SYNTHESIS, STRUCTURE, AND BIOLOGICAL PROPERTIES OF N-OXIDES OF SOME 2-SUBSTITUTED QUINOXALINES AND PYRAZINES

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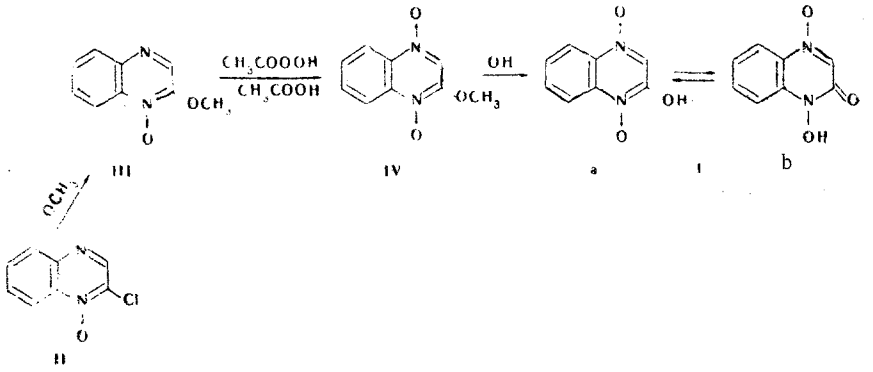
2-Methoxy- and 2-hydroxy-substituted quinoxaline and pyrazine N,N'-dioxides and N-oxides of a number of quinoxaline-2-carboxylic acid derivatives were synthesized in order to study their biological activity. It is shown that the N-monoxides and N,N'-dioxides of 2-hydroxy derivatives of quinoxaline exist primarily in the oxo form. Strong intramolecular hydrogen bonds were detected in the case of 1-N-oxides of 2-hydroxy and 2-carboxamido derivatives of quinoxaline. Substances with antibacterial and antituberculous activity were found among the synthesized compounds.

In contrast to the N-oxides of α- and γ-hydroxy derivatives of pyridine and quinoline [1], the 1-N-oxides of 2-hydroxyquinoxaline and 2-hydroxypyrazine did not display appreciable antibacterial action [2]. Inasmuch as the biological activity of some quinoxaline derivatives increases on passing from the monoxides to the N,N'-dioxides [2], it seemed of interest to synthesize and study the antibacterial action of the N,N'-dioxides of 2-hydroxy derivatives of quinoxaline and pyrazines.

The utilization of the method in [1, 3] for the synthesis of these compounds, which consists in N-oxidation of the corresponding 2-halo or 2-alkoxy derivatives and subsequent hydrolysis of the halogen or alkoxy groups, presented considerable difficulties, inasmuch as the oxidation of the N_1 nitrogen atom in the quinoxaline or pyrazine derivatives indicated above is difficult.

We were able to accomplish the synthesis of 2-hydroxyquinoxaline 1,4-dioxide (I) by using a practicable method for the preparation of 2-chloroquinoxaline 1-oxide (II) [4]. We obtained 2-methoxyquinoxaline 1-oxide (III) from II, after which we oxidized the N_4 nitrogen atom in it, and the resulting 2-methoxyquinoxaline 1,4-dioxide (IV) [5] was converted to I.

Similarly, we synthesized 2-methoxy- and 2-hydroxypyrazine 1,4-dioxides (VI and VII) from 2-methoxypyrazine 1-oxide (V) [6].



