decantation. The cuprous chloride was converted to cuprous

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[83]Clarke and Read, Organic Syntheses, Coll. Vol. 1, 2nd ed. (1941), p. 514.

cyanide as follows: the washed precipitate was suspended in 10 cc. of cold water and to the suspension there was added a solution of 3.25 g. (0.065 mole) of sodium cyanide in 5 cc. of water. While the resulting hot solution was allowed to cool, the aminoaryllead compound was diazotized as described below.

A suspension of 11.3 g. (0.02 mole) of triphenyl-p-aminophenyllead hydrochloride in a mixture of 2.2 cc. of concentrated hydrochloric acid and 25 g. of water and cracked ice was treated with a solution of 1.4 g. (0.0203 mole) of sodium nitrite in 4 cc. of water (to give a blue color with potassium iodide-starch paper). The resulting thick suspension was added to the cuprous cyanide solution which had been chilled to between 0 and 5° and covered with a layer of benzene. The mixture was stirred for a few minutes, allowed to warm up gradually to room temperature, and then heated to 50° and held at this temperature for thirty minutes. The reaction was then allowed to stand overnight, after which the benzene layer was separated. The aqueous suspension was shaken thoroughly with five 30-cc. portions of benzene in succession. The benzene-insoluble solid weighed 6.3 g. Since it was almost entirely insoluble in organic solvents it was discarded. The combined benzene extracts were dried over sodium sulfate and the solvent was allowed to evaporate. The sticky brown residue was stirred with absolute alcohol and 0.5 g. of insoluble material was removed by filtration. This melted at 222-226° and was shown to be tetraphenyllead by a mixed

melting point. The alcohol filtrate was decolorized with Norite and concentrated to a small volume. On cooling, a white crystalline precipitate was deposited. This was filtered off, but most of it dissolved when washed with a little alcohol on the filter. The small amount of solid remaining melted with turbidity at 155-157° and resolidified above this temperature. On further concentration of the mother liquor plus the washings and on subsequent cooling there was obtained more of the crystalline precipitate. This was washed with petroleum ether to give 0.6 g. of snow-white crystals which melted with turbidity at 155-160° and resolidified above this temperature. A third fraction obtained by further concentration weighed 0.15 g. and melted at 143-145° with turbidity. A lead analysis of the 0.5 g. fraction showed that the lead content was 44.95 per cent, which is much higher than the theoretical lead content of triphenyl-p-cyanophenyllead (38.38 per cent). It was thought that the product might be triphenyllead cyanide (lead content 44.64 per cent), but the material gave no qualitative tests for nitrogen or for cyanide ion.

Tetraphenyllead and nitrogen tetroxide

The nitrogen tetroxide used in this experiment and in the two following experiments was prepared by the method of Cundall.[84]

To a solution of 2 g. (0.0039 mole) of tetraphenyllead in 15 cc. of chloroform there was added gradually, with external cooling in an

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[84]Cundall, J. Chem. Soc., 59, 1076 (1891).

ice bath, a solution of 0.6 g. (0.0065 mole) of nitrogen tetroxide in 10 cc. of chloroform. The brown color of the nitrogen tetroxide was immediately replaced by a light, clear blue. A precipitate formed at once and the amount of this increased with standing. The reaction mixture was allowed to stand for two weeks after which the solid was filtered off. There was obtained a light tan, crystalline solid, weighing 1.73 g. The product had no definite melting point and gave qualitative tests for nitrogen and for the nitrate ion. A sample purified by crystallization from absolute alcohol and dried under vacuum at 100° was shown by analysis to contain 42.26 per cent lead. The theoretical value for diphenyllead dinitrate is 42.70 per cent. The weight of crude product represents a 92 per cent yield of diphenyllead dinitrate.

Triphenyl-p-hydroxymethylphenyllead and nitrogen tetroxide

The procedure employed in this and the following experiment was patterned after that described by Cohen and Calvert[85] for the oxidation of benzyl alcohol to benzaldehyde by means of nitrogen tetroxide.

To a solution of 2 g. (0.00367 mole) of triphenyl-p-hydroxymethylphenyllead in 10 cc. of chloroform there was added gradually,

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[85]Cohen and Calvert, ibid., 71, 1050 (1897).

with cooling in an ice bath, a solution of 0.0043 mole of nitrogen tetroxide in 15 cc. of chloroform. The solution immediately turned blue-green, and soon deposited an oil. The reaction mixture was allowed to stand three days during which time the oil originally deposited changed to an amorphous solid. The chloroform layer was decanted off and allowed to evaporate. Only a small amount of dark-colored residue remained; this was discarded. The chloroform-insoluble solid was an amorphous material melting at 170-190° with decomposition. It could not be crystallized, and no pure product was isolated from the reaction.

Triphenyl-p-β-hydroxyethylphenyllead and nitrogen tetroxide

A solution of 2 g. of triphenyl-p-β-hydroxyethylphenyllead in chloroform was treated with a chloroform solution of nitrogen tetroxide and the reaction was worked up in the manner described for the preceding experiment. A slight odor of phenylacetic acid was noted during the manipulation of this reaction mixture. The only product obtained was an amorphous solid which melted at 185-195° with decomposition and which was insoluble in chloroform. This material resembled the product from the reaction described directly above.

Triphenyllead chloride and γ-diethylaminopropyllithium

A solution of 20 g. (0.13 mole) of γ-diethylaminopropyl chloride in 60 cc. of ether was added to a stirred suspension of 1.9 g. (0.28 g. atom) of lithium in 40 cc. of ether. After a small amount of the halide

had been added the reaction mixture turned grey and warmed up slightly. The rest of the halide was added over thirty minutes, during which time the mixture became more opaque and remained somewhat warm but it did not reflux. At the end of this time color test I was faintly positive. The reaction mixture was stirred at room temperature for eight hours. A double titration was then run. The results indicated that an organolithium compound had been formed in approximately ten per cent yield, although the end points of the titrations were not sharp.

Of this preparation, 90 cc., containing approximately 0.012 mole of γ-diethylaminopropyllithium, was added quickly to 5.7 g. (0.012 mole) of triphenyllead chloride suspended in 25 cc. of ether. The reaction mixture warmed up slightly, but not all of the triphenyllead chloride went into solution. After three minutes the reaction was hydrolyzed with iced ammonium chloride solution, filtered from 1.2 g. of impure triphenyllead chloride, and the ether layer was separated and dried over sodium sulfate. The ether was evaporated and the unreacted γ-diethylaminopropyl chloride was removed by distillation under vacuum. The oily residue, weighing 3.8 g., was treated with petroleum ether to precipitate 0.35 g. of a solid (m.p. 187-220°) which appeared to be a mixture of triphenyllead chloride with a little tetraphenyllead. The greater part of the oil could not be crystallized.

