Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2018, **28**, 320–322

Mendeleev Communications

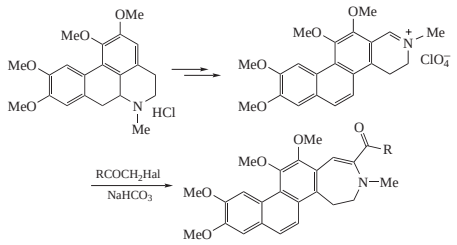
Synthesis of phenanthro[1,2-*d*]azepine derivatives containing a new heterocyclic system from the aporphine alkaloid glaucine

Alexander A. Zubenko,[a] Anatolii S. Morkovnik,*[b] Lyudmila N. Divaeva,[b] Viktor G. Kartsev,[c] Kirill Yu. Suponitsky[d] and Alexander I. Klimenko[e]

[a] *North-Caucasian Zonal Scientific Veterinary Institute, 346493 Novocherkassk, Russian Federation*
[b] *Institute of Physical and Organic Chemistry, Southern Federal University, 344090 Rostov-on-Don, Russian Federation. E-mail: asmork2@ipoc.rsu.ru*
[c] *InterBioScreen Ltd., 142432 Chernogolovka, Moscow Region, Russian Federation*
[d] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*
[e] *Don State Agrarian University, 346493 Novocherkassk, Russian Federation*

DOI: 10.1016/j.mencom.2018.05.031

Derivatives of phenanthro[1,2-*d*]azepine, a previously unknown heterocyclic system, can be easily obtained from aporphine alkaloids by successive pyridine–pyridine and pyridine–azepine recyclizations. The starting glaucine was used as an illustrative example.



About 50 pharmaceutical agents have been created from synthetic and natural azepines. They are either having practical applications or still being tested.[1–8] Examples of recently developed pharmaceuticals include Rucaparib, Omacetaxine, Galanthaminum, Eslicarbazepine, and Ivabradine used for treatment of ovarian cancer, leukemia, Alzheimer disease, epilepsy, and anisorhythmia, respectively. Recently synthesized substances, which are based on the azepine system, can be potential antitumor alkylating agents.[9]

Although the chemistry of azepines contains considerable achievements, which allow preparation of practically needed compounds, some simple fused azepine systems are still remaining understudied or even unknown. Phenanthroazepines are an example of the latter. Their structure combines two cyclic systems widespread in wildlife, *viz*. the phenanthrene and azepine ones, which makes them promising objects for molecular design of bioactive compounds.

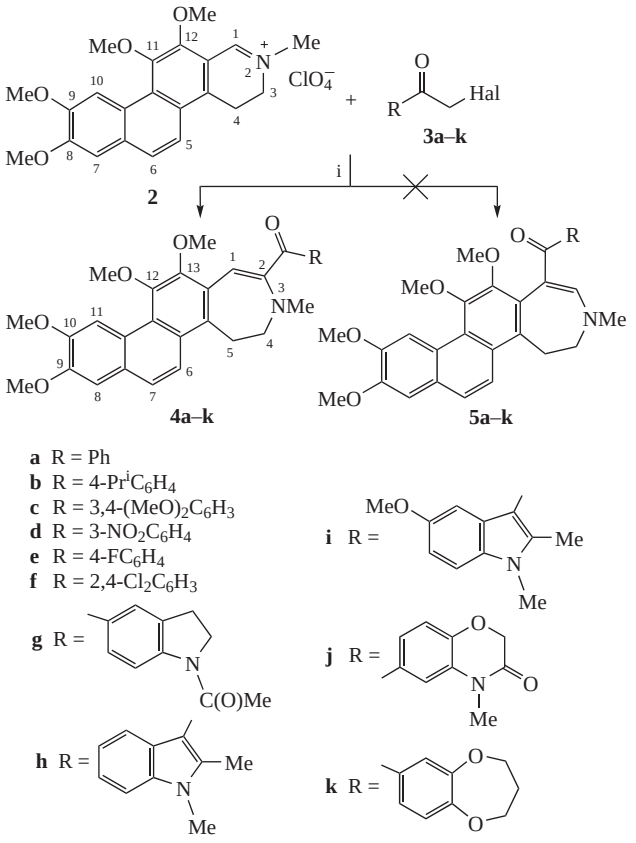
We have demonstrated in the present work that one among possible phenanthroazepine systems, the phenanthro[1,2-*d*]azepine, can be easily built from the tetracyclic aporphine (5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline) system *via* two successive recyclizations. The initial recyclization of the pyridine–pyridine type converts aporphines into quaternary salts of 3,4-dihydronaphtho[2,1-*f*]isoquinolinium, while the second one leads to expanding their heterocyclic ring to give phenanthro[1,2-*d*]-azepine derivatives.

