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Synthetic Approach to Preparation of Indole Derivatives Fused with a Bicyclo[3.3.1]nonane Framework

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Abstract—Synthetic procedures for *N*-(2-methoxy-6,7,8,9,10,11-hexahydro-5*H*-6,10-methanocycloocta[*b*]-indol-9-yl)acetamide were investigated. The desired product was obtained from the mono ethylene ketal of bicyclo[3.3.1]nonane-2,6-dione in a six-stage procedure involving as the key point the formation of an indole fragment on the bicyclo[3.3.1]nonane framework by Fischer reaction.

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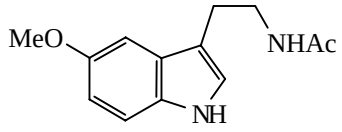
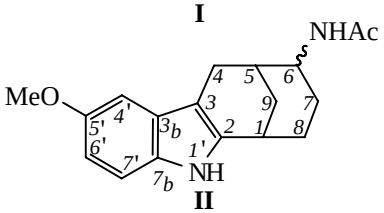
Melatonin [*N*-acetyl-5-methoxytryptamine (**I**)] is an endogeneous hormone endowed with chronobiotic, neuroprotection, immunostimulating, and anticancer activity; it is bonded in the body with three subtypes of protein receptor molecules. Recently intensive research is carried out worldwide directed on the preparation of synthetic substances possessing a high affinity and selectivity with respect to each of the melatonin receptors subtypes. In designing these compound a most common method is hampering of the conformational mobility of the melatonin side chain.

The target of the present study was a development of approaches to the synthesis of a "conformationaly limited" melatonin analog with an indole fragment fused to a bicyclo[3.3.1]-nonane framework: *N*-(2-methoxy-6,7,8,9,10,11-hexahydro-5*H*-6,10-methanocycloocta[*b*]-indol-9-yl)acetamide (**II**).

The published procedures for preparation of similar fused systems involve mainly building up of the polycyclic fragment on the indole structure (see, e.g., [1–4]). However an inverse method was described in [5–7]: indole fragment was built on the bicyclo- and azabicyclo[3.3.1]nonane framework by Fischer reaction; just this approach we chose for the synthesis of compound **II**.



I

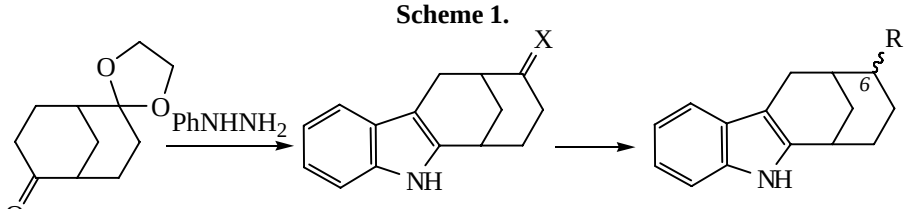


II

We studied first different methods of acetamide substituent formation in the position *6* of the bicyclo-[3.3.1]nonane skeleton fused with an unsubstituted indole (Scheme 1).

Initial ethylene ketal **III** was obtained by procedure [8] using toluene as solvent that resulted in some

Scheme 1.

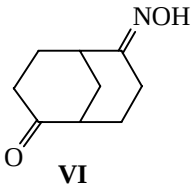


III **IVa–IVc** **Va–Vc**

IV, X = $O(CH_2)_2O$ (**a**), O (**b**), NOH (**c**); **V**, R = NH_2 (**a**), NHAc (**b**), OH (**c**).

improvement of the yield of the desired product. The attempt to carry out Fischer reaction with **III** as in [5] with phenylhydrazine in acetic acid at 80°C gave final product **IVa** with an impurity of the corresponding hydrazone. A more convenient preparation process was the reaction carried out in methanol in the presence of zinc chloride as a catalyst; this method provided indole derivative **IVa** in 53% yield.

