Chemistry of Heterocyclic Compounds, Vol. 46, No. 10, 2011

SYNTHESIS OF 2-HETARYL-3-(INDOL-1-YL)- AND -(3-PYRROL-1-YL)MALEIMIDES AND STUDY OF THEIR CONVERSIONS UNDER THE ACTION OF PROTIC ACIDS*

S. A. Lakatosh[1], E. E. Bykov[1], and M. N. Preobrazhenskaya[1]**

A series of 3-(indol-1-yl)maleimides has been synthesized, substituted at position 2 by residues of amines or various nitrogenous heterocycles. The possibility of obtaining new polycondensed heterocyclic structures from them has been studied. Experimental investigations confirmed theoretical predictions made on the basis of results of quantum-chemical calculations.

Keywords: indole, indolylmaleimides, quantum chemistry, cyclization reaction.

2-Aryl-3-indolylmaleimides, and also 2-aminoaryl-3-indolylmaleimides and their derivatives are of interest as potential inhibitors of protein kinases, which may serve as a basis for constructing new medicinal preparations. A series of derivatives of bis(indolyl)maleimides are undergoing clinical testing at present [1, 2]. Derivatives of bis(indol-1-yl)-, 2-alkylamino-3-(indol-1-yl)maleimides (for example compounds **1** and **2**) were synthesized previously [3]. It was shown that under the action of protic acids these compounds are cyclized with the formation of a diazepine seven-membered ring with annelated indoline and maleimide fragments (**3** and **4** respectively) in difference to bis(indol-3-yl)maleimides **5**, which form compounds with a six-membered central ring **6** under similar conditions [4] (Scheme 1).

In the present work the preparation is described of various 3,4-bis(hetaryl)maleimides, including 2-hetaryl-3-(indol-1-yl)maleimides, and also 2-amino-3-(indol-1-yl)maleimides, and the transformation of some of them under the action of protic acids has been studied. For the purpose of predicting the direction of cyclization of 2-hetaryl-3-(indol-1-yl)maleimides under the action of protic acids, quantum-chemical calculations were carried out of the electron density distribution at the reaction centers of hetarylmaleimides and their indoleninium cations formed on protonation, and also of the energy parameters of the respective cyclization reactions.

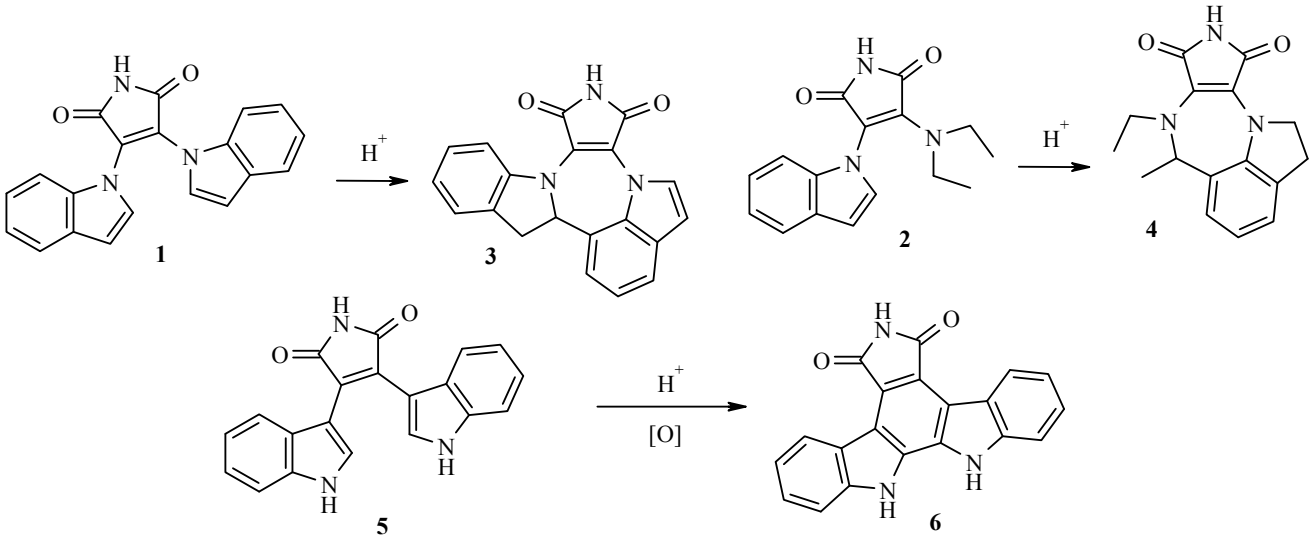
*Dedicated to the shining memory of A. N. Kost.

**To whom correspondence should be addressed, e-mail: mnp@space.ru.

[1] G. F. Gause Institute of New Antibiotics, Russian Academy of Medical Sciences, Moscow 119021, Russia.

