Chemistry of Heterocyclic Compounds, Vol. 39, No. 12, 2003

SYNTHESIS OF 2-(β-HETARYLAMINO-ETHYL)-3,5,6-TRICHLORO-1,4-BENZOQUINONES*

G. Karlivans and R. Valters

4,6,7-Trichloro-2-hetarylamino-5-hydroxy-2,3-dihydrobenzo[b]furans have been prepared from 4,6,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[b]furan and hetarylamines. Reductive opening of the dihydrobenzofuran ring in these compounds gave 3,5,6-trichloro-2-(β-hetarylaminoethyl)-hydroquinones. The latter could be oxidised to the target 3,5,6-trichloro-2-(β-hetarylaminoethyl)-1,4-benzoquinones which are novel 1,4-benzoquinone derivatives with intramolecular charge transfer.

Keywords: 4,6,7-trichloro-2-hetarylamino-5-hydroxy-2,3-dihydrobenzo[*b*]furans, 3,5,6-trichloro-2-(β-hetarylaminoethyl)-1,4-benzoquinones, intramolecular charge transfer, reductive ring opening, oxidation.

We have previously developed a method for the synthesis of 2-hetaryl-substituted trichloro-1,4-benzoquinones [1-3] based on 3,4,6,7-tetrachloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan which is readily prepared in two stages from chloranil [4]. The method includes the recyclization of the indicated dihydrobenzofuran with different bifunctional compounds and subsequent oxidation of the hydroquinone fragment in the products formed. In this way, hetaryl-substituted trichloro-1,4-benzoquinones were obtained with the rings of thiazole and thiazoline [5], selenazole [6], thiazoline-2-thione [7, 8], 1,3,4-thiadiazine [9], pyrazole [9], and 1,3-dithiol-2-one [10]. The molecules of these compounds show intramolecular charge transfer due to the presence in them of a covalently linked C–C bond of the electron-donor heterocycle and the electron-acceptor residue of the benzoquinone. This transition is achieved through a direct conjugative effect between both fragments and is reflected in the electronic spectra of the indicated hetaryl substituted compounds.

Our work concerns the synthesis of 2-(β-hetarylaminoethyl)-3,5,6-trichloro-1,4-benzoquinones, the molecules of which contain unconjugated electron-donor and electron-acceptor fragments separated by a $–CH_2CH_2NH–$ group. Results for the investigation of this type of compound with intramolecular charge transfer are summarized in the monograph [11]. In the section regarding a conformationally flexible structures with a three membered bridge (four σ-bonds), compounds containing fragments with relatively weak electron-acceptor (nitroaryl groups, 1,4-naphthoquinone derivatives) and electron-donor (aryl groups with electron donor substituents) properties were discussed [11, see p. 21].

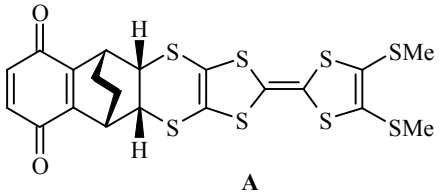
Systems were later synthesized with very strong electron-donors with tetrathiafulvalene derivative residues bonded to the 1,4-benzoquinone fragment either with conformationally flexible or rigid components with several σ-bonds. However, UV spectroscopy was unable to reveal an intramolecular charge transfer in any

* Dedicated to Professor J. Stradins on the occasion of his 70th birthday. We wish the respected celebrant good health and many years of productive work on behalf of Latvian science and culture.

Riga Technical University, Riga LV-1048, Latvia; e-mail: rvalters@latnet.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1837-1843, December, 2003. Original article submitted January 29, 2002.

