by linear least-squares fitting of the data.

Direct Photolysis of 3a. In 2 mL of degassed methylene chloride in a Pyrex tube was dissolved 1 mg of **3a**. The contents of the tube were irradiated under a nitrogen atmosphere with the light from a 550-W, high-pressure, Hanovia mercury lamp, which was passed through a Pyrex filter. After 20 min **3a** was completely decomposed. Analytical GLC showed that the only two products formed in >1% yield were **6a** and **7a**, which were present in a ratio of 3.3:1. Both products were shown to be stable to the reaction conditions.

Sensitized Photolysis of 3a. A mixture of 0.5 mg of **3a** and 15 mg benzophenone in 1 mL of degassed methylene chloride was irradiated as described above. Analytical GLC showed the major product (>98%) to be **6a**. A small amount (<2%) of **7a** was also formed.

Reduction of 4 to 5b with Diimide-d_2. To a 250-mL, three-necked flask, fitted with a condenser and a dropping funnel, were added 310 mg of **4** (1.1 mmol), 5.7 g of dipotassium azocarboxylate,[18] and 40 mL of 99.5% methanol-*O*-*d*. The reaction mixture was placed under a nitrogen atmosphere, and 2.5 mL of 98% acetic acid-*O*-*d* was added dropwise over 10 min. The reaction mixture was stirred for 45 min. Reduction proved very inefficient, and additional portions of 4.4 g dipotassium azocarboxylate and 2 mL of acetic acid-*O*-*d* were added five times as 45-min intervals. The reaction mixture was stirred overnight, and water was then added until all the solid dissolved. The mixture was extracted three times with 50-mL portions of methylene chloride, and the combined methylene chloride extracts were washed twice with 25-mL portions of 5% $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent under vacuum afforded 295 mg (95%) of a crystalline solid, which was used without purification.

Synthesis of 3b. The synthesis was carried out, starting with **5b**, in a manner identical with that described above for the preparation of **3a** from **5a**. The ^1H NMR spectrum of the product was similar to that of **3a**; but the resonance at δ 1.49 was reduced to 15% of its size in **3a**, the peak at δ 1.87 appeared as a singlet, and the resonance at δ 5.42 was a doublet with J = 6.0 Hz. The ^2H NMR spectrum displayed a resonance at δ 1.49, and the IR spectrum showed new bands at 2200, 2190, and 2180 cm^{-1}. The mass spectrum showed the product to consist of 70% d_2 molecules and 30% d_1: exact mass calcd for $C_8H_{10}D_2N_2$ 138.1126, found 138.1123; exact mass calcd for $C_8H_{11}DN_2$ 137.1063, found 137.1061.

Reduction of 9 to 7b with Diimide-d_2. In a 25-mL flask was placed 11 mg (0.1 mmol) of tricyclo[4.1.1.$0^{2,5}$]oct-3-ene (**9**), 250 mg (1.28 mmol) of dipotassium azodicarboxylate,[18] and 4 mL of 99.5% methanol-*O*-*d*. The reaction mixture was placed under an atmosphere of nitrogen, and 0.11 mL 98% acetic acid-*O*-*d* was added dropwise by syringe. The reaction mixture was stirred for 1 h and recharged once with 250 mg of dipotassium azodicarboxylate and 0.11 mL of acetic acid-*O*-*d*. The mixture was then stirred overnight at room temperature. Water was added slowly to dissolve the solid, and the resulting mixture was extracted with pentane. The pentane extracts were washed with 5% $NaHCO_3$ and dried over $MgSO_4$. Most of the pentane was removed by distillation, and 5.2 mg (47%) of **7b** was isolated by preparative GLC. The ^1H NMR spectrum of the product was the same as that described above for **7a**, except that the resonance at δ 1.42 appeared as a doublet, with J = 1.6 Hz, and the peak at δ 2.11 was nearly absent. The mass spectrum showed 90% d_2 molecules and 10% d_1.

Product Analysis in the Pyrolysis and Photolysis of 3b. These reactions were performed and the products separated as described above for **3a**. The vinyl hydrogens in **6b** were easily assigned on the basis of their coupling constants to the vinyl proton. Thus, the proton at δ 4.87 with J = 10.3 Hz was assigned as cis, while that at δ 4.92 with J = 17.2 Hz was assigned as trans. Both the ^1H and ^2H NMR spectra showed the ratio of these two resonances to be equal within experimental uncertainty. The ratios of **7b** to **7c** were determined by integrating the resonances at δ 1.42 and 2.11 in the ^2H NMR spectra of the mixture. The ratios corresponded closely to those obtained from integration of the ^1H NMR spectra, after correction of the latter for the presence of 30% of d_1 material. The ratios of **7b** to **7c** obtained for the pyrolysis and direct photolysis of **3b** are given in the text. So little **7** was formed in the sensitized photolysis that no attempt was made to assess its deuterium stereochemistry, especially since it seemed likely that this material resulted from some light absorption by the azo compound instead of by the sensitizer.

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Synthetic Studies on the Indole Alkaloid Vinoxine. Synthesis of 19,20-Dihydro-16-epivinoxine

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The synthesis of vinoxine analogues having the C-16 methoxycarbonyl substituent present in the alkaloid is reported. The key step in this synthesis is the mercuric acetate oxidation of appropriate methyl α-4-piperidyl-1-indoleacetates, which were prepared from 1-(4-pyridylmethyl)indoles through a three-step sequence involving methoxycarbonylation of the interannular methylene carbon, alkylation of the piperidine nitrogen, and hydrogenation of the resulting 4-alkylidene-1,4-dihydropyridine. The stereochemical aspects of 3-ethylpiperidines **13** and the vinoxine analogues **5**, **15**, and **16**, especially in regard to the relative configuration of the methine carbon α to the methoxycarbonyl group, are discussed.

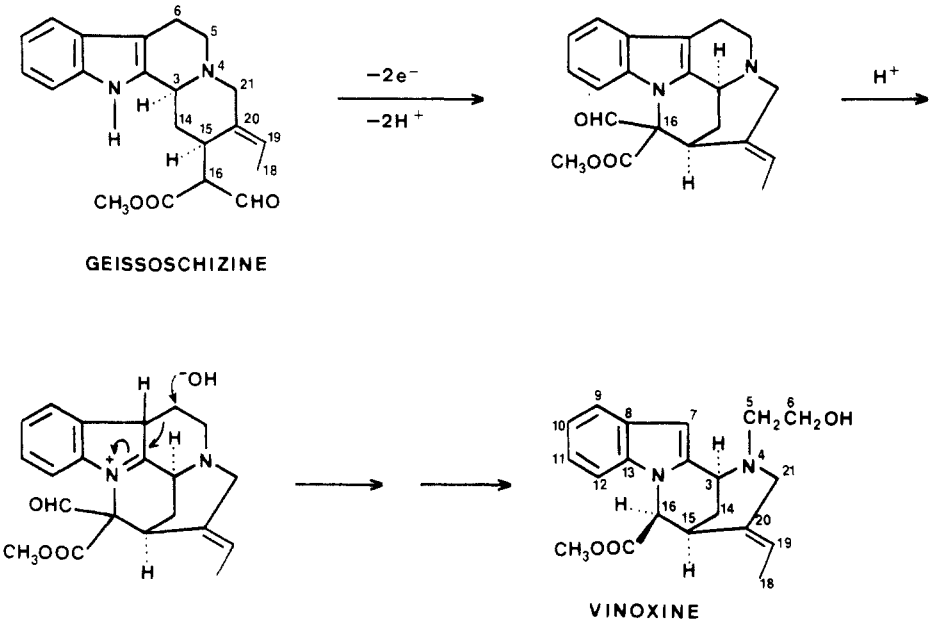
Vinoxine is a minor indole alkaloid isolated[1] in 1967 from *Vinca minor* L. Its unusual planar structure, lacking the characteristic tryptamine unit present in the greater part of indole alkaloids and having, as its pentacyclic analogue pleiocarpamine,[2,3] a C-16[4] methoxycarbonyl group and a

(1) Mokrý, J.; Kompiš, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2523.

(2) Hesse, M.; Philipsborn, W. v.; Schumann, D.; Spiteller, G.; Spiteller-Friedmann, M.; Taylor, W. I.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1964**, *47*, 878.

0022-3263/86/1951-2289$01.50/0

Scheme I



C-20 exocyclic (*E*)-ethylidene substituent, was established some years later.[5] From the biosynthetic standpoint, vinoxine can be considered to be formed from geissoschizine by oxidative ring closure between C-16 and the indole nitrogen followed by the loss of the formyl group and hydrolytic cleavage of the tryptamine bridge[6] (Scheme I). Recently, we have reported[7] the first total synthesis of vinoxine and its C-16 epimer as well as the reassignment of the relative configuration at carbon 16 of the alkaloid.

