1,1-Disubstituted-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indolecarboxylic Acid Esters and Ketones. The Base Catalyzed Transformation of 1-(2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indol]-2-yl)alkanones into 2-(4,9-Dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-alkylcyclohexanols

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Condensation of 1*H*-indole-3-ethanamines **1** with cyclic β-keto esters **2** under azeotropic conditions followed by acid-catalyzed ring closure of the resulting enamines **3** gave 2',3',4',9'-tetrahydrospiro[piperidine-3,1'-[1*H*]pyrido[3,4-*b*]indole]-4-carboxylic acid alkyl esters **4**. Condensation of **1** with 2-acylcycloalkanones **8** gave two types of enamines, **10** and **11**, respectively. Enamines **10** on treatment with acid gave 1-(2',3',4',9'-tetrahydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-alkylcyclohexanols **17**. Compounds **17** were further dehydrated to give cycloalkane derivatives **19**.

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In the course of research on drugs with antihypertensive properties, we were interested in the compounds resulting from condensation of 1*H*-indole-3-ethanamines (tryptamines), **1**, with β-keto esters **2** and subsequent acid-catalized transformation of the intermediate imino derivatives. The chemistry uncovered in these investigations is novel and is reported below.

We have found that condensation of **1** with an equimolar amount of **2** under azeotropic conditions gave enamine **3**. When the cyclic ketone ester constituted a 6-membered ring, the condensation occurred exclusively at the ketone carbonyl, leaving the ester function intact. With the 5-membered ring ketone, the condensation occurred both at the ketone to give **3** and at the ester function to give the ketone amide **6**, a minor product. Treatment of **3** with dry hydrogen chloride in chloroform or with trifluoroacetic

Scheme I

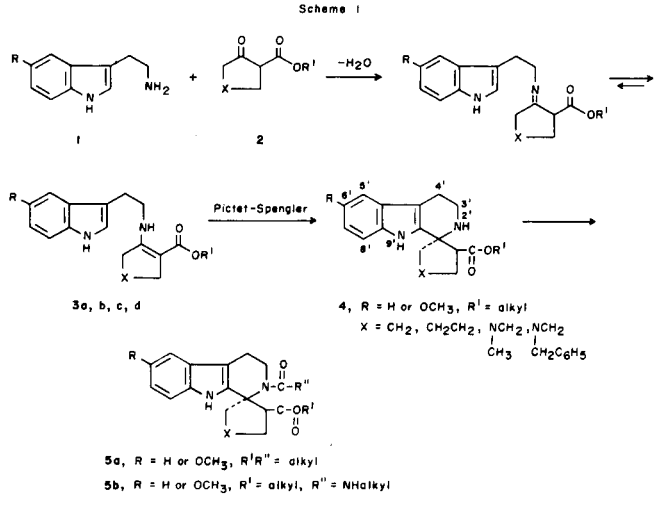
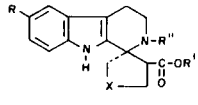


Table I

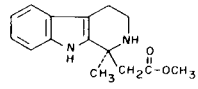
2,3,4,9-Tetrahydro-1-spiro-1*H*-pyrido[3,4-*b*]indole-Cycloalkane or Piperidine Carboxylic Acid Esters and Derivatives



Compound	R	R'	R''	X	Mp °C	% Yield	Empirical Formula	Analysis % Calcd./Found C	H	N
4a	H	C_2H_5	H	4-$(CH_2)_2$-	169-170	54	$C_{19}H_{24}N_2O_2$	73.04	7.74	8.97
								73.19	7.72	9.01
4b	H	C_2H_5	H	4-CH_2-	154-155	35	$C_{18}H_{22}N_2O_2$	72.45	7.43	9.36
								72.26	7.58	9.56
4c	OCH_3	CH_3	H	5-$CH_2N(CH_3)$-	161-162	70	$C_{19}H_{25}N_3O_3$	66.45	7.34	12.24
								66.39	7.27	12.18
4d	OCH_3	C_2H_5	H	5-$N(CH_2C_6H_5)$-CH_2-	158-159	70	$C_{26}H_{31}N_3O_3$	72.03	7.21	9.69
								71.80	7.16	9.55
5a	OCH_3	C_2H_5	-(O=C)CH_3	5-$N(CH_2C_6H_5)$-CH_2-	173-174	73	$C_{28}H_{33}N_3O_4$	70.71	6.99	8.84
								70.64	6.97	8.67
5b	OCH_3	C_2H_5	-(O=C)$NHCH_3$	5-$N(CH_2C_6H_5)$-CH_2-	189-190	71	$C_{28}H_{34}N_4O_4$	68.55	6.99	11.42
								68.69	7.06	11.61

acid produced spiro compounds **4** (Scheme I, Table I). Compounds **4** possess two chiral centers and could exist as a diastereoisomeric mixture; however, they have sharp melting points and display single spots on tlc and single peaks on hplc. Furthermore, as typical secondary amines compounds **4** react with acetic anhydride and alkyl ioscyanates at room temperature to give amides **5a** and ureas **5b**, respectively.

Condensation reactions of **1** with open-chain β-keto esters followed the same course as Scheme I and the product **7** was isolated.



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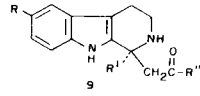
The above methodology was then applied to the reaction of **1** with cyclic β-diketones **8**. A previous report [1] had described the synthesis of 1-substituted-2,3,4,9-tetrahydro-1-(2-oxopropyl)-1*H*-pyrido[3,4-*b*]indoles **9** by condensation of **1** and 2,4-pentanediones fcllowed by a Pictet-Spengler [2] cyclization of the intermediate imine derivative.

This is analogous to the results obtained in the case of the open chain β-keto esters described above.



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We found that when **1** was condensed with one equivalent of 2-acylcycloalkanone **8** under azeotropic conditions, two series of enamines **10** and **11** were obtained in an approximate ratio 4:1 [3] (Tables II and III). Reaction with the cyclic ketone over the open chain ketone was favored

Scheme II

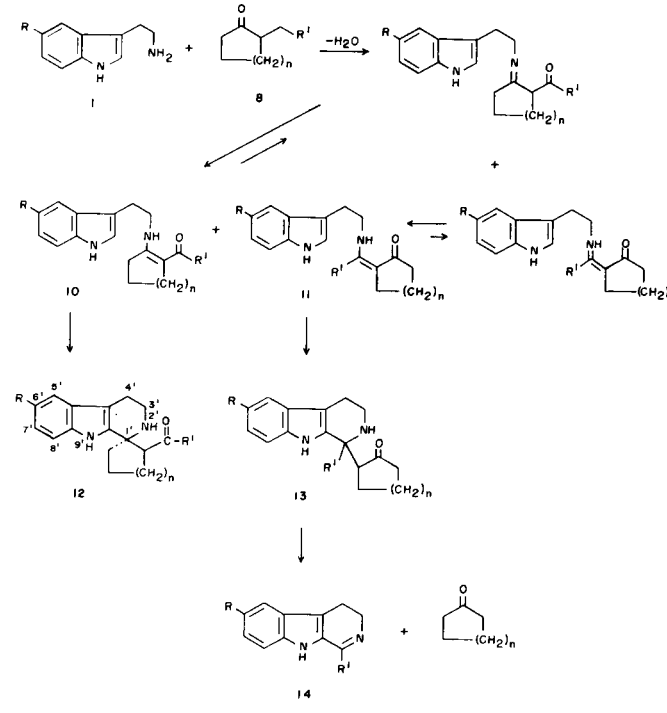
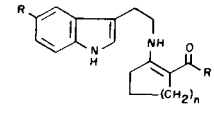


Table II

1-[2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-1-cycloalken-1-yl]alkanones **10**

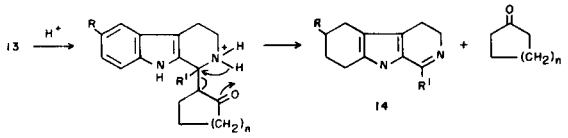


Compound	R	R'	n	Mp °C	% Yield	Empirical Formula	Analysis % Calcd./Found C	H	N
10a	H	CH_3	2	147-148	60	$C_{18}H_{22}N_2O$	76.56	7.85	9.92
							76.51	8.11	10.17
10b	OCH_3	OCH_3	2	161-162	59	$C_{19}H_{24}N_2O_2$	73.05	7.74	8.97
							73.19	7.88	8.98
10c	H	C_2H_5	2	131-132	70	$C_{19}H_{24}N_2O$	76.99	8.16	9.45
							77.19	8.18	9.18
10d	H	CH_2OCH_3	2	138-139	67	$C_{19}H_{24}N_2O_2$	73.05	7.74	8.97
							73.19	7.48	8.83
10e	OCH_3	CH_3	1	135-136	23 [a]	$C_{18}H_{22}N_2O_2$	72.45	7.43	9.39
							72.50	7.34	9.37
10f	OCH_3	CH_3	3	156-157	13 [b]	$C_{20}H_{26}N_2O_2$	73.59	8.03	8.58
							73.38	7.93	8.51

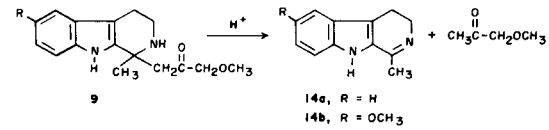
[a] In contrast to compounds **10a-d** (which constituted large majority and were isolated as primary products), compound **10e** was recovered from the mother liquor; hence low yield. [b] Direct fractional crystallization to obtain **10f** failed. Product **10f** was obtained in a pure form by chromatography over silica gel using dichloromethane-ethyl acetate (5:1) as an eluent.

in case of cyclohexanone type of β-diketones. Condensation of **1a** with 2-acetylcyclopentanone gave about 1:1 mixture of both positional isomers (**10e** and **11e**, respectively), while **1a** and 2-acetylcycloheptanone gave **10f** and **11f** in a ratio of 1:3, the latter being the first product isolated from the reaction mixture. Treatment of **10** with anhydrous hydrogen chloride in chloroform (method A) [4] or with trifluoroacetic acid (method B) gave **12**, essentially in a quantitative yield [5] (Scheme II, Table IV). Again, the possibility of diastereoisomeric mixtures existed because of the two chiral centers, but as with the β-keto esters, only a single isomer was isolated.

