Synthesis and Structure of Novel 1,2-Dihydrophthalazine Containing Betaines

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1,2-Dihydro-2-(4,5-dihydroimidazol-2yl)phthalazin-1-ol **1** reacts exothermically with dialkyl acetylenedicarboxylates to give 3-[2-(4,5-dihydro-1*H*-imidazol-3-ium-2-yl)-1,2-dihydro-1-phthalazin]-1,4-dialkoxy-1,4-dioxo-2-buten-2-olates **7** and **8**. Enolic ester compounds underwent further transesterification reactions with formation of the betaines **9** and **10**. The unequivocal structural assignement of these compounds was achieved by spectroscopic ^1H and ^{13}C nmr methods as well as X-ray analysis of **7**.

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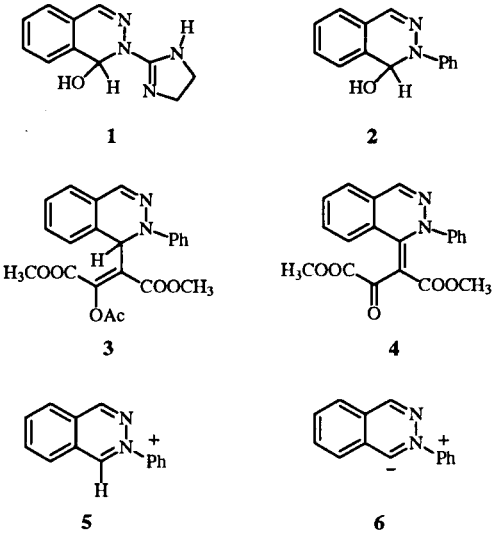
Pseudobases of heterocyclic amines constitute a valuable class of compounds with interesting chemical [1-8] and biological [9,10] properties. We have also described a facile synthesis of 1,2-dihydro-2-(4,5-dihydroimidazol-2yl)-phthalazin-1-ol **1** (Chart 1) which could be transformed into fused heterocyclic systems by reacting with C-H acids [11].

Recently, our attention has been drawn by a work of Butler and co-workers [6] on the reaction of 1,2-dihydro-2-phenylphthalazin-1-ol **2** (Chart 1) with dimethyl acetylenedicarboxylate. It was found that the reaction carried out in boiling acetonitrile, in the presence of acetic acid, led to the formation of phthalazine derivatives **3** and **4** in 7% and 15% yield respectively. Later products were thought to arise from addition of the phthalazinium **5** and acetate ion to dimethyl acetylenedicarboxylate or from addition of the ylide **6** followed by acetolysis of the initial adduct [6].

Chart 1



Results and Discussion.

When we subjected compound **1** to the reaction with dimethyl acetylenedicarboxylate in methanol, a slightly exothermic reaction took place which gave rise to the formation of a novel type of product **7** (50% yield) whose spectral properties did not allow ready structure determination. The presence of an eqivalent of methanol as a solvate further confused the interpretation of the spectra and elemental analysis. This material, however, could be recrystallized from nitromethane, with which did not form a solvate. Crystals suitable for X-ray analysis allowed structure determination, which showed **7** to be a 1,2-dihydrophthalazine containing betaine (Figure 1).

Similar reaction of the pseudobase **1** with diethyl acetylenedicarboxylate proceeded smoothly in anhydrous ethanol at room temperature furnishing the betaine **8** in 52% yield. It is noteworthy that monosubstituted acetylenes such as ethyl propiolate did not react analogously with pseudobase **1** and the betaines similar to **7** and **8** were not detected under the employed conditions.

The formation of the products **7** and **8** involves migration of an oxygen atom which could mechanistically be explained by the initial nucleophilic attack on the acetylene carbon atom by hydroxyl group of the pseudobase **1** (Scheme 1). Enol ether **A** thus formed breaks down with the formation of a tight ion pair **B** which then couples to give the intermediate **C**. Tautomerization of the later compound furnishes the final betaine. The mechanism involving ion pair of type **B** is supported by the finding that the reaction readily takes place in polar solvents (methanol, ethanol or acetone) where the formation of ions is favoured, and is hindered in nonpolar solvents such as benzene.

Analogous rearrangements have earlier been described for the reactions of dimethyl acetylenedicarboxylate with a series of benzimidazole [12] and phenanthridine *N*-oxides [13]. In these cases, however, *N*-oxides behaved as 1,3-dipols on reaction with electron deficient acetylenes, and therefore, the isoxazoline derivatives were suggested to be the key intermediates in a process involving N→C oxygen atom migration.

