

OXIDATIVE COUPLING IN 4a,9-DIAZA-1,2,4a,9a-TETRAHYDROFLUORENE DERIVATIVES.

2.* SYNTHESIS OF METHYLENEQUINONEIMINES

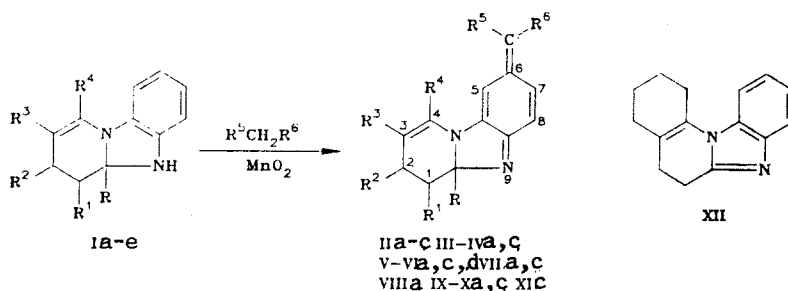
O. Yu. Slabko, L. V. Mezhennaya, V. A. Kaminskii,
and M. N. Tilichenko

UDC 547.833.3'781.5'678'
567.07:543.422.25

The oxidative coupling of 4a,9-diaza-1,2,4a,9a-tetrahydro-9H-fluorene derivatives with methylene-active compounds in the presence of MnO₂ leads to substituted (at the methylene group) 6-methylene-4a,9-diaza-1,2,4a,9a-tetrahydro-6H-fluorene derivatives. The corresponding 2,2-disubstituted 5-dicyanomethylene-3,5-dihydrobenzimidazoles were obtained in the reaction of 2,2-disubstituted benzimidazolines with malonitrile in the presence of MnO₂.

The most widely used methods for the synthesis of compounds containing a quinonemethide fragment are oxidation of p-substituted phenols [2, 3] and condensation of quinones with CH-active compounds [2-4]. The production of methylenequinoneimine structures in the reaction of malonitrile and cyanoacetic acid derivatives with quinoid compounds of the 2H-benzimidazole [5] and benzo[a]phenoxazin-9-one [6] series, which occurs via a process involving nucleophilic substitution, has been described. The formation of quinonemethide structures in the oxidative coupling of aromatic substrates with methylene-active compounds has not been described.

According to our data [1], 4a,9-diaza-1,2,4a,9a-tetrahydro-9H-fluorene derivatives readily undergo oxidative coupling with reagents that contain a primary amino group to give the corresponding quinonediimines. In the present communication we describe the reaction of diazahydrofluorenes Ia-e with a large number of CH-active compounds in the presence of MnO₂, as a result of which methylenequinoneimines – 6-methylene-4a,9-diaza-1,2,4a,9a-tetrahydro-6H-fluorene derivatives – are formed. Products of oxidative coupling of I with malonitrile (IIa-e), cyanoacetamide (IIIa, c, IVa, c), acetylacetone (Va, c, d), dibenzoylmethane (VIa, c, d), dimedone (VIIa, c), indan-1,3-dione (VIIIa), barbituric acid (IXa, c), and nitromethane (Xa, c, XIc) were obtained. The coupling of Ia, c with 5-nitrobarbituric acid is accompanied by elimination of a nitro group and leads to IXa, c. The synthesis of IIa, c, d has been previously cited in a brief report [7].



I—XI a R+R¹=R³+R⁴=(CH₂)₄, R²=H; b R+R¹=R³+R⁴=(CH₂)₄, R²=C₆H₅; c R+R¹=(CH₂)₄, R²=R⁴=C₆H₅, R³=H; d R=R²=R⁴=C₆H₅, R¹=R³=H; e R=(CH₃)₃C, R¹=H, R²=C₆H₅, R³+R⁴=(CH₂)₄; II R⁵=R⁶=CN; III R⁵=CONH₂, R⁶=CN; IV R⁵=CN, R⁶=CONH₂; V R⁵=R⁶=COCH₃; VI R⁵=R⁶=COC₆H₅; VII R⁵+R⁶=3,3-dimethylglutaryl; VIII R⁵+R⁶=phthalyl IX R⁵+R⁶=3-oxo-2,4-diazaglutaryl, X R⁵=NO₂, R⁶=H; XI R⁵=H, R⁶=NO₂

*See [1] for Communication 1.

