Methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6.—To an ice-cold mixture of 20 ml. of acetic anhydride, 8 ml. of glacial acetic acid and 0.5 ml. of concentrated sulfuric acid, 2.6 g. (0.012 mole) of methyl 2,4-methylene-D-glucarolactone-3,6[3] was added. The mixture was shaken for forty-five minutes at 0°. The solid dissolved and almost immediately a white precipitate was formed. It was filtered, washed with water and recrystallized from hot water. The yield was (2.1 g.) 68% of the theoretical amount; m. p. 190.6°–192°; $[\alpha]^{27.2}$D + 133 (*c*, 1.99; acetone).

Anal. Calcd. for $C_{10}H_{12}O_8$: C, 46.1; H, 4.6. Found: C, 46.1; H, 4.7.

N,N'-Dimethyl-2,4-methylene-D-glucarodiamide from Methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6.—In 30 ml. of ice-cold methanol 2.1 g. (0.008 mole) of methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6 was suspended. Methylamine was passed through the mixture until the solid dissolved. The solution was allowed to stand at 5–10° overnight. A white precipitate (0.5 g.) was formed; m. p. 217–218° (dec.). The filtrate was evaporated to dryness and crude product was recrystallized from methanol–ether. The yield was (2.1 g.) 95% of the theoretical amount; m. p. 223–224° (dec.) and a specific rotation $[\alpha]^{26.6}$D + 60.0° in methanol (*c*, 0.69), these data being in agreement with those previously found for the N,N'-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N'-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

Methyl-5-propionyl-2,4-methylene-D-glucarolactone-3,6.—To an ice-cold mixture of 35 ml. of propionic anhydride, 15 ml. of propionic acid and 1 ml. of concentrated sulfuric acid, 5.0 g. (0.023 mole) of methyl 2,4-methylene-D-glucarolactone-3,6 was added. The mixture was shaken for forty-five minutes at 0°. The solid dissolved and almost immediately a white precipitate was formed. It was filtered, washed with water and ether and recrystallized from hot water. The yield was (5.0 g.) 79% of the theoretical amount; m. p. 164.6–165.8°; $[\alpha]^{28.6}$D + 153° (*c*, 2.06; chloroform).

Anal. Calcd. for $C_{11}H_{14}O_8$: C, 48.2; H, 5.1. Found: C, 48.2; H, 5.3.

N,N'-Dimethyl-2,4-methylene-D-glucarodiamide from Methyl-5-propionyl-2,4-methylene-D-glucarolactone-3,6.—In 15 ml. of ice-cold methanol 0.6 g. of methyl 5-propionyl-2,4-methylene-D-glucarolactone-3,6 was suspended. Methylamine was passed through the mixture until the solid dissolved and the solution allowed to stand at 5–10° overnight. A white precipitate was formed; m. p. 223° (dec.). The crude product was recrystallized from methanol–ether and the specific rotation determined in methanol $[\alpha]^{27.2}$D + 61.7° (*c*, 1.03); these data are in agreement with those previously found for the N,N'-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N'-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

Summary

1. The nitric acid oxidation of 2,4:3,5-dimethylene-D-gluconic acid has been shown to yield 2,4-methylene-D-glucarolactone-3,6 in 67% yield.

2. An attempted controlled acetolysis of dimethyl-2,4-methylene-D-glucarate and of methyl 2,4-methylene-D-glucarolactone-3,6 did not remove the 2,4-methylene acetal ring.

3. Some N,N'-disubstituted-2,4-methylene-D-glucarodiamides have been prepared which appear to be new.

RIO PIEDRAS, PUERTO RICO RECEIVED APRIL 7, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE]

Some N-Aminophenylarsanilic Acids

BY ROBERT L. MCGEACHIN

Since it was found recently that Melarsen,[1,2] a diamino triazino derivative of *p*-arsanilic acid, is an effective trypanocidal agent, it was decided to study the preparation of some N-aminophenylarsanilic acids.

