dissolved in cold water (10 mL). The solution was acidified with 10% HCl and the water was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **4a**, which was identical with the authentic sample prepared above, 0.21 g (63%).

Elution of the second fraction gave 3-(*N*-ethylcarbamoyl)-1-methylpyridin-6-one (**6b**), which was recrystallized from ethyl acetate: 0.034 g (9%); mp 159 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.11 (3 H, t, J = 7 Hz), 3.49 (2 H, dq, J = 7, 2 Hz), 6.40 (1 H, d, J = 9.5 Hz), 7.87 (1 H, dd, J = 9.5, 3 Hz), 8.15 (1 H, br), 8.33 (1 H, d, J = 3 Hz); IR ν_{max} 3310 cm^{-1}; UV λ_{max} 296 (ϵ 5400), 229 nm (15 100), λ_{max} (0.1 N HCl) 296 (ϵ 5400), 229 nm (14 800), λ_{max} (0.1 N NaOH) 296 (ϵ 5500), 230 nm (15 700); mass spectrum, m/e 180 (M^+). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.99; H, 6.80; N, 15.61.

Elution of the third fraction gave **5b**, which was identical with the product prepared above, 0.053 g (16%).

Reaction of 3c with Sodium Ethoxide. A mixture of **3c** (0.446 g, 0.002 mol) in ethanolic sodium ethoxide [prepared from Na (0.092 g) in dry ethanol (55 mL)] was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The water was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **4b**, which was identical with the product prepared above, 0.240 g (66%).

Elution of the second fraction gave 2-methyl-3-(*N*-methylcarbamoyl)pyridin-6-one (**5c**): 0.063 g (19%); mp 255 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.37 (3 H, s), 2.71 (3 H, d, J = 4.5 Hz), 6.19 (1 H, d, J = 9.5 Hz), 7.56 (1 H, d, J = 9.5 Hz), 8.03 (1 H, br), 11.78 (1 H, br); IR ν_{max} 3400, 3300 cm^{-1}; UV λ_{max} 300 (ϵ 7100), 246 nm (10 700), λ_{max} (0.1 N HCl) 297 (ϵ 6700), 246 nm (9800), λ_{max} (0.1 N NaOH) 288 (ϵ 7700), 258 nm; mass spectrum, m/e 166 (M^+). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.92; H, 6.12; N, 16.90.

Acknowledgment. We thank Dr. M. Yogo, Faculty of Pharmacy, Meijo University, for ^{13}C NMR.

Registry No. **1a**, 4869-46-9; **1b**, 80981-21-1; **1c**, 23941-84-6; **2a**, 95387-35-2; **2b**, 95387-36-3; **2c**, 95387-37-4; **3a**, 95387-38-5; **3b**, 95387-39-6; **3c**, 95387-40-9; **4a**, 18617-50-0; **4b**, 3424-43-9; **5a**, 1007-18-7; **5b**, 95387-41-0; **5c**, 95387-42-1; **6a**, 62415-66-1; **6b**, 62415-68-3; $NH_2C(O)CH{=}PPh_3$, 38821-11-3; uracil, 66-22-8; 1-methyluracil, 615-77-0; 1,3-dimethyluracil, 874-14-6; 3-ethyl-1-methyluracil, 59495-24-8; 6-hydroxynicotinic acid, 5006-66-6.

Synthetic Applications of 2-Cyano-1,2,3,6-tetrahydropyridines. 2.[1] Synthesis of Isodasycarpidone and Related Systems, the Ervitsine Skeleton, and Its Benzo Analogue[2]

Joan Bosch,* Mario Rubiralta, Antonio Domingo, Jordi Bolôs, Ana Linares, Cristina Minguillôn, Mercedes Amat, and Josep Bonjoch

Department of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

Received July 12, 1984

The synthesis of isodasycarpidone (**8a**), *N*-demethylisodasycarpidone (**9a**), and their epi derivatives **8b** and **9b** is described. The condensation of an appropriate 2-cyano-1,2,3,6-tetrahydropyridine with indole and the conjugate addition of diethylcopper(I)–magnesium bromide to the resulting α,β-unsaturated esters constitute the key steps of this synthesis. A similar condensation from methyl 2-cyano-1-methyl-1,2,3,6-tetrahydropyridine-4-acetate (**11**) and indolylmagnesium iodide or (*m*-methoxyphenyl)magnesium bromide, followed by catalytic hydrogenation, hydrolysis, and PPA cyclization establishes synthetic routes to the tetracyclic framework (**16**) of the indole alkaloid ervitsine and its benzo analogue **19**.

