

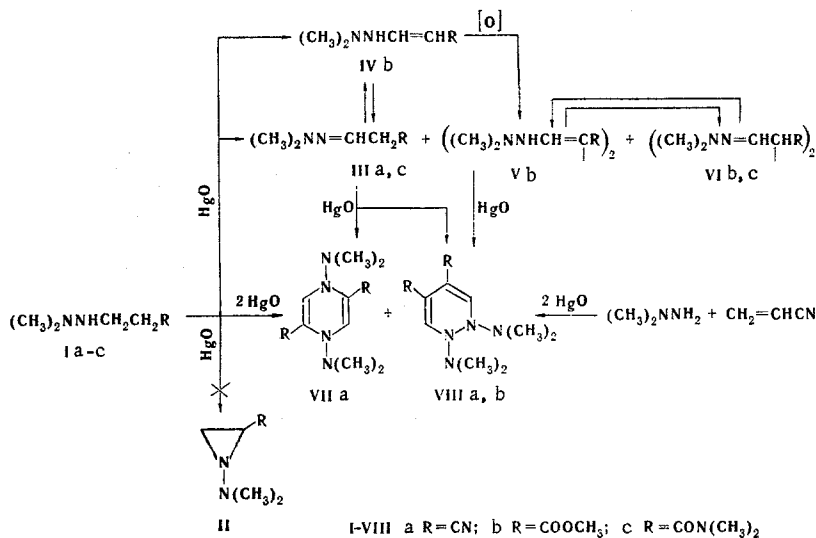
OXIDATION OF 1,1,2-TRISUBSTITUTED HYDRAZINES
AND 1,1-DIMETHYLHYDRAZONES
STABLE 1,4-HYDROPYRAZINE AND 1,2-DIHYDROPYRIDAZINE
SYSTEMS

S. A. Giller,* A. V. Ereemeev,
I. Ya. Kalvin'sh, V. G. Semenikhina,
É. É. Liepin'sh, T. M. Kupch,
and I. S. Yankovskaya

UDC 547.861:543.422.25:542.943

3-(N,N-Dimethylhydrazono)propionic acid and 1,4-bis-(dimethylamino)-3,5-dicyano-1,4-dihydropyrazine derivatives, 4,5-disubstituted 1,2-bis(dimethylamino)-1,2-dihydropyridazines, methyl β -(2,2-dimethylhydrazino)acrylate, bis[N,N-dimethyl-2,3-(2,2-dimethylhydrazono-methyl)succinamide], and dimethyl 1,4-(2,2-dimethylhydrazino)-1,3-butadiene-2,3-dicarboxylate were obtained by oxidation of 2'-substituted 1,1-dimethyl-2-ethylhydrazines.

Little study has been devoted to the oxidation of 1,1,2-trisubstituted hydrazines. In the present research we investigated the reaction of 2'-substituted 1,1-dimethyl-2-ethylhydrazines with yellow mercuric oxide. We used 1,1-dimethyl-2-(2-cyanoethyl)hydrazine (Ia), 1,1-dimethyl-2-(2-methoxycarbonyl)ethylhydrazine (Ib), and 1,1-dimethyl-2-(2-dimethylamidoethyl)hydrazine (Ic) as model compounds. It was established by PMR spectroscopy and gas-liquid chromatography (GLC) that the principal products of the reaction of hydrazines Ia-c with an equimolar amount of yellow mercuric oxide (with cooling) are hydrazones IIIa-c.



In contrast to acetoacetic ester dimethylhydrazone [1], hydrazones IIIa-c (Table 1) are not isomerized to an enehydrazine form at room temperature. However, a mixture of hydrazone IIIb with the isomeric enehydrazine IV and bis(enehydrazine) V is formed by vacuum distillation of IIIb or by oxidation of Ib at higher temperatures. Tautomeric conversion of enehydrazine IV to hydrazone IIIb is not observed when solutions of a chromatograph-

*Deceased.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 3, pp. 396-401, March, 1976. Original article submitted January 26, 1975.

This material is protected by copyright registered in the name of Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$7.50.

