min. Ether (50 ml) was then added to the solution, and the resulting precipitate was removed by filtration to give 3.7 g (83%) of a product with mp 91-92°C (dec.). Reprecipitation from methanol by the addition of ether gave a product with mp 93-94°C (dec.). Found: C 42.8; H 3.7%. $C_{16}H_{16}INO_4S$. Calculated: C 43.2; H 3.6%.

1-Methyl-2-chloroindole. A) A solution of 0.9 g (2 mmole) of (1-methyl-3-indolyl)phenyliodonium methosulfate and 0.17 g (4 mmole) of lithium chloride in 8 ml of DMSO was heated at 100°C for 2 h, after which it was cooled and poured into water. The aqueous mixture was extracted with benzene, and the extract was washed several times with water and dried with anhydrous magnesium sulfate. It was then evaporated to a minimal volume and separated chromatographically with a column filled with silica gel [elution with ether–petroleum ether (1:2)] to give 194 mg (60%) of 1-methyl-2-chloroindole with mp 63-64°C (mp 64-65°C [6]).

B) A mixture of 250 mg of 1-methyloxindole, 425 mg (C.2 ml) of phosphorus oxychloride, and 8 ml of chloroform was refluxed for 15 h, after which it was cooled and treated with 40 ml of a 5% solution of sodium hydrocarbonate. The organic layer was separated, and the aqueous layer was extracted with chloroform. The solvent was evaporated, and the residue was chromatographed with a column as in the preceding experiment to give 99 mg (35%) of 1-methyl-2-chloroindole with mp 62-63°C. The IR spectrum (mineral oil) was identical to the spectrum of a sample of the compound obtained in the preceding experiment.

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# MASS-SPECTROMETRIC DETERMINATION OF THE TAUTOMERIC FORMS OF ALKYL(ARYL)BENZAZOLYLAZOKETOXIMES


N. A. Klyuev, I. S. Shpileva,
L. I. Medvedeva, G. N. Lipunova,
and N. P. Bednyagina



UDC 543.51'547.789.8'785.5



A mass-spectrometric study of a series of alkyl(aryl)benzazolylazoketoximes as compared with arylazoketoxime was made. The ratios of the tautomers (oxime ⇄ nitroso) in the gas phase at the moment of vaporization of the samples were determined. It is shown that the ratios of the tautomers are determined by both the basicity of the heterocycle and the character of the substituent attached to the methylidyne carbon atom.


The quantitative ratios of the tautomers and the relationship between the position of the tautomeric equilibrium and the aggregate state of the substances are of undoubted interest in the study of the tautomerism of organic compounds [1]. Mass spectrometry has been used with increasing frequency for the solution of these problems in recent years. The ratios of the tautomers in the composition of the molecular ions ($M^+$) are evaluated quantitatively by summation of the relative intensities of the characteristic fragment that correspond to a certain form of tautomer with their subsequent normalization [2].


All-Union Scientific-Research Institute of Antibiotics, Moscow 113105. S. M. Kirov Ural Polytechnic Institute, Sverdlovsk 620002.


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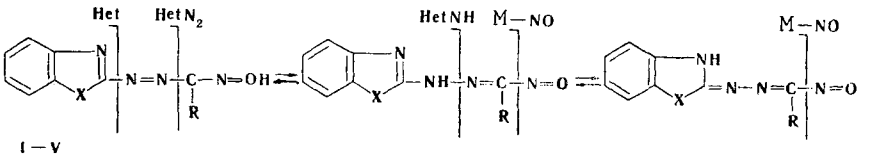
TABLE 1. Mass Spectra of I-VI*

