[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Organolead Compounds Containing Alcoholic Hydroxyl, Carboxyl and Dialkylamino Groups

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Organic compounds of lead have shown some promise in cancer therapy[2] but they suffer from two disadvantages in this application; these are their toxicity toward benign as well as malignant tissue and their insolubility in water. The present study is concerned with the preparation of organolead compounds containing water-solubilizing groups, with major emphasis on the purely organometallic members of the type R_3PbR'.

The preparation of organolead compounds containing groups such as hydroxyl, carboxyl, amino or sulfo is difficult because acidic reagents, generally required at some step in introduction of these groups, tend to bring about cleavage of the carbon–lead linkage. A further difficulty lies in the fact that Grignard reagents, employed as intermediates in the customary syntheses of organolead compounds from lead chloride or organolead halides, cannot be prepared directly from halides containing reactive functional groups.

We are now reporting the synthesis of some organolead compounds containing the alcoholic hydroxyl, the carboxyl, or the dialkylamino groups.

Alcoholic Hydroxyl Groups.—Prior to the present study the only known organolead compound containing an alcohol hydroxyl group was (2,3-dihydroxypropyl)-triphenyllead,[3] prepared in small yield by permanganate oxidation of (allyl)-triphenyllead in acetone. One phenolic organolead compound, (*o*-hydroxyphenyl)-triphenyllead, also has been reported. It was prepared[4,5] by reaction of triphenyllead chloride with the organolithium compound formed by halogen–metal interconversion of *o*-bromophenol with *n*-butyllithium; the same type of reaction failed with *p*-bromophenol.[5]

The preparation of organolead compounds containing hydroxyl groups attached through aliphatic groups to aromatic nuclei is of interest not only because the alcoholic hydroxyl is a hydrophilic group, but because it serves as an intermediate for the introduction of other, possibly more effective, water-solubilizing groups (for example, by oxidation to carboxyl). Extension of the halogen–metal interconversion reaction to phenylalkyl alcohols containing nuclear bromine[6] has made possible a general method of synthesizing organolead compounds containing the alcoholic hydroxyl group. The method is illustrated by equations for the preparation of (*p*-hydroxymethylphenyl)-triphenyllead from triphenyllead chloride and *p*-bromobenzyl alcohol.

$$p\text{-BrC}_6\text{H}_4\text{CH}_2\text{OH} + 2n\text{-C}_4\text{H}_9\text{Li} \longrightarrow p\text{-LiC}_6\text{H}_4\text{CH}_2\text{OLi} + n\text{-C}_4\text{H}_9\text{Br} + n\text{-C}_4\text{H}_{10} \quad (1)$$

$$(\text{C}_6\text{H}_5)_3\text{PbCl} + p\text{-LiC}_6\text{H}_4\text{CH}_2\text{OLi} \longrightarrow (\text{C}_6\text{H}_5)_3\text{PbC}_6\text{H}_4\text{CH}_2\text{OLi-}p + \text{LiCl} \quad (2)$$

$$(\text{C}_6\text{H}_5)_3\text{PbC}_6\text{H}_4\text{CH}_2\text{OLi-}p + \text{H}_2\text{O} \longrightarrow (\text{C}_6\text{H}_5)_3\text{PbC}_6\text{H}_4\text{CH}_2\text{OH-}p + \text{LiOH} \quad (3)$$

The yield of the *p*-hydroxymethyl compound was 63% from equimolar amounts of bromo alcohol and aryllead halide. Reactions 1, 2 and 3 are carried out in rapid succession in the same vessel without isolation of any of the intermediates.

By similar reaction of triphenyllead chloride with the organolithium compounds formed by interconversion of *o*- and *m*-bromobenzyl alcohols, *p*-bromophenethyl alcohol and *p*-bromo-α-methylbenzyl alcohol, (aryl)-triphenyllead compounds in which the dissimilar aryl group is *o*- or *m*-(hydroxymethyl)-phenyl, *p*-(α-hydroxyethyl)-phenyl or *p*-(β-hydroxyethyl)-phenyl were prepared in yields of 40 to 57% based on triphenyllead chloride.

It was found to be more convenient to separate unreacted bromophenyl alcohol (or phenyl alcohol formed by hydrolysis of excess interconversion product) from the (aryl)-triphenyllead compound than to separate unreacted triphenyllead chloride. Therefore, it is desirable to use 0.8 mole of triphenyllead chloride to one mole of the bromo alcohol (and 2 moles of *n*-butyllithium) in order to secure a high conversion of the organolead halide in reaction 2.

No (*n*-butyl)-triphenyllead was isolated from any of the reactions, although small amounts of it were no doubt formed from triphenyllead chloride by reaction with *n*-butyllithium not consumed in the interconversion (reaction 1).

