Ozonolysis of *N*-acetyl-2-(cyclopent-2-enyl)aniline

Akhat G. Mustafin,*[a] Denis I. D'yachenko,[b] Tat'yana V. Khakimova,[a] Leonid V. Spirikhin,[a] Gumer Yu. Ishmuratov,[a] Il'dus B. Abdrakhmanov[a] and Genrikh A. Tolstikov[a]

[a] *Institute of Organic Chemistry, Ufa Research Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. Fax: +7 3472 356 066; e-mail: chemorg@anrb.ru*

[b] *Bashkir State Agrarian University, 450001 Ufa, Russian Federation*

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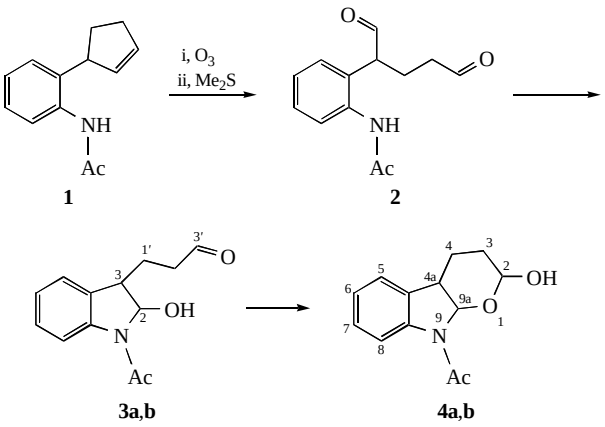
Double cyclization of *N*-acetyl-2-(cyclopent-2-enyl)aniline initiated by ozonolysis resulted in 9-acetyl-2-hydroxy-2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole.

Alkaloids containing oxygen cyclic fragments {alkaloids Daphniphyllum [(+)-codaphniphylline[1], ipecac alkaloids [deacetylisoipecoside[2]], Strychnos indole alkaloids[3–5]} are of considerable interest. The cyclization of *ortho*-alkenylarylamines is an effective method for the synthesis of heterocyclic structures.[6,7] To prepare natural compounds and their analogues[8,9] using alkenylarylamines, we studied the ozonolysis of *N*-acetyl-2-(cyclopent-2-enyl)aniline **1** in methanol at 0 °C. Previously, it was found that the ozonolysis of 2-alkenylanilines or their *N*-trifluoroacetyl derivatives with the subsequent treatment with dimethyl sulfide resulted in indole compounds and derivatives with the aldehyde function.[10,11] Indole derivatives were formed during the ozonolysis of 2-alkenylanilines *via* the interaction between the carbonyl group and the amino group, whereas in case of *N*-trifluoroacetyl derivatives, aldehydes, which undergo cyclization during the removal of the protecting trifluoroacetyl group, were formed.

An interesting fact of the double cyclization of **1** was found: the interaction of the amide group and the carbonyl group derived from the ozonolysis of compound **1** results in 2-hydroxy derivative of indoline **3**, which was cyclised into 9-acetyl-2-hydroxy-2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole **4** in 85% yield (Scheme 1).† Compounds **3a** and **3b** were identified in a mixture with product **4** by the ^{13}C NMR spectra recorded in the J-modulation mode without the known signals of compounds **4a** and **4b**. These equilibrium diastereomers were recrystallised from ethanol. The signals of compounds **3a** and **3b** are of different intensities (1:4); therefore, the signals of a higher intensity were assigned to one diastereomer and those of a lower intensity to the other. The compound with the upfield shifts of signals due to the carbon atoms C(2) and C(3) was identified as a *cis*-isomer.[12]



Scheme 1

The structure of compound **4** was assigned by ^{1}H and ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of **4** showed a doubled number of signals for practically all carbon atoms, the intensity ratio was approximately 1:5. These signals were assigned to two diastereomers **4a** and **4b**. The doubling of some proton signals at C(2), C(9a) and C(4a) was observed in the ^{1}H NMR spectrum.

The *cis*-coupling for the ring junction protons was determined from the values of 5.9 and 5.3 Hz for spin–spin coupling constants (SSCC) between protons at C(9a) and C(4a) for both of the diastereomers. In the ^{1}H NMR spectrum of a diastereomer with a higher intensity of signals (**4a**), the triplet proton signal at the carbon atom coupled with a hydroxyl group was observed. In this case, an anomeric effect is observed, *i.e.*, the hydroxyl group is axial[13] and *syn* positioned to the C(9a)–N bond of the indole ring. For minor diastereomer **4b**, the same proton appeared as a double doublet (*J* 2.3, 9.2 Hz). A higher SSCC value testified the axial–axial interaction between two protons. Thus, the minor diastereomer is shifted conformationally with the prevail of conformers with the equatorial hydroxyl group. In the ^{13}C NMR spectrum, the signals of carbon atoms C(2) and C(9a) for diastereomer **4a** were upfield positioned (91.02 and 83.13 ppm, respectively) in comparison with those of the minor isomer (92.93 and 87.81 ppm, respectively). The signals of C(2) and C(9a) for the major diastereomer were observed to appear

† A solution of *N*-acetyl-2-(cyclopent-2-enyl)aniline **1** (0.5 g, 2.5 mmol) in methanol (15 ml) was ozonised with an equimolar quantity of ozone at 0 °C and stirred until the starting product was disappeared (TLC control). Then, the reaction mixture was treated with dimethyl sulfide (1.6 ml), the solvent was evaporated on a rotary evaporator, the residue was washed with water (3×10 ml), the crystals were filtered off and dried in a vacuum. Recrystallisation from ethanol gave compound **4** in 85% yield (0.49 g); mp 136–137 °C. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM-300 spectrometer at 300 and 75.5 MHz, respectively; solvent $CDCl_3$; TMS as an internal standard.

