HETEROCYCLIC ENAMIDES — DERIVATIVES OF IMIDAZOLIDINE NITROSYL RADICALS: REACTIONS WITH NUCLEOPHILIC AND ELECTROPHILIC REAGENTS

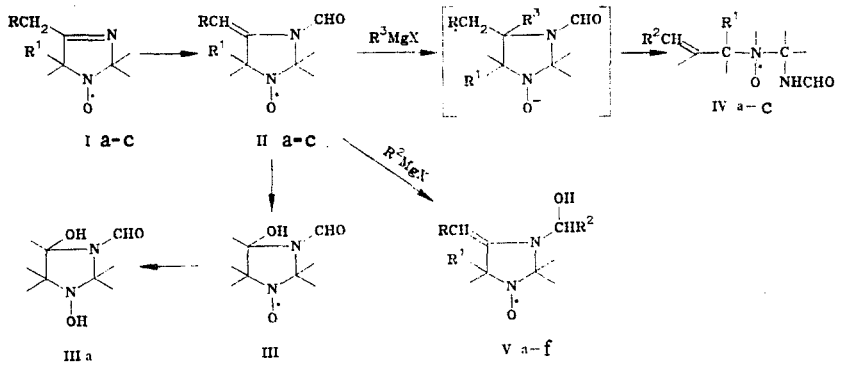
V. A. Reznikov, L. A. Vishnivetskaya, and L. B. Bolodarskii

UDC 547.781.3:541.515

The reactions of the heterocyclic enamides — 4-alkyliden-2,2,5,5-tetraalkyl-3-formylimidazolidin-1-oxyls — with organomagnesium and organolithium compounds takes place at two reaction centers — the N-formyl group and the C=C endocyclic carbon atom — to give three types of product: 3-imidazoline derivatives, substituted formyl derivatives, or acyclic nitroxyl radicals. Enamides with $POCl_3$ in DMF gives products of electrophilic substitution at the exocyclic methylene group with retention of the N-formyl.

The reaction of the 4-alkyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyls I with $POCl_3$ and DMF under conditions of the Vilsmeier reaction has been shown to give the enamides II [1]. Compounds containing the enamide group readily undergo photocyclization [2]. However, the reactivity of these compounds in the non-excited state has received very little attention, apart from reports on their bromination [3, 4], hydrogenation [5], and hydrolytic cleavage [6]. In the present work we have studied the reaction of the enamides II in the unexcited state with nucleophilic and electrophilic reagents.

Formylation of compounds Ia, followed by chromatographic separation of the reaction mixture on silica gel gave, in addition to the expected IIa, compound III; this was found to be the product of the addition of a molecule of water to the C=C bond of IIa (see [6]). The structure of compound III was confirmed from the PMR spectra of its diamagnetic analog IIIa, obtained by the reduction of the oxyl III with zinc. The ease of hydration of compound IIa, which occurred with retention of the heterocyclic structure, encouraged us to study the reaction of these compounds with other nucleophilic agents — organometallic compounds. It was shown that the reaction with organomagnesium and organolithium compounds proceeds in three directions: to give derivatives of the imidazoline I, or to give a product of the addition of the organometallic reagent — IV or V. The formation of the imidazoline I was observed in all cases; the relative amounts of the addition products was dependent on the structure of the substrate and the nature of the reagent; in some cases a mixture of compounds IV and V was obtained, and in others only one of them was formed. The product of deformylation of I apparently is a result of the addition of the organometallic reagent to the C=O bond,



Ia, IIa, Va—c R=H, $R^1=CH_3$, Ib, IIb Vd,e R=$R^1=CH_3$, Ic, IIc Vf R+$R^1=(CH_2)_3$; Va $R^2=C_4H_9$, b,e $R^2=C_6H_5$, c $R^2=C_2H_5$, d,f $R^2=CH_3$, IVa,b $R^1=CH_3$; a R^2=H, b $R^2=C_3H_7$; c $R^1+R^2=(CH_2)_3$

Novosibirsk Institute for Organic Chemistry, Siberian Section of the Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 620-624, May, 1988. Original article submitted December 19, 1986; revision submitted April 27, 1987.

