Chemistry of Heterocyclic Compounds, Vol. 36, No. 9, 2000

RECYCLIZATION OF 2-IMINO-2H-1-BENZOPYRANS UNDER THE ACTION OF NUCLEOPHILIC REAGENTS.

5.* INTERACTION OF 2-IMINOCOUMARIN-3-CARBOXAMIDE WITH ANTHRANILIC ACID AND ITS DERIVATIVES

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N-Substituted 2-iminocoumarins are formed on reacting 2-iminocoumarin-3-carboxamide with anthranilic acid, methyl anthranilate, anthranilamide, and anthranilonotrile. Depending on the reaction conditions these recyclize into the corresponding 3-substituted coumarins or are hydrolyzed to coumarin-3-carboxamide. An alternative synthesis of some of the compounds has been effected.

Keywords: anthranilic acid, 4(3H)-benzoxazinones, 2H-1-benzopyrans, 2-iminocoumarins, 4(3H)-quinazolinones, recyclization.

It was shown previously [1-5] that, depending on the conditions, 2-iminocoumarin-3-carboxamide is able to react with N-nucleophiles either with the formation of 2-N-substituted iminocoumarins (A_N-E reaction at the C=N bond) [1], or with fission of the iminolactone ring and the formation of compounds of linear structure (formally this is an S_N reaction of the OAr group as nucleophile at the imino group) [2]. In the first case the reaction occurs in the cold, and as a rule the reaction product is readily isolated from the reaction medium. In the second case a high temperature is required for the reaction (120-200°C) and the product is difficult to isolate due to its ability to undergo further conversions at these temperatures.

While continuing these investigations we studied the reaction of 2-iminocoumarin-3-carboxamide with anthranilic acid and its derivatives. On carrying out the reaction of 2-iminocoumarin-3-carboxamide (**1**) with anthranilic acid (**2**), anthranilamide (**3**), anthranilonitrile (**4a**), and methyl anthranilate (**4b**) in acetic acid the corresponding 2-N-substituted iminocoumarins **5**, **6**, **7a**, and **7b** were formed (Scheme 1, Table 1). Boiling compounds **5-7b** in acetic acid leads to a different final product. In the case of 2-[(N-2-carboxyphenyl)imino]-2H-1-benzopyran-3-carboxyamide (**5**) the reaction proceeds with fission of the iminolactone ring with the formation of 2-oxo-2H-1-benzopyran-3-(N-2-carboxyphenyl)carboxamide (**8**). In the case of 2-[(N-2-carbamoylphenyl)imino]-2H-1-benzopyran-3-carboxamide (**6**) the formation was observed of 2-(2-oxo-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one (**9**) due to nucleophilic attack of the amide group nitrogen atom of the anthranilamide residue at the carbon atom of the C=N bond (Scheme 2).

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* For communication 4, see [5].

