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Reaction of 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo-[4,5-*e*]-1,3-thiazolo[3,2-*b*]-1,2,4-triazine-2,7(1*H*,6*H*)-dione with isatins

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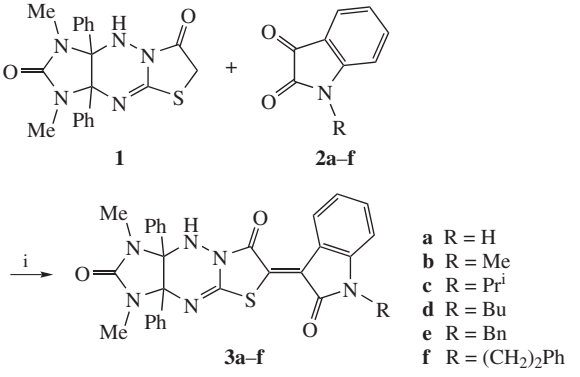
Condensation of 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]-1,3-thiazolo[3,2-*b*]-1,2,4-triazine-2,7(1*H*,6*H*)-dione with isatins afforded 6-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-3,3a,9,9a-tetrahydro-1,3-dimethyl-3a,9a-diphenylimidazo-[4,5-*e*]thiazolo[3,2-*b*]-1,2,4-triazine-2,7(1*H*,6*H*)-diones; a new conglomerate (space group $P2_12_12_1$) was found by an X-ray diffraction study.

Isatin and its metabolites are constituents of many natural substances. They are also components of many synthetic compounds exhibiting a wide range of biological activity including antiviral, antitumor and antiangiogenic, antibacterial, antitubercular, antifungal, antiaptotic, anticonvulsant, and anxyolytic activities. Isatin itself is an endogenously oxidized indole with a wide spectrum of behavioral and metabolic effects. It has a distinct and discontinuous distribution in the brain, peripheral tissues, and body fluids; isatin binding sites are also widely distributed.[1–3] Dyes, pesticides, medicinal preparations, *etc.*, were prepared starting from isatin derivatives.[2,3]

An antiviral drug Metisazon (thiosemicarbazide of *N*-methylisatin) is widely used in Russia.[4] That is why the synthesis of new compounds containing isatin moiety in combination with thiosemicarbazide remains relevant. We have recently synthesized 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]-1,3-thiazolo[3,2-*b*]-1,2,4-triazine-2,7(1*H*,6*H*)-dione **1**[5] bearing a thiosemicarbazide moiety annulated with a thiazole ring. The methylene group in this compound is highly reactive, and the tricycle **1** can be subjected to various chemical transformations, in particular those involving isatins. Such reactions have not been described in literature.

Here, we report on the condensation of tricycle **1** with isatins **2a–f** (Scheme 1).

The starting compound **1** was prepared by the reaction of $BrCH_2COOH$ with 5,7-dimethyl-4a,7a-diphenylperhydroimidazo-[4,5-*e*]-1,2,4-triazine-3,6-dione **4** accessible by condensation of thiosemicarbazide with 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidin-2-one.[6] Condensation of the tricycle **1** with isatins was carried out in boiling acetic acid for 1–2.5 h, which afforded earlier unknown 6-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-3,3a,9,9a-tetrahydro-1,3-dimethyl-3a,9a-diphenylimidazo[4,5-*e*]-thiazolo[3,2-*b*]-1,2,4-triazine-2,7(1*H*,6*H*)-diones **3a–f**.† The optimal time of 2.5 h provided yields of the targeted **3a–f** as high as 74–89%. This is indicative of a high reactivity of the methylene group in compound **1**.



Scheme 1 *Reagents and conditions*: i, glacial AcOH, reflux, 2.5 h.

† The ^{1}H NMR spectra were recorded on a Bruker Avance II 300 (300 MHz) and Bruker Avance II 600 (600.13 MHz) spectrometers. Chemical shifts were measured with reference to the residual protons of a DMSO-d_6 solvent (δ 2.50 ppm). HRMS (ESI) data were obtained on a MicrOTOF II (Bruker Daltonics) instrument.