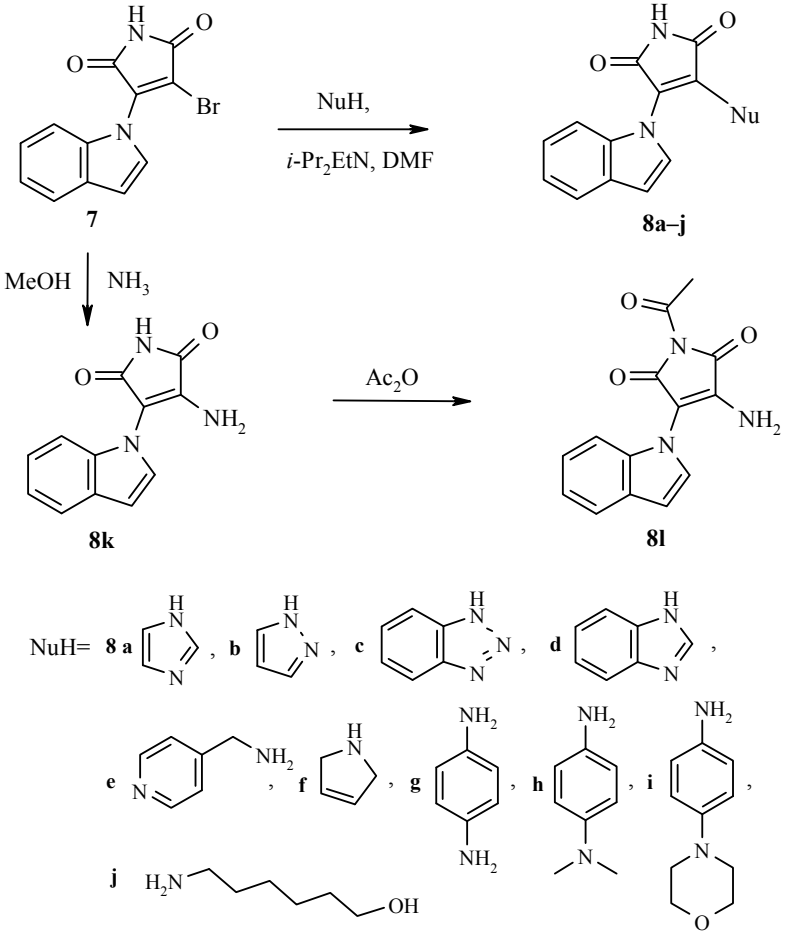
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1515-1525, October, 2010. Original article submitted August 17, 2010.

Scheme 1



Derivatives of (indol-1-yl)maleimide **8a-j** were obtained by the condensation of 2-bromo-3-(indol-1-yl)maleimide (**7**) with the appropriate amines or nitrogenous heterocycles in DMF on heating in the presence of ethyldiisopropylamine. 2-Amino-3-(indol-1-yl)maleimide (**8k**) was obtained by the interaction of compound **7** with ammonia in methanol at room temperature (Scheme 2).

