Summary

1. Fifteen alcohols have been carbonylated to acids containing one additional carbon atom, with carbon monoxide in the presence of nickel carbonyl, nickel chloride, and hydrochloric acid. Secondary aliphatic and alicyclic alcohols were carbonylated in an average yield of 75%, whereas the yields from primary and tertiary alcohols were from 30–60%.

2. The products formed generally were homogeneous and branched chain, *e. g.*, both butanol-1 and butanol-2 yielded 2-methylbutyric acid.

3. Aromatic alcohols were converted to alkylbenzenes and glycols to monocarboxylic acids under conditions that converted aliphatic alcohols to di- and tri-substituted acetic acids.

4. The carbonylation reaction appears to proceed through the dehydration of the alcohol to an olefin, which then is carbonylated to the acid.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE]

Organolead Compounds Containing an Azo Linkage

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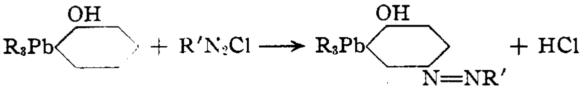
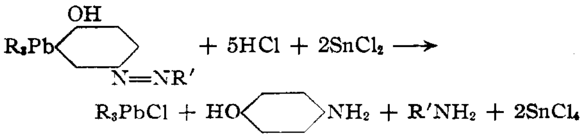
Since its introduction in the chemotherapeutic treatment of cancer by Bell[2] in 1922, lead has attracted more attention than any other metal in this particular field of therapeutics. The toxic side action of the required therapeutic doses has however militated against an extended use of this method of treatment. To circumvent this objection chemists have resorted to the preparation of compounds which contain the lead in highly masked form in complex molecules.[3] Syntheses of organolead compounds containing an azo linkage are described in the present paper.

The diazotization of triphenyl-*p*-aminophenyllead and its subsequent coupling with β-naphthol have been reported earlier.[4] A more convenient method of preparation of the azo-lead type of compound is the coupling of a diazonium salt with an aminoaryl- or hydroxyaryllead compound. The latter is conveniently prepared from a triaryllead halide and an aminoaryl- or hydroxyaryllithium compound.[5]

$$R_3PbX + R'Li \longrightarrow R_3PbR' + LiX$$



The position of coupling was determined by reductive cleavage with stannous chloride and hydrochloric acid. In each instance coupling took place *ortho* or *para* to the amino or hydroxyl group and *meta* to the lead atom



Experimental

General Information.—The titer of the *n*-butyllithium solutions used in this work was determined by the method of Gilman and Haubein.[6] The amount of R_3PbCl added to the organolithium solutions was equivalent to the amount of the halogen compound used in the interconversion. All melting points are uncorrected.

Triphenyl-*p*-aminophenyllead.—Three variations were used for the preparation of triphenyl-*p*-aminophenyllead.

Method 1.—This method, which involves adding anhydrous magnesium bromide to the *p*-aminophenyllithium solution, has been described.[4]

Method 2.—To 5.67 g. (0.033 mole) of *p*-bromoaniline in 25 ml. of ether was added dropwise 0.1 mole of *n*-butyllithium in 180 ml. of ether. After 60 ml. of the organometallic solution had been added, refluxing ceased and the remaining 120 ml. was added more rapidly. The mixture was stirred for an hour. A yellow, crystalline precipitate of the *p*-N,N-trithioaniline[5b] separated from the solution. The reaction flask was fitted with a stopcock at the bottom, by means of which the solid was filtered from the liquid. To the solid residue remaining in the flask was added 250 ml. of ether and then 10.3 g. (0.022 mole) of triphenyllead chloride. The mixture was stirred for one hour at room temperature and then hydrolyzed with cold, aqueous ammonium chloride. The organic layer was dried over sodium sulfate. Hydrogen chloride was cautiously passed into the dried ether solution, cooled in an ice-bath, to precipitate the hydrochloride of triphenyl-*p*-aminophenyllead. The hydrochloride was converted to the free amine by suspending it in water and adding dilute ammonium hydroxide. The yield of triphenyl-*p*-aminophenyllead thus obtained was 6 g. or 59%. After crystallization from a mixture of benzene and petroleum ether (b. p. 60–68°) the compound melted at 172°. A mixed melting point with the compound obtained by the first method showed no depression.

