2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indoles. II [1]. Reversible Transformation of 1-Alkyl-2-(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)cyclohexanol into 1-Alkylidene-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles

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Treatment of 2-(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-methylcyclohexanol (**2a**) with acetic anhydride or methyl isocyanate gave 2-acetyl-2,3,4,9-tetrahydro-1-(6-oxoheptylidene)-1*H*-pyrido[3,4-*b*]indole (**3**) or 1,3,4,9-tetrahydro-*N*-methyl-1-(6-oxoheptylidene)-2*H*-pyrido[3,4-*b*]indole-2-carboxamide (**4**), respectively. Simpler analogues, 1-alkyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indoles, **7**, subjected to identical reaction conditions, gave 2-acetyl-1-alkylidene-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles **8** and 1,3,4,9-tetrahydro-*N*-methyl-1-alkylidene-2*H*-pyrido[3,4-*b*]indole-2-carboxamides **9**, respectively. A limited lanthanide shift reagent study to determine stereochemical assignments was also performed.

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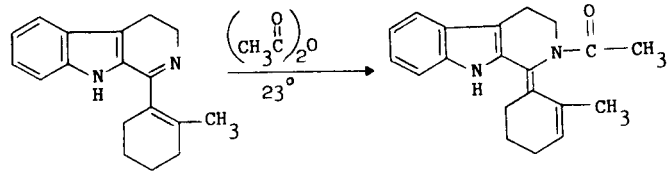
In the previous paper [1] we discussed the base-catalyzed irreversible rearrangement of β-amino ketone derivatives **1** into 4,9-dihydro-3*H*-pyrido[3,4-*b*]indoles **2**. This paper describes further transformation of **2a** into **3** and **4** and spectral studies which prove structural assignments. In addition, further chemical transformations of **3** and **4** are described (Scheme I).

Compound **2a** was selected for further studies as a representative of the rearranged products **2**. Treatment of **2a** with acetic anhydride at room temperature caused cleavage of the cyclohexane ring and resulted in the formation of an enamido ketone derivative **3**.

Apparently, the rupture occurred between the same carbon atoms which participated in ring closure during formation of **2a** [1]. Elemental analyses, mass, and other spectral data confirm structure **3** (see Experimental). In contrast to **2a**, the cyclohexene ring of its dehydration product **10** [1] did not undergo cleavage under the same conditions giving instead the enamido derivative **11**.



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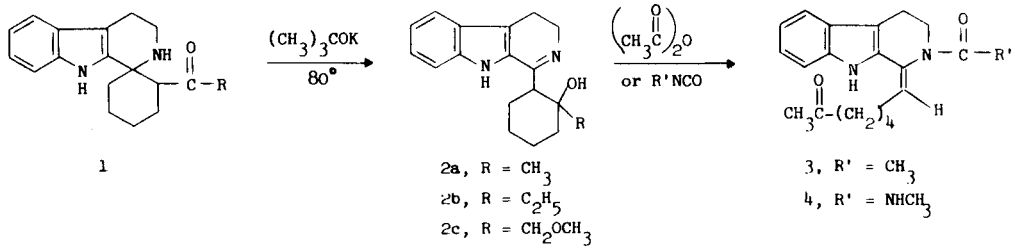
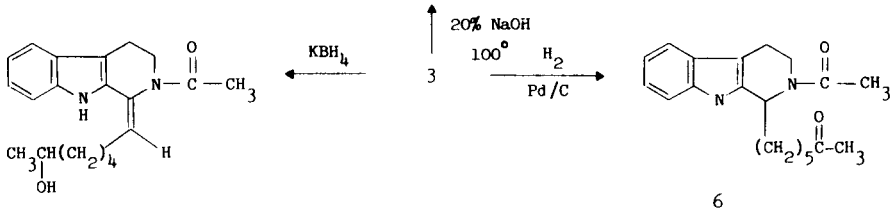
Scheme I



