TABLE 1. Condensed Pyrimidines IX, XII-XV, and XIX

Compound	mp., °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IX	192—194 [a]	63,1	5,6	22,7	$C_{10}H_{11}N_3O$	63,5	5,8	22,2	77
XII	225—227 [b]	61,8	5,3	24,2	$C_9H_9N_3O$	61,7	5,1	24,0	66
XIII	235—238 [b]	63,6	5,6	22,5	$C_{10}H_{11}N_3O$	63,5	5,8	22,2	67
XIV	202—205 [b]	65,2	6,5	20,9	$C_{11}H_{13}N_3O$	65,0	6,4	20,7	88
XV	242—245 [c]	62,4	6,4	24,1	$C_{12}H_{14}N_4O$	62,6	6,1	24,4	96
XIX	330[c]	65,1	6,13	20,8	$C_{11}H_{13}N_3O$	65,0	6,4	20,7	30

[a]From water. [b]From methanol. [c]From DMF.

mp 136-138°C (from alcohol). Found: C 60.6; H 7.0; N 23.9%. $C_9H_{13}N_3O$. Calculated: C 60.4; H 7.3; N 23.5%.

LITERATURE CITED

1. V. G. Granik, E. M. Peresleni, G. D. Kurochkina, A. M. Zhidkova, N. B. Marchenko, R. G. Glushkov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 3, 349 (1980).
2. B. Stanovnik and M. Tisler, Synthesis, 180 (1974).
3. V. A. Azimov, V. G. Granik, R. G. Glushkov, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 355 (1978).
4. A. N. Kost, R. S. Sagitullin, and G. G. Danagulyan, Khim. Geterotsikl. Soedin., No. 10, 1400 (1978).
5. V. G. Granik, N. B. Marchenko, T. F. Vlasova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 11, 1509 (1976).

HETEROCYCLIC DERIVATIVES OF PURINES.

3.* SYNTHESIS AND MASS SPECTROMETRIC STUDY OF IMIDAZO[1,2-]PURINE

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A mixture containing 65% 1-methyl-2-phenyl-5,7-dichloro- and 35% 1-methyl-2-phenyl-3,5,7-trichloroimidazo[1,2-f]purine (the percentages of the components were established by means of chromatographic mass-spectrometric analysis) was obtained by refluxing 1,8-dimethyl-2-phenylimidazo[1,2-f]xanthine in $POCl_3$ in the presence of excess PCl_5. Reduction of this mixture with concentrated HCl in the presence of red phosphorus leads to 1-methyl-2-phenylimidazo[1,2-f]purine, while heating with piperidine gives a mixture consisting of 55% 1-methyl-2-phenyl-6-piperidino-8-chloroimidazo[1,2-f]purine and 45% 1-methyl-2-phenyl-3,8-dichloro-6-piperidinoimidazo[1,2-f]purine. The IR, PMR, and mass spectra of the compounds obtained are discussed.

In a preceding communication [1] we demonstrated that imidazo[1,2-f]xanthine derivatives readily undergo electrophilic substitution. The behavior of imidazo[1,2-f]purine derivatives with respect to nucleophilic and electrophilic substitution reactions is of definite interest. The literature contains data on the synthesis of derivatives of imidazo[1,2-a]purine [2], imidazo[2,1-b]purine [3], and imidazo[2,1-i]purine [4, 5], whereas no information on the synthesis of imidazo[1,2-f]purine is available.

*See [1] for communication 2.

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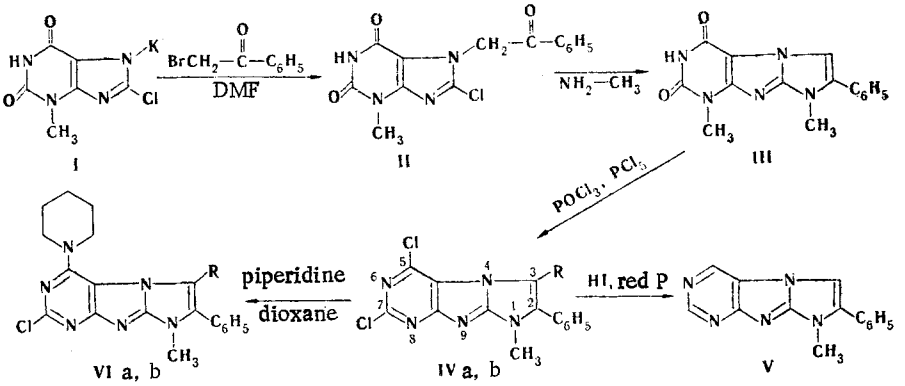
The synthesis and physicochemical properties of a new system, viz., the imidazo[1,2-f]-purine system (V), are described in this paper. A number of transformations that lead to the production of imidazo[1,2-f]purine V are shown in the scheme.



