phenyl-6-benzamidocinchoninate, colorless needles, m.p. 177–177.5° from ethanol, λ_{max} 280–281, 363–367 mμ, strong blue fluorescence under ultraviolet light.

Anal. Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.09; N, 7.07. Found: C, 75.75; H, 5.17; N, 7.22.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Preparation of Organolead Compounds Containing Water-solubilizing Groups

BY HENRY GILMAN AND LAWRENCE SUMMERS[1]

RECEIVED JUNE 6, 1952

A number of new organolead compounds of the type $(C_6H_5)_3PbR'$ were prepared from triphenyllead–lithium and alkyl halides. The R′ part was chosen such that it would contain functional groups conceivably capable of conversion into water-solubilizing structures. Triphenyl-*p*-bromobenzyllead did not react to form a Grignard reagent or organolithium compound. Triphenyl-ω-haloalkylleads could not be obtained in pure form by reaction of excess α,ω-dihaloalkane with triphenyllead–lithium. When the latter reagent was in excess, however, α,ω-bis-(triphenyllead)-alkanes were readily obtained. Triphenyl-γ-diethylminopropyllead was prepared from triphenyllead–lithium and γ-diethylaminopropyl chloride. It was cleaved by dilute aqueous hydrochloric acid to give crystalline diphenyl-γ-diethylaminopropyllead chloride hydrochloride. Some lead compounds containing tertiary amino groups were converted to quaternary ammonium iodides or methyl sulfate derivatives to give products sufficiently soluble for physiological testing. One of these, the methyl sulfate derivative of triphenyl-γ-diethylaminopropyllead, was extremely soluble in water.

In a study recently reported[2] from this Laboratory, it was shown that organolead compounds of the type R_3PbR' could be obtained in good yields by the reaction of triaryllead–lithium preparations with alkyl halides. The triaryllead–lithium component was formed by treatment of one mole of lead dichloride, at −10°, with three equivalents of the aryllithium compound in ether.

$$3RLi + PbCl_2 \longrightarrow R_3PbLi + 2LiCl$$

$$R_3PbLi + R'X \longrightarrow R_3PbR' + LiX$$

In these equations R = aryl and X = halogen. Investigation of these reactions led to the conclusion that the method should be generally applicable for R_3PbR' compounds in which R′ is an aliphatic structure containing no functional group which will react rapidly with aryllithium compounds. This latter requirement was due to the fact that the triaryllead–lithium preparations were found to behave as an equilibrium system containing RLi as well as R_3PbLi.

$$R_3PbLi \rightleftarrows R_2Pb + RLi$$

The present paper reports the application of this synthetic procedure to the preparation of some new organolead compounds of the type R_3PbR', where R′ contained functions conceivably capable of modification to produce water-solubilizing groups. The importance of this latter consideration for pharmacological evaluation has been discussed previously.[3] The compounds whose synthesis is described here include two water-soluble organolead derivatives which have been submitted for pharmacological testing elsewhere.

Halogen Compounds.—Of the structures allowable in the R′ group the most promising for our purposes appeared to be halogen atoms (which might be converted to other functions *via* the Grignard reaction) or tertiary amino groups. From triphenyllead–lithium and *p*-bromobenzyl chloride, triphenyl-*p*-bromobenzyllead was readily prepared. Attempts to form a Grignard reagent or organolithium compound from the triphenyl-*p*-bromobenzyllead did not succeed, however. In the only reported case[4] of unambiguous formation of a Grignard reagent from an organolead compound (triethyl-ϵ-bromoamyllead) the halogen atom was attached to an aliphatic carbon atom. Attempts were therefore made to obtain lead compounds containing a haloalkyl group by treatment of triphenyllead–lithium with excess polymethylene dihalide.

$$(C_6H_5)_3PbLi + X(CH_2)_nY \longrightarrow (C_6H_5)_3Pb(CH_2)_nY + LiX$$

(In this equation, X and Y are halogen atoms, which may or may not be of the same kind.) With an excess of a reagent such as trimethylene chlorobromide, triphenyllead–lithium reacted readily, but not cleanly according to the equation above. The products were mixtures, from which we could not isolate pure triphenyl-ω-haloalkylleads. In connection with this work, the corresponding α,ω-bis-(triphenyllead)-alkanes were prepared for comparison purposes. These compounds formed readily from excess triphenyllead–lithium and the polymethylene dihalide.