TABLE 1. Parameters of the PMR and IR Spectra of β -(2,2-Dimethylhydrazono)propionic Acid Derivatives

Compound	τ , ppm				ν , cm^{-1}		
	CH_2N	CH	CH_2	R	CH_2-N	$\text{C}=\text{N}$	R
IIIa	7,17	3,72	6,77	—	2805, 2845	1640	2200
IIIb	7,28	3,51	6,84	6,37	2800, 2840	1630	1745
IIIc	7,30	3,47	6,84	7,00, 7,17	2798, 2838	1650	

ically pure sample of it in chloroform are allowed to stand. This constitutes evidence for the presence of an appreciable barrier to isomerization of the enehydrazine to the hydrazone, and this is in good agreement with the literature data on the higher stabilities of enehydrazines stabilized by electron-acceptor groups [1]. Under the influence of air oxygen, enehydrazine IV is readily converted to bis(enehydrazine) V, which is partially isomerized to bis(hydrazone) VIb in solution.

In the oxidation of hydrazine Ic, bis(hydrazone) VIc was isolated as a side product. We also note that, in contrast to the dimethylhydrazones of β -dicarbonyl compounds [2], hydrazones IIIa-c and VIb, c and enehydrazines IV and V do not form mixtures of syn-anti and cis-trans isomers, respectively. A mixture of two isomers with identical melting points but different NMR and IR spectra was obtained by oxidation of hydrazine Ia with two equivalents of yellow mercuric oxide. From the alternative structures - 3,4-dicyano-1,2-cyclobutanedione bis(dimethylhydrazone), 1,3-dicyano-2,4-cyclobutanedione bis(dimethylhydrazone) VI, dihydropyrazine VII, and dihydropyridazine VIII - on the basis of measurements of the dipole moments and mass, H^1 NMR, and C^{13} NMR spectroscopic data we arrived at the unambiguous conclusion that a mixture of dihydropyrazine VII and dihydropyridazine VIIIa in a ratio of 9 : 1 is formed as a result of the oxidation of Ia. Similar results were obtained in the reaction of a chromatographically pure sample of hydrazone IIIa with one equivalent of yellow mercuric oxide. Only pyridazine VIIIb, which was also prepared by oxidation of hydrazone IIIb or enehydrazines IV and V, is formed in the oxidation of hydrazine Ib. The oxidative transformations of hydrazine Ic and hydrazone IIIc stop with the formation of bis(hydrazone) VIb, during prolonged storage of solutions of which the formation of the isomeric bis(enehydrazine) is not observed. We therefore propose that the oxidation of hydrazones IIIa-c takes place through a step involving prior isomerization to the enehydrazine; this isomerization takes place more readily, the stronger the acceptor properties of substituent R in the molecules of the starting compounds.

In most of the oxidation reactions of hydrazones that do not have labile hydrogen atoms attached to nitrogen the starting carbonyl compounds, azines, or nitroso derivatives are formed [3]. Consequently, the formation of dihydropyrazine and dihydropyridazine systems is a new type of oxidative transformation of hydrazones.

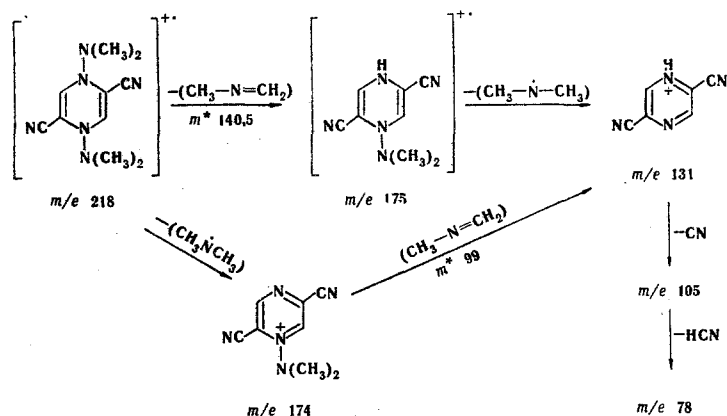
The 1,4-dihydropyrazine (VII) and 1,2-dihydropyridazines (VIIIa, b) obtained in this research are of 8π -electron pseudoaromatic systems [4, 5]. Their stability in both the solid state and in solution constitutes evidence for delocalization of the p electrons of nitrogen in the ring system. The bright-red color of VII and VIIIa and the leveling off of the absorption maxima in the shortwave region of the IR spectra are apparently explained by the presence of considerable conjugation. Heterocycles VII and VIIIa, b do not undergo addition reactions with 1,1-dimethylhydrazine, ammonia, and amines. We were also unable to obtain mineral acid salts of VII and VIIIa, b, and this indicates the reduced electron density on the nitrogen atoms as compared with tetrasubstituted hydrazines.