Starting chloro derivative VIII was first described in [7] as a side product formed in the reaction of pyrazine N,N'-dioxide (IX) with $POCl_3$ along with 2,6-dichloropyrazine. Later

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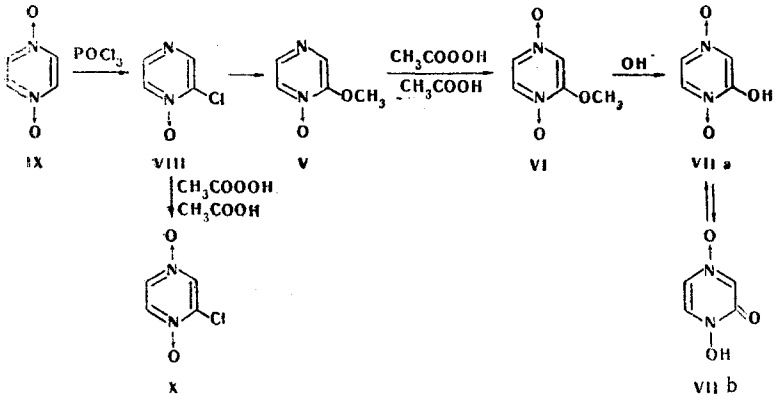
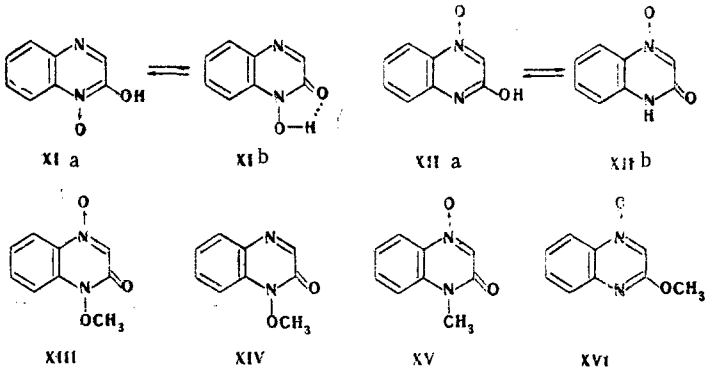
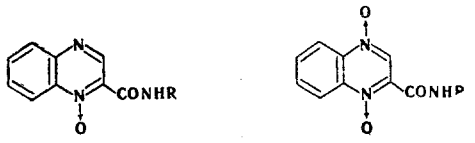


Okada and co-workers [8] obtained VIII in 25% yield. By changing the conditions of the reaction of N,N'-dioxide IX with $POCl_3$ we obtained chloro derivative VIII in about 45% yield. A variant of the synthesis of VI and VII through 2-chloropyrazine N,N'-dioxide (X) proved to hold little promise, inasmuch as the yield of X in the N-oxidation of VIII did not exceed 20%.

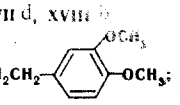


The spectra of the corresponding methylated derivatives of these compounds (XIII-XV) and the IR spectra of I, XI [9], and XII [10] (in the crystalline state and in solution) contain strong bands of an amide group at 1643-1686 cm^{-1}, which are absent in the spectra of model compounds with a fixed hydroxy structure (III, IV, and XVI). This constitutes evidence for the existence of the investigated 2-hydroxyquinoxaline N-oxides primarily in the oxo form (Ib, XIb, and XIIb) in the crystalline state and in solution. The $\nu C{=}O$ band in the spectra of crystalline XIb and solutions of XIb in $CHCl_3$ and CCl_4 is shifted to the lower-frequency region by 25-30 cm^{-1} as compared with the analogous band in the spectrum of its methylated derivative (XIV). There is a broad band of stretching vibrations of an associated hydroxyl group in the high-frequency region of the spectrum of XIb at 2500-2740 cm^{-1}; in a markedly dilute solution in CCl_4 (<0.02%) these bands are observed at 2500-3230 cm^{-1}, and the band of stretching vibrations of a free hydroxyl group is absent. This constitutes evidence for the existence of a strong intramolecular hydrogen bond in XIb. There is apparently a similar intramolecular hydrogen bond in N,N'-dioxide Ib, the spectra of which are close to the spectra of XIb with respect to the position of the $\nu C{=}O$ bands in the crystalline state and in solution and with respect to the position of the νOH band in the crystalline state. The possibility of the formation of an intramolecular hydrogen bond is excluded in the case of 4-oxide XIIb, and, in conformity with this, a band of stretching vibrations of a free NH group (3395 cm^{-1}) is observed in the spectrum of a dilute solution of it in $CHCl_3$. 2-Hydroxypyrazine N,N'-dioxide (VII) also exists in the oxo form, i.e., in the form of a cyclic hydroxamic acid (VIIb, $\nu C{=}O$ 1660 cm^{-1}), in the crystalline state.