Another possible side reaction is that of triphenyllead chloride with an alkoxide lithium atom instead of with organometallic lithium. From *p*-bromobenzyl alcohol there could be formed triphenyllead benzyloxide (I) or *p*-bromobenzyloxide (II). No indication of the presence of either

$$(\text{C}_6\text{H}_5)_3\text{PbCl} + \text{LiOCH}_2\text{C}_6\text{H}_4\text{Li-}p \longrightarrow (\text{C}_6\text{H}_5)_3\text{PbOCH}_2\text{C}_6\text{H}_4\text{Li-}p + \text{LiCl}$$

$$\xrightarrow{\text{H}_2\text{O}} \underset{\text{(I)}}{(\text{C}_6\text{H}_5)_3\text{PbOCH}_2\text{C}_6\text{H}_5}$$

$$(\text{C}_6\text{H}_5)_3\text{PbCl} + \text{LiOCH}_2\text{C}_6\text{H}_4\text{Br-}p \longrightarrow \underset{\text{(II)}}{(\text{C}_6\text{H}_5)_3\text{PbOCH}_2\text{C}_6\text{H}_4\text{Br-}p} + \text{LiCl}$$

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[1] Shell Chemical Corporation, Houston, Texas.

[2] Schmidt, "Medicine in Its Chemical Aspects," Bayer, Leverkusen, Germany, Vol. III, p. 400. This originally appeared in *Med. u. Chem. Abhandl. med.-chem. Forschungsstätten I. G. Farbenind.*, **3**, 418 (1936) [*C. A.*, **31**, 5866 (1937)].

[3] Austin, THIS JOURNAL, **53**, 3514 (1931).

[4] Leeper, *Iowa State Coll. J. Sci.*, **18**, 57 (1943).

[5] Stuckwisch, *ibid.*, **18**, 92 (1943).

[6] Gilman and Melstrom, THIS JOURNAL, **70**, 4177 (1948).

I or II or of triphenyllead hydroxide, which could be formed by hydrolysis of the alkoxides, was observed. Apparently the alkoxide lithium atom does not react or reacts only very slowly with the chlorine of triphenyllead chloride.

A small amount of tetraphenyllead was formed in each case, probably as a result of metal–metal interconversions which give rise to intermediates capable of reacting in the usual manner to form the tetraaryllead compound. The occurrence of metal–metal interconversion can be virtually prevented by converting the organolithium compound to a Grignard reagent by treatment with magnesium bromide[7] before carrying out the reaction with triphenyllead chloride. With the Grignard reagent metal–metal interconversion occurs only to a very limited extent. In the present work metal–metal interconversion and consequent formation of tetraphenyllead were minimized by employing short reaction periods; the reaction mixtures of organolead halide and organolithium compound were hydrolyzed after contact times of only about two minutes. It is also possible that the tetraphenyllead might form by disproportionation of an unsymmetrical organolead compound.

$$(C_6H_5)_3PbCl + RLi \longrightarrow (C_6H_5)_3PbR + LiCl$$
$$(C_6H_5)_3PbR + RLi \longrightarrow (C_6H_5)_2PbR_2 + C_6H_5Li$$
$$(C_6H_5)_3PbCl + C_6H_5Li \longrightarrow (C_6H_5)_4Pb + LiCl$$

$$RLi + MgBr_2 \longrightarrow RMgBr + LiBr$$

The preparation of (*p*-hydroxymethylphenyl)-triethyllead was attempted by an analogous procedure from triethyllead chloride and *p*-bromobenzyl alcohol. The crude product was an oil that decomposed on attempted distillation.

Carboxyl Groups.—Prior to the present study no simple tetraalkyl- or tetraaryl-lead compounds containing carboxyl groups were known. Leeper[4] prepared α,β-bis-(triphenylplumbyl)-succinic acid from hexaphenyldilead and maleic anhydride, but the disodium salt of the acid was only slightly soluble in hot water. All attempts by Austin[3] to prepare carboxyphenyllead compounds by permanganate oxidation of *o*- and *p*-tolyllead compounds were unsuccessful. It has been proposed[8] to synthesize carboxyphenyllead compounds by carbonation of an organolithium compound formed either by metalation of tetraphenyllead or by halogen–metal interconversion of bromophenyl-triphenyllead, as illustrated by the accompanying equations. Both of these procedures were unsatisfactory, since metal–metal interconversion took place more rapidly than either metalation or halogen–metal interconversion.

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

or

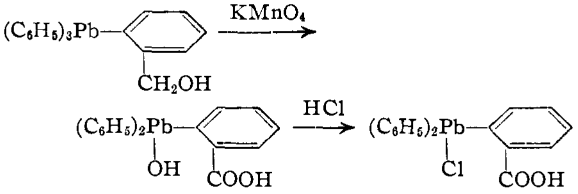
$$R_3PbC_6H_4Br + R'Li \longrightarrow R_3PbC_6H_4Li + R'Br$$

then

$$R_3PbC_6H_4Li + CO_2 \longrightarrow R_3PbC_6H_4COOLi$$

The new organolead compounds containing alcoholic hydroxyl groups seemed to offer more promising possibilities for oxidation than the tolyllead compounds studied by Austin. This possibility was realized in that permanganate oxidation of (*p*-hydroxymethylphenyl)-triphenyllead in acetone gave (*p*-carboxyphenyl)-triphenyllead in 25% yield. This constitutes the first successful preparation of a carboxyl-containing organolead compound by an oxidation reaction. The sodium and potassium salts of the carboxyphenyl compound were not appreciably soluble in water.

