

1-Substituted-2,3,4,9-tetrahydro-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indoles and
Their Base-catalyzed Rearrangements to
N-[2-[2-(1-Alkyl-3-oxobutenyl)-1*H*-indol-3-yl]ethyl]acetamides

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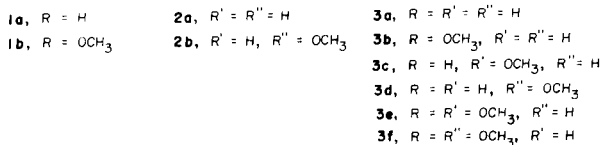
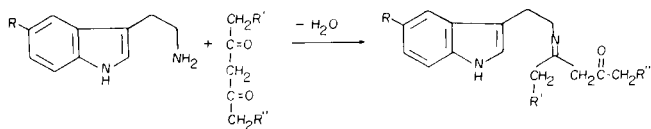
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The condensation of 1*H*-indole-3-ethanamines, **1**, with 2,4-pentanediones, **2**, gave enamines **3**. Acid catalyzed ring closure of **3** gave 1-(1-substituted-2,3,4,9-tetrahydro-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indoles **4**. Subsequent *N*-acetylation yielded **5** which sequentially produced 2,3-disubstituted indoles **6** and **7** resulting from C-N bond cleavage after treatment with sodium alkoxide in ethanol. Controlled catalytic hydrogenation of the latter gave saturated derivatives **8** and **9**.

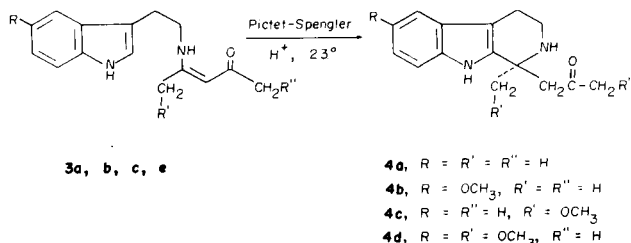
J. Heterocyclic Chem., **20**, 267 (1983).

This paper describes the synthesis of 1-substituted-2,3,4,9-tetrahydro-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indole derivatives **4**, subsequent *N*-acetylation to **5** and the base-catalyzed rearrangement of the latter to give 2,3-disubstituted indole derivatives **6** and **7**. Condensation of 1*H*-indole-3-ethanamines (tryptamines) **1a**, **b** with one equivalent of 2,4-pentanedione (**2a**) under azeotropic conditions gave a single series of compounds **3a** and **3b**. Condensation of **1a**, **b** with 1-methoxy-2,4-pentanedione (**2b**) gave two series of position isomers (**3c**, **e** and **3d**, **f**) in approximately equal amounts.

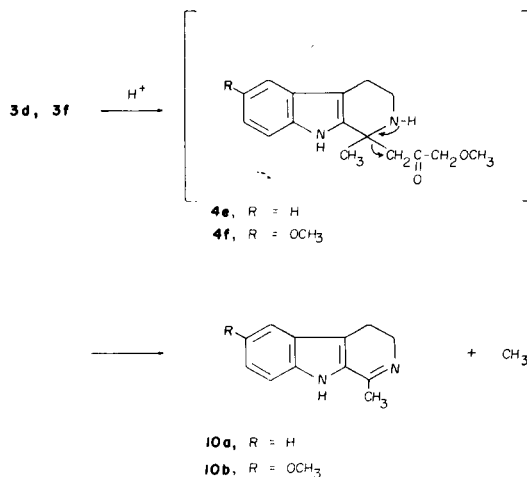


Accumulated spectral evidence established enamine (vinylogous amide) (**1**) structures, **3**, for the isomeric condensation products in solution (vinylic proton resonance at δ 4.90 to δ 5.20 for **3a-f**) and in the solid state (ν C=O at about 1612 cm⁻¹ and 1555 cm⁻¹) as well (see Experimental).

Ring closure could be effected under typical Pictet-Spengler reaction conditions (2) in which chloroform solutions of **3a**, **b**, **c**, **e**, were treated with dry hydrogen chloride at room temperature (Method A) (3). The products, 1-substituted-2,3,4,9-tetrahydro-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indoles, **4**, were isolated and characterized as hydrochloride salts. Likewise, the same cyclic products, **4**, were produced at room temperature where enamines, **3**, were dissolved in trifluoroacetic acid (Method B).

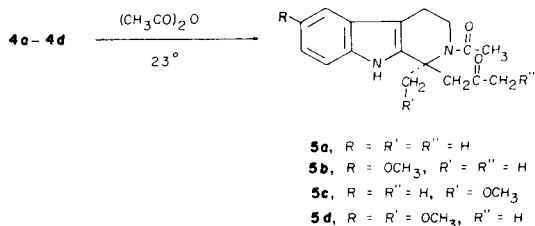


Under these conditions, isomeric enamines **3d**, **f** gave atypical results. The isolated products, 1-methyl-3*H*-pyrido[3,4-*d*]indoles (**10a**, **b**) are presumed to arise by loss of methoxy acetone from normal products, **4**. None of the typical products, **4**, could be detected in these reaction mixtures.



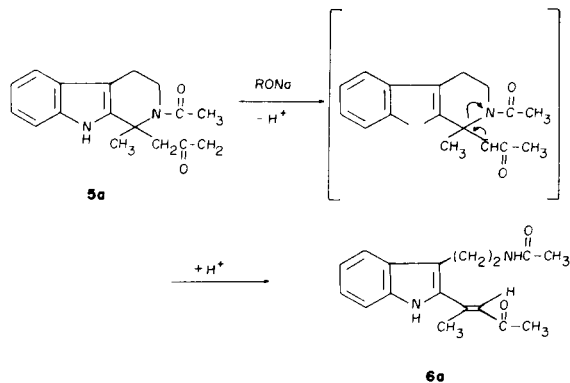
As typical Mannich bases, compounds **4a-d** are sensitive towards strong bases at room temperature and undergo a β -elimination of the acetone moiety to give the dihydroazacarbazoles corresponding to **10**. Compounds **4** could be stabilized by reduction to amino alcohols as exemplified by the transformation of **4a** to **11** (see Experimental).

