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2-Quinoxalinealdehyde and some Derivatives

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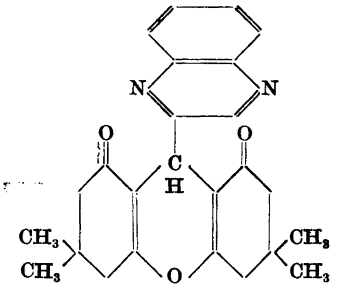
In connection with an investigation in this laboratory a need arose for 2-quinoxalinealdehyde. This compound was first reported by Borsche and Doeller [1] in 1939, who obtained it by oxidation of 2-methylquinoxaline with selenium dioxide in boiling xylene. Although a 25 % yield is reported for the reaction we have not, in spite of numerous attempts, been able to duplicate this yield. Moreover the yields tend to decrease further by increasing the amounts of the reacting components. The same year Müller and Varga [2] reported 2-quinoxalinealdehyde as a reaction product from the cleavage with lead tetraacetate of 2-(*d-arabo*)-tetrahydroxybutyl-quinoxaline, which in turn was prepared by condensation between *o*-phenylenediamine and fructose. This route to the aldehyde was checked too, but although the oxidative cleavage proceeded smoothly in good yields, the condensation in our hands gave yields quite mediocre. An experiment in which glucose was used in the condensation led to a 9 % yield. Hence an improved method for preparing the 2-quinoxalinealdehyde was deemed desirable and was found in carrying out the oxidation with selenium dioxide of 2-methylquinoxaline in aqueous dioxane at moderate temperature. Using this procedure yields of about 60 % were easily obtained.

For characterization Borsche and Doeller (*l. c.*) prepared the phenylhydrazone and the oxime while Müller and Varga (*l. c.*) report data for the phenylhydrazone and the semicarbazone. Apart from these few notations no observations have been found in the literature as to the properties and reactions of the aldehyde. On account of the somewhat anomalous behaviour of 3-hydroxy-2-quinoxalinealdehyde in forming derivatives, observed by Ohle [3], similar reactions with 2-quinoxalinealdehyde were studied. This investigation, however, did not disclose any irregularities in the reactions of the aldehyde. The hydrazone, azine, 2,4-dinitrophenylhydrazone and anil were formed in

excellent yields. Ohle (*l. c.*) mentions briefly and without any experimental evidence that 2-quinoxalinealdehyde like the 3-hydroxyaldehyde forms an aldazinehydrate, whereas we have been able to obtain only the normal azine as a nicely crystallizing yellow compound. By treatment of this with hot alcoholic potassium hydroxide a change in colour from yellow to red is observed, probably due to a tautomeric shift to the azo-structure as suggested by Ohle. In contradistinction to the hydroxyaldehyde, which with methone primarily gives a normal methonederivative that can be transformed into an anhydride quite readily, we obtain under various conditions always and only an anhydride to which the octahydroxanthene structure is ascribed:



3,6-tetramethyl-9-(2′-quinoxalyl)-
1,2,3,4,5,6,7,8-octahydroxanthenedione-1,8

It was found that 2-quinoxalinealdehyde condensed readily with *p*-aminobenzoic acid and its ethyl ester, *p*-aminobenzamide and sulfanilamide to Schiff bases. The reactions were performed in alcohol solution and gave yields close to the theoretical ones. The azomethines were obtained as nice crystalline, more or less yellow compounds, stable to alkali but quite sensitive to acidic reagents.

Several attempts at reduction of the azomethine double bond were made but none of them were successful. Invariably the reaction mixtures took on intensive blue and violet colours turning red by shaking with air. The occurrence of pigmented solutions by reduction of pyrazine derivatives is known from the literature and is undoubtedly due to at least partial reduction of the - C = N-bonds in the ringskeleton. Catalytic hydrogenation with different types of catalyst and solvent was attempted as well as milder procedures (sodium amalgam a. o.) but in all cases the ring seemed to be attacked more or at least as readily as the double bond in the side chain.