0009-3122/03/3912-1617$25.00©2003 Plenum Publishing Corporation

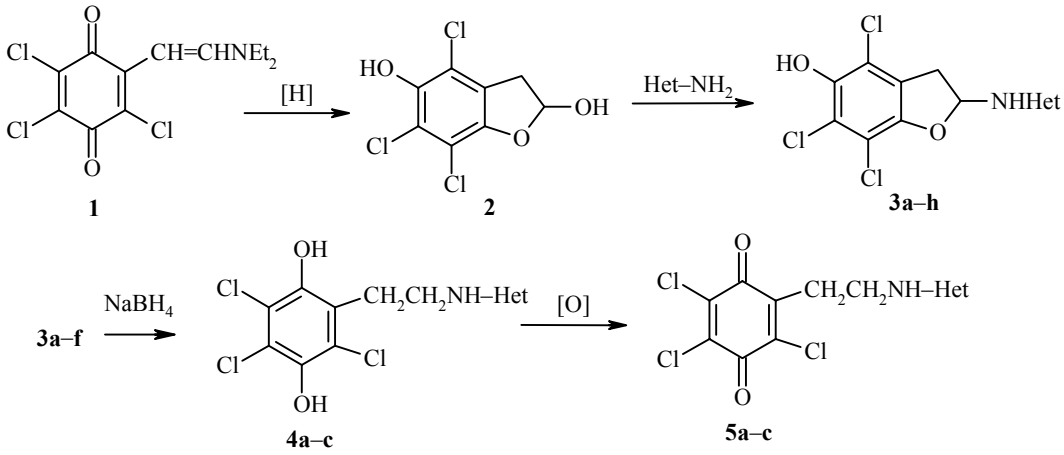
of these [12]. Compound **A** has recently been described [13] in the molecule of which the tetrathiafulvalene fragment is linked to the 1,4-benzoquinone fragment by a sterically rigid cyclic bridge.



A

The electronic spectrum of **A** shows an absorption peak at ~685 nm with ε ~ 310 indicating a weak intramolecular charge transfer. X-ray structural analysis has shown that charge transfer occurs through space thanks to the distorted folding of the molecule and partial overlap of the orbitals of the donor and acceptor fragments.

We were able to prepare 4,6,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan (**2**) *via* the reduction of the readily available [14] 3,5,6-trichloro-2-(β-diethylaminoethenyl)-1,4-benzoquinone (**1**) and sodium dithionite [15] or tin dichloride in concentrated hydrochloric acid [16].



3 **a** Het = 2-pyridyl, **b** Het = 3-pyridyl, **c** Het = 4-pyridyl, **d** Het = 1,2,4-triazol-3-yl, **e** Het = tetrazol-5-yl, **3f**, **4a**, **5a** Het = 2-pirimidyl, **3g**, **4b**, **5b** Het = 2-thiazolyl, **3h**, **4c**, **5c** Het = 6-quinolyl

Treatment of compound **2** with 2-, 3-, or 4-aminopyridines, 3-amino-1,2,4-triazole, 5-aminotetrazole, 2-aminopyrimidine, 2-aminothiazole, or 6-aminoquinoline gave good yields of the corresponding 4,6,7-trichloro-2-hetarylamino-5-hydroxy-2,3-dihydrobenzo[*b*]furans (**3a-h**) (Table 1).

In the ^{1}H NMR spectra of the compound **2** (see Experimental) and of **3a-h** (Table 2) the signals for the protons of the methylene group in position 3 of the heterocycle appear as two double doublets and this is related to their chemical non equivalence and the difference in the spin spin coupling of each of them with the proton on the chiral carbon atom at position 2. The latter appears as a multiplet (8 lines as a poorly resolved double doublet of doublets) because of its interaction with the non equivalent protons of the CH_2 group and also with the NH group proton.

Treatment of compounds **3f-h** with sodium borohydride in aqueous DMF solutions leads to a reductive opening of their dihydrobenzofuran ring and gives the corresponding 3,5,6-trichloro-2-(β-hetarylaminoethyl)hydroquinones **4a-c**. The structure of the latter was confirmed by their ^{1}H NMR spectra (Table 2) which showed two triplets for the methylene group protons, broadened signals for the OH and NH group protons, and signals for the protons of the corresponding heterocycle.

