

15. 2-Methoxy-4-carbethoxyaminophenylarsine Oxide. —2-Methoxy-4-carbethoxyaminophenylarsonic acid (1 g.) was suspended in dry ether (40 ml.) at room temperature and phosphorus trichloride (0.5 g.) added slowly with stirring. After one hour, the ether was evaporated, water added and the oxide filtered off.

### Summary

1. 2-Hydroxy-4-aminophenylarsine oxide and

eight derived oxides were prepared for the first time. Three derived oxides previously prepared were made again in purer form.

2. 2-Hydroxy-4-carbethoxyaminophenylarsonic acid and 2-hydroxy-4-aminophenylarsonic acid were prepared in purer form.

DETROIT, MICHIGAN

RECEIVED AUGUST 31, 1940

[CONTRIBUTION FROM THE BAILEY CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

## The Chlorination of Phenyl Ether and Orientation in 4-Chlorophenyl Ether

BY RAY Q. BREWSTER AND GLENN STEVENSON

Orientation in the phenyl ether series of compounds has been studied by several investigators.<sup>1</sup> Work upon the iodo and methoxy derivatives has been done in this Laboratory<sup>2</sup> and the present report contains results obtained with 4-chlorophenyl ether. Mailhe and Murat<sup>3</sup> chlorinated phenyl ether and obtained a mixture of products from which they succeeded in separating 4-chlorophenyl ether and a liquid dichloro compound which they assumed to be the 4,4' derivative. They make no mention of this latter solidifying upon cooling and very likely it was a mixture of 4,4'-dichlorophenyl ether and 3,4-dichlorophenyl ether. Our experiments have shown that chlorination of phenyl ether in acetic acid solution at room temperature gives chiefly monosubstitution at position 4 and that further reaction with chlorine introduces the second chlorine atom at either position 3 or position 4'. Likewise the bromination and nitration of 4-chlorophenyl ether yields a mixture of 3,4 and 4,4'-disubstitution products. In the case of iodination, however, by means of iodine chloride only the 4-chloro-4'-iodophenyl ether could be obtained.

### Experimental Part

**Chlorination of Phenyl Ether.**—The chlorination of phenyl ether in the absence of a solvent produced hopeless mixtures, while poor results were obtained in the presence of carbon tetrachloride. The use of acetic acid solution, however, was found to give chiefly the 4-chlorophenyl ether.

Two moles (340 g.) of phenyl ether was dissolved in 1000

(1) (a) Scarborough, *J. Chem. Soc.*, **132**, 2361 (1929); (b) Roberts and Turner, *ibid.*, **127**, 2004 (1925); (c) McCombie, Macmillan and Scarborough, *ibid.*, 529 (1931); (d) Groves, Turner and Sharp, *ibid.*, 512 (1929); (e) Fox and Turner, *ibid.*, 1853 (1930).

(2) (a) Brewster and Strain, *THIS JOURNAL*, **56**, 117 (1934); (b) Brewster and Choguill, *ibid.*, **61**, 2702 (1939).

(3) Mailhe and Murat, *Bull. soc. chim.*, [4] **11**, 329 (1912).

g. of glacial acetic acid and chlorine gas passed into the solution until the gain in weight (including that of the hydrogen chloride absorption apparatus) was 140–150 g. After standing overnight the chlorinated products were precipitated with water, washed well and dried. From three such lots (6 moles in all) which were combined and worked up together there were obtained by fractional distillation 50 g. of unchanged phenyl ether, 1105 g. of 4-chlorophenyl ether (I),<sup>4</sup> b. p. 146–150° (7 mm.), 15 g. of 4,4'-dichlorophenyl ether (II),<sup>5</sup> b. p. 168–172° (7 mm.), m. p. 30°, and 10 g. of 3,4,4'-trichlorophenyl ether (III), b. p. 180–190° (7 mm.), m. p. 46–47°. The position of all three chlorine atoms in compound III was proved by its preparation by the further chlorination of either 4,4'-dichlorophenyl ether (II) or 3,4-dichlorophenyl ether (V). The composition of all products was checked by analysis but analyses are here reported for only those substances which have not previously been recorded.

*Anal.*, III. Calcd. for C<sub>12</sub>H<sub>7</sub>OCl<sub>3</sub>: Cl, 38.94. Found: Cl, 38.65.

Any 2-chlorophenyl ether (IV) produced by this method of chlorination of phenyl ether must have been in small proportion as none was isolated. A sample prepared from 2-aminophenyl ether<sup>6</sup> was found to boil at 142–146° (12 mm.), and to melt at 47–48°.