EXPERIMENTAL

2-Quinoxalinealdehyde

A solution of 9.4 g of 2-methylquinoxaline in 45 ml of dioxane was heated to 70°. Under vigorous stirring a solution of 7.3 g of freshly sublimed selenium dioxide in 25 ml of dioxane and 5 ml of water was added dropwise over a 90 min. period. The temperature was raised to 85° and the stirring continued for about four hours at this temperature. After cooling the selenium was filtered off on a glass filter and the dioxane removed from the filtrate *in vacuo*. The residue was steam-distilled and about 3 l of filtrate were collected, saturated with sodium chloride and extracted thoroughly with ether. The etheral solution was dried over anhydrous sodium sulfate and the ether removed at diminished pressure. The crude product (6.2 g) was recrystallized from *n*-hexane and 5 g of large yellow needles were obtained. This product melts at 109°,* and is pure enough for most purposes. By sublimation *in vacuo* well formed and fairly large pale yellow prisms with m. p. 110° were obtained. The aldehyde has a characteristic, not unpleasant, smell and is advantageously kept well protected from light. Even then the preparation does not keep unchanged for a very long time.

2-Quinoxalinealdehyde-hydrazone

To 0.4 ml of hydrazine hydrate dissolved in 2 ml of water was added gradually by shaking a solution of 316 mg of the aldehyde in 2 ml of ethanol. The mixture was heated to boiling and concentrated somewhat. By cooling a crystalline product separated. After recrystallization from water containing a few drops of ethanol the product weighed 270 mg, corresponding to a 79 % yield. Long, pale yellow needles melting under the microscope at 151° after beginning sublimation from 142°. Macro-m. p. 156° under evolution of gas.

$C_9H_8N_4$ (172.2)	Calc.	C 62.77	H 4.68	N 32.54
	Found	» 62.64	» 4.76	» 32.60

2-Quinoxalinealdazine

To 158 mg of the aldehyde dissolved in 5 ml of ethanol was added 172 mg of 2-quinoxalinealdehyde hydrazone. Instantaneously the separation of yellow crystals starts, which after cooling and separation were recrystallized from a large volume of amyl acetate. Thus 256 mg of beautiful, long, yellow needles were obtained (82 % yield). The azine is very slightly soluble in ethanol and sparingly soluble in hot ether and benzene. In cold or hot aqueous alkali no colour change is observed, whereas boiling with ethanolic potassium hydroxide causes a reddish-brown colour, turning yellow again with acid.

On the hot stage under the microscope the azine shows a transformation point at ca. 240°. Sublimation starts at about 260°, and the compound melts at 265°. Macro-m. p. 270° (destr.)

$C_{18}H_{12}N_6$ (312.3)	Calc.	C 69.22	H 3.87	N 26.89
	Found	» 68.73	» 3.83	» 26.86

* All the reported »macro melting points» are uncorrigated and determined in an electrically heated bloc.

2-Quinoxalinealdehyde-2′,4′-dinitrophenylhydrazone

A solution of 79 mg of the aldehyde dissolved in 2 ml of ethanol was added to a hot solution of 100 mg of 2,4-dinitrophenylhydrazine in 6 ml of 2 N hydrochloric acid. A copious precipitate is formed momentarily. Yield after drying: 161 mg (95 %). Recrystallized from boiling toluene. Intensively yellow-orange prisms, melting under the microscope at 234—235°. Macro-m. p. 241° (destr.).

An alcoholic suspension of the derivative gives with traces of alkali a very intensive purple colour, disappearing again by acidification.