Method 3.—To 5.3 g. (0.031 mole) of *p*-bromoaniline in 30 ml. of ether was added dropwise 0.093 mole of *n*-butyllithium in 200 ml. of ether. The mixture was stirred at room temperature for one hour and was then poured into a suspension of 14.2 g. (0.03 mole) of triphenyllead chloride in ether. After three minutes the mixture was poured into cold water. The ether layer was separated and extracted with dilute hydrochloric acid to remove unreacted *p*-bromoaniline. (Triphenyl-*p*-aminophenyllead is insoluble in dilute hydrochloric acid.) Hydrogen chloride was passed into the dried ether solution to precipitate the hydrochloride of triphenyl-*p*-aminophenyllead. The free amine was obtained as described in Method 2. The yield was 9.5 g. or 60%. In the interconversion of *p*-bromoaniline the *n*-butyllithium solution must be clear, otherwise a gummy precipitate, difficult to work with, will be obtained.

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[2] Bell, *Lancet*, **203**, 1005 (1922); **206**, 267 (1924); **209**, 1003 (1925).

[3] Datnow, *Am. J. Cancer*, **24**, 531 (1935); Schmidt, *Med. u. Chem. Abhandl. med.-chem. Forschungsstaetten I. G. Farbenind.*, **3**, 418 (1936) [*C. A.*, **31**, 5866 (1939)].

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

[5] (a) Gilman and Arntzen, *ibid.*, **69**, 1537 (1947); (b) Gilman and Stuckwisch, *ibid.*, **71**, 2938 (1949).

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

Triphenyl-*o*-aminophenyllead.—To a solution of 8.6 g. (0.05 mole) of *o*-bromoaniline in 25 ml. of ether was added dropwise 0.15 mole of *n*-butyllithium in 175 ml. of ether. After forty-five minutes 18.9 g. (0.04 mole) of triphenyllead chloride was added to the reaction mixture. The mixture was stirred vigorously for three minutes and was then poured into an aqueous ammonium chloride solution. The ether layer was separated, extracted with dilute hydrochloric acid and then dried over sodium sulfate. When the ether was removed under reduced pressure, a solid residue was left behind. Fractional crystallization of the residue from ethanol gave 5.3 g. or a 50% yield (based on 40% interconversion of *o*-bromoaniline) of a solid melting at 164–165°.

Anal. Calcd. for $C_{24}H_{21}NPb$: Pb, 39.01. Found: Pb, 38.75.

In addition to the triphenyl-*o*-aminophenyllead there was isolated 6 g. of triphenyl-*n*-butyllead.

Triphenyl-*p*,N-methylaminophenyllead.—To a solution of 9.7 g. (0.05 mole) of *p*-bromo-N-methylaniline in 25 ml. of ether was added dropwise 0.1 mole of *n*-butyllithium in 150 ml. of ether. After one hour 18 g. (0.037 mole) of triphenyllead chloride was added to the solution. The reaction mixture was stirred at room temperature for three hours and then was hydrolyzed with cold, aqueous ammonium chloride. The ether layer was separated, extracted with 10% hydrochloric acid, and dried; the ether was removed at the water pump. The solid residue was extracted with hot methanol. The methanol-insoluble fraction, after being crystallized from benzene, melted at 224°. A mixed melting point with tetraphenyllead showed no depression. The yield of tetraphenyllead was 15%.

On cooling, the methanol extract deposited white crystals which melted at 90 to 96°. Two crystallizations from methanol gave a trace of material melting at 97–98°.

When the original methanol extract was concentrated more material was obtained. This proved to be triphenyl-*n*-butyllead.

A second run was made in which the mixture was hydrolyzed three minutes after the triphenyllead chloride had been added. The reaction was treated as in the first run. No tetraphenyllead was found in the reaction. After crystallization from methanol, the yield of triphenyl-*p*,N-methylaminophenyllead melting at 97–98° was 10%.