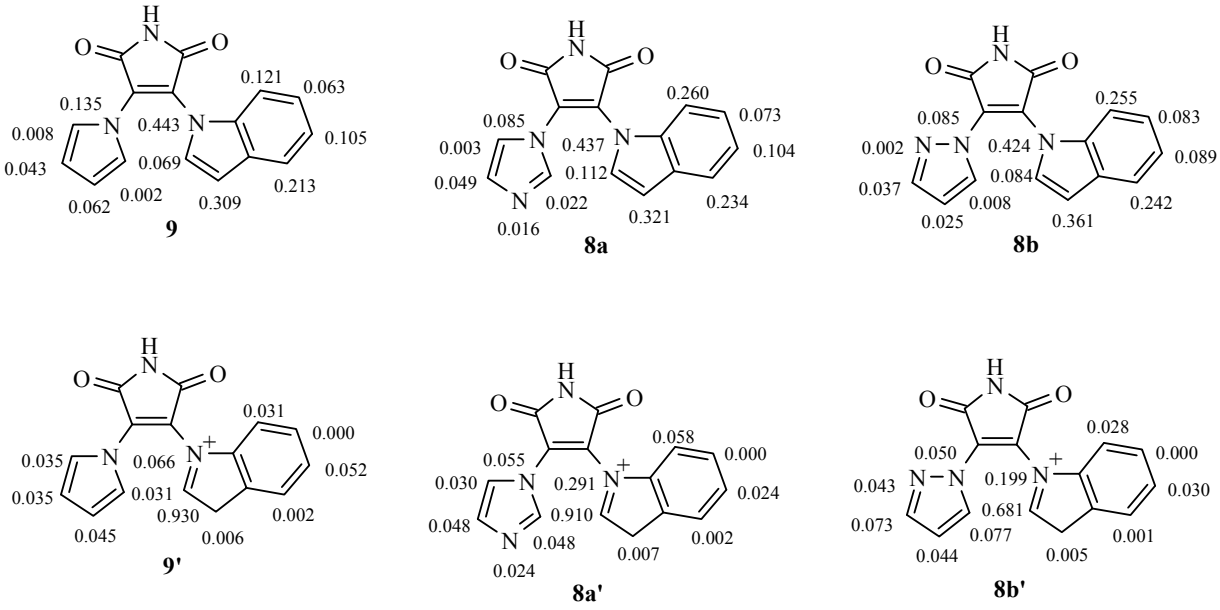
Scheme 2



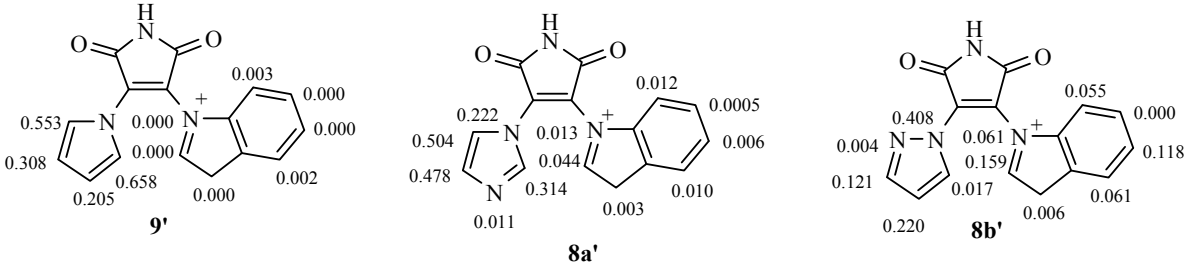
Heating compound **8k** in acetic anhydride led to acetylation at the maleimide nitrogen atom but not at the nitrogen in position 2 of the maleimide fragment. The possibility and direction of cyclization of analogs of 2-hetaryl-3-(indol-1-yl)maleimides, in which 2-hetaryl = pyrrol-1-yl (**9**), pyrazol-1-yl (**8b**), or imidazol-1-yl (**8a**), were investigated by methods of oquantum chemistry. Calculations of the distribution of limiting electron density in their HOMO were carried out in a study of the direction of protonation of these molecules.

In spite of the fact that the values of the Fukui indexes in pyrrolediones **8, 9** are greater at N(1) than at C(3), the C(3) atom must be considered to be the more nucleophilic, according to the results of calculations by the functional density method using B3LYP/6-31G(d) and the AM1 method. Consequently it may be suggested that protonation will occur at position 3 of the indole fragment of each of the molecules listed above.

To assess the reactivity of the conjugate acids of compounds **8a, 8b,** and **9** (**8a'**, **8b'**, and **9'** respectively) in intramolecular cyclization reactions the Fukui indices f were calculated for these particles corresponding to LUMO and HOMO – f_{LUMO} and f_{HOMO}.



Distribution of limiting electron density f_{LUMO} in cations **8a', 8b'**, and **9'**



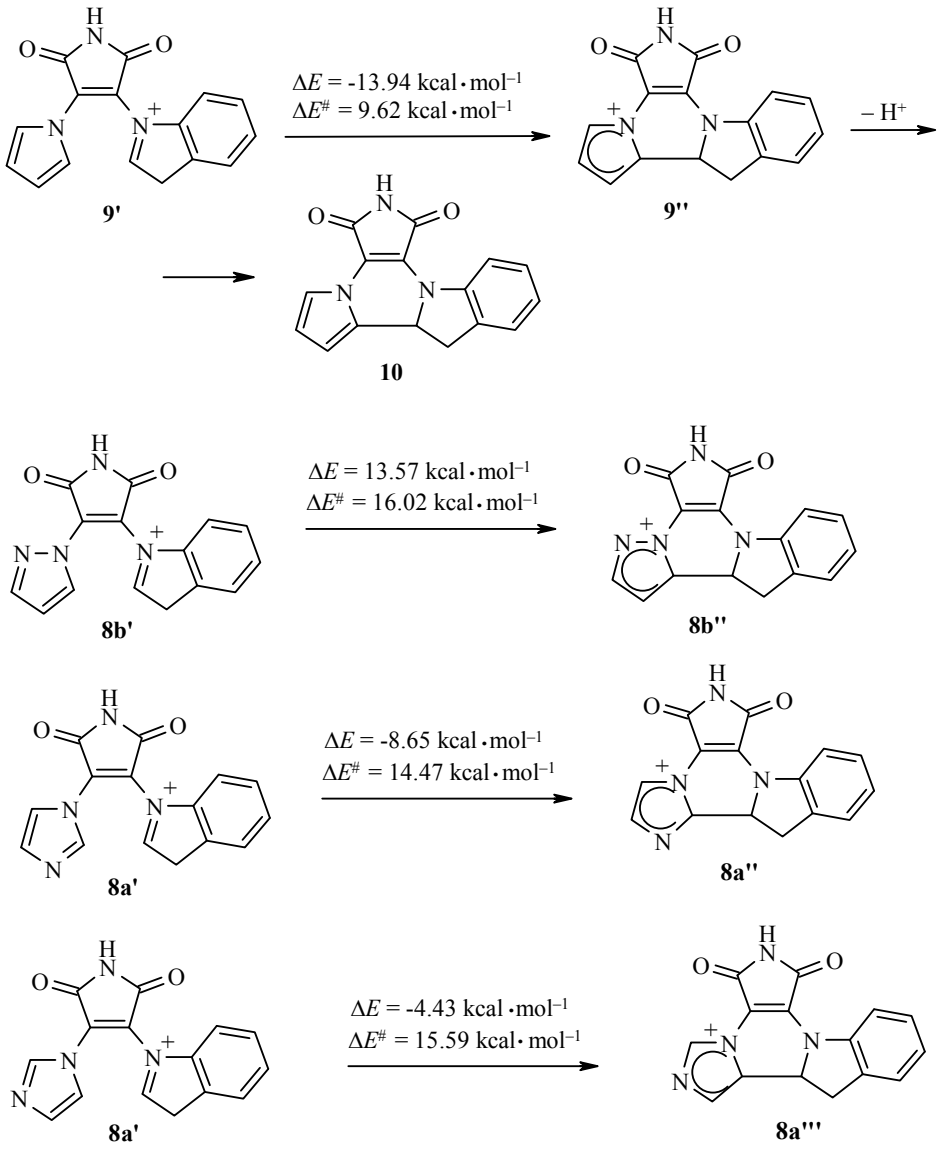
Distribution of limiting electron density f_{HOMO} in cations **8a', 8b'**, and **9'**