We tried two procedures for preparation of amine **Va**: a) a reductive amination of ketone **IVb**, and b) through oxime **IVc** with its subsequent reduction into amine. The reaction of ketone **IVb** with sodium borohydride in water-alcoholic ammonia solution resulted however in a product with an IR spectrum lacking the carbonyl group absorption band and with a broad absorption band at 3200–3400 cm^{-1}. The mass spectrum of the compound contained a peak with M^+ 227 and also a peak 209 [$M - H_2O]^+$, and the ^1H NMR spectrum, a broad singlet at δ 2.02 (OH) and a multiplet at δ 3.84 ppm. (HCOH). The signal of C–OH in the ^{13}C NMR spectrum appeared at δ 73 ppm. These spectral characteristics and the elemental analysis data indicate that in the reaction in question forms alcohol **Vc** previously described in [6].



VI

Next we tested the possibility to synthesize amine **Va** via oxime **IVc**. We also tried to prepare the latter by two alternative ways: by Fischer reaction of bicyclo[3.3.1]nonane-2,6-dione monooxime (**VI**), and from ketone **IVb**.

Compound **VI** was prepared by a standard procedure from ketal **III** and hydroxylamine hydrochloride in a water-alcohol medium in the presence of NaOH leading to the formation of mono ethylene ketal oxime of bicyclo-[3.3.1]nonane-2,6-dione* with the subsequent removal of the protective group. Fischer reaction with monooxime **VI** neither in the presence of acetic acid nor catalyzed by zinc chloride provided the desired oxime **IVc**. In the first case mainly the bicyclo[3.3.1]nonane-2,6-dione phenylhydrazone was obtained (mp 141–142°C [5] and *m*/*z* 332) and also the oxime of bicyclo[3.3.1]nonane-2,6-dione hydrazone [mass spectrum: 257 [M^+], 240 [M – OH]$^+$; IR spectrum: 3330 (NH of hydrazone), 1605 cm^{-1} (C=N)].

Oxime **IVc** was obtained in a quantitative yield from ketone **IVb** in a water-alcohol medium with hydroxylamine hydrochloride preliminary treated with K_2CO_3. The IR spectrum of oxime **IVc** contained a characteristic absorption band at 3400 cm^{-1} (NH of indole) on the background of the OH group absorption (3200–3500 cm^{-1}). In the ^1H NMR spectrum of oxime **IVc** a signal was observed at δ 4.12 ppm corresponding to the NOH proton, and in the ^{13}C NMR spectrum a signal at δ 163.77 ppm corresponded to C=N.

The oxime was reduced to the corresponding amine with lithium aluminum hydride in anhydrous THF. The oily amine **Va** obtained was further acetylated. The structure of compound **Va** was confirmed by mass spectra and by ^1H and ^{13}C NMR spectra.

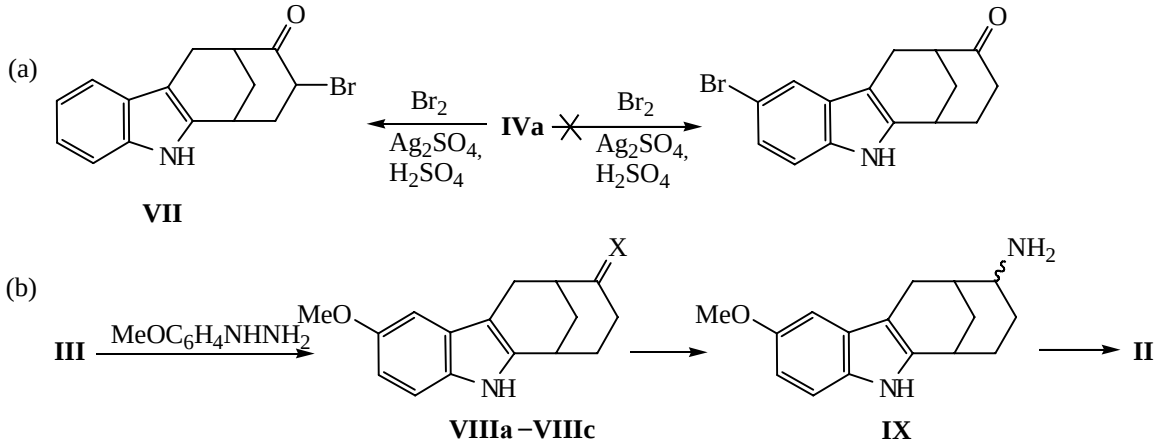
The acetylation of amine **Va** was carried out by treating with acetic anhydride in the presence of pyridine. The IR spectrum of compound **Vb** purified by chromatography contained the absorption band of the NH group from the indole fragment (3400 cm^{-1}) and absorption bands of amide groups C=O (1650) and NH (3330 cm^{-1}). The formation of amide **Vb** was also confirmed by ^1H NMR spectrum where appeared a broad singlet of the amide group NH proton at δ 5.67 ppm and a broad singlet at δ 4.07 ppm of $W_{1/2}$ 28.8 Hz corresponding to the H^6 proton of the *endo*-isomer of compound **Vb** (the assignment is based on [9]). A single isomer of compound **Vb** was yielded by chromatographic purification.

