STUDIES IN THE BENZODIAZINE SERIES

XVI.* SYNTHESIS OF QUINOXALIN-2-ONES CONTAINING A HYDROXY GROUP IN THE BENZO NUCLEUS

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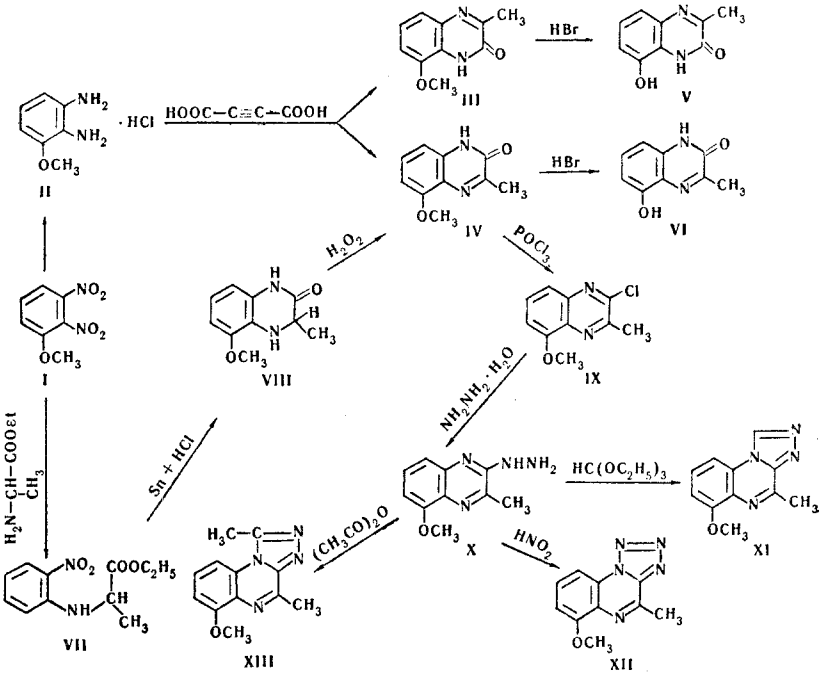
The reaction of acetylenedicarboxylic acid and 2,3-diaminoanisole has given two isomeric quinoxalin-2-ones, from which the corresponding 5- and 8-hydroxy derivatives have been obtained. Their structures have been shown by the independent synthesis of one of the isomers. Tetrazolo[4,5-a]- and s-triazolo[4,3-a]quinoxalines have been obtained.

Quinoxalinones with substituents in the benzo nucleus have been studied comparatively little, and quinoxalin-2-ones having hydroxy groups as substituents have not been described at all. Such compounds could be of interest as complex-forming agents. The present paper describes the synthesis of 5-hydroxy- and 8-hydroxy-3-methylquinoxalin-2-ones (IV and V) and some compounds obtained from them:



The quinoxalines mentioned were synthesized by the reaction between o-phenylenediamine and acetylenedicarboxylic acid (ADC) described previously [1,2]. The reaction of 2,3-diaminoanisole hydrochloride with ADC should have been expected to form two isomeric quinoxalinones (III and IV). The reaction did actually give a mixture of III and IV in approximately equal amounts. Their separation was successfully effected by virtue of their acidities: at pH 8 one of them passes into solution and the other remains undis-

*For Communication XV, see [10].

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solved. After separation and crystallization, the soluble isomer had mp 220-222°C, pK 9.82, and the other isomer mp 260-262°C, pK 9.95 (to obtain the pure substances, the separation had to be repeated two or three times, as a rule).

