Chemistry of Heterocyclic Compounds, Vol. 32, No. 7, 1996

NEW REACTIONS OF CYCLIZATION AND RECYCLIZATION OF DERIVATIVES OF 1,3-DIMETHYL-5,6-DIAMINOURACIL

N. N. Kolos, V. D. Orlov, V. A. Chebanov, O. V. Shishkin, V. P. Kuznetsov, and A. Yu. Kulikov

The reaction of 1,3-dimethyl-5,6-diaminouracils with chalcones produced 7,9-dimethyl-2,4-diaryl-1,7,9-triazaspiro[4,5]decene-1-6,8,10-triols. The transformation of these spiro-compounds to pyrimido[4,5-d]oxazoles was investigated.

The reactions of 1,3-dimethyl-5,6-diaminouracil (I) with aromatic α,β-unsaturated ketones were investigated earlier [1-3]; it was shown that the reaction of the diamine I with mesityl oxide and arylidenacetones [1, 2] leads to derivatives of pyrimido[4,5-b]-1,5-diazepine, whereas in the analogous reaction with chalcones hydrolysis of the 6-amino group of the diamine I, followed by the formation of pyrimido[4,5-d]oxazepines, was proposed.

Considering the ambiguity of the chemical behavior of the diamine I toward α,β-unsaturated ketones, we reproduced the conditions of the interaction of compound I with the chalcones (IIa-h) discussed in [3]. As a result we obtained products whose physicochemical characteristics (IR, UV, and partially PMR spectra, Tables 1, 2) and those of the compounds described earlier proved to be virtually identical. Thus, bands in the region of 1600-1618 cm^{-1}, which we assigned to the stretching vibrations of the C=N group, as well as intense bands of the stretching vibrations of the carbonyl groups in the region of 1630-1770 cm^{-1}, appear in the IR spectra of these products.

In the UV spectra of the compounds an absorption band sensitive to the electronic nature of the substituent R^1 is observed. On the PMR spectrograms of compounds IIIa-h, measured in DMSO-D_6, a typical ABX system is observed: quartets of protons of the methylene group, as well as a triplet of the methine proton (Table 2). The chemical shifts of the protons of the methylene group indicate a different anisotropic shielding of the H_A and H_B protons by substituents in the p-positions of the aromatic rings.

Thus, the spectral data, as well as elementary analysis for nitrogen, do not contradict the oxazepine structure proposed in [3]. However, x-ray crystallographic analysis of the product of the reaction of the diamine I with the chalcone IIg refuted this hypothesis. According to the data obtained (see below), compound IIIg is 7,9-dimethyl-2-phenyl-4-(p-bromophenyl)-1,7,9-triazaspiro[4,5]decene-1,6,8,10-trione.

In the IIIg molecule the pyrimidine ring is in the conformation of a nonuniformly flattened boat. The atoms $C_{(2)}$, $N_{(3)}$, $N_{(2)}$, $C_{(4)}$ lie in a plane with accuracy 0.015 Å, while the atoms $C_{(1)}$ and $C_{(3)}$ deviate from the plane by 0.35(1) and 0.14(1) Å, respectively. The five-membered ring has an envelope conformation. The deviation of the $C_{(7)}$ atom from the mean quadratic plane is 0.46(1) Å; the angle between the mean quadratic planes of the spiro-coupled rings is 82.7(6)°. The phenyl substituent is virtually coplanar with the $C_{(5)}=N_{(1)}$ double bond (torsional angle $N_{(1)}-C_{(5)}-C_{(15)}-C_{(14)}$ 175.0(2)°). The bromophenyl substituent at the $C_{(7)}$ atom has a pseudoequatorial orientation (torsional angle $N_{(1)}-C_{(1)}-C_{(7)}-C_{(21)}$ −176.2(7)°) and is rotated 34.8° relative to the $C_{(6)}-C_{(7)}$ bond (torsional angle $C_{(6)}-C_{(7)}-C_{(21)}-C_{(16)}$ 34.8°). Such an orientation of this substituent, as well as the distortions of the bond angles at the $C_{(7)}$ and $C_{(21)}$ atoms ($C_{(6)}-C_{(7)}-C_{(21)}$ 118.6°, $C_{(1)}-C_{(7)}-C_{(21)}$ 114.4°, $C_{(7)}-C_{(21)}-C_{(16)}$ 123.9°, $C_{(7)}-C_{(21)}-C_{(20)}$ 118.8°), are probably due to the shortened contacts $H_{(6A)}$-$H_{(16)}$ 2.1 Å (the sum of the van der Waals radii is 2.32 Å [6]), $C_{(3)}$-$C_{(20)}$ 3.33 Å (3.42 Å), $C_{(6)}$-$H_{(16)}$ 2.81 Å (2.87 Å), $C_{(4)}$-$C_{(16)}$ 3.09 Å (3.42 Å). Shortened contacts are also detected in crystals: $H_{(8b)}$-$O_{(3)}$ 2.30 Å (2.45), $H_{(9b)}$-$O_{(1)}$ 2.38 Å (2.45 Å), $C_{(6)}$-$H_{(14)}$ 2.65 Å (2.87 Å), $H_{(6a)}$-$C_{(16)}$ 2.73 Å (2.87 Å), $C_{(3)}$-$C_{(21)}$ 3.38 Å (3.42 Å).

