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REACTION OF 2-CHLORO-1-ALKYL-1*H*-INDOLE-3-CARBALDEHYDES WITH BARBITURIC ACIDS AND 5-METHYL-2-PHENYL-2,4-DIHYDROPYRAZOL-3-ONE. FORMATION OF COMPOUND WITH EXTREMELY SHORT INTRAMOLECULAR HYDROGEN BOND IN EIGHT-MEMBERED PSEUDOCYCLE

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Abstract – New indolin-2-one derivatives, containing in its molecules eight-membered pseudo-cycle with unusually short intramolecular hydrogen bond in OHO-bridge have been synthesized by reaction of 2-chloro-1-alkyl-1*H*-indole-3-carbaldehyde with barbituric acids or 5-methyl-2-phenyl-2,4-dihydropyrazol-3-one. Under the action of amines they undergo fragmentation to 5-aminomethylenebarbituric acids or 4-aminomethylenepyrazolones and 1-alkyl-1,3-dihydroindol-2-ones.

INTRODUCTION

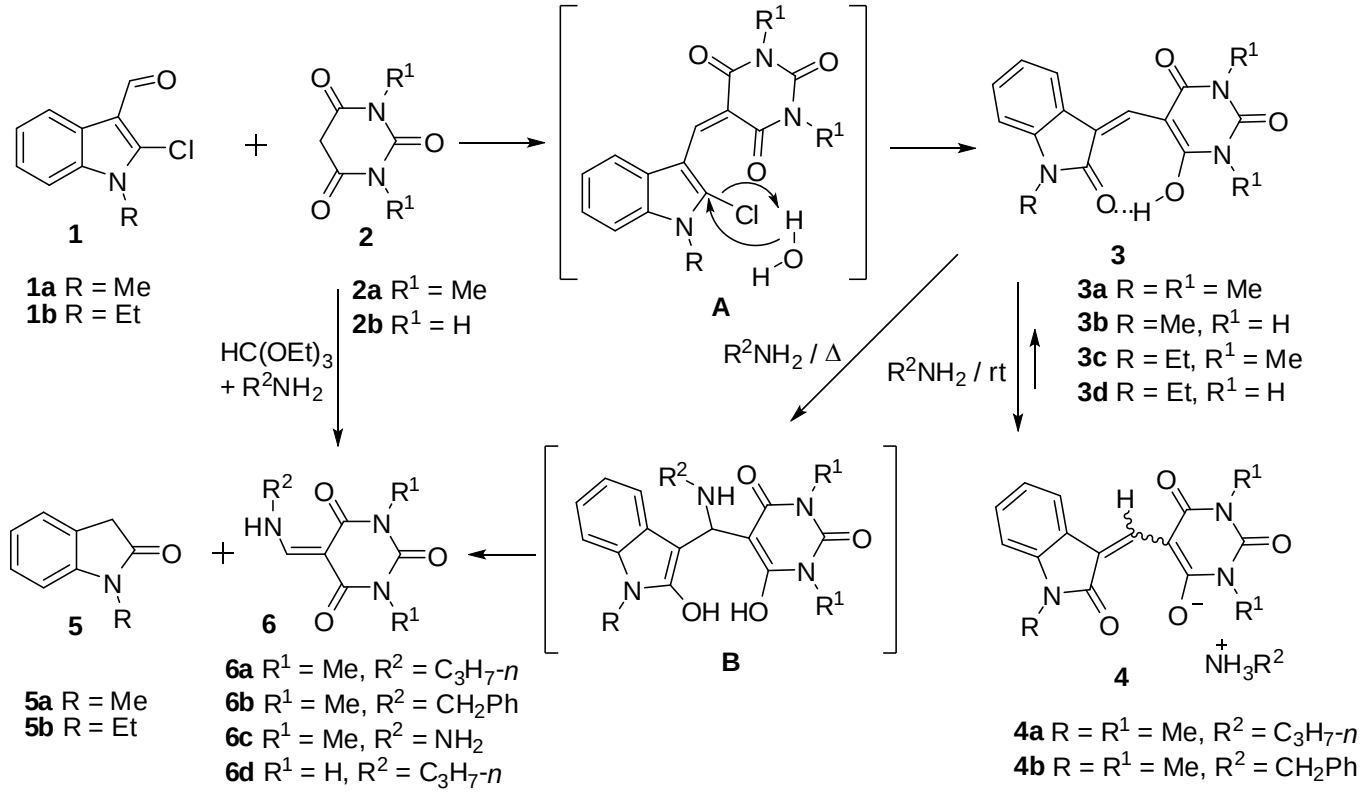
It is known, that 2-chloroindole-3-carbaldehydes react with CH-acids, such as malononitrile[1] and 1,3-dihydroindol-2-ones[2] to give Knoevenagel condensation products with retention of chlorine atom in a molecule. The products of the second reaction are of interest as anticancer drugs.[2]

To obtain such derivatives we have investigated reactions of 2-chloroindole-3-carbaldehydes **1a,b** with barbituric acids **2a,b** and 5-methyl-2-phenyl-2,4-dihydropyrazol-3-one **7**. We have surprisingly found that unlike the reactions described in the literature[1,2] products of other species were prepared. Elemental analysis, mass spectra, IR and NMR ^{1}H data have shown that these products include indole nucleus and

fragments of active methylene compounds but do not contain a chlorine atom. X-Ray analysis of the crystals, obtained by reacting of aldehyde **1b** with 1,3-dimethylbarbituric acid has sown this product (**3c**) contain a specific eight-membered heterocyclic ring system. The purpose of this paper is to describe the synthesis, structural features and some chemical properties of the compounds obtained.