Attempted preparation of triethyl-p-hydroxymethylphenyllead

A solution of 0.20 mole of n-butyllithium in 260 cc. of ether was added during ten minutes to a solution of 18.7 g. (0.1 mole) of

p-bromobenzyl alcohol in 45 cc. of ether. The reaction mixture was stirred for thirty minutes, and then 100 cc. of an ethereal solution containing an excess of magnesium bromide was added during fifteen minutes with vigorous stirring. A precipitate formed during the addition. After an additional fifteen minutes, 33.0 g. (0.1 mole) of triethyllead chloride was added fairly rapidly. Color test I was negative a few minutes after the addition of the organolead halide was complete, but the reaction was stirred for fifteen minutes and then hydrolyzed by pouring on iced ammonium chloride solution. The ether layer was separated and dried over sodium sulfate, and the ether was distilled off. Low-boiling products were removed by distillation over the steam bath under a vacuum of 1 mm. The residual oil, which weighed 42.5 g., was cooled in the ice box for thirty-six hours but only a trace of solid appeared. The oil was decanted from this solid, and distilled under a vacuum of 1 mm., using an oil bath the temperature of which was finally raised to 120°. A colorless oil distilled at 45 to 85° (vapor temperature), at which point the entire residue in the distillation flask decomposed and turned solid. The oil which had distilled weighed 15.5 g., and was probably chiefly triethyl-n-butyllead (n_D^{20} 1.5123),[86] since its refractive index at 20° was 1.5107.

Similar results, including decomposition of the residue in the distilling flask on attempted distillation of the product, were obtained

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[86] Grüttner and Krause, Ann., 415, 356 (1918).

from an experiment in which the organolithium compound resulting from the interconversion of p-bromobenzyl alcohol was not treated with magnesium bromide before addition of the triethyllead chloride.

Triethyl-p-bromophenyllead

Robinson[30] prepared crude triethyl-p-bromophenyllead by the procedure employed in the experiment described here. However, he was unable to distil or otherwise purify his product and therefore no constants have been reported for this compound.

In the first attempt to prepare pure triethyl-p-bromophenyllead, equivalent amounts of the Grignard reagent and triethyllead chloride were used. The high-boiling portion of the product was distilled under high vacuum, and the distillate collected as one large fraction. This product was shown by analysis to contain about four per cent more lead than the calculated value for pure triethyl-p-bromophenyllead. It appeared that some unreacted triethyllead chloride had distilled along with the desired product. The second preparation is described in detail below.

A Grignard reagent was prepared from 5.68 g. (0.234 g. atom) of magnesium and a solution of 47.2 g. (0.2 mole) of p-dibromobenzene in 225 cc. of ether. After all the halide had been added and the spontaneous reaction had ceased, the solution was refluxed for thirty minutes and then filtered from a slight excess of magnesium. To the filtered solution

there was added 52.8 g. (0.16 mole) of triethyllead chloride. The reaction mixture was stirred at room temperature for one hour and then hydrolyzed by pouring on iced ammonium chloride solution. The ether layer was removed and dried over sodium sulfate. The ether was evaporated and the remaining oil subjected to distillation under a vacuum of 3 mm. and up to a temperature of 125°. The residual oil was cooled for thirty-six hours in the ice box and then filtered through cotton from a small amount of solid into a small distilling flask. Under high vacuum distillation (about 0.002 mm.), the first three fractions collected weighed a total of 25.5 g. These fractions on cooling deposited a considerable amount of triethyllead chloride. The fourth fraction, which distilled at a bath temperature of 143°, was a clear, colorless liquid and weighed 21.5 g. This represents a 30 per cent yield of pure triethyl-p-bromophenyllead, based on the amount of triethyllead chloride used. The density (d_{27}^{20}) was 1.8586 and the refractive index (n_D^{20}) was 1.5968. The theoretical value of the molecular refraction, calculated from the atomic factors of Auwers and Eisenlohr[87] (using for the atomic refraction of lead the value 18.1, found by Grüttner and Krause[88] for lead in tetraethyllead), is 82.1. The observed value, based on the above values of the density and refractive index, was 82.5.

Anal. Calcd. for $C_{12}H_{19}BrPb$: Pb, 46.03. Found: Pb, 46.19.

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[87] Gilman, "Organic Chemistry," John Wiley and Sons, New York (1943), 2nd ed., vol. 2, p. 1751.

[88] Grüttner and Krause, Ann., 415, 343 (1918).

Reaction of triethyl-p-bromophenyllead with magnesium

Some preliminary experiments, as well as the work of Robinson,[30] indicated that triethyl-p-bromophenyllead does not react with magnesium in ether. Therefore, the activated copper-magnesium alloy[89] was used.

A solution of 6 g. (0.013 mole) of pure triethyl-p-bromophenyllead in 25 cc. of ether was added all at once to an excess (0.5 g.) of warm activated copper-magnesium alloy (87.5 per cent magnesium). Color test I was strongly positive after the reaction mixture had been stirred for four hours. After having been stirred at room temperature for a total time of ten hours, the reaction was carbonated by pouring on dry ice. The carbonation product was hydrolyzed with ammonium chloride solution, and the ether layer was separated and extracted with two 10-cc. portions of 10 per cent potassium hydroxide solution. Nitrogen was bubbled through the alkaline extract to remove dissolved ether. The solution was then cooled in an ice bath and carefully acidified with iced 10 per cent hydrochloric acid. There was formed a sticky precipitate which weighed 1.3 g., softened at 80-90°, and melted at 90-100°. This material seemed to decompose on attempted crystallization and no pure product was isolated.

In an earlier experiment using slightly impure triethyl-p-bromophenyllead, there was obtained, after carbonation and acidification

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[89]Gilman, Peterson, and Schulze, Rec. trav. chim., 47, 19 (1928).

of the alkaline extract, 1.3 g. of a white solid melting at 138-141°. This was crystallized from alcohol to give, in addition to decomposition products, 0.2 g. of solid melting at 140-143°. When this product was crystallized from petroleum ether containing a few drops of benzene there was obtained 0.1 g. of material which melted at 145-147°. A neutral equivalent determination on this material gave a value six times greater than the theoretical value for the expected triethyl-p-carboxyphenyllead.

Triethyllead-sodium and γ-diethylaminopropyl chloride

Triethyllead-sodium was prepared as follows: to a stirred mixture of 300 cc. of dry ether and 300 cc. of liquid ammonia there was added in small pieces 2.3 g. (0.1 g. atom) of sodium. To the dark blue solution thus formed there was added dropwise with stirring a solution of 16.2 g. (0.05 mole) of tetraethyllead in 30 cc. of ether. The reaction mixture was then stirred until the ammonia had evaporated and the solution had warmed up to room temperature.

