

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Metalation of 4-*t*-Butyldiphenyl Sulfone with *n*-Butyllithium¹

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The metalation of 4-*t*-butyldiphenyl sulfone by *n*-butyllithium results in introduction of the lithium atom in the positions *ortho* to the sulfone group, 69% of the metalation occurring in the unsubstituted ring and 31% in the ring containing the *t*-butyl group. This orientation is due to the deactivating influence toward metalation exerted by the *t*-butyl group through its inductive effect.

A large amount of experimental data has accumulated on the position of metalation of aromatic and heterocyclic nuclei by organoalkali compounds. These results have been rather well correlated by a mechanistic picture of the reaction involving nucleophilic² or perhaps better "protophilic"³ attack by the alkyl carbanion assisted by the metal cation. This picture further states that the principal factor controlling orientation and reactivity in the molecule being metalated is the inductive effect of substituents already present in the ring in increasing or decreasing the polarity of the carbon-to-hydrogen bonds at the various positions. Thus, such otherwise unrelated materials as trifluoromethylbenzene,² anisole,⁴ diphenyl sulfone⁵ and resorcinol dimethyl ether⁶ all metalate in the position *ortho* to the substituent(s) present due to the inductive electron-withdrawing tendency of the substituents allowing maximum polarization at the adjacent C-H bond.

An important test of these ideas has been offered in the metalation of compounds containing electron-releasing alkyl substituents. Conflicting reports have appeared in the literature on the results of metalation of isopropylbenzene. Morton and co-workers^{7,8} reported *ortho* and *para* metalation while Bryce-Smith³ indicated *meta* and *para* attack. These workers^{3,8} agree that *t*-butylbenzene metalates predominantly in the *p*-position and Bryce-Smith has shown by intermolecular competitive metalation that benzene is metalated in preference to *t*-butylbenzene.

It is the purpose of this paper to present some new evidence that the *t*-butyl group deactivates the ring to which it is attached. In order to do this we have adopted the technique used by Truce^{5,9} involving an intramolecular competition reaction on a monosubstituted diphenyl sulfone, namely, 4-*t*-butyldiphenyl sulfone. The sulfone group activates strongly the adjacent rings toward metalation, and the ratio of metalation in the two rings reflects the influence of a substituent present in the *p*-position of one ring. Thus Truce⁹ was able to demonstrate that the methyl group of phenyl *p*-tolyl sulfone caused a larger amount of metalation to occur

in the unsubstituted ring. If the metalation reaction is under the control of the inductive effect of groups already present in the ring, then the *t*-butyl group should show a stronger deactivation of the ring to which it is attached than that shown by the methyl group.

The metalation of 4-*t*-butyldiphenyl sulfone (I) (0.024 mole) was carried out with 0.010 mole of *n*-butyllithium at 0° for 15 minutes. The mixture was carbonated and the resulting mixed carboxylic acids isolated without disturbing the isomer ratio by crystallization. Neutralization equivalents of the mixed metalation acids indicated no dicarboxylic acid to be present. It was necessary to carry out the metalation so as to avoid demetalation since: (1) separation of the dicarboxylic acid might involve some loss of monocarboxylic acid and (2) further metalation of the monometalated product would probably occur at different rates in the two isomers thus disturbing the isomer ratio. Construction of a melting point-composition diagram using synthetic samples of 4-*t*-butyl-2'-carboxydiphenyl sulfone (II) and 4-*t*-butyl-2-carboxydiphenyl sulfone (III) indicated the mixed monocarboxylic acids from metalation to consist of 69% II and 31% III. Thus metalation of I occurs somewhat more than twice as fast in the unsubstituted benzene ring and this substantiates the idea that the *t*-butyl group deactivates the ring to which it is attached. This deactivation is greater than that exhibited by a methyl group, since Truce and Norman⁹ have shown that the metalation of 4-methyldiphenyl sulfone occurs 59% in the unsubstituted ring and 41% in the methyl substituted ring. It should be pointed out that these latter experiments were carried out so that at least 9 mole per cent. of dicarboxylic acid was formed and separated. The mixed monocarboxylic acids were subjected to crystallization before analysis, and no neutralization equivalent or other data were presented to show the ab-

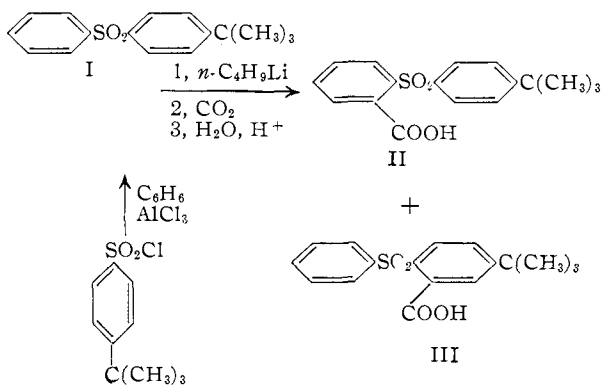


Fig. 1.

