2′,3′,4′,9′-Tetrahydrospiro[cyclohexane-1,1′-(1*H*)pyrido[3,4-*b*]indol]-2-ones and Their Transformations into 2,3,4,4a,5,6,9,14-Octahydro-4a-hydroxy-1*H*,8*H*-pyrido[3,4-*b*:2,1-*i*′]diindole-5-carbonitriles and 5-Substituted 2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo[2′,3′:3,4]-pyrido[1,2-*c*]benzimidazol-6-(5*H*)ones

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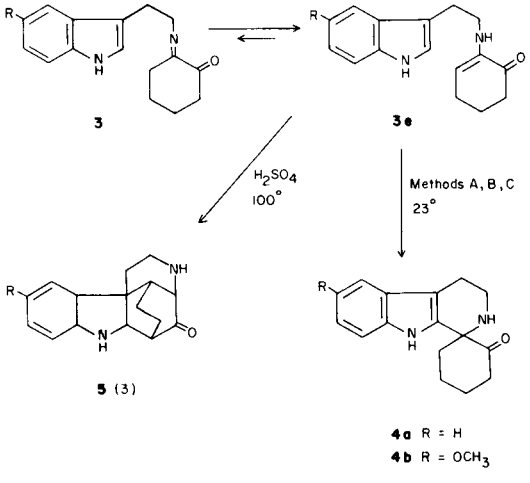
Received May 4, 1981

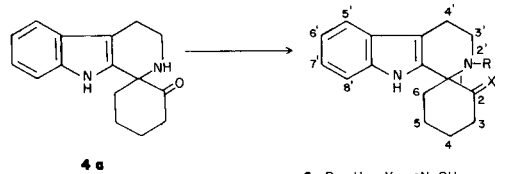
The condensation of 1*H*-indol-3-ethanamine derivatives **1** with 1,2-cyclohexanedione (**2**) and subsequent transformation of the resulting 2-[[2-(1*H*-indol-3-yl)ethyl]imino]cyclohexanones (**3**) into 2′,3′,4′,9′-tetrahydrospiro[cyclohexane-1,1′-(1*H*)pyrido[3,4-*b*]indol]-2-ones **4** using Pictet-Spengler (1) reaction conditions is described. The reaction of **4** with acrylonitrile gave a mixture of pentacyclic derivatives, 2,3,4,4a,5,6,9,14-octahydro-4a-hydroxy-1*H*,8*H*-pyrido[3,4-*b*:2,1-*i*′]diindole-5-carbonitriles **12**. Treatment of **4** with alkyl and aryl isocyanates (**14**) at room temperature gave 5-substituted-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo[2′,3′:3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)ones **16**. Dehydration of **16** gave 5-substituted-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2′,3′-3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)ones (**17**). Spectral and chemical evidence is presented to confirm structures **4**, **12**, **16**, and **17**.

J. Heterocyclic Chem., **18**, 1179 (1981).

One equivalent of 1,2-cyclohexanedione, **2**, gave approximately 80% yields of 2-[[2-(1*H*-indol-3-yl)ethyl]imino]-cyclohexanones, **3**, in the form of their enamine tautomers, **3e**, when it was treated with benzosubstituted-1*H*-indol-3-ethanamines, **1** under azeotropic conditions. Cyclic 2′,3′,4′,9′-tetrahydrospiro[cyclohexane-1,1′-(1*H*)-pyrido[3,4-*b*]indol]-2-ones, **4**, were produced in good yields when the precursor enamine, **3e** was exposed to three different acids: dry hydrogen chloride in chloroform (Method A) (2), trifluoroacetic acid (Method B), or sulfuric acid in alcohol (Method C). In contrast, **5**, 3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2-(1*H*)one, (3) was formed when more strenuous conditions were employed using neat sulfuric acid at 100°.



The structures of tetracyclic spiro derivatives **4** are proved by both chemical and spectral evidence. Compounds **4** have the characteristics of both ketones and amines. They form oximes **6** in the normal way and are reduced to secondary alcohols **7** by potassium borohydride in alcohol at room temperature. With acetic anhydride at 23°, compounds **4** give amido ketones **8**.



6 R = H, X = =N-OH
7 R = H, X = HOH
8 R = $COCH_3$, X = O
9 R = H, X = H_2
10 R = $COCH_3$, X = H_2

The presence of *N*-acetyl group in **8** causes a large deshielding effect on *N*-methylene protons (CH_2-3′). Furthermore, because of the rigidity and distortion of the heterocyclic ring, the chemical shifts of the two CH_2-3′ protons are separated by about 0.6 ppm. This *N*-methylene group takes the form of an AB quartet, each branch of which is further split by spin coupling with indole benzylic protons (CH_2-4′). Thus, the one C-3′ proton is seen as two apparent triplets at 4.12 (J = 4.2 Hz) and at 3.95 (J = 4.2 Hz) ppm, respectively, while the other C-3′ proton appears as an irregular quintet centered at *ca.* 3.45 ppm. The dissimilar patterns of the two protons reflect the different angles they make with the neighboring methylene protons (CH_2-4′). The unusual pattern of these *N*-methylene protons in **8** is also strongly influenced by the ketone function. Thus, the desoxy compound **10** merely exhibits a regular triplet (J = 6.5 Hz) at 3.73 due to CH_2-3′ and another at 2.80 (J = 6.5 Hz) ppm due to CH_2-4′. However,

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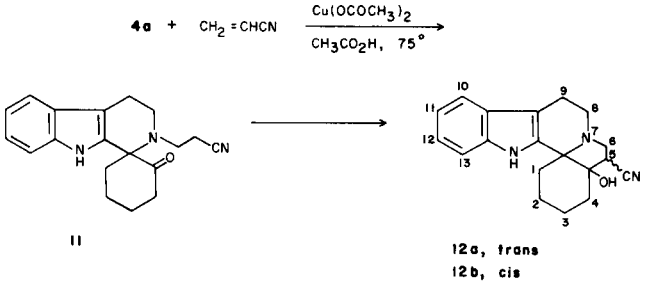
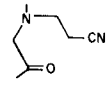
compound **10** exhibits a two-proton multiplet at 3.05 ppm, which is absent in the proton spectrum of the underivatized base as its hydrochloride salt **9**. The multiplet, therefore, is due to deshielding exerted by the amide carbonyl on two protons of the spiro ring. Depending on which chair forms the spiro ring can adopt, the axial protons on the two adjacent carbon atoms (C-2,6) or on the carbon atoms next removed (C-3,5) should fall within the shielding cone of the carbonyl group from inspection of molecular models. The remaining eight protons of the spiro ring are revealed as a narrow multiplet centered at 1.70 ppm and the methyl group of the acetamide function appears at 2.22 ppm.

The cyanoethylation reaction (4) of **4a** with acrylonitrile in the presence of cupric acetate and acetic acid gave 4′,9′-dihydro-2-oxospiro[cyclohexane-1,1′-(1*H*)pyrido-[3,4-*b*]indole]-2′-(3′*H*)propanenitrile, **11**. Compound **11** underwent spontaneous cyclization giving about equal proportions of the *trans* (**12a**) and *cis* (**12b**) isomers of the pentacyclic compound, 2,3,4,4a,5,6,9,14-octahydro-4a-hydroxy-1*H*,8*H*-pyrido[3,4-*b*:2,1-*i*′]diindole-5-carbonitrile.