In mass-spectroscopic studies it was established that pyrazine VII and pyridazine VIIIa have high stabilities with respect to electron impact. The fragmentation patterns of these systems are extremely similar, but there are slight differences in the percentages of fragments with $m/e < 150$. The major pro-

TABLE 2. β -(2,2-Dimethylhydrazono)propionic Acid Derivatives

Compound	bp, $^{\circ}\text{C}$ (pressure, mm)	n_D^{21}	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
IIIa	59-60 (3)	1,4768	$\text{C}_5\text{H}_9\text{N}_3$	53,8	8,2	37,9	54,0	8,1	37,8	79
IIIb	56 (3)	1,4668	$\text{C}_6\text{H}_{12}\text{N}_2\text{O}_2$	50,2	8,4	19,1	50,0	8,3	19,4	67
IIIc	92-96 (1)	1,4903	$\text{C}_7\text{H}_{15}\text{N}_3\text{O}$	53,4	9,7	26,6	53,5	9,6	26,7	63

cess is successive splitting out of dimethylamino groups, which for pyrazine VII can be represented by the following scheme:



A mixture of heterocycles VII and VIIIa is formed in the reaction of 1,1-dimethylhydrazine with acrylonitrile in the presence of two equivalents of yellow mercuric oxide. The substantial decrease in the yields of final products in this case can be explained by participation of the starting dimethylhydrazine in competitive oxidation and cyanoethylation reactions.

EXPERIMENTAL

The IR spectra of mineral oil or hexachlorobutadiene suspensions or liquid films of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of deuteriochloroform solutions were recorded with a Perkin-Elmer R 12B spectrometer with tetramethylsilane (TMS) as the internal standard. The C^{13} NMR spectra of deuteriochloroform solutions were recorded with a Bruker HX-90 spectrometer with TMS as the internal standard. The mass spectra were obtained with an MS-905 spectrometer at ionizing voltages of 14 and 70 eV with a system for introduction of the sample through the cylinder. Chromatographic analysis and isolation of the products were accomplished with a Pye Unicam 105 chromatograph with a flame-ionization detector. The 9.1-m long column with a diameter of 8 mm was filled with Fluoropak-80 (0.25-0.315 mm) modified with 10% E-301 or 1% Versamide-900. The thermostat temperature was 195°, and the carrier gas (helium) flow rate was 300 ml/min. The dipole moments of dioxane solutions of the compounds at 25° were measured with a Dipol' dipole meter.

Typical Experiments in the Oxidation of Hydrazines Ia-c. A 21.7-g (0.1 mole) sample of yellow mercuric oxide was added in portions with stirring and cooling (with ice water) in the course of 4-20 h to a mixture of 0.1 mole of hydrazine I and 30 g of anhydrous sodium sulfate in 100 ml of methylene chloride, after which the mixture was filtered, the solvent was removed from the filtrate by distillation, and the residue was vacuum fractionated. The physicochemical constants of the compounds obtained are presented in Table 2.

Dimethyl 1,4-Bis(2,2-dimethylhydrazino)-1,3-butadiene-2,3-dicarboxylate (V). The residue obtained after removal of hydrazone IIIb by distillation by the method presented above was triturated with methylene chloride, and the solid material was removed by filtration to give 5.9 g (20%) of colorless crystals with mp 154-156° (from ether). IR spectrum: 1584 and 3240 (NH), 1620 (C=C), 1682 (CO), and 2790 and 2840 cm^{-1} (NCH_3). PMR spectrum* (in d_6 -DMSO with TMS as the internal standard): τ 2.61 (d, $J=11.2$ Hz, CH), 3.36 (d, $J=11.2$ Hz, NH), 6.47 (s, COOCH_3), and 7.50 ppm (s, NCH_3). When the product was allowed to stand for 2 weeks in chloroform, an appreciable decrease in the intensity of the absorption bands at 1584, 3240, 1620, 1680, and 3240 cm^{-1} and the appearance of a strong band at 1735 cm^{-1} characteristic for the carbonyl group in an unconjugated ester group (compare with the IR spectrum of hydrazone IIIb) were observed in the IR spectrum of V. The ratio of the bis(enehydrazine) to the bis(hydrazone) was 1:3. Found: C 50.2; H 8.1; N 19.6%. $\text{C}_{12}\text{H}_{22}\text{N}_4\text{O}_4$. Calculated: C 50.0; H 8.3; N 19.4%.

