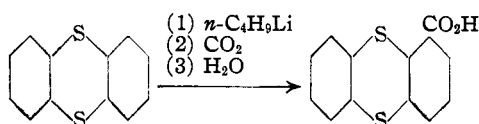


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

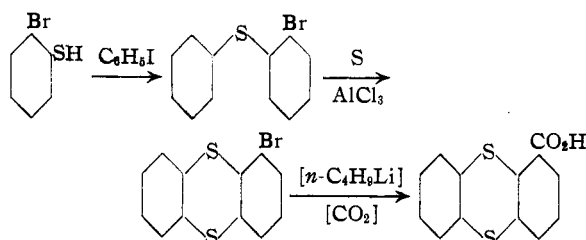
The Metalation of Thianthrene and Dibenz-*p*-dioxin¹

BY HENRY GILMAN AND C. G. STUCKWISCH

In the course of some studies on the metalation of polynuclear heterocyclic systems,^{2a,b} the metalation of thianthrene and dibenzo-*p*-dioxin by RLi compounds has been investigated. On the basis of earlier observations, it might have been predicted that the metalation of thianthrene would take place in the 1-position, or *ortho* to the hetero element. However, since notable exceptions to this generalization have been found in some sulfur-containing compounds,^{2b,c} the other position might have been involved. Actually, the metalation by *n*-butyllithium gave, subsequent to carbonation and hydrolysis, 1-thianthrenecarboxylic acid.



The structure of the acid was established as follows



Also the aminothianthrene obtained from thianthrenyllithium and α -methylhydroxylamine proved to be different from Krishna's^{2a} 2-aminothianthrene, the only other possible isomeric amine.

Bennett, Lesslie and Turner^{3b} had previously prepared a monocarboxylic acid of thianthrene by the action of phenylethylcarbonyl chloride and subsequent hydrolysis. We prepared some of the acid described by them and found it to be unlike the acid obtained by metalation. They did not establish the structure of their acid, and our

(1) Paper LI in the series "Relative Reactivities of Organometallic Compounds"; the preceding paper is in *J. Org. Chem.*, **8** (1943).

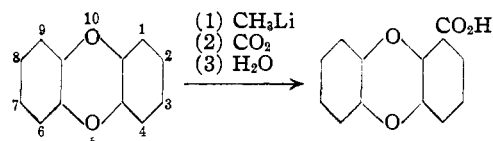
(2) (a) Gilman and Bebb, *THIS JOURNAL*, **61**, 109 (1939); (b) Gilman, Van Ess, Willis and Stuckwisch, *ibid.*, **62**, 2606 (1940); (c) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); Gilman, Jacoby, and Pacevitz, *ibid.*, **3**, 120 (1938); Gilman and Webb, *THIS JOURNAL*, **62**, 987 (1940).

(3) (a) Krishna, *J. Chem. Soc.*, **123**, 156 (1923); (b) Bennett, Lesslie and Turner, *ibid.*, 444 (1937).

metalation study shows that their acid was 2-thianthrenecarboxylic acid.

In one of our early experiments on the metalation of thianthrene we isolated and identified *n*-butyl mercaptan, di-*n*-butyl sulfide, and di-*n*-butyl tetrasulfide. The formation of these sulfur compounds was attributed to cleavage reactions effected by the *n*-butyllithium. However, we showed subsequently that the butyl-sulfur compounds were due to a reaction between sulfur and *n*-butyllithium. A careful purification of thianthrene is required to remove the sulfur used in its synthesis.

Dibenzo-*p*-dioxin.—Metalation of dibenzo-*p*-dioxin by *n*-butyllithium proceeds more intensively than the corresponding reaction with thianthrene, and leads largely to the formation of di-metalation products. For this reason, we turned to methylithium which is a distinctly milder metalating agent. The acid obtained from this reaction, subsequent to carbonation and hydrolysis, was shown to be unlike the dibenzo-*p*-dioxin-2-carboxylic acid prepared earlier by Tomita^{4a} by reliable ring closure synthesis. He also prepared the 2-acid by oxidation of the product resulting from the reaction of phthalylglycyl chloride with dibenzo-*p*-dioxin in the presence of aluminum chloride. We prepared some of the 2-acid by the latter procedure, and a comparison with our metalation acid showed the compounds to be different. This establishes the structure of the metalation acid



and is in agreement with the earlier generalizations² that metalation takes place *ortho* to oxygen in a heterocycle.

