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Condensation of 5,7-dimethyl-4a,7a-diphenyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-one with halogenoacetic acids

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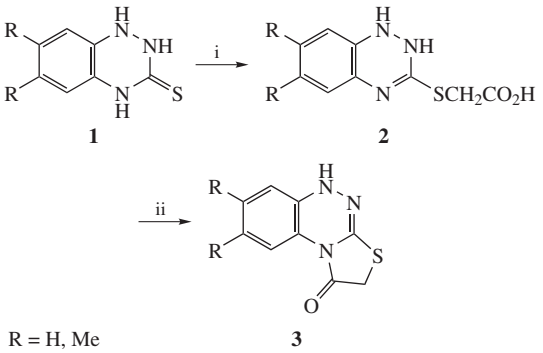
The reaction of 5,7-dimethyl-4a,7a-diphenyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-one with halogenoacetic acids was studied, and the directed synthesis of {(5,7-dimethyl-6-oxo-4a,7a-diphenyl-4,4a,5,6,7,7a-hexahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazin-3-yl)thio}acetic acid and 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]-1,3-thiazolo[3,2-*b*]-1,2,4-triazine-2,7(1*H*,6*H*)-dione was perfomed for the first time; the structures of title compounds were confirmed by the ^{1}H-{^{13}C} HMBC, ^{1}H-{^{15}N} HSQC, TOCSY, NOESY, HMBC, HSQCED NMR spectroscopy methods and XRD analysis of the tricyclic product.

New biologically active compounds such as anticancer agents, fungicides and bactericides were synthesized by S-alkylation of heterocycles containing NC(S)N-fragment with α,β-difunctional compounds.[1,2] Several examples of S-carboxymethylation of such heterocycles with bromo- and chloroacetic acids are known.[1–5] The reactions were usually performed in ethanol, sometimes in the presence of sodium acetate by boiling the reagents.[3–5] There are two examples of using aqueous KOH solution.[1,2] The interaction of these acids with the compounds containing the thioxotriazine cycle, which gave corresponding thiazolotriazines by the dehydration of initially formed heterocyclic derivatives of thioacetic acid, was described.[2,4,5] For instance, thioxobenzotriazine **1** was carboxymethylated at the sulfur atom with halogenoacetic acids to give thioacetic acids **2**, the further dehydration of **2** led to tricyclic products **3** using Ac_2O (Scheme 1).[4]

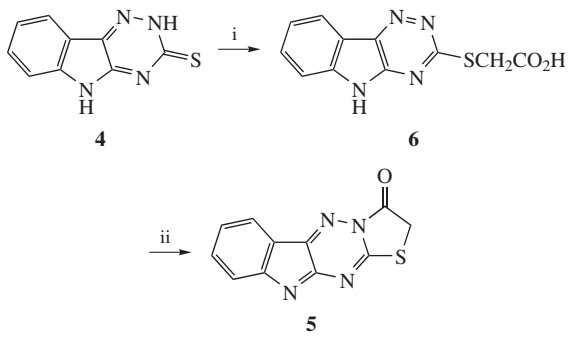
Cyclocondensation of triazinoindolthione **4** with chloroacetic acid gave thiazolotriazinoindole **5** *via* thioacetic acid **6** (Scheme 2).[2]

The aim of this work was to study the condensation of halogenoacetic acids with the 5,7-dimethyl-4a,7a-diphenyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-one and to elaborate procedures for the synthesis of {(5,7-dimethyl-6-oxo-4a,7a-diphenyl-4,4a,5,6,7,7a-hexahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazin-3-yl)thio}-acetic acid and 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 **2** **3**

Scheme 1 *Reagents and conditions*: i, $HalCH_2COOH$, EtOH, AcONa, reflux, 8 h; ii, Ac_2O, Py, reflux, 0.5 h.



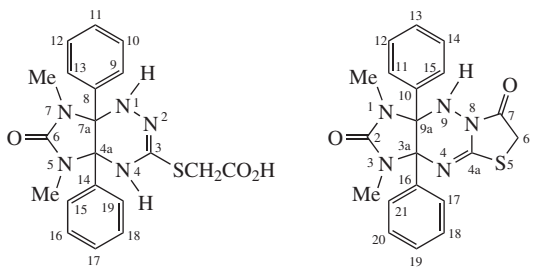
4 **6** **5**

Scheme 2 *Reagents and conditions*: i, $HalCH_2COOH$, 20% aq. KOH, reflux, 5 h; ii, Ac_2O, Py, heating, 0.25 h.

