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

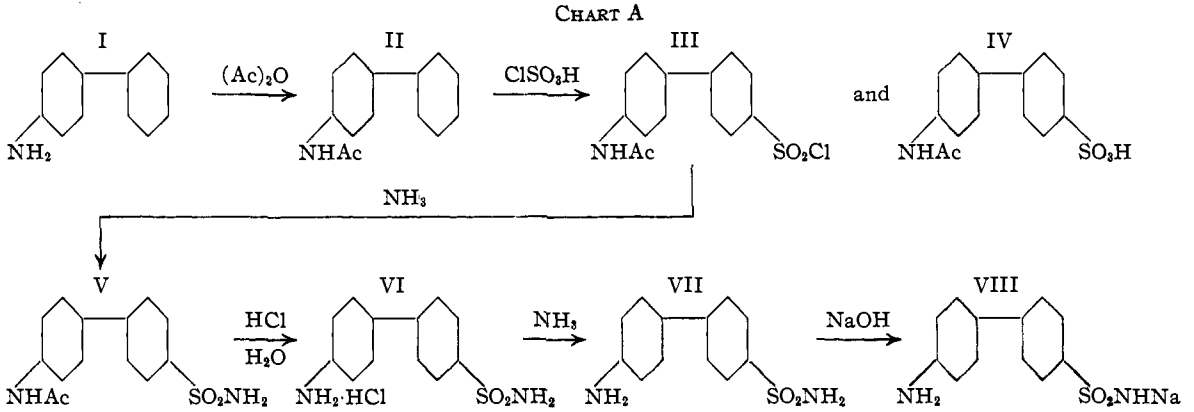
BY C. T. VAN METER, J. A. BIANCULLI AND ALEXANDER LOWY

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 action of these on various microörganisms. 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[1] 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).

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

CHART A



Experimental

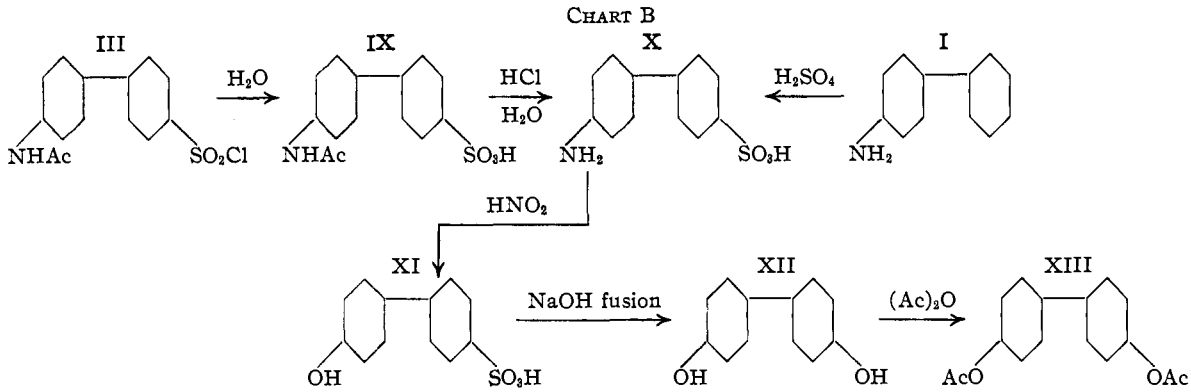
***n*-Acetoxenylamine (II).**—This was prepared directly from xenylamine (*p*-aminobiphenyl, Eastman Kodak Co. practical quality) according to the method of Heusler.[2] Four recrystallizations from 75% alcohol and then two from 95% alcohol yielded a white crystalline product, m. p. 173.6°.

***p*-(*p*-Acetaminophenyl)-benzenesulfonyl Chloride (III).**—This compound was prepared in a manner similar to that used for making *p*-aminobenzenesulfonyl chloride.[3] 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.

CHART B



was continued after all of (II) had been added until no more hydrogen chloride was evolved. The clear, liquid reaction mixture was poured very slowly with stirring onto crushed ice, the white, curdy solid was filtered off, washed several times with ice-cold water, and then dried as quickly as possible by working on porous plates. The dried reaction product was then extracted with boiling, anhydrous toluene; on cooling in an ice-bath, the filtrate deposited small, bright yellow crystals of (III). After two recrystallizations from toluene, 25 g. remained. The compound has no m. p.; it begins to decompose at 110°.

