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Syntheses of imidazo[4,5-*e*]-1,2,4-triazines *via* the reaction of 1,3-dimethyl-4,5-dihydroxy-4,5-diphenylimidazolidin-2-one with aminoguanidine and semicarbazide

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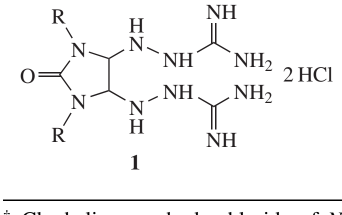
3-Imino-5,7-dimethyl-4a,7a-diphenylperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-one and 5,7-dimethyl-4a,7a-diphenylperhydroimidazo-[4,5-*e*]-1,2,4-triazine-3,6-dione were synthesized for the first time *via* the condensation of aminoguanidine and semicarbazide (as hydrochlorides) with 1,3-dimethyl-4,5-dihydroxy-4,5-diphenylimidazolidin-2-one, and a new conglomerate (space group $P2_1$) was found by XRD study.

Among the known pharmaceuticals, there are quite a lot of chemicals that contain guanidine and semicarbazide moieties. Drugs such as antihypertensive Clophelinum, antidiabetics Glibutidum and Metforminum, antibiotic Streptomycini, synthetic antimicrobial and antiparasitic Sulginum, Faringocept, Chloridinum, Bigumalum, *etc.* incorporate guanidine moieties.[†,1] Semicarbazone of 5-nitrofurfural (Furacilinum) possesses antimicrobial activity and semicarbazone of 1-methyl-3-hydroxy-2,3-dihydroindole-5,6-quinone (Adroxonum) impacts the tissue metabolism.[1] Imidazolidin-2-one derivatives display anticonvulsive, analgesic, herbicide and other activities.[1–4] The novel structures could enable new varieties of drugs containing the bioactive semicarbazide and guanidine moieties, and combining these with the imidazolidinone moiety in a single molecule could have interesting bioactivity.

Earlier, we studied the cyclocondensation of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-one (DHI) with thiosemicarbazide and showed a principal possibility of preparing derivatives of 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones.[5,6] However, aminoguanidine introduced into the reaction with DHI led to 4,5-bis(aminoguanidino)imidazolidin-2-ones **1** and 4-(guanidinoimino)imidazolidin-2-ones **2** rather than to imidazo[4,5-*e*]-1,2,4-triazines.[6–8]

Published data on the interaction between DHI and semicarbazide are unavailable. We investigated the condensation of 1,3-dimethyl-4,5-dihydroxy-4,5-diphenylimidazolidin-2-one with aminoguanidine and semicarbazide to synthesize new imidazotriazine derivatives.



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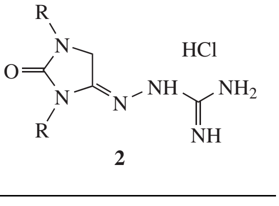

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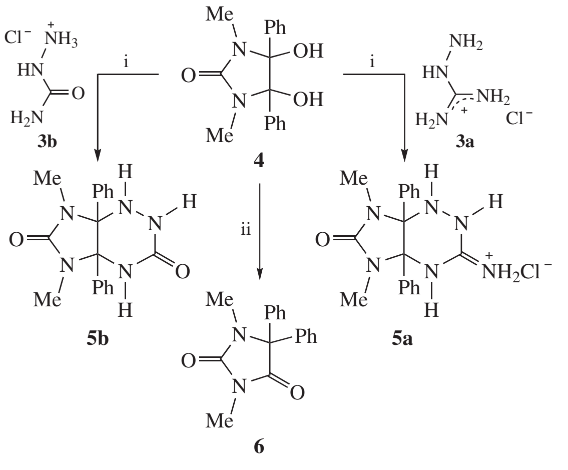
The interaction of aminoguanidine dihydrate **3a** and semicarbazide **3b** hydrochlorides with 1,3-dimethyl-4,5-diphenyl-DHI **4** was examined under different reaction conditions varying over the temperature range from 30 to 70 °C and reaction times from 0.5 to 7 h.

The condensation of compound **3a** with DHI **4** resulted in imidazotriazine **5a** with 90–92% yield both when the reaction mixture was boiled in methanol in the presence of HCl for 30 min and when it was kept at 40–45 °C during 1 h (Scheme 1).

