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FURYL ANALOGS OF α-PYRONO[2,3-*f*]ISOFLAVONES WITH AN AZOLE SUBSTITUENT IN THE α-PYRONE NUCLEUS

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The corresponding 9-azolyl-8-imino-4H,8H-pyrano[2,3-f]chromen-4-ones have been synthesized by the condensation of 7-hydroxy-3-(5-methoxycarbonyl-2-methylfuran-3-yl)-8-formylchromones with 2-aza-hetarylacetonitriles. Acid hydrolysis of the products led to the furyl analogs of 9-azolyl-α-pyrono-[2,3-f]isoflavones.

Keywords: 2-azolylacetonitriles, 9-azolyl-3-(5-methoxycarbonyl-2-methylfuran-3-yl)-4H,8H-pyrano-[2,3-*f*]chromen-4-ones, 8-formyl-7-hydroxychromones, α-pyrono[2,3-*f*]chromones, condensation.

The pyrano[2,3-*f*]chromene-4,8-dione system is the basis of the natural compounds clauzenidine [1, 2] and calomelanol D [3, 4]. It enters into the composition of the pyridylchromone alkaloid schumanniophytin, isolated from the roots and bark of *Schumanniophyton magnificum* and *S. problematicum* [5-7].

It is known that α-pyrono[2,3-*f*]flavones and isoflavones display bactericidal activity [8]. The same activity is also found for 2-hetarylpyrano[2,3-*f*]chromene-4,8-diones, including furyl analogs of α-pyrono-[2,3-*f*]flavones [9], which arouses interest in heterocyclic derivatives of this system.

As a continuation of our investigations in the area of heterocyclic analogs of isoflavones [10] and complex flavonoids [11, 12], in the present work we have synthesized furyl analogs of α-pyrono-[2,3-*f*]isoflavones containing azole substituents in position 9 of the molecule.

3-Furyl-7-hydroxychromones **1** and **2** were used as starting compounds, and were formylated with hexamethylenetetramine in acetic acid according to the Daff reaction. The formation of the corresponding 8-formyl-substituted products **3** and **4** (Table 1) was confirmed by the absence from the ^{1}H NMR spectra of these compounds, recorded in DMSO-d_6, of the singlet of the H-8 proton at 6.79 ppm characteristic of the initial chromones **1** and **2** (Table 2). The singlet of the formyl group proton was found at 10.48-10.52 ppm, and the signal of the OH group proton was displaced relative to the analogous signal of compounds **1** and **2** by almost 2 ppm towards low field, as the result of the formation of a chelated intramolecular hydrogen bond. Confirmation of the chelate structure of compounds **3** and **4** is their red-brown coloration with an alcoholic solution of iron(III) chloride and the presence of a broad band at 3080-3090 cm^{-1} in their IR spectra.

