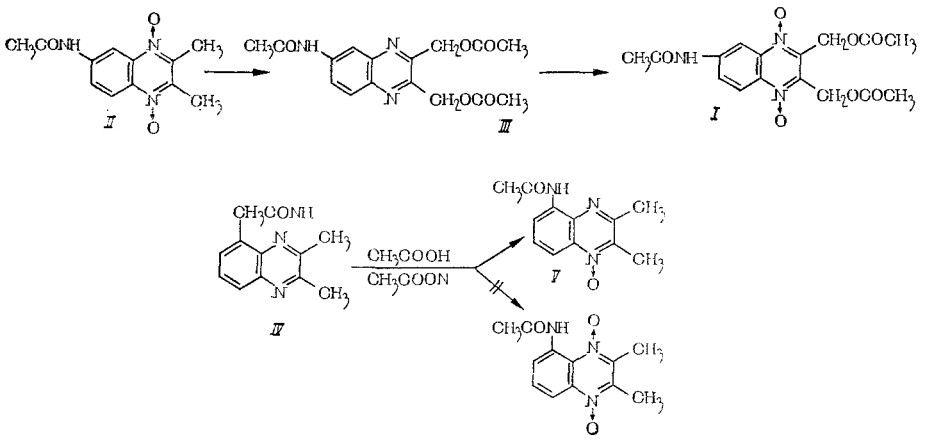
N-OXIDES OF THE QUINOXALINE SERIES.

XXI. SYNTHESIS AND PROPERTIES OF MONO- AND DI-N-OXIDES OF CERTAIN 2-SUBSTITUTED QUINOXALINES

A. S. Elina, I. S. Musatova, and L. G. Tsyrul'nikova

UDC 615.281:547.863.11].012.1:542.9

In connection with the high antimicrobial activity of quinoxaline di-N-oxides substituted in positions 2 and 3 by methyl, hydroxymethyl, or acetoxymethyl groups [1, 2], it appeared of interest to study the antibacterial activity of the corresponding derivatives of quinoxaline containing various substituents in the benzene portion of the molecule. It was shown previously that the introduction of methoxyl groups into positions 6 and 7 of the quinoxaline ring reduces the antibacterial activity of 2,3-dimethylquinoxaline di-N-oxide [2]. We undertook the synthesis of di-N-oxides of 2,3-bis(acetoxymethyl)-6-amino-(or 5-amino)-quinoxalines. The synthesis of 2,3-bis(acetoxymethyl)-6-acetylaminoquinoxaline 1,4-di-N-oxide (I) was carried out from 2,3-dimethyl-6-acetylaminoquinoxaline 1,4-di-N-oxide (II). Compound II on boiling with acetic anhydride underwent deoxidation of the ring nitrogens and simultaneous acetoxylation of the methyl groups. The formed 2,3-bis(acetoxymethyl)-6-acetylaminoquinoxaline (III) was then oxidized with a solution of peracetic acid and compound I was obtained.



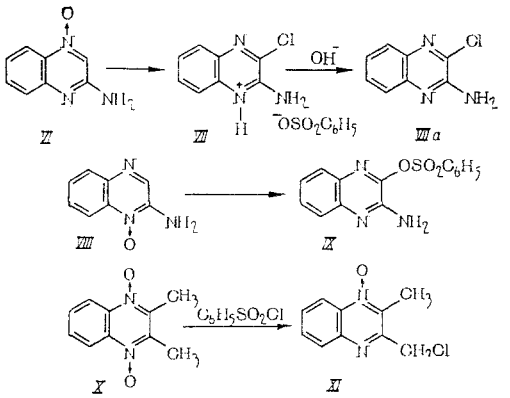
It was not possible to use an analogous scheme for the preparation of 2,3-bis(acetoxymethyl)-5-acetylaminoquinoxaline di-N-oxide since only the mono-N-oxide (V) was obtained from the N-oxidation of 2,3-dimethyl-5-acetylaminoquinoxaline (IV). Evidently, oxidation of ring N_4 is sterically hindered because of the presence of the acetylamino group in position 5.