The treatment of **4a-d** with acetic anhydride at room temperature gave amido ketone derivatives **5**. All of these compounds gave sharp melting points and only one spot on thin layer chromatography using several different solvent systems. Both **4** and **5** exhibit characteristic peculiarities in their pmr spectra. The methylene group attached to the indole ring (CH₂-4) usually resonates as a triplet, while the one attached to the nitrogen atom (CH₂-3) appears always as a multiplet. The methylene protons of the 2-propanone functionality are nonequivalent due to the adjacent chiral center and appear as an AB quartet. A

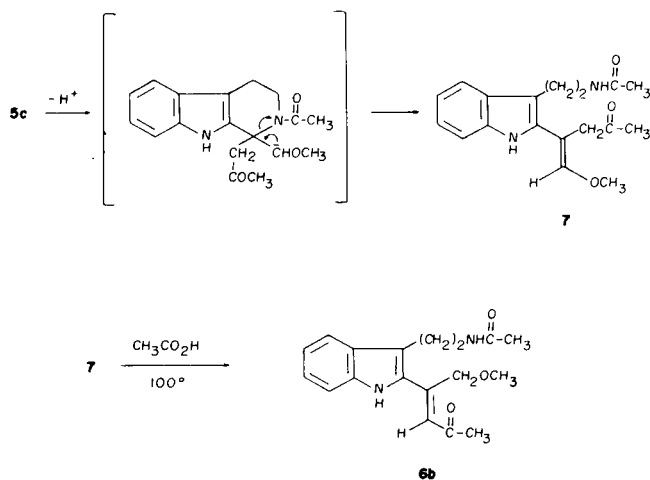


somewhat similar pattern of nonequivalency is also observed at the methylene group of methoxymethylene moiety (CH₃OCH₂-1) (see Experimental).

In contrast to the amino ketones **4**, the acetylated derivatives **5** are stable towards alkali at room temperature. However, when compound **5a** was treated with sodium alkoxide in refluxing absolute alcohol (conditions which are not expected to cause hydrolysis of the amido function), cleavage of the C-N bond of the tetrahydropyridine ring occurred to give an acyclic 2,3-disubstituted conjugated indole derivative **6a**. The analytical and spectral data are consistent with **6a**. The uv spectrum [217 nm ($\epsilon = 24,450$), 255 (8775), 351 (14570)] is characteristic for the conjugated indole (**4**). The infrared absorption spectrum displays two carbonyl absorptions at 1660 and 1650 cm⁻¹, due to the unsaturated ketone and amide, respectively. The proton magnetic resonance spectrum of **6a** shows a vinylic singlet resonating at δ 6.65 and all other protons are in full agreement with the structure (see Experimental). The initial formation of an anion from **5** leads to the cleavage of the C-N bond and results in a formal reverse Michael reaction to give **6a**.

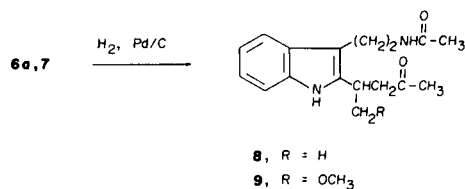


When the methoxy analog **5c** was subjected to similar reaction conditions and worked up in the absence of acid, cleavage of C-N bond took place, but the rearranged product **7** contained saturated ketone and enol ether functionalities in addition to the amide group. The uv spectrum again showed a conjugated indole. The ir spectrum indicated saturated ketone at 1702 cm⁻¹ and secondary amide at 1655 and 1545 cm⁻¹. The pmr spectrum fully confirms structure **7** (see Experimental). The formation of an enol ether **7** rather than α,β -unsaturated ketone would seem to indicate that the methylene group attached to the methoxy function is sufficiently activated to form an anion initially in preference to the ketone methylene group. Brief heating of **7** with glacial acetic acid results in the thermodynamically more stable tautomer **6b**.



All of the pmr and thin layer chromatography data indicate that olefins **6** and **7** exist as single *cis* or *trans* isomers. No studies were done to rigorously define the stereochemistry. We have chosen to draw the structure in the above form on steric grounds. Thus, the least hindered form is that in which the hydrogen rather than the methoxy or acetyl groups are *cis* to the bulky indole ring.

Compounds **6** and **7** were easily transformed to the saturated derivatives **8** and **9**, respectively, by the controlled catalytic hydrogenation using 5% palladium-on-charcoal catalyst in ethanol. The reduced products (**8** and **9**) display the normal indole absorption in the uv [225 nm (ϵ 37,200), 283 (8250) and 291 (7200)], saturated ketone (1702 cm⁻¹) in the ir, and absence of the vinylic proton in the pmr spectra (see Experimental).



EXPERIMENTAL

Physical constants, yields, and analytical values for the compounds below are reported in the individual examples. Melting points were determined using a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 doublebeam spectrograph. Unless otherwise stated, the former was determined as solution in 95% ethanol and the latter as Nujol mulls. The ¹H-nmr spectra were obtained on a Varian A-60 spectrometer in the solvents as indicated. Chemical shifts are reported in ppm, from TMS as an internal standard and are given in δ units. Aromatic protons are generally not reported and are included only in those instances where the emphasis of their differences and peculiarities is essential. Tlc was carried out on silica gel G (Stahl) using chloroform-ethyl acetate or toluene, acetone, heptane in varying proportions as the eluent. The chromatograms were developed in an iodine chamber.

Products 3 Derived from Condensation of 1H-Indole-3-ethanamines 1 with 2,4-Pentanediones 2.