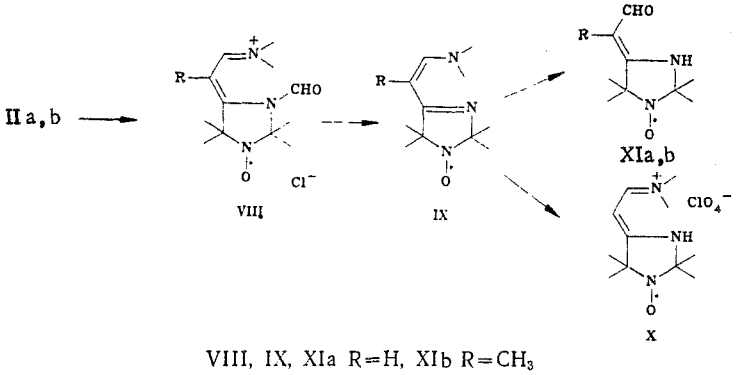
 0009-3122/88/2405-0504$12.50

followed by the heterolytic dissociation of the formamide group C=N bond. This is confirmed by the observation that the reaction of the enamide IIa and phenylmagnesium bromide gave a significant quantity of benzhydrol. The yield of the imidazolines I decreased on going from an organomagnesium to an organolithium reagent, while the yields of compounds IV and V correspondingly increased. The IR spectrum of compound IV contained bands corresponding to the amide group and the C=C bond at 1680-1710 cm^{-1}, an N–H bond vibration band at 3260 cm^{-1}, and a band due to the stretching vibration of the C=H olefin bond at 3010 cm^{-1}. In the PMR spectrum ($CDCl_3$) of the diamagnetic analog VIa, obtained by the reduction of compound IVa, was observed signals from the formamide group proton at 8.65 ppm and from the olefin protons at 4.74 ppm (2H). On the basis of these data, compound IV was assigned a structure corresponding to the product obtained from the opening of the imidazoline heterocyclic ring – an analog of di-tert-butylnitroxyl.

The IR spectrum of compound V contains an absorption band at 1640-1650 cm^{-1}, characteristic of vibrations of the C=C bond in enamines [7], and also a broad band at 3300-3600 cm^{-1} due to the vibration of the OH group. The PMR spectrum of the diamagnetic analog VIIe, obtained by the reduction of compound Ve, is very unusual – the anisotropic effect of the phenyl group gives rise to a signal from one of the methyl groups at position 2 of the heterocyclic ring at 0.43 ppm (3H), from the olefin proton at 2.57 ppm (1H, q, J = 7.5 Hz), and from the methyl group at the C=C bond at 1.31 ppm (3H, d, J = 7.5 Hz). In addition the spectrum contains singlets from the methyl group at 1.10, 1.25, and 1.32 ppm. Based on these data, compound V was assigned the structure 4-alkyliden-3-[1-hydroxyalkyl(phenyl)]-2,2,5,5-tetraalkylimidazolidine-1-oxyl. It should be noted that the reaction of the enamide IIb with phenyllithium gives two isomers (at the C=C bond) – compounds Ve and Ve*, which have different melting points and very similar IR spectra.

Thus in the reaction of the enamides II with organometallic compounds nucleophilic attack occurs either at the C=C bond (leading to opening of the heterocyclic ring), or at the C=O bond of the formyl group (leading either to the alcohol V, or to the imidazole I). It should be noted that in all cases the nitroxyl group in the enamide molecule was reduced by the organometallic reagent, following the oxidation of the reaction mixture with manganese dioxide, giving the paramagnetic product mentioned previously.

As noted earlier, the formyl group of the enamides II are readily cleaved by electrophilic reagents, among them protonic acids [3]. Splitting occurs probably owing to the formation of an unstable formylimine salt resulting from attack by an electrophilic agent. It is suggested that if electrophilic attack causes a proton to split off to give an enamide which is stabilized by conjugation, then the formyl group in the molecule is preserved. In order to study this possibility, the reaction of the enamides II with $POCl_3$ in DMF was investigated. It was shown that initially compound VIII is formed, and that in alkaline medium this loses a formyl group to give the enamine IX, which was separated, and characterized as the perchlorate X. The UV spectrum of compound X is similar to the spectra of compound VIII and enaminocarbonyl compounds of similar structure [8].