Compound I showed a much lower antimicrobial activity than the corresponding derivative of quinoxaline unsubstituted in the benzene ring (quinoxidine). Compound (V) also showed weak antibacterial activity.

In the search for accessible means of synthesis of quinoxaline derivatives and their N-oxides, the study of the reactions of the N-oxides of quinoxaline and its 2- or 2,3-substituted derivatives with organic acid chlorides was continued (previous communications [3, 4]). It was shown that the orientation and nature

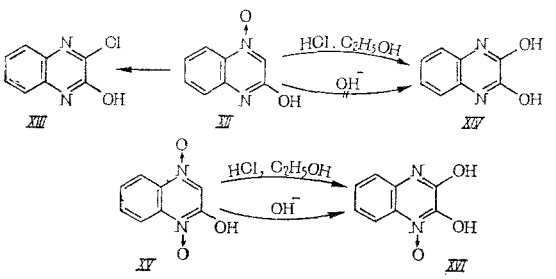
S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 5, No. 8, pp. 6-12, August, 1971. Original article submitted May 29, 1970.

of the substitution did not only depend on the nature of the acylating reagent and the substituent, but also on the position of the N-oxide group. Thus, 2-aminoquinoxaline 4-N-oxide (VI) on reacting with benzenesulfonyl chloride was converted into the benzenesulfonic acid salt of 2-amino-3-chloroquinoxaline (VII) while 2-aminoquinoxaline 1-N-oxide (VIII) reacted with the same acid chloride to form 2-amino-3-benzenesulfonyloxyquinoxaline (IX). 2-Chloromethyl-3-methylquinoxaline 4-N-oxide (XI) was prepared under analogous conditions from 2,3-dimethylquinoxaline 1,4-di-N-oxide (X).



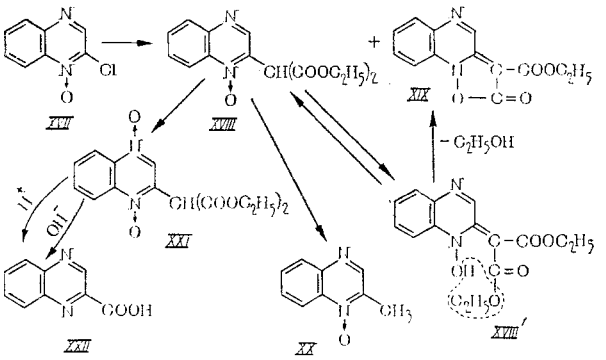
It was shown earlier that the 4-N-oxide and the 1,4-di-N-oxide of 2-phenylquinoxaline underwent deoxidation of nitrogen N_4 and chlorination in ring position 3 on heating with acetyl chloride or alcoholic hydrogen chloride solution [5]. We found that in the case of the N-oxides of 2-hydroxyquinoxaline such a similarity in the action of the above reagents is not observed since 2-hydroxyquinoxaline 4-N-oxide (XII) was converted into 2-hydroxy-3-chloroquinoxaline (XIII) by the action of acetyl chloride but formed 2,3-dihydroxyquinoxaline (XIV) on heating with alcoholic hydrogen chloride solution.

It was an interesting fact that 2-hydroxyquinoxaline 1,4-di-N-oxide (XV) underwent deoxidation of the N_4 nitrogen and ring hydroxylation not only on reacting with an alcoholic or aqueous solution of hydrogen chloride but also on heating in an aqueous solution of sodium or potassium hydroxide whereas (XII) was practically unchanged in aqueous alkaline solutions. We observed an analogous effect previously in the case of the 4-N-oxide and the 1,4-di-N-oxide of 2-aminoquinoxaline [6].



Thus, in the presence of acidic reagents the oxidation-reduction reactions of 2-amino- or 2-hydroxyquinoxalines took place when the N-oxide group and the substituent were in a meta position whereas, in order to achieve the analogous conversions in alkaline medium, a required condition was the presence of a second N-oxide group in a position ortho to the substituent.