**Chlorination of 4-Chlorophenyl Ether.**—Chlorine gas from a cylinder was passed through a solution of 102.5 g. (0.5 mole) of 4-chlorophenylether in 500 cc. of glacial acetic acid at room temperature until 35 g. of chlorine had been absorbed. The solution was allowed to stand overnight,

(4) Compound I was also obtained by the diazo reaction from 4-aminophenyl ether. Mailhe and Murat<sup>3</sup> prepared it along with other products by the chlorination of phenyl ether in carbon tetrachloride solution. Suter and Green<sup>6</sup> found that it could be made from potassium phenate and *p*-chloriodobenzene.

(5) An identical specimen of II was made in 50% yield from 4-chloro-4'-aminophenyl ether by the Sandmeyer method. According to our observations a repeatedly crystallized sample of 4-chloro-4'-acetaminophenyl ether melted at 115°. *Anal.* Calcd. for C<sub>14</sub>H<sub>11</sub>O<sub>2</sub>NCl: Cl, 13.58; N, 5.35. Found: Cl, 13.52; N, 5.37. Scarborough<sup>1a</sup> reports a melting point of 146°.

(6) Suter and Green, *THIS JOURNAL*, **59**, 2578 (1937), report 2-chlorophenyl ether as melting at 39°. By private correspondence Dr. Suter informed us that "further purification of the 2-chlorophenyl ether made from potassium phenoxide and *o*-chloro-iodobenzene raised the melting point to 46–47° and a mixed melting point with the material from 2-aminophenyl ether showed no depression."

then poured into water, washed, dried and fractionated. The products obtained were 52 g. of 3,4-dichlorophenyl ether (V), b. p. 160–163° (7 mm.), 30 g. of 4,4'-dichlorophenyl ether (II) and 18 g. of 3,4,4'-trichlorophenyl ether (III). The fact that the chlorine atoms in compound V are at positions 3 and 4 was established by the synthesis of another sample of this compound in the following manner. 3-Nitro-4-aminophenyl ether, prepared by nitration of 4-acetaminophenyl ether and hydrolysis, was converted into 3-nitro-4-chlorophenyl ether (VI), b. p. 208–211° (7 mm.). Reduction of VI with iron powder, water and a little ferric chloride gave a 90% yield of 3-amino-4-chlorophenyl ether (VII), b. p. 194–197° (3 mm.). The amino group in VII was then replaced by chlorine through the diazo reaction. Both samples of 3,4-dichlorophenyl ether were liquids of the same boiling point and upon bromination in acetic acid solution both gave the same 3,4-dichloro-4'-bromophenyl ether (XI), m. p. 52°, which was also obtained by chlorination of 4-chloro-4'-bromophenyl ether IX.

*Anal.* V. Calcd. for  $C_{12}H_9OCl_2$ : Cl, 29.71. Found: Cl, 29.62. VI. Calcd. for  $C_{12}H_9O_3NCl$ : Cl, 14.23. Found: Cl, 14.15. VII. Calcd. for  $C_{12}H_{10}ONCl$ : Cl, 16.17. Found: Cl, 16.24.

The benzoyl derivative of VII melted at 92°. *Anal.* Calcd. for  $C_{19}H_{14}O_2NCl$ : Cl, 10.97. Found: Cl, 11.00.

**Bromination of 4-Chlorophenyl Ether.**—One mole (160 g.) of bromine in 100 cc. of glacial acetic acid was added dropwise to a solution of one mole (205 g.) of 4-chlorophenyl ether in 300 cc. of glacial acetic acid. After standing for an hour with occasional gentle warming the solution was poured into a liter of water. By a process of washing, fractional distillation, partial freezing and recrystallization from ligroin, the precipitated crude oil was separated into 150 g. of the solid 4-chloro-4'-bromophenyl ether (IX), m. p. 42–43°, and 60 g. of the oily 4-chloro-3-bromophenyl ether (X), b. p. 165–168° (7 mm.). Proof of the structure of IX was established by its synthesis (1) by the chlorination of 4-bromophenyl ether and (2) through the diazo reaction from both 4-chloro-4'-aminophenyl ether and 4-bromo-4'-aminophenyl ether. Chlorination of IX or bromination of V gave identical specimens of 3,4-dichloro-4'-bromophenyl ether (XI).

The identity of compound X was proved by its preparation from VII by diazotization and treatment with cuprous bromide. Specimens of X made by the direct bromination of 4-chlorophenyl ether and from VII by the diazo reaction were liquids of the same boiling points and each upon further bromination in acetic acid solution gave identical samples of 4-chloro-3,4'-dibromophenyl ether (XII), m. p. 49°. Compound XII was also obtained by bromination of 4-chloro-4'-bromophenyl ether in acetic acid solution. All three specimens of XII showed no lowering of the melting point when mixed.