In the next stage we developed the way of indole fragment functionalization aiming at the preparation of the target compound **II**. We attempted to introduce a methoxy group into the position *5'* by the classic method of 5-substituted indoles synthesis via bromination of unsubstituted ethylene ketal **IVa** followed by replacement of the bromine by a methoxy group [10, 11] (Scheme 2, *a*).

After the bromination of compound **IVa** with bromine vapor in sulfuric acid in the presencd of silver sulfate [10, 11] we isolated two main products from the reaction mixture, the first one being oxoindole **IVb**. The second product gave a positive response to Beilstein's test, and its mass spectrum contained ion peaks of *m*/*z* 305 and 303 (30 and 27% respectively) thus corresponding to the empirical formula $C_{15}H_{14}BrNO$, and also peaks of ions formed on elimination of isotopes ^{79}Br and ^{81}Br from M^+ (226, 225, 224 of intensity 35.83 and 75% respectively). According to IR and ^1H NMR spectra the indole fragment did not suffer any changes in the reaction process, and the substitution occurred in the α-position with respect to the carbonyl. Obviously the bromination

* Yield of mono ethylene ketal oxime of bicyclo[3.3.1]nonane-2,6-dione was 67%. IR spectrum, cm^{-1}: 3100–3300 (OH), 1660 (C=N). Found, %: C 62.15; H 7.86; N 6.24. $C_{11}H_{17}NO_3$. Calculated, %: C 62.54; H 8.11; N 6.63.

Scheme 2.



X = $O(CH_2)_2O$ (**a**), O (**b**), NOH (**c**).

did not proceed at the tertiary position in the bridgehead; moreover, in the ^{1}H NMR spectrum a signal was observed of the H–C–Br proton at 4.5 ppm. Besides, in the region 2.7–3.45 ppm signals appeared belonging to protons H^1, H^{4a}, $H^{4\varepsilon}$, and H^5 of the bicyclo[3.3.1]nonane framework (assignment based on [9]) that are close in position to those observed in the spectra of compounds **IVa, IVb** and **Va, Vb**. All the data obtained confirm, that the bromination of ethylene ketal **IVa** occurred not in the aromatic ring but at a methylene group adjacent to a carbonyl (structure **VII**, Scheme 2, *a*).

The methoxy group was more successfully introduced into the indole fragment by Fischer reaction of compound **III** with 1-(4-methoxyphenyl)hydrazine hydrochloride in the presence of $ZnCl_2$. Compound **VIII**a was obtained as a result in 68% yield (Scheme 2, *b*). Its further treatment with 2 N H_2SO_4 at 50–60°C led to the formation of the corresponding ketone **VIIIb**. The signals of protons of OCH_3 groups were observed in the ^{1}H NMR spectra of both compounds **VIIIa** and **VIIIb** in the region 3.87 ppm.