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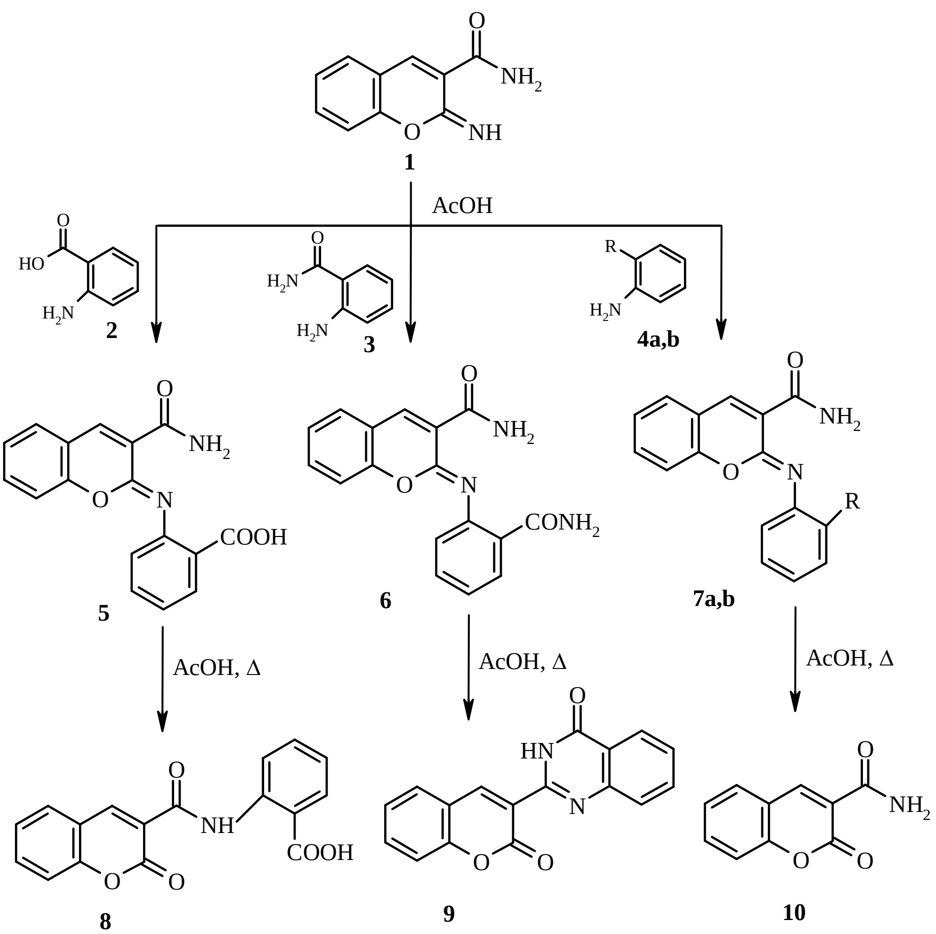
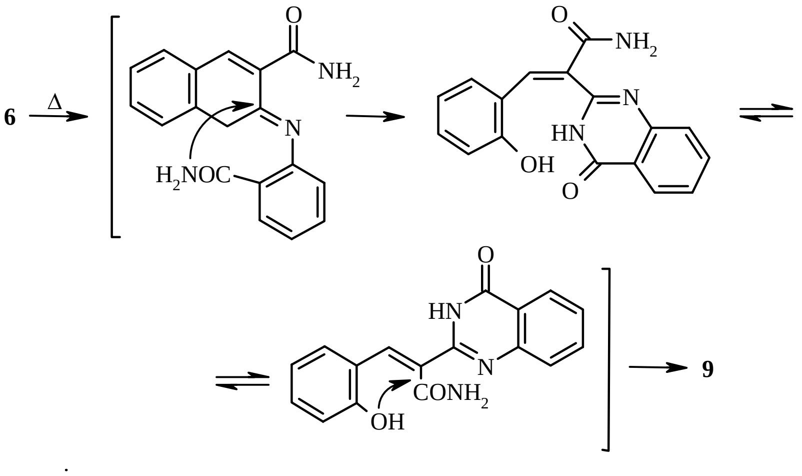
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1175-1181, September, 2000. Original article submitted May 12, 1999.