Anal. Calcd. for $C_{25}H_{22}NPb$: Pb, 38.07; N, 2.5. Found: Pb, 37.79; N, 2.6.

Besides some recovered triphenyllead chloride there was isolated 50% of triphenyl-*n*-butyllead.

Triphenyl-*o*-dimethylaminophenyllead.—To 0.5 g. of lithium suspended in 25 ml. of ether was added 5.6 g. (0.03 mole) of *o*-bromodimethylaniline in 50 ml. of ether. The mixture was heated gently to start the reaction and then the *o*-bromodimethylaniline was added at such a rate that gentle refluxing was maintained. After all of the amine had been added, stirring was continued for thirty minutes. The solution was filtered through glass wool and 5 ml. of the filtrate was hydrolyzed and titrated with standard acid. The yield of organometallic compound was 66%. The solution of organometallic compound thus prepared was added to 9.5 g. (0.02 mole) of triphenyllead chloride suspended in 50 ml. of ether. After 15 minutes the mixture was hydrolyzed with cold, aqueous ammonium chloride. The ether layer was separated and dried and the ether removed at reduced pressure. Crystallization of the residue from 95% ethanol gave 5.4 g. or 50% of triphenyl-*o*-dimethylaminophenyllead melting at 101–102°.

Anal. Calcd. for $C_{26}H_{25}NPb$: Pb, 37.1. Found: Pb, 36.9.

Triphenyl-*o*-hydroxyphenyllead.—To 7.8 g. (0.045 mole) of *o*-bromophenol in 50 ml. of ether was added dropwise 0.09 mole of *n*-butyllithium in 175 ml. of ether. After thirty minutes a slight excess of anhydrous magnesium bromide was added. To the mixture thus obtained was added 14 g. (0.03 mole) of triphenyllead chloride. The mixture was stirred at room temperature for two hours and then hydrolyzed with cold, aqueous ammonium chloride. The ether layer was dried and the ether removed at reduced pressure. The solid residue was extracted with 95% ethanol.

Seven grams of the material was insoluble in alcohol, contained no halogen, and melted at 231°. A quantitative lead analysis gave 43.7% lead. This agrees with the calculated value for triphenyllead carbonate. When boiled with concentrated hydrochloric acid, the compound evolved carbon dioxide and was converted to triphenyllead chloride. The alcohol-soluble portion after several crystallizations from an alcohol–petroleum ether mixture melted at 217–218° with decomposition. The yield of triphenyl-*o*-hydroxyphenyllead was 3 g. or 20%.

Anal. Calcd. for $C_{24}H_{20}OPb$: Pb, 38.98. Found: Pb, 38.81.

In a second preparation of triphenyl-*o*-hydroxyphenyllead, the magnesium bromide was omitted and the reaction was hydrolyzed three minutes after 0.05 mole of *o*-lithiolithiumphenoxide had been added to 0.05 mole of triphenyllead chloride. From this reaction the yield of triphenyl-*o*-hydroxyphenyllead was 70% and no high-melting material corresponding to that which was previously obtained was present.

Triphenyl-1-(2-hydroxynaphthyl)-azophenyl-4-lead.—The reported[4] diazotization of triphenyl-*p*-aminophenyllead and subsequent coupling with β-naphthol were carried out in dilute hydrochloric acid. Since the yield of dye was very small, a better means of diazotization was sought. When the aminoaryllead compound was dissolved in ethanol saturated with dry hydrogen chloride, treated with isoamyl nitrite at 0°, and then poured into a sodium hydroxide solution of β-naphthol, the yield of dye was no better. The same held true when 50% sulfuric acid was used as the reaction medium.

The following procedure gave the best results. Five-tenths of a gram of triphenyl-*p*-aminophenyllead was dissolved in 10 ml. of glacial acetic acid cooled to the freezing point. Sodium nitrite was then slowly added with stirring. The temperature was held between 15° and 20° for 15 minutes and the mixture was then poured into a sodium hydroxide solution containing 0.5 g. of β-naphthol. The solid which separated was filtered off and crystallized from dilute ethanol. The yield of dye melting at 135° (dec.)[4] was 0.2 g. or 35%.