| Compound | m/z values (relative intensities of the ion peaks in percent of the maximum peak) |
|---|---|
| I (sample-vaporization temperature | 41 (18,8), 42 (16,5), 43 (5,0), 44 (4,1), 45 (16,3), 50 (9,2), 51 (7,8), 52 (4,4), 57 (5,4), 58 (83,6), 62 (3,0), 63 (24,0), 64 (9,8), 69 (20,1), 70 (6,8), 75 (5,1), 76 (4,4), 77 (3,3), 78 (9,8), 82 (7,6), 90 (35,8), 91 (10,1), 95 (5,8), 96 (12,2), 104 (3,1), 105 (4,6), 107 (13,5), 108 (23,1), 109 (6,9), 122 (7,5), 123 (19,1), 133 (5,2), 134 (100,0), 135 (85,1), 136 (18,2), 137 (4,8), 148 (13,3), 149 (12,5), 150 (3,6), 151 (14,4), 162 (4,7), 175 (22,2), 190 (16,0), 192 (15,5), 203 (6,5), 220 (6,3). $W_M = 0{,}8$ |
| II (200°) | 41 (26,4), 42 (16,4), 43 (6,0), 44 (5,2), 45 (3,7), 50 (7,4), 51 (14,4), 52 (14,7), 53 (5,2), 55 (3,0), 57 (5,0), 58 (56,9), 62 (2,5), 63 (29,9), 64 (20,9), 65 (8,2), 71 (3,2), 75 (3,5), 76 (6,4), 77 (16,4), 78 (10,0), 79 (4,4), 89 (4,7), 90 (85,8), 91 (28,3), 92 (5,7), 103 (5,2), 104 (18,1), 105 (18,3), 106 (8,2), 116 (3,8), 117 (48,3), 118 (100,0), 119 (16,6), 131 (18,8), 132 (32,8), 133 (6,3), 134 (27,0), 145 (3,5), 158 (11,2), 172 (10,0), 173 (29,7), 174 (3,3), 175 (9,3), 203 (10,9). $W_M = 1{,}2$ |
| IIa | 50 (15,5), 51 (26,7), 52 (21,3), 53 (11,7), 55 (9,1), 56 (5,4), 57 (13,6), 58 (29,9), 59 (27,0), 62 (10,6), 63 (39,7), 64 (31,4), 65 (13,3), 66 (5,9), 67 (5,4), 69 (10,4), 71 (6,6), 75 (8,7), 76 (10,1), 77 (35,2), 78 (12,4), 79 (7,9), 89 (5,5), 90 (65,6), 91 (44,2), 92 (15,1), 93 (4,8), 103 (5,2), 104 (38,5), 105 (18,3), 106 (12,6), 107 (5,3), 117 (24,9), 118 (100,0), 119 (69,9), 120 (23,8), 121 (4,1), 131 (27,3), 132 (27,9), 133 (19,8), 134 (18,0), 135 (13,5), 136 (4,2), 145 (3,3), 158 (4,3), 159 (4,9), 172 (24,4), 173 (19,5), 174 (12,6), 175 (6,2), 176 (3,6), 203 (3,1), 204 (6,2), 205 (3,0) |
| III (210°) | 43 (7,7), 44 (11,7), 50 (15,7), 51 (29,4), 52 (13,5), 53 (5,2), 55 (3,9), 57 (8,9), 63 (15,8), 64 (13,0), 65 (7,5), 69 (4,1), 71 (5,2), 75 (7,2), 76 (30,5), 77 (100,0), 78 (15,7), 79 (4,0), 90 (33,2), 91 (18,1), 92 (6,2), 102 (4,2), 103 (56,0), 104 (49,1), 105 (26,5), 106 (5,9), 117 (21,0), 118 (52,8), 119 (12,1), 120 (13,3), 131 (37,3), 132 (36,5), 133 (8,5), 134 (7,3), 148 (6,5), 207 (5,1), 220 (14,9), 234 (35,4), 235 (34,3), 236 (3,8), 237 (4,6), 265 (0,9). $W_M = 0{,}1$ |
| IV (180°) | 41 (12,8), 42 (3,8), 43 (15,8), 44 (48,8), 50 (10,4), 51 (12,5), 52 (4,4), 55 (8,1), 56 (3,6), 57 (17,4), 63 (5,0), 64 (3,1), 65 (18,2), 69 (8,5), 70 (3,0), 71 (10,2), 76 (17,6), 77 (20,2), 78 (4,1), 81 (4,2), 90 (3,8), 91 (100,0), 92 (11,0), 102 (4,1), 103 (34,1), 104 (8,8), 105 (7,0), 119 (7,1), 196 (3,0), 205 (3,5), 206 (4,2), 207 (9,9), 208 (7,7), 220 (6,8), 222 (4,1), 223 (3,3), 224 (10,7), 324 (12,5), 325 (8,0), 326 (3,0), 355 (0,4). $W_M = 0{,}1$ |
| V (160°) | 43 (100,0), 44 (31,1), 50 (15,4), 51 (51,7), 52 (24,0), 53 (13,4), 54 (23,2), 63 (29,1), 64 (16,2), 65 (95,4), 66 (9,6), 68 (38,8), 70 (21,2), 71 (10,7), 75 (11,1), 76 (17,7), 77 (61,9), 78 (17,6), 86 (21,7), 89 (53,2), 90 (37,0), 91 (95,1), 92 (80,8), 103 (14,3), 104 (16,0), 105 (7,8), 106 (18,9), 117 (16,8), 118 (14,4), 119 (30,4), 145 (36,9), 196 (3,0), 205 (12,0), 206 (29,5), 207 (94,1), 208 (47,4), 209 (8,9), 220 (33,2), 221 (10,8), 222 (38,8), 223 (13,3), 224 (16,4), 275 (6,1), 276 (4,1), 289 (6,8), 290 (26,9), 291 (44,6), 292 (12,4), 293 (3,1), 321 (0,2). $W_M = 0{,}04$ |
| VI (130°) | 41 (5,7), 43 (12,2), 44 (16,1), 50 (12,0), 51 (28,1), 52 (6,8), 57 (5,5), 63 (5,0), 64 (10,8), 65 (17,1), 75 (10,9), 76 (15,9), 77 (100,0), 78 (27,1), 90 (4,2), 91 (18,1), 92 (40,3), 93 (3,8), 102 (17,8), 103 (6,4), 105 (39,4), 106 (6,4), 119 (19,7), 148 (4,0), 149 (6,6), 165 (8,4), 240 (3,0), 270 (0,4). $W_M = 0{,}1$ |

