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# SYNTHESIS OF 3-SUBSTITUTED 2-AMINO-1-HYDROXY-1*H*-INDOLE-5,6-DICARBONITRILES

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*A method of synthesizing new 3-substituted 2-amino-1-hydroxy-1H-indole-5,6-dicarbonitriles has been developed based on the reductive cyclization of substituted 4-cyanomethyl-5-nitrophthalonitriles.*

**Keywords:** 2,1-benzisoxazoles, 1-hydroxy-1*H*-indole-5,6-dicarbonitriles, phthalonitriles, *C*-nucleophilic substitution, reductive cyclization.

Interest in hydroxyindoles is determined by their role in biochemistry [1-4]. In the last time, investigations on the preparation of these heterocycles have been developing intensively. One of the main methods of synthesizing hydroxyindoles is the oxidation of 2,3-dihydroindoles, obtained by the reduction of the corresponding indoles [1]. One further direct method of synthesis of 1-hydroxyindoles [4] is the reductive cyclization of 2-nitrophenylketone [5], 2-nitrostyrene [6], and 2-cyano-2-(2-nitrophenyl)acetate [7] derivatives. There is not much information in the literature on the synthesis of substituted indole-5,6-dicarbo-nitriles [8-10], and data on the synthesis of 2-amino-1-hydroxy-1*H*-indole-5,6-dicarbonitriles are in altogether absent.

The aim of the present work was the synthesis of 2-amino-1-hydroxy-1*H*-indole-5,6-dicarbonitriles by the reductive cyclization of products of *C*-nucleophilic substitution of the bromine atom in 4-bromo-5-nitrophthalonitrile (**1**) (BNPN) with the sodium salts of 3-hydroxy-2-(4-R-phenyl)but-2-enenitriles **2a-d**. The characteristic special features of the chosen highly reactive substrate **1** in $S_NAr$ reactions were considered in [11-15]. It should be mentioned that the substituted *ortho*-dicarbonitriles are promising for obtaining hexazocyclanes [16], phthalocyanines [17, 18] and a series of other compounds containing anhydride, imide, isoindoline, and tetrazole fragments.

2-Amino-1-hydroxyindoles are obtained by the reductive cyclization of *ortho*-nitrobenzyl cyanides [7], therefore in the first stage of the investigation it was necessary for us to develop a method of synthesis of substituted 4-cyanomethyl-5-nitrophthalonitriles based on BNPN. The direct method of obtaining such

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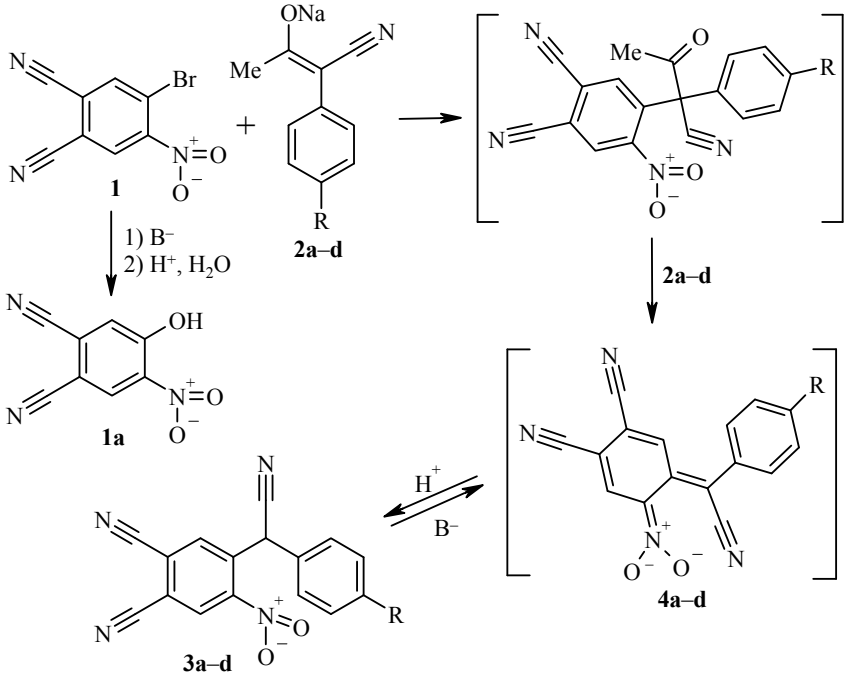
phthalonitriles is the nucleophilic substitution of the bromine atom in BNPN with benzyl cyanides. However classical methods of *C*-nucleophilic substitution according to Makosza (phase transfer catalysis) [19, 20] proved to be unacceptable for BNPN, since in the presence of aqueous base more favored was the nucleophilic substitution of the bromine atom by a hydroxyl group with the formation of 4-hydroxy-5-nitrophthalonitrile (**1a**) (Scheme 1) [18] as a main product. Also, benzyl cyanides, being CH-acids [20], possess low p*K*a values therefore on using dry potassium carbonate, formation of a *C*-nucleophile is probably reduced to the minimum while the interaction of BNPN and potassium carbonate appears to be predominant, resulting in the formation of a σ-complex [21, 22], which also gives nitrophenol **1a** as a main product upon hydrolysis. All attempts to carry out *C*-nucleophilic substitution of the bromine atom in BNPN using benzyl cyanides as nucleophiles were unsuccessful; therefore we have used the sodium salts **2a-d** obtained by Claisen condensation from benzyl cyanides and ethyl acetate. These salts are ambident nucleophiles (they have both *C*- and *O*-nucleophilic reaction centers). On interaction of BNPN dissolved in DMF with salts **2a-d** at room temperature, the formation of products **3a-d** with a characteristic dark-green color begins straight away, and the reaction is completely finished after 60-90 min (Scheme 1).

