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SYNTHESIS AND SOME PROPERTIES OF TETRAHYDROQUINAZOLINE 1,3-DIOXIDES

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It has previously been established that 1,3-dioxides of pyrimidines form as a result of the oxidation of products of the condensation of 1,3-hydroxylaminooximes with aldehydes [1]. In the present work this method was used for the synthesis of condensed pyrimidine 1,3-dioxides, viz., 5,6,7,8-tetrahydroquinazoline 1,3-dioxides, for which there is no information in the literature.

For this purpose we carried out the condensation of N-[(1-hydroxyiminocyclohex-2-yl)methyl]hydroxylamine (I) with carbonyl compounds [2]. The reaction of 1,3-hydroxylaminooxime I with formaldehyde, acetaldehyde, and acetone yielded condensation products (II-IV) with the splitting off of a water molecule. The PMR spectra of compounds II-IV point out that the condensation product with formaldehyde has the structure of 3-hydroxy-2,3,4,4a,5,6,7,8-octahydroquinazoline 1-oxide (cyclic form IIB), that with acetone is N-[(1-hydroxyiminocyclohex-2-yl)methyl]-α,α-dimethylnitrone (open form IVA), and the condensation product with acetaldehyde exists in a tautomeric mixture of open and cyclic forms (IIIA $\rightleftharpoons$ IIIB). Thus, the PMR spectrum of IIB in pyridine shows a broadened singlet of the protons of the methylene group in position 2 of the heterocycle at 4.92 ppm, and there are no signals (in D_2O) of the protons of the methylenenitrone group of open form IIA in the 6.0-7.0-ppm region [3]. The PMR spectrum of derivative IVA in D_2O has two signals of the protons of the methyl groups in the α,α-dimethylnitrone configuration at 2.10 and 2.19 ppm and does not show any signals of the protons in the geminal methyl groups of cyclic form IVB in the 1.4-1.7-ppm region [2, 4]. The PMR spectrum of compound III in D_2O shows a doublet of the protons of the methyl group and a quartet of the methine proton of the α-methylnitrone configuration of open form IIIA at 1.96 and 7.25 ppm ($J = 6.0$ Hz), respectively, whereas for cyclic form III there are two doublets of the protons of the methyl group in position 2 of the heterocycle: 1.49 ($J = 6.5$ Hz) and 1.53 ppm ($J = 6.5$ Hz) with a ~1:6 ratio. This points out the presence in the solution of two cyclic tautomeric forms, which are distinguished by the cis and trans orientations of the substituents in positions 2 and 4a of the heterocycle [5]. The constant of the tautomeric equilibrium ($K_T = [A]/[B]$) for III in D_2O is equal to 0.6, and that in pyridine is equal to 2.2.

It is noteworthy that the presence of a cyclohexane ring in 1,3-hydroxylaminooxime I caused an increase in the relative concentration of cyclic tautomer IIIB in the condensation product of III in comparison to the condensation product of the acyclic 1,3-hydroxylaminooxime which contains two methyl groups instead of the tetramethylene bridge (compare [2]).

Along with the bands at 1629 and 1623 cm^{-1}, which fit the stretching vibrations of the C=N bond in nitrones [6], the IR spectra (in KBr) of III and IV show bands at 1659 and 1657 cm^{-1}, respectively, of the stretching vibrations of a C=N bond in oximes [7], confirming structure IVA and suggesting that compound III also exists in open form IIIA in the crystalline state.

It could have been expected that the oxidation of II and III would produce tetrahydroquinazoline 1,3-dioxides V and VI, respectively [1]. It was found that the yields of 1,3-dioxides V and VI depend both on the solvent used [8] and on the oxidizing agent. When II was oxidized by active manganese dioxide in dioxane, 5,6,7,8-tetrahydro-

