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STUDIES ON THE SYNTHESIS OF *STRYCHNOS* INDOLE ALKALOIDS. INTRODUCTION OF THE FUNCTIONALIZED ONE-CARBON SUBSTITUENT AT C-16[1,2]

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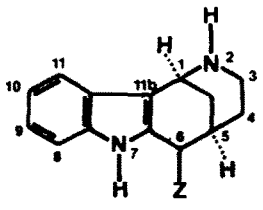
Abstract- A synthetic way for the construction of the tetracyclic 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole system I, having a methoxycarbonyl substituent at the C-6 position, is reported. The synthesis implies methoxycarbonylation of the interannular methylene carbon of an appropriate 2-(4-pyridylmethyl)indole, followed by alkylation of the pyridine nitrogen, catalytic hydrogenation and, finally, oxidative cyclization of the resulting 2-(4-piperidylmethyl)indole.

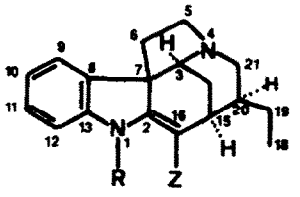
A structural feature of the majority of pentacyclic *Strychnos* indole alkaloids is the presence of a methoxycarbonyl (tubotaiwine, condylocarpine, akuammicine), formyl (strychnofluorine, fluorocurarine), or hydroxymethyl (geissoschizoline, retuline) substituent at the 16-position.[2]

In a previous paper[3] we have reported a new synthetic entry to the pentacyclic ring system of these alkaloids based on the closure of the five membered E ring in the last synthetic steps from a 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*] indole system such as I (Z = H) through introduction of a functionalized two carbon unit on the piperidine nitrogen atom followed by cyclization upon the indole 3-position. The extension of this strategy from a tetracyclic system I having an ethyl substituent on the piperidine β-position[4] would constitute a new synthesis of the simplest pentacyclic *Strychnos* indole alkaloids tubifoline, tubifolidine, and condyfoline, which lack the functionalized one-carbon substituent at C-16. In a similar way, operating from hexahydro-1,5-methanoazocino[4,3-*b*]indole systems (I) bearing a C-6[5] functionalized appendage, the above mentioned strategy would permit to synthesize the most complex alkaloids of this group.[6]



I

Systematic Numbering

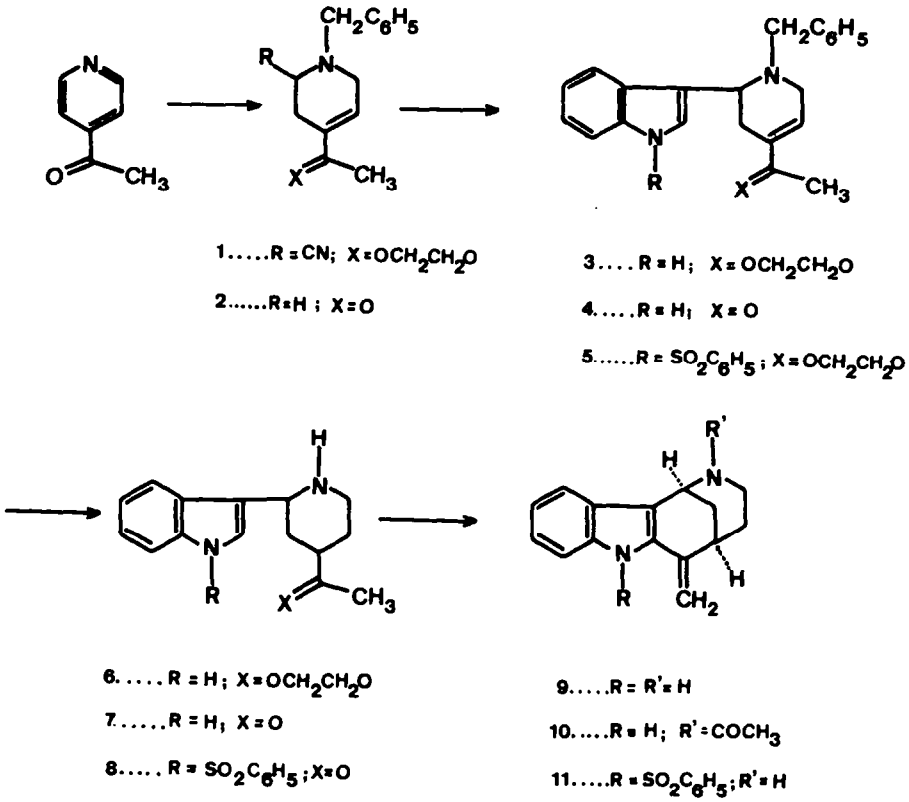


Biogenetic Numbering

R=Z=H; 2,16-dihydro .....TUBIFOLIDINE
R=CH_3; Z=CHO .....STRYCHNOFLUORINE
R=H; Z=CH_2OH; 2,16-dihydro..GEISSOSCHIZOLINE
R=H; Z=CO_2CH_3; 19,20-dehydro ....AKUAMMICINE

Scheme I

It seemed therefore of interest to establish an efficient route to tetracyclic systems of tipe I, having a functionalized one carbon substituent at C-6. The introduction of such substituent from a 6-oxo derivative (deethyldasycarpidone for example) proved to be difficult,[7] whereas nucleophilic substitution by cyano of the 6-hydroxy derivative of I (Z = OH) failed to give the desired product.[8] For this reason, in order to achieve the above synthetic goal, initially we intended to develop a synthetic sequence similar to that we had reported[9] for the synthesis of related C-6 unsubstituted tetracyclic systems (Scheme II). The 3-(2-piperidyl)indole moiety would be formed by condensation of indole and an appropriate 2-cyanotetrahydropyridine followed by reduction. Cyclization of the acetyl group upon indole 2-position would afford 20-deethyl-*N*-demethyluleine (9)[10] in a way similar to that reported in some syntheses of uleine[11] and its 20-epimer.[11,12] Finally, the conversion of the exocyclic methylene substituent into an hydroxymethyl group is a transformation that has previously been accomplished from uleine.[13]



Scheme II

The required 2-cyanotetrahydropyridine 1 was prepared from 4-acetylpyridine through a three-step sequence involving protection of the carbonyl group as its ethylene acetal, quaternization of the pyridine nitrogen with benzyl chloride and, finally, sodium borohydride reduction of the resulting pyridinium salt in the presence of an excess of cyanide ions.[14] As usual in similar reductive cyanations, tetrahydropyridine 2 was isolated as a by-product. Separation of compounds 1 and 2 was effected either by column chromatography or by acid extraction, taking advantage of the lower basic character of 2-cyanotetrahydropyridine 1 as a consequence of the electron withdrawing effect exerted by the cyano group. Amino nitrile 1 showed a weak IR absorption at 2220 cm^{-1} due to the cyano group, whereas the most significant features in the NMR spectrum were a singlet at

δ1.45 due to the methyl group and a broad signal at δ5.85 attributable to the vinyl proton.