Scheme 1




**a** R = H, **b** R = Me, **c** R = Cl, **d** R = OMe

It was determined experimentally that a twofold excess of salt **2** was necessary for the complete conversion of BNPN. The second mole of base (salt **2**) is probably required for the elimination of the acetyl group [23]. Elimination of the cyano group was not detected. Products **3a-d** were obtained after acidification of the reaction mixture in a yield not exceeding 60% (Table 1). Attempts to substantially increase the yield of the desired compounds **3a-d** by matching the ratio of reactants, solvents, bases, and the temperature regime were unsuccessful.

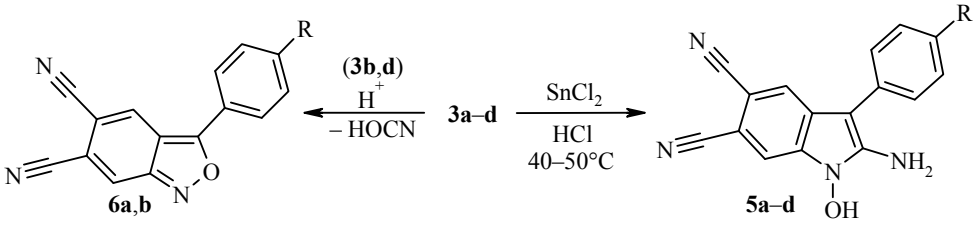
The product of *C*-substitution dominates, but the product of *O*-substitution was not isolated successfully (possibly due to the instability of the resulting enolic esters). It is necessary to mention that, in the reaction mixture, according to data of $^1$H NMR spectroscopy the methine proton characteristic of compounds **3** was not observed, that points to the quinoid form **4**, which is more advantageous for similar compounds in basic solutions [24-26]. Compounds **3a-d**, isolated after acidification of the reaction mixture, are white crystalline

substances, however, in polar solvents they are partially converted back into the quinoid form **4** (with characteristic intense green coloration, which on standing at room temperature for a day turns into a yellow-brown, which is apparently caused by oxidative polymerization of compounds **3**). UV spectra were recorded in various solvents for compounds **3b,d**. Thus, in chloroform solution, two absorption maxima were observed at $\lambda_{max1}$ 250 nm and $\lambda_{max2}$ 306 nm, but in DMSO solution two further maxima appeared at $\lambda_{max3}$ 422-420 nm and $\lambda_{max4}$ at 631-635 nm for compounds **3b** and **3d**, respectively, which confirmed the transition into the quinoid form.

Various methods exist for reducing the nitro group [7, 27, 28] for the synthesis of 1-hydroxyindole compounds, but under mild conditions hydroxylamine is usually formed first [28], and, after that, it is cyclized into 2-amino-1-hydroxyindole.

As reducing agent we chose divalent tin (Scheme 2), which reduces nitro groups more selectively, not affecting a cyano group. Compounds **3a-d** at 40-50°C in a solution of divalent tin in hydrochloric acid are reduced with simultaneous cyclization into the indole ring **5a-d**. As side products for compounds having donor substituents, substituted 2,1-benzisoxazole-5,6-dicarbonitriles **6a,b** were found in yields of up to 10%. It is known that analogous compounds are formed by the action of bases [29, 30] and on acidic decomposition of 1-hydroxyindoles [27]. Our attempts to synthesize 2,1-benzisoxazoles by the direct route on treating compounds **3** with sodium methylate were unsuccessful, but on heating compounds **3b,d** in an alcoholic solution of hydrochloric acid, 2,1-isoxazoles **6a,b** were obtained in low yield (up to 15%).