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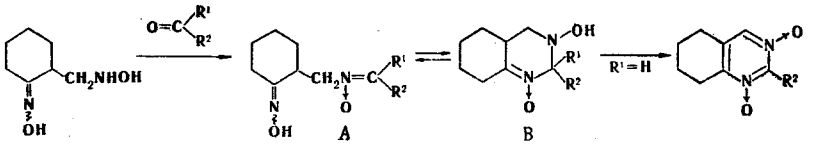
TABLE 1. Spectral Characteristics of Derivatives of 5,6,7,8-Tetrahydroquinazoline 1,3-Dioxide

Compound	PMR spectrum (in $CDCl_3$), δ ppm						IR spectrum, cm^{-1}*
	R^1	H^4	R^2	H^8	5-CH_2	6,7-CH_2CH_2	
V	H 8,92	7,89	H 2,5	—	3,0	1,4—2,1	1350, 1303, 1208, 1200, 1161
VI	CH_3 2,81	7,97	H 2,6	—	3,1	1,6—2,1	1318, 1167, 1126
VII	H 9,04	8,04	Br	5,65	2,7—3,0	1,9—2,5	1212, 1180
VIII	CH_3 2,81	8,06	Br	5,64	1,8—3,1		1288, 1129
IX	CH_3 2,79	8,11	CH_3COO 2,09	6,36	2,6—3,0	1,6—2,1	1319, 1244, 1132
X	CH_3 2,75	8,04	OH 5,17	5,01	2,5—2,9	1,6—2,3	1319, 1110

*The most intense absorption bands in the 1400-1100-cm^{-1} region are given.

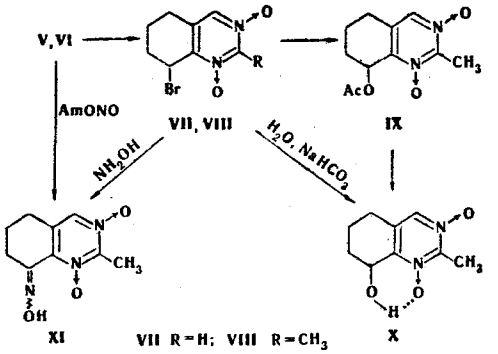


I II–IV A B V,VI

II $R^1=R^2=H$; III $R^1=H$, $R^2=CH_3$; IV $R^1=R^2=CH_3$; V $R^2=H$; VI $R^2=CH_3$

quinazoline 1,3-dioxide (V) formed with a 45% yield, and when III was oxidized under the same conditions, dioxide VI formed in trace amounts, whereas when the reaction was carried out in water, its yield was 28%. When nickel peroxide served as the oxidizing agent [9], 1,3-dioxide VI was obtained with a 52% yield in water and with a 25% yield in dioxane. However, under these conditions 1,3-dioxide V formed with lower yields than when the oxidation reaction was carried out with active manganese dioxide. The spectra data and the elemental analysis of compounds V and VI are in good agreement with the structure of 5,6,7,8-tetrahydroquinazoline 1,3-dioxides (Tables 1 and 2).

In the study of the properties of dioxides V and VI it was found that their treatment with N-bromosuccinimide or the application of a solution of bromine in chloroform to compound VI yields products of the replacement of a hydrogen atom by a bromine atom (VII and VIII) [10, 11]. The PMR spectra of these compounds (Table 1) and the further chemical conversions showed that the bromination resulted in the formation of 8-bromo derivatives VII and VIII. The reaction of bromo derivative VIII with potassium acetate in the presence of a catalytic amount of 18-crown-6 in acetonitrile produced acetoxy derivative IX, whose IR spectrum showed bands at 1735 (C=O) and 1244 cm^{-1} (C–O). The heating of IX in methanol in the presence of hydrochloric acid yielded hydroxy derivative X, whose IR spectrum displays only a characteristic band of an intramolecular hydrogen bond in the 3600-3200-cm^{-1} region regardless of the concentration (5% in $CHCl_3$ and 0.05% in CCl_4), pointing out position 8 for the hydroxy group in tetrahydroquinazoline X. The position of the hydroxy group in product X is consistent with the ability of this compound to produce colored complexes with copper salts. Compound X forms with a good yield when a solution of VIII in water is held in the presence of sodium bicarbonate.