Methyl β -(2,2-Dimethylhydrazino)acrylate (IV). A 43.7-g (0.3 mole) sample of Ia was added dropwise to a refluxing suspension of 65 g (0.3 mole) of yellow mercuric oxide and 200 g of anhydrous sodium sulfate in 500 ml of ether, after which the mixture was refluxed for 5 h. It was then filtered, and the fil-

*The following abbreviations are used here and subsequently: s is singlet, d is doublet, t is triplet, and m is multiplet.

trate was evaporated to 150 ml, cooled, and filtered to give 3.0 g (7%) of colorless crystals identical to an authentic sample of V obtained as indicated above. The filtrate was evaporated, and the residue was analyzed by gas-liquid chromatography (GLC). The mixture contained 6% enehydrazine IV, which was isolated by preparative GLC to give a colorless liquid with n_D^{26} 1.5107 and M^+ 144. IR spectrum: 1565 (NH), 1620 (C=C), 1700 (CO), and 2830 and 2870 cm^{-1} (NCH_3). The NH band in the shortwave portion of the IR spectrum is "diffuse"; this is also characteristic for the IR spectra of bis(enehydrazine) V in chloroform. PMR spectrum: τ 2.50 (d, $J=12.9$ Hz, CH), 5.44 (d, $J=12.9$ Hz, CH), 6.30 (s, COOCH_3), and 7.07 ppm (s, NCH_3). Found: C 50.1; H 8.2; N 20.0%. $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_2$. Calculated: C 50.0; H 8.3; N 19.4%.

Conversion of Enehydrazine IV to Bis(enehydrazine) V. Enehydrazine IV was allowed to stand in a U-tube at room temperature for 2 weeks, after which the resulting yellow crystalline mass was recrystallized from alcohol or ether to give colorless crystals that were identical to a genuine sample of V obtained as indicated above.

Bis[N,N-dimethyl-2,3-(2,2-dimethylhydrazonomethyl)succinamide](VIc). A) A 47.7-g (0.3 mole) sample of Ic was added dropwise to a suspension of 64.8 g (0.3 mole) of yellow mercuric oxide and 200 g of anhydrous sodium sulfate in 500 ml of ether, and the mixture was then refluxed for 18 h. The hot mixture was then filtered, evaporated to 150 ml, and cooled to give 3.0 g (6.5%) of colorless crystals with mp 144° (from ether). IR spectrum: 1600 (C=N), 1645 (CO), and 2790 and 2832 cm^{-1} (NCH_3). No changes were observed in the IR spectrum when VIb was allowed to stand in chloroform for 2 weeks. PMR spectrum: τ 3.49 (m, N=CH), 5.88 (m, CH), 6.87 and 7.07 [two singlets, $\text{CON}(\text{CH}_3)_2$], and 7.28 ppm (s, NCH_3). The resonance absorptions at 3.49 and 5.88 ppm form an AA'XX' system, the analysis of which gives the following spin-spin coupling constants (SSCC): 8.52 ($J_{\text{XX}'}$), 0 ($J_{\text{AA}'}$), 6.12 (J_{AX}), and -0.30 Hz ($J_{\text{XA}'}$). C^{13} NMR spectrum, δ : 171.5 (CO), 132.4 (N=C), 48.8 (C-2), 42.9 [$\text{NN}(\text{CH}_3)_2$], and 37.6 and 32.9 ppm (amide NCH_3). Found: C 54.0; H 9.1; N 27.0%. $\text{C}_{14}\text{H}_{28}\text{N}_6\text{O}_2$. Calculated: C 53.8; H 9.0; N 26.9%.

B) A 21.6-g (0.1 mole) sample of yellow mercuric oxide was added in portions with stirring to a mixture of 15.7 g (0.1 mole) of hydrazone IIIc and 60.0 g of anhydrous sodium sulfate in 250 ml of dioxane, and the mixture was refluxed for 18 h. It was then filtered, and the filtrate was evaporated. The residue was triturated with ether, the mixture was filtered, and the solid material was crystallized from ethanol to give 7.0 g (45%) of colorless crystals that did not depress the melting point of an authentic sample of VIc obtained by method A.

