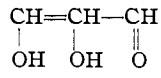
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HOWARD UNIVERSITY]

The Preparation and Properties of an Ene-diol. α-Phenyl-β-mesitoyl Acetylene Glycol

BY R. P. BARNES AND LEILA S. GREEN[1]

With the proof of the structure of ascorbic acid[2] there came a renewed interest in the chemistry of ene-diols.

Now heretofore, with the exception of reductone[3] (I), it has never been possible to isolate an ene-diol in an open chain compound except in a system with the chain —COCHOHCOCO—.[4]

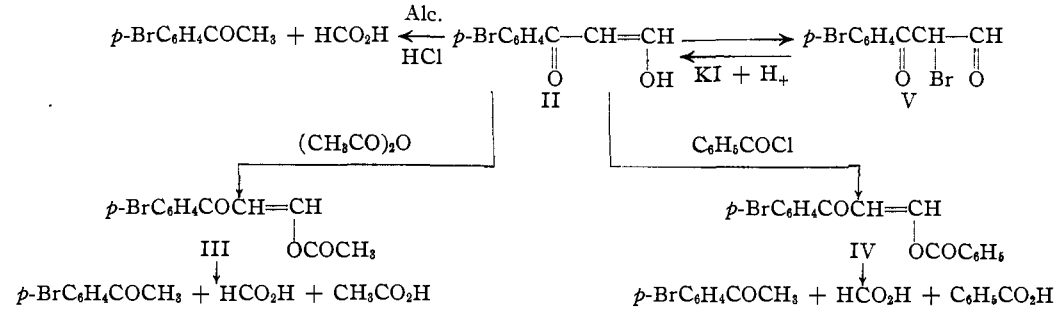


I

This investigation was undertaken in an attempt to make a new ene-diol with the same open chain carbon skeleton as is present in reductone. The likelihood of accomplishing this end seemed to lie in the possibility of obtaining a system with a chain —COCHOHCO— or —CHOHCOCO— with a hydrogen sufficiently active to shift. It had already been pointed out[5] that dibenzoylcarbinol, which contains the first of these chains, does not exist as an ene-diol. Kohler and Thompson[6] have shown that it is possible to follow, step by step, the isomerization of an hydroxy ketone in solution by way of an intermediate ene-diol, which, however, was too unstable to isolate.

More recently still, substances of an ene-diolic nature have been indicated in solution in connection with the reduction products of dimesitylbutanetrione enol and its methyl ethers.[7]

With a knowledge of the structure of reductone, and knowing that oxymethylene-*p*-bromoacetophenone (II) is enolic because of the presence of the very active aldehydic carbonyl group, we chose this substance as our starting material. The method of preparation of oxymethylene-*p*-bromoacetophenone[8] gives such poor yields that we had to modify the procedure in order to get sufficient material with which to work. This substance is 67% enolic; gives an O-acetate (III); an O-benzoate (IV); and a monobromo derivative (V). When the monobromo derivative, which is 100% enolic, was heated with potassium acetate in glacial acetic acid, decomposition with charring occurred, and no carbinol acetate could be isolated. We had hoped to hydrolyze the carbinol acetate to the carbinol which presumably would have shown some indications of an ene-diolic nature. The parent substance, as well as its acyl derivatives, is hydrolyzed in hydrochloric acid–alcoholic solution to *p*-bromoacetophenone



Kohler and Thompson[6] state that the group —CHCO-Mes promotes enolization and enhances the stability of the enol. Attention also has been called[9] not only to the activating influence of the mesityl nucleus upon an α-hydrogen in mesitylbenzylglyoxal and β-phenylbenzylmesitylglyoxal, but also to its stabilizing influence.

A similar activating effect on an α-halogen atom has also been observed in connection with the coupling reaction of α-bromo-β-phenylbenzyl-

(1) This report is the summary of a thesis presented in partial fulfilment of the requirements for the Master's Degree.

(2) (a) Hirst, *Chemistry and Industry*, **52**, 221 (1933); (b) Reichstein, Grüssner, and Oppenauer, *Helv. Chim. Acta*, **16**, 561, 1019 (1933); **17**, 510 (1934); (c) Haworth, *et al.*, *J. Chem. Soc.*, 1419 (1933); 62, 1192 (1934); (d) Reichstein and Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).

(3) Norrish and Griffiths, *J. Chem. Soc.*, 2837 (1928).