RESULTS AND DISCUSSION

The heating of starting materials **1a,b** with barbituric acids **2a,b** in butanol gave a 1,3-dihydroindol-2-ones **3a-d**. It is apparent, that the Knoevenagel products **A** formed at the initial stage underwent the conjugate addition of water followed by the elimination of HCl and formation of substances **3a-d** (Scheme 1).



Scheme 1

Barbituric acid moiety of compounds **3a-d** exists in the enol form. ^{1}H-NMR spectra in $CDCl_3$ of compounds **3a-d** include the signals of strongly unshielded protons of OH groups (17.75-17.80 ppm), connected by a hydrogen bond to the carbonyl group in the 2-position of the indole ring. The presence of hydrogen bonding has also been proven by two narrow singlets of *N*-methyl groups of barbituric acid fragments in products **3a** and **3c**. This demonstrates the fixation of the fragments by a hydrogen bond. The ^{1}H-NMR spectrum of compound **3a**, in DMSO-d_6 essentially differs from its spectrum in $CDCl_3$. The broad singlet of 6 protons of two NCH_3 groups of barbituric acid moiety, located at δ 3.32 ppm, may be explained

by the hindered rotation of this part of a molecule at room temperature in this solvent. It corresponds to the break of the H-bond, due to intermolecular association with DMSO.

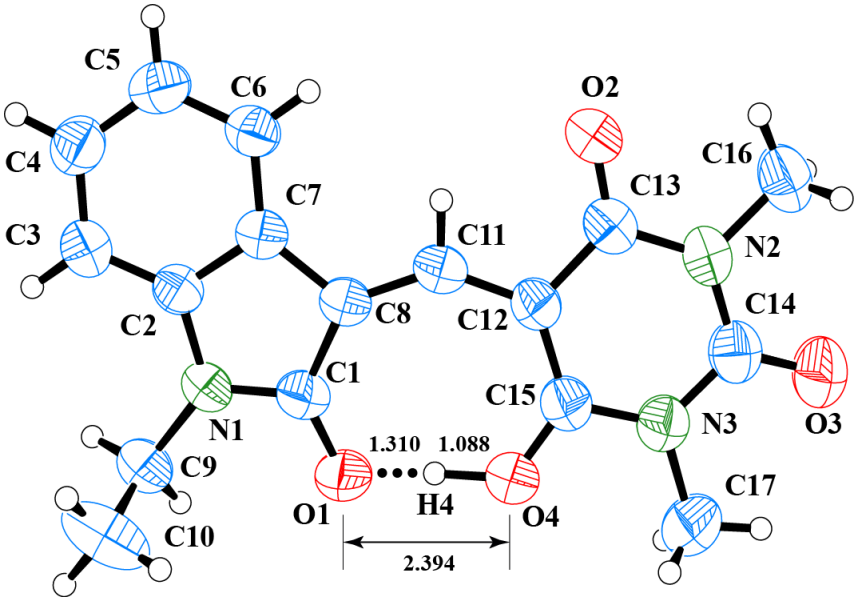


Figure 1. ORTEP view of structure **3c**

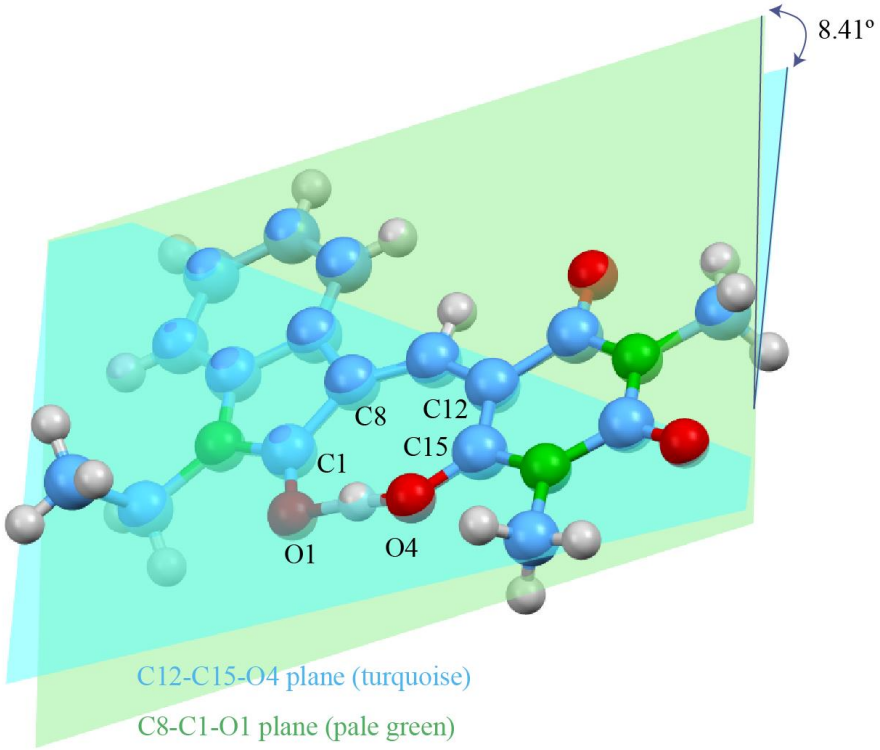


Figure 2. Ball and stick view of structure **3c**. Planes C8-C1-O1 and C12-C15-O4

