

Synthesis of new ring-fused thiocarbamates by condensation of 2-thioxo- and 2-oxo-1,3-dialkyl-4,5-dihydroxy-4,5-diphenylimidazolidines with KSCN

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Reaction of 2-thioxo or 2-oxo-1,3-dialkyl-4,5-dihydroxy-4,5-diphenylimidazolidines with KSCN in acidified MeOH affords 4,6-dialkyl-3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d]oxazole-2,5(3H)-dithiones or 4,6-dimethyl-3a,6a-diphenyl-2-thioxotetrahydro-2H-imidazo[4,5-d]oxazol-5(3H)-one, whose structure was proved by X-ray diffraction.

Substituted 4H-imidazo[4,5-d]oxazoles were patented as angiotensin II antagonists.¹ Hydrogenated derivatives of imidazo[4,5-d]oxazoles are represented by four types of compounds **1–4**,^{2–5} whose practical properties have not been studied. However, imidazolidin-2-one and ring-fused thiocarbamate fragments are known as parts of heterocyclic molecules **5–7** that exhibit various types of biological and pharmacological activity.^{6–12} Therefore, the synthesis of heterocycles containing both these fragments in one compound is of great interest.

The aim of this study was to obtain previously unknown 4,6-dialkyl-3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d]oxazole-2,5(3H)-dithiones **8a,b** and 4,6-dimethyl-3a,6a-diphenyl-2-thioxotetrahydro-2H-imidazo[4,5-d]oxazol-5(3H)-one **9**.

Two examples of similar compounds were reported in literature. Compound **3** was unexpectedly obtained as a side product in a very low yield from the Marckwald synthesis of 1-benzyl-5-hydroxymethyl-2-mercaptoimidazole by the reaction of 1,3-dihydroxyacetone with benzylamine hydrochloride and potassium

thiocyanate.⁴ Refluxing two equivalents of KSCN with 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidine-2-thione (DHIT) **10a** (see Scheme 1) in acidified THF afforded any of compounds **8a** or its isomer **11**,⁵ however, the authors were unable to unambiguously estimate the structures.

Here, the target imidazooxazolidithiones **8a,b** and thioxotetrahydroimidazooxazolone **9** were synthesized by simple cyclocondensation between DHIT **10a,b** or 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidin-2-one (DHI) **11** with KSCN and AcOH (Scheme 1).[†]

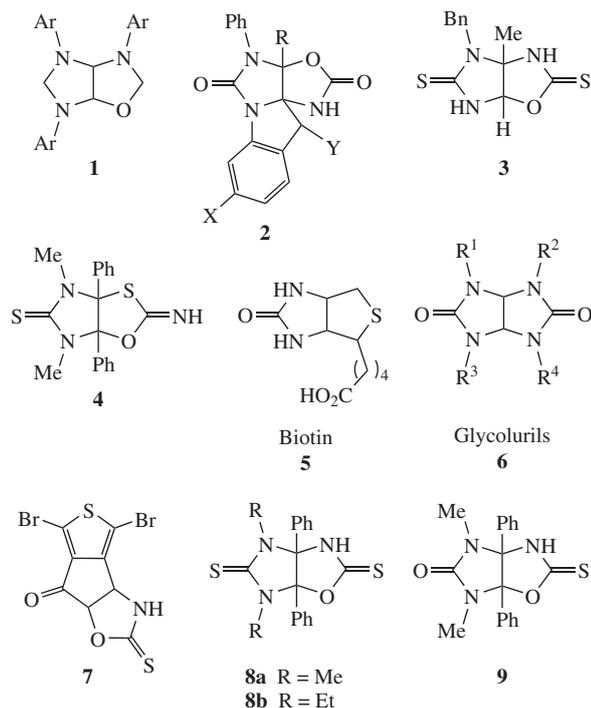
[†] General procedure for the synthesis of ring-fused thiocarbamates **8, 9**. To the solution of corresponding DHIT **10a,b** or DHI **11** (3.4 mmol, see refs. 13–15) and KSCN (0.42 g, 4.3 mmol) in MeOH (40 ml), AcOH (3 ml) was added at room temperature. The mixture was refluxed for 1 h, and then concentrated. The precipitate was filtered off and recrystallized from MeOH. The solid was filtered off and washed with MeOH.