Initially, condensation of 2-cyanotetrahydropyridine **1** with indole was effected in 50% aqueous acetic acid.[12b] Deprotection of the carbonyl group occurred under these conditions to give α,β-unsaturated ketone **3**, which proved to be slightly unstable. Its hydrogenation led to a complex mixture, from which 4-acetylpiperidine **7** was isolated in 20% yield.[15] In order to circumvent these difficulties and to preserve the protecting acetal group, the condensation step was carried out by using the indole Grignard reagent.[16] Operating in this manner, (tetrahydropyridyl)indole **4** was obtained in 64% yield. The most significant signals in the NMR spectrum of **4** were again a singlet at δ1.43 due to the methyl group and a broad absorption at δ5.77 due to the tetrahydropyridine vinyl proton.

Hydrogenation of **3** hydrochloride in the presence of palladium on charcoal brought about both tetrahydropyridine double bond reduction and hydrogenolysis of benzyl group to give in high yield a *cis* - *trans* diastereomeric mixture of piperidines **6** in which slightly predominated the *cis* isomer. Although only this isomer has the relative stereochemistry suitable for cyclization, this fact did not constitute a serious trouble because the *trans* isomer underwent epimerization to the more estable *cis*-**7**, having two equatorial substituents, during the next hydrolytic step.[17] Thus, when the isomeric mixture of acetals **6** was treated with hydrochloric acid, acetylpiperidine *cis*-**7** was obtained as the sole product. Its NMR spectrum showed, as the most significant data, a singlet at δ2.07 attributable to the methyl group of the acetyl substituent and a doublet of doublets at δ4.06 due to the axial C-2 methine proton. The stereochemical assignment of piperidines **6** and **7** was inferred from their ^{13}C-NMR data (Table 1), in particular from the shielding effects caused by the axial substituent in the *trans* isomer.

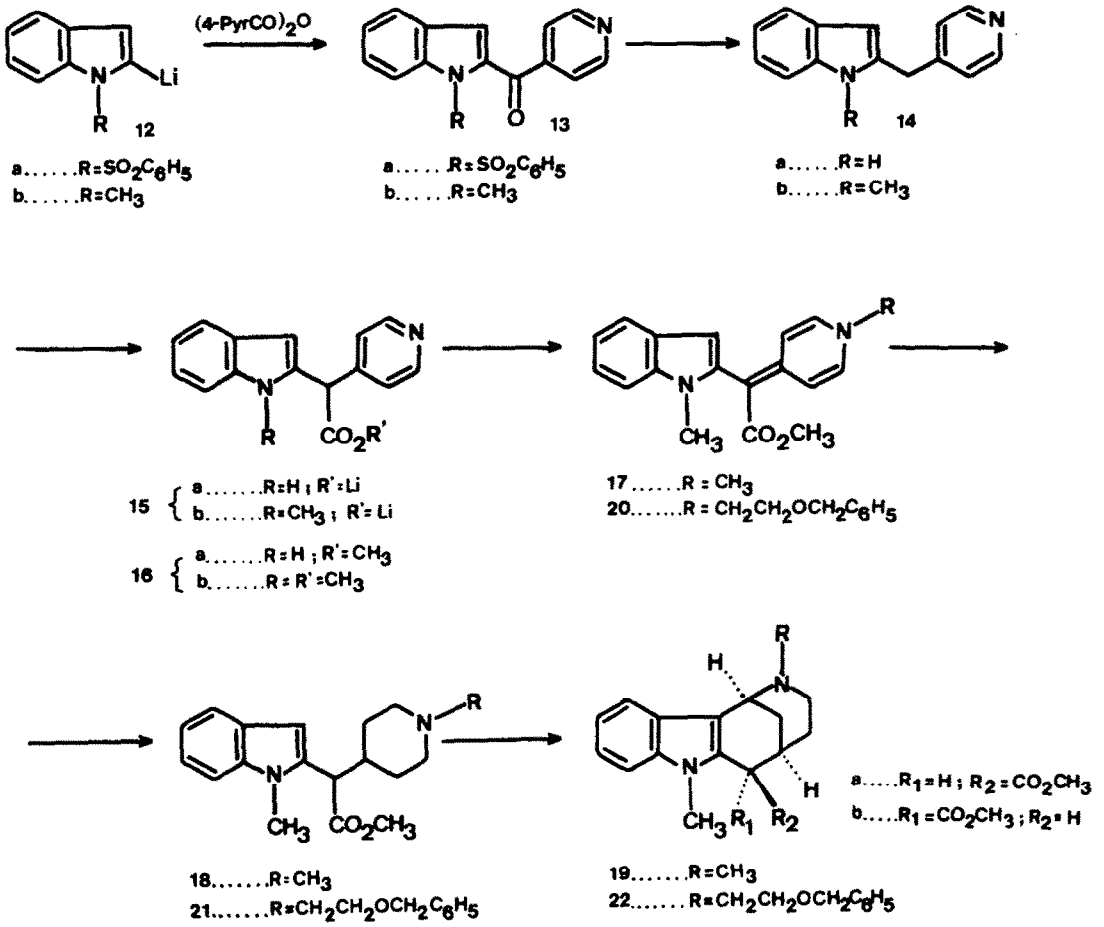
Table 1. ^{13}C-NMR Data of Piperidines 6 and 7