The resulting suspension, containing sodamide and approximately 0.05 mole of triethyllead-sodium in ether, was filtered through sintered glass into a stirred solution of 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride in 30 cc. of ether. When the first drops of the pale yellow solution of triethyllead-sodium were added to the halide, the reaction mixture turned orange in color. Soon it became opaque and almost black. After all the triethyllead-sodium had been added the reaction was stirred for one hour and then allowed to stand overnight. The solid was removed

by filtration, and the ether was distilled from the filtrate. The residual oil was distilled under a vacuum of 1 mm., at a bath temperature up to 90°, to give 2.1 g. of a liquid which distilled at 30-45° (vapor temperature) and which seemed to be unreacted γ-diethylaminopropyl chloride. The remaining oil was distilled under high vacuum (less than 0.001 mm.). The product, which came over at a bath temperature of 90° as a clear yellow oil, weighed 9.0 g. This material was shown to contain nitrogen by a sodium fusion test. The constants were as follows: n_D^{25} 1.5353; d_{27}^{25} 1.5429. The observed value of the molecular refraction, obtained from these constants, was 82.4. The theoretical value is 86.6. The lead content was shown by analysis to be 5 per cent higher than the theoretical value for triethyl-γ-diethylaminopropyllead. These results indicate that the product probably contained impurities such as hexaethyldilead and tetraethyllead.

In a preliminary experiment the reaction product decomposed and deposited metallic lead upon attempted distillation under a pressure of one millimeter.

Tetraphenyllead and fuming sulfuric acid

To 50 cc. of fuming sulfuric acid, cooled to -25°, there was added with stirring 10 g. (0.019 mole) of solid tetraphenyllead. The tetraphenyllead did not dissolve completely, and a viscous suspension was produced. After forty-five minutes the reaction mixture was allowed to warm up to 0° and was stirred at this temperature for forty-five

minutes longer. The now homogeneous solution was poured slowly, with vigorous stirring, on crushed ice. The slightly turbid solution was filtered from a trace of precipitate. The filtrate, which was still slightly turbid, was almost neutralized with a saturated aqueous solution of barium hydroxide. The barium sulfate was removed by filtration, and the filtrate was carefully treated with barium hydroxide and dilute sulfuric acid until further treatment with barium hydroxide gave no more barium sulfate and the solution was acidic to phenolphthalein and basic to litmus. A small additional amount of barium sulfate was removed by filtration, and the filtrate was evaporated to dryness. A white, solid residue was obtained. This was analyzed for barium and lead, but the results did not correspond to any possible compound. The lead content indicated a molecular weight of about 1700, assuming one atom of lead per molecule, whereas the molecular weight of the normal barium salt of a tetraphenyllead tetrasulfonic acid would be 1106. In addition, the ratio of barium to lead in the product (three atoms of barium to one atom of lead) was too great for the barium salt just mentioned (two atoms of barium to one atom of lead) or for the salt of any less completely sulfonated product. Although the conversion of tetraphenyllead to a product which was soluble in dilute sulfuric acid solution indicates that sulfonation unaccompanied by cleavage to lead sulfate had occurred, the products were not isolated in a pure enough condition for analysis to be significant.

Tetraphenyllead and chlorosulfonic acid

Finely pulverized tetraphenyllead (10 g., 0.019 mole) was added in small portions during five minutes to a large excess (25 cc.) of chlorosulfonic acid at -70°. With the addition of each portion of tetraphenyllead there was a rather violent reaction with sudden evolution of white fumes. The reaction mixture was stirred for five minutes after the addition was complete, and then carefully poured, with vigorous stirring, into 250 cc. of iced concentrated ammonium hydroxide, cooled in an ice-salt bath. There was obtained from this 5.45 g. of white solid which had no definite melting point and which was shown by qualitative tests not to contain sulfur or nitrogen. The solid was washed with hot chloroform and the chloroform filtrate evaporated to give 1.9 g. of tetraphenyllead. The remainder of the product was washed with ammonium acetate solution to remove inorganic lead salts. The residue, which weighed 2.5 g., was shown by lead analysis and by its conversion to tetraphenyllead with phenylmagnesium bromide to be diphenyllead dichloride.

Preparation of triphenyl-o-anisyllead

A Grignard reagent was prepared from 1.46 g. (0.06 g. atom) of magnesium and 11.22 g. (0.06 mole) of o-bromoanisole in 50 cc. of ether. To the clear solution there was added 23.70 g. (0.05 mole) of solid triphenyllead chloride. There was a rather vigorous refluxing of the

ether during the addition. An additional 50 cc. of ether was added and the mixture was stirred for one hour at the reflux temperature of ether. Then 50 cc. of toluene was added and refluxing was continued for one-half hour more. At the end of this time color test I was still positive. The reaction mixture was hydrolyzed by pouring on iced ammonium chloride solution. The hydrolysis product was filtered from 10.7 g. of crude product melting at 124-129°. This was crystallized from absolute alcohol to give 9.25 g. of pure triphenyl-o-anisyllead, melting at 128-129°.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 38.00. Found: Pb, 38.01.

The ether-toluene layer was separated from the aqueous layer of the original filtrate, dried, and evaporated. The toluene was removed by distillation under vacuum to leave an oil which solidified on cooling. The solid was crystallized from absolute alcohol to give 11.45 g. of rather impure product, melting at 121-124°. The total yield of crude triphenyl-o-anisyllead was 22.15 g. or 81 per cent, based on the triphenyllead chloride used.

Preparation of triphenyl-p-anisyllead

The preparation of triphenyl-p-anisyllead by means of the reaction of p-anisyllithium and triphenyllead chloride has been reported by Towne.[36]

In the present work, triphenyl-p-anisyllead was prepared by the reaction of p-anisylmagnesium bromide with triphenyllead chloride. The

procedure was similar to that described above for the preparation of the ortho isomer, and the amounts of materials were exactly the same. In the case of the para isomer the solid, formed as soon as the triphenyllead chloride was added to the solution of the Grignard reagent, was insoluble in ether and toluene, and, therefore, the reaction mixture was hydrolyzed by addition of ice and ammonium chloride to the previously cooled material in the reaction flask. The crude insoluble product weighed 21.0 g. (77 per cent) and melted at 146-150°. The dried ether-toluene layer yielded 2.5 g. of rather crude product, melting at 145-148°, making a total yield of 23.5 g. or 86 per cent. The pure compound, obtained by crystallization from absolute alcohol, melted at 150-151° with slight decomposition. Towne[36] reported that triphenyl-p-anisyllead melted at 152° with some decomposition.

Triphenyl-p-anisyllead and chlorosulfonic acid

Finely powdered triphenyl-p-anisyllead (5 g., 0.0092 mole) was added during five minutes to a large excess (25 cc.) of chlorosulfonic acid at -70°. There appeared to be a violent reaction with immediate evolution of white fumes. The reaction mixture was stirred for ten minutes and then poured slowly, with vigorous stirring, into 200 cc. of concentrated ammonium hydroxide, previously cooled in an ice-salt bath. The solid which separated weighed 2.8 g. and had no definite melting point. It was washed with chloroform and the chloroform washings were evaporated to give a small amount of red oil which was discarded. The

remainder of the solid was washed with ammonium acetate solution. The small amount of undissolved residue resembled the product obtained from the reaction of tetraphenyllead with chlorosulfonic acid (diphenyllead dichloride).