The X-ray analysis of compound **3c** (Figure 1) shows the presence of asymmetrical intramolecular hydrogen bond in a crystalline state. The distance between atoms O4 and H4 is 1.088 Å, while O1···H4 – 1.310 Å, which is considerably less than the sum of Van-der-Waals radii and indicates the presence of a "strong OHO bridge".[3] The formation of hydrogen bridge makes the molecule almost flat, the dihedral angle between the planes C1-C8-O1 and C12-C15-O4 is 8.41°, as shown in Figure 2. Since the hydrogen atom is located between O1 and O4, the angle C8-C11-C12 significantly deviates from its standard value (120 °) and is of 141.14°. Values of the remaining angles of the ring with a hydrogen bond vary between 109.81° - 133.57°, except for the angle O1-H4-O4 which is 173.49°.

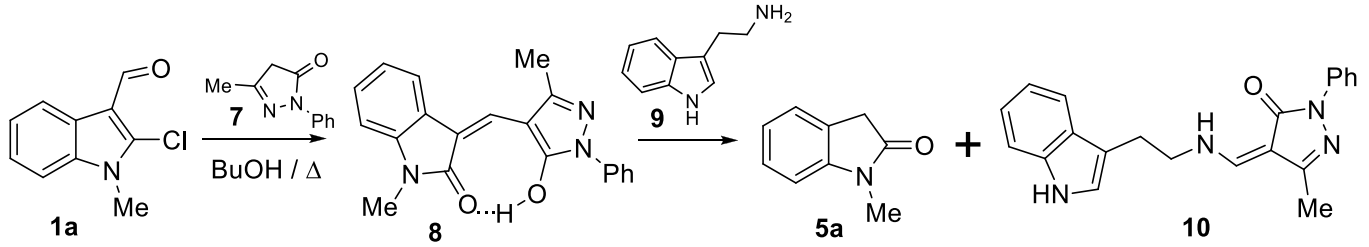
We have undertaken a literature search of substances similar in structure to our compound. According to database CCDC,[4] few structures having a conjugate system of carbonyl group, two double bonds and OH-function have been described.[5] They can be divided into three groups. The first includes compounds in which intramolecular hydrogen bonding is not occurring, and hence an eight-membered cycle does not form.[5a] In the second group two kinds of molecules with different interatomic distances O···O coexist in the crystal.[5b] In the third group the intramolecular hydrogen bond of the same type is formed in all molecules of the crystal.[5c-g] Our substance **3c** represents a third type of compounds. In this group only the one compound with two symmetrically placed pyrazolone rings is practically flat: the dihedral angle between planes analogous to shown in Figure 2 makes 0.13°.[5c] Most of compounds reported to be considerably twisted: the dihedral angle varies from 28.21° [5b] to 59.98°.[5g]

The shortest H-bond OHO in eight-membered pseudocycle among described molecules is 2.408 Å.[5c] In our compound **3c** distance between atoms O1 and O4 is 2.394 Å, indicating its unique structure.

We have investigated the reaction of derivatives **3a-d** with primary amines and hydrazine hydrate. Under mild conditions (at room temperature) compounds **4a,b** were obtained. They are ammonium salts of barbituric acid derivatives (Scheme 1). The structure of salts **4a,b** is confirmed by IR and ^{1}H-NMR spectra. In its IR spectra peaks at a long-wave part between 2527 and 3380 cm^{-1} correspond to NH_3^+ group vibrations. The ^{1}H-NMR spectrum of compound **4a** contains a broad singlet at δ 7.60 ppm, corresponding to the three protons of NH_3^+ group. In the ^{1}H-NMR spectrum of the product **4b** the similar signal is at 8.05 ppm. We have not determine a geometry of the exo-cyclic double bond attached at the 3-position of the indolin-2-one in products **4a,b**, because of their instability. It seems plausible negative charge distribution between the two oxygen atoms of the pyrimidine ring and the carbonyl group of the indole moiety. Heating of compounds **4a,b** in *n*-BuOH leads to their destruction up to 1,3-dihydroindol-2-ones **5a,b** and 5-aminomethylenebarbiturates **6a,b**. Compounds **6a-d** may be obtained at once from substances **3a-d** by their boiling with amines in *n*-BuOH (Scheme 1). Structure of compounds **6a,b** was proved using the oncoming synthesis – ternary condensation of barbituric acid **2a**, triethylorthoformate and the appropriate amine according to a known method.[6] Melting points and spectroscopic data of 1,3-dihydroindol-2-ones **5a,b** and the deliberately obtained samples[7] are the same.