(1) From a dissertation presented by Erwin A. Lehto in partial fulfillment of the requirements for the Ph.D. degree at the University of Tennessee.

(2) J. D. Roberts and D. Y. Curtin, *THIS JOURNAL*, **68**, 1658 (1946).

(3) D. Bryce-Smith, *J. Chem. Soc.*, 1079 (1954).

(4) H. Gilman and R. L. Bebb, *THIS JOURNAL*, **61**, 109 (1939).

(5) W. E. Truce and M. F. Amos, *ibid.*, **73**, 3013 (1951).

(6) H. Gilman, H. B. Willis, T. H. Cook, F. J. Webb and R. N. Meals, *ibid.*, **62**, 667 (1940).

(7) A. A. Morton, J. T. Massengale and M. L. Brown, *ibid.*, **67**, 1620 (1945).

(8) A. A. Morton and E. L. Little, *ibid.*, **71**, 487 (1949).

(9) W. E. Truce and O. L. Norman, *ibid.*, **78**, 6023 (1953).

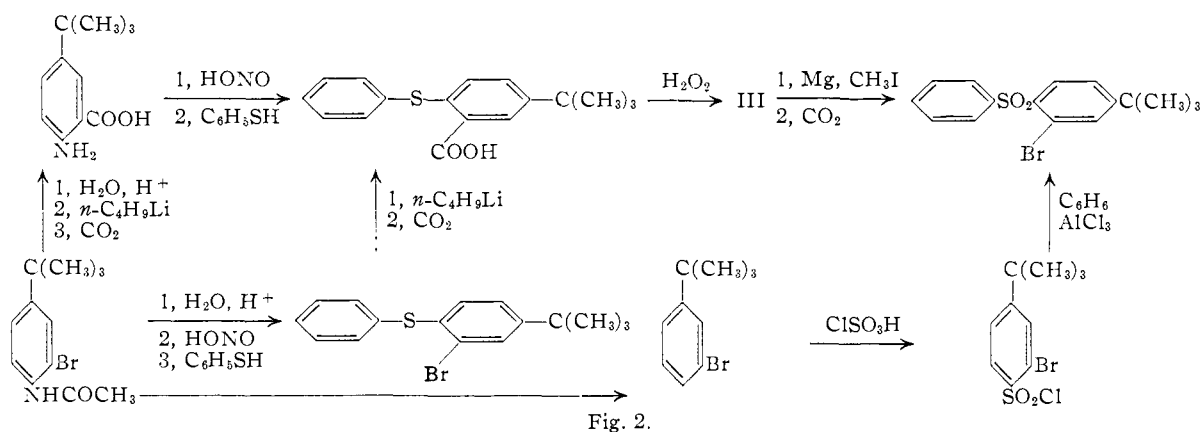


Fig. 2.

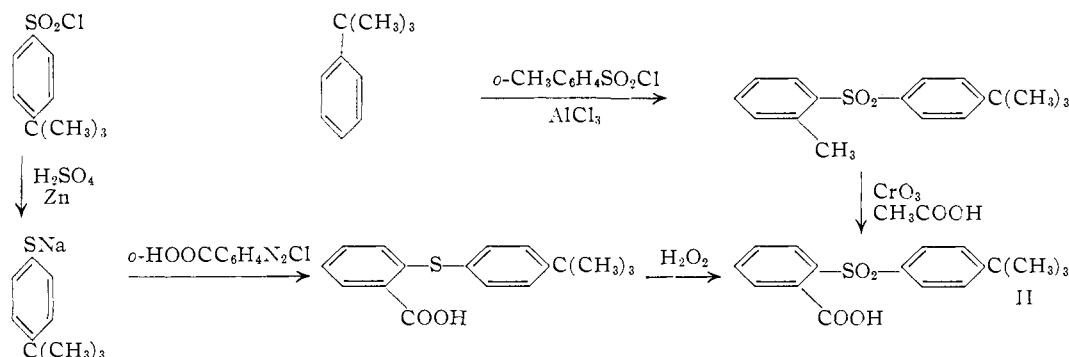


Fig. 3.

sence of some dicarboxylic acid in this fraction. Consequently, the results of our experiments and those of Truce and Norman⁹ may not be strictly comparable.