1-Acetyl-cis-*2-hydroxy-3-(3'-oxopropyl)indoline* **3a**: ^{13}C NMR ($CDCl_3$) δ: 18.32 [t, C(1′)], 23.11 [q, C(9)], 40.16 [d, C(3)], 42.05 [t, C(2′)], 91.57 [d, C(2)], 116.97 [d, C(7)], 123.00 [d, C(5)], 124.09 [d, C(4)], 127.96 [d, C(6)], 128.37 [s, C(3a)], 142.46 [s, C(7a)], 169.92 [s, C(8)], 200.86 [d, C(3′)].

1-Acetyl-trans-*2-hydroxy-3-(3'-oxopropyl)indoline* **3b**: ^{13}C NMR ($CDCl_3$) δ: 20.95 [t, C(1′)], 23.26 [q, C(9)], 40.56 [d, C(3)], 42.1 [t, C(2′)], 93.25 [d, C(2)], 116.96 [d, C(7)], 122.82 [d, C(5)], 124.01 [d, C(4)], 128.05 [d, C(6)], 128.38 [s, C(3a)], 142.64 [s, C(7a)], 170.36 [s, C(8)], 201.02 [d, C(3′)].

9-Acetyl-syn-*2-hydroxy-2,3,4,4a,9,9a-hexahydropyrano[2,3*-b*]indole* **4a**: ^{1}H NMR ($CDCl_3$) δ: 1.52–1.67 [m, 1H, C(3)H_a], 1.75–1.90 [m, 1H, C(3)H_b], 1.80–1.98 [m, 1H, C(4)H_a], 2.31 [s, 3H, C(11)H_3], 2.30–2.48 [m, 1H, C(4)H_b], 3.41 [dd, 1H, C(4a)H, *J* 7.05, 5.9 Hz], 4.99 [br. s, 1H, C(2)OH], 5.20 [t, 1H, C(2)H, *J* 4.8, 4.9 Hz], 5.89 [d, 1H, C(9a)H, *J* 5.9 Hz], 7.05–7.24 [m, 3H, C(5)H, C(6)H, C(7)H], 8.12 [d, 1H, C(8)H, *J* 7.95 Hz]. ^{13}C NMR ($CDCl_3$) δ: 18.09 [t, C(4)], 22.83 [q, C(2′)], 26.70 [t, C(3)], 39.84 [d, C(4a)], 83.13 [d, C(9a)], 91.02 [d, C(2)], 116.56 [d, C(8)], 122.88 [d, C(5)], 123.86 [d, C(6)], 127.51 [d, C(7)], 132.47 [s, C(4b)], 141.91 [s, C(8a)], 170.05 [s, C(10)].

N-Acetyl-anti-*2-hydroxy-2,3,4,4a,9,9a-hexahydropyrano[2,3*-b*]indole* **4b**: ^{1}H NMR ($CDCl_3$) δ: 1.52–1.67 [m, 1H, C(3)H_a], 1.75–1.90 [m, 1H, C(3)H_b], 1.80–1.98 [m, 1H, C(4)H_a], 2.39 [s, 3H, C(11)H_3], 2.30–2.48 [m, 1H, C(4)H_b], 3.18–3.35 [m, 1H, C(4a)H], 4.88 [dd, 1H, C(2)H, *J* 2.3, 9.2 Hz], 5.00 [br. s, 1H, C(2)OH], 5.70 [d, 1H, C(9a)H, *J* 5.3 Hz], 7.05–7.24 [m, 3H, C(5)H, C(6)H, C(7)H], 8.09 [d, 1H, C(8)H, *J* 7.8 Hz]. ^{13}C NMR ($CDCl_3$) δ: 20.60 [t, C(4)], 22.85 [q, C(2′)], 27.61 [t, C(3)], 38.45 [d, C(4a)], 87.81 [d, C(9a)], 92.93 [d, C(2)], 116.56 [d, C(8)], 122.51 [d, C(5)], 123.75 [d, C(6)], 127.51 [d, C(7)], 132.47 [s, C(4b)], 141.91 [s, C(8a)], 170.05 [s, C(10)]. For **4a** and **4b** found (%): C, 67.09; H, 6.25; N, 5.73. Calc. for $C_{13}H_{15}NO_3$ (%): C, 66.95; H, 6.44; N, 6.01.

in the higher field due to the effect of the 1,3-*syn*-interaction between the hydroxyl group and the C(9a)–N bond.[12]

Thus, the indole fragment and the hydroxyl group are positioned *syn* in diastereomer **4a**, and *anti* in diastereomer **4b**.

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