Khar'kov State University, Khar'kov 310077. Institute of Single Crystals, Academy of Sciences of Ukraine, Khar'kov 310141. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 978-983, July, 1996. Original article submitted February 20, 1996.

 0009-3122/96/3207-0838$15.00

TABLE 1. Characteristics of Compounds IIIa-h

Compound	Gross formula	Found N, %	Calculated N, %	mp, °C	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$) in isopropanol	Yield, %
					$\nu_{C=O}$	$\nu_{C=N}$		
IIIa	$C_{21}H_{21}N_3O_3$	11,5	11,6	230 (227...228)	1682, 1696, 1753	1615	245 (17,2)	82
IIIb	$C_{22}H_{21}N_3O_3$	11,3	11,2	206...207	1681, 1754	1612	256 (18,9)	74
IIIc	$C_{22}H_{21}N_3O_4$	10,6	10,7	259...260 (259)	1694, 1768	1615	262 (19,2)	67
IIId	$C_{21}H_{18}N_4O_5$	13,7	13,8	251...252	1635, 1701	1600	250 (17,3), 330 (14,8)	91
IIIe	$C_{22}H_{21}N_3O_3$	11,3	11,2	236...237	1675, 1754	1614	243 (15,5)	65
IIIf	$C_{22}H_{21}N_3O_4$	10,8	10,7	268...269 (225)	1681, 1714	1618	240 (13,8)	77
IIIg	$C_{21}H_{18}BrN_3O_3$	9,6	9,5	249...250 (245)	1681, 1735	1612	244 (20,8)	82
IIIh	$C_{21}H_{18}N_4O_5$	13,7	13,8	256...257	1681, 1702	1615	247 (12,2), 274 (15,0)	63

TABLE 2. PMR Spectra of the Compounds IIIa, b, d-h

Compound	Chemical shifts of protons, δ, ppm							SSCC, J, Hz		
	CH_3	CH_3	H_X	H_A	H_B	H_{Ar}	δ of group	AB	AX	BX
IIIa	2,56	3,21	4,03	3,58	3,50	7,13...8,00	—	-16,5	8,71	9,2
IIIb	2,58	3,21	3,98	3,59	3,51	7,00...7,99	2,27	-16,2	8,7	9,2
IIId	3,16	3,47	5,35	3,93	2,92	7,10...8,09	—	-14,6	5,2	5,7
IIIe	2,57	3,22	4,02	3,55	3,48	7,12...7,88	2,39	-16,8	8,8	9,0
IIIf	2,58	3,26	3,92	3,52	3,29	6,84...7,99	3,72	-16,3	8,7	8,8
IIIg	2,63	3,22	4,06	3,64	3,52	7,12...8,02	—	-17,0	8,5	9,1
IIIh	3,22	3,56	5,54	3,56	3,14	7,10...8,02	—	-14,9	5,4	5,8