TABLE 1. Characteristics of Compounds **3a-h, 4a-c, 5a-c**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C (dec.)	Yield, %
		C	H	Cl	N	S		
3a	$C_{13}H_9Cl_3N_2O_2$	46.85 / 47.09	2.82 / 2.74	32.43 / 32.08	8.34 / 8.45		187-188	78
3b	$C_{13}H_9Cl_3N_2O_2$	47.30 / 47.09	2.66 / 2.74	32.17 / 32.08	8.28 / 8.45		199-201	85
3c	$C_{13}H_9Cl_3N_2O_2$	47.38 / 47.09	2.87 / 2.74	32.37 / 32.08	8.67 / 8.45		237-239	41
3d	$C_{10}H_7Cl_3N_4O_2$	37.60 / 37.35	2.30 / 2.19	32.53 / 33.08	17.66 / 17.43		200-202	76
3e	$C_9H_6Cl_3N_5O_2$	33.77 / 33.51	1.96 / 1.88	32.69 / 32.98	22.02 / 21.71		221-222	76
3f	$C_{12}H_8Cl_3N_3O_2$	43.57 / 43.33	2.32 / 2.42	32.43 / 31.98	12.51 / 12.64		205-206	85
3g	$C_{11}H_7Cl_3N_2O_2S$	39.24 / 39.13	2.18 / 2.09	31.27 / 31.51	8.54 / 8.30	9.70 / 9.50	200-202	92
3h	$C_{17}H_{11}Cl_3N_2O_2$	53.55 / 53.50	3.00 / 2.91	27.37 / 27.87	7.18 / 7.34		218-220	93
4a	$C_{12}H_{10}Cl_3N_3O_2$	43.04 / 43.07	3.02 / 3.01	31.14 / 31.79	12.14 / 12.56		208-210	61
4b	$C_{11}H_9Cl_3N_2O_2S$	38.39 / 38.90	2.70 / 2.67	32.07 / 31.32	7.84 / 8.25	8.79 / 9.44	168-170	88
4c	$C_{17}H_{13}Cl_3N_2O_2$	53.24 / 53.22	3.39 / 3.42	27.59 / 27.73	7.19 / 7.30		218-220	92
5a	$C_{12}H_8Cl_3N_3O_2$	43.25 / 43.33	2.39 / 2.42	31.94 / 31.98	12.18 / 12.64		240-242	82
5b	$C_{11}H_7Cl_3N_2O_2S$	39.92 / 39.13	2.17 / 2.09	31.18 / 31.51	7.99 / 8.30	9.95 / 9.50	>250	70
5c	$C_{17}H_{11}Cl_3N_2O_2$	52.92 / 53.50	2.91 / 2.91	27.45 / 27.87	7.08 / 7.34		227-228	71

Oxidation of the hydroquinones **4a-c** with 1,4-benzoquinone gives the target 3,5,6-trichloro-2-(β-hetarylaminoethyl)-1,4-benzoquinone products (**5a-c**). Oxidation of **4** to **5** occurs in DMSO–ethanol solution in the presence of an equimolar amount of hydrochloric acid in order to protect the NH group *via* its protonation.

The ^{1}H NMR spectra of compounds **5a-c** (Table 2) show two triplets for the methylene groups, signals for the protons of the corresponding heterocycle, a broadened signal for the NH group, and the absence of OH group signals. The IR spectra of compounds **5a-c** (Table 2) show bands for the quinone C=O and C=C, the NH group, and C–H stretching vibrations.

Crystals of compounds **5a-c** showed a deeper shade of color than might have been expected from their molecular structure (**5a** red, **5b** dark violet, and **5c** blue). The presence in the UV spectra of compounds **5a-c** (see Experimental) of a low intensity absorption band in the range 438-539 nm points to a weak charge transfer. The UV spectra were recorded for solutions of different concentrations. The observed change in optical density of this band obeyed the Beer–Lambert law and can thus be assigned as an intramolecular charge transfer.

The absence of a direct conjugation between the π-electron systems of the donor and the acceptor in the molecules of compounds **5a-c** suggests that the intramolecular charge transfer is a result of orbital overlap through space.

Hence, in this report, we have suggested a novel method for the synthesis of 1,4-benzoquinone derivatives with intramolecular charge transfer. In these molecules the heterocyclic residue is linked to the benzoquinone fragment by a $–CH_2CH_2NH–$ bridge and the method is limited only by the availability of the corresponding aminoheterocycle.