The greatest values of f_{LUMO} for the represented indoleninium cations are centered at position 2 of the indole ring and the values of f_{HOMO} were maximal at position 2 of the pyrrole ring for cation **9'**, at position 5 of the imidazole fragment for cation **8a'** and in position 4 of the pyrazole fragment for cation **8b'**. In this way the

favorable directions for cyclization are 2-2', 2-5', and 2-4' for cations **9'**, **8a'**, and **8b'** respectively. It must be noted that the cyclization of **8b'** according to the 2-4' direction has a low probability due to the strong distortion of valence angles in the prospective product.

The activation barriers $\Delta E^{\#}$ and heats ΔE for intramolecular cyclization of cations **8a'**, **8b'**, and **9'** were also calculated and analyzed (Scheme 3).

Scheme 3

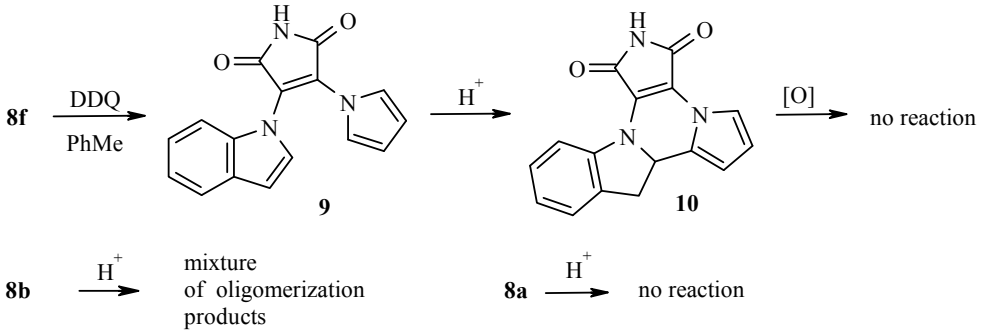


The calculations showed that $\Delta E^{\#}$ and ΔE for the intramolecular cyclization of the pyrrole system **9'** are lower than those of the **8a'** and **8b'** systems. A correlation was therefore established between the results of the calculation of energy parameters and the results of the calculation of the electron density distribution in the systems **8a'**, **8b'**, and **9'** (Scheme 3).

The condensation product **8f** on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave 2-(indol-1-yl)-3-(pyrrol-1-yl)maleimide (**9**) (Scheme 4). Treatment of imide **9** with trifluoroacetic acid in dichloromethane led to a derivative of pyrazine **10** with annelated pyrrole, maleimide, and indoline fragments,

namely 7*a*,8-dihydro-1H-dipyrrolo[2',1':3,4;3",4":5,6]pyrazino[1,2-*a*]indole-1,3(2H)-dione (Scheme 4). Conclusions on the structure of the product were made on the basis of analysis of the ^{1}H NMR spectra and double resonance spectra. In the spectrum of the product two one-proton doublets of doublets (3.28 and 3.74 ppm) were present, corresponding to the proton in position 3 of the indoline fragment, and also a one-proton triplet (5.33 ppm) corresponding to the proton in position 2 of the indoline fragment. The one-proton doublet (6.14), triplet (6.31), and multiplet (7.29 ppm) correspond to the protons in positions 3, 4, and 5 of the pyrrole fragment. Attempts to oxidize the indoline fragment in compound **10** to indole with the help of MnO_2 or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone did not lead to the desired product (Scheme 4).

Scheme 4



The pyrazole derivative **8b** (Scheme 4) was unchanged by the action of CF_3COOH in dichloromethane, but on treatment with MsOH gave a mixture of oligomerization products (data of mass spectroscopy). The imidazole derivative **8a** was unchanged by the action of protic acids.