Isatin derivatives **2b–f** were prepared by N-alkylation of isatin **2a**.[2]

*6-(2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene)-3,3a,9,9a-tetrahydro-1,3-dimethyl-3a,9a-diphenylimidazo[4,5-*e*]thiazolo[3,2-*b*]-1,2,4-triazine-2,7-(1*H*,6*H*)-diones* **3a–f** *(general procedure)*. A solution of the tricycle **1** (2 mmol) and isatin **2** (2 mmol) in 15 ml of AcOH was heated at reflux for 2.5 h. After cooling, the precipitate of **3** was filtered off, crystallized from AcOH and washed with water (5 ml).

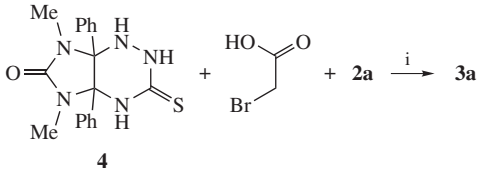
For **3a**: yield 86%, mp 258–260 °C (AcOH). ^{1}H NMR, δ: 2.63 (s, 6H, 2MeN), 6.74–7.40 (m, 13H, Ph), 7.83 (s, 1H, NH), 8.84 (d, 1H, Ph, *J* 8.1 Hz), 11.28 (s, 1H, HN_{indol}). HRMS, *m/z*: 523.1559 $[M + H]^+$ ($C_{28}H_{22}N_6O_3S$, Δ = 2.2 ppm).

For **3b**: yield 89%, mp 248–250 °C (AcOH). ^{1}H NMR (for the numeration of atoms, see Figure 1) δ: 2.63 [s, 3H, MeN(4)], 2.65 [s, 3H, MeN(1)], 3.29 [s, 3H, MeN(31)], 6.31–6.80 [m, 2H, C(11)H, C(15)H], 6.80–6.88 [m, 2H, C(17)H, C(21)H], 7.05–7.11 [m, 2H, C(18)H, C(20)H], 7.12–7.22 [m, 6H, C(12)H, C(13)H, C(14)H, C(19)H, C(34)H, C(36)H], 7.47–7.51 [m, 1H, C(35)H], 7.81 [s, 1H, N(6)H], 8.86 [d, 1H, C(33)H, *J* 8.1 Hz]. HRMS, *m/z*: 537.1702 $[M + H]^+$ ($C_{29}H_{24}N_6O_3S$, Δ = 0.18 ppm).

For **3c**: yield 78%, mp 310–312 °C (AcOH). ^{1}H NMR, δ: 1.42 (d, 6H, 2Me, *J* 6 Hz), 2.63 (s, 3H, MeN), 2.64 (s, 3H, MeN), 4.51–4.72 (m, 1H, CH), 6.69–7.50 (m, 13H, Ph), 7.81 (s, 1H, NH), 8.91 (d, 1H, Ph, *J* 8.1 Hz). HRMS, *m/z*: 565.2011 $[M + H]^+$ ($C_{31}H_{28}N_6O_3S$, Δ = 0.9 ppm).

For **3d**: yield 82%, mp 338–340 °C (AcOH). ^{1}H NMR, δ: 0.86–0.94 (m, 3H, Me), 1.25–1.39 (m, 2H, CH_2), 1.58–1.68 (m, 2H, CH_2), 2.64 (s, 3H, MeN), 2.65 (s, 3H, MeN), 3.78–3.87 (m, 2H, CH_2), 6.70–7.51 (m, 13H, Ph), 7.80 (s, 1H, NH), 8.89 (d, 1H, Ph, *J* 7.3 Hz). HRMS, *m/z*: 579.2177 $[M + H]^+$ ($C_{32}H_{30}N_6O_3S$, Δ = 0.7 ppm).

For **3e**: yield 74%, mp 208–210 °C (AcOH). ^{1}H NMR, δ: 2.65 (s, 3H, MeN), 2.66 (s, 3H, MeN), 5.02–5.14 (m, 2H, CH_2), 6.69–7.43 (m, 18H, Ph), 7.84 (s, 1H, NH), 8.91 (d, 1H, Ph, *J* 7.3 Hz). HRMS, *m/z*: 613.2008 $[M + H]^+$ ($C_{35}H_{28}N_6O_3S$, Δ = 1.0 ppm).



Scheme 2 *Reagents and conditions*: i, glacial AcOH, reflux, 3 h, AcONa.