In order to determine the structure of the isomers, the independent synthesis of one of them was carried out from 2,3-dinitroanisole (I). The process was based on literature information according to which the nitro groups present in positions 2 of 2,3-di- and 2,3,5-trinitroanisoles possess a high acidity and are replaced in the first case by an amino group in the reaction with alcoholic ammonia [3] and in the second case by a glycine residue in the reaction with the sodium salt of glycine [4]. By analogy with this, it could be considered with considerable probability that in the reaction between I and the ethyl ester of α-alanine the replacement of the nitro group in position 2 by an amino acid residue would take place. The reaction gave the ethyl ester of N-(2-methoxy-6-nitrophenyl)-α-alanine (VII). This compound was converted by reductive ring-closure (Sn + HCl) into 5-methoxy-3-methyl-1,2,3,4-tetrahydroquinoxalin-2-one (VIII), which was oxidized with hydrogen peroxide to a quinoxalin-2-one with mp 260-262°C, identical according to a mixed melting point and IR spectrum with the 5-methoxy-3-methylquinoxalinone (IV) isolated from the mixture of isomers. Consequently, the second isomer is 8-methoxy-3-methylquinoxaline-2-one (III).

The methyl groups in III and IV possess a considerable reactivity, which appears, for example, in their reactions with 5-nitrofurfural with the formation of the corresponding furylidene derivatives (XIV and XV).*

Both the isomers III and IV were demethylated in 47% HBr, giving 8-hydroxy-3-methylquinoxalin-2-one (V) and 5-hydroxy-3-methylquinoxalin-2-one (VI), respectively. In accordance with its structure, the 5-hydroxy derivative VI can form an intramolecular hydrogen bond and possesses complex-forming properties: with a solution of copper acetate, a yellow precipitate deposits, while the 8-hydroxy compound V merely colors a solution of a Cu^{2+} salt yellow. With phosphorus oxychloride, the quinoxalinones III and IV give chlorides (IX, XVI) which react smoothly with hydrazine hydrate to form the corresponding hydrazines (X, XVII).† The reactions of the latter with nitrous acid and orthoformic ester form, respectively, tetrazolo[4,5-a]quinoxaline (XII, XVIII) and s-triazolo[4,3-a]quinoxalines (IX, XIX). A difference in the behavior of the hydrazines X and XVII appears in their reaction with acetic anhydride: X forms 6-methoxy-1,4-dimethyl-s-triazolo[4,3-a]quinoxaline (XIII), while XVII is converted into di- and triacetyl derivatives (XX, XXI). This is evidently due to the fact that the more voluminous methoxy group in position 9 prevents the formation of a triazole ring and the successive replacement of the hydrogen of the hydrazine group by acyl residues (for a similar case, see [5]).

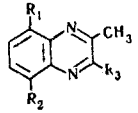
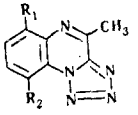
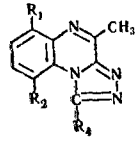
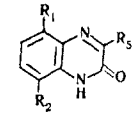
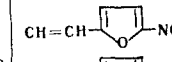
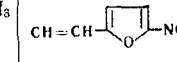
EXPERIMENTAL

5-Methoxy- and 8-Methoxy-3-methylquinoxalin-2-ones (IV and III). A solution of 1.14 g (0.01 mole) of acetylenedicarboxylic acid in 5 ml of water was added to a hot solution of 1.8 g (0.01 mole) of 2,3-diaminoanisole hydrochloride (II) [6, 7] in 10 ml of water. Pronounced foaming took place and a voluminous precipitate deposited. The mixture was boiled for 30 min and cooled, and 1.4 g (71%) of a mixture of IV and III with mp 200-230°C was filtered off. To separate the isomers, the mixture obtained was dissolved with heating in 30 ml of 2N HCl, and the solution was cooled and brought with concentrated ammonia to pH 8, after which 0.7 g of IV with mp 245-250°C was filtered off. Then the filtrate was acidified with 2N HCl to pH 3 and extracted with chloroform; the extract was dried with Na_2SO_4 and evaporated to one-fourth of its original volume, after which 0.6 g of III with mp 210-216°C was separated off. If, after the separation, the isomers had melting points differing from those given above, the separation was repeated. Crystallization from aqueous dimethylformamide (1:10) gave the pure isomers III and IV. Compound III forms colorless needles, mp 220-222°C. Found %: C 62.84; H 5.33; N 15.15. $C_{10}H_{10}N_2O$. Calculated %: C 63.15; H 5.29; N 14.73. $\nu_{C=O}$ 1668 cm^{-1}; ν_{NH} 3385 cm^{-1} (in chloroform). Compound IV forms colorless needles with mp 260-262°C. Found %: C 63.07; H 5.47; N 14.49. $\nu_{C=O}$ 1665 cm^{-1}; ν_{NH} 3383 cm^{-1} (in chloroform).