The hydroxymethyl group in (*o*-hydroxymethylphenyl)-triphenyllead underwent the expected oxidation by permanganate to carboxyl, but in addition one phenyl group was cleaved and replaced by hydroxyl, giving (*o*-carboxyphenyl)-diphenyllead hydroxide. Upon reaction with hydrogen chloride, the hydroxide formed (*o*-carboxyphenyl)-diphenyllead chloride which was converted to a well-defined crystalline methyl ester by reaction with diazomethane.



No pure products were isolated from similar oxidation of the *m*-hydroxymethyl compound.

Efforts to introduce the carboxyl group by more direct means, for example, by reaction of *p*-carboxyphenyllithium[9] (from *p*-iodobenzoic acid and butyllithium) with triphenyllead chloride or by carbonation of an organolithium compound derived from (*p*-bromophenyl)-triethyllead, were unsuccessful. However, a direct synthesis of (*p*-carboxyphenyl)-triphenyllead from the *p*-bromophenyl compound in 1.5% yield was carried out subsequent to the present work and has been reported.[10] This synthesis owed its success to the preparation of diethylbarium, which underwent interconversion with (*p*-bromophenyl)-triphenyllead. The resulting organobarium derivative of tetraphenyllead was carbonated and yielded the corresponding carboxylic acid.

We attempted to prepare (*p*-lithiophenyl)-triphenyllead by the reaction of triphenyllead chloride and phenylenedilithium (from *p*-dibromobenzene and two moles of *n*-butyllithium). No (*p*-carboxyphenyl)-triphenyllead was isolated after carbonation, but *p*-bis-(triphenylplumbyl)-benzene was obtained in small yield. This product must have been formed by reaction of two equivalents of triphenyllead chloride with one mole of phenylenedilithium.

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

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[7] Gilman and Stuckwisch, THIS JOURNAL, **64**, 1007 (1942).

[8] Gilman and Moore, THIS JOURNAL, **62**, 3206 (1940); Gilman, Moore and Jones, *ibid.*, **63**, 2482 (1941).

[9] Gilman and Arntzen, THIS JOURNAL, **69**, 1537 (1947).

[10] Gilman, Haubein, O'Donnell and Woods, THIS JOURNAL, **67**, 922 (1945).

No reaction was found to occur between the sodium derivative of malonic ester and triphenyllead chloride. The failure of the sodium enolate to react with the triaryllead chloride is not unexpected, in view of the above-mentioned observation that there was no metathesis between triphenyllead chloride and the alkoxide lithium atom of lithium *p*-lithiophenylalkoxides.

An attempt to prepare (*p*-cyanophenyl)-triphenyllead, a possible intermediate for hydrolysis to the carboxylic acid, by a Sandmeyer reaction on (*p*-aminophenyl)-triphenyllead[7] was unsuccessful.

Dialkylaminoalkyl Groups.—A few organolead compounds containing primary amino groups are known. These include di-(*m*-aminophenyl)-lead dihydroxide,[2] formed by reduction of di-(*m*-nitrophenyl)-lead oxide with titanium trichloride, and *o*- and *p*-aminophenyl-(triphenyl)-lead,[5,7] prepared from *o*- and *p*-bromoaniline via halogen–metal interconversion to form the aminophenyllithium compound and reaction of the latter with triphenyllead chloride. One alkylaminoaryllead compound[5] and a larger number of dialkylaminoaryllead compounds[5,11] are known. However, no purely aliphatic organolead compounds containing amino or substituted amino groups have been described.

We have succeeded in preparing two purely aliphatic organolead compounds containing dialkylaminoalkyl groups: namely, (β-diethylaminoethyl)-triethyllead and (γ-diethylaminopropyl)-triethyllead. These were obtained as colorless liquids, distillable under high vacuum, in yields of 29 and 54%, respectively, by addition of the appropriate dialkylaminoalkyl chloride to a solution of triethyllead-sodium in ether.

$$(C_2H_5)_3PbNa + (C_2H_5)_2NCH_2CH_2Cl \longrightarrow (C_2H_5)_3PbCH_2CH_2N(C_2H_5)_2 + NaCl$$

In tests carried out elsewhere[12] the γ-diethylaminopropyl compound was found to exhibit slight antimalarial activity.

Miscellaneous.—No organolead compounds containing the aldehyde or ketone groups are known. Attempts to introduce the aldehyde group, of interest as a possible intermediate in preparation of organolead carboxylic acids, were unsuccessful. The oxidation of some (hydroxyalkyl)-triphenyllead compounds by nitrogen tetroxide to the corresponding aldehydes was tried but gave no pure products. It is probable that both oxidation and cleavage occurred, since the relatively stable tetraphenyllead was cleaved by nitrogen tetroxide in chloroform with the formation of diphenyllead dinitrate.