	C-2	C-3	C-4	C-5	C-6	CH_3
cis-**6**	53.82	34.65	45.69	26.95	46.91	21.28
trans-**6**	48.93	30.99	39.92	26.75	41.34	21.68
cis-**7**	53.44	35.38	50.51	28.01	46.55	27.70

As expected, cyclization of acetylpiperidine *cis*-**7**, by heating in chloroform solution in the presence of *p*-toluenesulfonic acid, afforded the tetracyclic compound **9**, which was characterized as the N_b-acetyl derivative **10**. The NMR spectrum of **9** showed, as characteristic signals, two singlets due to the protons of the exocyclic methylene group and a broad signal at δ4.37 due to the bridgehead C-1 methine proton. Unfortunately, hydroboration of the 2-vinylindole **9** under usual conditions[13] led to a complex mixture from which the desired 6-hydroxymethyl derivative (**I**, Z = CH_2OH) could not be obtained. On the other hand, hydroboration of the presumably more estable N_a-phenylsulfonyl-2-vinylindole **11** could not be attempted since cyclization of N_a-protected acetylpiperidine **8** failed under a variety of conditions (BF_3-Et_2O, *p*-TsOH, or PPA), thus reflecting the deactivating effect of the benzenesulfonyl substituent.[18] The required piperidine **8** was prepared from **4** by sulfonylation of indole followed by catalytic hydrogenation, and hydrolysis of the acetal group.

The above unsuccessful results led us to consider an alternative strategy for the synthesis of functionalized tetracyclic systems of type **I**, based on the closure of ring C by formation of the C_1-C_{11b} bond in the last synthetic step through cyclization upon the indole 3-position of an iminium salt generated by

mercuric acetate oxidation from a suitable 2-(4-piperidylmethyl)indole.[19,20] The methoxycarbonyl group would be introduced from a 2-(4-pyridylmethyl)indole in an early stage of the synthesis by taking advantage of the acidic character of the interannular methylene protons. Following a similar strategy, in which the key synthetic steps were methoxycarbonylation of a (4-pyridylmethyl)indole and oxidative cyclization of an α-(4-piperidylmethyl)indoleacetate, we recently synthesized 19,20-dihydro-16-epivinoxine.[21]



Scheme III

The required pyridylmethylindole **14a**[22] was prepared[23] by reaction of 2-lithioindole **12a** with isonicotinic anhydride[24] followed by Wolff-Kishner reduction of the resulting ketone **13a**.[25] Deprotection of the indole nitrogen occurred under the reaction conditions. Carboxylation of **14a** through treatment with *n*-butyllithium and carbon dioxide gave the lithium carboxylate **15a**, which was characterized by NMR from the singlet at δ5.0 due to the interannular methine proton. However, treatment of **15a** with methanolic hydrogen chloride at room temperature did not afforded the expected ester **16a**. Instead, the pyridylmethylindole **14a** was recovered.[26] These results can be explained taking into account that both 2-indoleacetic acids[27] and 4-pyridineacetic acids,[28] especially when the pyridine nitrogen bears a positive charge, are prone to decarboxylation. On the other hand, the direct methoxycarbonylation of **14a** by using LDA as

a base and dimethyl carbonate as acylating agent was also ineffective , probably due to the presence of the acidic indole proton. For this reason, in order to introduce the required methoxycarbonyl substituent we decided to use the N_a- substituted pyridylmethylindole **14b**, which was prepared, as above, by condensation of the appropriate lithioindole **12b** with isonicotinic anhydride followed by Wolff-Kishner reduction[29] of the intermediate ketone **13b**.[30]

As expected, methoxycarbonylation of **14b** was satisfactorily accomplished by using potassium hydride as a base and dimethyl carbonate as acylating agent in refluxing toluene.[31] Under these conditions, the potassiun enolate derived from ester **16b** precipitates from the reaction mixture. After filtration and acidification, pure ester **16b** was obtained in 40% yield.[32] This experimental procedure allows an easy separation of ester **16b** from the starting pyridylmethylindole **14b**,[33] which was always recovered in some extension, and from 4-alkylidene-1,4-dihydropyridine **17**, which was obtained as a by-product. The alkylation by dimethyl carbonate of the activated pyridine nitrogen in the enolate derived from ester **16b** accounts for the formation of **17**. The IR spectrum of **16b** showed a strong absoption at 1740 cm^{-1} due to the ester carbonyl group, whereas the most significant signals in the NMR spectrum were three singlets, at δ 3.31, 3.62, and 6.29, attributable to the *N* and *O*-methyl groups and to the indole 3-proton, respectively.

Quaternization of **16b** with methyl iodide followed by treatment with base furnished the doubly vinylogous urethane **17**,[34] which was hydrogenated over platinum dioxide to give the piperidine **18**. Finally, oxidative cyclization of (piperidylmethyl)indole **18** by treatment with mercuric acetate-EDTA.2Na[35] in refluxing water as the solvent afforded, after the usual work-up with sodium borohydride, a nearly equimolecular C-6 epimeric mixture of tetracyclic bases **19**. The planar structure of **19** was evident from their spectroscopic data. The IR spectra showed a carbonyl absorption at 1730 cm^{-1}, whereas the ^1H NMR spectra exhibited an apparent triplet due to the bridgehead C-1 methine proton, which clearly indicated that cyclization had occurred. The relative configuration at carbon 6 was established from the multiplicity of the signal due to the C-6 methine proton, which appears as a doublet (J = 6.3 Hz) in **19a** (H-5/H-6 *cis* relationship) and as a singlet in **19b** (H-5/H-6 *trans* relationship).[36]

With a method in hand for the construction of tetracyclic hexahydro-1,5-methanoazocino[4,3-*b*]indole systems I having a C-6 methoxycarbonyl substituent, our next goal was to apply the same methodology to prepare the *N*-[2-(benzyloxy)ethyl] derivatives **22**. This substituent incorporates the functionalized two-carbon unit required for the subsequent elaboration of the five membered E ring present in pentacyclic *Strychnos* indole alkaloids.

As anticipated, alkylation of pyridine nitrogen of **16b** with benzyl 2-bromoethyl ether, followed by treatment with aqueous base, gave the 1,4-dihydropyridylene derivative **20**. As in the above N_b-methyl series, catalytic hydrogenation of **20** over platinum dioxide followed by oxidative cyclization of the resulting piperidine **21** with mercuric acetate-EDTA.2Na furnished an epimeric mixture of the desired tetracyclic compounds **22**, which can be envisaged as synthetic precursors of 20-deethylstrychnofluorine.

