Illinois Institute of Technology

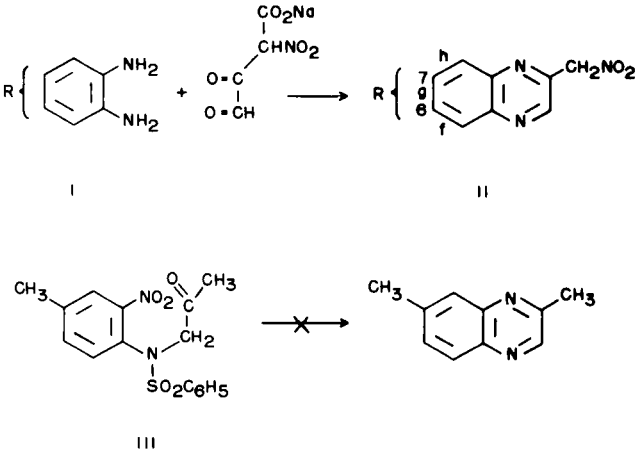
Derivatives of 2-Nitromethylquinoxaline. (1)

Paul E. Fanta and Chun-Shan Wang (2)

As an extension of our previous work (3), we have undertaken a study of the reaction of sodium 2-nitro-3-oxosuccinaldehydate with a variety of aromatic *vic*-diamines to give 2-nitromethylquinoxalines substituted in the carbocyclic ring. When an unsymmetrically substituted diamine is used in such a reaction, the formation of either of two isomers or a mixture of two isomer may be expected. The problems encountered in characterizing or separating such possible mixtures have been reported (4), and similar difficulties were encountered in the present work. The quinoxalines obtained are listed in Table I, with appropriate notation in the name where the structural ambiguity exists.

The product believed to be the mixture 2-nitromethyl-6(and 7)methylquinoxaline was converted to the 2-amino derivative by the sequence of reactions: nitromethyl → oxime → nitrile → amide → amine. The melting point of the substance obtained was about 10° lower than that of either 2-amino-6-methyl or 2-amino-7-methylquinoxaline, (5a) suggesting that the starting nitromethyl derivative is in fact a mixture of the two isomers. Furthermore, chromatography on alumina of the reaction product believed to be the mixture 2-nitromethyl-6(and 7)-methylquinoxaline gave five fractions of indistinguishable infrared spectra and progressively increasing melting point ranging from 127-128° for the first fraction to 158-159° for the fifth fraction, which comprised 50% of the total mixture. Since it has consistently been observed that 2,6-disubstituted quinoxalines have a higher melting point than their 2,7-isomers (5), it is reasonable to conclude that this particular reaction product consists of a mixture of isomers containing at least 50% of 2-nitromethyl-6-methylquinoxaline, melting at 158-159°.

A planned preparation of authentic 2,7-dimethylquinoxaline, which would have been useful in obtaining a definite structural assignment, failed when no identifiable product was isolated from the catalytic hydrogenation of III (6).



I II III

EXPERIMENTAL

Preparation of 2-Nitromethylquinoxalines.

In a typical procedure, a solution of equimolar amounts of the diamine and sodium 2-nitro-3-oxosuccinaldehydate in aqueous acetic acid was heated at 70° for two hours. The reaction mixture was thoroughly cooled and the product that precipitated was recrystallized from a suitable solvent such as ethanol, methanol, tetrahydrofuran, or acetone.

2-Amino-6(and 7)-methylquinoxaline.

Treatment of 6(and 7)-methyl-2-nitromethylquinoxaline with an excess of diazomethane in ether containing a little alcohol, followed by heating to remove the solvent and recrystallization of the residue from aqueous alcohol gave a 55% yield of 6(and 7)-methylquinoxaline-2-aldoxime, m.p. 212-214°.

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.35. Found: C, 64.01; H, 5.00; N, 22.05.

The aldoxime was dehydrated by refluxing for two hours in a solution of anhydrous sodium acetate in acetic anhydride to give 2-cyano-6(and 7)-methylquinoxaline, m.p. 78-80°, which was hydrolyzed by heating at 40° for 0.5 hour in concentrated hydrochloric acid followed by dilution with water. The crude product was recrystallized from aqueous alcohol, giving white, crystalline 6(and 7)-methylquinoxaline-2-carboxamide, m.p. 285-287°.