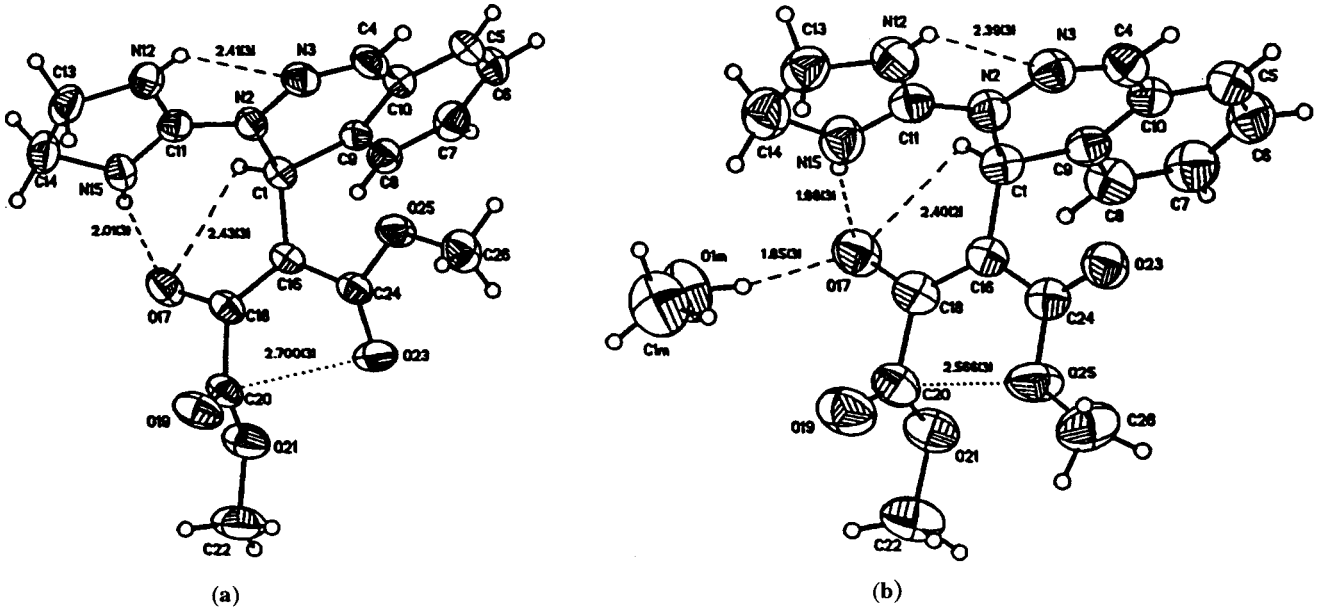
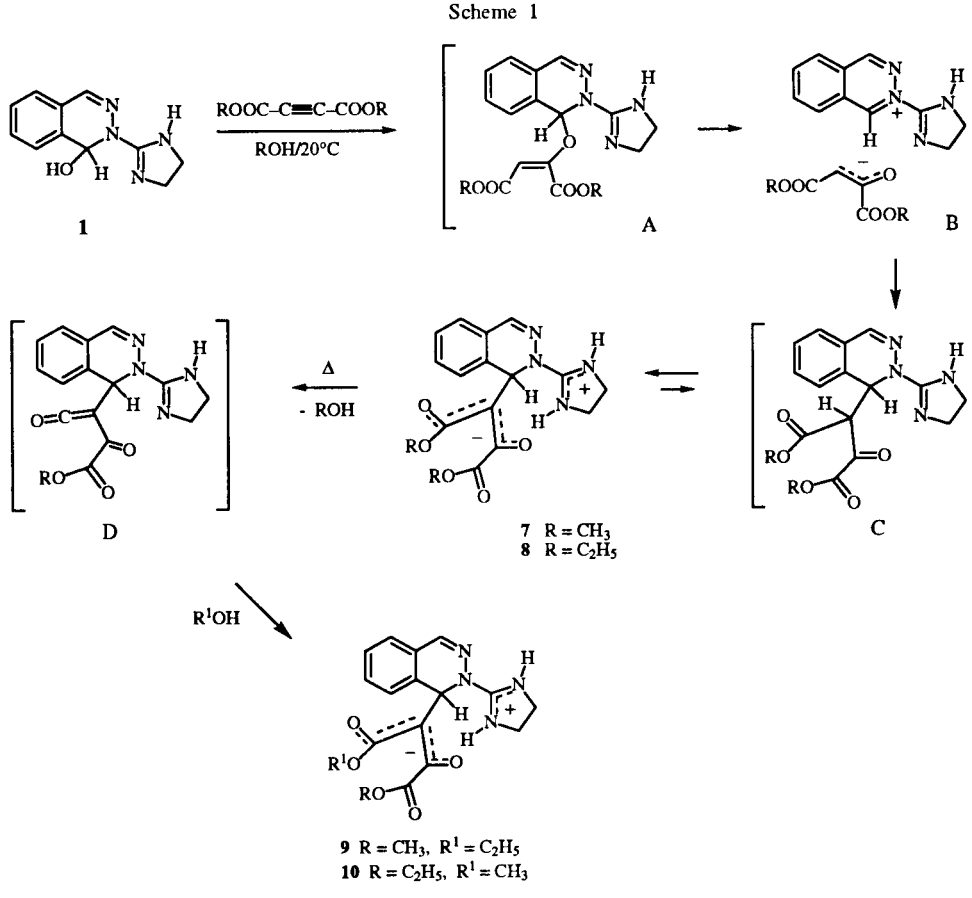


