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α-Thioureidoalkylation of Functionally Substituted Ureas: I. Tandem Cyclization and Esterification in Reactions of *N*-(Carboxyalkyl)ureas with 1,3-Dialkyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thiones in Alcohols

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Abstract—Acid-catalyzed reactions of *N*-(carboxyalkyl)ureas with 1,3-dialkyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thiones in methanol or propan-2-ol led to the formation of previously unknown ω-(4,6-dialkyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)alkanoic acids and their methyl and isopropyl esters. The structure of some esters was proved by X-ray analysis. Methyl (4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)acetate showed anxiolytic effect.

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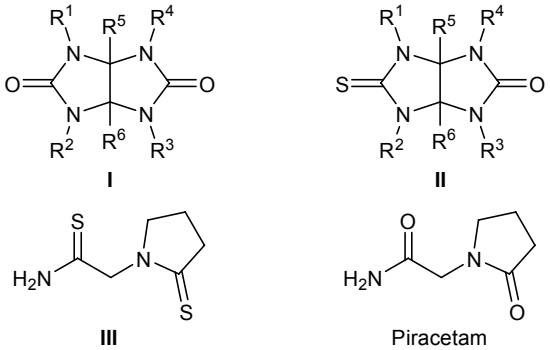
Glycolurils (**I**, octahydroimidazo[4,5-*d*]imidazole-2,5-diones) exhibit a broad spectrum of biological activity [1–4], in particular neurotropic [1], while 2,4,6,8-tetramethylglycoluril (Mebicar) is used in medical practice as minor tranquilizer [2]. 1,5-Diphenylglycolurils affect hepatic cytochrome P-450-dependent monooxygenase system [3]. Only a few examples of synthesis of thio analogs of glycolurils (5-thioxooctahydroimidazo[4,5-*d*]imidazol-2-ones **II**) were reported [5–7], though these compounds may also be important from the practical viewpoint. On the one hand (according to PASS), they could exhibit diverse pharmacological activity related to their effect on the central nervous system. On the other hand, it is known that, e.g., dithiopiracetam (**III**) possesses a higher nootropic activity than does Piracetam [8]. Therefore, synthesis of glycoluril thio analogs seems to be an important problem.

Glycolurils **I** can be synthesized by reaction of ureas with 4,5-dihydroxyimidazolidine-2-ones. In particular, reactions of *N*-alkyl- [9], *N*-(carboxyalkyl)- [10], *N*-(hydroxyalkyl)- [11], and *N*-(aminoalkyl)ureas [12] were reported. We recently described some specificities of the condensation of *N*-(carboxyalkyl)ureas with 4,5-dihydroxy-4,5-diphenylimidazolidin-2-ones: when these reactions were carried out in alcohols (methanol or propan-2-ol) the cyclization process leading to *N*-(carboxyalkyl)glycolurils was accompanied by esterification [13]. Analogous reactions of ureas with 4,5-dihydroxy-4,5-diphenylimidazolidine-2-thiones were not reported.

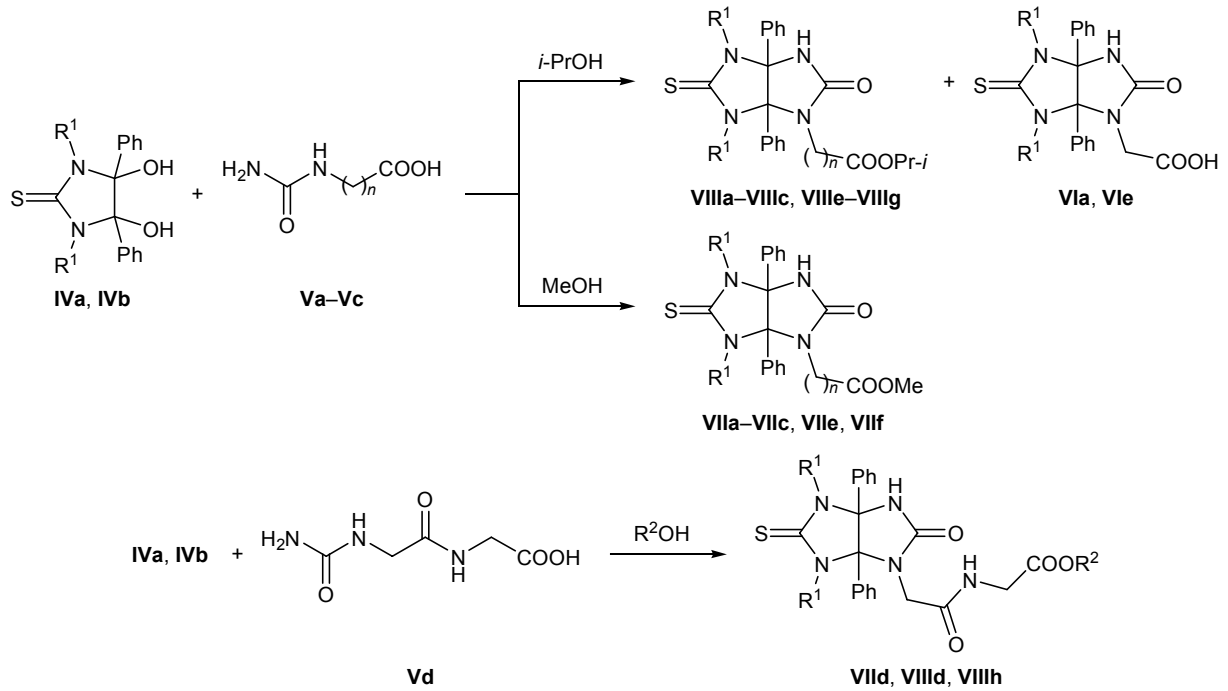
In the present work we examined the condensation of 1,3-dialkyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thiones **IVa** and **IVb** with ureido acids **Va**–**Vd** with a view to synthesize glycoluril thio analogs **VI** as potential biologically active substances. Reactions of ureas with 4,5-dihydroxy-4,5-diphenylimidazolidin-2-