$$2(C_6H_5)_3PbLi + X(CH_2)_nY \longrightarrow (C_6H_5)_3Pb(CH_2)_nPb(C_6H_5)_3 + LiX + LiY$$

Tertiary Amino Groups.—Organolead compounds containing aminoaryl,[3b] alkylaminoaryl,[3a] dialkylaminoaryl[5] or trialkylamino[3a] groups have been described. These lead-containing amines are weak bases, and will dissolve in water only if the solution is rather strongly acid. Such strongly acid solutions are presumably undesirable for physiological work, besides which the C–Pb bond is quite sensitive to acid cleavage. A method was therefore sought for forming, from these lead-containing amines, hydrophilic structures which would bring them into solution in water at a *p*H close to 7.0. Since the quaternary ammonium hydroxides are strong bases, it appeared that their salts with strong acids should fulfill the require-

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[1] E. I. du Pont Postgraduate Fellow, 1948–1950.

[2] H. Gilman, L. Summers and R. W. Leeper, *J. Org. Chem.*, **17**, 630 (1952).

[3] (a) H. Gilman and D. S. Melstrom, THIS JOURNAL, **72**, 2953 (1950); (b) H. Gilman and C. G. Stuckwisch, *ibid.*, **72**, 4553 (1950); **64**, 1007 (1942).

[4] G. Grüttner and E. Krause, *Ber.*, **49**, 2666 (1916).

[5] P. R. Austin, THIS JOURNAL, **54**, 3726 (1932).

ments. To test the hypothesis, tetra-*p*-dimethylaminophenyllead was converted, by use of methyl iodide, to the corresponding tetramethiodide. The reaction with methyl iodide took place readily, although the presence of four tertiary amino groups caused some difficulty in obtaining a product analyzing for the completely methylated compound. By rather prolonged treatment with a large excess of methyl iodide, this was accomplished. The tetramethiodide of tetra-*p*-dimethylaminophenyllead was soluble in water to the extent of about 0.5 g. per 100 ml., to give a stable solution with *p*H about 7.5.

Next the same type of experiment was tried with an unsymmetrical lead compound which contained a trialkylamino group. Treatment of triphenyllead-lithium with γ-diethylaminopropyl chloride gave, in 91% yield, triphenyl-γ-diethylaminopropyllead. This product was an oil which could not be distilled or caused to crystallize, so that it could not readily be purified. Its identity was established beyond question by the numerous experiments which were carried out with it.

Triphenyl-γ-diethylaminopropyllead was converted to a crystalline methyl iodide derivative. This product was insoluble in cold water. Treatment of it with moist silver oxide gave a stable aqueous solution. This solution contained the quaternary ammonium hydroxide, since on addition of hydriodic acid the original methyl iodide derivative was precipitated, but the quaternary base was apparently too soluble to be isolated. Treatment of this aqueous solution with sulfuric acid gave no precipitate. This observation suggested, not only that lead ion was absent (that is, decomposition had not occurred), but also that the quaternary ammonium sulfate must be quite soluble in water. Triphenyl-γ-diethylaminopropyllead was therefore converted, by means of dimethyl sulfate, to the corresponding methyl sulfate derivative.

$$(C_6H_5)_3PbHC_2CH_2CH_2N(C_2H_5)_2 + (CH_3)_2SO_4 \longrightarrow [(C_6H_5)_3PbCH_2CH_2CH\ N(C_2H_5)_2CH_3]^+[OSO_2OCH_3]^-$$

This derivative was a white crystalline solid, obtained in 70% yield based on lead chloride. It was insoluble in organic solvents such as benzene or ether, but soluble in methanol or ethylene glycol. The compound was extremely soluble in water, apparently in any proportion. A solution of 5.0 g. in 25 ml. of water had *p*H 5.7; after four days the *p*H had risen only to 6.9. Thereafter there was little change in *p*H, and after three months there was no visible precipitate in the solution. The compound appeared to be surface active, since its solution in water developed foam or suds on shaking. This substance, then, represented an organolead type in which the water-solubility was so great that the solubility problem essentially disappeared.

