

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

THE RELATION OF QUINOXALINE TO THE AMMONIA SYSTEM

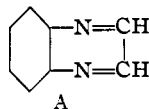
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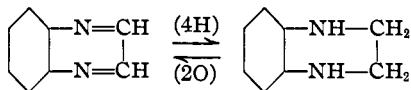
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In a recent article¹ the structure of quinoline was discussed from the standpoint of the ammonia system of compounds of Franklin and co-workers, and it was there pointed out that this compound contains the ammono aldehyde grouping —CH=N— , and so should be expected to display properties analogous to those of aldehydes of the water system. In the present work it is desired to apply similar reasoning to the structure of another heterocyclic compound, quinoxaline, and to present experimental confirmation.

From the conventional formula for quinoxaline, A, it is seen that two adjacent ammono aldehyde groups are present in the molecule, and hence it is to be regarded formally as an ammono 1,2-dialdehyde, or ammonoglyoxal.² Therefore the properties of quinoxaline, in so far as they involve the heterocyclic ring, should be those of an ammono glyoxal. Some previously known reactions are in accord with this analogy. Thus quinoxaline is synthesized by the action of *o*-phenylenediamine on glyoxal,³ a reaction which may be regarded as the ammonolysis of glyoxal by a substituted ammonia, the product being a substituted ammono glyoxal.



On reduction quinoxaline behaves as an ammono dialdehyde, yielding the corresponding ammono diprimary alcohol, 1,2,3,4-tetrahydroquinoxaline, which may be oxidized back to quinoxaline.⁴



Several new reactions of quinoxaline have been carried out, the results of which in the main substantiate still further the analogy between this compound and glyoxal.

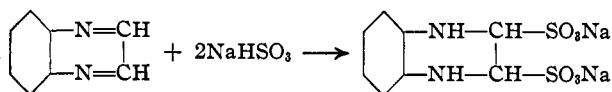
Quinoxaline and Bisulfites.—Glyoxal behaves as a typical dialdehyde in uniting with two equivalents of acid sulfites. Similarly, quinoxaline has been found to add very readily two equivalents of sodium bisulfite, the solid addition product being easily decomposed by bases with regeneration of quinoxaline.

¹ Bergstrom and McAllister, *THIS JOURNAL*, **52**, 2845 (1930).

² More correctly, it is to be regarded as an ammono dialdehyde diacetal, since the third valences of the nitrogen atoms are united to an *o*-phenylene group.

³ Hinsberg, *Ann.*, **237**, 327 (1887).

⁴ Merz and Ris, *Ber.*, **20**, 1191 (1887). See also Meisenheimer and Wieger, *J. prakt. Chem.*, [2] **102**, 45–62 (1921).



Quinoxaline.—This was prepared by the method of Hinsberg⁵ from glyoxal sodium bisulfite and *o*-phenylenediamine. The glyoxal was prepared by the method of Pollak,⁶ and the *o*-phenylenediamine according to the method of Hinsberg and König.⁶ The quinoxaline was obtained as a colorless crystalline mass, m. p. 32.0° (corr.),⁷ and boiling at 229° (corr.) at 760 mm. It was very soluble in water and organic solvents.

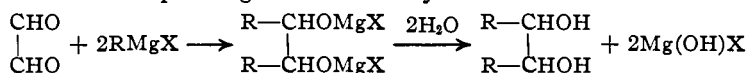
Quinoxaline Sodium Bisulfite.—Quinoxaline was added to a nearly saturated aqueous solution of slightly more than two equivalents of sodium bisulfite. Upon the addition of two volumes of ethyl alcohol, a very voluminous precipitate of fine white needles formed. This was filtered off, dissolved in a little water and reprecipitated with alcohol. Samples for analyses were dried in a vacuum over sulfuric acid.

Anal. Subs., 0.4839, 0.1667; Na₂SO₄, 0.2004, 0.0691. Calcd. for C₈H₈O₆N₂S₂Na₂: Na, 13.61. Found: Na, 13.41, 13.42.

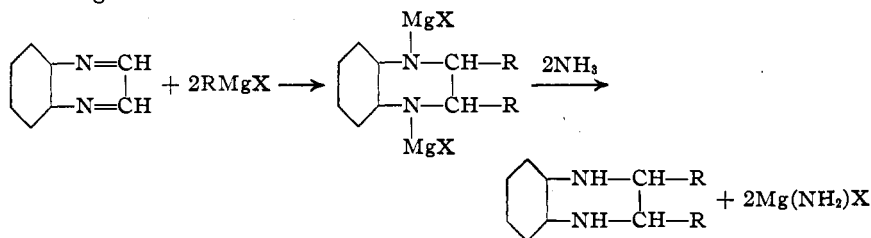
The product decomposed on heating. By treatment with aqueous solutions of bases, quinoxaline and a neutral sulfite were formed. Acids caused evolution of sulfur dioxide.