ones are usually carried out in water, lower alcohols, or their mixtures, depending on the solubility of the reactants, under conditions of acid catalysis (HCl) [9–13]. The condensation of acids **Va**–**Vd** with imidazolidinethiones **IVa** and **IVb** were performed by heating the reactants in boiling methanol or propan-2-ol (compounds **IV** are insoluble in water) in the presence of concentrated hydrochloric acid over a period of 1, 2, or 3 h. It was found that the formation of bicyclic thioglycolurils **VIa**–**VIh** was accompanied by esterification of the carboxy group [14] so that the major products were the corresponding methyl and isopropyl esters **VIIa**–**VIIf** and **VIIIa**–**VIIIh** (Scheme 1). The ^{1}H NMR spectra of esters **VII** and **VIII** lacked downfield signals assignable to OH proton in carboxy group (δ 12 ppm), but signals from MeO or *i*-PrO group were present. We succeeded in detecting and isolating only thioglycolurils **VIa** and **VIe** in the reactions of *N*-carbamoylglycine (**Va**) with compounds **IVa** and **IVb** in isopropyl alcohol; in both cases, esters **VIIIa** and **VIIIe** were also formed. The ratio of acids **VI** and esters **VIII** changed during the process. Complete esterification of the carboxy group in **VIa** and **VIb** required 8 or 10 h, respectively, which may be related to steric structure of both initial reactants and thioglycolurils **VIa** and **VIe**. All ureido acids **Va**–**Ve** reacted with compound **IVa** in boiling ethanol, whereas compound **IVb** reacted only with acids **Va** and **Vb** to produce methyl esters **VIIe** and **VIIf**, respectively. Compounds **IVa** and **IVb** turned out to be more reactive in propan-2-ol, and isopropyl esters **VIIIa**–**VIIIh** were formed from all ureido acids **Va**–**Vd**. The best yields of esters **VIIa**, **VIIb**, **VIIe**, and **VIIIb** (65, 59, 73, and 58%, respectively) were obtained by heating the reactants over a period of 1 h; compounds **VIId**, **VIIf**, **VIIId**, and **VIIIh** (35, 57, 65, and 77%, respectively) required heating over a period of 2 h; and esters **VIIc**, **VIIIc**, **VIIIf**, and **VIIIg** (51, 70, 66, and 67%, respectively) were isolated after heating for 3 h. When the reaction time was shortened from 1 h to 15 min, the yields of the corresponding esters were considerably lower, while initial ureido acids **Va**–**Vd** were partly recovered from the reaction mixtures.

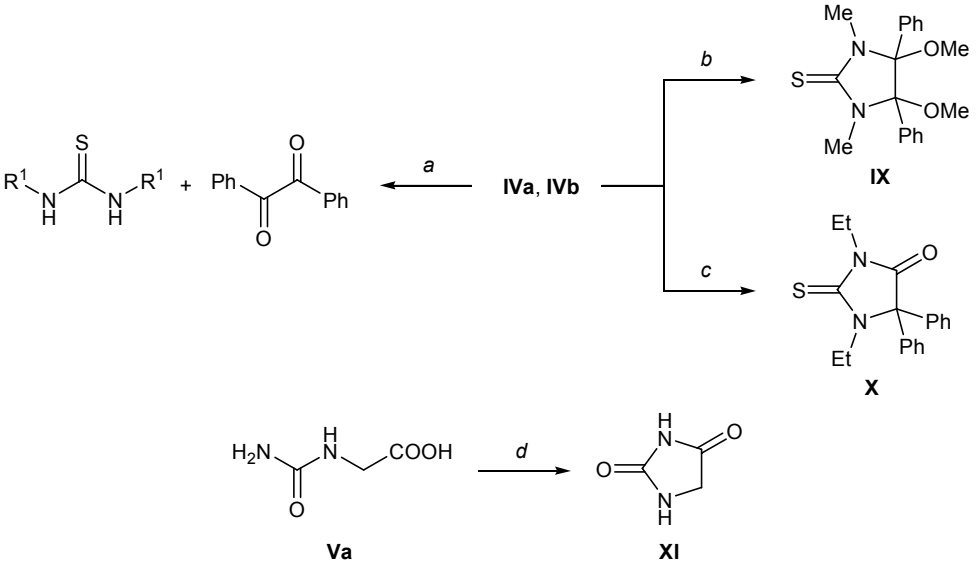
In all cases, the reactions were accompanied by side processes. Hydrolysis of compounds **IVa** and **IVb** to the corresponding ureas and benzil was observed in all reactions (Scheme 2, *a*), while other side reactions occurred only in some cases. 4,5-Dimethoxy-1,3-dimethyl-4,5-diphenylimidazolidine-2-thione (**IX**) was formed in methanol (Scheme 2, *b*), and it did not react with ureido acids. In the reactions of acids **Va**–**Vd** with compound **IVb** in isopropyl alcohol previously un-

Scheme 1.