V,VI VII, VIII IX XI X

VII R=H; VIII R=CH_3

TABLE 2. Compounds Synthesized

Compound	mp, °C[a]	UV spectrum, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
II	126—129	238 (3,98)	56,2	8,5	16,2	$C_8H_{14}N_2O_2$	56,5	8,3	16,5	83
III	137—139	235 (3,95)	59,0	8,8	15,5	$C_9H_{16}N_2O_2$	58,7	8,8	15,2	96
IV	124—127	238 (3,95)	60,6	9,2	14,3	$C_{10}H_{18}N_2O_2$	60,6	9,2	14,1	96
V	172—174	262 (4,40), 278 sh(4,13), 340 (2,82)	57,5	6,1	16,8	$C_8H_{10}N_2O_2$	57,8	6,1	16,9	45
VI	165—167	259 (4,41), 283 (4,03), 340 (3,03)	60,1	6,7	15,6	$C_9H_{12}N_2O_2$	60,0	6,7	15,5	52
VII	110decomp	271 (4,37), 298 (4,09)	39,6	3,9	11,3	$C_8H_9BrN_2O_2$[b]	39,2	3,7	11,4	31
VIII	123decomp	267 (4,37), 301 (4,05), 361 (3,21)	42,0	4,3	10,7	$C_9H_{11}BrN_2O_2$[c]	41,7	4,3	10,8	57
IX	173—175	264 (4,47), 287 (4,09), 354 (3,26)	55,3	5,9	11,7	$C_{11}H_{14}N_2O_4$	55,4	5,9	11,8	63
X	168—170	262 (4,40), 287 (4,01), 349 (3,15)	55,0	6,2	14,1	$C_9H_{12}N_2O_3$	55,1	6,2	14,3	63
XI	250decomp	273 (4,33), 330 (4,10), 349 (3,99)	51,6	5,6	20,1	$C_9H_{11}N_3O_3$	51,7	5,3	20,1	40

[a]Compound II crystallized from dioxane with one water molecule, which was lost upon heating in a vacuum; compound III was recrystallized from dioxane, IV and VI were recrystallized from ethyl acetate, XI was recrystallized from ethanol, and compounds V and VII-X were purified chromatographically. [b]Found: Br, 32.4%. Calculated: Br 32.6%. [c]Found: Br, 30.8%. Calculated: Br, 30.8%.

Thus, compounds VIII, IX, and X have the structures of 8-bromo-(VIII), 8-acetoxy- (IX), and 8-hydroxy-2-methyl-5,6,7,8-tetrahydroquinazoline 1,3-dioxide (X). It may be postulated that bromination product VII has the structure of 8-bromo-5,6,7,8-tetrahydroquinazoline 1,3-dioxide. The spectral data on the compounds obtained (Tables 1 and 2) are in agreement with these structures.

As in the case of alkylpyrimidines [13], the nitrosation of 1,3-dioxide VI by amyl nitrite in an acid medium produced oxime XI, which forms with a small yield when 8-bromo derivative VIII is treated with hydroxylamine [14]. Therefore, the nitrosation of dioxide VI also takes place at position 8 of the heterocycle, and oxime XI has the structure of 8-hydroxyimino-2-methyl-5,6,7,8-tetrahydroquinazoline 1,3-dioxide.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument, and the UV spectra were recorded on a Specord UV-vis spectrometer in ethanol. The PMR spectra were recorded on a Varian A-56-60A instrument in HMDS and tert-butanol (aqueous solutions) as internal references. 18-Crown-6, which is produced as the Experimental Chemical Production Facilities of the Novosibirsk Institute of Organic Chemistry, was used in the work.

N-[(1-Hydroxyiminocyclohex-2-yl)methyl]hydroxylamine (I). A solution of hydroxylamine (which was obtained by neutralizing 0.23 mole of hydroxylamine hydrochloride with an equimolar amount of sodium methoxide) in 200 ml of methanol was given an addition of a solution of 23.10 g (0.10 mole) of N-[(1-oxocyclohex-2-yl)-methyl]-α-phenylnitrone [15] in 100 ml of methanol over the course of 1 h. After 24 h the solvent was driven off, and the residue was treated with ether. The precipitate formed was filtered off, and 11.10 g (70%) of compound I with mp 131-133°C (from ethanol) were recorded from it by crystallization from ethyl acetate. Found: C, 53.4; H, 9.1; N, 17.6%. Calculated for $C_7H_{14}N_2O_2$: C, 53.1; H, 8.9; N, 17.7%.