In the course of our previous studies on the search for biologically active compounds in a series of N-oxides of quinoxaline-2-carboxylic and quinoxalyl-2-alkylcarboxylic acids and their derivatives [7-10], we synthesized,in addition, the N-oxides of certain N-substituted amides of quinoxaline-2-carboxylic acid. Possible methods of synthesis of mono- and di-N-oxides of quinoxalyl-2-acetic acid were also studied. It was shown that 2-chloroquinoxaline 1-N-oxide (XVII), in contrast to 2-chloroquinoxaline, reacts comparatively readily with sodiomalonic ester. Two substances are formed during the reaction: 2-(dicarbethoxymethyl)quinoxaline (XVIII) and 2-oxo-3-carbethoxy-2H, 10H-isoxazolo[2,3-a]quinoxaline (XIX). The structure of compounds XVIII and XIX was confirmed by the IR and PMR spectroscopic data. Compound (XVIII), owing to the presence of a mobile methine hydrogen, possessed clearly expressed acidic properties.



The formation of compound XIX in this reaction was evidence in favor of possible prototropic tautomeric rearrangements of (XVIII) of the type XVIII ⇌ XVIII[1] since closure of the isoxazoline ring might be realized by the cleavage of a molecule of alcohol from compound (XVIII) in the tautomeric form (XVIII)[1].

Compound (XVIII) was not successfully converted into quinoxalyl-2-acetic acid 1-N-oxide: it was practically unchanged at low temperatures in dilute acids and alkalies and, under more vigorous conditions, considerable resinification occurred. Moreover, under acidic hydrolysis conditions the formation of 2-methylquinoxaline 1-N-oxide (XX) or, in low yield, compound XIX was observed. 2-(Dicarbethoxymethyl)-quinoxaline di-N-oxide (XXI) was obtained on oxidizing (XVIII) with peracetic acid solution. We also failed to obtain quinoxalyl-2-acetic acid di-N-oxide from compound (XXI) since under acidic or alkaline conditions of hydrolysis (XXI) underwent deoxidation of both N-oxide groups accompanied by conversion of the dicarbethoxymethyl group into carboxyl; as a result quinoxalyl-2-carboxylic acid (XXII) was formed. The observed oxidation-reduction rearrangements of (XXI) are evidently also associated with a possibility of prototropic tautomeric rearrangements because there is a mobile methine hydrogen in this compound which is activated by the N-oxide and carbethoxyl groups. Similar oxidation-reduction reactions were observed by us previously in the case of the di-N-oxides of 2-hydroxymethyl- and 2,3-bis(hydroxymethyl) quinoxalines and 2-dihydroxymethylpyrazine.

EXPERIMENTAL

2,3-bis(Acetoxymethyl)-6-acetylaminoquinoxaline (III). A mixture of 43 ml of acetic anhydride and 20 ml of glacial acetic acid was added gradually with stirring to a solution of 14.00 g of II in 120 ml of glacial acetic acid at 110°C. The reaction mixture was then boiled for 20 min and evaporated almost to dryness under vacuum. The residue was ground with alcohol and the compound (III) which formed was filtered off. This gave 11.34 g (60%) of III with mp 159-160° (from acetone). Found, %: C 58.55; H 5.20; N 12.78. $C_{16}H_{17}N_3O_5$. Calculated, %: C 58.00; H 5.17; N 12.68.

2,3-bis(Acetoxymethyl)-6-acetylaminoquinoxaline 1,4-Di-N-oxide (I). To 116 ml of a 9.7% solution of peracetic acid in acetic acid was added 1.58 g of anhydrous sodium acetate, the mixture was stirred, then 8.17 g of compound (III) was added, and the mixture was heated at 55-60° for 20 h. At the end of the reaction the excess of active oxygen was decomposed with an aqueous solution of the calculated quantity of sodium thiosulfate and after this the acetic acid was almost completely distilled off in vacuum. The reaction mixture which remained was neutralized with sodium bicarbonate solution and extracted with chloroform. After drying, the chloroform solution was evaporated to dryness in vacuum. The residue was crystallized from dioxane. This gave 2.3 g (25.6%) of compound I with mp 208.5° (decomp.). Found, %: C 52.95; H 4.85; N 11.58. $C_{16}H_{17}N_3O_7$. Calculated, %: C 52.89; H 4.72; N 11.56.

