Reactions of α-perfluorophenylpyrylium perchlorates with hydrazine hydrate

*I. Yu. Kargapolova, K. S. Shmuilovich, I. V. Beregovaya, and N. A. Orlova**

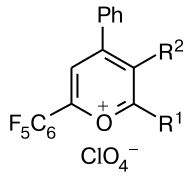
N. N. Vorozhtsov Institute of Organic Chemistry,
Siberian Branch of the Russian Academy of Sciences,
9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383) 330 9752. E-mail: ona@nioch.nsc.ru

Reactions of α-perfluorophenylpyrylium salts with hydrazine hydrate in ethanol afforded derivatives of 1,2-diazepine, dihydro-1*H*-pyrazole, and/or 1-aminopyridinium salts, depending on the steric characteristics of the substituent in the second α-position. 1-Amino-2-methyl-6-perfluorophenyl-4-phenylpyridinium perchlorate was used to obtain various pyridocyanines.

Key words: α-perfluorophenylpyrylium salts, perfluorophenyl-1,2-diazepines, polyfluorinated dihydro-1*H*-pyrazoles, 1-amino-2-methyl-6-perfluorophenylpyridinium perchlorate, fluorine-containing pyridocyanines.

Reactions of highly reactive pyrylium salts with various nitrogen-containing nucleophiles and binucleophiles are widely employed in the synthesis of not easily accessible aromatic and heterocyclic compounds.[1,2] The use of polyfluorinated pyrylium salts[3,4] in these reactions can afford earlier unknown polyfluorinated nitrogen-containing heterocycles and novel fluorophores. In the last few years, great interest has been shown in fluorescent labels for biological structures, the labels being produced by reactions of the pyrylium ring with amino-containing fragments of biomolecules.[5]

It is known that the pathway of reactions of pyrylium salts with hydrazines depends on the structure of the starting salt and the reaction conditions.[6—9] For instance, a reaction of 2,4,6-triphenylpyrylium perchlorate with hydrazine hydrate in ethanol gives a seven-membered cyclic product, *viz.*, 3,5,7-triphenyl-6*H*-1,2-diazepine.[6] Supposedly, the reaction passes through intermediate acyclic 5-hydrazono-1,3,5-triphenylpent-2-en-1-one. Depending on the ratio of the reagents, alkylpyrylium salts form under these conditions pyrazole derivatives and/or *N*-aminopyridinium salts.[8]



1a—d

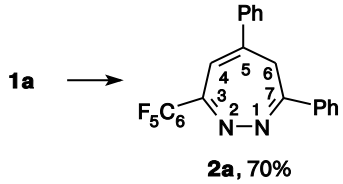
1	**a**	**b**	**d**	**c**
R^1	Ph	C_6F_5	Me	$R^1 + R^2$
R^2	H	H	H	$(CH_2)_4$

Results and Discussion

Earlier, reactions of α-perfluorophenylpyrylium salts with ammonia,[10] ammonium salts,[3] methylamine,[10] and hydroxylamine[11] have been investigated. In the present work, we studied room-temperature reactions of four pyrylium perchlorates of the general formula **1**, which contain one or two α-perfluorophenyl groups, with a twofold excess of hydrazine hydrate in ethanol.

We found that the reaction products largely depend on the structure of the starting salt. For instance, pyrylium salt **1a** yields, like a nonfluorinated analog,[6] 3-perfluorophenyl-5,7-diphenyl-4*H*-1,2-diazepine (**2a**) (Scheme 1).

Scheme 1



2a, 70%

Reagents and conditions: $NH_2NH_2 \cdot H_2O$, EtOH, 20 °C.

