CONNECTION BETWEEN THE STRUCTURE AND THE ANTIBACTERIAL ACTIVITY OF THE N-OXIDES OF QUINOXALINES. MOLECULAR STRUCTURE OF DIOXIDINE AND QUINOXIDINE

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UDC 615.281:547:863].011.1.07

The di-N-oxides of quinoxaline derivatives describe a specific class of chemotherapeutic agents [7]. The highly effective antibacterial preparation dioxidine [2,3-bis(hydroxymethyl)quinoxaline-1,4-di-N-oxide (I)] and quinoxidine [2,3-bis-(acetoxymethyl)quinoxaline-1,4-di-N-oxide (II)], which were developed at the VNIKhFI, appertain to compounds of this type; they are produced industrially and are successfully applied in medical practice for the treatment of purulent, wound, and burn infections [5, 8, 10]. Dioxidine and quinoxidine are preparations having a broad spectrum of antibacterial action and exhibit activity toward bacterial strains which are resistant to other chemotherapeutic medicinal agents including antibiotics. The peculiarity of the spectrum of antibacterial activity is evidently associated with features of the molecular structure and reactivity of the di-N-oxides of α-hydroxymethyl derivatives of quinoxaline. It was previously found that (II) is metabolized rapidly in the intestines, plasma, and liver, being converted to the main metabolite (I) via an intermediate product [1]. On the basis of these data and the comparison of the activity of (I) and (II), it was concluded that the antibacterial effect of (II) is determined by the activity of its main metabolite (I).

The investigation of the characteristic functional conversions of the biologically important quinoxaline-N-oxides showed that the presence of the hydroxymethyl group containing available protons in the α-position to the readily polarized N→O function is the main structural factor determining the capacity of dioxidine and its analogs to undergo a certain type of oxidation–reduction and photochemical reactions [3, 6, 9, 11-14]. It was established on the basis of the study of the EPR spectra of the anion-radicals formed by the electrochemical reduction of quinoxaline-di-N-oxides in DMF that a stepped reduction reaction with the sequential deoxidation of the nitrogen atoms is characteristic of the compounds containing the methyl or formyl groups in the pyrazine ring. Under the same conditions, the anion-radicals of the α-hydroxymethyl derivatives of quinoxaline undergo the intramolecular oxidative–reduction deoxidation reaction with the simultaneous conversion of the hydroxymethyl groups to aldehyde groups [9]. The ability of the N-oxides of the α-hydroxymethyl derivatives of quinoxaline to undergo the analogous conversion in the presence of alkaline reagents was found previously [6]. Our investigations showed that, in the acid media, (I) undergoes the same oxidation–reduction reaction proceeding in two sequential kinetically controlled stages as follows: the formation of the cyclic hemiacetal of 2-hydroxymethyl-3-formylquinoxaline-1-N-oxide and its conversion to the cyclic bishemiacetal of 2,3-diformylquinoxaline [11, 14]. When hydroxymethyl groups are substituted by the methyl or acetoxymethyl groups, the quinoxaline-N-oxides lose the ability to undergo this reaction. It was shown that the main process in the conversion of quinoxidine in both the alkaline and acidic media is the solvolysis reaction with the formation of dioxidine [14].

Features of the molecular structure are also shown by the high selectivity of the photochemical conversions of the biologically active quinoxaline-N-oxides [3, 4, 12, 13]. It was established that, depending on the character of the substituent at the pyrazine ring of the quinoxaline-di-N-oxides, they can undergo one of two types of photochemical rearrangements with the transfer of the oxygen of the N→O group to the pyrazine ring proceeding by different mechanisms: the isomerization with the migration of the substituent to the nitrogen of the heterocycle, and the rearrangement with the elimination of the substituent. Dioxidine and quinoxidine, for which the main structural difference is the presence and absence correspondingly of the available hydroxyl protons in the molecule, undergo different types of rearrangements, and one determined photo-reaction is characteristic of each preparation. The conception according to which the possibility of the formation of six-membered rings on account of the intramolecular hydrogen bonds in the molecules of dioxidine and its analogs determines the features of the photorarrangement mechanism with the elimination of the substituent was considered in [3, 4]. In connection with this, the principal interest is