TABLE 1. Data from the Electronic Spectra of II-XI and XIV

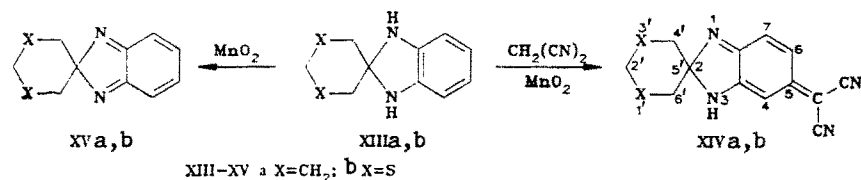
Compound	Electronic spectrum, λ_{\max} , nm (log ϵ)	Compound	Electronic spectrum, λ_{\max} , nm (log ϵ)	Compound	Electronic spectrum, λ_{\max} , nm (log ϵ)
IIa	590 (4,32)	Vc	530 (4,20)	IXa	626 (4,22)
IIb	584 (4,28)	Vd	500 (4,02)	IXc	636 (4,30)
IIc	560 (4,21)	VIa	602 (4,24)	Xa	633 (4,09)
II d	550 (4,26)	VIc	528 (4,16)	Xc	569 (4,29)
IIe	572 (4,14)	VI d	496 (4,14)	XIc	636 (3,97)
IIIa+IVa	593 (4,32)	VIIa	650 (4,30)	XIV a	522 (4,26)
IIIc+IVc	556 (4,22)	VIIc	609 (4,19)	XIV b	521 (4,34)
Va	586 (4,28)	VIIIa	678 (4,45)		

Oxidative coupling takes place readily at ordinary temperatures and proceeds selectively: the formation of small amounts of products of oxidation of I was noted only in individual cases. Only in the case of Ie the principal product of the reaction with malononitrile is benzimidazole derivative XII, which is formed by the readily occurring splitting out of the angular tert-butyl group [8]. The yields of methylenequinoneimines from Ia-d are usually rather high and are decreased only sometimes because of the low solubilities of the products and the difficulty involved in their separation from MnO_2 (IXa, c) or because of their decreased stabilities (Xa, c, XIc). In most cases we used inactivated MnO_2 ; the use of γ - MnO_2 sometimes (for example in the case of Ic, d) gives the best results. As in the synthesis of quinonediimines [1], the solvent has little effect on the course of the reaction, and its selection is determined primarily by considerations of the solubilities of the reagents and products.

Mixtures of Z (IIIa, c) and E (IVa, c) isomers (IIIa:IVa = 2:1, IIIc:IVc = 1:1) are formed in the oxidative coupling of Ia, c with cyanoacetamide. We were unable to separate the mixture of IIIa and IVa because of facile Z, E isomerization. Compound IVc is isolated from the mixture of isomers IIIc and IVc; this constitutes evidence for its greater configurational stability. The coupling of Ia with nitromethane initially gives only the Z isomer (Xa); a complex mixture of products is formed when the reaction is prolonged. The coupling of Ic with nitromethane leads to a mixture of stereoisomers Xc and XIc; Z isomer Xc predominates in the case of a brief reaction period, while E isomer XIc predominates when the reaction period is prolonged.

Judging from TLC, the oxidative coupling of Ia, c also takes place with acetoacetic and malonic esters, malonic acid diamide, 2-amino-4,6-dihydroxypyrimidine, and nitroethane; the reactions with 1,3-dithian-5-one, methylene iodide, and cyclohexane-1,2-dione proceed less selectively, and no reaction at all occurs with diphenylmethane, fluorene, methylenebisacrylamide, and bromoacetophenone – only products of oxidation of I are obtained in this case.

The reactions of malononitrile with dihydrobenzimidazole-2-spirocyclohexane (XIIIa) [9] and the previously undescribed dihydrobenzimidazole-2-spiro-5'-di-1',3'-thiane (XIIIb)* in the presence of MnO_2 lead to methylenequinoneimines – 5-dicyanomethylene-3,5-dihydrobenzimidazole derivatives XIVa, b. Compound XIVa was previously obtained [5] in the reaction of the corresponding 2H-benzimidazole XVa with malononitrile in the presence of MnO_2 (8 h, 30%). XIVa is formed directly from XIIIa faster and in better yield. In the case of XIIIb a 2H-benzimidazole derivative (XVb) was also isolated along with XIVb in the case of an insufficient excess amount of malononitrile.