The lead atom in compounds like diphenyllead dinitrate (and probably in tetraphenyllead) is *meta*-directing[13] and presumably has a deactivating effect on the benzene ring as far as nuclear substitution reactions are concerned. It has been reported[14] that a second aldehyde group can be introduced into benzaldehyde, containing the *meta*-orienting aldehyde group, under conditions like those of the Reimer–Tiemann reaction. Similar introduction of an aldehyde group into tetraphenyllead and into (*p*-anisyl)-triphenyllead, containing the activating methoxyl substituent, was attempted by means of chloroform and concentrated aqueous alkali under the conditions of the Reimer–Tiemann reaction, but the organolead compounds were recovered unchanged.

Incidental to this and related studies, we have prepared and are reporting (*p*-bromophenyl)-triethyllead, hitherto prepared only in impure form.[15] We are also reporting the preparation of (*o*-anisyl)-triphenyllead and (*p*-anisyl)-triphenyllead from the appropriate anisyl Grignard reagent and triphenyllead chloride. The *p*-anisyl compound has been prepared[16] from *p*-anisyllithium and triphenyllead chloride.

Experimental

Starting Materials.—Tetraphenyllead was prepared from phenylmagnesium bromide and lead chloride according to the directions of Setzer, Leeper and Gilman.[17] In preparations carried out on two to three times as large a scale as that reported by the above authors, yields of 50 to 65% were obtained (compared with a maximum yield of 83% in the smaller-scale reaction),[17] but it was necessary to provide extremely efficient stirring during and immediately after addition of the lead chloride to the Grignard reagent.

Triphenyllead chloride was prepared by a large-scale modification of the method of Gilman and Robinson.[18] In a typical preparation, a stream of dry hydrogen chloride was passed into a boiling solution of 245 g. of tetraphenyllead in 2600 cc. of chloroform for fifty-five minutes. There was then obtained 30 g. (15%) of insoluble diphenyllead dichloride; from the filtrate, by evaporation to dryness and crystallization of the residue from absolute alcohol, there was obtained 169 g. (75%) of triphenyllead chloride melting at 204–206°.

Triethyllead chloride was prepared by cleavage of tetraethyllead in ether with hydrogen chloride according to the procedure of Gilman and Robinson.[19]

Typical Procedure for Preparation of (Hydroxyalkylphenyl)-triphenyllead Compounds.—A solution of the appropriate bromophenylalkanol (0.1 mole) in 50 cc. of dry ether was added during ten to fifteen minutes at room temperature to two molar equivalents (0.2 mole) of *n*-butyllithium[20] in about 300 cc. of ether. The resulting solution was stirred for thirty to sixty minutes, and to it there was then added as rapidly as possible (about two minutes) 0.8 molar equivalent (0.08 mole) of solid triphenyllead chloride. The reaction mixture was hydrolyzed immediately (or within three minutes) by pouring on iced ammonium chloride solution. The hydrolysis product was filtered to remove 1.8 to 2.6 g. of solid consisting

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[11] Austin, THIS JOURNAL, **54**, 3726 (1932).

[12] Through the courtesy of Parke, Davis and Co.

[13] Vorländer, *Ber.*, **58**, 1893 (1925); Challenger and Rothstein, *J. Chem. Soc.*, 1258 (1934).

[14] Chaudhuri, THIS JOURNAL, **64**, 315 (1942); Rapson, Saunder and Stewart (*J. Chem. Soc.*, 74 (1944)) were unable to confirm the work of Chaudhuri.

[15] Unpublished studies by J. D. Robinson.

[16] Towne, *Iowa State Coll. J. Sci.*, **8**, 229 (1933).

[17] Setzer, Leeper and Gilman, THIS JOURNAL, **61**, 1609 (1939).

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

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

[20] (a) The titer of the butyllithium solutions was determined by the analytical procedure of Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944). (b) For an improved procedure for the preparation of *n*-butyllithium see Gilman, Beel, Brannen, Bullock, Dunn and Miller, *ibid.*, **71**, 1499 (1949).

chiefly of tetraphenyllead with a trace of triphenyllead chloride. The ether layer of the filtrate was separated, dried over sodium sulfate, and the ether removed by distillation. The oily residue, which usually solidified in part on cooling, was dissolved in hot alcohol and the solution was filtered to remove triphenyllead chloride. The filtrate upon cooling usually deposited the (hydroxyalkylphenyl)-triphenyllead compound as an amorphous or microcrystalline white solid.