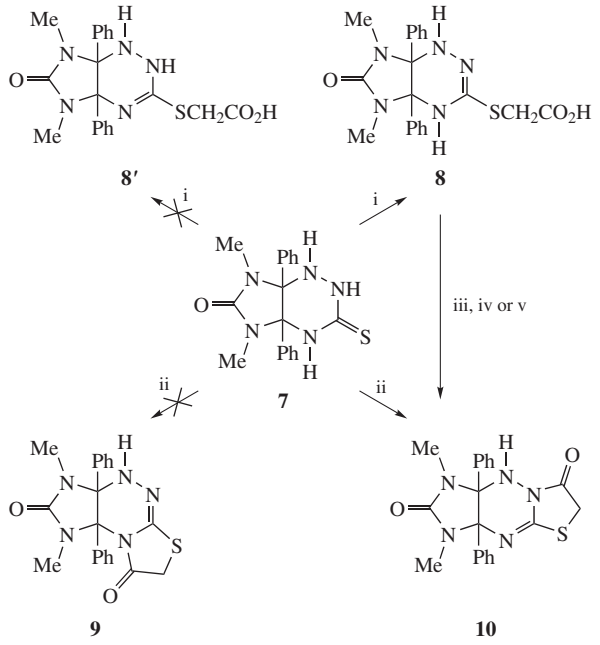
Based on the structure of thioxoimidazotriazine **7**, one can expect that the interaction of **7** with halogenoacetic acid under given conditions will lead to products **8**–**10** (Scheme 3).

Imidazotriazinone **7** was obtained by ureidoalkylation of thiosemicarbazide with 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidin-2-one according to an earlier developed procedure.[6] The interaction of compound **7** with halogenoacetic acids was explored when boiling it in anhydrous ethanol or acetic acid in the presence of AcONa for 1–8 h. As a result, the product containing the COOH group was formed in ethanol. This product can exist as isomers **8** or **8′**. With AcOH, we isolated the compound that could be one of regioisomers **9** and **10** based on ^{1}H and ^{13}C NMR spectra.

On the basis of the ^{1}H, ^{13}C and ^{15}N NMR spectra using HSQC and HMBC methods, the obtained product was assumed to be



8 **10**



Scheme 3 *Reagents and conditions*: i, $HalCH_2COOH$, EtOH, AcONa, reflux, 2 h (for $BrCH_2COOH$) or 6 h (for $ClCH_2COOH$); ii, $HalCH_2COOH$, AcOH, AcONa, reflux, 1.5 h (for $BrCH_2COOH$) or 2.5 h (for $ClCH_2COOH$); iii, Ac_2O, Py, reflux, 0.5 h; iv, AcOH, reflux, 1 h; v, Ac_2O, reflux, 0.5 h.

isomer **8**. The ^1H-{^{13}C} HMBC spectrum exhibited cross-peak between the narrow signal for the N(1)H proton and *ipso*-carbon atom C(8) of one of the benzene rings. The ^1H-{^{15}N} HMBC spectrum exhibited cross-peak between the narrow signal for the N(1)H proton and sp^2-nitrogen atom N(2), whereas the cross-peak with nitrogen atom N(4) of other NH group was not observed. This confirms that our product is isomer **8**.

The choice between the structures of **9** and **10** was made based on NOESY, TOCSY, HSQCED, HMBC ^1H and ^{13}C NMR spectra and quantum-chemical calculations. The correlation of the N(9)H proton was observed with both the C(7)=O and C(2)=O groups and also with the quaternary carbon atom C(4a). There are no cross-peaks of the N(9)H group with carbon atom C(6) of the CH_2 moiety. This is also indicative of the compound being regioisomer **10**. The experimental ^{13}C NMR spectrum of this particular product agrees with the values of chemical shifts calculated for the isolated molecule of **10** (the influence of solvent was not taken into account).