Scheme 2




**5a** R = H; **5b**, **6a** R = Me; **5c** R = Cl; **5d**, **6b** R = OMe

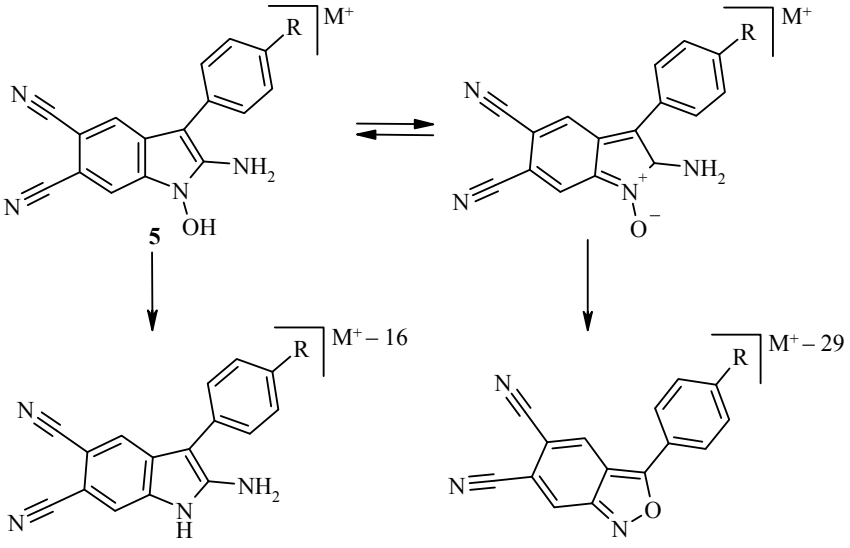
TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **3a-d, 5a-d, 6a,b**

| Compound | Empirical formula | Found, % / Calculated, % | | | Mp, ºC | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **3a** | $C_{16}H_8N_4O_2$ | 66.46 / 66.67 | 2.75 / 2.80 | 19.40 / 19.44 | 152-154 | 48 |
| **3b** | $C_{17}H_{10}N_4O_2$ | 67.43 / 67.55 | 3.21 / 3.33 | 18.46 / 18.53 | 163-165 | 54 |
| **3c** | $C_{16}H_7ClN_4O_2$ | 59.28 / 59.55 | 2.05 / 2.19 | 17.29 / 17.36 | 189-190 | 58 |
| **3d** | $C_{17}H_{10}N_4O_3$ | 64.02 / 64.15 | 3.14 / 3.17 | 17.50 / 17.60 | 202-205 | 46 |
| **5a** | $C_{16}H_{10}N_4O \cdot H_2O$ | 65.55 / 65.75 | 4.08 / 4.14 | 19.15 / 19.17 | 189-190 (decomp.) | 64 |
| **5b** | $C_{17}H_{12}N_4O \cdot H_2O$ | 66.47 / 66.66 | 4.53 / 4.61 | 18.24 / 18.29 | 209-211 (decomp.) | 68 |
| **5c** | $C_{16}H_9ClN_4O \cdot H_2O$ | 58.70 / 58.82 | 3.33 / 3.39 | 17.05 / 17.15 | 246-248 (decomp.) | 71 |
| **5d** | $C_{17}H_{12}N_4O_2 \cdot H_2O$ | 63.15 / 63.35 | 4.25 / 4.38 | 17.32 / 17.38 | 223-225 (decomp.) | 69 |
| **6a** | $C_{16}H_9N_3O$ | 73.98 / 74.12 | 3.41 / 3.50 | 16.19 / 16.21 | 161-163 | 15 |
| **6b** | $C_{16}H_9N_3O_2$ | 69.62 / 69.81 | 3.27 / 3.30 | 15.21 / 15.27 | 161-162 | 11 |