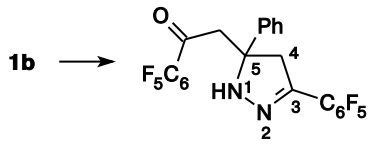
The structure of compound **2a** was determined from its ^1H and ^{19}F NMR spectra and elemental analysis data. The ^1H NMR spectrum of diazepine **2a** shows multiplets for two phenyl rings, the AB system of the methylene protons in position 6 (broadened doublets at δ 2.90 and 3.93 with the geminal coupling constant J = 12 Hz), and a singlet for the H(4) proton (δ 6.72), which is broadened because of its coupling with the C_6F_5 fragment. The ^{19}F NMR spectrum contains three signals with

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1383—1387, July, 2010.

an intensity ratio of 2 : 1 : 2 for the perfluorophenyl substituent.

Under the same conditions, compound **1b** with two α-C_6F_5 fragments mainly yields 1-perfluorophenyl-2-(3-perfluorophenyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-ethanone (**3b**) (Scheme 2).

Scheme 2

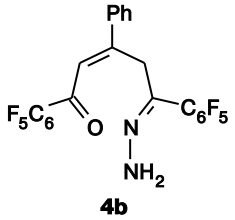


3b, 56%

Reagents and conditions: $NH_2NH_2 \cdot H_2O$, EtOH, 20 °C.

The IR spectrum of pyrazoline **3b** contains bands at 3303 (N—H stretches), 1693 (C=O stretches), and 1488 cm^{-1} (C_6F_5 stretches). The ^{19}F NMR spectrum exhibits signals for the F atoms of two nonequivalent C_6F_5 fragments. The ^1H NMR spectrum shows a multiplet for the phenyl ring and two AB systems of the methylene protons in the pyrazoline ring (δ 3.50 and 3.71, J = 16.5 Hz) and in the phenacyl fragment (δ 3.32 and 3.34, J = 16 Hz) (*cf.* Ref. 12). It should be noted that the signal for the NH proton is absent from the ^1H NMR spectrum in $CDCl_3$, probably, because of exchange processes with water impurities.

The formation of pyrazolines in reactions of triarylpyrylium salts with hydrazine hydrate has not previously been observed. It is very likely that the unexpected formation of pyrazoline **3b** in the reaction of pyrylium perchlorate **1b** with hydrazine hydrate is due to the mutual steric influences of two pentafluorophenyl substituents. As a result, the hydrazone fragment in the presumed intermediate 5-hydrazono-1,5-bis(perfluorophenyl)-3-phenylpent-2-en-1-one (**4b**) becomes non-coplanar with the rest of the molecule, which precludes closure of a seven-membered ring. Earlier,[11] we have observed a similar effect of two C_6F_5 substituents in a reaction of salt **1b** with hydroxylamine.

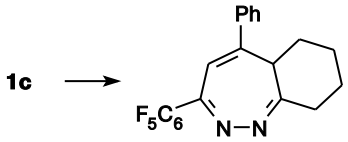


4b

Pyrylium perchlorate **1c** reacts with hydrazine hydrate to give 3-perfluorophenyl-5-phenyl-6,7,8,9-tetrahydro-4*H*-benzo[*c*][1,2]diazepine (**2c**) (Scheme 3).

Apparently, the predominant formation of diazepine **2c** is also due to the steric factor: the rigidly fixed alicyclic

Scheme 3



2c, 68%

Reagents and conditions: $NH_2NH_2 \cdot H_2O$, EtOH, 20 °C.

fragment favors the retention of the planar structure of the intermediate hydrazone.[11]

Unlike compound **1c**, methylpyrylium salt **1d** yields under these conditions a mixture of two isomeric diazepines **2d´** and **2d″**, which differ in the position of the double bond, 1-amino-2-methyl-6-perfluorophenyl-4-phenylpyridinium perchlorate (**5d**), and 6,7,8,9-tetrafluoro-2-methyl-3a-phenyl-3a,4-dihydropyrazolo[1,5-*a*]quinolin-5(3*H*)-one (**6d**) (^1H and ^{19}F NMR data). The formation of the last compound can be attributed to intramolecular nucleophilic displacement of the *o*-F atom in the perfluorophenyl ring of intermediate pyrazoline **3d** by the amino group of the pyrazoline ring (Scheme 4).