VIII, IX, XIa R=H, XIb R=CH_3

The enaminaldehyde XIa is formed when a solution of compound IX in aqueous 5% NaOH is allowed to stand (see [8]). Hydrolysis of the enamine group of compound IX also occurs when it is chromatographed on silica gel. Under analogous conditions, compound IIb is formylated to give the enaminaldehyde XIb.

Thus, the reaction of the enamide IIa with $POCl_3$ in DMF gives compound VIII; here the formyl group does not separate because of the formation of the enamine, which is conjugated with the imine group. This compound readily undergoes deformylation in aqueous-alkali solutions.

TABLE 1. Physicochemical Data for Compounds Synthesized

Compound	mp, °C*	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N (Cl)		C	H	N (Cl)	
IIc	80—82	63.1	8.4	13.0	$C_{11}H_{17}N_2O_2$	63.1	8.2	13.4	65
III	125—128	53.7	8.5	13.9	$C_9H_{17}N_2O_3$	53.8	8.5	13.9	5
IIIa	112—114	53.7	8.5	13.9	$C_9H_{18}N_2O_3$	53.5	8.9	13.9	75
IVa	87—88	59.9	9.3	13.9	$C_{10}H_{19}N_2O_2$	60.3	9.6	14.1	50
IVb	82—84	64.5	10.6	11.3	$C_{13}H_{25}N_2O_2$	64.7	10.4	11.6	30
IVc	90—92	63.9	9.5	12.3	$C_{12}H_{21}N_2O_2$	64.0	9.3	12.4	10
Va	oil	64.6	10.1	11.7	$C_{13}H_{25}N_2O_2$	64.7	10.4	11.6	30
Vb	68—69	68.7	8.0	10.7	$C_{15}H_{21}N_2O_2$	69.0	8.0	10.7	40
Vc	oil	62.2	9.6	12.8	$C_{11}H_{21}N_2O_2$	62.0	9.9	13.1	30
Vd	59—62	62.0	9.9	13.1	$C_{11}H_{21}N_2O_2$	62.0	9.9	13.1	60
Ve	83—85	69.5	8.4	9.9	$C_{16}H_{23}N_2O_2$	69.8	8.4	10.2	30
Ve*	119—121	69.5	8.4	10.0	$C_{16}H_{23}N_2O_2$	69.8	8.4	10.0	20
Vf	56—57	63.7	9.3	12.3	$C_{12}H_{21}N_2O_2$	64.0	9.3	12.4	20
VIa	93—95	59.9	9.6	13.6	$C_{10}H_{20}N_2O_2$	60.0	10.0	14.0	95
VIIb	160—162	68.6	8.2	10.4	$C_{15}H_{22}N_2O_2$	68.8	8.4	10.7	70
VIId	84—85	61.4	10.2	12.7	$C_{11}H_{22}N_2O_2$	61.7	10.3	13.1	90
VIIe	133—135	69.2	8.4	10.0	$C_{16}H_{24}N_2O_2$	69.5	8.7	10.1	90
VIII	195—196	52.3	8.0	15.7 (13.2)	$C_{12}H_{21}ClN_3O_2$	52.4	7.7	15.3 (12.9)	15
X	168—170	42.7	7.0	13.2 (11.0)	$C_{11}H_{21}ClN_3O_5$	42.5	6.8	13.5 (11.4)	10
XIb	130—131	61.2	8.8	14.4	$C_{10}H_{17}N_2O_2$	60.9	8.6	14.2	30

*Compounds II-V were recrystallized from hexane, VIIb, Ve, and XIb from a 1:3 mixture of ethyl acetate and hexane, VIII from acetonitrile, and X from alcohol.