The acid III was synthesized by three independent routes (Fig. 2) of which only the method starting from 2-bromo-4-*t*-butylaniline and proceeding through the halogen-metal interconversion reaction¹⁰ of 2-bromo-4-*t*-butyldiphenyl sulfide and *n*-butyllithium gave the product in good yield. The isomeric acid II was prepared by two independent routes as indicated in Fig. 3. The route involving coupling of sodium *p*-*t*-butylthiophenolate with diazotized anthranilic acid was the better one.

The authors wish to express their appreciation to the Research Corporation of New York for financial support of this investigation.

Experimental¹¹

***p*-*t*-Butylbenzenesulfonyl Chloride.**—The chlorosulfonation of *t*-butylbenzene followed the general procedure of Huntress and Carten.¹² To 67 g. (0.5 mole) of *t*-butylbenzene in 150 ml. of chloroform at 0° was added dropwise with stirring 175 g. (1.5 moles) of chlorosulfonic acid. After the chlorosulfonic acid had been added, the reaction mixture was allowed to warm slowly (12 hours) to room temperature with stirring. It was then poured over an excess of ice and the resulting organic and aqueous layers separated. The aqueous layer was extracted once with chloroform and the combined chloroform solutions washed with water. The volume of the chloroform solution was reduced by evaporation on the steam-bath, the solution cooled and

(10) R. G. Jones and H. Gilman in R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.

(11) Melting and boiling points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn., and Weiler and Strauss, Oxford, England.

(12) E. H. Huntress and F. H. Carten, THIS JOURNAL, **62**, 511 (1940)

crystallization allowed to occur. The crystallized solid weighed 93.5 g. (81%) and melted at 78–80° after drying *in vacuo* over concentrated sulfuric acid. Another preparation carried out in a similar fashion resulted in a 77% yield of the sulfonyl chloride.

A small amount of the sulfonyl chloride was converted to the sulfonamide which melted at 135–136° after crystallization from aqueous ethanol. The reported¹³ m.p. is 136–137°.

4-*t*-Butyldiphenyl Sulfone.—A solution of 58.1 g. (0.25 mole) of *p*-*t*-butylbenzenesulfonyl chloride in 300 ml. of benzene was placed in a 1-l. round-bottomed flask fitted with mechanical stirrer and reflux condenser. To this solution was added slowly with stirring 75 g. of anhydrous aluminum chloride. The reaction mixture was stirred at room temperature for one hour and then heated to reflux for two hours on the steam-bath. It was poured over an excess of ice and the unreacted benzene removed by steam distillation. The residue from the distillation, after two recrystallizations from methanol, weighed 49.2 g. (75%) and melted at 129–130°. Another run carried out in a similar manner resulted in a 68% yield.

Anal. Calcd. for C₁₆H₁₈O₂S: C, 70.07; H, 6.57. Found: C, 70.03, 69.84; H, 6.46, 6.76.

The method of preparation given above was found superior in yield of product to the Friedel-Crafts reaction of benzenesulfonyl chloride and *t*-butylbenzene.

Metalation of 4-*t*-Butyldiphenyl Sulfone.—To a well-stirred suspension of 6.7 g. (0.024 mole) of 4-*t*-butyldiphenyl sulfone in 250 ml. of dry ether at ice-bath temperature was added slowly 0.010 mole of an ethereal solution of *n*-butyllithium.¹⁴ A nitrogen atmosphere was used. After the *n*-butyllithium had been added, the reaction mixture was stirred at ice-bath temperature for 15 minutes and then carbonated by the addition of crushed solid carbon dioxide directly into the reaction flask. After removal of the ether and carbon dioxide, the residue was treated with water and filtered. The insoluble material weighed 5.7 g. and was unreacted sulfone melting at 128–130°. The aqueous filtrate

(13) E. H. Huntress and J. S. Autenrieth, *ibid.*, **63**, 3446 (1941).