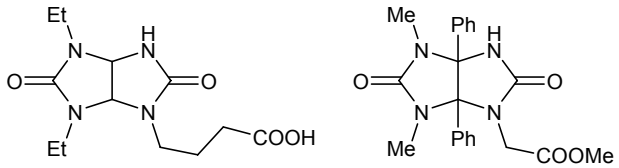
IV, R^1 = Me (**a**), Et (**b**); **V**, *n* = 1 (**a**), 2 (**b**), 3 (**c**); **VI**, R^1 = Me (**a**), Et (**e**); **VII**, **VIII**, R^1 = Me, *n* = 1 (**a**), 2 (**b**), 3 (**c**), R^1 = Et, *n* = 1 (**e**), 2 (**f**), 3 (**g**); **VII**, $R^1 = R^2$ = Me (**d**); **VIII**, R^1 = Me, R^2 = *i*-Pr (**d**), R^1 = Et, R^2 = *i*-Pr (**h**).

Scheme 2.



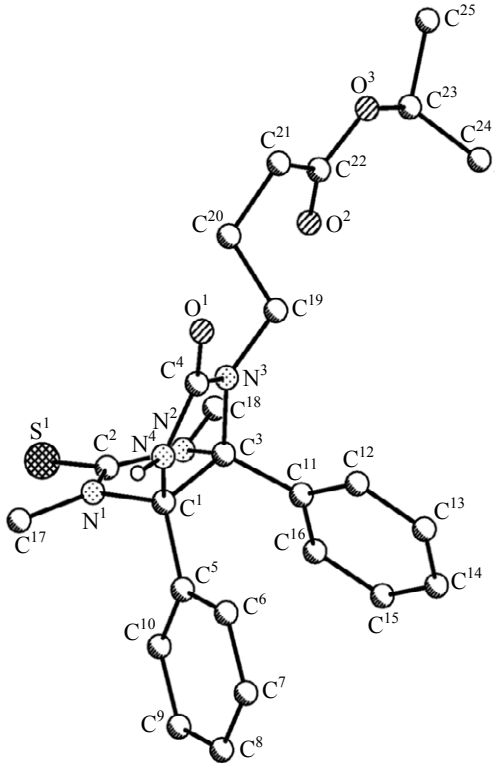
known 1,3-diethyl-5,5-diphenyl-2-thioxoimidazolidin-4-one (**X**) was formed (Scheme 2, *c*). In addition, prolonged heating of acid **Va** with imidazolidinethione **IVa** (8 h) or compound **IVb** (10 h) in isopropyl alcohol resulted in the formation of well known hydantoin **XI** via cyclization of the initial acid [9] (Scheme 2, *d*).

We succeeded in obtaining single crystals suitable for X-ray analysis only from isopropyl esters **VIIIc** and **VIIIg**. According to the X-ray diffraction data, these compounds crystallized as racemates (space group *P*1). Thioglycolurils **VIIIc** and **VIIIg** were characterized by slightly different molecular structures, though their geometric parameters were consistent with those typical of structurally related compounds [9–13, 15, 16]. The imidazolidine rings in molecule **VIIIc** have *twist* conformation with the C^1 and C^3 atoms deviating by 0.096(3)–0.167(3) and 0.149(3)–0.211(3) Å, respectively, from the plane formed by the other atoms in the ring. The imidazolidine rings in molecule **VIIIg** have *envelope* conformation, and deviations of the C^3 and C^1 atoms were 0.341(3) and 0.331(3) Å, respectively. The dihedral angle between the mean-square planes of the imidazolidine rings is 64.3(2)° in **VIIIc** and 68.6(2)° in **VIIIg**; in both molecules the phenyl groups on C^1 and C^3 are oriented *cis* with respect to each other. The isopropoxycarbonylpropyl groups on the N^3 atom in **VIIIc** and **VIIIg** have similar *synclinal* conformations with the torsion angle $C^{19}C^{20}C^{21}C^{22}$ equal to 70.9(2)° (**VIIIc**) or 78.0(2)° (**VIIIg**). The carbonyl group is *synperiplanar* to the C^{21}–C^{20} bond: the torsion angle $O^2C^{22}C^{21}C^{20}$ is 6.2 and 13.5° for **VIIIc** and **VIIIg**, respectively. Furthermore, orientation of the isopropoxycarbonyl group with respect to the bicyclic fragment is similar to that found for structurally related compound **XIII** which was presumed to crystallize as racemate taking into account steric repulsion between the carboxypropyl and ethyl substituents in chiral associate [15].