Since the enamines **3** exist in the enamine rather than in the imino form, the names used in this paper correspond to the former.

4-[[2-(1H-Indol-3-yl)ethyl]amino]-3-penten-2-one (3a).

A solution of 63.5 g (0.4 mole) of 1H-indole-3-ethanamine (tryptamine) and 40.0 g (0.4 mole) of 2,4-pentanedione in 150 ml of toluene was refluxed under nitrogen for 90 minutes while 0.72 ml of water separated in a Dean-Stark trap. The solvent was removed and the residue was crystallized from acetonitrile to give 77.8 g (80% yield) of pure 4-[[2-(1H-indol-3-yl)ethyl]amino]-3-penten-2-one (**3a**), mp 133-144°; uv (ethanol): λ max nm (ε) 221 (36,000), 283 sh (11,750), 290 sh (13,700), 312 (20,000); ir (nujol): 3190, 1608, 1552, 1300 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.80 (s, CH₃C=C, 3H), 1.98 (s, CH₃C=O, 3H), 3.00 (t, CH₂-indole, 2H, J = 6.0 Hz), 3.51 (q, CH₂NH, 2H, J = 6.0 Hz), 4.91 (s, vinylic, 1H), 7.20-7.60 (m, H-2 and 4 aromatic protons, 5H), 8.72 (broad, indole NH, 1H), 10.90 (m, CH₂NH, 1H).

Anal. Calcd. for C₁₅H₁₉N₂O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.43; H, 7.76; N, 11.73.

4-[[2-(5-Methoxy-1H-indol-3-yl)ethyl]amino]-3-penten-2-one (3b).

Following the procedure used for the preparation of **3a**, the 5-methoxy analog **3b** was obtained in 74% yield, after recrystallization from 2-propanol, mp 153-154°; uv (ethanol): λ max nm (ε) 222 (36,100), 283 sh (11,750), 312 (20,050); ir (nujol): 3190, 1609, 1552, 1310, cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.82 (s, CH₃-C-N, 3H), 1.98 (s, CH₃C=O, 3H), 3.00 (t, CH₂-indole, 2H, J = 6.0 Hz), 3.50 (q, CH₂NH, 2H, J = 6.0 Hz), 3.80 (s, CH₃O-5, 3H), 4.95 (s, vinylic, 1H), 6.95-7.55 (m, H-2 and 3 aromatic protons, 4H), 8.45 (broad, indole NH, 1H), 10.85 (m, CH₂NH, 1H).

Anal. Calcd. for C₁₆H₂₀N₂O₂: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.55; H, 7.34; N, 10.26.

4-[[2-(1H-Indol-3-yl)ethyl]amino]-5-methoxy-3-penten-2-one (3c).

A solution of 7.6 g (0.04 mole) of 1H-indol-3-ethanamine and 6.2 g (0.048 mole) of 1-methoxy-2,4-pentanedione in 125 ml of toluene was refluxed for 90 minutes until 0.72 ml of water had separated. Tlc (acetone, toluene, heptane, 3:2:1) showed two new spots at Rf = 0.26 (ca. 60%) and at Rf = 0.22 (ca. 40%), respectively. After the solvent was removed *in vacuo*, the semi-solid residue was crystallized from acetonitrile giving 6.2 g of white crystals which contained about 90% of the faster moving positional isomer, mp 112-114°. Three recrystallizations from ethanol gave 2.9 g of analytically and chromatographically (R_f = 0.26) pure 4-[[2-(1H-indol-3-yl)ethyl]amino]-5-methoxy-3-penten-2-one (**3c**), mp 119-120°; uv (ethanol): λ max nm (ε) 221 (36,750), 291 (16,650), 311 (17,800); ir (Nujol): 3140 (NH), 1605, 1562, 1548; ir (chloroform): 3420, 3360, 3200, (NH), 1610, 1570, 1545, cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.98 (s, CH₃C=O, 3H), 2.99 (t, CH₂-indole, 2H, J = 6.0 Hz), 3.23 (s, OCH₃,

3H), 3.50 (q, CH₂NH, 2H, J = 6.0 Hz), 3.81 (s, OCH₃, 2H), 5.03 (s, vinylic, 1H), 6.95-7.55 [H-2 (indole) and aromatic protons, 5H], 8.42 (broad, indole NH, 1H), 10.43 (m, broad, CH₂NH, 1H).

Anal. Calcd. for C₁₆H₂₀N₂O₂: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.88; H, 7.58; N, 10.49.

4-[[2-(1H-Indol-3-yl)ethyl]amino]-1-methoxy-3-penten-2-one (3d).

The combined mother liquors from **3c** were chromatographed over Florisil, ether-ethyl acetate (5:1) being used as an eluent. Fractions containing ca. 85% of the slower moving product (R_f = 0.22) were evaporated and triturated with ether giving 1.1 g of white crystals, mp 77-80°. Recrystallization from ether gave 0.8 g of analytically and chromatographically (R_f = 0.22) pure 4-[[2-(1H-indol-3-yl)ethyl]amino]-1-methoxy-3-penten-2-one (**3d**), mp 78-79°; uv (ethanol): λ max nm (ε) 221 (37,200), 284 sh (11,600), 291 (12,900), 315 (23,500); ir (nujol): 3150 (NH), 1613, 1548 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.76 (s, CH₃-C=C, 3H), 2.94 (t, CH₂-indole, 2H, J = 7.0 Hz), 3.35 (m, CH₂NH, OCH₃, 5H), 3.88 (s, CH₂OCH₃, 2H), 5.18 (s, vinylic, 1H), 6.90-7.60 [m, H-2 (indole), 4 aromatic protons, 5H], 8.08 (broad, indole NH, 1H), 11.08 (m, CH₂NH, 1H).

Anal. Calcd. for C₁₆H₂₀N₂O₂: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.57; H, 7.63; N, 10.02.