In order to search for biologically active compounds in the quinoxaline series we also accomplished the synthesis of the N-monoxides and N,N'-dioxides of quinoxaline-2-carboxylic acid derivatives — the amides, the hydrazide, and the corresponding hydroxamic acids (XVIIa-k and XVIIIa-h). The synthesis was accomplished by the action of amines, hydrazine hydrate, or hydroxylamine [11] on the 1-oxide or N,N'-dioxide of methyl quinoxaline-2-carboxylate (XIX or XX).



XVII XVIII

XVII, XVIII a R=H; XVII b R=NH_2; c R=OH; k R=$CH_2CH(OH)CH_2N(C_2H_5)_2$; XVII d, XVIII b R=$CH(CH_3)CH_2C_6H_5$; XVII, XVIII f R=$CH_2CH_2C_6H_5$; g R=$CH(CH_3)C_6H_5$; h R=  ; XVII e XVIII d R=$CH_2(CH_2)_2CH_2N(C_2H_5)_2$; XVII i, XVIII e R=$CH_2CH_2CH_2OH$; XVII j, XVIII c R=$CH_2(CH_2)_4CH_2OH$

Just as in the spectra of the previously synthesized quinoxaline-2-carboxamide and its 4-oxide (XXI and XXII) [12] recorded in the crystalline state and in solution, there are intense bands of $\nu_{C=O}$ stretching vibrations of an amide group (1666-1713 cm^{-1}) and, in the high-frequency region, ν_{NH_2} bands (3200-3530 cm^{-1}) in the IR spectra of the amides of the 1-oxide and 1,4-dioxide of quinoxaline-2-carboxylic acid (XVIIa and XVIIIa).

The ν_{NH_2} bands in the spectra of dilute solutions of XVIIa and XVIIIa in CCl_4 (about 0.002%) are found in the lower-frequency region as compared with corresponding bands in the spectra of XXI and XXII. This shift in the frequencies shows up particularly clearly during an examination of the position of the bands of symmetrical stretching vibrations ν_s) of the NH_2 group (ν_s 3290 and 3250 cm^{-1} in the spectra of XVIIa and XVIIIa, respectively, as compared with 3407 cm^{-1} in the spectra of XXI and XXII). These data speak in favor of the fact that, as in I and XI examined above, there are intramolecular hydrogen bonds in XVIIa and XVIIIa.

The antibacterial activity of the synthesized compounds was studied in *in vitro* experiments and in experiments on animals. The activities of all of the compounds were compared with the chemotherapeutic activity of 2,3-bis(acetoxymethyl)quinoxaline N,N'-dioxide (quinoxidine) and 2,3-bis(hydroxymethyl)quinoxaline N,N'-dioxide (dioxidine), which showed high antibacterial activity in previous studies and, after a thorough clinical study, were approved for medical application for acute purulent bacterial infections. The 1,4-dioxides of 2-hydroxy derivatives of quinoxaline and pyrazine (I and VII), which are analogs of aspergillic acid, do not have pronounced antibacterial activity. 2-Methoxyquinoxaline 1,4-dioxide (IV), which in experiments on animals in the case of a number of infections (including also experiments with staphylococcus strains that are resistant to antibiotics) gives rise to a a high chemotherapeutic effect close to the action of quinoxidine and dioxidine, seems of great interest. However, IV is somewhat more toxic, and this does not make it possible to recommend it for clinical study. The corresponding pyrazine derivative (VI) is inactive.