Barber[3] condensed 3-nitro-4-chlorophenylarsonic acid with certain aromatic amines to give N-phenylarsanilic acids but no studies on the condensation of dinitrochlorobenzene with *p*-arsanilic acid have been made. However, Linke[4] condensed dinitrochlorobenzene with *p*-aminobenzoic acid and Kogan, Voronov and Lyubiteleva[5] condensed dinitrochlorobenzene with *p*-aminophenol-3,5-disulfonic acid.

Heating *p*-arsanilic acid and 2,4-dinitrochlorobenzene in 5% aqueous sodium hydroxide for seven hours proved to be an unsatisfactory method since excessive hydrolysis of the 2,4-dinitrochlorobenzene to 2,4-dinitrophenol occurred under these conditions. Sodium acetate and calcium carbonate (in aqueous alcohol medium) were found to be satisfactory condensing agents, however, with the latter the better of the two since it produced less by-products than the sodium acetate and gave better yields of N-2,4-dinitrophenylarsanilic acid. N-2,4-Diaminophenylarsanilic acid was prepared from this dinitro compound.

It was found that 3-nitro-4-chlorophenylarsonic acid would react with *p*-aminodimethylaniline and *p*-aminodiethylaniline under conditions outlined by Barber[3] to give N-4-dimethylaminophenyl-3-nitroarsanilic acid and N-4-diethylaminophenyl-3-nitroarsanilic acid. Attempts to reduce the nitro groups in these compounds to amino groups were unsuccessful, however, presumably due to the instability of the products formed.

Experimental

N-2,4-Dinitrophenylarsanilic Acid (I). A.—Six grams of *p*-arsanilic acid, 5 g. of 2,4-dinitrochlorobenzene and

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[1] Friedheim, THIS JOURNAL, **66**, 1775 (1944).

[2] Banks, *et al.*, *ibid.*, **66**, 1771 (1944).

[3] Barber, *J. Chem. Soc.*, 471 (1929).

[4] Linke, *J. prakt. Chem.*, **91**, 202 (1915).

[5] Kogan, Voronov and Lyubiteleva, *Anilinokrasochnaya Prom.*, **3**, 153 (1933).

0.5 g. of calcium carbonate were added to 100 ml. of 50% aqueous ethyl alcohol and the mixture heated under reflux on a steam-bath for eight hours. The reaction mixture was cooled, diluted with 50 ml. of water and filtered. The residue was dissolved in 10% sodium hydroxide (the solution was deep blood-red in color), treated with 0.5 g. of activated charcoal and the solution filtered. On acidification of the solution to congo red with concd. hydrochloric acid, a canary-yellow solid precipitated. After allowing the acidified mixture to stand overnight in the ice-box, the product was filtered off and dried at 130° for twelve hours giving a yield of 3.8 g. (41%). This compound did not melt below 250°.

Anal.[6] Calcd. for $C_{12}H_{10}O_7N_3As$: As, 19.58. Found: As, 19.44.

B.—I was also prepared from *p*-arsanilic acid and 2,4-dinitrochlorobenzene using sodium acetate as the condensing agent. In this reaction a considerable quantity of a red-orange solid was formed as a by-product. The product was isolated and purified, the same procedure used in method A giving a yield of 30%.

Anal. Calcd. for $C_{12}H_{10}O_7N_3As$: As, 19.58. Found: As, 19.16.

N-2,4-Diaminophenylarsanilic Acid.—One gram of I was reduced using 10.1 g. of ferrous sulfate in the method of Jacobs, Heidelberger and Rolf.[7] The product was a dark-red solid which rapidly turned black in the presence of air. The yield was 0.3 g. (36%).

Anal. Calcd. for $C_{12}H_{14}O_3N_3As$: As, 23.22. Found: As, 23.10.