(14) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, *ibid.*, **71**, 1499 (1949).

was extracted with ether and acidified with dilute hydrochloric acid. The resulting aqueous mixture was extracted with ether and the ether extract washed twice with water. The ether layer was extracted with dilute aqueous sodium carbonate and the sodium carbonate extract acidified with dilute hydrochloric acid. The precipitated colorless semi-solid was extracted with ether, the ether extract washed three times with cold water and dried over anhydrous sodium sulfate. After removal of the ether, the residue was dried *in vacuo* over anhydrous calcium chloride. After a short time, it partially crystallized. This material still possessed the odor of valeric acid and it was heated on the steam-bath with 200 ml. of water. The residue liquefied and on continued heating, a colorless solid separated. A further treatment with 200 ml. of water in a similar manner, followed by collection of the solid material, yielded 0.7 g. melting at 154–190°. A mixture melting point with a small amount of 2-carboxy-4-*t*-butyldiphenyl sulfone gave a final melting point of 196° and with 2-carboxy-4'-*t*-butyldiphenyl sulfone, 186°.

Anal. Calcd. for C₁₇H₁₈O₂S: C, 64.15; H, 5.66; neut. equiv., 318. Found: C, 64.01, 64.29; H, 5.77, 5.74; neut. equiv., 320.

The aqueous filtrates (from treatment of the acidic solid above) were concentrated to approximately 100 ml., filtered (no residue) and cooled. There was obtained by crystallization approximately 80 mg. of crystalline solid melting at 153–177°.

Anal. Calcd. for C₁₇H₁₈O₂S: C, 64.15; H, 5.66. Found: C, 64.33; H, 5.64.

Further concentration and cooling of the aqueous mother liquor yielded no solid material.

Treatment of the crude mixed acids with cold water was found not to effect complete removal of valeric acid.

Several other metalation conditions were tried in which a larger molar proportion of *n*-butyllithium to sulfone was used at longer reaction times. In all cases appreciable dimetalation resulted as indicated by low neutralization equivalents on mixed metalation acids free of valeric acid.

A melting point-composition diagram (Fig. 4) was constructed from samples of 2-carboxy-4-*t*-butyldiphenyl sulfone and 2-carboxy-4'-*t*-butyldiphenyl sulfone from the data shown in Table I.¹⁵ The 0.7 g. of mixed acid, m.p. 154–190°, corresponds to a composition of 68% 2-carboxy-4'-*t*-butyldiphenyl sulfone and 32% of the 2,4-isomer. The 80 mg. isolated later, m.p. 153–177°, contains 74% of the 2,4-isomer II and 26% of the 2,4-isomer III. Addition of these fractions represents 69% of II and 31% of III. The data of Table I were collected by dissolving the weighed samples of acid in dry ether and evaporating the solvent. The melting range of the resulting mixture was determined on a Kofler hot-stage microscope. A plot of the data shows a smooth curve with a single eutectic at 20 mole per cent. 2-carboxy-4-*t*-butyldiphenyl sulfone (III).

2-*t*-Butylthioxanthone-5-dioxide.—Following the procedure described by Ullmann and Lehner,¹⁶ 1.0 g. of a mixture of monocarboxylic acids from metalation was heated on the steam-bath with 10 ml. of concentrated sulfuric acid until solution was effected. The solution was heated between 190 and 200° for 15 minutes and then poured over an excess of ice. The precipitated solid, after collection and recrystallization from absolute ethanol, weighed 0.6 g. and melted at 109–110°.

Anal. Calcd. for C₁₇H₁₆O₃S: C, 68.00; H, 5.33. Found: C, 68.01; H, 5.01.

2-Bromo-4-*t*-butylbenzenesulfonyl Chloride.—*m*-Bromo-*t*-butylbenzene was prepared in general accordance with the procedure of Larner and Peters¹⁷ by the sequence *p*-nitro-*t*-butylbenzene → *p*-*t*-butylaniline → *p*-*t*-butylacetanilide → 2-bromo-4-*t*-butylacetanilide → 2-bromo-4-*t*-butylaniline → *m*-bromo-*t*-butylbenzene.

To a well-stirred solution of 24.8 g. (0.12 mole) of *m*-bromo-*t*-butylbenzene in 200 ml. of chloroform was added

slowly at room temperature 50 g. of chlorosulfonic acid. After the addition was complete, the reaction mixture was stirred at room temperature for two hours and then heated to reflux on the steam-bath for two hours. It was poured over an excess of ice and the resulting organic and aqueous layers separated. After removal of the chloroform from the organic layer, an oily residue remained which crystallized on standing. Recrystallization from petroleum ether yielded 25.1 g. (67%) of crystalline solid melting at 67–68°. Conversion of a small amount of the sulfonyl chloride to the corresponding sulfonamide in the usual manner¹⁸ gave a crystalline solid, after recrystallization from dilute aqueous ethanol, melting at 109–110°.

