ACYLATION OF 1-HYDROXYAMINO-2-HYDROXYIMINOETHANES WITH α-HALO ACID CHLORIDES AND THE PREPARATION OF 1-HYDROXY-2-OXOTETRAHYDROPYRAZINE 4-OXIDES

A. Ya. Tikhonov, L. B. Volodarskii, and N. V. Belova

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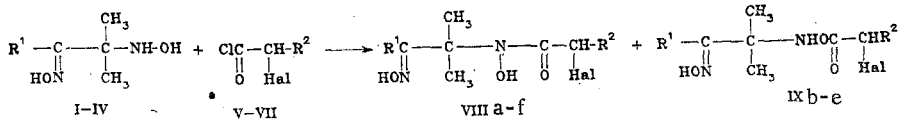
The acylation of 1-hydroxyamino-2-hydroxyiminoethanes with α-halo acid chlorides has given the products of N- and O-acylation at the hydroxyamino group. The action of bases on the products of N-acylation — N-(2-hydroxyiminoalkyl)-2-halohydroxamic acids — has given, depending on the conditions, 1-hydroxy-2-oxo-1,2,3,6- or -1,2,5,6-tetrahydropyrazine 4-oxides and 1,2-oxazetidin-3-ones.

The acylation of hydroxylamine derivatives by acid chlorides usually leads to hydroxamic acids [1], which possess a broad spectrum of biological activity [2] and in a number of cases may be considered as metabolites of amides and peptides [3, 4]. The capacity of hydroxamic acids for giving stable complexes with transition-metal ions is well known [4]. Continuing a study on the synthesis of heterocyclic compounds from 1-hydroxyamino-2-hydroxyiminoethanes [6], we have performed the acylation of the 1-hydroxyamino-2-hydroxyiminoethanes (I-IV) with the α-halo acid chlorides (V-VII) in order to obtain the N-(2-hydroxyiminoalkyl)-2-halohydroxamic acids (VIIIa-f). The cyclization of the compounds (VIII) could have been expected to form 1-hydroxy-2-oxo-1,2,3,6-tetrahydropyrazine 4-oxides (see [7, 8]).

When the 1-hydroxy-2-hydroxyiminoethanes (I-IV) were acylated with the α-halo acids chlorides (V-VII), the N-(2-hydroxyiminoalkyl)-2-halohydroxylamic acids (VIIIa-f) were formed. In addition to the hydroxamic acids (VIIIb-e) — the products of the N-acylation of the 1-hydroxyamino-2-hydroxyiminoethanes — 1-(2-haloacyloxyamino)-2-hydroxyiminoethanes (IXb-e) were also isolated.*



I-IV V-VII VIII a-f IX b-e

I, VIII a R^1=H; II, VIIIb, e, f, IXb, e R^1=CH_3; III, VIIIc, IXc R^1=CH_2CH_3; IV, VIIId, IXd R^1=C_6H_5; V, VIII a-d, IX b-d R^2=H, Hal=Cl; VI, VIII e, IXe, R^2=CH_3, Hal=Br; VII, VIII f R^2=CH_2CH_3, Hal=Br

The IR spectra of the hydroxamic acids (VIIIa-f) each show a band in the 1614-1655 cm^{-1} region (Table 1) corresponding to the stretching vibrations of the C=O bond of a hydroxamic group [10]. As was to be expected, these compounds gave a dark cherry-red color with an ethanolic solution of ferric chloride. The PMR spectra of compounds (VIIIa-d, f) in $(CD_3)_2SO$ each show two singlets in the 9.82-9.99 and 10.15-10.51 ppm, corresponding to the protons of hydroxamic and of oxime groupings (Table 1).

In the IR spectra of the 1-(acyloxyamino)-2-hydroxyiminoethanes (IXb-e) (Table 1), unlike those of the N-acyl compounds (VIII), the band of the stretching vibrations of the C=O bond is observed in the 1746-1766 cm^{-1} region, a position close to the C=O of an ester group. Compounds (IXb-e) did not give a dark cherry-red coloration with an ethanolic solution of ferric chloride. In the PMR spectra of (IXb, d) in $(CD_3)_2SO$ (Table 1), the signals of the protons of the oxime group and of the acyloxyamino group (—NH—O—) are observed at 10.92, 10.74, and at 7.93, 7.77,

*For a preliminary communication on the properties of the 1-(acyloxyamino)-2-hydroxyiminoethanes, see [9].