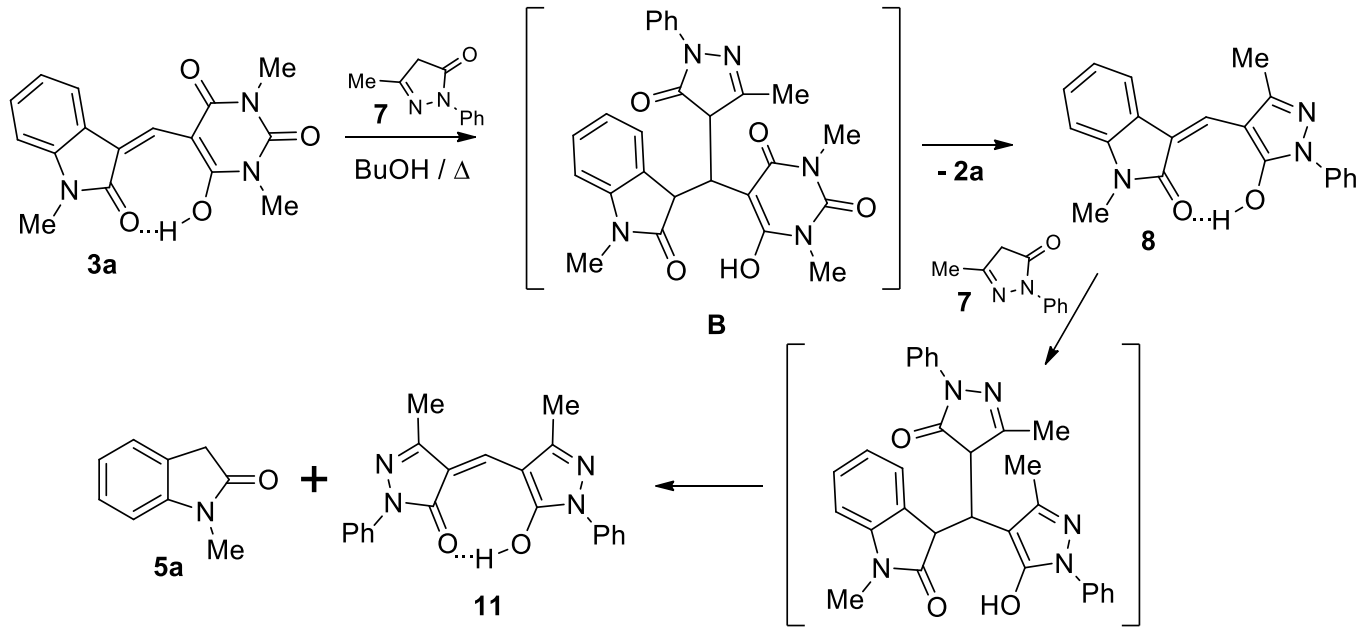
Reaction of aldehyde **1a** with 5-methyl-2-phenyl-2,4-dihydropyrazol-3-one **7** passes through the same pathway (as in the case of barbituric acids **2a,b**) to give the product **8** (Scheme 2). ^{1}H-NMR spectrum of compound **8** in $CDCl_3$ contains a signal of strongly unshielded enol proton at δ 16.10 ppm that confirms the presence of intramolecular hydrogen bond in this solvent. The signals of methyl protons at the indole nitrogen atom and pyrazolone cycle appear at δ 3.40 and 2.40 ppm, respectively. In contrast to compound **3a**, the product **8** in DMSO-d_6 partly retains the intramolecular hydrogen bond; duplication of the signals in ^{1}H-NMR spectrum indicates the presence of non-chelated conformer of this compound. So, in DMSO-d_6 NCH_3 group is characterized by singlets at δ 3.40 and 3.78 ppm, and CCH_3 group of pyrazolone cycle – by singlets at δ 2.25 and 2.40 ppm.

Reaction of compound **8** with tryptamine **9** proceeds as described above reacting compounds **3a,c** with amines and produces decomposition products **5a** and **10** (Scheme 2).



Scheme 2

Reaction of the compound **3a** with 5-methyl-2-phenyl-2,4-dihydropyrazol-3-one **7** led to formation of products **8** and **11** (Scheme 3).



Scheme 3

First, as in the case of reaction with amines, Michael addition to the double bond occurs. Elimination of dimethylbarbituric acid fragment **2a** from intermediate **B** gives compound **8** in 10% yield. Alongside with the product **8,** a substance **11** was obtained. Presumably, an anion, derived from pyrazolone **7** existing in a reaction mixture, attacks the double bond of the product **8**. A subsequent elimination of 1-methyl-1,3-dyhidroindol-2-one **5a** leads to the formation of substance **11** with yield of 9.5%. The melting point of the compound **11** is the same as described in the literature.[8] This reaction shows that the anion formed from pyrazolone **7** consistently displaces barbiturate and indolin-2-one fragments from the parent molecule **3a** to form the symmetrical thermodynamically stable product **11**.

In conclusion, the observed reactions may be used as a method for the synthesis of 1,3-dihydro-2*H*-indol-2-ones (oxindoles) containing heterocyclic moieties. A large number of such compounds exhibit useful pharmaceutical properties,[9] including anticancer,[10] analgesic,[11] anti-inflammatory,[12] and serotonergic.[13] Recently oxindoles have been actively investigated as antiglycation agents – preparations for the prevention of late diabetic complications.[14] As regards the compounds **3a-d**, they are derivatives of barbituric acid. The importance of such compounds for drug design is well known: they can be used as hypnotics, sedatives, anticonvulsants and anesthetics.[15] Recently, much attention is paid to the use of barbituric acid derivatives in coordination and supramolecular chemistries.[16] The metal complexes of barbituric acids possess antitumor activities.[17] When the substances **3a-d** will be used as ligands, they may be employed in this field.