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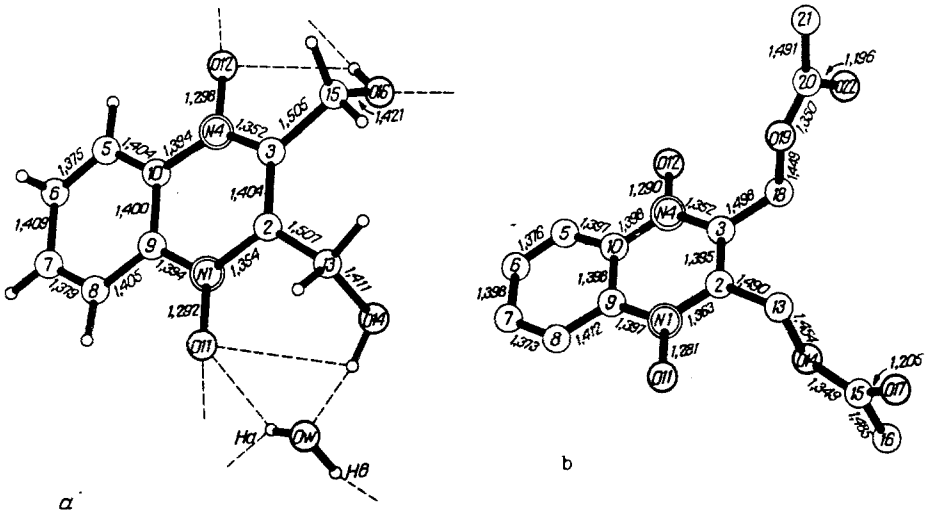

Fig. 1. Structure of the molecules (I) and (II) with the bond lengths: a) (I) (σ = 0.001 Å); b) (II) (σ = 0.003-0.004 Å).

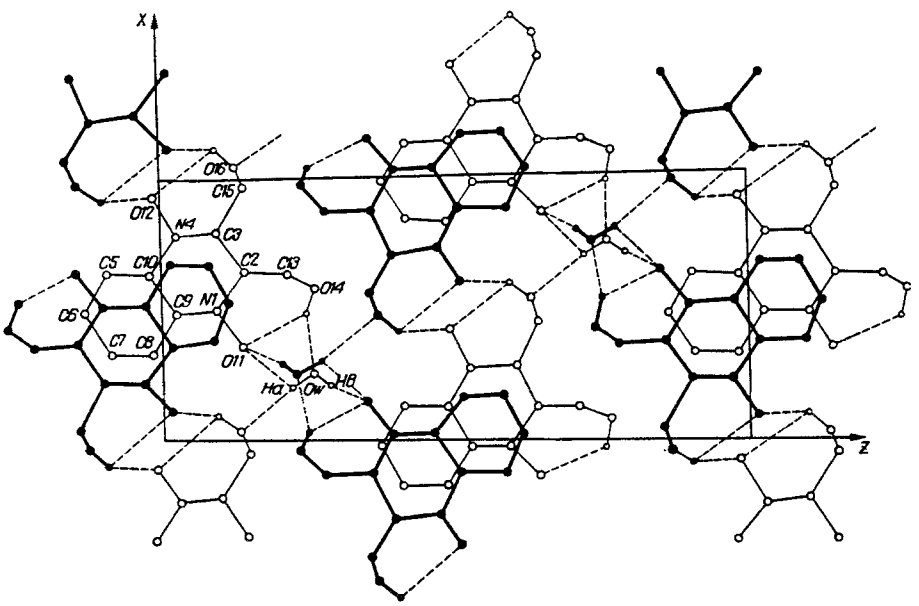

Fig. 2. Projection of the structure of the monohydrate of (I) on the (010) plane. The dash lines designate the hydrogen bonds. The bold lines distinguish the molecules of (I) situated closer to the observer.

presented by the comparison of the actual molecular structure of dioxidine and quinoxidine and the study of their relative ability to undergo intermolecular interactions of varying type. With this object, we performed an X-ray structural investigation of these preparations.