Compounds **12** were stable under experimental conditions and could be isolated as hydrochlorides or as free bases. By contrast, when enamine **11** was subjected to the same conditions, the initially cyclized products **13** could be isolated when the work-up was effected within a few minutes after the reaction was complete. However, when **13** was allowed to stand in acid solution for a longer time, they underwent β-elimination of cycloalkanones to give 4,9-dihydro-1-alkyl-3*H*-pyrido[3,4-*b*]indole **14** [6]. This could possibly occur through the following mechanisms:

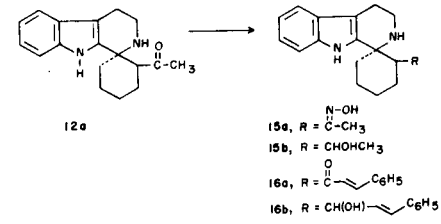


The extrusion of cycloalkanone from **13** to give **14** under such mild conditions may be due to the relief of the steric hindrance that is present in **13**. A somewhat similar situation was encountered previously [1] with elimination of methoxyacetone moiety from **9** to give **14**.



9 **14a**, R = H; **14b**, R = OCH_3

We wished to examine the chemistry of **12** in greater detail. Due to the presence of the ketone function, **12a** formed an oxime **15a** and it could be reduced to amino alcohol **15b**. Condensation of **12a** with benzaldehyde gave benzal derivative **16a**. The latter, on potassium borohydride reduction, gave vinyl alcohol **16b**.

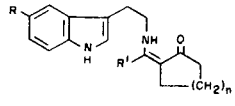


12a **15a**, R = C(=N-OH)-CH_3; **15b**, R = $CHOHCH_3$; **16a**, R = C(=O)-CH=CH-C_6H_5; **16b**, R = CH(OH)-CH=CH-C_6H_5

However, when compounds **12** were subjected to strong bases, like potassium *t*-butoxide or sodium hydride at elevated temperature, they underwent rearrangement to new products containing no carbonyl function but show-

Table III

1-[2-[[2-(1*H*-Indol-3-yl)ethyl]amino]alkylidene]cycloalkanones **11**

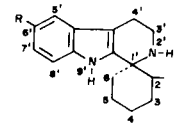


Compound	R	R'	n	Mp °C	% Yield	Empirical Formula	Analysis % Calcd./Found C	H	N
11a	H	CH_3	2	149-150	11 [a]	$C_{18}H_{22}N_2O$	76.56	7.85	9.92
							76.40	7.91	9.88
11b	OCH_3	CH_3	2	151-152	10.5 [a]	$C_{19}H_{24}N_2O_2$	73.05	7.74	8.97
							73.09	7.81	9.02
11c	H	C_2H_5	2	126-127	9	$C_{19}H_{24}N_2O$	76.99	8.16	9.45
							76.73	8.18	9.17
11d	H	CH_2OCH_3	2	150-151	8 [a]	$C_{19}H_{24}N_2O_2$	73.05	7.74	8.97
							73.01	7.80	9.03
11e	OCH_3	CH_3	1	155-156	25 [b]	$C_{18}H_{22}N_2O_2$	72.45	7.43	9.39
							72.48	7.37	9.34
11f	OCH_3	CH_3	3	135-136	37 [b]	$C_{20}H_{26}N_2O_2$	73.59	8.03	8.58
							73.73	7.77	8.63

[a] Although the ratio of enamines **10a-d** to **11a-d** was about 4:1 (as shown by ^1H nmr and tlc of the crude mixture), the low-yield of actually isolated minor positional isomers **11** is explained by the difficulty of isolating them in a pure form (free from **10**) by fractional crystallization. [b] Compounds **11e-f** were isolated first from the reaction mixture as primary products.

Table IV

1-[2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indole]-2-yl]alkanones and Derivatives

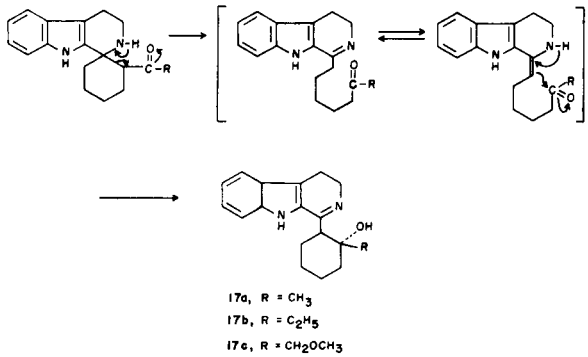


Compound	R	R'	Mp °C	% Yield	Empirical Formula	Analysis % Calcd./Found C	H	N
12a	H	-(O=C)-CH_3	151-152	78	$C_{18}H_{22}N_2O$	76.56	7.85	9.92
						76.52	7.72	9.96
12b	OCH_3	-(O=C)-CH_3	161-162	73	$C_{19}H_{24}N_2O_2$	73.05	7.74	8.97
						73.30	7.88	9.23
12c	H	-(O=C)-C_2H_5	172-173	74	$C_{19}H_{24}N_2O$	76.99	8.16	9.45
						77.25	8.36	9.61
12d	H	-(O=C)-CH_2OCH_3	176-177	51	$C_{19}H_{24}N_2O_2$	73.05	7.74	8.97
						72.88	7.80	9.08
15a	H	-(HON=C)-CH_3	200-201	67	$C_{18}H_{23}N_3O$·HCl [a]	64.75	7.53	12.81
						64.83	7.53	12.81
15b	H	$CH(OH)CH_3$	267-268 [c]	62.5	$C_{18}H_{24}N_2O$·HCl [b]	67.39	7.85	8.73
						67.47	8.09	8.44
16a	H	-(O=C)-CH=CH-C_6H_5 [d]	194-195	75	$C_{25}H_{26}N_2O$	81.04	7.07	7.56
						81.21	6.69	7.68
16b	H	-CHOH-CH=CH-C_6H_5 [d]	217-218	82	$C_{25}H_{28}N_2O$	80.61	7.58	7.52
						80.44	7.34	7.66

[a] Calcd: Cl^-, 10.62. Found: Cl^-, 10.64. [b] Calcd: Cl^-, 11.05. Found: Cl^-, 11.26. [c] Melts with decomposition.

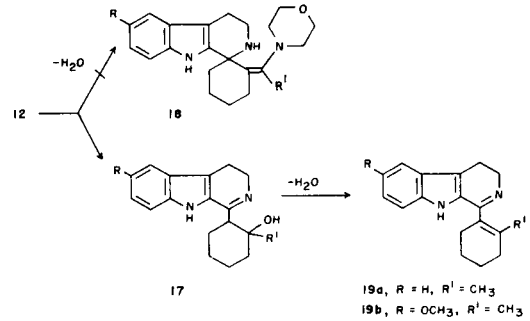
ing both the indole hydrogen and an hydroxyl function. The elemental analyses and molecular weights were unchanged from the starting ketones. Structure **17** was assigned based on microanalyses and ultraviolet, infrared and proton magnetic resonance spectra (see Experimental).

According to the mechanism proposed, the cleavage of the carbon-carbon bond in the first stage is similar to the eliminative formation of **14** from **13**. After cleavage, the resulting aliphatic chain possesses a carbonyl function at a favorable position, allowing cyclization to the six-membered ring to take place. However, since **12** has a spiro ring locked-in, it is considerably more stable than **13**. Hence more drastic conditions are needed to effect this transformation.



17a, R = CH_3
17b, R = C_2H_5
17c, R = CH_2OCH_3

Refluxing a solution of **12**, morpholine and traces of 4-toluenesulfonic acid in toluene under azeotropic conditions resulted in the formation of **19**. None of the expected enamine derivative **18** was formed. Reaction must have proceeded through the originally formed **17** followed by dehydration. As a confirmation, **17a** was subjected to the same reaction conditions to give **19a** as a sole product.

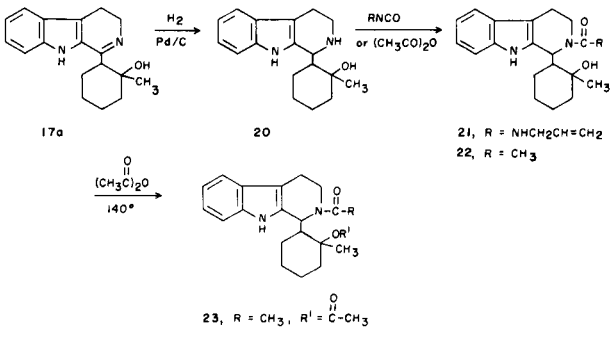


19a, R = H, R' = CH_3
19b, R = OCH_3, R' = CH_3

Upon catalytic hydrogenation (Pd/C), compound **17a** absorbed one mole of hydrogen to give the tetrahydro-1*H*-pyrido[3,4-*b*]indole derivative **20**. The carbon framework of this compound remained unchanged. Compound **20** was also obtained when **17a** was treated with potassium borohydride in methanol. Reduction from a single face of the molecule occurred in each case as evidenced by the formation of a single isomer (sharp melting point, tlc,

hplc).

Treatment of **20** with an alkyl isocyamate or with acetic anhydride at room temperature gave a urea **21** and amido **22** carbinols, respectively. On increasing the temperature to 140°, the latter was converted quantitatively to the amido ester **23**.



