[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE]

Organotin Compounds Containing Water-Solubilizing Groups: Some *m*-Hydroxyphenyl Derivatives

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Triphenyl-*m*-hydroxyphenyltin, diphenyldi-*m*-hydroxyphenyltin, phenyltri-*m*-hydroxyphenyltin, and tetra-*m*-hydroxyphenyltin have been prepared. All are insoluble in water while their solubility in base increases as the number of hydroxyphenyl groups increases. Triphenyl-*m*-hydroxyphenyltin reacts with ethyl bromoacetate to give ethyl *m*-triphenylstannylphenoxyacetate.

Pure azo-tin dyes could not be obtained from the reaction of triphenyl-*m*-hydroxyphenyltin with *p*-bromo-, *p*-carboxy-, and *p*-nitrobenzenediazonium fluoborate in neutral or sodium carbonate buffered solutions.

A true evaluation of the merits of organotin compounds as chemotherapeutic agents has been hindered considerably by their low solubility in water. For some time, investigators in this laboratory have been concerned with increasing the water solubility of organotin compounds by introducing water-solubilizing groups into the molecule.[1,2] This report is concerned with the preparation and properties of some *m*-hydroxyphenyl derivatives of tin.

Lithium *m*-lithiophenoxide (I) was prepared by means of a halogen-metal interconversion reaction. Subsequently, (I) was carbonated and the product was identified as *m*-hydroxybenzoic acid after acidification. Although no attempt has been made to determine the optimum conditions for the preparation of (I), it has been found, through carbonation studies, that a considerably better yield of this intermediate organometallic compound was obtained when *n*-butyllithium was added to *m*-bromophenol than when these reagents were mixed in the reversed order.

Tetra-*m*-hydroxyphenyltin (II) was prepared directly by means of the reaction of (I) with anhydrous tin(IV) chloride. The following equations are illustrative of this preparation:

$$m\text{-BrC}_6\text{H}_4\text{OH} + n\text{-C}_4\text{H}_9\text{Li} \longrightarrow m\text{-BrC}_6\text{H}_4\text{OLi} + n\text{-C}_4\text{H}_{10}$$

$$m\text{-BrC}_6\text{H}_4\text{OLi} + n\text{-C}_4\text{H}_9\text{Li} \longrightarrow \underset{\text{(I)}}{m\text{-LiOC}_6\text{H}_4\text{Li}} + n\text{-C}_4\text{H}_9\text{Br}$$

$$4(m\text{-LiOC}_6\text{H}_4\text{Li}) + \text{SnCl}_4 \longrightarrow (m\text{-LiOC}_6\text{H}_4)_4\text{Sn} + 4\text{LiCl}$$

$$(m\text{-LiOC}_6\text{H}_4)_4\text{Sn} \xrightarrow{\text{NH}_4\text{Cl (aqueous)}} \underset{\text{(II)}}{(m\text{-HOC}_6\text{H}_4)_4\text{Sn}}$$

Cleavage and redistribution reactions have been reported to occur when organolithium compounds, obtained through halogen-metal interconversion reactions, are reacted with organotin halides.[1] These undesirable side reactions do not occur if the organolithium derivative is first converted to the corresponding Grignard reagent. Triphenyl-*m*-hydroxyphenyltin (III), diphenyldi-*m*-hydroxyphenyltin (IV) and phenyltri-*m*-hydroxyphenyltin (V) were prepared, therefore, from the reaction of the Grignard reagent with the appropriate organotin chloride as indicated by the equations:

$$\text{(I)} + \text{MgBr}_2 \longrightarrow m\text{-LiOC}_6\text{H}_4\text{MgBr} + \text{LiBr}$$

$$y(m\text{-LiOC}_6\text{H}_4\text{MgBr}) + (\text{C}_6\text{H}_6)_{4-y}\text{SnCl}_y \longrightarrow (m\text{-LiOC}_6\text{H}_4)_y\text{Sn}(\text{C}_6\text{H}_5)_{4-y} + y(\text{MgBrCl})$$

$$(m\text{-LiOC}_6\text{H}_4)_y\text{Sn}(\text{C}_6\text{H}_5)_{4-y} \xrightarrow{\text{NH}_4\text{Cl aqueous}} (m\text{-HOC}_6\text{H}_4)_y\text{Sn}(\text{C}_6\text{H}_5)_{4-y}$$