One of the most accessible aporphine alkaloids, glaucine **1**, was selected as a convenient model to demonstrate advantages of the proposed synthetic approach. This compound was also used as a model in our previous work reporting the ability of aporphines to undergo the recyclization into 3,4-dihydronaphtho-[2,1-*f*]isoquinolinium salts.[10] That recyclization followed by the counterion exchange provides effective conversion of glaucine into 8,9,11,12-tetramethoxy-3,4-dihydronaphtho[2,1-*f*]isoquinolinium perchlorate **2**, which is the first known example of 3,4-dihydronaphtho[2,1-*f*]isoquinolinium salts and, at the same time, a highly reactive oxidized form of *O*,*O*-dimethyl substituted litebamine, the phenanthrene alkaloid.[11] Therefore, the proposed goal of this work in the case of glaucine can be achieved by a demonstration of the salt **2** ability to undergo further recyclization with expansion of one heterocyclic ring to the azepine cycle.

In case of structurally related to salt **2** 3,4-dihydroisoquinolinium[12,13] and 3,4-dihydro-β-carbolinium quaternary salts,[14] halomethyl derivatives RCH_2Hal containing electron-withdrawing group R are efficient reagents for such pyridine–azepine recyclizations. Reactions of 3,4-dihydronaphtho[2,1-*f*]isoquinolinium salts with these reagents should give 2-R-3,4-dihydrophenanthro[1,2-*d*]-azepines or, for R = Ac, their 1-R-isomers in case of concurrent 1,2-acyl rearrangement.[14–16] This rearrangement usually requires powerful electron-donating substituents in the acyl group and occurs due to the formation of carbocationic intermediates possessing a tetrahydroazepine structure prone to intra-cation 1,2-migration of the acyl group.

Experiments with various acylmethyl halides **3a**–**k** have revealed that salt **2** is actually capable of undergoing pyridine–azepine recyclization. It reacts with above halides even under mild conditions: upon refluxing an aqueous-ethanol solution of an equimolar mixture of a salt substrate and reagent in the presence of excess sodium hydrogen carbonate. However, perchlorate **2** demonstrates only one type of reactivity (Scheme 1)[†] unlike the two previously studied substrate types,[12,14] which can react in two ways. Independently of the presence of strong electron-donating substituents, salt **2** was in all cases converted only into the non-

[†] The general procedure for synthesizing compounds **4a**–**k** is provided in Online Supplementary Materials.



Scheme 1 *Reagents and conditions*: $RCOCH_2Hal$ (**3a**–**k**), $NaHCO_3$, aqueous ethanol (1:3 v/v), reflux, 3 h.

rearranged products with α-acyldihydroazepine structure, *viz*. 2-acyl-3,4-dihydrophenanthro[1,2-*d*]azepines **4a**–**k**, but not into their β-acyl-substituted isomers **5a**–**k**.

Such a behavior of perchlorate **2** indicates that the carbocationic intermediates formed from it undergo a direct deprotonation leading to non-rearranged products **4** under the reaction conditions rather than isomerization *via* acyl migration, which would give compounds **5**. One of the possible reasons for this phenomenon could be the slowness of the carbocationic isomerization step for salt **2**, which was confirmed by comparison of DFT-calculated (B3LYP/6-31G**) activation energies of the benzoyl group migration in the carbocationic intermediate of salt **2** ($\Delta E^{\neq}$ = 2.5 kcal mol^{-1}) and in a similar intermediate of cotarnine, the dihydroisoquinoline alkaloid ($\Delta E^{\neq}$ = 1.6 kcal mol^{-1}) that has a pronounced susceptibility to the bidirectional recyclization upon treatment with acyl methyl halides (the calculation details and the structures of two transition states for the carbocations are given in Online Suppplementary Materials).