2-Cyano-1,2,3,6-tetrahydropyridines are useful synthetic intermediates since they have proven to be synthons for 2,5-dihydropyridinium salts.[3] These compounds are easily accesible from the corresponding pyridinium salts by reductive cyanation by means of sodium borohydride in the presence of a large excess of cyanide ions.[4] They are able to react with Grignard reagents to give 2-substituted-1,2,3,6-tetrahydropyridines[5,6] or with activated aromatic rings such as indole itself[1] as Grignard reagent[1,6] or as alkali metal salt,[7] to give 3-(tetrahydro-2-pyridyl)indole systems. In this way, 2-cyano-1,2,3,6-tetrahydropyridines bearing a functionalized carbon substituent at the C-4 position have been elaborated to deethyldasycarpidone.[1] On the other hand, 2-cyano-1,2,3,6-tetrahydropyridines having an indol-3-ylethyl substituent at the nitrogen atom can be cyclized to the indolo[2,3-*a*]quinolizine skeleton,[8] whereas catalytic hydrogenation of the carbon–carbon double bond of 4-(indolylmethyl)-2-cyano-1,2,3,6-tetrahydropyridines followed by acid cyclization led to bridged polycyclic systems related to indole alkaloids.[9]

In this paper we wish to further illustrate some synthetic applications of 2-cyano-1,2,3,6-tetrahydropyridines: (a) The α,β-unsaturated ester moiety of methyl 2-(3-indolyl)tetrahydropyridine-4-carboxylates **3** and **4**, prepared from appropriate 2-cyano-1,2,3,6-tetrahydropyridines, allows the introduction of an ethyl substituent by means of conjugate addition of diethylcopper(I)–magnesium bromide. By this route we report efficient syntheses of isodasycarpidone (**8a**), *N*-demethylisodasycarpidone (**9a**), and their epiderivatives **8b** and **9b**, respectively. (b) We also describe the preparation of a 2-cyano-1,2,3,6-tetrahydropyridine (**11**), having a C-4 (alkoxycarbonyl)methyl substituent, and its condensation

(1) For the previous paper in this series, see: Feliz, M.; Bosch, J.; Mauleôn, D.; Amat, M.; Domingo, A. *J. Org. Chem.* **1982**, *47*, 2435.

(2) Presented in part at the 19th Reuniôn Bienal de la Real Sociedad Española de Quimica, Santander, Spain, 1982, and at the 3rd European Symposium on Organic Chemistry, Canterbury, England, 1983.

(3) For the synthesis and synthetic applications of 2-cyano-1,2,5,6-tetrahydropyridines, see: Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683 and references cited therein.

(4) (a) Fry, E. M. *J. Org. Chem.* **1963**, *28*, 1869. (b) Fry, E. M. *J. Org. Chem.* **1964**, *29*, 1647.

(5) Parfitt, R. T.; Walters, S. M. *J. Med. Chem.* **1971**, *14*, 565.

(6) Bosch, J.; Alvarez, M.; Llobera, R.; Feliz, M. *An. Quim.* **1979**, *75*, 712.

(7) Bosch, J.; Feliz, M. *An. Quim.* **1982**, *78C*, 240.

(8) (a) Beisler, J. A. *Tetrahedron* **1970**, *26*, 1961. (b) Fry, E. M.; Beisler, J. A. *J. Org. Chem.* **1970**, *35*, 2809. (c) Aschroft, W. R.; Joule, J. A. *Tetrahedron Lett.* **1980**, *21*, 2341.

(9) Bosch, J.; Feliz, M.; Bennasar, M.-L. *Tetrahedron* **1984**, *40*, 1419.

0022-3263/85/1950-1516$01.50/0

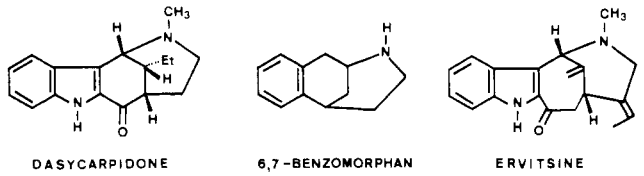


Figure 1.

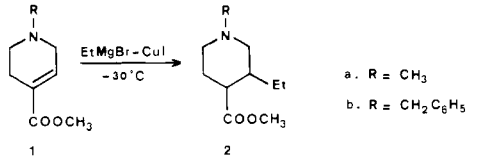


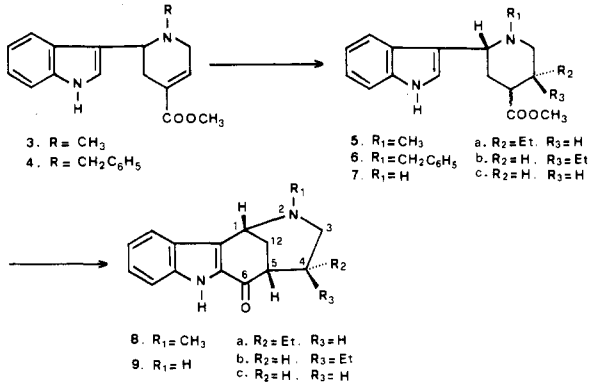
Figure 2.

with the indole Grignard reagent to give a 3-(tetrahydro-2-pyridyl)indole system **14** which has been further elaborated to the tetracyclic framework (**16**) of the indole alkaloid ervitsine. (c) A similar condensation with Grignard reagents of benzene derivatives constitutes a key step in the synthesis of the hexahydro-1,5-methano-2-benzazonine system, a new class of B-homobenzomorphans,[10] which are potential analgesics related to 6,7-benzomorphans.[11]