2,3-Dimethyl-5-aminoquinoxaline. A mixture of 1.9 g of 1,2,3-triaminobenzene dihydrochloride and 1.13 g of dimethylglyoxime was heated in 28 ml of 50% alcohol for 3 h at 78-82°. A solution of sodium hydroxide (2.5 N) was then added to the hot solution until the pH was 7.5-8 and the solid which precipitated was filtered off. The yield was 1.07 g (64%) with mp 164-165° (from aqueous methanol). Found, %: C 69.32; H 6.29; N 24.09. $C_{10}H_{11}N_3$. Calculated, %: C 69.30; H 6.35; N 24.20.

2,3-Dimethyl-5-acetylaminoquinoxaline (IV). To a suspension of 3.4 g of 2,3-dimethyl-5-aminoquinoxaline in 20 ml of anhydrous toluene was added 2.24 ml of acetic anhydride and the mixture was stirred for 2 h at 55-60°. The reaction mixture was cooled and the precipitate which separated was filtered off. This gave 3.43 g (81.2%) of compound (IV) with mp 197-198° (from methanol). Found, %: C 67.10; H 6.10; N 19.44. $C_{12}H_{13}N_3O$. Calculated, %: C 66.97; H 6.09; N 19.53.

2,3-Dimethyl-5-acetylaminoquinoxaline 1-N-Oxide (V). To 43.5 ml of a 9.7% solution of peracetic acid was first added, with stirring, 0.66 g of anhydrous sodium acetate, then 3 g of compound (IV), and the reaction mixture was heated for 10 h at 70-75°. The excess of active oxygen was decomposed with sodium thiosulfate, the acetic acid was distilled off in vacuum, the residue was neutralized with aqueous sodium bicarbonate solution, and extracted with chloroform. After removal of the chloroform, 2.9 g (90%) of compound V was obtained with mp 201-202° (from methanol). Found, %: C 62.19; H 5.88; N 18.24. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.33; H 5.67; N 18.17.

Reaction of 2-Aminoquinoxaline 4-N-Oxide (VI) with Benzenesulfonyl Chloride. Compound VI (0.5 g) was heated in 3 ml of benzenesulfonyl chloride for 6 h at 100° and 7 h at 125-130° until the original compound had disappeared (monitored chromatographically).* The reaction mixture was cooled, the precipitate was filtered off, and washed with ethyl acetate. This gave (VII) with mp 224-225° (decomp.; from methanol); the yield was 0.7 g (67%). Found, %: Cl 10.62; S 9.42. $C_8H_6ClN_3$. $C_6H_5SO_3H$. Calculated, %: Cl 10.48: S 9.47.

To compound (VII) (0.8 g) without a preliminary purification was added an aqueous solution of sodium bicarbonate. The precipitate which separated was filtered off, dried, and treated several times with boiling ether. The insoluble solid (0.1 g) was identical with the starting compound (VI). After evaporation of the ethereal solution 0.38 g (89.4%) of 2-amino-3-chloroquinoxaline (VIIa) was obtained with mp 149-150°. Found, %: C 53.28; H 3.40; N 23.47; Cl 19.77. $C_8H_6ClN_3$. Calculated, %: C 53.49; H 3.36; N 23.48; C 19.74.

IR spectrum: νNH_2 bands at 3500, 3310, and 3160 cm^{-1}; δNH_2 at 1642 cm^{-1}.

PMR spectrum:† there were no signals in the 8.6-8.3 ppm region where the pyrazine ring protons normally appear; the normal benzene ring multiplet showed at 7.33-7.95 ppm (spectrum measured in deuterochloroform).

Reaction of 2-Aminoquinoxaline 1-N-Oxide (VIII) with Benzenesulfonyl Chloride. A suspension of 1.78 g of compound (VIII) in 7 ml of benzenesulfonyl chloride was stirred for 48 h at 20-25°. The precipitate was filtered off, washed with benzenesulfonyl chloride, and then with ether. This gave 1.48 g (44.8%) of IX with mp 185-186° (from alcohol). Found, %: N 13.80; S 10.41. $C_{14}H_{11}N_3O_3S$. Calculated, %: N 13.94: S 10.62.