IV, VIa R = H; b R = Cl

The reaction of the potassium salt of 8-chloro-3-methylxanthine (I) with phenacyl bromide in dimethylformamide (DMF) gave 7-phenacyl-8-chloro-3-methylxanthine (II). The latter forms 1,8-dimethyl-2-phenyl-6H-imidazo[1,2-f]xanthine (III) when it is heated with 25% aqueous methylamine solution in a sealed ampul at 170-180°C.

A mixture of IVa,b is obtained when III is refluxed with excess PCl_5 in $POCl_3$. 1-Methyl-2-phenylimidazo[1,2-f]purine (V) was obtained by reduction of IVa, b with concentrated hydriodic acid in the presence of excess red phosphorus, while VIa, b were formed when IVa, b were refluxed briefly with piperidine in dioxane.

The absorption bands of the stretching vibrations of various groups ($\nu_{C=C}$ 1615, $\nu_{C=N}$ 1540, and $\nu_{C=O}$ 1700 cm^{-1}), as well as the asymmetrical (ν_{as} 3480 cm^{-1}) stretching vibrations of an associated NH grouping (a broad absorption band), show up distinctly in the IR spectrum of III. The stretching vibrations of CH_{arom} ($\nu_{CH_{arom}}$ 3070, 3040 cm^{-1}) and CH_3 (ν_{CH_3} 2960, 2835 cm^{-1}) groups are less clearly expressed. The assignment of the absorption bands in the IR spectrum was made on the basis of previous studies [6-8].

Signals of protons of an N-methyl group (3.41 ppm, s, 3H), of a phenyl substituent in the 2 position (7.42-7.71 ppm, m, 5H), and of a proton attached to the C_3 atom of the outer imidazole ring (7.75 ppm, s, 1H), as well as signals of a uracil fragment attached to the N_6 atom (9.25 ppm, broad s, 1H) and of a methyl group attached to the N_8 atom (3.7 ppm, s, 3H), are recorded in the PMR spectrum of III. The signals were identified on the basis of published spectra [9].

A molecular ion peak (M^+), which is the maximum peak, is recorded in the mass spectrum of III. The presence of a uracil ring in the molecule is confirmed by the characteristic elimination of NCO and NHCO particles from M^+ (via a mechanism of the "retrodiene fragmentation: type [10]) with subsequent splitting out of CO and CH_3NCO molecules. The elimination of a methyl group by $[(M - HNCO) - CO]^+$ (m/e 209)* and $[(M - HNCO) - CO - HCN]^+$ (182) ions, as well as the formation of ions with the $C_6H_5C{\equiv}\overset{+}{N}{-}CH_3$ (118) and $[C_6H_5C{=}CH]^+$ (102) structures, confirms that the methyl group is in the 1 position and that the phenyl group is in the 2 position.

The chlorination of III with excess $POCl_3$ and PCl_5 gives a compound with an IR spectrum in which stretching vibrations of NH and CH_{arom} bonds are absent and in which absorption bands of a methyl group virtually do not appear.

An analysis of the mass spectrum of this compound showed that it is not an individual substance but rather is a mixture of two substances. The principal substance (a) gives a triplet of M^+ peaks at 317, 319, and 321 and, judging from the ratio of the intensities of the M^+, $[M + 2]^+$, and $[M + 4]^+$ peaks (100:65:10), contains two chlorine atoms.

