STUDY OF STRUCTURE AND REACTIVITY OF SPIROBI-2(5*H*)-FURANONES*

Maria JAKUBCOVA[a], Daniel VEGH[a,**], Jan LESKO[b] and Vladimir MASTIHUBA[c]

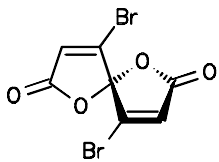
[a] *Department of Organic Chemistry, Slovak Technical University, 812 37 Bratislava, Slovak Republic*
[b] *Central Laboratories, Slovak Technical University, 812 37 Bratislava, Slovak Republic*
[c] *Department of Milk, Fats and Food Hygiene, Slovak Technical University, 812 37 Bratislava, Slovak Republic*

Received March 3, 1995
Accepted September 15, 1995

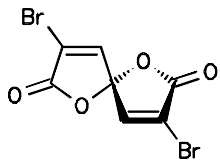
Reactions of 4,9-dibromo-1,6-dioxaspiro[4.4]nona-3,8-dien-2,7-dione (*I*) and 3,7-dibromo-1,6-dioxaspiro[4.4]nona-3,8-dien-2,7-dione (*II*) with nucleophiles yielding spirolactones *IIIa–IIIg* are described. The ring opening reactions of spirobilactones are discussed.

Spiroketals are important subunits of a growing variety of naturally occurring compounds of considerable importance and interest[1–3]. Halogenated 2(5*H*)-furanones have been studied extensively in the recent past, both as target compounds and as synthetic intermediates[4–6].

Recently[7] we published a new method for preparation of two halogenated spirobi-2(5*H*)-furanones: 4,9-dibromo-1,6-dioxaspiro[4.4]nona-3,8-dien-2,7-dione (*I*) and 3,7-



I



II

dibromo-1,6-dioxaspiro[4.4]nona-3,8-dien-2,7-dione (*II*). The structure of the compound *I* was confirmed by X-ray analysis[8]. Isomers *I* and *II* were distinguishable based

* Taken in part from the Ph.D. Thesis of M. J.

** The author to whom correspondence should be addressed.

on their EI mass spectra (Fig. 1); basic pathways of fragmentation of molecular ion of *II* are represented in Scheme 1. In contrast to mass spectrum of *II*, that of isomer *I* does not show fragments $[M - CO_2]^{+\bullet}$ with *m/z* 264* and $[M - CO_2 - CO]^{+\bullet}$ with *m/z* 236, but does show fragment *m/z* 240, not present in the spectrum of the compound *II*. The formation of fragment *m/z* 240 from $M^{+\bullet}$ confirms the existence of metastable transition involving the release of fragment with 68 mass units. This fragment, containing two bromine atoms, could have been created by rearrangement only.

Spirobilactones *I* and *II* differ in their reactivity towards nucleophiles. While *I* belongs to reactive compounds in nucleophilic substitution reactions, spirolactone *II* is not reactive under usual S_N reaction conditions. The only successful reaction of this skeleton was the opening of spirolactone ring resulting in the creation of 2,6-dibromo-4-oxo-2,5-heptadiendioic acid derivatives. However, our attempts to prepare mono- or