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TABLE 1. Spectral Characteristics of the Compounds (VIII-XIII) Synthesized

Compound	IR spectrum[a], cm^{-1}	UV spectrum λ_{max}, nm (log ε)	PMR spectrum, ppm (J, Hz)[b]				
			R^1	$C(CH_3)_2$	R^2	CH	NH, OH
VIIIa	1655 (C=O)	—	H 7,47 s	1,38s	H 4,36 s		9,99, 10,15
VIIIb	1647 (C=O)	—	CH_3 1,66 s	1,38s	H 4,32 s		9,91, 10,34
VIIIc	1639 (C=O)	—	CH_2 2,16 q (7,2) | CH_3 1,01 t (7,2)	1,37s	H 4,30 s		9,82, 10,22
VIIId	1635 (C=O)	—	C_6H_5 7,0—7,5 m	1,49s	H 4,26 s		9,85, 10,51
VIIIf	1614 (C=O)	—	CH_3 1,62 s	1,34s	CH_2 1,88 m | CH_3 0,86 t (7,2)	4,81 t (7,3)	9,96, 10,33
IXb	1766 (C=O)	—	CH_3 1,74 s	1,17s	H 4,32 s		7,93, 10,92
IXc	1763 (C=O)	—	CH_2 2,38 q (7,2) | CH_3 1,12 t (7,2)	1,30s	H 4,03 s		7,95
IXd	1760 (C=O)	—	C_6H_5 7,0—7,5 m	1,23s	H 4,38 s		7,77, 10,74
IXe	1746 (C=O)	—	CH_3 1,92 s	1,32s	CH_3 1,81 d (6,8)	4,41 q (6,8)	7,59, 8,62
X	1747 (C=O)	—	C_6H_5 7,0—7,5 m	1,47s	H 5,21 s		10,94
XIb	1682 (C=O)	237 (3,99)	CH_3 2,07 t (1,5)	1,45 s	H 4,46 q (1,5)		10,01
XIc	1676 (C=O)	242 (3,97)	CH_2 2,65 q (7,4) | CH_3 1,20 t (7,4)	1,60s	H 4,63 s		—
XId	1629 (C=N) 1687 (C=O)	247 (3,91)	C_6H_5 7,2—7,6 m	1,39s	H 4,69 s		10,07
XIf	1665 (C=O)	240 (3,94)	CH_3 2,01 d (1,5)	1,39s 1,42s	CH_2[c] m | CH_3 0,66 s (7,0)	4,28 m	9,98
XII	1723 (C=O)	—	—	1,86 s 1,90 s	H 4,57 s		10,71
XIIIa	1588 (C=N) 1663 (C=O)	261 (4,09)	H_2 4,16 s	1,26s	—	7,20 s	9,56
XIIIb	1583 (C=N) 1660 (C=O)	264 (4,15)	H 5,01 s | C_6H_5 7,44 s	1,07 s 1,54 s	—	7,37s	—

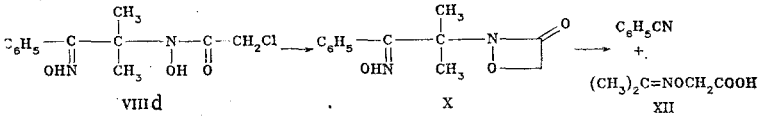
[a] In KBr; IR spectrum of (VIIIe) 1623 cm^{-1} (C=O). [b] The PMR spectra of (VIIIa-d, f), (IXb, d), (X), (XIb, d, f) and (XIIIa) were recorded in $(CD_3)_2SO$, those of (IXc, d) and (XII) in $CDCl_3$, that of (XIc) in D_2O, and that of (XIIId) in CD_3OD. [c] The determination of the chemical shift was difficult because of the superposition of the doublet signal of the protons of the methyl group.

ppm, respectively. The presence in the PMR spectra of (IXb, d) of the signal of the hydroxyl proton of the oxime groups is in harmony with the fact that these compounds are the products of the acylation of the 1-(acyloxyamino)-2-hydroxyiminoethanes (II, IV) at the oxygen atom of the hydroxyamino group and not at the oxygen atom of the oxime group.