5-Methoxy-4-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-3-penten-2-one (3e).

A solution of 19.0 g (0.1 mole) of 5-methoxy-1H-indole-3-ethanamine and 16.2 g (0.115 mole) of 1-methoxy-2,4-pentanedione in 10 ml of chloroform was refluxed under nitrogen. After 2 hours 1.8 ml of water was collected in a Dean-Stark trap. The tlc (acetone, toluene, heptane, 3:2:2) showed two new spots at R_f = 0.29 and 0.23 of about 1:1 ratio. After the removal of solvent, the residue was crystallized from diethyl ether giving 19.0 g of white crystals which contained both positional isomers, mp 78-85°. Recrystallization from ether-ethyl acetate (2:1) gave 12.1 g of product containing ca. 80% of the faster moving isomer (R_f = 0.29), mp 84-88°. Two additional recrystallizations from ether gave 5.4 g of analytically and chromatographically (R_f = 0.29) pure 5-methoxy-4-[[2-(5-methoxy-1H-3-yl)ethyl]amino]-3-penten-2-one (**3e**), mp 91-92°; uv (ethanol): λ max nm (ε) 223 (26,650), 309 (20,650); ir (nujol): 3190, 1614, 1552 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 2.00 (s, C=C-COCH₃, 3H), 2.98 (t, CH₂-indole, 2H, J = 7.5 Hz), 3.29 (s, CH₃OCH₃, 3H), 3.50 (m, CH₂NH, 2H), 3.82 (s, ArOCH₃, 3H), 3.88 (s, CH₃O, 2H), 5.13 (s, vinylic, 1H), 6.72-7.35 (m, H-2 and aromatic protons, 4H), 8.78 (broad, indole NH, 1H), 10.78 (broad, CH₂NH, 1H).

Anal. Calcd. for C₁₇H₂₂N₂O₃: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.68; H, 7.50; N, 9.38.

1-Methoxy-4-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-3-penten-2-one (3f).

The combined mother liquors from **3e** (containing ca. 65% of the slower moving isomer, R_f = 0.23) were chromatographed over Florisil, ether-ethyl acetate being used as an eluent. The combined fractions which contained predominantly slower moving isomer were evaporated and triturated with ethyl acetate to give 3.4 g of nearly pure isomer (R_f = 0.23), mp 102-104°. Further recrystallization from ethyl acetate gave 1.9 g of analytically and chromatographically (R_f = 0.23) pure 1-methoxy-4-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-3-penten-2-one (**3f**), mp 104-105°; uv (ethanol): λ max nm (ε) 222 (27,400), 281 sh (10,800), 311 (22,400); ir (nujol): 3190, 1614, 1552 cm⁻¹; ir (chloroform): 3480, 3320 (NH), 1610, 1562 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.82 (s, CH₃-C=C, 3H), 2.97 (t, CH₂-indole, 2H, J = 7.0 Hz), 3.45 (m, CH₂OCH₃ and CH₂NH, 5H), 3.83 (s, ArOCH₃, 3H), 3.88 (s, CH₃O, 2H), 5.21 (s, vinylic, 1H), 6.70-7.25 (m, H-2 and aromatic protons, 4H), 8.93 (broad, indole NH, 1H), 11.08 (broad, CH₂NH, 1H).

Anal. Calcd. for C₁₇H₂₂N₂O₃: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.70; H, 7.45; N, 9.38.

Pictet-Spengler Cyclization of Enamines 3 into 1,1-Disubstituted 2,3,4,9-Tetrahydro-9H-pyrido[3,4-b]indoles 4.

1-(2,3,4,9-Tetrahydro-1-methyl-1H-pyrido[3,4-b]indol-1-yl)-2-propanone

Hydrochloride (**4a**). (Method A).

This general procedure will be illustrative for the transformations of compounds **3** into **4**.

Dry hydrogen chloride was bubbled into a solution of 4.9 g (0.2 mole) of 4-[[2-(1*H*-indol-3-yl)ethyl]amino]-3-penten-2-one (**3a**) in 100 ml of chloroform at room temperature until pH equalled 1.0 (wet pH paper). After 30 minutes, 150 ml of ether was added and the resulting precipitate was collected by filtration. Recrystallization from 2-propanol-acetonitrile (1:1) gave 3.9 g (70% yield) of pure 1-(2,3,4,9-tetrahydro-1-methyl-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-propanone hydrochloride (**4a**) as off-white crystals, mp 257-258° dec; uv (ethanol): λ max nm (ϵ) 221 (36,500), 270-280 plateau (7200), 288.5 (5500); ir (nujol): 3200 (NH), 1714 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6): δ 1.80 (s, $\text{CH}_3\text{-C-N}$, 3H), 2.15 (s, $\text{CH}_3\text{C=O}$, 3H), 2.91 (t, $\text{CH}_2\text{-indole}$, 2H, $J = 5.0$ Hz), 3.40 (m, CH_2NH , 2H), 3.57 (s, $\text{CH}_2\text{C=O}$, 2H), 7.03 (m, H-6, H-8, 2H, aromatic), 7.37 (m, H-5, H-7, 2H, aromatic), 9.65 (broad *NH_2 , 2H), 11.40 (s, indole NH, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}\cdot\text{HCl}$: C, 64.62; H, 6.87; N, 10.05; Cl, 12.72. Found: C, 64.68; H, 6.78; N, 9.86; Cl, 12.64.

1-(2,3,4,9-Tetrahydro-6-methoxy-1-methyl-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-propanone Hydrochloride (**4b**). (Method B).