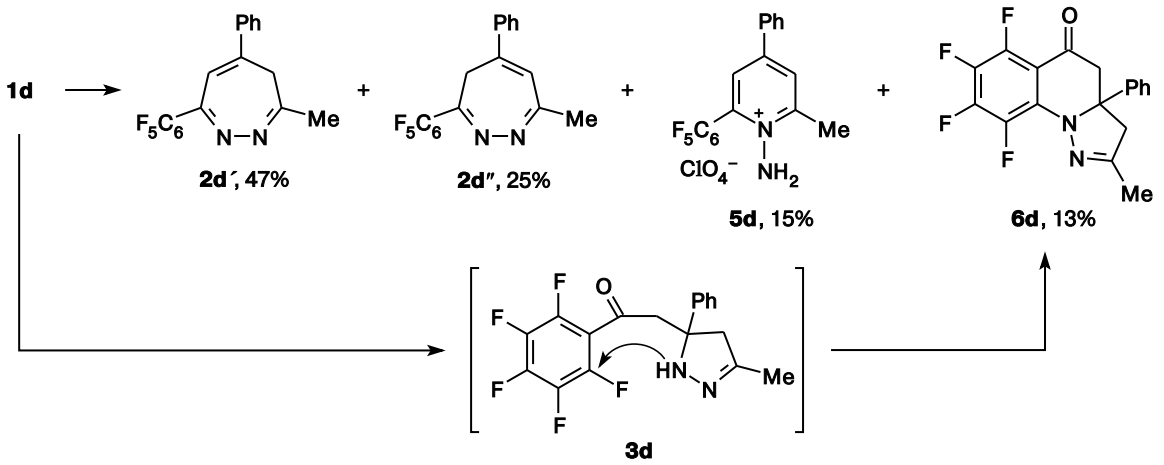
The formation of two isomers of diazepine (**2d**) was confirmed by their calculated total energies (PBE/3z): isomer **2d´** (−1300.20433 au) is more stable than isomer **2d″** (−1300.20341 au) only by 0.6 kcal mol^{-1}.

We isolated in the individual state only 3-methyl-7-perfluorophenyl-5-phenyl-4*H*-1,2-diazepine (**2d´**). Structure **2d″** was identified from the ^1H and ^{19}F NMR spectra of the reaction mixture. The ^1H NMR spectra of both isomers are similar; they exhibit singlets for the methyl groups, multiplets for the aromatic protons, broadened doublets of the AB systems for the methylene groups, and singlets for the methine protons. The signal for the H(6) atom of diazepine **2d´** is noticeably broader than the corresponding signal for diazepine **2d″** because of a coupling with the perfluorophenyl substituent.

The IR spectrum of 6,7,8,9-tetrafluoro-2-methyl-3a-phenyl-3a,4-dihydropyrazolo[1,5-*a*]quinolin-5(3*H*)-one (**6d**) contains intense bands at 1703 (C=O), 1642 (C=N), and 1495 cm^{-1} (C—F_{arom}). The ^{19}F NMR spectrum shows four signals of equal intensity for the F atoms of the annulated ring. The ^1H NMR spectrum exhibits two AB systems of the protons of two CH_2 groups in the heterocycles, a singlet for the methyl group, and signals for the aromatic protons of the phenyl ring. The IR spectrum of pyridinium salt **5d** contains intense bands due to the vibrations of the perchlorate anion, the amino group, and the C—F and C=N bonds.