Tetraphenyllead and sodium hydroxide in alcohol

This experiment was carried out in order to determine the stability of tetraphenyllead toward strong base. A mixture of 5 g. of tetraphenyllead, 20 g. of sodium hydroxide, and 100 cc. of 95 per cent alcohol was refluxed for three hours. At the end of this time the sodium hydroxide had dissolved and the color of the solution was pale orange. The mixture was poured into 400 cc. of water and filtered from 4.7 g. (94 per cent recovery) of pure tetraphenyllead.

Tetraphenyllead and sodium hydroxide in chloroform

This and the following experiment were carried out in an attempt to prepare organolead compounds containing the aldehyde group by a Reimer-Tiemann reaction.

To a solution of 25 g. (0.049 mole) of tetraphenyllead in 96 g. (0.8 mole) of chloroform there was added a warm solution of 80 g. (2 moles) of sodium hydroxide in 80 cc. of water. The mixture was stirred vigorously at reflux for six hours, allowed to stand overnight, and then distilled with steam until no more chloroform came over. The residual material was filtered and washed with water to give 24.6 g. (98 per cent recovery) of pure tetraphenyllead.

Triphenyl-p-anisyllead and potassium hydroxide in chloroform

A solution of 5 g. (0.0092 mole) of triphenyl-p-anisyllead in 20 g. (0.17 mole) of chloroform was treated with a solution of 22.5 g. (0.4 mole) of potassium hydroxide in 15 cc. of water. The mixture was refluxed over a steam bath, with vigorous stirring, for six hours, and allowed to stand overnight. It was then subjected to steam distillation to remove the chloroform. The residual material was filtered and washed with water to give 5 g. or a quantitative recovery of triphenyl-p-anisyllead.

DISCUSSION

Halogen-Metal Interconversion Reactions

The halogen-metal interconversion reaction between alkyllithium compounds and aromatic halides affords an excellent method for the preparation of organolithium compounds from halides which react only to a slight extent or not at all with lithium to form organolithium compounds or with magnesium to form Grignard reagents. In the present study the halogen-metal interconversion reaction has been extended to the preparation of organolithium compounds from (1) compounds containing "unreactive" halogen atoms, and (2) aromatic halides containing alcoholic hydroxyl groups.

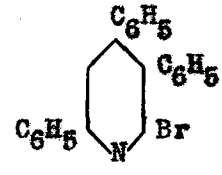
The fact that β-styryllithium was obtained from the reaction of β-bromostyrene (a halide of the unreactive vinyl type) with n-butyllithium in petroleum ether[54] suggested that the interconversion reaction might prove useful in the preparation of organolithium compounds from other unreactive halides. This has been found to be the case.

The organolithium compound and the corresponding acid have been prepared in good yield by interconversion and carbonation from 2,4,5-triphenyl-3-bromofuran, a compound which does not react with lithium[59]

or with magnesium,[90] and in which the bromine atom is unaffected by prolonged boiling with alcoholic potassium hydroxide.[90]

The corresponding triphenylchlorofuran also gave the organolithium compound when treated with n-butyllithium. The only other case of a halogen-metal interconversion in which the replacement of a chlorine atom by lithium has been demonstrated by carbonation and subsequent isolation of the acid is that of phenylethinyl chloride with n-butyllithium.[56] Wittig[91] has reported that such an interconversion occurs between o-chloroanisole and phenyllithium but the experimental details are as yet unpublished. Wittig and Witt[92] have recently shown, by isolation of chlorobenzene, that halogen-metal interconversion occurs between phenyllithium and the chlorides, carbon tetrachloride, phenyltrichloromethane, and diphenyldichloromethane.

The bromine atom in the highly-substituted 3,4,6-triphenyl-2-bromopyridine is rather unreactive, since it is but little affected by prolonged boiling with sodium methoxide or ethoxide, although sodium



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[90] Allen and Rosener, J. Am. Chem. Soc., 49, 2110 (1927).

[91] Wittig, Angew. Chem., 53, 241 (1940).

[92] Wittig and Witt, Ber., 74, 1474 (1941) [C. A., 36, 5802 (1942)].

butoxide effects replacement of the bromine by butoxyl.[58] Allen and Frame[59] have reported that this halide reacts slowly with lithium in ether to give a product which is decomposed by acid to form 2,4,5-triphenylpyridine but which does not react with carbon dioxide, aldehydes, or ketones. The present work shows that 3,4,6-triphenyl-2-bromopyridine, when treated with n-butyllithium in ether at -35°, gives a product which reacts with crushed solid carbon dioxide to give 3,4,6-triphenylpyridine-2-carboxylic acid in good yield.

Attempts to prepare a Grignard reagent from 2-bromobenzofuran have been unsuccessful.[60] By interconversion at -70° with short reaction time 2-benzofuryllithium has now been prepared in good yield, as shown by carbonation to give benzofuran-2-carboxylic acid. The method is not of preparative value as far as benzofuran-2-carboxylic acid is concerned, since the latter is an intermediate in the synthesis of 2-bromobenzofuran. However, the interconversion makes available a means of preparing other compounds containing the 2-benzofuryl group through the agency of 2-benzofuryllithium.

Reichstein and Baud[62] obtained a very small yield (one per cent) of the Grignard reagent from 3-bromobenzofuran by using copper-magnesium alloy. The chief reaction was a cleavage of the benzofuran nucleus to give o-ethinylphenol. The present work shows that the chief reaction between 3-bromobenzofuran and n-butyllithium also is cleavage. At room temperature the action of three moles of n-butyllithium on 3-bromo-benzofuran resulted in the isolation, after hydrolysis of the reaction

mixture, of a sixty-seven per cent yield of o-ethinylphenol. Even at low temperatures some cleavage occurs. From one short-time interconversion in ether at -70° there was isolated, after carbonation, an acid having the properties of benzofuran-3-carboxylic acid; however, this result could not be duplicated. In most cases (see Table I, page 55) the only acid found was benzofuran-2-carboxylic acid. The mechanism of formation of the 2-acid is probably similar to that postulated for the reaction of 3-bromodibenzofuran with n-butyllithium, in which case a mixture of 3- and 4-dibenzofurancarboxylic acids was obtained upon carbonation.[93]

The halogen-metal interconversion reaction has made possible the preparation of organolithium compounds from aromatic halides containing functional groups which have active hydrogen atoms. Among the halides of this type which have been studied are o- and p-bromophenol, p-iodophenol, o-bromobenzoic acid, o- and p-iodobenzoic acid,[17] o-bromoaniline,[47] p-bromoaniline,[48,94] and p-bromo-N-methylaniline.[47] In such cases it is necessary to use enough of the alkyllithium compound (RLi in the equation--usually n-butyllithium) not only to effect the replacement of the halogen atom by lithium but first to replace the active hydrogen atoms of the functional group.

$$p\text{-}BrC_6H_4OH + 2RLi \longrightarrow p\text{-}LiC_6H_4OLi + RH + RBr$$

It is necessary also to carry out the reaction at low temperatures in

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

[94]Gilman and Stuckwisch, ibid., 63, 2844 (1941).

the case of halides containing functional groups (such as the carboxyl) which are subject to addition of, and reduction by, active organometallic types.

