SHORT PAPER

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Synthesis of 1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one derivatives and their rearrangement to 2,3,5,6-tetrahydropyrrolo-[2,1-*a*]isoquinoline-3-carboxamides†

Rimgaile Degutyte[a], Algirdas Sackus[a]* and Ulf Berg[b]

[a]*Department of Organic Chemistry, Kaunas University of Technology, Kaunas LT-3028, Lithuania*

[b]*Organic Chemistry 1, Department of Chemistry, Lund University, PO Box 124, S-221 00 Lund, Sweden*

Condensation of 10b-methyl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one with aromatic aldehydes affords 10b-(2-arylethenyl)-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one derivatives, which on heating in ethanol easily transform to 2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-3-carboxamides.

Keywords: fused isoquinolines, fused imidazoles, fused pyrroles, rearrangements

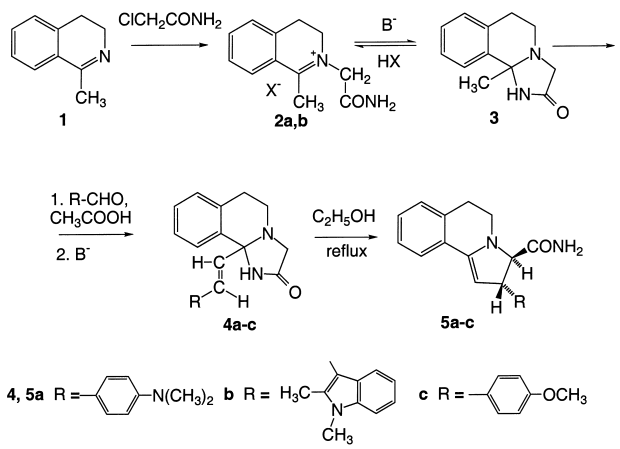
The 1,2,3,4-tetrahydroisoquinoline nucleus is present in a wide variety of biologically active compounds. In order to obtain pharmacologically relevant substances the development of new efficient methods for the synthesis of isoquinoline derivatives having fused to the a edge various saturated and aromatic heterocycles, including *inter alia* pyrrole[1] and pyrrolidine[2], pyridine[3], pyrazolidine[4], thiazolidine[5], piperazine[6], tetrahydroisoquinoline[7] and 1,2,4-triazole[8] rings, is of considerable current interest. It has been shown that imidazo- and pyrrolo[2,1-*a*]isoquinoline derivatives exhibit antidepressant activity[9]. The pyrrolo[2,1-*a*]isoquinoline ring system is present in the structures of the naturally occurring erythrinan and lamellarin alkaloids.[10]

Earlier the annelation of the imidazolidine ring to the isoquinoline nucleus by reaction of 3,4-dihydroisoquinoline or its 6,7-dimethoxy derivative with chloroacetamide has been reported.[11] 8,9-Dimethoxy-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinoline-2(3*H*)-one, synthesised in this manner, has been used in the preparation of the antidepressant 2,5-benzodiazonin-3-one.[12]

Here we report the synthesis of new 1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one derivatives and their unexpected rearrangement to 2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolines.

The synthesis of the starting 2-carbamoylmethyl-3,4-dihydroisoquinolinium chloride **(2a)** was carried out by the reaction of **1** with chloroacetamide. By treatment of an aqueous solution of the chloride **2a** with potassium hydroxide, addition of the amide nitrogen to C-1 of the isoquinoline ring takes place and 10b-methyl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one **(3)** is formed (Scheme 1).

The structure of the product **3** was proven by spectral data. An absorption band at 1700 cm^{-1}, which is due to a carbonyl group, and a band at 3155 cm^{-1} which corresponds to stretching vibrations of the N–H bond, are observed in the IR spectrum of **3**. Characteristic signals at ^{1}H NMR spectrum of **3** are a singlet of the methyl group at 1.66 and an AB-system ($|^2J|$ = 14.2 Hz) of diastereotopic geminal protons of the NCH_2CO moiety at 3.41-3.70 ppm. In the ^{13}C NMR spectrum of compound **3** the signals of the imidazolidine ring carbon atoms are at 53.60 (C-3), 76.43 (C-10b) and 174.22 ppm (C=O).