EXPERIMENTAL

IR spectra were taken on Varian 3100 FT-IR, Excalibur Series instrument by means of Attenuated Total Reflectance (ATR) method. NMR spectra were recorded on Varian Unity 300 spectrometer (300 MHz).

2-Chloro-1-methyl-1*H*-indole-3-carbaldehyde (1a). To a solution of 2-chloro-1*H*-indole-3-carbaldehyde[18] (12.56 g, 70 mmol) in DMSO (40 mL) was added a solution of sodium hydroxide (3.5 g, 87.5 mmol) in water (3.5 mL). Hereupon the temperature of a mixture rose up to 43 °C. After 10 min the temperature started to fall and the mixture became to darken. Through 30 min after addition of alkali a mixture was cooled up to 10 °C and dimethyl sulfate (8.46 mL, 87.5 mmol) was added dropwise for maintaining temperature not above 20 °C. A mixture was stirred at rt during 1 h, then warmed up to 55-60 °C. To a warm solution cold water (70 mL) was added dropwise. A precipitated product of light-pink color was filtered. Recrystallization from benzene and washing with petroleum ether (bp 40-70 °C) gave compound **1a** (11.52 g, 85%) as colorless crystals; mp 105 °C (lit. 89-91 °C[18]) IR 1645 (C=O), 1590 (C-C_{Ar}) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s, NCH_3), 7.24-7.37 (3H, m, H_{Ar}), 8.23-8.35 (1H, m, H-4_{Ind}), 10.10 (1H, s, CHO). *Anal*. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; Cl, 18.31; N, 7.23. Found: C, 62.00; H, 4.2; Cl, 18.30; N, 7.25.

2-Chloro-1-ethyl-1*H*-indole-3-carbaldehyde (1b). 2-Chloro-1*H*-indole-3-carbaldehyde[18] (15.72 g, 90 mmol) was treated with diethyl sulfate (14.8 mL, 110 mmol) in the described above manner to give **1b**. Recrystallization from *i*-PrOH gave pale beige crystals (14.3 g, 76%); mp 107 °C; IR 1645 (C=O), 1600, 1580 (C-C_{Ar}) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.43 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 4.30 (q, *J* = 7.4 Hz, 2H, $C\underline{H}_2CH_3$), 7.25-7.37 (m, 3H, $H_{Ar.}$), 8.30 (m, 1H, H-4_{Ind}), 10.15 (s, 1H, CHO). *Anal*. Calcd for $C_{11}H_{10}NClO$: C, 63.62; H, 4.85; N, 6.75; Cl, 17.07. Found: C, 63.40; H, 4.80; N, 6.80; Cl, 17.00.

6-Hydroxy-1,3-dimethyl-5-(1-methyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1*H*-pyrimidine-2,4-dione (3a). A mixture of 2-chloro-1-methyl-1*H*-indol-3-carbaldehyde **(1a)** (1.94 g, 10 mmol) and 1,3-dimethylbarbituric acid **2a** (1.56 g, 10 mmol) was refluxed in *n*-BuOH (15 mL) for 30 min. The yellow residue began to precipitate from hot solution. Recrystallization from benzene gave **3a** (2.1 g, 68%); mp 243-245 °C; IR 1700, 1633(C=O), 1600 (C-C_{Ar}) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.40 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 7.08-7.40 (m, 3H, H_{Ar}), 7.80 (d, *J* = 7.0 Hz, 1H, H-4_{Ind}), 8.6 (s, 1H, =CH-), 17.63 (s, 1H, OH). ^{1}H-NMR (DMSO-d_6) δ: 3.32 (br s, 6H, $2CH_3$), 3.55 (s, 3H, N_{Ind}-CH_3), 7.20 (m, 3H, H_{Ar}), 7.60 (d, 1H, H-4_{Ind}), 8.40 (s, 1H, =CH-), 17.55 (br s, 1H, OH). MS m/z: 313 (M). *Anal*. Calcd for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.30; H, 4.80; N, 13.40.

6-Hydroxy-5-(1-methyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1*H*-pyrimidine-2,4-dione (3b). The compound **1a** (0.29 g, 1.5 mmol) was refluxed in *n*-BuOH (2 mL) with barbituric acid **2b** (0.19 g, 1.5 mmol) in the described above manner to give **3b** (0.374 g, 87%) as a yellow residue, which was recrystallized from DMF. The crystals were refluxed in CCl_4 (15 mL) during 5 h for removal of DMF to give **3b**, mp 320 °C. IR 3200, 3290 (NH); 1700, 1660 (C=O), 1580 (C-C_{Ar}) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 3.5 (s, 3H, NCH_3), 7.10-7.28 (m, 3H, H_{Ar}), 7.60 (d, *J* = 7.1 Hz, 1H, H-4_{Ind}), 8.28 (s, 1H, =CH-), 11.10 (br s, 1H, NH), 11.60 (br s, 1H, NH), 17.78 (br s, 1H, OH). *Anal*. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.83; H 3.97; N, 14.85.

