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Mendeleev Commun., 2018, **28**, 83–85

Mendeleev Communications

Reaction of 2-methyl-3,4-dihydro-β-carbolin-2-ium iodide with acylmethyl halides controlled by electronic effects: a new route to 1,2-dihydroazepino[4,5-*b*]indoles

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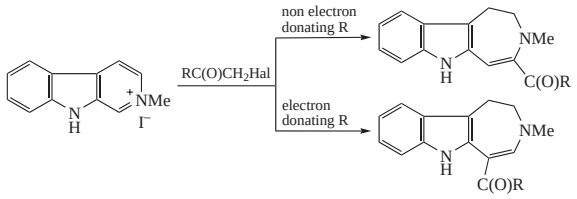
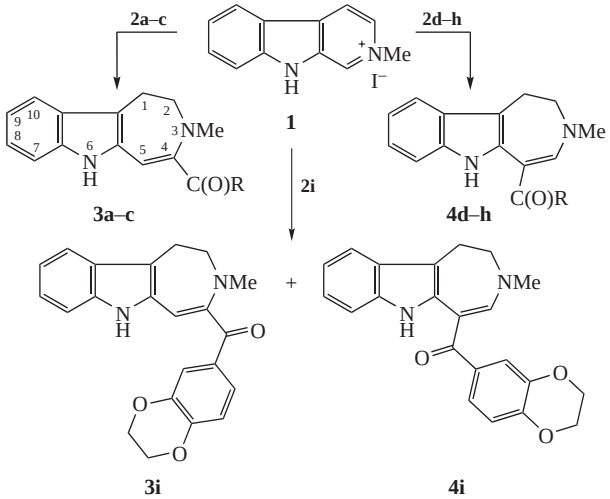
DOI: 10.1016/j.mencom.2018.01.028

2-Methyl-3,4-dihydro-β-carbolin-2-ium iodide in the reaction with aryl halomethyl ketones is converted into 4- or/and 5-acyl-1,2-dihydroazepino[4,5-*b*]indoles depending on the electron donating effect of substituents in the aryl moiety of the halomethyl ketone.



Azepino[4,5-*b*]indoles whose structure contains a privileged indole scaffold are of considerable interest in the search for new biologically active compounds. Annulated azepino[4,5-*b*]indole moiety is encountered in some alkaloids[1–3] and synthetic compounds, *e.g.*, paullones.[4,5] The latter are selective kinase inhibitors that are promising as anti-tumor agents.[6–8] Non-annelated azepino-[4,5-*b*]indoles have been reported in only one publication.[9] More information is available about their derivatives with a hydrogenated azepine ring,[10–15] some of which were found to be modulators of nuclear[16–18] and serotonin receptors.[19,20] These compounds are synthesized by the Fischer reaction[12] and by cyclocondensation of 2-methyl-3-formylindole with ethyl azidoacetate[21,22] or tryptamine derivatives with reagents such as ethyl bromopiruvate, 1-chlorobutane-2,3-dione,[11,17] or *tert*-butyl propargyl carbonate.[15] The miscellaneous reactions are as follows: intramolecular Friedel–Crafts reaction,[19,23] cyclization of *N*-propargyltryptamines in the presence of $AuCl_3$,[10] and rearrangement of 1,2-dihydrospiro-[indolo-3,3′-pyrrolidine] derivatives.[24]



a R = Ph
b R = 4-BrC_6H_4
c R = 4-$O_2NC_6H_4$
d R = 4-$MeOC_6H_4$
e R = 3,4-$(MeO)_2C_6H_3$
f R = indol-3-yl
g R = 1,2-dimethylindol-3-yl
h R = 1,2-dimethyl-5-methoxyindol-3-yl
i R = 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl

Scheme 1 *Reagents and conditions*: $RC(O)CH_2Hal$ **2a–i**, $NaHCO_3$, EtOH, H_2O, reflux.