1-Aminopyridinium perchlorate **5d** with an active α-methyl group was used in the synthesis of asymmetric pyridocyanines from 4-dimethylaminobenzaldehyde. The reaction in a mixture of acetic acid and acetic anhydride gives Schiff base **7**; the α-methyl group is inert under these

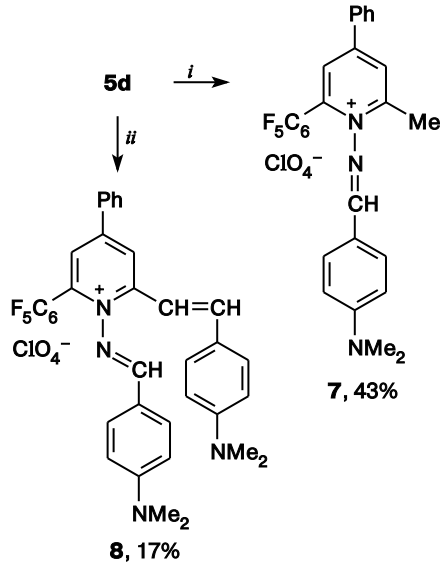
Scheme 4



Reagents and conditions: $NH_2NH_2 \cdot H_2O$, EtOH, 20 °C.

conditions. Pyridocyanine **8** was obtained in low yield by heating salt **5d** and 4-dimethylaminobenzaldehyde in AcOH—Ac_2O in the presence of anhydrous sodium acetate (Scheme 5).

Scheme 5



Reagents and conditions: *i*. $Me_2NC_6H_4CHO$, Ac_2O/AcOH, 100 °C; *ii*. $Me_2NC_6H_4CHO$, Ac_2O/AcOH, AcONa, 120 °C.

To sum up, α-perfluorophenylpyrylium salts easily react with hydrazine hydrate in ethanol to give a number of earlier unknown polyfluorinated nitrogen-containing heterocyclic compounds: diazepines, pyrazolines, and pyridinium salts; the reaction pathway depends on the steric characteristics of the substituent in the second α-position of the pyrylium ring. The pyrylium salt containing two α-perfluorophenyl substituents yields a pyrazoline derivative, in contrast to a nonfluorinated analog. 1-Amino-2-methyl-6-perfluorophenyl-4-phenylpyridinium perchlorate (**5d**) was employed in the synthesis of pyridocyanine dyes.

Experimental

NMR spectra were recorded on Bruker AC-200 instruments (200.13 (^{1}H) and 188.2 MHz (^{19}F)) in $CDCl_3$ and CD_3CN. The signals for the residual protons in $CDCl_3$ (δ 7.24) and CD_3CN (δ 1.96) were used as the internal standards. IR spectra were recorded on a Vector 22 instrument; electronic absorption spectra were recorded on a Hewlett-Packard 8453 spectrophotometer. High-resolution mass spectra were measured on a Finnigan Mat 8200 instrument (ion source temperature 314 °C, ionizing energy 70 eV, direct inlet probe).

Calculations with full optimization of the geometries of isomeric diazepines **2d′** and **2d″** were performed at the PBE/3z level with the Priroda program.[13]

Reactions of pyrylium perchlorates 1a—d with hydrazine hydrate (general procedure). A conical flask was charged with a solution of hydrazine hydrate (0.12 g, 2.0 mmol) in ethanol (5 mL). Then pyrylium salt **1a—d** (0.9 mmol) was added with stirring. The reaction mixture was stirred with a magnetic stirring bar for 30 min and cooled in a freezer. The precipitate that formed was filtered off and dried in air. The mother liquor was poured onto crushed ice. The resulting precipitate was filtered off or subjected to extraction with CH_2Cl_2, washed with water, and dried over $CaCl_2$. The solvent was removed on a rotary evaporator *in vacuo*. The products were analyzed by ^{1}H and ^{19}F NMR spectroscopy and purified by recrystallization of the precipitates. The yields, melting points, and elemental analysis data of the reaction products are given in Table 1. Their IR and NMR spectra are given in Table 2.