Acetamino group formation in compound **VIIIb** in order to obtain desired structure **II** was carried out similarly to the above procedure via oxime **VIIIc** prepared quantitatively from compound **VIIIb**. The reduction of compound **VIIIc** with lithium aluminum hydride gave amine **IX** that was without isolation brought into reaction with acetic anhydride in the presence of pyridine. We synthesized as a result the target product **II** whose NMR spectra show the formation of two (*endo*- and *exo*-) isomers of compound **II** with respect to acetamino group in a ratio 6:1 as confirmed also by chromato-mass spectral data. In the ^{1}H and ^{13}C NMR spectra of compound **II** the signals of all protons and all carbon atoms of the bicyclic fragment of both isomers of compound **II** are clearly seen (see EXPERIMENTAL). The value $W_{1/2}$ 29 Hz suggested [9] the prevalence of the *endo*-isomer **II** that we isolated in the individual state by chromatography.

Hence we developed in this study a preparative procedure for the synthesis of *N*-(2-methoxy-6,7,8,9,10,11-hexahydro-5*H*-6,10-methanocycloocta-[*b*]indol-9-yl)acetamide (**II**), potential analog of melatonin "with a limited conformational mobility".

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AMX-400 at operating frequencies 400 and 100 MHz respectively using HMDS as internal reference. IR spectra were recorded on spectrophotometers UR-20 and Specord 75 IR from mulls in mineral oil. Mass spectra were measured on a GC-MS instrument JMS-D300. The reaction progress was monitored by TLC on Silufol UV-254 plates. Separation by column chromatography was carried out on silica gel Lancaster (60–200 μm).

***N*-(2-Methoxy-6,7,8,9,10,11-hexahydro-5*H*-6,10-methanocycloocta[*b*]-indol-9-yl)acetamide (II)** was obtained in the same way as amide **Vb**, yield 30% calculated on oxime **VIIIc**. The product was purified by chromatography (eluent methanol–chlorpform, 1:20), mp 140°C. IR spectrum, cm^{-1}: 1660 (C=O), 3300 (NH of amide), 3390 (NH of indole).

Endo-isomer. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.62 br.s (1H, NH of indole), 7.20 d (1H, $H^{7'}$, *J* 8.60 Hz),

6.96 d (1H, H$^{4'}$, *J* 2.16 Hz), 6.80 d.d (1H, H$^{6'}$, *J* 2.54, 8.60 Hz), 5.51 br.s (1H, NH of amide), 4.08 m (1H, H^{6}, $W_{1/2}$, 29.0 Hz), 3.89 s (3H, OCH_3), 3.00 br.s (1H), 2.83 d.d (1H, HC$^{4\varepsilon}$, *J* 6.66, 16.63 Hz), 2.64 d (1H, H^{4a}, *J* 17.02 Hz), 2.60 br.s (1H), 2.10 m (1H), 2.03 s [3H, NC(O)CH_3], 2.00–1.07 m (5H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 169.41 (C=O), 153.94, 1137.52, 130.66, 127.47, 111.35, 110.67, 109.59, 100.10, 55.93 (C^{6}), 32.08, 31.13, 30.73, 28.42, 25.16, 20.88. Mass spectrum, *m*/*z* (I_{rel}, %): 298 (100) [*M*]$^+$, 281 (3), 254 (24), 238 (46), 224 (16), 210 (47), 198 (73), 183 (18), 167 (34).