1,2-Bis(dimethylamino)-4,5-dicyano-1,2-dihydropyrazine (VIIIa) and 1,4-Bis(dimethylamino)-3,5-dicyano-1,4-dihydropyrazine (VII). An 86.64-g (0.4 mole) sample of yellow mercuric oxide was added in portions with stirring and cooling to a mixture of 22.6 g (0.2 mole) of hydrazine Ia and 150 g of anhydrous sodium sulfate in 500 ml of dioxane, and the mixture was refluxed for 8 h. The hot mixture was filtered, and the filtrate was evaporated to 150 ml. The concentrated solution was cooled, and the resulting reddish-yellow plates were removed by filtration to give 4.0 g (9%) of VIIIa with mp 204° (dec., from dioxane). IR spectrum: 1538 (C=C) and 2215 cm^{-1} (CN). The degree of purity of the product was monitored by TLC on activity II aluminum oxide in a dioxane-methanol system (1:3) and also from the absence of the absorption maximum in the IR spectrum at 1215 cm^{-1} that is characteristic for VII. PMR spectrum (in d_6 -DMSO with cyclohexane as the internal standard), τ : 2.79 (s, CH) and 6.86 ppm (s, NCH_3). C^{13} NMR spectrum (in d_7 -DMF with TMS as the internal standard), δ : 123.2 (C_3 and C_6), 115.1 (C_4 and C_5), 116.9 ($\text{C}\equiv\text{N}$), and 43.0 ppm [$\text{N}(\text{CH}_3)_2$]. Mass spectrum [m/e (I, %)]: 219 (9), 218 (54), 175 (20), 174 (9), 160 (7), 159 (7), 145 (14), 134 (9), 132 (8), 131 (16), 117 (6), 107 (6), 106 (7), 105 (6), 77 (5), 58 (26), 51 (5), 47 (7), 45 (45), 44 (78), 43 (100), 42 (84), 41 (12). Found: C 55.1; H 6.5; N 38.3%. $\text{C}_{10}\text{H}_{14}\text{N}_6$. Calculated: C 55.0; H 6.4; N 38.5%. The filtrate was evaporated, and the residue was triturated with dioxane and filtered. The filtrate was evaporated, and the dark-red residue was crystallized from alcohol to give 36.0 g (83%) of red needles of VII with mp $204\text{--}205^\circ$ and $\mu=0$ D. IR spectrum: 1540 (C=C) and 2222 cm^{-1} (CN). The degree of purity of the product was monitored by means of TLC on activity II aluminum oxide in a dioxane-methanol system (1:3) and also from the absence of the absorption maximum in the IR spectrum at 860 cm^{-1} that is characteristic for VIIIa. PMR spectrum (in d_6 -DMSO with cyclohexane as the internal standard), τ : 2.96 (s, CH) and 6.86 ppm (s, NCH_3). C^{13} NMR spectrum (in d_7 -DMF with TMS as the internal standard), δ : 124.4 (C_2 and C_5), 116.2 (C_3 and C_6), 114.8 ($\text{C}\equiv\text{N}$), and 4.27 ppm [$\text{N}(\text{CH}_3)_2$]. Mass spectrum [m/e (I, %)]: 219 (7), 218 (55), 216 (6), 175 (21), 174 (9), 160 (7), 159 (7), 147 (6), 145 (11), 134 (10), 133 (6), 132 (8), 131 (22), 121 (5), 120 (8), 107 (6), 106 (8), 77 (5), 58 (38), 52 (6), 45 (55), 44 (86), 43 (100), 42 (83). Found: C 54.9; H 6.5; N 38.4%. $\text{C}_{10}\text{H}_{14}\text{N}_6$. Calculated: C 55.0; H 6.4; N 38.5%.