The overall synthetic problem associated with the synthesis of vinoxine can be subdivided as follows: (i) development of a general synthetic procedure to achieve the fundamental tetracyclic framework of the alkaloid; (ii) introduction of the C-16 methoxycarbonyl substituent with the appropriate stereochemical relationship; and (iii) elaboration of the (*E*)-ethylidene side chain.[8]

Our synthetic approaches to the tetracyclic ring skeleton of vinoxine imply closure of ring C by formation of the C_2–C_3 bond in the key synthetic step through intramolecular cyclization of a suitable iminium salt upon the indole 2-position. For this purpose, among the numerous methods of generating iminium salts we selected three of them: (a) the mercuric acetate oxidation of piperidines,[9] which has proved to be a general method for the synthesis of indole alkaloids;[10] (b) the acid treatment of 2-cyanopiperidines,[11] because it is known that α-amino nitriles can be considered as latent forms of iminium salts;[12] and (c) the regioselective protonation of 1,4-dihydropyridine resulting from nucleophilic attack of an ester α-anion at the 4-position of a pyridinium salt having an electron-withdrawing substituent at the 3-position.[13] The latter methodology has been successfully applied to the synthesis of vinoxine[7] since, when this substituent is 2-(methoxycarbonyl)vinyl, it can be further converted in a stereoselective manner[14] into the (*E*)-ethylidene group present in the alkaloid.

In the context of our studies on the synthesis of vinoxine and simplified analogues,[7,9,11] and continuing our interest on cyclizations promoted by mercuric acetate,[9,15] we planned to evaluate the effectiveness of this reagent for the synthesis of vinoxine analogues having the C-16 methoxycarbonyl substituent of the alkaloid. As synthetic goals we chose compounds **5** and **16** (the latter one constitutionally can be considered as a 19,20-dihydro derivative of the natural product[16]), although at the initial stages

(3) For the synthesis of pentacyclic alkaloids of the C-mavacurine group related to pleiocarpamine, see: (a) O'Rell, D. D.; Lee, F. G. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1972**, *94*, 3205. (b) Sakai, S.; Shinma, N. *Chem. Pharm. Bull.* **1974**, *22*, 3013. (c) Sakai, S.; Shinma, N. *Heterocycles* **1976**, *4*, 985. (d) Sakai, S.; Shinma, N. *Yakugaku Zasshi* **1978**, *98*, 950. (e) Calverley, M. J.; Banks, J. B.; Harley-Mason, J. *Tetrahedron Lett.* **1981**, *22*, 1635.

(4) The biogenetic numbering is used throughout this paper for the tetracyclic systems related to vinoxine: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(5) (a) Votický, Z.; Grossmann, E., Tomko, J.; Massiot, G.; Ahond, A.; Potier, P. *Tetrahedron Lett.* **1974**, 3923. (b) Votický, Z.; Grossmann, E.; Potier, P. *Collect. Czech. Chem. Commun.* **1977**, *42*, 548.

(6) Rahman, A. U.; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, 1983; p 65.

(7) Bosch, J.; Bennasar, M.-L.; Zulaica, E.; Feliz, M. *Tetrahedron Lett.* **1984**, *25*, 3119.

(8) For a review on the elaboration of the ethylidene substituent in the synthesis of indole alkaloids, see: Bosch, J.; Bennasar, M.-L. *Heterocycles* **1983**, *20*, 2471.

(9) (a) Bosch, J.; Feliz, M.; Bennasar, M.-L. *Heterocycles* **1982**, *19*, 853. (b) Bosch, J.; Mauleón, D.; Feliz, M.; Granados, R. *J. Org. Chem.* **1983**, *48*, 4836.

(10) See references cited in ref 9b.

(11) (a) Bosch, J.; Feliz, M.; Bennasar, M.-L. *Tetrahedron* **1984**, *40*, 1419. (b) Bennasar, M.-L.; Bosch, *Tetrahedron* **1986**, *42*, 637.

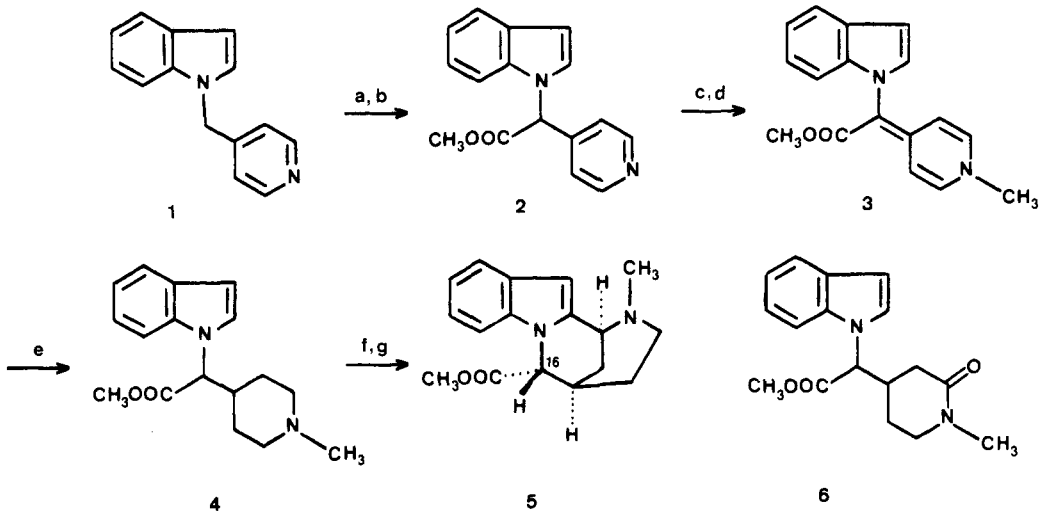
(12) See references cited in ref 11. For recent work in this field, see: (a) Koskinen, A.; Lounasmaa, M. *Tetrahedron* **1983**, *39*, 1627. (b) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683. (c) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392. (d) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolôs, J.; Linares, A.; Minguillôn, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516.

(13) For precedents of the use of this methodology in alkaloid synthesis, see: (a) Wenkert, E.; Chang, C. J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645. (b) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 5370. (c) Lounasmaa, M.; Koskinen, A. *Tetrahedron Lett.* **1982**, *23*, 349. (d) Wanner, M. J.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1983**, *39*, 3673. (e) Weller, D. D.; Ford, D. W. *Tetrahedron Lett.* **1984**, *25*, 2105. (f) Rosemberg, S. H.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 56. (g) Wenkert, E.; Michelotti, E. L.; Pyrek, J. S. *J. Org. Chem.* **1984**, *49*, 1832; (h) and references cited therein.

(14) This procedure has been previously applied to the synthesis of the (*E*)-ethylidene bearing indole alkaloids deplancheine[14a] and geissoschizine.[14b] (a) Besselièvre, R.; Cosson, J.-P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 63. (b) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.* **1980**, *102*, 7971.

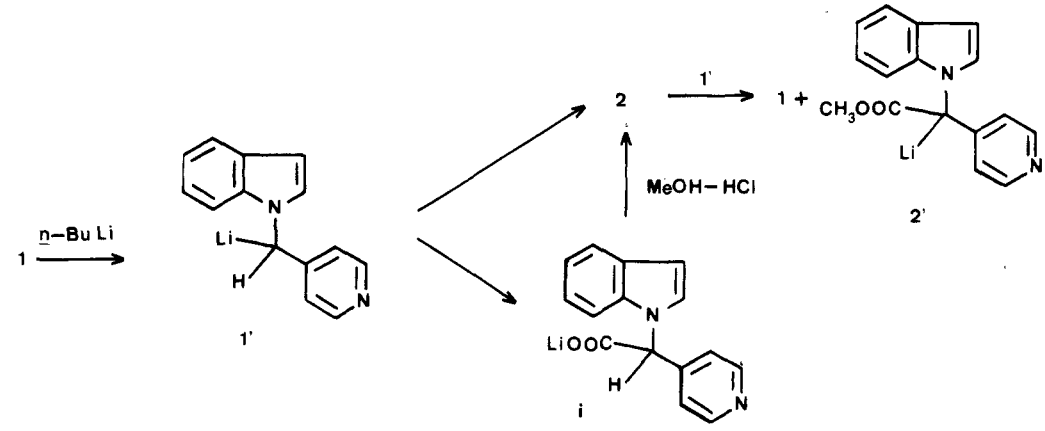
(15) (a) Bonjoch, J.; Casamitjana, N.; Bosch, J. *Tetrahedron* **1982**, *38*, 2883. (b) Bosch, J.; Domingo, A.; Granados, R. *J. Heterocycl. Chem.* **1983**, *20*, 887. (c) Bosch, J.; Bonjoch, J.; Díez, A.; Linares, A.; Moral, M.; Rubiralta, M. *Tetrahedron* **1985**, *41*, 1753.