A bathochromic shift of the absorption maximum in the visible region on passing from 2,4,9a-triphenyl derivatives (d) to 2,4-diphenyl-1-9a-tetramethylene derivatives (c) and then to an even greater degree on passing to 1,9a-3,4-bistetramethylene derivatives (a, b) (with the exception of the IXa and IXc pair) is characteristic for the electronic spectra of 6-methylenediazahydrofluorene derivatives (Table 1). This is probably associated with the different degrees of charge transfer from the donor $N_{(4a)}$

*Obtained by S. A. Shumakov from 1,3-dithian-5-one and o-phenylenediamine.

TABLE 2. Data from the PMR Spectra of II-XI

Com- pound	Chemical shift, ppm (SSCC, Hz)						other protons, s
	2-H	3-H, d	5-H	7-H	8-H, d (J = 10)	Ar-H, m	
IIb	3,40 t (10)	—	6,40 d (2)	7,44 dd (10; 2)	7,12	7,04 ... 7,36	—
IIe	3,51 d (9)	—	6,39 d (2)	7,42 dd (10; 2)	7,07	7,00 ... 7,34	—
IIIa	—*	—	7,92 d (2)	7,48 dd (10; 2)	7,06	—	—
IIIc	3,89 dd (10; 3,5)	5,55 (3,5)	6,78 d (2)	—**	7,10	7,20 ... 7,48	—
IVa	—	—	6,31 d (2)	8,91 dd (10; 2)	6,99	—	—
IVc	3,91 dd (10; 3,5)	5,55 (3,5)	5,23 d (2)	8,82 dd (10; 2)	7,03	7,20 ... 7,48	—
Va	—*	—	6,70 d (2)	7,41 dd (10; 2)	6,93	—	—
Vc	3,85 dd (10,5; 3,0)	5,45 (3,0)	4,91 d (2)	7,67 dd (10; 2)	6,95	7,20 ... 7,46	2,39 (6H, CH ₃)
Vd	3,38 qd (12; 5,7; 2,5)	5,50 (2,5)	5,13 d (2)	—**	6,90	7,15 ... 7,75	1,96 (3H, CH ₃); 2,23 (3H, CH ₃)
VIa	—*	—	6,68 d (2)	7,46 dd (10; 2)	6,92	7,25 ... 7,70	—
VIC	3,81 dd (10; 3,0)	5,32 (2,5)	4,81 d (2)	—**	6,87	7,10 ... 7,83	—
VId	3,33 qd (12; 5,7; 2,5)	5,38 (2,5)	4,95 d (2)	—**	6,79	7,10 ... 7,83	—
VIIa	—*	—	8,30 d (2)	8,18 dd (10; 2)	7,04	—	1,1 (6H, CH ₃)
VIIc	3,88 ⁺ dd (10; 3,5)	5,60 (3,5)	6,88 d ⁺ (1,8)	8,05 dd (10; 1,8)	7,07	7,18 ... 7,50	1,0 (6H, CH ₃)
VIIIa	—*	—	8,29 ⁺ s	9,15 d (10)	7,17	7,61 ... 7,78	—
IXa	—*	—	8,50s ⁺ ; 8,02 s	8,93 d (10)	7,30	—	—
IXc	4,08 dd (10; 3,0)	5,72 (3,0)	7,35 d (2)	8,88 dd (10; 2)	7,18	7,12 ... 7,50	—
Xa	—*	—	7,60 d (2)	6,73 dd (10; 2)	7,03	—	6,93 (C=CHNO ₂)
Xc	8,89 dd (10; 3,5)	5,55 (3,5)	6,36 d (2)	6,72 dd (10; 2)	7,03	7,20 ... 7,48	6,84 (C=CHNO ₂)
XIc	3,95 dd (10; 3,5)	5,70 (3,5)	5,80 d (2)	—	7,21	7,19 ... 7,53	6,44 (C=CHNO ₂)

*Overlapped by the signals of aliphatic protons.