The results here reported open a viable route to tetracyclic systems having rings A-D of pentacyclic *Strychnos* alkaloids and possessing the functionallized one carbon C-16 substituent present in a great number of these indole alkaloids.

EXPERIMENTAL

GENERAL. Melting points were determined in a capillary tube on a CTP-MP 300 hot

plate apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Perkin-Elmer R-24B (60 MHz) instrument or, when indicated, on a Varian XL-200 spectrometer using TMS as internal standard. ^{13}C-NMR spectra were determined on a Varian XL-200 spectrometer (50.3 MHz). The chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin Elmer 1430 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Column chromatography was carried out on SiO_2 (silica gel 60, 63-200 μm, Merck) or, when indicated, on Al_2O_3 (aluminium oxide 90, neutral, activity I, 63-300 μm, Merck). Flash chromatography was carried out on SiO_2 (silica gel 60, 40-63 μm, Machery-Nagel). TLC was performed on SiO_2 (silica gel 60, F_{254}, Merck), using 70:30:5 ether-acetone-diethylamine as developing solvent, and the spots were located with UV light or iodoplatinate reagent. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Instituto de Química Bio-Orgánica, Barcelona.

1-Benzyl-4-[1,1-(ethylenedioxy)ethyl] pyridinium Chloride. A solution of 4-acetylpyridine ethylene acetal[37] (50.8 g, 308 mmol) and benzyl chloride (42.9 g, 339 mmol) in absolute methanol (150 ml) was refluxed for 24 h. The solvent was removed and the resulting white solid was digested several times with boiling ether to give the title pyridinium salt (88 g, 98%) which was highly hygroscopic; mp 100-102ºC (anhydrous acetone); NMR ($CDCl_3$): 1.60 (s, 3H, CH_3), 3.50-4.07 (m, 4H, OCH_2CH_2O), 6.16 (s, 2H, NCH_2), 7.00-7.37 (m, 3H, H*m,p*-phenyl), 7.50-8.00 (m, 4H, H_o-phenyl, H_β-pyridine), 9.68 (d, 2H, H_α-pyridine). (Found: C, 63.81; H, 6.22; N, 4.82; Cl, 11.78. Calcd for $C_{16}H_{18}ClNO_2$. 1/2H_2O: C, 63.89; H, 6.36; N, 4.66; Cl,11.79).

1-Benzyl-4-[1,1-(ethylenedioxy)ethyl]-1,2,3,6-tetrahydropyridine-2-carbonitrile (1). Hydrochloric acid (6 N, 111.5 ml) was added dropwise to a stirred solution of sodium cyanide (36.4 g, 744 mmol) in water (230 ml), layered with ether (230 ml), and kept below 15ºC. To the resulting mixture a solution of the above pyridinium chloride (21.6 g, 74.4 mmol) in methanol (230 ml) and then sodium borohydride (2.8 g, 74.4 mmol) were added. The mixture was stirred at room temperature for 1 h, the ether was decanted, and the aqueous layer was extracted with ether. The combined etheral solutions were washed with aqueous 0.6 N hydrochloric acid, dried, and evaporated to give 1 (14.2 g, 67%); mp 71-73ºC (acetone); NMR ($CDCl_3$): 1.45 (s, 3H, CH_3), 2.40 (br, 2H, CH_2), 3.00-3.45 (m, 2H, NCH_2), 3.50-4.00 (m, 7H, OCH_2CH_2O, NCH, CH_2Ar), 5.85 (br, 1H, =CH), 7.25 (s, 5H, ArH); IR ($CHCl_3$): 2220 (cyano), 1680 (C=C): (Found: C, 72.17; H, 7.45; N, 9.85. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85). The acidic aqueous solution was basified with sodium carbonate and extracted with ether. The evaporation of the dried extracts gave the tetrahydropyridine 2 (3.73 g, 23%); NMR ($CDCl_3$): 2.17 (s, 3H, CH_3), 2.27-2.66 (m, 4H, CH_2), 3.00-3.36 (m, 2H, NCH_2), 3.47 (s, 2H, CH_2Ar), 6.53 (br, 1H, =CH), 7.00 (s, 5H, ArH); IR (NaCl): 1675 (C=O). The picrate melted at 145-148ºC (absolute ethanol). (Found: C, 54.12; H, 4.67; N, 12.37. Calcd for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.54; N, 12.61).

3-{1-Benzyl-4-[1,1-(ethylenedioxy)ethyl]-1,2,3,6-tetrahydro-2-pyridyl}indole (4). A solution of cyanotetrahydropyridine 2 (12.8 g, 45 mmol) in anhydrous methylene chloride (180 ml) was slowly added under nitrogen to a stirred solution of indolylmagnesium bromide (90 mmol) in an anhydrous 1:1 ether-methylene chloride mixture (200 ml) maintained at -10ºC. The resulting mixture was stirred at room temperature for 4 h, poured into ice-aqueous ammonium chloride, basified with ammonium hydroxide, and decanted. The aqueous layer was extracted with methylene chloride. The combined organic solutions were dried and evaporated to give an oil (24 g) which was chromatographed. Elution with 98:2 chloroform-methanol afforded the tetrahydropyridylindole **4** (10.8 g, 64%); NMR ($CDCl_3$): 1.43 (s, 3H, CH_3), 2.33-2.73 (m, 2H, CH_2), 2.73-3.27 (m, 2H, NCH_2), 3.47-4.07 (m, 7H, OCH_2CH_2O, CH_2Ar, NCH), 5.77 (br, 1H, =CH), 6.83-8.17 (m, 11H, ArH). A sample of **4** was dissolved in absolute ethanol and precipitated as the picrate. After recrystallization from absolute ethanol, the picrate of 4-acetyltetrahydropyridine **3** was obtained: mp 165-169ºC; NMR (DMSO): 2.33 (s, 3H, CH_3); IR (KBr): 1670 (C=O). (Found: C, 59.15; H, 4.61; N, 12.32: Calcd for $C_{28}H_{25}N_5O_8$ .1/2H_2O: C, 59.15; H, 4.61; N, 12.32).