Scheme II



Reagents: (a) n-BuLi, CO_2; (b) 1.2N MeOH–HCl; (c) CH_3I, acetone; (d) $Na_2CO_3 - H_2O$; (e) H_2, PtO_2; (f) $Hg(AcO)_2$, EDTA·2Na; (g) $NaBH_4$

Scheme III



of the work not only the relative configuration at C-16 in **5** and **16** was still unknown but also the reassignment of stereochemistry at C-16 in vinoxine had not still been effected.[7]

Results and Discussion

Synthetic Aspects. Scheme II outlines the reaction sequence we have developed for the synthesis of **5**.[17] The piperidine **4**, having the required methoxycarbonyl substituent, was prepared in three steps from (pyridylmethyl)indole **1**.[9b] The introduction of this substituent was effected in the earlier stage of the synthesis by taking advantage of the acidity of the interannular methylene protons in **1**. Thus, carboxylation of **1** through treatment with *n*-butyllithium and carbon dioxide, followed by esterification with a methanolic solution of hydrogen chloride, afforded ester **2**[18] in 73% yield. *n*-Butyllithium was considered as the base of choice[19] because, as it was evident by deuteration experiments,[20] monolithiation at the interannular methylene proton was complete at −30 °C. However, when dimethyl carbonate was used as acylating agent, the yield of **2** was only 30–40%. This fact can be explained by considering that the acylated product (**2** in our case) undergoes further ionization by the original carbanion (**1'**) to give the conjugate acid **1** and a new stabilized carbanion (**2'**).[21] The higher yield when using carbon dioxide can be rationalized by taking into account the lower acidity of the methine proton in the lithium carboxylate intermediate i as compared with **2** (Scheme III).

Due to its instability, ester **2** was only characterized by its spectroscopic data. The most significant signals were a IR absorption at 1745 cm^{-1} due to the ester carbonyl group and two singlets in the NMR spectrum, at δ 3.75 and 6.15, due to the *O*-methyl group and the interannular methine proton, respectively. Quaternization of **2** with methyl iodide gave an unstable pyridinium salt which was also characterized by its spectral data, especially from the

(16) A 19,20-dihydro derivative of vinoxine was prepared[5] in the context of the structural elucidation of the alkaloid, by catalytic hydrogenation of vinoxine. However, the relative configuration at C-20 was not discussed.

(17) For a preliminary report on this part of the work, see ref 9a.

(18) Attempts to obtain **2** by *N*-alkylation of indole with methyl α-bromo-4-pyridineacetate failed. This compound was obtained by bromination of methyl 4-pyridineacetate according to the procedure reported for the 2-substituted isomer: Edwards, O. E.; Chaput, M.; Clarke, F. H.; Singh, T. *Can. J. Chem.* **1957**, *32*, 785.

(19) The use of NaH, KH, or LDA as a base and dimethyl carbonate as acylating agent was ineffective.

(20) Sundberg, R. J.; Russel, H. F. *J. Org. Chem.* **1973**, *38*, 3324.

(21) (a) Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 4237. (b) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React. (N.Y.)* **1954**, *8*, 113.

NMR singlet (δ 4.3) due to the *N*-methyl group. However, treatment of the pyridinium salt with aqueous sodium carbonate afforded (66% yield from **2**) a crystalline solid which was identified as the 4-alkylidene-1,4-dihydropyridine **3**. The conversion of some pyridinium salts into dihydropyridylidene derivatives (anhydro bases) under alkaline conditions is a well-known process.[22,23]

Catalytic hydrogenation of **3** over platinum dioxide gave the piperidine **4** in excellent yield. Finally, oxidative cyclization of **4** by means of mercuric acetate was effected in the presence of EDTA·2Na to avoid the mercuriation[24] of the indole nucleus, at pH 3–4 (hydrolysis of $Hg(AcO)_2$–EDTA·2Na) in refluxing water as the solvent, being that the best set of conditions we had found in similar cyclizations to the fundamental tetracyclic skeleton of vinoxine.[9b] Subsequent addition of excess $NaBH_4$ in order to reduce the possible overoxidation products and to destroy the excess of $Hg(AcO)_2$ led, with abundant loss of material, to a mixture of the piperidine **4**, the piperidinone **6**, and the desired cyclized product **5** (9% yield after column chromatography). Both the recovery of the starting piperidine and the formation of lactams under mercuric acetate cyclization conditions have been previously observed and discussed.[9b] The lightly acidic reaction conditions could account for the low yield of recovered material in the above cyclization, due to the partial hydrolysis of the methoxycarbonyl group,[25] to give a water-soluble amino acid. The IR spectrum of **5** showed a carbonyl absorption at 1745 cm^{-1}, whereas the most significant signals in the NMR spectrum were an apparent triplet at δ 3.91 due to the C-3 methine proton, a doublet (J = 0.76 Hz) at δ 4.90 corresponding to the C-16 methine proton, and a singlet at δ 6.30 attributable to the C-7 (indole 3-position) proton[4] (see later for a discussion about the relative configuration at C-16).

With a method in hand for the construction of the tetracyclic ring system of vinoxine that allows the introduction of the methoxycarbonyl group present in the alkaloid, we decided to develop a similar approach to achieve the synthesis of a dihydro analogue of vinoxine.[26] For this purpose, we had to prepare 1-(piperidylmethyl)indole **13**, having an ethyl substituent on the piperidine 3-position. This was successfully achieved from methyl 3-ethyl-4-pyridinecarboxylate (**7**)[27] through the reaction sequence depicted in Scheme IV.

Lithium aluminum hydride reduction of ester **7** followed by treatment of the resulting alcohol **8** with thionyl chloride gave chloromethylpyridine hydrochloride **9**. Its condensation with indole was effected in dimethyl sulfoxide,[28] using potassium hydroxide as a base, according to the general procedure for the *N*-alkylation of indoles.[29] 1-(Pyridylmethyl)indole **10** was easily characterized by the singlet at δ 5.15 in the NMR spectrum, due to the interannular methylene protons, and was converted, as in the above deethyl series, into the ester **11** in 65% yield by carboxylation (*n*-BuLi, CO_2) followed by esterification.

Since it is known that the mercuric acetate–EDTA oxidation of *N*-(2-hydroxyethyl)piperidines is a good method of forming 2-piperidones,[30] in order to avoid the presence of a 2-hydroxyethyl substituent on the piperidine nitrogen during the cyclization step we planned to introduce the two-carbon chain on the nitrogen atom by alkylation of the pyridine ring with 2-bromoethyl acetate, as in our synthesis of vinoxine.[7] However, although pyridine **11** was easily quaternized at room temperature with methyl iodide to give, after treatment with aqueous sodium carbonate, the doubly vinylogous urethane **12a**, alkylation with 2-bromoethyl acetate proved to be difficult;[31] when alkylation of **11** was carried out by heating without solvent and the resulting pyridinium salt was basified, pure 4-alkylidene-1,4-dihydropyridine **12b** was isolated in 57% yield. The *Z* configuration for the exocyclic double bond of **12** was inferred from the chemical shift of the methyl (δ ~0.7) and methylene (δ ~1.2) protons of the ethyl substituent, which are strongly shielded by the indole ring.

Initially, the hydrogenation of **12b** was carried out in ethyl acetate solution by using platinum dioxide as catalyst. Under these conditions a complex mixture was obtained, from which the piperidine **13a** (12%), the tetrahydropyridine **14** (19%), the methyl 1-indoleacetate (**17**) as the major product (30%) were isolated by column chromatography. The unexpected formation of **17** can be explained by considering the initial hydrogenation of the exocyclic double bond of **12b** to give an unstable 1,4-dihydropyridine which undergoes an heterolytic fragmentation as illustrated in Scheme V.[32,33]

Inasmuch as in acidic solution 4-alkylidene-1,4-dihydropyridine **12b** should exist as the corresponding pyridinium salt, in order to avoid the above fragmentation we tried the hydrogenation of **12b** using acetic acid as the solvent. As expected, under these conditions the fragmentation product **17** was not detected, although a complex mixture was again obtained. Pure piperidines **13a** and **13b** were separated by column chromatography in 16% and 6% yield, respectively (their stereochemical assignment will be discussed later). Tetrahydropyridine **14** also appeared to be an undesirable byproduct (20%), resistant to further hydrogenation.[34]

Oxidative cyclization of the major piperidine **13a** was effected, as in the above deethyl series, by treatment with

(22) *Heterocyclic Compounds. Pyridine and its Derivatives. Part I*; Abramovitch, R. A., Ed.; John Wiley and Sons: New York, 1974; p 351.