(*p*-Hydroxymethylphenyl)-triphenyllead.—This compound was obtained in yields of 57 and 63% in duplicate experiments starting with 0.08 mole of *p*-bromobenzyl alcohol,[6] 0.16 mole of *n*-butyllithium, and 0.08 mole of triphenyllead chloride. The crude solid product (38 g.) was dissolved in 250 cc. of hot (not boiling) alcohol and filtered from a small amount of tetraphenyllead. The filtrate was heated to boiling and diluted with 75 cc. of hot water; on cooling, a reasonably pure product (27.5 g., 63%) was obtained having a melting point of 97–100°. After recrystallization first from benzene–petroleum ether and then from petroleum ether containing a little chloroform, an analytical sample, melting at 98–100°, was obtained.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 37.98. Found: Pb, 37.46, 37.66.

(*p*-Hydroxymethylphenyl)-triphenyllead is readily soluble in methyl or ethyl alcohol, benzene and chloroform, moderately soluble in ether, and insoluble in petroleum ether. Its melting point is somewhat variable, depending on the crystallization procedure and the method of melting point determination.

When (*p*-hydroxymethylphenyl)-triphenyllead was subjected to cleavage with one molar equivalent of bromine in pyridine at −15° (procedure of Grüttner),[21] there was obtained a 20% yield of *p*-bromobenzyl alcohol (identified by mixed m. p.) and a 48% yield of triphenyllead bromide (identified by mixed m. p. and by lead analysis).

When dry hydrogen chloride was passed for twelve minutes into a solution of (*p*-hydroxymethylphenyl)-triphenyllead in boiling chloroform, there was obtained 5% of diphenyllead dichloride, 28% of triphenyllead chloride, and 55% recovery of starting material.

(*o*-Hydroxymethylphenyl)-triphenyllead.—*o*-Bromobenzyl alcohol (m. p. 80–81°) was prepared from *o*-bromotoluene by a procedure exactly paralleling that described[6] for the preparation of *p*-bromobenzyl alcohol.

From 0.15 mole of *o*-bromobenzyl alcohol, 0.30 mole of butyllithium, and 0.12 mole of triphenyllead chloride there was obtained, after crystallization of the crude product from alcohol, 26.2 g. (40% yield) of (*o*-hydroxymethylphenyl)-triphenyllead melting at 133–136°. An additional 20.6 g. (31%) of less pure product was obtained by dilution of the mother liquor with water. The analytical sample, purified by an additional recrystallization from benzene–petroleum ether, melted at 134–136°.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 37.98. Found: Pb, 38.49.

In a second experiment on a slightly smaller scale, the yield of pure product was 45% and there was an additional 25% of less pure fraction.

(*m*-Hydroxymethylphenyl)-triphenyllead.—This compound was prepared in 41% yield from *m*-bromobenzyl alcohol[6] by the general procedure. After two recrystallizations from benzene–petroleum ether and one from methanol, the product melted at 113–114° with slight turbidity.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 37.98. Found: Pb, 38.46.

[*p*-(β-Hydroxyethyl)-phenyl]-triphenyllead.—This compound was prepared in 57% yield from *p*-bromophenethyl alcohol and triphenyllead chloride by the usual procedure. The product, after crystallization once from absolute alcohol and twice from benzene–petroleum ether, melted at 87–88°.

Anal. Calcd. for $C_{26}H_{24}OPb$: Pb, 37.02. Found: Pb, 37.03, 37.06.

[*p*-(α-Hydroxyethyl)-phenyl]-triphenyllead.—This compound was prepared in 52% yield from *p*-bromo-α-methylbenzyl alcohol[22] and triphenyllead chloride by the general procedure. The crude product was an oil that was extremely difficult to crystallize. Crystals were finally obtained by preparing a solution in methanol, adding water just short of turbidity at slightly above room temperature, and then cooling in the ice chest. After two such crystallizations, the product melted at 68–70°.

Anal. Calcd. for $C_{26}H_{24}OPb$: Pb, 37.02. Found: Pb, 37.22.

(*p*-Carboxyphenyl)-triphenyllead.—To a stirred solution of 10 g. (0.018 mole) of (*p*-hydroxymethylphenyl)-triphenyllead in 100 cc. of permanganate-stabilized acetone there was added in small portions over a period of five hours 4.2 g. (0.027 mole—a slight excess) of potassium permanganate. The permanganate color disappeared one-half hour after the last portion had been added, but 1 cc. of alcohol was then added to ensure complete decomposition of all the permanganate. The dark brown solid that had formed was separated by filtration and washed with acetone. The combined acetone solution and washings were evaporated and left only 1.5 g. of residue which appeared to be impure starting material. The original acetone-insoluble brown solid 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 warmed, diluted with water and cooled. There was obtained 2.6 g. (25% yield) of crystalline acid melting at 254–256°. The mother liquor upon concentration yielded an amorphous difficultly soluble solid that has not been identified. The crystalline fraction was recrystallized from alcohol, giving a pure sample of (*p*-carboxyphenyl)-triphenyllead. This changed crystalline form at 145–150° and melted to a viscous liquid at 256–258°.

Anal. Calcd. for $C_{25}H_{20}O_2Pb$: Pb, 37.03; neut. equiv., 560. Found: Pb, 36.73, 36.74; neut. equiv., 568, 569.

The sodium and potassium salts of the acid were moderately soluble in alcohol but insoluble in cold or hot water.

