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SYNTHESIS OF 5-AMINO-4-HETARYL-2,3-DIHYDRO-1H-3-PYRROLONES

A. V. Tverdokhlebov, A. B. Lyashenko, Yu. M. Volovenko, and A. A. Tolmachev

2-Hetaryl-3-oxo-4-phthalimidobutyronitriles (and pentanonitriles) were obtained with high yields by C-acylation of hetarylacetonitriles with N-phthaloylglycine and α-alanine chlorides respectively under the conditions of base catalysis. Hydrazinolysis of the phthaloyl protection in these compounds leads to the formation of 5-amino-4-hetaryl-2,3-dihydro-1H-3-pyrrolones.

Keywords: 5-amino-4-hetaryl-2,3-dihydro-1H-3-pyrrolones, hetarylacetonitriles, γ-phthalimidonitriles, N-phthaloylamino acids.

The interest in derivatives of 2-aminopyrrole has arisen in connection with their prospective use as medicines [1-8] and as components of dyes in photography [9-11]. The principal methods for the synthesis of these compounds are the condensation of methylene-active nitriles with derivatives of α-aminocarbonyl compounds [12-17] or amination of substituted 4-halobutyronitriles [18-24] or their synthetic equivalents [25-27]. Both approaches have been successfully applied to the synthesis of 1-R^1-2,2-R^2,R^3-5-amino-4-hetaryl-2,3-dihydro-3-pyrrolones [28-37]. However, they cannot be used for the production of similar derivatives unsubstituted at position 1 since, on the one hand, the N-unsubstituted α-aminocarbonyl compounds quickly dimerize to pyrazine derivatives and, on the other, the use of ammonia in the reaction together with the need for heat and a nonaqueous medium give rise to certain technical difficulties. For this reason we developed a different method for the synthesis of N-unsubstituted 2,3-dihydro-1H-3-pyrrolones **1a-h**, and this method is described here.

The key compounds in the synthesis of the dihydropyrrolones **1** are 2-hetaryl-3-oxo-4-phthalimidobutyronitriles **2a-e** and the corresponding pentanonitriles **2f-h**, obtained by acylation of the hetarylacetonitriles **3a-e** with the chlorides of N-phthaloylglycine **4a** and alanine **4b** (see the scheme). It should be noted that acylation of the sodium salts of simple methylene-active compounds with the chlorides [38-41] and esters [17, 42, 43] of protected α-amino acids was used earlier for construction of the pyrrole ring. However, the acid chlorides often gave the products from bis-C,C- and bis-C,O-acylation [38, 40] of complex mixtures [39], while the esters gave the enolates of the corresponding acyl derivatives. During transformation of the latter into the conjugate acids it was not always possible to avoid side processes associated with hydrolysis of the protecting groups [42, 43]. We obtained the monoacyl derivatives **2a-h** with yields of more than 90% as the only products (Scheme 1).

The composition and structure of the nitriles **2a-h** were confirmed by the results of elemental analysis (Table 1) and also by data from the IR and ^{1}H NMR spectra (Table 2). According to the spectral data, compounds **2a-h** exist exclusively in the form of NH tautomers with an intramolecular hydrogen bond, as known for the acyl derivatives of hetarylacetonitriles [44]. Thus, the ^{1}H NMR spectra of the butyronitriles **2a-e**

Taras Shevchenko Kiev University, Kiev, Ukraine; e-mail: atver@mail.univ.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1783-1790, December, 2004. Original article submitted December 27, 2001; revision submitted October 26, 2004.