*The ion peaks with intensities ⩾ 3% of the maximum peak are presented.

The aim of the present research was to make a mass-spectrometric study of the tautomerism of heterarylazoketoximes. It is known [3] that alkyl(aryl)benzazolylazoketoximes I-V exist in solutions in the form of three prototropic tautomers (the spatial isomers were not taken into account):




A (oxime form) B (amine form) C (imine form)

I X=S, R=$CH_3$; II X=NH, R=$CH_3$; III X=NH, R=$C_6H_5$; IV X=$NCH_2C_6H_5$, R=$C_6H_5$; V X=$NCH_2C_6H_5$, R=$CH(CH_3)_2$

Indeterminacy (as a consequence of rearrangements and secondary fragmentation processes) in the assignment of some of the ions to an individual form of isomer will exist in the fragmentation of the $M^+$ ions of I-V [4]. The sequence of the pathways of the fragmentation of

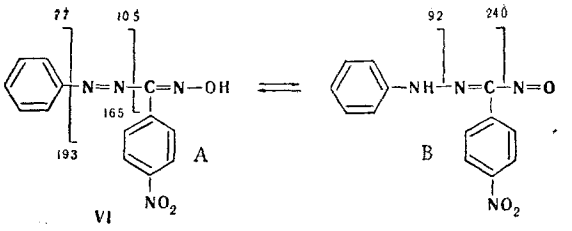
TABLE 2. Specific Ion Peaks That Characterize the Oxime and Amine-Imine Tautomeric Forms of the Molecular Ions ($M^+$) of I-V (intensities in percent of maximum peak in mass spectrum)*