The second substance is a high-molecular-weight compound that contains three chlorine atoms (the isotopic distribution for the M^+, $[M + 2]^+$, $[M + 4]^+$, and $[M + 6]^+$ peaks is 30:30:10:1). If one takes into account the fact that the coefficient of sensitivity to electron

*The numbers that characterize the ions are the mass-to-charge ratios.

impact is approximately the same for both compounds (IVa and (Vb) [12], their percentages in the mixture are 67 and 33%, respectively, according to the mass spectrum. The number of atoms in the molecules is also determined by the successive elimination of an element from M^+, which is recorded in the mass spectrum from the peaks of the $[M - Cl]^+$, $[M - 2Cl]^+$, and, in the case of IVb, $[M - 3Cl]^+$ ions. The processes involved in the elimination of chlorine atoms and other fragmentation pathways were monitored by the DADI technique [13]. The presence of ion peaks with m/e 102 and 118 in the mass spectrum of IVa, which are also observed in the mass spectrum of III, specifies unambiguously that the chlorine atoms are absent in the imidazole fragment of the molecule and that the molecule contains a methyl group in the N_1 position of the three-ring system. Substitution by a chlorine atom consequently occurs exclusively in the pyrimidine fragment of the molecule in this case.

In the case of IVb it may be assumed that tertiary substitution by a chlorine atom may take place in the 2 position of the phenyl ring or at the C_3 atom of the imidazole ring. The absence of $[C_6H_4Cl]^+$ (111) and $[CH_3\overset{+}{N}{\equiv}CC_6H_4Cl]$ (152) ion peaks in the mass spectrum indicates that substitution does not occur in the phenyl ring. This assumption is confirmed by the direct elimination of a $CH_3\overset{+}{N}{\equiv}CC_6H_5$ particle from M^+. All of the indicated mass-spectrometric characteristics make it possible to assign IVa and IVb structures, respectively, to the synthesized compounds.

The PMR spectrum (in d_6-DMSO) confirms this conclusion. Signals of protons in the form of singlets, viz., signals of a methyl group attached to the N_1 atom at δ 3.77 (IVa) and δ 3.63 ppm (IVb), are recorded in the strong-field region. A calculation of the PMR spectrum shows that the mixture contains 75% IVa. This represents completely satisfactory agreement with the results of the mass-spectrometric study. A singlet of a proton attached to the C_3 atom is recorded for the IVa component at δ 8.16 ppm. The presence of an unsubstituted phenyl ring is monitored by a multiplet at 7.48-7.80 ppm.

The reduction of IVa, b with concentrated hydriodic acid in the presence of red phosphorus leads to the formation of 1-methyl-2-phenylimidazo[1,2-f]purine (V).

A νCH_{arom} (3100 cm^{-1}) absorption band shows up distinctly in the IR spectrum of V, and this confirms that dehalogenation occurs; in addition, bands due to the vibrations of a hetaryl ring ($\nu_{C=C}$ 1650 and $\nu_{C=N}$ 1600 cm^{-1}) and a group of bands at 1540, 1465, 1370, and 1295 cm^{-1} are observed. Signals of protons attached to C_3, C_5, and C_7 at 8.09, 8.82, and 9.06 ppm, respectively, and signals of protons of a phenyl ring attached to C_2 (7.43-7.79 ppm, m, 5H) are observed in the PMR spectrum of V. In addition, the spectrum contains signals of protons of a methyl group attached to the N_1 atom (3.75 ppm, s, 3H).

An M^+ peak, which has the maximum intensity, is recorded in the mass spectrum of V. The mass number of M^+ corresponds to the value calculated for the proposed structure. The elimination of a hydrogen atom (248) (β cleavage relative to the hetaryl ring) and of a CH_3 group (234) from M^+ is characteristic for N-methyl-substituted pyrrole derivatives. The appearance of ion peaks with m/e 77, 102, 103, 104, and 118 proves the presence of the imidazole part of the molecule and establishes the position of the substituents in it. The subsequent detachment of two HCN molecules from M^+ (222 and 195, respectively) is specific for pyrimidines and purines [14, 15]. The presence of an intense M^{2+} peak (124.5) confirms the aromatic character of V. The stability of this compound with respect to electron impact (W_M 24.9%) attests that it has a high degree of aromatic character.