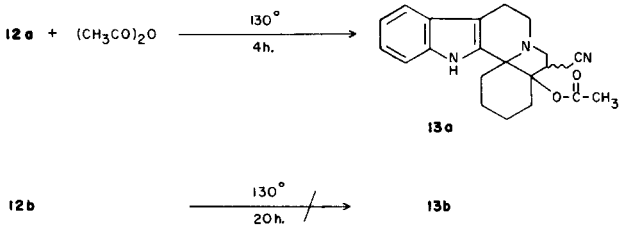


Acyclic derivative, **11**, which is a normal cyanoethylation product and an intermediate to **12a** and **12b**, could only be isolated in low (10%) yield under the conditions employed. Compound **11** could be easily converted into a mixture of **12a** and **12b** by heating briefly at 100° in the presence of acetic acid and cupric acetate (see Experimental). This facile cyclization indicates an absence of steric hindrance in the area of the carbonyl



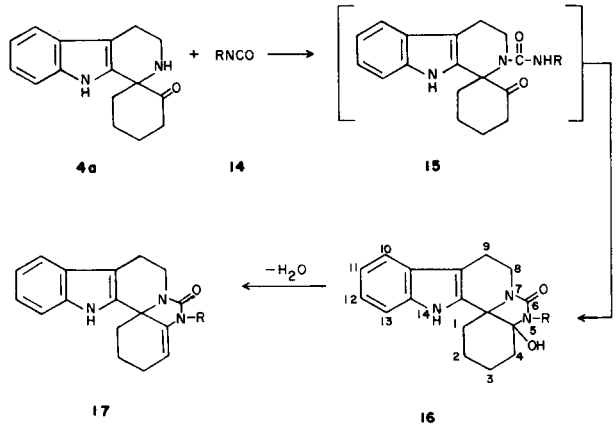
function and a favorable spatial relationship between the ring forming termini.

The spectral data of **12a** and **12b** are similar and of little use for differentiating between the two isomers. However, there are significant differences in their melting points and mobilities on thin layer chromatography (tlc). The tentative assignment of the *trans* **12a** and *cis* **12b** structures is based in part on physical characteristics: the *trans* isomer has lower solubility, lower mobility on tlc and a higher melting point. The assignment is also supported by chemical evidence: the *trans* isomer forms an acetate ester **13a** fairly easily, while the *cis* isomer (with the hydroxyl and cyano functions in close proximity) failed to react within 20 hours with refluxing acetic anhydride.



Although compounds **12** possess three asymmetric centers, raising the possibility of 4 *d,l*-pairs, they appear to be single isomers as evidenced by sharp melting points and single spots on tlc.

Treatment of **4a** with one equivalent of alkyl or aryl isocyanate **14** (5) at room temperature gave the urea ketone derivatives **15** which spontaneously cyclized to 5-substituted-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo[2′,3′:3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)ones, **16**, in relatively good yields (Table I). This extremely facile cyclization precluded the isolation of **15**.

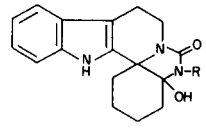


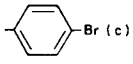
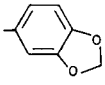
In contrast to compounds **12** (*a* and *b*) which are rather resistant to dehydration, the benzimidazol-6-(5*H*)one derivatives **16** eliminate water easily to give **17**. Olefins **17** are formed spontaneously under mild, neutral conditions where substituents R are alkyl or acyl groups bearing electron-releasing substituents. Intermediates **16** are stable when they contain aryl groups, R, bearing electron-withdrawing groups, but they can be converted to **17** by heating with traces of mineral acids or by heating with acetic anhydride (Table II).

The pentacyclic hydroxy derivatives **16** exhibit spectral patterns for the *N*-methylene protons (CH_2-8′), which are somewhat similar to the analogous (CH_2-3′) protons of the amide, **8**. However, because of the much greater rigidity of **16** where the imidazole carbonyl is fixed, the non-equivalency of these protons is even more pronounced.

Table I

5-Substituted-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)ones **16**

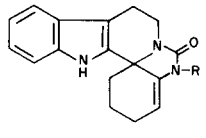


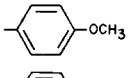
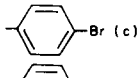
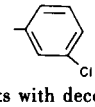
Compound	R	Empirical Formula	Mp °C	% Yield	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
16a		$C_{23}H_{22}BrN_3O_2$	211-212 (a)	66	61.07	4.90	9.30	61.36	5.02	9.45
16b		$C_{23}H_{22}ClN_3O_2$	222-223 (a)	67	67.73	5.54	10.30	67.90	5.40	10.30
16c		$C_{24}H_{23}N_3O_4 \cdot C_2H_6O$	143-144 (b)	38	67.37	6.31	9.07	67.28	6.43	8.89
16d	C_2H_5	$C_{19}H_{23}N_3O_2$	285-286 (a)	46	70.13	7.12	12.91	70.40	7.14	13.09

(a) Melts with decomposition. (b) Crystallized with 1 mole of ethanol. (c) Calcd: Br, 17.66. Found: Br, 17.80.

Table II

5-Substituted-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]imidazol-6-(5*H*)ones **17**

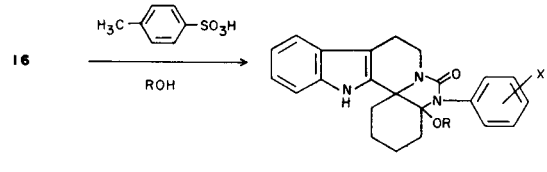


Compound	R	Empirical Formula	Mp °C	% Yield	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
17a	C_2H_5	$C_{19}H_{21}N_3O$	288-289 (a)	12.5 (b)	74.24	6.89	13.67	74.22	6.76	13.93
17b	CH_3	$C_{18}H_{19}N_3O$	299-300 (a)	79	73.69	6.53	14.33	73.64	6.55	14.06
17c	$CH_2CO_2C_2H_5$	$C_{21}H_{23}N_3O_3$	206-207 (a)	81	69.02	6.34	11.50	69.22	6.31	11.29
17d		$C_{24}H_{23}N_3O_2$	268-269 (a)	82	74.78	6.01	10.90	74.90	6.08	10.72
17e		$C_{23}H_{21}BrN_3O$	251-252 (a)	90	63.60	4.64	9.67	63.41	4.62	9.52
17f		$C_{23}H_{20}ClN_3O$	257-258 (a)	66	70.86	5.17	10.78	70.66	5.21	10.97

(a) Melts with decomposition. (b) The major product (46% yield) isolated from that reaction is 4a-hydroxy derivative **16d**, Table I. (c) Calcd: Br, 18.40. Found: Br, 18.55.

The separation of signals is now up to 1.00 ppm. The *N*-methylene group is an AB quartet (J_{gem} = 13.0 Hz), where each branch is a narrow multiplet caused by spin coupling with CH_2-indole protons (see Experimental). Compounds **16** exhibit carbonyl absorption at frequencies of 1695 to 1675 cm^{-1} which is a normal region for a five-membered ring lactam or urea (6a-d).

Compounds **16** could be converted to their ethers by heating briefly in alcohol in the presence of traces of mineral acids. This is exemplified by the transformation of **16a** and **16b** into the methoxy (**18a**) and ethoxy (**18b**) derivatives, respectively.