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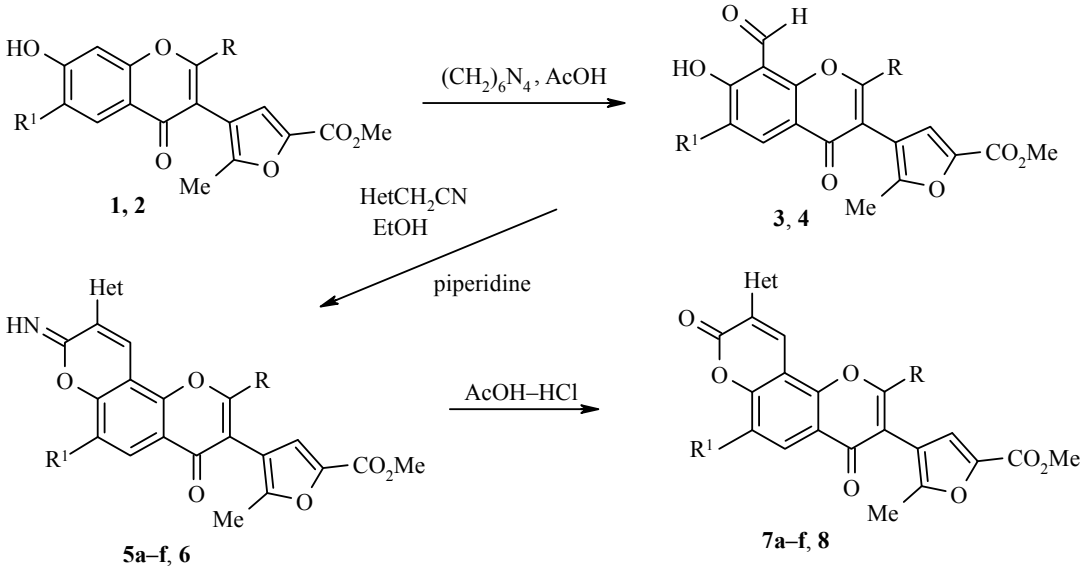
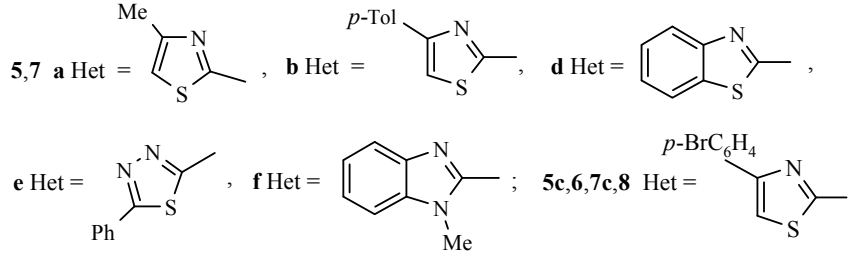
Previously, for the synthesis of the α-pyrono[2,3-*f*]isoflavone system, the initial 8-formyl-7-hydroxyisoflavones were put into a Perkin reaction under rigorous conditions [8, 15]. 9-Azahetaryl derivatives of this system were obtained by us under the mild conditions of the Knoevenagel reaction, on interacting 8-formyl-7-hydroxyisoflavones with 2-azahetarylacetonitriles in DMF with subsequent acid hydrolysis by the one-pot method [11]. In the present work the condensation of compounds **3** and **4** with 2-cyanomethyl derivatives of azoles (4-methyl-1,3-thiazole, 4-(4-methylphenyl)-1,3-thiazole, 4-(4-bromophenyl)-1,3-thiazole, benzothiazole, 5-phenyl-1,3,4-thiadiazole, and 1-methylbenzimidazole) was effected under even more mild conditions, in alcohol in the presence of catalytic amounts of piperidine. This permitted isolation of the intermediate 9-azolyl-8-imino-3-(5-methoxycarbonyl-2-methylfuran-3-yl)-4H,8H-pyrano[2,3-*f*]chromen-4-ones **5a-f**, **6**. Attempts to carry out hydrolysis of the imino group analogous to isoflavone derivatives [11] did not lead to the desired result. On boiling a suspension of compound **6** in a mixture of DMF – 3% aqueous H_2SO_4 for 5 h only one half was hydrolyzed and after 27 h 70%.



1,**3**,**5**,**7** R = R¹ = H; **2**,**4**,**6**,**8** R = CF_3, R¹ = Me;



Chromatographically pure 9-azolyl-3-(5-methoxycarbonyl-2-methylfuran-3-yl)-4H,8H-pyrano[2,3-*f*]chromene-4,8-diones **7a-f**, **8** were obtained in high yield on boiling the corresponding 8-imino derivatives **5a-f**, **6** in a mixture of acetic and 36% hydrochloric acid for 5-10 min.

The 8-imino derivatives **5a-f**, **6** and their hydrolysis products **7a-f**, **8** were high melting substances, poorly soluble in organic solvents, possessing a blue fluorescence in UV light. In the ^{1}H NMR spectra of these compounds, recorded in CF_3CO_2D, the same set of signals was observed for the protons of the chromone, furan, and azole fragments of the molecule, and also a low-field characteristic singlet for the H-10 proton. For the