Compounds XVIIIa,d,e and the previously synthesized 1,4-dioxide of the piperidinomethylamide, N-methylpiperazinomethylamide, and morpholinomethylamide of quinoxaline-2-carboxylic acid [13] displayed antibacterial activity, but the observed activity was inferior to that of quinoxidine and dioxidine. The N-oxides of the amides and hydrazide of quinoxaline-2-carboxylic acid (XVIIIa,b and XVIIb) display high *in vitro* tuberculostatic action in concentrations of 1 μg/ml and lower.

EXPERIMENTAL

The IR spectra of mineral oil suspensions or solutions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. Chromatography was carried out on paper in a butanol—5% CH_3COOH system (1:1) with development in UV light.

2-Methoxyquinoxaline 1-Oxide (III). A solution of 0.7 g (3.87 mmole) of II in 4 ml of anhydrous methanol was added gradually to a solution of 0.09 g (3.92 mmole) of Na in 2 ml of anhydrous methanol, after which the mixture was stirred at 22° for 1 h and at 55° for 1 h. The solution was then cooled, and the resulting precipitate was removed by filtration to give III.

2-Methoxyquinoxaline 1,4-Dioxide (IV). An 0.4-g sample of sodium acetate, 0.01 g of $Na_4P_2O_7$, and 2 g (11 mmole) of III were added to 24 ml (31.6 mmole) of a 10% solution of peracetic acid, after which the mixture was heated at 35° for 25 h. The solvent was then re-

moved *in vacuo* at 40° until the volume of the mixture was one third of the original volume, and the residual mixture was neutralized with $NaHCO_3$ solution and extracted with chloroform. The chloroform was removed from the extract to give IV.

2-Hydroxyquinoxaline 1,4-Dioxide (I). A mixture of 1 g (5.2 mmole) of IV in 8 ml of 2.5 N NaOH solution was stirred at 22° until the solid had dissolved completely (about 1.5 h), after which the solution was filtered and the filtrate was acidified to pH 1-2 to give I, which gave an intense cherry-red coloration with $FeCl_3$.

1-Methoxy-2-oxo-1,2-dihydroquinoxaline (XIV). A solution of 0.5 g (3.1 mmole) of XI in 7.5 ml of 4% NaOH and 7.5 ml of methanol was shaken with 1.5 ml of CH_3I at 25° for 5 h, after which the reaction solution was vacuum evaporated to one half its initial volume and extracted with chloroform. Removal of the chloroform from the extract gave XIV.

1-Methoxy-2-oxo-1,2-dihydroquinoxaline 4-Oxide (XIII). A mixture of 0.55 g (3.6 mmole) of I, 9 ml of 2.5 N NaOH, 18 ml of methanol, and 7.2 ml of CH_3I was shaken at 25° for 13 h, after which it was worked up as in the preparation of XIV to give XIII.

Reaction of Pyrazine 1,4-Dioxide (IX) with $POCl_3$. A 3-g (27 mmole) sample of IX was added to 10.5 ml (110 mmole) of $POCl_3$ heated to 60°, after which the mixture was stirred at 72° for 1 h. The temperature was then gradually raised to 95°, upon which a spontaneous rise in the temperature to 105° was observed, and the solid material dissolved. Heating was then discontinued, and the solution was allowed to stand at 25° for 18 h. It was then poured over ice, and the aqueous mixture was neutralized with concentrated NH_4OH to give 1.67 g (42%) of 2,6-dichloropyrazine with mp 54-56° [7, 8]. The filtrate was extracted with chloroform, and the solvent was removed from the extract to give 1.44 g (42%) of VIII with mp 133-134° (from methanol).