The 9*H*-pyrido[3,4-*b*]indoles with a spiro 6-membered ring system described above are thus seen to undergo some interesting chemical transformation. Irreversible cleavage at the carbon next to the carbonyl under the influence of strong bases is seen, with the subsequent formation of the cyclohexanol derivatives. The latter could be dehydrated to the cyclohexene derivatives.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover melting point apparatus which was calibrated against known standards. The ultraviolet (uv) and infrared (ir) spectra were obtained, respectively with a Beckman DK-1 spectrograph. The ^{1}H nmr spectra were obtained on a Varian A-60 and a Bruker WH90 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. In some instances when there were nonresolvable multiplicities or overlappings of the aliphatic protons, they were not reported.

Products **4**, Derived from Condensation of 1*H*-Indole-3-ethanamines (Tryptamines) **1** with β-Keto Esters **2** (Table I).

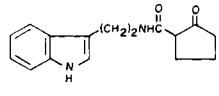
Since the condensation of **1** with **2** gave single imino derivatives **3** (except amide **6**), there were not always attempts to purify and isolate them. Consequently, in some cases the cyclization to **4** was accomplished in the same reaction pot after the prior removal of solvent. The preparation of **4a** will illustrate the general procedure.

Ethyl 2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indole]-2-carboxylic Acid, Ethyl Ester (**4a**). (Method A).

A solution of 4.0 g (0.025 mole) of 1*H*-indole-3-ethanamine (**1a**) and 4.2 g (0.025 mole) of ethyl 2-oxocyclohexanecarboxylate in 100 ml of benzene was refluxed under nitrogen for 2 hours while the theoretical volume of water had separated in a Dean-Stark trap. The solution was evaporated *in vacuo* to give ethyl 2-[[2-(1*H*-indol-3-yl)ethyl]amino]-1-cyclohexene-1-carboxylic acid ethyl ester (**3a**, Scheme I) as an off-white oil; ir (chloroform): 3350, 3215 (NH), 1647, 1592 (NH-C=C-C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.09 (1*H*, N*H*-indole), 9.10 (1*H*, CH_2NH). This enamino ester derivative **3a** was taken up with 50 ml of chloroform and treated with dry hydrogen chloride for 5 minutes to cause the temperature to rise to 45°. After 24 hours at room temperature, the dark solution was made basic with sodium bicarbonate at 0°; the chloroform phase was dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from 2-propanol gave 4.2 g of ethyl 2',3',4',9'-tetrahydroisospiro-[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indole]-2-carboxylic acid, ethyl ester (**4a**) as white crystals, mp 169-170°; uv (ethanol): λ max nm (ε) 226 (36,650), 283 (8640), 292 (7250); ir (potassium bromide): 3420, 3320 (NH), 1705 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.70 (t, J = 7.0 Hz, 3H, CH_2CH_3), 3.80 (m, 2H, CH_2CH_3), 7.05-7.55 (m, 4H, aromatic), 7.82 (s, 1H, N*H*-indole); mass spectrum, m/z 312.

2',3',4',9'-Tetrahydrospiro[cyclopentane-1,1'-[1*H*]pyrido[3,4-*b*]indole]-2-carboxylic Acid, Ethyl Ester (**4b**).

A solution of 6.0 g (0.0375 mole) of 1*H*-indole-3-ethanamine (**1a**) and 5.4 g (0.0375 mole) of ethyl 2-oxocyclopentanecarboxylate (**2b**) in 120 ml of benzene was refluxed under nitrogen for 1.5 hours while the theoretical volume of water had separated in a Dean-Stark trap. After the solution was evaporated *in vacuo* the gummy residue was refluxed with 25 ml of diisopropyl ether to give, after cooling, 1.4 g (14% yield) of *N*-[2-(1*H*-indol-3-yl)ethyl]-2-oxocyclopentanecarboxamide (**6**) as white crystals, mp 114-115°; uv (ethanol): λ max nm (ε) 222 (27,300), 283 (6800); ir (chloroform): 3420, 3350, (NH), 1740, 1655, 1540 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.70-2.45 (m, 6H, cyclopentanone moiety), 2.98 (m, 3H, CH_2-indole proton of cyclopentanone α to the carbonyl,



6

3.58 (m, 2H, CH_2-indole), 6.79 (m, 1H, N*H*C=O), 7.05-7.70 [m, 5H, 4H, aromatic and *H*-2 (indole)], 8.20 (1H, NH-indole); ms: m/z 270.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 7.10; H, 6.78; N, 10.33.

The filtrate from **6** containing predominantly 2-[[2-(1*H*-indol-3-yl)-ethyl]amino]-1-cyclopentene-1-carboxylic acid ethyl ester (**3b**, Scheme I) was evaporated and the residue was dissolved in 10 ml of trifluoroacetic acid. After 3 days at 23°, the solution was neutralized with aqueous ammonia at 0°, and extracted with 150 ml of ethyl acetate. The extract was dried over sodium sulfate and evaporated to give 7.8 g of **4a** as yellow cake. Crystallization from benzene gave 2.7 g of 2',3',4',9'-tetrahydrospiro[cyclopentane-1,1'-[1*H*]pyrido[3,4-*b*]indole]-2-carboxylic acid ethyl ester (**4b**) as white crystals, mp 154-155°; uv (ethanol): λ max nm (ε) 227 (36,640), 283 (8640), 292 (7240); ir (chloroform): 3410, 3230 (NH), 1725 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.00 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.69 (t, J = 4.5 Hz, 2H, CH_2-4'), 2.98-3.28 (m, 3H, *H*-2), 3.90-4.13 (m, 2H, CH_2CH_3), 7.05-7.50 (m, 4H, aromatic), 7.84 (s, 1H, N*H*-indole); ^{13}C nmr (deuteriochloroform): δ 13.9, 21.9, 22.8, 27.4, 39.7, 40.3, 53.6, 60.3, 64.2, 110.4, 110.7, 118.1, 119.2, 121.6, 127.5, 135.8, 136.5, 173.1; ms: m/z 298.

2',3',4',9'-Tetrahydro-6'-methoxy-1-methylspiro[piperidine-4,1'-[1*H*]pyrido[3,4-*b*]indole]-2-carboxylic Acid, Methyl Ester (**4c**).

A solution of 8.6 g (0.05 mole) of 9.5 g (0.05 mole) of 5-methoxy-1*H*-indole-3-ethanamine (**1b**) and 8.6 g (0.05 mole) of methyl 1-methyl-4-oxo-3-piperidinecarboxylate (free base, freshly regenerated from **2c**-hydrochloride) in 200 ml of benzene was refluxed under nitrogen for 2 hours while the theoretical volume of water had separated. After the solution was evaporated *in vacuo*, the brown residue recrystallized from acetonitrile to give 14.2 g (83% yield) of **3c** as off-white crystals, mp 131-138°. An analytical sample of 1,2,5,6-tetrahydro-4-[[2-(5-methoxy-1*H*-indol-3-yl)ethyl]amino]-1-methyl-3-pyridinecarboxylic acid, methyl ester (**3c**, Scheme I) was obtained by recrystallization from acetonitrile, mp

139-140°; uv (ethanol): λ max nm (ε) 226 (25,740), 299 (20,050); ir (chloroform): δ 3410, 3220 (NH), 1635, 1590 (NH-C=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, NCH_3), 3.60 (s, 3H, $COOCH_3$), 3.78 (s, 3H, 3 CH_3O-5), 6.60-7.20 (m, 4H, *H*-2 and 3H, aromatic), 7.70 (1H, N*H*-indole), 9.50 (m, 1H, CH_2NH); ms: m/z 243.

To a solution of 7.9 g (0.022 mole) of **3c** in 110 ml of chloroform was added 10 ml of trifluoroacetic acid. After 24 hours at 23°, the solution was made basic with aqueous ammonia at 0°. The chloroform phase was washed, dried over sodium sulfate and the solvent removed *in vacuo*. Crystallization of the residue from acetonitrile gave 6.9 g of 2',3',4',9'-tetrahydro-6'-methoxy-1-methylspiro[piperidine-4,1'-[1*H*]pyrido[3,4-*b*]indole-3-carboxylic acid, methyl ester (**4c**), mp 158-160°. Recrystallization from acetonitrile gave 5.5 g of pure **4c**, mp 161-162°; uv (ethanol): λ max nm (ε) 227 (27,680), 280 (9200); ir (chloroform): 3420, 3220 (NH), 1718 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H, NCH_3), 3.32 (s, 3H, $COOCH_3$), 3.78 (s, 3H, CH_3O-6'), 6.68-7.40 (m, 3H, aromatic), 8.28 (1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 22.8, 35.1, 45.7, 48.9, 50.0, 51.2, 52.3, 55.3, 99.8, 107.8, 110.1, 111.4, 127.0, 130.7, 139.4, 152.8, 172.4; ms: m/z 343.

2',3',4',9'-Tetrahydro-6'-methoxy-1-(phenylmethyl)spiro[piperidine-3,1'-[1*H*]pyrido[3,4-*b*]indole]-4-carboxylic Acid, Ethyl Ester (**4d**).

The same procedure as for the preparation of **4c** was followed. Thus, 4.8 g (0.04 mole) of **1b** and 5.0 g (0.04 mole) of ethyl 1-(phenylmethyl)-3-oxo-4-piperidinecarboxylate (**2d**) gave 1,2,3,4-tetrahydro-5-[[2-(1*H*-indol-3-yl)-ethyl]amino]-1-(phenylmethyl)-4-pyridinecarboxylic acid, ethyl ester (**3d**, Scheme I) as an off-white oil; ir (chloroform): 3345, 3270 (NH), 1644, 1583 (NH-C=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.98 (1H, N*H*-indole), 8.80 (t, J = 4.0 Hz, 1H, CH_2NH); ms: m/z 433.