3-{1-Benzyl-4-[1,1-(ethylenedioxy)ethyl]-1,2,3,6-tetrahydro-2-pyridyl}-1-(phenylsulfonyl)indole (5). Aqueous 50% sodium hydroxide (30 ml) was added to a solution of **4** (1 g, 2.67 mmol) and tetrabutylammonium bisulfate (98 mg) in benzene (100 ml). The mixture was stirred at room temperature for 10 min. Then, a solution of benzenesulfonyl chloride (0.73 g, 4.14 mmol) in benzene (45 ml) was added and the mixture was stirred at room temperature for 14 h. The organic layer was separated, washed with brine, dried, and evaporated to give **5** as an oil (1.26 g, 91%); NMR (CCl_4): 1.35 (s, 3H, CH_3), 3.70 (br, 4H, OCH_2CH_2O) 5.70 (br, 1H, =CH), 6.40-7.90 (m, 15H, ArH); IR ($CHCl_3$): 1375 and 1175 (SO_2N). The picrate melted at 176-179ºC (absolute methanol-ethanol). (Found: C, 58.33; H, 4.44; N, 9.44; S, 4.30. Calcd for $C_{36}H_{33}N_5O_{11}S$: C, 58.13; H, 4.47; N, 9.42; S, 4.31).

cis-**3-(4-Acetyl-2-piperidyl)indole (*cis*-7).** A solution of 3, hydrochloride (5.5 g, 13.4 mmol) in absolute methanol (200 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (1 g). When

the solution had absorbed the required volume of hydrogen, the catalyst was filtered off and the filtrate was evaporated. The resulting residue was dissolved in methylene chloride and washed with aqueous 10% sodium carbonate solution. The organic layer was dried and evaporated to give the piperidine **6** as a mixture of diastereomers (3.42 g, 89%); NMR (200 MHz, $CDCl_3$): 1.28 and 1.29 (2 s, 3H, CH_3), 4.01 (m, 4H, OCH_2CH_2O), 4.64 (apparent t, 1H, NCH), 6.67-7.97 (m, 5H, ArH).

A solution of the above mixture (3 g, 10.5 mmol) in methanol (35 ml) and aqueous 20% hydrochloric acid (75 ml) was stirred at 60ºC for 1 h. The solution was concentrated, basified with aqueous 2 N sodium hydroxide and extracted with methylene chloride. The organic layer was dried and evaporated to give the acetylpiperidine *cis*-**7** (2.5 g, 98%); NMR ($CDCl_3$): 2.07 (s, 3H, CH_3), 4.06 (dd, J=4, 11 Hz, 1H, NCH), 6.73-7.70 (m, 5H, ArH), 8.73 (br, 1H, NH); IR ($CHCl_3$): 1705 (C=O). The picrate melted at 188-190ºC (absolute ethanol). (Found: C, 53.67; H, 4.55; N, 14.53. Calcd for $C_{21}H_{21}N_5O_8$: C, 53.50; H, 4.49; N, 14.86).

3-(4-Acetyl-2-piperidyl)-1-(phenylsulfonyl)indole (8). Operating as above, a solution of **5** hydrochloride (3.8 g, 7 mmol) was hydrogenated to give a solid (2.7 g) which was dissolved in methanol (30 ml) and aqueous 20% hydrochloric acid (50 ml). After being stirred at 70ºC for 30 min, the reaction mixture was worked-up as above to give the piperidine **8** (2.4 g, 90%); NMR ($CDCl_3$): 2.03 (s, 3H, CH_3), 6.83-7.85 (m, 10H, ArH); IR ($CHCl_3$): 1705 (C=O), 1370 and 1170 (SO_2N). The picrate melted at 115-119º (absolute ethanol). (Found: C, 53.40; H, 4.21; N, 11.12. Calcd for $C_{27}H_{25}N_5O_{10}S$: C, 53.02; H, 4.12; N, 11.46).

6-Methylene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (9). A solution of acetylpiperidine **7** (1g, 4.1 mmol) and *p*-toluenesulfonic acid (3.3 g, 19 mmol) in dry chloroform (750 ml) was refluxed for 24 h under nitrogen. The mixture was cooled, poured into aqueous 2 N ammonium hydroxide (250 ml) and extracted with chloroform. The organic extracts were dried evaporated to give an oil which was chromatographed through alumina. On elution with 2:8 benzene-chloroform, **9** (0.66 g, 72%) was obtained; NMR ($CDCl_3$): 4.37 (apparent t, 1H, NCH), 4.83 (s, 1H, =CH), 5.13 (s, 1H, =CH). Attempts to purify and characterize **9** as a picrate or hydrochloride failed. A solution of acetyl chloride (0.15 ml, 1.9 mmol) in methylene chloride (6 ml) was added to a solution of **9** (0.19 g, 0.8 mmol) in methylene chloride (15 ml) and aqueous 1 N sodium hydroxide (5 ml). The resulting mixture was stirred at room temperature for 5 h. The organic layer was separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with brine, dried, and evaporated to give the acetyl derivative **10** (230 mg, 72%); mp 225-228ºC (anhydrous acetone), NMR (200 MHz, $CDCl_3$-CD_3OD): 2.46 and 2.87 (2 s, 3H, CH_3), 5.49 and 5.51 (2 s, 1H, =CH), 5.93 and 6.01 (2 s, 1H, =CH), 5.75 and 6.75 (2 apparent t, 1H, NCH), 7.33-8.00 (m, 5H, ArH); IR ($CHCl_3$): 3465 (NH), 1620 (C=O). (Found: C, 75.97; H, 7.19; N, 10.05. Calcd for $C_{17}H_{18}N_2O$. $1/5H_2O$: C, 75.64; H, 6.86; N, 10.37).