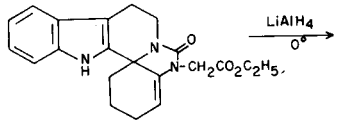


18a R = CH_3, X = 4-Br
18b R = C_2H_5, X = 3-Cl

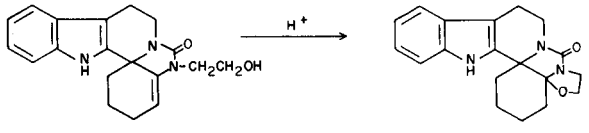
The dehydration products, **17**, show resonance patterns for the *N*-methylene protons (CH_2-8) which are similar to those of **16**. Moreover, they exhibit a vinylic proton signal,

usually as a triplet (J = 3.5 Hz) or as a multiplet. Olefins **17** display distinctive infrared absorption in the double bond region. In addition to strong amide I absorption at 1675-1695 cm^{-1}, absorption of higher frequency and moderate intensity is present at 1710-1720 cm^{-1}. The latter band is absent in precursors **16** which requires that it be associated with the enamido function present in **17**. Spectral data for close structural analogs have not been reported. However, olefinic absorption of perfluoro olefins has been assigned at 1740 cm^{-1} (7). The extinction coefficients of **17** are more intense than those of **16** in analogy to 1-vinyl-2-pyrrolidinone versus 1-butyl-2-pyrrolidinone (6d).

Compound **17c**, when subjected to controlled reduction conditions, gave the terminal alcohol **19** without affecting the imidazol-6-one ring. Along with **19**, a minor hexacyclic product, presumably **20**, was obtained in about 15% yield. Product **20** has the same empirical formula as **19**, and it lacks vinyl proton. Further, the distinctive infrared absorption of **17c** (1720 cm^{-1}) is absent. Other features of the ^{1}H-nmr and ultra-violet spectra likewise support structure **20**. Formation of **20** could be rationalized as follows: protonation at the β-carbon of the enamine function causes a shift of electrons and activates the α-position towards the nucleophilic attack by the oxygen atom.



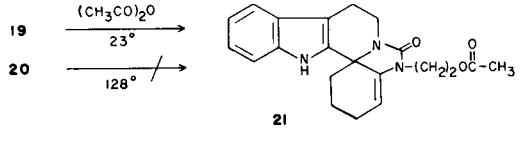
17c



19 20

Since no acid was used during the work-up process, it was felt that traces of hydrogen chloride present in commercial chloroform (the extraction solvent) might have catalyzed the cyclization. This was confirmed when alcohol **19** was dissolved in chloroform containing a small amount of hydrogen chloride. Quantitative conversion to compound **20** was effected within 5 hours at room temperature and within 5 minutes at 65°.

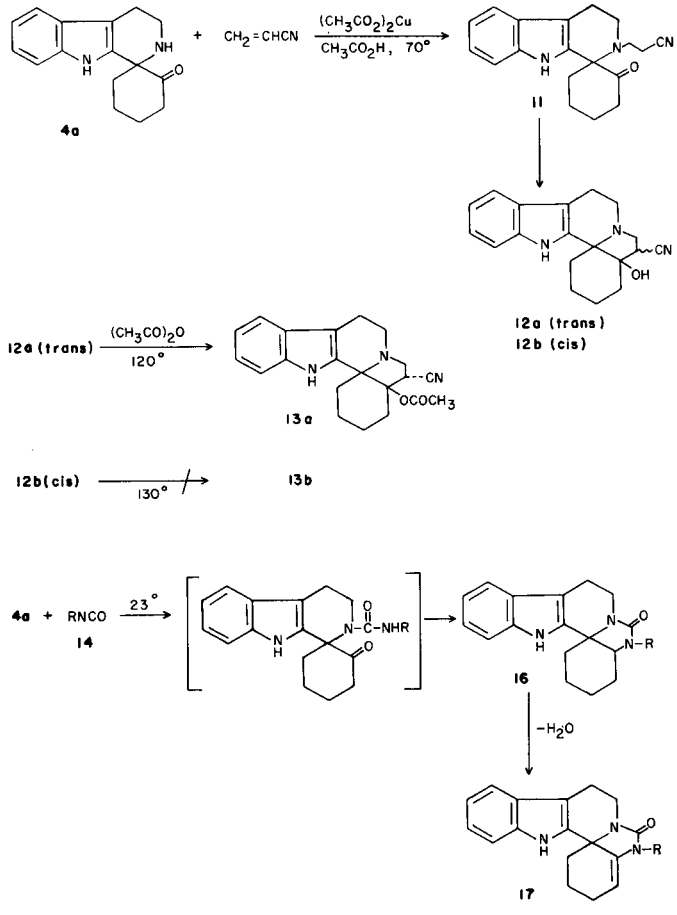
The 5-(2-hydroxyethyl) derivative **19** was converted to its acetate ester **21** by reaction with acetic anhydride at room temperature. However, compound **20** failed to react with acetic anhydride within 10 hours at reflux.



21

The sequence of reactions is presented in Scheme I.

Scheme I



EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. Infrared (ir) and ultraviolet (uv) spectra were obtained, respectively with a Beckman DK-1 spectrograph. Proton magnetic resonance (^{1}H-nmr) spectra were recorded on a Varian A-60 and a Bruker WH90 spectrometers with tetramethylsilane as an internal reference. The mass spectra were recorded on a Finnigan 1015 Quadrupole mass spectrometer. Thin layer chromatography (tlc) was carried out on silica gel G (Stahl) using toluene, acetone, and heptane or methanol and acetonitrile in varying proportions. The chromatograms were developed in an iodine chamber. The proton magnetic resonances of aromatic protons were generally not included. The lone protons were specified only in those instances when their resonances were clearly separated from envelopes of other protons or if they were shown in close proximity to other resonances but disappeared on deuterium oxide-exchange.

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

A solution of 16.0 g (0.1 mole) of 1*H*-indole-3-ethanamine (tryptamine) (**1**) and 11.2 g (0.1 mole) of 1,2-cyclohexanedione (**2**) in 200 ml of toluene was refluxed under nitrogen for 90 minutes, while 1.8 ml of water separated in a Dean-Stark trap. After the solvent was removed *in vacuo*, the residue was crystallized from ethanol giving 19.3 g (75% yield) of 2-[[2-(1*H*-indol-3-yl)ethyl]imino]cyclohexanone (**3a**) as off-white crystals, mp 132-133°. Concentration of the mother liquor and cooling gave 1.7 g

(total yield, 82%) of additional product **3a**, mp 130-132°; uv (ethanol): λ max nm (ε) 222 (25,500), 280 (8000), 298 (7830), 309 sh (6700); ir (potassium bromide): 3390, 3370 (NH), 1670 (C=O), 1628 (C=C-NH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.23 (m, broad, 1H, deuterium oxide-exchangeable, NH), 5.49 (t, J = 6.0 Hz, 1H, vinylic), 8.20 (1H, indole NH) ppm.

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.33; H, 7.21; N, 10.94.

Cyclization of Schiff Base **3a**. Method A.

To a solution of 2-[[2-(1*H*-indol-3-yl)ethyl]imino]cyclohexanone (**3a**) (7.63 g, 0.03 mole) in 75 ml of dry chloroform was introduced dry hydrogen chloride for 4 minutes until fumes began to appear. The subsequent thin layer chromatography (tlc, silica gel G; acetone, toluene, heptane, 2:1:1) showed complete reaction, the new product **4a** having slower mobility (Rf = 0.4) than the starting **3a** (Rf = 0.55). The solution was treated with ice, made basic with ammonium hydroxide and separated. The chloroform phase was washed, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from ethanol gave 5.1 g of pure 2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-(1*H*)pyrido-[3,4-*b*]indol]-2-one (**4a**) as white crystals, mp 185-186° dec. Concentration of the mother liquor to a low volume gave 1.9 g (total yield, 79%) of additional product **4a**, mp 183-185° dec; uv (ethanol): λ max nm (ε) 222 (37,800), 275 sh (7000), 281 (7750), 289 (7400); uv (ethanolic hydrogen chloride): 221 (39,600), 270 (7750), 279 (7410), 288 (7330); ir (potassium bromide): 3480 (NH), 1713 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.81 (1H, deuterium oxide-exchangeable, ArN*H*), 1.6 (1H, deuterium oxide-exchangeable, N*H*-2') ppm; mass spectrum, m/e 254.