1 2a, R = CH_3; 2b, R = C_2H_5; 2c, R = CH_2OCH_3 3, R' = CH_3; 4, R' = $NHCH_3$



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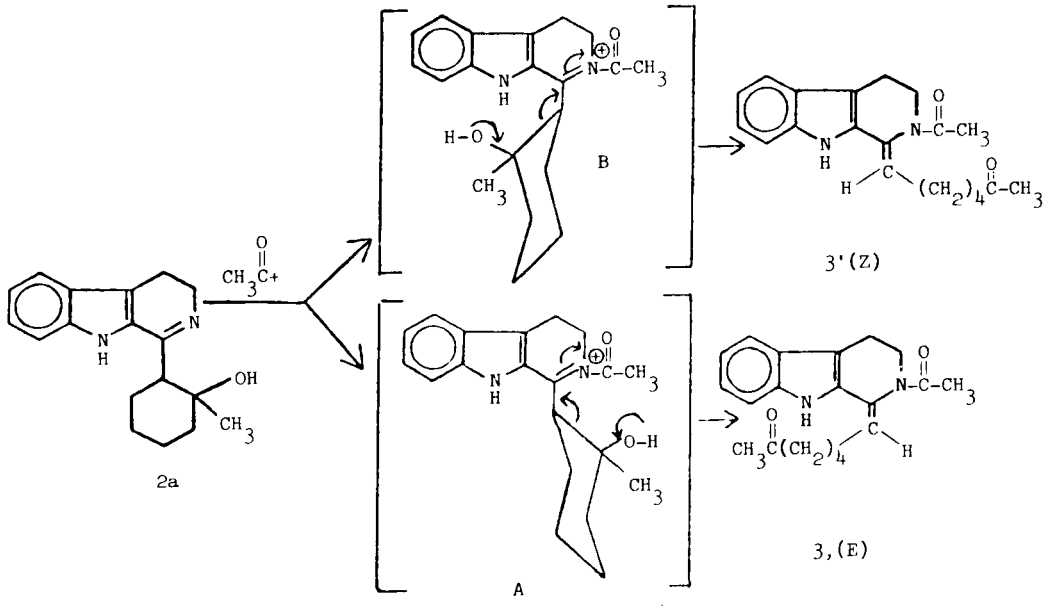


The configuration about the double bond of **3**, *cis* (*Z*) or *trans* (*E*) can be assigned by considering the possible transition states leading to its formation. The bonds undergoing transformation must be coplanar in the transition state. Two conformations, **A** and **B**, allow coplanarity. Conformation **B** is not likely because of steric crowding between the indole moiety and substituents on the cyclohexyl ring. Thus, **A** is the probable conformation undergoing reaction leading to the *E* (*trans*) product **3**.

Mechanistically, the rearrangement of **2a** to **3** can be rationalized in the following way. Addition of the acetyl group creates a positive charge on the α-carbon (**A** or **B**). Neutralization of this charge becomes a driving force for the C-C bond cleavage and electron shifts shown below.

The resulting enamido ketone **3** was a single stereoisomer as demonstrated by tlc, hplc, sharp melting point and spectral data. Assignment of the *E*-configuration to this isomer was confirmed by the lanthanide shifted ^{1}H nmr experiment [2].

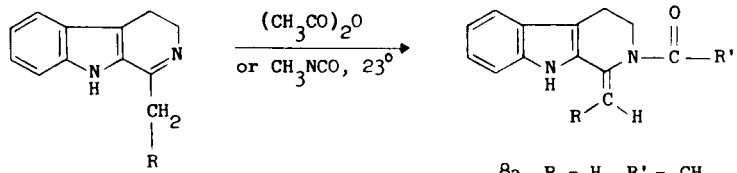
A similar transformation occurred when **2a** was treated with alkyl isocyanate to give urea ketone **4**. Compound **4** was also a single stereoisomer. Assignment of the *E*-configuration was confirmed by shift reagent studies on this compound as well.

In addition to **3** and **4**, the simple analogues **8** and **9**, were prepared under similar reaction conditions from the corresponding dihydro derivatives **7** [1,4,5]. The lanthanide induced spectra (LIS) of **8** and **9** using Eu(fod)$_3$ [3] were also recorded for comparison and are discussed in the section "Structural Stereochemical Studies".

It was also found that **3** and **8b** could be transformed into their more thermally stable stereoisomers **3'** and **8b'**, respectively, by refluxing acetic anhydride. While the infrared, mass and ^{13}C nmr spectra of **3'** and **8b'** are very similar to the precursors **3** and **8b**, their ^{1}H nmr spectra differ considerably. The allyl methylene group of **3'** and allyl methyl group of **8b'** resonate at higher fields and the vinylic protons at lower fields than their stereoisomers **3** and **8b**, respectively (for further details see Experimental).

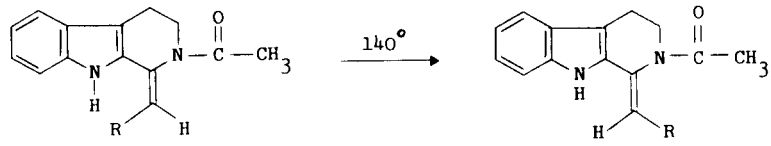
Structural Stereochemical Studies.

Analysis of the ^{1}H nmr spectra of compounds **3, 4, 8b** and **9b** have shown their vinylic protons to resonate within a relatively narrow range (δ 5.45-5.75). To obtain more



7a, R = H
7b, R = CH_3

8a, R = H, R' = CH_3
8b, R, R' = CH_3
9a, R = H, R' = $NHCH_3$
9b, R = CH_3, R' = $NHCH_3$



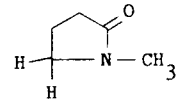
3, R = $(CH_2)_4C(=O)CH_3$
8b, R = CH_3

3', R = $-(CH_2)_4C(=O)CH_3$
8b, R = CH_3

stereochemical information, we have done several ^1H nmr experiments using Eu(fod)$_3$ in varying concentrations. As is well-known [2,17], the lanthanide complexes induce paramagnetic shifts in the nmr spectra of polar organic molecules. Although the induced shifts are a composite of dipolar (pseudo-contact, "through space") and contact interactions [6,7], the contributions of the latter are negligible.