Anal. Calcd. for C₁₂H₁₄BrNO₂S: C, 41.10; H, 4.79; N, 4.79. Found: C, 41.04; H, 4.68; N, 4.93.

2-Bromo-4-*t*-butylphenyl Sulfone.—A solution composed of 5.0 g. (0.016 mole) of 2-bromo-4-*t*-butylbenzenesulfonyl chloride and 50 ml. of benzene was warmed to 70° on the steam-bath. After removal from the bath, 10 g. of anhydrous aluminum chloride was added slowly with stirring. The reaction mixture was stirred at room temperature until the evolution of hydrogen chloride had ceased and then heated to reflux on the steam-bath for 30 minutes. The mixture was poured over an excess of ice and the excess benzene was removed by distillation with steam. Recrystallization of the solid residue from the distillation from 95% ethanol yielded 3.6 g. (63%) melting at 110–111°.

Anal. Calcd. for C₁₆H₁₇BrO₂S: C, 54.39; H, 4.82. Found: C, 54.43, 54.48; H, 4.74, 4.91.

2-Bromo-4-*t*-butyldiphenyl Sulfide.—The procedure followed for the preparation of this compound was in general that employed by Ziegler¹⁹ for the preparation of 2-carboxy-diphenyl sulfide. A solution of 19.0 g. (0.07 mole) of 2-bromo-4-*t*-butylanilinium hydrochloride in 200 ml. of water and 15 ml. of concentrated hydrochloric acid was diazotized in the usual manner at 0° by the slow addition (with stirring) of a solution of 4.8 g. of sodium nitrite in 30 ml. of water. After completion of diazotization, a solution of aqueous sodium acetate was added to neutralize the free acid.²⁰ The solution was filtered and added slowly to a solution of 8.4 g. (0.08 mole) of thiophenol and 30 g. of sodium hydroxide in 100 ml. of water kept at 70° on the steam-bath. After the addition was complete, the mixture was heated on the steam-bath for two hours, made acidic with concentrated hydrochloric acid, cooled and extracted with ether. The ether extract, after removal of the ether, was dissolved in a solution composed of 150 ml. of 95% ethanol and 30 ml. of concentrated hydrochloric acid. The solution was heated to boiling on the steam-bath and 35 g. of zinc dust was added at such a rate that the mixture was kept at vigorous ebullition. After the zinc had been added, the mixture was heated to reflux for 15 minutes and then filtered while hot. The filtrate was distilled with steam to remove any unreacted thiophenol and the residue from the distillation, after cooling, was extracted with ether. The ethereal extract was washed with dilute aqueous sodium hydroxide and water, and then dried over anhydrous sodium sulfate. After removal of the ether, there remained 5.2 g. of a yellow oil. This compound was characterized by its conversion to 2-carboxy-4-*t*-butyldiphenyl sulfide.

2-Carboxy-4-*t*-butyldiphenyl Sulfide. a. From 2-Bromo-4-*t*-butyldiphenyl Sulfide.—A solution of 5.2 g. (0.016 mole) of crude 2-bromo-4-*t*-butyldiphenyl sulfide in 100 ml. of dry ether was added slowly with stirring to an ethereal solution of 0.05 mole of *n*-butyllithium.¹⁴ A nitrogen atmosphere was used and the reaction flask was immersed in an acetone-solid carbon dioxide bath kept between –50 and –60°. After the solution of *n*-butyllithium had been added, the reaction mixture was stirred at a bath temperature of –50 to –60° for 15 minutes. Carbonation was accomplished by pouring over a slurry of ether and crushed solid carbon dioxide. After the carbon dioxide had evaporated, water was added and the ethereal and aqueous layers were separated. The aqueous layer on acidification with concentrated hydrochloric acid yielded 2.1 g. of a light brown solid melt-

(15) Figure 4 and Table I have been deposited as Document No. 5116 with the ADI Auxiliary Publication Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document No. and by remitting in advance \$1.25 for photoprints or \$1.25 for 35 mm. microfilm, by check or money order payable to the Chief.

(16) F. Ullmann and A. Lehner, *Ber.*, **38**, 729 (1905).