Taking into account the available data[7] on the synthesis of analogous compounds by one-step condensation of imidazotriazine **4** with bromoacetic acid and aldehydes (RC_6H_4CHO) in a boiling organic solvent with dry AcONa, we attempted the straightforward condensation of the isatin **2a** with compound **4** and bromoacetic acid (Scheme 2). The yield of **3a**, however, dropped from 89% to 38%. Therefore, such a three-component synthesis of compounds **3b**–**f** was not even tried.

The structures of **3a**–**f** were established by ^{1}H NMR spectroscopy and HRMS data. It is to be mentioned that the ^{1}H NMR spectra display a strong downfield shift of proton signals at the C(33) atom (8.84–8.91), which is characteristic of proximity of the carbonyl group C(25)=O(37) (Figure 1).

To prove this assumption, an X-ray diffraction analysis‡ was performed for compounds **3a** and **3f** (Figure 2). According to the results obtained, compound **3a** crystallizes as a conglomerate (space group $P2_12_12_1$) with two solvate molecules of acetic acid, whereas compound **3f** as a racemate (space group $P2_1/c$) with one solvate molecule of DMSO. Examination of the geometric parameters of the heterocycle in **3a** and **3f** showed

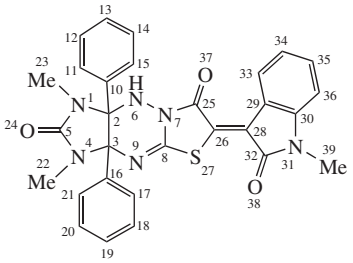


Figure 1 A schematic representation of compound **3b** with the labeling scheme for the C, O, and N atoms used for the description of the ^{1}H NMR spectra.

that they are within the values expected for the compounds of this type.[6] The conformations of the imidazole ring and the triazine moiety are an envelope [the C(3) atom deviates by 0.50(1) Å in **3a** and by 0.49(1) Å in **3f**] and a half-chair [the deviations of the C(2) and N(6) atoms are 0.22(1)–0.27(1) and 0.33(1)–0.40(1) Å], respectively; the other heterocycles are flat within 0.01(1) Å. The nitrogen atoms N(1), N(7), and N(31) are planar with the sums of the valence angles being 357.6(1)–360.0(1)°. The N(4) atom is slightly piramidalized; the corresponding value is 348.1(1)° in **3a** and 349.5(1)° in **3f**. The piramidalization of the N(6) atom (its hydrogen atom is in the axial position to the triazine plane) is even more pronounced – the sum of its valence angles reaches 331.5(1) and 328.6(1)° in **3a** and **3f**, respectively.

The planarity of the indole-thiazole moiety allows for the relatively strong intramolecular O(38)···S(27) binding [O···S 2.642(2) Å in **3a** and 2.702(2) Å in **3f**] to occur. Its formation is usually described as a charge transfer from a lone pair of the oxygen atom to the σ*-orbital of the C(8)–S(27) bond. The additional stabilization of such a molecular conformation is achieved through rather weak intramolecular contact C(33)–H···O(37)=C(27) [C···O 2.965(3) and 2.955(3) Å, ∠CHO 134° and 133° in **3a** and **3f**, respectively] that was anticipated on the basis of the NMR data in solution and was indeed observed in the crystals of **3a** and **3f** (Figure 2). In **3a**, the same oxygen O(37) also forms the intermolecular hydrogen bond (of the similar strength) with the NH group of the indole fragment (N···O 2.810(3) Å, ∠NHO 148°). In **3f**, there is no intermolecular hydrogen bond involving this atom; instead, there are two

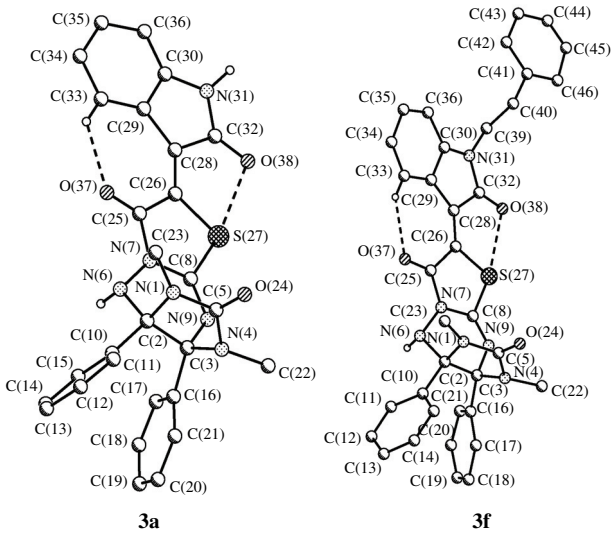


Figure 2 General views of compounds **3a** and **3f**. The hydrogen atoms except for those of the NH groups and those at the C(33) atoms as well as the solvate molecules (AcOH in **3a** and DMSO in **3f**) are omitted for clarity.