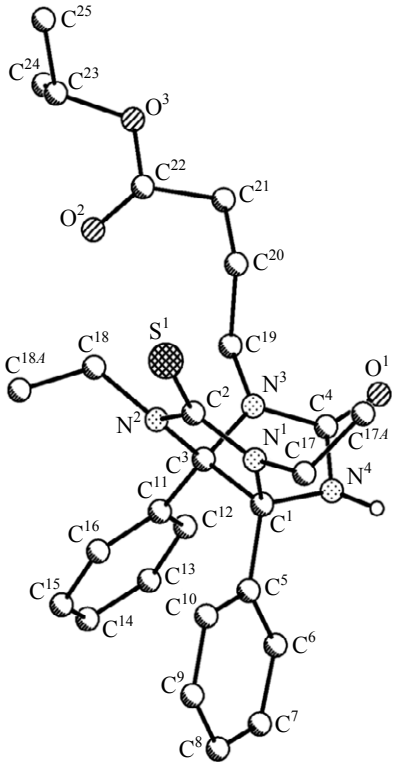


In fact, molecules **VIIIc** and **VIIIg** in crystal are linked to form centrosymmetric dimers by medium-strength hydrogen bond N^4–H···O^1 [N···O 2.8714(18) and 2.852(2) Å, ∠NHO 164 and 174° for **VIIIc** and **VIIIg**, respectively]. These dimers are linked to each other via numerous weak C–H···O, C–H···S, C–H···H–C, and C–H···π (for **VIIIc**) contacts leading to formation of three-dimensional network.

Pharmacological testing of methyl (4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]-imidazol-1-yl)acetate (**VIIa**) and methyl (4,6-dimethyl-2,5-dioxo-3a,6a-diphenyloctahydroimidazo[4,5-*d*]-imidazol-1-yl)acetate (**XIV**) [13] taken for comparison showed that both compounds are almost nontoxic (LD_{50} > 1000 mg/kg). Glycoluril **XIV** revealed no appreciable neuroprotective effect on the behavior of animals exposed to hypoxic stress, while thioglycoluril **VIIa** exhibited anxiolytic effect.



VIIIc



VIIIg

Molecular structures of isopropyl 4-(4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)butanoate (**VIIIc**) and isopropyl 4-(4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)butanoate (**VIIIg**) according to the X-ray diffraction data

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300.13 and 75.5 MHz, respectively using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The melting points were determined on a Sanyo Gallenkamp melting point apparatus. The X-ray diffraction data for compounds **VIIIc** and **VIIIg** were obtained on a Smart 1000 CCD diffractometer (MoK_α irradiation, graphite monochromator, ω-scanning). The structures were solved by the direct method and were refined by F^2_{hkl} by the least-squares procedure in full-matrix anisotropic approximation. Hydrogen atoms in the NH groups were localized by Fourier difference syntheses of electron density. The positions of hydrogen atoms in methyl and methylene groups were calculated on the basis of geometry considerations. The positions of all hydrogen atoms were refined according to the riding model. The principal crystallographic data and refinement parameters are given in table. All calculations were performed using SHELXTL PLUS software package [17].

Pharmacological assays were performed at the Institute of Technical Chemistry (Ural Division, Russian Academy of Sciences) in 20–22-g white outbred mice.

1,3-Dialkyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thiones **IVa** and **IVb** were synthesized by condensation of *N*,*N*′-dimethyl- and *N*,*N*′-diethylthioureas with 1,2-diphenylethane-1,2-dione [18, 19]. Ureido acids **Va**–**Vd** were obtained by reaction of the corresponding amino acids [glycine, β-alanine, γ-aminobutyric acid, and *N*-(aminoacetyl)glycine] with potassium cyanate [20].

Thioglycolurils VIa and VIe (*general procedure***).** A solution of 4 mmol of imidazolidinethione **IVa** or **IVb** and 4 mmol of ureido acid **Va** in 40 ml of isopropyl alcohol containing 0.6 ml of concentrated hydrochloric acid was heated for 1 h under reflux. The mixture was evaporated to dryness, the residue was treated with diethyl ether to remove benzil, the precipitate (a mixture of compounds **VIa** and **VIIIa** or **VIe** and **VIIIe**) was treated with 5 ml of 5% aqueous alkali under stirring over a period of 5 min at room temperature, and the precipitate (ester **VIIIa** or **VIIIe**) was filtered off. The filtrate was acidified to pH 1 by

adding concentrated hydrochloric acid, and the precipitate (acid **VIa** or **VIe**) was filtered off.

(4,6-Dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)acetic acid (VIa). Yield 0.62 g (39%), mp 297–299°C. ^{1}H NMR spectrum, δ, ppm: 2.92 s and 3.01 s (3H each, NMe), 3.54 d and 4.01 d (1H each, CH_2, J = 18 Hz), 6.60–6.90 m (4H, H_{arom}), 6.93–7.17 m (6H, H_{arom}), 8.90 s (1H, NH), 12.69 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 31.04 and 32.28 (NMe), 43.63 (CH_2), 86.61 and 90.19 (C^{3a}, C^{6a}); 127.21, 127.84, 128.02, 128.40, 128.61, 128.82, 132.46, 134.17 (C_{arom}); 158.25 (C^5), 170.05 (COOH), 183.15 (C^2). Found, %: C 60.54; H 5.19; N 14.19; S 8.00. $C_{20}H_{20}N_4O_3S$. Calculated, %: C 60.59; H 5.08; N 14.13; S 8.09.