TABLE 2. IR and ^{1}H NMR Spectra of Compounds **3-5**

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum*, δ, ppm (*J*, Hz)
3a	3388 (NH), 2670-2520 (br, OH), 1614, 1582, 1532	3.11 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 3.60 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.50-6.90 (3H, m, 2-H + 3-, 5-H$_{Het}$); 7.50 (1H, dt, 4-H$_{Het}$); 7.91 (1H, d, ^3J = 10, NH); 8.05 (1H, dt, 6-H$_{Het}$); 9.70 (1H, br. s, OH)
3b	3315 (NH), 2480 (br, OH), 1597, 1537	3.20 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 3.65 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.45 (1H, ddd, 2-H); 7.20 (2H, m, 4-, 5-H$_{Het}$); 7.50 (1H, d, ^3J = 10, NH); 7.95 (1H, t, 6-H$_{Het}$); 8.15 (1H, m, 2-H$_{Het}$); 9.70 (1H, br. s, OH)
3c	3344 (NH), 2480 (br, OH), 1616, 1588, 1528	3.13 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 3.60 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.45 (1H, ddd, 2-H); 6.73 (2H, dd, 3-, 5-H$_{Het}$); 7.90 (1H, d, ^3J = 10, NH); 8.16 (2H, dd, 2-, 6-H$_{Het}$); 9.50 (1H, br. s, OH)
3d	3516 (NH), 3284 (NH), 3120-2750 (br, OH), 1590, 1558, 1516	3.13 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 3.56 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.45 (1H, m, 2-H); 7.70 (1H, br. s, NH); 8.15 (1H, s, 5-H$_{Het}$); 9.60 (1H, br. s, OH); 13.00 (1H, br. s, NH$_{Het}$)
3e	3412 (NH), 3264 (NH), 3076-2780 (br, OH), 1638, 1544	3.17 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 3.67 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.33 (1H, m, 2-H); 8.63 (1H, d, ^3J = 10, NH); 9.80 (1H, br. s, OH); 15.40 (1H, br. s, NH$_{Het}$)
3f	3332 (NH), 3260, 2976 (br, OH), 1590, 1522	3.24 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 3.58 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.78 (2H, m, 2-H + 5-H$_{Het}$); 8.38 (2H, d, 4-, 6-H$_{Het}$); 8.47 (1H, d, ^3J = 10, NH); 9.70 (1H, br. s, OH)
3g	3384, 3248 (NH), 2470 (br, OH), 1557, 1515	3.11 (1H, dd, ^2J = 17, ^3J=6, 3-H); 3.64 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.45 (1H, ddd, 2-H); 6.80 (1H, d, ^3J = 4, 4-H$_{Het}$); 7.11 (1H, d, ^3J = 4, 5-H$_{Het}$); 8.90 (1H, d, ^3J = 10, NH); 9.80 (1H, br. s, OH)
3h	3300 (NH), 3087-2967 (CH quinoline), 2450 (br, OH), 1632,1588, 1554, 1502	3.22 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 3.71 (1H, dd, ^2J = 17, ^3J = 8, 3-H); 6.53 (1H, ddd, 2-H); 7.20-8.60 (6H, m, H$_{Het}$); 7.69 (1H, d, ^3J = 10, NH); 9.80 (1H, br. s, OH)
4a	3423 (NH), 3175 (br, OH), 1594, 1528	3.00 (2H, t, ^3J = 6, CH$_2$); 3.33 (2H, t, ^3J = 6, CH$_2$); 6.53 (1H, t, 5-H$_{Het}$); 7.20 (1H, br. t, NH); 8.24 (2H, d, 4-, 6-H$_{Het}$)
4b	3240, 3140 (NH, OH), 1612, 1566, 1510	3.04 (2H, t, ^3J = 4, CH$_2$); 3.29 (2H, t, ^3J = 4, CH$_2$); 6.60 (1H, d, ^3J = 4, 4-H$_{Het}$); 7.00 (1H, d, ^3J = 4, 5-H$_{Het}$); 7.80 (1H, br. t, NH); 9.90 (2H, br. s, OH)
4c	3383 (NH), 2960-2860 (CH quinoline), 2580 (br, OH), 1624, 1548	3.12 (2H, t, ^3J = 4, CH$_2$); 3.25 (2H, t, ^3J = 4, CH$_2$); 6.42 (1H, br. t, NH); 6.80-8.50 (6H, m, H$_{Het}$); 9.50 (1H, br. s, OH); 9.70 (1H, br. s, OH)
5a	3235 (NH), 3140-2930, 1660 (C=O quinone), 1573 (C=C quinone), 1537	3.06 (2H, t, ^3J = 6, CH$_2$); 3.63 (2H, t, ^3J = 6, CH$_2$); 5.42 (1H, br. t, NH); 6.49 (1H, t, 5-H$_{Het}$); 8.18 (2H, d, 4-, 6-H$_{Het}$)
5b	3207 (NH), 3115, 3067, 2947, 2916, 1682 and 1670 (C=O), 1596, 1572 (C=C quinone)	3.50 (4H, two overlapping triplets, ^3J = 6, 2CH$_2$); 6.56 (1H, d, ^3J = 4, 4-H$_{Het}$); 6.87 (1H, d, ^3J = 4, 5-H$_{Het}$); 7.60 (1H, br. t, NH)
5c	3275 (NH), 3100-3020, 1660 (C=O), 1620, 1560 (C=C quinone)	3.17 (2H, t, ^3J = 6, CH$_2$); 4.20 (2H, t, ^3J = 6, CH$_2$); 7.50-9.00 (6H, H$_{Het}$); 9.70 (1H, br. t, NH)