(23) For examples, see: (a) Jones, A.; Katritzky, A. R. *Aust. J. Chem.* **1964**, *17*, 455. (b) Ban, Y.; Kimura, T. *Chem. Pharm. Bull.* **1968**, *16*, 549. (c) Stupnipova, T. V.; Rybenko, L. A.; Kost, A. N.; Sagitullin, R. S.; Kolodin, A. I.; Marshtupa, V. P. *Chem. Heterocycl. Comp.* **1980**, *16*, 585. (d) Stupnipova, T. V.; Zemskii, B. P.; Vysostskii, Y. B.; Sagitullin, R. S.; Lopatinskaya, K. I. *Chem. Heterocycl. Comp.* **1980**, *16*, 743.

(24) (a) Ramachandran, L. K.; Witkop, B. *Biochem. J.* **1964**, *3*, 1603. (b) Kirby, G. W.; Shah, S. W. *J. Chem. Soc., Chem. Commun.* **1965**, 381. (c) Remers, W. A. In *Indoles. Part I*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; p 126. (d) Powers, J. C. ref 24c, Part II, 1972; p 152.

(25) For examples of cyclizations promoted by mercuric acetate on structures having a methoxycarbonyl substituent, see: (a) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708. (b) Gutzwiller, J.; Pizzolato, G.; Uskoković, M. *J. Am. Chem. Soc.* **1971**, *93*, 5907. (c) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron* **1973**, *29*, 2015. (d) Uskoković, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Pruess, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742. (e) Imanishi, T.; Inoue, M.; Wada, Y.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 1925.

(26) This part of the work was presented in a preliminary form at the Third European Symposium on Organic Chemistry (ESOC III), Canterbury, England, 1983.

(27) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, 2738.

(28) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499.

(29) (a) Cardillo, B.; Casnati, G.; Pochini, A.; Ricca, A. *Tetrahedron* **1967**, *23*, 3771. (b) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; pp 19–31.

(30) (a) Leonard, N. J.; Conrow, K.; Savers, R. L. *J. Am. Chem. Soc.* **1958**, *80*, 5185. (b) Mohrle, H. *Arch. Pharm.* **1966**, *299*, 122. (c) Fujii, T.; Hiraga, T.; Ohba, M. *Chem. Pharm. Bull.* **1981**, *29*, 2691; (d) and references cited therein.

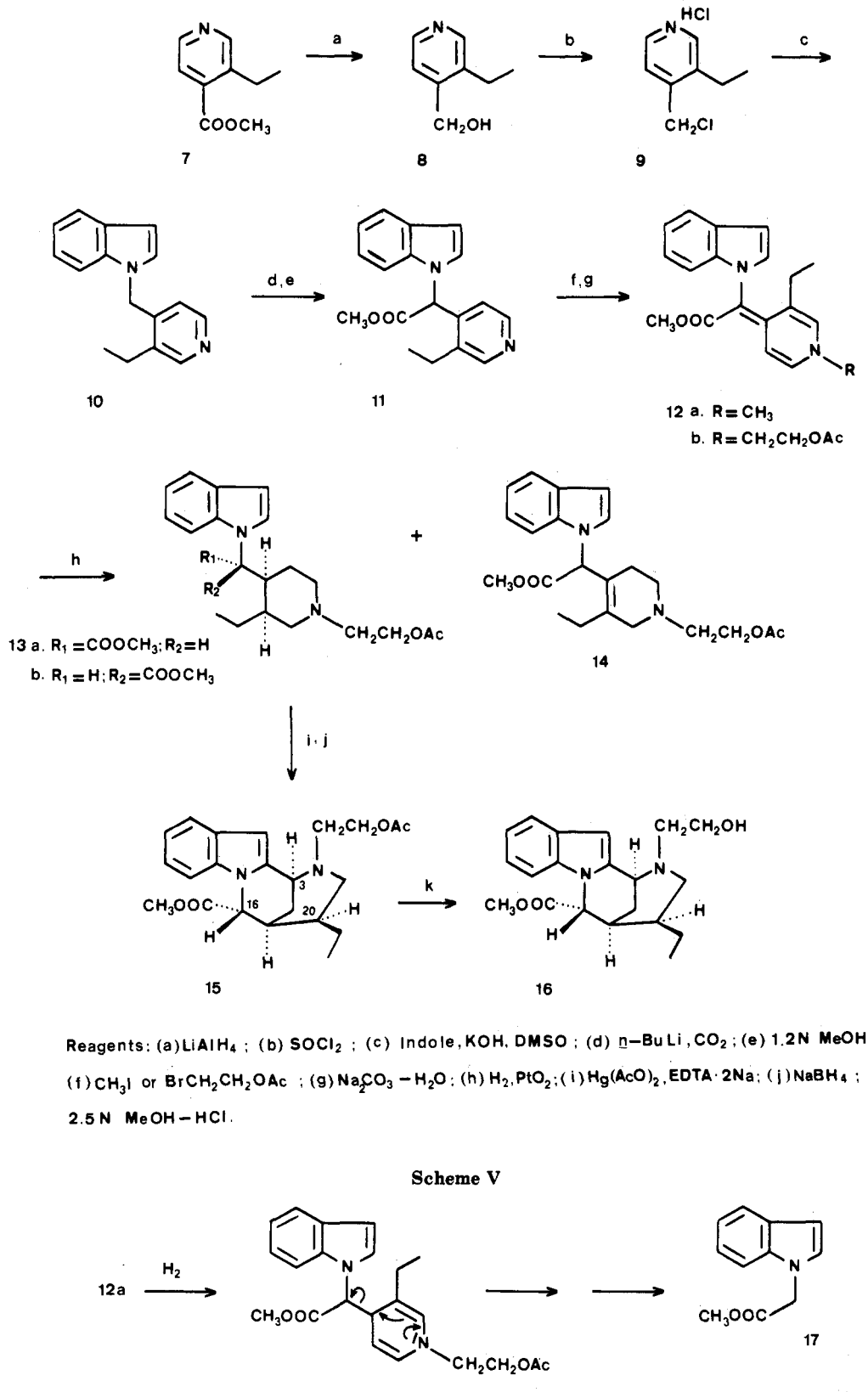
(31) Alkylation failed when refluxing acetone, methanol, or toluene in the presence of potassium iodide, were used as solvents.

(32) A similar fragmentation from a dimethyl 1,4-dihydro-4-pyridinemalonate system has been previously observed: see ref 13a.

(33) It is worth mentioning that this process is the reverse to that constitutes the key step in our synthesis of vinoxine.[7] A 2-(methoxycarbonyl)vinyl, instead of ethyl, was the substituent at the pyridine 3-position.

(34) Attempts to saturate its tetrasubstituted double bond under hydrogen pressure in acidic medium failed.

Scheme IV



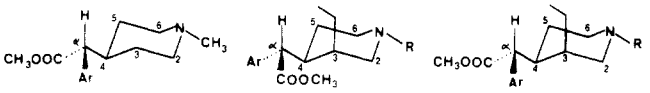
Reagents: (a) $LiAlH_4$; (b) $SOCl_2$; (c) Indole, KOH, DMSO ; (d) n-BuLi, CO_2 ; (e) 1.2N MeOH–HCl (f) CH_3I or $BrCH_2CH_2OAc$; (g) $Na_2CO_3 - H_2O$; (h) H_2, PtO_2 ; (i) $Hg(AcO)_2$, EDTA·2Na; (j) $NaBH_4$; (k) 2.5 N MeOH–HCl.

Scheme V

$Hg(AcO)_2$–EDTA in aqueous solution. After the usual workup with sodium borohydride, a complex mixture was obtained, from which 19,20-dihydro-16-epivinoxine acetate (**15**) and 19,20-dihydro-16-epivinoxine (**16**) were isolated in 11% overall yield. Formation of the latter product evidenced that hydrolysis of ester groups occurs during cyclization. Finally, acetate **15** was converted in 90% yield into 19,20-dihydro-16-epivinoxine (**16**) by treatment with methanolic hydrogen chloride at room temperature.