On the basis of *o*-metalation of an oxygen heterocycle, three structures are possible for the dibasic acids obtained when dibenzo-*p*-dioxin is metalated by *n*-butyllithium. These are the 1,4-diacid, the 1,6-diacid, and the 1,9-diacid. An at-

(4) (a) Tomita, *J. Pharm. Soc. Japan*, **56**, 814 (1936); **57**, 609 (1937) [*C. A.*, **32**, 8426 (1938); **33**, 2898 (1939)]; (b) *ibid.*, **52**, 429 (1932) [*C. A.*, **26**, 4589 (1932)].

tempt was made to synthesize the 1,6-diacid by the dry distillation of the sodium salt of methyl 3-bromosalicylate. The negative results were probably due in this case to steric hindrance.

Experimental

Preparation of *n*-Butyllithium.—It has been observed that *n*-butyllithium can be prepared in a shorter time and in an improved yield by a simple cooling operation. *n*-Butyl bromide was added to lithium suspended in ether until a rapid rate of reflux was obtained. The reaction flask was then immersed in an ice-water-bath and the *n*-butyl bromide was added at a rate to maintain gentle refluxing. When all the RX compound had been added, the cooling bath was removed and stirring was continued until refluxing ceased. In preparations using 0.3 mole of *n*-butyl bromide, the time of preparation was reduced from two and one-half hours to forty minutes, and the average yield was increased by 10%.

A chief disadvantage of this procedure is the formation of a large quantity of colloidal lithium which makes filtration to a clear solution more difficult. The general results obtained in the preparation of methylithium and ethyllithium are comparable to those reported for *n*-butyllithium. With aryllithium compounds, the cooling procedure is successful with anisyl types, but apparently not worth while with *p*-dimethylaminophenyllithium.

Metalation of Thianthrene.—After refluxing a solution of 8.64 g. (0.04 mole) of thianthrene⁵ and 0.08 mole of *n*-butyllithium in 250 cc. of ether for twenty-four hours, the mixture was poured upon solid, crushed carbon dioxide. Extraction with 10% potassium hydroxide followed by acidification with concd. hydrochloric acid yielded 6.5 g. of a solid melting between 190 and 198°. This mixture of mono- and dibasic acids was triturated with benzene to remove the mono-acid, which melted at 217–218° after crystallization from ethanol.

Anal. Calcd. for C₁₂H₈O₂S₂: S, 24.42; neut. equiv., 262. Found: S, 24.34; neut. equiv., 261.5.

Decarboxylation of the 1-thianthrenecarboxylic acid gave thianthrene (mixed m. p.).

1-Bromothianthrene.—First *o*-bromothiophenol⁶ was prepared in 55% yield. From this was obtained *o*-bromodiphenyl sulfide as follows. *o*-Bromothiophenol (18.9 g., 0.1 mole) was dissolved in 75 cc. of ethanol containing 6 g. of potassium hydroxide. The ethanol was removed by distillation, and to the residue was added 100 cc. of xylene, 0.5 g. of copper bronze, and 31.5 g. (0.15 mole) of iodobenzene. After stirring and refluxing the mixture for twenty hours, cooling, washing with 10% potassium hydroxide and with water, the organic layer was dried over sodium sulfate and then distilled to yield 17.3 g. (65%) of *o*-bromodiphenyl sulfide distilling at 203° (6 mm.).

The 1-bromothianthrene (m. p. 145°) was prepared in 20% yield from *o*-bromodiphenyl sulfide in essential accordance with the preparation of thianthrene⁵ from diphenyl sulfide, sulfur, and aluminum chloride.

Anal. Calcd. for C₁₂H₇S₂: Br, 27.02; S, 21.69. Found: Br, 27.13; S, 21.53.

1-Bromothianthrene and *n*-Butyllithium.—To a solution of 0.032 mole of *n*-butyllithium in 50 cc. of ether was added slowly with stirring 2.95 g. (0.01 mole) of 1-bromothianthrene in 30 cc. of benzene. When addition was completed, the solution was stirred and refluxed for 15 minutes, and then poured on crushed, solid carbon dioxide. The yield of acidic material was 1.8 g. or 50%. After crystallization from dilute ethanol the acid melted at 213–215°, and showed no depression in mixed m. p. with the acid obtained by metalation of thianthrene.