| $M^+$ ion | Compound | | | | |
|---|---|---|---|---|---|
| | I | II | III | IV | V |
| M+ | 220 (6,3) | 203 (10,9) | 265 (0,9) | 355 (0,4) | 321 (0,2) |
| Ions corresponding to the oxime form (A) | | | | | |
| $[Het]^+$ | 134 (100,0) | 117 (48,3) | 117 (21,0) | 207 (9,9) | 207 (9,9) |
| $[HetN_2]^+$ | 162 (4,7) | 145 (3,5) | 145 (1,0) | 235 (1,8) | 235 (2,1) |
| $[M-Het]^+$ | — | — | 148 (6,5) | — | — |
| $[M-HetN_2]^+$ | 58 (83,6) | 58 (56,9) | 120 (13,4) | 120 (1,8) | 86 (21,7) |
| $[M-OH]^+$ | 203 (6,5) | — | — | — | — |
| $[M-N_2]^+$ | 192 (15,5) | 175 (9,3) | 237 (4,6) | 237 (1,0) | 293 (3,1) |
| $[(M-N_2)-OH]^+$ | 175 (22,2) | 158 (11,2) | 220 (14,9) | 310 (2,1) | 276 (4,1) |
| ΣA | 232,5 | 129,2 | 61,4 | 16,6 | 125,1 |
| Ions corresponding to the amine (B) and imine (B') forms | | | | | |
| $[M-NO]^+$ | 190 (16,0) | 173 (29,7) | 235 (34,3) | 325 (8,0) | 291 (44,6) |
| $[M-NOH]^+$ | 189 (2,9) | 172 (10,4) | 234 (35,4) | 324 (12,5) | 290 (26,9) |
| $[HetN]^+$ | 148 (13,3) | 131 (18,6) | 131 (37,3) | 221 (2,2) | 221 (10,8) |
| $[HetNH]^+$ | 149 (12,5) | 132 (32,8) | 132 (36,4) | 222 (4,1) | 222 (38,8) |
| ΣB + ΣC | 44,7 | 91,5 | 143,4 | 26,8 | 121,1 |
| ΣA : (ΣB + ΣC) | 83,9 : 16,1 | 58,5 : 41,5 | 30,0 : 70,0 | 38,3 : 61,7 | 50,8 : 49,2 |
| IR and PMR [3] | Form A | Form A | Form A | A⇄C | Form A |

*The empirical compositions of the ions indicated in the table were confirmed by data from high-resolution mass spectrometry in the case of I and III.

the $M^+$ and fragment ions must therefore be traced in the first stage of the investigation by means of a study of the spectra of the metastable ions with the aid of the DADI technique [5].

As a model compound we selected arylazoketoxime VI, which can exist in the form of two tautomers, a fact that simplifies the interpretation of the mass spectrum significantly. The affiliation of VI (form A) simultaneously




with oximes and azo compounds dictates the necessity for an approach for the elucidation of the mass spectrum with allowance for the principles of fragmentation that are characteristic for each of these groups [6-11]. Form A will be determined by the following ion peaks: 77* ($[C_6H_5]^+$), 105 ($[C_6H_5N_2]^+$), 165 ($[M - C_6H_5N_2]^+$), and 193 ($[M - C_6H_5]^+$) (α cleavage relative to the azo group), as well as 148 ($[M - C_6H_5N_2 - OH]^+$) and 149 ($[M - C_6H_5N_2 - O]^+$) (secondary processes that characterize the oxime grouping). We will designate their overall contribution to the total ion current as ΣA. Amine structure B, which contains hydrazone and nitroso groupings, is characterized by the following set of ions: 91 ($[C_6H_5N]^+$), 92 ($[C_6H_5NH]^+$), and 240 ($M - NO]^+$). The absence of $[M - NO_2]^+$ or $[M - NO - CO]^+$ fragment ions [12] excludes the formation of this ion due to the nitro group in the nitrophenyl substituent. The total fraction of the intensities of the ion peaks corresponding to form B in the total ion current is designated by ΣB. The other relatively intense ion peaks in the mass spectrum of VI are associated with secondary processes involving the fragmentation of the 165 and 149 ions: $[M - C_6H_5N_2 - NO_2]^+$ (the value determined was 119.0385, and the value calculated for the composition $C_7H_5NO$ was 119.0371) and $[M - C_6H_5N_2 - NO_2, - OH]^+$ (the value determined was 102.0429, and the value calculated for the composition $C_7H_4N$ was 102.0469). The complete mass spectrum of the compound is presented in Table 1.