Scheme 1

When compound **3** was condensed with aromatic aldehydes under acidic conditions with subsequent basic workup, 10b-(2-arylethenyl)-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one derivatives were formed. It can be assumed that the first stage of this reaction is the ring-opening of the imidazolidine ring and condensation of the active 1-methyl group of the 3,4-dihydroisoquinolinium cation (**2**) with the carbonyl group of the aldehyde. Cleavage of the annelated ring by protic acid is confirmed by the fact that treatment of the compound **3** with perchloric acid gives perchlorate 2b (X = ClO_4). Reaction of **3** with 4-dimethylaminobenzaldehyde and 1,2-dimethylindole-3-carboxaldehyde in acetic acid, treatment of the reaction mixture with potassium hydroxide, and crystallisation from acetone afforded compounds 4a,b, correspondingly. As in the case of compound 3, ^{1}H NMR spectrum of 4a contains an AB quartet (geminal $|^2J|$ = 14.5 Hz) in the region of 3.22–3.75 ppm. The ethene protons give a corresponding AB quartet in the region of 5.93–6.42 ppm with vicinal ^3J = 16.0 Hz, which verifies their *trans* orientation.

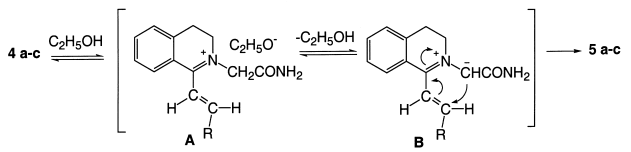
When compounds **4a,b** were crystallised from ethanol a new product was formed. It was found that in boiling ethanol 10b-(2-arylethenyl)-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones (**4a,b**) rearrange in 30 min to 2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-3-carboxamides (**5a,b**). Compound **5c** was synthesised in a similar way.

The structures of **5a–c** were established from the spectral evidence. The ^{1}H NMR spectrum of **5b** showed a

* To receive any correspondence. Fax +370 7451 432

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

characteristic ABX pattern of the three pyrroline ring protons consisting of a doublet at 3.90 (J = 11.2 Hz, 3-H), a doublet of doublets at 4.55 (J = 11.2 and 2.4 Hz, 2-H) and a doublet at 5.50 ppm (J = 2.4 Hz, 1-H). ^{13}C NMR spectrum of **5b** shows signals of the pyrroline ring carbon atoms at 45.83 (C-2), 75.86 (C-3), 101.62 (C-1) and the signal of C-10b at 133 ppm. The relative 2,3-*trans* stereochemistry of **5a–c** was based upon the vicinal coupling constants in the pyrroline ring. For example, the dihedral angles in the five membered ring obtained from MM3 optimised structure of *trans* **5c** are 77° for H–$C_{(1)}$–$C_{(2)}$–H and 150° for H–$C_{(2)}$–$C_{(3)}$–H. In this case, the Karplus equation in the version of Bothner-By[13] gives coupling constants $^3J_{1,2}$ = 2.8 and $^3J_{2,3}$ = 10.3 Hz, respectively, which are in a good agreement with the experimental data ($^3J_{1,2}$ = 2.4, $^3J_{2,3}$ = 11.1 Hz).



Scheme 2

The recyclisation of **4a–c** to **5a–c** can be rationalised as follows (Scheme 2). The imidazo[2,1-a]isoquinolin-2-ones **4a–c** in ethanol exist in equilibrium with the open-chain form **A**. Removal of an acidic proton from the methylene group located between the positively charged nitrogen atom and the electron-attracting carbonyl group affords the azomethine ylid **B**. Finally, the ylid attacks the partially positive carbon atom to give heterocyclic enamines **5a–c**.

Experimental

All melting points were determined in an open capillary and are uncorrected. The IR spectra were measured with a Perkin Elmer 325 spectrometer (KBr pellets). ^{1}H NMR spectra were run on Varian XL-200 (200 MHz) and Bruker WH-360 (360 MHz) spectrometers; ^{13}C NMR spectra were registered on a Bruker WH-360 (90.5 MHz) spectrometer. Chemical shifts, in ppm, were measured relative to tetramethylsilane (TMS).

2-Carbamoylmethyl-1-methyl-3,4-dihydroisoquinolinium chloride (**2a**): A mixture of 1-methyl-3,4-dihydroisoquinoline (29.04 g, 0.2 mol) and α-chloroacetamide (22.44 g, 0.24 mol) in acetonitrile (45 ml) was heated to reflux for 6h. The reaction mixture was cooled, crystalline material filtered off, washed with acetonitrile and dried to give 34.0 g (71%) of the title compound, m.p. 204–205°C (isopropyl alcohol). IR (KBr): 3260 (N–H), 3135 (N–H), 1685 cm^{-1} (C=O). ^{1}H NMR spectrum (CF_3COOH): 2.56 (3H, s, 1-CH_3); 3.26 (2H, t, J 7.0 Hz, CH_2); 3.77 (2H, t, J 7.0 Hz, CH_2); 4.77 (2H, s, CH_2CO); 6.61–7.74 ppm (6H, m, ArH, NH_2). Calcd. for $C_{12}H_{15}ClN_2O$: C, 60.38; H, 6.33; Cl, 14.85 %. Found: C, 60.18; H, 6.54; Cl, 14.90 %.