The best yields of 85 and 90% for acid **8** were achieved on reflux with $BrCH_2COOH$ (for 2 h) and $ClCH_2COOH$ (for 6 h), respectively. This result indicates that the reaction of bicycle **7** with the halogenoacetic acids occurs regiospecifically with the formation of acid **8**.

The best yields of tricycle **10** reaching 75 and 63% were obtained on reflux with $BrCH_2COOH$ (for 1.5 h) and $ClCH_2COOH$ (for 2.5 h), respectively. Compound **10** precipitates from reaction mixtures immediately after its formation. Therefore, one can assume that tricycle **10** is formed regiospecifically. The residues of reaction mixtures are resinification products.

Compound **10** was also obtained by boiling acid **8** in AcOH, Ac_2O or Ac_2O and Py, the best yield (83%) of tricycle **10** being achieved when using Ac_2O.

The mass spectra of synthesized compounds correspond to the structures of **8** and **10** in molecular and intense heavy fragment ions peaks.

Moreover, the structure of the regioisomer **10** was confirmed by the X-ray diffraction analysis of its crystals obtained from the solution of **10** in [$^2H_6$]DMSO and that of **10** in benzene. In both cases, compound **10** crystallized with one solvent moiety

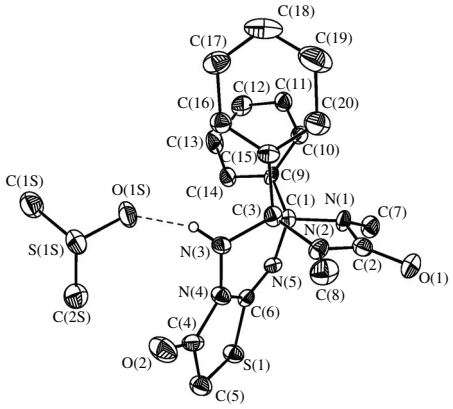


Figure 1 General view of compound **10**·DMSO in representation of atoms *via* thermal ellipsoids at 50% probability level. Hydrogen atoms except for that of the NH group are omitted for clarity. Selected bond lengths (Å) and angles (°) are: C(1)–C(3) 1.585(3), N(1)–C(1) 1.459(3), N(1)–C(2) 1.379(3), N(2)–C(2) 1.365(3), N(2)–C(3) 1.455(3), N(3)–C(3) 1.452(3), N(3)–N(4) 1.408(2), N(4)–C(6) 1.391(3), N(4)–C(4) 1.370(3), C(4)–C(5) 1.512(3), S(1)–C(5) 1.813(2), S(1)–C(6) 1.761(2), N(5)–C(6) 1.262(3), N(5)–C(1) 1.482(3); N(2)–C(2)–N(1) 108.28(18), N(4)–N(3)–C(3) 111.35(16), C(6)–N(5)–C(1) 119.35(18), C(4)–C(5)–S(1) 107.99(15).

(DMSO or benzene) per one molecule of the product (Figures 1 and 2) giving the crystallosolvates **10**·DMSO and **10**·Bz. Examination of the molecular geometry of **10**·DMSO and **10**·Bz revealed that the bond lengths of the octahydroimidazotriazine-thiazole fragment (with the maximum difference for the two forms being 0.01 Å) are typical of such a type of the heterocycles.[7]

The conformation of the imidazole cycle is twisted with the angles between the C(1)N(1)C(2) and C(2)N(2)C(3) planes of 19.0(2)° in **10**·DMSO and 21.1(2)° in **10**·Bz. The triazine moiety is also twisted; the N(3)/C(3) atoms deviates from the plane of the others by 0.23(1)/–0.24(1) Å and 0.38(1)/–0.37(1) Å in **10**·DMSO and **10**·Bz, respectively. In contrast, the thiazole cycle is flattened and the deviations of atoms from its mean plane do not exceed 0.06(1) Å [0.07(1) Å in the case of the crystallosolvate with benzene]. The hydrogen-bearing N(3) atom is markedly piramidalized: the sum of the bond angles at N(3) is 330.0(1)° in **10**·DMSO or 325.6(1)° in **10**·Bz. For comparison, the same value for one of the imidazole nitrogens, N(1), is 351.0(1)° [349.6(1)° for the benzene analogue], while for the others it is more than 357°. The mutual disposition of the phenyl sustituents is a cisoid one as it was observed in other cases.