Scheme 5

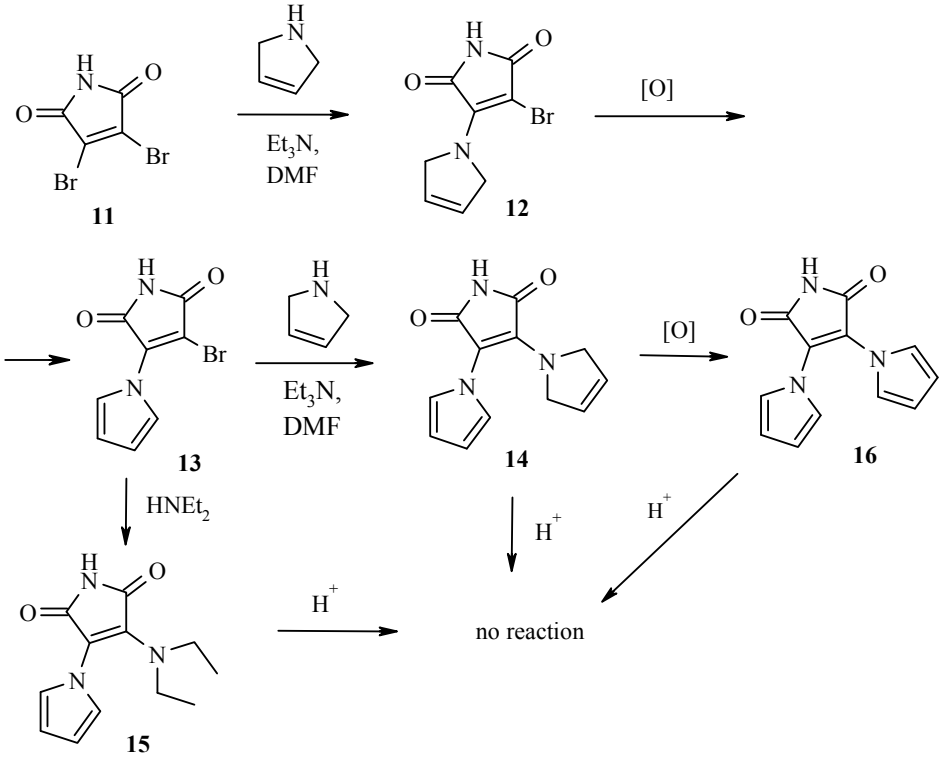


TABLE 1. Physicochemical Characteristics of the Obtained Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
8a	$C_{15}H_{10}N_4O_2$	64.78 / 64.74	3.57 / 3.62	20.23 / 20.13	233-235	70
8b	$C_{15}H_{10}N_4O_2$	64.79 / 64.74	3.68 / 3.62	20.19 / 20.13	148-149	75
8c	$C_{18}H_{11}N_5O_2$	65.72 / 65.65	3.30 / 3.37	21.20 / 21.27	199-200	83
8d	$C_{19}H_{12}N_4O_2$	69.62 / 69.51	3.58 / 3.68	17.15 / 17.06	245-246	74
8e	$C_{18}H_{14}N_4O_2$	67.88 / 67.91	4.49 / 4.43	17.64 / 17.60	214-215	80
8f	$C_{16}H_{13}N_3O_2$	68.79 / 68.81	4.72 / 4.69	15.09 / 15.05	209-210	69
8g	$C_{18}H_{14}N_4O_2$	67.96 / 67.91	4.42 / 4.43	17.61 / 17.60	180-181 (dec.)	77
8h	$C_{20}H_{18}N_4O_2$	69.39 / 69.35	5.29 / 5.24	16.13 / 16.17	189-190	75
8i	$C_{22}H_{20}N_4O_3$	68.09 / 68.03	5.22 / 5.19	14.38 / 14.42	221-222	76
8j	$C_{18}H_{21}N_3O_3$	66.09 / 66.04	6.55 / 6.47	12.89 / 12.84	110-112	73
8k	$C_{12}H_9N_3O_2$	63.47 / 63.43	4.02 / 3.99	18.41 / 18.49	185-186	80
8l	$C_{14}H_{11}N_3O_3$	62.40 / 62.45	4.14 / 4.12	15.68 / 15.61	221-222	68
9	$C_{16}H_{11}N_3O_2$	69.34 / 69.31	3.95 / 4.00	15.18 / 15.15	225-226	85
10	$C_{16}H_{11}N_3O_2$	69.39 / 69.31	4.03 / 4.00	15.09 / 15.15	229-230	62
12	$C_8H_7BrN_2O_2$	39.59 / 39.53	2.94 / 2.90	11.49 / 11.53	163-164	70
13	$C_8H_5BrN_2O_2$	39.92 / 39.86	2.03 / 2.09	11.67 / 11.62	135-136	72
14	$C_{12}H_{11}N_3O_2$	62.90 / 62.87	4.80 / 4.84	18.32 / 18.33	219-220	75
15	$C_{12}H_{15}N_3O_2$	61.82 / 61.79	6.50 / 6.48	17.97 / 18.01	187-188	92
16	$C_{12}H_9N_3O_2$	63.46 / 63.43	4.02 / 3.99	18.51 / 18.49	143-144	76