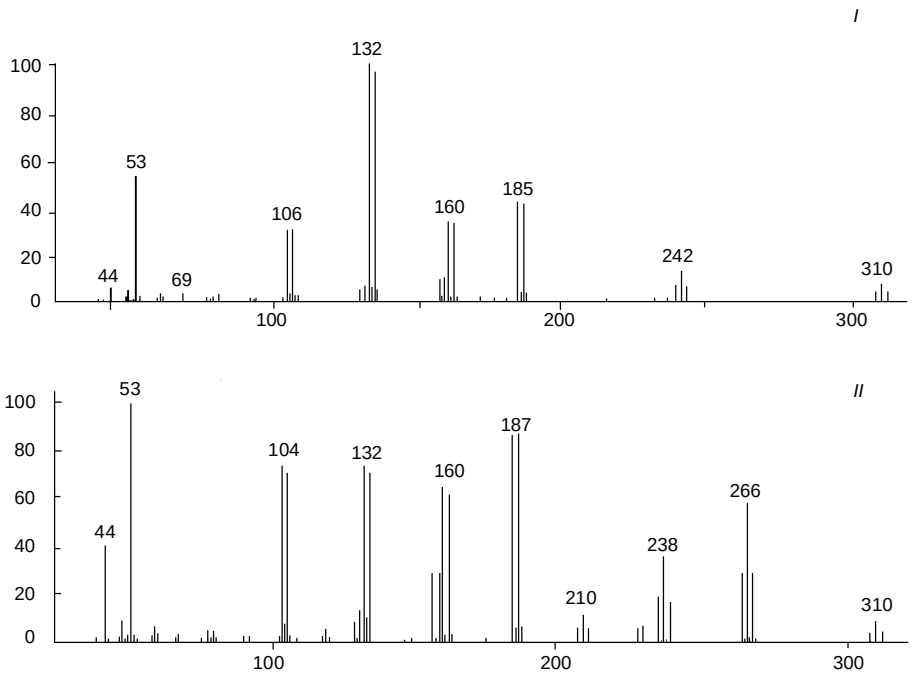
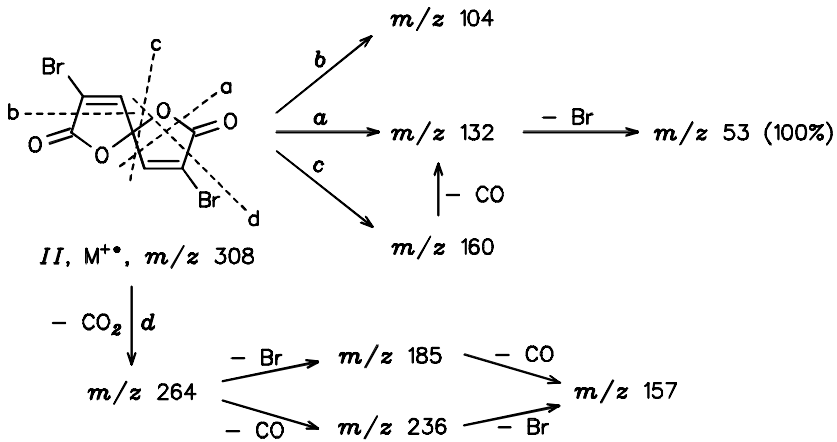


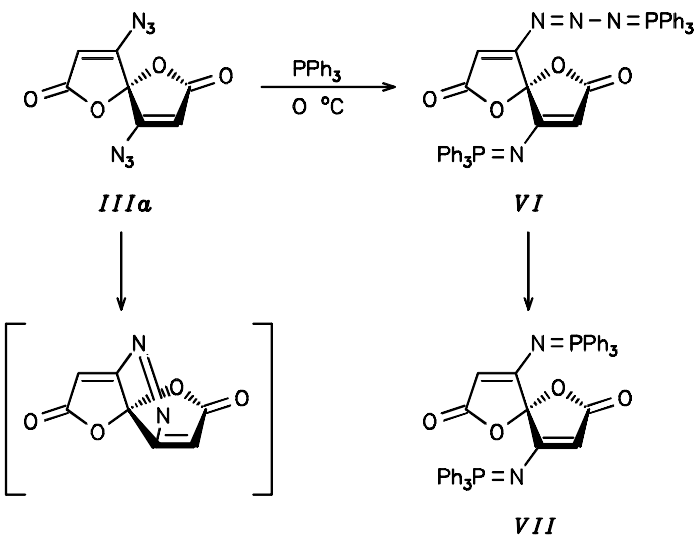
FIG. 1
EI mass spectra of 4,9-dibromo-1,6-dioxaspiro[4.4]nona-3,8-dien-2,7-dione (*I*) and 3,7-dibromo-1,6-dioxaspiro[4.4]nona-3,8-dien-2,7-dione (*II*)

* In all fragments containing bromine the given data correspond to isotope ^{79}Br.

diesters of these acids by the lipase-catalyzed methanolysis of lactone rings were unsuccessful. The paper presents nucleophilic substitution of furanone halogen in the molecule of *I* with various types of nucleophiles. The reactivity of *I* with iodine anion, oxygen (CH_3O^-, *p*-$CH_3C_6H_4O^-$), sulfur (*p*-$CH_3C_6H_4S^-$, $C_4H_9S^-$), nitrogen ($-N_3$, –NCS, secondary and tertiary amines) and phosphorus (PPh_3) nucleophiles containing reagents in the system acetone–water and in dry toluene or benzene was investigated, forming



