Found: Pb, 63.8; $CO_3$, 18.4 (carbonate analysis by decomposition of the compound with acid and absorption of $CO_2$ on ascarite).

**Triethyllead Carbonate and Bicarbonate.**—Triethyllead carbonate could not be prepared from triethyllead hydroxide by simple treatment with carbon dioxide; the product consisted mainly of triethyllead bicarbonate.

*Anal.* Calcd. for $(C_2H_5)_3PbHCO_3$: Pb, 58.3; $CO_3$, 16.9. Found: Pb, 59.7; $CO_3$, 14.6 (corresponding to about 82% $(C_2H_5)_3PbHCO_3$ and 18% $((C_2H_5)_3Pb)_2CO_3$).

After storage for seventy-two hours in a vacuum desiccator over activated alumina, the material was largely converted to triethyllead carbonate.

*Anal.* Calcd. for $((C_2H_5)_3Pb)_2CO_3$: Pb, 63.9; $CO_3$, 9.2. Found: Pb, 63.2; $CO_3$, 9.6 (corresponding to 91% $((C_2H_5)_3Pb)_2CO_3$ and 9% $(C_2H_5)_3PbHCO_3$).

**Triethyllead Cyanide.**—A solution of 19.5 g. (0.30 mole) of potassium cyanide in 35 ml. of water was added to a solution of 66.0 g. (0.20 mole) of triethyllead chloride in 3500 ml. of water. The white precipitate was separated by filtration and dried *in vacuo;* yield, 77%.

*Anal.* Calcd. for $(C_2H_5)_3PbCN$: Pb, 64.7; CN, 8.1. Found: Pb, 64.5; CN, 7.4.

**Triethyllead Sulfide.**—A cold solution of 10.6 g. (0.04 mole) of sodium sulfide nonahydrate in 350 ml. of water was added dropwise to a solution of 13.9 (0.04 mole) of triethyllead chloride in 700 ml. of water, stirred and cooled in an ice-bath. The product, a yellow oil, was dissolved with ether and filtered, and the ether was evaporated *in vacuo;* this procedure was repeated. The residue was a photosensitive, yellow-green liquid; f. p. −45.1° (uncor.), $n^{20}_D$ 1.6249, and $d^{20}_4$ 2.05; yield, 86%.

*Anal.* Calcd. for $((C_2H_5)_3Pb)_2S$: Pb, 66.8; S, 5.2. Found: Pb, 66.8; S, 5.0.

**Triethyllead Sulfate.**[11]—Air was bubbled for forty hours through a solution of 68.3 g. (0.11 mole) of triethyllead sulfide in 1000 ml. of dry ether in a darkroom. Evaporation losses were made up by the addition of ether from time to time. Triethyllead sulfate precipitated as a white solid and was separated by filtration through a sintered-glass Büchner funnel. After being washed several times with ether, the product was dried *in vacuo;* yield, 55%. After recrystallization from water, the product was chloride-free. Contrary to a statement by Klippel,[9b,9c] the material was found to be soluble to the extent of 5.5% in water at room temperature.

*Anal.* Calcd. for $((C_2H_5)_3Pb)_2SO_4$: Pb, 60.5; $SO_4$, 14.0. Found: Pb, 60.4; $SO_4$, 14.2.

**Trimethyllead Acetate.**—A mixture of 29.4 g. (0.11 mole) of tetramethyllead with excess glacial acetic acid was refluxed for about five minutes under nitrogen, during which time the reaction mixture set to a solid mass. The excess acetic acid was removed *in vacuo*, leaving glistening white crystals which were recrystallized from water; m. p. 183–184°; yield, 84%.

*Anal.* Calcd. for $(CH_3)_3PbCO_2CH_3$: Pb, 66.6. Found: Pb, 66.9.

## Summary

Improved methods of preparation of some alkyllead salts have been developed, and the following new alkyllead salts have been prepared: diethyllead dihydroxide, diethyllead carbonate, triethyllead bicarbonate and trimethyllead acetate.

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[11] This method of preparing triethyllead sulfate was discovered by Mr. J. V. Capinjola, to whom the authors are indebted.

DETROIT, MICHIGAN RECEIVED OCTOBER 24, 1944

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[CONTRIBUTION FROM THE LABORATORIES OF WALLACE & TIERNAN CO.]

# Diethylstilbestrol and Related Compounds

BY MARTIN RUBIN, A. KOZLOWSKI AND M. R. SALMON

Since the original preparation of diethylstilbestrol by Dodds, *et al.*,[1] several alternative procedures[2] of which the simplest is that described by Kharasch and Kleiman,[3] have been reported. The method described in this communication, although lengthy, is characterized by good yields and several points of particular interest.