*The antitubercular activity of these compounds has been investigated. Compound XIV showed activity in vitro in a dilution of 1:1 million in the absence of blood serum; in the presence of serum the activity fell considerably.

† A review of the reactions described is given in the scheme only for the isomer IV, the reactions for the isomer III being analogous; the products of the reactions are described in Table 1 (IX-XIX) and the the Experimental (XX, XXI).

TABLE 1. Quinoxaline Derivatives

Formula	Compound	R_1	R_2	R_3 (R_4, R_5)	Form of the crystals	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
								C	H	N	C	H	N	
	IX	OCH_3	H	Cl	Needles a	94—96		57,50	4,50	13,41	57,56	4,35	13,43	85
	XVI	H	OCH_3	Cl	Needles a	124—126	$C_{10}H_9N_2O$	57,33	4,31	13,33				90
	X	OCH_3	H	$NHNH_2$	Plates a	198—201	$C_{17}H_{15}N_5O_3$	60,43	4,72	20,88e	60,53	4,48	20,76	85
	XVII	H	OCH_3	$NHNH_2$	Prisms a	152—155		60,58	4,38	21,16e				70
	XII	OCH_3	H	—	Needles b	220—221	$C_{10}H_9N_5O$	55,55	4,19	33,01	55,81	4,22	32,54	80
	XVIII	H	OCH_3	—	Prisms b	207—208		55,80	4,17	32,69				78
	XI	OCH_3	H	H	Needles a	259—260	$C_{11}H_{10}N_4O$	61,60	4,72	26,01	61,69	4,70	26,15	90
	XIX	H	OCH_3	H	Needles c	223—224	$C_{12}H_{12}N_2O_4$	61,26	4,90	26,39				70
	XIII	OCH_3	H	CH_3	Needles c	244—245		52,80	5,40		63,14	5,30	24,55	80
	XV	OCH_3	H		Needles d	281—282	$C_{15}H_{11}N_3O_5$	57,68	3,83	13,87	57,51	3,54	13,41	79
	XIV	H	OCH_3		Needles d	289—290		57,23	3,70	13,78				80

a. From ethanol.
b. From acetone.
c. From water.
d. From DMFA containing water.
e. The analysis for the hydrazones with p-nitrobenzaldehyde is given.

5-Hydroxy- and 8-Hydroxy-3-methylquinoxalin-2-ones (VI and V). A mixture of 0.57 g (0.003 mole) of IV or III and 5 ml of 47% HBr was heated at the boil for 6 h, the mixture was cooled and filtered, and the residue was washed with hot water and then with sodium carbonate solution. This gave 0.37 g (70%) of product. The hydroxy compound VI forms colorless needles (from ethanol), mp 252-254°C. Found %: C 61.11; H 4.78; N 15.94. $C_9H_8N_2O_2$. Calculated %: C 61.36; H 4.58; N 15.90. $\nu_{C=O}$ 1660 cm^{-1}; ν_{OH} 3467 cm^{-1}; ν_{NH} 3390 cm^{-1} (in chloroform). An ethanolic solution of VI gives a yellow precipitate with an ethanolic solution of copper acetate. The hydroxy compound V forms colorless needles (from water), mp 236-237°C. Found %: C 61.27; H 4.69; N 16.12. $\nu_{C=O}$ 1664 cm^{-1}. Broad band in the 3200-2800 cm^{-1} region, showing the presence of associated OH and NH groups. In view of the poor solubility of the substance in chloroform, its spectrum was taken only for the crystalline state. It colored a solution of copper acetate dark yellow.

Compounds IX-XIX were obtained by the usual methods [8, 9]. The melting points, analytical resuls, and yields are given in Table 1.