SCHEME 1

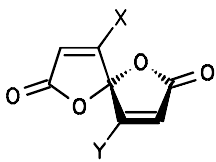


SCHEME 2

4,9-disubstituted bifuranones *IIIa–IIIg*. Azide anion and tertiary amines (except pyridine) easily react with the compound *I* giving substitution products *IIIa*, *IIIe*, *IIIf* in excellent yields. The reaction with triphenylphosphines proceeds smoothly as well, affording the derivative *IIIg*. The compound *IIIf* was found to be a monosubstituted product in spite of two equivalents of the reagent used for the reaction. Reactions of *I* with iodide and isothiocyanate anions and sulfur nucleophiles resulted generally in poor yields of substitution product (I^-, SCN^-, *p*-$CH_3C_6H_4S^-$) or did not proceed at all ($C_4H_9S^-$).

Reactions of *I* with secondary amines (dimethylamine, piperidine, morpholine) even at lower temperatures (–15 °C) in dry benzene gave a mixture of acyclic products due to substitution and addition side reactions. Reactions of *I* with oxygen nucleophiles (CH_3O^-, *p*-$CH_3C_6H_4O^-$) led preferentially to ring opening of *I* as well. Reactions of spirobilactones *I* and *II* with methanol in the presence of $NaHCO_3$ afforded also the ring opening products – halogenated 4-oxoheptanedioic monoesters *IV* and *V*, respectively.

As a part of our study of reactivity of *IIIa* and for its structure confirmation we carried out a reaction with two equivalents of triphenylphosphine in diethyl ether at 0 °C. The spirobilactone *VI* bearing one phosphazine and one iminophosphorane group in its



III

	X	Y
IIIa	N_3	N_3
IIIb	NCS	NCS
IIIc	I	I
IIId	*p*-$CH_3C_6H_4S$	*p*-$CH_3C_6H_4S$
IIIe	$N^{(+)}(CH_3)_3Br^{(-)}$	$N^{(+)}(CH_3)_3Br^{(-)}$
IIIf	Br	*p*-$(N(CH_3)_2)C_5H_4N^{(+)}Br^{(-)}$
IIIg	Br	$P^{(+)}Ph_3Br^{(-)}$

$HOOC-CH=CBr-CO-CBr=CH-COOCH_3$

IV

$HOOC-CBr=CH-CO-CH=CBr-COOCH_3$

V

molecule was isolated, as an intermediate en route to bisiminophosphorane *VII* (Scheme 2). The structure of *VI* was assigned only based on elemental analysis, since dissolution of *VI* in $(CD_3)_2SO$ for NMR analysis caused immediate formation of *VII*. For preparative purposes, a reflux in diethyl ether for two hours was sufficient to convert *VI* to *VII* in quantitative yield. Bisiminophosphorane *VII*, due to its steric properties[9], does not participate in reactions characteristic for iminophosporanes. The heating of *VII* with carbon disulfide in a sealed Pyrex pressure tube for 6 h at 100 °C followed by sonication yielded only starting material quantitatively. Similarly, aqueous hydrolysis failed as well. The thermal decomposition of spirodiazide *IIIa* in refluxing toluene gave red crystalline substance characterized by the same melting point as the starting compound *IIIa*, but without interdecomposition at 127–129 °C. Elemental analysis corresponded to the formula $C_7H_2N_2O_4$ and the band characteristic of azide group disappeared in the IR spectra. Its probable structure is given in Scheme 2.