2-Chloropyrazine 1,4-Dioxide (X). An 0.23-g sample of sodium acetate, 0.01 g of $Na_4P_2O_7$, and 1 g (8 mmole) of VIII were added successively to 15.5 ml of 10.5% (24 mmole) peracetic acid, after which the mixture was heated at 70° for 7 h and at 80° for 5 h. It was then filtered, and the solvent was removed *in vacuo* until the volume of the mixture was one fourth of the original volume (at 45°). The residue was evaporated to dryness at 22°, and the dry material was treated with a mixture of ether and methanol. The resulting solid was extracted several times with heated ether to remove the unchanged VIII. Workup gave X. PMR spectrum (in D_2O), δ, ppm: 8.59 (3-H), 8.12 (5-H), and 8.29 (6-H); $J_{3,5}$ 2.7 Hz, $J_{3,6}$ 0.5 Hz, and $J_{5,6}$ 5.8 Hz. Compounds X, VIII, and 2-hydroxypyrazine 1-oxide were detected chromatographically in the methanol solution after separation of the precipitate.

2-Methoxypyrazine 1,4-Dioxide (VI). An 0.34-g sample of sodium acetate, 0.01 g of $Na_4P_2O_7$, and 1 g (8 mmole) of V were added successively to 22 ml of 10.5% (27 mmole) peracetic acid, after which the mixture was heated at 60° for 17 h. It was then cooled to 20° and filtered, and ether was added to the filtrate until no more turbidity was produced. The resulting precipitate was removed by filtration to give VI.

2-Hydroxypyrazine 1,4-Dioxide (VII). A mixture of 0.57 g (4 mmole) of VI and 1.6 ml of 2.5 N NaOH solution was allowed to stand at 25° for 1 h until the solid material had dissolved completely. The solution was then acidified with 2.5 N HCl to pH 2, and the resulting solid was removed by filtration to give 0.36 g (70%) of VII with mp 238-239° (dec., from aqueous alcohol). The product gave an intense cherry-red coloration with $FeCl_3$. IR spectrum, cm^{-1}: 1658 (amide $\nu_{C=O}$) and 3110. PMR spectrum (in CF_3COOH), δ, ppm: 8.42 (3-H), 7.81 (5-H), and 8.24 (6-H); $J_{3,5}$ 1.9 Hz, $J_{5,6}$ 5.5 Hz.

Quinoxaline-2-carboxamide 1-Oxide (XVIIa). A mixture of 2.7 g (13.2 mmole) of XIX in 27 ml of 18% alcoholic NH_3 was allowed to stand at 25° for 24 h, after which it was cooled, and XVIIa was removed by filtration.

Quinoxaline-2-carboxylic Acid Hydrazide 1-Oxide (XVIIb). A mixture of 2 g (9.8 mmole) of XIX and 1 ml of $NH_2NH_2 \cdot H_2O$ in 30 ml of anhydrous alcohol was allowed to stand at 25° for 24 h, after which it was worked up to give XVIIb.

Quinoxaline-2-hydroxamic Acid 1-Oxide (XVIIc). A solution of 3.12 g of KOH in 46 ml of methanol and 3 g (14.7 mmole) of XIX were added successively to 2.6 g (36.4 mmole) of $NH_2OH \cdot HCl$ in 20 ml of methanol, after which the mixture was allowed to stand at 25° for 24 h. Workup of the mixture gave the potassium salt, from which XVIIc was isolated in the usual manner.