*Anal.* IX. Calcd. for  $C_{12}H_9OClBr$ : Cl, 12.53; Br, 28.22. Found: Cl, 12.48; Br, 28.09. X. Isomeric with IX. Found: Cl, 12.60; Br, 12.38. XI. Calcd. for  $C_{12}H_7OCl_2Br$ : Cl, 22.33; Br, 25.14. Found: Cl, 22.39; Br, 25.24. XII. Calcd. for  $C_{12}H_7OClBr_2$ : Cl, 9.80; Br, 44.16. Found: Cl, 9.74; Br, 43.90.

**Iodination of 4-Chlorophenyl Ether.**—To a solution of 20.5 g. (0.1 mole) of 4-chlorophenyl ether (I) in 100 cc. of

glacial acetic acid was added 17 g. of iodine monochloride in 50 cc. of acetic acid and the liquid boiled for eight hours. The cooled solution was then poured into water and the precipitated solid material purified by washing and crystallization from 95% ethyl alcohol. There was thus obtained 30 g. (91% yield) of 4-chloro-4'-iodophenyl ether (XIII), m. p. 68°. No other product could be isolated. A counter-synthesis of compound (XIII) by the passage of chlorine into a solution of 30 g. (0.1 mole) of 4-iodophenyl ether in 200 cc. of glacial acetic acid until the system had absorbed 7 g. (0.1 mole) of chlorine gave first a heavy mass of yellow crystals of 4-iodophenyl ether dichloride, melting with decomposition at 95–97°, which upon dissolution in hot ethyl alcohol and chilling deposited colorless plates of 4-chloro-4'-iodophenyl ether (XIII). Mixing these crystals with compound (XIII) produced no lowering of the melting point. Compound (XIII) also was prepared from 4-chloro-4'-aminophenyl ether through the diazo synthesis.

*Anal.* XIII. Calcd. for  $C_{12}H_9OClI$ : Cl, 10.75; I, 38.46. Found: Cl, 10.66; I, 38.14.

For purposes of comparison samples of 3-iodo-4-chlorophenyl ether (XIV, b. p. 196–200° (3 mm.)), 2'-iodo-4-chlorophenyl ether (XV, b. p. 193–196° (3 mm.)),<sup>7</sup> and 2-iodo-4-chlorophenyl ether (XVI, m. p. 42°)<sup>8</sup> were made through the diazo synthesis from 3-amino-4-chlorophenyl ether (VII), 2'-amino-4-chlorophenyl ether, and 2-amino-4-chlorophenyl ether, respectively. The formation of small quantities of compound XIV would be expected by the iodination of 4-chlorophenyl ether, though none of this substance could be found in the product.

*Anal.* XIV. Calcd. for  $C_{11}H_9OClI$ : Cl, 10.75; I, 38.46. Found: Cl, 10.64; I, 38.10. XV. Isomeric with XIV. Found: Cl, 10.59; I, 37.89. XVI. Another isomer of XIV. Found: Cl, 10.78; I, 38.58.

Further iodination of either (XIII) or (XIV) by boiling in acetic acid solution with iodine monochloride gave 4-chloro-3,4'-diiodophenyl ether (XVII), m. p. 73°.

*Anal.* XVII. Calcd. for  $C_{12}H_7OClI_2$ : Cl, 7.78; I, 55.65. Found: Cl, 7.72; I, 55.23.

**Nitration of 4-Chlorophenyl Ether.**—To a solution of 21 g. (0.1 mole) of 4-chlorophenyl ether in 50 cc. of glacial acetic acid and 50 cc. of acetic anhydride was slowly added a solution of 7 cc. of fuming nitric acid ( $D = 1.5$ ) in 7 cc. of acetic acid. The solution was stirred mechanically and the temperature kept below 55° by external cooling. After standing for one hour the solution was poured into water and the oil separated. Three such lots were combined, washed, dried, and fractionated at 4 mm. pressure into the following fractions: I up to 175°, 23 g. consisting chiefly

(7) In the synthesis of XV 4-chloro-2'-nitrophenyl ether was prepared from *o*-nitrochlorobenzene and *p*-chlorophenol by the method of Raiford and Colbert, *THIS JOURNAL*, **48**, 2652 (1926), and reduced to the amino compound as described by McCombie, Macmillan and Scarborough.<sup>10</sup> For the diazotization the 4-chloro-2'-aminophenyl ether (23 g.) was dissolved in a solution of 200 cc. of glacial acetic acid, 50 cc. of water and 125 cc. of concentrated hydrochloric acid, cooled to 5° and diazotized with 7 g. of sodium nitrite in a little water. Other diazotizations in this work were done in this same manner.