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.75; H, 7.34; N, 10.83.

Method B.

To a solution of 5.0 g (0.02 mole) of **3a** in 30 ml of chloroform was added 5 ml of trifluoroacetic acid and the light brown solution was allowed to stand at 23° for 3 hours. Ice (20 g) was added and the mixture was made basic with sodium carbonate. The product **4a** was extracted with 60 ml of chloroform, the extract was washed, dried over sodium sulfate and evaporated. The residue was crystallized from 2-propanol giving 3.9 g (76% yield) of pure **4a**, mp 185-186° dec.

Method C.

To a solution of **3a** (1.0 g) in 20 ml of methanol was added 5 ml of concentrated sulfuric acid and the resulting light-red solution was allowed to stand at 23° for 2 hours. The solvent was removed under roto evaporator at 30°. The residue was taken up with ice-water, made basic with aqueous ammonia and extracted with 50 ml of chlorofom. The extract was washed, dried over sodium sulfate and evaporated. Crystallization of the residue from methanol gave 0.5 g (50% yield) of **4a** as white crystals, mp 185-186°. The product **4a** obtained by methods B and C was identical in all respects with that obtained by method A.

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

A stirred solution of 9.5 g (0.05 mole) of 5-methoxy-1*H*-indol-3-ethanamine (**1b**) (5-methoxytryptamine), 5.8 g (0.055 mole) of 1,2-cyclohexanedione in 120 ml of chloroform was refluxed for 2 hours, while the theoretical volume of water separated in a Dean-Stark trap. The solvent was removed and the brown residue was refluxed with 200 ml of ether. The ethereal extract was decanted from the insoluble gum and evaporated to dryness. Crystallization of the residue from methanol gave 8.9 g (55% yield) of 2-[[2-(5-methoxy-1*H*-indol-3-yl)ethyl]imino]cyclohexanone (**3b**) as off-white crystals, mp 111-113°; uv (ethanol): λ max nm (ε) 222 (25,500), 280 (8000), 298 (7830), 309 sh (6700), 334 (2900); ir chloroform: 3470, 3380 (NH), 1666 (C=O), 1624 (C=C-NH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.22 (1H, broad m, deuterium oxide-exchangeable, N*H*), 5.49 (t, J = 6.0 Hz, 1H, vinylic), 8.20 (1H, deuterium oxide-exchangeable, ArN*H*) ppm.

By applying of method A, the Schiff base **3b** was converted to 2',3',4',9'-tetrahydro-6'-methoxyspiro[cyclohexane-1,1'-(1*H*)pyrido[3,2-*b*]-indol]-2-one (**4b**) in 75% yield, mp 209-210.5°, dec; uv (ethanol): λ max nm (ε) 227 (28,800), 279 (9000), 294 sh (7800); ir (chloroform): 3500, 3390 (NH), 1708 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.80 (1H, deuterium oxide-exchangeable, ArN*H*), 3.85 (3H, OCH_3), 1.60 (1H, deuterium oxide-exchangeable, N*H*-2') ppm.

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 72.07; H, 7.21; N, 9.92.

2-[[2-(5-Acetyl-1*H*-indol-3-yl)ethyl]imino]cyclohexanone (**3c**).

A solution of 6.67 g (0.03 mole) of 1-[3-(2-aminoethyl)-1*H*-indol-5-yl]-ethanone (**1c**) and 3.9 g (0.033 mole) of 1,2-cyclohexanedione in 125 ml of toluene was refluxed for 2 hours while the theoretical volume of water had separated. After the solvent was evaporated *in vacuo*, the residue was crystallized from ethanol giving 3.3 g (42% yield) of pure 2-[[2-(5-acetyl-1*H*-indol-3-yl)ethyl]imino]cyclohexanone (**3c**) as off-white crystals, mp 154-156°; uv (ethanol): λ max nm (ε) 221 (25,500), 279 (8000), 298 (7830), 334 (2900); ir (nujol): 3380, 3350 (NH), 1675 (broad, C=O), 1630 (C=C-NH) cm^{-1}; ^{1}H-nmr (deuterioacetone): δ 10.45 (1H, deuterium oxide-exchangeable, ArN*H*), 5.48 (t, J = 5.0 Hz, 1H, vinylic), 4.2 (broad m, 1H, deuterium oxide-exchangeable, CH=C-N*H*) ppm.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.21; H, 7.00; N, 9.47.

All attempts to convert **3c** into the spiro derivative **4a** by applying methods A, B, and C with various modifications were unsuccessful. In most cases starting imine **3c** was recovered or, when reactions were performed in the presence of water, the Schiff base **3c** was hydrolyzed into its components.

2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]indol]-2-one Oxime (**6**).

A solution of 0.5 g of **4a**, 0.5 g hydroxylamine hydrochloride and 2 ml of pyridine in 25 ml of absolute ethanol was refluxed for 3 hours. The infrared absorption spectrum showed absence of the carbonyl function. The solution was evaporated to dryness. The residue was taken up with cold sodium bicarbonate solution and the off-white crystalline product was collected by filtration, mp 204-205° dec. Tlc (methanol-acetonitrile, 1:2) showed one spot only, Rf = 0.3. Recrystallization from 2-propanol gave 0.35 g of pure 2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-(1*H*)-pyrido[3,4-*b*]indol]-2-one oxime (**6**) as nearly white crystals, mp 205-206° dec; uv (ethanol): λ max nm (ε) 222 (37,850), 281 (7500), 289 (7500); ir (potassium bromide): 3415, 3300 (OH, NH) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.72 (1H, O*H*), 10.43 (1H, ArN*H*), 3.30 (1H, N*H*-2') ppm. All three protons exchange with deuterium oxide; mass spectrum, m/e 269.

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.38; H, 6.94; N, 15.45.

2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]indol]-2-ol (**7**).

To a stirred solution of 1.27 g (0.005 mole) of (**4a**) in 50 ml of methanol was added 0.2 g of potassium borohydride and continued to stir at 23° for 1 hour. The tlc (ethyl acetate-acetonitrile, 4:1) showed complete conversion, the new product having slower mobility (Rf = 0.3) than the starting ketone **4a**. The solution was adjusted to *p*H 7.0 with acetic acid and evaporated to dryness *in vacuo*. The colorless solid was taken up with cold water, stirred for 1 hour and filtered to give 1.1 g of **7** as white crystals, mp 197-198° dec. Recrystallization from 2-propanol gave 0.9 g (71% yield) of pure **7**, mp 198-199° dec; uv (ethanol): λ max nm (ε) 224 (36,200), 281 (7450); ir (potassium bromide): 3580 (OH), 3460, 3370, 3190 (NH); ^{1}H-nmr (DMSO-d_6): δ 10.58 (1H, ArNH), 4.30 (d, J = 5.5 Hz, 1H, deuterium oxide-exchangeable, O*H*), 3.90 (m, 1H, H-2), 3.31 (1H, deuterium oxide-exchangeable, N*H*) ppm.

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.89; H, 7.74; N, 10.84.