2,3-Bis(pyrrol-1-yl)maleimide (**16**) and 2-diethylamino-3-(pyrrol-1-yl)maleimide (**15**), analogs of the previously synthesized 2,3-bis(indol-1-yl)maleimide (**1**) and 2-diethylamino-3-(indol-1-yl)maleimide (**2**), were obtained from pyrroline and 2,3-dibromomaleimide (**11**) by sequential replacement of bromine atoms and aromatization (Scheme 5) with the aim of studying the possibility of obtaining cyclization products from them analogous to compounds **3** and **4.**

However, treatment of compounds **15** or **16** with trifluoroacetic acid did not lead to a cyclization product similar to **3** or **4**. On using stronger acids and more rigorous conditions (heating) resinification was observed.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 (400 and 100 MHz respectively) in DMSO-d_6, internal standard was TMS. Melting points were determined on a Buchi SMP-20 instrument and are given uncorrected. Analytical TLC was carried out on plates of silica gel F254 (Merck), column

TABLE 2. ^{1}H NMR Spectra of the Obtained Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)
8a	6.80 (1H, dd, *J* = 8.3, *J* = 0.7); 6.84 (1H, d, *J* = 3.5); 6.95-7.04 (3H, m); 7.14 (1H, t, *J* = 7.5); 7.52 (1H, d, *J* = 3.5); 7.64 (1H, d, *J* = 7.7); 7.76 (1H, s); 11.71 (1H, s)
8b	6.56 (1H, dd, *J* = 2.6, *J* = 1.7); 6.71 (1H, d, *J* = 8.4); 6.74 (1H, dd, *J* = 3.4, *J* = 0.9); 6.95 (1H, t, *J* = 7.8); 7.08 (1H, t, *J* = 7.8); 7.52 (1H, d, *J* = 3.5); 7.58 (1H, d, *J* = 7.8); 7.61 (1H, d, *J* = 1.8); 8.36 (1H, d, *J* = 3.5); 11.63 (1H, s)
8c	6.25 (1H, d, *J* = 8.4); 6.65 (1H, t, *J* = 7.6); 6.85 (1H, d, *J* = 3.1); 6.97 (1H, t, *J* = 7.3); 7.39-7.43 (1H, m); 7.49-7.54 (3H, m); 7.71 (1H, d, *J* = 3.1); 8.09 (1H, d, *J* = 8.4); 11.94 (1H, s)
8d	6.55 (1H, d, *J* = 8.1); 6.69 (1H, d, *J* = 7.9); 6.76 (1H, t, *J* = 7.4); 6.82 (1H, d, *J* = 3.4); 6.85 (1H, t, *J* = 7.5); 6.94 (1H, t, *J* = 7.4); 7.07 (1H, t, *J* = 7.6); 7.49 (1H, d, *J* = 7.9); 7.60 (1H, d, *J* = 8.0); 7.69 (1H, d, *J* = 3.4); 8.53 (1H, s); 11.80 (1H, s)
8e	3.93 (2H, br. s); 6.48 (1H, d, *J* = 2.7); 6.65 (2H, d, *J* = 5.1); 6.99-7.07 (4H, m); 7.53 (1H, m); 8.22 (2H, d, *J* = 5.5); 8.43 (1H, t, *J* = 6.7); 10.77 (1H, s)
8f	4.58 (4H, s); 5.76 (2H, s); 6.58 (1H, d, *J* = 3.1); 7.09 (1H, t, *J* = 7.5); 7.16 (1H, t, *J* = 7.5); 7.30 (1H, d, *J* = 7.6); 7.34 (1H, d, *J* = 3.2); 7.59 (1H, d, *J* = 7.6); 10.71 (1H, s)
8g	4.82 (2H, s); 6.04 (2H, d, *J* = 8.9); 6.34 (1H, d, *J* = 3.3); 6.60 (2H, d, *J* = 8.8); 6.82 (1H, s); 6.89 (1H, d, *J* = 3.3); 6.99 (1H, t, *J* = 7.1); 7.03 (1H, t, *J* = 8.1); 7.11 (1H, d, *J* = 8.3); 7.41 (1H, d, *J* = 6.0); 9.73 (1H, s); 10.74 (1H, s)
8h	2.61 (6H, s); 6.02 (2H, d, *J* = 8.9); 6.32 (1H, d, *J* = 3.3); 6.52 (2H, d, *J* = 8.8); 6.79 (1H, s); 6.87 (1H, d, *J* = 3.3); 6.95 (1H, t, *J* = 7.1); 7.01 (1H, t, *J* = 8.1); 7.11 (1H, d, *J* = 8.3); 7.41 (1H, d, *J* = 6.0); 9.65 (1H, s); 10.54 (1H, s)
8i	2.77 (4H, t, *J* = 4.7); 3.6 (4H, t, *J* = 4.7); 6.23 (2H, d, *J* = 8.7); 6.37 (1H, d, *J* = 3.3); 6.52 (2H, d, *J* = 8.8); 6.91-7.00 (3H, m); 7.07 (1H, d, *J* = 8.1); 7.40 (1H, d, *J* = 8.1); 9.59 (1H, s); 10.84 (1H, s)
8j	0.63-0.73 (2H, m); 0.79-0.87 (2H, m); 1.04-1.18 (4H, m); 2.55 (2H, m); 3.20-3.24 (2H, m); 4.29 (1H, t, *J* = 5.2); 6.59 (1H, d, *J* = 3.1); 7.08 (1H, t, *J* = 7.4); 7.15 (1H, t, *J* = 7.4); 7.24 (1H, d, *J* = 7.9); 7.31 (1H, d, *J* = 3.2); 7.59 (1H, d, *J* = 7.8); 7.90 (1H, t, *J* = 6.3); 10.64 (1H, s)
8k	6.62 (1H, d, *J* = 3.3); 7.07-7.14 (2H, m); 7.17 (2H, m); 7.28 (1H, d, *J* = 3.3); 7.36 (2H, s); 7.62 (1H, d, *J* = 7.9); 10.55 (1H, s)
8l	2.46 (3H, s); 6.66 (1H, d, *J* = 3.3); 7.12 (1H, t, *J* = 7.25); 7.18 (1H, t, *J* = 7.28); 7.26 (1H, d, *J* = 7.1); 7.29 (1H, d, *J* = 3.2); 7.63 (1H, d, *J* = 7.5); 7.78 (2H, s)
9	6.19 (2H, t, *J* = 2.3); 6.80 (1H, d, *J* = 3.3); 6.83 (2H, t, *J* = 2.2); 6.97 (1H, d, *J* = 8.1); 7.04 (1H, t, *J* = 7.1); 7.13 (1H, t, *J* = 7.2); 7.47 (1H, d, *J* = 3.3); 7.64 (1H, d, *J* = 7.7); 11.53 (1H, s)
10	3.28 (1H, dd, *J* = 15.7, *J* = 9.7); 3.74 (1H, dd, *J* = 15.7, *J* = 9.5); 5.33 (1H, t, *J* = 9.6); 6.14 (1H, d, *J* = 3.3); 6.31 (1H, t, *J* = 3.1); 6.92 (1H, t, *J* = 7.3); 7.14 (1H, t, *J* = 7.3); 7.21 (1H, d, *J* = 7.3); 7.29 (1H, m); 7.93 (1H, d, *J* = 7.3); 10.7 (1H, s)
12	4.66 (4H, s); 5.95 (2H, s); 10.78 (1H, s)
13	6.39 (2H, s); 7.62 (2H, s); 11.56 (1H, s)
14	4.16 (4H, s); 5.86 (2H, s); 6.11 (2H, t, *J* = 2.0); 6.78 (2H, t, *J* = 2.1); 10.60 (1H, s)
15	1.01 (6H, t, *J* = 7.0); 3.28 (4H, q, *J* = 7.0); 6.13 (2H, t, *J* = 2.0); 6.74 (2H, t, *J* = 2.0); 10.61 (1H, s)
16	6.32 (4H, t, *J* = 2.2); 6.87 (4H, t, *J* = 2.2); 11.43 (1H, s)