1-(Phenylsulfonyl)-2-indolyl 4-Pyridyl Ketone (13a). A solution of lithioindole **12a**, prepared[38] from 1-(phenylsulfonyl)indole (20 g, 77.8 mmol) and LDA (85 mmol) in tetrahydrofuran (200 ml), was slowly added under nitrogen to a suspension of isonicotinic anhydride (21.3 g, 93.4 mmol) in tetrahydrofuran (100 ml) cooled at -78ºC. The resulting mixture was stirred at -78ºC for 30 min and at room temperature for 4 h. Then, water (450 ml) was added and the mixture was concentrated at reduced pressure and extracted with methylene chloride. The organic phase was extracted with aqueous 10% hydrochloric acid, dried, and evaporated to give an oil which was chromatographed in a flash column using chloroform as the eluent. The first fractions gave 1-(phenylsulfonyl)indole (3.8 g), and then pure **13a** (21.3 g, 75%) was obtained as a solid; mp 110-113ºC (carbon tetrachloride); NMR ($CDCl_3$): 6.80 (s, 1H, H-3 indole), 6.90-8.40 (m, 11H, ArH), 8.63 (d, J=8 Hz, 2H, H_α-pyridine); IR (KBr): 1670 (C=O), 1375 and 1175 (SO_2N). The hydrochloride melted at 192-195ºC (acetone-ether). (Found: C, 60.56; H, 3.76; N, 7.00; S, 8.17; Cl, 8.70. Calcd for $C_{20}H_{15}ClN_2O_3S$: C, 60.22; H, 3.79; N, 7.02; S, 8.04; Cl, 8.89). The acidic aqueous solution was basified with aqueous 50% sodium hydroxide and extracted with methylene chloride. The extract was dried and evaporated to give ***N,N*-diisopropylisonicotinamide** (3.8 g); NMR ($CDCl_3$): 1.41 (d, 12H, CH_3), 3.45 (m, 2H, CH), 7.00 (d, J=5 Hz, 2H, H_β-pyridine), 8.46 (d, J=5 Hz, 2H, H_α-pyridine): IR (KBr): 1630 (C=O): The picrate melted at 165-167ºC (absolute ethanol). (Found: C, 49.61; H, 4.81; N, 16.06. Calcd for $C_{18}H_{21}N_5O_8$: C, 49.65; H, 4.82; N, 16.09).

When the reaction was effected by reversing the order of addition of the reagents, the yield of ketone **13a** decreased to 46% and **bis[1-(phenylsulfonyl)-2-indolyl]-4-pyridylmethanol**, coming from attack of lithioindole **12a** upon the initially formed ketone **13a**, was also obtained (14 % yield) after column chromatography (8:2 benzene-chloroform as eluent); mp 140-142ºC (chloroform-ether); NMR ($CDCl_3$): 5.96 (s, 2H, H-3 indole), 6.83-8.16 (m, 20H, ArH), 8.43 (d, J=5.6 Hz, 2H, H_α-pyridine); IR (KBr): 3420 (OH), 1370 and 1170 (SO_2N). (Found: C, 66.06; H, 4.18; N, 6.62; S, 10.45. Calcd for $C_{34}H_{25}N_3O_5S_2$: C, 65.89; H, 4.07; N, 6.78; S, 10.35).

1-Methyl-2-indolyl 4-Pyridyl Ketone (13b). A solution of lithioindole **12b**, prepared[39] from 1-methylindole (7.2 g, 55 mmol) and *n*-butyllithium (64.3 mmol) in tetrahydrofuran (80 ml) was allowed to react as above with isonicotinic anhydride (15 g, 65.7 mmol) in tetrahydrofuran (100 ml). The mixture was poured into ice-

water, concentrated, and extracted with ether. The etheral solution was extracted with aqueous 10% hydrochloric acid and evaporated to give 1-methylindole (1.7 g). The aqueous solution was basified with aqueous 50% sodium hydroxide and extracted with ether. Evaporation of the dried extracts gave the ketone **13b** (9.5 g, 73%). The product was identified by melting point and comparison of its IR and NMR spectra with those previously reported.[25a,b]

2-(4-Pyridylmethyl)indole (14a). A solution of ketone **13a** (10.3 g, 28.4 mmol), 80% hydrazine hydrate (9.5 ml), and potassium hydroxide (9.5 g, 167 mmol) in diethylene glycol (150 ml) was stirred under nitrogen at 120-140ºC for 6 h. After cooling, the mixture was poured into ice-water (400 ml) and extracted with ether. The extract was washed with water, dried, and evaporated to give a red oil which was chromatographed. Elution with chloroform afforded **14a** as a solid (3.8 g, 64%). The product was identified by melting point[22] and comparison of its IR and NMR spectra with those previously reported.[22b]

1-Methyl-2-(4-pyridylmethyl)indole (14b) was prepared by the published procedure;[29] MNR (CCl_4): 3.23 (s, 3H, NCH_3), 3.80 (s, 2H, CH_2), 6.00 (s, 1H, H-3 indole), 6.63-7.40 (m, 6H, ArH), 8.16 (d, J=5 Hz, H_α-pyridine).

Lithium α-(4-Pyridyl)-2-indoleacetate (15a). *n*-Butyllithium (1.6 M, 12.5 ml, 20 mmol) was added dropwise under nitrogen to a cooled (-30ºC) solution of **14a** (2.16 g, 10.3 mmol) in anhydrous tetrahydrofuran (54 ml). The mixture was gradually warmed to -10ºC, stirred at this temperature for 45 min, saturated with a stream of dry carbon dioxide, and then maintained at room temperature for 1 h. The reaction mixture was diluted with water, concentrated, and extracted with ether. Evaporation of the aqueous solution gave **15a** as a solid (1.3 g, 49%); NMR (D_2O): 5.00 (s, 1H, CHCO), 6.16 (s, 1H, H-3 indole), 6.60-7.56 (m, 6H, ArH), 8.33 (d, J=5.6 Hz, 2H, H_α-pyridine).