1-[4-(Dimethylamino)benzylideneamino]-2-methyl-6-perfluorophenyl-4-phenylpyridinium perchlorate (7). 4-Dimethyl-

Table 1. Reactions of pyrylium salts **1a—d** with hydrazine hydrate. Yields, melting points, elemental analysis data, and mass spectra of the products

Pyrylium salt	Reaction product[a]	Yield (%)	M.p./°C (solvent)[b]	Found / Calculated (%)				Molecular formula	MS[c]
				C	H	F	N		
1a	**2a**	70	180—182 (ethanol)	67.02 66.99	3.31 3.18	22.48 23.04	6.72 6.79	$C_{23}H_{13}F_5N_2$	412.10039 412.09988
1b	**3b**	56	104—106 (heptane)	53.06 53.09	2.07 1.94	36.39 36.51	5.25 5.38	$C_{23}H_{10}F_{10}N_2O$	521.0474 521.0473
1c	**2c**	68	171—174 (heptane)	64.50 64.61	3.95 3.81	24.48 24.34	7.17 7.18	$C_{21}H_{15}F_5N_2$	390.11531 390.11553
1d	**2d´**	21	127—128 (hexane)	61.20 61.71	3.26 3.17	27.16 27.12	8.08 8.00	$C_{18}H_{11}F_5N_2$	350.08503 350.08423
	5d	11	249—250 (ethanol)	47.47 47.96	2.96 2.68	27.40 27.04	3.92 3.99	$C_{18}H_{12}ClF_5N_2O_4$	—
	6d	6	119—122 (hexane)	—	—	—	—	$C_{18}H_{12}F_4N_2O$	348.0889 348.0880

[a] Salt **5d** was isolated by washing the precipitate formed with ether. Compounds **2d´** and **6d** were isolated by column chromatography of the ethereal fraction on Al_2O_3 with benzene as an eluent.
[b] The solvent for recrystallization.
[c] Found/calculated, m/z, $[M]^+$/M.

Table 2. IR and ^1H and ^{19}F NMR spectra of compounds **2a,c,d´,d´´**, **3b**, **5d**, and **6d**

Compound	IR, ν/cm^{-1} (solvent)	^1H NMR		^{19}F NMR	
		Solvent	δ (J/Hz)	Solvent	δ*
2a	1652 (C=N), 1523 (C_6F_5) ($CHCl_3$)	$CDCl_3$	2.90, 3.93 (AB system, 2 H, C(4)H_2, J = 12.0); 6.72 (s, 1 H, H(6)); 7.10—8.10 (m, 10 H, 2 Ph)	$CDCl_3$	0.92, 10.20, 21.64 (2 : 1 : 2)
2c	1651 (C=N), 1496, 1522 (C_6F_5)	$CDCl_3$	1.58 (1 H), 1.82—1.90 (2 H), 2.06 (1 H), 2.24 (1 H), 2.54—2.66 (2 H) and 2.80 (1 H) (all m, 4 (CH_2)); 2.90, 3.33 (AB system, 2 H, C(4)H_2, J_1 = 12.0, J_2 = 3.0); 7.11—7.32 (5 H, Ph)	$CDCl_3$	0.54, 9.45, 21.07 (2 : 1 : 2)
2d´	1654 (C=N), 1507, 1519 (C_6F_5) ($CHCl_3$)	CD_3CN	2.07 (s, 3 H, Me); 2.31, 3.89 (AB system, 2 H, C(4)H_2, J = 14.0); 6.49 (s, 1 H, H(6)); 7.45—7.65 (m, 5 H, Ph)	CD_3CN	1.50, 12.97, 21.31 (2 : 1 : 2)
2d´´		CD_3CN	2.32 (s, 3 H, Me); 2.81 and 3.81 (AB system, 2 H, C(4)H_2, J = 13.0); 6.45 (s, 1 H, H(6)); 7.34—7.47 (m, 5 H, Ph)	CD_3CN	0.97, 9.35, 21.85 (2 : 1 : 2)
3b	3303 (N—H), 1693 (C=O), 1488 (C_6F_5) ($CHCl_3$)	$CDCl_3$	3.32, 3.34 (AB system, 2 H, $C_6F_5COCH_2$, J = 16.0); 3.50, 3.71 (AB system, 2 H, C(4)H_2, J = 16.5); 7.26—7.42 (m, 5 H, Ph)	$CDCl_3$	0.00, 2.15, 7.98, 13.93, 21.32, 22.10 (2 : 2 : 1 : 1 : 2 : 2)
5d	3347 (NH_2), 1629 (C=N), 1507, 1526 (C_6F_5), 1104 (ClO_4^-) (KBr)	CD_3CN	2.89 (s, 3 H, C(2)Me); 6.18 (s, 2 H, NH_2); 7.64—7.91 (m, 5 H, Ph); 8.22 (d, 1 H, H(3), J = 2.0); 8.33 (d, 1 H, H(5), J = 2.0)	CD_3CN	0.00, 9.42, 24.32 (2 : 1 : 2)
6d	1703 (C=O), 1642 (C=N), 1495 (C_6F_5) ($CHCl_3$)	CD_3CN	2.06 (s, 3 H, Me); 3.06, 3.24 (AB system, 2 H, CH_2, J = 18.0); 3.15, 3.39 (AB system, 2 H, CH_2, J = 15.0); 7.28—7.42 (m, 5 H, Ph)	CD_3CN	–5.77, 14.05, 15.15, 19.74 (1 : 1 : 1 : 1)