On hydrolysis in dilute hydrochloric acid IX was converted into a compound identical in R_f and IR spectrum with 2-amino-3-hydroxyquinoxaline prepared by a known method [11].

Reaction of 2,3-Dimethylquinoxaline Di-N-oxide (X) with Benezenesulfonyl Chloride. A mixture of compound (X) (0.5 g) and 2 ml of benzenesulfonyl chloride was left for 24 h at 20-25°. The precipitate was filtered off, washed with a small quantity of benzenesulfonyl chloride, then with ethyl acetate, and neutralized to pH 7 with aqueous sodium bicarbonate solution. This gave 0.36 g (65.5%) of (XI) with mp 181-182° (from alcohol). Found, %: N 13.45; Cl 16.97. $C_{10}H_9ClN_2O$. Calculated, %: N 13.4; Cl 17.00.

PMR spectrum: the signal of the protons of the CH_2 group was at δ 4.95 ppm and the benzene ring multiplet was at 7.5-8.3 ppm.

Reaction of 2-Hydroxyquinoxaline 4-N-Oxide (XII) with Acetyl Chloride. Compound (XII) (0.3 g) in 5 ml of acetyl chloride was boiled for 20 h, the mixture was cooled, and the precipitate filtered off. This gave 0.25 g (75.7%) of (XIII) with mp 262-263°. Found, %: N 15.43: Cl 19.23. $C_8H_5ClN_2O$. Calculated, %: N 15.5; Cl 19.68.

IR spectrum: the amide $\nu C=O$ was at 1700 cm^{-1}.

PMR spectrum: signals for pyrazine ring protons in the 8.6-8.3 ppm region were absent; the multiplet of the benzene ring protons appeared at 7.02-7.73 ppm.

Oxidation-Reduction Reactions of 2-Hydroxyquinoxaline Di-N-oxide (XV) in Acidic or Alkaline Medium. a. Compound (XV) (0.4 g) in 4 ml of a saturated alcoholic solution of hydrogen chloride was boiled for 6 h until the original compound had disappeared (the reaction was monitored by chromatography). The mixture

*All the chromatography was carried out on paper in the system butanol–5% acetic acid solution (1:1). The chromatograms were visualized in UV light.

† The PMR spectra were measured on a JNM4H-100 instrument mainly in a solution of a mixture of dimethyl sulfoxide and carbon tetrachloride with tetramethylsilane as internal standard; chemical shifts are given in the δ scale.

was cooled and 0.18 g of precipitate was filtered off. After evaporation of the solvent in vacuum and grinding of the residue with methanol, an additional 0.2 g of the same substance was obtained (total yield 95%); the formed substance was identical in melting point (287-288°; decomp.), R_f, and IR spectrum with 2,3-dihydroxyquinoxaline 1-N-oxide (XVI) prepared by another means [6]. b. Compound XV (0.2 g) in 2 ml of 2.5 N aqueous sodium hydroxide solution was boiled until the starting compound had disappeared (~ 10-12 h). The reaction solution was treated with activated carbon and filtered and the filtrate was acidified to pH 1. This gave 0.15 g (75%) of a substance identical in melting point and R_f to compound (XVI).

Reaction of 2-Chloroquinoxaline 1-N-Oxide (XVII) with Sodiomalonic Ester. To sodiomalonic ester (prepared from 0.13 g of sodium and 0.9 g of malonic ester) in 17 ml of anhydrous toluene was added compound (XVII) (1 g) at 40° and the reaction mixture was stirred for 30 min at 20-25° and for 1 h at 70-75°. After cooling to 10° a precipitate separated, this was dissolved in water, filtered, and the filtrate acidified to pH 2. This gave 0.37 g of (XVIII) with mp 84.5-85° (from aqueous methanol). Found, %: C 58.79; H 5.24; N 9.20. $C_{15}H_{16}N_2O_5$. Calculated, %: C 59.10; H 5.31; N 9.20.

In the IR spectrum the $\nu C=O$ band of the ester group was at 1742 cm^{-1}.

PMR spectrum: CH_3, $\delta = 1.31$ ppm, triplet; $COOCH_2CH_3$, $\delta = 4.30$ ppm, quartet; CH, $\delta = 5.60$ ppm, singlet; $H_{(3)}$, $\delta = 8.84$ ppm, singlet; $\delta = 7.8$-8.57 ppm, multiplet from benzene ring protons.