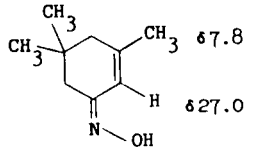
The presence of the indole proton, which is known to be rather inert to the shift reagents [8], was not expected to interfere to any significant extent. In the case of compounds **3** and **4** there are two main centers of complexations between Eu(fod)$_3$ and the ketone and amide functionalities. However, since the ketone carbonyl is sufficiently removed from the protons of interest, its effect could be ignored.

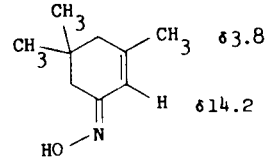
Amides are known to protonate on the carbonyl oxygen [9] due to extensive delocalization of the lone pair electrons on the nitrogen atom. It was expected that the shift reagent would complex with the basic lone pair electrons on the oxygen atom [10]. This is exemplified by the dramatic difference between the *cis* and *trans* protons of 1-methyl-2-pyrrolidinone [11]



δ5.49 δ10.12

and by the *cis* (*syn*) and *trans* (*anti*) oximes [12a-b].





For our study we selected Eu(fod)$_3$ as the shift reagent since the concomitant line broadening is relatively small [13] and its higher Lewis acidity induced by fluorinated substituents cause larger induced shifts [14]. Since we were interested in studying qualitative rather than quantitative relationships, the concentration of shift reagent with respect to the substrates was quite small. Consequently, the resulting shifts are the average of complexed and free substrates.

Addition of increasing amounts of a solution of Eu(fod)$_3$ in deuteriochloroform to solutions of **3, 4, 8a, 8b** and **8b'** in the same solvent caused downfield shifts of all the neighboring protons to the amide function. As expected, the most affected protons by the LSR were those of an acetyl methyl group and of an *N*-methylene group (CH_2-3). Since they resonate as a singlet and a distinct triplet, respectively, they did not overlap with the protons in which we were particularly interested (vinylic and allylic). The protons directly attached to the ketone function were distinctly different and did not interfere with our measurements.

The ^1H nmr spectrum of **3** displays a remarkable regularity of its protons and their splitting patterns. For example, the CH_2-4 and CH_2-5 of the side chain appear as an envelope at δ 1.40-1.85; the two methyl groups are shown as singlets at δ 2.15 and δ 2.20. The two side-chain methylene groups (CH_2-3 and CH_2-6) are equivalent and appear as a narrow multiplet at δ 2.53. The ring methylene

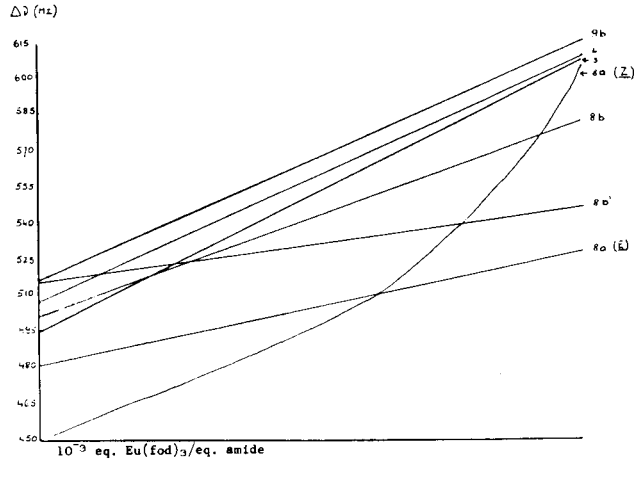


Figure 1. The induced chemical shifts, Δν, versus the amount of added shift reagent for the vinylic protons of amides **3, 8a, 8b, 8b'** and of ureas **4** and **9b**. The starting points at left indicate the corresponding resonances in the same solvent without Eu(fod)$_3$. 10^{-3} equivalents of Eu(fod)$_3$/equivalent of amides as a 2% solution in deuteriochloroform and as a 1% solution of ureas in deuteriochloroform. Data from direct comparison of **3** and **3'** shift experiments are omitted due to scalar differences in Eu(fod)$_3$ concentration. All spectra for this graph were recorded on a Bruker WH90 spectrometer.

groups (CH_2-4 and CH_2-3) appear as triplets (J = 6.5 Hz) at δ 2.95 and δ 4.12, respectively, while the vinylic proton resonates as a triplet (J = 7.5 Hz) at δ 5.50. With the shift reagent [Eu(fod)$_3$] the vinylic proton underwent the paramagnetic shift of Δ = 1.28 ppm (Figure 1) while the allylic methylene group sustained a shift of Δ = 0.60 ppm.