(4) (a) Karrer and v. Segesser, *Helv. Chim. Acta*, **18**, 273 (1935); (b) Karrer and Musante, *ibid.*, p. 1140; (c) A. H. Blatt, THIS JOURNAL, **57**, 1103 (1935); **58**, 1894 (1936).

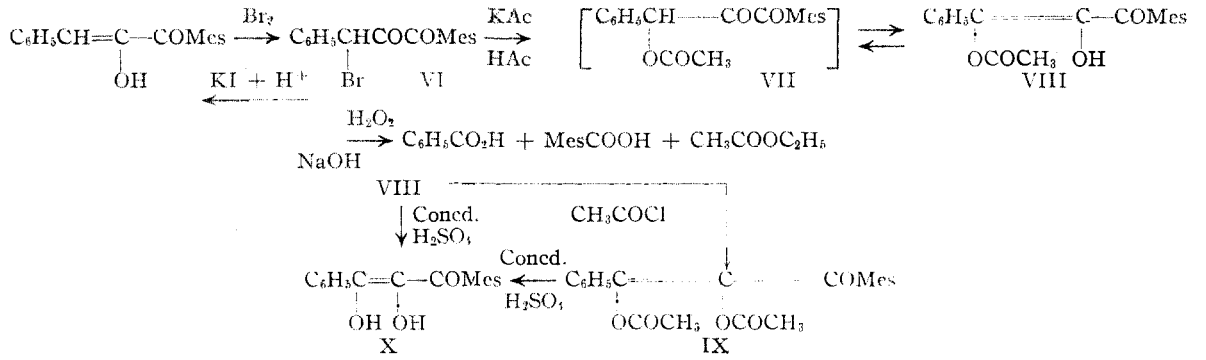
(5) A. H. Blatt and W. Lincoln Hawkins, *ibid.*, **58**, 81 (1936).

(6) E. P. Kohler and R. B. Thompson, *ibid.*, **59**, 887 (1937).

(7) Robert E. Lutz and John L. Wood, *ibid.*, **60**, 705 (1938).

(8) Erich Benary, *Ber.*, **61**, 2252 (1928).

(9) (a) R. P. Barnes, THIS JOURNAL, **57**, 937 (1935), (b) **60**, 1168 (1938).



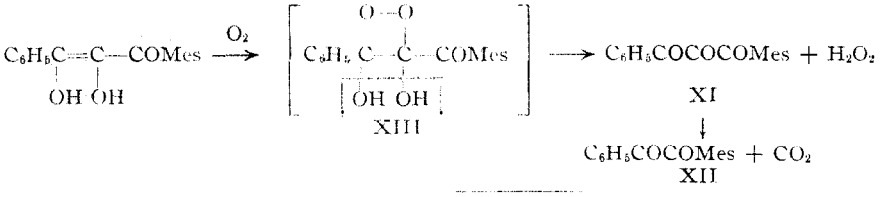
glyoxal[6] and the substitution reaction[9b] whereby it has been possible to obtain an α-oxy-α-diketone and its acetate, in spite of the fact that generally substitution on a methylene group α- to a carbonyl group has a tendency to decrease the activity of remaining substituents. Therefore we set out to test this effect on α-bromobenzylmesitylglyoxal (VI).

The enolic modification of benzylmesitylglyoxal was brominated in cold absolute ethereal solution, producing a golden-yellow oil (VI) which could not be crystallized from any solvent. In acetone solution with hydriodic acid this product is easily reduced to the parent enol. The golden-yellow monobromo compound is 24% enolic. It was dissolved in glacial acetic acid and refluxed with an excess of freshly fused potassium acetate, whereupon potassium bromide separated out. There was no noticeable change in color of the solution. Contrary to the opinion held by Kohler and Brown,[10] and contrary to the mechanism proposed by Blatt,[11] this α-bromo-α-diketone reacts by way of a direct substitution reaction to produce the acetate (VII) of the α-oxy-α-diketone. This substance could not be obtained solid. Its methyl alcoholic solution is of a deep red-wine color. On standing overnight in the cold, this solution deposits a beautiful pale peach-colored solid (VIII), which gives a cherry-red color with alcoholic ferric chloride, and is 100% enolic. This enolic modification of the acetate (VIII) is hydrolyzed simultaneously and cleaved by means of alkaline hydrogen peroxide with the production of benzoic and trimethylbenzoic acids and ethyl acetate.