B) A 1.71-g (8.2 mmole) sample of yellow mercuric oxide was added in portions to a mixture of 0.911 g (8.2 mmole) of a chromatographically pure sample of hydrazone IIIa and 10 g of anhydrous sodium sulfate in 30 ml of dioxane, after which the mixture was stirred and refluxed for 8 h. The reaction products were isolated by the method presented above to give 0.075 g (8.4%) of a yellowish-red plates identical, with respect to their PMR and IR spectra, to an authentic sample of VIIIa obtained by method A presented above and 0.76 g (85%) of red needles identical to an authentic sample of VII obtained by method A.

1,2-Bis(dimethylamino)-4,5-di(methoxycarbonyl)pyridazine (VIIIb). A) A 43.3-g (0.2 mole) sample of yellow mercuric oxide was added in portions with stirring to a mixture of 14.6 g (0.1 mole) of hydrazone Ib and 30 g of anhydrous sodium sulfate in 100 ml of dioxane, and the mixture was then refluxed for 12 h. The hot mixture was filtered, the solvent was removed by evaporation, and the residue was crystallized from absolute ethanol to give 20.4 g (72%) of yellow crystals with mp 147-148°, $\mu = 2.75 \pm 0.05$ D, and M^+ 284. IR spectrum: 1564 (C=C) and 1735 cm^{-1} (CO). PMR spectrum, τ : 2.80 (s, CH), 6.21 (s, COOCH_3), and 7.05 ppm (s, NCH_3). C^{13} NMR spectrum, δ : 168.0 (CO), 129.3 (C_4 and C_5), 127.0 (C_3 and C_6), 51.8 (OCH_3), and 42.4 ppm [$\text{N}(\text{CH}_3)_2$]. Found: C 51.0; H 7.2; N 19.6%. $\text{C}_{12}\text{H}_{20}\text{N}_4\text{O}_4$. Calculated: C 50.7; H 7.0; N 19.7%.

B) A 0.74-g (3.4 mmole) sample of yellow mercuric oxide was added in portions with stirring to a mixture of 0.5 g (3.4 mmole) of chromatographically pure enehydrazine IV and 5 g of anhydrous sodium sulfate in 20 ml of dioxane, and the mixture was then refluxed for 12 h. The reaction product was isolated by method A to give 0.36 g (75%) of yellow crystals that did not depress the melting point of an authentic sample of VIIIb obtained by method A.

C) A 1.19-g (5.5 mmole) sample of yellow mercuric oxide was added in portions with stirring to a mixture of 1.57 g (5.5 mmole) of bis(enehydrazine) V and 8 g of anhydrous sodium sulfate in 30 ml of dioxane, and the mixture was then refluxed for 12 h. The reaction product was isolated by method A to give 1.07 g (70%) of yellow needles that did not depress the melting point of an authentic sample of VIIIb.

Reaction of 1,1-Dimethylhydrazine with Acrylonitrile in the Presence of Yellow Mercuric Oxide. A 21.6-g (0.1 mole) sample of yellow mercuric oxide was added with stirring and cooling to a mixture of 76 ml (0.1 mole) of 1,1-dimethylhydrazine and 33.3 ml (0.5 mole) of acrylonitrile in 100 ml of ether, and the mixture was then allowed to stand at room temperature for 18 h. The solvent was evaporated, and the dry residue was extracted with alcohol. The extract was evaporated, and the dry residue was triturated with 150 ml of dioxane. The mixture was filtered to give 0.61 g (2.8%) of reddish plates that were identical to an authentic sample of VII. The mother liquor was evaporated, the residue was triturated with dioxane, and the mixture was filtered. The filtrate was evaporated, and the residue was crystallized from alcohol to give 5.5 g (25%) of red needles of VIIIa that were identical to an authentic sample.

LITERATURE CITED

1. T. A. Favorskaya, S. I. Yakimovich, and V. A. Khrustalev, Material from the Third All-Union Conference on the Investigation of the Structures of Organic Compounds by Physical Methods (FIMIS) [in Russian], Kazan (1971), p. 321.
2. Yu. P. Kitaev and B. I. Buzykin, Hydrazones [in Russian], Moscow (1974), p. 87.
3. Yu. P. Kitaev and B. I. Buzykin, Hydrazones [in Russian], Moscow (1974), p. 291.
4. J. W. Lown, M. H. Akhtar, and R. S. McDaniel, J. Org. Chem., **39**, 1998 (1974).
5. M. Tisler and B. Stanovnik, Advances in Heterocyclic Chemistry, Vol. 9 (1968), p. 305.