Quinoxaline reacted slowly with sulfurous acid, yielding some sulfuric acid, and an amorphous blue solid which was not further investigated.

Quinoxaline and the Grignard Reagent.—Monomeric glyoxal reacts with two equivalents of a Grignard reagent,⁸ the product yielding on hydrolysis the corresponding *dl*-di-secondary alcohol.



Quinoxaline has been found to behave in precisely analogous fashion, giving as the final product the corresponding *dl*-ammono di-secondary alcohol,^{8a} *i. e.*, *dl*-1,2,3,4-tetrahydro-2,3-dialkyl-(or aryl)-quinoxaline, in good yield. *dl*-Tetrahydro-diphenyl- and *dl*-tetrahydro-dimethylquinoxalines were thus prepared, and the method is suggested for the synthesis of other homologs.



⁵ Pollak, *Monatsh.*, **15**, 469 (1894).

⁶ Hinsberg and König, *Ber.*, **28**, 2947 (1895).

⁷ Hinsberg gives 27° as the melting point.

⁸ Wren and Still, *J. Chem. Soc.*, **103**, 1770 (1913).

^{8a} Strictly speaking, if the phenylene group is taken into consideration in the naming, we should speak of the di-alkyltetrahydroquinoxalines as mixed ammono di-secondary alcohol-dihydric phenols.

dl-1,2,3,4-Tetrahydro-2,3-diphenylquinoxaline.—Three grams of quinoxaline in absolute ether was added slowly to ethereal phenylmagnesium bromide (2.2 equivalents) in an atmosphere of nitrogen. The reaction was immediate and vigorous, with precipitation of a semi-solid dark brown addition compound. After two hours' standing this was decomposed by careful addition of liquid ammonia (water may also be used). The ammonia was evaporated and the product was extracted with ordinary ether, leaving a residue of ammono basic magnesium bromide. The ether solution was steam distilled, ether first coming over and finally a little diphenyl, the residue being a clear brown gum, vitreous when cold. It was treated with hot concentrated hydrochloric acid and the resulting solid hydrochloride was recrystallized from glacial acetic acid as fine white needles. This was then decomposed with hot aqueous ammonia, regenerating the free base as a colorless vitreous mass, very difficult to crystallize. It was obtained from alcohol as colorless plates, m. p. 106° (corr.). With alcoholic silver nitrate it gave a fine green color and a silver mirror. By acetylation with acetic anhydride and crystallization of the product from alcohol, fine white needles were obtained, m. p. 170° (corr.).

The above properties agree with those of *dl*-tetrahydro-diphenylquinoxaline, described by Hinsberg and König^{9a} and Bennett and Gibson.^{9b} A sample of this compound prepared by the method of Hinsberg and König proved to be identical with the above product. In particular, the diacetyl derivative from each melted at 170° (corr.), and gave the same mixed melting point, proving their identity: yield of *dl*-tetrahydro-diphenylquinoxaline by the Grignard reaction, 70% of the theoretical.

dl-1,2,3,4-Tetrahydro-2,3-dimethylquinoxaline.—Three grams of quinoxaline in absolute ether was slowly added to ethereal methylmagnesium iodide (2.2 equivalents) in an atmosphere of nitrogen. The addition product settled out rapidly as a dark oil, and after an hour was decomposed with liquid ammonia as above. The product was extracted with ether, which was then evaporated off in a vacuum desiccator, leaving a partially crystalline red residue. This was dissolved in 25 cc. of hot alcohol and added to a solution of 2.8 g. of crystalline oxalic acid in 10 cc. of hot alcohol. After several hours in the cold, the copious crystalline precipitate (oxalate of the base) was filtered off, washed and recrystallized from alcohol. After filtration, the precipitate was decomposed with aqueous ammonia, the free base then being extracted from the solution with benzene. Evaporation of the benzene left a yellowish crystalline mass, which could be crystallized from ligroin or water as fine colorless plates, m. p. 101° (corr.). With aqueous ferric chloride a magnificent blue coloration was produced.

Gibson¹⁰ gives 101° as the melting point of *dl*-1,2,3,4-tetrahydro-2,3-dimethylquinoxaline. A sample of this compound prepared by Gibson's method from 2,3-dimethylquinoxaline proved to be identical with the above product. Each melted sharply at 101° (corr.), as did a mixture of equal quantities, showing their identity. The yield of *dl*-tetrahydro-dimethylquinoxaline by the Grignard reaction was 50% of the theoretical.