This enamine ester **3d** was converted to **4d** in the same vessel (after the solvent was first removed) by trifluoroacetic acid. Two recrystallizations from 2-propanol gave pure **4d** as white crystals, mp 158-159°; uv (ethanol): λ max nm (ε) 225 (28,050), 280 (9350); ir (chloroform): 3490, 3350 (NH), 1725 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.02 (t, J = 7.5 Hz), 3.58 (s, 2H, $CH_2NC_6H_5$), 3.82 (s, 3H, CH_3O-6'), 6.70-7.35 (m, 3H, aromatic), 9.25 (1H, N*H*-indole); ms: m/z 433.

2'-Acetyl-2',3',4',9'-tetrahydro-6'-methoxy-1-(phenylmethyl)spiro[piperidine-3,1'-[1*H*]pyrido[3,4-*b*]indole]-4-carboxylic Acid, Ethyl Ester (**5a**).

A solution of 1.0 g of **4d**, and 0.5 g of acetic anhydride in 15 ml of dichloromethane was allowed to stand at 23° for two days. After the solution was evaporated *in vacuo*, the residue was recrystallized twice from ethanol to give 0.8 g of **5a**, mp 173-174°; uv (ethanol): λ max nm (ε) 223 (29,660), 276 (8950); ir (potassium bromide): 3220 (NH), 1731 (ester C=O), 1663 (amide C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.03 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.09 (CH_3C=O), 3.74 (OCH_3), 6.78-6.87 (m, 2H, aromatic), 7.16-7.40 (m, 6H, aromatic), 11.10 (s, 1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 13.9, 21.3, 25.0, 25.6, 38.3, 42.6, 45.4, 50.3, 55.4, 58.1, 59.5, 61.1, 62.0, 99.7, 106.5, 110.9, 112.0, 126.1, 127.1, 128.2, 129.2, 129.9, 137.8, 138.7, 153.1, 169.6, 171.0; ms: m/z 475.

2',3',4',9'-Tetrahydro-6'-methoxy-2'-[(methylamino)carbonyl]-1-(phenylmethyl)spiro[piperidine-3,1'-[1*H*]pyrido[3,4-*b*]indole]-4-carboxylic Acid, Ethyl Ester (**5b**).

A solution of 5.2 g (0.012 mole) of **4d**, 1.0 g (0.223 mole) of methyl isocyanate and 1 drop of triethylamine in 24 ml of dichloromethane was allowed to stand for three days at 23°. Methanol (0.5 ml) was added to destroy excess isocyanate and the solution was evaporated to dryness. Crystallization of the solid residue from ethyl acetate gave 4.2 g of **5b** as white crystals, mp 189-190°; uv (ethanol): λ max nm (ε) 224 (29,650), 276 (9000); ir (potassium bromide): 3415, 3290 (NH), 1729 ($COOC_2H_5$), 1632 (NHC=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.98 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.50 (d, J = 4.0 Hz, $NHCH_3$), 3.34 (s, N-$CH_2C_6H_5$), 3.71 (s, CH_3O-6'), 6.65-7.38 (m, 8H, aromatic), 7.62 (q, J = 4.0 Hz, 1H, $NHCH_3$), 11.00 (s, 1H, N*H*-indole).

2,3,4,9-Tetrahydro-1-methyl-1*H*-pyrido[3,4-*b*]indole-1-acetic Acid, Methyl Ester, Trifluoroacetate Salt (**7**).

A solution of 8.0 g (0.05 mole) fo **1a** and 6.4 g (0.055 mole) of methyl acetoacetate in 70 ml of benzene was refluxed under nitrogen for 2 hours while 0.9 ml of water had separated. The solution was evaporated *in vacuo* to give 3-[[2-(1*H*-indol-3-yl)ethyl]amino]-2-butenoic acid methyl ester as a noncrystallizable semisolid. This residue was taken up with 100 ml of anhydrous ether and treated with 10 ml of trifluoroacetic acid. After 20 hours at room temperature, 13.9 g (75% yield) of **7** was obtained as a trifluoroacetate salt, mp 190-191° dec. An analytical sample of **7** as white crystals was obtained by recrystallization from 2-propanol, mp 191-192° dec; uv (ethanol): λ max nm (ε) 220.5 (37,250), 271 (7100), 279 (7050), 289 (5250); ir (nujol): 3280 (NH), 1730 (ester C=O), 1670 (CF_3COO^-) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.78 (s, 3H, C-CH_3), 2.90 (m, 2H, CH_2-4), 3.20 (m, 2H, CH_2C=O), 3.35-3.65 (m, 5H, CH_2-3 and CH_3OC=O), 6.85-7.45 (m, 4H, aromatic), 11.20 (s, 1H, N*H*-indole).

Anal. Calcd. for $C_{15}H_{18}N_2O_2 \cdot CF_3COOH$: C, 54.8; H, 5.14; N, 7.52. Found: C, 54.73; H, 5.14; N, 7.42.

Products **12** and **13** Resulting from Condensation of 1*H*-Indole-3-ethanamines **1** with 2-Acylcycloalkanones **8**. General Procedure.

1-[2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-1-cyaloalken-1-yl]alkanones **10** (Table II) and 2-[1-[[2-(1*H*-Indol-3-yl)ethyl]amino]alkylidene]cycloalkanones **11** (Table III).

1-[2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-1-cyclohexen-1-yl]ethanone (Schiff Base **10a**).

A solution of 13.0 g (0.0815 mole) of 1*H*-indole-3-ethanamine (**1a**) of 2-acetylcyclohexanone (**8a**) in 180 ml of toluene was refluxed under nitrogen for 1.5 hours using a Dean-Stark trap to remove 1.5 ml of water formed. Thin layer chromatography (tlc; silic gel G; benzene-acetone-heptane, 1:1:1) showed two new spots at Rf = 0.3, and at Rf = 0.23 in an approximate ratio of 4:1. After the solvent was removed, the residue was crystallized from acetonitrile giving 16.0 g of product containing *ca.* 95% of the faster moving component (Rf = 0.3), mp 140-141°. Recrystallization from ethanol gave 13.6 g (60% yield) of analytical and chromatographically pure (Rf = 0.3) **10a**, mp 147-148°; uv (ethanol): λ max nm (ε) 221 (35,900), 274 sh (6500), 282 (7450), 290 (7200), 333 (18,200); ir (nujol): 3150 (NH), 1597, 1552 (NH-C=C-C=O) cm^{-1}; ir (chloroform): 3490 (NH), 1601, 1565 (NH-C=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45-1.65 (m, 4H, CH_2-4 and CH_2-5 of cyclohexane moiety), 2.10 (3H, CH_3), 2.20-2.48 (m, 4H, CH_2-4 and CH_2-5 of cyclohexane moiety), 3.11 (2H, t, J = 7.5 Hz, CH_2-indole), 3.53 (m, 2H, CH_2NH), 7.10-7.67 [5H, H-2 (indole) and 4H, aromatic], 8.77 (1H, N*H*-indole), 10.52 (1H, broad, CH_2NH).

2-[1-[[2-(1*H*-Indol-3-yl)ethyl]amino]ethylidene]cyclohexanone (Schiff Base **11a**).

The original filtrate (from **10a**) was concentrated to a low volume to give 5.1 g of crystals consisting of about 1:1 mixture of **10a** and **11a**, mp 126-129°. Recrystallization from acetonitrile gave 3.6 g of predominantly slower moving isomer, mp 145-148°. Recrystallization from methanol gave 2.5 g of pure **11a** (Rf = 0.23) as white crystals, mp 149-150°; uv (ethanol): λ max nm (ε) 221 (36,400), 275 sh (6400), 282 (7200), 290 (7200), 335 (18,200); ir (nujol): 3150, 1596, 1540, 1250 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45-1.70 (m, 4H, CH_2-4 and CH_2-5 of cyclohexane moiety), 1.84 (s, 3H, CH_3), 2.10-2.40 (m, 4H, CH_2-3 and CH_2-6 of cyclohexane moiety), 3.02 (2H, t, J = 7.5 Hz, 2H, CH_2-indole), 3.52 (m, 2H, CH_2NH), 7.05-7.65 [m, 5H, H-2 (indole) and 4H, aromatic], 9.30 (1H, N*H*-indole), 12.30 (m, 1H, CH_2NH).

1-[2-[[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]amino]-1-cyclohexen-1-yl]ethanone (**10b**).

By following the above general procedure, a solution of 47.5 g (0.25 mole) of **1b** and 38.5 g (0.275 mole) of **8a** in 300 ml of toluene gave, on concentration to a low volume and cooling, 50.5 g of off-white solid containing about 95% of **10b** (Rf = 0.5), mp 159-161°. Recrystallization from 2-propanol gave 45.6 g of chromatographically pure **10b** as white

crystals, mp 161-162°; uv (ethanol): λ max nm (ε) 225 (21,800), 280 (7100), 333 (16,600); ir (nujol): 3160 (NH), 1593, 1550 (NHC=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.51 (m, narrow, 4H, CH_2-4 and CH_2-5), 1.94 (s, 3H, CH_3C=O), 2.24, 2.34 (m, m, 4H, CH_2-3 and CH_2-6), 2.88 (2H, t, J = 7.2 Hz, 2*H*, CH_2-indole), 3.46 (m, 2H, CH_2NH), 3.77 (s, 3H, CH_3O), 6.69, 6.74 (dd, J = 10.0 Hz, and 2.4 Hz, 1H, H-6'), 7.03 [d, J = 2.3 Hz, 1H, H-2 (indole)], 7.16 (d, J = 2.4 Hz, 1H, H-4'), 7.23 (d, J = 9.0 Hz, 1H, H-7'), 10.72 (d, J = 2.3 Hz, 1H, N*H*-indole), 11.46 (t, J = 5.5 Hz, CH_2N*H*); ms: m/z (M^+ + 1) 313.

2-[1-[[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]amino]ethylidene]cyclohexanone (**11b**).