10b-Methyl-1,5,6,10b-tetrahydroimidazo[2,1-a]isoquinolin-2(3H)-one (**3**): To a solution of chloride **2a** (23.87 g, 0.1 mol) in ice-cooled water (150 ml) was added saturated sodium carbonate solution until pH 9 was attained. The product was extracted with chloroform (4 × 100 ml) and the extract dried with magnesium sulfate. The solvent was evaporated and the residue crystallised from ethanol to yield 16.81 g (83%) of **3**, m.p. 149–150°C. ^{1}H NMR ($CDCl_3$): 1.66 (3H, s, CH_3); 2.59–3.25 (4H, m, CH_2CH_2); 3.41–3.70 (2H, AB-system, ($|J_{AB}|$ 14.2 Hz, NCH_2CO); 7.06–7.30 (4H, m, ArH); 8.95 ppm (1H, broad s, NH). ^{13}C NMR ($CDCl_3$): 24.21 (CH_3); 30.25 (C-6); 44.30 (C-5); 53.60 (C-3); 76.43 (C-10b); 126.42; 126.98; 127.20; 128.68 (C-7; C-8; C-9; C-10); 132.89; 138.93 (C-10a, C-6a); 174.22 ppm (C=O). Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85%. Found: C, 71.36; H, 7.01; N, 14.11%.

2-Carbamoylmethyl-1-methyl-3,4-dihydroisoquinolinium perchlorate (**2b**): To a solution of compound **3** (1.01 g, 5 mmol) in ethanol (8 ml) was added dropwise 30% perchloric acid until pH 2. After keeping at 5°C for 5 h the crystalline product was filtered off and recrystallised from ethanol to yield 1.00 g (66%) of perchlorate, m.p. 219–220 °C (dec.). IR (KBr): 3420 (N–H), 3300 (N–H), 1690 (C=O), 1095, 650 cm^{-1} (ClO_4^-). Calcd. for $C_{12}H_{15}ClN_2O_5$: C, 47.61; H, 4.99; Cl, 11.71%. Found: C, 47.90; H, 5.02; Cl, 11.80%. The ^{1}H NMR spectrum of perchlorate **2b** in CF_3COOH is identical to the spectrum of chloride **2a** in the same solvent.

10b-[2-(4-Dimethylaminophenyl)ethenyl]-1,5,6,10b-tetrahydroimidazo[2,1-a]isoquinolin-2(3H)-one (**4a**): A solution of **3** (2.02 g, 10 mmol) and 4-dimethylaminobenzaldehyde (1.64 g, 11 mmol) in a mixture of glacial acetic acid (10 ml) and acetic anhydride (1 ml) was heated at 100°C for 4h. The reaction mixture was poured into water (60 ml) and basified to pH 9-10 with 10% potassium hydroxide. The crystalline solid separated was filtered off and crystallised from acetone to give 0.94 g (29%) of **4a** with mp 147–148°C. IR (KBr): 3160 (N-H), 1700 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$) : 2.73–3.29 (4H, m, CH_2CH_2); 2.93 (6H, s, 2 × N-CH_3); 3.22–3.75 (2H, AB-system, J_{AB} 14.5 Hz, CH_2CO); 5.93–6.42 (2H, AB-system, J_{AB} 16.0 Hz, CH=CH); 6.50–7.30 (8H, m, ArH); 7.83 ppm (1H, broad s, NH). Calcd. for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60%. Found: C, 75.81; H, 6.77; N, 12.72 %.