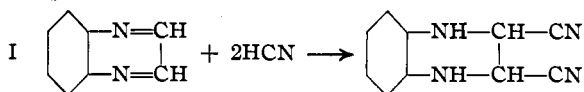
Quinoxaline and Hydrocyanic Acid.—Glyoxal was found by Pollak⁵ to react with two equivalents of hydrocyanic acid, yielding two optically isomeric dicyanohydrins, the dinitriles of *dl*-tartaric and meso-tartaric acid, respectively.

Quinoxaline has been found to behave in similar fashion, adding two equivalents of hydrogen cyanide to give only one ammono dicyanohydrin,

⁹ (a) Hinsberg and König, *Ber.*, 27, 2181 (1894); (b) Bennett and Gibson, *J. Chem. Soc.*, 123, 1570 (1923).

¹⁰ Gibson, *ibid.*, 342 (1927).

the hitherto unknown 1,2,3,4-tetrahydro-2,3-dicyanoquinoxaline in accordance with the equation



(The optical constitution of this substance was not determined.) This substance was shown to be a secondary diamine, but attempts to saponify it to the corresponding acid were fruitless.

1,2,3,4-Tetrahydrodicyanoquinoxaline.—Ten grams of pure quinoxaline, 7 g. (3.4 equivalents) of anhydrous hydrogen cyanide,¹¹ and 20 cc. of absolute alcohol were sealed in a bomb tube, which was then heated for two hours at 100° and allowed to stand overnight. The resulting clear yellowish solution was transferred to a beaker and evaporated to dryness in a vacuum desiccator, leaving a crystalline residue. This was extracted twice with carbon tetrachloride (to remove unchanged quinoxaline), and the residue was recrystallized once from water. It was finally purified by precipitation from saturated ether solution by the addition of several volumes of carbon tetrachloride. The crystals so obtained were white prismatic needles, odorless and tasteless, very soluble in alcohol and hot water, moderately soluble in ether, slightly soluble in benzene and cold water and insoluble in carbon tetrachloride. The substance melted at 168.5° (corr.) without appreciable decomposition, but the liquid decomposed above 200°.

Anal. Subs., 0.1416, 0.1455: CO₂, 0.3388, 0.3480; H₂O, 0.0574, 0.0603. Subs. 0.1023, 0.1060: 0.09537 *N* HCl (Kjeldahl), 23.16, 24.00 cc. Calcd. for C₁₀H₈N₄: C, 65.19; H, 4.39; N, 30.42. Found: C, 65.25, 65.22; H, 4.54, 4.64; N, 30.25, 30.25.

The yield was about 30%, irrespective of the time of heating. Apparently an equilibrium between quinoxaline, hydrogen cyanide and the addition compound was reached.

The compound did not dissolve in dilute acids and bases. A water solution yielded with nitrous acid an immediate yellow precipitate which gave the Liebermann reaction. The diacetyl derivative was prepared by heating with excess acetic anhydride at 100°. The remaining anhydride was decomposed with alcohol, and the ethyl acetate was removed by evaporation. The gummy residue was dissolved in alcohol and reprecipitated with water. Several repetitions of this process gave colorless prisms, m. p. 93.5° (corr.), very soluble in alcohol, but insoluble in water.

Anal. Subs., 0.0927, 0.0618: 0.09537 *N* HCl (Kjeldahl), 15.10, 9.95 cc. Calcd. for C₁₄H₁₂N₄O₂: N, 20.90. Found: N, 21.76, 21.51.

Attempts to saponify tetrahydro-dicyanoquinoxaline were unsuccessful. Strong bases decomposed it into metal cyanide and quinoxaline, as did a solution of two equivalents of potassium amide in liquid ammonia. Heating with strong hydrochloric acid caused decomposition to a dark tarry mass.

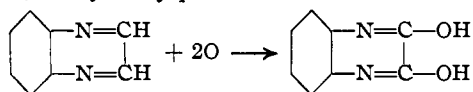
Oxidation of Quinoxaline

Glyoxal is readily oxidized, first to glyoxalic and then to oxalic acid. Quinoxaline was reported by Hinsberg⁸ to be resistant to chromic acid, while Gabriel and Sonn¹² found that alkaline permanganate solutions disrupted the benzene ring, yielding a pyrazine-dicarboxylic acid. In the present investigation it was found that by the action of a suitable agent, such as ammonium persulfate, quinoxaline undergoes an oxidation analogous to

¹¹ "Organic Syntheses," John Wiley and Sons, Inc., New York, 1927, Vol. VII, p. 50.

¹² Gabriel and Sonn, *Ber.*, 40, 4850 (1907).

that of glyoxal, yielding an *o*-phenylene ester of a mixed aquo-ammono oxalic acid, *i. e.*, 2,3-dihydroxyquinoxaline.



