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Sulfaquinoxaline. II. A New Synthesis of 2-Aminoquinoxaline[1]

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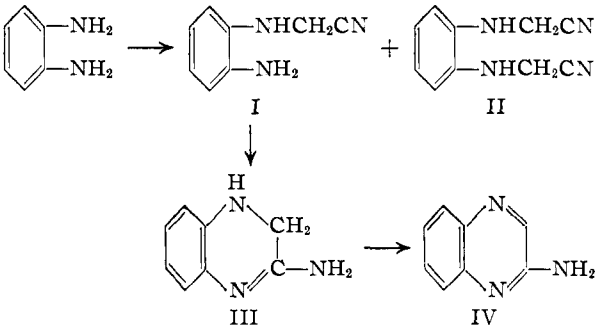
A new three step synthesis of 2-aminoquinoxaline has been described which consists of the formation of N-cyanomethyl-*o*-phenylenediamine followed by cyclization to 2-amino-3,4-dihydoquinoxaline and dehydrogenation of the latter. The method has been applied to the synthesis of alkyl-substituted 2-aminoquinoxalines.

The drug 2-sulfanilamidoquinoxaline first attracted attention as a prophylactic agent in avian malaria[2] because of its unique pharmacological properties.[3] More recently sulfaquinoxaline has proved valuable in veterinary medicine and especially for use against coccidia of chickens and turkeys and for control of acute cholera of chicks and turkeys.[4]

The 2-aminoquinoxaline (IV) used in preparation of sulfaquinoxaline was originally obtained from alloxazine by cleavage with concentrated sulfuric acid or by decarboxylation of the 2-aminoquinoxaline-3-carboxylic acid produced by cleavage of alloxazine with ammonia.[1] Both of these alternatives are relatively expensive, involve difficultly controlled reactions and give only mediocre yields. Synthesis of 2-aminoquinoxaline by chlorination of 2-hydroxyquinoxaline followed by amination of the 2-chloroquinoxaline has been employed but it suffers from the lack of a practical synthesis of the hydroxyquinoxaline.[5]

Unsuccessful attempts to obtain 2-aminoquinoxaline from the reaction of *o*-phenylenediamine with glyoxylic nitrile or dichloroacetonitrile, as well as fruitless attempts to aminate quinoxaline with sodamide have also been reported.[6]

A new and practical three step synthesis has now been devised which gives 2-aminoquinoxaline in 65% yield from *o*-phenylenediamine. Formaldehyde and hydrogen cyanide react with *o*-phenylenediamine in aqueous methanol at a *p*H of about 6.5 to give crude N-cyanomethyl-*o*-phenylenediamine in 90–93% yield. This product, which is a mixture containing 80–85% N-cyanomethyl-*o*-phenylenediamine (I) while the remainder is N,N′-dicyanomethyl-*o*-phenylenediamine (II), is cyclized to 2-amino-3,4-dihydroquinoxaline (III) by treatment with potassium hydroxide in methanol solution. The 2-amino-3,4-dihydroquinoxaline (III) need not be isolated for conversion to 2-aminoquinoxaline since addition of hydrogen peroxide to the cyclization solution in the presence of a catalytic amount of a transfer agent such as ferric ion brings about the required dehydrogenation. 2-Aminoquinoxaline is obtained in 70–75% yield from the crude N-cyanomethyl-*o*-phenylenediamine by this scheme and the product is sufficiently pure for conversion to sulfaquinoxaline without further purification.



The cyanide reaction is carried out by generating hydrogen cyanide *in situ* from hydrochloric acid and sodium cyanide. The *p*H must then be adjusted to about 6.5 since operation at either higher or lower *p*H results in sharply reduced yields. Hydrogen cyanide itself may be conveniently employed since this reagent automatically provides the correct acidity for the reaction.

N-Cyanomethyl-*o*-phenylenediamine was also prepared by reaction of *o*-phenylenediamine with chloroacetonitrile or glycolonitrile but neither method was comparable to that using formaldehyde and hydrogen cyanide. These alternate methods gave similar mixtures of the mono- and dicyanomethyl derivatives of *o*-phenylenediamine.