The enamine **3b** (5.45 g, 0.02 mole) was dissolved in 25 ml of trifluoroacetic acid with external cooling and the solution was allowed to stand at room temperature for 2 hours. Ice-water was added, the mixture was made basic with potassium carbonate and extracted twice with 50 ml of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and treated with ethanolic hydrogen chloride to about pH 1.5. After 20 hours at 5°, the resulting off-white crystals (5.2 g) were collected, mp 186-187° dec. Recrystallization from 2-propanol gave 4.4 g (71% yield) of **4b** as nearly white crystals, mp 188-189° dec; uv (ethanol): λ max nm (ϵ) 222 (36,500), 270-281 plateau (7200), 289 (5550); ir (nujol): 1710 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6): δ 1.76 (s, $\text{CH}_3\text{-C-N}$, 3H), 2.14 (s, $\text{CH}_3\text{C=O}$, 3H), 2.88 (t, $\text{CH}_2\text{-indole}$, 2H, $J = 5.0$ Hz), 3.42 (m, CH_2NH , 2H), 3.53 (s, $\text{CH}_2\text{C=O}$, 2H), 3.70 (s, CH_3O), 6.70 (dd, H-7, 1H, $J = 8.0$ and 1.8 Hz), 6.89 (d, H-5, 1H, $J = 1.8$ Hz), 7.18 (d, H-8, 1H, $J = 8.0$ Hz), 9.53 (broad, 2H, *NH_2), 11.20 (s, indole NH, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\cdot\text{HCl}$: C, 62.23; H, 6.85; N, 9.07. Found: C, 62.30; H, 7.13; N, 8.92.

1-[2,3,4,9-Tetrahydro-1-(methoxymethyl)-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-propanone Hydrochloride (**4c**).

Dry hydrogen chloride was bubbled into a solution of 2.7 g (0.01 mole) of 4-[[2-(1*H*-indol-3-yl)ethyl]amino]-5-methoxy-3-penten-2-one (**3c**) in 100 ml of chloroform for 3 minutes (pH 1.0) and allowed to stand at 25° for 1 hour. Ether (200 ml) was added and the nearly white precipitate (2.9 g) was collected by filtration, mp 173-175°. Recrystallization from 2-propanol-acetone (2:1) gave 2.2 g (71% yield) of pure 1-[2,3,4,9-tetrahydro-1-(methoxymethyl)-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-propanone hydrochloride (**4c**), mp 176-177° dec; uv (ethanol): λ max nm (ϵ) 221 (28,000), 272 (9000), 294 sh (5000), 307 sh (3900); ir (nujol): 1712 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6): δ 2.11 (s, CH_2COCH_3 , 3H), 2.90 (t, $\text{CH}_2\text{-indole}$, 2H, $J = 6.5$ Hz), 3.24 (s, CH_3O , 3H), 3.52 (m, CH_2COCH_3 and CH_2NH , 4H), 3.90, 4.08 (dd, CH_2O , 2H, $J = 10.0$ Hz), 6.90-7.55 (m, 4 aromatic protons), 9.70 (broad, 2H, *NH_2 , 2H), 11.30 (s, indole NH, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\cdot\text{HCl}$: C, 62.23; H, 6.85; N, 9.07; Found: C, 62.09; H, 6.93; N, 9.01.

1-[2,3,4,9-Tetrahydro-6-methoxy-1-(methoxymethyl)-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-propanone Hydrochloride (**4d**).

By using procedure A, 3.0 g (0.011 mole) of 5-methoxy-4-[[2-(5-methoxy-1*H*-indol-3-yl)ethyl]amino]-3-penten-2-one (**3e**) gave 3.8 g of crude **4d**, mp 162-163° dec. Recrystallization from 2-propanol gave 2.7 g (80% yield) of pure **4d** as off-white crystals, mp 163-164° dec; uv (ethanol): λ max nm (ϵ) 220 (28,000), 272 (9000), 295 sh (5000), 307 sh (3900); ir (nujol): 1715 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6): δ 2.12 (s, CH_2COCH_3 , 3H), 2.91 (t, $\text{CH}_2\text{-indole}$, 2H, $J = 6.0$ Hz), 3.24 (s, CH_2OCH_3 , 3H), 3.50 (m, CH_2COCH_3 and CH_2N , 4H), 3.73 (s, ArOCH_3 , 3H), 3.87, 4.07 (dd, $\text{CH}_2\text{-OCH}_3$, 2H, $J = 10.0$

Hz), 6.74 (dd, H-7, 1H, $J = 8.0$ and 1.8 Hz), 6.92 (d, H-5, 1H, $J = 1.8$ Hz), 7.23 (d, H-8, 1H, $J = 8.0$ Hz), 9.65 (broad, 2H, *NH_2), 11.20 (s, indole NH, 1H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3\cdot\text{HCl}$: C, 60.26; H, 6.84; N, 8.27; Cl, 10.46. Found: C, 60.10; H, 6.62; N, 8.18; Cl, 10.49.

2-Acetyl-2,3,4,9-tetrahydro-1-methyl-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indole (**5a**).

To a suspension of 8.1 g (0.029 mole) of **4a** in 150 ml of chloroform was added aqueous potassium bicarbonate at 0° until pH 8.5 and the two phases were quickly separated. After the chloroform phase was dried with sodium sulfate, 8 ml of acetic anhydride and 5 drops of triethylamine were added and the solution was allowed to stand at 23° for 20 hours. Ice-water was added and pH was adjusted to 8.0 by the addition of aqueous ammonia. The organic phase was washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. The solid residue was crystallized from ethyl acetate giving 7.1 g (86% yield) of pure amido ketone derivative **5a** as white crystals, mp 175-176°; uv (ethanol): λ max nm (ϵ) 222 (38,600), 276 (7800), 288 sh (6050); ir (nujol): 3280 (NH), 1700 (ketone C=O), 1630, 1618 (amide C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6): δ 1.66 (s, 1- CH_3 , 3H), 1.74 (s, CH_3COCH_3 , 3H), 2.08 (s, NCOCH_3 , 3H), 2.69 (t, $\text{CH}_2\text{-indole}$, 2H, $J = 6.0$ Hz), 3.09, 4.13 (dd, CH_2COCH_3 , 2H, $J_{gem} = 16.0$ Hz), 3.62 (m, CH_2N , 2H), 6.95 (m, H-6, H-8, 2H, aromatic), 7.30 (m, 2H, H-5, H-6, 2H, aromatic), 10.80 (indole NH, 1H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.99; H, 7.08; N, 10.08.