The bond lengths (Fig. 1) and bond angles (Table 1) in the molecules (I) and (II) are in good agreement with the values of the analogous parameters in the previously investigated structures of the quinoxaline-di-N-oxides, particularly in 6-chloro-3-ethoxycarbonyl-2-methoxyquinoxaline-1,4-di-N-oxide [16-18], and are close to the standard values [15]. The quinoxaline bicycle is practically planar: the dihedral angle between the planes of the six-membered rings is equal to 1.2° in (I) and 1.3° in (II). The presence of sufficiently bulky substituents at the positions 2 and 3 of the quinoxaline system produces certain steric difficulty. As a consequence of this, the oxygen atoms of the N→O groups deviate from the plane of the pyrazine ring by −0.039(1) Å and −0.054(1) Å in (I) and by −0.076(2) Å and 0.035(2) Å in (II). Deviations from this plane which are similar in magnitude are also

TABLE 1. Bond Angles (in Degrees) in the Molecules (I) and (II).

I		II	
C(2)N(1)C(9)	120,2 (1)	C(2)N(1)C(9)	118,5 (2)
C(2)N(1)O (11)	121,4 (1)	C(2)N(1)O(11)	121,4 (2)
C(9)N(1)O(11)	118,4 (1)	C(9)N(1)O(11)	120,2 (2)
N(1)C(2)C(3)	120,2 (1)	N(1)C(2)C(3)	120,8 (2)
N(1)C(2)C(13)	115,5 (1)	N(1)C(2)C(13)	115,8 (2)
C(3)C(2)C(13)	124,3 (1)	C (3)2(2)2(13)	123,4 (2)
C(2)C(3)N(4)	120,6 (1)	C(2)2(3)N(4)	121,5 (2)
C(2)C(3)C(15)	125,1 (1)	C(2)C(3)C(18)	122,9 (2)
N(4)C(3)C(15)	114,3 (1)	N(4)C(3)C(18)	115,6 (2)
C(3)N(4)C(10)	120,0 (1)	C(3)N(4)C(10)	119,0 (2)
C(3)N(4)O(12)	120,6 (1)	C(3)N(4)O(12)	121,7 (2)
C(10)N(4)O(12)	119,4 (1)	C(10)N(4)O(12)	119,3 (2)
C(10)C(5)C(6)	118,7 (1)	C(10)C(5)C(6)	118,2 (3)
C(5)C(6)C(7)	121,5 (1)	C(5)C(6)C(7)	121,2 (3)
C(6)C(7)C(8)	120,2 (1)	C(6)C(7)C(8)	121,3 (3)
C(7)C(8)C(9)	119,0 (1)	C(7)C(8)C(9)	118,3 (3)
N(1)C(9)C(8)	121,5 (1)	N(1)C(9)C(8)	119,6 (3)
N(1)C(9)C(10)	120,2 (1)	N(1)C(9)C(10)	120,6 (2)
C(8)C(9)C(10)	119,0 (1)	C(8)C(9)C(10)	119,8 (3)
N(4)C(10)C(5)	120,2 (1)	N(4)C(10)C(5)	119,3 (2)
N (4)C(10)C(9)	119,6 (1)	N(4)C(10)C(9)	119,5 (2)
C(5)C(10)C(9)	120,2 (1)	C(5)C(10)C(9)	121,1 (3)
C(2)C(13)O(14)	112,5 (1)	C(2)C(13)O(14)	107,1 (2)
		C(13)O(14)C(15)	115,6 (2)
		O(14)C(15)C(16)	111,4 (2)
		O(14)C(15)O(17)	122,8 (3)
		C(16)C(15)O(17)	125,8 (3)
C(3)C(15)O(16)	111,0 (1)	C(3)C(18)O(19)	106,1 (2)
		C(18)O(19)C(20)	114,9 (2)
		O(19)C(20)C(21)	110,9 (2)
		O(19)C(20)O(22)	123,4 (3)
		C(21)C(20)O(22)	125,7 (3)