(17) B. W. Larner and A. T. Peters, *J. Chem. Soc.*, 680 (1952).

(18) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 186.

(19) J. H. Ziegler, *Ber.*, **23**, 2469 (1890).

(20) G. E. Hilbert and T. B. Johnson, *THIS JOURNAL*, **51**, 1526 (1929).

ing at 174–201°. Recrystallization of this material from benzene gave 1.6 g. (35%) of an almost colorless crystalline solid melting at 205–206°.

Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.33; H, 6.29. Found: C, 71.24, 71.09; H, 6.46, 6.41.

b. From 2-Bromo-4-*t*-butylaniline.—Following the procedure described by Gilman and Stuckwisch,²¹ an ethereal solution of 0.32 mole of *n*-butyllithium was added slowly with stirring to a solution of 19.2 g. (0.08 mole) of 2-bromo-4-*t*-butylaniline in 200 ml. of dry ether at room temperature. An atmosphere of nitrogen was used. After the addition of *n*-butyllithium was complete, the reaction mixture was carbonated by pouring over a slurry of ether and crushed solid carbon dioxide. After the carbon dioxide had evaporated, excess water was added and the aqueous layer was extracted twice with ether and acidified with 1:1 hydrochloric acid until just neutral. This resulted in the separation of a light yellow solid which was collected by filtration and diazotized in the usual manner at 0°. After completion of diazotization, an aqueous solution of sodium acetate was added to neutralize the free acid²⁰ and the resulting solution was added to a solution of 4.8 g. of thiophenol and 25 g. of sodium hydroxide in 100 ml. of water kept at 70° on the steam-bath. The mixture was heated on the steam-bath for one hour and then filtered. The filtrate was acidified with concentrated hydrochloric acid and the precipitate collected by filtration. This material, after one crystallization from benzene, weighed 0.7 g. and melted at 194–201°. A recrystallization from methanol yielded 0.3 g. melting at 205–206°. A mixture melting point with the product obtained from 2-bromo-4-*t*-butyldiphenyl sulfide, melting point 205–206°, was 205–206°.

2-Carboxy-4-*t*-butyldiphenyl Sulfone (III). **a. From 2-Bromo-4-*t*-butyldiphenyl Sulfone.**—To 0.5 g. of magnesium turnings in 25 ml. of dry ether was added slowly with stirring 1.5 g. of 2-bromo-4-*t*-butyldiphenyl sulfone. There was no apparent reaction even on heating the mixture to reflux. A small amount of methyl iodide was added and the mixture heated once more to reflux. Presently reaction commenced and continued without the application of heat. When there was no further visible indication of reaction, crushed solid carbon dioxide was added to the mixture. After the removal of the ether and carbon dioxide, the residue was acidified with 20% sulfuric acid. When the magnesium had dissolved completely, the mixture was made alkaline by the addition of aqueous sodium hydroxide and the solution filtered. Acidification of the filtrate with 1:1 hydrochloric acid resulted in the precipitation of a tan-colored solid. It was collected by filtration and reprecipitated from an aqueous solution of sodium carbonate by means of dilute hydrochloric acid. This gave a small amount of colorless crystalline solid melting at 241–242°.

Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 64.15; H, 5.66. Found: C, 64.00; H, 5.45.

b. From Oxidation of 2-Carboxy-4-*t*-butyldiphenyl Sulfide.—One and one-half grams (0.005 mole) of 2-carboxy-4-*t*-butyldiphenyl sulfide dissolved in 50 ml. of glacial acetic acid was heated to 80° on the steam-bath and then 15 ml. of 30% hydrogen peroxide was added slowly. The solution was heated on the steam-bath for one hour and, after the addition of another 10 ml. of 30% hydrogen peroxide, then to reflux for one hour. The reaction mixture was poured into an excess of water and the precipitated solid, weighing 0.8 g. (45%) and melting at 241–242°, was collected by filtration. A mixture melting point with the product obtained from 2-bromo-4-*t*-butyldiphenyl sulfone, melting at 241–242°, was 241–242°. The yield obtained from another preparation carried out in a similar manner was 55%.