chromatography on silica gel Merck 60. Extracts were dried over anhydrous Na_2SO_4 and were evaporated under reduced pressure. Commercial reagents (Acros, Fluka) and solvents (Khimmed) were used. Elemental analysis was carried out in the analytical laboratory of the Center for Drug Chemistry of the All-Russia Research Institute of Pharmaceutical Chemistry.

Synthesis of 2-Substituted 3-(Indol-1-yl)maleimides 8a-j (General Method). The appropriate nucleophile (1.2 equiv.) and $Et(2\text{-}Pr)_2N$ (1.2 equiv.) were added to a solution of 2-bromo-3-(indol-1-yl)maleimide (**7**) (290 mg, 1 mmol) in DMF (10 ml), the reaction mixture was stirred at 60°C, checking the

progress of the reaction by TLC (eluent *n*-hexane–ethyl acetate, 1:1), until complete conversion of the initial imide **7**. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 ml), washed with 0.1 N HCl (2×20 ml), with saturated $NaHCO_3$ solution (10 ml), dried and evaporated. The residue was recrystallized from 2-PrOH.

2-Amino-3-(indol-1-yl)maleimide (8k). A solution of compound **7** (100 mg, 0.34 mmol) in saturated ammonia in methanol solution (5 ml) was stirred at room temperature until complete disappearance of the initial compound **7** (3-4 h). The reaction mixture was filtered and evaporated. The residue was dissolved in ethyl acetate (10 ml) and washed with 0.1 N HCl (2×3 ml), with saturated $NaHCO_3$ solution (5 ml), dried, and evaporated. The residue was recrystallized from 2-PrOH. Compound **8k** (63 mg, 0.28 mmol) was obtained as a yellow solid (yield 80%).

N-Acetyl-2-amino-3-(indol-1-yl)- maleimide (8l). A solution of imide **8k** (30 mg, 0.13 mmol) in acetic anhydride (3 ml) was heated at 70°C for 2 h. The mixture was cooled to ~20°C and poured into saturated $NaHCO_3$ solution (50 ml). After decomposition of the excess of acetic anhydride, the reaction product was extracted with ethyl acetate (2×10 ml), the organic extracts were dried and evaporated. The residue was recrystallized from 2-PrOH. Compound **8l** (24 mg, 0.09 mmol) was obtained as a yellow solid (yield 68%).