Methyl 1-Methyl-α-(4-pyridyl)-2-indoleacetate (16b). A solution of **14b** (4.2 g, 19 mmol) in anhydrous toluene (20 ml) was slowly added under nitrogen to a suspension of potassium hydride (1.5 g, 37.5 mmol) in toluene (10 ml). The resulting mixture was refluxed for 10 min. Then, a solution of dimethyl carbonate (4.5 g, 49 mmol) and a few drops of absolute methanol in anhydrous toluene (5 ml) were added. The mixture was refluxed for 7 h, cooled, and filtered. The solid was washed several times with anhydrous toluene and dried. The combined organic solutions were evaporated to give 2 g of **14b**. The dry potassium salt was decomposed by cautious addition of cold aqueous 50% acetic acid. The mixture was diluted with water and extracted with methylene chloride. The extract was successively washed with aqueous 20% sodium carbonate solution and brine, dried, and evaporated to afford **16b** (2.1 g, 40%); mp 83-84ºC (benzene); NMR ($CDCl_3$): 3.31 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 5.04 (s, 1H, $CHCO_2$), 6.29 (s, 1H, H-3 indole), 6.80-7.60 (m, 6H, ArH), 8.34 (br, 2H, H_α-pyridine). IR ($CHCl_3$): 1740 (C=O). (Found: C, 72.73; H, 5.89; N, 9.67. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99).

Methyl 1-Methyl-α-(1-methyl-1,4-dihydro-4-pyridylidene)-2-indoleacetate (17). A solution of methyl iodide (2.5 ml. 43 mmol) in anhydrous benzene (45 ml) was added to a solution of **16a** (2.7 g, 9.6 mmol) in anhydrous acetone (24 ml). The solution was stirred at room temperature for 15 h and evaporated. The residue was partitioned between aqueous potassium carbonate and ether. The organic phase was extracted with 2 N hydrochloric acid. The resulting aqueous solution was basified with potassium carbonate and extracted with ether. The extract was dried and evaporated to give **17a** (1.85 g, 65%); mp 159-160ºC (benzene); NMR (200 MHz, $CDCl_3$): 3.42 (s, 3H, NCH_3), 3.50 (s, 3H; NCH_3), 3.58 (s, 3H OCH_3), 5.95 (dd, J=8, 2.6 Hz, 1H, H-3 pyridine), 3.61 (d, J=0.8Hz, 1H, H-3 indole), 6.56 (dd, J=8, 2 Hz, 1H, H-2 pyridine), 6.87 (dd, J=8, 2Hz, 1H, H-5 pyridine), 7.03-7.36 (m, 3H, ArH), 7.58 (ddd, 1H, H-7 indole), 8.26 (dd, J=8, 2.6 Hz, 1H, H-6 pyridine); IR (KBr): 1655 (C=O), 1620 (C=C). (Found: C, 73.64; H, 6.15; N, 9.57. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52).

Methyl 1-Methyl-α-(1-methyl-4-piperidyl)-2-indoleacetate (18). A solution of **17** (1.67 g, 5.6 mmol) in a 2:1 mixture of methanol-chloroform (200 ml) was hydrogenated over PtO_2 (117 mg) at room temperature and atmospheric pressure. When the solution had absorbed the required volume of hydrogen, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography. On elution with 99:1 chloroform-methanol, piperidine **18** (1.03 g, 61%) was obtained; NMR ($CDCl_3$): 2.13 (s, 3H, NCH_3), 3.43 (s, 3H, NCH_3), 3.50 (s, 3H, OCH_3), 6.26 (s, 1H, H-3 indole), 6.66-7.50 (m, 4H, ArH); IR ($CHCl_3$): 1730 (C=O): The picrate melted at 210-211ºC (methanol). (Found: C, 53.47; H, 5.26; N, 13.13. Calcd for $C_{24}H_{27}N_5O_9 \cdot 1/2H_2O$: C, 53.53; H, 5.24; N,13.01).

Methyl 2,7-Dimethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-*b*]indole-6-carboxylate (19). A solution of piperidine **18** (0.74 g, 2.5 mmol), mercuric acetate (8.2 g, 25 mmol), and EDTA.2Na.$2H_2O$ (10.1 g, 27 mmol) in water (180 ml) was stirred at 100ºC for 90 min under nitrogen. The mixture was cooled and poured into a solution of sodium borohydride in methanol. The precipitate was filtered through Hyflo-Supercel (Machery-Nagel) and washed several times with methanol. The combined solutions were concentrated and extracted with chloroform. Evaporation of the dried extracts gave an oil which was chromatographed. Elution

with 98:2 chloroform-methanol gave **19** as a mixture of isomers enriched in **19b** (150 mg, 20%); NMR (200 MHz, $CDCl_3$): 2.30 (s, 3H, NCH_3), 3.59 (s, 1H, H-6), 3.61 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 4.26 (apparent t, 1H, H-1), 7.66-7.04 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$): 29.51, 31.23, 31.37, 33.29 (t), 45.12 (q), 45.72 (d), 46.77 (t), 52.06 (d), 52.97 (q), 107.46 (s), 109.49 (d), 119.93 (d), 119.99 (d), 121.91 (d), 128.16 (s), 134.76 (s), 137.75 (s),173.56 (s); IR ($CHCl_3$): 1730 (C=0). Elution with 95:5 chloroform-methanol gave **19** as a mixture of isomers enriched in **19a** (160 mg, 21%); ^1H NMR (200 MHz, $CDCl_3$): 2.41 (s, 3H, NCH_3), 3.60 (s, 3H, NCH_3) 3.85 (s, 3H, OCH_3), 4.19 (d, J=6.3 Hz, 1H, H-6), 4.47 (apparent t, 1H, H-1), 7.16-7.54 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$): 29.51, 30.22, 30.88, 34.74 (t), 44.77 (q), 45.72 (d), 46.93 (t), 52.54 (q), 52.71 (d), 107.28 (s), 109.48 (d), 119.35 (d), 120.19 (d), 122.04 (d), 127.94(s), 135.10 (s), 137.84 (s), 173.56 (s); IR ($CHCl_3$): 1730 (C=0) The picrate melted at 192-194ºC (methanol). (Found: C, 54.68; H, 4.57; N, 13.41. Calcd for $C_{24}H_{25}N_5O_9$: C, 54.64; H, 4.78; N, 13.28).