One of the reasons for the formation of the 1-(acyloxyamino)-2-hydroxyiminoethanes (IX) in appreciable amounts is the steric screening of the nitrogen atom of the hydroxylamino group [1]. The lowering of the yields of the hydroxamic acids (VIIIb, e, f) in the sequence (VIIIb) > (VIIIc), (VIIIf) on the acylation of the 1-hydroxyamino-2-hydroxyiminoethane (II) with the acid chlorides (V-VII) having substituents with different volumes, must be mentioned. The relative amount of the 1-(acyloxyamino)-2-hydroxyiminoethane (IX) increased when the acetate of the 1-hydroxyamino-2-hydroxyiminoethane (II) was used instead of the free base (II), which is possibly due to a lowering of the nucleophilicity of the nitrogen atom of the hydroxylamino group as the result of its protonation [1].

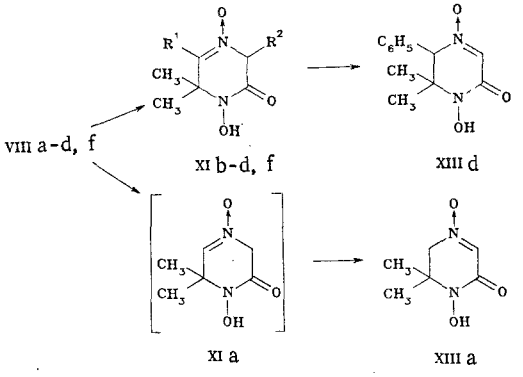
When compound (VIIId) was treated with an equimolar amount of 1N NaOH under the conditions given by Gnichtel et al. [7], a compound (X) with the empirical composition $C_{12}H_{14}N_2O_3$ corresponding to 1,2,3,6-tetrahydropyrazine 4-oxide (XId) was isolated. However, the absence of an absorption maximum for compound (X) above 220 nm, which must be due to the presence of the α-phenylnitrone group in compound (XId) [11], the singlet of the proton of the hydroxy group observed in the PMR spectrum in $(CD_3)_2SO$ at 10.94 ppm (Table 1), and also the high-frequency po-

sition of the band of the stretching vibrations of the C=O bond at 1747 cm^{-1} [12] showed that (X) had the structure of 2-(2-hydroxyimino-1,1-dimethyl-2-phenylethyl)-1,2-oxazetidin-3-one. The formation of 1,2-oxazetidin-3-ones has been observed previously in the acylation of N-substituted hydroxylamines with α-chlorodiphenylacetyl chloride [12]. On storage, compound (X) underwent degradation with the formation of benzonitrile and isopropylideneaminooxyacetic acid (XII) [13].



The 1-hydroxy-2-oxo-1,2,3,6-tetrahydropyrazine 4-oxides (XIb-d, f) were obtained with yields of 47-83% when the 2-halohydroxamic acids (VIIIb-d, f) were added to an aqueous or ethanolic solution of a base present in excess. However, in this case as well 1,2-oxazetidin-3-ones were formed, as was confirmed by the isolation of (X) in the production of compound (XId).

In the IR spectra of (XIb-d, f) (Table 1), the band of the stretching vibrations of the C=O of the cyclic hydroxamic group is observed in the 1665-1687 cm^{-1} region [2], which corresponds to a high-frequency shift by 35-52 cm^{-1} in comparison with the initial (VIIIb-d, f). In the IR spectrum (XId) there is a band at 1629 cm^{-1} which can be assigned to the stretching vibrations of the C=N bond of the nitrone group [11]. In compounds (XIb, c, and f), apparently, this band is masked by the band of the stretching vibrations of the C=O bond. In the UV spectra of (XIb, c, and f) (Table 1), each containing an alkylnitrone group in its heterocycle, an absorption maximum is observed in the 237-242 nm region, and in compound (XId) (with an α-phenylnitrone group) one at 247 nm, which corresponds to a displacement of the absorption maximum in the short-wave direction by 40-50 nm in comparison with the acyclic α-phenylnitrones [11]. This is apparently due to the departure of the benzene ring in compound (XId) from conjugation with the nitrone group.



Similar changes have been observed previously in UV spectra of 4-phenyltetrahydropyrimidine 3-oxides [14]. The PMR spectra of (XIb-d, f) (Table 1) agree with the structure of 1-hydroxy-2-oxo-1,2,3,6-tetrahydropyrazine 4-oxides. Thus, for example, the spin–spin coupling (J = 1.5 Hz) between the protons of the methyl group in position 5 and the methylene protons in position 3 of the heterocycle in (XIb) is possible only for a cyclic structure [11]. The same interaction is also observed for (XIf).