The structures of compounds **3, 5, 6** were confirmed by data of NMR spectroscopy and mass spectrometry (Tables 2-4). It is necessary to mention that recording of spectra for compounds **3** is possible only in $CDCl_3$ (in DMSO-$d_6$ solution, the formation of a mixture of products difficult to identify was observed 2-3 h after dissolution). However, their solubility in $CDCl_3$ was minimal so that it was not possible to record $^{13}C$ NMR spectra for the majority of compounds. In the $^1H$ NMR spectra of freshly prepared samples of compounds **3** signals were observed for aromatic protons in the 8.10-8.40 ppm region, two singlets for the phthalonitrile fragment, at 7.00-7.50 ppm for the second benzene ring, and a singlet for the methine proton in the 6.1 ppm region. Signals for the OH group were observed for 2-amino-1-hydroxyindoles **5** in $^1H$ NMR spectra as a singlet in the 11.70-11.80 ppm region and a broadened singlet for $NH_2$ at 6.60-6.90 ppm, and also signals of the protons of the phthalonitrile ring shifted upfield at 7.70-7.90 ppm. In the $^{13}C$ NMR spectra of compounds **3, 5, 6** all the carbon signals characteristic of these compounds were present. A precise assignment of the signals of the protons and carbon atoms was made for the case of compound **5c** with the aid of two-dimensional spectroscopy (ROESY, HSQC, HMBC).

The mass spectra of compounds **3** were characterized by low intensity signals of the molecular ion, and further fragmentation occurs through the formation of a quinoid form. The $[M\text{-}OH]^+$ signal was the most intense. The presence of a hydroxyl group in indoles **5** followed from analysis of those mass spectra in which the most intense signals were $[M\text{-}O]^+$ and $[M\text{-}CH\text{-}NH_2]^+$ (Scheme 3), corresponding to products of decomposition of the quinoid form.

Scheme 3




Determination of the orientation of substituents in 2-amino-1-hydroxyindoles was performed by the single crystal X-ray structural analysis for the case of compound **5a**. In the crystal, compound **5a** exists as a monohydrate (Fig. 1). The indole fragment has a planar structure. The effect of donor and acceptor substituents leads to significant redistribution of bond lengths in the six-membered ring of the indole fragment. The C(3)–C(8) and C(5)–C(6) bonds are significantly longer than the remainder (Table 5). The N(1)–C(8) and C(2)–C(3) bonds are somewhat shortened, while the C(1)–C(2) bond is elongated relative to the mean length values for such bonds (1.372, 1.434, and 1.364 Å, respectively [31]). The amino group is characterized by a nonplanar structure (sum of the angles at the nitrogen atom is 355.1°), the hydroxyl group is rotated perpendicularly (torsion angle C(1)–N(1)–O(1)–H(1) is equal to 91.6°) relative to the indole fragment. Apparently, such a structure is governed by the participation of donor substituents in hydrogen bonding. However, the H(1)N atom does not form an H-bond, which may be caused by steric factors from the presence of a phenyl substituent adjacent to the $NH_2$

group. The phenyl group is disordered over two positions with equal occupancies, however, both components are rotated relative to the indole fragment on opposite sides by 37.95(9) and 38.09(7)°.

In the crystal structure, the H-bonded layers are formed parallel to the *ab* crystallographic plane (Fig. 2) by the water and compound **5a** molecules (Tables 5, 6). The interactions between the layers are brought about by hydrogen bonds and Van der Waals forces.

TABLE 2. $^{1}$H NMR Spectra of the Synthesized Compounds **3a-d**, **5a-d**, **6b,d***