A halogen-metal interconversion is effected by the addition of two moles of n-butyllithium to one mole of a nuclearly bromine-substituted phenylalkyl alcohol such as p-bromobenzyl alcohol, for example. The reaction has been studied with three primary alcohols, namely, p- and m-bromobenzyl alcohol, and p-bromophenethyl alcohol ($p\text{-}BrC_6H_4CH_2CH_2OH$), and with one secondary alcohol, p-bromo-α-methylbenzyl alcohol ($p\text{-}BrC_6H_4CHOHCH_3$). The yields of interconversion products, as determined by carbonation and isolation of the corresponding carboxylic acids, range from 18 to 52 per cent. However, the actual yields are greater than these results indicate, since the interconversion products, when treated with triphenyllead chloride instead of with carbon dioxide, were converted into the expected unsymmetrical organolead compounds in yields of 41 to 63 per cent. The halogen-metal interconversion of o-bromobenzyl alcohol, although not studied by carbonation of the reaction product, has been established by the reaction of the interconversion product with triphenyllead chloride to produce triphenyl-o-hydroxymethylphenyllead in a yield of 70 per cent.

Results have been obtained which indicate that p-bromobenzenesulfonamide undergoes halogen-metal interconversion when treated with two moles of n-butyllithium. However, it was not possible to isolate pure p-carboxybenzenesulfonamide from the carbonated reaction mixture.

The occurrence of a halogen-metal interconversion to the extent of ten per cent between p-bromobenzonitrile and n-butyllithium in ether at -70° has been established by the isolation, after carbonation, of an acid in 17 per cent yield which was converted to dimethyl terephthalate in 60 per cent yield upon treatment with diazomethane. The terephthalic acid must have resulted from the hydrolysis of p-cyanobenzoic acid during the heating of the alkaline extract of the latter to remove dissolved ether. No interconversion of p-bromobenzonitrile occurred when a

$$p\text{-}BrC_6H_4CN + RLi \longrightarrow p\text{-}LiC_6H_4CN + RBr$$

$$p\text{-}LiC_6H_4CN + CO_2 \longrightarrow p\text{-}LiOOCC_6H_4CN$$

$$p\text{-}LiOOCC_6H_4CN + KOH + 2H_2O \longrightarrow p\text{-}LiOOCC_6H_4COOK + NH_4OH$$

mixture of ether and benzene was used as solvent.

Organolead Compounds

Organolead compounds containing alcoholic hydroxyl groups

The preparation of organolead compounds containing alcoholic hydroxyl groups attached through aliphatic groups to aromatic nuclei is of interest not only because the hydroxyl group is a water-solubilizing group, but also because the compounds with this group might serve as intermediates in the preparation of types containing other, and perhaps more effective, water-solubilising groups. Before the present study, the only known organolead compound containing the alcoholic hydroxyl group was triphenyl-2,3-dihydroxypropyllead, prepared by Austin[40] in a small yield by permanganate oxidation of triphenylallyllead.

The extension of the halogen-metal interconversion reaction to phenylalkyl alcohols containing bromine as a nuclear substituent makes available a general method for the synthesis of unsymmetrical organolead compounds containing the alcoholic hydroxyl group. The method is illustrated by the equation for the preparation of triphenyl-p-hydroxymethylphenyllead from triphenyllead chloride and the product of interconversion of p-bromobenzyl alcohol with n-butyllithium.

$$p\text{-}BrC_6H_4CH_2OH + 2n\text{-}C_4H_9Li \longrightarrow p\text{-}LiC_6H_4CH_2OLi + n\text{-}C_4H_9Br + n\text{-}C_4H_{10}$$

$$(C_6H_5)_3PbCl + p\text{-}LiC_6H_4CH_2OLi \longrightarrow (C_6H_5)_3PbC_6H_4CH_2OLi\text{-}p + LiCl$$

$$(C_6H_5)_3PbC_6H_4CH_2OLi + H_2O \longrightarrow (C_6H_5)_3PbC_6H_4CH_2OH\text{-}p + LiOH$$

It was found advantageous to use about eight-tenths of a mole of triphenyllead chloride to one mole of the bromoalcohol (and two moles of n-butyllithium), since by this means the necessity of separating appreciable amounts of unreacted triphenyllead chloride from the desired product was avoided. It was more convenient to separate unreacted bromoalcohol (or benzyl alcohol formed by hydrolysis of unreacted interconversion product) from the desired organolead compound than it was to separate excess triphenyllead chloride. Although an excess of n-butyllithium must have been present in every case, assuming that the interconversions did not go to the extent of one hundred per cent, no triphenyl-n-butyllead was isolated from any of these reactions. The butyllead compound was probably formed, but because of its low melting point and relatively great solubility this compound remained in the mother liquors from the crystallization of the hydroxyalkylphenyllead compounds.

A side reaction which might have been expected to occur was that of the alkoxide lithium atom, instead of the organometallic lithium atom, with the triphenyllead chloride to give a triphenyllead alkoxide which is still an organolithium compound.

$$(C_6H_5)_3PbCl + p\text{-}LiC_6H_4CH_2OLi \longrightarrow (C_6H_5)_3PbOCH_2C_6H_4Li\text{-}p + LiCl$$

This product would form triphenyllead benzoxide (or "benzylate") upon hydrolysis. No evidence for the formation of such a compound, which is an isomer of triphenyl-p-hydroxymethylphenyllead but which would probably be unstable in the presence of water, was observed. The formation of triphenyllead p-bromobenzoxide according to the following equation might also be expected to occur to some extent:

$$(C_6H_5)_3PbCl + p\text{-}BrC_6H_4CH_2OLi \longrightarrow (C_6H_5)_3PbOCH_2C_6H_4Br\text{-}p + LiCl$$

However, no halogen-containing product was found in any of these reactions. The fact that no benzoxide or p-bromobenzoxide was found indicates that the alkoxide lithium atom does not react with the chlorine atom of triphenyllead chloride or that such a reaction is much slower than that of the organometallic lithium atom with triphenyllead chloride.