In this study, we have shown for *N*-methyl-3,4-dihydro-β-carbolinium iodide **1** as an example that quaternary salts of 3,4-dihydro-β-carbolines can serve as convenient starting compounds for synthesizing two types of 1,2-dihydroazepino[4,5-*b*]-indoles, namely, their 4- and 5-acyl derivatives. According to the SciFinder database, the few reported structures of this kind include 5-acetyl-1,1-dimethyl-1,2-dihydroazepino[4,5-*b*]indole obtained from a tryptamine derivative, as well as two N-substituted derivatives of the former.[22]

The synthetic approach that we suggest relies on a base-catalyzed one-pot reaction of a 3,4-dihydro-β-carbolinium salt induced by an acylmethyl halide and involving expansion of a dihydropyridine ring to a dihydroazepine one. To demonstrate the potential of the pyridine–azepine recyclization in question, we used not only salt **1** but also a series of acylmethyl halides with general formula $RC(O)CH_2Cl(Br)$ **2a–i** (Scheme 1). Recyclization readily occurs upon refluxing a water-ethanolic solution of equimolar amounts of salt **1** and halo ketone **2** containing excess $NaHCO_3$.[†] Apart from the synthetic valuability of the reaction, it is also of theoretical interest since it belongs to rather a rare type of processes whose mechanism and direction are efficiently

[†] *(1,2-Dihydroazepino[4,5-*b*]indolyl)arylmethanones* **3a–c**,**i**, **4d–i** (*general synthetic procedure*). A mixture of 2-methyl-3,4-dihydro-β-carbolin-2-ium iodide **1** (1.25 g, 14 mmol), α-halo ketone **2** (4 mmol) and $NaHCO_3$ (1.2 g, 14 mmol) in a mixture of EtOH (15 ml) and H_2O (5 ml) was refluxed for 1–3 h with stirring (TLC monitoring). After the reaction was complete, the mixture was treated with water (30 ml). The resulting precipitate of an acyl derivative was filtered off, washed with water (3×20 ml), dried and recrystallized (see Online Supplementary Materials).

controlled by the electronic effect of substituents. In the system in question, this allows one to perform selective syntheses of two types of acyl derivatives of 1,2-dihydroazepino[4,5-*b*]indole from the same quarternary salt.

If the substituent R in the acyl group of the reactant does not possess evident electron donating properties (halo ketones **2a–c**), salt **1** is converted to 4-acyl-1,2-dihydroazepino[4,5-*b*]indoles **3a–c** (68–80%) due to a RE–recyclization (RE is ring expansion). In halo ketones **2d–i**, the substituent is electron donating, which can cause 1,2-acylic skeletal rearrangement and switching the reaction to the (RE + AR)-recyclization mode (AR is acyl rearrangement) leading to 5-acyl-1,2-dihydroazepino[4,5-*b*]indoles **4** in 57–70% yields (see Scheme 1). Halo ketone **2i** bearing obviously electron donating substituent R gives rise to both 5- (**4i**) and 4-acyl (**3i**) derivatives in ~4 : 1 ratio (^{1}H NMR). In comparison with 5-acyl isomers **4**, 4-acyl derivatives **3** are characterized by considerably lower deshielding of the spin-uncoupled olefin protons. These values can be diagnostic as they vary within δ 7.2–7.4 (DMSO-d_6, series **4**) and 6.2–6.4 ppm (series **3**).

The structure of isomeric acylazepinoindoles was determined by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry (see Online Supplementary Materials), and also by single crystal X-ray diffraction analysis in the case of compounds **3a** and **4g** that represent both series of ketones (Figure 1).‡

Note that salt **1** is already the second azinium substrate after the dihydroisoquinolinium alkaloid cotarnine[25] whose ability to undergo pyridine–azepine recyclization induced by acylmethyl halides was demonstrated. Transition to reagents with an electron donating substituent switches the reaction from the (RE) mode to the (RE + AR) mode also in the case of cotarnine.