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.35. Found: C, 64.13; H, 4.91; N, 22.08.

The Hofmann degradation of the amide, carried out in the usual way gave 2-amino-6(and 7)-methylquinoxaline, pale yellow solid m.p. 170-172° after recrystallization from methanol and vacuum sublimation. The reported melting point of 2-amino-6-methylquinoxaline is 181-182° and of the 7-isomer is 179-180° (5a).

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.80. Found: C, 67.61; H, 6.16.

6(And 7)-methylquinoxaline-2-carboxylic acid was obtained by oxidation of the nitromethyl derivative with sodium dichromate in aqueous sulfuric acid, m.p. 180-188°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.79. Found: C, 63.82; H, 4.34; N, 14.58.

4-Methyl-2-nitro-*N*-acetonyl-*N*-benzenesulfonylaniline (III).

Heating 4-methyl-2-nitroaniline with two equivalents of benzenesulfonyl chloride in dry pyridine gave a 90% yield of the *N*,*N*-dibenzenesulfonyl derivative, m.p. 206-208° after several successive recrystallizations from acetic acid.

Anal. Calcd. for $C_{19}H_{16}N_2O_6S_2$: C, 52.76; H, 3.63; N, 6.48. Found: C, 52.95; H, 3.56; N, 6.65.

The dibenzenesulfonyl derivative was refluxed for 0.5 hour with 1*N* alcoholic potassium hydroxide. Dilution with water, cooling and acidification with hydrochloric acid gave a 91% yield of the monobenzenesulfonyl derivative, m.p. 100-102° after recrystallization from methanol.

TABLE I

Quinoxalines Prepared by the Reaction of Sodium 2-Nitro-3-oxosuccinaldehydate with Aromatic *vic*-Diamines

Diamine Used (I)	2-Nitromethylquinoxaline Obtained (II)	M.P.	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
2,3-Naphthalenediamine	benzo[g]-	216-218	65.26	3.79	17.56	65.27	3.84	17.56
1,2-Naphthalenediamine	benzo[f and/or h]-	139-140	65.26	3.79	17.56	65.35	3.81	17.24
3,4-Toluenediamine	6(and 7)methyl-	146-148	59.11	4.47	20.68	59.41	4.57	20.70
4-Nitro-*o*-phenylenediamine	6(and/or 7)nitro-	210-212	46.16	2.58	23.93	46.29	2.58	23.48
4-Chloro-*o*-phenylenediamine	6(and/or 7)chloro-	149-151	48.34	2.71		48.56	2.95	
3,4-Diaminobenzoic acid	-6(and/or 7)carboxylic acid	300	51.51	3.03	18.02	51.43	3.31	17.98
4,5-Diamino-1,3-dimethyl-2,6-Dioxo-1,2,3,4-tetrahydropyrimidine	1,3-Dimethyl-2,4-dioxo-5(and/or 6)nitromethyl-1,2,3,4-tetrahydropteridine (monohydrate)	205-207	40.15	4.11	26.01	40.48	4.02	25.90

Anal. Calcd. for $C_{13}H_{12}N_2O_4S$: C, 53.41; H, 4.14; N, 9.59. Found: C, 53.60; H, 4.06; N, 9.98.

The sodium salt of the above compound was prepared by heating it with a solution of sodium ethoxide in absolute ethanol. Recrystallization from methanol gave a yellow powder, m.p. 295-296°, yield 92%. Mixing 20 g. of the dry sodium salt and 25 ml. of bromoacetone without solvent resulted in an exothermic reaction, which was completed by heating for one hour at 70°. Recrystallization of the product from methanol gave a 68% yield of 4-methyl-2-nitro-*N*-acetonyl-*N*-benzenesulfonylaniline. The analytical sample, m.p. 146-148°, was obtained by three successive recrystallizations from methanol.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04. Found: C, 55.30; H, 4.61; N, 7.99.

Attempted hydrogenation of this compound gave an intractable or tarry product from which no characterizable substance could be isolated.

REFERENCES

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(6) The reaction sequence was patterned after the reported preparation of 7-chloro-2-methylquinoxaline, ref. 5b.

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