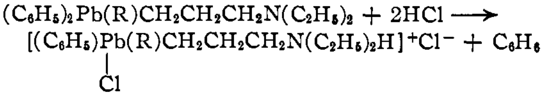
It was found that the dialkylaminoaryl group did not exert as strong a water-solubilizing effect as a trialkylamino group. Triphenyl-*p*-dimethylaminophenyllead was converted to a methyl sulfate derivative, but this product was almost insoluble in water.

Other Reactions of Triphenyl-γ-diethylaminopropyllead.—The phenyl groups in triphenyl-γ-diethylaminopropyllead were very readily removed by the action of acid. Treatment of the compound with hydrogen chloride in benzene caused complete cleavage to give lead chloride. One phenyl group could be cleaved by simply shaking the material with cold dilute aqueous hydrochloric acid. Diphenyl-γ-diethylaminopropyllead chloride hydrochloride was thus obtained as stable white crystals.

$$(C_6H_5)_3PbCH_2CH_2CH_2N(C_2H_5)_2 + 2HCl \longrightarrow [(C_6H_5)_2Pb(Cl)CH_2CH_2CH_2N(C_2H_5)_2H]^+Cl^- + C_6H_6$$

This compound is of interest in connection with the still unsolved problem of preparation of a lead compound with optical activity due to an unsymmetrical arrangement of groups around a lead atom. It is a crystalline material with three different groups around lead, and containing reactive functions through which further changes might be effected. Thus a series of reactions such as

$$[(C_6H_5)_2Pb(Cl)CH_2CH_2CH_2N(C_2H_5)_2H]^+Cl^- + 2RMgX \longrightarrow (C_6H_5)_2Pb(R)CH_2CH_2CH_2N(C_2H_5)_2 + 2MgXCl + RH$$



$$(C_6H_5)_2Pb(R)CH_2CH_2CH_2N(C_2H_5)_2 + 2HCl \longrightarrow [(C_6H_5)\underset{\displaystyle Cl}{Pb}(R)CH_2CH_2CH_2N(C_2H_5)_2H]^+Cl^- + C_6H_6$$

(R = alkyl) would lead to a compound having four different groups around the lead atom, containing also a basic group through which resolution might be possible. The Pb–Cl bond in diphenyl-γ-diethylaminopropyllead chloride hydrochloride did react normally with active organometallic compounds, as was shown by the conversion of the hydrochloride back to triphenyl-γ-diethylaminopropyllead by the action of phenyllithium. The series of reactions indicated above was attempted with R = ethyl or benzyl. In these cases, although the Grignard reaction again proceeded in an apparently normal manner, the impure oily product could neither be crystallized nor cleaved to give a crystalline hydrochloride.

Experimental

The starting materials were pure commercial chemicals, except in those cases where a method of preparation is indicated below. The lead chloride, a powdered reagent-grade material, was used as received, without special treatment. Phenyllithium was prepared as usual,[6] in diethyl ether, and was titrated to determine the exact concentration. All reactions involving phenyllithium were carried out, up to the hydrolysis step, under dry nitrogen.

Melting points are uncorrected.

Triphenyl-*p*-bromobenzyllead.—Lead chloride, 11.1 g. (0.04 mole), and 30 ml. of ethyl ether were placed in a reaction flask equipped with an efficient glass stirrer with a semi-circular blade (Ace Glass Co., No. 8245). The reaction flask was cooled in an ice–salt-bath whose temperature was kept at −10°, while 0.120 mole of phenyllithium in 113 ml. of ether was added over a period of one hour, with constant stirring. To this triphenyllead-lithium preparation[1] there was added, still at the same temperature, 9.0 g. (0.04 mole plus 10%) of *p*-bromobenzyl chloride in 50 ml. of ether. The solution was refluxed for one hour, then cooled in ice and hydrolyzed by addition of dilute aqueous ammonium chloride solution. The ether layer was separated, washed with water, and dried on Drierite. Removal of the ether left a yellow oil containing mushy white crystals. This was crystallized from absolute ethanol; yield 16.3 g. (67%), m.p. 66–68°, color somewhat yellowish.