Exo-isomer. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.62 br.s (1H, NH of indole), 7.19 d (1H, H$^{7'}$, *J* 8.84 Hz), 6.93 d (1H, H$^{4'}$, *J* 2.53 Hz), 6.80 d.d (1H, H$^{6'}$, *J* 2.54, 8.60 Hz), 5.90 br.s (1H, NH of amide), 4.04 m (1H, H^{6}, $W_{1/2}$ 23.5 Hz), 3.89 s (3H, OCH_3), 3.05 d.d (1H, CH$^{4\varepsilon}$, *J* 7.32, 16.68 Hz), 3.04 br.s (1H), 2.65 d (1H, HC^{4a}, *J* 16.93 Hz), 2.41 br.s (1H), 2.10 m (1H), 2.06 s [3H, NC(O)CH_3], 2.00–1.24 m (5H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 196.44 (C=O), 136.54, 135.63, 127.13, 121.06, 119.18, 117.65, 110.76, 109.69, 51.84 (C–NH), 32.13, 31.16, 30.70, 28.32, 25.11, 23.64, 20.85. Mass spectrum, *m*/*z* (I_{rel}, %): 298 (33) [*M*]$^+$, 280 (1), 253 (1), 239 (100), 224 (6), 210 (13), 198 (54), 182 (10), 167 (14).

5',6',7',8',10',11'-Hexahydrospiro(1,3-dioxolane-2,9'-[6,10]methanocycloocta[*b*]indole) (IVa). To a solution of 0.3 g (1.53 mmol) of mono ethylene ketal **III** in 3 ml of methanol was added at stirring 0.165 g (1.53 mmol) of phenylhydrazine and 0.75 g (5.50 mmol) of anhydrous $ZnCl_2$. The mixture was boiled for 6 h, washed with water and methanol. Yield 0.22 g (53%), mp 184–186°C (EtOH) (185–187°C [5]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.66 br.s (1H, NH), 7.48 d (1H, H$^{7'}$, *J* 7.58 Hz), 7.30 d (1H, H$^{4'}$, *J* 7.33 Hz), 7.16–7.07 m (2H, H$^{5',6'}$), 4.00 m [4H, $(OCH_2)_2$], 3.05–1.45 m (10H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 136.00, 135.52, 127.54, 120.84, 119.06, 117.90, 111.30, 110.44, 109.06, 64.30 (OCH_2CH_2O), 38.52, 30.38, 29.87, 28.52, 28.32, 22.24. Mass spectrum, *m*/*z* (I_{rel}, %): 269 (100) [*M*]$^+$, 236 (5), 254 (71), 210 (50), 200 (40).

5',6',7',8',10',11'-Hexahydro-9*H*-6,10-methanocycloocta[*b*]indole-9-one (IVb) was obtained as described in [5], yield 88%, mp 145–147°C (EtOH) (151–153°C [5]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.49 br.s (1H, NH), 7.47 d (1H, H$^{7'}$, *J* 7.82 Hz), 7.33 d (1H, H$^{4'}$, *J* 7.82 Hz), 7.18 t, 7.13 t (2H, H$^{5',6'}$, *J* 7.05 Hz), 3.24 br.s (1H), 3.13 d.d (1H, H$^{4\varepsilon}$, *J* 6.65, 16.44 Hz), 3.03 br.s (1H), 2.83 d (1H, H^{4a}, *J* 16.63 Hz), 2.37–2.10 m (6H). Mass spectrum, *m*/*z* (I_{rel}, %): 225 (65) [*M*]$^+$, 197 (37), 168 (100), 167(175), 156 (12).

5',6',7',8',10',11'-Hexahydro-9*H*-6,10-methanocycloocta[*b*]indole-9-one oxime (IVc). To a solution of 0.14 g (2.00 mmol) of hydroxylamine hydrochloride in 5 ml of ethanol was added at stirring 0.14 g (1.00 mmol) of K_2CO_3 and then dropwise, a solution of 0.40 g (1.78 mmol) of compound **IVb** in 10 ml of ethanol. The reaction mixture was stirred for 3 h, then 20 ml of water was added, extracted with CH_2Cl_2, the organic layer was dried over Na_2SO_4, and the solution was evaporated on a rotary evaporator. The crude product was subjected to chromatography (eluent benzene–ethyl acetate, 3:1) to isolate 0.30 g (70%) of oxime **IVc** as colorless crystals, mp 125°C. IR spectrum, cm^{-1}: 3400 (NH of indole) on the background 3200–3500 (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.78 br.s (1H, NH), 7.48 d (1H, H$^{7'}$, *J* 8.02 Hz), 7.34 d (1H, H$^{4'}$, *J* 7.83 Hz), 7.18, 7.12 t (2H, H$^{5',6'}$, *J* 7.24 Hz), 4.12 br.s (1H, NOH), 3.25–1.60 m (10H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 163.77 (C=N), 135.67, 134.86, 127.25, 121.41, 119.41, 117.97, 110,66, 109.21 (C^{3}), 34.64, 32.53, 30.25, 29.08, 27.44, 26.25. Found, %: C 75.03; H 6.55; N 11.37. $C_{15}H_{16}N_2O$. Calculated, %: C 75.00; H 6.67; N 11.67.