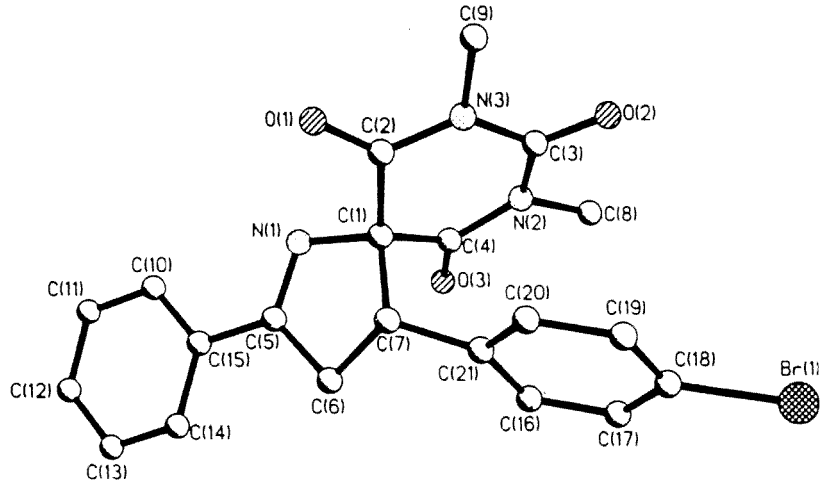
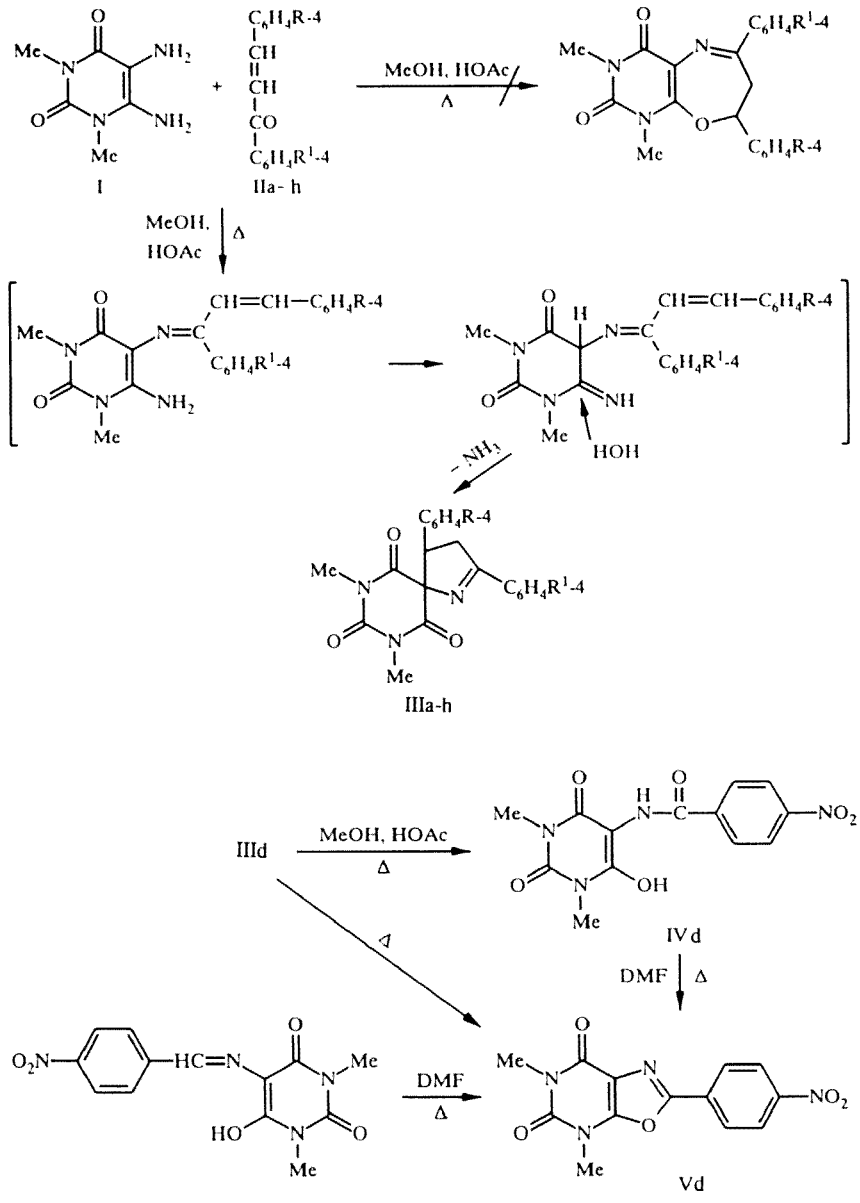


Fig. 1. Molecular structure of compound IIIg.