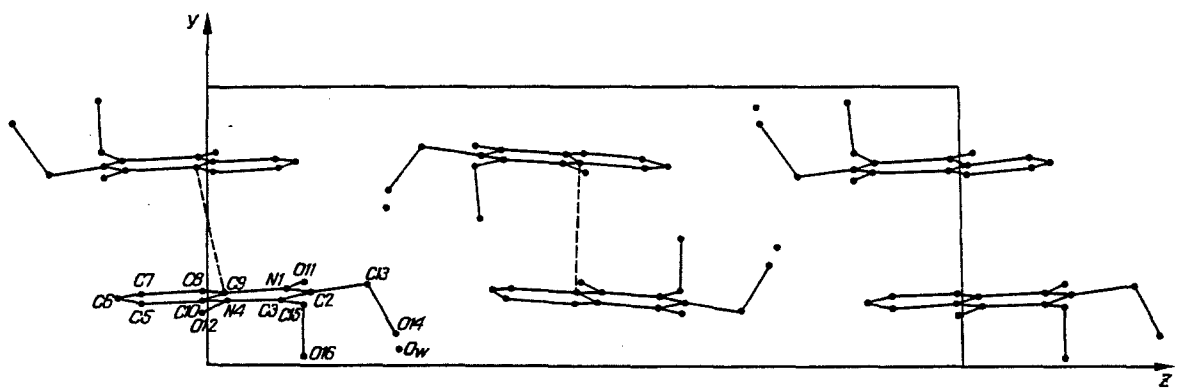

Fig. 3. Projection of the structure of the monohydrate of (I) on the (100) plane, showing the stacking interaction.

observed for the methylene C atoms of the hydroxymethyl [0.024(1) Å and −0.041(1) Å] and acetoxymethyl [0.086(2) Å and −0.055(3) Å] groups. The acetoxymethyl groups in (II) have the elongated planar–transoid conformation [the torsion angles C(2)C(13)–O(14)C(15) −151.7(4), C(13)O(14)–C(16) 177.5(4), C(3)C(18)–O(19)C(20) −170.1(4), C(18)O(19)–C(20) −176.2(4)] and the anti orientation in relation to the pyrazine nucleus [the distances from the O(14) and O(19) atoms to the mean plane of the quinoxaline system comprise −1.254(2) Å and 1.319(2) Å]. The planes of the two acetoxymethyl groups are thereby approximately perpendicular to the plane of the quinoxaline system: the dihedral angles are equal to 93.6° and 89.1°.

In contrast, the hydroxymethyl groups in the molecule of (I) have the syn orientation in relation to the quinoxaline system [the oxygen atoms of the hydroxyl groups O(14) and O(16) deviate from the plane of the pyrazine ring by −1.198(1) Å and −1.321(1) Å]. The conformation of the hydroxymethyl substituents in the molecule of (I) is determined by the formation of

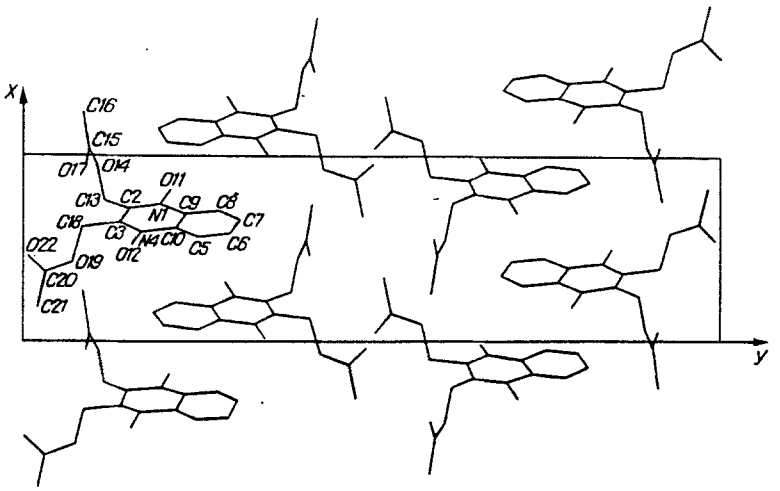

Fig. 4. Projection of the structure of (II) on the (001) plane.