The alcoholysis of anisaldehyde cyanhydrin by aliphatic alcohols and hydrogen chloride has been found to form the ethers of the expected α-hydroxy esters.[4] The reaction of these alkyl-α-alkoxy-*p*-methoxyphenylacetic esters with the ethyl Grignard reagent proceeded normally. Pinacol rearrangement of the 4-anisyl-4-alkoxyhexanol-3 formed gave anisyl-4-hexanone-3 as in the case of the non-etherified glycol.[5] The condensation of *p*-halogen anisole with anisyl-4-hexanone-3 by means of sodium in petroleum ether to give 3,4-dianisyl-hexanol-3 offered some advantages in yield and ease of manipulation over the Grignard reagent for this same reaction.[6] This carbinol was dehydrated by heating with potassium acid sulfate to a mixture of crystalline *trans* and other liquid isomers[2c] of diethylstilbestrol dimethyl ether. By use of a combination of iodine and certain metallic halides, notably ferric chloride, the liquid isomers of diethylstilbestrol dimethyl ether could be rearranged in good yield to the desired crystalline *trans* isomer.

Demethylation of the *trans*-diethylstilbestrol dimethyl ether by sodium or sodium hydroxide in boiling carbitol resulted in a mixture in which the monomethyl ether of diethylstilbestrol[7] predominated. This is in contrast to the reaction carried out in ethanol or diethylene glycol and

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[1] Dodds, Golberg, Lawson and Robinson, *Proc. Roy. Soc.* (London), **B127**, 152 (1939).

[2] (a) Kerschbaum, Kleedorfer, Prillinger, Wessely and Zajic, *Naturwissenschaften*, **27**, 131 (1939); (b) Wessely and Kleedorfer, *ibid.*, **27**, 567 (1939); (c) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940); (d) Kuwada, Sasagawa, *J. Pharm. Soc.*, Japan, **60**, 27 (1940); (e) Kuwada, Sasagawa and Nisikawa, *ibid.*, **60**, 553 (1940); (f) Peteri, *J. Chem. Soc.*, 833 (1940).

[3] Kharasch and Kleiman, THIS JOURNAL, **65**, 11 (1943).

[4] The analogous conversion under similar conditions of anisyl alcohol to anisyl ether has been ascribed to the influence of the *p*-methoxyl group: Quelet and Allard, *Bull. soc. chim.*, [5] **4**, 1468 (1937).

[5] Tiffeneau, Levy and Weill, *ibid.*, [4] **49**, 1709 (1931).

[6] Fieser and Christiansen, U. S. Patent 2,248,019 (1941).

[7] Reid and Wilson, THIS JOURNAL, **64**, 1625 (1942).

alkali in which diethylstilbestrol is the major product.[8]

## Experimental

Melting points and boiling points are uncorrected.

**Butyl α-Butoxy-*p*-methoxyphenylacetate.**—Ten grams of sodium was dissolved in 6000 cc. of commercial *n*-butanol. After cooling to 18°, 800 cc. of liquid hydrocyanic acid was added. To the mixture was added 1815 cc. of anisic aldehyde at 20–25°. After stirring at 25° for thirty minutes, the temperature was lowered and maintained at 15° while 550 g. of dry hydrogen chloride was added. During the further addition of 550 g. of dry hydrogen chloride the temperature was allowed to rise to 40°. The mixture was then refluxed for three hours, cooled and diluted with 6 liters of water. The water layer was drawn off, the solvent evaporated, and the residue distilled *in vacuo*. The fraction boiling 160–180° at 0.8 mm. was collected; yield 3600 g.

*Anal.* Calcd. for $C_{17}H_{26}O_4$: C, 69.35; H, 8.91; sapn. no., 190.8. Found: C, 69.65; H, 9.03; sapn. no., 195.7.

**α-Butoxy-*p*-methoxybenzyl Cyanide.**—The substitution of sulfuric acid for dry hydrogen chloride in the reaction described above halted the reaction at the stage of the ether of anisaldehyde cyanhydrin. The product was a clear, colorless oil, boiling point 120–125°, 0.2 mm.

*Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.24; H, 7.83. Found: C, 70.90; H, 7.72.

**Anisyl-4-hexanone-3.**—To the Grignard reagent, prepared in a 25-qt. enameled pot fitted with a reflux condenser, a stirrer and dropping funnel in the top and a discharge valve in the bottom, from 625 g. of magnesium turnings, 8 liters of dry ether and 1650 g. of ethyl chloride was added 3000 g. of butyl α-butoxy-*p*-methoxyphenylacetate at such a rate as to maintain a gentle ether reflux. After stirring for one hour the reaction product was decomposed by adding it with vigorous stirring to 3 liters of 30% sulfuric acid while simultaneously distilling off the ether. The oily layer was then separated and added to 3 liters of 30% sulfuric acid. The mixture was heated and the distillate boiling below 92° was discarded. Following the addition of 500 cc. of water the pinacol rearrangement was completed by refluxing for four hours. The oily layer was then separated, washed with water and distilled *in vacuo*. The ketone was collected at 115–135°, 1.0 mm., yield, 1500 g. (75%).

The semicarbazone melted at 132°. Mixed melting point with an authentic sample[5] showed no depression.