II, IIIa—d R = H, a R^1 = H, b R^1 = Me, c R^1 = OMe, d R^1 = NO_2; II, IIIe-h R^1 = H, e R = Me, f R = OMe, g R = Br, h R = NO_2

The formation of the spiro-products IIIa-h can be represented as follows. The amino group in position 5 of the diamine I is more nucleophilic, and azomethines are readily formed precisely at it [4], whereas the amino group in position 6 of this diamine can participate in imine-amine tautomerism. Hydrolysis of the imino group, followed by heterocyclization, leads to the formation of spiro-compounds IIIa-h.

The spiro-compounds IIIa-h are not thermodynamically stable. This is manifested especially in the case of the product IIId, heating of which in alcohol in the presence of catalytic amounts of acetic acid leads to compound IVd, identified as the N-(1,3-dimethylbarbituryl)amide of p-nitrobenzoic acid. In the IR spectrum of this compound, bands of the secondary amino group, as well as bands of symmetrical and asymmetrical vibrations of the nitro group, distinctly appear.

The formation of compound IVd occurs as a result of the splitting out of a molecule of styrene from substance IIId, and not of acetophenone, as might have been assumed. To prove this fact we investigated the reaction solution by gas-liquid chromatography. In a quantitative analysis using a method of normalization it was determined that the ratio of styrene and acetophenone is 98:2.

TABLE 3. Coordinates of the Atoms ($\times 10^4$) in Compound IIIg

Atom	x	y	z
Br(1)	3344(1)	8418(1)	5198(1)
O(1)	1558(6)	15755(5)	372(4)
O(2)	4919(6)	13464(5)	2898(4)
O(3)	5596(6)	11818(5)	-56(4)
N(1)	3011(6)	13868(5)	-878(4)
N(2)	5353(6)	12691(5)	1390(4)
N(3)	3239(6)	14634(5)	1645(4)
C(1)	3058(8)	13424(7)	282(5)
C(2)	2552(8)	14744(7)	742(5)
C(3)	4487(8)	13583(7)	2046(5)
C(4)	4792(8)	12599(7)	499(5)
C(5)	2245(8)	12944(7)	-1098(4)
C(6)	1601(9)	11755(7)	-146(5)
C(7)	1634(8)	12347(6)	805(4)
C(8)	6861(9)	11716(7)	1744(6)
C(9)	2544(9)	15750(8)	2246(6)
C(10)	2629(10)	14200(8)	-3055(5)
C(11)	2474(12)	14306(9)	-4113(6)
C(12)	1767(11)	13229(10)	-4312(6)
C(13)	1232(9)	12088(8)	-3493(6)
C(14)	1378(9)	11991(7)	-2447(5)
C(15)	2088(8)	13063(7)	-2220(5)
C(16)	2999(9)	9978(7)	1956(5)
C(17)	3394(9)	9143(7)	2935(5)
C(18)	2716(9)	9552(7)	3871(5)
C(19)	1585(8)	10807(7)	3815(5)
C(20)	1187(8)	11662(7)	2821(5)
C(21)	1933(8)	11287(7)	1861(5)

TABLE 4. Bond Lengths in Compound IIIg

Bond	Length, Å	Bond	Length, Å
Br(1)—C(18)	1,888(6)	O(1)—C(2)	1,205(7)
O(2)—C(3)	1,211(9)	O(3)—C(4)	1,227(8)
N(1)—C(5)	1,301(9)	N(1)—C(1)	1,469(8)
N(2)—C(3)	1,410(9)	N(2)—C(4)	1,376(9)
N(2)—C(8)	1,472(8)	N(3)—C(2)	1,383(9)
N(3)—C(3)	1,371(8)	N(3)—C(9)	1,500(9)
C(2)—C(1)	1,54(1)	C(4)—C(1)	1,524(8)
C(5)—C(6)	1,507(8)	C(5)—C(15)	1,483(9)
C(6)—C(7)	1,54(1)	C(7)—C(1)	1,600(9)
C(7)—C(21)	1,505(7)	C(10)—C(11)	1,40(1)
C(10)—C(15)	1,371(8)	C(11)—C(12)	1,39(2)
C(12)—C(13)	1,36(1)	C(13)—C(14)	1,38(1)
C(14)—C(15)	1,40(1)	C(21)—C(16)	1,396(9)
C(21)—C(20)	1,413(9)	C(16)—C(17)	1,373(8)
C(20)—C(19)	1,396(8)	C(17)—C(18)	1,39(1)