Phenanthroazepines **4a**–**k** were obtained in 66–81% yields as crystalline compounds with colors ranging from pale yellow to red. The structure of the simplest phenanthroazepine **4a** was proven by single-crystal X-ray diffraction analysis (Figure 1).‡

‡ *Crystallographic data for* **1**: $C_{30}H_{29}NO_5$, orthorhombic, space group *Pca*2$_1$: *a* = 27.970(2), *b* =10.7154(6) and *c* = 8.0399(4) Å, *V* = 2409.7(2)Å^3, *Z* = 4, *M* = 483.54, d_{calc} = 1.333 g cm^{-3}, wR_2 = 0.0974 calculated on F^2_{hkl} for all 6346 independent reflections with $2\theta < 58.0°$ [GOF = 1.027, *R* = 0.0389 calculated on F_{hkl} for 5642 reflections with $I > 2\sigma(I)$]. X-ray diffraction study was carried out with a SMART APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, graphite monochromator, ω-scans] at 120 K.

CCDC 1582583 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.

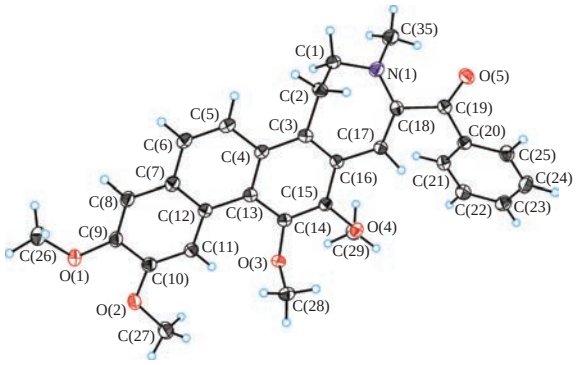


Figure 1 Molecular structure of compound **4a** with atoms represented by thermal ellipsoids (*p* = 50%).

The structural similarity of acyl derivatives **4b**–**k** followed from the analysis of their NMR spectra with account of the data acquired in our previous reports,[12,14] which revealed that α-acyldihydroazepines have almost 1 ppm lower chemical shifts for the lone olefin proton at the azepine ring than those of their β-acyl isomers.

Similar but even more significant differences are also characteristic of the ^{13}C atom bound to the proton indicated above. This was shown by both ^{13}C NMR spectra of various available to us α- and β-acylazepines and the results of SOS-DFPT-IGLO(II)[17] (B3LYP/6-31G**//PW-91–PW-91) quantum-chemical calculations on two model isomeric structures **4e** and **5e**. The calculated chemical shifts for the characteristic CH-moiety were 117.55, 6.93 (**4e**), and 147.02, 7.81 (**5e**) (gas phase conditions). The corresponding experimental values for phenanthroazepine **4e** (δ of 102.91 and 6.22; DMSO-d_6) were considerably smaller than the calculated ones, which was due to the polar solvent effect. Similar chemical shifts for the considered CH-moiety were also observed for other phenanthroazepines **4**. It should be also noted that the signals from the characteristic ^{13}C atom in various acyldihydroazepines can be conveniently identified by their two-dimensional HSQC ^{13}C–^{1}H NMR spectra.

Therefore, the presented results have completely confirmed that the aporphine alkaloids can be used as the good starting material in the synthesis of various phenanthro[1,2-*d*]azepines according to the proposed protocol involving the two successive recyclizations.

This work was supported by the Russian Foundation for Basic Research (grant no. 16-03-00828). The experimental data were acquired using the equipment of the 'Molecular Spectroscopy' User Facilities Center at the Southern Federal University, Rostov-on-Don.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.031.