1-Thianthrenyllithium and α -Methylhydroxylamine.—To a solution of 0.2 mole of *n*-butyllithium in 250 cc. of ether was added 21.6 g. (0.1 mole) of thianthrene. The mixture was stirred and heated at reflux temperature for twenty hours. Analysis showed the solution to contain 0.08 mole of RLi compound. After adding slowly to this solution, 1.25 g. (0.0266 mole) of α -methylhydroxylamine⁷ in 10 cc. of ether, cooled in an ice-bath, Color Test I⁸ showed reaction to be complete in one hour. Subsequent to hydrolysis, the ether layer was separated, dried, and treated with dry hydrogen chloride to precipitate 5.5 g. (75%) of the crystalline amine hydrochloride which melted with decomposition at 231°. The 1-aminothianthrene obtained from the hydrochloride by the action of dilute ammonium hydroxide melted at 139° after crystallization from dilute ethanol.

Anal. Calcd. for C₁₂H₇NS₂: N, 6.66. Found: N, 6.62.

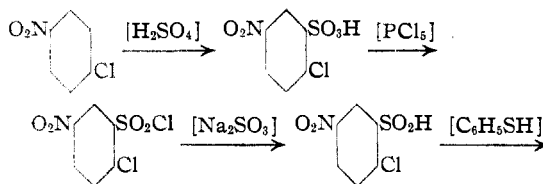
1-N⁴-Acetylsulfanilamidothianthrene.—To a solution of 2.31 g. (0.01 mole) of 1-aminothianthrene in 25 cc. of acetone was added 2.9 g. (0.012 mole) of *p*-acetaminobenzenesulfonyl chloride and 5 cc. of pyridine.⁹ After standing for several hours, the mixture was diluted with 200 cc. of water, and the precipitate which separated was washed successively with 5% sodium carbonate solution, 10% hydrochloric acid, and water. Crystallization from dilute ethanol gave 2.5 g. (58%) of the sulfanilamide compound which melted at 154°.

Anal. Calcd. for C₂₀H₁₅O₃N₂S₃: N, 6.57. Found: N, 6.45.

1-Sulfanilamidothianthrene.—The acetyl derivative was hydrolyzed by boiling for one hour with 10% sodium hydroxide to give an 80% yield of compound which decomposed when heated above 120°.

Anal. Calcd. for C₁₅H₁₄O₂N₂S₃: N, 7.29. Found: N, 7.21.

2-Aminothianthrene.—This amine was prepared by the following transformations, in essential accordance with the procedure of Krishna.^{3a} The yields for these steps, none of which was reported,^{3a} are as follows: sulfonation of *p*-



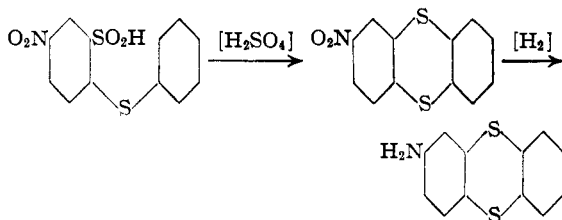
(7) Sheverdina and Kochechkov, *J. Gen. Chem.* (U. S. S. R.), **8**, 1825 (1938).

(8) Gilman and Schulze, *THIS JOURNAL*, **47**, 2002 (1925).

(9) Winterbottom, *ibid.*, **62**, 160 (1940).

(5) Dougherty and Hammond, *THIS JOURNAL*, **57**, 117 (1935).

(6) Schwarzenbach and Egli, *Helv. Chim. Acta*, **17**, 1176 (1934).



nitrochlorobenzene, 88%; preparation of the sulfonyl chloride, 96%; reduction of the sulfonyl chloride, 84%; condensation with thiophenol, 90%; dehydration, 95%; and reduction of 2-nitrothianthrene, 78%.

2-N⁴-Acetylsulfanilamidothianthrene.—This compound was prepared by a procedure identical with that used for the 1-aminothianthrene. The yield was 62%; and the melting point after two crystallizations from dil. ethanol was 163°.

Anal. Calcd. for C₂₀H₁₆O₃N₂S₃: N, 6.57. Found: N, 6.49.

2-Sulfanilamidothianthrene.—Hydrolysis of the acetyl compound by boiling for one hour with 10% sodium hydroxide gave an 85% yield of 2-sulfanilamidothianthrene which decomposed when heated above 125°.

Anal. Calcd. for C₁₈H₁₄O₂N₂S₃: N, 7.29. Found: N, 7.14.

4-N⁴-Acetylsulfanilamidophenoxathiin.—When 4-aminophenoxathiin^{1b} was treated with *p*-acetaminobenzene-sulfonyl chloride as described above there resulted an 81% yield of the product which melted at 192°.

Anal. Calcd. for C₂₀H₁₆O₄N₂S₂: N, 6.82. Found: N, 6.75.

4-Sulfanilamidophenoxathiin.—Hydrolysis of the acetyl derivative by boiling for one hour with 10% sodium hydroxide gave an 87% yield of the de-acylated product which melted at 168° after several recrystallizations from dilute ethanol.