The ^{1}H nmr spectrum obtained for compound **3'** was not as informative as that obtained for **3** owing to the large number of multiple and isochronous signals in the range of δ 1.30-3.20. The signals of interest, however, could easily be discerned. In this isomer, the vinylic proton occurs as a multiplet at δ 5.66 and the deshielded one *N*-methylene proton occurs as a compressed multiplet resembling a distorted AB quartet at δ 5.08.

The ^{1}H nmr spectrum of **8b** also displays a regular pattern similar to **3** except for the absence of the side chain (for details see Experimental). In the presence of Eu(fod)$_3$ the vinylic proton was shifted downfield by Δ = 0.90 ppm and the allylic methyl group underwent a shift 0.52 ppm. Although both shifts of **8b** are of somewhat lesser magnitude than those of **3**, there is some parallelism between **3** and **8b** in accordance with the similarity of conditions of their formation (23°).

In sharp contrast to **8b**, the ^{1}H nmr spectrum of **8b'** displays an irregular pattern. The allylic methyl group resonates at δ 1.88 (d, J = 7.5 Hz). While the CH_2-4 group resonates at a comparable field to that of **8b** (δ 3.05, m), the two protons of the *N*-methylene group are nonequivalent and show a large difference in their chemical shifts. One proton of NCH_2 appears as a multiplet at a higher than expected field (δ 2.68) while another proton shows an unusually large downfield shift at δ 5.05 (m). The dissimilar patterns of the two NCH_2 protons reflect the different angles which they make with the neighboring methylene protons (CH_2-4) as well as with the amide carbonyl due to distortion of the ring. A similar, albeit less extreme situation, was noted previously [16].

With Eu(fod)$_3$ the allylic methyl shift of **8b'** was of the same magnitude as that of **8b**. However, the vinylic proton underwent only a negligible shift (Δ = 0.34 ppm) when the same proportion of reagent was used. This unusually small downfield shift is in agreement with the assumption that **8b'** has *Z*-configuration. Consequently, it is expected that the proton farther removed from the complexation site would be less affected than one located on the same side of the double bond as the LSR-amide moiety.

The above assumption was further confirmed by the analysis of Eu(fod)$_3$ shifted spectra of amide **8a**. The two methylene protons are, as expected, nonequivalent and appear as widely separated doublets (J = 2.0 Hz) at δ 5.00 and δ 5.35, respectively. With gradually increasing amounts of Eu(fod)$_3$, the upfield proton (δ 5.00) moved downfield much faster than the lower-field one (δ 5.35), eventually overtaking it to give a total shift of Δ = 1.73 ppm. The lower-field proton at the same time underwent only about one-third of this shift (Δ = 0.52 ppm). These data indicate that the originally upfield vinylic proton was on the same side of the double bond as the LSR-amide moiety (*Z*-relationship). The behavior of the *cis* (*Z*) proton of **8a** is consistent with the assignment of configurations for **3**, **8b** and **8b'**.

The urea derivatives **4** and **9b** show regular patterns in their ^{1}H nmr spectra. With Eu(fod)$_3$, the vinylic protons of **4** and **9b** underwent similar chemical shifts to **3** and **8b**, *i.e.*, Δ = 1.19 ppm and Δ = 1.12 ppm, respectively. Because of low solubility in deuteriochloroform, the spectra of urea **9a** could not be recorded for comparison with **4** and **9b**.

Finally, a direct comparison of sensitivity to the europium shift reagent was made between the two exo methylene isomers of compound **3** utilizing a 200 MHz spectrometer. Compounds **3** and **3'** were prepared as 0.055-0.06 molar solutions in deuteriochloroform containing 0.03% v/v tetramethylsilane (TMS) as an internal standard. After normal spectra were acquired, the deuteriochloroform solutions were made approximately 0.004 molar in Eu(fod)$_3$, and a second spectrum obtained with identical spectrometer configuration. As observed for the simple isomers **8a** and **8b**, the vinyl proton in the *E* isomer **3** resonates at higher field and is more sensitive to lanthanide concentration than the corresponding proton in the *Z* isomer.

A Varian XL200, equipped with a tunable probe was configured to obtain proton spectra in dilute deuteriochloroform solution. Compound **3** was prepared as a 0.059 molar solution in deuteriochloroform, a spectrum was obtained, Eu(fod)$_3$ (0.0029 g, 6.5 mole %) added, and a shifted spectrum obtained. The vinyl proton was observed as a triplet (δ 5.49, 1H, J = 7.5 Hz) which remained a triplet, though with some loss of resolution, and moved to δ 5.75, a downfield shift of Δ = 0.259 ppm, or 0.04 ppm per mole % shift reagent.

Compound **3'** was prepared as a 0.056 molar solution in deuteriochloroform, a spectrum was obtained, Eu(fod)$_3$ (0.003 g, 7.2 mole %) added, and a shifted spectrum obtained. The vinyl proton was observed as a multiplet (δ 5.74-5.57, 1H) which also remained a multiplet with some broadening of the signal, which moved to δ 5.98-5.78, a downfield shift of Δ = 0.233 ppm, or 0.03 ppm per mole % shift reagent.