The proposed planar structure for **15** an **16** was evident from their spectroscopic data. The most significant signals in the ^1H NMR spectra of these tetracyclic bases were (i) in a singlet at δ 6.1 corresponding to the indole 3-proton, which demonstrated that cyclization had occurred; (ii) an apparent triplet at δ 3.9 due to the bridgehead C-3 methine proton, thus clearly indicating that the desired regioisomer had been obtained; and (iii) a singlet at δ 4.8 due to the C-16 methine proton (see later for a discussion about the

Table I. ^{13}C NMR Data of Methyl α-4-Piperidyl-1-indoleacetates



4 13a 13b

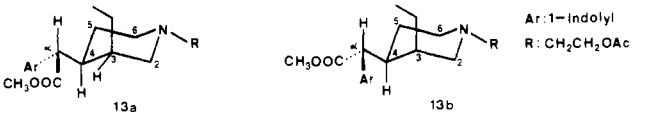
Ar: 1-indolyl
R: CH_2CH_2OAc

carbon	4	13a	13b
C-2	54.97	56.55	56.55
C-3	28.45	37.62	35.89
C-4	38.13	41.69	41.69
C-5	29.43	23.85	24.98
C-6	55.05	54.22	54.09
C-α	63.01	59.87	59.87
OCH_3	52.27	52.23	52.23
Ind C-2	125.55	125.66	125.66
Ind C-3	102.95	102.97	102.97
Ind C-3a	128.32	128.41	128.41
Ind C-4	121.02	120.98	120.98
Ind C-5	121.94	121.96	121.96
Ind C-6	119.90	119.87	119.87
Ind C-7	109.21	109.24	109.24
Ind C-7a	136.67	136.34	136.34
NCH_3	46.14		
NCH_2		55.69	55.69
CH_2OH		61.90	61.86
CH_2CH_3		17.94	17.81
CH_2CH_3		12.25	11.65
CH_3CO		20.98	20.98
CO	170.44	170.87	170.87
		171.04	171.04

relative configuration of this center).

Stereochemical Aspects. At this point it is worth commenting upon some stereochemical aspects of piperidines **13** and the simplified vinoxine analogues **5**, **15**, and **16**, especially with regard to the relative configuration of the methine carbon α to the methoxycarbonyl group.

As discussed above, two stereoisomeric piperidines were isolated after hydrogenation of **12b**. Their stereochemical assignment as **13a** and **13b** was inferred from their ^1H and ^{13}C NMR data. The ^1H NMR spectra (200 MHz)[35] of both



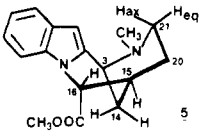
13a 13b

isomers showed the interannular methine (C-α) proton resonance as a doublet, whose coupling constant (12 Hz) clearly reflects an anti relationship with the C-4 piperidine proton. The relative configuration of the interannular methine carbon was inferred from the strong shielding effect caused by the indole ring upon the protons on the piperidine 5-position in **13a** (δ 1.32 and 0.80 for the axial and equatorial protons, respectively; compare with δ 1.70 and 1.48 in **13b**) and the ethyl substituent in **13b** (δ 0.5 for the methyl and δ 1.10 and 1.70 for the methylene protons; compare with δ 0.96 and 1.58, respectively, in **13a**). Finally, the axial orientation of the ethyl group in **13a** was established from the multiplicity and coupling constants of H-4ax (triplet of doublets) and H-2ax (broad doublet).

On the other hand, the ^{13}C NMR chemical shifts of **13a**, **13b**, and the deethyl analogue **4** are given in Table I. These data are in agreement with the assigned planar structures and confirm the axial disposition of the ethyl substituent in both isomers. Thus, substitution at the piperidine 3-position by an ethyl group produces an upfield γ-effect shift upon the interannular methine carbon (−3.14 ppm) and the piperidine C-5 (∼−4.5 ppm) resonances. Such characteristic upfield shifts provide a good indication of the axial position of the ethyl substituent.

Concerning the mechanism of formation of these piperidines, it is interesting to note that both the stereochemical relationship between C-α and C-4 in the piperidine **13a** resulting from hydrogenation of **12b** in neutral medium and the formation of 3,4-cis-disubstituted piperidines **13a** and **13b** during the hydrogenation under acid conditions reflect a syn hydrogen uptake, either upon the exocyclic double bond of 4-alkylidene-1,4-dihydropyridine **12b** or upon the tetrasubstituted double bond of the corresponding pyridinium salt, respectively.

Although oxidative cyclization of piperidine **4** could lead to a C-16 epimeric mixture of tetracyclic bases, only isomer **5** was detected and isolated from the reaction mixture. Assignment of the relative configuration of C-16 in **5**, as



5

the opposite to that of vinoxine, was established from the coupling constant of the doublet corresponding to the 16-methine proton in the 200-MHz NMR spectrum. Thus, the observed $J_{15,16}$ was 0.76 Hz, a value similar to that reported for 16-epivinoxine[7] and 16-epipleiocarpamine[2] (H-15/H-16 trans relationship; J = 1.14 and 1.5 Hz, respectively) but different to that observed in vinoxine[5,7] and pleiocarpamine[2] (H-15/H-16 cis relationship; J = 6.14 and 4 Hz, respectively). Furthermore, this coupling constant is in fair agreement with that expected from the Karplus equation for the stereochemical disposition depicted in **5** ($H-C_{15}-C_{16}-H$ dihedral angle ∼80°).

The above stereochemical assignment is in good agreement with the shielding (−4.08 ppm) of C-14 in the ^{13}C NMR spectrum of **5** by a γ-effect induced by the methoxycarbonyl group,[36] as compared with the base value for the corresponding tetracyclic compound unsubstituted at C-16[9] (Table II). A similar γ-effect (−3.24 ppm) was observed in 16-epivinoxine as compared with vinoxine.[7] The absence of a related γ-effect at C-20 in **5**, observable in vinoxine,[7] rules out the opposite relative configuration at C-16.

Finally, it is worth mentioning that the relative configuration at C-16 in **5** appeared to be stable toward base, as it was evident after epimerization experiments with sodium methoxide in methanol. Since this fact has been considered of diagnostic value in the 16-epipleiocarpamine series,[2,3] the most stable H-15/H-16 trans stereochemistry of **5** was definitively concluded.

The spectroscopic criteria discussed above were used to establish the relative configuration at C-16 in the dihydro analogues of vinoxine **15** and **16**. In these cases the 60-MHz NMR spectra were examined, the H-16 resonance being observed as a singlet. The equatorial orientation of the C-20 ethyl substituent follows from the cis relationship between substituents at positions 3 and 4 in the starting piperidine **13a**.[37] Accordingly, in the ^{13}C NMR spectrum of **15** a negligible γ-effect shift in carbon 14 was observed to be produced by the ethyl group.

(35) See Experimental Section for a detailed assignment of the spectra. All assignments were confirmed by irradiation experiments.

(36) Ahond, A.; Bui, A.-M.; Potier, P.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1976**, *41*, 1878.

(37) However, it should be noted that this center (C-20) can undergo epimerization during the mercuric acetate treatment. Overoxidation of the initial cyclized product **15** could lead to an iminium salt, which could epimerize through the corresponding enamine (double bond between C-20 and C-21).

Table II. ^{13}C NMR Data of Vinoxine and Simplified Analogues

C		5	15	16-epivinoxine[a]	vinoxine[a]
C-2	132.81	131.60	132.60	131.95	133.81
C-3	53.36	53.07	52.25	51.82	51.80
C-5			53.73	56.49	56.50
C-6			62.44	57.93	57.96
C-7	100.31	101.53	101.45	101.42	101.76
C-8	127.55	127.75	127.80	127.79	128.06
C-9	120.29	120.67	120.70	120.74	120.58
C-10	120.83	121.54	121.55	120.86	121.62
C-11	119.64	120.18	120.21	120.35	120.33
C-12	108.74	108.49	108.48	108.61	110.02
C-13	136.17	136.20	136.04	136.27	136.51
C-14	32.20	28.12	29.70	27.76	31.00
C-15	25.02	29.46	34.50	31.80	31.10
C-16	47.98	60.19	61.40	59.90	60.03
C-18			12.60	12.59	12.58
C-19			25.52	121.77	122.32
C-20	30.96	31.88	42.72	135.08	133.19
C-21	47.84	47.56	49.10	54.34	54.97
OCH_3		52.47	52.58	52.71	52.21
CO		171.64	171.81		170.13
			170.81		
NCH_3	43.49	43.21			
CH_3CO			21.01		

[a] Reference 7. These assignments were confirmed by heteronuclear correlated ^1H-^{13}C NMR spectrum.