[2-(4,6-Dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)-1-oxoethylamino]acetic acid (VIe). Yield 0.32 g (18%), mp 288–290°C. ^{1}H NMR spectrum, δ, ppm: 2.91 s and 2.95 s (3H each, NMe), 3.52 d and 4.15 d (1H each, CH_2, J = 17.3 Hz), 3.68–3.85 m (2H, CH_2), 6.60–6.93 m (4H, H_{arom}), 6.95–7.20 m (6H, H_{arom}), 8.09 t (1H, NH, J = 5.5 Hz), 8.88 s (1H, NH), 12.55 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 30.95 and 32.30 (NMe), 40.65 (CH_2), 44.28 (CH_2), 86.46 and 90.37 (C^{3a}, C^{6a}); 127.56, 128.01, 128.40, 128.58, 128.78, 132.38, 134.18 (C_{arom}); 158.37 and 167.90 (C=O), 170.98 (COOH), 183.07 (C=S). Found, %: C 58.20; H 5.16; N 15.41; S 7.14. $C_{22}H_{23}N_5O_4S$. Calculated, %: C 58.26; H 5.11; N 15.44; S 7.07.

Methyl and isopropyl (4,6-dialkyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)alkanoates VIIa–VIIf and VIIIa–VIIIh (*general procedure*). A solution of 4 mmol of compound **IVa** or **IVb** and 4 mmol of ureido acid **Va**–**Vd** in 20 ml of methanol or 40 ml of propan-2-ol containing 0.6 ml of concentrated hydrochloric acid was heated for 1 h (in the synthesis of **VIIa**, **VIIb**, **VIIe**, and **VIIIb**), 2 h (in the synthesis of **VIId**, **VIIf**, **VIIId**, and **VIIIh**), 3 h (in the synthesis of **VIIc**, **VIIIc**, **VIIIf**, and **VIIIg**), 8 h (in the synthesis of **VIIIa**), or 10 h (in the synthesis of **VIIIe**). The mixture was kept for 3 days at room temperature, and the precipitate was filtered off, washed on a filter with diethyl ether to remove benzil, and recrystallized from methanol. After separation of ester **VIIIe**–**VIIIh**, the filtrate was kept for 3 days, and the precipitate of hydantoin **X** was filtered off.

Methyl (4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)acetate (VIIa). Yield 1.07 g (65%), mp 292–294°C. ^{1}H NMR spectrum, δ, ppm: 2.93 s and 2.98 s (3H each, NMe), 3.65 s (3H, OMe), 3.77 d and 4.25 d (1H each, CH_2, J = 17.8 Hz), 6.62–6.99 m (4H, H_{arom}), 7.01–7.23 m (6H, H_{arom}), 8.92 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 31.01 and 32.31 (NMe), 43.47 (CH_2), 52.03 (OMe), 86.74 and 90.11 (C^{3a}, C^{6a}); 127.18, 127.76, 128.05, 128.42, 128.67, 128.85, 132.28, 133.98 (C_{arom}); 158.18 (C^2), 169.30 (COO), 183.00 (C^5). Found, %: C 61.36; H 5.39; N 13.68; S 7.74. $C_{21}H_{22}N_4O_3S$. Calculated, %: C 61.44; H 5.40; N 13.65; S 7.81.

Methyl 3-(4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)propanoate (VIIb). Yield 1.00 g (59%), mp 205–207°C. ^{1}H NMR spectrum, δ, ppm: 2.42–2.54 m (1H, CH_2),

Principal crystallographic data and refinement parameters for compounds **VIIIc** and **VIIIg**

Parameter	**VIIIc**	**VIIIg**
Formula	$C_{25}H_{30}N_4O_3S$	$C_{27}H_{34}N_4O_3S$
Molecular weight	466.59	494.64
Temperature, K	120	100
Crystal system	Triclinic	Triclinic
Space group	*P*-1	*P*-1
Z	2	2
a, Å	8.5592(6)	9.2016(15)
b, Å	11.2734(7)	9.7183(16)
c, Å	12.9535(8)	15.919(3)
α, deg	75.9490(10)	93.158(8)
β, deg	87.0650(10)	90.050(10)
γ, deg	82.4420(10)	113.261(6)
V, Å^3	1201.73(13)	1305.4(4)
d_{calc}, g/cm^3	1.289	1.258
μ, cm^{-1}	1.69	1.59
F(000)	496	528
$2\theta_{max}$, deg	58	58
Total number of reflections	13251	14476
Number of independent reflections	6346	6917
Number of reflections with $I > 2\sigma(I)$	4615	4327
Number of refined parameters	302	320
R_1	0.0519	0.0563
wR_2	0.1092	0.1417
Goodness of fit	1.007	1.008
Residual electron density, $e\times$Å^{-3} (d_{max}/d_{min})	0.369/–0.270	0.753/–0.597

2.67–2.77 m (1H, CH_2), 2.90 s and 3.08 s (3H each, NMe), 3.01–3.11 m (1H, CH_2), 3.56 s (3H, OMe), 3.64–3.75 m (1H, CH_2), 6.58–6.90 m (4H, H_{arom}), 6.92–7.21 m (6H, H_{arom}), 8.85 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 30.76 and 32.63 (NMe), 33.52 (CH_2), 38.27 (CH_2), 51.45 (OMe), 86.69 and 90.52 (C^{3a}, C^{6a}); 128.10, 128.44, 128.74, 128.86, 132.19, 133.59 (C_{arom}); 158.56 (C^2), 170.99 (COO), 182.96 (C^5). Found, %: C 62.19; H 5.74; N 13.27; S 7.40. $C_{22}H_{24}N_4O_3S$. Calculated, %: C 62.24; H 5.70; N 13.20; S 7.55.