* ^{1}H NMR spectrum of compound **5a** was recorded in $CDCl_3$ and the remaining compounds in DMSO-d_6.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument for a suspension in nujol (1900-1500 cm^{-1} region, NaCl prism) or in hexachlorobutadiene (3800-2000 cm^{-1} region, LiF prism). Electronic spectra were taken on a Specord M-40 instrument for solutions in ethanol, chloroform, or dioxane at a concentration of 2.5×10^{-5} M. ^{1}H NMR spectra were obtained on a Mercury BB 200 instrument (200 MHz) with TMS as internal standard. The purity of the compounds was monitored using TLC on Silufol UV-254 silica gel plates with acetone-hexane eluent and visualization by UV light and iodine vapor.

4,6,7-Trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan (2). A solution of tin dichloride (3 g) in concentrated hydrochloric acid (15 ml) was added dropwise with stirring (magnetic stirrer) over 10 min to a solution of the benzoquinone **1** (2 g, 6.5 mmol) [14] in glacial acetic acid (25 ml) at 20°C. The initially blue solution became colorless. The reaction mixture was stirred at 20°C for 3 h, diluted with water (100 ml), and extracted with ether (2 × 50 ml). The extract was washed with water (5 × 50 ml), dried over anhydrous calcium chloride, evaporated in vacuo (rotary evaporator, bath temperature ~40°C), and the residue was dissolved in toluene (50 ml). The precipitated solid formed after standing for 20 h at 0°C was separated, washed with benzene and then hexane, and dried to give colorless crystals (1.2 g, 72%); mp 169-170°C. Repeated crystallizations from benzene gave compound **2** (1.0 g, 60%); mp 172-173°C (lit. mp 166-167°C [15], 168-170°C [16]). IR spectrum, ν, cm^{-1}: 3520 (2-OH), 3360 (br, 5-OH), 1608, 1578. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.82 (1H, dd, ^2J = 17, ^3J = 3, 3-H); 3.40 (1H, dd, ^2J = 17, ^3J = 6, 3-H); 6.06 (1H, ddd, $^3J_{C-C}$ = 6, $^3J_{C-C}$ = 3, $^3J_{C-O}$ = 6, 2-H); 7.60 (1H, d, ^3J = 6, 2-OH); 9.70 (1H, br. s, 5-OH).

4,6,7-Trichloro-2-hetarylamino-5-hydroxy-2,3-dihydrobenzo[*b*]furans (3a-h) (General Method). Compound **2** (1 g, 4 mmol) was dissolved in ethanol (20 ml) and the corresponding hetarylamine (4 mmol) was added. The reaction mixture was refluxed using a condenser for 2 h, cooled, and then held at 0°C (compounds **3a-d**) or at 20°C (compounds **3f-h**) for 20 h. The precipitated solid was separated, washed with ethanol, and dried. For the separation of compound **3e** the reaction mixture was evaporated to dryness in vacuo, the residue was treated with hot acetonitrile (10 ml), and the insoluble product **3e** was filtered off and dried.

3,5,6-Trichloro-2-(β-hetarylaminoethyl)hydroquinones (4a-c) (General Method). A solution of the corresponding compound **3f-h** (1 mmol) in DMF (10 ml) was added dropwise with stirring over 10 min to a solution of sodium borohydride (0.4 g, 10 mmol) in water (10 ml) at 20°C. The reaction mixture was stirred for 3 h at 20°C, formic acid (1 ml) was carefully added, and then water (50 ml). The precipitated product **4a-c** was separated, washed with water, and dried. UV spectrum (in ethanol, c = 2.5×10^{-5} M), λ_{max}, nm (log ε): **4a** 235 (4.46), 304 (4.06); **4b**: 263 (3.83), 305 (3.60); **4c** 255 (4.67), 296 (4.14), 371 (3.76).