2'-Acetyl-2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]-indol]-2-one (**8**).

A solution of 0.3 g of **4a** and 2 ml of acetic anhydride in 20 ml of

chloroform was allowed to stand at 23° for 20 hours. Ice was added and the mixture was made basic with ammonium hydroxide. The chloroform phase was washed, dried over sodium sulfate and evaporated. Crystallization of the residue from ethyl acetate gave 0.2 g of pure **8**, mp 249-250° dec; uv (ethanol): λ max nm (ε) 224 (37,200), 275 sh (5550), 282 (7280), 291 (6600); ir (potassium bromide): 3380, 3320 (NH), 1678 (ketone C=O), 1625 ($NCOCH_3$) cm^{-1}; (chloroform): 3480, 3450 (NH), 1702 (ketone C=O), 1652, 1630 (amide C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.42 (1H, ArN*H*), 4.12, 4.02 (tt, J = 12.0 Hz and 4.2 Hz, 1H, H-3'), 3.42 (m, 1H, H-3'), 2.10 ($COCH_3$) ppm.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.05; H, 7.01; N, 9.61.

2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]indole] Hydrochloride (**9a**).

A solution of 1.6 g (0.01 mole) of **1** and 1.5 g (0.015 mole) of cyclohexanone in 50 ml of toluene was refluxed for 3 hours while the theoretical volume of water had separated. After the solvent was removed *in vacuo*, the residue was taken up with 30 ml of dry chloroform and treated with dry hydrogen chloride for 3 minutes. Ether (50 ml) was added and the light purple precipitate of the spiro derivative as a hydrochloride **9** was collected (2.6 g), mp 277-278° dec. Recrystallization from 2-propanol gave 2.3 g (82% yield) of pure **9**, mp 280-281° dec [lit (8) mp 279-281°]; uv (methanol): λ max nm (ε) 221 (38,380), 271 (7710), 278 (7390), 288 (5700); ^{1}H-nmr (DMSO-d_6): δ 11.12 (1H, ArN*H*), 9.52 (2H, $\overset{+}{N}H_2$), 3.35 (m, 2H, CH_2N), 2.28 (t, J = 5.0 Hz, CH_2-indole) ppm.

Anal. Calcd. for $C_{16}H_{20}N_2$·HCl: C, 69.42; H, 7.65; N, 10.12. Found: C, 69.14; H, 7.41; N, 10.09.

A free base **9b** was obtained by neutralization of the hydrochloride, extraction with ether and recrystallization from cyclohexane. The product **9b** as white crystals melts at 132-132.5°; uv (methanol): λ max nm (ε) 224 (33,600), 281 (7300), 289 (6110); ir (potassium bromide): 3406, 3395 (NH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.60 (ArN*H*), 3.12 (t, J = 5.5 Hz, 2H, CH_2-N), 2.66 (t, J = 5.5 Hz, 2H, CH_2-indole), 1.33 (deuterium oxide-exchangeable, N*H*-2') ppm.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.77; H, 8.27; N, 11.70.

2'-Acetyl-2',3',4',9'-tetrahydrospirocyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]-indole (**10**).

A solution of 1.38 g (0.005 mole) of **9**, 1.5 ml of acetic anhydride and 3 ml of triethylamine in 30 ml of ethyl acetate was allowed to stand for 3 days at 23°, after which time the tlc (2-propanol-acetonitrile, 1:2) showed complete reaction Rf = 0.5 (Rf_9 = 0.15). Cold water (30 ml) was added and the reaction mixture was stirred for 1 hour at 23° to hydrolyze excess anhydride. After the two phases were separated, the organic layer was washed, dried over sodium sulfate and evaporated *in vacuo*. Recrystallization of the residue from ethanol gave 1.0 g (72% yield) of pure **10** as white crystals, mp 162-163°; uv (ethanol): λ max nm (ε) 225 (40,760), 281 (8020); ir (potassium bromide): 3420 (NH), 1639 (C=O) cm^{-1}; (chloroform): 3515, 3485 (NH), 1649 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.73 (t, J = 5.5 Hz, 2H, NCH_2), 2.80 (t, J = 5.5 Hz, 2H, CH_2-4'), 2.20 (3H, CH_3) ppm.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.58; H, 7.63; N, 9.92.

Reaction of 2',3',4',9'-Tetrahydrospiro[cyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]-indol]-2-one (**4a**) with Acrylonitrile.

2,3,4,4a,5,6,9,14-Octahydro-4a-hydroxy-1*H*,8*H*-pyrido[3,4-*b*:2,1-*i'*]diindole-5-carbonitriles (**12a**, *trans* isomer and **12b**, *cis* isomer).

A stirred mixture of 10.1 g (0.04 mole) of **4a**, 2.7 g (0.044 mole) of acrylonitrile, 1.0 g of cupric acetate and 5 ml of glacial acetic acid in 100 ml of tetrahydrofuran was refluxed for 2 hours. The infrared absorption spectrum showed absence of the carbonyl function. Tlc (acetone, toluene, heptane, 2:2:1) showed two new spots at Rf = 0.4 and Rf = 0.55, respectively of about the same proportions. The solvent was evaporated; the residue was taken up with saturated sodium bicarbonate and extracted twice with 175 ml of ethyl acetate. The combined extracts were washed, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from 2-propanol gave 2.9 g of 2,3,4,4a,5,6,9,14-octahydro-4a-hydroxy-1*H*,8*H*-pyrido[3,4-*b*:2,1-*i'*]diindole-5-carbonitrile (**12a**, trans isomer) as white crystals of analytical and chromatographic (Rf = 0.4) purity, mp 218-219° dec; uv (ethanol): λ max nm (ε) 226 (36,580), 283 (8400), 290 (7100); ir (potassium bromide): 3440 (NH, OH), 2248 (CN); ^{1}H-nmr (DMSO-d_6): δ 9.86 (1H, ArN*H*), 5.76 (1H, deuterium oxide-exchangeable, O*H*) ppm; mass spectrum, m/e 307.

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.36; H, 6.92; N, 13.71.

The filtrate from *trans* isomer (**12a**) on concentration to a low volume and cooling gave 1.8 g of predominantly faster moving product (Rf = 0.55), mp 200-201° dec. Recrystallization from 2-propanol gave 1.5 g of analytically and chromatographically (Rf = 0.55) pure **12b** *(cis* isomer) as white crystals, mp 204-205° dec; uv (ethanol): λ max nm (ε) 225 (38,150), 281 (8340), 289 (6980); ir (chloroform): 3600 (OH), 3465 (NH), 2242 (CN); ^{1}H-nmr (DMSO): δ 10.02 (1H, ArN*H*), 5.99 (1H, deuterium oxide-exchangeable, O*H*) ppm; mass spectrum, m/e 307.

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.37; H, 6.94; N, 13.78.

The filtrate from isomer **12b** was evaporated to dryness and triturated with hot ethanol giving 0.5 g of the carbonyl compound, mp 176-177° dec. Recrystallization from ethanol gave 0.3 g of pure (Rf = 0.32) 4',9'-dihydro-2-oxospiro[cyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]indole]-2'-(3'*H*)propanenitrile (**11**) as a normal cyanoethylation product, mp 178-179° dec; uv (ethanol): λ max nm (ε) 225 (38,150), 281 (8340), 289 (6980); ir (chloroform): 3460 (NH), 2240 (CN), 1704 (C=O) cm^{-1}.

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.35; H, 7.18; N, 13.89.

Transformation of **11** into **12** (**a** and **b**).