The reaction of organolithium compounds, prepared by halogen-metal interconversion, with triphenyllead chloride resulted in the formation of a small amount of tetraphenyllead in every case. This is probably due to the occurrence of metal-metal interconversion reactions which give rise to intermediates capable of reacting in the usual manner to form the R_4Pb compound.

$$(C_6H_5)_3PbCl + RLi \longrightarrow (C_6H_5)_3PbR + LiCl$$

$$(C_6H_5)_3PbR + RLi \longrightarrow (C_6H_5)_2PbR_2 + C_6H_5Li$$

$$(C_6H_5)_3PbCl + C_6H_5Li \longrightarrow (C_6H_5)_4Pb + LiCl$$

The occurrence of this series of reactions can be avoided by conversion of the organolithium compound to the Grignard reagent by treatment with magnesium bromide.[48] Arntzen[17] found it necessary to adopt this procedure in order to secure satisfactory yields of unsymmetrical organotin compounds from the reaction of organotin halides with the products of halogen-metal interconversion reactions. In the case of organolead compounds the formation of tetraphenyllead has been minimized by making the time of reaction relatively short, that is, by hydrolyzing the reaction mixture after the triphenyllead chloride and organolithium compound have been in contact for about two minutes.

Although organolead compounds of the type $(C_6H_5)_3PbR$, which are solids and can usually be purified by recrystallization, were obtained in relatively good yields from the reaction of triphenyllead chloride with organolithium compounds formed by halogen-metal interconversion, the analogous preparation of liquid organolead compounds of the type $(C_2H_5)_3PbR$ is in general not successful. The compounds must be purified by distillation; however, they often decompose upon attempted distillation under a pressure of one millimeter, whereas under high-vacuum distillation no separation from some of the by-products is effected. The compound, triethyl-*p*-hydroxymethylphenyllead, has not been isolated. It was probably formed in the reaction of triethyllead chloride with the organo-

lithium compound obtained from p-bromobenzyl alcohol, but decomposition occurred when attempts were made to distil the reaction product under a pressure of one millimeter.

The melting points of the triphenylhydroxyalkylphenyllead compounds show some interesting relationships. In the hydroxymethyl series, in which the ortho, meta, and para isomers have been prepared, the ortho isomer has the highest melting point (134-136°). The meta isomer melts at 113-114° and the para isomer at 98-100°. This is in agreement with the observation that, in general, the ortho isomer in a pair of substituted tetraaryllead compounds has a higher melting point than the para isomer. The triphenylanisyllead compounds constitute an exception to this generalization. Triphenyl-o-anisyllead, the preparation of which is described in this thesis, melts at 128-129°, whereas Towne[36] reported that the para isomer melted at 152° with some decomposition. Of the two triphenylhydroxyethylphenyllead compounds which were prepared, triphenyl-p-β-hydroxyethylphenyllead, a phenethyl alcohol derivative, melted at 87-88°, and the triphenyl-p-α-hydroxyethylphenyllead, the only secondary alcohol prepared, melted at 68-70° or almost twenty degrees lower than the isomeric primary alcohol.

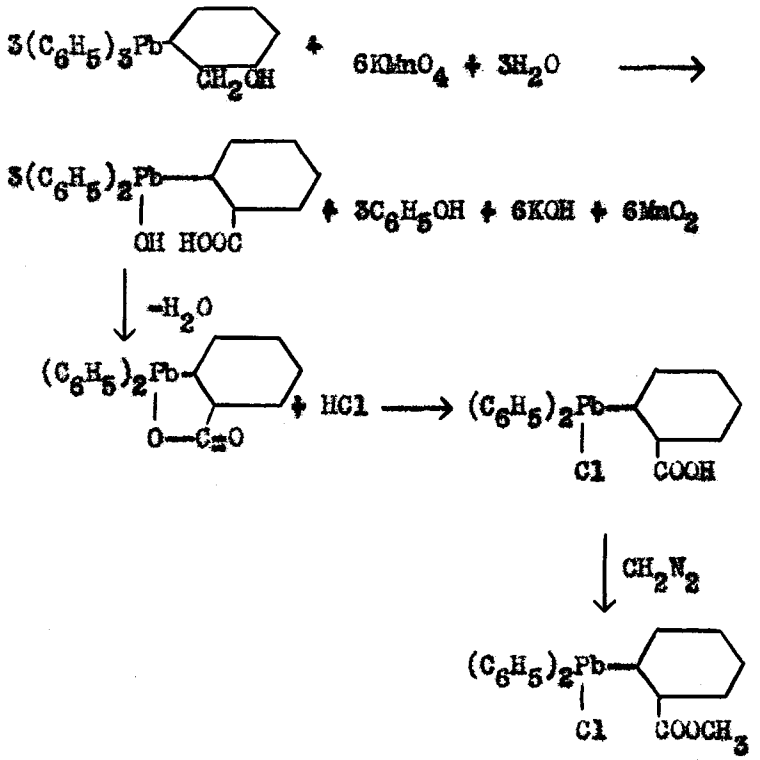
Organolead compounds containing carboxyl groups

Several workers have attempted to prepare organolead compounds containing the carboxyl group without success. The oxidation of tolyllead compounds with permanganate in acetone was unsuccessful (see

page 30). However, it was thought that the hydroxymethylphenyl compounds, in which the aliphatic side chain is already partially oxidized, might be more readily oxidized to carboxyphenyl compounds. The oxidation of triphenyl-p-hydroxymethylphenyllead with potassium permanganate was successfully carried out to give a 25 per cent yield of triphenyl-p-carboxyphenyllead. The acid and its sodium and potassium salts were insoluble in water. The free acid reacted with diazomethane to form the methyl ester. Arntzen[17] was able to oxidize triphenyl-p-hydroxymethylphenyltin to triphenyl-p-carboxyphenyltin in a yield of 44 per cent by using the conditions that were found to give the desired oxidation in the organolead series.

The oxidation of triphenyl-o-hydroxymethylphenyllead by a similar procedure resulted in the formation of the inner anhydride of diphenyl-o-carboxyphenyllead hydroxide. The formation of this compound involves oxidation of the hydroxymethyl group to a carboxyl group and simultaneous cleavage of one phenyl group. In the equations below, the cleaved phenyl group is shown as having been converted to phenol. This is hypothetical since no phenol was isolated from the reaction; however, if phenol were formed it would immediately be oxidized further by any permanganate present. The diphenyl-o-carboxyphenyllead hydroxide postulated as the oxidation product was not isolated since it formed the anhydride spontaneously. Treatment of the anhydride with concentrated hydrochloric acid in absolute alcohol gave diphenyl-o-carboxyphenyllead

chloride which reacted with diazomethane to form the methyl ester.



Arntzen[18] has carried out a similar series of reactions starting with triphenyl-o-hydroxymethylphenyltin.

One attempt was made to oxidize triphenyl-m-hydroxymethylphenyllead to triphenyl-m-carboxyphenyllead but this was unsuccessful. The organolead compound decomposed to give an acetone-insoluble product but no pure material could be isolated from the reaction.

It was thought that triphenylcarboxyphenyllead compounds could be prepared more conveniently by oxidation of triphenylmethoxymethylphenyllead compounds, because the latter might possibly be prepared from the reaction of triphenyllead chloride with the Grignard reagent prepared directly from bromobenzyl methyl ethers. If this could be done, a halogen-metal

interconversion would not be necessary. However, the yield of Grignard reagent obtained from o-bromobenzyl methyl ether was so small that none of the desired organolead compound could be prepared from it. Supniewski and Adams[95] were unable to prepare Grignard reagents from o- and p-bromobenzyl methyl ether.