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
3	$C_{17}H_{12}O_7$	61.90 / 62.20	3.89 / 3.68	—	—	189-190	56
4	$C_{19}H_{13}F_3O_7$	64.01 / 64.04	4.50 / 4.53	—	—	201-202	77
5a	$C_{23}H_{16}N_2O_6S$	61.37 / 61.60	3.72 / 3.60	6.12 / 6.25	7.23 / 7.15	263-264	76
5b	$C_{29}H_{20}N_2O_6S$	66.16 / 66.40	3.84 / 3.84	5.38 / 5.34	6.14 / 6.11	250-251	73
5c	$C_{28}H_{17}BrN_2O_6S$	56.83 / 57.06	2.89 / 2.91	4.91 / 4.75	5.49 / 5.44	261-262	83
5d	$C_{26}H_{16}N_2O_6S$	64.18 / 64.46	3.35 / 3.33	6.03 / 5.78	6.44 / 6.62	285-290 (dec)	70
5e	$C_{27}H_{17}N_3O_6S$	63.41 / 63.40	3.38 / 3.35	8.19 / 8.21	6.28 / 6.27	250-255 (dec)	75
5f	$C_{27}H_{19}N_3O_6$	67.66 / 67.36	4.09 / 3.98	8.52 / 8.73	—	269-270	58
6	$C_{30}H_{18}BrF_3N_2O_6S$	—	—	4.24 / 4.17	4.79 / 4.78	>300	85
7a	$C_{23}H_{15}NO_7S$	61.24 / 61.47	3.37 / 3.36	3.24 / 3.12	6.92 / 7.13	>300	82
7b	$C_{29}H_{19}NO_7S$	66.11 / 66.28	3.57 / 3.64	2.46 / 2.67	6.21 / 6.10	278-279	73
7c	$C_{28}H_{16}BrNO_7S$	56.73 / 56.96	2.74 / 2.73	2.34 / 2.37	5.53 / 5.43	>300	80
7d	$C_{26}H_{15}NO_7S$	64.07 / 64.33	3.12 / 3.11	2.78 / 2.89	6.54 / 6.60	>300	66
7e	$C_{27}H_{16}N_2O_7S$	62.99 / 63.28	3.13 / 3.15	5.68 / 5.47	6.19 / 6.26	>300	67
7f	$C_{27}H_{18}N_2O_7$	66.93 / 67.22	4.06 / 3.76	5.80 / 5.81	—	>300	67
8	$C_{30}H_{17}BrF_3NO_7S$	—	—	2.15 / 2.08	4.89 / 4.77	>300	67

8-imino derivatives **5a-f**, **6** this signal was found in the 9.32-9.53 ppm region, but for α-pyrono[2,3-*f*]chromones **7a-f**, **8** it was displaced by 0.5 ppm towards low field. In the ^{1}H NMR spectra of imino derivatives **5a** and **6**, recorded in DMSO-d_6, the singlet of the H-10 proton was recorded at 8.81-8.82, but at lower field the signal of the NH group proton was observed at 9.14-9.34 ppm, disappearing on adding D_2O.

3-Furyl-8-imino-4H,8H-pyrano[2,3-*f*]chromones have therefore been synthesized by interacting 8-formyl-3-furyl-7-hydroxychromones with 2-azolyl-acetonitriles. Acid hydrolysis of the products led to the furyl analogs of α-pyrono[2,3-*f*]isoflavones containing an azole substituent in the α-pyrone nucleus.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in KBr disks. The ^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) spectrometer in DMSO-d_6 and CF_3CO_2D, internal standard was TMS. The purity of the obtained compounds was checked by TLC on Silufol UV-254 plates in the system chloroform–methanol, 9:1.

8-Formyl-7-hydroxy-3-(5-methoxycarbonyl-2-methylfuran-3-yl)chromen-4-ones 3, 4 (General Method). A solution of the appropriate 7-hydroxy-3-(5-methoxycarbonyl-2-methylfuran-3-yl)chromone **1, 2** (5 mmol) and hexamethylenetetramine (7 g, 50 mmol) in acetic acid (20 ml) was maintained on a boiling

