[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of Some Quinoxaline Derivatives

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In view of the recent articles by English workers[2,3] we wish to report a number of quinoxaline derivatives which were synthesized in this Laboratory prior to the publications of these investigators.

The method selected for the preparation of most of the quinoxalines involved: the condensation of a nuclear substituted *o*-nitroaniline with monobromoacetic acid; the reduction of the N-(*o*-nitrophenyl)-glycine thus prepared to the corresponding 1,2,3,4-tetrahydro-2-ketoquinoxaline; the oxidation of the tetrahydro compound to the 2-hydroxyquinoxaline; the conversion of the hydroxy derivative to the corresponding 2-chloroquinoxaline; and finally, the reaction of the 2-chloroquinoxaline with various amines to yield the compounds listed in Table I.

TABLE I

R	R′	M. p.,[a] °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$C_5H_{10}N$[b]	CH_3O–	66–68	96	69.11	68.99	7.05	7.04
$C_5H_{10}N$[b]	Cl–	114–115	82	63.03	63.34	5.70	5.54
$C_5H_{10}N$[b]	H–	59–60.5	96	73.21	73.23	7.09	6.95
$-NH(CH_2)_3N(C_2H_5)_2$[c]	CH_3O–	177–178	77	47.44	47.59	6.33	6.24
$-O(CH_2)_2N(CH_3)_2$[c]	CH_3O–	203.5–205	97	43.20	43.05	5.18	5.15
$-O(CH_2)_2N(CH_3)_2$	Cl–	72–73	63	57.26	57.18	5.61	5.41

[a] Melting points not corrected. [b] 1-Piperidino. [c] Melting point and analysis refer to the methyl iodide derivative.

Because of the demonstrated reactivity of the methyl group in 2-methylquinoxaline with aromatic aldehydes, it seemed probable that the former would undergo the Mannich reaction. 2-(2-Diethylaminoethyl)-quinoxaline was therefore produced by the reaction of 2-methylquinoxaline with diethylamine hydrochloride and formalin. Bost and Towell[4] found that 2,3-dimethylquinoxaline does not undergo the Mannich reaction with methylamine hydrochloride and formalin.

Experimental

N-(2-Nitro-4-methoxyphenyl)-glycine[3] (I).—Prepared in 89% yield from 2-nitro-4-methoxyaniline and monobromoacetic acid; m. p. 183–184° (dec.).

N-(2-Nitro-4-chlorophenyl)-glycine[2] (II).—Prepared in 24% yield from 2-nitro-4-chloroaniline and monobromoacetic acid; m. p. 195–196° (dec.).

1,2,3,4-Tetrahydro-2-keto-7-methoxyquinoxaline[5] (III).—To a mixture of 9.0 g. of I, 18 g. of tin and 30 ml. of ethanol, 40 ml. of concd. hydrochloric acid was added in small portions. After the addition of the acid had been completed, the mixture was refluxed two hours, diluted with an equal volume of water and the tin removed from the solution by precipitation with hydrogen sulfide. The product was precipitated from the filtrate by the addition of solid sodium carbonate; yield 6.0 g. (85%). After recrystallization from ethanol, white needles were obtained, m. p. 178–181°.

Anal. Calcd. for $C_9H_{10}O_2N_2$: C, 60.66; H, 5.66. Found: C, 61.03; H, 5.56.

1,2,3,4-Tetrahydro-2-keto-7-chloroquinoxaline[6] (IV) was prepared similarly, but precipitation of the tin was not necessary in this case since the desired product separated from the reaction mixture upon dilution with water; yield 89%. After recrystallization from ethanol, this compound was obtained as silvery plates melting at 214–216°.

Anal. Calcd. for $C_8H_7ON_2Cl$: C, 52.61; H, 3.86. Found: C, 52.73; H, 3.97.