A proposed synthesis of triphenyl-p-carboxyphenyllead involved the reaction of triphenyllead chloride with the organolithium compound formed by interconversion of p-iodobenzoic acid. None of the desired compound was obtained from this reaction. It is probable that the reaction of the organolead halide with the organolithium compound is very slow at the low temperature (-70°) at which the interconversion was carried out, and that as the reaction mixture is warmed the chief reaction occurs intermolecularly between the carboxyl groups and the organometallic lithium atoms.

The following equations represent another proposed synthesis of triphenyl-p-carboxyphenyllead:

$$p\text{-}BrC_6H_4Br + 2RLi \longrightarrow p\text{-}LiC_6H_4Li + 2RBr$$

$$p\text{-}LiC_6H_4Li + (C_6H_5)_3PbCl \longrightarrow (C_6H_5)_3PbC_6H_4Li\text{-}p + LiCl$$

$$(C_6H_5)_3PbC_6H_4Li\text{-}p + CO_2 \longrightarrow (C_6H_5)_3PbC_6H_4COOLi\text{-}p$$

In spite of the fact that only one mole of triphenyllead chloride was used per mole of p-dibromobenzene, the only new organolead compound found in the reaction products was p-phenylenedi-(triphenyllead).

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[95]Supniewski and Adams, J. Am. Chem. Soc., 48, 507 (1926).

The formation of this product would result from the reaction of two molecules of triphenyllead chloride with one molecule of p-phenylenedilithium.

$$p\text{-}LiC_6H_4Li + 2(C_6H_5)_3PbCl \longrightarrow (C_6H_5)_3PbC_6H_4Pb(C_6H_5)_3\text{-}p + 2LiCl$$

It was thought that triphenyl-p-carboxyphenyllead might be prepared by alkaline hydrolysis of triphenyl-p-cyanophenyllead, provided the latter could be formed by a Sandmeyer reaction using the diazonium salt from triphenyl-p-aminophenyllead and cuprous cyanide. However, the synthesis of the cyanophenyllead compound could not be accomplished. Most of the product was an amorphous, non-melting substance. The only crystalline material isolated was shown by analysis to be a cleavage product, since its lead content was considerably greater than that of triphenyl-p-aminophenyllead or any other tetraaryllead compound. Conditions under which an aminophenyllead compound can be diazotized in good yields have not been found. The synthesis of triphenyl-p-cyanophenyllead from triphenyllead chloride and p-cyanophenyllithium was not attempted because of the low yield of the organolithium compound obtained by interconversion of p-bromobenzonitrile.

Robinson[30] prepared impure triethyl-p-bromophenyllead by the reaction of p-bromophenylmagnesium bromide with triethyllead chloride. Since the product decomposed on attempted distillation, Robinson tried to prepare a Grignard reagent from magnesium and some of the impure product. He hoped to obtain triethyl-p-carboxyphenyllead by carbonation of the Grignard reagent, but the triethyl-p-bromophenyllead did not react with magnesium. The experimental part of this thesis describes the preparation

of triethyl-p-bromophenyllead by the method of Robinson, followed by high-vacuum distillation to give a pure product. The compound reacted with activated copper-magnesium alloy to give a Grignard reagent, as shown by a positive color test (I), but no pure carboxylic acid could be isolated from the reaction mixture.

Studies of miscellaneous types of organolead compounds

No organolead compounds containing the aldehyde or ketone groups have been prepared. The oxidation of two hydroxyalkylphenyllead compounds by nitrogen tetroxide to the corresponding aldehydes was attempted but no pure product was obtained. It seems probable that both oxidation and cleavage occurred, since the relatively stable tetraphenyllead was cleaved by nitrogen tetroxide in chloroform to give a good yield of diphenyllead dinitrate.

The oxidation of hydroxyalkyllead compounds by mild and selective oxidizing agents (selenium dioxide, for example) is a promising field for future research leading to the synthesis of organolead aldehydes and ketones, as well as of other interesting types such as the phenylacetic acid derivative, $(C_6H_5)_3PbC_6H_4CH_2COOH$-p.

Chaudhuri[96] was able to introduce a second aldehyde group into benzaldehyde by means of a Reimer-Tiemann reaction, thus synthesizing phthalaldehydes. The aldehyde group is meta-orienting and accordingly

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[96]Chaudhuri, J. Am. Chem. Soc., 64, 315 (1942).

it is an inactivating group. It was thought, therefore, that an aldehyde group might be similarly introduced into tetraphenyllead or its derivatives, in which the lead atom may be considered a moderately inactivating group. However, both tetraphenyllead and triphenyl-p-anisyllead were recovered unchanged after having been refluxed for six hours with chloroform and concentrated aqueous alkali.

The sulfonic acid group is one of the most effective water-solubilising groups known. No organolead compounds containing this group have yet been prepared. The treatment of tetraphenyllead with fuming sulfuric acid at a relatively low temperature resulted in the conversion of the organolead compound to a form in which it was soluble in aqueous sulfuric acid. Sulfonation must have occurred, because if cleavage had occurred exclusively the products would have been insoluble organolead salts or lead sulfate.

The chlorosulfonation of some organolead compounds was also attempted. Since it appeared probable that the sulfonyl chloride grouping in any organolead sulfonyl chloride formed might bring about cleavage of carbon-lead linkages, the reaction mixture was poured, while still cold, into concentrated ammonium hydroxide in order to convert the sulfonyl chloride to a sulfonamide. The only product isolated from the reaction of tetraphenyllead with chlorosulfonic acid was the cleavage product, diphenyllead dichloride, and with triphenyl-p-anisyllead the chief reaction also seemed to be cleavage.

No aminoalkyllead compounds have been prepared. Two syntheses, illustrated by the equations below, were proposed for organolead compounds containing the diethylaminopropyl group.

(1) $(C_6H_5)_3PbCl + (C_2H_5)_2N(CH_2)_3Li \longrightarrow (C_6H_5)_3Pb(CH_2)_3N(C_2H_5)_2 + LiCl$

(2) $(C_2H_5)_3PbNa + (C_2H_5)_2N(CH_2)_3Cl \longrightarrow (C_2H_5)_3Pb(CH_2)_3N(C_2H_5)_2 + NaCl$

The synthesis illustrated in the first equation was unsuccessful because the organolithium compound (as well as the Grignard reagent) could not be prepared in practicable yield from γ-diethylaminopropyl chloride. The second reaction showed promise, but the product decomposed on attempted distillation under a vacuum of one millimeter, and under high-vacuum distillation the desired organolead compound could not be obtained free of by-products. The chief of these by-products was probably hexaethyldilead.

SUMMARY

A review of the literature concerning studies of the preparation of organogermanium, organotin, and organolead compounds containing water-solubilizing groups has been made.

Halogen-metal interconversion reactions have been effected between n-butyllithium and (1) compounds containing unreactive halogen atoms and (2) aromatic halides containing alcoholic hydroxyl groups.