Assuming that both substrates react with acylmethyl halides **2** in the same way, we can describe the reaction involving salt **1** by Scheme 2 similar to the scheme suggested previously for cotarnine and justified by quantum-chemical methods.[25] The process starts with hydroxylation of a quarternary salt to give pseudo-base **5** that is further converted to open-chain tautomer **6**. The latter is alkylated at the secondary amino group with halo ketone **2**. The resulting *N*-acylmethyl derivative **7** then undergoes

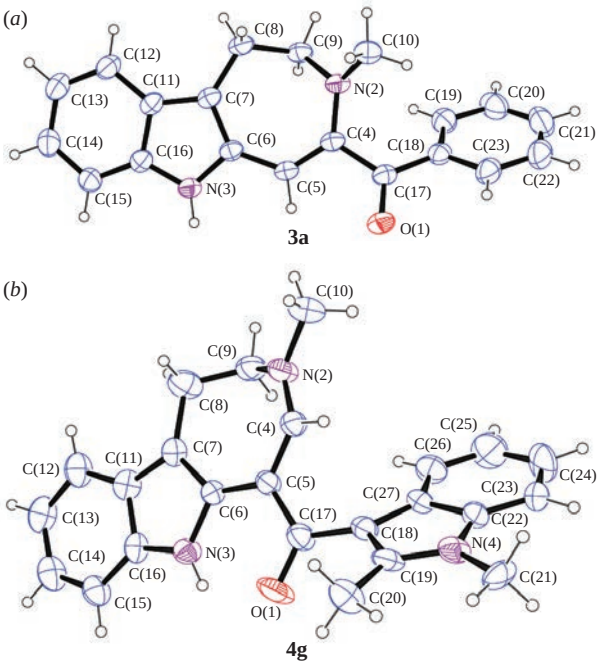
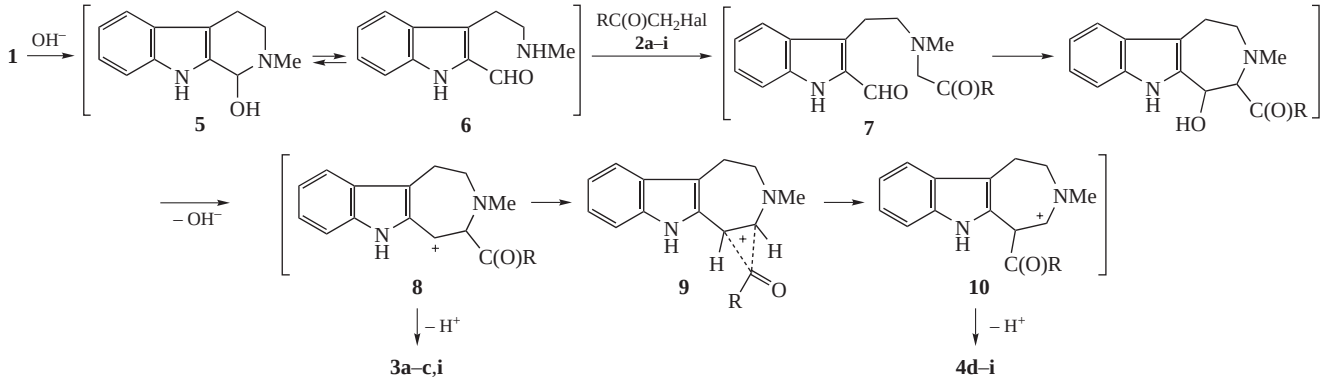


Figure 1 Molecular structure of compounds (*a*) **3a** and (*b*) **4g** according to single crystal X-ray data (ellipsoids at 30% probability).

a base-catalyzed intramolecular aldol reaction with closure of the tetrahydroazepine ring. The acyl-containing azepine type carbocation **8**, which has dual reactivity and corresponds to a bifurcational point on the reaction coordinate, plays a key role at subsequent stages. If the substituent R of acyl group does not contain electron donating groups, carbocation **8** is deprotonated to 4-acyl derivative **3**. Otherwise, acyl intra-cation 1,2-migration *via* the transition state **9** becomes a faster process. Isomeric carbocation **10** is the primary rearrangement product that is further deprotonated to an (RE + AR)-recyclization product, *viz.*, 5-acylazepinoindole **4**. Note that the transition state for cotarnine similar to **9** was localized by quantum-chemical methods[25] and