**Diethylstilbestrol Dimethyl Ether (I).**—In the usual manner 686 g. of sodium was powdered under toluene. The toluene was decanted and 225 g. of *p*-chloroanisole in 2 liters of 30–60° petroleum ether was added. The mixture was heated until gentle refluxing began. A mixture of 2000 g. of *p*-chloroanisole and 3000 g. of anisyl-4-hexanone-3 was then added at a rate sufficient to maintain the reflux. During the course of the addition four 500-cc. portions of petroleum ether were added. After stirring overnight the excess sodium was destroyed by the addition of 1 liter of ethanol. After washing with 4 liters of water the solvents were distilled and the residue fractionated. The distillate boiling below 105°, 0.5 mm. was discarded. The fraction 105–135°, 0.5 mm. (1700 g.) consisted largely of recovered anisyl-4-hexanone-3. To the residue was added 500 g. of potassium bisulfate. Dehydration was complete after heating at 180–215° for one hour. The liquid was decanted from inorganic salt and distilled *in vacuo*. A mixture of crystalline *trans*-diethylstilbestrol dimethyl ether and liquid isomers (1193 g.) was collected at 160–190°, 0.8 mm.

The distillate was diluted with an equal volume of petroleum ether and allowed to crystallize overnight in the ice box. The crystalline *trans*-diethylstilbestrol dimethyl ether was removed by filtration. The petroleum ether filtrate was heated to 140° to remove the solvent and 1 g. of iodine and 1 g. of ferric chloride added. Heating and stirring was continued for one hour. After cooling, the mixture was diluted with an equal volume of petroleum ether and set in the ice box to crystallize. Repetition of the process resulted in an over-all conversion of the mixed liquid isomers of diethylstilbestrol dimethyl ether to 80% of the crystalline *trans* isomer, melting at 123–124° on recrystallization from 60–90° petroleum ether. A mixed melting point with an authentic specimen showed no depression.

Substitution of antimony pentachloride, aluminum chloride and boron trifluoride in combination with iodine was also highly effective for the conversion to the *trans* isomer.

**Diethylstilbestrol (II) and Diethylstilbestrol Monomethyl Ether (III).**—A mixture of 3.5 liters of "carbitol" solvent and 485 g. of potassium hydroxide was heated, with stirring, until 500 cc. of distillate had been collected. Diethylstilbestrol dimethyl ether was added (1 kg.) and the solution refluxed for four hours. After cooling to 120° the mixture was poured into 3 liters of ethanol and 6 liters of water. Filtration after one and one-half hours of stirring gave 300 g. of recovered (I). The filtrate was diluted to 38 liters, acidified with concentrated hydrochloric acid and the precipitate which separated collected on a filter. The precipitate, consisting of (II) and (III), was slurried for three hours in 26.5 liters of water containing 177 g. of potassium hydroxide and 340 g. of filter cell. Filtration removed the monomethyl ether and the filter cell. Acidification of the filtrate with concentrated hydrochloric acid gave 200 g. of crude diethylstilbestrol. On recrystallization from benzene the product melted at 169–171°. There was no melting point depression on admixture with an authentic sample.[1]

The monomethyl ether was eluted from the precipitate by stirring for one hour with a solution of 5 liters of water, 5 liters of alcohol and 133 g. of potassium hydroxide. The mixture was filtered, the filtrate diluted to 38 liters, acidified with concentrated hydrochloric acid and filtered. The monomethyl ether weighed 300 g. The crude material was recrystallized from 70% ethanol, melted *in vacuo*, diluted with 300 cc. of benzene and 300 cc. of 60–90° petroleum ether and allowed to crystallize overnight in the ice box. The pure material melted at 116–117° (250 g.).

*Anal.* Calcd. for $C_{19}H_{22}O_2$: $OCH_3$, 10.99. Found: $OCH_3$, 10.95, 11.05.

The **acetate**, prepared by heating with acetic anhydride, upon recrystallization from petroleum ether, melted at 115.5–116.5°.

*Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.77; H, 7.40. Found: C, 77.77; H, 7.50.

The **propionate**, prepared by reaction with propionic anhydride, upon recrystallization from petroleum ether, melted at 76–77°.

*Anal.* Calcd. for $C_{22}H_{26}O_3$: C, 78.10; H, 7.69. Found: C, 77.76; H, 7.60.

The **butyrate**, prepared by reaction with butyric anhydride, melted at 64–65°.

*Anal.* Calcd. for $C_{23}H_{28}O_3$: C, 78.41; H, 8.01. Found: C, 78.43; H, 8.00.

The **p-bromobenzoate**, prepared by reaction of (III) and *p*-bromobenzoyl chloride in pyridine, on crystallization from petroleum ether, melted at 131–131.5°.

*Anal.* Calcd. for $C_{26}H_{25}O_3Br$: C, 67.31; H, 5.42; Br, 17.17. Found: C, 66.92; H, 5.48; Br, 16.36.

Microanalyses were carried out by Mr. S. Gottlieb.

## Summary

A synthesis of diethylstilbestrol and diethylstilbestrol monomethyl ether has been described.

BELLEVILLE, N. J. RECEIVED AUGUST 31, 1944

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(8) Corse, U. S. Patent 2,325,307 (1943).