**Overlapped by the signals of aromatic protons.

TABLE 3. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	Compound	Empirical formula	mp, °C
IIb	C ₂₈ H ₂₆ N ₄	220*	VIIa	C ₂₇ H ₃₂ N ₂ O ₂	200*
IIe	C ₂₈ H ₂₆ N ₄	138...140	VIIc	C ₃₅ H ₃₄ N ₂ O ₂	162...164
IIIa + IVa	C ₂₂ H ₂₄ N ₄ O	221...223	VIIa	C ₂₈ H ₂₆ N ₂ O ₂	192...194
IIIc	C ₃₀ H ₂₆ N ₄ O	248...250	IXa	C ₂₃ H ₂₄ N ₄ O ₃	400*
Va	C ₂₄ H ₂₆ N ₂ O ₂	121...122	IXc	C ₃₁ H ₂₆ N ₄ O ₃	400*
Vc	C ₃₂ H ₃₀ N ₂ O ₂	198...199	Xa	C ₂₆ H ₂₃ N ₃ O ₂	200*
Vd	C ₃₄ H ₂₈ N ₂ O ₂	157...158	Xc	C ₂₈ H ₂₅ N ₃ O ₂	202...204
VIa	C ₃₄ H ₃₂ N ₂ O ₂	171...172	XIc	C ₂₈ H ₂₅ N ₃ O ₂	232...234
VIc	C ₄₂ H ₃₄ N ₂ O ₂	201...202	XIIIb	C ₁₀ H ₁₂ N ₂ S ₂	158...159
VId	C ₄₄ H ₃₂ N ₂ O ₂	190...191	XIVb	C ₁₃ O ₁₆ N ₄ S ₂	212...214
			XVb	C ₁₀ H ₁₀ N ₂ S ₂	233...235

*Decomposes.

TABLE 4. Conditions of Synthesis and Yields of Methylenequinoneimines

Synthesized compound	Reagent: I, mole/mole	Solvent	Reaction time, h	Yield, %
IIa	2:1	Benzene	1,0	98
IIb	2,5:1	Benzene	1,0	89
IIc	2:1	Benzene	1,0	93
IId	2:1	Benzene*	1,0	76
IIe	2,5:1	Benzene	1,0	25
IIIa+IVa	2:1	Ethanol	1,5	97
IIIc+IVc	4:1	Acetone	1,0	99
Va	2,5:1	Benzene	2,0	93
Vc	3:1	Benzene*	1,0	75
Vd	3:1	Benzene	2,0	88
VIa	2:1	Benzene	1,5	95
VIc	2:1	Benzene	1,5	98
VId	3:1	Benzene	1,5	80
VIIa	1,5:1	Benzene	1,5	95
VIIc	2:1	Ethanol	1,0	71
VIIIa	1:1	Acetone	1,5	76
IXa	2:1	DMF**	1,0	46
IXc	2:1	DMF	1,5	49
Xa	7:1	Chloroform	0,08	55
Xc+XIc	6:1	Ether	0,08	48
Xc+XIc	20:1	Chloroform*	2,5	44
XIVa	1,5:1**	Chloroform*	1,0	67
XIVb	3:1**	Benzene	—	—

*Using γ -MnO₂.

**Malononitrile: XIII, mole/mole.

atom to the acceptor R⁵ and R⁶ groups; this difference is possibly due to the geometries of the molecules [1]. A significant bathochromic shift was noted on passing from Z-nitromethylenequinoneimine Xc to E isomer XIc. The absorption maxima of XIVa, b are shifted hypsochromically as compared with the absorption maxima of II; this is evidently explained by the presence in the latter of an enamine fragment conjugated with the quinoid structure.

The IR spectra of methylenequinoneimines II-XI contain absorption bands of enamine C(3)=C(4) bonds in the form of a band of medium intensity at 1636-1665 cm⁻¹, of a quinoid structure in the form of two and sometimes three bands of high intensity at 1550-1630 cm⁻¹, and of functional groups of a methylene fragment. The spectra of XIVa, b do not contain an absorption band of an enamine bond but do contain absorption bands of an NH group. The absorption bands of cyano groups are separated in the spectra of mineral oil suspensions of dicyanomethylene derivatives II and XIV (with the exception of IIa), while the cyano groups in the spectra of solutions give one band (a narrow singlet) at 2207-2220 cm⁻¹.

The most informative signals in the PMR spectra of the methylenequinoneimines (Table 2) coincide, in principle, with the signals of the analogous protons in the spectra of quinonediimines [1]. The character of the signals of the quinoid 5-H, 7-H, and 8-H protons in the spectra of II-XI confirms the p-quinoid structure of these compounds. A significant weak-field shift of the signals of the 5-H and 7-H protons, which are syn-oriented with respect to the CO groups of the cyclic dicarbonyl fragment (VII-IX), the carboxamido group (III and IV), and the nitro group (X and XI), was noted; this is due to the deshielding effect of these groups. This makes it possible to establish the configurations of the stereoisomeric compounds (III and IV and X and XI), as well as the ratios of the isomers in their mixtures. The location of the signals of the 5-H proton in the spectra of the c and d compounds at stronger field than in the spectra of the remaining compounds is explained by shielding of this proton by the benzene ring bonded in the 4 position.