| Compound | Chemical shifts, δ, ppm (*J*, Hz) |
|---|---|
| **3a** | 6.13 (1H, s, CH); 7.28-7.31 (2H, m, H Ph); 7.43-7.47 (3H, m, H Ph); 8.11 (1H, s, H-3); 8.42 (1H, s, H-6) |
| **3b** | 2.48 (3H, s, $CH_3$); 6.09 (1H, s, CH); 7.16 (2H, d, $^3J$ = 8.0, H-3',5'); 7.24 (2H, d, $^3J$ = 8.0, H-2',6'); 8.11 (1H, s, H-3); 8.41 (1H, s, H-6) |
| **3c** | 6.12 (1H, s, CH); 7.25 (2H, d, $^3J$ = 8.5, H-3',5'); 7.44 (2H, d, $^3J$ = 8.5, H-2',6'); 8.13 (1H, s, H-3); 8.44 (1H, s, H-6) |
| **3d** | 3.82 (1H, s, $OCH_3$); 6.06 (1H, s, CH); 6.94 (2H, d, $^3J$ = 8.8, H-3',5'); 7.20 (2H, d, $^3J$ = 8.8, H-2',6'); 8.11 (1H, s, H-3); 8.41 (1H, s, H-6) |
| **5a** | 6.77 (2H, s, $NH_2$); 7.25 (1H, t, $^3J$ = 7.7, H Ph); 7.44 (2H, t, $^3J$ = 7.7, H Ph); 7.54 (2H, d, $^3J$ = 7.7, H Ph); 7.74 (1H, s, H-7); 7.90 (1H, s, H-4); 11.76 (1H, s, OH) |
| **5b** | 2.33 (3H, s, $CH_3$); 6.60 (2H, br. s, $NH_2$); 7.28 (2H, d, $^3J$ = 8.0, H-3',5'); 7.42 (2H, d, $^3J$ = 8.0, H-2',6'); 7.71 (1H, s, H-7); 7.81 (1H, s, H-4); 11.75 (1H, s, OH) |
| **5c** | 6.85 (2H, s, $NH_2$); 7.47 (2H, d, $^3J$ = 8.5, H-3',5'); 7.56 (2H, d, $^3J$ = 8.5, H-2',6'); 7.75 (1H, s, H-7); 7.91 (1H, s, H-4); 11.77 (1H, s, OH) |
| **5d** | 3.80 (3H, s, $OCH_3$); 6.65 (2H, s, $NH_2$); 7.01 (2H, d, $^3J$ = 8.8, H-3',5'); 7.44 (2H, d, $^3J$ = 8.8, H-2',6'); 7.71 (1H, s, H-7); 7.79 (1H, s, H-4); 11.70 (1H, s, OH) |
| **6a** | 2.47 (3H, s, $CH_3$); 7.47 (2H, d, $^3J$ = 8.1, H-3',5'); 8.14 (2H, d, $^3J$ = 8.1, H-2',6'); 8.73 (1H, s, H-4); 9.22 (1H, s, H-7) |
| **6b** | 3.93 (3H, s, $OCH_3$); 7.19 (2H, d, $^3J$ = 8.8, H-3',5'); 8.20 (2H, d, $^3J$ = 8.8, H-2',6'); 8.74 (1H, s, H-7); 9.24 (1H, s, H-4) |

*Solvents: $CDCl_3$ (compounds **3a-d**) and DMSO-$d_6$ (compounds **5a-d** and **6a,b**).

TABLE 3. $^{13}$C NMR Spectra of the Synthesized Compounds **3a,d, 5a,c,d, 6b***

| Compound | Chemical shifts, δ, ppm |
|---|---|
| **3a** | 38.2 (CH); 112.9; 113.2; 116.6; 117.6; 120.7; 127.9 (C-3',5'); 129.9 (C-4'); 130.1 (C-2',6'); 130.3 (C-6); 131.5 (C-4); 136.0 (C-3); 136.4 (C-1'); 149.3 (C-5) |
| **3d** | 37.6 (CH); 55.4 ($OCH_3$); 112.9; 113.2; 115.4; 116.8; 117.4; 120.6; 123.1; 129.3; 130.2; 135.9; 136.9; 149.2 (C-5); 160.6 (C-4') |
| **5a** | 90.4 (C-3); 99.3 (C-6); 104.5 (C-5); 111.2 (C-7); 118.2 (C≡N); 118.5 (C≡N); 120.2 (C-4); 124.9 (C-3a); 125.3 (C-4'); 127.5 (C-2',6'); 129.0 (C-3',5'); 130.7 (C-7a); 133.1 (C-1'); 146.3 (C-2) |
| **5c** | 89.2 (C-3); 99.7 (C-6); 104.6 (C-5); 111.3 (C-7); 118.1 (C≡N); 118.4 (C≡N); 120.2 (C-4); 124.7 (C-3a); 128.9 (C-3',5'); 129.3 (C-2',6'); 129.5 (C-4'); 130.8 (C-7a); 132.0 (C-1'); 146.5 (C-2) |
| **5d** | 55.2 ($OCH_3$); 90.3 (C-3); 98.9 (C-6); 104.3 (C-5); 111.1 (C-7); 114.5 (C-3',5'); 118.2 (C≡N); 118.6 (C≡N); 120.1 (C-4); 125.0 (C-3a); 125.2 (C-4'); 128.9 (C-2',6'); 130.4 (C-7a); 146.1 (C-2); 157.2 (C-1') |
| **6b** | 55.7 ($OCH_3$); 106.0 (C-5); 111.9 (C-6); 113.8; 115.2 (C-3',5'); 115.6 (C-3a); 116.2 (C≡N); 118.2 (C≡N); 125.4 (C-7); 129.4 (C-2',6'); 133.9 (C-4); 154.7 (C-3); 162.6 (C-7a); 168.8 (C-4') |

*Solvents: $CDCl_3$ (compounds **3a,d**) and DMSO-$d_6$ (compounds **5a,c,d** and **6b**).