(*p*-Carbomethoxyphenyl)-triphenyllead.—The methyl ester was prepared from the acid by treatment with ethereal diazomethane. The product (79% yield), obtained as white crystals from alcohol, melted at 125–127°.

Anal. Calcd. for $C_{26}H_{22}O_2Pb$: Pb, 36.12. Found: Pb, 36.50.

(*o*-Carboxyphenyl)-diphenyllead Hydroxide.—(*o*-Hydroxymethylphenyl)-triphenyllead (10 g.) in 100 cc. of acetone was treated with 4 g. (a slight excess) of potassium permanganate over a period of five hours. Since the permanganate color persisted, the mixture was allowed to stand overnight and was then treated with 1 cc. of alcohol to decompose excess oxidizing agent. The dark brown solid was removed, and the acetone filtrate was evaporated to dryness. The residue was extracted with hot alcohol; the remaining insoluble white solid (3.2 g., 35% yield) consisted of the hydroxide melting at 300–305° to a turbid liquid. It was insoluble in the common organic solvents and could not be crystallized.

Anal. Calcd. for $C_{19}H_{16}O_3Pb$: Pb, 41.48. Found: Pb, 41.72.

The alcohol-soluble portion of the residue and the material that had been extracted by alcohol from the dark brown solid were both treated by the procedure used for the isolation of (*p*-carboxyphenyl)-triphenyllead. There was obtained a total of 1.7 g. of solid melting at 288–295° with evolution of gas. This unidentified material was insoluble in the common solvents and did not react with diazomethane. It may consist of the inner anhydride of (*o*-carboxyphenyl)-diphenyllead hydroxide.

(*o*-Carboxyphenyl)-diphenyllead Chloride.—A 1-g. portion of the hydroxide was suspended in 25 cc. of absolute alcohol and treated with a few cc. of concentrated hydrochloric acid. Most of the solid dissolved. The filtrate

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(21) Grüttner, *Ber.*, **51**, 1298 (1918).

(22) Ziegler and Tiemann, *Ber.*, **55**, 3406 (1922).

was diluted with 6 N hydrochloric acid and cooled. There was deposited 0.9 g. (87% yield) of white crystalline chloride. This product changed crystalline form at 145° and melted to a turbid, viscous liquid at 210–220°. It gave off hydrogen chloride when treated with cold concentrated sulfuric acid.

Anal. Calcd. for $C_{19}H_{15}O_2ClPb$: Pb, 40.00. Found: Pb, 40.69.

(*o*-**Carbomethoxyphenyl)-diphenyllead Chloride.**—The methyl ester was prepared from 0.5 g. of the above-described chloride with ethereal diazomethane. The product, crystallized from methanol, weighed 0.43 g. (84% yield) and melted at 170–171°. It dissolved in cold concentrated sulfuric acid with evolution of hydrogen chloride, forming a clear, colorless solution.

Anal. Calcd. for $C_{20}H_{17}O_2ClPb$: Pb, 38.95. Found: Pb, 39.06.

p-**Bis-(triphenylplumbyl)-benzene.**—*p*-Phenylenedilithium was prepared from 0.067 mole of *p*-dibromobenzene and 0.20 mole of *n*-butyllithium in 500 cc. of ether. After the mixture had been stirred for one hour and then allowed to stand for eighteen hours, titration[20a] of aliquot portions showed that practically no butyllithium remained and that all the dibromide had been converted to the dilithium compound. To the solution there was added during five minutes 0.067 mole of triphenyllead chloride. The mixture was stirred for forty-five minutes and then carbonated by pouring on Dry Ice. The ether suspension was mixed with 10% potassium hydroxide and filtered from 18 g. of insoluble white solid. The potassium hydroxide layer was separated and carefully acidified; there was precipitated only 1.45 g. of product that did not contain lead and showed the melting point behavior of terephthalic acid (sublimed *ca.* 300°). The 18 g. of non-acidic solid was extracted with boiling absolute alcohol to remove triphenyllead chloride, and the residue was crystallized from 400 cc. of hot chloroform. There was obtained 2.9 g. (9% yield) of white, crystalline *p*-bis-(triphenylplumbyl)-benzene melting at 285–288°.

Anal. Calcd. for $C_{42}H_{34}Pb_2$: Pb, 43.48. Found: Pb, 43.91, 43.92.

(β-**Diethylaminoethyl)-triethyllead.**—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 resulting dark blue solution 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 to room temperature. The resulting suspension was filtered from sodamide.

To the filtrate, containing about 0.05 mole of triethyllead-sodium, there was added dropwise with cooling in an ice-bath 6.8 g. (0.05 mole) of β-diethylaminoethyl chloride[23] (b. p. 82–84°) in 30 cc. of ether. The cooling bath was removed, the mixture was allowed to warm to room temperature, and the now dark-colored solution was stirred for two hours and then allowed to stand overnight. It was hydrolyzed with water and the ether layer was separated, dried over sodium sulfate and distilled. The residue left after removal of the ether was distilled under high vacuum. The first fraction (5.7 g., 29% yield) was taken at a bath temperature of 85–90° under a pressure of 0.001 mm. It consisted of pure (β-diethylaminoethyl)-triethyllead and had a density (d^{25}_{25}) of 1.459 and a refractive index (n^{20}D) of 1.5235.