References

1 J. H. Shah, R. M. Hindupur and H. N. Pati, *Curr. Bioact. Compd.*, 2015, **11**, 170.
2 S. Singh, J. Goo, V. Gajulapati, T.-S. Chang, K. Lee and Y. Choi, *Anticancer Agents Med. Chem.*, 2016, **16**, 539.
3 A. O. Plunkett, *Nat. Prod. Rep.*, 1994, **11**, 581.
4 E. Kaltenegger, B. Brem, K. Mereiter, H. Kalchhauser, H. Kählig, O. Hofer, S. Vajrodaya and H. Greger, *Phytochemistry*, 2003, **63**, 803.
5 *The Total Synthesis of Natural Products*, ed. J. ApSimon, Wiley-Interscience, New York, 1977, vol. 3, p. 243.
6 *Dictionary of Alkaloids*, 2nd edn., eds. J. Buckingham, K. H. Baggaley, A. D. Roberts and L. F. Szabo, CRC Press, Boca Raton, FL, 2010.

7 R. A. Pilli, G. B. Rosso and M. Da Conceiçâo F. De Oliveira, in *The Alkaloids: Chemistry and Physiology*, ed. G. A. Cordell, Elsevier, Amsterdam, 2005, vol. 62, p. 77.
8 https://www.drugbank.ca.
9 O. A. Shemyakina, O. G. Volostnykh, A. V. Stepanov, A. G. Mal'kina, I. A. Ushakov, K. A. Apartsin, V. V. Kireeva and B. A. Trofimov, *Mendeleev Commun*., 2018, **28**, 128.
10 A. A. Zubenko, A. S. Morkovnik, L. N. Divaeva, V. G. Kartsev, L. G. Kuzmina, G. S. Borodkin and A. I. Klimenko, *Mendeleev Commun*., 2018, **28**, 58.
11 (*a*) W. M. Whaley and M. Meadow, *J. Org. Chem*., 1954, **19**, 661; (*b*) E. Martínez, J. C. Estévez, R. J. Estévez and L. Castedo, *Tetrahedron*, 2001, **57**, 1973; (*c*) E. Martínez, J. C. Estévez, R. J. Estévez and L. Castedo, *Tetrahedron*, 2001, **57**, 1981; (*d*) M. C. Pampín, J. C. Estévez, R. J. Estévez, M. Maestro and L. Castedo, *Tetrahedron*, 2003, **59**, 7231.
12 V. G. Kartsev, A. A. Zubenko, A. S. Morkovnik and L. N. Divaeva, *Tetrahedron Lett*., 2015, **56**, 6988.
13 A. A. Zubenko, V. G. Kartsev, A. S. Morkovnik, L. N. Divaeva, D. V. Alexeenko, K. Yu. Suponitsky, G. S. Borodkin and A. I. Klimenko, *Tetrahedron Lett*., 2017, **58**, 1233.
14 A. A. Zubenko, A. S. Morkovnik, L. N. Divaeva, V. G. Kartsev, G. S. Borodkin and A. I. Klimenko, *Mendeleev Commun*., 2018, **28**, 83.
15 A. A. Zubenko, V. G. Kartsev, A. S. Morkovnik, L. N. Divaeva and K. Yu. Suponitsky, *ChemistrySelect*, 2016, **1**, 2560.
16 A. A. Zubenko, L. N. Divaeva, A. S. Morkovnik, V. G. Kartsev, Y. D. Drobin, N. M. Serbinovskaya, L. N. Fetisov, A. N. Bodryakov, M. A. Bodryakova and L. A. Lyashenko, *Russ. J. Bioorg. Chem*., 2017, **43**, 311 (*Bioorg. Khim*., 2017, **43**, 311).
17 (*a*) A. A. Granovsky, *Firefly version 7.1.G*, http://classic.chem.msu.su/gran/firefly/index.html; (*b*) M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, Jr., *J. Comput. Chem*., 1993, **14**, 1347; (*c*) V. G. Malkin, O. L. Malkina, M. E. Casida and D. R. Salahub, *J. Am. Chem. Soc*., 1994, **116**, 5898.

Received: 10th November 2017; Com. 17/5401