The cyclization of the 2-chlorohydroxamic acid (VIIIa) led to a different result. The absorption with a maximum at 261 nm observed in the UV spectrum of compound (XIIIa) showed conjugation of the nitrone group with the hydroxamic group (see [15]), and the band at 1588 cm^{-1} observed in the IR spectrum can be assigned to the stretching vibration of the C=N bond of a conjugated nitrone group [11]. In the PMR spectrum of (XIIIa), the singlet signal of the protons of the methylene group appears at 4.16 ppm, i.e., upfield by approximately 0.3-0.5 ppm in comparison with compounds (XIb, c). These results permit compound (XIIIa) to be ascribed the structure of 1-hydroxy-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydropyrazine 4-oxide. Apparently, under the reaction conditions, the 1-hydroxy-6,6-dimethyl-2-oxo-1,2,3,6-tetrahydropyrazine 4-oxide (XIa) first formed undergoes isomerization [11] with the production of (XIIIa). It might be expected that such an isomerization could also take place for the other 1-hydroxy-2-oxo-1,2,3,6-tetrahydropyrazine 4-oxides (XI). In actual fact, on treatment with a twofold excess of sodium ethanolate, compound (XId) underwent isomerization with the formation of the sodium salt

TABLE 2. Characteristics of the Compounds (VIII-XIII) Synthesized

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl(Br)	N		C	H	Cl(Br)	N	
VIIIa	112—114[a]	37,2	5,7	18,1	14,7	$C_6H_{11}ClN_2O_3$	37,0	5,7	18,2	14,4	23
VIIIb	172—174[b]	40,0	6,2	17,3	13,4	$C_7H_{13}ClN_2O_3$	40,3	6,3	17,0	13,4	44
VIIIc	175—178[b]	43,2	6,8	16,0	12,5	$C_8H_{15}ClN_2O_3$	43,2	6,8	15,9	12,6	35
VIIId	140—142a	53,2	5,6	13,2	10,2	$C_{12}H_{15}ClN_2O_3$	53,2	5,6	13,1	10,4	44
VIIIe	162—164[b]	36,0	5,7	29,8	10,8	$C_8H_{15}BrN_2O_3$	36,0	5,7	29,9	10,5	9
VIIIf	178—180[b]	38,3	6,5	27,9	10,2	$C_9H_{17}BrN_2O_3$	38,4	6,1	28,4	10,0	14
IXb	89—91[c]	40,2	6,2	17,0	13,7	$C_7H_{13}ClN_2O_3$	40,3	6,3	17,0	13,4	22
IXc	73—75[c]	43,0	6,9	16,1	12,6	$C_8H_{15}ClN_2O_3$	43,2	6,8	15,9	12,6	13
IXd	117—119[c]	52,9	5,6	13,5	10,4	$C_{12}H_{15}ClN_2O_3$	53,2	5,6	13,1	10,4	23
IXe	57—60[c]	35,7	5,5	30,2	10,3	$C_8H_{15}BrN_2O_3$	36,0	5,7	29,9	10,5	50
X	117—120[c]	61,6	5,9	—	11,9	$C_{12}H_{14}N_2O_3$	61,5	6,0	—	12,0	54
XIb	201—203[d]	49,1	7,0	—	16,5	$C_7H_{12}N_2O_3$	48,8	7,0	—	16,3	83
XIc	166—168[b]	51,8	7,7	—	14,7	$C_8H_{14}N_2O_3$	51,6	7,6	—	15,0	69
XId	222—224[d]	61,4	6,0	—	12,0	$C_{12}H_{14}N_2O_3$	61,5	6,0	—	12,0	52
XIf	197—200[b]	54,1	8,2	—	13,8	$C_9H_{16}N_2O_3$	54,0	8,1	—	14,0	56
XII	75—76[e]	45,6	6,9	—	10,9	$C_5H_9NO_3$	45,8	6,9	—	10,7	30
XIIIa	144—147[d]	45,5	6,2	—	17,9	$C_6H_{10}N_2O_3$	45,6	6,4	—	17,7	52
XIIId	174—177[a]	61,6	6,1	—	12,0	$C_{12}H_{14}N_2O_3$	61,5	6,0	—	12,0	73

[a] From ethyl acetate. [b] From dioxane. [c] By reprecipitation from chloroform with hexane (pentane). [d] From ethanol. [e] According to [13], mp 76°C.

of compound (XIIId), from which, by neutralization, 1-hydroxy-6,6-dimethyl-2-oxo-5-phenyl-1, 2,5,6-tetrahydropyrazine 4-oxide (XIIId) was obtained. Compound (XIIId) was formed and was isolated with a yield of 9% in the preparation of (XId). The spectral characteristics for compound (XIIId) do not contradict the structure deduced (Table 1).