After separation of compound (XVIII), the reaction solution was evaporated to dryness in vacuum, the residue was treated with water, and the insoluble precipitate filtered off. This gave 0.27 g (19%) of XIX with mp 188-189° (from aqueous methanol). Found, %: C 60.63; H 3.93; N 11.06. $C_{13}H_{10}N_2O_4$. Calculated, %: C 60.4; H 3.91; N 10.83.

In the IR spectrum there were strong bands at 1800 and 1695 cm^{-1} which can be attributed to the valence vibrations of the C=O groups of the ester radical and the isoxazolone ring.

PMR spectrum: CH_3, $\delta = 1.42$ ppm, triplet; $COOCH_2CH_3$, $\delta = 4.42$ ppm, quartet; H_4, $\delta = 9.55$ ppm, singlet (the signal of the proton $H_{(3)}$ evidently shifts to the region of weak field on account of the effect of the anisotropic C=O group); $\delta = 7.70$-8.16 ppm, multiplet from benzene ring protons.

The aqueous solution remaining after the separation of compound (XIX) was acidified to pH 1.2 and extracted with chloroform; the residue after removal of the chloroform was treated with 2.5 N sodium hydroxide solution, cooled, and the sodium salt of compound XVIII was filtered off; an additional 0.14 g of compound (XVIII) was obtained from the aqueous solutions on acidification. The total yield of (XVIII) was 0.51 g (30.4%).

2-Methylquinoxaline 1-N-Oxide (XX) from Compound (XVIII). Compound (XVIII) (5.17 g) in a mixture of 70 ml of 2.5 N hydrochloric acid and 70 ml of alcohol was boiled for 4 h with stirring, the solution was clarified with activated carbon, filtered, and evaporated to dryness under vacuum. The residue was neutralized with aqueous sodium bicarbonate solution to pH 7 and extracted with chloroform. After removal of the chloroform 2.24 g (82.5%) of compound XX was obtained with mp 97-98° (from petroleum ether). Found, %: C 67.34; H 4.89; N 17.59. $C_9H_8N_2O$. Calculated, %: C 67.60; H 5.00; N 17.48.

Compound (XX) and the substance obtained from it on N-oxidation with a solution of peracetic acid were identical in R_f and mixed melting point with samples of 2-methylquinoxaline 1-N-oxide and 1,4-di-N-oxide respectively.

The main spot detected by paper chromatography of the reaction solution from heating compound (XVIII) in a mixture of 2 ml of 2.5 N hydrochloric acid and 2 ml of alcohol at 70° for 2 h was identical with the starting compound (XVIII), a weaker spot was compound (XIX).

2-(Dicarbethoxymethyl)quinoxaline 1,4-Di-N-oxide (XXI). Sodium acetate (0.15 g) and 10 ml of 10% peracetic acid solution were mixed, then compound (XVIII) (1 g) was added, and the mixture heated at 50-55° for 8 h. The reaction solution was evaporated to one half the original volume in vacuum at 40°, saturated aqueous sodium bicarbonate solution was added until pH 5.5-6, and compound (XXI) (0.98 g, 92.3%) was filtered off with mp 153.5-154.5° (from methanol). Found, %: N 8.75. $C_{15}H_{16}N_2O_6$. Calculated, %: N 8.76.

In the IR spectrum there was a strong band for $\nu C=O$ at 1753 cm^{-1}.

PMR spectrum: CH_3, $\delta = 1.31$ ppm, triplet; $COOCH_2$, $\delta = 4.37$ ppm, quartet; CH, $\delta = 6.19$ ppm, singlet; H_3, $\delta = 8.60$ ppm, singlet; multiplet of benzene ring protons, $\delta = 7.89$-8.55 ppm.

Conversion of Compound XXI into Quinoxaline-2-carboxylic Acid (XXII). a. Compound (XXI) (2 g) was heated at 75-80° in 20 ml of 98% acetic acid to which 0.15 ml of sulfuric acid (sp. gr. 1.82) had been added until the starting compound had disappeared (~20 h, monitored by chromatography). After cooling the colorless crystalline substance (0.81 g, 74.4%) was filtered off and had mp 208-208.5. Found, %: C 61.97; H 3.32; N 15.91. $C_9H_6N_2O_2$. Calculated, %: C 62.1; H 3.48; N 16.08.