N-4-Dimethylaminophenyl-3-nitroarsanilic Acid.—Four grams of 3-nitro-4-chlorophenylarsonic acid was dissolved in 10 ml. of 10% sodium hydroxide and 8 ml. of water, 3 ml. of *p*-aminodimethylaniline added and the mixture heated under reflux in an oil-bath at 140° for eight hours. On addition of concd. hydrochloric acid to the neutral point, a sticky dark-brown solid precipitated. This product was purified by twice redissolving in 5% sodium hydroxide, charcoaling the solution, filtering and reacidifying. The red-brown solid was filtered off, washed well with water and alcohol and dried at 100° for twenty-four hours to yield 3 g. of product (56%).

Anal. Calcd. for $C_{14}H_{16}O_5N_3As$: As, 19.40. Found: As, 19.29.

N-4-Diethylaminophenyl-3-nitroarsanilic Acid.—This product was prepared by the same method used for the dimethylamino compound. It was a red-brown solid. The yield was 3.5 g. (60%).

Anal. Calcd. for $C_{16}H_{20}O_5N_3As$: As, 18.32. Found: As, 18.36.

Summary

The reaction of *p*-arsanilic acid with 2,4-dinitrochlorobenzene to form N-2,4-dinitrophenylarsanilic acid has been studied. N-2,4-Diaminophenylarsanilic acid has been prepared.

N-4-Dimethylaminophenyl-3-nitroarsanilic acid and N-4-diethylaminophenyl-3-nitroarsanilic acid have been prepared.

LOUISVILLE, KY. RECEIVED AUGUST 3, 1949

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[6] Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

[7] Jacobs, Heidelberger and Rolf, *ibid.*, **40**, 1581 (1918).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

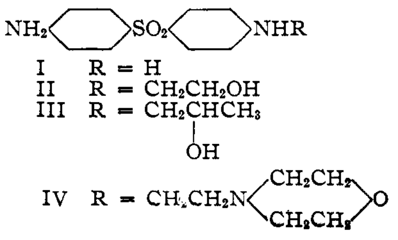
Monosubstituted Diaminodiphenyl Sulfones

BY JOHN WEIJLARD AND EDWARD SWANEZY

The antistreptococcal and antitubercular efficacy of substituted 4,4′-diaminodiphenyl sulfones appears to be increased if one amino group is free; consequently a number of monosubstituted diaminodiphenyl sulfones have been reported upon recently.[1,2] These compounds have generally been prepared either by reducing 4-nitro-4′-halodiphenyl sulfone followed by reaction of the resultant 4-amino-4′-halodiphenyl sulfone with the requisite amine,[1] or by alkylation of 4-nitro-4′-aminodiphenyl sulfone followed by reduction of the nitro group.[2] In either case the methods are laborious, the replacement reactions are often sluggish and the yields poor. This is particularly noticeable when 4-nitro-4′-aminodiphenyl sulfone is subjected to hydroxyethylation with compounds such as ethylene bromohydrin.[2]

A simple and rapid method has now been found for these compounds consisting of treating the readily available 4-acetylaminobenzene sulfonyl chloride with monochlorobenzene in presence of aluminum chloride to give 4-acetylamino-4′-chlorodiphenyl sulfone in 88% yield and of reacting the latter with, for instance, ethanolamine or isopropanolamine in presence of copper to yield the corresponding 4-amino-4′-(β-hydroxyethylamino)- or (β-hydroxypropylamino)-diphenyl sulfone, respectively, in 70 to 85% yields. Other amines, such as N-aminoethylmorpholine, reacted readily to give 4-amino-4′-(β-morpholineëthylamino)-diphenyl sulfone in high yield. With ammonia water, 4,4′-diaminodiphenyl sulfone was obtained in good yield. It is noteworthy that deacetylation takes place simultaneously with the alkylations.

A simplified method for the preparation of the parent substance, 4,4′-diaminodiphenyl sulfone, is thus available, and in addition a general method for preparing a large number of monosubstituted diaminodiphenyl sulfones, by selecting the proper amine and catalyst. The preparation of four compounds in this class is described.



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[1] Amstutz, Fehnel and Woods, THIS JOURNAL, **69**, 1922 (1947).

[2] Jackson, *ibid.*, **70**, 680 (1948).