(III), (IV), and (V)

The crude reaction mixtures obtained from the preparation of (II), (III), (IV), and (V) had a considerable amount of *n*-butyl bromide as well as some phenolic materials present as by-products of the reaction. The *n*-butyl bromide could not be removed by distillation, for, in the vicinity of 90° extensive decomposition occurred and the resulting resin could not be purified. It was found more effective, therefore, to concentrate the hydrolyzed reaction mixture between 40 and 50° under reduced pressure in order to avoid excessive decomposition of the desired product. The decomposition observed is attributed to the cleavage of the carbon-tin bond by the acidic phenols present in the crude reaction mixture. The cleavage of groups from organotin compounds by acidic reagents is dependent upon the nature of the groups attached, with aryl groups being more readily removed than alkyl groups.[3,4] Thus, although the cleavage of tetraethyltin with phenol gave an 8% yield of cleavage product under more drastic conditions,[5] a higher degree of cleavage would be expected with the aromatic organotin compounds reported here.

The *m*-hydroxyphenyl derivatives of tin (II), (III), (IV), and (V) were all insoluble in water. Their solubility in aqueous sodium hydroxide, however, increased as the number of hydroxy groups in the molecule increased. Triphenyl-*m*-hydroxyphen-

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[1] H. Gilman and C. E. Arntzen, *J. Org. Chem.*, **15**, 994 (1950).

[2] H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, **77**, 3228 (1955).

[3] Z. M. Manulkin, *J. Gen. Chem.* (*U.S.S.R.*), **16**, 235 (1946) [*Chem. Abstr.*, **41**, 90 (1947)]; R. H. Bullard and F. R. Holden, *J. Am. Chem. Soc.*, **53**, 3150 (1931).

[4] M. S. Kharasch and A. L. Flenner, *J. Am. Chem. Soc.*, **54**, 674 (1932); Meals, *J. Org. Chem.*, **9**, 211 (1944).

[5] R. Sasin and G. S. Sasin, *J. Org. Chem.*, **20**, 770 (1955).

yltin (III) was very slightly soluble in 5% aqueous sodium hydroxide; on the other hand, diphenyldi-*m*-hydroxyphenyltin (IV), phenyltri-*m*-hydroxyphenyltin (V), and tetra-*m*-hydroxyphenyltin (II) were soluble in the same medium to the extent of approximately 10, 13, and 15 parts per hundred, respectively.

The preparation of triphenyl-*m*-hydroxyphenyltin (III) reported herein completes this series of isomeric hydroxyphenyl derivatives of tin. The other two isomers were reported earlier.[1,6] It is interesting to observe that the melting points of these three isomeric compounds do not follow the same trend that has been observed with the three isomeric dimethylaminophenyltriphenyltin compounds.[1,6,7] The melting points of both sets of isomeric compounds have been given in Table I. Triphenyl-*m*-dimethylaminophenyltin is the lowest melting isomer of this series of amino derivatives, while the corresponding hydroxy derivative (III) is the highest melting isomer of the hydroxy series.

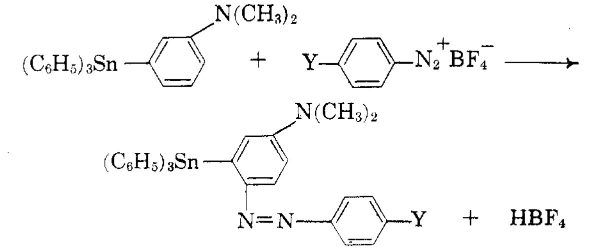
TABLE I

MELTING POINTS OF SOME ISOMERIC $Y\text{-}C_6H_4Sn(C_6H_5)_3$ COMPOUNDS

Position of Substitution	Melting Point °C. When "Y" is	
	Hydroxy group	Dimethylamino group
ortho-	dec. 176–177°	110–112°
meta-	207–208°	90–91°
para-	201–203°	132–134°

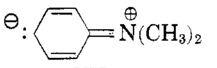
Sodium *m*-triphenylstannylphenoxide [the sodium salt of (III)] reacted smoothly with ethyl bromoacetate to give a 41% yield of ethyl *m*-triphenylstannylphenoxyacetate (VI).