Compound **11** (0.02 g) and 0.05 g of cupric acetate in 5 ml of glacial acetic acid were heated at 100° for 30 minutes. The infrared spectrum revealed absence of the carbonyl function and tlc showed two spots corresponding to **12a** (Rf = 0.4) and **12b** (Rf = 0.55), respectively. *trans*-4a-(Acetyloxy)-2,3,4,4a,5,6,9,14-octahydro-1*H*,8*H*-pyrido[3,4-*b*:2,1-*i'*]diindole-5-carbonitrile (**13a**).

A solution of 0.3 g of **12a** *(trans* isomer) in 6 ml of acetic anhydride was refluxed for 4 hours and the excess reagent was removed *in vacuo*. The residue was taken with cold water, made basic with ammonium hydroxide and extracted with 25 ml of ethyl acetate. The extract was washed, dried over sodium sulfate, and concentrated to a low volume to give, on cooling, analytically pure *trans* ester **13a** as white crystals, mp 207-208° dec; uv (ethanol): λ max nm (ε) 226 (36,600), 283 (8450), 291 (7150); ir (chloroform): 3420 (NH), 2245 (CN), 1740 (C=O) cm^{-1}.

Anal. Calcd. for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.10; H, 6.61; N, 11.85.

Attempts to convert **12b** (*cis* isomer) to its ester **12b** by boiling anhydride for 20 hours were unsuccessful. Starting **12b** was recovered along with decomposition products.

5-(4-Bromophenyl)-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo-[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**16a**) (Table I).

A solution of 6.0 g (0.024 mole) of **4a**, 5.0 g (0.0264 mole) of 4-bromophenyl isocyanate and 5 drops of triethylamine in 120 ml of dry ethyl acetate was allowed to stand for 3 days at room temperature. The tlc (silica gel G; acetone, benzene, heptane, 3:2:1) showed complete reaction, the new product having faster mobility (Rf = 0.55) than the starting material **4a** (Rf = 0.45). Methanol (0.5 ml) was added and the solution was evaporated *in vacuo*. Trituration of the residue with 2-propanol gave 10.1 g of **16a**, mp 208-210° dec. Recrystallization from toluene gave 8.8 g (66% yield) of pure **16a**, mp 211-212° dec; uv (ethanol): λ max nm (ε) 217 (48,200), 222 sh (47,300), 275 (9730), 282 (9650), 291 (7450); ir (potassium bromide): 3450 (OH), 3325 (NH), 1686 (C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.66 (1H, ArNH), 4.17, 4.04 (mm, 1H, H-8), 3.10 (mm, 1H, H-8), 3.23 (1H, deuterium oxide-exchangeable, O*H*); (deuteriochloroform): δ 9.65 (1H, ArN*H*), 5.13 (1H, O*H*) ppm.

5-(3-Chlorophenyl)-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo-[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**16b**).

Following the procedure used for the preparation of 4-bromo analog (**16a**), **16b** was obtained in 67% yield, mp 222-223° dec; uv (ethanol): λ max nm (ε) 217 (48,200), 222 sh (47,200), 275 (9720), 282 (9650), 291 (7480): ir (nujol): 3500 (OH), 3220 (NH), 1688 (C=O) cm^{-1}; 'H-nmr (DMSO-d_6): δ 10.56 (1H, ArN*H*), 5.98 (1H, deuterium oxide-exchangeable, O*H*) ppm.

5-(1,3-Benzodioxol-5-yl)-2,3,4,4a,9,14-octahydro-4a-hydroxy-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one, Compound with Ethanol (**16c**).

A solution of 7.62 g (0.03 mole) of **4a** and 4.9 g (0.03 mole) of 1,3-benzodioxol-5-yl isocyanate in 120 ml of dry tetrahydrofuran was allowed to stand at room temperature for 4 days. The resulting white crystals (**16c**, 38% yield) were collected, mp 143-144° dec. Recrystallization from ethanol gave analytically pure product **16c** containing one mole of ethanol, mp 143-144°; uv (ethanol): λ max nm (ε) 223 (51,700), 283 (13,650), 291 (12,750); ir (nujol): 3300, 3250, 3120 (OH, NH), 1675 (C=O) cm^{-1}; 'H-nmr (deuteriochloroform): δ 9.80 (1H, ArN*H*), 5.89 (1H, deuterium oxide-exchangeable, O*H*-4a), 3.60 (q, J = 7.0 Hz, 2H, CH_2CH_3), 1.17 (t, J = 7.0 Hz, 3H, CH_2CH_3) ppm.

5-Ethyl-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo[2',3':3,4]pyrido-[1,2-*c*]benzimidazol-6-(5*H*)one (**16d**).

A solution of 7.62 g (0.03 mole) of **4a**, 2.55 g (0.036 mole) of ethyl isocyanate and 5 drops of triethylamine in 100 ml of dry ethyl acetate was allowed to stand at room temperature for 2 days. Tlc (toluene, acetone, heptane, 2:2:1) showed absence of **4a** (Rf = 0.33) and presence of two new products, Rf = 0.23 (*ca.* 70%) and Rf = 0.4 (*ca.* 30%), respectively. A few drops of ethanol was added to destroy excess isocyanate and the solution was concentrated to about 40 ml. After 2 days at 23°, 5.4 g of crystalline product, mp 279-280° dec, was obtained whose tlc indicated *ca.* 97% of slower moving component, Rf = 0.23. Recrystallization from acetonitrile gave 4.5 g (46% yield) of analytically and chromatographically (Rf = 0.23) pure 5-ethyl-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**16d**), mp 285-286° dec; uv (ethanol): λ max nm (ε) 224 (46,750), 278 (7900), 285 (8000), 293 (6800); ir (chloroform): 3550 (OH), 3465 (NH), 1680 cm^{-1}; 'H-nmr (DMSO-d_6): δ 10.61 (1H, ArN*H*), 4.05, 3.92 (mm, 1H, H-8), 3.60 (1H, broad, deuterium oxide-exchangeable, O*H*), 0.98 (t, J = 7.0 Hz, 3H, CH_2CH_3) ppm.

5-Ethyl-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]imidazol-6-(5*H*)one (**17a**).

The combined mother liquors of the 4a-hydroxy derivative **16d**, containing predominantly the faster moving product (Rf = 0.4), were evaporated to dryness. Trituration with hot acetonitrile gave 1.6 g of off-white material, mp 284-285° dec. Recrystallization from ethyl acetate gave 1.2 g (12.5% yield) of pure (Rf = 0.4) dehydration product, 5-ethyl-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]imidazol-6-(5*H*)one (**17a**), mp 288-289° dec; uv (ethanol): λ max nm (ε) 226 (46,520), 277 sh (7600), 284 (7950), 294 (6750); ir (chloroform): 3470 (NH), 1718 (C=C-NCO), 1683 (C=O) cm^{-1}; 'H-nmr (DMSO-d_6): δ 10.52 (1H, ArN*H*), 4.95 (t, J = 3.0 Hz, 1H, vinylic), 4.08, 3.90 (mm, 1H, H-8), 0.94 (t, J = 7.0 Hz, 3H, CH_2CH_3) ppm.

Isolation of **16d** and **17a** represents an example where both products were obtained from the same reaction.

2,3,9,14-Tetrahydro-5-methyl-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]imidazol-6-(5*H*)one (**17b**).