Isolation of pure N-cyanomethyl-*o*-phenylenediamine (free from contaminating dicyanomethyl compound) by crystallization was both difficult and wasteful, but it could be accomplished readily *via* the quite insoluble N-cyanomethyl-*o*-phenylenediamine *p*-toluenesulfonate. The pure monocyano compound gave 2-aminoquinoxaline in 85% yield by cyclization and dehydrogenation. However, for the synthesis of 2-aminoquinoxaline there is no advantage in such purification since the contaminating dicyanomethyl compound does not interfere in the subsequent steps. Even pure N,N′-dicyanomethyl-*o*-phenylenediamine, prepared by further treatment of crude N-cyanomethyl-*o*-phenylenediamine with formaldehyde and hydrogen cyanide, gave no crystalline product after cyclization and dehydrogenation in the usual manner.

It is of considerable interest that we have been unable to achieve this cyclization in any solvent but methanol. This specificity is in marked contrast to the situation with the alkaline catalyst. Thus sodium hydroxide, potassium hydroxide, sodium methylate, trimethylphenyl- and trimethylbenzylammonium hydroxide have all been found

(1) For the preceding paper in this series see Weijlard, Tishler and Erickson, THIS JOURNAL, **66**, 1957 (1944).

(2) SN 3078, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Ed., J. W. Edwards, 1946.

(3) Seeler, Mushett, Graessle and Silber, *J. Pharmacol.*, **82**, 357 (1944); Mushett and Silber, *ibid.*, **91**, 84 (1947); Smith and Robinson, *Proc. Exptl. Biol. Med.*, **57**, 292 (1944); Silber and Clark, *Am. J. Med. Sci.*, **209**, 813 (1945); *Arch. Biochem.*, **10**, 9 (1946).

(4) Peterson, *Am. J. Vet. Res.*, **9**, 77 (1948); Grumbles, Delaplane and Higgins, *Poultry Sci.*, **27**, 411 (1948); *ibid.*, **27**, 605 (1948); Peterson, *Vet. Med.*, **44**, 126 (1949); Armstrong, *ibid.*, **44**, 306 (1949); Delaplane and Higgins, *Cornell Vet.*, **38**, 267 (1948); Moore, *ibid.*, **39**, 223 (1949).

(5) Perkin and Riley, *J. Chem. Soc.*, **123**, 2399 (1923); Gowenlock, Newbold and Spring, *ibid.*, 622 (1945); Platt, *ibid.*, 1310 (1948); Wolf, Pfister, Beutel, Wilson, Robinson and Stevens, THIS JOURNAL, **71**, 6 (1949).

(6) Jensen, *Acta Chem. Scand.*, **2**, 91 (1948).

satisfactory. It appears likely that any strong base having sufficient solubility can be used. However, from experiments using potassium hydroxide in ethyl, isopropyl or *n*-butyl alcohol and sodium ethylate in ethyl alcohol, neither 2-amino-3,4-dihydroquinoxaline nor 2-aminoquinoxaline could be obtained. Oily and tarry products resulted, and in no case was any crystalline substance isolated.

The reaction involved in this cyclization, addition of an aromatic amine to a nitrile group with formation of a cyclic amidine, is similar to the formation of 2-aminoquinoline from *o*-aminocinnamonitrile as described by Pschorr.[7] Cyclization of *o*-aminocinnamonitrile was carried out with sodium ethylate in alcohol at the boiling point of the mixture.

Dehydrogenation of the 2-amino-3,4-dihydroquinoxaline is preferably done with hydrogen peroxide and a trace of transfer agent, but air or oxygen can be substituted for the former. In the absence of a transfer agent, the reaction is very slow and yields are slightly lower than normal. Satisfactory results were obtained with trace amounts of ferrous chloride, ferric sulfate or lead dioxide, employed as carriers, whereas manganese dioxide or manganese chloride were less satisfactory.

From one run, in which dehydrogenation was apparently incomplete, a nicely crystalline lemon yellow substance was isolated which melted higher than either 2-aminoquinoxaline or its dihydro derivative, and which gave only the former on further oxidation. This product was shown to be a molecular compound of 2-aminoquinoxaline and 2-amino-3,4-dihydroquinoxaline since it crystallized out when equimolecular amounts of these compounds were combined in methanol solution. The resemblance to the formation of quinhydrone is immediately evident.