By applying the same general method as for the preparation of **5a**, the following amido ketones were prepared.

2-Acetyl-2,3,4,9-tetrahydro-6-methoxy-1-methyl-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indole (**5b**).

Compound **5b** was prepared from **4b** in 82% yield as white crystals after recrystallization from 2-propanol, mp 188-189° dec; uv (ethanol): λ max nm (ϵ) 221 (38,620), 276 (7800), 288 sh (6050); ir (nujol): 3270 (NH), 1707 (ketone C=O), 1632 (amide C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6): δ 1.68 (s, $\text{CH}_3\text{C=C}$, 3H), 1.77 (s, $\text{CH}_3\text{C=O}$, 3H), 2.10 (s, CH_3CON , 3H), 2.68 (t, $\text{CH}_2\text{-indole}$, 2H, $J = 5.0$ Hz), 3.60, 4.10 (dd, $\text{CH}_2\text{C=O}$, 2H, $J = 15.0$ Hz), 3.55 (m, CH_2N , 2H), 3.72 (s, $\text{CH}_2\text{O-6}$, 3H), 6.60 (dd, H-7, 1H, $J = 8.0$ and 2.0 Hz), 6.85 (d, H-5, 1H, $J = 2.0$ Hz), 7.13 (d, H-8, 1H, $J = 8.0$ Hz), 10.65 (s, indole NH, 1H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.96; H, 6.89; N, 8.92.

2-Acetyl-2,3,4,9-tetrahydro-1-(methoxymethyl)-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indole (**5c**).

Compound **4c** gave 85% of crude yield of **5c**, mp 168-170° dec. Recrystallization from acetonitrile-ethyl acetate gave pure **5c** (76% yield) as white crystals, mp 170-171° dec; uv (ethanol): λ max nm (ϵ) 223 (39,000), 274 sh (8200), 282 (8400), 291 (6750); ir (chloroform): 3390 (NH), 1709 (ketone C=O), 1639 (amide C=O) cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 1.87 (s, CH_2COCH_3 , 3H), 2.20 (s, NCOCH_3 , 3H), 2.82 (m, $\text{CH}_2\text{-indole}$, 2H), 3.32 (s, OCH_3 , 3H), 3.68, 4.25 (dd, OCH_2 , 2H, $J_{gem} = 9.0$ Hz), 3.90 (m, CH_2N , 2H), 6.95-7.50 (m, aromatic, 4H), 8.65 (s, indole NH); $^1\text{H-nmr}$ (DMSO- d_6): δ 1.75 (s, $\text{CH}_3\text{C=O}$, 3H), 2.12 (s, CH_3CON , 3H), 2.70 (t, $\text{CH}_2\text{-indole}$, 2H, $J = 5.0$ Hz), 3.00, 4.15 (dd, OCH_2 , 2H, $J_{gem} = 9.0$ Hz), 3.10 (s, OCH_3 , 3H), 3.75 (m, $\text{CH}_2\text{C=O}$, CH_2N , 4H), 7.00 (m, H-6, H-8, 2H aromatic), 7.35 (m, H-5, H-7, 2H aromatic), 10.80 (s, indole NH, 1H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.69; H, 6.76; N, 8.85.

2-Acetyl-2,3,4,9-tetrahydro-6-methoxy-1-(methoxymethyl)-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indole (**5d**).

Compound **5d** was obtained from **4d** (62% yield) as white crystals after recrystallization from ethanol, mp 144-145°; uv (ethanol): λ max nm (ϵ) 225 (29,100), 277 (9150), 296 sh (7000), 308 sh (4000); ir (nujol): 3250 (NH), 1705 (ketone C=O), 1630, 1614 (NC=O); ir (chloroform): 3410 (NH), 1720 (ketone C=O), 1640 (NC=O) cm^{-1} .

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.37; H, 7.11; N, 8.39.

Base Catalyzed Cleavage of Amido Ketones 5.

N-[2-[2-(1-Methyl-3-oxo-1-butenyl)-1H-indol-3-yl]ethyl]acetamide (6a).

A solution of 5.7 g (0.02 mole) of 2-acetyl-2,3,4,9-tetrahydro-1-methyl-1-(2-oxopropyl)-1H-pyrido[3,4-b]indole (5a) and 5.0 g of sodium methoxide in 50 ml of absolute ethanol was refluxed for 2 hours and subsequently the solvent was evaporated *in vacuo*. Cold water was added and the product was extracted twice with 75 ml of chloroform. The combined extracts were washed with water, dried over sodium sulfate and evaporated to dryness. The solid residue was crystallized from ethyl acetate to give 2.4 g of analytically and chromatographically ($R_f = 0.25$, chloroform-ethyl acetate, 3:1) pure N-[2-[2-(1-methyl-3-oxo-1-butenyl)-1H-indol-1-yl]ethyl]acetamide (6a) as pale yellow crystals, mp 161-162°. Concentration of the mother liquor and cooling gave 1.1 g (total yield: 61%) of additional product, mp 160-161°; uv (ethanol): λ max nm (ϵ) 217 (24,450), 255 (8775), 351 (14,570); ir (nujol): 3320 (NH), 1660 (C=C-COCH₃), 1650, 1570 (NHCOCH₃) cm⁻¹; ¹H-nmr (DMSO-d₆): δ 1.80 (s, CH₃C=C, 3H), 2.28 (s, CH₃CO, 3H), 2.52 (s, CH₃CON, 3H), 3.02 (m, CH₂-indole, 2H), 3.24 (m, CH₂N, 2H), 6.65 (s, vinylic, 1H), 7.00-7.60 (m, 4H aromatic), 8.00 (t, CH₂NH, 1H, J = 6.0 Hz, deuterium oxide-exchangeable), 11.04 (s, indole NH, 1H).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 72.02; H, 7.20; N, 9.99.