Conclusion. Although the mercuric acetate cyclization of methyl α-4-piperidyl-1-indoleacetates has proved to be a method for the synthesis of vinoxine analogues having the C-16 methoxycarbonyl substituent present in the alkaloid, this synthetic approach has some important limitations: (a) low yield in the hydrogenation step when a substituent is present on the piperidine 3-position; (b) low yield, with abundant loss of material, in the cyclization step [Furthermore, although formation of unnatural regioisomers having the ethyl substituent at the methylene bridge was not detected, it cannot be definitively excluded]; (c) through this synthetic approach, the elaboration of the ethylidene substituent of vinoxine seems to be a difficult task; and (d) the relative configuration at C-16 resulting after cyclization is the opposite to that found in vinoxine.

Experimental Section

General Methods. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ at 60 MHz or, when indicated, at 200 MHz using Me_4Si as internal standard. ^{13}C NMR spectra were recorded at 50.3 MHz. The chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. For IR spectra only noteworthy absorptions (reciprocal centimeters) are listed. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder. TLC and column chromatography were carried out on SiO_2 (silica gel, Merck, 63–200 μm), and the spots were located with UV light or iodoplatinate reagent.

Methyl α-4-Pyridyl-1-indoleacetate (2). *n*-BuLi (2 N, 48 mL, 96.1 mmol) was added dropwise under N_2 to a cooled (−30 °C) solution of 1-(4-pyridylmethyl)indole (1)[9b] (10 g, 48 mmol) in anhydrous THF (250 mL). The resulting solution was allowed to rise to −10 °C, stirred for 45 min, saturated with a stream of CO_2, and then allowed to stand at room temperature for 1 h. The resulting suspension was diluted with H_2O (20 mL) and evaporated to give a semisolid residue which was dissolved in H_2O and extracted with Et_2O. Evaporation of the dried ethereal extract gave 3.3 g of the starting pyridylmethylindole 1. The aqueous phase was evaporated to dryness and the resulting solid was dried over P_2O_5, dissolved in methanolic HCl (1.2 N, 450 mL), and stirred at room temperature for 17 h. The solution was evaporated, and the resulting residue was dissolved in H_2O, basified with solid Na_2CO_3, and extracted with Et_2O to give the ester 2: 9.3 g (73%); IR ($CHCl_3$) 1745 (CO); NMR 3.75 (s, 3 H, OCH_3), 6.15 (s, 1 H, CH), 6.5 (d, J = 4 Hz, 1 H, indole H-3), 6.95–7.25 (m, 6 H, indole and H-β pyridine), 7.4–7.85 (m, 1 H, indole H-4), 8.5 (d, J = 6 Hz, 2 H, H-α pyridine).

Methyl α-(1-Methyl-1,4-dihydro-4-pyridylidene)-1-indoleacetate (3). A solution of CH_3I (8.6 mL, 0.15 mol) in anhydrous benzene (15 mL) was added dropwise to a solution of 2 (9.28 g, 34.8 mmol) in anhydrous acetone (80 mL). The mixture was stirred at room temperature for 10 h and evaporated to dryness. The residue was dissolved in H_2O, basified with solid Na_2CO_3, and extracted with Et_2O. The ethereal layers were extracted with 5% HCl, and the acidic aqueous phase was basified with solid Na_2CO_3 and extracted with Et_2O. The organic extracts were dried and evaporated to give 3: 6.5 g (66%); mp 168–169 °C (acetone–Et_2O); IR (KBr) 1620 (C=C), 1660 (CO); NMR 3.3 (s, 3 H, NCH_3), 3.45 (s, 3 H, OCH_3), 5.2 (dd, J = 2 and 8 Hz, 1 H, pyridine H-3), 6.35–6.55 (m, 2 H, indole H-3, pyridine H-2), 6.75–7.25 (m, 5 H, indole, pyridine H-5), 7.35–7.75 (m, 1 H, indole H-4), 8.1 (dd, J = 2 and 8 Hz, 1 H, pyridine H-6). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.81; H, 5.75; N, 10.00. Found: C, 72.58; H, 5.74; N, 9.85.

Methyl α-(1-Methyl-4-piperidyl)-1-indoleacetate (4). A solution of 3 (3.5 g, 12 mmol) in MeOH (200 mL) was hydrogenated over PtO_2 (175 mg) at atmospheric pressure. When the absorption ceased, the catalyst was filtered off and the solvent was evaporated to give piperidine 4: 3.4 g (95%); IR ($CHCl_3$) 1735 (CO); NMR 2.25 (s, 3 H, NCH_3), 3.55 (s, 3 H, OCH_3), 4.7 (d, J = 9 Hz, 1 H, CH), 6.45 (d, J = 4 Hz, 1 H, indole H-3), 6.95 (d, J = 4 Hz, 1 H, indole H-2), 7.05–7.75 (m, 4 H, indole). For the picrate: mp 186–187 °C (acetone–Et_2O). Anal. Calcd for $C_{23}H_{25}N_5O_9$: C, 53.59; H, 4.88; N, 13.58. Found: C, 53.52; H, 5.01; N, 13.17.

Oxidative Cyclization of Piperidine 4. A solution of the piperidine 4 (2.5 g, 8.74 mmol), $Hg(AcO)_2$ (13.9 g, 43 mmol), and EDTA·Na_2·$2H_2O$ (17.2 g, 46 mmol) in H_2O (300 mL) was stirred at 90–100 °C for 45 min. The mixture was cooled and poured into a solution of $NaBH_4$ (0.5 g) in MeOH (100 mL). The precipitate was filtered and washed with MeOH. The combined filtrate and washings were concentrated to 70 mL and extracted

with CH_2Cl_2. The extracts were dried and evaporated to give an oil (1.69 g) which was chromatographed. Elution with 99:1 $CHCl_3$–MeOH afforded piperidinone **6**: 0.3 g (11%); mp 198 °C (Et_2O–acetone); IR (KBr) 1740 (CO, ester), 1630 (CO, amide); NMR 2.85 (s, 3 H, NCH_3), 3.55 (s, 3 H, OCH_3), 4.7 (d, J = 9 Hz, 1 H, CH), 6.4 (d, J = 4 Hz, 1 H, indole H-3), 6.25–7.25 (m, 4 H, indole), 7.35–7.7 (m, 1 H, indole H-4). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.32. Found: C, 67.79; H, 6.74; N, 9.13. Elution with 98:2 $CHCl_3$–MeOH gave **methyl (1*RS*,2*SR*,6*SR*)-5-methyl-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1-carboxylate (5)**: 0.2 g (9%); IR ($CHCl_3$) 1745 (CO); NMR (200 MHz) 1.70–2.60 (complex signal, 7 H, aliphatic), 2.24 (s, 3 H, NCH_3), 3.66 (s, 3 H, OCH_3), 3.91(apparent t, J = 1 Hz, 1 H, H-3), 4.90 (d, J = 0.76 Hz, 1 H, H-16), 6.30 (s, 1 H, H-7), 7.00–7.20 (m, 3 H, indole), 7.56 (d, J = 7 Hz, 1 H, H-9). For the picrate: mp 201–202 °C (acetone–Et_2O). Anal. Calcd for $C_{23}H_{23}N_5O_9$: C, 53.80; H, 4.51; N, 13.64. Found: C, 54.02; H, 4.58; N, 13.39. On elution with 97:3 $CHCl_3$–MeOH, the starting piperidine **4** (0.35 g) was recovered.

3-Ethyl-4-pyridinemethanol (8). A solution of methyl 3-ethyl-4-pyridinecarboxylate[27] (**7**, 18 g, 0.11 mol) in anhydrous Et_2O (250 mL) was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (10.35 g, 0.27 mol) in anhydrous Et_2O (250 mL). The mixture was stirred at room temperature for 10 min, and then AcOEt (38 g, 0.43 mol) and H_2O (19.6 mL, 1.09 mol) were added dropwise (ice bath). The mixture was stirred for 15 min and filtered, and the aluminium salts were digested with boiling Et_2O (3 × 100 mL). The whole ethereal extracts were dried and evaporated to give an oil (15.7 g) which was chromatographed. Elution with 7:3 benzene–$CHCl_3$ gave alcohol **8**: 6.87 g (46%); mp 52–53.5 °C (Et_2O); IR ($CHCl_3$) 3500–3100 (OH); NMR 1.2 (t, J = 7 Hz, 3 H, CH_3), 2.55 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.7 (s, 2 H, CH_2OH), 5.6 (s, 1 H, OH), 7.35 (d, J = 5 Hz, 1 H, H-5), 8.15 (s, 1 H, H-2), 8.25 (d, J = 5 Hz, 1 H, H-6). Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.96; H, 8.16; N, 10.19.