Anal. Calcd. for $C_{14}H_{12}ClNO_3S$: N, 4.52; S, 10.35; Cl, 11.18. Found: N, 4.46, 4.70; S, 10.22, 10.23; Cl, 11.33, 11.11.

p-(*p*-**Acetaminophenyl**)-**benzenesulfonamide** (V).—To a finely powdered mixture of 16 g. of pure (III) and 32 g. of ammonium carbonate, 200 cc. of concd. ammonium hydroxide was added. The mixture was stirred at room temperature for one hour and then at 40° for two hours. During this time the original faint yellow color due to (III) gradually disappeared; the mixture became white and somewhat gelatinous. After cooling to room temperature, the insoluble portion of the reaction mixture was filtered off, washed twice with cold water, and crystallized from 75% alcohol. Two recrystallizations from 75% alcohol yielded finally 12 g. of white crystalline (V), m. p. 289° with decomposition. A small quantity of (V) prepared by passing ammonia gas into a toluene solution of (III) showed the same properties as the (V) prepared as above; m. p. and mixed m. p. 289° with decomposition.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: N, 9.65; S, 10.80. Found: N, 9.66, 9.59; S, 10.85, 11.14.

p-(*p*-**Aminophenyl**)-**benzenesulfonamide** (VII).—Six grams of (V), 100 cc. of water, and 100 cc. of concd. hydrochloric acid were refluxed for three hours. While still warm, the reaction mixture was filtered and rendered alkaline at once by the addition of concd. ammonium hydroxide. Compound (VII) was thus formed as a white, flocculent precipitate; the mixture was cooled to room temperature, (VII) filtered off and washed with cold water. The crude product was crystallized three times from 95% alcohol containing a small amount of decolorizing carbon. There resulted 3 g. of (VII), m. p. 261° with slight decomposition.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.02; H, 4.87; N, 11.29; S, 12.92. Found: C, 58.29, 58.00; H, 4.90, 5.15; N, 11.24, 11.37, 11.36; S, 12.99, 13.14.

Properties of (VII).—It crystallizes in short, white needles; at 20°, 1 g. dissolves in about 60 cc. of acetone, 300 cc. of methyl alcohol, 500 cc. of ethyl alcohol, 2000 cc. of ether, and 5000 cc. of chloroform; it is practically insoluble in benzene and in water at 20°. One gram dissolves in about 1100 cc. of boiling water and in 125 cc. of boiling alcohol. The aqueous solution is neutral to litmus. Solutions in methyl and ethyl alcohols exhibit a blue fluorescence. It is diazotizable, and when the diazonium chloride is coupled with alkaline β-naphthol, a reddish-orange azo compound precipitates. (VII) dissolves easily in hot, 20% hydrochloric acid, from which at least 90% of the dissolved material separates on cooling in an ice-bath as the hydrochloride (VI) in glistening plates. (VI) is easily soluble in water and reacts at once with ammonia to give (VII). On warming (VII) with sodium hydroxide solution there results a solution from which (VIII) is obtained in minute crystals or as a white amorphous mass. Addition of acid to a solution of (VIII) precipitates (VII) immediately.

Anal. of (VIII). Calcd. for $C_{12}H_{11}N_2O_2SNa$: Na, 8.52. Found: Na, 8.67, 8.64.

Direct Synthesis of (VII).—Starting with 20 g. of (II) and using the same reagents and experimental conditions described above but not isolating and purifying the intermediates (III), (V) and (VI), there resulted after decolorizing and crystallizing three times from 95% alcohol, 14 g. (VII), m. p. 261–262° with decomposition. A mixed m. p. of this product with (VII) as obtained from pure (V) showed no depression.

Determination of Configuration.—(Chart B). Since in (II) the acetamino group was known to be para, the only problem here was to determine which hydrogen of biphenyl had been attacked by the chlorosulfonic acid. Two grams of (II) was treated with 10 cc. of chlorosulfonic acid as described above. The (III) thus obtained was refluxed with 20% hydrochloric acid for five hours, during which time (III) was hydrolyzed to (IX) and simultaneously deacetylated to (X) which crystallized out on cooling. About 1 g. of (X) so obtained was dissolved in hot water, sodium hydroxide solution added till neutral, and the solution evaporated to dryness. The dried sodium salt of (X) thus prepared was diazotized according to a method used by Shoppee.[4] The resulting solid diazosulfonate was dispersed in 400 cc. of water and heated.

(4) Shoppee, *J. Chem. Soc.*, 43 (1933).