Anal. Calcd. for C₁₈H₁₄O₃N₂S₂: N, 7.61. Found: N, 7.69.

***n*-Butyllithium and Sulfur.**—From one of the first reactions between thianthrene and *n*-butyllithium there were isolated and identified the following compounds: *n*-butyl mercaptan, di-*n*-butyl sulfide, and di-*n*-butyl tetrasulfide. An authentic specimen of the tetrasulfide was prepared from *n*-butyl mercaptan and sulfur chloride in accordance with the directions of Bezzi.¹⁰ However, when the thianthrene was subsequently purified by digestion with concd. sodium hydroxide prior to crystallization from glacial acetic acid, there was no formation of mercaptans and sulfides. Mr. R. V. Christian has shown that *n*-butyllithium reacts with sulfur to give a mixture of mercaptans, sulfides, and polysulfides.

Preparation of Dibenzo-*p*-dioxin.—This compound has been synthesized from pyrocatechol and *o*-dibromobenzene, and by the condensation of potassium *o*-bromophenoxide in the presence of copper acetate at 200°. ^{4b} A less expensive and more convenient procedure is the dry distillation of sodium *o*-chlorophenoxide.¹¹

(10) Bezzi, *Gazz. chim. ital.*, **65**, 693 (1935) [*C. A.* **30**, 2171 (1936)].

(11) The authors are grateful to Dr. E. Britton for suggestions and for a liberal supply of *o*-chlorophenol.

Sodium hydroxide (40 g., 1.0 mole) was dissolved in a minimum volume of methanol. To this solution was added 128 g. (1.0 mole) of *o*-chlorophenol. The sodium salt of the phenol was precipitated by the addition of petroleum ether (b. p. 68–76°). The dry salt was placed in a Claisen flask provided with a 16 mm. side-arm. The flask was evacuated to 4 mm. and gradually heated in a metal bath to 250°. Thirty-one grams or a 37% yield of dibenzo-*p*-dioxin was distilled in this manner. Crystallization from ethanol gave 27 g. of pure product melting at 119°.

Dimetalation of Dibenzo-*p*-dioxin.—To a solution of 0.25 mole of *n*-butyllithium in 300 cc. of ether was added 18.4 g. (0.1 mole) of dibenzo-*p*-dioxin. The mixture was stirred and refluxed for twelve hours. After carbonation there was isolated by conventional procedures, 15 g. of acidic material melting between 213–230°. Crystallization from various solvents did not appreciably alter the melting point range. Accordingly, the acidic mixture was esterified with methanol in the presence of dry hydrogen chloride. Twelve grams of the acidic material yielded 10 g. of esterified product melting between 97–130°. Extraction by ether of the mixture of esters yielded 6 g. of an ether-soluble fraction which melted at 142–143°. Hydrolysis of this ester gave 5.5 g. or 20% of an acid melting at 297–298°.

Anal. Calcd. for C₁₄H₈O₆: neut. equiv., 136. Found: neut. equiv., 140.

Decarboxylation of the acid in the presence of soda-lime gave dibenzo-*p*-dioxin (mixed m. p.).

The ether insoluble fraction (3 g.) which melted from 175 to 190° was extracted with 95% ethanol, and the ethanol insoluble material (2 g.) melted at 202–204°. Hydrolysis of this compound gave 1.8 g. (7%) of an acid which did not melt at 335°.

Anal. Calcd. for C₁₄H₈O₆: neut. equiv., 136. Found: neut. equiv., 142.

Decarboxylation of this dibasic acid yielded dibenzo-*p*-dioxin (mixed m. p.).

When equivalent quantities of *n*-butyllithium and dibenzo-*p*-dioxin were used in the metalation, the yield of dibasic acids was reduced by 50%. However, the lower melting material obtained by this procedure, presumably mono-basic acid, could not be purified.

Monometalation of Dibenzo-*p*-dioxin.—To a solution of 0.05 mole of methylithium in 100 cc. of ether was added 5.5 g. (0.03 mole) of dibenzo-*p*-dioxin. The solution was stirred and refluxed for seven hours. Subsequent to carbonation, the reaction mixture was worked up by conventional procedures to yield 0.7 g. (10%) of an acid melting at 210°.

Anal. Calcd. for C₁₃H₈O₄: neut. equiv., 228. Found: neut. equiv., 230.

Decarboxylation of the acid gave dibenzo-*p*-dioxin (mixed m. p.).

The methyl ester, prepared from the acid and diazomethane, melted at 86°.