When the monoacetate (VIII) is refluxed with acetyl chloride it is converted quantitatively into the diacetate (IX). This substance is a pale lemon-yellow solid which produces no color with alcoholic ferric chloride. These acetates are recovered unchanged after refluxing their alcoholic solutions with both hydrochloric and sulfuric acids.

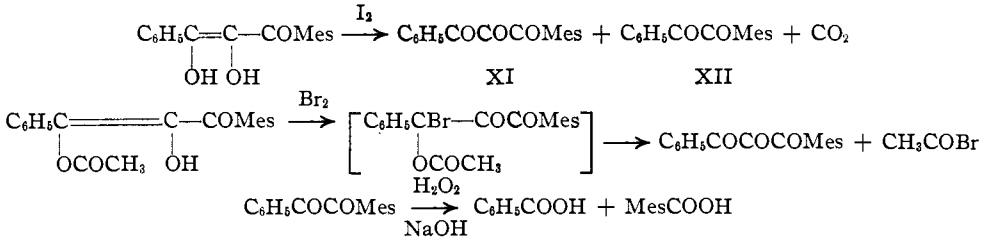
Both the mono- and diacetates dissolve in concd. sulfuric acid with the production of deep orange-colored solutions. When poured over finely crushed ice, an odor of ethyl acetate and a light yellow solid are formed. The yellow solid is the ene-diol (X). It gives a deep greenish-blue color with alcoholic ferric chloride, and is 37% ene-diolic in methyl alcoholic solution as indicated by titration with standard iodine solution.

The ene-diol (X) is not a very stable substance. In the solid state or in solution in peroxide-free ether, it quite readily undergoes autoxidation with production of the tri- and diketones,[12] (XI) and (XII), respectively, and hydrogen peroxide. The course of the reaction is best followed in peroxide-free ether, for thus an acidulated potassium iodide solution rapidly colors up red due to the peroxide oxidation of hydriodic acid to free iodine. The oxidizing substance must be hydrogen peroxide, since oxidation by means of the organic peroxide (XIII) probably would result in a cleavage of the molecule to benzoic and mesitylglyoxylic acids.



(10) E. P. Kohler and F. W. Brown, THIS JOURNAL, **55**, 4299 (1933).
(11) A. H. Blatt, *J. Wash. Acad. Sci.*, **28**, 1 (1938).
(12) Gray and Fuson, THIS JOURNAL, **56**, 739 (1934); Weinstock and Fuson, *ibid.*, **58**, 1233 (1936).

The ene-diol (X) also suffers oxidation in an acidulated iodine solution. The products of this reaction are the tri- and diketones (XI) and (XII), respectively. The triketone is a deep orange-colored solid, melting at 94°; the diketone is pale yellow and melts at 134°. When the monoacetate (VIII) is brominated in chloroform and heated, the resulting yellow compound is exclusively the diketone. The diketone (XII) is cleaved quantitatively by alkaline hydrogen peroxide to benzoic and trimethylbenzoic acids.



This behavior of the triketone (XI) is consistent with what is known of the chemistry of polyketones, for Gray and Fuson[13] have found that dimesityl tetraketone (XIV) upon heating in alcoholic or glacial acetic acid solution is changed into the corresponding triketone (XV). It seems therefore that dimesityl triketone is far more stable than phenylmesityl triketone, a fact which still further substantiates the stabilizing effect of the mesityl group.

$$\underset{\text{XIV}}{\text{MesCOCOCOCOMes}} \longrightarrow \underset{\text{XV}}{\text{MesCOCOCOMes}}$$

Further investigation of the properties of this ene-diol and its derivatives is in progress.

Experimental

Preparation of Oxymethylene-*p*-bromoacetophenone (II).—A solution of 7.0 g. of metallic sodium in a mixture of 30 cc. of absolute alcohol and 100 cc. of absolute benzene was obtained on long refluxing. It solidified on cooling. To this crystalline mass was added 52 g. of *p*-bromoacetophenone dissolved in 35 g. of pure ethyl formate. The reaction mixture warmed up; the alcoholate dissolved; the solution became brown and a crystal meal was formed. It was allowed to stand overnight at room temperature, and was then filtered and washed with alcohol and finally with ether. The yield was 52 g. of cream colored solid. This sodium compound was dissolved in a large volume of water, filtered and acidified with cold dilute sulfuric acid with rapid stirring. A yield of 45 g. of hard yellow needles, melting at 71°, was obtained. Kurt Myer titrations show that this compound is 67% enolic.