Organometallic compounds of silicon,[8] tin,[1,7] and lead[9] containing an azo linkage have been prepared. The first azo-tin dye of this type to be obtained resulted from the reaction of triphenyl-*p*-dimethylaminophenyltin with *p*-nitrobenzenediazonium chloride[1] in an acetate buffered solution. Subsequent work[7] has shown that *p*-substituted benzenediazonium fluoborates could be used to advantage in reactions with triphenyl-*m*-dimethylaminophenyltin according to the equations:

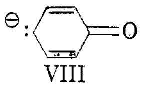


In order to explore further the scope and limitations of the formation of azo-tin dyes using *p*-substituted benzenediazonium fluoborates, this coupling reaction with triphenyl-*m*-hydroxyphenyltin (III) has been investigated. Under conditions analogous to those reported[7] for the preparation of triphenyl-3-dimethylamino-6-(4′-nitrophenylazo)-phenyltin, (III) did not couple with either *p*-bromo-, *p*-carboxy- or *p*-nitrobenzenediazonium fluoborate. The starting material (III) was recovered in yields of 86, 89.5, and 92%, respectively.

Since the coupling of diazonium salts with aromatic amines and with phenols is dependent upon the availability of resonance structures (VII) and (VIII), respectively, one finds that aromatic amines couple best in the *p*H range 4 to 7, while the phenols couple best in the range of from 5 to 9.[10] The differences observed in the behavior of (III) and triphenyl-*m*-dimethylaminophenyltin under the conditions used in *Run I* were understandable.



VII



VIII

An effort was made to move into a more favorable *p*H range for the coupling of (III). Thus, the reaction of *p*-bromo-, *p*-carboxy-, and *p*-nitrobenzenediazonium fluoborate with (III) in the presence of sodium carbonate as a buffer was investigated (*Run II*). In these reactions, the starting material (III) was recovered in yields ranging from 60 to 80%. In addition, however, a red oil was obtained in each coupling reaction attempted. Some tin-containing materials were present in these oils, as indicated by a qualitative test for tin.[11] Unfortunately, they could not be resolved into any pure components.

The possibility has been considered that a sodium or potassium salt of (III) might be used effectively in coupling reactions with *p*-substituted benzenediazonium fluoborates. Investigations of this possibility are now under way.

EXPERIMENTAL[12]

Diphenyltin dichloride.[13] In a 1-l. flask, equipped with an air condenser, were placed 214 g. (0.50 mole) of tetraphenyltin and 130.5 g. (0.50 mole) of anhydrous tin (IV) chloride. The mixture was heated gradually to 180°, over a period of 1 hr., and held at 180° for a period of 2 hr. It was cooled and crystallized from petroleum ether (b.p. 57–70°). After recrystallization from the same solvent, 274 g. (83%) of diphenyltin dichloride was obtained, melting at 42–44°. A mixture melting point with an authentic specimen was not not depressed.

Phenyltin trichloride.[13] In a 1-l. flask fitted with an air

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(6) C. E. Arntzen, *Iowa State Coll. J. Sci.*, **18**, 6 (1943) [*Chem. Abstr.*, **38**, 61 (1944)].

(7) H. Gilman and S. D. Rosenberg, *J. Am. Chem. Soc.*, **74**, 5580 (1952).

(8) S. V. Sunthankar and H. Gilman, *J. Org. Chem.*, **15**, 1200 (1950); see also B. N. Dolgov and O. K. Panina, *J. Gen. Chem.* (*U.S.S.R.*), **18**, 1129 (1948).

(9) H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, 64, 1007 (1942); 72, 4553 (1950).

(10) K. H. Saunders, "The Aromatic Diazo Compounds," 2nd Edition, Edward Arnold and Co., London, 1949, p. 196.

(11) Gilman and Goreau, *J. Org. Chem.*, **17**, 1470 (1952).