Attempted Preparation of Triphenyl-1-(2-hydroxynaphthyl)-azophenyl-2-lead.—To a solution of 2.0 g. of triphenyl-*o*-aminophenyllead in glacial acetic acid cooled to 15° was added 1.0 g. of sodium nitrite. The mixture was allowed to stand for fifteen minutes and was then poured into an alkaline solution containing 1.0 g. of β-naphthol. The yellow solution was filtered and the residue crystallized from ethanol. No appreciable quantity of dye was isolated. The alcohol-insoluble fraction was crystallized from chloroform. A mixed melting point with tetraphenyllead showed no depression. The alcohol-soluble portion yielded triphenyllead acetate, and on dilution with petroleum ether, triphenyl-*o*-hydroxyphenyllead.

Triphenyl-1-[2-hydroxy-3,5-di-(*p*-nitrophenylazo)-phenyl]-lead.—*p*-Nitroaniline (5.0 g.) was diazotized in the usual manner. The diazotized solution was then added to a mixture of 5.3 g. (0.1 mole) of triphenyl-*o*-hydroxyphenyllead, 20 ml. of ethyl acetate, 20 ml. of 95% ethanol, and 40 ml. of 10% sodium hydroxide solution. A deep, blood-red color was immediately obtained. The mixture was stirred rapidly until all the ethyl acetate had evaporated. This took about two hours. The solid residue was then collected on a filter and washed thoroughly with water and cold 50% ethanol. The dark red powder which remained on the filter was crystallized from ethanol containing a small amount of acetic acid. The compound decomposed above 180°. The yield was 7.1 g. or 86%.

Anal. Calcd. for $C_{36}H_{26}O_5N_6Pb$: Pb, 24.9; N, 10.1. Found: Pb, 24.6; N, 9.9.

The analysis of the compound showed that two molecules of *p*-nitrobenzenediazonium chloride had coupled with the lead compound.

TABLE I

REACTIONS OF DIAZONIUM SALTS WITH TRIPHENYL-*o*-HYDROXYPHENYLLEAD AND TRIPHENYL-*o*-DIMETHYLAMINOPHENYLLEAD[a]

Organolead compound	Diazonium salt	Coupling position	Yield, %	Analyses, % Pb Calcd.	Analyses, % Pb Found
$(C_6H_5)_3Pb$-*o*-C_6H_4OH	*p*-$ClC_6H_4N_2Cl$	5	45	30.9	30.8
$(C_6H_5)_3Pb$-*o*-C_6H_4OH	*p*-$BrC_6H_4N_2Cl$	5	48	28.9	28.6
$(C_6H_5)_3Pb$-*o*-C_6H_4OH	*p*-$IC_6H_4N_2Cl$	5	50	25.9	25.5
$(C_6H_5)_3Pb$-*o*-C_6H_4OH	*p*-$HOOCC_6H_4N_2Cl$	5	15	..[b]	..[b]
$(C_6H_5)_3Pb$-*o*-$C_6H_4N(CH_3)_2$	*p*-$ClC_6H_4N_2Cl$	5	51	29.9	29.6
$(C_6H_5)_3Pb$-*o*-$C_6H_4N(CH_3)_2$	*p*-$BrC_6H_4N_2Cl$	5	57	28.0	27.7
$(C_6H_5)_3Pb$-*o*-$C_6H_4N(CH_3)_2$	*p*-$IC_6H_4N_2Cl$	5	60	27.2	27.0
$(C_6H_5)_3Pb$-*o*-$C_6H_4N(CH_3)_2$	*p*-$HOOCC_6H_4N_2Cl$	5	57	29.8	29.6

[a] All of the dyes listed in this table range from brown to red in color. [b] Since difficulty was encountered in obtaining a good qualitative test for nitrogen in this particular compound, a quantitative analysis for nitrogen was carried out. *Anal.* Calcd. for $C_{31}H_{24}O_3N_2Pb$: N, 4.1. Found: N, 3.9. The compound is easily soluble in dilute, aqueous sodium hydroxide.