$C_{15}H_{10}N_6O_4$ (318.3) Calc. N 24.85 Found N 24.86

2-Quinoxalinealdehyde-anil

By heating together 47.4 mg of the aldehyde and 27.9 mg of freshly distilled aniline in 0.3 ml of ethanol for a short time a crystalline product was obtained. Recrystallized from 0.5 ml of ethanol it consisted of yellow-brownish, flat prisms weighing 54 mg (77 %)

Micro-m. p. 130° Macro-m. p. 133°

$C_{15}H_{11}N_3$ (233.3)	Calc.	C 77.23	H 4.75	N 18.01
	Found	» 76.85	» 4.85	» 17.85

Methone derivative

To a solution of 140 mg of methone in 1 ml of ethanol and 2 ml of water was added 79 mg of the aldehyde in 2 ml of ethanol. The mixture was heated to boiling and one drop of piperidine was added. The separation of crystals starts and after recrystallization from 70 % ethanol there was obtained 92 mg of colourless prisms having the structure indicated above. Under the microscope sublimation takes place from 190° to 225°, the sublimate forming rectangular plates which melt sharply at 231°. Macro-m. p. 229°.

$C_{25}H_{26}O_3N_2$ (402.5)	Calc.	C 74.60	H 6.51	N 6.96
	Found	» 74.59	» 6.49	» 6.99

N-(2-quinoxalylmethylene)-*p*-aminobenzoic acid

A mixture of 500 mg of the aldehyde and 435 mg of *p*-aminobenzoic acid in 5 ml of ethanol was heated to boiling for one hour. After cooling 812 mg of lemon yellow rods had separated. Recrystallized from dioxane. Under the microscope the yellow prims are observed sublimating at 180° to fine, thin needles. These sublimate in turn from 220° until all has disappeared at 240°. Macro-m. p. 285° (destr.)

$C_{16}H_{11}O_2N_3$ (277.3)	Calc.	C 69.30	H 4.00	N 15.15
	Found	» 69.55	» 4.07	» 15.30

Ethyl N-(2-quinoxalylmethylene)-*p*-aminobenzoate

Dissolved in 3 ml of ethanol 316 mg of the aldehyde and 330 mg of ethyl *p*-aminobenzoate were boiled for about 3 hours. The reaction mixture was then taken to dryness *in vacuo* and the residue recrystallized from *n*-hexane. Clusters of yellow needles were obtained by slow cooling, weighing 216 mg. From the mother liquor an additional crop (30 mg) was isolated. Total yield: 40 %.

Micro-m. p. 137° Macro-m. p. 139°

$C_{18}H_{15}N_3O_2$ (305.3) Calc. N 13.76 Found N 13.61

Treatment of the ester with 2 *N* sodium hydroxide at 80° gave the corresponding acid mentioned above.

N^4-(2-quinoxalylmethylene)-aminobenzamide

Heating for a few minutes a solution of 79 mg of the aldehyde and 70.3 mg of *p*-aminobenzamide in 3 ml of ethanol gave 118 mg (85 %) of lemon yellow crystals. Recrystallized from dioxane. Rectangular plates melting under the microscope from 244—252°. Macro-m. p. 245-252° (destr.)

$C_{16}H_{12}N_4O$ (276.3)	Calc.	C 69.55	H 4.38	N 20.28
	Found	» 70.42	» 4.48	» 20.28

N^4-(2-quinoxalylmethylene)-sulfanilamide

Seventy nine milligrams of the aldehyde were heated for a short time to boiling with 86 mg of sulfanilamide in 3 ml of ethanol. A precipitate was formed rapidly but dissolved again by prolonged heating. After concentration to a small volume 102 mg (65 %) of pale yellow crystals were isolated. Recrystallized from a small volume of dioxane. Small prisms melting on the hot stage at 220°. Macro-m. p. 227° (destr.)

$C_{15}H_{12}O_2N_4S$ (312.3)	Calc.	N 17.94	S 10.26
	Found	» 18.27	» 10.50

SUMMARY

An improved method for the preparation of 2-quinoxalinealdehyde is described.

Different derivatives and condensation products of the aldehyde are reported.

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REFERENCES

1. Borsche, W., and Doeller, W. *Ann.* **537** (1939) 39.
2. Müller, A., and Varga, I. *Ber.* **72** (1939) 1999.
3. Ohle, H. *Ber.* **76** (1943) 624.

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