Figure 1. Structure of **7** in its unsolvated crystal (a) and in the methanol solvate (b).

Scheme 1



Betaines **7** and **8** contain enolic ester group which is known to undergo facile transesterification reaction involving rate-determining elimination of alkohol to give acylketen as a reactive intermediate [14-16]. Thus, we found

that heating the methyl ester **7** in boiling ethanol for 0.5 hour produced diester **9** and similar reaction of diethyl ester **8** in boiling methanol furnished product **10** (Scheme 1).

The structures of the betaines **7**, **8**, **9** and **10** were confirmed by elemental analyses and the ir and nmr spectra. For example, ir spectrum of **8** exhibits two carbonyl absorptions at 1723 and 1644, and a strong band at 1504 cm^{-1} corresponding to the carbon-oxygen stretching in enolate anions [17]. The ^1H nmr spectrum shows two triplets in ratio 1:1, integrating each for three protons at δ = 0.78 and 1.2 ppm, a quartet of two methylene protons of 1-ethoxy group at δ = 3.6 ppm, and a broadened singlet integrating for four protons of imidazoline methylene protons at δ = 3.7 ppm. Due to presence of asymmetric center at carbon atom C-1 of 1,2-dihydrophthalazine moiety, the methylene protons of 4-ethoxy group exhibit chemical shift nonequivalence [18] and appear as a multiplet at δ = 4.0-4.2 ppm. An analogous geminal nonequivalence is observed for methylene protons of 4-ethoxy group in ^1H nmr spectrum of **9** (*vide infra*).

Crystal structure analysis. Compound **7** gives two crystalline forms - an unsolvated one, **7a**, when recrystallized from nitromethane and a 1:1 methanol solvate **7b** when recrystallized from methanol. In both cases **7** exists in the zwitterionic form with the positive charge delocalized at the protonated guanidine fragment and negative charge at the dimethyl 2-oxobutanedioate part of the molecule. The geometry of the latter fragment strongly resembles that observed in dimethyl 3-(2-phenyl-1,2-dihydrophthalazine-1-ylidene)-2-oxobutanedioate **4** (Chart 1) where the major contribution to the molecular ground state comes from the dipolar form due to the torsional twist of the ylidene linkage (62(and >C=C< bond of 1.471 Å) with the negative charge delocalized among carbonyl groups at the acyclic end of the ylidene [6]. The zwitterionic structure of **7** is stabilized by intramolecular hydrogen bond between O17 and N15-H of the imidazolidinium fragment. The ORTEP drawings of **7** in the two crystal structures are shown in Figure 1. The disposition of substituents at the partially double bond C16-C18 is *E* in both structures but the two molecules differ in the configuration about partially double bond C16-C24 which is *E* in the methanol solvate and *Z* in the unsolvated form [torsion angles C18-C16-C24-O23 are 16.1(4) and -170.7(2) [in **7a** and **7b** respectively]. The two ester groups of the dimethyl 2-oxobutanedioate fragment are approximately perpendicular as often observed for diesters of maleic or *o*-phthalic acids. Such orientation of the ester groups usually leads to a short intramolecular contact between the carbonyl carbon atom of one ester group and the carbonyl or etheral oxygen atom of the second ester group. There is a significant difference in this contact between the two structures - for the *E* isomer this distance is 2.566(3) Å and in the *Z* isomer it is much longer [2.700(3) Å]. Despite this difference, bond lengths and angles in the two structures show a good agreement.