*Here and subsequently in the text and in the scheme, the numbers that characterize the ions are the mass-to-charge ratios (m/z).

It must be noted that rearrangement processes that lead to the formation of $[M - OH]^+$, $[M - HCN]^+$, $[M - CO]^+$. and $[M - HCNO]^+$ ions, are recorded for various ketoximes, and are realized by means of a four- [7, 13] or five-center [14-16] mechanism, were not observed in this specific case.

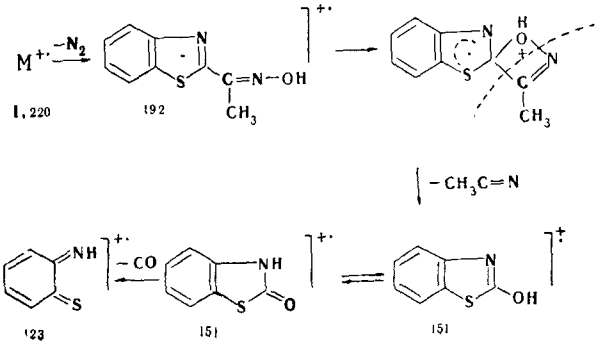
It is also known that Beckmann rearrangement, which leads, as a rule, to the formation of substituted amides, is characteristic for oximes. This reaction has been studied thoroughly for solutions, but it was recently established that the rearrangement also takes place in the gas phase for some ketoximes [17, 18]. In the case of arylazoketoxime VI fragmentation products due to a Beckmann rearrangement are not observed in the mass spectra.

Thus our interpretation of the principal fragment ions (the empirical compositions of the ions were confirmed by high-resolution mass spectra) in the mass spectrum of VI (Table 1) constitutes evidence for the existence in the gas phase of two tautomeric forms of $M^+$, viz., A and B in a ratio of $\Sigma A:\Sigma B = 72.2:27.8$.

The fragmentation pattern becomes complicated substantially when a heterocyclic residue is introduced in the azoketoxime molecule. However, peaks of ions formed via a unique mechanism are observed in the mass spectra of I-V (Table 2). In analogy with the mass spectrum of the model compound the peaks of $[Het]^+$, $[HetN_2]^+$, $[M - Het]^+$, and $[M - HetN_2]^+$ ions correspond to oxime form A. The primary fragmentation processes due to the elimination of an OH group [9, 14-16] (the value determined for I was 203.0378, while the value calculated for the composition $C_9H_7N_4S$ was 203.0391) and to the ejection of an $N_2$ molecule (the value determined for I was 192.0352, while the value calculated for the composition $C_9H_8N_2OS$ was 192.0357) can be ascribed to the same $M^+$ form. The formation of an $M - N_2^+$ ion is specific for some compounds that contain an azo group [9, 19]. The secondary ion that develops in the elimination of a hydroxy group from the $[M - N_2]^+$ ion the value determined for I was 175.0313, while the value calculated for the composition $C_9H_7N_2S$ was 175.0330 can also be adopted as diagnostic in the determination of the A form.

Starting from the analogy with VI, the ions of the $[HetN]^+$, $[HetNH]^+$ and $[M - NO]^+$ form will be affiliated with a tautomer of the B or C form. The elimination of an NOH particle from $M^+$ (the value determined for I was 189.0366, while the value calculated for the composition $C_9H_7N_3S$ was 189.0361) can also be assigned to the same forms. We were unable to find a mass-spectrometric difference between tautomers B and C in the case of I-V. It may only be assumed that the high intensities of the $[HetH]^+$ and $[HetNH]^+$ ions are due to the preponderant percentage of the B form, since it is known [20-22] that the azine N—N bond (form CO undergoes considerably less destruction in the first step of the fragmentation of $M^+$.