Target imidazotriazine **5b** was produced from semicarbazide hydrochloride **3b** and DHI **4** in methanol at 40–45 °C for 1 h in a maximum yield of about 50%. Higher reaction temperature, *e.g.*, reaction mixture boiling during 30 min, entailed a conversion of DHI **4** to 1,3-dimethyl-4,5-diphenylimidazolidin-2-one **6** that did not react with semicarbazide under the reaction conditions. The generation of hydantoin **6** may be explained by a rearrangement of the pinacoline type.[9]

The structure of the synthesized compounds was ascertained by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy,[‡] and the structure of **5a** was additionally confirmed by XRD study.[§] According to its results, the geometry of the cationic moiety of



Scheme 1 *Reagents and conditions*: i, MeOH, HCl, 40–45 °C, 1 h, ii, MeOH, HCl, 80 °C, 30 min.

[†] Clophelinum – hydrochloride of *N*-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine, Glibutidum – hydrochloride of *N*-butylimidodicarbonimidic diamide, Metforminum – *N*,*N*-dimethylimidodicarbonimidic diamide, Sulginum – 4-amino-*N*-[amino(imino)methyl]benzenesylfonamide, Faringocept – 2-{4-[(aminocarbonothioyl)hydrazono]cyclohexa-2,5-dien-1-ylidene}hydrazinecarboximidamide, Chloridinum – 5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine, Bigumalum – hydrochloride of *N*-(4-chlorophenyl)-*N*′-isopropylimidodicarbonimidic diamide.

5a (Figure 1) is very similar to that in its analogue with 5,7-dimethyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones.[5] The conformation of the imidazole cycle is twist; the N(1) and N(2) atoms deviate from the plane of the three carbons by 0.37(1) and –0.32(1) Å, respectively. The conformation of the triazine moiety can also be described as twist. The angle between mean planes formed by N(3), N(4), N(5) and one of the carbon atoms is 21.4(1)°. Note that two hydrogen atoms belonging to the N(4)H and N(5)H groups of the triazine fragment are in the equatorial plane with the H(3N) atom which is an axial one. The sum of the CNC and CNH angles is 339.0(1)° for N(3) atom, 353.3(1) and 351.1(1)° for N(4) and N(5), respectively. The mutual disposition of the phenyl substituents is a cisoid one with the torsion angle C(7)C(1)C(3)C(13) of 30.0(1)°.

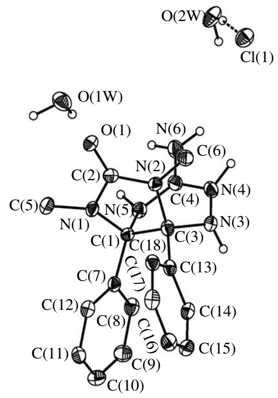


Figure 1 General view of compound **5a** in representation of atoms *via* thermal ellipsoids at 50% probability level.

Salt **5a** crystallizes with two solvate water molecules per molecule of the product and this governs the supramolecular organization in the crystal. Cations of **5a** are assembled into double chains *via* N(6)–H(6NA)···O(1) bonds [N···O 2.873(3) Å; NHO 152(1)°]. These associates are additionally stabilized by hydrogen bonds with H_2O(2W) water molecule [N···O 2.919(4)–2.955(4) Å; NHO 159(1)–165(1)°] serving as both the donor and acceptor of proton. The cationic species also participate in the formation of the H-bond with the second water molecule, namely, N(4)–H(4N)···O(1W) one with the N···O distance and NHO angle of 2.771(3) Å and 159°, respectively. The interionic H-bonds [N···Cl 3.238(3) Å; NHCl 172(1)°] and those between the water molecules and chloride anions [O···Cl 3.206(3)–3.248(3) Å; OHCl 143(1)–173(1)°] interlink the above water-cationic chains leading to the formation of the 3D framework.

Thus, the research on the condensation of 1,3-dimethyl-4,5-dihydroxy-4,5-diphenylimidazolidin-2-one with aminoguanidine and semicarbazide (as hydrochlorides) allowed us to synthesize 3-imino-5,7-dimethyl-4a,7a-diphenylperhydroimidazo-[4,5-*e*]-1,2,4-triazin-6-one and 5,7-dimethyl-4a,7a-diphenylperhydroimidazo[4,5-*e*]-1,2,4-triazine-3,6-dione. Their structures were analyzed by XRD and a new conglomerate **5a** was found.