TABLE 2. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)*
1	2	3
3	3090 (CHO···HO), 1710 (C=O ester), 1645 (C=O)	[2.43 (3H, s, 2'-CH_3); 3.83 (3H, s, CO_2CH_3); 7.07 (1H, d, *J* = 8.8, H-6); 7.34 (1H, s, H-4'); 8.24 (1H, d, *J* = 8.8, H-5); 8.42 (1H, s, H-2); 10.52 (1H, s, CHO); 12.25 (1H, s, OH)]
4	3080 (CHO···HO), 1740 (C=O ester), 1660, 1630 (C=O)	[2.26 (3H, s, 6-CH_3); 2.34 (3H, s, 2'-CH_3); 3.83 (3H, s, CO_2CH_3); 7.08 (1H, s, H-4'); 8.11 (1H, s, H-5); 10.48 (1H, s, CHO); 12.77 (1H, s, OH)]
5a	3250 (=N–H), 1740 (C=O ester), 1650 ($C=O_\gamma$)	2.45 (3H, s, 2'-CH_3); 2.69 (3H, s, 4"-CH_3); 4.07 (3H, s, CO_2CH_3); 7.48 (1H, s, H-4'); 7.57 (1H, s, H-5"); 7.87 (1H, d, *J* = 9.2, H-6); 8.45 (1H, s, H-2); 8.91 (1H, d, *J* = 9.2, H-5); 9.32 (1H, s, H-10) [2.48 (3H, s, 2'-CH_3); 2.52 (s, 4"-CH_3, DMCO); 3.86 (3H, s, CO_2CH_3); 7.34 (2H, m, H-4',6); 7.40 (1H, s, H-5"); 8.20 (1H, d, *J* = 8.8, H-5); 8.59 (1H, s, H-2); 8.82 (1H, s, H-10); 9.14 (1H, s, NH)]
5b	3300 (=N–H), 1720 (C=O ester), 1640 ($C=O_\gamma$)	2.42 (3H, s, 4'"-CH_3); 2.46 (3H, s, 2'-CH_3); 4.07 (3H, s, CO_2CH_3); 7.35 (2H, d, *J* = 8.0, *m*-H Tol); 7.49 (1H, s, H-4'); 7.76 (2H, d, *J* = 8.0, *o*-H Tol); 7.89 (1H, d, *J* = 9.2, H-6); 7.90 (1H, s, H-5"); 8.49 (1H, s, H-2); 8.90 (1H, d, *J* = 9.2, H-5); 9.37 (1H, s, H-10)
5c	3300 (=N–H), 1720 (C=O ester), 1640 ($C=O_\gamma$)	2.49 (3H, s, 2'-CH_3); 4.10 (3H, s, CO_2CH_3); 7.52 (1H, s, H-4'); 7.64 (2H, d, *J* = 8.0, *m*-H C_6H_4Br); 7.78 (2H, d, *J* = 8.0, *o*-H C_6H_4Br); 7.91 (1H, d, *J* = 8.8, H-6); 7.97 (1H, s, H-5"); 8.52 (1H, s, H-2); 8.92 (1H, d, *J* = 8.8, H-5); 9.38 (1H, s, H-10)
5d	3280 (=N–H), 1710 (C=O ester), 1650 ($C=O_\gamma$)	2.49 (3H, s, 2'-CH_3); 4.10 (3H, s, CO_2CH_3); 7.52 (1H, s, H-4'); 7.69-7.77 (2H, m, H-5",6"); 7.92 (1H, d, *J* = 9.2, H-6); 8.11 (1H, d, *J* = 7.6, H-7"); 8.25 (1H, d, *J* = 7.6, H-4"); 8.53 (1H, s, H-2); 8.94 (1H, d, *J* = 9.2, H-5); 9.46 (1H, s, H-10)
5e	3290 (=N–H), 1710 (C=O ester), 1655 ($C=O_\gamma$)	2.48 (3H, s, 2'-CH_3); 4.09 (3H, s, CO_2CH_3); 7.50 (1H, s, H-4'); 7.69 (2H, t, *J* = 7.6, *m*-H Ph); 7.80 (1H, t, *J* = 7.6, *p*-H Ph); 7.94 (1H, d, *J* = 9.0, H-6); 8.07 (2H, d, *J* = 7.6, *o*-H Ph); 8.50 (1H, s, H-2); 9.00 (1H, d, *J* = 9.0, H-5); 9.53 (1H, s, H-10)
5f	3300 (=N–H), 1705 (C=O ester), 1650 ($C=O_\gamma$)	2.45 (3H, s, 2'-CH_3); 4.08 (3H, s, CO_2CH_3); 4.28 (3H, s, NCH_3); 7.48 (1H, s, H-4'); 7.76 (1H, d, *J* = 8.8, H-6); 7.87-7.97 (4H, m, H-4",5",6",7"); 8.40 (1H, s, H-2); 8.86 (1H, d, *J* = 8.8, H-5); 9.26 (1H, s, H-10)
6	3325 (=N–H), 1725 (C=O ester), 1660 ($C=O_\gamma$)	2.35 (3H, s, 6-CH_3); 2.81 (3H, s, 2'-CH_3); 4.12 (3H, s, CO_2CH_3); 7.37 (1H, s, H-4'); 7.68 (2H, d, *J* = 8.4, *m*-H C_6H_4Br); 7.79 (2H, d, *J* = 8.4, *o*-H C_6H_4Br); 7.98 (1H, s, H-5"); 8.70 (1H, s, H-5); 9.32 (1H, s, H-10) [2.28 (3H, s, 6-CH_3); 2.52 (s, 2'-CH_3, DMCO); 3.84 (3H, s, CO_2CH_3); 7.12 (1H, s, H-4'); 7.61 (2H, d, *J* = 8.4, *m*-H C_6H_4Br); 7.98 (2H, d, *J* = 8.4, *o*-H C_6H_4Br); 8.03 (1H, s, H-5"); 8.25 (1H, s, H-5); 8.81 (1H, s, H-10); 9.34 (1H, s, NH)]
7a	1740 ($C=O_\alpha$), 1710 (C=O ester), 1660 ($C=O_\gamma$)	2.50 (3H, s, 2'-CH_3); 2.83 (3H, s, 4"-CH_3); 4.12 (3H, s, CO_2CH_3); 7.52 (1H, s, H-4'); 7.79 (1H, d, *J* = 9.2, H-6); 7.82 (1H, s, H-5"); 8.48 (1H, s, H-2); 8.88 (1H, d, *J* = 9.2, H-5); 9.75 (1H, s, H-10)
7b	1725 ($C=O_\alpha$ + ester), 1645 ($C=O_\gamma$)	2.48 (3H, s, 4'"-CH_3); 2.50 (3H, s, 2'-CH_3); 4.09 (3H, s, CO_2CH_3); 7.49 (2H, d, *J* = 8.0, *m*-H Tol); 7.50 (1H, s, H-4'); 7.71 (2H, d, *J* = 8.0, *o*-H Tol); 7.77 (1H, d, *J* = 9.2, H-6); 8.13 (1H, s, H-5"); 8.45 (1H, s, H-2); 8.88 (1H, d, *J* = 9.2, H-5); 9.91 (1H, s, H-10)
7c	1730 ($C=O_\alpha$+ester), 1660 ($C=O_\gamma$)	2.48 (3H, s, 2'-CH_3); 4.09 (3H, s, CO_2CH_3); 7.51 (1H, s, H-4'); 7.72 (2H, d, *J* = 8.0, *m*-H C_6H_4Br); 7.77 (1H, d, *J* = 9.2, H-6); 7.83 (2H, d, *J* = 8.0, *o*-H C_6H_4Br); 8.21 (1H, s, H-5"); 8.46 (1H, s, H-2); 8.88 (1H, d, *J* = 9.2, H-5); 9.94 (1H, s, H-10)