The method described appears to be general and it has been successfully applied to the synthesis of a number of alkyl, halo and alkoxy substituted 2-aminoquinoxalines also reported to have been prepared by other methods.[5,8] Of special interest is the exclusive formation of 2-amino-8-methylquinoxaline, m.p. 135.5–136°, from 3-methyl-1,2-diaminobenzene. From the glyoxalate synthesis,[5] only the isomer of melting point 202–203° is obtained, and this compound has been shown by Platt and Sharp[8] to be 2-amino-5-methylquinoxaline. These authors also isolated a low melting isomer from the mixture obtained by sulfuric acid cleavage of a mixture of 5- and 8-methylalloxazines. From comparison of the melting points, it appears likely, as Platt and Sharp pointed out, that their product (m.p. 129°) was essentially 2-amino-8-methylquinoxaline contaminated with some of the 5-methyl isomer.

Experimental

Crude N-Cyanomethyl-*o*-phenylenediamine. A. Formaldehyde and Hydrogen Cyanide.—A mixture of 540 g. (5 moles) of *o*-phenylenediamine and 486 cc. of methanol was stirred and the temperature held below 30° while 486 cc. of concentrated hydrochloric acid was added gradually. A solution of 294 g. (5.7 moles) of sodium cyanide (95%) in 700 cc. of water was then added over fifteen to 30 minutes while the temperature was held below 30°. The thin slurry of *o*-phenylenediamine which resulted was carefully adjusted to a *p*H of 6.5 and then warmed to 40–45°. Aqueous formaldehyde (417 g., 5.14 moles, 36–38%) was added gradually over twenty-five or 30 minutes. The reaction is mildly exothermic and proceeds with solution of the *o*-phenylenediamine followed by precipitation of crude N-cyanomethyl-*o*-phenylenediamine. A temperature of 40–45° was maintained throughout the addition, after which the mixture was stirred an additional hour without cooling but below the 45° maximum temperature. The slurry was cooled to 0–5° for an hour, filtered and washed free of inorganic salts with ice-water. The weight of pale tan granular product after drying at 50° was 662 g. (90% yield), m.p. 103–106°.

This material was found by solubility analysis to be about 80% N-cyanomethyl-*o*-phenylenediamine, while the remainder was largely N,N'-dicyanomethyl-*o*-phenylenediamine.

B. Glycolonitrile.—A mixture of 250 cc. of water, 135 g. (0.125 mole) of *o*-phenylenediamine and 142.5 g. (0.125 mole) of commercial 50% aqueous glycolonitrile was warmed to 30–35° and the *p*H adjusted to 6.5–6.7 by addition of dilute sodium hydroxide solution. The reaction mixture was then warmed to 60–65° and held within this range for two hours by application of heat or cooling as necessary. Mild heat evolution occurred for about an hour after 60° was reached. The diamine dissolved at about 50° and after about 20 minutes at 60–65° an oil separated and upon seeding gradually turned crystalline. After two hours at 60–65°, the slurry was cooled to room temperature for two hours, filtered and the residue washed with water. After drying at 45–50°, the sandy pale brown product weighed 151–156.5 g. (82–85%), m.p. 101–105°.

Solubility analysis[9] indicated the composition to be 80% N-cyanomethyl-*o*-phenylenediamine, 14% N,N'-dicyanomethyl-*o*-phenylenediamine and the rest an unidentified dark and tarry material.

N-Cyanomethyl-*o*-phenylenediamine *p*-Toluenesulfonate.—A suspension of 1048 g. (5.5 moles) of *p*-toluenesulfonyl chloride in 1670 cc. of water was stirred and heated under reflux on the steam-bath until formation of a clear solution indicated that hydrolysis was complete. A hot solution of 736 g. (5 moles) of crude N-cyanomethyl-*o*-phenylenediamine in 1 l. of methanol was added to the *p*-toluenesulfonic acid solution whereupon the *p*-toluenesulfonate crystallized out in thick rods. The slurry was stirred at 0–5° for an hour and then filtered and washed with two 500-cc. portions of methanol–water (1:2). The product weighed 1354.5 g. (84.7% yield), m.p. 178–180°.

For recrystallization, 400 cc. of water was heated to 90° and 63.6 g. of the crude *p*-toluenesulfonate added. Solution occurred in a few minutes (long heating caused darkening and a dark product) and after filtration and refrigeration the *p*-toluenesulfonate was collected, washed and dried; weight 55.1 g. (86.5% recovery), m.p. 179–181°. A small sample further purified by recrystallization from methanol gave slender white needles of m.p. 181.5–182.5°.