Anal. Calcd. for C₁₄H₁₀O₈: C, 69.42; H, 4.13. Found: C, 69.38; H, 4.19.

Methyl 3-Bromosalicylate.—3-Bromosalicylic acid was

prepared in essential accordance with the three-stage procedure of Meldrum and Shah.¹²

The methyl ester was prepared from the acid with methanol and hydrogen chloride in 92% yield. After crystallization from dilute methanol, the ester melted at 62°.

Anal. Calcd. for C₈H₇O₃Br: Br, 34.6. Found: Br, 34.4.

In an attempt to prepare dibenzo-*p*-dioxin-1,6-dicarboxylic acid, there was added to a solution made up by dissolving one g. of sodium in 10 cc. of methanol, 9.2 g. (0.04 mole) of methyl 3-bromosalicylate. The methanol was removed at reduced pressure, and the residue was subjected to dry distillation. The material gradually charred and no product distilled when the bath temperature reached 300°.

(12) Meldrum and Shah, *J. Chem. Soc.*, **123**, 1990 (1923). We had no appreciable success in preparing the acid by the method of Sen and Ray, *J. Indian Chem. Soc.*, **9**, 173 (1932).

Summary

Metalation of thianthrene by *n*-butyllithium followed by carbonation and hydrolysis, gives 1-thianthrenecarboxylic acid, the structure of which was established by a ring-closure synthesis. Accordingly, the other thianthrenecarboxylic acid prepared by earlier workers by a modified Friedel-Crafts reaction must be the 2-acid. Incidentally, it was shown that sulfur with *n*-butyllithium gives *n*-butyl mercaptan, di-*n*-butyl sulfide, and di-*n*-butyl tetrasulfide.

Dibenzo-*p*-dioxin is mono-metalated by methyl-lithium in the 1-position. With *n*-butyllithium, two dimetalation products are formed.

AMES, IOWA

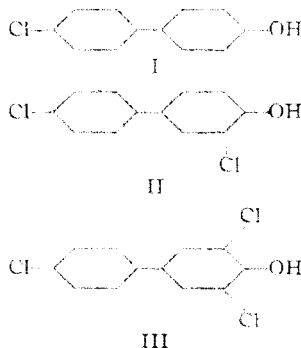
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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF TEXAS AND SOUTHWESTERN LOUISIANA INSTITUTE]

Studies in the Biphenyl Series. III. The Attempted Chlorination of the Acetate, Benzoate and Benzenesulfonate of 4-(4-Chlorophenyl)-phenol: 2-Chloro-4-(4-chlorophenyl)-phenol¹

BY CORA MAY SEGURA SAVOY¹ AND JOHN LEO ABERNETHY

In connection with the study of the relationship of bactericidal activity² to structure of certain halogenated phenylphenols it was desirable to prepare 2-chloro-4-(4-chlorophenyl)-phenol (II). This was readily accomplished by chlorination of 4-(4-chlorophenyl)-phenol (I). Further chlorination gave rise to the known 2,6-dichloro-4-(4-chlorophenyl)-phenol (III), which incidentally served to prove the structure of II.



(1) The main portion of this investigation was the subject of a research course taken by Mrs. Savoy while working toward the degree of Master of Arts at the University of Texas. Present address: Department of Chemistry, Southwestern Louisiana Institute, Lafayette, Louisiana.

(2) Professor O. B. Williams of the Department of Bacteriology of the University of Texas is directing the testing of the phenol coefficients of these substances in an independent investigation.

In previous investigations,³ in this series it has been demonstrated that chlorination of the 4-phenylphenyl esters introduces chlorine in the 4'-position of the biphenyl nucleus. It was of interest to see if utilization of these same mild chlorinating conditions would introduce chlorine ortho to the ester linkage, if the 4'-position was already substituted with chlorine. Hence the acetate, benzoate and benzenesulfonate of II were subjected to the chlorination procedure, using iodine as the catalyst and carbon tetrachloride as the solvent. None of the anticipated esters resulted. This would lend support to the view that the ester linkage hinders the 3-position.

Although none of the 2-chloro-4-(4-chlorophenyl) esters were identified in the reaction products of the chlorination of the esters of II, these esters were readily prepared by respective acetylation, benzoylation and benzenesulfonation of I.

Acknowledgment.—The authors are indebted to the Research Institute of the University of Texas for a grant which made this investigation possible. We are indebted to Professor H. R. Henze for assistance during the progress of this investigation.

(3) Savoy and Abernethy, *THIS JOURNAL*, **64**, 2219, 2719 (1942).