Scheme 1



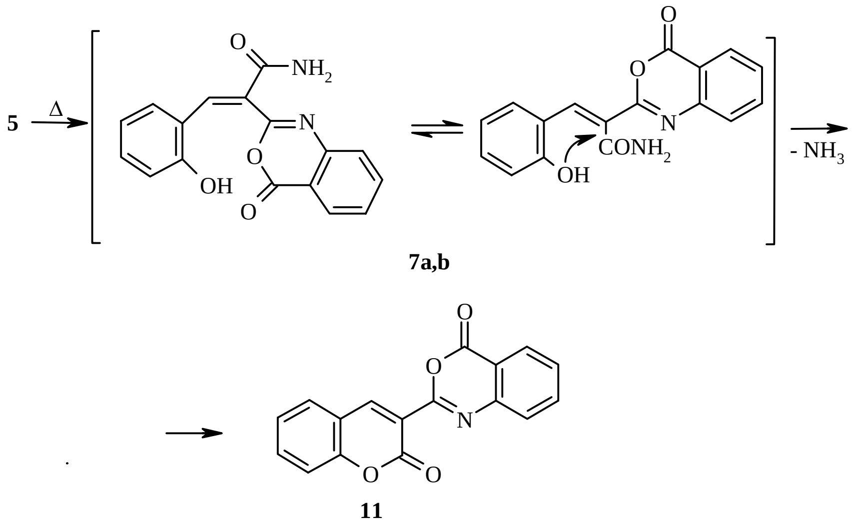
a R = CN, **b** R = COOCH$_3$

Scheme 2



It follows from the mechanism suggested that formation of 2-(2-oxo-2H-1-benzopyran-3-yl)-4H-3,1-benzoxazin-4-one (**11**) must be expected on boiling compound **5** in acetic acid. However, due to the presence of a certain amount of water in the acetic acid, reaction does not take place in this direction. Benzoxazinone **11** was successfully obtained on carrying out the reaction in acetic anhydride (Scheme 3).

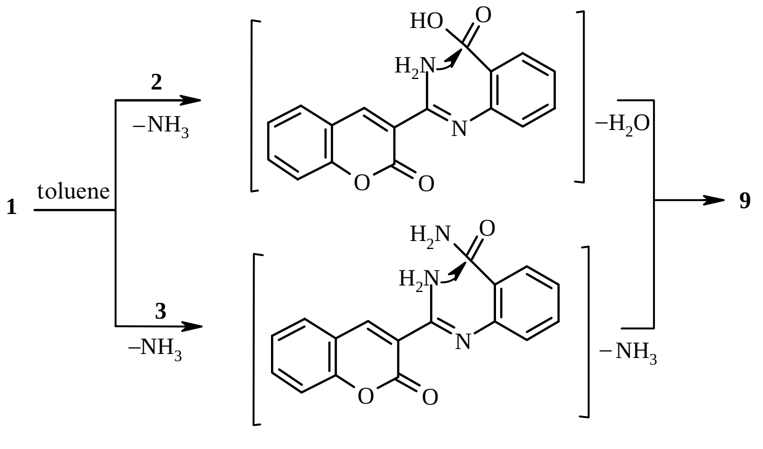
Scheme 3



In the case of compounds **7a,b** containing carbomethoxy and cyano groups, recyclization is impossible since boiling in acetic acid leads to hydrolysis and the formation of coumarin-3-carboxamide (**10**).

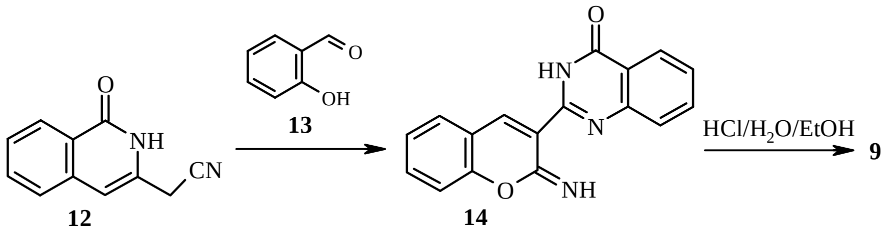
Recyclization of 2-iminocoumarin-3-carboxamide **1** by the action of anthranilic acid **2** and anthranilamide **3** on boiling in a nonpolar solvent (toluene) occurs predominantly through the stage of forming the appropriate intermediates, *viz*. amidines [2], further cyclization of which leads in both cases to 2-(2-oxo-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one (**9**) (Scheme 4). However the use of toluene as reaction medium makes sense only in the case of anthranilic acid, since significant resinification occurs in the case of anthranilamide and the yield of product is significantly lower than on carrying out the reaction in acetic acid.

Scheme 4



With the aim of confirming the structure of the obtained 2-(2-oxo-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one **9**, we have carried out an alternative synthesis of it by Knoevenagel condensation of 2-cyanomethyl-4(3H)-quinazolin-2-one (**12**) [6] with salicylic aldehyde (**13**) and subsequent acid hydrolysis of the resulting 2-(2-imino-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one (**14**) (Scheme 5).

Scheme 5



There were characteristic bands in the IR spectra of the 2-N-substituted iminocoumarins **5-7** (Table 1) for N–H at 3100-3400 cm^{-1}, for C=O at 1660-1720 cm^{-1}, and for C=N at 1640 cm^{-1}. In the IR spectra of quinazolinone **9** and benzoxazinone **11** there is no N–H band and a lactone C=O absorption appears at 1700 cm^{-1}.