Results and Discussion

Synthesis of Isodasycarpidone, *N*-Demethylisodasycarpidone, and Their Epi Derivatives.[12] In a previous paper[1] we described the preparation of 3-(tetrahydro-2-pyridyl)indoles **3** and **4** by condensation of an appropriate 2-cyano-1,2,3,6-tetrahydropyridine with indole. The introduction of an ethyl substituent on the α,β-unsaturated ester moiety of these tetrahydropyridines followed by cyclization upon the indole 2-position would constitute a new synthesis[13] of isodasycarpidone (**8a**) and the first of its *N*-demethyl analogues **9a** and **9b**. These compounds possess the tetracyclic ring system of the *Strychnos* indole alkaloids uleine and dasycarpidone.[14,15] On the other hand, *N*-demethylisodasycarpidone (**9a**) can be considered as a synthetic precursor of pentacyclic *Strychnos* indole alkaloids exemplified by tubifoline. Thus, integration of two appropriately functionalized carbon atoms on the piperidine nitrogen atom followed by cyclization upon the indole 3-position could constitute a new synthetic entry[16] to these alkaloids, similar to that developed for the synthesis of pentacyclic alkaloids in the *Aspidosperma* series.[17]

Scheme I



Although the conjugate addition of organocopper reagents to α,β-unsaturated ketones is a well-established reaction,[18] the conjugate addition to α,β-unsaturated esters has received comparatively few synthetic applications.[19] For this reason, to test the efficiency of the conjugate addition of diethylcopper(I)–magnesium bromide for the introduction of the ethyl side chain we initially tried the reaction with the model tetrahydropyridines **1a** and **1b**, which were easily prepared by sodium borohydride reduction of the corresponding pyridinium salts. When a 4:2:1 molar ratio of ethylmagnesium bromide, cuprous iodide, and tetrahydropyridine was used, the reaction was highly regioselective. In each case, 3-ethylpiperidines **2** (**a** and **b**) were obtained in good yield as a diastereomeric mixture.[20]

In an identical manner, the conjugate addition to the unsaturated ester **3** afforded in excellent yield a nearly equimolecular mixture of diastereomers, **5a** and **5b**, which without separation were saponified and cyclized with PPA to the so-called isodasycarpidone (**8a**) and epiisodasycarpidone (**8b**). These tetracyclic bases were separated by column chromatography (17% and 18% yield, respectively) and showed melting points coincident with those

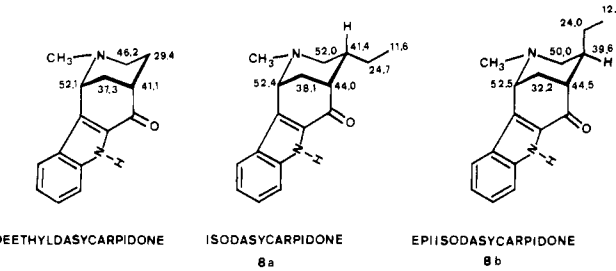


Figure 3. ^{13}C NMR data.

(10) The synthesis of B-homobenzomorphans having other skeletal types has been described: (a) 2,3,4,5,6,7-Hexahydro-1,5-methano-1*H*-4-benzazonine: Smith, F. J.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2141. (b) 2,3,4,5,6,7-Hexahydro-2,6-methano-1*H*-3-benzazonine: Proctor, G. R.; Smith, F. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1754.

(11) Palmer, D. C.; Strauss, M. *J. Chem. Rev.* **1977**, *77*, 1.

(12) (a) For clarity the IUPAC numbering system instead of the biogenetic one[12b] is used for the tetracyclic compounds **8**, **9**, and **16**. (b) Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(13) Kametani, T.; Suzuki, T. *J. Org. Chem.* **1971**, *36*, 1291.

(14) Joule, J. A.; Ohashi, M.; Gilbert, B.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1717.

(15) For the synthesis of these alkaloids and their epi derivatives, see: (a) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, 2738. (b) Dolby, L. J.; Biere, H. *J. Org. Chem.* **1970**, *35*, 3843. (c) Kametani, T.; Suzuki, T. *Chem. Pharm. Bull.* **1971**, *19*, 1424. (d) Büchi, G.; Gould, S. J.; Näf, F. *J. Am. Chem. Soc.* **1971** *93*, 2492. (e) Natsume, M.; Kitagawa, Y. *Tetrahedron Lett.* **1980**, *21*, 839. (f) Harris, M.; Besselièvre, R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1981**, *22*, 331. (g) See also ref 3 and 13.

(16) For the synthesis of pentacyclic *Strychnos* indole alkaloids, see: (a) Van Tamelen, E. E.; Dolby, L. J.; Lawton, R. G. *Tetrahedron Lett.* **1960**, 30. (b) Harley-Mason, J. *Pure Appl. Chem.* **1975**, *41*, 167. (c) Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057. (d) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. (e) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881. (f) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657.

(17) (a) Ziegler, F. E.; Spitzen, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (b) Husson, H.-P.; Thal, C.; Potier, P.; Wenkert, E. *J. Chem. Soc., Chem. Commun.* **1970**, 480. (c) Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, *17*, 111. (d) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 1140. (e) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. (f) Magnus, P.; Pappalardo, P. *J. Am. Chem. Soc.* **1983**, *105*, 6525. (g) Utsunomiya, I.; Natsume, M. *Heterocycles* **1984**, *21*, 726.