On the basis of this study with the shift reagent, it has been shown that amides **3** and **8b** have the *E*-configuration while amides **3'** and **8b'** (obtained by thermal transformation from **3** and **8b**, respectively) have the *Z*-configuration.

Since the formation and response to shift reagent of the ureas **4** and **9b** are so similar to the amides **3** and **8b**, we

conclude that **4** and **9b** also have the *E*-configuration.

Alkaline hydrolysis of **3** resulted in recovery of **2a**. The potassium borohydride reduction of **3** gave alcohol **5** without affecting the double bond. The selectively controlled catalytic hydrogenation of **3** gave the saturated amido derivative **6**.

As expected, both stereoisomeric amides **8b** and **8b'** gave a single dihydro derivative **7b** on hydrolysis.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover melting point apparatus which was calibrated against known standards and are uncorrected. The ultraviolet (uv) and infrared (ir) spectra were obtained on a Beckman DK-1 spectograph. The ^{1}H nmr spectra were obtained on either a Varian A-60, and a Bruker WH90, or Varian XL200 spectrometers with tetramethylsilane as an internal reference. Carbon magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker WH90 with a 22.63 MHz operating frequency in deuteriochloroform or deuterated dimethylsulfoxide (DMSO-d_6). The mass spectra were recorded on a Finnigan 1015 Quadrupole Mass Spectrometer. Tlc was carried out on silica gel G (Stahl) and the chromatograms were developed in an iodine chamber. The assignment of protons in the ^{1}H nmr spectra was done whenever the signals were distinctly separated and there was sufficient resolution.

Reactions of 2-(4,9-Dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-methylcyclohexanol (**2a**).

(*E*)-2-Acetyl-2,3,4,9-tetrahydro-1-(6-oxoheptylidene)-1*H*-pyrido[3,4-*b*]indole (**3**).

A solution of 2.0 g (0.0071 mole) of 2-(4,9-dihydro-3*H*-pyrido[3,4-*b*]-indol-1-yl)-1-methylcyclohexanol (**2a**), 3.0 g of acetic anhydride and 3 drops of triethylamine in 20 ml of ethyl acetate was allowed to stand at 25° for two days. The resulting white crystals (1.3 g, mp 158-159°) were collected by filtration. To the filtrate was added ice-water and aqueous ammonia to *p*H 8.5, and separated. The organic phase was washed, dried over sodium sulfate and concentrated to a low volume giving 0.6 g of additional product, mp 158-159°. Recrystallization of the combined crops from ethyl acetate gave 1.6 g (69% yield) of pure ketoamide **3**, mp 159-160°; uv (methanol): λ max nm (ε) 225.5 (21,200), 303 sh (17,000), 309 (17,200); ir (nujol): 3240 (NH), 1711 (ketone C=O), 1630 (amide C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.15 (3H, COCH_3), 2.20 (3H, N-COCH_3), 2.45 [t, J = 6.5 Hz, 4H, C=C-CH_2-(CH$_2$)$_2$ and CH_2-C=O], 2.85 (t, J = 6.5 Hz, 2H, CH_2-indole), 4.07 (t, J = 6.5 Hz, 2H, CH_2-N), 5.45 (t, J = 7.5 Hz, 1H, vinylic), 9.06 (1H, NH-indole); mass spectrum, m/z 324. Tlc (ethyl acetate) showed one spot, R_f = 0.5.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.63. Found: C, 74.17; H, 7.50; N, 8.88.

(*Z*)-2-Acetyl-2,3,4,9-tetrahydro-1-(6-oxoheptylidene)-1*H*-pyrido[3,4-*b*]indole (**3'**). (Method B).

A solution of 0.8 g of **3** in 20 ml of triethylamine was refluxed under nitrogen for 12 hours and subsequently evaporated to dryness. The dark residue was taken up with dichloromethane, filtered through the silica gel and evaporated. Crystallization of the residue from ethyl acetate-cyclohexane (2:1) gave the analytically and chromatographically pure (R_f = 0.55) stereoisomer **3'**, mp 101-102°; uv (methanol): λ max nm (ε) 225 (21,200), 309 (17,200); ir (potassium bromide): 3240 (NH), 1711 (ketone C=O), 1630 (amide C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.30-3.20 (m, 4H), 2.07 (s, 3H, CH_3), 2.15 (s, 3H, embedded in m 2.12-2.19 integral), 2.34-2.49 (m, 3H), 2.66-2.72 (m, 1H), 3.04-3.11 (m, 2H), 5.08 (compressed multiplet, appearing as an irregular AB quartet, 1H), 5.59-5.57 (m, 1H, vinylic), 7.05-7.50 (m, 4H, aromatic), 8.45 (1H, NH-indole); ms: m/z 324.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.63. Found: C, 74.15; H, 7.26; N, 8.65.