1-(3-Ethyl-4-pyridylmethyl)indole (10). A solution of the alcohol **8** (13.75 g, 0.1 mol) in $SOCl_2$ (46 mL) was refluxed for 90 min. The resulting mixture was cooled and evaporated to give the highly hygroscopic hydrochloride **9**: 17 g (88%).

Indole (28.3 g, 0.24 mol) was added under N_2 to a solution of ground KOH (48 g, 0.85 mol) in anhydrous Me_2SO (250 mL). The resulting mixture was stirred at room temperature for 90 min and then the hydrochloride **9** (17 g, 88 mmol) was added portionwise. The suspension was stirred at room temperature for 4 h, poured into ice–H_2O, and extracted with Et_2O. The ethereal layers were extracted with 10% HCl, and the acidic aqueous phase was basified with concentrated NH_4OH and extracted with Et_2O. The organic extracts were dried and evaporated to give a solid (19.2 g) which was chromatographed. Elution with 6:4 benzene–$CHCl_3$ afforded (pyridylmethyl)indole **10**: 14.2 g (68%); mp 79.5–80.5 °C (hexane–Et_2O); NMR 1.2 (t, J = 7 Hz, 3 H, CH_3), 2.65 (q, J = 7 Hz, 2 H, CH_2CH_3), 5.15 (s, 2 H, $ArCH_2$), 6.25 (d, J = 5 Hz, 1 H, pyridine H-5), 6.45 (d, J = 4 Hz, 1 H, indole H-3), 6.8–7.2 (m, 4 H, indole), 7.4–7.7 (m, 1 H, indole H-4), 8.2 (d, J = 5 Hz, 1 H, pyridine H-6), 8.3 (s, 1 H, pyridine H-2). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.35; H, 6.86; N, 11.72.

Methyl α-(3-Ethyl-4-pyridyl)-1-indoleacetate (11). Operating as in the above deethyl series, from (pyridylmethyl)indole **10** (11.5 g, 48.6 mmol) the ester **11** was obtained: 9.35 g (65%); mp 127–128.5 °C (CH_2Cl_2–Et_2O); IR (KBr) 1750 (CO); NMR 1.1 (t, J = 7 Hz, 3 H, CH_3), 2.5 (q, J = 7 Hz, 2 H, CH_2), 3.7 (s, 3 H, OCH_3), 6.2 (s, 1 H, CH), 6.4 (d, J = 4 Hz, 1 H, indole H-3), 6.7 (d, J = 4 Hz, 1 H, indole H-2), 6.9–7.2 (m, 4 H, indole and pyridine H-5), 7.3–7.6 (m, 1 H, indole H-4), 8.3 (d, J = 5 Hz, 1 H, pyridine H-6), 8.35 (s, 1 H, pyridine H-2). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.51. Found: C, 73.14; H, 6.13; N, 9.52.

Methyl (*Z*)-α-(3-Ethyl-1-methyl-1,4-dihydro-4-pyridylidene)-1-indoleacetate (12a). Operating as in the above deethyl series, from ester **11** (0.3 g, 1.02 mmol) and CH_3I (0.25 mL, 4.4 mmol) **12a** was obtained: 0.15 g (42%); mp 162–163 °C (Et_2O–acetone); IR (KBr) 1620 (C=C), 1660 (CO); NMR 0.7 (t, J = 7 Hz, 3 H, CH_3), 1.25 (q, J = 7 Hz, 2 H, CH_2) 3.3 (s, 3 H, NCH_3), 3.4 (s, 3 H, OCH_3), 6.3–6.6 (m, 2 H, pyridine H-2, indole H-3), 6.75 (dd, J = 1 and 8 Hz, 1 H, pyridine H-5), 6.9–7.2 (m, 4 H, indole), 7.3–7.7 (m, 1 H, indole H-4), 8.3 (d, J = 8 Hz, 1 H, pyridine H-6). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.53; N, 9.08. Found: C, 74.05; H, 6.54; N, 9.06.

Methyl (*Z*)-α-[1-(2-Acetoxyethyl)-3-ethyl-1,4-dihydro-4-pyridylidene]-1-indoleacetate (12b). A mixture of **11** (3 g, 10.2 mmol) and 2-bromoethyl acetate (10 mL, 15.14 g, 90 mmol) was heated at 90–100 °C for 5 h. The reaction mixture was poured into saturated Na_2CO_3 solution and extracted with Et_2O. The ethereal layers were extracted with 10% HCl, and the acidic aqueous phase was basified with solid Na_2CO_3 and extracted with Et_2O. The organic extracts were dried and evaporated to give **12b**: 2.2 g (57%); mp 132–133 °C (Et_2O–acetone); IR (KBr) 1620 (C=C), 1660 (conjugated CO), 1735 (CO); NMR 0.65 (t, J = 7 Hz, 3 H, CH_3), 1.2 (q, J = 7 Hz, 2 H, CH_2CH_3), 2.1 (s, 3 H, CH_3CO), 3.4 (s, 3 H, OCH_3), 3.75 (t, J = 6 Hz, 2 H, CH_2N), 4.2 (t, J = 6 Hz, 2 H, CH_2O), 6.3–6.6 (m, 2 H, pyridine H-2 and indole H-3), 6.75 (dd, J = 1 and 8 Hz, 1 H, pyridine H-5), 6.9–7.2 (m, 4 H, indole), 7.6–7.7 (m, 1 H, indole H-4), 8.3 (d, J = 8 Hz, 1 H, pyridyne H-6). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.35; N, 7.36. Found: C, 69.54; H, 6.47; N, 7.47.

Catalytic Hydrogenation of 12b. Method A. A mixture of **12b** (2.8 g, 7.5 mmol) in AcOEt (60 mL) and PtO_2 (142 mg) was shaken at room temperature under H_2 at atmospheric pressure. When the absorption ceased, the catalyst was filtered off, and the filtrate was evaporated to give an oil which was chromatographed: (i) Elution with 9:1 C_6H_6–$CHCl_3$ gave **methyl 1-indoleacetate (17)**: 0.43 g (30%); IR (NaCl) 1730 (CO); NMR 3.6 (s, 3 H, OCH_3), 4.65 (s, 2 H, CH_2), 6.4 (d, J = 4 Hz, 1 H, indole H-3), 6.9 (d, J = 4 Hz, 1 H, indole H-2), 7.0–7.3 (m, 3 H, indole), 7.3–7.7 (m, 1 H, indole H-4). (ii) Elution with 7:3 C_6H_6–$CHCl_3$ gave **methyl (α*RS*,3*SR*,4*SR*)-α-[1-(2-acetoxyethyl)-3-ethyl-4-piperidyl]-1-indoleacetate (13a)**: 0.34 g (12%); IR (NaCl) 1730 (CO); NMR (200 MHz) 0.80 (br d, J = 14 Hz, 1 H, H-5eq), 0.96 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.32 (qd, J = 4, 12, 12, and 14 Hz, 1 H, H-5ax), 1.58 (m, 2 H, CH_2CH_3), 1.90 (td, J = 3, 12, and 12 Hz, 1 H, H-6ax), 2.02 (s, 3 H, CH_3CO), 2.08 (br d, J = 14 Hz, 1 H, H-2ax), 2.42 (td, J = 4, 12, and 12 Hz, 1 H, H-4ax), 2.54 (m, 2 H, CH_2N), 2.72 (br d, J = 12 Hz, 1 H, H-6eq), 3.00 (br d, J = 14 Hz, 1 H, H-2 eq), 3.70 (s, 3 H, OCH_3), 4.12 (t, J = 5 Hz, 2 H, CH_2O), 4.92 (d, J = 12 Hz, 1 H, CH), 6.58 (d, J = 4 Hz, 1 H, indole H-3), 7.04–7.44 (m, 4 H, indole), 7.60 (d, J = 5 Hz, 1 H, indole H-4). For the oxalate: mp 170–171 °C (absolute ethanol). Anal. Calcd for $C_{24}H_{32}N_2O_8$: C, 60.50; H, 6.76; N, 5.80. Found: C, 60.57; H, 6.77; N, 5.80. (iii) Finally, elution with 3:7 C_6H_6–$CHCl_3$ afforded **methyl α-[1-(2-acetoxyethyl)-3-ethyl-1,2,5,6-tetrahydro-4-pyridyl]-1-indoleacetate (14)**: 0.56 g (19%); IR (NaCl) 1730 (CO); NMR 0.85 (t, J = 7 Hz, 3 H, CH_2CH_3), 2.0 (s, 3 H, CH_3CO), 2.5 (t, J = 6 Hz, 2 H, CH_2N), 3.6 (s, 3 H, OCH_3), 4.0 (t, J = 6 Hz, 2 H, CH_2O), 5.8 (s, 1 H, CH), 6.35 (d, J = 4 Hz, 1 H, indole H-3), 6.8–7.2 (m, 4 H, indole), 7.3–7.6 (m, 1 H, indole H-4). For the oxalate: mp 103–104 °C (absolute ethanol). Anal. Calcd for $C_{24}H_{30}N_2O_8$: C, 60.73; H, 6.37; N, 5.98. Found: C, 60.49; H, 6.45; N, 5.80.