TABLE 4. Mass Spectra of Compounds **3a-d**, **5a-d, 6b,d**

| Compound | *m/z* ($I_{rel}$, %) |
|---|---|
| **3a** | 288 $[M]^+$ (1.4), 271 $[M-17]^+$ (100), 254 (70), 245 (26) 240 (37), 231 (8), 217 (66), 213 (30), 77 (46) |
| **3b** | 302 $[M]^+$ (4), 285 $[M-17]^+$ (55), 268 (55), 258 (32), 240 (62), 230 (75), 213 (21), 201 (20), 176 (16), 119 (12), 107 (15), 103 (21), 91 (82), 77 (62), 65 (66), 63 (50), 51 (58), 39 (100) |
| **3c** | 322 $[M]^+$ (3), 307 (10), 305 $[M-17]^+$ (34), 288 (43), 279 (19), 251 (41), 240 (100), 233 (46), 216 (67), 202 (20), 188 (10), 139 (8), 123 (8), 111 (19), 99 (10), 87 (9), 75 (25) |
| **3d** | 318 $[M]^+$ (38), 301 $[M-17]^+$ (100), 284 (98), 275 (59), 270 (30), 256 (30), 254 (42), 232 (95), 228 (40), 201 (62), 175 (23), 123 (39), 92 (24), 77 (34) |
| **5a** | 274 $[M]^+$ (18), 258 $[M-16]^+$ (98), 257 (58), 245 $[M-29]^+$ (44), 230 (28), 217 (12), 105 (31), 77 (99), 51 (76), 44 (100) |
| **5b** | 288 $[M]^+$ (1.4), 272 $[M-16]^+$ (100), 255(18), 91 (24), 65 (19) |
| **5c** | 308 $[M]^+$ (2), 294 (17), 292 $[M-16]^+$ (59), 256 (37), 216 (16), 202 (22), 176 (21), 139 (68), 128 (50), 113 (52), 111 (100), 101 (35), 75 (90) |
| **5d** | 304 $[M]^+$ (24), 288 $[M-16]^+$ (100), 273 $[M-29]^+$ (54), 256 (22), 232 (18), 217 (12), 204 (9), 191 (7), 135 (5), 92 (5), 63 (15) |
| **6a** | 259 $[M]^+$ (67), 230 $[M-N-O]^+$ (40), 172 (27), 91 (68), 89 (30) |
| **6b** | 275 $[M]^+$ (98), 232 (100), 204 (87), 178 (48), 177 (38), 92 (71), 77 (22), 64 (71) |

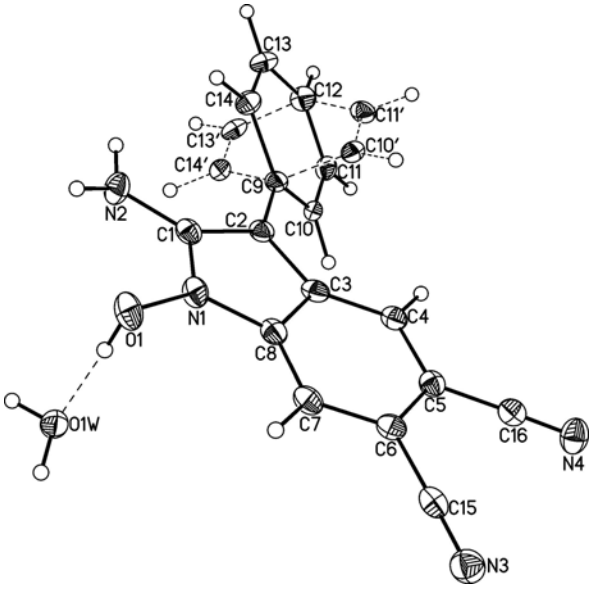



Fig. 1. General form of the monohydrate **5a**·$H_2O$, representing atoms by ellipsoidal atomic displacements with 50% probability. The second component of the disordered phenyl fragment is shown by dashed lines.

We have therefore established that on interacting BNPN with the sodium salts of 3-hydroxy-2-(4-R-phenyl)but-2-enenitriles in DMF solution a *C*-nucleophilic substitution of the bromine atom occurs in 4-bromo-5-nitrophthalonitrile with the formation, as the main reaction product, of substituted 4-cyanomethyl-5-nitrophthalonitriles, which on chemical reduction of the nitro group led to 3-substituted 2-amino-1-hydroxy-1*H*-indol-5,6-dicarbonitrile. The obtained 4-cyanomethyl-5-nitrophthalonitriles are transformed under the action of base into the quinoid form, and under the action of strong acids they are cyclized into 2,1-benzisoxazoles.