* The intensity ratios are given in parentheses.

aminobenzaldehyde (0.09 g, 0.6 mmol) was added to a suspension of 1-aminopyridinium perchlorate **5d** (0.09 g, 0.2 mmol) in AcOH—Ac_2O (1 : 1 v/v, 0.5 mL). The reaction mixture was heated at 110—120 °C (bath temperature) for 3 h, cooled to room temperature, and triturated with ether (10 mL). The resulting precipitate of a bright yellow dye was filtered off and purified by column chromatography on Al_2O_3 with $CHCl_3$—MeCN (10 : 1) as an eluent. Yield 0.05 g (43%), m.p. 117—120 °C. UV-VIS (CH_2Cl_2), λ_{max}/nm (logε): 387 (5.15), 415_{tr} (4.87). ^{1}H NMR ($CDCl_3$), δ: 2.85 (s, 3 H, C(2)Me); 3.09 (s, 6 H, NMe_2); 6.65 and 7.67 (2 H each, AB system, 4 H_{arom}, J = 9 Hz); 7.47—7.86 (m, 5 H, Ph); 7.98 (d, 1 H, H(3), J = 1 Hz); 8.22 (d, 1 H, H(5), J = 1 Hz); 8.65 (s, C<u>H</u>=N). ^{19}F NMR (CD_3CN), δ: 2.78, 14.70, 26.75; intensity ratio 2 : 1 : 2. Found (%): C, 55.50; H, 3.91; Cl, 6.06; F, 16.31; N, 7.01. $C_{27}H_{21}ClF_5N_3O_4$. Calculated (%): C, 55.73; H, 3.64; Cl, 6.09; F, 16.32; N, 7.22.

1-[4-(Dimethylamino)benzylideneamino]-2-[4-(dimethylamino)styryl]-6-perfluorophenyl-4-phenylpyridinium perchlorate (8). A mixture of 1-aminopyridinium perchlorate **5d** (0.10 g, 0.23 mmol), 4-dimethylaminobenzaldehyde (0.10 g, 0.69 mmol), and freshly calcined MeCOONa (0.10 g, 1.28 mmol) in AcOH—Ac_2O (1 : 1 v/v, 1 mL) was heated at 110—120 °C (bath temperature) for 1.5 h. The reaction mixture was cooled, washed with water to remove the excess of MeCOONa and then with ether, and dissolved in acetonitrile. The product was precipitated with ether. The yield of dye **8** was 0.028 g (17%), dark green crystals (m.p. 208—210 °C) producing a dark pink solution in $CHCl_3$. UV-VIS (CH_2Cl_2), λ_{max}/nm (logε): 548 (4.37). ^{1}H NMR (CD_3CN), δ: 2.92 (s, 6 H, NMe_2); 3.03 (s, 6 H, NMe_2); 6.64—6.72 (m, 5 H, 4 H_{arom} + —CH=); 7.33 (d, 2 H_{arom}, J = 8 Hz); 7.47 (d, 2 H_{arom}, J = 8 Hz); 7.66—7.68 (m, 3 H(Ph)); 7.92—8.04 (m, 5 H, 2 H(Ph) + H(3) + —CH= + N=C<u>H</u>); 8.61 (d, 1 H, H(5), J = 1 Hz). ^{19}F NMR (CD_3CN), δ: 2.19, 14.09, 24.64, 25.72; intensity ratio 2 : 1 : 1 : 1. Found (%): C, 60.21; H, 4.20; F, 13.07; N, 7.63. $C_{36}H_{30}ClF_5N_4O_4$. Calculated (%): C, 60.63; H, 4.24; F, 13.32; N, 7.86.