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
I	240—241 (dec., from alcohol)	53,4	3,5	15,4	$C_8H_6N_2O_3$	53,8	3,4	15,7	54
III	135—136 (from methanol)	60,9	4,5	16,1	$C_9H_8N_2O_2$	61,3	4,6	15,9	69
IV	171—172 (from alcohol)	56,1	4,2	14,4	$C_9H_8N_2O_3$	55,8	4,2	14,6	46
VI	181—182 (dec., from alcohol)	42,6	4,4	19,7	$C_5H_6N_2O_3$	42,5	4,3	19,7	78
X	191—192 (dec., from alcohol)	32,5	2,1	18,6	$C_4H_3ClN_2O_2$	32,8	2,1	19,1	20
XIII	192—193 (from alcohol)	56,1	4,1	14,2	$C_9H_8N_2O_3$	56,3	4,2	14,6	50
XIV	102—103 (from alcohol)	61,3	4,6	15,9	$C_9H_8N_2O_2$	61,3	4,5	15,8	64
XVIIa	227—228 (from alcohol)	57,0	3,6	22,3	$C_9H_7N_3O_3$	57,1	3,7	22,2	94
XVIIb	177—178 from aqueous alcohol)	53,0	3,8	27,6	$C_9H_8N_4O_2$	52,9	3,9	27,4	95
XVIIc	207—208 (from acetic acid)	52,8	3,5	20,8	$C_9H_7N_3O_3$	52,7	3,4	20,5	92
XVIId	131—132 (from methanol)	70,6	5,6	13,6	$C_{18}H_{17}N_3O_2$	70,3	5,6	13,7	91.5
XVIIe	166,5—167,5 (from alcohol)	58,1	7,2	15,7	$C_{17}H_{24}N_4O_2 \cdot HCl$	57,9	7,1	15,8	81
XVIIf	120,5—121,5 (from alcohol)	69,7	5,3	14,2	$C_{17}H_{15}N_3O_2$	69,6	5,2	14,3	70
XVIIg	159—160 (from alcohol)	69,9	5,4	14,4	$C_{17}H_{15}N_3O_2$	69,6	5,2	14,3	61,4
XVIIh	127—128 (from alcohol)	64,5	5,4	12,1	$C_{19}H_{19}N_3O_4$	64,6	5,4	11,9	91,6
XVIIi	109—110,5 (from acetone	58,4	5,2	17,1	$C_{12}H_{13}N_3O_3$	58,3	5,3	17,0	98
XVIIj	87—88 (from aqueous acetone)	62,5	6,4	14,5	$C_{15}H_{19}N_3O_3$	62,3	6,6	14,5	91
XVIIk	187—188	54,3	6,7	16,1	$C_{16}H_{22}N_4O_3 \cdot HCl$	54,2	6,3	15,9	65
XVIIIa	252 (dec., from 35% alcohol)	52,9	3,7	20,5	$C_9H_7N_3O_3$	52,6	3,4	20,5	98,6
XVIIIb	111—112 (from methanol)	67,1	5,4	12,8	$C_{18}H_{17}N_3O_3$	66,9	5,3	13,0	84
XVIIIc	123—124 (from alcohol)	58,8	6,2	13,9	$C_{15}H_{19}N_3O_4$	59,0	6,3	13,8	70
XVIIIJ	99,5—100,5 (from acetone)	61,4	7,0	16,5	$C_{17}H_{24}N_4O_3$	61,4	7,3	16,9	72
Hydrochloride XVIIId	197 (dec., from alcohol)				$C_{17}H_{24}N_4O_3 \cdot HCl$				
XVIIIe	147—148 (from alcohol)	55,0	5,1	15,7	$C_{12}H_{13}N_3O_4$	54,7	5,0	16,0	98
XVIIIf	189—190 (from alcohol)	66,2	5,2	13,7	$C_{17}H_{15}N_3O_3$	66,0	4,9	13,6	93
XVIIIg	162.5—163,5 (from alcohol)	65,8	4,6	13,5	$C_{17}H_{15}N_3O_3$	66,0	4,9	13,6	71,5
XVIIIh	173—174 (from alcohol)	61,9	5,0	11,3	$C_{19}H_{19}N_3O_5$	61,8	5,2	11,4	98

Quinoxaline-2-carboxylic Acid N-(β-Phenylisopropyl)amide 1-Oxide (XVIId). A mixture of 3.28 g (16 mmole) of XIX and 4.4 g (26 mmole) of 80% β-phenylisopropylamine in 40 ml of anhydrous alcohol was refluxed for 6-7 h, after which it was worked up to give XVIId.