2-(Indol-1-yl)-3-(pyrrol-1-yl)maleimide (9). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (200 mg, 0.88 mmol) was added to a solution of compound **8f** (200 mg, 0.72 mmol) in toluene (50 ml). The reaction mixture was stirred while boiling for 2 h, cooled to room temperature, washed with a saturated solution of $NaHSO_3$ (2×10 ml), with a saturated solution of $NaHCO_3$ (4×5 ml), dried, and evaporated. The residue was recrystallized from 2-PrOH. Product **9** (179 mg, 0.61 mmol) was obtained as a dark-red solid (yield 85%).

7*a*,8-Dihydro-1H-dipyrrolo[2',1':3,4;3",4":5,6]pyrazino[1,2-*a*]indole-1,3(2H)-dione (10). Trifluoroacetic acid (2 ml) was added to a solution of imide **9** (100 mg, 0.36 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred for 2 h at room temperature, and then evaporated. The residue was dissoloved in ethyl acetate (10 ml), and the solution washed with saturated $NaHCO_3$ solution (2×5 ml), then dried, and evaporated. The solid was recrystallized from toluene. Product **10** (62 mg, 0.22 mmol) was obtained as a dark-red solid (yield 62%).

2-Bromo-3-(2,5-dihydropyrrol-1-yl)maleimide (12). Pyrroline (300 mg, 4.3 mmol) and triethylamine (430 mg, 4.3 mmol) were added to a solution of 3,4-dibromomaleimide (1 g, 3.9 mmol) in DMF (20 ml). The reaction mixture was stirred for 3 h at room temperature, then diluted with ethyl acetate (150 ml). The mixture was washed with saturated citric acid solution (2×20 ml), with saturated $NaHCO_3$ solution (2×30 ml), dried, and evaporated. The residue was recrystallized from 2-PrOH. Imide **12** (663 mg, 2.7 mmol) was obtained as a yellow solid (yield 70%).

2-Bromo-3-(pyrrol-1-yl)maleimide (13). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (530 mg, 2.3 mmol) was added to a solution of compound **12** (500 mg, 2.1 mmol) in toluene (50 ml). The reaction mixture was stirred while boiling for 2 h, cooled to room temperature, washed with saturated $NaHSO_3$ solution (2×10 ml), with saturated $NaHCO_3$ solution (4×10 ml), dried, and evaporated. The residue was recrystallized from 2-PrOH. Imide **13** (363 mg, 1.51 mmol) was obtained as a yellow solid (yield 72%).

2-(2,5-Dihydropyrrol-1-yl)-3-(pyrrol-1-yl)maleimide (14). Pyrroline (112 mg, 1.6 mmol) and triethylamine (160 mg, 1.6 mmol) were added to a solution of imide **13** (300 mg, 1.3 mmol) in DMF (10 ml). The reaction mixture was stirred for 3 h at room temperature, diluted with ethyl acetate (100 ml), washed with saturated citric acid solution (2×20 ml), with saturated $NaHCO_3$ solution (2×30 ml), dried, and evaporated. The residue was recrystallized from 2-PrOH. Compound **14** (223 mg, 0.98 mmol) was obtained as a yellow solid (yield 75%).

2-Diethylamino-3-(pyrrol-1-yl)maleimide (15). Diethylamine (220 mg, 3 mmol) was added to a solution of imide **13** (300 mg, 1.3 mmol) in DMF (10 ml). The reaction mixture was stirred for 3 h at room temperature, diluted with ethyl acetate (100 ml), washed with saturated citric acid solution (2×20 ml), with saturated $NaHCO_3$ solution (2×30 ml), dried, and evaporated. The residue was recrystallized from 2-PrOH. Imide **15** (280 mg, 1.2 mmol) was obtained as a yellow solid (yield 92%).

2,3-Bis(pyrrol-1-yl)maleimide (16). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (220 mg, 0.97 mmol) was added to a solution of compound **14** (200 mg, 0.87 mmol) in toluene (50 ml). The reaction mixture was stirred while boiling for 2 h, cooled to room temperature, washed with a saturated solution of $NaHSO_3$ (2×10 ml), with saturated $NaHCO_3$ solution (4×10 ml), dried, and evaporated. The residue was recrystallized from 2-PrOH. Compound **16** (150 mg, 0.66 mmol) was obtained as a yellow solid (yield 76%).

The work was supported by the Federal Agency for Science and Innovation (State Contract 02.512.12.2035 from May 12, 2009), and also by Grant NSh-5290-2010.4.

REFERENCES

1. P. Goekjian and M. Jirousek, *Expert Opin. Invest. Drugs,* **10**, 2117 (2001).
2. H. Nakano and S. Omura, *J. Antibiot.*, **62**, 17 (2009).
3. S. A. Lakatosh, Y. N. Luzhikov, and M. N. Preobrazhenskaya, *Org. Biomol. Chem.* **1**, 826 (2003).
4. J. Bergman, *Chem. Scripta*, **27**, 539 (1987).
5. R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 2437 (1964).