(18) (a) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1. (b) Erdik, E. *Tetrahedron* **1984**, *40*, 641.

(19) (a) Liu, S.-H. *J. Org. Chem.* **1977**, *42*, 3209. (b) Costerousse, G.; Buendia, J.; Toromanoff, E.; Martel, J. *Bull. Soc. Chim. Fr.* **1978**, 355. (c) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

(20) When a catalytic amount (3% molar with respect to **1b**) of cuprous iodide was used, 1-(1-benzyl-3-ethyl-4-piperidyl)-1-propanone was isolated in 60% yield. Its formation can be accounted for by considering an initial 1,2-addition followed by an 1,4-addition to the resulting α,β-unsaturated ketone. This ketone was also formed as the main product in the absence of cuprous iodide.

previously described.[13] The stereochemical assignments are in good agreement with the shielding of C-12 (δ32.2) in the ^{13}C NMR spectrum of **8b**, as compared with **8a** (δ38.1), by a γ effect[21] induced by the axial ethyl group. Furthermore, the chemical shift of the methyl component of the ethyl group reflects the relative configuration at C-4.[22] Due to its simplicity and the few synthetic steps this synthesis of isodasycarpidone improves that previously reported.[13]

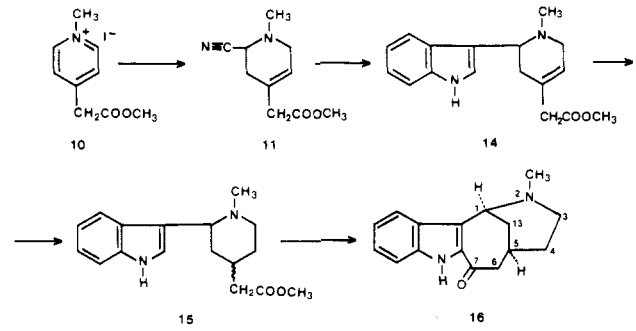
The introduction of the ethyl side chain into **4** was achieved in 85% yield to give a complex mixture of diastereomers, which were partially separated by column chromatography into **6a** and **6b**. The stereochemical assignment was effected when these amino esters were independently converted (~30% overall yield), by catalytic debenzylation followed by saponification and cyclization, into the tetracyclic derivatives **9a** and **9b**, respectively. The relative configuration at C-4 in **9** was inferred from the chemical shift of the methylene protons of the ethyl side chain in the NMR spectrum (60 MHz). In **9b**, a compound having an axial ethyl group, the signal corresponding to these protons appear at a field (δ >1.4) lower than in the isomer **9a** (δ <1.4) due to the anisotropic effect of the piperidine nitrogen lone pair. In the later isomer, the small chemical shift difference between methylene and methyl protons accounts for the observed multiplicity of the signal due to the methyl group, which appears as an apparent broad singlet instead of as a clear triplet as in **9b**.[23] The same effect was observed when the 60-MHz NMR spectra of iso- and epiisodasycarpidone (**8a** and **8b**, respectively) were compared.

The moderate yields of the above cyclizations raises a question regarding whether the 2,4-trans-substituted piperidines *trans*-**5a,b**, *trans*-**7a**, and *trans*-**7b** undergo isomerization to the most stable cis diastereomers[24] under the alkaline conditions of the saponification step or under the acid conditions of the cyclization reaction. Obviously, only the diastereomers of **5a,b**, **7a**, and **7b**, in which the substituents at C-2 and C-4 are cis can undergo cyclization to give **8a,b**, **9a**, and **9b**, respectively.

In order to address the above question, inasmuch as it was not possible to separate the C-2/C-4 cis–trans diastereomeric mixtures of the piperidines **5a,b**, **7a**, and **7b** (see Experimental Section) we turned over attention to the more simplified, closely related 2,4-disubstituted piperidine model **7c**. In this case, the cis and trans diastereomers had been previously separated and characterized,[1] although cyclization to the corresponding tetracyclic ketone **9c** had been effected in 25% yield from an approximately 5:1 mixture of cis–trans esters **7c**.

When pure *cis*-**7c** was subjected to alkaline hydrolysis and then to PPA cyclization, ketone **9c** was isolated in 38% yield. Similar treatment of pure *trans*-**7c** afforded **9c** in 37% yield.[25]

Scheme II



This result clearly indicated that epimerization at the C-4 piperidine position in the trans isomer had been produced. The same should be true for 2,4-trans-substituted piperidines *trans*-**5a,b**, *trans*-**7a**, and *trans*-**7b** in their cyclizations to **8a,b**, **9a**, and **9b**, respectivley.