Anal. Calcd. for $C_{12}H_{29}NPb$: Pb, 52.52; *MR*, 82.0.[24] Found: Pb, 52.22; *MR*, 82.6.

A second fraction (1.6 g.) taken at 90–110° (0.001 mm.) was higher in refractive index and had considerably greater than the theoretical lead content.

(γ-**Diethylaminopropyl)-triethyllead.**—A solution of 0.05 mole of triethyllead-sodium in ether was prepared as described in the preceding section. To this there was added with cooling 6.5 g. (0.043 mole) of γ-diethylaminopropyl chloride (less than the equivalent amount was used inadvertently). A white precipitate formed gradually. After the mixture had warmed to room temperature and then been stirred for two hours, it was hydrolyzed with water and worked up as described for the diethylaminoethyl compound. From the ether layer there was obtained a residue which distilled at a bath temperature of about 90° under a pressure of less than 0.001 mm. The distillate was taken in two fractions, of which the first (9.5 g., 54% yield) was pure (γ-diethylaminopropyl)-triethyllead having a density (d^{28}_{28}) of 1.432 and a refractive index (n^{20}D) of 1.5229.

Anal. Calcd. for $C_{13}H_{31}NPb$: Pb, 50.71; *MR*, 86.6.[24] Found: Pb, 50.77, 50.91; *MR*, 87.0.

The second fraction (3 g.) contained 53.27% lead.

In preliminary experiments it was found that lower yields of product were obtained when the triethyllead-sodium was added to the dialkylaminopropyl chloride, and that the product decomposed upon attempted distillation under a pressure of 1 mm.

Reaction of Tetraphenyllead and Nitrogen Tetroxide.—To a solution of 2 g. of tetraphenyllead in 15 cc. of chloroform there was added gradually, with ice cooling, a solution of 0.6 g. (1.7 molar equivalents) of nitrogen tetroxide in 10 cc. of chloroform. The brown color of the tetroxide was immediately replaced by a light, clear blue. A precipitate formed at once and increased gradually in amount. After the mixture had stood at room temperature for two weeks the solid was separated. It was a light tan, crystalline material (1.73 g.) and consisted chiefly of diphenyllead dinitrate. It had no definite melting point and gave qualitative tests for nitrogen and for nitrate ion. A sample purified by crystallization from absolute alcohol and dried under vacuum at 100° was analyzed.

Anal. Calcd. for $C_{12}H_{10}N_2O_6Pb$: Pb, 42.69. Found: Pb, 42.26.

(*p*-**Bromophenyl)-triethyllead.**—*p*-Bromophenylmagnesium bromide 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. The solution was refluxed for thirty minutes and then filtered from excess magnesium. To the filtrate 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 separated and dried and the ether was removed. The residual oil was cooled, filtered from a small amount of solid, and the filtrate was distilled under a vacuum of 0.002 mm. The first three fractions collected (total weight, 25.5 g.) deposited a considerable amount of solid triethyllead chloride. The fourth fraction, which distilled at a bath temperature of 143° (0.002 mm.), was a clear, colorless liquid. It weighed 21.5 g.; this is a 30% yield of (*p*-bromophenyl)-triethyllead, based on triethyllead chloride. It had a density (d^{20}_{27}) of 1.8586 and a refractive index (n^{20}D) of 1.5968.

Anal. Calcd. for $C_{12}H_{19}BrPb$: Pb, 46.01; *MR*, 82.1.[24] Found: Pb, 46.19; *MR*, 82.5.

The pure (*p*-bromophenyl)-triethyllead did not react with magnesium in ether, but it did react with activated copper–magnesium alloy[25] in ether. After a reaction period of ten hours the resulting Grignard reagent was carbonated, but the small amount of acidic product could not be purified.

(*o*-**Anisyl)-triphenyllead.**—*o*-Anisylmagnesium bromide was prepared from 11.2 g. (0.06 mole) of *o*-bromoanisole in 50 cc. of ether. To the clear solution there was added 23.7 g. (0.05 mole) of triphenyllead chloride. After the

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[23] Prepared from β-diethylaminoethanol and thionyl chloride in chloroform by a modification of the procedure of Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

[24] Calculated using the atomic factors of Auwers and Eisenlohr (Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 1751) and, for lead, the value 18.1 found by Grüttner and Krause, *Ann.*, **415**, 343 (1918), for the lead atom in tetraethyllead.

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

initial brief period of vigorous refluxing, the mixture was diluted with 50 cc. of ether and 50 cc. of toluene and then heated at reflux for one hour. After hydrolysis by pouring on iced ammonium chloride, part of the product was recovered by filtration and the remainder by evaporation of the ether–toluene layer. The total yield of (*o*-anisyl)-triphenyllead was 22.1 g. (81% yield). A portion crystallized from absolute alcohol melted at 128–129°.