(*E*)-1,3,4,9-Tetrahydro-*N*-methyl-1-(6-oxoheptylidene)-2*H*-pyrido[3,4-*b*]-indole-2-carboxamide (**4**).

A solution of 0.6 g of **2a** and 2.0 g of methyl isocyanate in 25 ml of dichloromethane was allowed to stand overnight at 23°. After the solvent and excess isocyanate were removed, the residue was crystallized from acetonitrile to give 0.5 g (69% yield) of pure urea ketone derivative **4** as white crystals, mp 150-151°; uv (methanol): λ max nm (ε) 228 (21,300), 248 (13,800), 304 (24,600), 312 (24,200); ir (nujol): 3380, 3230 (NH), 1709 (ketone C=O), 1631, 1528 (CH$_3$NHC=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.30-1.75 (m, broad envelope, 4H, 3,4-methylene groups of the ketone chain), 2.12 (s, 3H, CH_3C=O), 2.16-2.50 (m, 4H, 2,5-methylene groups of the ketone chain), 2.80 (m, 5H, CH_3-NH and CH_2-indole), 4.03 (2H, t, J = 4.5 Hz, CH_2-N), 5.07 (q, J = 4.5 Hz, 1H, CH$_3$-N*H*), 5.63 (t, J = 7.5 Hz, 1H, vinylic) 7.10-7.55 (m, 4H, aromatic), 8.82 (1H, N*H*-indole); ms: m/z 339.

Anal. Calcd. for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.43; N, 12.38. Found: C, 70.62; H, 7.26; N, 12.46.

2-Acetyl-2,3,4,9-tetrahydro-1-methylene-1*H*-pyrido[3,4-*b*]indole (**8a**).

A solution of 1.3 g of 4,9-dihydro-1-methyl-3*H*-pyrido[3,4-*b*]indole (**7a**) [1,4] and 2.0 ml of acetic anhydride in 25 ml of dichloromethane was allowed to stand at 23° overnight. The contents were poured onto ice-water and made basic with potassium bicarbonate. The organic extract was dried over sodium sulfate and evaporated to give 1.4 g of off-white solid. Crystallization from acetonitrile gave 1.1 g (70% yield) of pure **8a**, mp 216-217° dec; uv (methanol): λ max nm (ε) 227 (24,500), 304 (19,700); ir (potassium bromide): 3420, 3300 (NH), 1645, 1622 (C=C-N-C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3C=O), 2.86 (t, J = 6.0 Hz, 2H, CH_2-indole), 4.13 (t, J = 6.0 Hz, 2H, CH_2N), 5.00 (d, J = 2.0 Hz, 1H, vinylic), 5.33 (d, J = 2.0 Hz, 1H, vinylic), 6.98-7.50 (m, 4H, aromatic), 8.37 (1H, N*H*-indole); ms: m/z 226.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.22; H, 6.23; N, 12.46.

(*E*)-2-Acetyl-1-ethylidene-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**8b**).

In an analogous manner 1-ethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*indole (**7b**) [1,5] and acetic anhydride gave **8b** essentially in quantitative yield. Recrystallization from 2-propanol gave 82% of analytically and chromatographically (silica gel; ethyl acetate-acetonitrile, 1:1, R_f = 0.45) pure **8b** as white crystals, mp 219-220° dec; uv (methanol): λ max nm (ε) 228 (23,800), 304 (19,900), 310 (19,900); ir (chloroform): 3510 (NH), 1640 (C=C-N-C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.04 (s, 3H, CH_3C=O), 2.09 (d, J = 7.5 Hz, 3H, CH_3CH=C), 2.73 (t, J = 6.0 Hz, 2H, CH_2-indole), 3.85 (t, J = 6.0 Hz, 2H, CH_2N), 5.56 (q, J = 7.5 Hz, 1H, vinylic), 6.65-7.40 (m, 4H, aromatic), 10.60 (1H, N*H*-indole); (deuteriochloroform): δ 2.18 (m, 6H, CH_3C=O and CH_3CH=C overlapping), 2.89 (t, J = 6.0 Hz, CH_2-indole), 4.08 (t, J = 6.0 Hz, 2H, CH_2N), 5.53 (q, J = 7.5 Hz, 1H, vinylic), 7.02-7.58 (m, 4H, aromatic), 8.29 (1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 14.7, 23.7 (2CH_3), 21.8, 43.7 (2CH_2), 13.5, 119.8, 120.4, 120.8, 123.9, 127.3, 131.0, 133.5, 138.8, 170.7 (C=O); ms: m/z 240.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.09; H, 6.76; N, 11.65.

(*Z*)-2-Acetyl-1-ethylidene-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**8b'**). Method A.