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[6] R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 353 (1951).

Anal. Calcd. for $C_{25}H_{21}BrPb$: Br, 13.1; Pb, 34.1. Found: Br, 13.2; Pb, 34.3.

Triphenyl-*p*-bromobenzyllead, 6.1 g. (0.01 mole) in 35 ml. of ether was refluxed and stirred under nitrogen for three hours with 0.5 g. of magnesium turnings and a crystal of iodine. Color Test I[7] remained negative, and there was no suggestion of reaction. A few drops of methylmagnesium iodide solution were finally added, but this still did not catalyze the reaction. The mixture was treated with water and worked up as usual, to give only starting material.

Triphenyl-*p*-bromobenzyllead, 6.1 g. (0.01 mole), was stirred for two hours at room temperature in 30 ml. of ether, under nitrogen, with 0.3 g. of lithium metal, freshly cut into small pieces. Since there was no evidence of reaction, the mixture was refluxed for five hours. The lithium became coated black, especially on the freshly cut edges, but no other change was apparent. Working up of the mixture gave only recovered starting material.

1,3-Bis-(triphenyllead)-propane.—Triphenyllead–lithium was prepared by the addition of 0.120 mole of phenyllithium in 113 ml. of ether to 11.1 g. (0.04 mole) of lead chloride in 30 ml. of ether at −10°. There was then added 4.0 g. (0.02 mole) of 1,3-dibromopropane, and the mixture was stirred for 15 minutes in the cold, then refluxed for one hour, hydrolyzed and worked up as above to give an oily crude product. This was extracted with two portions (100 and 50 ml.) of hot ethanol. The extracts on cooling yielded the product as a liquid which solidified in the refrigerator, weight 8.4 g. The residue unextracted by the ethanol was dissolved in petroleum ether (indicating absence of tetraphenyllead), and by addition of ethanol there was obtained an additional 2.2 g. of product. The total yield was thus 10.6 g. (58%), m.p. 90–92°. Because the material came out of solution in recrystallization solvents as an oil, final purification for analysis required four more crystallizations from ethanol–petroleum ether mixtures. The final white crystals had m.p. 94–95°.

Anal. Calcd. for $C_{39}H_{36}Pb_2$: Pb, 45.1. Found: Pb, 44.9.

Triphenyllead–Lithium and Excess 1,3-Dihalopropanes.—Triphenyllead–lithium was prepared as above from 0.04 mole of lead chloride and 0.120 mole of phenyllithium in ether. To this preparation there was added 8.9 g. (0.04 mole, plus 10%) of 1,3-dibromopropane, and after 15 minutes stirring in the cold the mixture was hydrolyzed and worked up as above. The yellow oil obtained as crude product was crystallized from ethanol, to give 7.3 g. of white powder, m.p. 65–80°. Further attempts to purify this material by crystallization gave no product having a definite melting point.

In another experiment, 1-bromo-3-chloropropane (12.6 g., 0.08 mole) was added to the triphenyllead–lithium preparation obtained from 0.04 mole of lead chloride, and after 20 minutes in the cold the mixture was hydrolyzed and worked up. There was obtained a white solid, 28.2 g., m.p. 65–71°. Recrystallization from ethanol–petroleum ether mixtures gave products with wide melting-point ranges in the neighborhood of 55–65°. Repeated experiments always gave results of this nature. In another case, triphenyllead–lithium was prepared from 0.06 mole of lead chloride and 0.180 mole of phenyllithium in 171 ml. of ether, and to this there was added 9.5 g. (0.06 mole) of 1-bromo-2-chloropropane. After 1.5 hours under reflux, the mixture was hydrolyzed and worked up. The product, 10.5 g. of white crystals, m.p. 68–71°, had a halogen content close to that required for triphenyl-γ-chloropropyllead.

Anal. Calcd. for $C_{21}H_{21}PbCl$: Pb, 40.2; Cl, 6.9. Found: Pb, 40.1; halogen calculated as Cl, 6.4.