The ^{1}H NMR spectra (Table 2) are characterized by the presence of overlapping signals for the protons of the ABCD systems of the coumarin and anthranilate (quinazolone/benzoxazinone) fragments in the 7.00-8.50 ppm region. In addition, signals for the NH_2 group protons were observed in the spectra of the 2-N-substituted iminocoumarins **5-7** as broadened singlets at 9.20 and 7.70 ppm, which were absent in the spectra of the corresponding recyclization products. Data of mass spectrometry (Table 3) were used in certain cases to confirm structures.

The recyclization of 2-iminocoumarin-3-carboxamide under the action of anthranilic acid and anthranilamide therefore leads to 2-(2-oxo-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one which may serve as an alternative method to obtaining it according to Knoevenagel. And the recyclization of 2-[(N-2-carboxyphenyl)imino]-2H-1-benzopyran-3-carboxamide makes possible the preparation of other 3-substituted coumarins, such as 2-(2-oxo-2H-1-benzopyran-3-yl)-4H-3,1-benzoxazin-4-one.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp,°C	IR spectra (KBr), cm^{-1} (assignments)	UV spectrum (ethanol) λ_{max}, nm (ε, M·cm^{-1})	Yield, % (method)
5	$C_{17}H_{12}N_2O_4$	191-192	3300 (NH+OH) 3160 (NH) 1700 (C=O) 1670 (C=O)	249 (18400) 365 (6450)	62
6	$C_{17}H_{13}N_3O_3$	244-246	3392 (NH) 3168 (NH) 1640 (C=O$^+$C=N) 1588 (C=C)	290 (13310) 359 (9210)	82
7a	$C_{17}H_{11}N_3O_2$	214-217	3256 (NH) 3112 (NH) 2232 (C≡N) 1696 (C=O) 1644 (C=N) 1592 (C=C)	291 (11700) 359 (7480)	68
7b	$C_{18}H_{14}N_2O_4$	170-173	3424 (NH) 3272 (NH) 1716 (C=O) 1688 (C=O) 1608 (C=C)	292 (15140) 357 (9460)	61
8	$C_{17}H_{11}NO_5$	275-276*	3266 (NH) 1731 (C=O) 1696 (C=O) 1673 (C=O)	296 (13170) 335 (13510)	91 (A) 82 (B)
9	$C_{17}H_{10}N_2O_3$	275-277	3254 (NH) 1706 (C=O) 1690 (C=O) 1606 (C=C)	218 (30303) 298 (10710) 353 (11430)	70 (A) 78 (B) 47 (C) 56 (D) 89 (E)
11	$C_{17}H_9NO_4$	203-204*^{2}	3063 (CH) 1749 (C=O) 1599 (C=C)	220 (21333) 349 (14500)	77
14	$C_{17}H_{11}N_3O_2$	225-228	3435 (NH) 3319 (NH) 3060 (CH) 1689 (C=O) 1678 (C=N) 1655 (C=N) 1599 (C=C)	218 (29140) 378 (11100)	74

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* Mp 278°C according to [7].

* Mp 197°C according to [7].