A solution of 1.3 g of **8b** in 25 ml of acetic anhydride was refluxed for 3 hours and subsequently evaporated to dryness. The dark solid residue was taken up with 25 ml of tetrahydrofuran, filtered through the silica gel and evaporated. Crystallization of the residue from 2-propanol gave 0.7 g (54% yield) of analytically and chromatographically pure (R_f = 0.52) stereoisomer **8b'** as white crystals, mp 242-243° dec [lit [15], mp 242-243° dec]; uv (methanol): λ max nm (ε) 228 (23,800), 304 (19,900), 310 (19,900); ir (potassium bromide): 3410, 3240 (NH), 1672, 1638 (C=C-N-C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.79 (d, J = 7.0 Hz, 3H, CH_3CH=C), 1.96 (s, 3H, CH_3C=O), 2.76 (m, 2H, CH_2-indole), 3.80 (m, 1H, one of CH_2N-C=O), 4.85 (m, 1H, one of CH_2N-C=O), 5.97 (q, J = 6.0 Hz, 1H, vinylic), 6.90-7.45 (m, 4H, aromatic), 11.10 (1H, N*H*-indole);

^{1}H nmr (deuteriochloroform): 1.88 (d, J = 7.0 Hz, 3H, CH_3CH=C), 2.08 (s, 3H, CH_3C=O), 2.68 (m, 1H, one of CH_2N-C=O), 3.08 (m, 2H, CH_2-indole), 5.05 (m, 1H, one of CH_2N-C=O), 5.75 (q, J = 7.0 Hz, 1H, vinylic), 7.05-7.50 (m, 4H, aromatic), 8.12 (1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 13.5, 21.2 (2CH_3), 20.8, 43.2 (2CH_2), 111.0, 114.5, 118.5, 118.8, 123.7 (5CH), 109.9, 126.5, 130.8, 132.9, 136.5 (5 C quat.), 169.8 (C=O); ms: m/z 240.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.98; H, 6.57; N, 11.54.

Method B.

A solution of 1.2 g of **8b** in 20 ml of triethylamine was refluxed under nitrogen until starting material was no longer present (10 hours, tlc). The solution was evaporated, the residue in dichloromethane solution was filtered through the silica gel and the solvent evaporated. Crystallization of the residue from acetonitrile gave 0.5 g (42% yield) of pure **8b'**, mp 242-243° dec. This product is identical in all respects with that obtained from **8b** in refluxing acetic anhydride.

1,3,4,9-Tetrahydro-*N*-methyl-1-methylene-2*H*-pyrido[3,4-*b*]indole-2-carboxamide (**9a**).

A solution of 0.4 g of **7a** and 1 ml of methyl isocyanate in 25 ml of dichloromethane was allowed to stand overnight at 23°. After the solvent and excess reagent were removed under nitrogen, the residue was crystallized from ethyl acetate to give 0.4 g (80% yield) of **9a** as nearly white crystals, mp 231-232° dec; uv (methanol): λ max nm (ε) 228 (20,900), 302 (21,950), 311 (21,400); ir (potassium bromide): 3440, 3330 (NH), 1640, 1617, 1530 (C=C-N-CONH) cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.61; H, 6.32; N, 17.23.

(*E*)-1-Ethylidene-1,3,4,9-tetrahydro-*N*-methyl-2*H*-pyrido[3,4-*b*]indole-2-carboxamide (**9b**).

A solution of 0.63 g of **7b** and 1 ml of methyl isocyanate in 25 ml of ethyl acetate was allowed to stand overnight at 23°. Methanol (1 ml) was added to destroy excess isocyanate and the solution was concentrated to a low volume to give, on cooling, 0.6 g (78% yield) of **9b**, mp 219-220° dec. An analytical sample, mp 220-221° dec, was obtained by recrystlization from 2-propanol-isopropyl ether; uv (methanol): λ max nm (ε) 228 (20,900), 303 (22,000), 311 (21,400); ir (potassium bromide): 3440, 3340 (NH), 1641, 1617, 1531 (NHC=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.87 (d, J = 7.5 Hz, 3H, CH_3=C), 2.82 (d, J = 5.5 Hz, 3H, CH_3NH), 2.85 (t, J = 5.5 Hz, 2H, CH_2-indole), 4.01 (t, J = 5.5 Hz, 2H, CH_2N), 4.93 (m, 1H, CH_3N*H*), 5.73 (q, J = 7.5 Hz, 1H, CH_3C*H*=C), 7.05-7.52 (m, 4H, aromatic), 7.93 (1H, N*H*-indole); ms: m/z 255.

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.39; H, 6.63; N, 16.45.

2-Acetyl-2,3,4,9-tetrahydro-1-(2-methyl-2-cyclohexen-1-ylidene)-1*H*-pyrido[3,4-*b*]indole (**11**).