Methyl 4-(4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)-butanoate (VIIc). Yield 0.89 g (51%), mp 227–229°C. ^1H NMR spectrum, δ, ppm: 1.56–1.73 m (1H, CH_2), 1.84–1.97 m (1H, CH_2), 2.26–2.38 m (2H, CH_2), 2.72–2.82 m (1H, CH_2), 2.93 s and 3.09 s (3H, NMe), 3.36–3.57 m (1H, CH_2), 3.54 s (3H, OMe), 6.60–6.93 m (4H, H_{arom}), 6.95–7.26 m (6H, H_{arom}), 8.75 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 24.47 (CH_2), 30.45 (CH_2), 30.61 and 32.60 (NMe), 41.54 (CH_2), 51.24 (OMe), 86.70 and 90.55 (C^{3a}, C^{6a}); 127.00, 128.12, 128.37, 128.74, 128.79, 132.37, 133.55 (C_{arom}); 158.61 (C^2), 172.83 (COO), 182.90 (C^5). Found, %: C 63.08; H 5.95; N 12.72; S 7.25. $C_{23}H_{26}N_4O_3S$. Calculated, %: C 62.99; H 5.98; N 12.78; S 7.31.

Methyl [2-(4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)-1-oxoethylamino]acetate (VIId). Yield 0.65 g (35%), mp 271–273°C. ^1H NMR spectrum, δ, ppm: 2.91 s and 2.96 s (3H each, NMe), 3.58 d and 4.16 d (1H each, CH_2, J = 16.9 Hz), 3.62 s (3H, OMe), 3.74–3.93 m (2H, CH_2), 6.60–6.93 m (4H, H_{arom}), 6.95–7.20 m (6H, H_{arom}), 8.21 t (1H, NH, J = 6.7 Hz), 8.87 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 30.95 and 32.22 (NMe), 40.59 (CH_2), 44.29 (CH_2), 51.64 (OMe), 86.48 and 90.37 (C^{3a}, C^{6a}); 127.17, 128.01, 128.41, 128.58, 128.79, 132.38, 134.18 (C_{arom}); 158.36 and 168.08 (CO), 170.08 (COO), 183.08 (C=S). Found, %: C 59.19; H 5.34; N 15.03; S 6.75. $C_{23}H_{25}N_5O_4S$. Calculated, %: C 59.08; H 5.39; N 14.98; S 6.86.

Methyl (4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)acetate (VIIe). Yield 1.28 g (73%), mp 215–217°C. ^1H NMR spectrum, δ, ppm: 1.15–1.29 m (6H, Me), 3.05–3.76 m (4H, $CH_3C\mathbf{H}_2$), 3.66 s (3H, OMe), 3.77 d and 4.28 d (1H each, CH_2, J = 17.8 Hz), 6.76–6.94 m (4H, H_{arom}), 6.96–7.23 m (6H, H_{arom}), 8.80 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.54 and 14.19 (Me); 39.69, 40.11, 42.99 (CH_2); 52.13 (OMe); 87.48, 91.03 (C^{3a}, C^{6a}); 127.05, 127.22, 127.43, 127.79, 128.00, 128.33, 128.86, 129.06, 132.44, 134.25 (C_{arom}); 158.28 (C^2); 169.28 (COO); 182.94 (C^5). Found, %: C 62.88; H 5.94; N 12.82; S 7.27. $C_{23}H_{26}N_4O_3S$. Calculated, %: C 62.99; H 5.98; N 12.78; S 7.31.

Methyl 3-(4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)propanoate (VIIf). Yield 1.03 g (57%), mp 230–232°C. ^1H NMR spectrum, δ, ppm: 1.16 t (3H, Me, J = 6.6 Hz), 1.32 t (3H, Me, J = 7.4 Hz), 2.50– 2.70 m (2H, CH_2), 3.01–3.16 m (1H, CH_2), 3.11–3.26 m (1H, CH_2), 3.40–3.47 m (1H, CH_2), 3.44–3.52 m (1H, CH_2), 3.57 s (3H, OMe), 3.54–3.71 m (1H, CH_2), 3.68–3.86 m (1H, CH_2), 6.68–6.92 m (4H, H_{arom}), 6.94–7.25 m (6H, H_{arom}), 8.71 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.50, 14.39 (Me); 33.57, 37.68, 40.38 (CH_2); 51.50 (OCH_3); 87.21, 91.66 (C^{3a}, C^{6a}); 126.98, 127.16, 127.71, 127.94, 128.05, 128.33, 128.91, 129.03, 132.21, 133.80 (C_{arom}); 158.61 (C^2); 171.03 (COO); 182.61 (C^5). Found, %: C 63.74; H 6.28; N 12.37; S 7.01. $C_{24}H_{28}N_4O_3S$. Calculated, %: C 63.69; H 6.24; N 12.38; S 7.09.

Isopropyl (4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)acetate (VIIIa). Yield 1.38 g (79%), mp 239–241°C. ^1H NMR spectrum, δ, ppm: 1.19 d and 1.22 d (3H each, Me, J = 6.4 Hz), 2.94 s and 3.00 s (3H each, NMe), 3.73 d and 4.19 d (1H each, CH_2, J = 17.8 Hz), 4.85–4.98 m (1H, OCH), 6.60–6.93 m (4H, H_{arom}), 6.95–7.20 m (6H, H_{arom}), 8.94 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.39 and 21.45 (Me), 30.99 and 32.27 (NMe), 43.84 (CH_2), 68.35 (OCH), 86.76 and 90.04 (C^{3a}, C^{6a}); 127.16, 127.76, 128.03, 128.38, 128.65, 128.82, 132.35, 134.04 (C_{arom}); 158.15 (C^2), 168.15 (COO), 183.14 (C^5). Found, %: C 62.94; H 5.85; N 12.80; S 7.36. $C_{23}H_{26}N_4O_3S$. Calculated, %: C 62.99; H 5.98; N 12.78; S 7.31.