(12) All melting and boiling points are uncorrected.

(13) These procedures are based on those by B. A. Kocheshkov, *Ber.*, **62**, 996 (1926), and particularly by H. Zimmer and H. Sparmann, *Chem. Ber.*, **87**, 645 (1954). They are adapted from modifications by T. C. Wu.

condenser, a thermometer, and a mechanical stirrer were placed 177 g. (0.415 mole) of tetraphenyltin and 326 g. (1.25 moles) of anhydrous tin (IV) chloride. The reaction mixture was heated with stirring at 150° for 3 hr.; then the product was purified by distillation. Phenyltin trichloride was obtained in a 354 g. yield (71%), boiling at 96–97°/1.4 mm.

Lithium m-lithiophenoxide (I). Run I. Eighty ml. of an ethereal solution containing 0.08 mole of *n*-butyllithium was added to a cold, well stirred solution of 6.92 g. (0.04 mole) of *m*-bromophenol in 25 ml. of ether. The cooling bath was removed and the reaction mixture was stirred at room temperature for 8 hr. after the addition had been completed. The product was poured jetwise into a solid carbon dioxide-ether slurry. The carbonated mixture was hydrolyzed after it had reached room temperature, the aqueous phase was separated, and the ethereal layer was extracted with 25 ml. of 10% sodium hydroxide. The combined aqueous phase was saturated with carbon dioxide and the phenols separated by ethereal extraction. The product obtained on acidification of the aqueous layer was recrystallized from ethanol-water to yield 2.71 g. (49%) of *m*-hydroxybenzoic acid, melting at 198–199.5°. A mixture melting point with an authentic specimen showed no depression.

Run II. This run was identical with the reaction described in *Run I* with the single exception that the *m*-bromophenol was added to the *n*-butyllithium. *m*-Hydroxybenzoic acid was obtained in a crude yield of 2.22 g. (40%), melting over the range of 187–193°. Recrystallization from ethanol-water gave 2.01 g. (36.5%) of *m*-hydroxybenzoic acid melting at 195–197°.

Tetra-m-hydroxyphenyltin (II). To a cold, well stirred solution of 52 g. (0.30 mole) of *m*-bromophenol in 50 ml. of ether was added 580 ml. of an ethereal solution containing 0.60 mole of *n*-butyllithium. The reaction mixture was stirred at room temperature overnight; then a solution containing 15.5 g. (0.058 mole) of anhydrous tin (IV) chloride dissolved in 100 ml. of benzene was added. The resulting suspension was heated at the reflux temperature for a 4-hr. period, and hydrolyzed by pouring it into an ice cold solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with 200 ml. of ether. The organic layers were combined and dried for 24 hr. over calcium sulfate. The ether was removed and the *n*-butyl bromide was distilled under reduced pressure. The black oily residue was crystallized from chloroform–petroleum ether (b.p. 57–70°), with difficulty, to yield 14.0 g. (48.5%) of crude tetra-*m*-hydroxyphenyltin (II) melting between 170 and 182°. Recrystallization from a mixture (1:1) of chloroform–petroleum ether (b.p. 57–70°) gave 11.0 g. of product melting over the range of 180–184° with decomposition.

Recrystallization from a mixture of ethanol and benzene gave a product whose decomposition point depended on the rate of heating. When the melting point bath was heated at the rate of one degree per min. the compound decomposed between 170 and 173°; on the other hand, if the bath was heated at the rate of 4° per min., the product melted at 178–179° with decomposition. Further recrystallization of this product did not change the decomposition point.

Anal. Calcd. for $C_{24}H_{20}O_4Sn$: Sn, 24.17. Found:[14] Sn, 24.12, 24.22.