A general method for the preparation of triphenylhydroxyalkylphenyllead compounds has been described.

The oxidation of triphenylhydroxyalkylphenyllead compounds by potassium permanganate has been studied. Some carboxyphenyllead compounds have been prepared by this reaction.

Several proposed syntheses of triphenylcarboxyphenyllead compounds have been investigated.

Pure triethyl-p-bromophenyllead has been prepared and the reaction of this compound with copper-magnesium alloy has been studied.

The synthesis of aminoalkyllead compounds has been attempted. One of the studies showed promise, but a pure product was not obtained.

The sulfonation and chlorosulfonation of some organolead compounds have been attempted.

Attempts to introduce the aldehyde group into some organolead compounds by means of a Reimer-Tiemann reaction have been unsuccessful. It has been shown that tetraphenyllead and triphenyl-p-anisyllead are stable toward strong alkali.

APPENDIX

The following letter from Dr. E.J. Crane, in reply to a request for recommendations concerning the nomenclature of RMOOH compounds, was received after the historical part of this thesis had been completed.

COPY January 25, 1943

Dr. Donald S. Melstrom
Iowa State College
Ames, Iowa

Dear Dr. Melstrom:

I am at last in a position to send you an answer to your letter of December 15. As explained in my letter of December 21 delay seemed necessary as we have been in the midst of our annual index rush and our hands have been extra full because we were short-handed. The index period is truly a strenuous one here. If we had known the answer to your inquiry offhand, I could, of course, have found time to write, but since it was necessary to do some investigating there just was not time.

We prefer the germanonic, stannonic, and plumbonic names over germanic, stannic and plumbic. For several years now we

have been trying to get the names of such acids into uniformity with benzenesulfonic acid. Our names for the compounds are:

CH_3GeOOH methanegermanonic acid

CH_3SnOOH methanestannonic acid

CH_3PbOOH methaneplumbonic acid

During the period of the third Decennial Index we named germanium compounds of this type as though the Ge took the place of a carbon atom in the chain. Thus CH_3GeOOH was called germanoacetic acid, and $CH_2(GeOOH)_2$, germanomalonic acid (now called methanedigermanonic acid). We have also preferred methanesiliconic acid for CH_3SiOOH over silicoacetic acid.

The germanonic, etc., names seem better than germanic, etc., as they are more in line with sulfonic, arsonic, etc., and are more significantly organic names.

Dr. Leonard T. Capell of this office devotes a good share of his time to the indexing of chemical compounds and this work involves systematic naming. I have had his help in getting ready to answer your letter.

Sincerely yours,

E.J. Crane,
Editor of Chemical
Abstracts

The following is a copy of the author's reply.

January 28, 1943

Dr. E.J. Crane
Editor, Chemical Abstracts
The Ohio State University
Columbus, Ohio

Dear Dr. Crane:

Thank you for your letter of January 25. I appreciate your kindness in taking the time for the investigation necessary to the answering of my question relative to the nomenclature of RMOOH compounds. I feel that the use of the germanonic names, etc., which you prefer to germanic, etc., as more significantly organic names, is highly desirable.

Although the acceptance of the name benzenesulfonic acid for the compound $C_6H_5SO_3H$ would require the use of the names suggested in your letter (methanegermanonic, methanestannonic, and methaneplumbonic acids), this system of nomenclature would seem to be at variance with the established practice, in the case of organometallic compounds, of using as prefix the name of the organic radical or radicals attached to the metal (phenylsodium, tetraethyltin, etc.).

It might be mentioned that the system of nomenclature you have suggested affords no general name for RMOOH compounds in which R is an aryl group. Compounds of the type RSnOOH, in which R is an alkyl group, might be called alkanestannonic acids, but one would hesitate to use the term "phenestannonic acids" for the cases in which

R is aryl, even if the term "phenes" were accepted as a general name for aromatic hydrocarbons. If the name of the radical could be used as prefix, the compounds of the type RSnOOH would be called simply alkylstannonic and arylstannonic acids.

The papers of C.S. Hamilton and co-workers, published in the Journal of the American Chemical Society, employ a system of nomenclature for "-onic acids" in which the name of the radical is used as prefix. (For example, phenylphosphonic acid, phenylarsonic acid, etc.)

I should like to know whether you feel that there are serious objections to the use of names like methylgermanonic, phenylstannonic, and ethylplumbonic acids.

Thank you for your consideration.

Yours very truly,

Donald S. Melstrom

The correspondence was closed with the following letter from Dr. E.J. Crane and the accompanying copy of a letter from Dr. Austin M. Patterson to Dr. Crane.

COPY February 16, 1943

Mr. Donald S. Melstrom
Iowa State College
Ames, Iowa

Dear Mr. Melstrom:

As explained in my letter of February 2, your letter of January 28 together with our earlier correspondence has been shown to Dr. Austin M. Patterson, whose advice we often seek in connection with nomenclature questions. I am enclosing a copy of the letter which I have just received from him. I guess there is nothing which I can add except that I should like to express the hope that you will join the procession in the tendency towards the "ane" names.

With best wishes, I am

Sincerely yours,

E.J. Crane

COPY February 11, 1943

Dr. E.J. Crane
"Chemical Abstracts"
Ohio State University
Columbus, Ohio

Dear Jay:

The copies of the correspondence with Mr. Donald S. Melstrom arrived when I was very busy and were put aside into a drawer and over-

looked temporarily; I regret the delay.

I agree fully with your letter to him of January 25. I think my answer to his letter to you of January 28 would be that Rule 47 of the Definitive Report provides for such names as "methanesulfonic acid," benzenetellurinic acid," etc. rather than "methylsulfonic," "phenyltellurinic," etc. and it seems fair to assume that the same practice should be extended to the germanonic, stannonic and plumbonic acids. This seems especially appropriate for the acids of the Group IV metals, since we do not say "methylcarboxylic acid" but "methanecarboxylic acid" (in French acide méthanecarbonique, in German Methancarbonsäure) as one alternative systematic name for acetic acid.

Rule 47 does not conflict with Rule 48 which prescribes such names as tetraethyltin, because the presence of the acid functional group changes the character of the name.

It is true that there is no general name for aromatic stannonic acids corresponding to the name "alkanestannonic acids," because there is no generally accepted short class name for the aromatic hydrocarbons and the Definitive Report did not provide one. "Phene" is a synonym for "benzene," which would be an objection to its use in the class sense. By analogy the term should be "arene," but I would not favor its use until after it had been discussed and approved by an authoritative body. I think we can continue to manage with the adjective "aromatic."

Mr. Melstrom will have plenty of company if he uses the "yl" names rather than the "ane" names, as the weight of usage is probably still in favor of the former (in the aliphatic series). But a strong tendency is in evidence today to adopt the IUC nomenclature, and this case seems an opportunity to help promote greater consistency.

Sincerely,

Austin M. Patterson