Anal. Calcd. for $C_{15}H_{17}O_3N_3S$: C, 56.40; H, 5.37; N, 13.17. Found: C, 56.37; H, 5.10; N, 13.22.

N-Cyanomethyl-*o*-phenylenediamine (I).—Ten grams of N-cyanomethyl-*o*-phenylenediamine *p*-toluenesulfonate, m.p. 179–181°, was suspended in 10 cc. of water and stirred for an hour after addition of 20 cc. of 2.5 *N* sodium hydroxide. The free base was collected, washed and dried, weight 4.1 g. (89% yield), m.p. 109.5–111.5°. Solution in hot isopropyl alcohol (4 cc. per gram) followed by filtration and crystallization at 0–5° gave lustrous pale yellow plates of m.p. 110.5–111.5° in 94% recovery. This material was found 96% pure by solubility analysis.

Anal. Calcd. for $C_8H_9N_3$: C, 65.27; H, 6.16; N, 28.54. Found: C, 64.91; H, 6.17; N, 28.63.

A sample further purified by sublimation (97.4% by solubility analysis) showed no change in melting point and was very pale yellow in color.

Dilute solutions of N-cyanomethyl-*o*-phenylenediamine in 2.5 *N* hydrochloric acid give an immediate blood red color on addition of small amounts of sodium nitrite, lead dioxide

(7) Pschorr, *Ber.*, **31**, 1289 (1898).

(8) Platt and Sharp, *J. Chem. Soc.*, 2129 (1948).

(9) T. J. Webb, *Anal. Chem.*, **20**, 100 (1948).

or ferric chloride. When hydrogen peroxide is added, color development occurs more slowly. *o*-Phenylenediamine exhibits a very similar behavior with these oxidizing agents.

2-Aminoquinoxaline.—A solution of 14.0 g. of potassium hydroxide in 600 cc. of methanol was prepared in a flask equipped with stirrer, thermometer, condenser and nitrogen inlet. Under a nitrogen atmosphere and with the temperature at 35–40°, 66.3 g. (0.45 mole) of crude N-cyanomethyl-*o*-phenylenediamine was added and stirring continued until solution was complete. The solution was then held at 35–40° under a slight positive nitrogen pressure for 15 to 20 hours. After this period, treatment of a few drops of the solution with dilute hydrochloric acid and sodium nitrite produced only a pale orange color, showing essentially complete reaction of the cyanomethyl compound.

To the reaction mixture maintained at 25–30° was added 0.6 g. of finely ground ferrous chloride and then over a period of four hours, 152 g. of 10% hydrogen peroxide solution. The slight excess of peroxide was removed by the addition of sodium bisulfite (0.5 g.). The reaction mixture was treated with 3.0 g. of Norite and filtered to give a clear but dark brown solution having an ammoniacal odor.

The mixture was subjected to distillation to remove the methanol until the liquid temperature reached 80°. At this point 300 cc. of water was added and distillation continued until the liquid temperature reached 96°. After stirring the resulting mixture at room temperature for several hours, the product was collected and washed free of alkali; weight 45.5–48.8 g.; 70–75% yield; m.p. 155–157°. This material is about 95% pure (solubility analysis).

Identical treatment of purified (94%) N-cyanomethyl-*o*-phenylenediamine gave 2-aminoquinoxaline in 84.7% yield.

N,N'-Dicyanomethyl-*o*-phenylenediamine.—A solution of 36.8 g. (0.25 mole) of crude N-cyanomethyl-*o*-phenylenediamine in 115 cc. of 2.5 *N* hydrochloric acid and 130 cc. of methanol was warmed to 50° and a solution of 14.7 g. of sodium cyanide in 25 cc. of water added over ten minutes. After adjustment of the *p*H to 6.5 with dilute hydrochloric acid, 21 g. of 36–38% formaldehyde was added over 15 minutes while the temperature was held between 55 and 65°. The crystalline slurry was stirred an additional hour and then stored in the refrigerator overnight. The product weighed 40.4 g. (86.8% yield), m.p. 127–130°.