Isopropyl 3-(4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)propanoate (VIIIb). Yield 1.05 g (58%), mp 190–192°C. ^1H NMR spectrum, δ, ppm: 1.16 d (6H, Me, J = 6.2 Hz), 2.36–2.47 m and 2.61–2.71 m (1H each, CH_2), 2.92 s and 3.09 s (3H each, NMe), 3.00–3.10 m and 3.49–3.59 m (1H each, CH_2), 3.64–3.74 m (1H, OCH), 6.60–6.93 m (4H, H_{arom}), 6.95–7.20 m (6H, H_{arom}), 8.86 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.49 (Me), 30.75 and 32.65 (NMe), 33.98 (CH_2), 38.16 (CH_2), 67.42 (OCH), 86.72 and 90.48 (C^{3a}, C^{6a}); 127.06, 127.31, 127.77, 128.10, 128.44, 128.74, 128.86, 132.19, 133.57 (C_{arom}); 158.54 (C^2), 170.09 (COO), 182.95 (C^5). Found, %: C 63.76; H 6.22;

N 12.35; S 7.11. $C_{24}H_{28}N_4O_3S$. Calculated, %: C 63.69; H 6.24; N 12.38; S 7.09.

Isopropyl 4-(4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)-butanoate (VIIIc). Yield 1.30 g (70%), mp 186–188°C. ^{1}H NMR spectrum, δ, ppm: 1.11 d and 1.12 d (3H, Me, J = 5.9 Hz), 1.55–1.70 m (1H, CH_2), 1.82–1.96 m (1H, CH_2), 2.24–2.28 m (2H, CH_2), 2.71–2.81 m (1H, CH_2), 2.93 s and 3.09 s (3H each, NMe), 3.39–3.52 m (1H, CH_2), 4.75–4.89 m (1H, CH), 6.60–6.93 m (4H, H_{arom}), 6.95–7.20 m (6H, H_{arom}), 8.78 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.53 (Me), 24.57 (CH_2), 30.65 (NMe), 31.05 (CH_2), 32.65 (NMe), 41.59 (CH_2), 67.09 (OCH), 86.70 and 90.58 (C^{3a}, C^{6a}); 127.03, 128.14, 128.40, 128.77, 128.82, 132.38, 133.58 (C_{arom}); 158.65 (C^2), 171.88 (COO), 182.91 (C^5). Found, %: C 64.33; H 6.53; N 11.97; S 6.90. $C_{25}H_{30}N_4O_3S$. Calculated, %: C 64.35; H 6.48; N 12.01; S 6.87.

Isopropyl [2-(4,6-dimethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)-1-oxoethylamino]acetate (VIIId). Yield 1.29 g (65%), mp 225–227°C. ^{1}H NMR spectrum, δ, ppm: 1.18 d (6H, Me, J = 5.9 Hz), 2.91 s and 2.95 s (3H each, NMe), 3.52 d and 4.16 d (1H each, CH_2, J = 16.9 Hz), 3.71–3.88 m (2H, CH_2), 4.83–4.95 m (1H, OCH), 6.60–6.93 m (4H, H_{arom}), 6.95–7.20 m (6H, H_{arom}), 8.23 t (1H, NH, J = 5.7 Hz), 8.90 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.52 (Me), 30.92 and 32.30 (NMe), 40.91 (CH_2), 44.29 (CH_2), 67.98 (OCH), 86.49 and 90.36 (C^{3a}, C^{6a}); 127.16, 128.02, 128.42, 128.61, 128.81, 132.41, 134.19 (C_{arom}); 158.37 and 168.04 (C=O), 169.13 [C(O)O], 183.07 (C=S). Found, %: C 60.66; H 5.93; N 14.10; S 6.39. $C_{25}H_{29}N_5O_4S$. Calculated, %: C 60.59; H 5.90; N 14.13; S 6.47.

Isopropyl (4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)acetate (VIIIe). Yield 1.29 g (69%), mp 199–201°C. ^{1}H NMR spectrum, δ, ppm: 1.11–1.31 m (12H, Me), 3.03–3.19 m (1H, CH_2), 3.24–3.35 m and 3.53–3.67 m (1H each, CH_2), 3.65– 3.76 m (2H, CH_2), 3.77 d and 4.11 d (1H each, CH_2, J = 17.6 Hz), 4.88–5.00 m (1H, OCH), 6.70–6.93 m (4H, H_{arom}), 6.95–7.25 m (6H, H_{arom}), 8.82 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.56, 14.11 (Me); 21.48 (2C, Me); 39.78, 40.00, 43.53 (CH_2); 68.34 (OCH); 87.38, 91.07 (C^{3a}, C^{6a}); 127.43, 127.78, 127.85, 128.23, 128.75, 128.93, 132.47, 134.33 (C_{arom}); 158.19 (C^2); 168.05 (COO); 182.85 (C^5). Found, %: C 64.41; H 6.46; N 11.93; S 6.90. $C_{25}H_{30}N_4O_3S$. Calculated, %: C 64.35; H 6.48; N 12.01; S 6.87.