TABLE 2. ^{1}H NMR Spectra (DMSO-d_6) of the Compounds Synthesized, ppm

Com-pound	1H, s, 4-H	H_{arom}	Other protons
5	8.42	7.90 (1H, dd, 5-H); 7.64 (1H, dd, ArH); 7.48-7.41 (2H, m); 7.22-7.10 (3H, m); 6.98 (1H, d, H-8)	9.21 (1H, br. s, NH$_2$); 7.62 (1H, br. s, NH$_2$)
6	8.41	7.78-7.75 (2H, m, NH + ArH); 7.64-7.40 (3H, m); 7.28-7.07 (5H, m, NH + ArH)	9.02 (1H, br. s, NH$_2$); 7.83 (1H, br. s, NH$_2$)
7a	8.67	7.77 (1H, d, 5-H); 7.68 (1H, t, 7-H); 7.62-7.50 (3H, m); 7.32-7.22 (2H, m); 7.12 (1H, d, 8-H)	9.06 (1H, br. s, NH$_2$); 7.83 (1H, br. s, NH$_2$)
8b	8.52	7.88 (1H, d, 5-H); 7.73 (1H, d, ArH); 7.52 (1H, t, ArH); 7.45 (1H, t, ArH); 7.26-7.17 (3H, m); 6.98 (1H, d, 8-H)	9.17 (1H, br. s, NH$_2$); 7.76 (1H, br. s, NH$_2$); 3.71 (3H, s, OCH$_3$)
8	8.85	8.65 (1H, d, ArH); 8.05 (1H, d, ArH); 7.94 (1H, d, 5-H); 7.73 (1H, t, 7-H); 7.56 (1H, t, ArH); 7.39 (2H, m, 6-H + 8-H)	13.52 (1H, br. s, NH)
9	8.97	8.18 (1H, m, ArH); 8.03 (1H, d, ArH); 7.90 (1H, d, ArH); 7.79 (2H, m); 7.58 (2H, m); 7.49 (1H, m, ArH)	12.07 (1H, br. s, NH)
11	8.86	8.20 (1H, d, ArH); 7.96-7.92 (2H, m, ArH); 7.74-7.69 (2H, m, ArH); 7.65 (1H, t, ArH); 7.43-7.38 (2H, m, 6-H + 8-H)	
14	8.96	8.14 (1H, d, 5-H); 7.73-7.68 (3H, m); 7.54 (1H, t, ArH); 7.46 (1H, t, ArH); 7.28-7.22 (2H, m, 6-H + 8-H)	14.04 (1H, s, –NH–); 8.98 (1H, s, =NH)

TABLE 3. Mass Spectra of Some of the Compounds Synthesized

Compound	*m/z* (I_{rel}, %)
5	308 (M$^+$, 46), 291 (55), 264 (37), 248 (86), 220 (100), 189 (43), 173 (36), 145 (54), 119 (42), 89 (34), 65 (28), 44 (36)
8	309 (M$^+$, 27), 264 (10), 173 (100), 119 (26), 101 (27), 89 (22), 63 (10)
9	290 (M$^+$, 83), 262 (17), 145 (8), 119 (100), 92 (19), 76 (5), 53 (10)
14	289 (M$^+$, 76), 272 (100), 171 (10), 146 (30), 119 (62), 92 (19), 77 (6), 63 (9)

TABLE 4. Results of Elemental Analysis of the Compounds Synthesized

Compound	Empirical formula	Mol. wt.	Nitrogen content, %	
			Found	Calculated
5	$C_{17}H_{12}N_2O_4$	308.30	9.15	9.09
6	$C_{17}H_{13}N_3O_3$	307.31	13.58	13.67
7a	$C_{17}H_{11}N_3O_2$	289.30	14.45	14.52
7b	$C_{18}H_{14}N_2O_4$	322.32	8.63	8.69
8	$C_{17}H_{11}NO_5$	309.28	4.58	4.53
9	$C_{17}H_{10}N_2O_3$	290.28	99.59	9.65
11	$C_{17}H_9NO_4$	291.27	4.77	4.81
14	$C_{17}H_{11}N_3O_2$	289.30	14.61	14.52

EXPERIMENTAL

The IR spectra of the compounds synthesized were recorded on a Specord M 80 spectrometer in KBr disks. The UV spectra were recorded on a Specord M 40 instrument in ethanol. The ^{1}H NMR spectra were drawn on a Varian WXR 400 instrument in DMSO-d_6, internal standard being TMS. The mass spectra were recorded on a

Finnigan MAT 4615B instrument, ionization energy was 70 eV, on ballistic heating of the sample. The characteristics of the compounds obtained are given in Tables 1-4.

2-[(N-2-Carboxyphenyl)imino]coumarin-3-carboxamide (5). 2-Iminocoumarin-3-carboxamide **1** (1.88 g, 0.01 mol) was added to a solution of anthranilic acid **2** (1.37 g, 0.01 mol) in acetic acid (10 ml). The solution was stirred vigorously. The precipitated solid compound **5** was filtered off, washed thoroughly with water, then with alcohol, and dried. Compounds **6** and **7a,b** were obtained similarly.