TABLE I
Characteristic data of compounds *III*

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found				
			% C	% H	% Br	% N	% S
IIIa	$C_7H_2N_6O_4$	162–165	35.91	0.86	–	35.91	–
	(234.1)	97	35.88	0.93	–	35.87	–
IIIb	$C_9H_2N_2O_4S_2$	134–137	40.60	0.76	–	10.52	24.08
	(266.3)	29	40.58	0.84	–	10.47	24.05
IIIc	$C_7H_2I_2O_4$	171–173	20.82	0.50	–	–	–
	(403.9)	10	21.04	0.56	–	–	–
IIId	$C_{19}H_{16}O_4S_2$	187–189	61.27	4.33	–	–	17.22
	(372.5)	21	61.17	4.35	–	–	17.25
IIIe	$C_{13}H_{20}Br_2N_2O_4$	129–132	36.47	4.71	37.33	6.54	–
	(428.1)	64	36.54	4.67	37.48	6.61	–
IIIf	$C_{14}H_{12}Br_2N_2O_4$	181–184	38.92	2.80	36.99	6.48	–
	(432.1)	95	39.12	2.91	36.86	6.51	–
IIIg	$C_{25}H_{17}Br_2O_4P$	156–159	52.48	2.99	27.93	–	–
	(572.2)	82	53.29	3.27	27.09	–	–

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are corrected. The IR spectra, ($\tilde{\nu}$, cm^{-1}) were recorded on a FTIR PU 9802/25 (Philips) spectrophotometer using KBr technique (0.5 mg/300 mg KBr). UV spectra (λ_{max}, nm; log ε) were obtained with M-40 (Zeiss, Jena) spectrophotometer in methanol. The ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and $(CD_3)_2SO$ on a Tesla BS 487 C (80 MHz) spectrometer. The chemical shifts (δ) are reported in ppm, using TMS and HMDS as internal reference. EI mass spectra were taken with a MS25RFA (Kratos, Manchester) instrument provided with a direct inlet system at ionization energy 70 eV. The yields and physicochemical data of compounds *IIIa–IIIg* are given in Table I.

4,9-Diazido-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione (*IIIa*)

Sodium azide (0.3 g, 3.9 mmol) in water (5 ml) was added dropwise to the stirred solution of the compound *I* (0.6 g, 1.94 mmol) in acetone (20 ml) at ambient temperature. White solid formed within 30 min. After 1 h of an additional stirring the solid was filtered off, washed with acetone giving 0.44 g (97%) of the product *IIIa*, m.p. (dec.) 127–129 °C. UV spectrum: 265 (3.38). IR spectrum: 2 140 (N_3), 1 800 (C=O), 1 630 (C=C), 1 185 (C–O). ^1H NMR spectrum ($(CD_3)_2SO$): 6.58 s, 2 H (=CH). ^{13}C NMR spectrum: 165.85 (C=O), 159.61 (C-4), 105.01 (C-3), 101.9 (C-5). Mass spectrum (*m/z*): 266 (M^+).

4,9-Diisothiocyanato-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione (*IIIb*)

Sodium thiocyanate (0.2 g, 2.47 mmol) in water (5 ml) was added dropwise to the compound *I* (0.4 g, 1.29 mmol) dissolved in acetone (15 ml) at 0 °C under continual stirring. After 20 h stirring the solvent was distilled off and the residual solid was dissolved in water (10 ml). The solution was extracted with ether, organic layers were combined, dried over sodium sulfate and concentrated. Column chromatography on silica gel with chloroform as eluant gave 0.1 g (29%) of pure compound *IIIb*. UV spectrum: 256 (3.28). IR spectrum: 2 090 (NCS), 1 785 (C=O), 1 610 (C=O), 1 210 (C–O). ^1H NMR spectrum ($CDCl_3$): 6.63 s, 2 H (=CH).

4,9-Diiodo-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione (*IIIc*)

Sodium iodide (0.3 g, 2.00 mmol) in water (5 ml) was added dropwise to the compound *I* (0.3 g, 0.97 mmol) in acetone (10 ml) at laboratory temperature. The mixture was stirred for 10 h, then sonicated for 30 min and stirred for additional 10 h. Evaporation of acetone, extraction by ether and column chromatography (chloroform as eluant) of the solid residue on silica gel gave 0.05 g (10%) of product. UV spectrum: 233 (3.01). IR spectrum: 1 788 (C=O), 1 609 (C=O), 1 215 (C–O). ^1H NMR spectrum ($CDCl_3$): 6.59 s, 2 H (=CH).