The original filtrate (from 50.5 g of **10b**) was evaporated and the residue was recrystallized twice from 2-propanol, and finally, from acetonitrile to give 8.5 g of chromatographically pure (Rf = 0.45) of **11b**, mp 135-136°; uv (ethanol): λ max nm (ε) 222 (34,500), 282 (7200), 290 (7200), 333 (16,550); ir (nujol): 3250 (NH), 1605, 1559 (NHC=C-C=O); ^1H nmr (deuteriochloroform): δ 2.02 (s, 3H, CH_3-C-NH), 3.02 (t, J = 7.3 Hz, 2H, CH_2-indole), 3.55 (m, 2H, CH_2NH), 3.90 (s, 3H, CH_3O), 6.75-7.30 [m, 4H, H-2 (indole) and 3H aromatic], 8.28 (1H, broad, 1H, N*H*-indole), 10.50 (m, 1H, CH_2N*H*); ms: m/z 312.

1-[2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-1-cyclohexen-1-yl]propanone (**10c**).

A solution of 32.0 g (0.2 mole) **1a** and 33.9 g (0.22 mole) of 2-(1-oxopropyl)cyclohexanone (**8b**) in 200 ml of dry toluene was refluxed under nitrogen for 2 hours until the theoretical volume of water had separated. The tlc (acetone:heptane:benzene, 3:2:2) showed two new spots at Rf = 0.4 and at Rf = 0.35 in a ratio of about 1:5. After the solvent was removed, the semisolid residue was crystallized from acetonitrile giving 41.3 g (70% yield) of chromatographically pure (Rf = 0.4) **10c**, mp 130-131°. An analytical sample was obtained by recrystallization from ethanol, mp 131-132°; uv (ethanol): λ max nm (ε) 221 (37,000), 282 (8200), 290 (8300), 333 (17,400); ir (nujol): 3215 (NH), 1597, 1542 (NHC=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.91 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.30 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.05 (t, J = 7.5 Hz, 2H, CH_2-indole), 3.50 (m, 2H, CH_2NH), 8.76 (1H, N*H*-indole), 10.51 (broad, 1H, CH_2N*H*).

2-[1-[[2-(1*H*-Indol-3-yl)ethyl]amino]propylidene]cyclohexanone (**11c**).

The filtrate from **10c** was evaporated to dryness and triturated with hot ethyl acetate to give 6.1 g of off white crystals consisting of about 85% of the slower moving isomer (Rf = 0.35). Two recrystallizations from ethyl acetate-diisopropyl ether (2:1) gave pure **11c** as nearly white crystals, mp 124-126°; uv (ethanol): λ max nm (ε) 221 (36,950), 282 (8200), 290 (8250), 332 (17,400); ir (nujol): 3220 (NH), 1608, 1559 (NHC=C-C=O); ^1H nmr (deuteriochloroform): δ 0.95 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.29 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.09 (t, J = 7.5 Hz, 2H, CH_2-indole), 3.52 (m, 2H, CH_2NH), 8.80 (1H, N*H*-indole), 10.60 (m, 1H, CH_2N*H*); ms: m/z 296.

1-[2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-1-cyclohexen-1-yl]-2-methoxyethanone (**10d**).

A solution of 16.0 g (0.1 mole) of **1a** and 18.0 g (0.115 mole) of 2-(methoxyacetyl)cyclohexanone (**8c**) in 180 ml of toluene was refluxed under nitrogen for 2 hours while the theoretical volume of water had separated. After the solvent was removed, the residue was refluxed with 120 ml of ether for 1 hour to give, on cooling, 26.3 g of off-white crystals, mp 126-128°. The tlc showed about 90% of the slower moving spot, Rf = 0.22. Two recrystallizations from methanol gave 13.8 g of analytically and chromatographically (Rf = 0.22) pure **10d** as white crystals, mp 138-139°; uv (ethanol): λ max nm (ε) 221 (36,000), 280-284 plateau (7400), 290 (7500), 334 (16,500); ir (nujol): 3490, 3290 (NH), 1607, 1570 (NH-C=C-C=O), 1118 (OCH_3) cm^{-1}; ms: m/z 312.

1-[2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-2-methoxyethylidene]cyclohexanone (**11d**).

The original filtrate (of 26.3 g of **10d**) was evaporated to dryness and passed over the florisil column, ether-ethyl acetate (4:1) being used as eluents. Fractions 1-5, containing predominantly faster-moving product were triturated with acetonitrile to give 2.6 g of **11d** (Rf = 0.28), mp 148-149°. Recrystallization from acetonitrile gave pure **11d** as white crystals, mp 150-151°; uv (ethanol): λ max nm (ε) 218.5 (34,650), 272.5 sh (7800), 280 (8400) 288 (7800); ir (chloroform): 3520, 3150 (NH), 1598, 1550 (NHC=C-C=O), 1090 (CH_3O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.60-1.80 (m, 4H, CH_2-4 and CH_2-5), 2.23-2.55 (m, 4H, CH_2-3, CH_2-6), 3.10 (t, J = 7.0 Hz, 2H, CH_2-indole), 3.32 (s, 3H, CH_3), 3.65 (m, 2H, CH_2NH), 4.08 (s, 2H, CH_2O), 7.10-7.70 (m, 4H, aromatic), 3.80 (1H, N*H*-indole), 11.8 (m, 1H, CH_2N*H*); ms: m/z 312.

2-[1-[[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]amino]ethylidene]cyclopentanone (**11e**).

A solution of 5.7 g (0.03 mole) of **1b** and 4.2 g (0.033 mole) of 2-acetylcyclopentanone (**8d**) in 100 ml of toluene was refluxed under nitrogen for 2 hours while the theoretical volume of water had separated. After the solvent was removed, the residue was triturated with hot acetonitrile to give 4.3 g of solid, mp 145-147°. The tlc (acetonitrile-ethyl acetate, 1:5) showed the solid and the mother liquor having similar mobility (Rf = 0.4). Two recrystallizations from 2-propanol gave 2.3 g of **11e**, mp 155-156°; ir (nujol): 3210, 3180 (NH), 1620, 1538 (NHC=C-C=O); ^1H nmr (deuteriochloroform): δ 1.69-1.86 (m, 2H, CH_2-4), 2.03 (s, 3H, CH_3-C-NH), 2.36-2.58 (m, 4H, CH_2-3 and CH_2-5), 2.97 (t, J = 8.0 Hz, 2H, CH_2-indole), 3.50 (m, 2H, CH_2NH), 3.86 (s, 3H, OCH_3), 6.82-7.27 [m, 4H, 3 aromatic and H-2 (indole)], 8.44 (1H, N*H*-indole), 9.60 (m, 1H, CH_2N*H*); ms: m/z 298.

1-[2-[[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]amino]-1-cyclopenten-1-yl]ethanone (**10e**).

The filtrate from 2.3 g of **11e** was filtered through the silica gel to remove some impurities, and evaporated. The residue was crystallized twice from acetonitrile and then from 2-propanol-diisopropyl ether to give 2.1 g of **10e** as white, shiny crystals, mp 132-133°; ir (nujol): 1623, 1576 (NH-C=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.75-1.86 (m, 2H, CH_2-4), 1.85 (s, 3H, CH_3C=O), 2.56-2.65 (m, 4H, CH_2-3 and CH_2-5), 2.99 (t, J = 8.0 Hz, 2H, CH_2-indole), 3.52 (m, 2H, CH_2NH), 3.85 (s, 3H, OCH_3), 6.82-7.27 (m, 4H, 3H aromatic and H-2 indole), 8.43 (1H, NH-indole), 10.52 (m, 1H, CH_2N*H*); ms: m/z 298.

2-[1-[[2-(5-Methoxy-1*H*-Indol-3-yl)ethyl]amino]ethylidene]cycloheptanone (**11f**).

A solution of 5.7 g (0.03 mole) of **1b** and 5.1 g (0.033 mole) of 2-acetylcycloheptanone (**8e**) in 100 ml of toluene was refluxed under nitrogen for 2 hours with water separator and subsequently evaporated *in vacuo*. The resulting dark residue was taken up with 200 ml of dichloromethane, treated with charcoal, and evaporated. Trituration of the residue with hot acetonitrile gave 4.7 g of off-white solid, mp 134-135°. The tlc (acetonitrile-ethyl acetate, 1:5) showed a faster moving spot at Rf = 0.5 (*ca.* 95%). Recrystallization from 2-propanol gave 3.6 g of pure 2-[1-[[2-(5-methoxy-1*H*-indol-3-yl)ethyl]amino]ethylidene]cycloheptanone (**11f**) as nearly white crystals, mp 135-136°; ir (nujol): 3215 (NH), 1608, 1559 (NH-C=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (m, 2H, CH_2-5), 1.67 (m, 4H, CH_2-4 and CH_2-6), 1.92 (s, 3H, CH_3-C-N), 2.32 (m, 2H, CH_2-3), 2.51 (m, 2H, CH_2-7), 3.03 (t, J = 7.0 Hz, 2H, CH_2-indole), 3.56 (m, 2H, CH_2NH), 3.87 (s, 3H, OCH_3), 6.82-7.27 [m, 4H, 3H, aromatic and H-2 (indole)], 8.31 (1H, N*H*-indole), 11.95 (m, 1H, CH_2N*H*); ms: m/z 326.

1-[2-[[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]amino]-1-cyclohepten-1-yl]ethanone (**10f**).