N-[2-[2-[(1-Methoxymethylene)-3-oxobutyl]-1H-indol-3-yl]ethyl]acetamide (7).

A solution of 0.8 g of 2-acetyl-2,3,4,9-tetrahydro-1-(methoxymethyl)-1-(2-oxopropyl)-1H-pyrido[3,4-b]indole (5c) and 0.8 g of sodium methoxide in 25 ml of ethanol was refluxed under nitrogen for 90 minutes. The (chloroform-ethyl acetate, 3:1) showed complete reaction, the new product having slower mobility ($R_f = 0.28$) than the starting material ($R_f = 0.35$). The solvent was evaporated, the residue was taken up with cold water, and the product was extracted twice with 25 ml of dichloromethane. The combined extracts were dried over sodium sulfate and evaporated to dryness. The residue was triturated with ethyl acetate to give 0.4 g of 7 as off-white crystals, mp 165-167°. An analytical sample, melting at 167-168°, was obtained by recrystallization from ethyl acetate; uv (ethanol): λ max nm (ϵ) 216 (24,480), 256 (8780), 352 (14,570); ir (nujol): 3320, 3270 (NH), 1702 (ketone C=O), 1655, 1545 (NHC=O) cm⁻¹; ir (chloroform): 3420 (NH), 1710 (ketone C=O), 1670, 1530 (NHC=O) cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.87 (s, CH₂COCH₃, 3H), 2.23 (s, NHCOCH₃, 3H), 2.98 (t, CH₂-indole, 2H, J = 7.0 Hz), 3.50 (m, CH₂NH, 2H), 3.57 (s, CH₂COCH₃, 2H), 3.73 (s, OCH₃, 3H), 6.33 (broad, NHCOCH₃, 1H, deuterium oxide-exchangeable), 6.50 (s, vinylic, 1H), 6.90-7.45 (m, 4H aromatic), 9.24 (indole NH).

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 69.05; H, 6.91; N, 9.01.

N-[2-[2-[(1-Methoxymethyl)-3-oxo-1-butenyl]-1H-indol-3-yl]ethyl]acetamide (6b).

A solution of 0.2 g of N-[2-[2-[(1-methoxymethylene)-3-oxobutyl]-1H-indol-3-yl]ethyl]acetamide (7) in 3 ml of glacial acetic acid was heated at 100° for 15 minutes and subsequently the solution was evaporated *in vacuo*. The residue was taken up with cold water, made basic with potassium bicarbonate and extracted with chloroform. The extract was dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from isopropyl ether-ethyl acetate (2:1) gave the conjugated ketone derivative 6b as off-white crystals, mp 156-157°; uv (ethanol): λ max nm (ϵ) 255 (8780), 352 (14,570); ir (nujol): 3320 (NH), 1662 (C=C-COCH₃), 1650, 1570 (NHCOCH₃) cm⁻¹.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.39; H, 7.16; N, 9.07.

Controlled Catalytic Hydrogenation of Compounds 6 and 7.

N-[2-[2-(1-Methyl-3-oxobutyl)-1H-indol-3-yl]ethyl]acetamide (8).

A solution of 1.0 g of N-[2-[2-(1-methyl-3-oxo-1-butenyl)-1H-indol-3-yl]ethyl]acetamide (6a) in 25 ml of ethanol was hydrogenated over 0.1 g of 5% palladium-on-charcoal at atmospheric pressure until one molar equivalent of hydrogen was absorbed (90 minutes). After the catalyst was removed, the filtrate was evaporated *in vacuo*. Trituration of the residue with ethyl acetate-diethyl ether gave 0.6 g of white crystals, mp 114-115°. Recrystallization from ethyl acetate-diethyl ether (1:2) gave pure N-[2-[2-(1-methyl-3-oxobutyl)-1H-indol-3-yl]ethyl]acetamide 8 as white crystals, mp 115-116°; uv (ethanol): λ max nm (ϵ) 225 (37,200), 275 sh (7600), 282 (8250), 290 (7250); ir (nujol): 3375, 3300 (NH), 1711 (ketone C=O), 1652, 1531 (NHC=O) cm⁻¹; ir (chloroform): 3450, 3340 (NH), 1714 (ketone C=O), 1662, 1532 (NHC=O) cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.27 (d, CH₃CH, J = 7.0 Hz), 1.90 (s, CH₂COCH₃, 3H), 2.00 (s, NHCOCH₃, 3H), 2.90 (m, CH₃COCH₂ and CH₂-indole, 4H), 3.55 (m, CH₃CONHCH₂ and CH₂CHCH₃, 3H), 6.63 (t, NH, 1H, J = 6.0 Hz), 9.38 (indole NH, 1H).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.47; H, 7.98; N, 9.69.

N-[2-[2-[(1-Methoxymethyl)-3-oxobutyl]-1H-indol-3-yl]ethyl]acetamide (9).

The same procedure was followed as for the preparation of 8. Thus, 1.0 g of N-[2-[2-[(1-methoxymethylene)-3-oxobutyl]-1H-indol-3-yl]ethyl]acetamide (7) gave 0.45 g of N-[2-[2-[(1-methoxymethyl)-3-oxobutyl]-1H-indol-3-yl]ethyl]acetamide 9 as white crystals, mp 126-127°; uv (ethanol): λ max nm (ϵ) 225 (37,800), 275 sh (7750), 283 (8250), 291 (7200); ir (nujol): 3340, 3290 (NH), 1698 (ketone C=O), 1649, 1558 (NHC=O); ir (chloroform): 3430, 3350 (NH), 1714 (ketone C=O), 1661, 1533 (NHC=O) cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.90 (s, CH₂COCH₃, 3H), 2.12 (s, NHCOCH₃, 3H), 3.00 (m, 2.98, CH₂COCH₃ and CH₂-indole, 4H), 3.33 (s, CH₃O, 3H), 3.65 (m, CH₂N, CHCH₂, 5H).