The Acetate of Oxymethylene-*p*-bromoacetophenone (III).—A solution of 5.0 g. of oxymethylene-*p*-bromoacetophenone was made by warming with the smallest possible amount of acetic anhydride. To the solution was added one drop of concd. sulfuric acid. The solution turned red and became hot. The mass solidified. It was dried overnight *in vacuo*, yielding 6.2 g. of crude solid. It was crystallized from methyl alcohol in glistening light yellow scales melting at 125°.

Anal. Calcd. for $C_{11}H_9O_3Br$: C, 48.8; H, 3.4. Found: C, 49.0; H, 3.4.

This substance decolorizes permanganate and bromine solutions. It produces no immediate color with alcoholic ferric chloride, but a cherry-red color slowly develops on standing. It is hydrolyzed completely by alcoholic hydrochloric acid to ethyl acetate and *p*-bromoacetophenone, identified by comparison with an authentic sample.

The Benzoate of Oxymethylene-*p*-bromoacetophenone (IV).—To a solution of 2.27 g. of the oxymethylene-*p*-bromoacetophenone in 50 cc. of ether was added 2 g. of benzoyl chloride. Slowly and with constant shaking, 10% sodium hydroxide was added dropwise to this ethereal solution. With the addition of each drop of alkali an orange-red color was produced. The color disappeared on shaking. The addition of sodium hydroxide was continued until the aqueous layer was permanently alkaline. A yellow solid separated out. The ether was blown off, the solid filtered and washed with sodium hydroxide solution and finally with water. The crude dry material weighed 3.5 g. It was recrystallized from methyl alcohol in bright yellow crystals, melting at 112°.

Anal. Calcd. for $C_{16}H_{11}O_3Br$: C, 58.0; H, 3.4. Found: C, 58.4; H, 3.7.

The benzoate also reduces potassium permanganate, adds bromine and very slowly develops a cherry-red color with alcoholic ferric chloride. It is completely hydrolyzed by alcoholic hydrochloric acid to ethyl benzoate and *p*-bromoacetophenone, identified by comparison with an authentic sample.

α-Bromo-oxymethylene-*p*-bromoacetophenone (V).—To a chilled solution of 16.5 g. of bromine in 150 cc. of chloroform was added slowly and with rapid stirring 20 g. of the sodium derivative of oxymethylene-*p*-bromoacetophenone. The solution finally became colorless. Sodium bromide was formed. The suspension was filtered and the sodium bromide washed thoroughly with chloroform. The chloroform was evaporated and the colorless glassy residue was taken up in hot glacial acetic acid from which it crystallized in shining colorless crystals, melting at 112°.

Anal. Calcd. for $C_9H_6O_2Br_2$: C, 35.3; H, 2.0. Found: C, 35.9; H, 2.5.

The bromo compound gives a beautiful light red color in alcoholic ferric chloride solution. In acetone solution it is reduced quantitatively to oxymethylene-*p*-bromoacetophenone by means of potassium iodide in acid solution.

A differential Kurt Meyer titration indicates that the

(13) Gray and Fuson, THIS JOURNAL, **56**, 2100 (1934).

bromo compound is 100% enolic, for two atoms of iodine are liberated per mole of bromo compound.

α-Bromobenzylmesitylglyoxal (VI).—An absolute ethereal solution of 15.5 g. of benzylmesitylglyoxal in 100 cc. of absolute ether was chilled and treated dropwise with the calculated quantity of bromine. With the addition of each drop of bromine the red color faded on shaking. Finally copious fumes of hydrogen bromide were given off. The hydrogen bromide and ether were pumped off, leaving 20.2 g. of a golden-yellow oil which could not be crystallized from any solvent.

Anal. Calcd. for $C_{18}H_{17}O_2Br$: C, 62.3; H, 4.9. Found: C, 62.3; H, 5.1.

The bromo compound gives a red color with alcoholic ferric chloride, and is easily reduced by hydriodic acid to the parent α-diketone. Differential titrations show it to be 24% enolic.

The Acetate of α-Oxybenzylmesityl-α-diketone (VII–VIII).—The bromo compound above (20.2 g.) was dissolved in 100 cc. of glacial acetic acid and refluxed for thirty minutes with 40 g. of freshly fused potassium acetate. Potassium bromide crystallized out. The solution was allowed to cool and was poured into a large volume of water. A deep yellow oil separated out. The yield was 15 g. It was dissolved in methyl alcohol, producing a deep red wine-colored solution, which could not be crystallized immediately. On standing overnight in the cold, however, a very pale peach-colored crystalline solid separated out. The yield was 11 g., melting at 71°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2. Found: C, 74.3; H, 6.4.