Scheme 2

‡ *Crystallographic data for* **3a**: crystals of $C_{20}H_{18}N_2O$ (M = 302.36) are monoclinic, space group $P2_1/n$, at 293 K: a = 15.720(2), b = 6.688(1) and c = 15.911(1) Å, β = 104.83(1)°, V = 1617.1(3) Å^3, Z = 15, d_{calc} = = 1.242 g cm^{-3}, μ(MoKα) = 0.08 mm^{-1}, F(000) = 640. Total of 3266 reflections were measured and 2425 independent reflections (R_{int} = 0.036) were used in a further refinement. The refinement converged to wR_2 = = 0.1568 and GOF = 1.07 for all independent reflections [R_1 = 0.0614 was calculated against F for 1990 observed reflections with $I > 2\sigma(I)$].

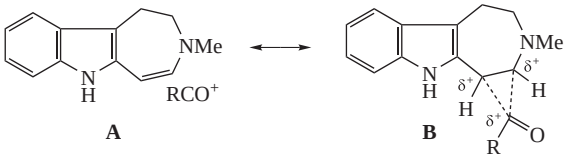
Crystallographic data for **4g**: crystals of $C_{24}H_{23}N_3O$ (M = 369.46) are monoclinic, space group $P2_1/n$, at 293 K: a = 7.1880(14), b = 9.1980(18) and c = 29.760(6)Å, β = 92.93(3)°, V = 1965.0(7) Å^3, Z = 4, d_{calc} = = 1.198 g cm^{-3}, μ(MoKα) = 0.08 mm^{-1}, F(000) = 748. Total of 5046 reflections were measured and 3852 independent reflections (R_{int} = 0.047) were used in a further refinement. The refinement converged to wR_2 = = 0.2495 and GOF = 0.945 for all independent reflections [R_1 = 0.0875 was calculated against F for 1243 observed reflections with $I > 2\sigma(I)$].

The measurements were made on a KM-4 (KumA Diffraction) diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXL97[26] using a full-matrix least-squares procedure based on F^2. The hydrogen atom positions were fixed geometrically at calculated distances and using the riding model.

CCDC 1535545 and 1535547 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.

proved to be quite a low-energy structure. The promoting effect of an electron donating substituent R on acyl migration is due to an electron density shift from the acyl group to the tricyclic core that occurs in carbocation **8**. This results in a decrease in the energy of transition state **9**, since the formation of structures of this kind requires exactly such an electron density redistribution.[25]

In comparison with cotarnine, salt **1** is more inclined to (RE + AR)-reactions. This follows from the fact that it reacts with *p*-methoxyphenacyl bromide **2d** to afford only an 'anomalous' (RE + AR)-product **4d**, whereas cotarnine in a similar reaction under the same conditions gives mainly an RE-product.[25] This difference is apparently due to a higher π-donor ability of the hydrogenated azepino-indole system **A** that is the basis of the structure of carbocation **8** in comparison with the hydrogenated 3-benzazepine structure that is formed in the case of cotarnine. This should favor a lower energy of the transition state **9** due to more efficient stabilization of the resonance structure **B** with a partial positive charge on the azepine ring.



Let us note the synthetic elegance of (RE + AR)-recyclizations that provide a tool for rather a dramatic one-pot conversion of quarternary azinium salts involving both the rearrangement of cyclic system with hetero-ring expansion and a rearrangement of the carbon skeleton. Meantime, the use of this reaction is still hindered by the fact that it has been studied insufficiently. Therefore, the results of our study are an important contribution to filling this gap.

The general conclusion that follows from the data considered above in the context of the chemistry of azepino[4,5-*b*]indoles is that quaternary 3,4-dihydro-β-carbolin-2-ium salts should be promising starting compounds for the synthesis of 1,2-dihydro-azepino[4,5-*b*]indoles containing an active acyl group at 4- and 5-positions.

This work was supported by the Russian Foundation for Basic Research (grant no. 16-03-00828). The authors acknowledge the Center for Collective Use 'Molecular Spectroscopy' of Southern Federal University for measuring NMR spectra and InterBioScreen Ltd. for provision of the starting reagents.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.028.

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Received: 13th March 2017; Com. 17/5199