6-Hydroxy-1,3-dimethyl-5-(1-ethyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1*H*-pyrimidine-2,4-dione (3c). The compound **1b** (0.415 g, 2 mmol) was heated with 1,3-dimethylbarbituric acid **2a** (0.312 g, 2 mmol) in *n*-BuOH (3 mL) in the described above manner (preparation of **3a**) to give compound **3c**. Recrystallization from *i*-PrOH gave yellow crystals (0.584 g, 80%), mp 250 °C; IR 1700, 1640 (C=O), 1600, 1590 (C–C_{Ar}) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.40 (t, *J* = 7.4 Hz, 3H, $C\underline{H}_3CH_2$), 3.45 (s, 3H, NCH_3), 3.55 (s, 3H, NCH_3), 4.10 (q, *J* = 7.4 Hz, 2H, $CH_3C\underline{H}_2$), 7.10 – 7.35 (m, 3H, H_{Ar}), 7.70 (d, *J* = 7.0 Hz, 1H, H-4_{Ind}), 8.60 (s, 1H, =CH-), 17.68 (s, 1H, OH). *Anal*. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.30; H, 5.30; N, 12.70. Crystal data: FW = 327.34, monoclinic, space group P2(1)/n a = 9.2686(8) Å, b = 6.9221(6) Å, c = 24.256(2) Å, α = 90°, β = 91.022(2)°, γ = 90°, V= 1556.0(2) $Å^3$, Z = 4, D_x = 1.397 Mg/m^3. T = 293(2) K, wavelength 0.71073 Å. Absorption coefficient 0.102 mm^{-1}, F (000) = 688. Crystal size: 0.40 x 0.05 x 0.05 mm. R (int) = 0.0406. Final R indices [I>2 sigma (I)] R_1 = 0.0481, R_{w2} = 0.1232. R indices (all

data) R_1 = 0.0742, R_{w2} = 0.1372. Extinction coefficient - 0.11 (2). Largest diff. peak and hole 0.216 and -0.193 e/ Å^3. Refinement method - full-matrix least-squares on F^2. Goodness-of-fit on F^2 1.014. Deposition number CCDC-1031039 for compound No. **3c**. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

6-Hydroxy-5-(1-ethyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-1*H*-pyrimidine-2,4-dione (3d). The compound **1b** (0.387 g, 2 mmol) was refluxed with barbituric acid **2b** (0.256 g, 2 mmol) in the described above manner (preparation of **3a**) to give **3d**. Residue was recrystallized from DMF and then refluxed in CCl_4 (15 mL) during 5 h for removal of DMF. Yield 0.42 g (70%), mp 320 °C. IR 3280, 3200, 3050 (NH, OH), 1700, 1660 (C=O), 1590, 1610, 1600 (C – C_{Ar}) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.35 (t, J = 7.4 Hz, 3H, C<u>H</u>$_3$CH$_2$), 4.05 (q, J = 7.4 Hz, 2H, CH$_3$C<u>H</u>$_2$), 7.10–7.30 (m, 3H, H_{Ar}), 7.60 (d, J = 7.2 Hz, 1H, H-4$_{Ind}$), 8.30 (s, 1H, =CH-), 11.10 (s, 1H, NH), 11.60 (s, 1H, NH), 17.78 (br s, 1H, OH). *Anal*. Calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.10; H, 4.40; N, 14.10.

1,3-Dimethyl-5-(1-methyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,6-dioxohexahydropyrimidin-4-ol 1-propylammonium salt (4a). To a solution of compound **3a** (0.94 g, 3 mmol) in $CHCl_3$ (10 mL) was added 1-propylamine (0.3 mL, 3.6 mmol) and reaction mixture was left over night at rt. Yellow crystals of **4a** were collected by filtration. Yield - 0.96 g (89%), mp 245-248 °C. IR 3100, 2527 (NH_3^+), 1670, 1660, 1650 (C=O), 1550 (C-C_{Ar}) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.90 (t, J = 7.3 Hz, 3H, C<u>H</u>$_3$CH$_2$CH$_2$NH$_3^+$), 1.55 (m, 2H, CH$_3$C<u>H</u>$_2$CH$_2$NH$_3^+$), 2.70 (t, J = 7.5 Hz, 2H, CH$_3$CH$_2$C<u>H</u>$_2$NH$_3^+$), 3.20 (s, 6H, 2NCH$_3$), 3.22 (s, 3H, N$_{Ind}$CH$_3$), 6.70-7.00 (m, 4H, H_{Ind}), 7.60 (br s, 3H, NH_3^+), 7.80 (s, 1H, =CH-). *Anal*. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.37; H, 6.62; N, 15.72.

1,3-Dimethyl-5-(1-methyl-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,6-dioxohexahydropyrimidin-4-ol benzylammonium salt (4b). The compound **3a** (0.31 g, 1 mmol) was reacted with benzylamine (0.11 mL, 1 mmol) in the described above manner to give **4b.** Yield - 0.348 g (87%), mp 243-245 °C. IR 3380, 3170, 2648 (NH_3^+), 1660, 1610 (C=O), 1600, 1580 (C-C_{Ar}) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 3.20 (s, 6H, 2NCH$_3$), 3.23 (s, 3H, N$_{Ind}$CH$_3$), 3.96 (s, 2H, C<u>H</u>$_2$Ph), 6.70-7.00 (m, 4H, H_{Ind}), 7.30-7.45 (m, 5H, H_{Ar}), 7.80 (s, 1H, =CH-), 8.05 (br s, 3H, -NH_3^+). *Anal*. Calcd for $C_{23}H_{24}N_4O_4$: C, 65.70; H, 5.75; N, 13.33. Found: C, 65.62; H, 5.81; N, 13.43.