In addition to the synthesis of imidazo[1,2-f]purine, it was also of interest to study the lability of the chlorine atoms in IVa, b. Monosubstitution occurs when the mixture of these compounds is heated briefly with excess piperidine, as evidenced by an analysis of their mass spectra. Signals of two M^+ ions are observed in it: 400:402:404 (with the isotope distribution that is characteristic for the presence of two chlorine atoms) and 366:368 (with the isotope distribution that is characteristic for one chlorine atom). The recorded M^+ peaks provide evidence that monosubstitution is characteristic for both components.

The following characteristic absorption bands appear in the IR spectrum of a mixture of VIa and VIb: νCH_{arom} 3070, ν_{CH_3} 2950, ν_{CH_2} 2860, $\nu_{C=C}$ 1645, and $\nu_{C=N}$ 1595 cm^{-1}. Substitution by piperidine is manifested in the mass spectrum by fragmention peaks with m/e 84, 70, 57, and 56 [16] and $[M - 56]^+$ and $[M - 83]^+$ ion peaks. The presence of ions with m/e 102 and 118 constitutes evidence in favor of the fact that one component of the mixture of VIa and VIb does not contain halogen in the 3 position. This is once again confirmed by direct elimination

of $C_6H_5{\equiv}CH$ particles from the M^+ ion with lower mass (264, which was proved by the DADI technique). A $ClC{\equiv}CPh$ particle is split out from the M^+ ion with greater mass (400), which indicates that the chlorine atom is in the 3 position. The direct elimination of chlorine from the M^+ ions of both components (365 and 331), from the $[M - CH_3NC - C_6H_5]^+$ ion (247 and 213), and from the $[M - C_5H_9N]^+$ ion (282 and 248) constitutes convincing evidence for the presence of a chlorine atom in the 7 position of both components.

The position of the piperidine ring in the pyrimidine ring of the molecule is determined by the formation of $[M - ClCN]^+$ ions (305 for VIa and 339 for VIb). The ratios of the intensities of the M^+ peaks of VIa and VIb are approximately the same. A semiquantitative calculation shows that they are present in the mixture in 55 and 45% amounts, respectively. The data from mass spectrometry are in good agreement with the results of PMR spectroscopy. Signals of protons of the methylene group of a piperidine ring (1.63-1.84 ppm, m), of a methyl group attached to the N_1 atom (3.67 ppm, s) for VIb, of a methyl group attached to the N_1 atom (3.78 ppm, s) for VIa, and C_8H (7.78 ppm, s), as well as signals of aromatic protons (7.48-7.80 ppm, m) of a phenyl ring, are observed in the PMR spectrum.

The set of data presented above unambiguously determines the individuality of the synthesized compound and completely confirms the proposed structure of V.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Bruker WH-90 spectrometer with tetramethylsilane as the standard. Some of the PMR spectra were recorded with a Varian model T-60 spectrometer (60 MHz) with CF_3COOH as the solvent. The mass spectra were recorded with a Varian MAT-311A spectrometer with direct introduction of the samples into the ion source. The spectra were recorded under standard conditions: The accelerating voltage was 3 kV, the cathode emission current was 300 μA, and the ionizing voltage was 70 eV.

8-Chloro-3-methylxanthine Potassium Salt (I). A 2.0-g (1 mmole) sample of 8-chloro-3-methylxanthine [17] was dissolved by heating in 30 ml of water containing 0.68 g (1.2 mmole) of KOH, and the solution was cooled and poured into 200 ml of acetone. The precipitate was removed by filtration to give 2.15 g (90.3%) of a product with mp 350°C (dec.).

7-Phenacyl-8-chloro-3-methylxanthine (II). A mixture of 2.38 g (1 mmole) of salt I and 2.2 g (1.2 mmole) of ω-phenacyl bromide was refluxed in 40 ml of DMF for 30 min, after which the mixture was cooled, and the precipitate was removed by filtration and washed with ether and water to give 2.4 g (72%) of a product with mp 297-299°C (dec., from aqueous DMF). IR spectrum (KBr pellet): 3420 (NH), 1710, 1695 (C=O); 1640 (C=N); 1605 cm^{-1} (C=C). Found: C 52.6; H 3.7; Cl 10.9; N 17.3%. $C_{14}H_{11}ClN_4O_3$. Calculated: C 52.8; H 3.5; Cl 11.1; N 17.6%.