TABLE 2 (continued)

1	2	3
7d	1740 ($C=O_{\alpha}$), 1710 (C=O ester), 1650 ($C=O_{\gamma}$)	2.49 (3H, s, 2'-CH_3); 4.10 (3H, s, CO_2CH_3); 7.51 (1H, s, H-4'); 7.80 (1H, d, *J* = 8.8, H-6); 7.96 (1H, t, *J* = 8.0, H-6"); 8.04 (1H, t, *J* = 8.0, H-5"); 8.32 (1H, d, *J* = 8.0, H-7"); 8.42 (1H, d, *J* = 8.0, H-4"); 8.49 (1H, s, H-2); 8.92 (1H, d, *J* = 8.8, H-5); 9.89 (1H, s, H-10)
7e	1725 ($C=O_{\alpha}$+ester), 1645 ($C=O_{\gamma}$)	2.49 (3H, s, 2'-CH_3); 4.10 (3H, s, CO_2CH_3); 7.51 (1H, s, H-4'); 7.79-7.83 (3H, m, *m*-H Ph, H-6); 7.97 (1H, t, *J* = 7.6, *p*-H Ph); 8.19 (2H, d, *J* = 7.6, *o*-H Ph); 8.50 (1H, s, H-2); 8.87 (1H, d, *J* = 9.2, H-5); 9.90 (1H, s, H-10)
7f	1730 ($C=O_{\alpha}$+ester), 1645 ($C=O_{\gamma}$)	2.47 (3H, s, 2'-CH_3); 4.09 (3H, s, CO_2CH_3); 4.32 (3H, s, NCH_3); 7.49 (1H, s, H-4'); 7.77 (1H, d, *J* = 9.2, H-6); 7.86-8.01 (4H, m, H-4",5",6",7"); 8.43 (1H, s, H-2); 8.87 (1H, d, *J* = 9.2, H-5); 9.41 (1H, s, H-10)
8	1730 ($C=O_{\alpha}$+ester), 1640 ($C=O_{\gamma}$)	2.29 (3H, s, 6-CH_3); 2.76 (3H, s, 2'-CH_3); 4.09 (3H, s, CO_2CH_3); 7.35 (1H, s, H-4'); 7.66 (2H, d, *J* = 8.4, *m*-H C_6H_4Br); 7.83 (2H, d, *J* = 8.4, *o*-H C_6H_4Br); 8.39 (1H, s, H-5"); 8.68 (1H, s, H-5); 9.80 (1H, s, H-10)