intramolecular H-bonds due to the available hydroxyl hydrogen atoms of the hydroxymethyl groups and the oxygen atoms of the N-oxide functions. Two intramolecular H-bonds are realized in the structure (I): O(14)H...O(11) and O(16)H...O(12) with the closing of the two six-membered rings (cf. Fig. 1a). The H-bond O(14)H...O(11) [O...O 2.998(1) Å, H...O 2.61(2) Å, OHO 111(2)°] is thereby significantly weakened by comparison with the O(16)H...O(12) bond [O...O 2.895(1) Å, H...O 2.43(2) Å, OHO 123(2)°] due to the competition with the molecule of water "introduced" at the first of these H-bonds which emerges as an acceptor of the hydroxyl hydrogen atom HO(14) [O_w...O(14) 2.716(1) Å, H...O 1.90(2) Å, OHO_w 172(2)°] and as the donor of the hydrogen atom H_a in the H-bond with the oxygen atom of the group N(1)→O(11) [O_w...O(11) 2.854(1) Å, H_a...O_a 2.54(2) Å, OHO_w 105(1)°]. Therefore, the hydroxyl hydrogen atom of the hydroxymethyl group at C(2) participates in the formation of the unsymmetrical fork H-bond.

The fork H-bond in the structure of the monohydrate of (I) also involves the participation of the hydroxyl hydrogen atom of the hydroxymethyl group at C(3), which forms the intermolecular H-bond O(16)H...O(12) (2−x, −y, −z) (Fig. 2) with the oxygen atom of the N→O group of another molecule of (I) [O...O 2.890(1) Å, H...O 2.24(2) Å, OHO 148(2)°], besides the intramolecular H-bond indicated above. A molecule of the water of crystallization also participates in the formation of several hydrogen bonds with the molecules of (I). The hydrogen atom H_a of the water molecule, which participates in the H-bond with the oxygen atom of the N(1)→O(11) group of one molecule of (I), simultaneously participates in the H-bond OH_a...O(16) (x−1, y, z) with the O(16) oxygen atom of the hydroxymethyl group of another molecule of (I) [O_w...O(16) 2.925(1) Å, H_a...O(16) 2.19(2) Å, OHO_w 154(2)°]. Moreover, the second hydrogen atom H_b, of the water molecule forms the H-bond O_wH_b...O(11) ($^1/_2$−x, $^1/_2$ + y, $^1/_2$−z) with another molecule of (I) [O_w...O(11) 2.821(1) Å, H_b...O(11) 1.96(2) Å, OHO_w 172(2)°].

On account of the H-bonds considered (besides the last), the molecules of (I) and water unite in double chains along the crystallographic direction [20$\bar{1}$], and these chains are in layers parallel to the (010) (cf. Fig. 2). The stacking interaction with the distances 3.928(2) Å and 3.350(2) Å between the planes of the quinoxaline nuclei disposed in the antiparallel position is accomplished in the chains indicated, besides the H-bonding via the water molecules between the molecules of (I) linked by the centers of symmetry of the type 000 and $^1/_2{}^1/_2$0 (Fig. 3). The molecules of (I) and the water of crystallization, pertaining to the different layers (010), form a three-dimensional framework in the crystal on account of the H-bonds of the type indicated last.

The stacking interaction is also accomplished in the structure (II) between the molecules connected by the sliding surfaces d (Fig. 4). The distance between the planes of the quinoxaline nuclei equals 3.382(2) Å.

Therefore, the main differences between the structures (I) and (II) comprise the following.

1. The molecule of (I) is the synisomer, whereas the molecule of (II) has the antiorientation of the more bulky acetoxymethyl groups.

2. A system of intramolecular and intermolecular H-bonds is observed in the structure of (I); the system includes the H-bonds with water molecules in which (I) emerges both as an acceptor and as a donor of active hydrogen atoms. The molecule of (II), which does not have active hydrogen atoms, may only participate with the H-bonds, in principle, as their acceptor; this is not however realized in the structure (II) due to the absence of donor molecules of water.