2-Methyl-4-*t*-butyldiphenyl Sulfone.—*o*-Toluenesulfonyl chloride (b.p. 143–145° at 25 mm.) was prepared in 75% yield in accordance with the procedure of Lee and Dougherty²² for conversion of aromatic thiols to the corresponding sulfonyl chlorides. A solution of 38.0 g. (0.20 mole) of *o*-toluenesulfonyl chloride and 35 g. of *t*-butylbenzene was warmed to 70° on the steam-bath. After removal from the steam-bath, 50 g. of anhydrous aluminum chloride was added in small portions with vigorous stirring. Shortly

after the addition was complete, the reaction mixture partially solidified and was poured immediately into an excess of cold water. The unreacted *t*-butylbenzene was removed by steam distillation. The water-insoluble residue was washed with petroleum ether and recrystallized twice from methanol, yielding 30.7 g. (52%) melting at 103–104°.

Anal. Calcd. for $C_{17}H_{20}O_2S$: C, 70.83; H, 6.94. Found: C, 70.76; H, 7.03.

Following in general the procedure described by Newell,²³ 14.4 g. (0.05 mole) of 2-methyl-4-*t*-butyldiphenyl sulfone was dissolved in the minimum amount of glacial acetic acid and heated almost to boiling. Then a solution of 15 g. of chromium trioxide dissolved in the minimum amount of glacial acetic acid was added slowly with stirring. After the addition was complete, the reaction mixture was heated to reflux for 16 hours and then poured into an excess of cold water. The precipitated crystalline solid was collected by filtration, dissolved in aqueous sodium carbonate solution, the solution filtered and the filtrate acidified with dilute hydrochloric acid. The solid precipitate was recrystallized from benzene giving 0.3 g. of crystalline acid melting at 168–169°. This material is further characterized below.

***p*-*t*-Butylthiophenol.**—This compound was prepared according to the procedure given by Seneor, Rapport and Koepfli²⁴ for the preparation of *p*-chlorothiophenol. To a mixture of 23.2 g. (0.10 mole) of *p*-*t*-butylbenzenesulfonyl chloride, 240 g. of ice and 50 ml. of concentrated sulfuric acid was added (30 minutes) with stirring 40 g. of zinc dust. The temperature of the reaction mixture was held at 0° throughout this operation and for two hours after the addition of the zinc. The mixture was then heated carefully to reflux and the resulting crystalline precipitate separated by filtration. The precipitate was suspended in a boiling mixture of 240 ml. of water and 45 ml. of concentrated sulfuric acid and then 40 g. of zinc was added in small portions. After the mixture had been steam distilled, the distillate was extracted with ether and the ether extract dried over anhydrous sodium sulfate. Removal of the ether left 9.8 g. (59%) of a colorless liquid. This compound was characterized by conversion to 2-carboxy-4-*t*-butyldiphenyl sulfide.

2-Carboxy-4-*t*-butyldiphenyl Sulfide.—Following the general procedure of Ziegler¹⁹ and using some modifications reported by Hilbert and Johnson,²⁰ 8.1 g. (0.59 mole) of anthranilic acid was added to a solution of 60 ml. of water and 10 ml. of concentrated hydrochloric acid. The solution was diazotized at 0° by the slow addition of a solution of 5.6 g. of sodium nitrite in 25 ml. of water. After completion of diazotization, an aqueous solution of sodium acetate was added to neutralize the free acid. The solution of the diazonium salt was added to a solution (warmed to 70°) of 9.8 g. (0.059 mole) of *p*-*t*-butylthiophenol and 5.0 g. of sodium hydroxide in 30 ml. of water. After the addition was complete, the reaction mixture was heated on the steam-bath for one hour. The mixture was filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate was collected by filtration and, after one recrystallization from glacial acetic acid and one from benzene, there was obtained 4.8 g. (27%) of crystalline solid melting at 193–194°. Another run carried out in a similar manner resulted in a yield of 36%.

Anal. Calcd. $C_{17}H_{18}O_2S$: C, 71.33; H, 6.29; neut. equiv., 286. Found: C, 71.37, 71.45; H, 6.19, 6.14; neut. equiv., 288.

2-Carboxy-4-*t*-butyldiphenyl Sulfone.—To a solution of 3.5 g. of 2-carboxy-4-*t*-butyldiphenyl sulfide in 50 ml. of glacial acetic acid heated to 80° on the steam-bath was added slowly 15 ml. of 30% hydrogen peroxide. The resulting solution was heated on the steam-bath for 30 minutes and, after the addition of another 15 ml. of 30% hydrogen peroxide, for 30 additional minutes. The solution was heated to reflux for two hours and poured into an excess of cold water. The precipitated solid was collected by filtration and recrystallized from benzene, yielding 2.6 g. (67%) of a crystalline solid melting at 168–169°. A mixture melting point of this solid with the material obtained from chromic acid oxidation of 2-methyl-4-*t*-butyldiphenyl sulfone, melting point 168–169°, was 168–169°.