The formation of 151 ions in the fragmentation of I (the value determined was 151.0065, and the value calculated for the composition $C_7H_5NOS$ was 151.0092), as well as 135 and 123 ions (the value determined was 123.0135, and the value calculated for the composition $C_6H_5NS$ was 123.0142), is associated with rearrangement processes (Table 1). The 135 ion has the benzothiazole structure, the fragmentation of which was examined in [23], and the interpretation of the peaks of the 134, 108, 107, 94, 90, and 76 daughter ions that are formed during its subsequent fragmentation is therefore not difficult. The formation of 151 and 123 ions is due to the following rearrangement process (the course of the rearrangement was confirmed by a study of the spectra of the metastable ions):




Thus the rearrangement processes previously observed for aldoximes and ketoximes [14-16] are realized only partially in the step involving the formation of the $[M - N_2]^+$ ion, and, as a consequence of this, cannot affect the ratio of the tautomeric forms in $M^+$. For I, $\Sigma A:(\Sigma B + \Sigma C) = 83.8:16.1$ (Table 2). An analysis of the mass spectrum of I (Table 1) shows

that Beckmann rearrangement [17, 18] is not realized in this case either (α cleavage relative to the keto group), since $[M - CH_3]^+$, $[M - COCH_3]^+$, and $[M - CH_3NH]^+$ are not observed, and the $COCH_3^+$ ion peak (43) is of low intensity.

The character of the fragmentation of the $M^+$ ions of II makes it possible to estimate the ratio of the tautomers: ΣA:(ΣB:ΣC) = 58.5:41.5 (Table 2). The development of 134 and 106 ions is explained by a rearrangement process similar to that observed in the fragmentation of I (the 151 and 123 ions). In this case also ion peaks due to a Beckmann rearrangement are not found in the mass spectrum.

To arrive at a more accurate estimate of the ratio of the B or C form of $M^+$ we attempted to use a deuterium-labeled sample of II (IIa, Table 1). A calculation of isotope exchange for $M^+$ [24] shows that IIa contains 25% undeuterated compound, 50% monodeuterated analog, and 25% dideuterated analog. The presence of the dideuterated compound indicates the possibility of deuterium exchange of both the hydrogen atom of the hydroxy group and the hydrogen atom of the imino group. The monodeuterated compound may contain the label in one of these groups. A comparison of the intensities of the 174 and 173 and 159 and 158 ion peaks determines the presence of the deuterium label in the hydroxy group, while a comparison of the 133 and 132 and 145 and 146 ion peaks indicates deuterium exchange of the hydrogen atom of the imino group (Table 1). The ratio of the two monodeuterated products is ∿1:1, and this demonstrates the approximately identical acidities of the hydroxy and imino groups in the tautomers. In a situation such as this it is impossible to accurately calculate the percentage of retention of the deuterium label for the $[Het]^+$, $[HetNH]^+$, and $[Het - HCN]^+$ ions, which determine the B form in the mass spectrum of IIa. However, considering the increased intensities of the 91, 92, 119, 120, and 133 ion peaks (Table 1), it may be assumed that the B form dominates.

