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Synthesis of indole derivatives fused with bicyclo[3.2.1]octane framework

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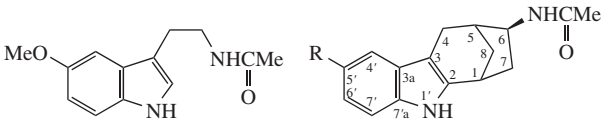
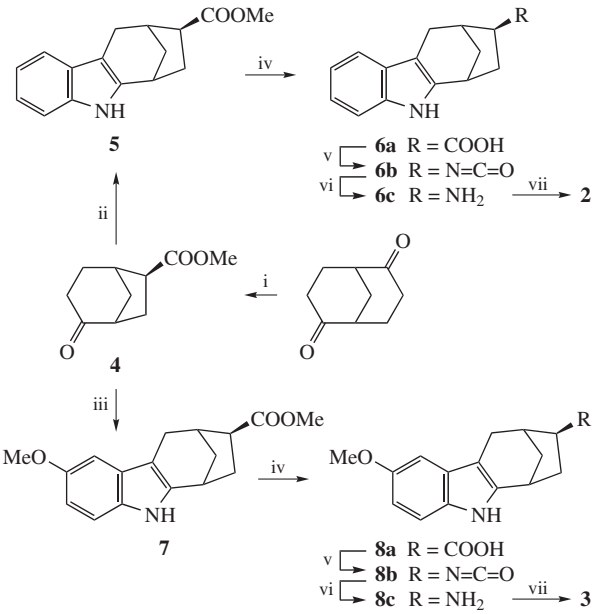
Two six-step syntheses of 6-acetylamino(indolo[2,3-*b*])bicyclo[3.2.1]oct-2-ene **2** and 6-acetylamino(5′-methoxyindolo[2,3-*b*])-bicyclo[3.2.1]oct-2-ene **3** are presented, and the crystal structure of compound **2** is described.

Melatonin (*N*-acetyl-5-methoxytryptamine) **1** is an endogenous hormone possessing chronobiologic activity (circadian rhythms coordination) and also neuroprotective, immune regulatory, antioxidant and oncostatic properties. Conformational restriction of the melatonin molecule is widely used for the design of its physiologically active and receptors subtype selective analogues.[1] Recently, we suggested to use for this purpose an 'inclusion' of structure **1** side chain into the bridgehead core and obtained the melatonin analogue with indole fragment fused with bicyclo[3.3.1]nonane.[2,3] Here, we present the synthesis of the compounds with bicyclo[3.2.1]octane framework, namely, *exo*-6-acetylamino(indolo[2,3-*b*])bicyclo[3.2.1]oct-2-ene **2** and *exo*-6-acetylamino(5′-methoxyindolo[2,3-*b*])bicyclo[3.2.1]oct-2-ene **3**.†



1 **2** R = H, **3** R = OMe

To obtain structures **2** and **3**, we decided to use the Fischer indolization on the bridgehead core, which has not been studied previously for bicyclo[3.2.1]octane framework. This synthetic pathway required 6-substituted bicyclo[3.2.1]octan-2-one as an initial compound. The ring constriction in ready available bicyclo[3.3.1]nonane-2,6-dione by thallium nitrate[4,5] was selected as a convenient method for its synthesis (Scheme 1). This reaction, in accordance with published data,[4,5] led to the formation of *exo*-isomer of methyl 2-oxobicyclo[3.2.1]octane-6-carboxylate **4**.



Scheme 1 *Reagents and conditions*: i, $Tl(NO_3)_3$, MeOH, 10 h, room temperature, 63%; ii, $PhNHNH_2$·HCl, AcOH, 90–100 °C, 30–40 min, 74%; iii, $MeOC_6H_4NHNH_2$·HCl, AcOH, 90–100 °C, 30–40 min, 52%; iv, NaOH, MeOH–H_2O, room temperature, 92% for **6a**, 94% for **8a**; v, ClCOOEt, NEt_3, THF, –10 °C, 30 min, then NaN_3, H_2O, –10 °C, 1 h, then toluene, reflux, 30 min, 63% for **6b**, 67% for **8b**; vi, HCl, H_2O, 60 °C cooling to room temperature, 56% for **6c**, 54% for **8c**; vii, Ac_2O, room temperature, 20 h, 69% for **2**, 70% for **3**.

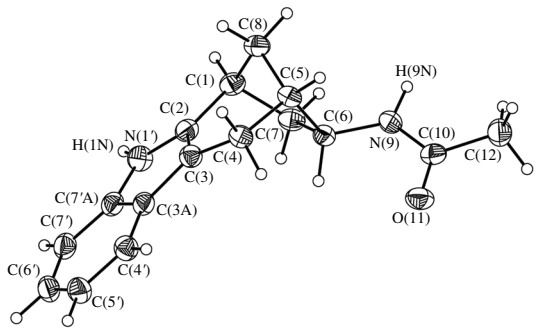


Figure 1 The general view of **2** in representation of atoms by thermal ellipsoids ($p = 50\%$). Selected bond lengths (Å): N(1′)–C(2) 1.375(2), N(1′)–C(7′A) 1.383(2), C(2)–C(3) 1.364(2), C(3)–C(3A) 1.434(2), C(6)–N(9) 1.451(2).