TABLE 2. Spectral Data for Synthesized Compounds

Compound	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (lg ε)	Compound	IR spectrum, cm^{-1}		UV spectrum λ_{max}, nm (lg ε)
				C=C	C=N (C=O)	
IIc	1680 (C=O)	234 (4,09)	Va	1640		
III	1640—1670 (C=O), 3400 (OH)		Vb	1650		
IIIa	1660 (C=O)		Vc	1645		
IVa	1650, 1680, 1710 (C=O, C=C), 3340 (NH), 3010, 3020 (H—C=C)	232 (3,87)	Vd	1640		
			Ve	1640		
			Ve*	1640		
IVb	1640, 1670, 1695 (C=O, C=C), 3260 (NH), 3010 (H—C=C)	232 (3,82)	Vf	1645		
			VIIb	1650		
IVc	1665, 1680, 1695 (C=O, C=C), 3270 (NH), 3005, 3015 (H—C=C)		VIII	1610	1660	333 (4,57)
			X	1600	1650	330 (4,61)
			XIb	1580	1650	302 (4,50)

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (0.25% in KBr pellets and 5% in CCl_4 solution), UV spectra were taken in ethanol solution on a Specord UV-vis; PMR spectra were recorded on a Varian A-56-60A on solutions in $CDCl_3$. Chromatography was carried out on Chemapol silica gel. Data for the compounds synthesized are given in Tables 1 and 2.

1,2,3,5,6,7-Hexahydro-1-oxyl-2,2,7a-trimethyl-3-formylbenzimidazole (IIc) was obtained from the imidazoline Ic by the method described in [3] for the preparation of IIa.

4-Hydroxy-2,2,4,5,5-pentamethyl-3-formylimidazolidine-1-oxyl (III). The reaction mixture, obtained by the formylation of the imidazoline Ia by method [3], was chromatographed on a silica gel column (40/100), and eluted with chloroform to give first the enamide IIa (Yield 80%) and then compound III.

1,4-Dihydroxy-2,2,4,5,5-pentamethyl-3-formylimidazolidine (IIIa). To a solution of 1 mmole of III in 10 ml of methanol was added 1 g (15 mmole) of powdered zinc and 0.3 g (6 mmole) of NH_4Cl, the mixture stirred for 0.5 hours, and filtered. The filtrate was evaporated, the residue treated with 15 ml of water, and extracted with $CHCl_3$ (3 × 15 ml). The extract was dried over $MgSO_4$, the solvent removed, hexane added to the residue, and the precipitated diamagnetic derivative IIIa filtered off. PMR spectrum: five singlets from the methyl groups at 0.95 (3H), 0.98 (3H), 1.32 (3H), 1.37 ppm (6H), and protons from the two OH groups at 5.77 and 7.62 ppm.

The nitroxyl radicals IV and V were reduced in the same way.

Reaction of the Enamides II with Organometallic Reagents. To a solution of 40 mmole of the organometallic compound in 40 ml of absolute ether was added dropwise with mixing a solution of 10 mmole of the enamide II in absolute ether. In the case of the organolithium derivatives the reaction was carried out in an argon atmosphere. After mixing for 1 hour, the reaction mixture was decomposed with water, the organic layer separated, and the aqueous layer extracted with ether (4 × 15 ml). The extract was dried over $MgSO_4$, the drying agent filtered off, and to the solution was added 5 g (70 mmole) of MnO_2. After stirring for 2 hours at 20°C, the excess oxidizing agent was filtered off, and the solvent evaporated. The mixture obtained was separated by chromatography on a silica gel column (100/250 fraction), eluted with $CHCl_3$ or an ether–hexane mixture, and the colored band collected. First to come off the column was the starting enamide (~5%), followed by compounds IV, V, and the imidazoline I. The reaction of compound IIa with methylmagnesium iodide gave N-(2-aminoformylpropyl-2)-N-(2,3-dimethylbuten-1-yl-3)nitroxyl (IVa), with butylmagnesium bromide gave N-(2-aminoformylpropyl-2)-N-(2,3-dimethylhepten-3-yl-2)nitroxyl (IVb) and 4-methyliden-3-(1-hydroxypentyl)2,2,5,5-tetramethylimidazolidine-1-oxyl (Va), with phenyllithium gave 3-(1-hydroxybenzyl)-4-methyliden-2,2,5,5-tetramethylimidazolidine-1-oxyl (Vb), with ethylmagnesium bromide gave 3-(1-hydroxypropyl)-4-methyliden-2,2,5,5-tetramethylimidazolidine-1-oxyl (Vc). The reaction of the enamide IIb with methyllithium gave 3-(1-hydroxyethyl)-2,2,5,5-tetramethyl-4-ethylidenimidazolidine-1-oxyl (Vd), with phenyllithium gave two isomers of 3-(1-hydroxybenzyl)-2,2,5,5-tetramethyl-4-ethylidenimidazolidine-1-oxyl (Ve and Ve*). The reaction of the enamide IIc with methylmagnesium iodide gave N-(2-aminoformylpropyl-2)-N-(2,3-dimethylcyclohexen-1-yl-3)nitroxyl (IVc), and with methyllithium gave 3-(1-hydroxyethyl)-1,2,3,5,6,7-hexahydro-2,2,7a-trimethyl-1-hydroxybenzimidazole (Vf).