An analysis of the mass spectra of III-V shows that the trend of the dissociative ionization remained virtually unchanged as compared with the examined spectra of I and II (Tables 1 and 2). Calculations of the overall intensities that determine the contribution of the tautomers to $M^+$ [ΣA:(ΣB + ΣC)] gives 30.0:70.0 for III, 38.3:61.7 for IV, and 50.8:49.2 for V. The rearrangement process that is observed for I and II and is due to the successive splitting out of RCN and CO particles from the $[M - N_2]^+$ ion is also realized in this case. In the mass spectrum of III the 103, 106, and 134 ion peaks have precise masses of 103.0414, 106.0538, and 134.0476, respectively, in agreement with the empirical compositions of the $[C_6H_5CN]^+$, $[C_6H_6N_2]^+$, and $[C_7H_6N_2O]^+$ ions. A similar rearrangement process is also recorded in the mass spectra of IV and V (Table 1):

$$[M-N_2]^+ \xrightarrow{-C_6H_5CN} 224 \xrightarrow{-CO} 196;\quad [M-N_2]^+ \xrightarrow{-C_3H_7CN} 224 \xrightarrow{-CO} 196.$$

The presence of a 105 ion peak in the mass spectra of III and IV is associated with the elimination of an HCN molecule by the $[HetNH]^+$ ions to give $[C_6H_5N_2]^+$ ions (with a determined value of 105.0432 and a calculated value of 105.0452) and is not in agreement with an ion with the composition $[C_6H_5CO]^+$, which could have been formed during a Beckmann rearrangement. The 250 ion peak is not recorded in the mass spectrum of V, i.e., the indicated rearrangement also does not occur for this oxime in the gas phase (Table 1).

Out study showed that for heterarylazoketoximes I-V in the gas phase at the moment of vaporization of the samples the overall contribution of the tautomers that exist in the nitroso form becomes more appreciable as compared with solutions. The ratios of the tautomers are determined by both the basicity of the heterocycle and the character of the substituent attached to the methylidyne carbon atom. It should also be noted that Beckmann rearrangement in the gas phase is not observed for any of the investigated oximes.

## EXPERIMENTAL

The mass-spectrometric study was made with a Varian MAT-311A spectrometer having "inverse" geometry in the construction of the magnetic and electrostatic sectors, which made it possible to obtain the spectra of the metastable ions (the DADI technique). The following standard recording conditions were used: an accelerating voltage of 3 kV, a cathode emission current of 300 μA, an ionizing-electron energy of 70 eV, and a sample-vaporization temperature of 80-210°C. A system for direct introduction of the substances into the ion source was used. The high-resolution mass spectra were obtained under the same conditions: M/ΔM = 15,000 with polyphosphoric acid as the standard. The deuteration of II was carried out directly in the mass spectrometer by adding a solution of $CD_3OD$ to the crucible containing the sample.

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# SYNTHESIS OF NUCLEOSIDES OF SUBSTITUTED 3-HYDROXYPYRAZOLES

F. F. Blanko, I. A. Korbukh,
M. N. Preobrazhenskaya, and H. Dorn

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N-Glucoside analogs of the antibiotic pyrazofurine were obtained by fusion of 3-hydroxy-4-ethoxycarbonylpyrazole with tetra-O-acetyl-β-D-ribofuranose in the presence of iodine.

In connection with the fact that the antitumorigenic activity of the antibiotic pyrazofurine (the C-nucleoside of 4-hydroxy-5-carbamoylpyrazole) is well known, the preparation of its N-glycoside analogs seems of interest [1].

As the starting compound for their synthesis we used 3-hydroxy-4-ethoxycarbonylpyrazole (I). 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-3-hydroxy-4-ethoxycarbonylpyrazole (IIa) was obtained by fusion of pyrazole I with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose at 160°C for 30 min *in vacuo* in the presence of iodine. Triacetate IIa was converted to 1-β-D-ribofuranosyl-3-hydroxy-4-ethoxycarbonylpyrazole (IIb) by the action of an alcohol solution of sodium ethoxide. 1-β-D-Ribofuranosyl-3-hydroxy-4-carbamoylpyrazole (IIc) is formed by ammonolysis

Oncologic Science Center, Academy of Medical Sciences of the USSR, Moscow 115478. Central Institute of Organic Chemistry, Academy of Sciences of the German Democratic Republic, Berlin-Adlershof 1199. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1512-1514, November, 1981. Original article submitted April 3, 1981.

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