In order to investigate if this epimerization had occurred during the alkaline hydrolysis[26] of the ester group of *trans*-**7c** or during the acid cyclization step, the piperidinecarboxylic acids resulting from saponification of esters *cis*-**7c** and *trans*-**7c** were independently reesterified with excess diazomethane in ether–methanol. In both cases an approximately 6:1 identical mixture of esters *cis*-**7c** and *trans*-**7c** was obtained, thus pointing out that epimerization of *trans*-**7c** takes places during the alkaline hydrolysis of the ester group. As byproducts (15% yield), a similar ratio of the *N*-methyl derivatives *cis*- and *trans*-**5c** were also obtained.[27,28]

Synthesis of the Fundamental Tetracyclic Skeleton of Ervitsine[12] and Its Benzo Analogue. Ervitsine is a minor alkaloid isolated[29] in 1977 from *Pandaca boiteaui*, lacking the characteristic tryptamine unit present in the greater part of indole alkaloids. No synthesis for ervitsine has been described yet.[30] Since a 3-(2-piperidyl)indole moiety can be visualized in the tetracyclic structure of ervitsine, it seemed interesting to apply our methodology based on the reactivity of 2-cyano-1,2,3,6-tetrahydropyridines to elaborate the fundamental skeleton (**16**) of this alkaloid.

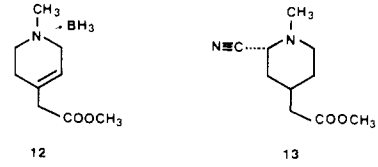


Figure 4.

(21) (a) A similar γ-effect was observed in the tandem ibogaine/epiibogamine[21b] and dregamine/tabernaenontanine.[21c] (b) Wenkert, E.; Cochran, D. W.; Hagaman, E. W.; Filho, R. B.; Matos, F. J.; Madruga, M. I. *Helv. Chim. Acta* **1976**, *59*, 2437. (c) Ahond, A.; Bui, A.-M.; Potier, P.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1976**, *41*, 1878.

(22) (a) The ca. 1-ppm difference of C-18 chemical shifts has been shown earlier to be diagnostic of the C-20 stereochemistry in corynantheoid alkaloids,[22b] ochrolifuanines,[22c] and vobasine-like indole alkaloids.[21c] (b) Wenkert, E.; Bindra, J. S.; Chang, C.-J.; Cochran, D. W.; Schell, F. M. *Acc. Chem. Res.* **1974**, *7*, 46. (c) Koch, M. C.; Plat, M. M.; Préaux, N.; Gottlieb, H. E.; Hagaman, E. W.; Schell, F. M.; Wenkert, E. *J. Org. Chem.* **1975**, *40*, 2836.

(23) The same effect has been observed in corynantheidine-type alkaloids: Lee, C. M.; Trager, W. F.; Beckett, A. H. *Tetrahedron* **1967**, *23*, 375.

(24) We acknowledge the suggestion of one reviewer concerning this question.

(25) These yields refer to product purified by column chromatography. The higher yields obtained in these experiments compared with that previously reported[1] can be attributed to two factors: (i) cyclizations were carried out with chromatographically pure esters **7c**, and (ii) a nitrogen stream was passed through the reaction mixture during the PPA treatment in order to sweep the hydrogen chloride generated from potassium chloride that impurified the crude amino acid.

(26) See, for example: Janot, M.-M.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1949**, 509.

(27) Identified by comparison (NMR, TLC) with samples prepared unambiguously.[1]

(28) The methylation of secondary amines with diazomethane in the presence of a Lewis acid is a known process: Müller, E.; Huber-Emden, H.; Rundel, W. *Liebigs Ann. Chem.* **1959**, *623*, 34. In our case, the piperidine nitrogen would compite with the carboxylate ion toward methylation.

(29) Andriantsiferana, M.; Besselièvre, R.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1977**, 2587.

(30) (a) Harris, M.; Grierson, D. S.; Riche, C.: Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 1957. (b) See also ref 3. (c) The preparation of methyl 2-(3-indolyl)-1-methyl-5-methylenepiperidine-4-acetate as potential intermediate of an ervitsine analogue has been reported: Suzuki, T.; Sato, E.; Goto, K.; Unno, K.; Kametani, T. *Heterocycles* **1980**, *14*, 433.

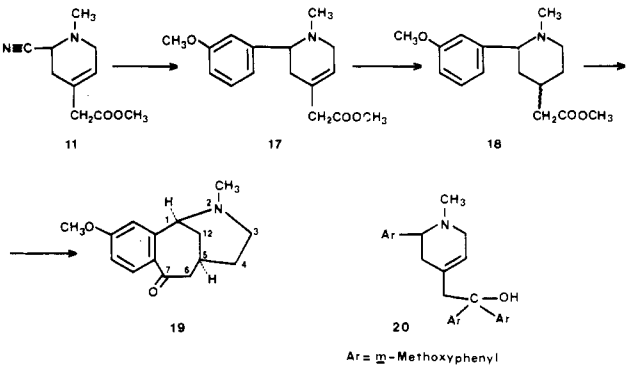
2-Cyanotetrahydropyridine 11, having a C-4 (methoxycarbonyl)methyl substituent suitable for constructing the 7-membered C ring of 16, was chosen as the starting material. This cyanotetrahydropyridine was prepared in 60% yield by quaternization of methyl 4-pyridineacetate followed by reductive cyanation.[4] The IR spectrum of 11 shows absorptions at 2210 and 1725 cm^{-1} for the cyano and ester carbonyl groups, respectively, whereas the most characteristic signals in the NMR spectrum were two singlets at δ 3.55 and 2.30 due to *O*- and *N*-methyl groups, respectively, a doublet of doublets at δ 3.75 corresponding to the 2-methine proton, and a broad signal at δ 5.50 due to the vinyl proton. As usual in these reactions aminoborane 12 was isolated as a byproduct. Transformation of 2-cyanotetrahydropyridine 11 into the corresponding 3-(tetrahydro-2-pyridyl)indole 14 was carried out in 78% yield[31] by condensation with indolylmagnesium iodide in ether–dichloromethane solution, according to our previously developed procedure.[1]