1,8-Dimethyl-6H-2-phenylimidazo[1,2-f]xanthine (III). Ethanol (50 ml) and 15-20 ml of a 25% aqueous solution of methylamine were added to a 3.3 g (1 mmole) of II, and the mixture was heated in a sealed ampul at 170-180°C for 8 h. It was then cooled, and the precipitate was removed by filtration and washed with water and acetone to give 2.7 g (81%) of a product with mp 339-340°C (dec., from glacial acetic CH_3COOH). Found: C 61.1; H 4.4; N 23.6%. $C_{15}H_{13}N_5O_2$. Calculated: C 61.1; H 4.4; N 23.7%.

5,7-Dichloro- and 3,5,7-Trichloro-1-methyl-2-phenylimidazo[1,2-f]purine (IVa, b). A 26.5-g (9 mmole) sample of III was heated in 150 ml of $POCl_3$ until it dissolved (for 3-5 h), after which the solution was cooled to room temperature and treated with 37.4 g (18 mmole) of PCl_2, and the mixture was refluxed for 5 h. The $POCl_3$ was removed by distillation to dryness *in vacuo*, and the residue was treated with cold water. The aqueous mixture was neutralized with a saturated solution of $NaHCO_3$, and the precipitate was removed by filtration and washed with water to give 24.5 g of a mixture of IVa, b.

1-Methyl-2-phenylimidazo[1,2-f]purine (V). A 6.0-g sample of the mixture of IVa and IVb was heated in 150 ml of concentrated HCl until it dissolved, after which 3.0 g of red phosphorus was added, and the mixture was refluxed for 1 h. The hot mixture was filtered, and the filtrate was cooled and neutralized with 25% ammonium hydroxide. The precipitate was removed by filtration to give 3.1 g of a product with mp 301-302°C (dec., from DMF) and R_f 0.37 [n-butanol–formic acid–water (77:10:13)]. Found: C 67.4; H 4.5; N 28.2%. $C_{14}H_{11}N_5$. Calculated: C 67.5; H 4.4; N 28.0%.

TABLE 1. Mass Spectra of the Synthesized Compounds

Compound	m/e values (intensities of the ion peaks in percent of the maximum peak)*
III	Temp. of heating of the admission system (THAS) 190°C 39 (5,7); 40 (8,7); 41 (6,8); 42 (14,2); 50 (3,9); 51 (10,0); 52 (5,5); 53 (3,4); 55 (5,7); 57 (3,1); 63 (4,6); 67 (9,1); 69 (5,8); 70 (9,0); 75 (4,0); 76 (8,4); 77 (29,7); 78 (5,2); 80 (3,8); 82 (5,5); 85 (3,1); 89 (6,6); 91 (5,4); 91,5 (3,8); 96 (7,8); 101 (7,0); 102 (17,0); 103 (7,5); 104 (3,8); 115 (5,2); 116 (8,6); 117 (3,1); 118 (25,0); 126 (19,6); 126,5 (3,2); 127 (3,1); 128 (11,4); 129 (4,2); 130 (4,4); 141 (3,5); 142 (3,3); 147,5 (9,7); 155 (5,0); 182 (7,1); 183 (6,6); 184 (7,8); 195 (3,4); 196 (9,4); 197 (18,2); 198 (3,6); 209 (7,0); 223 (39,0); 224 (45,6); 225 (20,0); 251 (11,9); 252 (9,2); 253 (7,3); 295 (100,0); 296 (24,0). W_m 12.0.
IV a, b	THAS 150° 50 (4,7); 51 (10,2); 63 (6,3); 76 (9,2); 77 (21,6); 89 (11,2); 91 (3,6); 101 (3,3); 102 (13,2); 103 (10,5); 104 (11,1); 118 (12,8); 136 (6,5); 158,5 (9,6); 159 (3,4); 159,5 (6,4); 175,5 (4,2); 176,5 (3,5); 233 (4,5); 235 (4,8); 246 (3,0); 247 (12,6); 281 (3,8); 282 (8,7); 284 (3,0); 302 (13,3); 304 (8,1); 316 (10,0); 317 (100,0); 318 (31,4); 319 (64,4); 320 (16,5); 321 (5,8); 351 (50,3); 352 (11,0); 353 (50,0); 354 (8,1); 355 (16,7); 356 (3,1). W_m 10.7 for IVa, 6.3 for IVb.
V	THAS 160° 39 (4,0); 42 (3,0); 51 (7,1); 52 (3,8); 63 (3,4); 76 (4,7); 77 (19,1); 89 (5,6); 102 (9,0); 103 (4,9); 104 (10,2); 111 (12,9); 116 (4,8); 118 (7,6); 120 (3,0); 124,5 (8,9); 128 (4,0); 131 (6,0); 153 (3,6); 180 (3,2); 195 (4,3); 221 (3,0); 222 (4,5); 234 (15,6); 248 (15,4); 249 (100,0); 250 (17,9). W_m 24.9.
VI a, b	THAS 165° 39 (3,8); 40 (5,2); 41 (8,6); 42 (4,3); 44 (3,5); 55 (5,4); 56 (3,6); 57 (3,2); 77 (7,8); 84 (100,0); 85 (6,3); 102 (4,0); 103 (7,6); 104 (3,1); 118 (12,2); 153 (3,4); 213 (3,2); 247 (4,0); 248 (12,2); 264 (4,1); 282 (20,5); 283 (12,3); 284 (9,1); 305 (3,6); 310 (8,4); 311 (5,2); 312 (3,5); 317 (15,4); 318 (6,1); 319 (11,1); 331 (3,2); 337 (10,0); 344 (11,6); 345 (4,4); 346 (7,5); 347 (3,0); 351 (3,0); 365 (20,6); 366 (20,3); 367 (10,2); 368 (6,5); 371 (6,6); 373 (4,2); 400 (17,2); 401 (4,3); 402 (10,8). W_m 3,0 for VIa, 2.6 for VIb.

