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Systems with annulated thioxo azepinone moiety: an access through heterocyclic carbodithioate ring expansion

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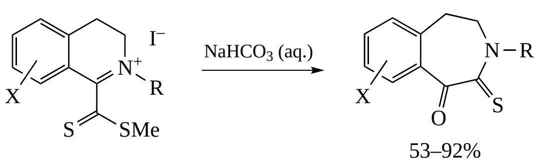
New 1-oxo-2-thioxo-1,2,4,5-tetrahydrobenz[*d*]azepine and 1-oxo-2-thioxo-1,2,4,5-tetrahydroazepino[4,5-*b*]indole derivatives were conveniently obtained by the novel recyclization reaction of (methylthio)carbonothioyl-substituted heterocyclic quaternary salts with expansion of the dihydropyridine ring.



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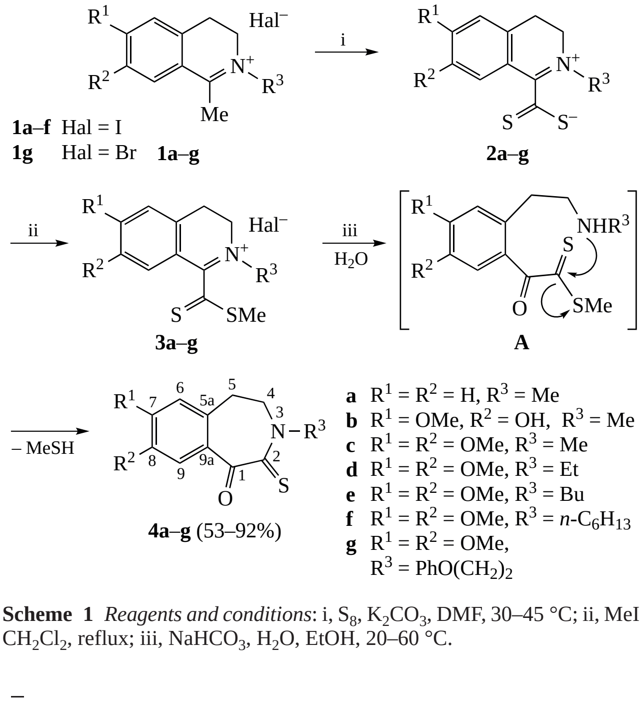
Derivatives of fused and monocyclic azepines with a hydrogenated azepine ring are very attractive objects in the search for new pharmacologically active compounds.[1,2] To date, over 70 drugs created on their basis are in clinical use or undergo testing.[3] Some of them have been approved, for example, Ivabradine as a cardioactive drug with a unique mechanism of action, Ajmaline as an antiarrhythmic agent, Tolazamide as an antidiabetic drug, Besifloxacin as an ophthalmic antibiotic, Bazedoxifene as a selective estrogen receptor modulator, the Galantamine alkaloid used to relieve the symptoms of Alzheimer’s disease, *etc*.

The methods for the molecular design of (hydro)azepine systems are mainly based on cyclization reactions with closure of the azepine ring or expansion of smaller rings.[4,5] In particular, various electrocyclizations,[6] cyclizations through the intramolecular Prins,[7] Heck reactions,[8] intramolecular alkylation[9] and the oxidative coupling of phenols are widely used for this purpose.[10,11] Nevertheless, the development of new convenient ways for constructing an azepine cycle, especially a functionalized one, is still relevant, since it allows one to achieve a greater structural diversification of available azepines, in particular by expanding the options of their conversion with preservation of the azepine system, for example, by annulation of other cyclic systems to it. In this respect, structures with two adjacent functionalized positions in the azepine ring, in particular, with thioxo and oxo groups at these positions, are of particular interest.