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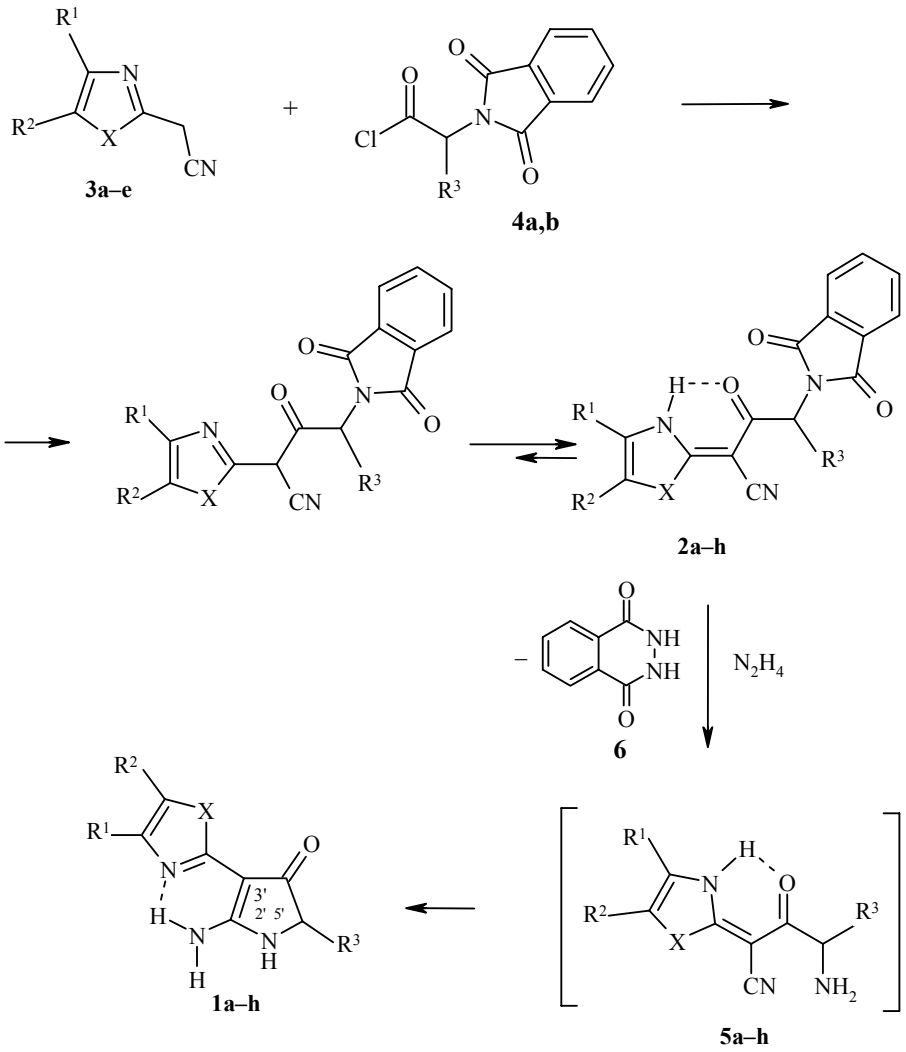
Scheme 1



1-3 a,f X = NH, **b,g** X = NMe, **c-e,h** X = S; **a-c,f-h** $R^1 + R^2$ = –CH=CHCH=CH–,
d R^1 = 4-BrC_6H_4, **e** R^1 = 3,4-$(MeO)_2C_6H_3$; **d**,**e** R^2 = H; **1a-e – 3a-e**, **4a** R^3 = H, **1f-h – 3f-h**, **4b** R^3 = Me

contain a two-proton singlet for the methylene group in the region of 4.60-4.75 ppm, a four-proton symmetrical multiplet for the phthaloyl fragment at 7.85-7.90 ppm, and a signal for the chelated proton in the region of 12.8-13.2 ppm. (It exchanges with D_2O.) In the ^1H NMR spectra of the pentanonitriles **2f-h** instead of the signal for the methylene group there are signals of an AX_3 spin system at 5.15-5.25 ppm (a quartet) and 1.60-1.80 ppm (a doublet). The protons of the heterocyclic substituent absorb in their characteristic regions. The IR spectra of compounds **2a**-**h** contain a strong band for the stretching vibrations of the conjugated nitrile group at 2180-2200 cm^{-1} and also two bands for the symmetrical and asymmetrical stretching vibrations of the CO–N–CO system at 1700-1720 and 1760-1780 cm^{-1} respectively. We assigned the strong band in the region of 1600-1625 cm^{-1} to the stretching vibrations of the carbonyl group attached to the NH group by a hydrogen bond. Such a significant shift toward lower frequencies in relation to the average value for a conjugated carbonyl group is due, first, to its inclusion in the β-enamino ketone fragment and, second, to its participation in an intramolecular hydrogen bond.