(8) For the preparation of XVI 4-chloro-2-nitrophenyl ether was first made from 2-nitro-1,4-dichlorobenzene and potassium phenate. This was then reduced and diazotized.

of the original 4-chlorophenyl ether; II 175–185°, 11 g., made up mostly of 4-chloro-3-nitrophenyl ether (VI) and some dichlorophenyl ether produced by disproportionation; and III 185–200°, 23 g., which solidified on cooling and after recrystallization from ligroin proved to be 4-chloro-4'-nitrophenyl ether, m. p. 76°. A mixture of this product and a sample of 4-chloro-4-nitrophenyl ether prepared by the Ullmann reaction or by chlorination of 4-nitrophenyl ether showed no lowering of the melting point.

The 4-chloro-3-nitrophenyl ether in fraction II could not be separated from the dichlorophenyl ether by distillation so it was reduced to the amino compound (VII) and made into the benzoyl derivative. The specimen of the benzoyl derivative, m. p. 92°, showed no depression

of the melting point when mixed with sample synthesized from 3-nitro-4-aminophenyl ether.

### Summary

Methods of chlorinating phenyl ether and separating pure products have been devised and the orienting influence of the chlorine atom in 4-chlorophenyl ether has been studied. A second substituent enters the nucleus either at position 3 or position 4' with the latter isomer usually predominating. The structure of all new compounds was established by several methods of synthesis.

LAWRENCE, KANSAS

RECEIVED AUGUST 8, 1940

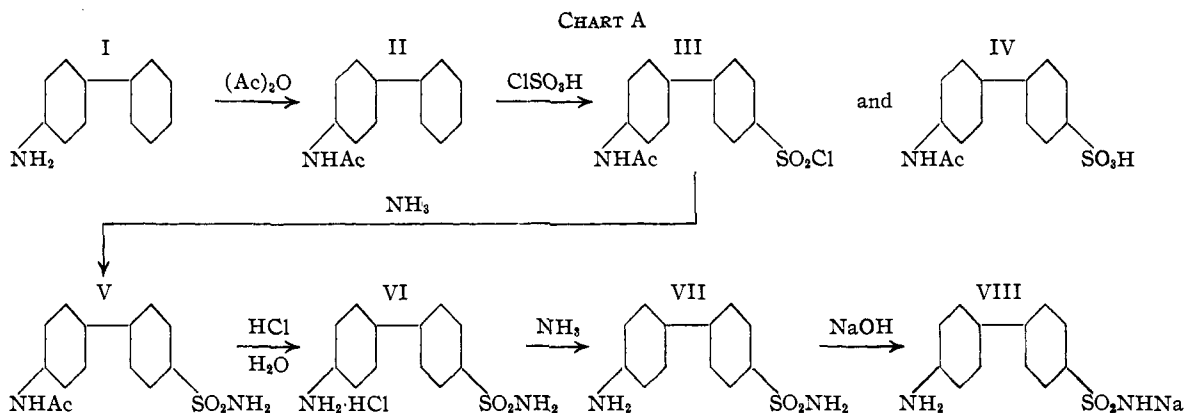
[CONTRIBUTION No. 407 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

## *p*-(*p*-Aminophenyl)-benzenesulfonamide and Derivatives. I

BY C. T. VAN METER, J. A. BIANCULLI AND ALEXANDER LOWY

The primary purposes of this study were (1) to prepare the analog of sulfanilamide in the biphenyl series, (2) to prepare various substituted derivatives of the same, and (3) to study the ac-

In order to determine the relative positions of the substituent groups on the biphenyl nucleus, the operations indicated in chart B were performed.



tion of these on various microorganisms. The present paper deals with the synthesis of the parent molecule of the series, *p*-(*p*-aminophenyl)-benzenesulfonamide. Possible bactericidal properties of this structure are now being investigated and will be reported later. Various substituted derivatives of this parent molecule are also in process of preparation and will be reported later. Furthermore, it seemed desirable to determine whether or not the general method for preparing aminosulfonamides in the benzene series<sup>1</sup> was applicable to the biphenyl series. Chart A shows the formulas and reactions of the analogous types of compounds of the biphenyl series as prepared.

(1) Baine, *J. Chem. Education*, **16**, 278 (1939).

### Experimental

*n*-Acetoxenylamine (II).—This was prepared directly from xenylamine (*p*-aminobiphenyl, Eastman Kodak Co. practical quality) according to the method of Heusler.<sup>2</sup> Four recrystallizations from 75% alcohol and then two from 95% alcohol yielded a white crystalline product, m. p. 173.6°.

*p*-(*p*-Acetaminophenyl)-benzenesulfonyl Chloride (III).—This compound was prepared in a manner similar to that used for making *p*-aminobenzenesulfonyl chloride.<sup>3</sup> Forty grams of (II) was finely pulverized and added slowly during one hour to 200 cc. of chlorosulfonic acid in a flask immersed in ice and equipped with a mechanical stirrer. The temperature was kept below 5°, and stirring

(2) Heusler, *Ann.*, **260**, 233 (1890).

(3) Marvel, *et al.*, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1925, Vol. V, p. 3.