Triphenyl-m-hydroxyphenyltin (III). To a cold, well stirred solution of 49.5 g. (0.286 mole) of *m*-bromophenol in 60 ml. of ether was added 830 ml. of an ethereal solution containing 0.572 mole of *n*-butyllithium. The reaction mixture was stirred at room temperature for 12 hr., then treated with 450 ml. of an ethereal solution containing 0.572 mole of anhydrous magnesium bromide (I). One-half hr. later, 57 g. (0.148 mole) of triphenyltin chloride suspended in 250 ml. of ether was added. Next, the mixture was heated at the reflux temperature for a 3-hr. period and then hydrolyzed by pouring it into an ice cold solution of ammonium chloride. The organic layer was separated and dried over anhydrous sodium sulfate. The ether was removed by distillation and the residue was digested with 100 ml. of 95% ethanol; then it was cooled and filtered to remove the unreacted materials. The solid obtained was crystallized from chloroform to yield 37.9 g. (55%) of crude triphenyl-*m*-hydroxyphenyltin (III), melting over the range of 197–203°. After recrystallization from chloroform, 34.3 g. (49.5%) of pure (III), melting at 207–208°, was obtained.

Anal. Calcd. for $C_{24}H_{20}OSn$: Sn, 26.79. Found: Sn, 26.79, 26.85.

Diphenyldi-m-hydroxyphenyltin (IV). The preparation of (IV) followed the same general procedure outlined for the preparation of (III). After 69 g. (0.40 mole) of *m*-bromophenol had been treated with 0.80 mole of *n*-butyllithium, and the mixture had been stirred at room temperature overnight, 0.8 mole of anhydrous magnesium bromide in 435 ml. of ether was added. One-half hr. later, 250 ml. of an ethereal solution containing 34.4 g. (0.1 mole) of diphenyltin dichloride was added. The resulting mixture was heated at the reflux temperature for a period of 3 hr. and then hydrolyzed by slowly pouring it into an ice cold solution of ammonium chloride. The organic layer was separated and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the residue was digested with 100 ml. of 75% methanol. The solution was cooled, the methanol removed by decantation, and the residual oil was crystallized from a mixture (1:3) of chloroform–petroleum ether (b.p. 57–70°) to give 19.6 g. (42.7%) of crude (IV), melting between 180 and 187°. After two recrystallizations from petroleum ether (b.p. 57–70°), 16 g. (35%) of pure diphenyldi-*m*-hydroxyphenyltin (IV) was obtained. The melting point of this compound was somewhat dependent on the rate of heating of the bath. When the temperature of the melting point bath was raised at a rate of 4° per min., the product melted at 201–203°, whereas when the temperature of the bath was raised at a rate of 1° per min., the product melted at 189–190°.

Anal. Calcd. for $C_{24}H_{20}O_2Sn$: Sn, 25.85. Found: Sn, 25.82, 25.82.

Phenyltri-m-hydroxyphenyltin (V). The preparation of (V) followed the same general procedure outlined for the preparation of (III). After 83 g. (0.62 mole) of *m*-bromophenol had been treated with 1.24 moles of *n*-butyllithium, and the reaction mixture had been stirred at room temperature overnight, 1.30 moles of anhydrous magnesium bromide in 620 ml. of ether was added. One-half hr. later, 125 ml. of a benzene solution containing 30 g. (0.10 mole) of phenyltin trichloride was added. The mixture was heated at the reflux temperature for 4 hr., cooled, then poured slowly into an ice cold solution of aqueous ammonium chloride. The organic layer was separated and dried for 24 hr. over calcium sulfate, filtered, and concentrated, first, at atmospheric pressure, then under reduced pressure at 50°. The product was then crystallized from a (1:1) mixture of chloroform–petroleum ether (b.p. 57–70°) to yield 23.2 g. (48%) of crude (V), melting over the range 140–152°. After two recrystallizations from the same solvent pair, 19.3 g. (40.5%) of pure product was obtained, melting at 203–205°.

Anal. Calcd. for $C_{24}H_{20}O_3Sn$: Sn, 24.98. Found: Sn, 24.93, 24.96.

Ethyl m-triphenylstannylphenoxyacetate (VI). Five-tenths of a gram (0.022 mole) of freshly cut sodium was dissolved in 25 ml. of absolute ethanol, and the resulting solution was added slowly to a well stirred solution of 8.86 g. (0.02 mole) of triphenyl-*m*-hydroxyphenyltin (III) in 200 ml. of absolute ethanol. To the resulting suspension of sodium *m*-triphenylstannylphenoxide was added 5 g. (0.03 mole) of ethyl bromoacetate, and the mixture was heated at the reflux temperature for a period of 2 hr. It was then concentrated by distillation until crystals began to form and then drowned with

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[14] The organotin compounds were analyzed by decomposing a sample with concentrated sulfuric acid followed by ignition to stannic oxide according to a recently described procedure by H. Gilman and S. D. Rosenberg, *J. Am. Chem. Soc.*, **75**, 3692 (1953).