The Diacetyl and Triacetyl Derivatives of 2-Hydrazino-8-methoxy-3-methylquinoxaline (XX, XXI). 0.38 g (0.002 mole) of XVII was boiled with acetic anhydride for 2 h 30 min, the mixture was cooled, and 0.25 g of (43%) of compound XX was filtered off. Colorless crystals from a mixture of dimethylformamide and water (2 :1), mp 260-261°C. Found %: C 57.62; H 5.67; N 19.42. $C_{14}H_{16}N_4O_3$. Calculated %: C 58.32; H 5.59; N 19.44. The mother solution after the separation of the diacetyl derivative XX was evaporated to one-third of its original volume, and 0.2 g (30%) of the triacetyl derivative was filtered off; mp 175-176°C, colorless crystals (from ethanol). Found %: C 58.46; H 5.59; N 17.31. $C_{16}H_{18}N_4O_4$. Calculated %: C 58.30; H 5.47; N 17.00.

Ethyl Ester of N-(6-Methoxy-2-nitrophenyl)-α-alanine (VII). A mixture of 5 g (0.024 mole) of 2,3-dinitroanisole [6] and 6 ml of the ethyl ester of α-alanine was heated to the boil. The reaction began vigorously and foaming took place, after the end of which the mixture was kept at the boil for 20 min and was then poured into cold water; an oil separated out which rapidly solidified, and 5.5 g (87%) of dark red solid was filtered off. It was distilled at 210°C (30 mm), mp 57-60°C; lustrous red crystals. Found %: C 53.73; H 5.60; N 10.93. $C_{12}H_{16}N_2O_5$. Calculated %: C 53.72; H 6.01; N 10.44.

5-Methoxy-3-methylquinoxalin-2-one (IV). A mixture of 3 g (0.011 mole) of VII, 6 g of granulated tin, and 6 ml of concentrated hydrochloric acid was heated at the boil for 1 h 30 min, diluted twofold with cold water, made alkaline with NaOH until a precipitate began to deposit (pH 2), and extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated to one-fourth of its original volume, after which 1.8 g of 5-methoxy-3-methyl-1,2,3,4-tetrahydroquinoxalin-2-one (VIII) (gray precipitate, mp about 70°C) was filtered off, and was subjected to oxidation without purification. A mixture of 0.7 g of VIII, 7 ml of 2N NaOH, and 1 ml of 30% hydrogen peroxide was heated in the water bath for 30 min. Then it was cooled and acidified with 2N HCl to pH 3, and 0.6 g (73.5% calculated on the initial VII) of IV was filtered off. Colorless needles from aqueous dimethylformamide. Found %: C 63.32; H 5.46; N 14.58. mp 260-262°C. The IR spectrum coincided completely with that of compound IV obtained by the reaction of 2,3-diaminoanisole with ADC.

LITERATURE CITED

1. Y. Iwanami, Nippon Kagaku Zasshi, 83, 161 (1962); C. A., 59, 3920b (1963).
2. N. G. Koshel and I. Ya. Postovskii, KhGS [Chemistry of Heterocyclic Compounds], 6, 684 (1970).
3. A. Bantlin, Ber., 11, 2106 (1878).
4. L. Horner, U. Schwenk, and E. Junghans, Ann., 579, 212 (1953).
5. K. T. Potts and S. W. Schneller, J. Heterocycl.Chem., 1968, 469.
6. D. L. Vivian, G. Y. Greenberg, and J. L. Hartwell, J. Org. Chem., 16, 1 (1951).
7. F. Wrede and E. Strack, Ber., 62, 2057 (1929).
8. N. G. Koshel, E. G. Kovalev, and I. Ya. Postovskii, KhGS [Chemistry of Heterocyclic Compounds], 6, 851 (1970).
9. D. I. Shino and S. Tagami, J. Am. Chem. Soc., 82, 4044 (1960).
10. B. V. Golomolzin and I. Ya. Postovskii, KhGS [Chemistry of Heterocyclic Compounds], 6, 855 (1970).