Anal. Calcd. for $C_{25}H_{22}OPb$: Pb, 37.98. Found: Pb, 38.01.

(*p*-Anisyl)-triphenyllead.—This compound was prepared like the *o*-anisyl compound, with substitution of *p*-bromoanisole for *o*-bromoanisole. The original reaction product was insoluble in ether–toluene; therefore, hydrolysis was effected by addition of ice and ammonium chloride solution to the reaction mixture. The crude product (86% yield) was recrystallized from alcohol and then melted at 150–151° with slight decomposition. Towne[16] reported a melting point of 152° with some decomposition.

Summary

1. Five (hydroxyalkylphenyl)-triphenyllead compounds have been prepared by the reaction of triphenyllead chloride with the organolithium compounds formed by halogen-metal interconversion between bromophenylalkanols and *n*-butyllithium.

2. (*p* - Hydroxymethylphenyl) - triphenyllead has been oxidized by permanganate in acetone to (*p*-carboxyphenyl)-triphenyllead, and (*o*-hydroxymethylphenyl)-triphenyllead has been similarly oxidized to (*o*-carboxyphenyl)-diphenyllead hydroxide.

3. (β-Diethylaminoethyl)-triethyllead and (γ-diethylaminopropyl)-triethyllead have been prepared by reaction of triethyllead-sodium with the appropriate dialkylaminoalkyl chloride.

4. (*p*-Bromophenyl)-triethyllead, prepared from *p*-bromophenylmagnesium bromide and triethyllead chloride, reacted with activated copper–magnesium alloy but the product could not be converted to an acid by carbonation.

AMES, IOWA RECEIVED NOVEMBER 7, 1949

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

Quaternary Intermediates in the Alkylation of Certain Esters by Tertiary Amines

BY H. R. SNYDER, ERNEST L. ELIEL AND ROBERT E. CARNAHAN*

In a previous report it was noted that 1-methylgramine reacts with cyanoacetic ester and with other esters containing active methylene or methinyl groups. The product, after hydrolysis and decarboxylation, was 1-methylindole-3(β)-propionic acid or a derivative of it. In an attempt to elucidate the mechanism of such alkylations the investigation has been continued and extended to reactions of benzyldimethylamine.

Benzyldimethylamine was found to react with tricarbethoxymethane at a temperature (180–200°) somewhat above that (160–170°) required with 1-methylgramine. Hydrolysis and decarboxylation of the products converted them to hydrocinnamic acid and dibenzylacetic acid. During the course of the alkylation gases were evolved; carbon dioxide and the tertiary amine dimethylethylamine were identified as components of the gaseous mixture. The secondary amine dimethylamine was not found. Similarly, the basic gas evolved during the alkylation of methyl cyanoacetate with 1-methylgramine, described earlier,[1] has been shown to be the tertiary amine trimethylamine. Finally, the alkylation of methyl cyanoacetate by benzyldimethylamine was found to occur with the evolution of the tertiary amine trimethylamine.

The formation of a tertiary amine in each of these reactions indicates that the first step in the alkylation is the reaction of the ester[2] with the amine to give the quaternary ammonium salt of an acid (equation 1), and the quaternary ammonium cation is the active alkylating agent. The anion of the acid or another molecule

$$C_6H_5CH_2N(CH_3)_2 + NCCH_2CO_2CH_3 \longrightarrow C_6H_5CH_2\overset{+}{N}(CH_3)_3 + NCCH_2CO_2^- \quad (1)$$

of the original ester may be alkylated by the cation. Decarboxylation of one or more of the anionic species at the high temperature employed and some dialkylation lead to the formation of the mixture of hydrocinnamonitrile and dibenzylacetonitrile. Support for this interpretation of the reaction was found in the fact that the thermal decomposition of benzyltrimethylammonium cyanoacetate occurred in the expected fashion, yielding a mixture of the same nitriles. The participation of esters in this reaction is, of course, not excluded, inasmuch as it is known[3] that quaternary ammonium salts of acids generate esters on thermal decomposition.

A free radical mechanism recently has been suggested for thermal alkylations with benzyl bromide.[4] Although it seemed unlikely that such a mechanism was operative in the present alkylations, because of the presence of amines, a test was made by carrying out parallel experiments

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[1] For the preceding paper in this series see Snyder and Eliel, THIS JOURNAL, **71**, 663 (1949).

[2] (a) Willstätter and Kahn, *Ber.*, **35**, 2757 (1902); (b) Hammett and Pfluger, THIS JOURNAL, **55**, 4079 (1933).

[3] (a) Prelog and Piantanida, *Z. physiol. Chem.*, **244**, 56 (1936); (b) Lawson and Collie, *J. Chem. Soc.*, **53**, 624 (1888).

[4] McElvain and Schroeder, THIS JOURNAL, **71**, 47 (1949).