Selected pertinent crystallographic data for the compound **7** are tabulated in Table 1.

Table 1

Bond Lengths [Å] and Angles [°] for Compounds **7a** and **7b**

a) bond lengths

Compound	7a	7b
C(1)-C(16)	1.500(3)	1.513(3)
C(1)-N(2)	1.501(3)	1.500(2)
C(1)-C(9)	1.508(3)	1.505 (3)
N(2)-C(1 1)	1.336(3)	1.342(3
N(2)-N(3)	1.391(3)	1.393(2)
N(3)-C(4)	1.264(3)	1.279(3)
C(4)-C(1O)	1.454(4)	1.453(3)
C(5)-C(10)	1.378(4)	1.388(3)
C(5)-C(6)	1.383(4)	1.378(4)
C(6)-C(7)	1.382(4)	1.378(4)
C(7)-C(8)	1.379(4)	1.381(4)
C(8)-C(9)	1.382(3)	1.388(3)
C(9)-C(10)	1.392(3)	1.397(3)
C(11)-N(15)	1.315(3)	1.328(3)
C(11)-N(12)	1.324(3)	1.316(3)
N(12)-C(13)	1.461(4)	1.452(3)
C(13)-C(14)	1.512(4)	1.524(4)
C(14)-N(15)	1.461(4)	1.455(3)
C(16)-C(18)	1.381(3)	1.385(3)
C(16)-C(24)	1.443(4)	1.435(3)
O(17)-C(18)	1.272(3)	1.280(3)
C(18)-C(20)	1.514(4)	1.520(3)
O(19)-C(20)	1.202(3)	1.195(3)
C(20)-0(21)	1.326(3)	1.326(3)
O(21)-C(22)	1.448(4)	1.439(3)
O(23)-C(24)	1.212(3)	1.213(2)
C(24)-0(25)	1.350(3)	1.355(3)
O(25)-C(26)	1.428(3)	1.425(3)
O(1M)-C(1M)		1.403(4)

b) bond angles

Compound	7a	7b
C(16)-C(1)-N(2)	114.5(2)	113.5(2)
C(16)-C(1)-C(9)	115.4(2)	112.9(2)
N(2)-C(1)-C(9)	107.9(2)	109.6(2)
C(11)-N(2)-N(3)	112.9(2)	113.2(2)
C(11)-N(2)-C(1)	121.3(2)	120.4(2)
N(3)-N(2)-C(1)	125.4(2)	126.2(2)
C(4)-N(3)-N(2)	115.7(2)	116.1(2)
N(3)-C(4)-C(10)	125.8(3)	126.5(2)
C(10)-C(5)-C(6)	120.2(3)	120.4(2)
C(7)-C(6)-C(5)	119.8(3)	119.7(3)
C(8)-C(7)-C(6)	119.8(3)	120.3(2)
C(7)-C(8)-C(9)	120.9(3)	120.8(2)
C(8)-C(9)-C(10)	118.8(2)	118.6(2)
C(8)-C(9)-C(1)	120.4(2)	119.8(2)
C(10)-C(9)-C(1)	120.7(2)	121.6(2)
C(5)-C(10)-C(9)	120.4(2)	120.1(2)
C(5)-C(10)-C(4)	121.7(2)	122.2(2)
C(9)-C(10)-C(4)	118.0(2)	117.6(2)
N(15)-C(11)-N(12)	112.2(2)	111.5(2)
N(15)-C(11)-N(2)	124.6(2)	124.1(2)
N(12)-C(11)-N(2)	123.2(2)	124.5(2)
C(11)-N(12)-C(13)	109.4(2)	111.0(2)
N(12)-C(13)-C(14)	101.8(2)	102.6(2)
N(15)-C(14)-C(13)	102.6(2)	102.7(2)
C(11)-N(15)-C(14)	109.3(2)	110.4(2)
C(18)-C(16)-C(24)	120.1(2)	124.9(2)
C(18)-C(16)-C(1)	118.6(2)	118.1(2)
C(24)-C(16)-C(1)	121.3(2)	117.0(2)
O(17)-C(18)-C(16)	125.9(2)	124.5(2)
O(17)-C(18)-C(20)	112.9(2)	112.7(2)
C(16)-C(18)-C(20)	120.7(2)	122.7(2)
O(19)-C(20)-O(21)	123.3(2)	124.5(2)
O(19)-C(20)-C(18)	122.4(2)	123.0(2)
O(21)-C(20)-C(18)	113.8(2)	112.1(2)
C(20)-O(21)-C(22)	114.5(3)	116.4(2)
O(23)-C(24)-O(25)	121.5(2)	120.9(2)
O(23)-C(24)-C(16)	127.5(2)	124.9(2)
O(25)-C(24)-C(16)	111.0(2)	114.2(2)
C(24)-O(25)-C(26)	118.4(2)	116.8(2)

EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were obtained from Specord M80 spectrophotometer in potassium bromide pellets, and nmr spectra were recorded in dimethyl-d_6 sulfoxide on a Varian Gemini 200 spectrometer at 200 and 50 MHz for ^1H and ^{13}C respectively. Chemical Shifts are recorded in ppm (δ) relative to tetramethylsilane as internal standard. All compounds were analyzed for C, H and values found were within (0.3% of theoretical values.

3-[2-(4,5-Dihydro-1*H*-imidazol-3-ium-2-yl)-1,2-dihydro-1-phthalazin]-1,4-dimethoxy-1,4-dioxo-2-buten-2-olate (**7**).

To a suspension of the phthalazine pseudobase **1** [11] (1 g, 4.6 mmoles) in anhydrous methanol (10 ml) was added dropwise with stirring dimethyl acetylenedicarboxylate (0.8 ml, 4.6 mmoles). The reaction mixture was stirred for 4 hours at ambient temperature and the product that precipitated was collected by filtration, washed with methanol, dried and purified by crystallization from nitromethane. Betaine **7a** thus obtained (0.83 g, 50%) had mp 210-212°; ir: λ 3344, 1712, 1640, 1504, 1192, 1112; ^{1}H nmr: δ 3.12 (s, 3H, CH_3), 3.56 ((s, 3H, CH_3), 3.71 (br s, 4H, imidazoline CH_2), 6.19 (s, 1H, CH), 6.96 (d, 1H, CH), 7.27-7.47 (m., 3H, CH), 7.88 (s, 1H, CH), 8.6 (br s, 1H, NH), 9.7 (br s, 1H, NH); ^{13}C nmr: δ 42.9, 49.0, 50.8, 51.2, 99.1, 123.6, 125.8, 127.2, 131.3, 134.2, 143.5, 158.3, 167.3, 169.0, 174.6;

Anal. Calcd. for $C_{17}H_{18}N_4O_5$: C, 56.97; H, 5.06. Found: C, 56.81; H, 4.88.

Recrystallization of the Compound **7a** from methanol led to the formation of 1:1 methanol solvate **7b**, mp 207-208° dec; ir: δ 3152, 1728, 1644, 1504, 1215, 1104.

3-[2-(4,5-Dihydro-1*H*-imidazol-3-ium-2-yl)-1,2-dihydro-1-phthalazin]-1,4-diethoxy-1,4-dioxo-2-buten-2-olate (**8**).

To a suspension of the pseudobase **1** (1.g, 4.6 mmoles) in anhydrous ethanol (10 ml) was added with stirring diethyl acetylenedicarboxylate (0.85 ml, 4.6 mmoles). The reaction mixture was stirred for 6 hours at room temperature. The solid that precipitared was collected by filtration, washed with ethanol and purified by crystallization from ethanol to afford betaine **8** (0.92 g, 52%), mp 205-207°; ir: δ 3400, 3295, 2984, 1723, 1644, 1488, 1280, 1195, 1112; ^{1}H nmr: δ 0.78 (t, 3H, CH_3), 1.2 (t, 3H, CH_3), 3.6 (q, 2H, CH_2), 3.7 (br s, 4H, imidazoilne CH_2), 4.0-4.2 (m., 2H, CH_2), 6.2 (s, 1H, CH), 6.9 (d, 1H, CH), 7.3-7.5 (m., 3H, CH), 7.9 (s, 1H, CH), 8.6 (br s, 1H, NH), 9.7 (br s, 1H, NH); ^{13}C nmr: δ 13.92, 13.98, 43.1, 51.3, 57.3, 59.3, 99.1, 123.7, 125.9, 127.1, 131.7, 134.5, 143.6, 158.4, 167.0, 168.6, 174.8.

Anal. Calcd. for $C_{19}H_{22}N_4O_5$: C, 59.05; H, 5.74. Found: C, 59.31; H, 5.52.

3-[2-(4,5-Dihydro-1*H*-imidazol-3-ium-2-yl)-1,2-dihydro-1-phthalazin]-4-ethoxy-1-methoxy-1,4-dioxo-2-buten-2-olate (**9**).