6',7',8',9',10',11'-Hexahydro-5*H*-6,10-methanocycloocta[*b*]indol-9-amine (Va). To a dispersion of 0.28 g (7.37 mmol) of $LiAlH_4$ in 10 ml of anhydrous THF was added dropwise at stirring a solution of 0.6 g (2.5 mmol) of oxime **IVc** in 10 ml of anhydrous THF, the reaction mixture was boiled for 6.5 h. On cooling with ice 1.5 ml of water–THF mixture, 1:1, was added, the mixture was boiled for 1 h, the precipitate was filtered off and washed with hot THF. The combined filtrates were dried over Na_2SO_4, and the solution was evaporated on a rotary evaporator to obtain 0.56 g (99%) of yellow oily substance. On treating with ethyl acetate solid amine **Va** crystallized (yield ~30%). IR spectrum, cm^{-1}: 3390 br (NH) on a background of wide absorption in the region 3100–3450 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 10.52 br.s (1H, NH), 7.35 d (1H, H$^{7'}$, *J* 7.33 Hz), 7.23 d (1H, H$^{4'}$, *J* 8.08 Hz), 6.97, 6.91 t (2H, H$^{5',6'}$, *J* 7.58 , 7.08 Hz), 2.96 m (2H, H^{1,4a}), 2.84 m (1H, H^{6}), 2.55 d.d (1H, H$^{4\varepsilon}$, *J* 6.83, 16.43 Hz), 2.08–0.80 m (10H, framework, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 137.72, 135.95, 127.39, 120.16, 118.26, 117.67, 111.13, 109.37, 53.99 (C^{6}), 34.79, 32.92, 30.95, 28.63, 28.36, 19.37. Mass spectrum, *m*/*z* (I_{rel}, %): 226 (100) [*M*]$^+$, 209 (70), 194 (20), 180 (75), 168 (95).

***N*-(6',7',8',9',10',11'-Hexahydro-5*H*-6,10-methanocycloocta[*b*]indol-9-yl)acetamide (Vb).**

A mixture of 0.11 g of oily amine **Va**, 2 ml of pyridine, and 1 ml of Ac_2O was stirred for 12 h at room temperature, then it was evaporated, and Et_2O was added. The ether solution was washed with 1 N HCl and 5% NaOH solution, dried over Na_2SO_4, and evaporated in a vacuum. The oily residue was subjected to chromatography (eluent methanol–chloroform, 1:9) to isolate 0.05 g (38%) of yellow crystals, mp 170°C. IR spectrum, cm^{-1}: 1650 (C=O), 3280 (NH of amide), 3400 (NH of indole). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.89 br.s (1H, NH of indole), 7.49 d (1H, $H^{7'}$, *J* 6.82 Hz), 7.31 d (1H, $H^{4'}$, *J* 7.58 Hz), 7.13 m (2H, $H^{5',6'}$), 5.67 br.s (1H, NHAc), 4.07 br.s (1H, H^6, $W_{1/2}$ 28.8 Hz), 3.00 br.s (1H), 2.85 d.d (1H, $H^{4\varepsilon}$, *J* 6.32, 16.68 Hz), 2.67 d (1H, H^{4a}, *J* 16.68 Hz), 2.57 br.s (1H), 2.07 m (1H), 2.01 s (3H, CH_3), 1.93–1.10 m (5H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 169.44 (C=O), 136.54, 135.63, 127.13, 121.06, 119.18, 117.65, 110.76, 109.69, 51.84 (C^6), 32.13, 31.16, 30.70, 28.32, 25.11, 23.64, 20.85. Mass spectrum, *m*/*z* (I_{rel}, %): 268 (100) $[M]^+$, 253, 225, 209, 194, 180, 168.