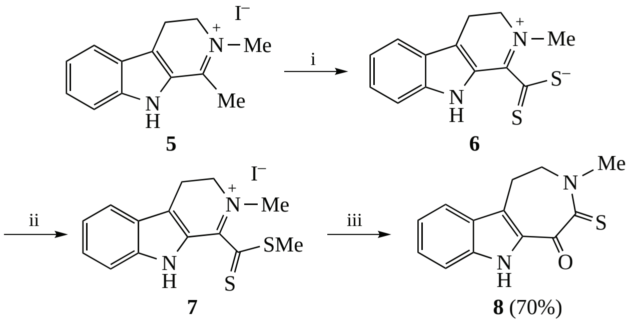
In this work performed as a continuation of our previous studies in the chemistry of azepines,[12] we suggested a new method for constructing two hitherto unknown systems with a fused 1,2,4,5-tetrahydro-1-oxo-2-thioxobenz[*d*]azepine ring, namely, 1-oxo-2-thioxo-1,2,4,5-tetrahydrobenz[*d*]azepine, and 2-oxo-1-thioxo-1,2,4,5-tetrahydroazepino[4,5-*b*]indole. It should be noted that analogous 2,3,5,6-tetrahydro-1,6-methanobenzo[*c*]azocine derivative was previously synthesized by replacement of one of the two adjacent oxo groups in 2,3,5,6-tetrahydro-1,6-methanobenzo[*c*]azocine precursor by a thioxo group.[13] We propose herein the constructing of the azepine ring right in the required bifunctionalized state. The starting compounds are the quaternary salts of 1-methyl-3,4-dihydroisoquinolines **1a–g** (Scheme 1) or harmalan analogue, 1-methyl-3,4-dihydro-β-carboline **5** (Scheme 2).

To convert these salts to the final oxo thioxo derivatives, we performed a three-stage transformation. The first stage involved the dithiocarboxylate functionalization of the C-methyl group by



a $R^1 = R^2 = H$, $R^3 = Me$
b $R^1 = OMe$, $R^2 = OH$, $R^3 = Me$
c $R^1 = R^2 = OMe$, $R^3 = Me$
d $R^1 = R^2 = OMe$, $R^3 = Et$
e $R^1 = R^2 = OMe$, $R^3 = Bu$
f $R^1 = R^2 = OMe$, $R^3 = n\text{-}C_6H_{13}$
g $R^1 = R^2 = OMe$, $R^3 = PhO(CH_2)_2$

Scheme 1 *Reagents and conditions*: i, S_8, K_2CO_3, DMF, 30–45 °C; ii, MeI, CH_2Cl_2, reflux; iii, $NaHCO_3$, H_2O, EtOH, 20–60 °C.



Scheme 2 *Reagents and conditions*: i, S_8, K_2CO_3, DMF, 30–45 °C; ii, MeI, CH_2Cl_2, reflux; iii, $NaHCO_3$, H_2O, EtOH, boiling.

oxidation with elemental sulfur using the method that we previously developed,[14] which is applicable both for quaternary azinium and azolium salts. Further, the dithiocarboxylate betaines **2a–h** obtained in this manner (see Scheme 1) were subjected to esterification to afford products **3a–h** with a group –C(=S)SMe. The final key stage of the synthesis is based on the liability of these functionalized salts to undergo an ANRORC-type recyclization that readily occurs in a weakly basic medium. It involves the expansion of the dihydropyridine ring and its replacement with a bifunctionalized hydrogenated azepine ring. This recyclization occurs most commonly even at nearly-room temperature in an aqueous-alcoholic medium and in the presence of $NaHCO_3$. It allows one to obtain fairly good yields of N-substituted 3-oxo-2-thioxo-1,2,4,5-tetrahydrobenzo[*d*]-azepines **4a–g**, or in the case of carbolinium salt **7**, their 1,2,4,5-tetrahydroazepino[4,5-*d*]indole analogue **8** (see Scheme 2).

In the course of this reaction, salts **3a–g** or **7** undergo a nucleophilic opening of the dihydropyridinium ring at the C=N bond, followed by azepine cyclization of their open forms, methyl esters of N-substituted *o*-(β-methylaminoethyl)phenyl-dithioglyoxalic acids **A** or (for salt **7**) their indole analogue, which occurs *via* the intramolecular thioacylation mechanism. Since some salts (**3** and **7**) are not sufficiently stable, it is more convenient in these cases to perform the synthesis without their isolation by combining the methylation and recyclization stages as part of the overall one-pot process. In this manner, oxo thioxo derivatives **4a**,**c**,**f**,**g** and **8** were synthesized. The advantages of the method reported here include the simplicity of the procedure, high efficiency, no need for expensive reagents or catalysts, and the fact that the resulting hydrogenated azepine ring is doubly functionalized (for details, see Online Supplementary Materials).

The structure of the obtained azepines was confirmed by X-ray single crystal analysis of representative compound **4c** (Figure 1)† and their high-resolution ESI mass and one- and two-dimensional NMR spectra.