It gives a red wine-colored solution with alcoholic ferric chloride and is 100% enolic. It is recovered unchanged after refluxing its alcoholic hydrochloric or alcoholic sulfuric acid solution for one hour.

Upon treatment with alkaline hydrogen peroxide an odor of ethyl acetate is observed and the compound is cleaved, yielding benzoic and trimethylbenzoic acids, each of which was identified by comparison with authentic samples.

The Diacetate of α-Phenyl-β-mesitoylacetylene Glycol (IX).—Excess acetyl chloride was added to 3 g. of the acetate of α-oxybenzyl-α-diketone in which it dissolved. It was refluxed for thirty minutes. The acetyl chloride was pumped off over solid sodium hydroxide. A glassy residue was left. It was dissolved in hot methyl alcohol from which it crystallized in pale lemon-yellow crystals, melting at 131°.

Anal. Calcd. for $C_{22}H_{22}O_5$: C, 72.1; H, 6.0. Found: C, 72.1; H, 6.4.

It produces no color with alcoholic ferric chloride, but reduces permanganate and adds bromine. When refluxed in alcoholic hydrochloric or alcoholic sulfuric acid solution, it is recovered unchanged.

α-Phenyl-β-mesitoylacetylene Glycol (X).—To 30 cc. of chilled concd. sulfuric acid was added 2.5 g. of the monoacetate. In three minutes, with stirring, a deep orange-red transparent solution resulted. This solution was poured over finely crushed ice, with the production of a light yellow solid. The suspension was allowed to stand overnight in the cold protected from air. A granular crystalline solid was obtained on filtering and washing with iced water. The yield was 2.2 g., melting at 79–80°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.4; H, 6.9.

This substance produces a deep green-blue color with alcoholic ferric chloride. The color fades slowly to yellow.

Iodine Titration of Ene-diol.—The following samples of the ene-diol were dissolved in 20 cc. of 95% alcohol each and acidified with 3 cc. of 10% sulfuric acid. Excess of standard iodine solution was then added, and the unused iodine titrated immediately with standard thiosulfate, 1.0 cc. of *N* iodine = 0.142 g. of ene-diol.

No.	Wt. of sample, g.	Vol. of *N* I used as 0.1056 *N* I, cc.	Vol. of *N* thio required as 0.1003 *N* thio, cc.	Vol. of I used up, cc.	% Ene-diol
I	0.0168	1.7334	1.6890	0.0444	37.48
II	.0714	1.8846	1.6990	.1856	36.49
				Mean	36.98

The Tri- and Diketones (XI and XII).—These polyketones are obtained under a variety of conditions.

When the solid ene-diol is exposed to atmospheric oxygen it becomes sticky and finally solidifies. It then produces no color with alcoholic ferric chloride. This solid upon solution in methyl alcohol and chilling gives a deep orange solid, melting at 94°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.14; H, 5.7. Found: C, 77.03; H, 5.8.

The mother liquor from this crystallization on concentrating gives a light yellow solid melting at 134°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4. Found: C, 81.1; H, 6.6.

It is sparingly soluble in methyl alcohol. It is cleaved quantitatively by alkaline hydrogen peroxide to benzoic and trimethylbenzoic acids, identified by comparison with authentic samples.

When an ethereal solution of the ene-diol is allowed to stand for a few minutes, it loses its ability to produce color with alcoholic ferric chloride. It liberates iodine very rapidly from an acidulated potassium iodide solution; and on evaporation leaves a residue which upon crystallization from methyl alcohol yields a deep orange solid, melting at 94° and a lighter yellow substance whose melting point is 134°. Mixed melting points with the above analyzed samples are unchanged.

A solution of 2 g. of the ene-diol in 30 cc. of alcohol was acidified with 5 cc. of 10% sulfuric acid. To this solution approximately 0.1 *N* iodine was added slowly. The alcoholic solution decolorized the iodine solution very rapidly. Finally it was allowed to stand overnight in the presence of excess iodine. Deep orange crystals melting at 94° were obtained. The mother liquor from a recrystallization gave the 134° product.