Similarly, condensation of 2-cyanotetrahydropyridine 11 with (*m*-methoxyphenyl)magnesium bromide in THF at room temperature gave 2-(*m*-methoxyphenyl)-1,2,3,6-tetrahydropyridine 17 in 70% yield. When the reaction was carried out at reflux temperature, the tertiary alcohol 20, formed by nucleophilic attack of the Grignard reagent on the ester group, was isolated as a byproduct.

Catalytic hydrogenation of tetrahydropyridines 14 and 17 was effected in the presence of platinum oxide to afford approximately equimolecular cis–trans mixtures of piperidines 15 and 18, respectively, which were chromatographically separated. The NMR spectra (200 MHz) clearly differentiates the two epimers of 15. Thus, in the trans isomer the signals due to the C-2 methine proton (δ 3.85) and the side chain methylene group (δ 2.55) appear at a lower field relative to the cis isomer (δ3.45 and 2.3, respectively). These data reflect the deshielding effect[32] caused by the axial substituent at C-4 upon the axial proton at C-2 and agree with the known generalization that proton resonances for equatorial methylene substituents undergo a small upfield shift (~0.2 ppm) as compared to the corresponding axial substituents.[33] Similar chemical shift differences were observed for the two epimers of 18 (see Experimental Section).

In order to investigate if the ratio of the cis isomer in the mixture of piperidines 18 could be improved, an alternative reaction sequence consisting of catalytic hydrogenation of 2-cyanotetrahydropyridine 11 followed by condensation of the resulting 2-cyanopiperidine with the Grignard reagent was studied. Catalytic hydrogenation of 11 was carried out at atmospheric pressure in methanolic solution in the presence of 10% palladium on charcoal[34] to give methyl *trans*-2-cyano-4-piperidineacetate 13 in 53% yield. The signal for the C-2 methine proton in the NMR spectrum appeared at δ 3.85 as an apparent triplet with J = 3.2 Hz, clearly indicating the equatorial orientation of this proton and, therefore, that the cyano group was positioned axially.[35] However, when 2-cyanopiperidine 13 was allowed to react with the Grignard reagent of *m*-methoxybromobenzene, the only product isolated was the piperidine *trans*-18, whose formation can be accounted for by considering that approach of the aryl group occurs from the most accessible face of the iminium salt generated from 2-cyanopiperidine 13. In this context it is worth commenting that condensation of 2-cyanotetrahydropyridines or 2-cyanopiperidines with Grignard reagents of benzene derivatives constitutes a new synthetic entry to 2-arylpiperidines.[36]

Scheme III



Finally, alkaline hydrolysis of the diastereomeric cis–trans mixtures of piperidines 15 and 18 followed by PPA cyclization of the resulting amino acids afforded, as expected, the 7-membered cyclic ketones 16 and 19, respectively. The poor yields of these cyclizations can be explained by considering that, in contrast to 2-substituted-4-piperidinecarboxylates, the trans isomers of 2-substituted-4-piperidineacetates 15 and 18 cannot undergo cyclization since epimerization at C-4 of the piperidine ring is not possible.[37]

In the IR spectrum of 16 a carbonyl absorption at 1650 cm^{-1}, characteristic of a 2-acylindole moiety, was observed. On the other hand, its NMR spectrum (200 MHz) showed a doublet of doublets at δ 4.77 corresponding to the bridgehead proton adjacent to the indole nucleus and the signals to the diastereotopic C-6 methylene protons, which appear as two doublet of doublets at δ 2.80 and 3.04. In the tetracyclic base 19 these protons at C-6 appear as a complex system at δ ~2.85, the most significative signal of the spectrum being the broad doublet at δ 3.98 corresponding to the methine proton of bridgehead C-1.