Evolution of nitrogen commenced at about 85°. Heating was continued until no more nitrogen was evolved; the solution was then neutralized with sodium hydroxide and evaporated to dryness when there remained as a residue about 1 g. of the sodium salt of (XI). This pulverized residue was gradually added to 3 g. of fused sodium hydroxide to which about 10% of water had been added, sufficient heat being used to just maintain fluidity in the reaction mixture. The melt was dissolved in about 500 cc. of water and carbon dioxide passed in when a crude form of (XII) precipitated as a dirty white amorphous material. This was collected, dissolved in warm sodium hydroxide solution, filtered, and rendered acid with hydrochloric acid. The milky liquid was now heated whereupon (XII) went into solution and the tarry matter coagulated. On filtering and cooling, the filtrate deposited (XII) as a white amorphous product which showed itself to have the qualitative properties of *p,p'*-diphenol.[5] Without further purification, the material showed a m. p. range of 267–271°, thus identifying it with the *p,p'*-diphenol, m. p. 272°.[5] As a further check, the diphenol so obtained was dissolved in 10 cc. of acetic anhydride and refluxed for two hours. The reaction product was then treated with water when crude (XIII) precipitated. This was recrystallized from dilute alcohol, and the short white needles thus obtained showed a m. p. of 160°. This corresponds with the m. p. (159–160°) as given in Beilstein.[6] In addition, another specimen of (X) prepared by another process[7] was treated similarly. It behaved in exactly the same manner as the (X) produced in the above synthesis, giving rise ultimately to (XII) and (XIII). Mixed m. p. on the two samples of (XII) and of (XIII) from the two specimens of (X) showed no depression.

(5) Beilstein, "Handbuch der organischen Chemie," fourth edition, Band VI, System No. 563, p. 991.

(6) *Ibid.*, p. 992.

(7) Shoppee, *J. Chem. Soc.*, 43 (1933).

PITTSBURGH, PENNA. RECEIVED JULY 31, 1940

Summary

1. The synthesis of the analog to sulfanilamide in the biphenyl series has been effected.

2. The reaction between *n*-acetoxenylamine and chlorosulfonic acid has been studied, the position of attack under the conditions employed has been determined, and conditions have been established for a 60% conversion to the *p*-(*p*-acetaminophenyl)-benzenesulfonyl chloride.

3. The following new compounds have been prepared and reported: (a) *p*-(*p*-acetaminophenyl)-benzenesulfonyl chloride, (b) *p*-(*p*-acetaminophenyl)-benzenesulfonamide, and (c) *p*-(*p*-aminophenyl)-benzenesulfonamide. The hydrochloride and sodium salt of (c) have also been prepared.

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER LABORATORY OF LEHIGH UNIVERSITY]

Optical Rotation of Aliphatic Acid Salts of Triethylenediamine-Cobaltic Hydroxide. Further Evidence for Ring Structure in Aliphatic Series

BY JAMES P. McREYNOLDS AND JOHN R. WITMEYER

The use of a ring form in aliphatic compounds to explain certain well-known irregularities in properties, as developed by Smith[1] and amplified in terms of optical activity by Smith and McReynolds,[2] indicates that a qualitative prediction of the character of the curve showing molecular rotation as a function of chain length can be made for the aliphatic acid salts of an optically active strong base. The treatment would call for a different $\Delta[M]_D$ (change in molecular rotation upon the addition of one CH_2 group) between the propionate and the butyrate than between the acetate and the propionate since the butyrate would be the first ion in the series to contain the postulated ring. A further irregularity in $\Delta[M]_D$ should appear between butyrate and valerate since the valerate ring would be the first to contain an asymmetric carbon atom. After the valerate the $\Delta[M]_D$ values should again become regular since the only variable is in the length of the chain attached to the asymmetric atom of the ring.

Triethylenediamine-cobaltic hydroxide has been shown to be a strong base by Lamb and Yngve.[3] It should also be readily obtained in an optically active form.

(1) Smith, THIS JOURNAL, **61**, 254, 1176 (1939); **62**, 1136 (1940).

(2) Smith and McReynolds, *ibid.*, **61**, 1963 (1939).

Experimental

Preparation of Compounds.—Dextro-triethylenediamine-cobaltic bromide was prepared by the method of Werner.[4] From this compound dextro-triethylenediamine-cobaltic hydroxide was prepared by the method which Jörgensen[5] used to obtain the racemic form. The hydroxide was quite stable to racemization in solution at room temperature but racemized upon heating or long standing. The specific rotation $[\alpha]_D$ for a freshly prepared 1% solution was +173°, for a solution which had stood

(3) Lamb and Yngve, *ibid.*, **43**, 2358 (1921).

(4) Werner, *Ber.*, **45**, 125–128 (1912).

(5) Jörgensen, *J. prakt. Chem.*, [2] **39**, 12 (1889).