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‡ The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C). Chemical shifts were measured with reference to the residual protons of a [$^2H_6$]DMSO solvent (δ 2.50 ppm). Melting points were determined with a Gallenkamp instrument (Sanyo). Commercially available compound **3b** from ACROS and dihydrate of hydrochloride of aminoguanidine **3a** synthesized at the Institute of Reagents were used. The solvents were used without preliminary purification. Starting DHI **4** was synthesized similarly to the described procedure.[10]

*Synthesis of 3-imino-5,7-dimethyl-4a,7a-diphenylperhydroimidazo-[4,5-*e*]-1,2,4-triazin-6-one* **5a**. A solution of DHI **4** (0.03 mol) and aminoguanidine hydrochloride dihydrate **3a** (0.03 mol) in 150 ml MeOH with ten drops of concentrated HCl was heated at 40–45 °C for 1 h and concentrated *in vacuo*. After cooling the oily residue was triturated with 50 ml Et_2O. White precipitate of **5a** was filtered off. Yield 93–95%, mp 224–226 °C (MeOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.63 (s, 3H, MeN), 2.68 (s, 3H, MeN), 6.85–7.12 (m, 11H, 2Ph + HN), 7.99 (s, 2H, H_2NCl), 9.75 (s, 1H, HN), 10.11 (s, 1H, HN). ^{13}C{^{1}H} NMR ([$^2H_6$]DMSO) δ: 25.9 (MeN), 26.2 (MeN), 80.7 (CH), 84.2 (CH), 126.2 (C_{Ph}), 127.7 (C_{Ph}), 127.8 (C_{Ph}), 127.9 (C_{Ph}), 128.0 (C_{Ph}), 128.2 (C_{Ph}), 128.4 (C_{Ph}), 133.9 (C_{Ph}), 134.7 (C_{Ph}), 157.8 (C=O), 158.1 (C=N). Found (%): C, 52.88; H, 6.14; Cl, 8.69; N, 20.50. Calc. for $C_{18}H_{25}ClN_6O_3$ (%): C, 52.87; H, 6.16; Cl, 8.67; N, 20.55.

*Synthesis of 5,7-dimethyl-4a,7a-diphenylperhydroimidazo[4,5-*e*]-1,2,4-triazine-3,6-dione* **5b**. A solution of DHI **4** (0.07 mol) and semicarbazide hydrochloride **3b** (0.07 mol) in 300 ml MeOH was heated at 40–45 °C for 1 h. After cooling white precipitate of **5b** was filtered off. Yield 49–52%, mp 275–276 °C (MeOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.58 (s, 3H, MeN), 2.59 (s, 3H, MeN), 6.41 (s, 1H, HN), 6.99 (br. s, 10H, 2Ph), 7.62 [s, 1H, HN(4)], 8.17 [s, 1H, HN(2)]. ^{13}C{^{1}H} NMR ([$^2H_6$]DMSO) δ: 25.7 (MeN), 26.1 (MeN), 83.3 (CH), 84.5 (CH), 126.4 (C_{Ph}), 126.5 (C_{Ph}), 127.3 (C_{Ph}), 127.4 (C_{Ph}), 127.5 (C_{Ph}), 128.0 (C_{Ph}), 135.8 (C_{Ph}), 137.2 (C_{Ph}), 158.9 (C=O), 160.0 (C=O). Found (%): C, 64.05; H, 5.69; N, 20.79. Calc. for $C_{18}H_{19}N_5O_2$ (%): C, 64.08; H, 5.68; N, 20.76.

§ *Crystallographic data*. Crystals of **5a** ($C_{18}H_{25}ClN_6O_3$, $M = 408.89$) are monoclinic, space group $P2_1$, at 120 K: $a = 8.2145(6)$, $b = 9.8678(6)$ and $c = 12.5084(8)$ Å, $\beta = 96.929(5)°$, $V = 1006.51(12)$ Å^3, $Z = 2$ ($Z' = 1$), $d_{calc} = 1.349$ g cm^{-3}, μ(MoKα) = 2.22 cm^{-1}, $F(000) = 432$. Intensities of 8322 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$] and 4680 independent reflections [$R_{int} = 0.0272$] were used in further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms of NH groups and those of water molecules 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 respectively the equivalent thermal parameters of the carbon atoms to which corresponding *H* atoms are bonded. For **5a** the refinement converged to $wR_2 = 0.1203$ and GOF = 1.008 for all independent reflections [$R_1 = 0.0489$ was calculated against F for 3846 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[11]

CCDC 745851 contains 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, 2009.

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