To a solution of 12.0 g (0.047 mole) of 2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-(1*H*)pyrido[3,4-*b*]indol]-2-one (**4a**) in 150 ml of dry tetrahydrofuran was added 3.0 g of methyl isocyanate below 30° and the solution was allowed to stand for 4 days at room temperature. The resulting off-white crystals (9.3 g) were collected by filtration, mp 298-299° dec. Evaporation of the filtrate and trituration with ethanol gave 1.6 g of an additional product (total yield: 79%), mp 296-297°. An analytical sample of 2,3,9,14-tetrahydro-5-methyl-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]imidazol-6-(5*H*)one (**17b**) as white crystals was obtained by recrystallization from ethanol, mp 299-300°; uv (ethanol): λ max nm (ε) 226 (46,520), 277 sh (7600), 284 (7960), 294 (6750); ir (chloroform): 3470 (NH), 1720 (CH=C-NCO), 1684 (C=O) cm^{-1}; 'H-nmr (DMSO-d_6): δ 10.50 (1H, ArN*H*), 4.89 (t, J = 3.0 Hz, 1H, vinylic), 4.05, 3.92 (mm, 1H, H-8), 3.30 (m, 1H, H-8), 2.71 (CH_3) ppm; mass spectrum, m/e 293. This preparation of **17b** represents an example of spontaneous and total elimination of water from the 4a-hydroxy intermediate which could not be isolated under these mild experimental conditions.

Ethyl 2,3,9,14-Tetrahydro-6-oxo-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazole-5-(6*H*)acetate (**17c**).

To a solution of 12.7 g (0.05 mole) of **4a** in 150 ml of dry ethyl acetate was added 6.8 g (0.0525 mole) of ethyl isocyanatoacetate with external cooling and allowed to stand for 24 hours at room temperature. The resulting white crystals of **17c** (13.2 g) were collected, mp 204-205° dec. Evaporation of the filtrate to dryness and trituration with hot acetonitrile gave 1.7 g (total yield: 81%) of an additional crop of **17c** mp 204-205° dec. An analytical sample of **17c**, mp 206-207° dec, was obtained by recrystallization from acetonitrile; uv (ethanol): λ max nm (ε) 223 (44,250), 274 (7750), 281 (8000), 289 (6700); ir (nujol): 3310 (NH), 1745 (ester C=O), 1717 (C=C-NCO), 1678 (C=O) cm^{-1}; (chloroform): 1751 (ester C=O), 1721 (C=C-NCO), 1686 (C=O) cm^{-1}; 'H-nmr (deuteriochloroform): δ 8.15 (1H, ArN*H*), 4.89 (t, J = 3.3 Hz, 1H, vinylic), 4.15, 4.07 (mm, 1H, H-8), 1.18 (t, 3H, CH_2CH_3) ppm.

5-(4-Methoxyphenyl)-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido-[1,2-*c*]benzimidazol-6-(5*H*)one (**17d**).

To a solution of 5.08 g (0.02 mole) of **4a** in 100 ml of dry tetrahydrofuran was added 3.23 g (0.022 mole) of 4-methoxyphenyl isocyanate and allowed to stand 2 days at 23°. After the addition of ten drops of methanol, the solution was evaporated *in vacuo* and crystallized from acetonitrile giving 6.6 g (82% yield) of crude product, mp 268-269° dec. Recrystallization from ethyl acetate gave analytically pure **17d** as white crystals, mp 269-270° dec; uv (ethanol): λ max nm (ε) 225 (55,050), 263 (12,700), 280 sh (11,200), 290 (8700); ir (chloroform): 3470 (NH), 1722 (C=C-NCO), 1685 (C=O), 1250, 1035 (C-OCH_3) cm^{-1}; 'H-nmr (DMSO-d_6): δ 10.68 (1H, ArN*H*), 4.80 (t, J = 3.0 Hz, 1H, vinylic), 4.12, 3.98 (mm, 1H, H-8), 3.40 (m, 1H, H-8), 3.67 (3H, CH_3O) ppm.

5-(4-Bromophenyl)-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido-[1,2-*c*]benzimidazol-6-(5*H*)one (**17e**).

A solution of 3.0 g of 5-(4-bromophenyl)-2,3,4,4a,9,14-hexahydro-4a-hydroxy-6*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**16a**) and 0.2 g of 4-methylbenzenesulfonic acid in 120 ml of benzene was refluxed for 1 hour, while 0.12 ml of water separated in a Dean-Stark trap. After cooling to room temperature, the solution was washed with dilute sodium hydroxide, dried with sodium sulfate and concentrated to a low volume to give 2.6 g (90% yield) of pure 5-(4-bromophenyl)-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**17e**) as white, shiny crystals, mp 251-252° dec; uv (ethanol): λ max nm (ε) 222 (46,950), 273 (14,500), 280 sh (13,600), 290 (9850); ir (nujol): 3270 (NH), 1708 (C=C-NCO), 1678 (C=O) cm^{-1}; 'H-nmr (DMSO-d_6): δ 9.90, 4.95 (t, J = 3.2 Hz, 1H, vinylic), 4.14, 4.01 (mm, 1H, H-8), 3.10 (m, 1H, H-8) ppm.

Compound **17e** was also obtained in 85% yield when starting material **16a** was refluxed with acetic anhydride in an attempt to form an acetate ester. No ester was formed, however, and the total **16a** underwent elimination of water giving **17e**.

5-(3-Chlorophenyl)-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido-[1,2-*d*]benzimidazol-6-(5*H*)one (**17f**).

On applying the same reaction conditions as for the preparation of 4-bromo analog (**17e**), 66% of **17f**, as off-white crystals, was obtained, mp 257-258° dec; uv (ethanol): λ max nm (ε) 223 (46,950), 273 (14,480), 280

sh (13,600), 290 (9840); ir (potassium bromide): 3340, 3297 (NH), 1715 (C=C-NCO), 1685 (C=O) cm^{-1}; 'H-nmr (DMSO-d_6): 10.64 (1H, ArN*H*), 5.10 (t, J = 3.0 Hz, 1H, vinylic) ppm.

5-(4-Bromophenyl)-2,3,4,4a,9,14-hexahydro-4a-methoxy-1*H*,8*H*-indolo-[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**18a**).

A solution of 1.0 g of 5-(4-bromophenyl)-2,3,4,4a,9,14-hexahydro-4a-hydroxy-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**16a**) and 0.1 g of 4-methylbenzenesulfonic acid monohydrate in 50 ml of absolute methanol was refluxed for 4 hours. After 20 hours at room temperature, the resulting white shiny crystals (0.7 g) of the methoxy derivative **18a** of analytical purity were collected, mp 249-250° dec; uv (ethanol): λ max nm (ε) 225 (39,750), 248 (25,720), 267-275 plateau (10,720), 282 sh (10,400), 291 (8150); ir (nujol): 3320 (NH), 1680 (C=O); chloroform): 3465 (NH), 1698 (C=O) cm^{-1}; 'H-nmr (DMSO-d_6): δ 11.03 (1H, ArN*H*), 4.30, 4.18 (mm, 1H, H-8), 3.33 (OCH_3), 3.25 (m, 1H, H-8) ppm.

Anal. Calcd. for $C_{24}H_{24}BrN_3O_2$: C, 61.81; H, 5.19; N, 9.01; Br, 17.13. Found: C, 61.82; H, 5.17; N, 9.00; Br, 17.32.

5-(3-Chlorophenyl)-2,3,4,4a,9,10-hexahydro-4a-ethoxy-1*H*,8*H*-indolo-[2',3':3,4]pyrido[1,2-*c*]benzimidazol-6-(5*H*)one (**18b**).