Three grams of the dye was suspended in 10 ml. of hot water, and 8 g. of stannous chloride in 20 ml. of hot concentrated hydrochloric acid was added. The mixture was warmed until decolorization had taken place and was then filtered. The filtrate was made alkaline with sodium hydroxide and then extracted with ether. The water layer was next saturated with carbon dioxide and again extracted with ether. The ether extract was dried and the ether was evaporated. The residue was crystallized from dilute ethanol. The melting point was 79–80°. The picrate melted at 120°. This corresponds to the melting point of the picrate of 2,4-diaminophenol.[7] A mixed melting point with an authentic specimen[7] showed no depression.

Triphenyl-1-[2-dimethylamino-5-(*p*-nitrophenylazo)-phenyl]-lead.—To a vigorously stirred suspension of 5.58 g. (0.01 mole) of triphenyl-*o*-dimethylaminophenyllead in a solution containing 75 ml. of water, 75 ml. of ethanol, 50 ml. of ethyl acetate, and 3 g. of sodium acetate was added 2 g. of *p*-nitroaniline diazotized in the usual manner. A deep-red color immediately appeared. After fifteen minutes air was bubbled through the mixture to expel the ethyl acetate. The gummy solid was filtered from the aqueous mixture and was dried on a porous plate. The dried material was boiled with ethanol to remove any of the starting lead compound, was then filtered and the residue was washed with water and dried. The yield of dark red dye was 4.2 g. or 70%.

Anal. Calcd. for $C_{32}H_{28}O_2N_4Pb$: N, 7.9. Found: N, 8.2.

Three grams of the dye was suspended in hot water (10 ml.) and 8 g. of stannous chloride in 20 ml. of hot concentrated hydrochloric acid was added. The mixture was warmed until decolorization was complete. The solid residue was collected on a filter. The filtrate was made basic with sodium hydroxide and then was extracted with ether. The ether layer was dried over sodium sulfate and the ether was evaporated. The crude bases were warmed on a water-bath with 1 g. of acetic anhydride. This mixture was diluted with water and filtered. The filtrate was neutralized with sodium carbonate to precipitate *p*-dimethylaminoacetanilide. This compound, when crystallized from hot water, melted at 130°. A mixed melting point with an authentic specimen[8] showed no depression.

Additional dyes, obtained from triphenyl-*o*-hydroxyphenyllead and triphenyl-*o*-dimethylaminophenyllead in essential accordance with the procedures described above, are listed in Table I. All of the dyes gradually decomposed when heated above 140°.

Acknowledgment.—The authors are grateful to Dr. William H. Woglom, Department of Cancer Research, Columbia University, New York, for tests of physiological action. The only compound which was sufficiently soluble for testing purposes, with the technique used, was the sodium salt of triphenyl-1-[2-hydroxy-5-(*p*-carboxyphenylazo)-phenyl]-lead (footnote "*b*," Table I). This compound was tested on four mice with spontaneous mammary carcinoma. In three the tumors grew in the usual way; in the fourth the tumor grew smaller, but this was not an unusual occurrence in this strain of mice. Accordingly, it appears that this particular compound has no curative properties against this type of cancer in mice. The compound did not appear to be toxic in the doses given (9 mg. twice weekly), but it was noticed that about twenty minutes after the injection the urine became wine-red, remained so for four or five hours, and then gradually returned to normal. Microscopic examination disclosed no blood in the urine.

The authors are also grateful to Lawrence Summers for assistance.

Summary

1. Several hydroxy- and aminoaryllead compounds have been prepared.

2. The coupling of diazonium salts with hydroxy- and aminoaryllead compounds has been described.

3. The structure of the coupling products was determined.

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(7) Lumière, *Compt. rend.*, **116**, 1204 (1893).

(8) Gattermann and Wieland, "Laboratory Methods in Organic Chemistry," The Macmillan Company, New York, N. Y., 1937, p. 302.