2-Oxo-2H-1-benzopyran-3-(N-2-carboxyphenyl)-carboxamide (8). A. A solution of compound **5** (0.31 g, 1 mmol) in acetic acid (3 ml) was boiled for 20-30 min. Water (5 ml) was added to the cooled reaction mixture. The precipitated residue was filtered off, washed thoroughly with water, and dried. The solid was recrystallized from acetic acid.

B. A solution of 2-iminocoumarin-3-carboxamide **1** (1.88 g, 0.01 mol) and anthranilic acid **2** (1.37 g, 0.01 mol) in acetic acid (10 ml) was boiled for 1 h. The mixture was then processed as described above.

2-(2-Oxo-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one (9). A. A solution of compound **6** (0.31 g, 1 mmol) in acetic acid (5 ml) was boiled for 20-30 min. The precipitated solid was filtered off, washed thoroughly with water, and dried. The compound was recrystallized from a butanol–DMF mixture.

B. A solution of 2-iminocoumarin-3-carboxamide **1** (1.88 g, 0.01 mol) and anthranilamide **3** (1.36 g, 0.01 mol) in acetic acid (10 ml) was boiled for 1 h. The mixture was then processed as described above.

C. A solution of 2-iminocoumarin-3-carboxamide **1** (0.28 g, 1.5 mmol) and anthranilic acid **2** (0.37 g, 1.7 mmol) in dry toluene (10 ml) was boiled for 5-6 h using a Dean and Stark head. Evolution of ammonia was observed in the course of the reaction. After cooling the reaction mixture, the precipitated solid was filtered off, dried, and recrystallized.

D. A solution of 2-iminocoumarin-3-carboxamide **1** (0.28 g, 1.5 mmol) and anthranilamide **3** (0.20 g, 1.5 mmol) in dry toluene (10 ml) was boiled for 5-6 h. The mixture was then processed as described above.

E. A solution of compound **14** (0.29 g, 1 mmol) in isopropyl alcohol (30 ml) was boiled with aqueous hydrochloric acid (1 : 1) for 3 h. After cooling, the reaction mixture was filtered, the precipitated solid was thoroughly washed with water, dried, and recrystallized.

2-(2-Oxo-2H-1-benzopyran-3-yl)-4H-3,1-benzoxazin-4-one (11). A solution of compound **5** (0.31 g, 1 mmol) in acetic anhydride (3 ml) was boiled for 30 min. The precipitated solid was filtered off, thoroughly washed with water, then with alcohol, and dried.

2-(2-Imino-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one (14). Salicylic aldehyde (1.04 ml, 0.01 mol) and piperidine (3-4 drops) were added to a solution of 2-cyanomethyl-4(3H)-quinazolin-2-one **12** (1.85 g, 0.01 mol) in isopropyl alcohol (20 ml). The solution was stirred vigorously. The precipitated solid was filtered off, washed with isopropyl alcohol, and dried. The product was recrystallized from 1-butanol.

REFERENCES

1. V. A. Zubkov, S. N. Kovalenko, V. P. Chernykh, and S. M. Ivkov, *Khim. Geterotsikl. Soedin.*, 760 (1994).
2. S. N. Kovalenko, V. A. Zubkov, V. P. Chernykh, A. V. Turov, and S. M. Ivkov, *Khim. Geterotsikl. Soedin.*, 186 (1996).
3. S. N. Kovalenko, V. P. Chernykh, A. E. Shkarlat, I. V. Ukrainets, V. I. Gridasov, and S. A. Rudnev, *Khim. Geterotsikl. Soedin.,* 916 (1998).
4. S. N. Kovalenko, M. V. Vasil'ev, I. V. Sorokina, V. P. Chernykh, A. V. Turov, and S. A. Rudnev, *Khim. Geterotsikl. Soedin.*, 1664 (1998).
5. S. N. Kovalenko, K. M. Sytnik, V. M. Nikitchenko, S. V. Rusanova, V. P. Chernykh, and A. O. Porokhnyak, *Khim. Geterotsikl. Soedin.*, 190 (1999).
6. M. A. A. Aziz, H. A. Daboun, and S. M. A. Gawad, *J. Prakt. Chem.,* **332**, 610 (1990).
7. M. R. Selim, F. M. Aly, A. H. Bedair, and F. A. Abu-Shanab, *J. Indian Chem. Soc.*, **69**, 688 (1992).