10b-[2-(1,2-Dimethylindol-3-yl)ethenyl]-1,5,6,10b-tetrahydroimidazo[2,1-a]isoquinolin-2(3H)-one (**4b**): The reaction of **3** (2.02 g, 10 mmol) and 1,2-dimethylindole-3-carboxaldehyde (1.90 g, 11 mmol) was carried out according to the procedure described for the compound **4a** and yielded 2.57 g (72%) of the title compound, mp 170–171°C (acetone). IR (KBr): 3145 (N–H), 1700 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 2.31 (3H, s, CH_3); 2.67–3.29 (4H, m, CH_2CH_2); 3.33; 3.71 (2H, AB system, ($|^2J_{AB}|$ 14.5 Hz, CH_2CO); 3.58 (3H, s, CH_3); 6.24; 6.64 (2H, AB system, J_{AB} 16.0 Hz, CH=CH); 7.22–7.35 (8H, m, ArH); 7.75 ppm (1H, broad s, NH). Calcd. for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49 %. Found: C, 77.35; H, 6.68 %.

(2R,3S*)-2-(4-Dimethylaminophenyl)-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline-3-carboxamide* (**5a**) Compound **4a** (1.0 g, 3 mmol) was refluxed for 30 min in ethanol (10 ml). After reducing the solvent in volume to 2–3 ml, the residue was kept at 3 °C for 2 h. The separated crystalline solid was filtered off and dried to yield 0.68 g (68%) of the title compound with m.p. 181–182°C. IR (KBr): 3350 (N–H), 3180 (N–H), 1655 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 2.61–3.33 (4H, m, CH_2CH_2); 2.88 (6H, s, 2 × N-CH_3); 3.54 (1H, d, J 11.2 Hz, 3-H); 4.12 (1H, dd, J 11.2, 2.4 Hz, 2-H); 5.30 (1H, d, J 2.4 Hz; H-1); 6.10 (1H, broad s, NH); 6.61–7.30 ppm (9H, m, ArH, NH). Calcd. for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60 %. Found: C, 75.43; H, 7.01; N, 12.70 %.

(2R, 3S*)-2-(1,2-Dimethylindol-3-yl)-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline-3-carboxamide* (**5b**) was obtained similarly to **5a** from **4b** (1.07 g , 3 mmol) in 0.59 g (55%) yield with mp 201–202°C (from ethanol). IR (KBr): 3410 (N-H), 3150 (N-H); 1680 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$): 2.43 (3H, s, CH_3); 2.82–3.42 (4H, m, CH_2CH_2); 3.68 (3H, s, CH_3); 3.90 (1H, d, J 11.2 Hz, 3-H); 4.55 (1H, dd, J 11.2, 2.4 Hz, 2-H); 5.50 (1H, d, J 2.4 Hz, 1-H); 6.07 (1H, broad s, NH); 6.84 (1H, broad s, NH); 6.95–7.78 ppm (8H, m, ArH). ^{13}C NMR spectrum ($CDCl_3$): 10.38 (CH_3), 29.38 (CH_3), 29.94 (CH_2), 45.83 (C-2), 47.73 (CH_2); 75.86 (C-3), 101.62 (C-1), 108.64 (CH), 110.56 (CH), 118.39 (CH), 119.15 (CH), 120.35 (CH), 124.84 (CH), 126.23 (CH), 126.70 (CH), 127.70 (C), 127.95 (CH), 128.57 (CH), 133.31 (C), 133.83 (C), 136.96 (C), 144.34 (C), 175.93 ppm (C=O). Calcd. for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.75 %. Found: C, 77.49; H, 6.33; N, 11.66 %.

(2R,3S*)-2-(4-Methoxyphenyl)-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline-3-carboxamide* (**5c**): A solution of **3** (1.01 g, 5 mmol) and 4-methoxybenzaldehyde (0.75 g, 5.5 mmol) in a mixture of glacial acetic acid (5 ml) and acetic anhydride (1 ml) was heated at 100°C for 4h. The reaction mixture was poured into ice-cooled water (50 ml) and basified with 10% potassium hydroxide until pH 9–10. The solid that separated was filtered off, dissolved in ethanol (10 ml) and refluxed for 30 min. After reducing the solvent in volume to 2 ml the residue was kept at 3°C for 24 h. The crystalline material separated was filtered off and dried to yield 0.44 g (27%) of the title compound **5c** with m.p. 165–167°C. IR (KBr) : 3400 (N-H), 3180 (N-H); 1660 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$): 2.76–3.40 (4H, m, CH_2CH_2); 3.56 (1H, d, J 11.1 Hz, 3-H), 3.78 (3H, s, OCH_3); 4.19 (1H, dd, J 11.1, 2.4 Hz, 2-H), 5.33 (1H, d, J 2.4 Hz, H-1); 5.92 (1H, broad s, NH); 6.80–7.54 ppm (9H, m, ArH, NH). Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74 %. Found: C, 74.79; H, 6.55; N, 8.62 %.

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