The obtained compound (XXII), its ethyl ester and amide were identical chromatographically and in mixed melting point with samples of quinoxaline-2-carboxylic acid and its appropriate derivatives which had been synthesized by the reported methods [7].

b. Compound XXI (0.5 g) was stood in 2.5 ml of 2.5 N sodium hydroxide solution for 2.5 h at 22°, the mixture was then cooled, and the sodium salt of compound XXII was filtered off; acidification of an aqueous solution of the salt gave 0.15 g of the free acid (XXII). After separation of the sodium salt, the reaction solution was acidified and yielded an additional 0.03 g of compound (XXII). The total yield of (XXII) was 0.18 g (66.8%).

Conversion of Compound (XVIII) into Compound (XIX). Compound XVIII (0.5 g) in a mixture of 2.5 ml of 98% acetic acid and 0.15 g of sulfuric acid (sp. gr. 1.82) was heated at 75-80° for 4 h. The reaction mixture was cooled and the precipitate filtered off; the weight was 0.15 g (35.5%) with mp 179-180° (from alcohol). The obtained compound was identical in mixed melting point and R_f with compound (XIX). After separation of compound (XIX), the main reaction solution was evaporated in vacuum, the residue was neutralized with sodium bicarbonate solution until pH 6-6.5, and the precipitate which separated was filtered off; this was crystallized from a mixture of ether and petroleum ether. The yield was 0.15 g (30%) of a substance identical in mixed melting point and R_f with the starting compound (XVIII).

Morpholinomethylamide of Quinoxaline-2-carboxylic Acid 1-N-Oxide (XXIII). A mixture of 1.5 g of quinoxaline-2-carboxyamide 1-N-oxide, 1.4 ml of morpholine, and 2 ml of 38% formalin solution in 20 ml of methanol was boiled for 10 h, then cooled, and 1.1 g of compound (XXIII) was filtered off with mp 135-136° (from alcohol). Found, %: C 58.18; H 5.49; N 19.14. $C_{14}H_{16}N_4O_3$. Calculated, %: C 58.32; H 5.59; N 19.44.

3'-Methoxy-4'-hydroxybenzylidenehydrazide of Quinoxaline-2-carboxylic Acid 1-N-Oxide (XXIV). A mixture of 1.2 g of quinoxaline-2-carboxyhydrazide 1-N-oxide and 0.9 g of vanillin in 24 ml of anhydrous alcohol was boiled for 10 h, cooled, and 1.44 g of compound (XXIV) was filtered off with mp 255-256° (purified by repeated boiling in alcohol). Found, %: C 60.00; H 4.39; N 16.34. $C_{17}H_{14}N_4O_4$. Calculated, %: C 60.35; H 4.17; N 16.56.

Piperidinomethylamide of Quinoxaline-2-carboxylic Acid 1,4-Di-N-oxide (XXV). A mixture of 2.2 ml of piperidine, 2.2 ml of 37% formalin, and 20 ml of anhydrous alcohol was added to 0.72 g of quinoxaline-2-carboxyamide 1,4-di-N-oxide. The reaction mixture was boiled for 7 h, cooled, and compound (XXV) was filtered off with mp 230° (decomp.; from anhydrous alcohol). Found, %: C 59.28; H 5.83; N 18.76. $C_{15}H_{18}N_4O_3$. Calculated, %: C 59.63; H 6.01; N 18.53.

N'-Methylpiperazinomethylamide of Quinoxaline-2-carboxylic Acid 1,4-Di-N-oxide (XXVI). A mixture of 1.3 g of quinoxaline-2-carboxyamide 1,4-di-N-oxide, 3.2 ml of N-methylpiperazine, and 3.2 ml of 37% formalin solution was stirred in 13 ml of anhydrous alcohol for 5 h at 65°, then cooled, and 1 g of compound XXVI was filtered off with mp 167-168°. Compound (XXVI) was unstable; therefore it was purified by washing several times with anhydrous alcohol at 20-22°. Found, %: C 56.47; H 6.01; N 21.80. $C_{15}H_{19}N_5O_3$. Calculated, %: C 56.80; H 6.03; N 22.07.