(21) H. Gilman and C. G. Stuckwisch, *This Journal*, **71**, 2934 (1949).

(22) S. W. Lee and G. Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

(23) L. C. Newell, *Am. Chem. J.*, **20**, 302 (1898).

(24) A. E. Seneor, M. M. Rapport and J. B. Koepfli, *J. Biol. Chem.*, **167**, 232 (1947).

Anal. Calcd. for $C_{11}H_{18}O_4S$: C, 64.15; H, 5.66; neut. equiv., 318. Found: C, 64.08, 64.35; H, 5.63, 5.54; neut. equiv., 316. KNOXVILLE, TENNESSEE

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Preparation of Some 10-Substituted Phenoxazines¹

BY HENRY GILMAN AND LEONARD O. MOORE²

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An improved procedure for the synthesis and purification of phenoxazine has been developed which is applicable to the preparation of larger amounts than previously reported. Several 10-alkyl- and 10-arylphenoxazines have been prepared. Iodine has been shown to have little, if any, catalytic activity in the preparation of 10-arylphenoxazines from aryl bromides.

In the study of the chemistry of phenoxazine it was desired to use variously 10-substituted compounds for comparison of substitution reactions and also to use the aryl derivatives for testing as solutes in liquid scintillators.³

Phenoxazine was made first by Bernthsen⁴ in 1887, and, though known for many years, has not had a systematic study made of its chemistry. Oxazine dyes, which are derivatives of phenoxazine, are widely used at present as biological stains.⁵ They have been studied for staining brain tumors,⁶ and as tuberculostatic agents.⁷ In general the reactions of phenoxazine which have been studied have related directly to these dyes. The majority of reactions studied have been cyclization, oxidation-reduction to oxazonium salts, and some substitution of the oxazonium compounds.

Related heterocycles containing an N-H bond have been used quite extensively in reactions to prepare N-substituted compounds. Carbazole⁸ and phenothiazine⁹ both have had various alkyl and aryl groups substituted for the hydrogen on the nitrogen. Relatively few N-substituted derivatives of phenoxazine have been prepared. Morris and Snyder¹⁰ prepared several 10-sulfolanyl- and 10-

sulfolenylphenoxazines from phenoxazine and various sulfone compounds in a basic solution. All other 10-substituted phenoxazines have been prepared by cyclization. Some 10-benzyl derivatives¹¹ were prepared for testing as tuberculostatic agents; some 10-(nitrophenyl)-phenoxazines¹² and one 10-methyl derivative¹³ were prepared in studies of a cyclization mechanism.

We have studied the preparation of phenoxazine, varying the methods reported in the literature.¹⁴ The best method for large amounts is to heat an equimolar mixture of *o*-aminophenol and *o*-aminophenol hydrochloride, allowing the water produced to distil. The completion of the reaction can be determined by measuring the amount of water produced. The addition of sea sand to facilitate extraction of the mass decreased the yield as also did heating the reaction for an extended length of time. The purification by chromatography was much less tedious than the methods reported in the literature. This procedure consistently gave 26 to 30% of a relatively pure product in runs of 0.5 to 2.5 moles.

In light of the patent by Waterman and Vivian¹⁵ as well as their articles¹⁶ on the preparation of phenothiazines and carbazoles from aromatic nitro compounds, attempts were made to produce phenoxazine from *o*-nitrophenyl phenyl ether. Heating this ether with powdered iron or ferrous oxalate yielded no phenoxazine.

The alkyl phenoxazines were prepared in liquid ammonia using 10-phenoxazylsodium, prepared from sodium amide and phenoxazine, with an alkyl iodide or a benzyl chloride.¹⁷ Phenoxazine, similar to carbazole, is not acidic enough to condense with ethyl iodide in a refluxing acetone solution of potassium hydroxide, as do nitrocarbazoles.¹⁸

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(2) Du Pont Teaching Fellow, 1956-1957.

(3) F. Newton Hayes, *Intern. J. Applied Radiation Isotopes*, **1**, 46 (1956). Evaluation of these compounds for scintillator activity is being made by Wright N. Langham, F. N. Hayes and D. G. Ott of the Los Alamos Scientific Laboratory who will report the results later.

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