This analysis served to establish the presence of halogen, but this halogen may have consisted in part of bromine. The product did not behave as a pure material, but exhibited the same behavior as the other samples when attempts were made to purify it.

In none of these experiments was there more than a trace of insoluble residue after hydrolysis (yellow residues at this point indicate incomplete reaction of triphenyllead–lithium with the RX compound[2]).

1,4-Bis-(triphenyllead)-butane.—1-Bromo-4-chlorobutane, 3.4 g. (0.02 mole), was added over a period of 40 minutes to the cold triphenyllead–lithium preparation obtained as above from 0.04 mole of lead chloride. After one hour under reflux, the mixture was hydrolyzed and worked up. Fractional crystallization of the solid crude product from ethanol–petroleum ether mixtures gave 8.6 g. (46%) of white crystals, m.p. 134–136°.

Anal. Calcd. for $C_{40}H_{38}Pb_2$: Pb, 44.4. Found: Pb, 44.2.

Triphenyllead–Lithium and Excess 1-Bromo-4-chlorobutane.—1-Bromo-4-chlorobutane, 13.7 g. (0.08 mole) was added all at once to the cold triphenyllead–lithium preparation obtained from 0.04 mole of lead chloride, and stirred for 20 minutes before it was hydrolyzed and worked up. Fractional crystallization of the crude product in this case led to a less soluble fraction with a high m.p. (100–125°) and a low-melting (50–60°) fraction, neither of which could be purified.

Tetramethiodide of Tetra-*p*-dimethylaminophenyllead.—Tetra-*p*-dimethylaminophenyllead,[2,6] 13.8 g. (0.02 mole), was dissolved in 50 ml. of methyl iodide in a 2000-ml. three-neck flask equipped with stirrer and reflux condenser, and the solution was allowed to stand for one hour after warming slightly. Methanol, 1000 ml., was added to the whitish paste which formed, and the mixture was stirred and refluxed for 12 hours, and filtered hot. The filtrate was cooled in ice–salt, and there crystallized 9.9 g. of slightly yellow product, which was recrystallized from 820 ml. of methanol to give 5.3 g. of white needles, m.p. 187–189° (which is the m.p. of tetra-*p*-dimethylaminophenyllead). The residue from the initial hot filtration was replaced in the reaction flask and refluxed again for 12 hours with 1000 ml. of methanol containing 10 ml. of methyl iodide. Hot filtration now left little residue, and the filtrate on cooling yielded 7.9 g. of pure white product, m.p. 187–189°; total yield, 13.2 g. (53% calculated from tetra-*p*-dimethylaminophenyllead).

Anal. Calcd. for $C_{36}H_{52}NI_4Pb$: I, 40.4. Found: I, 40.4.

The product was soluble in water or methanol to the extent of about 0.5 g. per 100 ml., and somewhat more soluble in either solvent hot. It was insoluble in benzene or ether. The saturated aqueous solution had *p*H 7.5, and showed no precipitate after one month standing, while the *p*H rose only to 8.1.

Triphenyl-γ-diethylaminopropyllead.—To 27.8 g. (0.10 mole) of lead chloride, stirred in 80 ml. of ether at −10°, there was added 0.30 mole of phenyllithium in 276 ml. of ether, over a period of one hour. There was then added, in one portion, 15.0 g. (0.10 mole) of γ-diethylaminopropyl chloride (prepared by a modification of a previously described[8] method, and freshly distilled just before use). The mixture was stirred 10 minutes in the cold, refluxed for 1.5 hours, cooled, and hydrolyzed by addition of cold dilute aqueous ammonium chloride. The ether layer was separated and dried and the ether was removed, finally at reduced pressure. This left the crude triphenyl-γ-diethylaminopropyllead as a yellow oil, 50.5 g. (91%).

Anal. Calcd. for $C_{25}H_{31}NPb$: Pb, 37.5. Found: Pb, 36.0.

The preparation was repeated several times with similar results. The crude liquid did not solidify at Dry Ice temperatures, and attempts to crystallize it from ethanol or petroleum ether were fruitless. Attempts at distillation under reduced pressure led to decomposition. Qualitative tests showed nitrogen present in the material.