Isopropyl 3-(4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)propanoate (VIIIf). Yield 1.27 g (66%), mp 197–199°C. ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, Me, J = 6.9 Hz), 1.16 d (6H, Me, J = 6.3 Hz), 1.32 t (3H, Me, J = 6.8 Hz), 2.41–2.65 m (2H, CH_2), 3.01–3.14 m (1H, CH_2), 3.11–3.23 m (2H, CH_2), 3.35–3.45 m (1H, CH_2), 3.43–3.56 m (2H, CH_2), 3.59–3.69 m (1H, CH_2), 3.71–3.82 m (1H, CH_2), 4.79–4.92 m (1H, OCH), 6.63–6.95 m (4H, H_{arom}), 6.97–7.23 m (6H, H_{arom}), 8.70 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.47, 14.37 (Me); 21.57 (2C, Me); 34.00, 37.59, 39.36 (CH_2); 67.45 (OCH); 87.24, 91.64 (C^{3a}, C^{6a}); 127.31, 127.77, 128.06, 128.31, 128.91, 129.03, 132.30, 133.89 (C_{arom}); 158.58 (C^2); 170.09 (COO); 182.68 (C^5). Found, %: C 64.90; H 6.76; N 11.63; S 6.72. $C_{26}H_{32}N_4O_3S$. Calculated, %: C 64.97; H 6.71; N 11.66; S 6.67.

Isopropyl 4-(4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)butanoate (VIIIg). Yield 1.32 g (67%), mp 187–189°C. ^{1}H NMR spectrum, δ, ppm: 1.13 d (6H, Me, J = 6.2 Hz), 1.17 t and 1.33 t (3H each, Me, J = 7 Hz), 1.71–1.81 m (1H, CH_2), 2.24–2.29 m (2H, CH_2), 2.83–2.96 m (1H, CH_2), 3.00–3.14 m (1H, CH_2), 3.18–3.32 m (1H, CH_2), 3.44–3.54 m (1H, CH_2), 3.57–3.68 m (1H, CH_2), 3.75–3.87 m (1H, CH_2), 4.78–4.91 m (1H, OCH), 6.67–6.92 m (4H, H_{arom}), 6.94–7.24 m (6H, H_{arom}), 8.61 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.52, 14.55 (Me); 21.52 (2C, Me); 24.56, 31.14, 38.98, 39.17, 40.94 (CH_2); 66.96 (OCH); 87.10, 91.80 (C^{3a}, C^{6a}); 127.20, 127.74, 128.07, 128.18, 128.88, 128.93, 132.44, 133.91 (C_{arom}); 158.71 (C^2); 171.83 (COO); 182.74 (C^5). Found, %: C 65.68; H 6.90; N 11.20; S 6.43. $C_{27}H_{34}N_4O_3S$. Calculated, %: C 65.56; H 6.93; N 11.33; S 6.48.

Isopropyl [2-(4,6-diethyl-2-oxo-3a,6a-diphenyl-5-thioxooctahydroimidazo[4,5-*d*]imidazol-1-yl)-1-oxoethylamino]acetate (VIIIh). Yield 1.61 g (77%), mp 211–213°C. ^{1}H NMR spectrum, δ, ppm: 1.16 t (3H, Me, J = 7.3 Hz), 1.19 d (3H, Me, J = 5.5 Hz), 1.19 d (3H, Me, J = 6.4 Hz), 1.27 t (3H, Me, J = 6.4 Hz), 3.09–3.27 m (2H, CH_2), 3.57–3.70 m (2H, CH_2), 3.75–3.89 m (4H, CH_2), 4.82–4.97 m (1H, OCH), 6.76–6.98 m (4H, H_{arom}), 7.00–7.29 m (6H, H_{arom}), 8.15 t (1H, NH, J = 5.5 Hz), 8.75 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.51, 14.04 (Me); 21.50 (2C, Me); 25.44, 40.87, 43.79 (CH_2); 67.96 (OCH); 87.11, 91.35 (C^{3a}, C^{6a}); 127.51, 127.74, 128.03, 128.20, 128.62, 128.85, 132.45, 134.44 (C_{arom}); 158.39, 167.91 (C=O);

169.09 (COO); 182.94 (C=S). Found, %: C 61.99; H 6.46; N 13.30; S 6.01. $C_{27}H_{33}N_5O_4S$. Calculated, %: C 61.93; H 6.35; N 13.37; S 6.12.

1,3-Diethyl-5,5-diphenyl-2-thioxoimidazolidin-4-one (X). Yield 0.05–0.08 g (4–6%), mp 133–135°C. ^{1}H NMR spectrum, δ, ppm: 0.46 t (3H, Me, J = 7 Hz), 1.15 t (3H, Me, J = 7.3 Hz), 3.71–3.84 m (2H, CH_2), 3.78–3.89 m (2H, CH_2), 7.12–7.23 m (4H, H_{arom}), 7.43–7.54 m (6H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.70 and 12.67 (Me), 36.57 and 40.24 (CH_2), 76.21 (C^5); 127.96, 129.10, 129.16, 135.72 (C_{arom}); 173.41 (C^4), 179.69 (C^2). Found, %: C 70.26; H 6.19; N 8.67; S 9.93. $C_{19}H_{20}N_2OS$. Calculated, %: C 70.34; H 6.21; N 8.63; S 9.88.

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