TABLE 1. The Characteristics of 5-Amino-4-hetaryl-3-oxo-2,3-dihydro-1H-pyrrolones **1a-h**, 2-Hetaryl-3-oxo-4-phthalimidobutyronitriles **2a-e**, and the Pentanonitriles **2f-h**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield %
		C	H	N	S		
1a	$C_{11}H_{10}N_4O$	61.69 / 61.67	4.79 / 4.71	26.09 / 26.15		273	57
1b	$C_{12}H_{12}N_4O$	63.21 / 63.15	5.26 / 5.30	24.49 / 24.55		261	50
1c	$C_{11}H_9N_3OS$	57.08 / 57.13	3.99 / 3.92	18.07 / 18.17	13.87 / 13.86	>300	61
1d*[2]	$C_{13}H_{10}BrN_3OS$	46.37 / 46.44	3.03 / 3.00	12.55 / 12.50	9.49 / 9.54	248	43
1e	$C_{15}H_{15}N_3O_3S$	56.79 / 56.77	4.69 / 4.76	13.18 / 13.24	10.16 / 10.10	226	44
1f	$C_{12}H_{12}N_4O$	63.13 / 63.15	5.22 / 5.30	24.43 / 24.55		>300	50
1g	$C_{13}H_{14}N_4O$	64.52 / 64.45	5.89 / 5.82	23.05 / 23.12		238	51
1h	$C_{12}H_{11}N_3OS$	58.68 / 58.76	4.53 / 4.52	17.10 / 17.13	13.01 / 13.07	297	41
2a	$C_{19}H_{12}N_4O_3$	66.24 / 66.28	3.48 / 3.51	16.34 / 16.27		>300	97
2b	$C_{20}H_{14}N_4O_3$	67.09 / 67.03	4.01 / 3.94	15.62 / 15.63		>300	95
2c	$C_{19}H_{11}N_3O_3S$	63.19 / 63.15	2.99 / 3.07	11.60 / 11.63	8.91 / 8.87	>300	98
2d*[3]	$C_{21}H_{12}BrN_3O_3S$	54.06 / 54.09	2.62 / 2.59	8.94 / 9.01	6.93 / 6.88	259	93
2e	$C_{23}H_{17}N_3O_5S$	61.78 / 61.74	3.84 / 3.83	9.33 / 9.39	7.12 / 7.17	231	93
2f	$C_{20}H_{14}N_4O_3$	66.94 / 67.03	4.06 / 3.94	15.67 / 15.63		>300	93
2g	$C_{21}H_{16}N_4O_3$	67.80 / 67.73	4.31 / 4.33	14.98 / 15.05		242	91
2h	$C_{20}H_{13}N_3O_3S$	63.92 / 63.99	3.52 / 3.49	11.11 / 11.19	8.48 / 8.54	271	91

* Compounds **1a**,**b** were identical with those described in [45] (IR spectra and mixed melting tests).

*[2] Found, %: Br 23.66. Calculated, %: Br 23.77.

*[3] Found, %: Br 17.10. Calculated, %: Br 17.14.

Removal of the phthaloyl protection from the phthalimidonitriles **2a-h** leads to the formation of the intermediates **5a-h**, having the structures of γ-amino nitriles. According to data in [18-24, 28-37], such aminonitriles undergo heterocyclization on account of intramolecular addition of the amino group to the nitrile group, which in this case should lead to the formation of the desired pyrrolones **1**. In fact, the desired products **1a-h** were obtained with yields of 40-60% by the action of a 3-4-fold excess of hydrazine hydrate on compounds **2a-h**. It should be noted that according to TLC and ^{1}H NMR spectra this transformation takes place quantitatively. The moderate yields of the products **1a-h** indicated above are due to losses that arise during their purification from the second product – phthalazinedione **6**. We isolated the latter from the reaction mixture with yields of 60-70%. It is noticeable that reaction of the excess hydrazine hydrate either with the β-oxonitrile fragment of compounds **2a-h** or with the carbonyl group of the pyrrolones **1a-h** was not observed in the course of the reaction. This agrees with data for derivatives of 5-amino-3-pyrrolones substituted at position 1 [36].