EXPERIMENTAL*

IR spectra were recorded on a UR-20 instrument, and UV spectra on a Specord UV-Vis spectrometer in ethanol. PMR spectra were recorded on a Varian A-56-60A instrument with HMDS and tert-butanol (aqueous solution) as internal standards. The course of the reactions was monitored on Silufol UV-254 plates, the spots being revealed in UV light and with iodine vapor. The investigation was carried out with the 1-hydroxyamino-2-hydroxyiminoethanes (I-IV) produced in the Experimental Chemical Factory of the Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Academy of Sciences of the USSR. The spectral characteristics of compounds (VIII-XIII) are given in Table 1, and the yields, melting points, and results of elementary analysis in Table 2.

N-(1,1-Dimethyl-2-hydroxyiminoethyl)-2-chloroacethydroxamic Acid (VIIIa). With cooling in an ice bath and stirring, a solution of 9.6 ml (127 mmole) of chloroacetyl chloride (V) in 60 ml of tetrahydrofuran was added over 50 min to a solution of 15.0 g (127 mmole) of (I) and 17.7 ml (127 mmole) of triethylamine in 300 ml of tetrahydrofuran. Then the mixture was stirred without cooling at room temperature for 2 h, the precipitate was filtered off and washed, the filtrate was evaporated, the residue was dissolved in ethyl acetate, the solution was washed with water, dried with magnesium sulfate, and evaporated, and the residue was dissolved in ether. The precipitate that deposited from the ethereal solution was filtered off, giving 5.70 g of (VIIIa).

N-(1,1-Dimethyl-2-hydroxyiminopropyl)-2-bromobutanohydroxamic Acid (VIIIf) was obtained similarly.

N-(1,1-Dimethyl-2-hydroxyiminopropyl)-2-chloroacethydroxamic Acid (VIIIb) and 3-Methyl-3-(O-chloroacetylhydroxyamino)butan-2-one Oxime (IXb). With cooling in an ice bath and stirring, a solution of 3.50 g (31.1 mmole) of chloroacetyl chloride (V) in 50 ml of tetrahydrofuran was added over 35 min to a solution of 4.10 g (31.1 mmole) of (II) and 4.35 ml (31.1 mmole) of triethylamine in 150 ml of tetrahydrofuran. The mixture was stirred for 2 h and the precipitate was filtered off. The filtrate was evaporated and the residue was treated with 40 ml of chloroform and 5 ml of water; the resulting precipitate was filtered off and

*With the participation of G. I. Teselkina.

was washed with water and chloroform to give 2.85 g of (VIIIb). The chloroform solution was separated off, washed with water, dried with magnesium sulfate and evaporated, and the residue was triturated in a mixture of diethyl ether and petroleum ether; the resulting precipitate was filtered off to give 1.43 g of (IXb)* (in the isolation of the mixture of (VIIIb) and (IXb) they were separated by treatment with chloroform (IXb) being soluble readily in chloroform and (VIIIb) to only a limited extent).

Compounds (VIIIc-e) and (IXc-e) were obtained similarly. When the acetate of the 1-hydroxyamino-2-hydroxyiminoethane (II) was used, 15% of (VIIIb) and 49% of (IX) were obtained.

2-(2-Hydroxyimino-1,1-dimethyl-2-phenylethyl)-1,2-oxazetidin-3-one (X). With stirring, 25 ml of 1 N NaOH was added to a solution of 6.0 g (22.2 mmole) of (VIIId) in 60 ml of dioxane, the mixture was kept for 2 h and was then neutralized with 1 N HCl and evaporated, and the residue was treated with ethyl acetate and washed with water. The ethyl acetate solution was dried with magnesium sulfate and evaporated, the residue was triturated in a mixture of diethyl ether and petroleum ether (3:2), and the precipitate was filtered off. Yield 2.80 g of (X).

Benzonitrile and Isopropylideneaminooxyacetic Acid (XII). On prolonged storage, 1.20 g (5.13 mmole) of (X) underwent degradation with the formation of a mixture of compounds from which 0.20 g of (XII) was isolated by treatment with benzene. The benzene solution was evaporated and chromatography of the residue on a column of silica gel (with chloroform as eluent) gave 0.19 g (36%) of benzonitrile.