A solution of 1 g. of the ene-diol in 10 cc. of chloroform was treated in the cold with 0.6 g. of bromine in 5 cc. of chloroform. The chloroform solution avidly absorbed each drop of the bromine. Hydrogen bromide was evolved. The chloroform was pumped off and the residue taken up in methyl alcohol. The product of this crystallization was exclusively the light yellow substance, melting point and mixed melting point with the above analyzed sample unchanged.

A solution of the ene-diol in alcoholic ferric chloride produces a deep green-blue color which gradually fades to yellow on standing. Evaporation of this solution yields a light yellow solid, melting point and mixed melting point with the above 134° melting compound unchanged.

Summary

Herein are reported the preparation and properties of a new ene-diol having the open chain —C=C—C— (OH OH O), and some further evidences of the activating influence of the mesityl nucleus upon α-substituents together with its stabilizing effects on the resulting compound.

WASHINGTON, D. C. RECEIVED MAY 10, 1938

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Derivatives of 4-Aminobenzenesulfonanilide. I

BY G. L. WEBSTER AND L. D. POWERS

Following the observation made by Trefouel, Trefouel, Nitti and Bovet[1] that 4-aminobenzenesulfonamide was a valuable therapeutic agent in the treatment of infections caused by the β-hemolytic streptococcus, a large number of derivatives and analogs of this compound were tested in the search for other compounds which would be effective against the same and other organisms. Biological tests have shown only a few substances which have comparable action against bacterial organisms of any type.

It has been shown by Buttle, Gray and Stephenson[2] and by Rosenthal, Bauer and Branham[3] that, when given in equal molecular doses, 4-aminobenzenesulfonanilide is just as effective against pneumococcic infections in mice as is 4-aminobenzenesulfonamide. It has also been shown[1,3] that the presence of an amino group para to the sulfonamide group is necessary for therapeutic action.

Only a few derivatives of 4-aminobenzenesulfonanilide, in which an amino or a nitro group has been substituted for a hydrogen atom of the anilide ring, have been reported in the literature. Whitby[4] has published results on the protective action of the tartrates of 4,4′-diaminobenzenesulfonanilide and 4,3′-diaminobenzenesulfonanilide against experimental infections in mice and Bauer and Rosenthal[5] have reported their results with the first of these two diamines and with 4-aminobenzenesulfon-4′-nitroanilide. The authors of these papers presented no syntheses or chemical characterization of these compounds.

We have prepared a series of derivatives of 4-aminobenzenesulfonanilide in which a hydrogen atom of the anilide ring has been substituted with a nitro, amino or hydroxyl group in the hope that biological tests might disclose active chemotherapeutic agents.

Preliminary reports to us have indicated that several of these compounds show some slight protective action against experimental streptococcal infections in mice and one, 4-acetaminobenzenesulfon-4′-aminoanilide, has been described as moderately effective.[6] A more detailed report will be published elsewhere by Dr. Long.

Nitro derivatives of 4-acetaminobenzenesulfonanilide were prepared by the action of 4-acetaminobenzenesulfonchloride on a hot solution of the nitroaniline in dimethylaniline.

The corresponding amino derivatives were prepared by the ferrous hydroxide reduction method of Jacobs and Heidelberger.[7]

The hydroxyl derivatives of 4-acetaminobenzenesulfonanilide were prepared by the action of 4-acetaminobenzenesulfonchloride on a hot aqueous solution of the corresponding aminophenol and also by the method used for preparing the nitro derivatives.

Preparation of derivatives of 4-aminobenzenesulfonanilide was accomplished by boiling the acetamino compounds with an alcoholic solution of hydrochloric acid.

Diazotization of 4-acetaminobenzenesulfon-3′-aminoanilide and heating the resulting solution yielded the corresponding 3′-hydroxy derivative. Diazotization of 4-acetaminobenzenesulfon-4′-aminoanilide and boiling the diazonium solution

(1) Trefouel, Trefouel, Nitti and Bovet, *Compt. rend. soc. biol.*, **120**, 756 (1935).

(2) Buttle, Gray and Stephenson, *Lancet*, I, 1286 (1936).

(3) Rosenthal, Bauer and Branham, *U. S. Pub. Health Repts.*, **52**, 662 (1937).

(4) Whitby, *Lancet*, I, 1517 (1937).

(5) Bauer and Rosenthal, *U. S. Pub. Health Repts.*, **53**, 40 (1938).

(6) Private communication from Dr. Perrin H. Long, The Johns Hopkins Hospital.

(7) Jacobs and Heidelberger, THIS JOURNAL, **39**, 1435 (1917).