Methiodide of Triphenyl-γ-diethylaminopropyllead.—The triphenyl-γ-diethylaminopropyllead prepared as above from 8.3 g. (0.03 mole) of lead chloride was dissolved in 20 ml. of methyl iodide. After 10 minutes standing the white mass was washed by decantation through a filter, first with petroleum ether and then with ethyl ether. The residue was dissolved in 200 ml. of hot absolute ethanol, filtered hot and allowed to crystallize after addition of 250 ml. of hot petroleum ether. The yield was 15.3 g. (74% calculated from lead chloride) of small shining pearly plates, m.p. 153–155°.

Anal. Calcd. for $C_{26}H_{34}NIPb$: Pb, 29.8. Found: Pb, 29.5.

The product was insoluble in cold water, although it could be crystallized from water.

Methyl Sulfate Derivative from Triphenyl-γ-diethylaminopropyllead.—The triphenyl-γ-diethylaminopropyllead prepared as above from 20.9 g. (0.075 mole) of lead

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[7] H. Gilman and F. Schulze, This Journal, **47**, 2002 (1925).

[8] H. Gilman and D. A. Shirley, *ibid.*, **66**, 888 (1944).

chloride was dissolved in 75 ml. of benzene, and this solution was added to a solution of 10.4 g. (0.075 mole, plus 10%) of freshly distilled dimethyl sulfate in 25 ml. of benzene, with mild cooling in water. After 1.5 hours stirring at room temperature, the mixture was heated just to refluxing to dissolve the precipitate, and the white crystals (40 g.) which formed on cooling were collected on a filter and recrystallized from 100 ml. of benzene. The yield was 36.0 g. (70% calculated from lead chloride), m.p. 137–138°.

Anal. Calcd. for $C_{27}H_{37}O_4NSPb$: Pb, 30.5; S, 4.7. Found: Pb, 30.2; S, 4.9.

This derivative was very soluble in methanol or ethanol, soluble in hot benzene, insoluble in cold benzene or in petroleum ether. It was very soluble in water. A sample of the solid moistened with even a few drops of water passed into a clear solution which foamed on shaking. The *p*H of a solution of 5 g. of the material in 100 ml. of water was 5.7 immediately after preparation, 6.9 after 4 days, and 7.2 after 11 days. After 3 months this solution showed no precipitate.

Methyl Sulfate Derivative from Triphenyl-*p*-dimethylaminophenyllead.—Triphenyl-*p*-dimethylaminophenyllead,[6] 8.4 g. (0.015 mole), in 25 ml. of benzene was added rapidly with shaking to 1.9 g. (0.015 mole plus 10%) of dimethyl sulfate in 10 ml. of benzene. After one hour at room temperature and 20 minutes under reflux, the product precipitated as a bulky solid, which was filtered out, washed with ether, and recrystallized from ethanol. The yield was 3.5 g. (34%) of white, pearly, very fine fibers or needles, m.p. 241–243°. The solubility in water was less than 0.1 g. per 100 ml., although the material nevertheless caused foaming when shaken with water.

Anal. Calcd. for $C_{28}H_{31}O_4NSPb$: S, 4.7; Pb, 30.3. Found: S, 4.6; Pb, 29.8.

Diphenyl-γ-diethylaminopropyllead Chloride Hydrochloride.—Triphenyl-γ-diethylaminopropyllead, 30.0 g., was dissolved in 20 ml. of ether and washed twice with 100-ml. portions of cold 5% aqueous hydrochloric acid. The oil which formed was withdrawn with the aqueous layers, and the combined aqueous layers were shaken until crystallization of the oil was complete (about 30 minutes). The product was filtered out and recrystallized from 450 ml. of 95% ethanol; yield 18.2 g. (61%).

Anal. Calcd. for $C_{19}H_{27}NCl_2Pb$: Cl, 12.9; Pb, 37.8. Found: Cl, 12.9; Pb, 38.0.

Heated in a capillary tube, this material gradually turned brown, but did not melt up to 240°.