Chloride of 4-(2-N,N-Dimethyliminethyliden)-2,2,5,5-tetramethyl-3-formylimidazolidine-1-oxyl (VIII). Dry DMF (3 ml, 40 mmole) was cooled to 0°C and 0.84 ml (9.3 mmole) of $POCl_3$ added dropwise with stirring. After stirring for a further 0.25 hour, the solution was again cooled to 0°C and a solution of 1 g (5.5 mmole) of the enamide IIa in 3 ml of DMF was added dropwise. The cooling was discontinued and stirring continued for 1 hour at 20°C. The reaction mixture was diluted with 100 ml of $CHCl_3$, and washed with 5% $NaHCO_3$ solution. To the aqueous solution was added a further 50 ml of $CHCl_3$ and 5 g of dry $NaHCO_3$. The mixture was shaken and the organic layer separated. The combined extracts were dried over $MgSO_4$ for 0.25 hours and the solvent then distilled off. The residue was treated with ethyl acetate, and the precipitated compound VIII filtered off. Chromatographic separation of the filtrate gave 0.5 g of enaminoaldehyde XIa.

Perchlorate of 4-(2-N,N-Dimethyliminethyliden)-2,2,5,5-tetramethylimidazolidine-1-oxyl (X) and 4-(2-Oxoethyliden)-2,2,5,5-tetramethylimidazolidine-1-oxyl (XIa). The reaction described above, was carried out using 1.83 g (10 mmole) of the enamide IIa with 1.5 ml (16.5 mmole) of $POCl_3$ and 7 ml of DMF. At the end of the reaction, the reaction mixture was poured into a mixture of ice and 10% NaOH (30 ml), and extracted with $CHCl_3$ (3 × 25 ml). The extract was washed with water, dried with $MgSO_4$ and evaporated. The mixture of compounds was separated by chromatography on silica gel (150 ml, 40/100, eluent – $CHCl_3$), which gave successively 0.3 g of the starting enamide IIa, 0.9 g of the enaminoaldehyde XIa and 0.2 g of the enamine IX. The latter was dissolved in 1 ml of ethanol and 2-3 drops of 57% $HClO_4$ solution added. The precipitated perchlorate X was filtered off, and washed with dry ether.

When the reaction mixture was allowed to stand on the column for 12 hours, compound IX could not be isolated; instead, 0.3 g of the starting enamide IIa and 1 g of the enaminoaldehyde XIa were obtained.

2,2,5,5-Tetramethyl-4-(1-formyliden-1)imidazolidine-1-oxyl (XIb) was obtained in the same way as compound XIa, from 1 g (5.1 mmole) of the enamide IIb, 2.4 ml (26 mmole) of $POCl_3$ and 12 ml of DMF. The reaction mixture was kept at 20°C for 48 hours, poured into a mixture of 50 g of ice and 20 ml of 10% NaOH, and extracted with $CHCl_3$ (3 × 25 ml). The extract was dried with $MgSO_4$ and evaporated to dryness. The residue was dissolved in $CHCl_3$, transferred to a silica gel column (150 ml, 40/100), and kept for 12 hours, then eluted with $CHCl_3$ to give compound XIb.