4,6-Dimethyl-3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d]oxazole-2,5(3H)-dithione **8a**: colourless prisms unstable in air (– MeOH), white powder, yield 86%, mp 223–225 °C (decomp.). ¹H NMR (DMSO-*d*₆) δ: 3.00 (s, 3H, Me), 3.01 (s, 3H, Me), 3.17 (s, 3H, Me), 6.82–6.97 (m, 4H, Ph), 7.13–7.28 (m, 6H, Ph), 12.05 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ: 31.18, 31.60, 48.58 (Me), 90.07, 107.66 (C–C bridge), 126.68, 126.78, 128.55, 128.66, 129.58, 129.76, 131.06, 131.12 (Ph), 183.43, 187.28 (C=S). HRMS, *m/z*: 356.0885 [M+H]⁺ (calc. for C₁₈H₁₈N₃OS₂, *m/z*: 356.0891).

4,6-Diethyl-3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d]oxazole-2,5(3H)-dithione **8b**: colourless prisms, yield 80%, mp 243–245 °C (decomp.). ¹H NMR (DMSO-*d*₆) δ: 1.13 (t, 3H, Me, *J* 7.0 Hz), 1.22 (t, 3H, Me, *J* 7.0 Hz), 3.08–3.22 (m, 2H, CH₂), 3.81–3.97 (m, 2H, CH₂), 6.79–6.93 (m, 4H, Ph), 7.12–7.28 (m, 6H, Ph), 11.50–12.40 (br. s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ: 13.30, 13.50 (Me), 39.79, 39.95 (CH₂) 91.00, 108.20 (C–C), 126.88, 126.99, 128.39, 128.49, 129.54, 129.67, 131.20, 131.73 (Ph), 182.30, 187.18 (C=S). MS, *m/z* (%): 383 [M⁺] (39), 324 (44), 308 (56), 279 (52), 253 (100), 194 (67), 166 (78). Found (%): C, 62.59; H, 5.59; N, 10.91; S, 16.68. Calc. for C₂₀H₂₁N₃OS₂ (%): C, 62.63; H, 5.52; N, 10.96; S, 16.72.

4,6-Dimethyl-3a,6a-diphenyl-2-thioxotetrahydro-2H-imidazo[4,5-d]oxazol-5(3H)-one **9**: colourless hexagonal prisms, yield 84%, mp 227–230 °C. ¹H NMR (DMSO-*d*₆) δ: 2.70 (s, 6H, Me), 6.92–7.00 (m, 4H, Ph), 7.12–7.22 (m, 6H, Ph), 11.50–12.50 (br. s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ: 26.93, 27.48 (Me), 86.81, 106.19 (C–C bridge), 127.29, 127.35, 127.41, 127.61, 128.79, 128.84, 129.60, 129.86, 132.07, 132.42 (Ph), 157.85 (C=O), 188.23 (C=S). MS, *m/z* (%): 339 [M⁺] (32), 280 (15), 264 (21), 223 (13), 203 (31), 194 (40), 165 (18), 118 (100). Found (%): C, 63.68; H, 5.00; N, 12.34; S, 9.49. Calc. for C₁₈H₁₇N₃O₂S (%): C, 63.70; H, 5.05; N, 12.38; S, 9.45.

For details, see Online Supplementary Materials.