A solution of 0.5 g of **14b** and 10 ml of 4-methylbenzenesulfonic acid monohydrate in 20 ml of absolute ethanol was refluxed for 1 hour. Tlc (toluene, acetone, heptane, 2:2:1) showed complete conversion, the new product **18b** having faster mobility (Rf = 0.55) than starting **16b** (Rf = 0.4). After the solution was evaporated to dryness *in vacuo*, the residue was crystallized from acetonitrile giving 0.4 g of pure ethoxy derivative **18b** as nearly white crystals, mp 259-260° dec; uv (ethanol): λ max nm (ε) 225 (29,760), 248 (26,740), 266-274 plateau (10,720), 290 (8200); ir (chloroform): 3465 (NH), 1698 (C=O) cm^{-1}; 'H-nmr (deuteriochloroform): δ 7.95 (1H, ArN*H*), 4.30 (m, 1H, H-8), 3.70 (q, J = 6.5 Hz, CH_2CH$_3$), 3.30 (m, 1H, H-8), 1.20 (t, J = 6.5 Hz, CH$_2$CH_3) ppm.

Anal. Calcd. for $C_{25}H_{26}ClN_3O_2$: C, 68.87; H, 5.78; N, 9.64. Found: C, 68.77; H, 6.02; N, 9.58.

Controlled Lithium Aluminum Hydride Reduction of Ethyl 2,3,9,14-Tetrahydro-6-oxo-1*H*,8*H*-indolo[2',3':3,4]pyrido[1,2-*c*]benzimidazole-5-(6*H*)acetate (**17c**).

A mixture of 7.3 g (0.02 mole) of **17c** and 1.5 g of lithium aluminum hydride (Aluminum Corporation of America) in 125 ml of anhydrous tetrahydrofuran was stirred at 0° for 30 minutes. The infrared absorption spectrum showed disppearance of an ester function and presence of an amide band at 1677 cm^{-1}. Tlc (acetone, toluene, heptane, 2:2:1) showed two new spots at Rf = 0.3 (*ca.* 65%) and Rf = 0.45 (*ca* 35%), respectively. Ethyl acetate (10 ml) was added cautiously at 0° followed by the addition of 50 ml of water. The products were extracted twice with 200 ml of chloroform. The combined extracts were washed, dried over sodium sulfate, and evaporated *in vacuo*. The colorless residue was crystallized from ethyl acetate giving 3.3 g (51% yield) of pure (Rf = 0.3) hydroxy derivative, 2,3,9,14-tetrahydro-5-(2-hydroxyethyl)-1*H*,8*H*-indolo-[2',3':3,4]pyrido[1,2-*c*]benzimidazol-5-(6*H*)one (**19**) as white crystals, mp 253-254° dec; uv (ethanol): λ max nm (ε) 223 (51,000), 275 sh (8800), 282 (8900), 291 (7600); ir (nujol): 3390, 3280, (OH, NH), 1716 (C=C-NCO), 1677 (C=O), 1055 (OH) cm^{-1}; 'H-nmr (DMSO-d_6): δ 10.65 (1H, ArN*H*), 5.10 (t, J = 3.0 Hz, 1H, vinylic), 4.65 (broad, deuterium oxide-exchangeable, 1H, O*H*) ppm.

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.54; N, 12.99. Found: C, 70.54; H, 6.62; N, 13.22.

2,3,8,13,14,15,16,17-Octahydro-5*H*,7*H*-indolo[2',3':3,4]pyrido[1,2-*c*]oxazolo[2,3-*i*]benzimidazol-5-one (**20**). Isolation from Reaction Mixture.

The mother liquor from the unsaturated 5-(2-hydroxyethyl)benzimidazol-5-(6*H*)one derivative **19**, containing predominantly fast moving product (Rf = 0.45), was evaporated to dryness and triturated with acetonitrile giving 1.7 g of white crystals, mp 256-258° dec. Tlc indicated about 95% purity. Recrystallization from acetonitrile gave pure (Rf = 0.45) hexacyclic derivative, 2,3,8,13,14,15,16,17-octahydro-5*H*,7*H*-indolo[2',3':3,4]pyrido[1,2-*c*]oxazolo[2,3-*i*]benzimidazol-5-one (**20**), mp 263-264° dec; uv (ethanol): λ max nm (ε) 224.5 (41,400), 275 sh (7760), 282 (8000), 290 (6520); ir (chloroform): 3400 (NH), 1689 (C=O), 1030 (R-OCH$_2$-) cm^{-1}; 'H-nmr (deuteriochloroform): δ 8.66 (1H, ArN*H*) ppm; (DMSO-d_6): 10.80 (1H, ArN*H*), 3.95 (R-O-CH_2-) ppm.

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.54; N, 12.99. Found: C, 70.57; H, 6.59; N, 13.03.

The complexities of overlapping signals did not permit further assignment of higher field protons. However, there are two major differences from starting **17c** and all compounds **17** in general: the high frequency band (*ca.* 1715 cm^{-1}) in the infrared and the vinylic proton in 'H-nmr spectra are absent in **20**.

Direct Preparation of Compound **20** from **19**.

To a solution of 0.5 g of **19** in 25 ml of chloroform was added 5 drops of chloroform saturated with dry hydrogen chloride and allowed to stand for 5 hours at room temperatue. Tlc showed complete reaction. The solution was shaken up with potassium bicarbonate, washed with water, dried, and evaporated. Crystallization of the residue from acetonitrile gave 0.3 g of pure **20**, mp 263-264° dec. A mixture melting point with the analytical sample of **20** described above was not depressed and the spectra are identical.

5-[2-(Acetyloxy)ethyl]-2,3,9,14-tetrahydro-1*H*,8*H*-indolo[2',3':3,4]pyrido-[1,2-*c*]benzimidazol-5-(4*H*)one (**21**).

A solution of **19** (0.4 g) and 2 ml of acetic anhydride in 40 ml of ethyl acetate was allowed to stand for 4 days at room temperature. Water and sodium bicarbonate were added and the two layers separated. The organic phase was washed, dried over sodium sulfate, and evaporated *in vacuo*. Crystallization of the residue from ethanol gave pure acetate ester **21** as white crystals, mp 231-232° dec; uv (ethanol): λ max nm (ε) 224 (37,600), 283 (6800), 291 (5720); ir (potassium bromide): 3230 (NH), 1743 (ester C=O), 1716 (C=C-NCO), 1683 (amide C=O), 1236 (OCOCH$_3$) cm^{-1}; 'H-nmr (deuteriochloroform): δ 7.95 (1H, ArN*H*), 4.90 (t, J = 3.5 Hz, 1H, vinylic), 1.67 (3H, CH_3); (DMSO-d_6): δ 10.35 (1H, ArN*H*), 5.00 (m, 1H, vinylic), 1.64 (3H, CH_3) ppm.

Anal. Calcd. for $C_{21}H_{23}N_2O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 68.94; H, 6.34; N, 11.57.

Acknowledgments.

The author wishes to thank Professor E. L. Eliel for most helpful discussions. Special thanks are due to Mrs. U. Zeek for microanalyses, Ms. S. England, Dr. R. C. Greenough, Messrs. R. Puchalski, R. E. Saville, E. Schoeb, A. B. Scott, and R. DeSimone for the determination of spectra.

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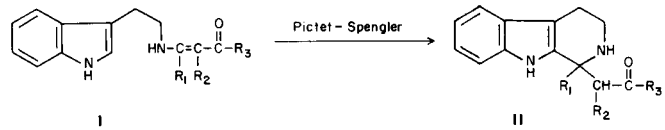

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