1-Hydroxy-6,6-dimethyl-2-oxo-1,2,3,6-tetrahydropyrazine 4-Oxides (XIb-d, f). With stirring, 5 mmole of one of (VIIIb-d, f) (or a solution of (VIIId) in ethanol) was added in portions to the solution of 10 mmole of sodium ethanolate in 10 ml of ethanol. The mixture was kept for 30 min-1 h (3 h for (VIIIf)), and was neutralized with 1 N HCl in ethanol, the precipitate of sodium chloride† was eliminated by centrifugation, the solvent was evaporated, the residue was triturated with ethyl acetate (or with a mixture of ethyl acetate and ether), and the precipitate was filtered off. This gave (XIb-d and f). The filtrate after the separation of (XI), by evaporation and chromatography of the residue on a column of silica gel (with chloroform as eluent), yielded 9% of (XIIId).

1-Hydroxy-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydropyrazine 4-oxide (XIIIa) was obtained similarly.

1-Hydroxy-6,6-dimethyl-2-oxo-5-phenyl-1,2,3,6-tetrahydropyrazine 4-Oxide (XId). At the rate at which it dissolved, 3.0 g (11.1 mmole) of (VIIId) was added to 20 ml of 1 N aqueous NaOH. The solution was kept for 1 h and was neutralized with 1 N HCl, and the resulting precipitate was filtered off to give 0.50 g (19%) of (X). The filtrate was saturated with sodium chloride, and the resulting precipitate was filtered off to give 1.12 g (44%) of (XId). Extraction of the aqueous solution with chloroform gave an additional 0.08 g (3% of (XId).

1-Hydroxy-6,6-dimethyl-2-oxo-5-phenyl-1,2,5,6-tetrahydropyrazine 4-Oxide (XIIId). To 0.50 g (2.14 mmole) of compound (XId) was added 0.29 g (4.3 mmole) of sodium ethanolate in 10 ml of ethanol, the mixture was kept for 2 h, and the resulting precipitate of the sodium salt of compound (XIIId) was filtered off; yield 0.47 g (69%), mp 224-226°C (from ethanol). UV spectrum λ_{max} 263 nm (log ε 4.09). A solution of 0.20 g (0.86 mmole) of the sodium salt of (XIIId) in 2 ml of water was neutralized with 1 N HCl, the solution was saturated with sodium chloride, extracted with chloroform, dried with magnesium sulfate, and evaporated. This gave 0.11 g of (XIIId).

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*On storage, (IXb and d) were converted into the 1-hydroxyamino-2-hydroxyiminoethane (II) salts of the corresponding α-halo acids.

†Compound (XId) precipitated with the sodium chloride, and it was separated by treating the precipitate with a small amount of water.

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CHARACTERISTIC VIBRATIONS OF 2-MONOSUBSTITUTED PYRIMIDINES

V. I. Berezin and V. V. Berezin

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The frequency intervals of the localization of the bands of the characteristic and noncharacteristic vibrations of 2-substituted pyrimidines have been determined on the basis of calculated and analysis of experimental results. A theoretical interpretation of the bands according to the form of the vibrations has been given and the groups of characteristic and noncharacteristic vibrations of the aromatic skeleton of the 2-monosubstituted pyrimidines has been established. For the noncharacteristic vibrations, groups of substituents with different regions of localization of the frequencies of the aromatic skeleton have been isolated.

A special role belongs to pyrimidine derivatives in many biological processes. In the last few decades, in view of the creation of drugs based on them, great attention has been devoted to the study of the spectral properties of the substituted pyrimidines. The establishment of groups of characteristic and noncharacteristic frequencies for substituted pyrimidines will permit the solution of important chemical and pharmaceutical problems on the identification of pyrimidine derivatives and the performance of spectral monitoring of the process of synthesizing complex compounds. All this means that the question of the characteristic nature of the vibrations is acquiring great importance.

In the present investigation we have continued a study of the characteristic nature of the vibrations of nitrogen heterocycles begun previously [1]. A number of other authors have turned to the same question in one form or another [2-7]. However, they approached the evaluation of the characteristic nature of the vibrations only from the qualitative aspects. In our work we have proposed quantitative criteria.

To answer the question of the characteristic nature of the vibrations of 2-substituted pyrimidines we must have reliable information on the fundamental frequencies. The proposed assignments for a number of monosubstituted pyrimidines [3-9] are either incomplete and are contradictory in the assignments of certain bands or they are insufficiently convincing because of the absence of a theoretical foundation. All this leads to the necessity for approaching the assignment of the fundamental frequencies from unitary positions based on theoretical calculations.

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