^{1}H NMR spectra were recorded in CF_3COOD, values recorded in DMSO-d_6 are in square brackets.

water bath for 12 h, poured into a mixture of 36% HCl–H_2O, 1:1 (24 ml), boiled for 5 min (product **4** was not boiled), diluted with water (40 ml), and after several hours the precipitated solid was filtered off. The product was recrystallized from methanol.

9-Azolyl-8-imino-3-(5-methoxycarbonyl-2-methylfuran-3-yl)-4H,8H-pyrano[2,3-*f*]chromen-4-ones 5a-f, 6 (General Method). The appropriate 2-azolylacetonitrile (1 mmol) and piperidine (3 drops) were added to a solution of chromone **3** (1 mmol) in ethanol (50 ml) or chromone **4** in 2-propanol (2 ml). The mixture was left for 24 h at room temperature, the precipitated solid was filtered off, and washed with alcohol.

9-Azolyl-3-(5-methoxycarbonyl-2-methyl-furan-3-yl)-4H,8H-pyrano[2,3-*f*]chromen-4,8-diones 7a-f, 8 (General Method). A solution of the appropriate pyranochromen-4-one **5a-f, 6** (1 mmol) in a mixture of acetic (5 ml) and 36% hydrochloric acid (1 ml) was boiled for 5-10 min, cooled, the precipitated solid was filtered off, washed with water, and with methanol.

REFERENCES

1. B. S. Joshi and V. N. Kamat, *Tetrahedron Lett.*, **7**, 5767 (1966).
2. B. S. Joshi, V. N. Kamat, and A. K. Saksena, *Tetrahedron*, **23**, 4785 (1967).
3. F. Asai, M. Iinuma, T. Tanaka, and M. Mizuno, *Heterocycles*, **33**, 229 (1992).
4. M. Iinuma, T. Tanaka, and F. Asai, *Phytochemistry*, **36**, 941 (1994).
5. E. Schlittler and U. Spitaler, *Tetrahedron Lett.*, **19**, 2911 (1978).
6. P. J. Houghton, *Planta Medica*, **53**, 264 (1987).
7. T. R. Kelly and M. H. Kim, *J. Org. Chem.*, **57**, 1593 (1992).
8. M. Vijava Lakshmi and N. V. Subba Rao, *Curr. Sci.*, **42**, 19 (1973).
9. K. A. Thakar and N. R. Manjaramkar, *Indian J. Chem.*, **9**, 892 (1971).
10. T. V. Shokol, N. V. Gorbulenko, T. M. Tkachuk, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 455 (2009). [*Chem. Heterocycl. Comp.*, **45**, 370 (2009)].
11. T. V. Shokol, V. A. Turov, V. V. Semenyuchenko, and V. P. Khilya, *Khim. Prir. Soedin.*, 544 (2006).

12. T. V. Shokol, O. A. Lozinskii, A. V. Turov, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 1361 (2009). [*Chem. Heterocycl. Comp.*, **45**, 1089 (2009)].
13. S. Rangaswami and T. R. Seshadry, *Proc. Indian Acad. Sci.*, **9A**, 7 (1939).
14. M. Krishnamurty and T. R. Seshadry, *J. Sci. Ind. Res.*, **14B**, 258 (1955).
15. Y. Kawase, T. Sekiba, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **31**, 997 (1958).