Quinoxaline-2-carboxylic Acid N-(δ-Diethylaminobutyl)amide 1-Oxide Hydrochloride (XVIIe). A mixture of 2 g (9.8 mmole) of XIX, 1.86 g (12.9 mmole) of δ-diethylaminobutylamine, and 30 ml of anhydrous alcohol was refluxed for 4.5 h, after which the solution was evaporated. Alcoholic HCl solution was added to the residue, and the mixture was triturated with ether. Workup gave hydrochloride XVIIe.

Quinoxaline-2-carboxylic Acid N-(γ-Diethylamino-β-hydroxypropyl)amide 1-Oxide Hydrochloride (XVIIk). A mixture of 0.8 g (3.9 mmole) of XIX, 0.68 g (4.7 mmole) of γ-diethylamino-β-hydroxypropylamine, and 8 ml of anhydrous alcohol was refluxed for 9 h, after which the solution was evaporated, and 20% alcoholic HCl and acetone were added to the residue. Workup gave XVIIk.

Quinoxaline-2-carboxamide 1,4-Dioxide (XVIIIa). A mixture of 0.6 g (2.72 mmole) of XX and 12 ml of 16% alcoholic NH_3 was allowed to stand at 25° for 2 days, after which it was cooled and worked up to give XVIIIa.

Quinoxaline-2-carboxylic Acid N-(β-Phenylisopropyl)amide 1,4-Dioxide (XVIIIb). A mixture of 3 g (15.4 mmole) of XX and 4.2 g (31 mmole) of β-phenylisopropylamine in 20 ml of anhydrous alcohol was refluxed for 4 h, after which it was worked up to give XVIIIb.

Compounds XVIIf-j and XVIIIc-h. These compounds were obtained by the method described for the preparation of XVIId. See Table 1 for the results.

LITERATURE CITED

1. K. G. Cunningham, G. T. Newbold, F. S. Spring, and J. Stark, J. Chem. Soc., 2091 (1949).
2. A. S. Elina and E. N. Padeiskaya, Proceedings of the S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow, No. 2 [in Russian], Moscow (1971), p. 197.
3. W. A. Lott and E. Shaw, J. Amer. Chem. Soc., 71, 70 (1949).
4. A. S. Elina, Zh. Obshch. Khim., 34, 2809 (1964).
5. A. S. Elina, E. N. Padeiskaya, O. Yu. Magidson, G. N. Pershin, K. A. Belozerova, and V. I. Fatneva, USSR Author's Certificate No. 320,495 (1970); Byul. Izobr., No. 34 (1972).
6. B. Klein, E. O'Donnel, and J. M. Gordon, J. Org. Chem., 29, 2623 (1964).
7. L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, Gazz. Chim. Ital., 91, 1431 (1961); Chem. Abstr., 57, 2223e (1962).
8. S. Okada, A. Kosasayama, T. Konno, and F. Uchimaru, Chem. Pharm. Bull., 19, 1337 (1971); Ref. Zh. Khim., 3Zh439 (1972).
9. A. S. Elina, Zh. Obshch. Khim., 32, 2956 (1962).
10. J. K. Landquist, J. Chem. Soc., 2830 (1953).
11. A. S. Elina, T. N. Zykova, O. Yu. Magidson, G. N. Pershin, L. G. Tsyrul'nikova, and V. I. Fatneva, USSR Author's Certificate No. 235767 (1967); Byul. Izobr., No. 2, 204 (1970).
12. A. S. Elina and O. Yu. Magidson, Zh. Obshch. Khim., 25, 161 (1955).
13. A. S. Elina, I. S. Musatova, and L. G. Tsyrul'nikova, Khim.-Farmats. Zh., No. 8, 6 (1971).