The composition and structure of compounds **1a-h** were supported by data from elemental analysis (Table 1), the ^{1}H NMR spectra (Table 2), and also by the identity of the pyrrolones **1a**,**b** with samples that we synthesized earlier by a different more complicated method [45]. In the IR spectra of the derivatives **1a-h** there is strong absorption above 3000 cm^{-1}, due to the stretching vibrations of the N–H bonds, and there is also a strong broad band in the region of 1560-1600 cm^{-1}, which is not present in the spectra of the initial nitriles **2a-h**. It is probably due to the deformation vibrations of the primary amino group, although it is quite likely that it may also include the stretching vibrations of the strongly polarized [17, 46] C=C bond of the pyrrolone ring. In some cases this band has a clearly defined shoulder at 1640-1645 cm^{-1}, which can be assigned to the stretching vibrations of the carbonyl group contained in the β-enamino ketone fragment. The absence of the absorption of the conjugated nitrile group in the IR spectra of compounds **1a-h** indicates conclusively that it participates in heterocyclization. The signals of the phthaloyl residue are absent both in the IR spectra and in the ^{1}H NMR spectra of the dihydropyrrolones **1a-h**. The ^{1}H NMR spectra of compounds **1a-e** in DMSO-d_6 contain a

TABLE 2. The ^{1}H NMR Spectra of Compounds **1a-h** and **2a-h**

Com-pound	Chemical shifts, δ, ppm SSCC, *J*, Hz)
1a	3.80 (2H, s, CH_2); 7.04 (2H, m, H_{arom}); 7.48 (2H, m, H_{arom}); 7.61 (1H, s, H-1); 8.07 (2H, s, NH_2); 11.80 (1H, s, NH)
1b	3.75 (2H, s, CH_2); 3.92 (3H, s, NCH_3); 7.17 (2H, m, H_{arom}); 7.49 (3H, NH and 2H_{arom}); 7.92 (2H, s, NH_2)
1c	3.75 (2H, s, CH_2); 7.17 (1H, deg. t, *J* = 7.8, H_{arom}-6); 7.33 (1H, deg. t, *J* = 7.8, H_{arom}-5); 7.69 (2H, m, NH and H_{arom}-7); 7.83 (1H, d, *J* = 7.8, H_{arom}-4); 8.07 (1H, s, H_{NH2}); 8.27 (1H, s, H_{NH2}···N)
1d	3.73 (2H, s, CH_2); 7.42 (1H, s, H-5); 7.64 (3H, m, H_{arom}-3,5 and NH); 7.94 (3H, m, H_{arom}-2,6 and H_{NH2}); 8.19 (1H, s, H_{NH2}···N)
1e	3.71 (2H, s, CH_2); 3.79 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 6.94 (1H, d, *J* = 8.1, H_{arom}-5); 7.36 (1H, s, H-5); 7.45 (3H, NH and H_{arom}-2,6); 7.86 (1H, s, H_{NH2}); 8.12 (1H, s, H_{NH2}···N)
1f	1.31 (3H, d, *J* = 7.0, CH_3); 3.99 (1H, q, *J* = 7.0, C<u>H</u>CH_3); 7.31 (2H, m, H_{arom}); 7.66 (2H, m, H_{arom}); 8.19 (2H, s, NH and H_{NH2}); 8.49 (1H, s, H_{NH2}···N); 11.21 (1H, s, H-1)
1g	1.28 (3H, d, *J* = 7.2, CH_3); 3.71 (1H, q, *J* = 7.2, C<u>H</u>CH_3); 3.93 (3H, s, NCH_3); 7.09 (2H, m, H_{arom}-5,6); 7.34 (1H, m, H_{arom}-7); 7.42 (1H, m, H_{arom}-4); 7.64 (1H, s, NH); 7.72 (1H, s, H_{NH2}); 8.33 (1H, s, H_{NH2}···N)
1h	1.29 (3H, d, *J* = 6.8, CH_3); 3.79 (1H, q, *J* = 6.8, C<u>H</u>CH_3); 7.21 (1H, deg. t, *J* = 7.5, H_{arom}-6); 7.34 (1H, deg. t, *J* = 7.5, H_{arom}-5); 7.71 (1H, d, *J* = 7.5, H_{arom}-7); 7.88 (2H, m, NH and H_{arom}-4); 8.07 (1H, s, H_{NH2}); 8.29 (1H, s, H_{NH2}···N)
2a	4.64 (2H, s, CH_2); 7.24 (2H, m, H_{arom}); 7.48 (2H, m, H_{arom}); 7.91 (4H, m, Phth); 12.90 (2H, s, 2NH)
2b	3.97 (3H, s, NCH_3); 4.70 (2H, s, CH_2); 7.32 (2H, m, H_{arom}); 7.60 (2H, m, H_{arom}); 7.90 (4H, m, Phth); 13.10 (1H, s, NH)
2c	4.72 (2H, s, CH_2); 7.42 (2H, m, H_{arom}-5,6); 7.71 (1H, d, *J* = 8.0, H_{arom}-4); 7.89 (5H, m, H_{arom}-7 and Phth); 12.84 (1H, s, NH)
2d	4.69 (2H, s, CH_2); 7.50 (1H, s, H-5); 7.69 (4H, br. s, H_{arom}); 7.90 (4H, m, Phth); 12.93 (1H, s, NH)
2e	3.81 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 4.67 (2H, s, CH_2); 7.00 (1H, d, *J* = 8.4, H_{arom}-5); 7.28 (3H, m, H_{arom}-2,6 and H-5); 7.89 (4H, m, Phth); 12.50 (1H, s, NH)
2f	1.73 (3H, d, *J* = 7.6, CH_3); 5.17 (1H, q, *J* = 7.6, C<u>H</u>CH_3); 7.24 (2H, m, H_{arom}); 7.49 (2H, m, H_{arom}); 7.87 (4H, m, Phth); 12.80 (2H, s, NH)
2g	1.79 (3H, d, *J* = 7.2, CH_3); 3.98 (3H, s, NCH_3); 5.25 (1H, q, *J* = 7.2, C<u>H</u>CH_3); 7.27 (2H, m, H_{arom}-5,6); 7.53 (1H, d, *J* = 7.5, H_{arom}-4); 7.64 (1H, d, *J* = 7.2, H_{arom}-7); 7.85 (4H, m, Phth); 13.25 (1H, s, NH)
2h	1.67 (3H, d, *J* = 7.2, CH_3); 5.18 (1H, q, *J* = 7.2, C<u>H</u>CH_3); 7.31 (1H, deg. t, *J* = 7.5, H_{arom}-6); 7.44 (1H, deg. t, *J* = 7.5, H_{arom}-5); 7.64 (1H, d, *J* = 7.5, H_{arom}-4); 7.86 (5H, m, H_{arom}-7 and Phth); 12.76 (1H, s, NH)