Method B. A solution of **12b** (3.3 g, 8.6 mmol) in AcOH (60 mL) was hydrogenated at room temperature and atmospheric pressure over PtO_2 (165 mg). When the absorption ceased, the catalyst was filtered off and the solution was diluted with H_2O, basified with solid Na_2CO_3, and extracted with Et_2O. Evaporation of the dried extracts gave an oil (3 g) which was chromatographed: (i) On elution with 7:3 C_6H_6–$CHCl_3$, the piperidine **13a** (0.53 g, 16%) was obtained. (ii) On elution with 4:6 C_6H_6–$CHCl_3$ **methyl (α*SR*,3*SR*,4*SR*)-α-[1-(2-acetoxyethyl)-3-ethyl-4-piperidyl]-1-indoleacetate (13b)** was obtained: 0.2 g (6.3%); NMR (200 MHz) 0.50 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.10 (m, 1 H, CH_2CH_3), 1.48 (br d, J = 14 Hz, 1 H, H-5eq), 1.70 (m, 3 H, H-3eq, H-5ax, and CH_2CH_3), 2.01 (masked, 1 H, H-2ax), 2.04 (s, 3 H, CH_3CO), 2.10 (br t, J = 13 Hz, 1 H, H-6ax), 2.54 (m, 3 H, CH_2N and H-4ax), 2.88 (br d, J = 14 Hz, 1 H, H-2eq), 3.00 (m, 1 H, H-6eq), 3.66 (s, 3 H, OCH_3), 4.14 (m, 2 H, CH_2O), 4.90 (d, J = 12 Hz, 1 H, CH), 6.56 (d, J = 4 Hz, 1 H, indole H-3), 7.02–7.42 (m, 4 H, indole), 7.60 (d, J = 6 Hz, 1 H, indole H-4). (iii) Finally, on elution with 3:7 C_6H_6–$CHCl_3$, the tetrahydropyridine **14** was isolated: 0.65 g (20%).

Oxidative Cyclization of Piperidine 13a. The piperidine **13a** (0.82 g, 2.12 mmol) was allowed to react, as in the above deethyl series, with $Hg(AcO)_2$ (1.62 g, 5 mmol) and EDTA·

$Na_2 \cdot 2H_2O$ (1.94 g, 5.2 mmol). After the usual workup, an oil was obtained (0.64 g), which was chromatographed. Elution with 7:3 C_6H_6–$CHCl_3$ gave **19,20-dihydro-16-epivinoxine acetate (15)**: 50 mg (6%); IR ($CHCl_3$) 1730 (CO); NMR 1.0 (t, J = 7 Hz, 3 H, H-18), 2.0 (s, 3 H, CH_3CO), 3.6 (s, 3 H, OCH_3), 3.9 (apparent t, 1 H, H-3), 4.1 (t, J = 6 Hz, 2 H, H-6), 4.8 (s, 1 H, H-16), 6.1 (s, 1 H, H-7), 6.9–7.2 (m, 3 H, indole), 7.3–7.7 (m, 1 H, H-9). For the oxalate: mp 142–143 °C (acetone). Anal. Calcd for $C_{24}H_{30}N_2O_8$: C, 60.73; H, 6.37; N, 5.98. Found: C, 60.56; H, 6.39; N, 5.76. Elution with 1:9 C_6H_6–$CHCl_3$ afforded **19,20-dihydro-16-epivinoxine (16)**: 40 mg (5%); IR ($CHCl_3$) 1730 (CO), 3200–3600 (OH); NMR 1.0 (t, J = 7 Hz, 3 H, H-18), 3.6 (t, J = 6 Hz, 2 H, H-6), 3.6 (s, 3 H, OCH_3), 3.9 (apparent t, 1 H, H-3), 4.8 (s, 1 H, H-16), 6.15 (s, 1 H, H-7), 6.9–7.2 (m, 3 H, indole), 7.3–7.7 (m, 1 H, H-9). For the oxalate: mp 162–163 °C (acetone–C_6H_6). Anal. Calcd for $C_{22}H_{22}N_2O_7 \cdot {}^1/_4C_6H_6$: C, 62.40; H, 6.58; N, 6.19. Found: C, 62.12; H, 6.94; N, 5.86.

19,20-Dihydro-16-epivinoxine (16). A solution of the acetate **15** (50 mg, 0.13 mmol) in methanolic hydrogen chloride (2.5 N, 5 mL) was stirred at room temperature for 5 h. The solvent was evaporated and the resulting oily residue was dissolved in water, basified with Na_2CO_3 solution, and extracted with Et_2O. Evaporation of the dried extracts gave **16**: 40 mg (90%).

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A Short, Flexible Route to Symmetrically and Unsymmetrically Substituted Diphoshatidylglycerols (Cardiolipins)

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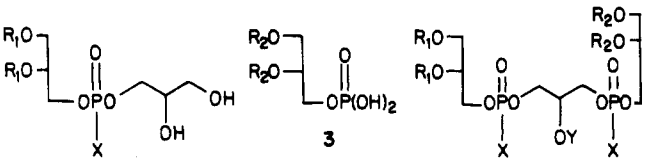
Phosphatidylglycerol methyl esters **2a,b** undergo selective phosphorylation on the primary alcohol with phosphatidic acid **3a** to give, after methylation of the crude product for purposes of purification and then didemethylation, symmetrically substituted DPG **5a** and unsymmetrically substituted DPG **5b**, respectively, in moderate overall yield.

The ready availability of chemically well-defined complex lipids is important to many areas of biochemical and biomedical research. The diphoshatidylglycerols (DPGs, also called cardiolipins) constitute a class of complex phospholipids occurring mainly in the heart and skeletal muscles, usually associated with membranes of subcellular fractions showing high metabolic activity, for example, the mitochondria.[1,2] The several synthetic approaches described to date[1,3,4] have led to symmetrically substituted DPGs. We report herein a versatile synthetic approach that leads to either symmetrically or unsymmetrically substituted, chemically well-defined DPGs. This approach allows for the preparation of DPGs that bear, for example, a biophysical probe (nitroxide spin-label, fluorescent label, etc.) in one of the four chains. Only one such labeled DPG, a nitroxide spin-labeled derivative, has been described to date.[5] This was derived in low overall yield from natural cardiolipin (a mixture) by a somewhat difficult to control hydrolysis with a phospholipase A_2 followed by reesterification with a nitroxide spin-labeled fatty acid.

Our approach involves the coupling of a phosphatidylglycerol (PG) methyl ester with a phosphatidic acid (PA) as the key step. Several synthetic routes to chemically well-defined PGs and PAs have been described.[4] That many naturally derived as well as synthetic PGs and PAs are also available commercially enhances their value as starting materials for DPG synthesis.

In the event, L-α-phosphatidyl-DL-glycerol (dipalmitoyl) **1a** (NH_4^+ salt) was converted into methyl ester **2a** by acidification followed by treatment with diazomethane.



1, X = $O^-NH_4^+$
2, X = OCH_3

4, X = OCH_3, Y = H
5, X = O^-Na^+, Y = H
6, X = OCH_3, Y = Ac

a, R_1 = R_2 = palmitoyl
b, R_1 = oleoyl, R_2 = palmitoyl
c, R_1R_2 = mixture of long chain saturated and unsaturated acyl groups

Ester **2a** underwent a selective TPS-promoted phosphorylation[6] on the primary alcohol group with L-α-phosphatidic acid (dipalmitoyl) **3a**. To facilitate purification, the crude monomethyl ester product was methylated with diazomethane to give dimethyl ester **4a**. Ester **4a** underwent selective didemethylation with NaI in hot 2-butanone,[7] giving the symmetrically substituted DPG **5a**.

In order to confirm the position of phosphorylation of **2a** natural cardiolipin (**5c**) was converted into dimethyl ester **4c**,[8] a portion of which was acetylated to give **6c**.

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