2,3-Dihydroxyquinoxaline.—With warm ammoniacal silver nitrate solutions quinoxaline gave a fine silver mirror, but for convenience in isolating the reaction product recourse was had to ammonium persulfate as the oxidizing agent: 1.3 g. of quinoxaline and 15 g. of ammonium persulfate were dissolved in 50 cc. of water, which was then slowly heated to boiling. The solution gradually turned red and deposited a slight brown precipitate. After a few minutes it was cooled and filtered. The filtrate, after evaporation to a small bulk, was nearly neutralized with aqueous ammonia. The resulting precipitate was recrystallized from water, in the form of fine white needles, melting above 300°. This product was shown to be 2,3-dihydroxyquinoxaline¹³ by converting it into 2,3-dichloroquinoxaline.¹⁴ The substance was heated with excess phosphorus pentachloride at 180° for a few minutes. The melt was decomposed with ice and washed with water. Extraction of the residue with benzene and evaporation of the latter gave a white solid. This was recrystallized from petroleum ether, appearing as fine white needles, m. p. 149.8° (corr.). This substance was 2,3-dichloroquinoxaline, as was shown by the unaltered melting point when it was mixed with a sample of pure 2,3-dichloroquinoxaline, m. p. 149.8° (corr.), prepared by the method of Hinsberg and Pollak.¹⁴ The yield of dihydroxyquinoxaline was about 30% of the theoretical.

Attempts to nitridize quinoxaline in liquid ammonia solution with iodine or ammonium azide were unsuccessful.

Quinoxaline and Potassium Amide.—In the presence of bases glyoxal undergoes an internal Cannizzaro reaction, yielding glycolic acid. Quinoxaline might be expected to undergo an analogous reaction with ammono bases, such as potassium amide, in liquid ammonia, but this was not found to be the case. The reaction of quinoxaline with potassium amide in liquid ammonia apparently follows a complex course, which has not been definitely established. When small amounts (less than one equivalent) of potassium amide were used, the quinoxaline was converted into a viscous, resinous substance. It is suggested that this may be the result of a polymerization of the quinoxaline induced by the ammono base. When two or more equivalents of potassium amide were used, two products were obtained, a dark tarry substance, and a white crystalline precipitate. The latter upon hydrolysis yielded potassium hydroxide and an organic compound which appeared to be fluorubin, described by Hinsberg and Schwantes.¹⁵ Fluorubin is to be regarded as a derivative of ammono oxalic acid, and as a nitridation product of quinoxaline. Inasmuch as no gaseous hydrogen was obtained, equivalent reduction must have taken place, and it is suggested

¹³ Bladin, *Ber.*, 18, 674 (1885).

¹⁴ Hinsberg and Pollak, *ibid.*, 29, 784 (1896). 2-Hydroxyquinoxaline also yields 2,3-dichloroquinoxaline on fusion with phosphorus pentachloride [Motylewski, *ibid.*, 41, 800 (1908)]. However, 2-hydroxyquinoxaline melts at 269°, whereas the compound obtained melted above 300°.

¹⁵ Hinsberg and Schwantes, *ibid.*, 36, 4048 (1903).

Pyrazine was not attacked by iodine in liquid ammonia, although it is to be noted that it can be oxidized in water solution.²¹

Potassium amide in liquid ammonia reacts with pyrazine to form an opaque dirty green solution from which no definite products were isolated.

Discussion

The experimental evidence presented in this article shows the striking analogy between the reactions of glyoxal and those of quinoxaline, substantiating the consideration of the latter as a substituted ammono glyoxal. The usefulness of the ammonia system viewpoint in the study of this and similar heterocyclic compounds is evident. It is intended to show in a later communication how derivatives of quinoxaline may be studied in the same manner.

A point of interest is that in the reactions presented here quinoxaline showed a reactivity more resembling that of an open-chain aldimine than that of a cyclic compound. (Compare the relative inertness of naphthalene, quinoline, etc.) This would seem to indicate definitely the presence of two true double bonds in the heterocyclic ring of quinoxaline.

Summary

1. The behavior of quinoxaline as an ammono glyoxal has been demonstrated by several new reactions. Thus it has been found to add two equivalents of bisulfites, Grignard reagents and hydrogen cyanide, and to undergo oxidation to *o*-phenylene oxamide. Quinoxaline has been found to react with potassium amide, probably in the sense of the Cannizzaro reaction.

2. A new method for the preparation of *dl*-1,2,3,4-tetrahydro-2,3-di-alkyl (or diaryl) quinoxalines has been discovered.

3. The following new compounds have been prepared: quinoxaline sodium bisulfite and 1,2,3,4-tetrahydro-2,3-dicyanoquinoxaline.

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²¹ Stöhr, *J. prakt. Chem.*, [2] 51, 449 (1895).