* Phth – phthaloyl.

two-proton singlet for the methylene group at 3.7-3.8 ppm,* whereas the methyl-substituted compounds **1f-h** are characterized by the signals of an AX_3 system at 3.7-3.9* (a quartet) and 1.25-1.30 ppm (a doublet). Signals for the proton at position 1 of the dihydropyrrolone ring and the protons of the amino group are observed in the ^{1}H NMR spectra of compounds **1a-h** in the form of three one-proton singlets (one narrow and two broad) in the region of 7.5-8.5 ppm. The latter clearly belong to the protons of the amino group, which are magnetically nonequivalent as a result of the formation of an intramolecular hydrogen bond, as was observed earlier for analogous systems [28-37]. The protons of the heterocyclic substituent resonate in their characteristic regions. Thus, according to the spectral data, the dihydropyrrolones **1a-h** exist exclusively in the amino ketone tautomeric form both in the solid phase and in solution.

Thus, the present investigation resulted in the development of a two-stage preparative method for the synthesis of 2-(2-amino-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)benzimidazoles **1a**,**b**,**f**,**g**, the thiazoles **1d**,**e**, and the benzothiazoles **c**,**h**, involving the acylation of hetarylacetonitriles with the chlorides of N-phthaloyl-protected amino acids followed by removal of the protection from the obtained products **2a-h** by hydrazinolysis. The method is based on readily obtainable starting compounds, and the overall yield of the targeted products in the two stages amounts to 45-50%.

EXPERIMENTAL

The IR spectra were obtained on a Pye-Unicam SP 3-300 instrument for tablets in potassium bromide. The ^{1}H NMR spectra were recorded in DMSO-d_6 on Bruker WP-100SY (100 MHz) and Varian VXR-300 (300 MHz) instruments.

The reactions and the individuality of the obtained compounds were monitored by TLC on Silufol UV-254 plates in 9:1 benzene–ethanol. The melting points were determined in sealed capillaries in Thiele melting point apparatus, previously heated to 180-200°C, and the substances melted almost exactly at the melting point; when the capillary was heated slowly from room temperature, the substances melted over a wide range on account of partial decomposition.

The hetarylacetonitriles **3b-d** were synthesized by the usual methods [47-49]. Phthaloylglycine and phthaloylalanine were obtained from the respective amino acids and were converted into the chlorides **4a**,**b** by standard procedures. Benzimidazol-2-ylacetonitrile **3a** and cyanothioacetamide are commercially available and were used without additional purification.