1-Methyl-1,3-dihydroindol-2-one (5a), 1,3-dimethyl-5-propylaminomethylenepyrimidine-2,4,6-trione (6a) *(Method A)***.** The mixture of compound **3a** (0.31 g, 1 mmol) and 1-propylamine (0.1 mL, 1.2 mmol) in *n*-BuOH (3 mL) was refluxed for 1 h. White powder was filtered and recrystallized from *i*-PrOH to give **6a**. Yield - 0.12 g (53%), mp 145 °C. IR 3170 (NH), 1630, 1650, 1670 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.00 (t, J = 7.3 Hz, 3H, C<u>H</u>$_3$CH$_2$CH$_2$), 1.70 (m, 2H, CH$_3$C<u>H</u>$_2$CH$_2$), 3.33 (s, 6H, 2NCH$_3$), 3.42 (m, 2H, CH$_3$CH$_2$C<u>H</u>$_2$), 8.20 (d, J = 10.3 Hz, 1H, =CH-), 10.31 (br s, 1H, NH). MS *m/z*: 225 (M^+). *Anal*. Calcd

for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.20; H, 6.7; N, 18.70. Mother liquor was evaporated *in vacuo* up to dryness. The residue was purified by column chromatography on Al_2O_3 (eluent – $CHCl_3$, column - d=2 cm, l=20 cm, R_f = 0.79). The first fraction was collected and the solvent evaporated. The residue of **5a** was recrystallized from *i*-PrOH to give colorless needles (0.062 g, 46%); mp 86 °C (lit. mp 86 °C).[7]

1,3-Dimethyl-5-propylaminomethylenepyrimidine-2,4,6-trione (6a) *(Method B)* The mixture of 1-propylamine (0.17 mL, 2 mmol), 1,3-dimethylbarbituric acid **2a** (0.312 g, 2 mmol) and triethyl orthoformate (0.4 mL, 2.5 mmol) was refluxed for 15 min in EtOH (2.5 mL). Filtered residue of **6a** was recrystallized from EtOH, to give **6a** as colorless crystals 0.315 g (70%), mp 145 ºC; Spectral data for compound **6a,** obtained by both methods are the same.

1-Ethyl-1,3-dihydroindol-2-one (5b), 5-hydrazinomethylene-1,3-dimethylpyrimidine-2,4,6-trione (6c). The mixture of compound **3c** (0.655 g, 2 mmol) and hydrazine hydrate (0.1 mL, 2 mmol) in $CHCl_3$ (10 mL) was left for 24 h at rt. Precipitated residue of crude product **6c** was filtered and purified by column chromatography on Al_2O_3 [eluent – $CHCl_3$ /MeOH (8 : 2), column - d=2 cm, l=20 cm, R_f = 0.65]. The first colorless fraction was collected and the solvent was evaporated. Recrystallization from EtOH gave compound **6c** (0.05 g, 13%), mp 135 °C. *Anal*. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.30; H, 5.10; N, 28.40. IR 3310, 3250 (NH_2), 3200 (NH), 1680, 1650, 1610 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 2.90 (s, 6H, $2NCH_3$), 5.50 (s, 2H, NH_2), 8.10 (s, 1H, -CH=), 11.15 (br d, J = 10.2 Hz, 1H, NH). MS m/z: 198 (M). Filtrate was evaporated *in vacuo* and residue was recrystallized from benzene/petroleum ether (bp 40-70 °C) (5:1) to give colorless needles of compound **5b** (0.05g, 17%); mp 96 °C (lit. mp 96 ºC).[7]

5-(Benzylaminomethylene)-1,3-dimethylpyrimidine-2,4,6-trione (6b) *Method A*: The mixture of compound **3a** (0.31 g, 1 mmol) and benzylamine (0.11 mL, 1 mmol) was refluxed in *n*-BuOH in the manner used for preparation of compound **6a** (*Method A)* to give **6b**. Yield - 0.238 g (87%).

Method B: The mixture of benzylamine (0.22 mL, 2mmol), 1,3-dimethylpyrimidine-2,4,6-trione (0.312 g, 2 mmol) and triethyl orthoformate (0.4 mL, 2.5 mmol) was refluxed in EtOH in the manner used for preparation of compound **6a** *(Method B)* to give **6b**. Yield - 0.437 g (80%), mp 160 °C. IR 3170 (NH), 1600, 1590 (C-C_{Ar}), 1650, 1680 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.28 (s, 3H, NCH_3), 3.32 (s, 3H, NCH_3), 4.63 (d, J = 11.3 Hz, 2H, CH_2Ph), 7.20-7.45 (m, 5H, H_{Ar}), 8.30 (1H, d, J = 10.2 Hz, =CH-), 10.54 (br s, 1H, NH). *Anal*. Calcd for $C_{14}H_{15}N_3O_3$: C 61.53; H 5.53; N 15.38. Found: C, 61.59; H, 5.40; N, 15.40.