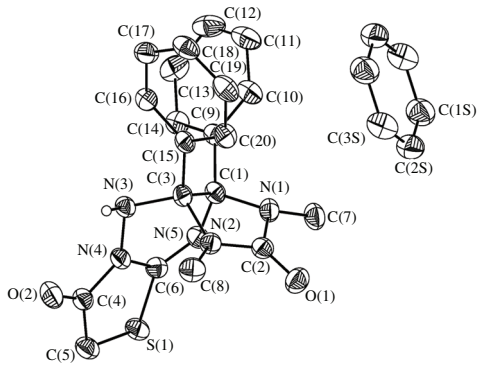


Figure 2 General view of compound **10**·Bz in representation of atoms *via* thermal ellipsoids at 50% probability level. Hydrogen atoms except for that of the NH group are omitted for clarity. Selected bond lengths (Å) and angles (°) are: C(1)–C(3) 1.578(3), N(1)–C(1) 1.468(2), N(1)–C(2) 1.378(3), N(2)–C(2) 1.363(2), N(2)–C(3) 1.453(2), N(3)–C(3) 1.465(2), N(3)–N(4) 1.410(2), N(4)–C(6) 1.380(2), N(4)–C(4) 1.368(2), C(4)–C(5) 1.502(3), S(1)–C(5) 1.824(2), S(1)–C(6) 1.763(2), N(5)–C(6) 1.269(2), N(5)–C(1) 1.482(2); N(2)–C(2)–N(1) 108.39(16), N(4)–N(3)–C(3) 109.82(14), C(6)–N(5)–C(1) 119.31(16), C(4)–C(5)–S(1) 108.15(13).

Supramolecular organization in the crystal of **10**·DMSO is governed by rather strong H-bond with the solvate molecule [N(3)···O(1S) 2.834(3) Å, Figure 1] and a number of weak contacts, such as C–H···O, C–H···N, C–H···S, C–H···π, and H···H ones, completing the formation of the 3D framework. In the case of the **10**·Bz crystallosolvate, despite the presence of the convenient donors and acceptors of proton, there are no H-bonds between the species and the strongest intermolecular interaction is C(2)–O(1)···S(1) binding [S···O 3.163(2) Å]. The latter leads to the formation of the centrosymmetric dimers, which are further held together by means of weaker contacts of the same types as those in the crystal of **10**·DMSO. The solvate benzene species are bound to the molecules of the product *via* the H···H contacts.

Thus, as a result of the detailed study of the condensation of $HalCH_2COOH$ with imidazotriazinone **7**, we have established that the reaction occurs regiospecifically depending on reaction conditions. Carboxyethylation at the sulfur atom of compound **7** occurs by carrying out the reaction in EtOH, while tricycle **10** is formed in AcOH. Compound **10** was obtained from acid **8** regiospecifically. Structures of compounds **8** and **10** were proved using NMR spectroscopy (^{1}H-{^{13}C} HSQC, ^{1}H-{^{15}N} HSQC, TOCSY, NOESY and HMBC, HSQCED).† X-ray analysis of **10** was also carried out.‡

† 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 NMR spectra). Chemical shifts were measured with reference to the residual protons of a [$^2H_6$]DMSO solvent (δ 2.50 ppm). Mass spectra were measured on an MS 30 spectrometer. Melting points were determined in a GALLENKAMP instrument (Sanyo).

Commercially available compounds (thiosemicarbazide, EtOH, AcONa, $BrCH_2COOH$, $ClCH_2COOH$, AcOH, Ac_2O, Py) supplied by ACROS were used in the syntheses. The solvents were used without preliminary purification.

The crystals for XRD study were prepared by crystallizing compound **10** from [$^2H_6$]DMSO and benzene.