4-(3,4-Dimethoxyphenyl)thiazol-2-ylacetonitrile (3e). To a warm solution (40-50°C) of cyanothioacetamide (10 g, 0.1 mol) in ethanol (80 ml) we added 3,4-dimethoxyphenacyl bromide (25.9 g, 0.1 mol) [50]. The mixture heated and boiled for a few minutes, and the hydrobromide of compound **3e** was precipitated. The reaction mass was kept on a boiling water bath for a further 1 h and was then cooled. The precipitated salt **3e**·HBr was filtered off. The salt was suspended in 15-20% aqueous ammonia for 40 min and was then filtered off and washed with water. After recrystallization from 2-propanol 22 g (85%) of the product **3e** was obtained; mp 101°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.80 (3H, s, CH_3O); 3.84 (3H, s, CH_3O); 4.52 (2H, s, CH_2); 6.96 (1H, d, J = 8.4, 5-H_{arom}); 7.49 (2H, m, 2,6-H_{arom}); 7.90 (1H, s, 5-H). Found %: C 60.01; H 4.61; N 10.69; S 12.38. $C_{13}H_{12}N_2O_2S$. Calculated %: C 59.98; H 4.65; N 10.76; S 12.32.

2-Hetaryl-3-oxo-4-phthalimidobutyronitriles (2a-e) and Pentanonitriles (2f-h) (General Procedure). To a warm solution (~50°C) of the hetarylacetonitrile **3a-e** (0.01 mol) and pyridine (0.8 ml, 0.01 mol) in dioxane (30-60 ml) we added the acid chloride **4a** or **4b** (0.01 mol). The obtained mixture was kept

* In the ^{1}H NMR spectra of the nitriles **2a-h** the respective protons resonate 0.9-1.4 ppm downfield. This is probably due to the descreening effect of the magnetically anisotropic carbonyl groups of the phthalimide fragment.

on a boiling water bath for 1.5-2 h and cooled. The precipitate was filtered off and washed thoroughly with water. After recrystallization from dioxane (for **2a-e**) or alcohol (for **2f-h**) we obtained the phthalimidonitriles **2a-h**.

2-(2-Amino-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)benzimidazole (1a), 2-(2-Amino-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)-1-methylbenzimidazole (1b), 2-(2-Amino-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)benzothiazole (1c), 2-(2-Amino-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)-4-(4-bromophenyl)thiazole (1d), 2-(2-Amino-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)-4-(3,4-dimethoxyphenyl)thiazole (1e), 2-(2-Amino-5-methyl-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)benzimidazole (1f), 2-(2-Amino-5-methyl-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)-1-methylbenzimidazole (1g), and 2-(2-Amino-5-methyl-4-oxo-4,5-dihydro-1H-pyrrol-3-yl)benzothiazole (1h). A (for compounds **1a**,**b**,**d-g**). To a solution of phthalimidonitrile **2** (0.005 mol) in *n*-butanol (25 ml) we added hydrazine hydrate (1 ml, 0.02 mol). The obtained mixture was heated on a boiling water bath for 1.5 h. After cooling the precipitate that separated was filtered off, washed with *n*-butanol, and recrystallized from *n*-butanol. We obtained ~0.5 g (~60%) of the phthalazinedione **6**. The combined filtrates were evaporated to dryness under vacuum. The residue was rubbed with ether, filtered, and recrystallized from ethanol (for **1a**,**b**,**f**,**g**) of glacial acetic acid (for **1d**,**e**), after which the analytically pure pyrrolones (**1a**,**b**,**d-g**) were obtained.

B (for compounds (**1c**,**d**,**e**,**h**). To a solution of the phthalimidonitrile **2** (0.005 mol) in dioxane (30 ml) we added hydrazine hydrate (1 ml, 0.02 mol). The obtained mixture was kept on a boiling water bath for 2 h. After cooling the precipitate was filtered off and recrystallized from glacial acetic acid. (Compounds **1e**,**h** were recrystallized twice.) The pyrrolones **1c**,**d**,**e**,**h** were obtained with yields comparable with the yields of the corresponding samples obtained by method A. By evaporation of the mother solution under vacuum followed by recrystallization of the residue from *n*-butanol it is possible to obtain the phthalazinedione **6** with an overall yield of 60-70%.

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