Compound **7** (0.5 g, 1.3 mmoles) was dissolved in anhydrous ethanol (15 ml) and the solution was refluxed for 0.5 h. After cooling, the solid that precipitated was separated by suction, washed with cold ethanol, dried and purified by recrystallization from ethanol. Betaine **9** was obtained (0.4 g., 77%), mp 154-156°; ir δ 3248, 1720, 1640, 1504, 1208, 1104; ^{1}H nmr: δ 1.2 (t, 3H, CH_3), 3.1 (s, 3H, CH_3), 3.7 (br s, 4H, imidazoline CH_2), 4.0-4.2 (m, 2H, CH_2), 6.2 (s, 1H, CH), 6.9 (d, 1H, CH), 7.3-7.5 (m, 3H, CH), 7.9 (s, 1H, CH), 8.6 (br s, 1H, NH), 9.7 (br s, 1H, NH).

Anal. Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.05; H, 5.41. Found: C, 57.88; H, 5.19.

3-[2-(4,5-Dihydro-1*H*-imidazol-3-ium-2-yl)-1,2-dihydro-1-phthalazin]-1-ethoxy-4-methoxy-1,4-dioxo-2-buten-2-olate (**10**).

Compound **8** (0.5 g, 1.3 mmoles) was dissolved in anhydrous methanol (10 ml) and the resulting solution was heated under reflux for 15 minutes. After cooling to room temperature, the solid that precipitated was collected by filtration, washed with methanol, dried and recrystallized from methanol to yield 0.35 g (73%) of betaine **10**, mp 209-212°; ir: δ 3408, 1728, 1644, 1204, 1104; ^{1}H nmr: δ 0.8 (t, 3H, CH_3), 3.57 (q, 2H, CH_2), 3.59 (s, 3H, CH_3), 3.69 (br s, 4H, imidazoline CH_2), 6.2 (s, 1H, CH), 6.6 (d, 1H, CH), 7.3-7.45 (m, 3H, CH), 7.9 (s, 1H, CH), 8.6 (br s, 1H, NH), 9.7 (br s, 1H, NH).

Anal. Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.05; H, 5.41. Found: C, 57.94; H, 5.27.

X-ray Structure Analysis of Compound **7**.

Crystal data for $C_{17}H_{18}N_4O_5$ (**7a**): monoclinic, space group P21/c, a = 7.290(1), b =19.588(4), c =11.820(2) Ĺ, (=105.54(3), (V = 1626.2(5) Ĺ3, Z = 4, dx = 1.464 g cm^{-3}, ((MoKα =0.110 mm^{-1}, T= 293K. Data were collected on Kuma KM-4 diffractometer for crystal with dimensions 0.25 x 0.25 x 0.2 mm up to 2(max = 48). Out of 2696 measured reflections 2168 independent reflections with I positive have been used in further calculations. The structure was solved by direct methods with the program SHELXS-86 [19]. Full-matrix least-squares refinement was carried out on F2 with SHELXL-93 [20]. Hydrogen atoms have been located on (F map and their parameters included in the refinement process. Final R indices for reflections with I>2(I) and 307 refined parameters are: R1 = 0.036, wR2 = 0.088 (R1 = 0.084, wR2 = 0.116 for all data) [21]. Intramolecular interatomic distances and angles for nonhydrogen atoms are given in Table 1.

Crystal data for $C_{17}H_{18}N_4O_5$•CH_3OH (**7b**): monoclinic, space group P21/c, a = 8.945(2), b = 14.253(3), c = 15.130(3) Ĺ, (=90.40(3), (V = 1928.9(7) Ĺ3, Z = 4, dx = 1.344 g cm^{-3}, (CuKα = 0.860 mm-1, T = 293K. Data were collected on Kuma KM-4 diffractometer for crystal with dimensions 0.5 x 0.4 x 0.4 mm up to 2(max =140). Crystals were unstable and therefore were sealed in a glass capillary. Out of 3447 measured reflections 2989 independent reflections with I positive have been used in further calculations. The structure was solved by direct methods with the program SHELXS-86 [19]. Full-matrix least-squares refinement was carried out on F2 with SHELXL-93 [20]. Hydrogen atoms have been located on (F map and their parameters included in the refinement process. Final R indices for reflections with I>2(I) and 342 refined parameters are: R1 = 0.047, wR2 = 0.131 (R1 = 0.067, wR2 = 0.147 for all data) [21].

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