*The peaks with intensities greater than 3% are presented.

7-Chloro-1-methyl-2-phenyl-6-piperidinoimidazo[1,2-f]purine (VIa) and 3,7-Dichloro-1-methyl-2-phenyl-6-piperidinoimidazo[1,2-f]purine (VIb). A 3.0-g sample of the mixture of IVa and IVb in 50 ml of dioxane was refluxed with 10 ml of piperidine for 20 min, after which the mixture was cooled and poured into 150 ml of water. The precipitate was removed by filtration to give 2.8 g of product.

LITERATURE CITED

1. Yu. V. Strokin, B. A. Priimenko, A. K. Sheinkman, and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 10, 1404 (1979).
2. C. R. Frihart, A. M. Feinberg, and K. Nakanishi, J. Org. Chem., 43, 1644 (1978).
3. P. D. Sattsangi, N. J. Leonard, and C. R. Frihart, J. Org. Chem., 42, 3292 (1977).
4. L. Shaw and B. M. Smallwood, J. Chem. Soc., No. 16, 2206 (1970).
5. N. K. Kochetkov, V. N. Shibaev, and A. A. Kost, Tetrahedron Lett., No. 22, 1993 (1971).
6. J. S. Connolly and H. Linschitz, J. Heterocycl. Chem., 9, 379 (1972).
7. E. R. Blaut and M. Field, J. Am. Chem. Soc., 72, 479 (1950).
8. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen (1958).
9. T. J. Butterham, NMR Spectra of Sample Heterocycles, New York—London—Sydney—Toronto (1974).
10. J. Heiss, K.-P. Zeller, and W. Voelter, Org. Mass Spectrom., 3, 181 (1970).
11. L. A. Gutorov, L. A. Nikolaeva, and E. S. Golovchinskaya, Khim. Farm. Zh., No. 2, 17 (1971).
12. A. A. Polyakov and R. A. Khmel'nitskii, Mass Spectrometry in Organic Chemistry [in Russian], Khimiya, Moscow (1972).
13. N. A. Klyuev, E. N. Istratov, V. P. Suboch, V. L. Rusinov, and V. A. Zyryanov, Zh. Org. Khim., 13, 1501 (1977).
14. J. R. Williams and J. E. Ayling, J. Heterocycl. Chem., 10, 827 (1973).
15. J. Rice and L. Dudek, J. Am. Chem. Soc., 89, 2719 (1967).
16. H. Budzikiewicz, C. Djerassi, and D. H. Williams, Interpretation of the Mass Spectra of Organic Compounds, Holden—Day, San Francisco (1964).
17. E. Fischer and F. Ach, Ber., 31, 1980 (1898).