2-Hydroxy-7-methoxyquinoxaline[5] (V).—A mixture of III (10 g.), 125 g. of 8% aqueous sodium hydroxide and 113 m. of 3% hydrogen peroxide solution was heated on the steam-bath for two hours. The reddish-brown solution was made acidic while still hot by the slow addition of acetic acid. After cooling, the precipitated product was collected by filtration; yield 9.9 g. (quantitative). The compound was purified through the sodium salt and by recrystallization from ethanol, m. p. 232–234°.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58. Found: C, 61.63; H, 4.62.

2-Hydroxy-7-chloroquinoxaline[6] (VI) was prepared and purified in the same manner as V. The yield of white crystals melting at 261–263° was almost quantitative.

Anal. Calcd. for $C_8H_5N_2OCl$: C, 53.20; H, 2.79. Found: C, 53.44; H, 2.83.

2-Chloro-7-methoxyquinoxaline[3] (VII).—This compound was prepared in 86% yields by the reaction of phosphorus oxychloride with V, m. p. 100.5–102°.

Anal. Calcd. for $C_9H_7ON_2Cl$: C, 55.54; H, 3.63. Found: C, 55.74; H, 3.77.

2,7-Dichloroquinoxaline[2] (VIII) was prepared and purified by the same method as outlined for VII; yield 65%, m. p. 140–141°.

Procedure for the Preparation of 2-Piperidinoquinoxalines.—One gram of the 2-chloroquinoxaline was added to 5 ml. of piperidine and the mixture was allowed to stand twenty-four hours at room temperature. Ten milliliters of anhydrous ether was added and the mixture filtered. The filtrate was concentrated at the water-pump and then

(1) Parke, Davis and Company Fellow.

(2) Crowther, Curd, Davey and Stacey, *J. Chem. Soc.*, 1260 (1949).

(3) Curd, Davey and Stacey, *ibid.*, 1271 (1949).

(4) Bost and Towell, THIS JOURNAL, **70**, 903 (1948).

(5) Prepared by a different method from that of Curd, *et al.*[3]

(6) Synthesized by a different method from that described by Crowther, *et al.*[2]

poured onto 50 g. of ice. The precipitated product was collected by filtration and recrystallized from Barnsdall-6 or ethanol.

Procedure for the Preparation of 2-(3-Diethylaminopropylamino)-quinoxalines.—The 2-chloroquinoxaline (2–3 g.) was heated with 2 equivalents of 3-diethylaminopropylamine on the steam-bath for three hours. The reaction mixture was treated with 20 ml. of 2 *N* hydrochloric acid and filtered. The filtrate was cooled in an ice-bath and made basic by the slow addition of aqueous 20% sodium hydroxide. The oil which separated was extracted with 50 ml. of ether. The ether solution was washed with five 10-ml. portions of water, dried with magnesium sulfate and the ether evaporated. The oil thus obtained was treated with slightly more than one equivalent of methyl iodide in the cold, and warmed carefully on the steam-bath if no reaction occurred initially. The methyl iodide derivatives were recrystallized from absolute ethanol.

Procedure for the Preparation of 2-(2-Dimethylaminoethoxy)-quinoxalines.—The 2-chloroquinoxaline (0.0075 mole) was added to 10 ml. of 2-dimethylaminoethanol containing a slight excess of sodium. The mixture was allowed to stand twenty-four hours at room temperature and then heated one hour on the steam-bath. The reaction mixture was poured into 50 ml. of ice-water. 2-(2-Dimethylaminoethoxy)-7-chloroquinoxaline separated as a solid and was collected by filtration and recrystallized from Barnsdall-6. 2-(2-Dimethylaminoethoxy)-7-methoxyquinoxaline was obtained as an oil and was isolated in the same manner as described in the previous procedure.

2-(2-Diethylaminoethyl)-quinoxaline (IX).—2-Methylquinoxaline was prepared from *o*-phenylenediamine and isonitrosoacetone[7] by the procedure of Borsche and Doeller.[8] 2-Methylquinoxaline (7.2 g.) was added to 7.7 g. of diethylamine hydrochloride and 10 ml. of formalin. The mixture was refluxed and stirred twenty hours. It was diluted with 50 ml. of water, treated with charcoal and filtered. The filtrate was extracted with two 50-ml. portions of ether. The aqueous layer was made basic by the addition of 50–60 ml. of aqueous 10% sodium hydroxide. The mixture was extracted with three 50-ml. portions of ether, the ether solution dried with magnesium sulfate, treated with charcoal, filtered and the ether evaporated. The residue was distilled at reduced pressure. A yellow oil was obtained, distilling at 168–172° (9 mm.). The yield was 3.6 g. (31%). For analysis, a monopicrate was prepared in ethanol. After recrystallization from ethanol, bright yellow needles were obtained melting at 141–143°.