LITERATURE CITED

1. V. A. Reznikov and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1437 (1982).

2. G. R. Lenz, Synthesis, No. 7, 489 (1978).
3. B. A. Reznikov and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 11, 2565 (1984).
4. H. Böhme and G. Berg, Berichte, 99, 2127 (1966).
5. R. B. Ainscow, R. B. Brettle, and S. M. Shibib, J. Chem. Soc., Perkin Trans. 1, No. 8, 1781 (1985).
6. V. M. Csizmadia, K. M. Koshy, K. C. M. Lau, R. A. McClelland, V. J. Nowlan, and T. T. Tidwell, J. Am. Chem. Soc., 101, 974 (1979).
7. Enamines: Synthesis, Structure, and Reactions, ed. A. G. Cook, Dekker, New York–London (1969), p. 38.
8. V. A. Reznikov, T. I. Reznikova, and L. B. Volodarskii, Zh. Org. Khim., 78, 2135 (1982).

STUDIES ON THE SERIES OF AZOLES AND AZINES.

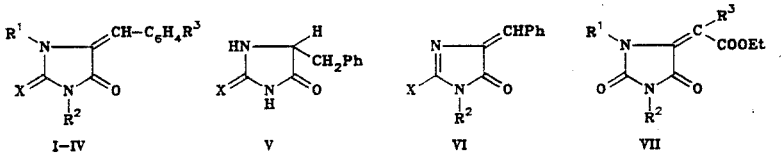
65.* MASS SPECTRA OF 5-ARYLIDENE-, 5-ETHOXYCARBONYLMETHYLENE-HYDANTOINS AND THEIR DERIVATIVES

V. S. Mirzoryan, R. G. Melik-Ogandzhanyan, T. N. Rusavskaya, G. V. Rutkovskii, and B. A. Ivin

UDC 543.51:547.783.07

The mass spectra of 5-m- and p-substituted benzylidenehydantoins, their thio analogs and 5-carbethoxymethylenehydantoins with a substituent at the α-carbon atom of the side chain were studied. The fragmentation of the molecular ions of 5-arylidenehydantoins proceeds in one direction, splitting of the X=C–NR–C=O fragment, irrespective of the substituent in the benzene ring. The peak intensity of the fragmentary ions formed from the molecular ions is linearly dependent on the σ-constants of the substituent. The direction of the fragmentation of 5-ethoxycarbonylmethylenehydantoins markedly depends on the substituent at the α-carbon atom in the side chain that determines the stability of the hydantoin ring and the carboethoxyl group. The fragmentation of these compounds under electron impact proceeds by five paths, related to splitting of fragments $O=C_{(2)}NCH_{(4)}=O$, C_2H_4, C_2H_5O, C_2H_5OH, and $COOC_2H_5$.

The mass spectra of hydantoins, their aryl, alkyl, and thio derivatives were fairly thoroughly investigated in [2-4]. Depending on the nature of the substituent, the fragmentation of these compounds under electron impact can proceed by three paths: with the splitting of the fragments $X=C_{(2)}N_{(3)}RC_{(4)}=O$ (X = O, S), NHCO or CO, respectively. Data on the



I–IV V VI VII

I, III, Va X=O, II, IV, Vb X=S, VIa,b X=MeS; I, II $R^1=R^2=H$; a $R^2=4\text{-}NO_2$; b R^3=3-Br; c R^3=3-Cl; d R^3=3-COOH; e R^3=4-Br; f R^3=4-Cl; g R^3=4-I; h R^3=3-OH; i R^3=2-OMe; j $R^3=H$; k R^3=4-Me; l R^3=4-OMe; m R^3=3-OMe–4-OH; n R^3=3-OMe; o $R^3=4\text{-}NEt_2$; III, IV a R^1=Me, $R^2=R^3=H$; b $R^1=R^3=H$, R^2=Me; VI a $R^2=H$; b R^2=Me; VII a-i $R^1=R^2=H$, a $R^3=NO_2$; b R^3=Cl; c R^3=F; d $R^3=H$; e R^3=Ph; f R^3=Me; g R^2=OMe; h R^2=OPh; i R^3=OH; j $R^2=R^3=H$, R^1=Me; k $R^1=R^3=H$, R^2=Me; l $R^1=H$, R^2=Me, R^3=Ph; m $R^1=R^2$=Me, R^3=OPh

*See [1] for Communication 64.

A. L. Mndzhoyan Academy of the Armenian SSR, Erevan 375014. Leningrad Chemical Pharmaceutical Institute, Leningrad, 197022. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 625-631, May, 1988. Original article submitted April 2, 1986; revision submitted October 8, 1987.

 0009-3122/88/2405-0508$12.50