3,5,6-Trichloro-2-(β-hetarylaminoethyl)-1,4-benzoquinones (5a-c) (General Method). A solution of the corresponding compound **4a-c** (1 mmol) in DMSO (8 ml) at 20°C was treated with concentrated hydrochloric acid (0.12 ml, 1.5 mmol) and a solution of 1,4-benzoquinone (0.16 g, 1.5 mmol) in ethanol (8 ml) was then added dropwise with stirring over 5 min. The reaction mixture was stirred for 2 h at 20°C and diluted with water (50 ml). The precipitated crystalline solid compounds **5a,c** were separated, washed with water, and dried.

Compound 5b. After the dilution with water the reaction mixture was extracted with benzene (50 ml) and the extract was dried over anhydrous $MgSO_4$ and evaporated in vacuo to a volume of ~10 ml. Hot petroleum ether (~30 ml) was added to the hot concentrate and the mixture was held at 0°C for 20 h. The precipitated product **5b** was separated and washed with petroleum ether.

UV spectrum, λ_{max}, nm (log ε): **5a** (in chloroform, c = 2.5×10^{-5} M) 287 (4.54), 334 (3.04), 438 (2.82); **5b** (in chloroform, c = 2.5×10^{-5} M) 286 (4.26), 359 (2.73), 514 (2.60); **5c** (in dioxane, c = 2.5×10^{-5} M) 282 (4.29), 357 (3.62), 539 (2.73).

REFERENCES

1. G. A. Karlivan, R. E. Valter, and M. F. Utinan, *Khim. Geterotsikl. Soedin.*, 849 (1985).
2. R. E. Valter, G. A. Karlivan, M. F. Utinan, and Yu. V. Gulbis, *Sib. Khim. Zh.*, No. 4, 39 (1992).
3. R. Valters, G. Karlivans, J. Gulbis, M. Utinans, and A. Bace, *Phosph., Sulfur and Silicon*, **95** & **96**, 457 (1994).
4. R. E. Valter, E. E. Liepin'sh, G. A. Karlivan, V. R. Zin'kovska, and M. F. Utinan, *Zh. Org. Khim.*, **21**, 436 (1985).
5. M. F. Utinan, R. E. Valter, G. A. Karlivan, E. E. Liepin'sh, and A. S. Edzhinya, *Khim. Geterotsikl. Soedin.*, 692 (1988).
6. M. F. Utinan, R. E. Valter, and G. A. Karlivan, *Khim. Geterotsikl. Soedin.*, 1430 (1989).
7. Yu. V. Gulbis, R. E. Valter, G. A. Karlivan, and M. F. Utinan, *Khim. Geterotsikl. Soedin.*, 111 (1994).
8. Yu. V. Gulbis and R. E. Valters, *Khim. Geterotsikl. Soedin.*, 1556 (2001).
9. G. Karlivans, J. Gulbis, R. Valters, A. Bace, and R. Kampare, *Latv. J. Chem.*, 99 (1994).
10. G. A. Karlivan, R. E. Valter, and Yu. V. Gulbis, *Khim. Geterotsikl. Soedin.*, 1055 (1998).
11. Ya. F. Freimanis, *Organic Compounds with Intramolecular Charge Transfer* [in Russian], Riga: Zinatne (1985).
12. M. R. Bryce, *Adv. Mater.*, **11**, 11 (1999).
13. E. Tsiperman, T. Regev, J. Y. Becker, J. Bernstein, A. Ellern, V. Khodorkovsky, A. Shames, and L. Shapiro, *Chem. Commun.*, 1125 (1999).
14. D. Buckley, H. B. Henbest, and P. Slade, *J. Chem. Soc.*, 4891 (1957).
15. D. Buckley, S. Dunstan, and H. B. Henbest, *J. Chem. Soc.*, 4880 (1957).
16. E. P. Fokin and E. P. Prudchenko, *Zh. Org. Khim.*, **6**, 1251 (1970).