Experimental Section

General Methods. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H NMR spectra were measured on a Perkin-Elmer R-24B (60 MHz) instrument or, when indicated, on a Varian XL-200 spectrometer. ^{13}C NMR spectra were recorded with a Varian XL-200 spectrometer. Unless otherwise noted NMR spectra were recorded in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were taken on a Perkin-Elmer 577 spectrometer. Mass spectra were recorded on a

(31) When the condensation was effected with indole itself in AcOH–H_2O for 24 h at room temperature the yield decreased to 45%.
(32) Booth, H. *Tetrahedron* **1966**, *22*, 615.
(33) Branca, S. J.; Smith, III, A. B. *J. Org. Chem.* **1977**, *42*, 1026.
(34) See ref 9 and references cited therein. When the hydrogenation was effected at 10 atm the yield of 13 decreased and abundant methyl 1-methyl-4-piperidineacetate was formed.
(35) The axial preference of a cyano group, as well as the facile equatorial–axial epimerization of this group in 2-cyanopiperidines, has been previously observed: (a) Reference 9 and references cited therein. (b) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392.
(36) For other procedures, inter alia see: (a) Overberger, C. G.; Herin, L. P. *J. Org. Chem.* **1962**, *27*, 417. (b) Joshi, K.; Rao, V. A.; Anand, N. *Indian J. Chem.* **1973**, *11*, 1222. (c) Evans, D. A.; Domeier, L. A. *Org. Synth.* **1974**, *54*, 93. (d) Malmberg, M.; Nyberg, K. *J. Chem. Soc., Chem. Commun.* **1979**, 167. (e) Scully, Jr., F. E. *J. Org. Chem.* **1980**, *45*, 1515. (f) Achini, R. *Helv. Chim. Acta* **1981**, *64*, 2203. (g) Bosch, J.; Rubiralta, M.; Moral, M.; Valls, M. *J. Heterocycl. Chem.* **1983**, *20*, 595.
(37) In fact, although the cis–trans isomerization of the same 5-ethyl-2-oxo-4-piperidineacetic acids under acid hydrolytic conditions or on thermal treatment (180 °C) has been reported, the process cannot operate in our case since the equilibration is attained by lactam ring opening followed by ring closure with participation of the exocyclic carboxyl group: Fujii, T.; Yoshifuji, S. *Tetrahedron* **1980**, *36*, 1539 and references cited therein.

Hewlett-Packard 5930A mass spectrometer. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ powder. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck, 63–200 μm), and the spots were located by TLC with UV light or iodoplatinate reagent. Preparation TLC was performed on silica gel plates $60F_{254}$ (Merck), layer thickness 2 mm, using 7:3 ether–acetone as developing solvent. All distillations were effected using a Büchi GKR-50 Kugelrohr apparatus. The temperatures cited are the maximum temperatures of the oven during the distillation. Microanalyses were performed by Instituto de Química Bio-Orgánica, Barcelona.

Methyl 1-Methyl-1,2,3,6-tetrahydropyridine-4-carboxylate (1a).[38] To an ice bath cooled solution of 1-methyl-4-(methoxycarbonyl)pyridinium iodide[39] (9.08 g, 32 mmol) in MeOH (100 mL) was added $NaBH_4$ (2 g, 53 mmol) portionwise. The resulting solution was stirred for 3 h at room temperature, the solvent was removed at reduced pressure, H_2O (100 mL) was added, and the aqueous basic solution was extracted with ether. Evaporation of the dried ethereal extracts gave an oil which was purified by distillation to yield **1a**: 4.61 g (91%); bp 100–110 °C (0.1 mmHg); IR (NaCl) 1710 (CO) cm^{-1}; NMR (CCl_4) δ 2.20 (s, 3 H, NCH_3), 2.2–2.7 (m, 4 H, 5- and 6-CH_2), 2.8–3.2 (m, 2 H, 2-CH_2), 3.60 (s, 3 H, OCH_3), 6.70 (m, 1 H, =CH). For the hydrochloride: mp 185–187 °C (acetone–Et_2O). Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.13; H, 7.36; N. 7.31; Cl, 18.50. Found: C, 49.89; H, 7.31; N, 7.00; Cl, 18.81.

Methyl 1-Benzyl-1,2,3,6-tetrahydropyridine-4-carboxylate (1b). By use of the above procedure, from 1-benzyl-4-(methoxycarbonyl)pyridinium chloride[1] (10 g, 38 mmol), MeOH (100 mL), and $NaBH_4$ (2.15 g, 57 mmol) tetrahydropyridine **1b** was obtained: 7.15 g (81%) bp 175–180 °C (0.07 mmHg); IR (NaCl) 1710 (CO) cm^{-1}; NMR (CCl_4) δ 2.2–2.8 (m, 4 H, 5- and 6-CH_2), 3.0–3.3 (m, 2 H, 2-CH_2), 3.45 (s, 2 H, $ArCH_2$), 3.53 (s, 3 H, OCH_3), 6.65 (m, 1 H, =CH), 7.08 (s, 5 H, ArH). For the hydrochloride: mp 185–187 °C (acetone). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.77; N, 5.23; Cl, 13.24. Found: C, 62.76; H, 6.90; N, 5.38; Cl, 13.50.