Boiling the product IVd in DMFA leads to the formation of 5,7-dimethyl-2-(4-nitrophenyl)-4,6-dioxopyrimido[4,5-d]oxazole (Vd), identified with the aid of the IR and PMR spectra. Thus, two singlets of the methyl groups with chemical shifts 3.22 and 3.45 ppm, respectively, as well as a singlet of the aromatic protons in the region of 8.27 ppm, equal in intensity to the four protons, appear in the PMR spectrum of compound Vd.

Compound Vd proved identical with the products obtained in cyclization of 5-(4-nitrobenzylidenamino)-1,3-dimethylbarbituric acid in DMFA [5]. Transformation to the pyrimido[4,5-d]oxazole Vd is also observed in the thermolysis of the spiro-product IIId, apparently also accompanied by splitting out of a styrene molecule.

TABLE 5. Bond Angles (deg) in Compound IIIg

Angle	ω	Angle	ω
C(5)—N(1)—C(1)	108,4(5)	C(3)—N(2)—C(4)	123,8(5)
C(3)—N(2)—C(8)	117,2(6)	C(4)—N(2)—C(8)	118,7(5)
C(2)—N(3)—C(3)	125,7(6)	C(2)—N(3)—C(9)	117,2(5)
C(3)—N(3)—C(9)	117,1(6)	O(1)—C(2)—N(3)	123,0(6)
O(1)—C(2)—C(1)	121,9(6)	N(3)—C(2)—C(1)	115,0(5)
O(2)—C(3)—N(2)	120,2(5)	O(2)—C(3)—N(3)	122,4(6)
N(2)—C(3)—N(3)	117,2(6)	O(3)—C(4)—N(2)	121,6(6)
O(3)—C(4)—C(1)	121,5(7)	N(2)—C(4)—C(1)	116,7(5)
N(1)—C(5)—C(6)	115,3(6)	N(1)—C(5)—C(15)	120,9(5)
C(6)—C(5)—C(15)	123,7(6)	C(5)—C(6)—C(7)	102,5(6)
C(6)—C(7)—C(1)	100,4(4)	C(6)—C(7)—C(21)	118,6(5)
C(1)—C(7)—C(21)	114,4(5)	C(11)—C(10)—C(15)	121,3(8)
C(10)—C(11)—C(12)	118,9(7)	C(11)—C(12)—C(13)	120,6(8)
C(12)—C(13)—C(14)	120,3(8)	C(13)—C(14)—C(15)	120,4(6)
C(5)—C(15)—C(10)	121,6(7)	C(5)—C(15)—C(14)	119,9(5)
C(10)—C(15)—C(14)	118,5(7)	N(1)—C(1)—C(2)	110,3(4)
N(1)—C(1)—C(4)	109,9(5)	C(2)—C(1)—C(4)	113,9(6)
N(1)—C(1)—C(7)	105,6(5)	C(2)—C(1)—C(7)	108,0(4)
C(4)—C(1)—C(7)	108,9(5)	C(7)—C(21)—C(16)	123,9(5)
C(7)—C(21)—C(20)	118,8(5)	C(16)—C(21)—C(20)	117,1(5)
C(21)—C(16)—C(17)	121,2(6)	C(21)—C(20)—C(19)	121,4(5)
C(16)—C(17)—C(18)	121,3(6)	Br(1)—C(18)—C(17)	120,4(5)
Br(1)—C(18)—C(19)	120,5(5)	C(17)—C(18)—C(19)	119,1(5)
C(20)—C(19)—C(18)	119,7(6)		

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer in tablets of KBr; the electronic absorption spectra were taken on a Specord M-40 instrument in isopropyl alcohol in chloroform at concentrations of the substances $1\text{-}5\cdot10^{-5}$ M; the PMR spectra were taken on a Bruker AC-200 MHz instrument in DMSO-D_6, with TMS as the internal standard. The purity of the compounds obtained was monitored by thin-layer chromatography on Silufol UV-254 plates, with the solvent chloroform.