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.52; H, 7.66; N, 9.02.

Cyclization of Enamines 3 Accompanied by Elimination of Methoxy Acetone to Give 4,9-Dihydro-1-methyl-3H-pyrido[3,4-b]indoles 10.

4,9-Dihydro-1-methyl-3H-pyrido[3,4-b]indole (10a).

To a solution of 0.9 g of 1-methoxy-4-[[2-(1H-indol-3-yl)ethyl]amino]-3-penten-2-one (3d) in 50 ml of chloroform was introduced dry hydrogen chloride for 2 minutes at 25°. Ice-water was added and the mixture was made basic with potassium bicarbonate. The chloroform phase was washed, dried over sodium sulfate and evaporated. Trituration of the dark residue with ethyl acetate gave 0.4 g of off-white crystals, mp 181-182°. Recrystallization from 2-propanol-acetonitrile (1:2) gave pure 4,9-dihydro-1-methyl-3H-pyrido[3,4-b]indole (10a), mp 182-183° [lit (5a), mp 182-183°; (5b), 181-182°; (5c) 180-181°]; uv (ethanol): λ max nm (ϵ) 235 (15,850), 238 sh (15,600), 315 (15,200); uv (ethanolic HCl): 244 (10,750), 345 (21,200); ir (chloroform): 3490 (NH), 1627 (C=N) cm⁻¹; ¹H-nmr (deuteriochloroform): δ 2.33 (s, CH₃, 3H), 2.83 (t, CH₂-indole, 2H, J = 8.0 Hz), 2.95 (t, CH₂N, 2H, J = 8.0 Hz), 6.95-7.40 (m, 4 aromatic protons), 8.52 (indole NH, 1H).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.15; H, 6.57; N, 15.20. Found: C, 78.17; H, 6.52; N, 15.04.

4,9-Dihydro-6-methoxy-1-methyl-3H-pyrido[3,4-b]indole (10b).

To a solution of 1.2 g of 1-methoxy-4-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-3-penten-2-one (3f) in 25 ml of chloroform was introduced dry hydrogen chloride for 4 minutes at 23° and the solution was made basic immediately by the addition of aqueous ammonia at 0°. The chloroform extract was washed, dried over sodium sulfate and evaporated to dryness. Trituration of the residue with ethyl acetate gave 0.5 g of off-white crystals, mp 205-208°. Recrystallization from acetonitrile gave 0.3 g of pure 4,9-dihydro-6-methoxy-1-methyl-3H-pyrido[3,4-b]indole (10b), mp 208-209°; uv (ethanol): λ max nm (ϵ) 235 (15,850), 239 sh (15,600), 316 (15,250); ir (chloroform): 3490 (NH), 1613 (C=N), 1020 (OCH₃) cm⁻¹; ¹H-nmr (deuteriochloroform): δ 2.32 (s, CH₃-C=N, 3H), 2.78 (t, CH₂-

indole, 2H, J = 7.5 Hz), 3.93 (m, CH₂N, CH₃O, 5H), 6.80 (dd, H-7, 1H, J = 8.0 and 2.0 Hz), 6.83 (d, H-5, 1H, J = 2.0 Hz), 7.20 (d, H-8, 1H, J = 8.0 Hz), 10.04 (indole NH, 1H).

Anal. Calcd. for C₁₃H₁₄N₂O: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.71; H, 6.59; N, 13.26.

2,3,4,9-Tetrahydro- α ,1-dimethyl-1H-pyrido[3,4-b]indole-1-ethanol (II).

To a stirred solution of 8.0 g (0.0285 mole) of 1-(2,3,4,9-tetrahydro-1-methyl-1H-pyrido[3,4-b]indol-1-yl)-2-propanone hydrochloride (4a) in 100 ml of methanol was added 2.0 g of potassium borohydride portionwise at 0° and then allowed to warm up to room temperature within one hour. The solution was evaporated *in vacuo* at 28°, the residue was taken up with cold water and the resulting white crystals (7.6 g) were collected, mp 208-210°. Two recrystallizations from acetonitrile gave 6.2 g (78% yield) of pure II, mp 210-211°; uv (ethanol): λ max nm (ϵ) 225 (36,300), 274 sh (7180), 280 (7390), 289 (600); ir (nujol): 3200 (broad, NH, OH), 1069 (C-O) cm⁻¹; ¹H-nmr (DMSO-d₆): δ 1.02 (d, CH₃CHOH, 3H, J = 6.0 Hz), 1.46 (s, CH₃-C-N, 3H), 1.70 (m, CH₂CHO, 2H), 2.66 (t, CH₂-indole, 2H, J = 4.5 Hz), 2.98 (m, CH₂N, 2H), 4.05 (m, CHOH, 1H), 6.55 (broad, OH, 1H), 6.90 (m, H-6, H-8, 2H, aromatic), 7.25 (m, H-5, H-7, 2H, aromatic), 10.60 (indole NH, 1H).

Anal. Calcd. for C₁₃H₂₀N₂O: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.99; H, 8.41; N, 11.50.

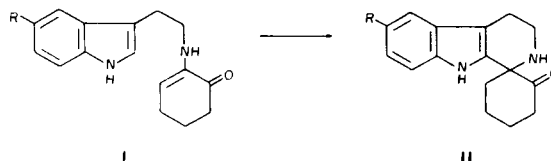
In contrast to aminoketones 4 which are very sensitive to alkali, compound II remained unchanged after refluxing in aqueous ethanolic sodium hydroxide for 5 hours.

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