One's attention is directed to the difference in the spectral characteristics of the methylene fragment of some of the a compounds from the corresponding data for the analogous c and d compounds. In the PMR spectrum of Va the signals of the two CH₃ groups give one narrow singlet (6H), while in the spectra of Vc, d separate signals of two CH₃ groups (3H each) are observed; the ¹³C NMR spectrum of VIa contains only one signal of the carbon atom of a CO group at 195.4 ppm, while the spectrum of VIc contains two signals at 194.4 and 195.4 ppm. This makes it possible to assume that the C₍₆₎=C₍₁₀₎ bond order decreases in compounds a as a consequence of the greatest degree of charge transfer from the N_(4a) atom to the R⁵ and R⁶ groups, which leads to a decrease in the barrier to rotation about this bond and is responsible for the facile Z, E isomerization and averaging of the signals of the Z and E atoms in the NMR spectra. A smaller degree of charge transfer is proposed for compounds c and d [1], and this leads to the development of separated signals of the Z and E atoms. This is in agreement with the above-mentioned ease of interconversion of IIIa and IVa and with the possibility of isolation of IVc. A double set of signals of quinoid protons is observed in the PMR spectrum of IXa; this indicates the presence of two isomeric forms (in a ratio of 2:1). This may be associated with the existence of the barbituric fragment in both tricarbonyl and hydroxy carbonyl forms.

The PMR spectrum of XIVa coincides with the spectrum presented in [5]. The following signals are noted in the spectrum of XIVb: signals of the quinoid protons 4-H at 6.28 ppm (d, J = 2 Hz), 6-H at 7.42 ppm (dd, J = 9.5 and 2 Hz), and 7-H at 7.08 ppm (d, J = 9.5 Hz); a signal of the proton of an NH group at 7.95 ppm (narrow s); signals of protons of dithiane fragment 2'-H_{eq} at 4.07 ppm (d, J = 14 Hz), 2'-H_{ax} at 3.52 ppm (dt, J = 14 and 2 Hz), 4'-H_{eq} and 6'-H_{eq} at 3.56 ppm (2H, d, J = 14 Hz), 4'-H_{ax} and 6'-H_{ax} at 2.40 ppm (2H, dd, J = 14 and 2 Hz). In conformity with its symmetrical structure, the spectrum of isobenzimidazole XVb is much simpler: the signal of the 2'-H protons has the form of a singlet (2H) at 4.03 ppm, the 4'-H and 6'-H protons also give a singlet (4H) at 2.97 ppm, and the o-quinoid protons give two multiplets (2H each) at 7.07 and 7.26 ppm.

The molecular masses of the synthesized compounds determined by mass spectrometry (with the exception of IXa, b, the mass spectra of which could not be recorded because of their nonvolatility) were in agreement with the calculated values.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform and suspensions in mineral oil were recorded with a Specord IR-75 spectrometer. The electronic spectra of solutions in DMF (for IXa, c) and in chloroform (for the remaining compounds) were obtained with a Perkin-Elmer-555 spectrophotometer. The NMR spectra of solutions in deuteriochloroform and d₆-DMSO were recorded with a Bruker WM-250 spectrometer. The mass spectra were obtained with an LKB-9000 spectrometer at an ionization energy of 70 eV by direct introduction of the samples into the ion source. The course of the reactions and the purity of the products obtained were monitored by TLC on Silufol plates.

The characteristics of the remaining synthesized compounds are presented in Table 3. The results of elementary analysis of II-XV for C, H, and N were in agreement with the calculated values.

9a-R-1-R¹-2-R²-3-R³-4-R⁴-6-(R⁵, R⁶-Methylene)-4a-9-diaza-1,2,4a,9a,tetrahydro-6H-fluorenes (II-XI). The conditions used to carry out the reactions are presented in Table 4. A 10- to 15-fold excess of MnO₂ was added with stirring to a solution of the corresponding I and the methylene-active compound (15-30 ml of the solvent per 0.5 g of I), after which the mixture was stirred at room temperature until the spot of the starting I vanished on the thin-layer chromatogram. The MnO₂ was removed by filtration and washed until the filtrate was almost colorless (in the synthesis of III and IV the MnO₂ was washed with DMF, while in the remaining cases it was washed with the solvent in which the reaction was carried out). In the synthesis of Xa, c separation of the MnO₂ must be carried out rapidly after completion of the reaction. In the synthesis of IIe, III, and IV the combined filtrate was poured into water, whereas in the synthesis of IXc it was poured into 0.5% HCl, and the precipitated products were removed by filtration. In the remaining cases the solvent was removed from the combined filtrate by distillation at ordinary (in the case of IIa-d) or reduced (in the case of V-VIII and IXa)