4,9-Bis(*p*-methylphenylthio)-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione (*IIId*)

Sodium *p*-methylbenzenethiolate (0.37 g, 2.58 mmol) in acetone (10 ml) was added dropwise to the compound *I* (0.4 g, 1.29 mmol) in acetone (20 ml) and the resulting solution was stirred for 2 days at laboratory temperature. The reaction mixture was then concentrated on vacuum rotatory vaporator, diluted with 20 ml water and extracted with ether. The extract was then dried over sodium sulfate, concentrated and purified by column chromatography on silica gel with chloroform as eluant. Crystallization from toluene gave 0.1 g (21%) of compound *IIId*. UV spectrum: 229 (3.29), 269 (2.54). IR spectrum: 1 763 (C=O), 1 651 (C=C), 1 593 (arom.), 1 152 (C–O–C). ^1H NMR spectrum ($CDCl_3$): 2.31 s, 3 H (CH_3); 7.09 d, 2 H (arom.); 7.39 d, 2 H (arom.); 7.33 s, 2 H (=CH).

1,6-Dioxaspiro[4.4]nona-3,8-diene-2,7-dione-4,9-bis(trimethylammonium) Dibromide (*IIIe*)

Dry benzene (15 ml) saturated with trimethylamine (0.3 g, 5.1 mmol) was added to the compound *I* (0.4 g, 1.29 mmol) in benzene (15 ml). A precipitate formed after overnight standing was crystallized from ethanol–ether giving 0.35 g (64%) of dibromide *IIIe*. UV spectrum: 227 (2.84). IR spectrum: 1 767 (C=O), 1 630 (C=N), 1 211 (C–O–C). ^{1}H NMR spectrum ($(CD_3)_2SO$): 3.06 s, 18 H (CH_3); 7.23 s, 2 H (=CH).

9-Bromo-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione-4-*p*-(*N*,*N*-dimethylamino)pyridinium Bromide (*IIIf*)

p-(*N*,*N*-Dimethylamino)pyridine (0.47 g, 3.87 mmol) in dry toluene (15 ml) was quickly added to the compound *I* (0.6 g, 1.94 mmol) in minimum of dry toluene. White solid precipitate was crystallized from ethanol–ether to give 0.8 g (95%) of *IIIf*. IR spectrum: 1 781 (C=O), 1 643 (C=C), 1 177 (C–O). ^{1}H NMR spectrum ($(CD_3)_2SO$): 3.36 s, 6 H (CH_3); 7.23 d, 2 H (arom.); 7.36 s, 1 H (=CH); 7.62 s, 1 H (=CH); 8.24 d, 2 H (arom.).

9-Bromo-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione-4-triphenylphosphinium Bromide (*IIIg*)

Triphenylphosphine (0.18 g, 0.7 mmol) in dry benzene (20 ml) was added to the compound *I* (0.2 g, 0.64 mmol) in dry benzene (10 ml). The resulting solution was stirred at laboratory temperature for 48 h giving 0.3 g (82%) of light green crystals of compound *IIIg*. UV spectrum: 228 (3.16), 263 (2.65). IR spectrum: 1 796 (C=O), 1 644 (C=C), 1 586 (arom.), 1 203 (C–O). ^{1}H NMR spectrum ($(CD_3)_2SO$): 7.31 s, 1 H (=CH); 7.77 s, 1 H (=CH); 7.35–8.20 m, 15 H (arom.).

General Procedure for Preparation of *IV* and *V* via Ring Opening of *I* and *II*

Sodium bicarbonate (0.2 g) was suspended in absolute methanol (20 ml) containing the compound *I* (or *II*) (0.4 g, 1.28 mmol) at 0 °C. After 3 h stirring at ambient temperature the solvent was distilled off. The residue was neutralized by 5 ml of 5% HCl, extracted with ethyl acetate and crystallized.

3,5-Dibromo-4-oxo-2,5-heptadiendioic acid monomethyl ester (IV). Yield 0.07 g (16%), m.p. 149–151 °C (petroleum ether). For $C_8H_6Br_2O_5$ (341.9) calculated: 28.10% C, 1.77% H, 46.74% Br; found: 28.36% C, 1.84% H, 46.63% Br. IR spectrum: 3 117 (OH), 1 740 (C=O), 1 638 (C=C). ^{1}H NMR spectrum ($(CD_3)_2SO$): 3.74 s, 3 H (CH_3); 7.41 s, 1 H (=CH); 7.55 s, 1 H (=CH).