TABLE 2. Coordinates of the Atoms ($\cdot 10^4$, and for the H Atoms $\cdot 10^3$) and Their Equivalent Isotropic Temperature Parameters (B_{eq}, Å^2) in the Structure of the Monohydrate of (I)

Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
N(1)	4943 (1)	2746 (1)	1036 (1)	0,971 (1)	H(5)	726 (2)	214 (3)	—109 (1)	2,6 (4)
C(2)	6427 (1)	2734 (1)	1397 (1)	1,01 (1)	H(6)	471 (3)	208 (4)	—180 (1)	4,4 (6)
C(3)	7889 (1)	2495 (1)	1014 (1)	1,04 (1)	H(7)	223 (2)	250 (3)	—110 (1)	2,2 (4)
N(4)	7839 (1)	2307 (1)	281 (1)	1,06 (1)	H(8)	232 (3)	287 (3)	15 (1)	3,9 (5)
C(5)	6271 (1)	2248 (1)	—865 (1)	1,34 (2)	H(13A)	746 (2)	337 (3)	242 (1)	2,2 (4)
C(6)	4757 (1)	2289 (2)	—1225 (1)	1,52 (2)	H(13B)	564 (2)	412 (3)	230 (1)	1,9 (4)
C(7)	3276 (1)	2459 (1)	—845 (1)	1,48 (2)	H(14)	479 (3)	114 (3)	254 (1)	3,7 (5)
C(8)	3322 (1)	2604 (1)	—96 (1)	1,25 (2)	H(15A)	954 (2)	273 (3)	186 (1)	2,1 (4)
C(9)	4861 (1)	2756 (1)	279 (1)	0,97 (1)	H(15,B)	1025 (2)	331 (3)	111 (1)	1,8 (3)
C(10)	6325 (1)	2381 (1)	—102 (1)	1,01 (1)	H(16)	1042 (2)	20 (3)	94 (1)	3,5 (5)
O(11)	3576 (1)	2901 (1)	1378 (1)	1,41 (1)	H(01)	212 (2)	24 (3)	288 (1)	2,8 (5)
O(12)	9186 (1)	2038 (1)	—72 (1)	1,54 (1)	H(02)	215 (4)	45 (4)	219 (2)	4,3 (5)
C(13)	6363 (1)	2956 (2)	2212 (1)	1,26 (2)					
O(14)	5805 (1)	1225 (1)	2556 (1)	1,66 (1)					
C(15)	9600 (1)	2370 (1)	1357 (1)	1,33 (2)					
O(16)	10224 (1)	410 (1)	1326 (1)	1,48 (1)					
O	2481 (1)	693 (1)	2596 (1)	2,11 (2)					

TABLE 3. Coordinates of the Atoms ($\cdot 10^4$, and for the H Atoms $\cdot 10^3$) and Their Equivalent Temperature Parameters (B_{eq}, Å^2) in the Structure (II)

Atom	x	y	z	B_{eq}	Atom	x	y	z
N (1)	2387 (3)	6972 (1)	4244 (4)	2,14 (5)	H (5)	10 (6)	740 (1)	1026 (7)
C (2)	2098 (3)	6500 (1)	4657 (4)	2,03 (6)	H (6)	38 (5)	821 (2)	955 (7)
C (3)	1386 (3)	6359 (1)	6483 (4)	1,89 (5)	H (7)	150 (5)	846 (1)	623 (7)
N (4)	870 (3)	6683 (1)	7861 (3)	1,88 (4)	H (8)	268 (6)	791 (1)	390 (8)
C (5)	574 (4)	7507 (1)	8879 (5)	2,45 (6)	H (13A)	238 (6)	635 (2)	165 (7)
C (6)	786 (4)	7985 (1)	8434 (6)	3,09 (8)	H (13B)	186 (5)	584 (1)	336 (7)
C (7)	1501 (4)	8132 (1)	6611 (6)	3,18 (7)	H (16A)	803 (5)	594 (1)	98 (7)
C (8)	2032 (4)	7805 (1)	5205 (6)	2,74 (7)	H (16B)	769 (6)	555 (1)	183 (7)
C (9)	1842 (4)	7313 (1)	5642 (5)	2,03 (6)	H (16C)	791 (5)	600 (1)	315 (8)
C (10)	1102 (4)	7171 (1)	7460 (4)	1,92 (5)	H (18A)	143 (5)	580 (1)	861 (7)
O (11)	3151 (3)	7105 (1)	2624 (4)	3,09 (5)	H (18B)	202 (5)	562 (1)	613 (7)
O (12)	133 (3)	6555 (1)	9516 (3)	2,58 (5)	H (21A)	—380 (5)	500 (1)	771 (8)
C (13)	2588 (4)	6158 (1)	3052 (5)	2,59 (6)	H (21B)	—310 (6)	499 (1)	562 (7)
O (14)	4557 (3)	6055 (1)	3243 (3)	2,44 (4)	H (21C)	—396 (5)	543 (1)	661 (7)
C (15)	5439 (4)	5937 (1)	1551 (4)	2,16 (5)				
C (16)	7453 (4)	5861 (1)	1889 (5)	3,12 (7)				
O (17)	4646 (3)	5901 (1)	—15 (3)	2,85 (5)				
C (18)	1146 (4)	5844 (1)	7055 (5)	2,40 (6)				
O (19)	—768 (3)	5726 (1)	6625 (3)	2,10 (4)				
C (20)	—1337 (4)	5298 (1)	7326 (5)	2,33 (6)				
C (21)	—3279 (5)	5194 (1)	6696 (6)	3,03 (7)				
O (22)	—377 (3)	5040 (1)	830 (4)	3,19 (5)				