A solution of 2.0 g of 4,9-dihydro-1-(2-methyl-1-cyclohexen-1-yl)-3*H*-pyrido[3,4-*b*]indole (**10**) [1] and 5 ml of acetic anhydride in 25 ml of ethyl acetate was allowed to stand at 23° for 2 days. The mixture was then stirred with cold water to destroy excess anhydride and separated. The aqueous phase was reextracted with 25 ml of ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated to a low volume to give 1.5 g of **11** as off-white crystals, mp 226-227°; uv (methanol): λ max nm (ε) 258 (14,000), 326 (24,400); ir (nujol): 3200 (NH), 1638, 1625 (C=C-N-C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.88 (m, 1H, vinylic), 7.03-7.50 (m, 4H, aromatic), 8.00 (1H, N*H*-indole); ^{13}C nmr (deuteriochloroform): δ 21.5, 21.7, 22.0, 22.2, 26.1, 28.6, 44.3, 110.8, 113.5, 118.9, 119.9, 123.0, 126.5, 126.7, 131.6, 132.6, 136.7, 172.5 (C=O); ms: m/z 306.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.48; H, 7.19; N, 9.20.

(*E*)-2-Acetyl-2,3,4,9-tetrahydro-1-(6-hydroxyheptylidene)-1*H*-pyrido-[3,4-*b*]indole (**5**). By Potassium Borohydride Reduction of **3**.

To a stirred solution of 0.5 g of (*E*)-2-acetyl-2,3,4,9-tetrahydro-1-(6-oxoheptylidene)-1*H*-pyrido[3,4-*b*]indole (**3**) in 25 ml of methanol was added 0.5 g of potassium borohydride. After 3 hours at 25°, the infrared spectrum indicated absence of the ketone function. The solvent was removed *in vacuo*, the residue was taken up with cold water and extracted with 50 ml of ethyl acetate. The extract was dried over sodium sulfate and concentrated to a low volume to give 0.3 g of pure enamido alcohol derivative **5**, mp 172-173°; uv (methanol): λ max nm (ε) 228 (24,650), 244 infl (18,500), 304 (21,900), 311 (22,050); ir (chloroform): 3610, 3540, 3360 (OH, NH), 1633 (C=C-N-C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.05 (d, J = 6.5 Hz, 3H, CH_3CH), 2.06 (s, 3H, CH_3C=O), 2.77 (t, J = 6.0 Hz, 2H, CH_2-indole), 3.98 (t, J = 6.0 Hz, 2H, CH_2N), 4.39 (1H, deuterium oxide-exchangeable, OH), 5.58 (t, J = 7.5 Hz, 1H, vinylic), 7.10-7.65 (m, 4H, aromatic), 10.55 (1H, N*H*-indole); ms: m/z 326.

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.30; H, 7.85; N, 8.67.

2-Acetyl-2,3,4,9-tetrahydro-1-(6-oxoheptyl)-1*H*-pyrido[3,4-*b*]indole (**6**). Controlled Catalytic Hydrogenation of **3**.

One g of **3** was hydrogenated over 0.1 g of palladium-on-charcoal (5%) in ethanol at atmospheric pressure until one molar equivalent of hydrogen was absorbed (20 minutes). After the catalyst was removed, the solution was evaporated *in vacuo*. Trituration of the colorless semisolid residue with ether gave 0.8 g (80% yield) of white crystals, mp 125-126°. An analytical sample of **6**, mp 126-127°, was obtained by recrystallization from ethyl acetate; uv (methanol): λ max nm (ε) 225 (41,000), 274 sh (7900), 282 (8050), 291 (6500); ir (nujol): 3280 (NH), 1713 (ketone C=O), 1630 (amide C=O) cm^{-1}; ms: m/z 326.

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.55. Found: C, 73.61; H, 8.25; N, 8.85.

Transformation of 2-Acetyl-2,3,4,9-tetrahydro-1-(6-oxoheptylidene)-1*H*-pyrido[3,4-*b*]indole (**3**) into 2-(4,9-Dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-methylcyclohexanol (**2a**).

A solution of 1.0 g of **3** in 30 ml of ethanol and 10 ml of 20% aqueous sodium hydroxide was refluxed for 3 hours. Cold water was added and the product was extracted twice with 50 ml of chloroform. The combined extracts were washed, dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from ethyl acetate gave 0.4 g (46% yield) of **2a** as white crystals, mp 150-151° dec. A mixture mp with an authentic sample [1] was not depressed and the spectra are identical.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; H, 9.92. Found: C, 76.61; H, 7.78; H, 9.96.

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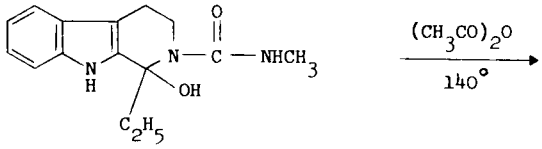

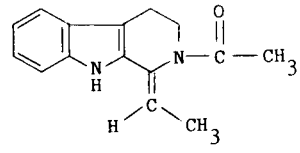

dehydration-transamidation was assumed to have *E* (*trans*) configuration. On the basis of ^{1}H nmr and shift reagent studies, its configuration has to be reassigned as that of *Z* (*cis*) as shown above.

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