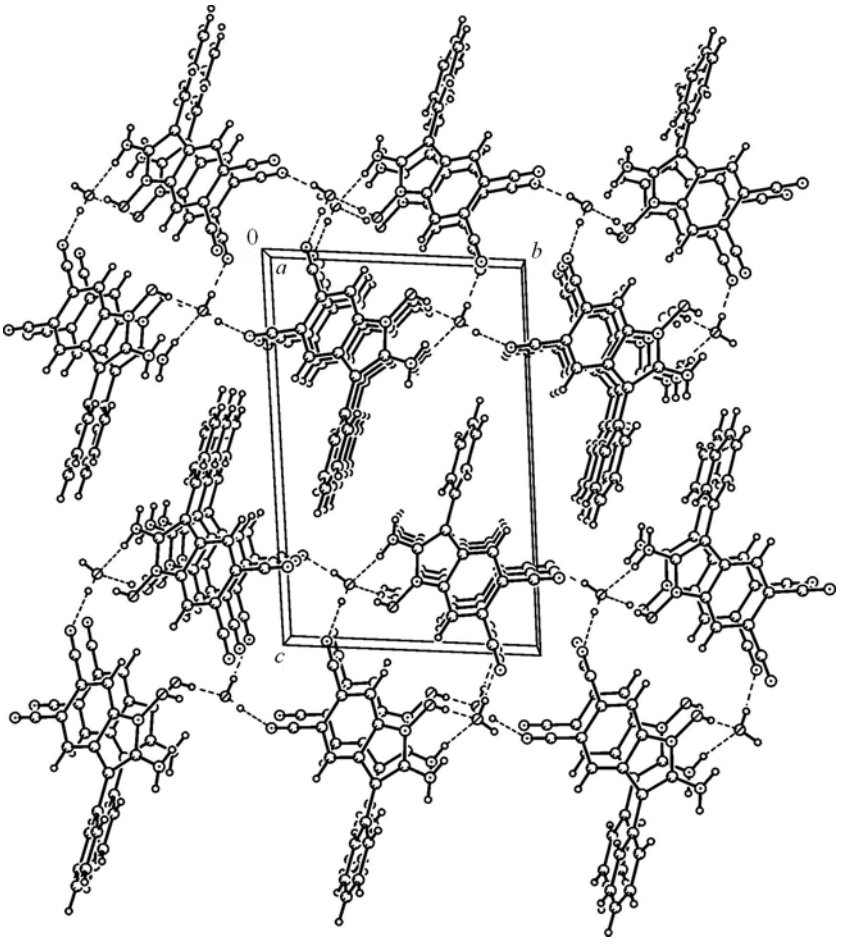



Fig. 2. Fragment of the crystal packing of hydrate **5a**·$H_2O$. The second component of the disordered phenyl fragment is not shown.

TABLE 5. Bond Lengths (*l*) in the Molecule of **5a**·$H_2O$

| Bond | *l*, Å | Bond | *l*, Å |
|---|---|---|---|
| C(3)–C(4) | 1.394(2) | C(3)–C(8) | 1.427(2) |
| C(4)–C(5) | 1.390(2) | N(1)–C(8) | 1.365(2) |
| C(5)–C(6) | 1.422(2) | C(2)–C(3) | 1.434(2) |
| C(6)–C(7) | 1.389(2) | C(1)–C(2) | 1.364(2) |
| C(7)–C(8) | 1.372(2) | | |

TABLE 6. Interatomic Distances and Angles in the **5a**·$H_2O$ Molecule

| H-bond | O(N)···O(N), Å | H···O(N), Å | ∠O(N)–H···O(N), deg. |
|---|---|---|---|
| O(1)–H(1)···O(1)W | 2.607(2) | 1.76 | 178 |
| N(2)–H(2)N···O(1)W | 3.079(2) | 2.21 | 161 |
| O(1)W–H(1)W···N(4) | 2.845(2) | 2.03 | 162 |
| O(1)W–H(2)W···N(3) | 2.833(2) | 1.99 | 174 |

## EXPERIMENTAL

The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX-500 instrument (at 500 and 125 MHz, respectively) in $CDCl_3$ or DMSO-$d_6$ solution at 30°C, internal standard was TMS or the residual signals of the solvent (2.50 ppm for DMSO-$d_6$ or 7.26 ppm for $CDCl_3$ in $^1H$ NMR spectra, 39.5 ppm for DMSO-$d_6$ in $^{13}C$ NMR spectra). Mass spectra were recorded on a Finnigan MAT Incos 50 chromato-mass spectrometer at an ionizing voltage of 70 eV and ionization chamber temperature of 100-220°C. Elemental analysis was carried out on a Perkin–Elmer 2400 instrument.