3. The difference in the relative volume of the substituents at the positions 2 and 3 of the quinoxaline nucleus evidently influences the capacity of the molecules of (I) and (II) for the intermolecular stacking interaction, which is more marked in the case of (I).

The combination of the experimental data obtained and the results of the preceding investigations [3-9, 11-14] permits the conclusion that the capacity for the formation of intramolecular and intermolecular H-bonds and the stacking interaction, which is determined by a key fragment of the molecular structure, evidently plays a fundamental role in the dynamics of the characteristic functional conversions and in the mechanism of antibacterial action of dioxidine and its analogs.

EXPERIMENTAL

Crystals suitable for the investigation were obtained from the aqueous-ethanolic solution of (I) and the ethanolic solution of (II); the x-ray structural investigation showed that (I) is the monohydrate of 2,3-bis(hydroxymethyl)quinoxaline-1,4-di-N-oxide, $C_{10}H_{10}N_2O_4 \cdot H_2O$, and (II) is 2,3-bis(acetoxymethyl)-quinoxaline-1,4-di-N-oxide, $C_{14}H_{14}N_2O_6$. The parameters of the unit cells and intensities of the reflections were measured on a "Syntex $P2_1$" four-circle automatic diffractometer (USA) at the temperature of 153 K [λ MoK_α, graphite monochromator, $\theta/2\theta$-scanning, $2\theta_{max}$ 66 and 60° correspondingly for the crystals of

the monohydrate (I) and the crystals of (II)]. The crystals of the monohydrate (I) are monoclinic: a = 8.091(2), b = 6.768(2), and c = 18.370(6) Å, β = 91.72(3)°, V = 1005.4(5) Å^3, z = 4, d_{calc} = 1.59 g/cm^3, space group $P2_1/n$. The crystals of (II) are rhombic: a = 7.208(2), b = 27.921(1), and c = 6.765(3) Å, V = 1361.4(9) Å^3, z = 4, d_{calc} = 1.50 g/cm^3, space group $Pna2_1$.

Both structures were interpreted by the direct method using the MULTAN program, and they were specified by the ICs in the anisotropic block-diagonal approximation for non-hydrogen atoms. The positions of all the hydrogen atoms were found in the difference Fourier synthesis, and they were specified by the ICs in the isotropic approximation with the fixed B_{iso} = 5 Å^2 in the structure (II), and in the anisotropic approximation in the structure (I). All calculations were performed using the INEXTL program [2] on the "Eclipse S/200" computer of the firm "Data General Corp." (USA). The final values of the divergence factors were as follows: for the crystals of the monohydrate (I), R = 4.1%, R = 5.9% from the 2906 reflections with $I > 3\sigma$, and for the crystals of (II), R = 4.4%, R_w = 5.3% from the 1683 reflections with $I > 3\sigma$. The coordinates of the atoms in the structures (I) and (II) are presented in the Tables 2 and 3 correspondingly.

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