*{(5,7-Dimethyl-6-oxo-4a,7a-diphenyl-4,4a,5,6,7,7a-hexahydro-1*H*-imidazo-[4,5-*e*]-1,2,4-triazin-3-yl)thio}acetic acid* **8**: yield: 85% (using $BrCH_2COOH$) or 90% (using $ClCH_2COOH$), mp 243–245 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.52 [s, 3H, Me–N(5)], 2.53 [s, 3H, Me–N(2)], 3.75 (m, 2H, CH_2), 6.83 [d, 2H, *o*-Ph–C(15) and *o*-Ph–C(19), *J* 8.1 Hz], 7.05 [m, 8H, Ph–C(9–13, 16–18)], 7.15 [s, 1H, N(1)H], 7.93 [s, 1H, N(4)H], 12.85 (br. s, 1H, COOH). ^{13}C {^{1}H} NMR ([$^2H_6$]DMSO) δ: 25.4 (Me), 25.7 (Me), 32.6 (SCH_2), 82.4 [C(7a)], 83.6 [C(4a)], 127.1 [C(Ph)], 127.6 [C(Ph)], 127.8 [C(Ph)], 127.9 [C(Ph)], 128.2 [C(Ph)], 135.9 [C(14)], 136.9 [C(8)], 145.1 (CS), 158.2 [C(6)], 170.2 (COOH). MS, *m*/*z* (%): 411 (M^+, 3), 316 (15), 278 (35), 264 (100), 249 (12), 234 (10), 207 (21), 118 (35), 104 (15), 101 (24), 59 (45).

*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* **10**: yield: 75% (using $BrCH_2COOH$) or 63% (using $ClCH_2COOH$) or 83% (by boiling of compound **8** in Ac_2O), mp 280–282 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.56 [s, 3H, Me–N(3)], 2.58 [s, 3H, Me–N(1)], 4.18 (m, 2H, CH_2), 6.70 [d, 2H, *o*-Ph–C(17, 21), *J* 6.9 Hz], 6.78 [d, 2H, *o*-Ph–C(11, 15), *J* 7.3 Hz], 7.02–7.15 (m, 6H, Ph), 7.37 (s, 1H, NH). ^{13}C {^{1}H} NMR ([$^2H_6$]DMSO) δ: 25.1 (Me), 25.8 (Me), 30.0 [C(6)], 79.3 [C(9a)], 81.2 [C(3a)], 126.1 [C(Ph)], 127.1 [C(Ph)], 127.6 [C(Ph)], 127.7 [C(Ph)], 127.8 [C(Ph)], 128.0 [C(Ph)], 134.2 [C(Ph)], 135.4 [C(Ph)], 151.0 [C(4a)], 159.1 [C(2)], 165.8 [C(7)]. MS, *m*/*z* (%): 392 [(M^+ – 1), 2], 316 (6), 278 (24), 265 (21), 264 (100), 249 (11), 207 (31), 118 (52), 104 (17), 77 (30), 51 (38).

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‡ *Crystallographic data*. Crystals of **10**·DMSO ($C_{22}H_{25}N_5O_3S_2$, M = 471.59) are monoclinic, space group $P2_1/n$, at 120 K: a = 8.8821(7), b = 15.4896(13) and c = 16.4553(13) Å, β = 90.588(5)°, V = 2263.8(3) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.384 g cm^{-3}, μ(MoKα) = 2.70 cm^{-1}, F(000) = 992. Intensities of 23005 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$] and 5458 independent reflections (R_{int} = 0.0430) were used in further refinement.

Crystals of **10**·Bz ($C_{23}H_{22}N_5O_2S$, M = 432.52) are monoclinic, space group $P2_1/n$, at 120 K: a = 15.8295(13), b = 8.3843(7) and c = 16.6669(13) Å, β = 112.721(5)°, V = 2040.4(3) Å^3, Z = 4 (Z' = 1/2), d_{calc} = 1.408 g cm^{-3}, μ(MoKα) = 1.91 cm^{-1}, F(000) = 908. Intensities of 18316 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = = 0.71072 Å, ω-scans, $2\theta < 56°$] and 4916 independent reflections (R_{int} = = 0.0389) were used in further refinement.

The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atom of NH group was located from the Fourier density synthesis. 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 **10**·DMSO the refinement converged to wR_2 = 0.1329 and GOF = 1.001 for all independent reflections [R_1 = 0.0532 was calculated against F for 3638 observed reflections with $I > 2\sigma(I)$]. For **10**·Bz the refinement converged to wR_2 = 0.1224 and GOF = 1.002 for all independent reflections [R_1 = 0.0478 was calculated against F for 3251 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[8]

CCDC 758605 and 758606 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.