2,6-Dibromo-4-oxo-2,5-heptadiendioic acid monomethyl ester (V). Yield 0.19 g (43%), m.p. 183–186 °C (toluene). For $C_8H_6Br_2O_5$ (341.9) calculated: 28.10% C, 1.77% H, 46.74% Br; found: 28.21% C, 1.92% H, 46.53% Br. IR spectrum: 3 112 (OH), 1 796, 1 750 (C=O), 1 612 (C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$): 3.78 s, 3 H (CH_3); 7.21 s, 1 H (=CH); 7.32 s, 1 H (=CH).

In an alternative method, using acidic conditions, the compound *I* (0.2 g, 0.64 mmol) was dissolved in methanol (20 ml) and concentrated hydrochloric acid (1 ml) was added. After 8 h reflux the solvent was evaporated and the residue was extracted with ethyl acetate. Crystallization from petroleum ether gave 0.05 g (25%) of the product *IV*.

4-Triphenylphosphazino-9-triphenylphosphino-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione (*VI*) and 4,9-Bis(triphenylphosphino)-1,6-dioxaspiro[4.4]nona-3,8-diene-2,7-dione (*VII*)

Triphenylphosphine (0.45 g, 1.71 mmol) in ether (5 ml) was slowly added to the compound *IIIa* (0.2 g, 0.85 mmol) in ether (80 ml) at 0 °C. Yellow crystals of the product *VI* separated within 15 min. M.p. 348–350 °C, for $C_{43}H_{32}N_4O_4P_2$ (730.7) calculated: 70.68% C, 4.41% H, 7.67% N; found: 69.38% C, 4.53% H, 8.02% N. IR spectrum: 1 759, 1 746 (C=O), 1 591, 1 570 (C=C), 1 210 (C–O). Further reflux of

the reaction mixture for 2 h in ether gave white crystalline product (0.58 g, 98%), m.p. 348–350 °C. For $C_{43}H_{32}N_2O_4P_2$ (702.7) calculated: 47.21% C, 1.13% H, 15.73% N; found: 47.02% C, 1.61% H, 15.14% N. UV spectrum: 248 (3.14), 296 (3.51). IR spectrum: 1 742 (C=O), 1 591 (C=C), 1 203 (C–O). ^{1}H NMR spectrum ($(CD_3)_2SO$): 7.51 s, 2 H (=CH); 7.39–7.75 m, 30 H (arom.). ^{13}C NMR spectrum: 97.94 (C-5), 134.34 (C-4), 136.32, 138.66, 138.90, 141.72 (arom.), 142.77 (C-3), 182.05 (C=O). Mass spectrum (*m/z*): 702 ($M^{+\bullet}$).

Decomposition of the Compound *IIIa* in Toluene

The spiro derivative *IIIa* (0.2 g, 0.86 mmol) suspended in 30 ml absolute toluene was refluxed for 4 h and the solvent was distilled off giving 0.15 g (98%) of red-orange powder, m.p. 165 °C. For $C_7H_2N_2O_4$ (178.1) calculated: 47.21% C, 1.13% H, 15.73% N; found: 47.02% C, 1.61% H, 15.41% N.

REFERENCES

1. Pale P., Chuche J.: Tetrahedron Lett. *29*, 2947 (1988).
2. Perron F., Albizati K. F.: J. Org. Chem. *54*, 2044 (1989).
3. Lawson E. N., Kitching W., Kennard C. H. L., Byriel K. A.: J. Org. Chem. *58*, 2501 (1993).
4. Black T. H., McDermott T. S.: Synth. Commun. *20*, 2959 (1990).
5. Cardellach J., Estopa C., Font J., Moreno-MaEas M., Ortuno R. M., Sanchez-Ferrando F., Valle S., Vilamajo L.: Tetrahedron *38*, 2377 (1982).
6. Font J., Sanchez-Ferrando F., Segura C., Piniella J. F., Jeffrey G. A., Ruble J. R.: J. Heterocycl. Chem. *27*, 183 (1990).
7. Jakubcova M., Vegh D., Kozisek J., Dvorsky A.: Synth. Commun. *24*, 1333 (1994).
8. Kozisek J., Dvorsky A., Vegh D., Jakubcova M., Jecny J.: Acta Crystallogr. *49*, 990 (1993).
9. Molina P., Vilaplana M. J.: Synthesis *1994*, 1197.