Compounds IIIa-h were produced according to the procedure of [3].

X-Ray Crystallographic Investigation. Crystals of compound IIIg are triclinic. At 20°C a = 8.070(2) Å, b = 9.730(3) Å, c = 13.213(4) Å, α = 72.71(0)°, β = 78.38(0)°, γ = 80.09(0)°, V = 963.3(4) Å^3, d_{calc} = 1.518 g/cm^3, space group $P\bar{1}$, Z = 2. The parameters of the unit cell and the intensities of 1759 independent reflections with $F > 4\sigma(F)$ were measured on a Siemens P3/PC automatic four-circle diffractometer (MoK α radiation, graphite monochromator, $\theta/2\theta$ scanning, $2\theta_{max}$ = 45°). The structure was interpreted by a direct method using the SHELXTL PLUS software complex. The positions of the hydrogen atoms were detected from a differential synthesis of the electron density and were subsequently refined according to the "rider" model. Refinement defined according to the "rider" model. Refinement by full-matrix MNK in an anisotropic approximation for nonhydrogen atoms was performed up to R = 0.038 (R_w = 0.034, S = 1.47). The coordinates of the nonhydrogen atoms are presented in Table 3.

Gas-Liquid Chromatography. Measurements were performed on a Tsvet-550M series gas chromatograph with flame-ionization detector. The column was a glass spiral (length 3 cm, diameter 6 mm), filled with a sorbent — 5% SE-30 Interton-Super. The temperature of the column thermostat was 110°C. The temperature of the thermostats of the evaporator and detector was 210°C. The carrier gas was helium, and the gas velocity 30±1 ml/min. The chromatograms were recorded with a KXPU and were treated using the SAA-05-01 system of automatic analysis. The volume of the sample was 5 ml. The sample was introduced with an MSh-10 microsyringe.

N-(1,3-Dimethylbarbituryl)amide of p-Nitrobenzoic Acid (IVd). A 1.0 g portion of the spiro-compound IIId in 40 ml of methanol with an addition of 1-2 ml of acetic acid was boiled until the precipitate dissolved completely (approximately 1.5 h). The solvent was evaporated to half its volume. We obtained 0.5 g (70%) of yellow crystals of compound IVd with mp 211-212°C. IR spectrum: 3399 (NH), 1648, 1687 (CO), 1338, 1523 cm^{-1} (NO_2). Found, %: N 18.3. $C_{13}H_{12}N_4O_5$. Calculated, %: N 18.4.

2-(4-Nitrophenyl)-5,7-dimethyl-4,6-dioxopyrimido[4,5-d]oxazole (Vd). A 0.4 g portion of compound IVd was dissolved in 20 ml of DMFA and heated for 30 min. The mixture was cooled, and the product was precipitated with water. The light-yellow crystals that precipitated were recrystallized from methanol. We obtained 0.25 g (60%) of compound Vd with mp > 300°C. Lit.: mp > 300°C [5]. IR spectrum: 1662, 1722 (CO), 1602 (C=N), 1345, 1529 cm^{-1} (NO_2). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$, chloroform): 262 (14.0), 359 (18.1). PMR spectrum (DMSO-D_6): 3.22 (3H, s, CH_3), 3.45 (3H, s, CH_3), 8.27 ppm (4H, s, CH arom.). Found, %: N 18.6. $C_{13}H_{10}N_4O_5$. Calculated, %: N 18.5.

REFERENCES

1. Q. Q. Dang, R. C. Gaugolle, and T. R. Dang, Compt. Rend, **274**, 885 (1972).
2. V. D. Orlov and I. Z. Paniashvili, Khim. Geterotsikl. Soedin., No. 2, 241 (1985).
3. V. D. Orlov, I. Z. Paniashvili, and P. A. Grigorov, Khim. Geterotsiki. Soedin., No. 5, 671 (1983).
4. K. Senga, J. Sato, K. Shimizu, and S. Nishigaki, Heterocycles, **6**, No. 11, 1919 (1977).
5. K. Senga, J. Sato, and K. Shimizu, Chem. Pharm. Bull., **28**, No. 6, 1905 (1980).
6. P. M. Zorkii and Yu. V. Zefirov, Uspekhi Khim., **58**, No. 5, 713 (1989).