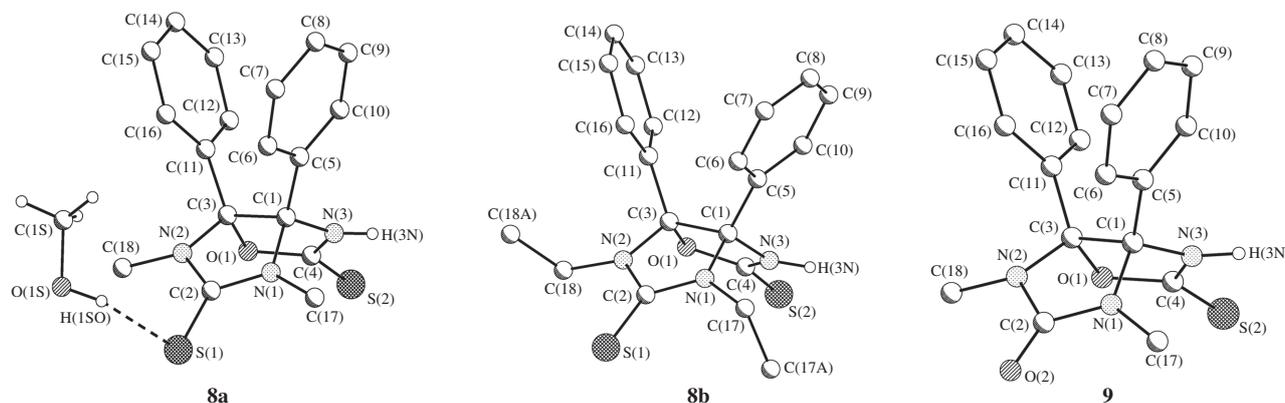
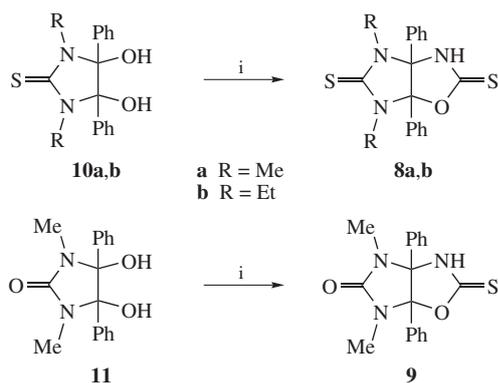


Figure 1 General view of compounds **8a** (with a solvate methanol molecule), **8b** and **9**.

Reactants **10a,b** or **11** and KSCN in the ratios 1:1 or 1:1.25 were refluxed in MeOH in the presence of AcOH for 0.5 to 1 h to furnish the desired products **8a,b** or **9**.[†] The highest yields of 80–86% were achieved when excess of KSCN (1.25 equiv.) was used and reaction duration was 1 h. Acetic acid serves as both a reagent (for activation of DHI and DHI) and a solvent. No bicyclic compound **4** or related compounds were detected in the ¹H NMR spectra of the reaction mixtures after evaporation to dryness. On reproduction the literature⁵ experiment we confirmed that imidazooxazolidithione **8a** was the reaction product rather than compound **4**.



Scheme 1 Reagents and conditions: i, KSCN, AcOH, MeOH, reflux, 1 h.

The structures of the obtained compounds **8, 9** were proved by elemental analysis, a combination of ¹H and ¹³C NMR spectra and X-ray diffraction (Figure 1).[‡] The latter showed that their molecular geometry is rather similar with the bond lengths varying by no more than 0.01 Å. As expected, the largest discrepancy was observed for compound **8b** with ethyl substituents. Indeed, the conformations of the imidazo and oxazole moieties in the two

others were an envelope [with the atom C(3) deviated by 0.29(1) Å in **8a** and 0.35(1) Å in **9**] and a twist [with the atoms C(1) and C(3) deviated by 0.17(1) and –0.16(1) Å in **8a** and by 0.22(1) and –0.18(1) Å in **9**], respectively. In compound **8b**, both these heterocycles were flat within 0.02 Å. The angle between their mean planes varied from 64.4(1)° in **8b** to 68.2(1)–70.0(2)° in **8a** and **9**. At the same time, in all three cases the nitrogen atoms have a flattened environment; the sum of their bond angles were 355.1(1)–360.0(2)°.

At the supramolecular level, compound **8a** becomes more different from **9**, as it crystallizes with a solvate methanol molecule in a 1:1 ratio. Therefore, the main motif in its crystal packing is methanol-assisted chains formed through N–H…O [N(3)…O(1S) 2.790(2) Å, ∠NHO 165(1)°] and O–H…S [O(1S)…S(1) 3.2794(15) Å, ∠OHS 140(1)°] hydrogen bonds, while in **9** these are chains of the target molecules hold by a N–H…O bond [N(3)…O(2) 2.745(2) Å, ∠NHO 168(1)°]. In the case of compound **8b**, the molecules in its crystal form finite aggregates, which are H-bonded centrosymmetric dimers stabilized by two N–H…S bonds [N(3)…S(2) 3.353(3) Å, ∠NHS 169(1)°] and assembled with others into a 3D framework by numerous less directional and weaker contacts. The latter is also true for compounds **8a** and **9**.