The original filtrate from 4.7 g of **11f** (which contained a 1:1 mixture of both positional isomers) was evaporated and the residue triturated with hot ethyl acetate to give 3.5 g of a mixture of **10f** and **11f** (about 1:1). Attempts to separate both isomers directly by fractional crystallization were unsuccessful. Chromatography over silica gel, using dichloromethane-ethyl acetate (5:1) as eluents, gave 1.3 g of chromatographically pure (Rf = 0.4) **10f** as white crystals, mp 156-157°; ir (nujol): 3220 (NH), 1602, 1555 (NH-C=C-C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.18 (s,

3H, CH_3C=O), 3.05 (t, J = 7.0 Hz, 2H, CH_2-indole), 3.65 (m, 2H, CH_2NH), 3.90 (s, 3H, OCH_3), 6.85-7.35 [m, 4H, 3H, aromatic and H-2 (indole)], 8.45 (1H, N*H*-indole), 12.20 (m, 1H, CH_2NH); ms: m/z 326.

Preparation of 1,1-Disubstituted-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles **12**.

The detailed description of cyclization of **10a** into **12a** (Method A) will illustrate the general procedure for preparation of compounds **12a-d**.

1-(2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indol]-2-yl)ethanone (**12a**). Method A.

To a solution of 12.9 g (0.05 mole) of **10a** in 200 ml of dry chloroform was introduced hydrogen chloride gas for 6 minutes, causing the temperature to rise to 40°. After 10 minutes at 30°, the tlc (ethyl acetate-acetonitrile, 5:1) showed complete cyclization, the new product having a higher Rf (0.45) than the starting enamine **10a** (Rf = 0.4). Anhydrous ether (200 ml) was added to the cooled, brown solution, and the resulting, faintly yellow precipitate was collected by filtration. Recrystallization from acetonitrile gave 11.4 g of 1-(2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indol]-2-yl)ethanone hydrochloride (**12a**) as white crystals, mp 182-183° dec. An analytical sample, melting at 183-184° dec, was obtained by recrystallization from acetonitrile; uv (ethanol): λ max nm (ε) 221 (37,500), 271 (8100), 280 sh (7800), 289 sh (6000); ir (nujol): 3110 (NH), 1695 (C=O) cm^{-1}.

Anal. Calcd. for $C_{18}H_{22}N_2O \cdot HCl$: C, 67.81; H, 7.27; N, 8.79; Cl^-, 11.2. Found: C, 67.81; H, 7.48; N, 8.77; Cl^-, 10.88.

A free base **12a** was obtained by suspending the hydrochloride in chloroform and treatment with potassium bicarbonate. The chloroform phase was dried over sodium sulfate and evaporated to dryness. The residual cake was crystallized from ethanol giving white crystals of analytical purity, mp 151-152°; uv (ethanol): λ max nm (ε) 225 (37,000), 273 sh (7900), 281 (8120), 290 (6560); ir (chloroform): 3475, 3350 (NH), 1704 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.71 (CH_3), 2.32 (amine N*H*, *deuterium oxide exchangeable*), *7.10-7.55 (m, 4H, aromatic), 7.98 (1H, NH*-indole); ^{13}C nmr (DMSO-d_6): δ 20.5, 22.7, 22.9, 24.7, 35.5, 38.9 ($6CH_2$), 30.8 (CH_3), 54.1 (quat, C-1), 56.0 (CH-2), 107.7, 126.8, 135.4, 139.6 (4 CH, aromatic), 110.9, 117.6, 118.2, 120.5 (4 C quat, aromatic), 211.6 (C=O).

1-(2',3',4',9'-Tetrahydro-6'-methoxyspiro[cyclohexane-1,1'-[1*H*]pyrido-[3,4-*b*]indol]-2-yl)ethanone (**12b**).

Following the same procedure as for the preparation of **12a**, compound **12b** was obtained from **10b** and isolated as a base, after recrystallization from ethyl acetate, mp 161-162°; uv (ethanol): λ max nm (ε) 226 (27,500), 279 (9,300), 295 sh (7950), 307 sh (4250); ir (chloroform): 3470 (NH), 1698 (C=O), 1148 (OCH_3); ^1H nmr (deuteriochloroform): δ 1.75 (s, CH_3C=O), 2.25 (1H, amine N*H*, deuterium oxide exchangeable), 3.82 (s, 3H, OCH_3), 6.70-7.20 (m, 3H, aromatic), 7.80 (1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 20.5, 22.7, 22.9, 24.7, 35.5, 38.7 ($6CH_2$), 30.8 (CH_3), 54.1 (quat, C-1), 55.3 (OCH_3), 55.9 (C-2), 99.8, 110.3, 111.5 (4 CH, aromatic), 107.6, 127.0, 130.4, 140.3, 152.9 (4 C quat, aromatic), 211.6 (C=O); ms: m/z 312.

1-(2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indol]-2-yl)-1-propanone (**12c**).

By applying Method A above, **12c** base was obtained from **10c** as off-white crystals, after recrystallization from ethyl acetate, mp 172-173°; uv (ethanol): λ max nm (ε) 225 (37,500), 275 sh (7950), 282 (8400), 290 (7600); ir (nujol): 3320 (NH), 1682 (C=O); ir (chloroform): 3440 (NH), 1698 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ (t, J = 7.5 Hz, 3H, CH_2CH_3), 7.10-7.50 (m, 4H, aromatic), 8.30 (1H, N*H*-indole); ms: m/z 296.

2-Methoxy-1-(2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido-[3,4-*b*]indol]-2-yl)ethanone (**12d**). Method B.

To a solution of 4.7 g (0.015 mole) of **10d** in 50 ml of chloroform was added 5 ml of trifluoroacetic acid and allowed to stand at 25° for 3 hours, after which time the cyclization was complete. The mixture was made basic with aqueous ammonia at 0°. The chloroform phase was washed, dried over sodium sulfate and evaporated. Trituration of the residue with acetonitrile gave 3.5 g of off-white crystals, mp 171-274°. Recrystallization from acetonitrile gave pure **12d** as white crystals, mp 176-177°; uv (ethanol): λ max nm (ε) 225 (30,400), 275 sh (6300), 283 (6800), 291 (6400); ir (chloroform): 3500, 3360 (NH), 1712 (C=O); ^1H nmr (DMSO-d_6): δ 2.78 (s, 3H, OCH_3), 312, 382 (dd, J = 18.0 Hz, 2H, CH_2OCH_3), 6.88-7.06 (m, 2H, H-6, H-7, aromatic), 7.32 (d, J = 8.8 Hz, 2H, H-5, H-8, aromatic), 10.97 (s, 1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 20.4, 22.8, 24.6, 35.2, 38.2, 38.7, 38.8, 39.1, 39.5, 39.9, 40.2, 40.3, 40.7, 52.1, 54.1, 57.8, 76.5, 108.1, 110.9, 117.7, 118.4, 120.8, 126.7, 135.4, 138.9, 210.5; ms: m/z 312.

Products Obtained from Enamines **11** by using Pictet-Spengler Reaction Conditions.

The description below will illustrate different outcome by using slight modifications of the same general reaction.

2-[2,3,4,9-Tetrahydro-1-methyl-1*H*-pyrido[3,4-*b*]indol-1-yl]cyclohexanone (**13a**, Scheme II). Method A.

To a solution of 0.8 g of **11a** in 25 ml of chloroform was introduced dry hydrogen chloride for 6 minutes and immediately it was made basic with sodium bicarbonate at 0°. The chloroform phase was washed, dried over sodium sulfate and evaporated. Trituration of the residue with acetonitrile gave 0.5 g of off-white solid, mp 147-149°. Recrystallization from ethyl acetate gave pure **13a** as nearly white crystals, mp 149-150°; uv (ethanol): λ max nm (ε) 225 (36,500), 273 sh (7900), 280 (8,100), 290 (6500); ir (chloroform): 3480, 3350 (NH), 1702 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.53 (CH_3), 2.15 (amine N*H*, deuterium oxide-exchangeable), 8.01 (1H, N*H*-indole); ms: m/z 282.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.63; H, 7.81; N, 9.78.

4,9-Dihydro-1-methyl-3*H*-pyrido[3,4-*b*]indole (**14a**). From Enamine **11a**, (Method A'-Delayed Work-up, Scheme II).

To a solution of 0.4 g of **11a** in 25 ml of chloroform was introduced dry hydrogen chloride for 5 minutes and the solution was allowed to stay for 24 hours at 25°. The dark reaction mixture was made basic with aqueous sodium bicarbonate at 0° and separated. The chloroform layer was washed, dried over sodium sulfate and evaporated. Trituration with 2-propanol gave 0.2 g of pale yellow crystals, mp 181-182°. Recrystallization from ethyl acetate gave pure 4,9-dihydro-1-methyl-3*H*-pyrido[3,4-*b*]indole (**14a**), mp 182-183°, which is identical in all respects to the product obtained previously [1].

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.15; H, 6.57; N, 15.20. Found: C, 78.23; H, 6.59; N, 15.17.

4,9-Dihydro-6-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole (**14b**). From Enamine **11b**. (Method B'-Delayed Work-up).

A solution of 0.5 g **11b** in 10 ml of chloroform was treated with 2 ml of trifluoroacetic acid and allowed to stand overnight at 23°. The mixture was taken up with ice-water, made basic with potassium bicarbonate and separated. The aqueous layer was reextracted with chloroform and the combined extracts were dried over sodium sulfate and evaporated. Trituration of the residue with ethyl acetate gave 0.2 g of **14b**, mp 206-208°. Recrystallization from acetonitrile gave pure **14b** as off-white crystals, mp 208-209° [lit [1] mp 208-209°].

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.69; H, 6.62; N, 13.14.

1-Ethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (**14c**, Scheme II).