pressure or by evaporation at room temperature (in the case of X and XI). Compound VIIIa was purified by column chromatography on silica gel (5/40) by elution with chloroform; the isolation of Xa and the separation of Xc and XIc and IIe and XII were carried out by preparative TLC on activity II Al_2O_3 in a hexane-ethyl acetate system. Compound IIIc was isolated by preparative TLC on silica gel (5/40) in a hexane-ethyl acetate system; the solutions obtained in the chromatographic isolation of IIe, Xa, c, and XIc were evaporated at room temperature. In the remaining compounds from benzene-hexane. The methylenequinoneimines obtained were crystalline compounds, most of which were soluble in chloroform and acetone, somewhat less soluble in ethanol, and only slightly soluble in hexane; IXa, c were quite soluble only in DMF and DMSO. Compounds IIe, Xa, c, and XIc decomposed in solutions at 40°C. Compound XII was identical to a genuine sample [8].

Dihydrobenzimidazole-2-spiro-5'-di-1',3'-thiane (XIIIb). A hot solution of 2.8 g (26 mmoles) of o-phenylenediamine in 30 ml of ethanol was added to a hot solution of 3.6 g (30 mmoles) of 1,3-dithian-5-one in 30 ml of ethanol, after which the mixture was cooled to precipitate acicular crystals; after 2 h, they were removed by filtration, washed with ethanol, and dried. The yield was 4.4 g (76%).

2,2-Disubstituted 5-Dicyanomethylene-3,5-dihydrobenzimidazoles (XIVa, b) and 2H-Benzimidazole-2-spiro-5'-di-1',3'-thiane (XVb). The oxidative coupling of XIIIa, b with malononitrile was carried out as described above for I (see Table 4). After removal of the MnO_2 by filtration and washing, the solvent was removed from the combined filtrate by distillation, and the residue was recrystallized from benzene (in the case of XIVa) or ethanol-DMF (in the case of XIVb). According to the IR and PMR spectral data, XIVa was identical to the previously described compound [5]; the product had mp 220°C (with sublimation) (mp 210°C [5]). In the reaction of XIIIb with a smaller excess of malononitrile (malononitrile:XIIIb molar ratio = 1.3:1) in the presence of MnO_2 in acetone, after separation of the MnO_2 , the reaction products were washed initially with acetone until the wash solution was slightly colored, and then with chloroform. The acetone wash solution contained primarily XIVb, while the chloroform solution contained primarily XVb. The chloroform was removed by distillation, and the residue was recrystallized from benzene-hexane; XVb was isolated in 19% yield.

Compounds IIa, c, d were previously described in [7].

LITERATURE CITED

1. O. Yu. Slabko, V. A. Kaminskii, and M. N. Tilichenko, *Khim. Geterotsikl. Soedin.*, No. 11, 1500 (1989).
2. S. Patai (ed.), *The Chemistry of the Quinonoid Compounds*, London-New York (1974), p. 1145.
3. A. A. Volod'kin and V. V. Ershov, *Usp. Khim.* **57**, 595 (1988).
4. Y. Yamashita, T. Suzuki, G. Saito, and T. Mukai, *Techn. Rep. ISSP, A, N 1657* (1986); *Ref. Zh. Khim.*, 7Zh74 (1987).
5. K. E. Davies, G. E. Domany, M. Farhat, J. A. Herbert, A. M. Jefferson, M. A. Gutierrez, and H. Sushitzky, *J. Chem. Soc., Perkin 1*, No. 11, 2465 (1984).
6. V. I. Vysokov, G. B. Afanas'eva, and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.*, No. 4, 538 (1988).
7. V. A. Kaminskii, O. Yu. Slabko, S. É. Kraeva, and M. N. Tilichenko, *Zh. Org. Khim.* **24**, 228 (1988).
8. V. A. Kaminskii, T. V. Zabolotnova, T. V. Novikova, and M. N. Tilichenko, *Zh. Org. Khim.* **17**, 670 (1981).
9. H. A. Staab and F. Vögtle, *Chem. Ber.* **98**, 2681 (1965).