This work was financially supported by the Federal Agency for Science and Innovations (State Contract No. 02.513.11.3167) and the Siberian Branch of the Russian Academy of Sciences (Integrating Project No. 65).

References

1. A. T. Balaban, A. Dinculescu, G. N. Dorofeenko, G. W. Fischer, A. V. Koblik, V. V. Mezheritskii, W. Schroth, *Pyrylium Salts: Syntheses, Reactions, and Physical Properties*, in *Adv. Heterocycl. Chem*., Ed. A. R. Katrizky, Suppl. 2, Academic Press, New York, 1982, 434 pp.
2. G. N. Dorofeenko, E. I. Sadekova, E. V. Kuznetsov, *Preparativnaya khimiya pirilievykh solei* [*The Preparative Chemistry of Pyrylium Salts*], Izd. Rostov. Univ., Rostov-on-Don, 1972, 234 pp. (in Russian).
3. V. M. Vlasov, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* [*Bulletin of the Siberian Branch of the Academy of Sciences of the USSR, Division of Chemical Sciences*], 1971, 96 (in Russian).
4. N. A. Orlova, T. N. Gerasimova, M. A. Kudinova, A. I. Tolmachev, *Zh. Org. Khim.*, 1990, **26**, 1313 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1990, **26**].
5. B. K. Hofelschweiger, *The Pyrylium Dyes: A New Class of Biolabels. Synthesis, Spectroscopy, and Application as Labels and in General Protein Assay*, PhD Diss., Regensburg, Germany, 2005.
6. A. T. Balaban, *Tetrahedron*, 1968, **24**, 5059.
7. E. A. Zvezdina, M. P. Zhdanova, O. S. Anisimova, G. N. Dorofeenko, *Khim. Geterotsikl. Soedin.,* 1983, 695 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1983, **19**, 564].
8. G. N. Dorofeenko, A. N. Narkevich, Yu. A. Zhdanov, O. E. Shelepin, T. G. Soroka, *Khim. Geterotsikl. Soedin., Sb. 2: Kislorodsoderzhashchie Geterotsikl.*, 1970, 223 [*Chem. Heterocycl. Compd., Proc. 2: Oxygen-Containing Heterocycles* (*Engl. Transl.*), 1970].
9. S. V. Tolkunov, S. Yu. Suikov, M. Yu. Zubritskii, V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 1998, 1137 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1998, **34**, 983].
10. I. Yu. Kargapolova, N. A. Orlova, T. N. Gerasimova, *Khim. Geterotsikl. Soedin.*, 1991, 1100 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1991, **27**, 883].
11. I. Yu. Kargapolova, K. S. Shmuilovich, N. A. Orlova, M. M. Shakirov, T. V. Rybalova, V. V. Shelkovnikov, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 402 [*Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 412].
12. A. T. Balaban, W. Silhan, *Tetrahedron*, 1970, **26**, 743.
13. D. N. Laikov, *Chem. Phys. Lett.*, 1997, **281**, 151.

Received June 11, 2009;
in revised form March 10, 2010