The starting BNPN was synthesized by the procedure of [32], sodium salts **2a-d** were synthesized analogously to the procedure of [33].

**4-(Cyanophenylmethyl)-5-nitrophthalonitrile (3a), 4-(Cyano-*p*-tolylmethyl)-5-nitrophthalonitrile (3b), 4-[(4-Chlorophenyl)cyanomethyl]-5-nitrophthalonitrile (3c), and 4-[(4-Methoxyphenyl)cyano-methyl]-5-nitrophthalonitrile (3d) (General Method)**. Compound **2a-d** (2.2 mmol) was added to a solution of BNPN (1 mmol) in DMF (3 ml), and the mixture was stirred at room temperature for 1-2 h, then poured into cold water (10 ml) containing AcOH (0.5 ml). The separated resiny solid was extracted with $CH_2Cl_2$, washed thoroughly with water, and chromatographed on silica gel with eluent hexane–$CH_2Cl_2$, 2:1. The solvent was evaporated, and the residual solid was recrystallized from alcohol.

**2-Amino-1-hydroxy-3-phenyl-1*H*-indole-5,6-dicarbonitrile (5a), 2-Amino-1-hydroxy-3-*p*-tolyl-1*H*-indole-5,6-dicarbonitrile (5b), 2-Amino-3-(4-chlorophenyl)-1-hydroxy-1*H*-indole-5,6-dicarbonitrile (5c), and 2-Amino-1-hydroxy-3-(4-methoxyphenyl)-1*H*-indole-5,6-dicarbonitrile (5d) (General Method)**. EtOH (2 ml) was added to a solution of $SnCl_2$ (4 mmol) in conc. HCl (2 ml), and compound **3a-d** (1 mmol) was added portionwise at such a rate that the solution heated spontaneously to not higher than 40-50°C. The mixture was maintained at this temperature for 1-2 h, and diluted with water (5 ml), the precipitated solid was filtered off, and recrystallized from alcohol.

**3-*p*-Tolylbenzo[*c*]isoxazole-5,6-dicarbonitrile (6a) and 3-(4-Methoxyphenyl)benzo[*c*]isoxazole-5,6-dicarbonitrile (6b) (General Method).** Conc. HCl (1 ml) was added to a suspension of compound **3b,d** (1 mmol) in EtOH (10 ml) and the mixture was refluxed for 2-6 h (check by TLC, petroleum ether–ethyl acetate, 1:1) until complete disappearance of the starting compound. The mixture was cooled, diluted with water (10 ml), the precipitated solid was separated and chromatographed on silica gel, eluent hexane–$CH_2Cl_2$, 1:2. The solvent was evaporated and the residual solid was recrystallized from alcohol.

**X-ray Structural Analysis.** Crystals of **5a**·$H_2O$ ($C_{16}H_{11}N_4O·H_2O$) at 100 K are triclinic: $a$ = 4.7298(4) Å, $b$ = 9.8790(9) Å, $c$ = 15.2145(15) Å, α = 84.829(2)°, β = 81.839(2)°, γ = 8.088(2)°, $V$ = 700.69(11) Å$^3$, $Z$ = 2, space group $P1$, μ = 0.096 mm$^{-1}$, $d_{calc}$ = 1.385 g·cm$^{-3}$. The intensities of 7743 reflections were collected on a SMART APEX2 CCD diffractometer (λ(MoKα) = 0.71073 Å, graphite monochromator, ω-scanning, 2θ < 58°). Treatment of the initial array of measurement intensities was carried out with the programs SAINT and SADABS, included in the APEX2 program package [34]. The structure was solved by the direct method and refined by the least squares method in an anisotropic approximation for non-hydrogen atoms on $F^2_{hkl}$. Hydrogen atoms were placed in geometrically calculated positions, with the exception of hydrogen atoms at oxygen and nitrogen atoms, the positions of which were localized from an electron density difference synthesis and were then normalized at a distance of 0.85 (for O–H) and 0.9 Å (for N–H). The positions of all hydrogen atoms were refined within the riding model ($U_{iso}$(H) = $nU_{eq}$(C)(O)(N), where $n$ = 1.5 for oxygen atoms, $n$ = 1.2 for C, N atoms). There were 3368 independent reflections ($R_{int}$ = 0.0417) in the refinement. The convergence of refinement at each independent reflection is w$R_2$ = 0.1180 ($R_1$ = 0.0446 at 2210 reflections with $I > 2\sigma(I)$). All calculations were carried out using the SHELXTL program [35].

The X-ray structural analysis data have been deposited in the Cambridge Crystallographic Data Center (deposition CCDC 810378).

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