† For procedures and characteristics of compounds, see Online Supplementary Materials.

means of Curtius rearrangement. Amine **6c** was subjected to the acylation with acetic anhydride to give compound **2**.

The structure and stereochemistry of **2** was unambiguously proved by X-ray diffraction analysis.‡ According to these data, the acetamide group in **2** has, as expected *exo*-configuration [*i.e*. located in equatorial position with amine hydrogen atom oriented towards the bridgehead C(8) atom] (Figure 1). The six-membered ring C(8)C(5)C(4)C(3)C(2)C(1) of the bicyclic fragment has Zefirov–Palyulin puckering parameters[6] (calculated by RICON program[7]) $S_2 = 0.947$, $\theta = 33.3°$, $\psi_2 = 14.1°$, $\sigma = 1.7$, which correspond to the ring conformation intermediate between envelope and half-chair. The five-membered ring C(8)C(1)-C(7)C(6)C(5) puckering parameters: $S_2 = 0.671$, $\psi_2 = 13.0°$, $\sigma = 0.2$ indicate that the ring conformation is intermediate between twist and envelope. Bond lengths in the indole cycle are close to the corresponding ones in the previously studied by us 6-oxoindolo[2,3-*b*]bicyclo[3.3.1]non-2-ene oxime.[3]

The molecules in crystal are assembled by means of N–H···O hydrogen bonds [N(9)···O(11) (–x + 1/2, *y* – 1/2, *z*) is 2.839(2) Å, N(9)H(9N)O(11) 169.4°] formed between amide groups into chains directed along the crystallographic axis *b*. Unexpectedly, in addition to these hydrogen bonds the rather unusual N–H···π contacts were observed in the chains. Indeed, the NH group of indole cycle due to the absence of the suitable hydrogen acceptor participates in the formation of shortened contact with C(6′) atom with the H···C separation being 2.40 Å and almost linear NHC angle (177°) (Figure 2).

Finally, the elaborated procedure was used for obtaining compound **3**. The Fischer reaction of **4** with 1-(4-methoxyphenyl)hydrazine hydrocloride in acetic acid gave methoxy-substituted template **7**. The 6-carbomethoxy group transformation in **7** was carried out analogously to the method discussed above through the synthesis of corresponding acid **8a**, isocyanate **8b** and amine **8c**. The acetylation of the latter led to compound **3** in 70% yield.

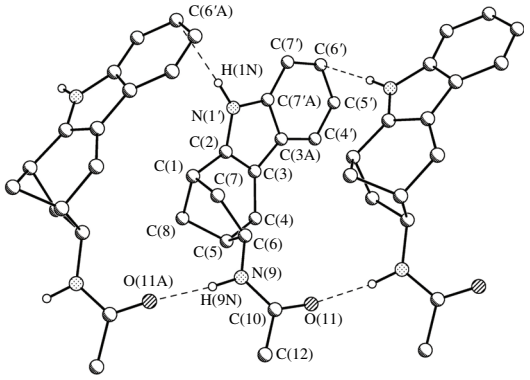


Figure 2 The N–H···O and N–H···π bonded chains in the crystal of **2**.

In summary, a convenient method of synthesis of *exo*-6-acetylamino(indolo[2,3-*b*])bicyclo[3.2.1]oct-2-ene **2** and *exo*-6-acetylamino(5′-methoxyindolo[2,3-*b*])bicyclo[3.2.1]oct-2-ene **3** – putative melatonin conformationally rigid analogue was elaborated.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.01.004.

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‡ *Crystal data for* **2**. Crystals of **2** ($C_{16}H_{18}N_2O$, $M = 254.32$) are orthorhombic, space group *Pbca*, at 120 K, $a = 7.4133(9)$, $b = 9.3988(10)$ and $c = 38.403(5)$ Å, $V = 2675.8(6)$ Å^3, $Z = 8$ ($Z' = 1$), $d_{calc} = 1.263$ g cm^{-3}, μ(MoKα) = 0.80 cm^{-1}. Intensities of 14120 reflections were measured with SMART 1000 CCD [λ(MoKα) = 0.71072 Å, $2\theta < 58°$] and 3535 independent reflections ($R_{int} = 0.0423$) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The positions of the CH and CH_2 hydrogen atoms were calculated from geometrical point of view while NH ones were located from the Fourier density synthesis. The refinement converged to $wR_2 = 0.1428$ and GOF = 1.001 for all independent reflections [$R_1 = 0.0423$ was calculated against F for 2129 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 713077 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.