Monooxime of bicyclo[3.3.1]nonane-2,6-dione (VI) was prepared from the oxime of mono ethylene ketal of bicyclo-[3.3.1]nonane-2,6-dione (see the text) by procedure [5], yield 94%. IR spectrum, cm^{-1}: 3400 br (OH), 1700 (C=O) br, sh 1650 (C=N). Mass spectrum, *m*/*z* (I_{rel}, %): 167 $[M]^+$, 150 $[M - OH]^+$. Found, %: C 64.18; H 7.57; N 7.97. $C_9H_{13}NO_2$. Calculated, %: C 64.65; H 7.83; N 8.37. *M* 167.21.

8-Bromo-5,6,7,8,10,11-hexahydro-9H-6,10-methanocycloocta[b]indol-9-one (VII). To 10 ml of concn. H_2SO_4 was added 1 g (3.70 mmol) of ethylene ketal **IVa** and 1.16 g of silver sulfate, and a flow of bromine vapor (0.6 g) with air was passed through the mixture. The reaction mixture was poured on ice, the precipitate was separated and washed with $CHCl_3$. The filtrate was extracted with $CHCl_3$, the organic layer was passed through a bed of silica gel. The solution was evaporated in a vacuum to obtain 0.96 g of dark-brown oily substance which was subjected to chromatography (eluent hexane–ethyl acetate, 2:1) to give ketone **IVb** and compound **VII**. IR spectrum, cm^{-1}: 3400 (NH), 1720 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 8.08 br.s (1H, NH), 7.46 d (1H, *J* 7.80 Hz), 7.37 d (1H, *J* 8.00 Hz), 7.22 t (1H, *J* 7.54 Hz), 7.13 t (1H, *J* 7.34 Hz), 4.49 m (1H, H^7), 3.39 br.s (1H), 3.23 br.s (1H), 3.15 d.d (1H, H^{4e}, *J* 6.85, 16.38 Hz), 2.83 d (1H, H^{4a}, J 16.20 Hz), 2.80–2.18 m (4H). Mass spectrum, *m*/*z* (I_{rel}, %): 305 (30) $[M + 1]^+$, 303 (27), 226 (35), 225 (83), 224 (75).

2'-Methoxy-5',6',7',8',10',11'-hexahydrospiro-(1,3-dioxolane-2,9'-[6,10]methanocycloocta[b]-indole) (VIIIa). To a solution of 0.97 g (4.95 mmol) of mono ethylene ketal **VI** in 12 ml of methanol under argon was added at stirring 0.95 g (5.44 mmol) of 4-methoxyphenylhydrazine hydrochloride, 0.376 g (2.72 mmol) of K_2CO_3, and 2.28 g (16.72 mmol) of anhydrous $ZnCl_2$. The mixture was boiled for 4 h, the precipitate was filtered off, washed with water and methanol. Yield 1.0 g (68%), colorless crystals, mp 160–162°C. IR spectrum, cm^{-1}: 3400 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.56 br.s (1H, NH), 7.19 d (1H, $H^{7'}$, *J* 8.84 Hz), 6.95 d (1H, $H^{4'}$, *J* 2.27 Hz), 6.79 d.d (1H, $H^{6'}$, *J* 2.28, 8.59 Hz), 4.00 m (4H, OCH_2CH_2O), 3.87 s (3H, OCH_3), 2.97 m (2H), 2.86 d.d (1H, $H^{4\varepsilon}$, *J* 6.83, 16.68 Hz), 2.24–1.48 m (7H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 153.90, 137.26, 130.69, 127.92, 111.23, 111.14, 110.67, 109.26, 100.35, 64.33 (OCH_2CH_2O), 55.95 (OCH_3), 36.49, 30.44, 29.80, 28.81, 28.55, 22.52. Found, %: C 72.32; H 7.10; N 4.72. $C_{18}H_{21}NO_3$. Calculated, %: C 72.24; H 7.02; N 4.68.