Recrystallization of 25 g. from 175 cc. of ethyl acetate (2 g. Norite) gave, after cooling to 0–5°, 65% recovery of material of m.p. 132.5–134°. A sample of this product recrystallized from isopropyl alcohol formed very pale yellow diamond-shaped prisms of m.p. 133.5–135°. The purity by solubility analysis was 99.3 ± 0.2%.

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.74; H, 5.23; N, 30.33.

N,N'-Dicyanomethyl-*o*-phenylenediamine is difficultly soluble in hot water or hot benzene. It dissolves readily in ethyl acetate, somewhat less readily in methanol or ethanol, and still less readily in isopropyl alcohol.

2-Amino-3,4-dihydroquinoxaline.—A suspension of 7.4 g. (0.05 mole) of crude N-cyanomethyl-*o*-phenylenediamine in 65 cc. of methanol was stirred and treated with a solution of 3.1 g. (0.055 mole) of KOH in 50 cc. of methanol. After standing at room temperature for 24 hours under a nitrogen atmosphere, the clear solution was concentrated to dryness (nitrogen atmosphere) under reduced pressure. The residue was slurried with a little water and the crude product collected by filtration. After washing and drying *in vacuo*, the weight was 5.5 g. (74.3% of theory), m.p. 140–142°.

This material gave no color when treated with sodium nitrite in dilute acid solution. It was readily dissolved by dilute hydrochloric acid, pyridine or isopropyl alcohol, less easily by ethyl acetate or benzene. Recrystallization from benzene and petroleum ether gave pale yellow needles, m.p. 142–144°.

Anal. Calcd. for $C_8H_9N_3$: C, 65.27; H, 6.16; N, 28.54. Found: C, 65.12; H, 6.08; N, 28.63, 28.43.

The melting point of this material is not sharply defined, probably due to the tendency to oxidize. The typical hard prisms obtained from ethyl acetate melted at 148–154°. A sample prepared by sublimation at 155° and 0.3 mm. sintered at 140°, melted partially at 143–145° and finally gave a clear melt at 151°.

A small sample (0.5 g.) refluxed for 1.5 hours with 10 cc. of 10% sodium hydroxide solution evolved ammonia. After acidification with acetic acid and refrigeration, tan needles separated which, after washing and drying at 100°, weighed 0.42 g., m.p. 136–138°. A mixed melting point with authentic 2-hydroxy-3,4-dihydroquinoxaline was not depressed. By recrystallizing from water and drying at low temperature, the monohydrate of 2-hydroxy-3,4-dihydroquinoxaline, m.p. *ca.* 100° was obtained.

Molecular Compound of 2-Aminoquinoxaline and 2-Amino-3,4-dihydroquinoxaline.—A cyclization solution which had been exposed to air for a day and then concentrated to dryness without an inert atmosphere, yielded 0.82 g. (from 1.47 g. crude N-cyanomethyl-*o*-phenylenediamine) of lemon yellow material of m.p. 158–160° with decomposition. Mixtures with 2-aminoquinoxaline and its dihydro derivative melted lower. Oxidation with ferric chloride yielded only 2-aminoquinoxaline.

A warm solution of 0.436 g. (0.003 mole) of 2-aminoquinoxaline (m.p. 154–156°) in 2 cc. of methanol was treated with 0.442 g. (0.003 mole) of 2-amino-3,4-dihydroquinoxaline (m.p. 140–143°). A clear solution was formed from which very soon a yellow-orange crystalline product separated; m.p. 162–163°. When mixed with a sample of the above product, no change in m.p. was observed.

2-Amino-8-methylquinoxaline.—N-(2-Amino-3-methylphenyl)-glycine nitrile was prepared from 3-methyl-1,2-diaminobenzene using hydrogen cyanide and formaldehyde exactly as described for the unsubstituted compound. The crude product, m.p. 74–84°, was cyclized using potassium hydroxide and the resulting dihydro compound oxidized with hydrogen peroxide to give crude 2-amino-8-methylquinoxaline, m.p. 129–131°, in 51% yield. Recrystallization from benzene gave material of m.p. 135.5–136° which was shown by analysis to be the monohydrate.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.70. Found: C, 61.33; H, 5.95; N, 23.30.

After drying at 100° and 1–2 mm. anhydrous material of identical melting point was obtained.

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70. Found: C, 68.01; H, 5.79.

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