This preparation was repeated several times, always with essentially the same result.

Of this product, 1.1 g. (0.002 mole), was suspended in 35 ml. of ether and cooled in ice while 0.004 mole of phenyllithium in ether was added with stirring. After 20 minutes refluxing, the mixture was worked up, and gave as product a yellow oil. This was treated with 1 g. of dimethyl sulfate in benzene, and there resulted 0.4 g. of white solid, m.p. 139–140°, which did not depress the melting point of a sample of the methyl sulfate derivative of triphenyl-γ-diethylaminopropyllead.

In a similar way, a reaction was carried out between diphenyl-γ-diethylaminopropyllead chloride hydrochloride (5.5 g., 0.01 mole) and ethylmagnesium bromide (0.02 mole, plus 10%). The product was again an oily liquid, and could not be caused to crystallize. It was dissolved in ether and treated in a separatory funnel with two portions of cold 5% hydrochloric acid. As in the case of triphenyl-γ-diethylaminopropyllead, an insoluble layer separated immediately, and this was withdrawn with the water layer. In this case, the product would not crystallize on cooling, shaking, scratching, or standing in the refrigerator.

A corresponding reaction was carried out between diphenyl-γ-diethylaminopropyllead chloride hydrochloride and benzylmagnesium chloride. The oily product from this reaction was divided into portions which were treated, respectively, with methyl iodide, dimethyl sulfate or 5% hydrochloric acid. None of the products were crystalline.

Ames, Iowa

[Contribution from the School of Pharmacy, University of North Carolina]

Palladium Catalysis. IV.[1] Change in the Behavior of Palladium-on-Charcoal in Hydrogenation Reactions[2]

By Walter H. Hartung and Yen-tsai Chang[3]

Received February 6, 1952

During the past 18 years there developed a change in the qualitative behavior of palladium-on-charcoal catalysts which has been difficult to demonstrate convincingly. Previous results, for example, with α-oximino ketones showed that when three moles of hydrogen was taken up practically quantitative yields of the corresponding amino alcohol were formed; or if two moles of hydrogen was taken up, practically pure amino ketone was formed. Now with catalysts similarly prepared from pure palladium chloride, α-oximinopropiophenone takes up about two moles of hydrogen, but the product consists of approximately equal amounts of amino alcohol and oximino alcohol. The addition of platinum or rhodium to the palladium gives catalysts which, judging by results, somewhat approximate those employed earlier. α-Oximinopropiophenone reduced in alkaline medium forms good yields of amino alcohol.

It has been impossible until now to confirm by convincing experiments the suspicion, which developed shortly after the last paper in this series was published,[1] that the character of hydrogenation reactions in which palladium-on-charcoal was employed was changing. This has now been shown for α-oximinopropiophenone, and the results with this compound lend support to the belief that it may be true in other respects also.

The conversion of α-oximino ketones of structure Ar–CO–CR:NOH with palladium catalysts to the corresponding physiologically active amino alcohols, Ar–CHOH–CHR–NH_2, has become an accepted procedure.[4,5] If the Ar group is phenyl or tolyl the amino alcohol is formed directly unless the reaction is stopped earlier; at 2 moles of hydrogen, practically pure almost quantitative yields of amino ketone are formed. If the aromatic portion is substituted with hydroxyl or alkoxyl the reaction stops at the amino ketone, which may then be further hydrogenated with fresh catalyst in aqueous solution to the amino alcohol. It is to be stressed here that when two molar equivalents of hydrogen was taken up and the reaction was carried out in acidic medium only the amino ketone was identified

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(1) For no. III see W. H. Hartung and F. S. Crossley, This Journal, **56**, 158 (1934).

(2) The authors are grateful to Sharp and Dohme for a grant to the North Carolina Pharmaceutical Research Foundation for assistance in these studies.

(3) Fellow, American Foundation for Pharmaceutical Education, 1948–1951.

(4) W. H. Hartung, J. C. Munch and others, This Journal, **51**, 2262 (1929); **53**, 4149 (1931).

(5) R. Baltzly and J. S. Buck, *ibid.*, **62**, 164 (1940).