For **3f**: yield 82%, mp 325–327 °C (AcOH). ^{1}H NMR, δ: 2.64 (s, 3H, MeN), 2.65 (s, 3H, MeN), 2.90–3.01 (m, 2H, CH_2), 3.69–4.09 (m, 2H, CH_2), 6.71–7.48 (m, 18H, Ph), 7.78 (s, 1H, NH), 8.85 (d, 1H, Ph, J 8.2 Hz). HRMS, *m/z*: 627.2169 $[M + H]^+$ ($C_{36}H_{30}N_6O_3S$, Δ = 0.6 ppm).

‡ *Crystallographic data*. Crystals of **3a** ($C_{32}H_{30}N_6O_7S$, M = 642.68), obtained by crystallization from AcOH, orthorhombic, space group $P2_12_12_1$, at 120 K: a = 14.2245(15), b = 14.5479(16) and c = 14.9888(17) Å, V = = 3101.7(6) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.376 g cm^{-3}, μ(MoKα) = 1.63 cm^{-1}, F(000) = 1344. Intensities of 16418 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 54°$] and 6757 independent reflections [R_{int} = 0.0501] were used in further refinement.

Crystals of **3f** ($C_{38}H_{36}N_6O_4S_2$, M = 704.85), obtained by crystallization from DMSO, monoclinic, space group $P2_1/c$, at 120 K: a = 9.9523(6), b = 21.6482(12) and c = 16.3203(9) Å, β = 97.8360(10)°, V = 3483.4(3) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.344 g cm^{-3}, μ(MoKα) = 2.03 cm^{-1}, F(000) = 1480. Intensities of 38360 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 58°$] and 9259 independent reflections (R_{int} = 0.0248) were used in further refinement.

The structures were solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atoms of NH and OH groups were located from the Fourier density synthesis and refined in isotropic approximation. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation in riding model with the U_{iso}(H) parameters equal to $1.2U_{eq}(C_i)$, for methyl groups equal to $1.5U_{eq}(C_{ii})$, where $U(C_i)$ and $U(C_{ii})$ are the equivalent thermal parameters of the carbon atoms to which corresponding H atoms are bonded. For **3a** the refinement converged to wR_2 = 0.0856 and GOF = 0.877 for all independent reflections [R_1 = 0.0462 was calculated against F for 3302 observed reflections with $I > 2\sigma(I)$]. For **3f** the refinement converged to wR_2 = 0.1256 and GOF = 1.005 for all independent reflections [R_1 = 0.0495 was calculated against F for 7257 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[8]

CCDC 786200 and 786201 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

weaker C–H···O(37) contacts with the smallest C···O distance equal to 3.226(3) Å. The similar situation was observed for the third C=O group. In **3a**, it binds to one of the molecules of the acetic acid, the latter forming the hydrogen bond with the second solvate molecule. The corresponding values of the O···O distances and the ∠OHO angles are 2.584(3) Å and 171°, 2.555(3) Å and 172°. Thus, formed infinite H-bonded chains consist of the molecules of **3a** and those of the acetic acid. In **3f**, two C–H···O(24) contacts [C···O 3.402(3) and 3.445(3) Å] are also present instead of the hydrogen bond; the solvate DMSO molecule is hold in a crystal by means of the N–H···O hydrogen bond [N···O 2.901(3) Å, ∠NHO 165°]. The latter leads to the formation of the H-bonded **3f**–DMSO pairs. The above supramolecular associates in these two crystals are further assembled into the 3D-framework by a number of weak C–H···O, C–H···π, and C=O···π (in **3a**) or π···π (in **3f**) contacts.

In summary, condensation of the tricyclic thiazolidinone **1** with isatins **2a**–**f** revealed the high reactivity of the methylene group in the molecule of compound **1**, which may promote synthesis of other valuable chemicals based on this compound.

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