2-Methoxy-5,6,7,8,10,11-hexahydro-9*H*-6,10-methanocycloocta[b]indol-9-one (VIIIb) was obtained by procedure [5] from compound **VIIIa**. Yield 82%, mp 170–172°C. IR spectrum, cm^{-1}: 3390 (NH), 1690 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.80 br.s (1H, NH), 7.19 d (1H, $H^{7'}$, *J* 8.81 Hz), 6.95 d (1H, $H^{4'}$, *J* 1.96 Hz), 6.79 d.d (1H, $H^{6'}$, *J* 2.34, 8.81 Hz), 3.87 s (3H, OCH_3), 3.20 br.s (1H), 3.09 d.d (1H, $H^{4\varepsilon}$, *J* 6.85, 16.43 Hz), 3.02 br.s (1H), 2.80 d (1H, $H^{4'a}$, *J* 16.24 Hz), 2.36–2.06 m (6H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 213.68 (C=O), 154.18, 136.04, 130.85, 127.49, 111.55, 111.38, 108.15, 100.24, 55.79 (CH_3), 44.58, 36.65, 32.25, 31.96, 28.45, 25.13. Mass spectrum, *m*/*z* (I_{rel}, %): 255 (100) $[M]^+$, 238 (5), 227 (12), 212 (10), 198 (100), 183 (25), 167 (20). Found, %: C 75.05; H 7.00; N 5.24. $C_{16}H_{17}NO_2$. Calculated, %: C 75.29; H 6.67; N 5.49. *M* 255.

(9*E*)-2-Methoxy-5,6,7,8,10,11-hexahydro-9*H*-6,10-methanocycloocta[*b*]indol-9-one oxime (VIIIc) was obtained similarly to oxime **IVc** in 96% yield. The compound was purified by chromatography (eluent benzene–ethyl acetate, 3:1) through a thin layer of silica gel (1 cm). mp 170° C. IR spectrum, cm^{-1}: 3400 (NH), 3200–3450 (OH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.67 br.s (1H, NH), 7.21 d (1H, $H^{7'}$, *J* 8.34 Hz), 6.92 d (1H, $H^{4'}$, *J* 2.53 Hz), 6.82 d.d (1H, $H^{6'}$, *J* 2.53, 8.59 Hz), 4.12 br.s (1H, NOH), 3.86 s (3H, OCH_3), 3.24–1.61 m (10H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 163.66 (C=N), 154.03, 136.43, 130.78, 128.35, 111.30, 109.09, 109.09, 100.25, 55.91, 34.64, 32.51, 30.31, 29.72, 29.19, 27.51. Found, %: C 71.30; H 6.81; N 10.42. $C_{16}H_{18}N_2O_2$. Calculated, %: C 71.11; H 6.67; N 10.37.

2-Methoxy-6,7,8,9,10,11-hexahydro-5H-6,10-methanocycloocta[b]indol-9-amine (IX). To a dispersion of 0.14 g (5.00 mmol) of $LiAlH_4$ in 10 ml of anhydrous THF was added dropwise at stirring a solution of 0.45 g (1.67 mmol) of compound **VIIIc** in 10 ml of THF, and the mixture was boiled for 6.5 h. On cooling with ice 0.8 ml of water–THF mixture, 1:1, was added, the mixture was boiled for 1 h, the precipitate was filtered off and washed with hot THF. The combined filtrates were dried over Na_2SO_4, and the solution was evaporated on a rotary evaporator to obtain 0.38 g of yellow oily substance that was used in the synthesis of compound **II** without isolation.

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