Morpholinomethylamide of Quinoxaline-2-carboxylic Acid 1,4-Di-N-oxide (XXVII). A mixture of 1.2 ml of morpholine, 1.68 ml of 37% formalin solution, and 30 ml of anhydrous alcohol was added to 1.2 g of quinoxaline-2-carboxyamide 1,4-di-N-oxide. The reaction mixture was boiled for 6 h, than a further 1.2 ml of morpholine and 1.68 ml of formalin was added, and the mixture boiled for a further 7 h. After cooling, the compound (XXVII) which separated was filtered off; the yield was 1.34 g with mp 185-186° (from alcohol). Found, %: C 55.33; H 5.49; N 18.64. $C_{14}H_{16}N_4O_4$. Calculated, %: C 55.25; H 5.30; N 18.41.

3'-Methoxy-4'-hydroxybenzylidenehydrazide of Quinoxaline-2-carboxylic Acid 1,4-Di-N-oxide (XXVIII). To a solution of 0.9 g of methyl quinoxaline-2-carboxylate 1,4-di-N-oxide in 36 ml of methanol heated to 50°, 0.9 ml of hydrazine hydrate was added gradually with stirring. The reaction mixture was then stirred for 1 h at 20-25° after which it was cooled and 0.99 g of quinoxaline-2-carboxyhydrazide 1,4-

di-N-oxide was filtered off. To the obtained substance 0.87 g of vanillin and 30 ml of anhydrous alcohol were added and the reaction mixture was boiled for 3.5 h. This gave 1.44 g of compound (XXVIII) with mp 254° (decomp.; from acetic acid). Found, %: C 57.62; H 4.05; N 15.83. $C_{17}H_{14}N_4O_5$. Calculated, %: C 57.62; H 3.98; N 15.81.

β-Phenylisopropylamide of Quinoxaline-2-carboxylic Acid 4-N-Oxide (XXIX). A mixture of 0.7 g of ethyl quinoxaline-2-carboxylate 4-N-oxide and 0.6 g of β-phenylisopropylamine in 6.5 ml of anhydrous alcohol was boiled for 26.5 h. This gave 0.54 g of compound XXIX with mp 112.5-113.5° (from alcohol). Found, %: 70.23; H 5.65; N 13.78. $C_{18}H_{17}N_3O_2$. Calculated, %: C 70.36; H 5.58; N 13.67.

LITERATURE CITED

1. J. Francis, J. K. Landquist, A. A. Levi, J. A. Silk, and J. M. Thorp, Biochem. J., 63, 455 (1956).
2. E. N. Padeiskaya, A. S. Elina, G. N. Pershin, L. G. Tsyrul'nikova, and K. A. Belozerova, Farmakol. i Toksikol., No. 5, 617 (1967).
3. A. S. Elina, Zh. Obshch. Khim., 34, 2809 (1964).
4. A. S. Elina, Khim. Geterotsikl. Soedin., No. 4, 724 (1967).
5. Y. Ahmad, M. S. Habib, Ziauddin Bakhtiari, and Bushra Bakhtiari, J. Org. Chem., 31, 2613 (1966).
6. A. S. Elina and L. G. Tsyrul'nikova, Zh. Obshch. Khim., 33, 1544 (1963).
7. A. S. Elina and O. Yu. Magidson, Zh. Obshch. Khim., 25, 161 (1955).
8. A. S. Elina and L. G. Tsyrul'nikova, Khim. Farmats. Zh., No. 11, 36 (1967).
9. A. S. Elina, L. G. Tsyrul'nikova, E. N. Padeiskaya, et al., Author's certificate No. 235767 (1967); Izobreteniya, No. 2, 204 (1970).
10. A. S. Elina, Zh. Obshch. Khim., 29, 2763 (1959).
11. J. R. Stevens, K. Pfister, and F. J. Wolf, J. Amer. Chem. Soc., 68, 1035 (1946).