Methyl α-{1-[2-(Benzyloxy)ethyl]-4-piperidyl}-1-methyl-2-indoleacetate (21). A solution of **16b** (2 g, 7 mmol) in benzyl 2-bromoethyl ether (13.8 g, 64 mmol) was stirred at 95-100ºC for 5 h, after which the excess of ether was distilled (50-60ºC/ 0.01 mm Hg). The residue was worked-up as in the above N_b-methyl series to give an oil which was chromatographed. On elution with chloroform, compound **20** was obtained (1.18 g, 40%); NMR (200 MHz, $CDCl_3$): 3.52 (s, 3H, NCH_3), 3.59 (s, 3H, OCH_3), 3.62 (t, 2H, NCH_2), 3.71 (t, 2H, OCH_2), 4.48 (s, 2H, $ArCH_2$), 5.97 (dd, J=8, 2 Hz, 1H, H-3 pyridine), 6.33 (d, J=0.8 Hz, 1H, H-3 indole), 6.63 (dd, J=8, 1.5 Hz, H-2 pyridine), 6.92 (dd, J=8, 1.5 Hz, 1H, H-5 pyridine), 7.13-7.58 (m, 8H, ArH), 7.61 (ddd, 1H, H-7 indole), 8.26 (dd, J=8, 2 Hz, 1H, H-6 pyridine); IR ($CHCl_3$): 1655 (C=0), 1610 (C=C). A solution of **20** (1.3 g, 3 mmol) in methanol (70 ml) was hydrogenated over PtO_2 (91 mg) as in the above N_b-methyl series. The usual work-up afforded an oil which was chromatographed. On elution with 99:1 chloroform-methanol, the piperidine **21** (1 g, 77%) was obtained; NMR ($CDCl_3$): 2.43 (t, 2H, NCH_2), 3.45 (s, 3H, NCH_3), 3.53 (s, 3H, OCH_3), 4.26 (s, 2H, $ArCH_2$), 6.23 (s, 1H, H-3 indole), 6.50-7.66 (m, 9H, ArH); IR ($CHCl_3$): 1725 (C=0). The oxalate melted at 86-88ºC (acetone-ether). (Found: C, 64.87; H, 7.08; N, 4.58. Calcd for $C_{28}H_{34}N_2O_7 \cdot 2C_3H_6O$: C, 65.16; H, 7.40; N, 4.47).

Methyl 2-[2-(Benzyloxy)ethyl]-7-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-6-carboxylate (22). A solution of piperidine 21 (0.64 g, 1.5 mmol), mercuric acetate (5 g, 16 mmol), and EDTA.2Na.$2H_2O$ (6.2 g, 16.7 mmol) in water (160 ml) was allowed to react as in the above N_b-methyl series to give an oil which was chromatographed. On elution with 99:1 chloroform-methanol, a mixture of epimers **22a** and **22b** was obtained (330 mg, 52%); ^1H NMR (200 MHz, $CDCl_3$): 3.56 and 3.58 (2 s, 3H, NCH_3), 3.69 and 3.80 (2 s, 3H, OCH_3), 4.10 (d, J=6.1 Hz, H_α-6), 4.41 and 4.49 (2 apparent t, 1H, H-1), 4.54 and 4.56 (2 s, 2H, CH_2Ar), 6.95-7.65 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, isomer **22a**[40]): 28.32 (C-4), 28.87 (C-5), 30.32 ($N-CH_3$), 33.39 (C-12), 44.72 (C-3), 45.00 (C-6), 52.25 (OCH_3), 52.46 (C-1), 55.86 (NCH_2), 67.54 (OCH_2), 73.23 (CH_2Ar), 106.00 (C-11b), 109.08 (C-8), 118.85 (C-11), 119.95 (C-9), 121.70 (C-10), 126.89 (C-11a), 127.60 (C-*o*), 127.78 (C-*p*), 128.07 (C-*m*), 135.20 (C-6a), 137.30 (C-*i*), 138.17 (C-7a), 172.79 (C=0); ^{13}C NMR ($CDCl_3$, isomer **22b**[40]): 29.68 (NCH_3), 30.07 (C-4), 30.22 (C-12), 30.91 (C-5), 44.72 (C-3), 45.00 (C-6), 51.33 (C-1), 52.08 (OCH_3), 56.08 (NCH_2), 68.07 (OCH_2), 73.22 (CH_2Ar), 106.00 (C-11b), 108.95 (C-8), 119.39 (C-11), 119.68 (C-9), 121.48 (C-10), 126.89 (C-11a), 127.60 (C-*o*), 127.78 (C-*p*), 128.07 (C-*m*), 135.20 (C-6a), 137.30 (C-*i*), 138.17 (C-7a), 172.79 (C=0); IR ($CHCl_3$): 1725 (C=0). The picrate melted at 74-75ºC (acetone). (Found: C, 59.41; H, 5.28; N, 9.85. Calcd for $C_{32}H_{33}N_5O_{10} \cdot C_3H_6O$: C, 59.55, H, 5,57, N, 9.93).

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31. As in the above N_a-demethyl series, carboxylation of **14b** (*n*-BuLi, CO_2) gave a carboxylate salt **15b** (50% yield), which underwent decarboxylation on treatment with methanolic hydrogen chloride; NMR (D_2O): 3.30 (s, 3H, CH_3), 4.85 (s, 1H, CHCO), 5.95 (s, 1H, H-3 indole), 6.40-7.50 (m, 6H, indole, H_β-pyridine), 8.25 (d, 2H, H_α-pyridine).
32. For the use of this experimental procedure for alkoxycarbonylation, see: M. C. Wani, P. E. Ronman, J. T. Lindley, and M. E. Wall, *J. Med. Chem.* **1980**, *23*, 554.
33. The use of LDA or *n*-BuLi as a base in THF solution gave also mixtures of compounds **14b** and **16b**, which showed to be difficult to separate by column chromatography.
34. For the formation of similar 4-alkylidene-1,4-dihydropyridine derivatives, see reference 21. See also references cited therein.
35. For similar cyclizations and leading references, see references 19-21 and references cited therein.
36. These multiplicities are in fair agreement with those expected from the Karplus equation for the H-C_5-C_6-H dihedral angle in **19a** and **19b**, respectively. For similar stereochemical assignments in related tetracyclic systems, see references 8, 19, and 21.
37. R. Besselièvre and H.-P. Husson, *Tetrahedron* **1981**, *37*, 241.
38. M. G. Saulnier and G. W. Gribble, *J. Org. Chem.* **1982**, *47*, 757.
39. D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.* **1953**, *75*, 375.
40. Data obtained from the spectrum of an isomeric mixture enriched in **22a**.