The signals in 1D spectra were assigned taking the two-dimensional spectra of compound **4a** into account. According to the HMBC ^{15}N–^{1}H spectrum, the chemical shift of the ^{15}N nucleus in **4a** is 158.1 ppm when referenced to $^{15}NH_3$. Moreover, this nucleus is coupled quite strongly with the methyl group and much more weakly, with two methylene groups. A feature of the ^{1}H NMR spectra of oxo thioxo azepines **4a–g**, **8**, likewise salts **1a–g**, **5** and betaines **2a–g**, **6**, is that the cyclic ethylene bridge in them is represented by two triplets for methylene groups. At the same time, in isolated functionalized salts **3a–g** all the protons of that bridge have different chemical shifts. This fact can be attributed to a noticeable tetrahedral geometry of the C(1) electrophilic atom of the isoquinoline system of these salts due to its attractive interaction with rather a nucleophilic iodide ion, as well as with the adjacent second electrophilic center (C=S group). Moreover, this interaction in betaines **2a–g**, **6** is apparently much weakened by a certain repulsive component due to the negative charge of the dithiocarboxylate group (more detail for spectral information is provided in Online Supplementary Materials).

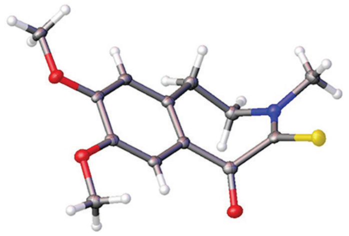


Figure 1 Molecular structure of compound **4c**.

It is worthy of note that the 1-oxo-2-thioxo-1,2,4,5-tetra-hydrobenzo[*d*]azepines **4a–g** have a close structural relationship with the recently discovered plant alkaloid from the bulbs of *Corydalis decumbens* plant (poppy family; used in Chinese traditional medicine) that has the 7,8-methylenedioxy-3-methyl-2,3,4,5-tetrahydrobenz[*d*]azepine-1,2-dione structure.[19]

To conclude, the results of this study open up a simple way to fused 1-oxo-2-thioxo-1,2,4,5-tetrahydroazepines and their azepino[4,5-*b*]indole analogues, which makes them promising for biological investigations as well as for preparation of new analogous functionalized hydrogenated fused azepines.

The preparation of this publication and supporting materials, the study of the recyclization of salts **3**, **7**, the synthesis of thioxo derivatives **4**, **8** and the determination of their structure by NMR were carried out with financial support from the Russian Foundation for Basic Research (grant no. 20-03-00657). The synthesis of salts **1**, **3**, **7** and betaines **2**, **6** was carried out at the North-Caucasian Zonal Research Veterinary Institute (SKZNIVI) with financial support from the Program for Fundamental Scientific Research of the State Academies of Sciences for 2013–2020 (grant no. 0710-2019-0044). The structures of the compounds obtained were confirmed using the equipment of the Center for Molecular Spectroscopy of the Southern Federal University (Rostov-on-Don) and single-crystal X-ray diffraction equipment of the North-Caucasus Federal University (Stavropol).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.07.036.

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† *Crystal data for* **4b**. $C_{13}H_{15}NO_3S$ (M = 265.32 g mol^{-1}): orthorhombic, space group *Pbca* (no. 61), a = 7.7726(2), b = 16.3989(5) and c = 19.1123(7) Å, V = 2436.09(13) Å^3, Z = 8, T = 99.99(13) K, μ(CuKα) = 2.375 mm^{-1}, D_{calc} = 1.447 g cm^{-3}, 16162 reflections measured (9.254° ⩽ 2θ ⩽ 152.026°), 2530 unique (R_{int} = 0.0607, R_σ = 0.0309) which were used in all calculations. The final R_1 was 0.0457 [$I > 2\sigma(I)$] and wR_2 was 0.1153 (all data).

The experimental data were obtained on an Agilent SuperNova diffractometer using a microfocus X-ray source with a copper anode and an Atlas S2 two-dimensional CCD detector at 99.99(13) K. The reflections were collected, unit cell parameters determined and refined using the specialized CrysAlisPro 1.171.38.41 software suite (Rigaku Oxford Diffraction, 2015).[15] The structures were solved using the ShelXT program (Sheldrick, 2015)[16] and refined with the ShelXL program (Sheldrick, 2015).[17] Molecular graphics and presentation of structures for the publication were performed with the Olex2 ver. 1.2.10 software suite.[18]

CCDC 2049405 [crystal from mixed solvents (1 : 1 methanol/*n*-propanol)] contains 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.

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