5-Propylaminomethylenepyrimidine-2,4,6-trione (6d). The mixture of compound **3b** (0.29 g, 1 mmol) and 1-propylamine (0.12 mL, 1.5 mmol) was refluxed in *n*-BuOH in the manner used for preparation of **6a** (*Method A)*. Filtered residue was recrystallized from DMF to give **6d**. Yield - 0.084 g (43%), mp 260 °C. IR 3300, 3260, 3060, 3000 (NH_3^+), 1700, 1640, 1610 (C=O), 1590 (C-C_{Ar}) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.90

(t, J = 7.3 Hz, 3H, C<u>H</u>$_3$CH$_2$CH$_2$), 1.64 (m, 2H, CH$_3$C<u>H</u>$_2$CH$_2$), 3.45 (m, 2H, CH$_3$CH$_2$C<u>H</u>$_2$), 8.10 (d, 1H, J = 10.1 Hz, -CH=), 10.15 (m, 1H, N<u>H</u>CH$_2$CH$_2$CH$_3$), 10.32 (d, 1H, NH), 10.45 (s, 1H, NH). *Anal*. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.65; H, 5.56; N, 21.44.

3-(5-Hydroxy-3-methyl-1-phenyl-*1H*-pyrazol-4-ylmethylene-1-methyl-1,3-dihydroindol-2-one (8). The mixture of compound **1a** (1.93g, 10 mmol) and 5-methyl-2-phenyl-2*H*-pyrazol-3-one **7** (1.74 g, 10 mmol) was refluxed in *n*-BuOH (15 mL) for 2 h and then cooled. Yellow crystals were collected by filtration and recrystallized from benzene, washing by petroleum ether (bp 40-70 °C) to give compound **8** (1 g, 30%), mp 150-152 °C. IR 1640 (C=O), 1605, 1550 (C-C$_{Ar}$) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ: 2.40 (s, 3H, C-CH$_3$), 3.40 (s, 3H, N-CH$_3$), 6.90-7.95 (m, 10H, H$_{Ar}$), 16.10 (s, 1H, OH). ^{1}H-NMR (DMSO-d_6) δ: 2.15 and 2.40 (s + s, together 3H, C-CH$_3$), 3.40 and 3.75 (s + s, together 3H, N-CH$_3$), 7.00-7.90 (m, 10H, H$_{Ar}$), 16.20 (s, 1H, OH). MS *m/z*: 331 (M). *Anal*. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.58; H, 5.18; N, 12.59.

4-{[2-(1*H*-Indol-3-yl)ethylamino]-methylene}-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one (10). The mixture of compound **8** (0.33 g, 1 mmol) and tryptamine **9** (0.16 g, 1 mmol) was refluxed in *n*-BuOH (3 mL) for 3 h. Formed residue was filtered. Recrystallization from *n*-BuOH with charcoal gave **10** as colorless crystals. Yield - 0.146 g (42%), mp 198 °C. IR 3373 (NH), 1633(C=O), 1584, 1567 (C-C$_{Ar}$) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ: 2.05 (s, 3H, CH$_3$), 3.15 (t, J = 7.4 Hz, 2H, NHCH$_2$C<u>H</u>$_{2Ind}$), 3.70 (m, 2H, NHC<u>H</u>$_2$CH$_{2\,Ind}$), 7.02-7.28 (m, 5H, H$_{Ar}$), 7.32-7.43 (m, 4H, H$_{Ar}$), 7.60 (d, 1H, H-4$_{Ind}$), 7.96 (d, J = 10.1 Hz, 1H, -CH=), 7.98 (d, J = 9.0 Hz, 1H, H-4$_{Ind}$), 8.15 (s, 1H, NH$_{Ind}$), 9.90 (br s, 1H, NH). *Anal*. Calcd for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.36; H, 5.77; N, 16.35.

5-Methyl-4-[(5-methyl-3-oxo-2-phenyl-2,4-dihydro-*3H*-pyrazol-4-yl)methylene]-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (11), 3-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-ylmethylene-1-methyl-1,3-dihydroindol-2-one (8). The mixture of compound **3a** (0.31 g, 1 mmol) and 5-methyl-2-phenyl-2*H*-pyrazol-3-one **7** (0.17 g, 1 mmol) was refluxed in chlorobenzene (3 mL) for 4 h and left overnight. Yellow residue was filtered off and divided by column chromatography on Al$_2$O$_3$ (eluent – CHCl$_3$, column - d=2 cm, l=70 cm) First fraction (R$_f$ = 0.73) was separated and the solvent was removed *in vacuo*. Residue was recrystallized from benzene/petroleum ether (bp 40-70 °C) (1/2) to give compound **11** (0.034 g, 9.5%), mp 178-180 °C (lit. mp 178-180 °C).[8] ^{1}H-NMR (CDCl$_3$) δ: 2.29-2.45 (s, 6H, 2CH$_3$), 7.20-8.00 (m, 11H, 10H$_{Ar}$, -CH=), 17.95 (s, 1H, OH). MS m/z: 358 (M). The second yellow fraction (R$_f$ = 0.23) was collected and the solvent was evaporated. The residue was recrystallized from benzene to give compound **8**. Yield - 0.032 g (10%); mp 150-152 °C; spectral data are the same as in the described above protocol.

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