Anal. Calcd. for $C_{14}H_{19}N_3 \cdot C_6H_3O_7N_3$: C, 52.40; H. 4.84. Found: C, 52.69; H, 4.88.

(7) Freon, *Ann. chim.*, **11**, 460 (1939).

(8) Borsche and Doeller, *Ann.*, **537**, 42 (1938).

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Summary

1. The synthesis of various 2-piperidino, 2-(3-diethylaminopropylamino)- and 2-(2-dimethylaminoethoxy)-quinoxalines, as well as the intermediates used in preparing these compounds, has been described.

2. 2-(2-Diethylaminoethyl)-quinoxaline has been prepared by the utilization of 2-methylquinoxaline in a Mannich reaction.

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Spectral Changes of Pinacyanol Chloride in Sodium Silicate–Salt Solutions

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Pinacyanol chloride is a cationic dye which is blue in water but becomes purple in the presence of colloidal electrolytes such as the siliceous soluble silicates.[1,2] This change in the color of an adsorbed dye depending on the nature of the stainable substrate is the phenomenon which P. Ehrlich called metachromasy. It is attributable to interaction, probably involving both electrostatic, van der Waals, and hydrogen bonding forces of a dimeric or polymeric form of the dye with oppositely charged colloidal electrolyte micelles.[2] Dyes which show metachromasy disobey the usual form of Beers law for a single absorbing species in aqueous solution, due to the formation of molecular aggregates of the dye ion with increasing concentration.[3] The characteristic absorption bands of such dyes are frequently attributed to monomeric, dimeric and polymeric forms,[4,5,6,7,8] and regarded as characteristic of these species. However, these same absorption bands are generally apparent in organic solvents where there is no evidence of dimerization or polymerization, so that the bands generally attributed to dimers or polymers may be due to vibrationally coupled transitions proper to the monomeric ions which are, however, enhanced in the dimer or trimer.[9]

In a previous publication[2] we have shown that the addition of sodium chloride, sulfate or trisodium phosphate decreases the effect of a sodium silicate ($Na_2O \cdot 3.3SiO_2$) on the absorption spectra of pinacyanol chloride, and that the effects of these salts are different at the same ionic strength. This paper reports the effects of fourteen electrolytes, three of which form micelles in aqueous solution, on the absorption spectra of 1×10^{-5} *M* pinacyanol chloride in water and in a 0.01 *M* solution of the sodium silicate with a silica to alkali (Na_2O) molecular ratio of 3.3.

Experimental

The sodium silicate used was the commercially

(1) R. C. Merrill, R. W. Spencer and R. Getty, THIS JOURNAL, **70**, 2460 (1948).

(2) R. C. Merrill and R. W. Spencer, *ibid.*, **70**, 3683 (1948).

(3) L. Michaelis and S. Granick, *ibid.*, **67**, 1212 (1945).

(4) G. Scheibe, *Kolloid Z.*, **82**, 1 (1938).

(5) W. L. Lewschin, *Acta Physicochem. U. S. S. R.*, **1**, 685 (1934).

(6) S. M. Solov'ev, *J. Gen. Chem. (U. S. S. R.)*, **16**, 1405 (1946); *C. A.*, **41**, 4716 (1947).

(7) H. O. Dickinson, *Trans. Faraday Soc.*, **43**, 486 (1947).

(8) E. Rabinowitch and L. R. Epstein, THIS JOURNAL, **63**, 69 (1941).

(9) S. E. Sheppard and A. L. Geddes, *ibid.*, **66**, 2003 (1944).