A solution of 1.0 g **11c** in 25 ml of chloroform was saturated with dry hydrogen chloride for 5 minutes at 10° and allowed to stand at 10° until starting materials was consumed (7 hours). The mixture was taken up with ice-water, made basic with potassium bicarbonate, and separated. The chloroform phase was washed, dried over sodium sulfate and evaporated. The residue was triturated with acetonitrile to give 0.4 g of **14c** as off-white crystals, mp 164-166°. An analytically pure **14c** was obtained by recrystallization from acetonitrile, mp 168-169° [lit [7] mp 172-173°]; uv (ethanol): λ max nm (ε) 235 (14,600), 315 (14,200); uv (ethanolic hydrogen chloride): 245 (9900), 341 (21,400); ir (chloroform): 3480 (NH), 1560

(C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (t, J = 7.5 Hz, 3H, CH_3), 2.75 (m, 4H, CH_2CH_3 and CH_2-indole), 3.87 (t, J = 7.5 Hz, 2H, CH_2N), 8.79 (1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 10.5, 18.9, 27.7, 47.6, 112.3, 114.1, 119.3, 119.4, 123.3, 125.0, 128.7, 136.4, 160.8.

2-[2,3,4,9-Tetrahydro-1-(methoxymethyl)-1*H*-pyrido[3,4-*b*]indol-1-yl]cyclohexanone (**13d**).

The same procedure as for the preparation of **13a** was followed. Thus, 0.6 g of **11d** gave 0.4 g of crude **13d**, mp 148-150°. Recrystallization from ethyl acetate gave pure **13d**, mp 151-152°; uv (ethanol): λ max nm (ε) 225 (30,400), 283 (6800), 292 (6400); ir (chloroform): 3485, 3360 (NH), 1713 (C=O) cm^{-1}; ms: m/z 282.

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 73.20; H, 7.96; N, 9.14.

Enamines **11e** and **11f** required longer reaction time for their consumption (5 and 7 hours, respectively, at 23°). However, in both cases there was an extensive decomposition and the only isolable product in a low yield (10-15%) was **14b** as a result of extrusion of cyclopentanone and cycloheptanone, respectively.

1-(2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indol]-2-yl)ethanone Oxime (**15a**).

Product **15a** hydrochloride was obtained in 67% yield as white, fluffy crystals using standard conditions, mp 204-205°; uv (ethanol): λ max nm (ε) 221, (37,600), 275 (7450), 289 (5800).

2',3',4',9'-Tetrahydro-α-methylspiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]-indole]-2-methanol, Hydrochloride (**15b**).

A mixture of 8.5 g (0.03 mole) of **15a** and 2.5 g of potassium borohydride in 100 ml of 2-propanol was stirred for 3 hours at 23°. After the solution was evaporated *in vacuo* at 30°, the residue was taken up with cold water and the resulting white precipitate was separated by filtration. The solid was redissolved in 75 ml of acetonitrile and dry hydrogen chloride was introduced to *p*H 2.0 to give, on standing for 20 hours, 5.9 g of white crystals, mp 265-267° dec. An analytical sample of **15b** was obtained by recrystallization from methanol, mp 267-268° dec; uv (ethanol); nmr (ε) 223 (37,000), 273 (7950), 280 (8000), 289 (6500); ^1H nmr (DMSO-d_6): δ 0.50 (d, J = 7.5 Hz, 3H, CH_3), 7.08-7.55 (m, 4H, aromatic), 9.20 (broad, 2H, NH_2), 11.35 (1H, N*H*-indole); ms: m/z 284.

3-Phenyl-1-(2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]-indol-2-yl)-3-propen-1-one (**16a**).

A solution of 11.3 g (0.04 mole) of **12a**, 8 g of benzaldehyde and 4 ml of 40% aqueous sodium hydroxide in 180 ml of ethanol was heated on a steam bath for 5 minutes. After the solution was allowed to cool and stand at 23° overnight, the resulting light yellow crystals (11.1 g, 75% yield) were collected by filtration, mp 193-194°. An analytical sample, mp 194-195°, was obtained by recrystallization from ethanol; uv (ethanol): λ max nm (ε) 226 (31,000), 343 sh (14,500), 292 (18,200); ir (nujol): 3300 (NH), 1666, 1595 (C=C-C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.08 (d, J = 16.0 Hz, 1H, vinylic), 6.85-7.40 (m, 10H, 1H, vinylic and 9H, aromatic), 11.07 (1H, N*H*-indole); ms: m/z ($M^+ + 1$), 371 (100%).

2',3',4',9'-Tetrahydro-α-(2-phenylethenyl)spiro[cyclohexane-1,1'-[1*H*]pyrido[3,4-*b*]indol]-2-methanol (**16b**).

A mixture of 7.8 g (0.02 mole) of **16a** and 1.8 g of potassium borohydride in 75 ml of methanol was stirred for 3 hours at 23°. After the solvent was removed *in vacuo*, the residue was taken up with cold water and the white solid (7.4 g) was collected by filtration, mp 214-216°. Crystallization from ethanol gave 6.4 g (82% yield) of pure **16b**, mp 217-218°; ^1H nmr (DMSO-d_6): δ 3.95 (d, J = 7.0 Hz, 1H, C*H*-OH), 5.50 and 5.66 (dd, J = 16.0 Hz and 7.0 Hz, 1H, C*H*-CHOH), 6.13 (d, J = 16.0 Hz, 1H, C*H*-C_6H_5), 6.45 (1H, deuterium oxide-exchangeable, O*H*), 6.65-7.45 (m, 9H, aromatic), 10.83 (1H, N*H*-indole); ms: m/z 372.

2-(4,9-Dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-methylcyclohexanol (**17a**).

Method A.

A solution of 8.5 g (0.03 mole) of **12a** and 5.0 g of potassium *t*-butoxide (MSA Research Corporation) in 50 ml of *t*-butyl alcohol was refluxed for 3 hours. The tlc (acetonitrile-ethyl acetate, 1:1) showed absence of the starting **12a** (Rf = 0.5), the new product having a lower Rf (0.3). After the solution was evaporated, the residue was taken up with cold water and extracted twice with 75 ml of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated *in vacuo*. The residue was crystallized from 2-propanol-ethyl acetate giving 5.1 g (65% yield) of **17a** as off-white crystals, mp 150-151°; uv (ethanol): λ max nm (ε) 236 (15,800), 241 sh (15,500), 306.5 (15,200); uv (ethanol·HCl): 245 (12,800), 353 (24,000); ir (chloroform): 3490, 3220 (OH, NH), 1620, 1605, 1550 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.26-1.75 (m, 8H, cyclohexane moiety), 2.74 (t, J = 8.5 Hz, 2H, CH_2-4), 2.92 (m, 1H, C*H*C-OH), 3.72 (m, 2H, CH_2-3), 5.77 (s, 1H, deuterium oxide-exchangeable, O*H*), 6.95-7.65 (m, 4H, aromatic), 11.40 (s, 1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 18.6, 21.1, 25.3, 27.9, 39.7, 46.8 (6 CH_2), 29.7 (CH_3), 46.8 (CH-2), 69.8 (C-1), 112.3, 119.5, 119.7, 123.9 (4CH, aromatic), 115.3, 124.8, 128.3, 136.6 (4C quat, aromatic), 166.1 (C-1); ms: m/z 282.

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.79; H, 7.94; N, 10.10.

Method B.

A solution of 5.6 g (0.02 mole) of **12a** and 1.0 g of sodium hydride (Ventron Corp., 57% in paraffin oil) in 50 ml of dry tetrahydrofuran was refluxed for 3 hours and subsequently evaporated to dryness *in vacuo*. The residue was taken up with cold water and extracted with 100 ml of ethyl ethyl acetate. The extract was dried over sodium sulfate and evaporated *in vacuo*. Crystallization of the residue from 2-propanol gave 3.4 g (61% yield) of **17a**, mp 150-151°. A mixture mp, spectra, and tlc were identical to the product obtained by Method A.

2-(4,9-Dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-ethylcyclohexanol (**17b**).

By following Method B, 8.0 g (0.027 mole) of **12c** gave 5.2 g of crude **17b**. Recrystallization from diisopropyl ether-ethyl acetate gave 4.7 g (59% yield) of pure **17b** as off-white crystals, mp 133-134°; uv (ethanol): λ max nm (ε) 236 (15,800), 241 sh (15,550), 307 (15,200); ir (chloroform): 3510, 3290 (OH, NH), 1622, 1606, 1550 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.73 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.10-1.75 (m, 10H, 8H of cyclohexane moiety and CH_2CH_3), 2.74 (t, J = 8.5 Hz, 2H, CH_2-4), 2.95 (m, 1H, C*H* C-OH), 3.72 (m, 2H, CH_2-3), 5.77 (s, 1H, deuterium oxide-exchangeable, O*H*), 7,02, 7.17 (mm, 2H, H-6 and H-7), 7.41, 7.45 (dd, J = 8.0 Hz, 2H, H-5 and H-8), 11.43 (s, 1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 8.0, 18.6, 20.9, 25.4, 28.3, 34.2, 34.6, 38.3, 46.8, 72.2, 112.4, 115.3, 119.7, 124.0, 124.9, 128.3, 136.7, 166.2; ms: m/z 296.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.01; H, 8.18; N, 9.36.

2-(4,9-Dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-(methoxymethyl)cyclohexanol (**17c**).

By following Method A, compound **17c** was obtained from **12d** in 56% yield, mp 163-164. An analytical sample was obtained by recrystallization from 2-propanol, mp 164-165°; uv (ethanol): λ max nm (ε) 236 (14,800), 319 (14,850); uv (ethanol·HCl): 245 (12,000), 353 (21,600); ^1H nmr (deuteriochloroform): δ 1.45-1.90 (m, 8H, cyclohexane moiety), 2.80 (m, 3H, CH_2-4 and C*H*-C-OH), 3.25 (CH_3), 2.95-4.10 (non-resolvable multiplicity, 7H, CH_2-3, CH_2O, CH_3), 5.30 (deuterium oxide-exchangeable, O*H*), 7,15-7.65 (m, 4H, aromatic), 9.10 (1H, N*H*-indole); ms: m/z 312.

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.74. Found: C, 73.10; H, 7.71; H, 8.68.