Condensation of I with Formaldehyde, Acetaldehyde, and Acetone. These condensation reactions were carried out in analogy to [2] by adding, 1,3-hydroxylaminooxime I to solutions of formaldehyde and acetaldehyde in 99.5% ethanol and acetone.

5,6,7,8-Tetrahydroquinazoline 1,3-Dioxide (V). Compound V was obtained by oxidizing II by active manganese dioxide under the conditions in [1] in dioxane with pyridine with a 45% yield.

2-Methyl-5,6,7,8-tetrahydroquinazoline 1,3-dioxide (VI). A suspension of 18.6 g (0.0204 mole) of nickel sesquioxide [16] in 70 ml of water was added with stirring to a solution of 3.13 g (0.017 mole) of compound III in 80 ml of water. After 1 h the suspension was filtered off, and after the filtrate was saturated with sodium chloride, it was extracted with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated, and the residue was treated with an acetone–ether mixture. Dioxide VI was filtered off, and the yield was 1.59 g.

In an analogous manner 1,3-dioxide V was obtained with a ~5% yield by oxidizing II with active manganese dioxide or nickel sesquioxide in water.

8-Bromo-2-methyl-5,6,7,8-tetrahydroquinazoline 1,3-Dioxide (VIII). A. A solution of 0.93 g (5.8 mmole) of bromine in 20 ml of chloroform was added with stirring to a solution of 0.90 g (5.0 mmole) of VI in 60 ml of chloroform, and the mixture was held for 1 h. The reaction mixture was washed with a 3% solution of sodium dicarbonate and water. The chloroform solution was dried over magnesium sulfate and evaporated, and 0.73 g of VIII was isolated by chromatographing the residue in a column with silica gel (the eluent was chloroform).

B. A solution of 0.20 g (1.11 mmole) of VI and 0.29 g (1.63 mmole) of N-bromosuccinimide in 20 ml of chloroform with a catalytic amount of concentrated sulfuric acid was stirred for 4 h. Compound VIII was isolated as in experiment A, and its weight was 0.085 g (29%).

8-Bromo-5,6,7,8-tetrahydroquinazoline 1,3-Dioxide (VII). Compound VII was obtained from V in an analogous manner.

8-Acetoxy-2-methyl-5,6,7,8-tetrahydroquinazoline 1,3-Dioxide (IX). A catalytic amount of 18-crown-6 was added to a suspension of 0.57 g (5.8 mmole) of potassium acetate in 25 ml of acetonitrile. After 15 min, 0.50 g (1.93 mmole) of VIII was added, and the mixture was stirred for 70 h. The precipitate was filtered off, the filtrate was evaporated, and 0.29 g of product IX was recovered by chromatographing the residue in a column with silica gel (the eluent was a 50:1 chloroform–methanol mixture).

8-Hydroxy-2-methyl-5,6,7,8-tetrahydroquinazoline 1,3-Dioxide (X). A. A solution of 0.15 g (0.63 mmole) of IX in 7 ml of methanol was boiled for 16 h, and 0.4 ml of a 5% hydrochloric acid solution was added in small portions during this time. The solvent was evaporated, and 0.027 g (18%) of the original compound IX and 0.045 g (37%) of X were isolated by preparative thin-layer chromatography on silica gel (the eluent was a 5:5:3:2 chloroform–acetone–methanol–ether mixture).

B. A solution of 1.0 g (3.87 mmole) of VIII in 70 ml of water was given an addition of 17 ml of a 3% solution of sodium bicarbonate and held for 6 days at room temperature. Then the solution was heated for 1 h 30 min at 70°C. After cooling, the solution was extracted with chloroform, and the chloroform solution was dried over magnesium sulfate. After the solvent was evaporated, 0.48 g of compound X was isolated by chromatographing the residue in a column with silica gel (the eluent was chloroform).