TABLE II

PREPARATIVE DETAILS ON THE ATTEMPTED COUPLING OF TRIPHENYL-*m*-HYDROXYPHENYLTIN IN A NEUTRAL MEDIUM

Benzene Diazonium Fluoborate	Grams	Mole	Over-all Reaction Time	Grams of (III) Recovered	Yield of (III) Recovered	M.P. of (III) Recovered
p-Bromo-	2.71	0.01	4 hr.	3.80	86%	203–205°
p-Carboxy-	2.36	0.01	4 hr.	3.98	89.5%	202–205°
p-Nitro-	2.37	0.01	3 hr.	4.09	92%	201–205°

TABLE III

PREPARATIVE DETAILS ON THE ATTEMPTED COUPLING OF TRIPHENYL-*m*-HYDROXYPHENYLTIN IN A SODIUM CARBONATE BUFFERED MEDIUM

Benzene Diazonium Fluoborate	Grams	Mole	Over-all Reaction Time	Grams of Red Oil Obtained	Grams of (III) Recovered	Yield of (III) Recovered	M.P. of (III) Recovered
p-Bromo-	2.71	0.01	4 hr.	1.83	2.90	67%	201–204°
p-Carboxy-	2.36	0.01	4 hr.	1.61	2.81	63%	201–204°
p-Nitro-	2.37	0.01	4 hr.	0.91	3.51	79%	199–204°

water. The precipitated solid was removed by filtration and recrystallized from ethanol to give 6.5 g. (41%) of crude (VI) melting between 91 and 95°. After two recrystallizations from 95% ethanol, 5.1 g. (32%) of pure product was obtained, melting at 97–98°.

Anal. Calcd. for $C_{28}H_{26}O_3Sn$: Sn, 22.43. Found: Sn, 22.62, 22.56.

Reactions of triphenyl-m-hydroxyphenyltin with p-substituted benzenediazonium fluoborates. Run I: In the absence of a buffer. In a 600-ml. beaker was placed 4.43 g. (0.01 mole) of triphenyl-*m*-hydroxyphenyltin (III) dissolved in 60 ml. of dioxane. The solution was cooled in ice and a solution containing 0.01 mole of the *p*-substituted benzenediazonium fluoborate dissolved in 300 ml. of a 50% dioxane-water was added dropwise, with vigorous stirring. No color changes occurred. The ice bath was removed and the reaction mixture was stirred at room temperature for 2 hr. and then poured into 500 ml. of ice water. The product was removed by filtration and purified by recrystallization from a mixture (1:1) of chloroform–petroleum ether (b.p. 57–70°). The products obtained from the reaction of *p*-bromo-, *p*-carboxy-, and *p*-nitrobenzenediazonium fluoborate with (III) have been given in Table II along with other pertinent data.

Run II: Sodium carbonate buffered medium. In a 600-ml. beaker was placed 4.43 g. (0.01 mole) of triphenyl-*m*-hydroxyphenyltin (III) in 100 ml. of dioxane. To this was added 3.2 g. (0.03 mole) of sodium carbonate in 30 ml. of water. Then 0.01 mole of the *p*-substituted benzenediazonium fluoborate dissolved in 300 ml. of a 50% solution of dioxane-water was added dropwise. Two hr. after the addition had been completed, the mixture was poured into 500 ml. of ice water and the product was separated by carefully decanting off the water layer. The deep red, oily solid obtained was recrystallized twice from methanol and then once from chloroform to obtain the recovered (III) reported in Table III. On concentration of the mother liquors of recrystallization, a red viscous oil was obtained. This red oil gave a qualitative test[11] for tin. Attempts to isolate a pure product from this oil by crystallization as well as by chromatography were unsuccessful.

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