Given the reported⁴ mechanism of formation of compound **3** and the result we obtained, one can assume that heterocycles **8a,b** and **9** are formed as follows (Scheme 2). The first step is the formation of carbenium-iminium cation **A**, which reacts with the NCS anion acting as N-nucleophile to give an adduct **B**. A nucleophilic attack by the oxygen lone electron pair on the electrophilic center in the adduct **B** completes the formation of the oxazolone ring.

Thus, upon investigating new reactions of DHI and DHI with KSCN and AcOH, we proposed a method for the synthesis

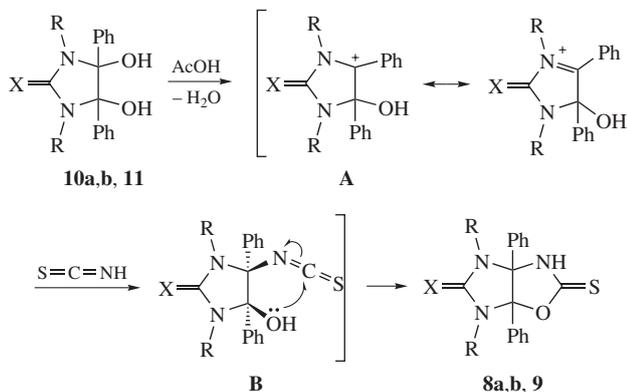
[‡] X-ray diffraction data. Experiments were carried out with a SMART 1000 CCD diffractometer using graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å, ω -scans) at 120 K. The structures were solved by direct method and refined by the full-matrix least-squares against F^2 in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms of NH groups in all cases and of OH group of a solvate methanol molecule in **8a** were found in difference Fourier synthesis; the H(C) atom positions were calculated. All hydrogen atoms were refined in isotropic approximation in riding model. All calculations were performed using the SHELXTL software.¹⁶

For **8a**: crystals of C₁₉H₂₁N₃O₂S₂ ($M = 387.51$) are monoclinic, space group $P2_1/n$, $a = 8.0624(4)$, $b = 15.8738(7)$ and $c = 15.0658(7)$ Å, $\beta = 93.7220(10)^\circ$, $V = 1924.07(16)$ Å³, $d_{\text{calc}} = 1.338$ g cm⁻³, $Z = 4$, $\mu(\text{MoK}\alpha) = 2.95$ cm⁻¹, $F(000) = 816$, $2\theta_{\text{max}} = 58^\circ$. 20975 reflections were measured, from which 5106 were independent, 4047 reflections with $I > 2\sigma(I)$. The refinement converged to $R_1 = 0.0467$, $wR_2 = 0.1228$, GOF = 1.004.

For **8b**: crystals of C₂₀H₂₁N₃OS₂ ($M = 383.52$) are triclinic, space group $P\bar{1}$, $a = 8.934(5)$, $b = 9.096(5)$ and $c = 13.718(9)$ Å, $\alpha = 73.824(11)^\circ$, $\beta = 81.107(13)^\circ$, $\gamma = 65.090(8)^\circ$, $V = 970.1(10)$ Å³, $d_{\text{calc}} = 1.313$ g cm⁻³, $Z = 2$, $\mu(\text{MoK}\alpha) = 2.88$ cm⁻¹, $F(000) = 404$, $2\theta_{\text{max}} = 58^\circ$. 5382 reflections were measured, from which 5382 were independent, 4372 reflections with $I > 2\sigma(I)$. The refinement converged to $R_1 = 0.0353$, $wR_2 = 0.0900$, GOF = 1.004.

For **9**: crystals of C₁₈H₁₇N₃O₂S ($M = 339.41$) are monoclinic, space group $P2_1/n$, $a = 9.6933(7)$, $b = 11.9078(9)$ and $c = 14.7807(11)$ Å, $\beta = 96.327(2)^\circ$, $V = 1695.7(2)$ Å³, $d_{\text{calc}} = 1.329$ g cm⁻³, $Z = 4$, $\mu(\text{MoK}\alpha) = 2.06$ cm⁻¹, $F(000) = 712$, $2\theta_{\text{max}} = 58^\circ$. 18391 reflections were measured, from which 4490 were independent, 2943 reflections with $I > 2\sigma(I)$. The refinement converged to $R_1 = 0.0519$, $wR_2 = 0.1247$, GOF = 0.999.

CCDC 949131–949133 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2014.



Scheme 2

of imidazooxazolidithiones **8a,b** and thioxotetrahydroimidazo-oxazolone **9**.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.02.014.

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