8-Hydroxyimino-2-methyl-5,6,7,8-tetrahydroquinazoline 1,3-Dioxide (XI). A solution of 0.11 g (3 mmole) of HCl in 5 ml of absolute ethanol at 0°C was given additions of 0.20 g (1.11 mmole) VI and then of a solution of 0.26 g (2.22 mmole) of amyl nitrite in 5 ml of absolute ethanol and stirred for 2 h at 0°C. The precipitate of XI formed was filtered and washed with ethanol. The yield was 0.092 g.

Compound XI formed with a 5% yield when a solution of VIII was held with a 1.5-fold excess of free hydroxyl amine over the course of 4 days at room temperature.

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MASS-SPECTROMETRIC STUDY OF ANTIBIOTICS OF THE PYRIMIDO[5,4-e]-asym-TRIAZINE SERIES

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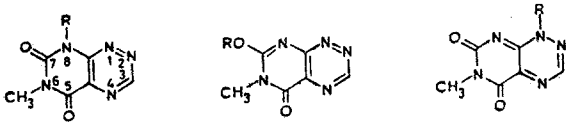
It has previously [1, 2] been reported that the methylation of rheumycin (Ia) by diazomethane yields three individual monomethylation products, which have been identified as 1,6-dimethylpyrimido[5,4-e] [1,2,4]triazine-5,7-dione (IIIa), which is known as the antibiotic xanthothricin [3] or toxoflavin, 6,8-dimethylpyrimido[5,4-e] [1,2,4]triazine-5,7-dione (Ic), which is known as the antibiotic fervenulin [5, 6] or planomycin [7], and 6-methyl-7-methoxypyrimido[5,4-e] [1,2,4]triazin-5-one (IIa), whose synonym is 7-methoxyrheumycin [2].



I a R=H; b R=D; c R=CH_3; d R=CH_2D; II a R=CH_3; b R=CH_2D; III a R=CH_3; b R=CH_2D

In order to further study the products of the chemical and biological conversion of antibiotics Ia, Ic, IIa, and IIIa, it is necessary to find analytical criteria, which would make it possible to identify compounds with very similar structures. This was the goal of the present investigation and presupposes the use of mass spectrometry [8].

Antibiotics Ia, Ic, IIa, and IIIa are distinguished by a low resistance to electron impact (W_M) (Table 1) in comparison to derivatives of uracil [9] and pyrimidine [10, 11]. This finding is evidence that the molecular ion (M^+) exists predominantly in the keto form, which is in complete agreement with the ground-state structure of the molecules under study. The appreciable decrease in the value of W_M in compound IIa is due to the appearance of addition fragmentation paths owing to the presence of the methoxy group in the uracil part of the molecule [12].

The directions for the fragmentation of M^+ for each antibiotic have been determined with the aid of an investigation of the mass spectra of metastable ions (the DADI technique) [13, 14] (Table 2). It was rigorously provided that the initial act in the fragmentation of M^+ is due to the loss of 28 amu (i.e., a CO or N_2 molecule). The elimination of a CO molecule is characteristic of most cyclic ketones of the hetaryl series. This is dictated not only by the predominant localization of the charge in M^+ on the more electronegative oxygen atom, but also to the formation of the energetically favorable pseudomolecular ion $[M-CO]^+$, which has the structure of a heteroaromatic five-membered ring. However, as the data from high-resolution mass spectrometry showed (Table 3), in the case of compounds Ia, Ic, and IIa, the triazine part of the molecule undergoes destruction with the elimination of an N_2 molecule, and the elimination of a CO molecule is characteristic only of compound IIIa.

In this connection it seemed of interest to compare the energetics of the two processes (Table 4). The value we determined for ΔE [the difference between the appearance potential (AP) of the fragment ion and the ionization potential (IP) of the molecule] for the process $M^+ \xrightarrow{-N_2} [M-N_2]^+$ in the case of compound Ia is small

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