4,9-Dihydro-1-(2-methyl-1-cyclohexen-1-yl)-3*H*-pyrido[3,4-*b*]indole (**19a**).

A solution of 14.1 g (0.05 mole) of **12a**, 10 ml of morpholine and 0.5 g of 4-toluenesulfonic acid in 200 ml of toluene was refluxed for 6 hours while 0.9 ml of water separated in a Dean-Stark trap. After the solution

was evaporated, the dark residue was taken up with cold water and extracted with 150 ml of chloroform. The chloroform extract was dried over sodium sulfate, filtered through silica gel, and evaporated. Trituration of the residue with 2-propanol gave 5.1 g of **19a** as off-white crystals, mp 202-204°. Recrystallization from ethyl acetate gave 4.9 g (37% yield) of pure **17a** as white crystals, mp 204-205°; uv (ethanol): λ max nm (ε) 237 (17,000), 320 (14,750); uv (ethanol·HCl): 246 (10,650), 359 (21,400); ^{1}H nmr (deuteriochloroform): δ 1.71 (CH_3), 1.73-2.50 (m, 8H, cyclohexane moiety), 2.95 (t, J = 8.5 Hz, 2H, CH_2-4), 3.98 (t, J = 8.5 Hz, 2H, CH_2-3), 7.10-7.65 (m, 4H, aromatic), 9.10 (1H, N*H*-indole); ms: m/z 264.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 82.03; H, 7.92; N, 10.36.

4,9-Dihydro-6-methoxy-1-(2-methyl-1-cyclohexen-1-yl)-3*H*-pyrido[3,4-*b*]-indole (**19b**).

By following the same procedure as for the preparation of **19c**, the spiro ketone **12b** gave **19b** as white crystals in 44% yield, after recrystallization from 2-propanol, mp 176-177° dec; uv (ethanol): λ max nm (ε) 233 sh (14,250), 330 (16,300); ^{1}H nmr (DMSO-d_6): δ 1.42 (s, 3H, CH_3), 1.65 (m, narrow, 4H), 1.95-2.15 (m, 4H), 2.72 (t, J = 8.0 Hz, 2H, CH_4), 3.73 (t, J = 8.0 Hz, 5H, CH_2-3 and OCH_3), 6.79 (dd, J = 8.5 and 1.5 Hz, 1H, H-7), 6.99 (d, J = 1.5 Hz, 1H, H-5), 7.27 (d, J = 8.5 Hz, 1H, H-8), 10.65 (s, 1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 18.9, 20.5, 22.3, 28.3, 30.7, 48.0, 55.3, 100.1, 113.2, 113.6, 114.3, 125.2, 128.9, 129.1, 131.6, 131.7, 153.5, 161.8; ms: m/z 294.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.80; H, 7.47; N, 9.64.

Transformation of **17a** into **19a**.

A solution of 0.6 g of **17a**, 2 ml of morpholine and 0.1 g of 4-toluenesulfonic acid in 50 ml of toluene was refluxed with water separator for 3 hours and subsequently evaporated to dryness. The dark residue was taken up with water, extracted with 25 ml of dichloromethane and evaporated. Trituration of the residue with 2-propanol gave 0.3 g of **19a** as off-white crystals, mp 203-204°. Recrystallization from 2-propanol gave pure **19a**, mp 204-205° which is identical in all respects to analytical product **19a** obtained by direct method from **12a**.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.83; H, 7.56; N, 10.65.

1-Methyl-2-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)cyclohexanol (**20**).

A solution of 2.82 g (0.1 mole) of 2-(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-1-methylcyclohexanol (**17a**) in 20 ml of ethanol was hydrogenated over 0.1 g of palladium-on-carcoal at atmospheric pressure until the hydrogen uptake ceased (1 hour). The tlc showed slower moving product (Rf = 0.45) than the starting material (Rf = 0.55). After the catalyst was removed, the filtrate was evaporated *in vacuo*. Crystallization of the residue from ethyl acetate gave 1.7 g (60% yield) of **20** as white crystals, mp 211.5-212° dec; uv (ethanol): λ max nm (ε) 226 (34,520), 282 (8050), 2905 (6900); ^{1}H nmr (DMSO-d_6): δ 0.98 (3H, CH_3), 1.75 (CH_2-N*H*), 4.34 (1H, O*H*, deuterium oxide-exchangeable), 10.70 (1H, N*H*-indole); ^{13}C nmr (DMSO-d_6): δ 21.4, 22.0, 25.6, 26.3, 41.1, 43.5 (6 CH_2), 29.7 (CH_3), 48.5 (CH-2), 56.1 (N-C-1), 71.0 (C-1), 110.8, 117.3, 118.2, 120.1 (4CH, aromatic), 107.3, 127.0, 135.1, 136.3 (4 quat, aromatic); ms: m/z 284.

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.07; H, 8.51; N, 9.85. Found: C, 76.29; H, 8.37; N, 10.01.

1,3,4,9-Tetrahydro-1-(2-hydroxy-2-methylcyclohexyl)-*N*-2-propenyl-2*H*-pyrido[3,4-*b*]indole-2-carboxamide (**21**).

A solution of 4.0 g (0.04 mole) of **20** and 2.5 g (0.03 mole) of allyl isocyanate in 45 ml of anhydrous tetrahydrofuran was allowed to stand overnight at 23°. Methanol (1 ml) was added to destroy excess isocyanate and the solution was evaporated to dryness *in vacuo*. Crystallization of the residue from acetonitrile gave 3.3 g (65% yield) of pure cyclohexanol urea derivative **21** as off-white crystals, mp 223-224° dec; uv (ethanol): λ max nm (ε) 226 (41,500), 282 (8000), 290 (6650); ir (nujol): 3350 (OH, NH), 1630, 1595, 1586, 1530 (CONH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.33 (CH_3), 1.10-1.78 (m, 11H, CH_3 and 8H of cyclohexane moiety), 2.68 (m, 2H, CH_2-4), 3.37 (m, 2H), 3.72 (m, 2H, NHCH_2C=C), 4.12 (m, 1H, vinylic), 4.69 (s, 1H, deuterium oxide-exchangeable, O*H*), 5.02 (m, 2H, vinylic), 5.60 (d, J = 3.5 Hz, 1H, H-1), 6.79 (t, J = 5.5 Hz, 1H, deuterium oxide-exchangeable, CH$_2$N*H*), 6.90-7.10 (m, 2H, H-6, H-7), 7.35 (t, J = 7.5 Hz, 2H, H-5, H-8), 10.46 (1H, N*H*-indole); ms: m/z 367.

Anal. Calcd. for $C_{22}H_{29}N_3O_2$: C, 71.90; H, 7.95; N, 11.44. Found: C, 71.96; H, 7.90; N, 11.45.

2-Acetyl-2,3,4,9-tetrahydro-1-(2-hydroxy-2-methylcyclohexyl)-1*H*-pyrido-[3,4-*b*]indole (**22**).

A solution of 1.4 g (0.005 mole) of **20** and 2 ml of acetic anhydride was allowed to stand 20 hours at room temperature. The contents were poured onto ice, made basic with aqueous ammonia and extracted with 50 ml of ethyl acetate. The extract was dried over sodium sulfate and evaporated *in vacuo*. Crystallization of the residue from ether-ethyl acetate gave 1.2 g (76% yield) of pure amido alcohol derivative **22**, mp 245-246° dec; uv (ethanol): λ max nm (ε) 225 (46,800), 274 sh (9050), 282 (9300), 291 (7600); ir (nujol): 3300-3190 (OH, NH), 1614 (C=O) cm^{-1}; ms: m/e 316.

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.59. Found: C, 73.59; H, 7.81; N, 8.53.

2-Acetyl-1-[2-(acetyloxy)-2-methylcyclohexyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**23**).

A solution of 1.0 g of **20** in 20 ml of acetic anhydride was refluxed for 6 hours. After cooling, 50 ml of ether was added and the solution was allowed to stand in refrigerator overnight. The resulting white crystals of **23** (0.9 g, 79% yield) were collected by filtration, mp 217-218°. An analytical sample was obtained by recrystallization from diisopropyl ether-ethyl acetate, mp 218-219°; uv (ethanol): λ max nm (ε) 225 (45,900), 282 (9300), 289 (7750); ir (chloroform): 3450 (NH), 1737 (ester, C=O), 1630 (amide C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.56 (3H, CH_3-2), 2.06 (3H, NCOCH_3), 2.15 (3H, OCOCH_3), 5.89 (d, 1H, J = 6.0 Hz, C*H*-1), 6.85-7.40 (m, 4H, aromatic), 10.28 (1H, N*H*-indole); ms: m/e 358.

Anal. Calcd. for $C_{22}H_{26}N_3O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 72.00; H, 7.85; N, 7.39.

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[1] G. Bobowski, *J. Heterocyclic Chem.*, **20**, 267 (1983).

[2] W. M. Whaley and T. R. Govindachari, "Organic Reactions", Coll Vol **6**, John Wiley and Sons, Inc., New York, NY, 1951, pp 151-190.

[3] The ratio of **10** to **11** as determined by tlc and ^{1}H nmr of the crude mixture was only approximate. However, the amount of isolated minor isomer **11** by direct crystallization was much less (*cf.* Table III) since a considerable amount of it *invariably* remained in the mother liquor.

[4] This method was used successfully for the cyclization of enamines derived from 1*H*-indol-3-ethanamines and 1,2-cyclohexanedione. G. Bobowski, *J. Heterocyclic Chem.*, **18**, 1179 (1981).

[5] As shown in Table IV, yields of isolated pure products **12** are considerably lower since some decomposition unavoidably occurred under reaction conditions.

[6] In case of **11f** (7-membered ring), the elimination of cycloheptanone occurred immediately after cyclization was complete to give **14b**.

[7] E. Späth and E. Lederer, *Ber.*, **63**, 2120 (1930).