Methyl 3-Ethyl-1-methyl-4-piperidinecarboxylate (2a). A solution of ethylmagnesium bromide, freshly prepared from EtBr (2.16 g, 19.8 mmol) and magnesium (0.45 g, 18.5 mmol) in anhydrous Et_2O (15 mL), was added dropwise under N_2 to a stirred suspension of CuI (1.23 g, 6.45 mmol) in anhydrous Et_2O (15 mL) at −30 °C. The mixture was stirred at −30 °C for 30 min and then a solution of tetrahydropyridine **1a** (0.5 g, 3.22 mmol) in anhydrous Et_2O (10 mL) was added dropwise. After stirring at −30 °C for 6 h the reaction mixture was poured into an aqueous NH_4Cl solution. The ethereal layer was separated and the aqueous solution was extracted with $CHCl_3$. The combined organic extracts were washed with brine and aqueous NH_4Cl solution, dried, and evaporated to give **2a** as an epimeric mixture: 0.45 g (80%); bp 210–215 °C (10 mmHg). A pure isomer was isolated by column chromatography: IR (NaCl) 1735 (CO) cm^{-1}; NMR (CCl_4) δ 0.95 (br, 3 H, CH_2CH_3), 2.10 (s, 3 H, NCH_3), 3.52 (s, 3 H, OCH_3). For the hydrochloride: mp 138–140 °C (acetone–Et_2O). Anal. Calcd for $C_{10}H_{20}ClNO_2$: C, 54.17; H, 9.10; N, 6.32; Cl, 16.00. Found: C, 53.95; H, 9.11; H, 6.40; Cl, 16.21.

Methyl 1-Benzyl-3-ethyl-4-piperidinecarboxylate (2b). This material was prepared as an epimeric mixture by the above procedure from tetrahydropyridine **1b** (0.74 g, 3.22 mmol): 0.65 g (78%); bp 200–220 °C (0.2 mmHg). A pure isomer was isolated by column chromatography: IR (NaCl) 1730 (CO) cm^{-1}; NMR (CCl_4) δ 0.92 (m, 3 H, CH_2CH_3), 3.28 and 3.44 (2 d, J = 14 Hz, 2 H, $ArCH_2$), 3.55 (s, 3 H, OCH_3), 7.15 (s, 5 H, ArH); MS, m/e (relative intensity) 261 (6), 170 (47), 110 (21), 91 (100). For the hydrochloride: mp 153–154 °C (acetone). Anal. Calcd for $C_{16}H_{24}ClNO_2$: C, 64.52; H, 8.12; N, 4.70; Cl, 11.90. Found: C, 64.50; H, 8.04; N, 4.98; Cl, 11.72.

Methyl 5-Ethyl-2-(3-indolyl)-1-methyl-4-piperidinecarboxylate (5). Operating as above, from EtBr (8 g, 73 mmol), magnesium (1.7 g, 70 mmol), CuI (4.65 g, 24.4 mmol), and methyl 2-(3-indolyl)-1-methyl-1,2,3,6-tetrahydropyridine-4-carboxylate (**3**,[1] 2 g, 7.4 mmol) in anhydrous THF (75 mL), a nearly equimolecular mixture of piperidines **5a** and **5b**[13] was obtained after column chromatography by using 97:3 CH_2Cl_2–MeOH as eluent: 1.98 g (89%); IR ($CHCl_3$) 3480 (NH), 1720 (CO) cm^{-1}; NMR δ 1.00 (br, 3 H, CH_2CH_3), 2.00 and 2.05 (2 s, 3 H, NCH_3), 3.56 and 3.65 (2 s, 3 H, OCH_3), 6.6–7.4 (m, 4 H, indole), 7.70 (m, 1 H, indole), 8.40 (br, 1 H, NH).

Methyl 1-Benzyl-5-ethyl-2-(3-indolyl)-4-piperidinecarboxylate (6). Operating as above, from EtBr (30.2 g, 0.28 mol), magnesium (6.6 g, 0.27 mol), CuI (18.1 g, 95 mmol), and methyl 1-benzyl-2-(3-indolyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (**4**,[1] 10 g, 28 mmol) in anhydrous THF (210 mL), a solid (11 g) which by ^1H NMR was found to be a mixture of epimers was obtained. Column chromatography with chloroform as eluent afforded **6a** (2.71 g): IR (KBr) 3340 (NH), 1700 (CO) cm^{-1}; NMR δ 0.66 and 0.77 (2 t, 3 H, CH_2CH_3), 3.20 and 3.86 (2 d, J = 13 Hz, 2 H, $ArCH_2$), 3.56 and 3.63 (2 s, 3 H, OCH_3), 6.9–7.3 (m, 9 H, ArH), 7.7–8.2 (m, 2 H, indole and NH). For the hydrochloride: mp 182–186 °C (acetone–MeOH). Anal. Calcd for $C_{24}H_{29}ClN_2O_2$: C, 69.80; H, 7.08; N, 6.78; Cl, 8.58. Found: C, 69.83; H, 7.17; N, 6.82; Cl, 8.67. Later, 4.81 g of a mixture of **6a** and **6b** was obtained. Finally, elution with 99:1 $CHCl_3$–MeOH gave 1.68 g of **6b**: IR ($CHCl_3$) 3480 (NH), 1720 (CO) cm^{-1}; NMR δ 0.95 (br t, 3 H, CH_2CH_3), 3.0–4.0 (m, 2 H, $ArCH_2$), 3.63 (s, 3 H, OCH_3), 6.8–7.3 (m, 9 H, ArH), 7.60 (m, 1 H, indole), 8.35 (br, 1 H, NH). For the hydrochloride: mp 220–222 °C (Et_2O–MeOH). Anal. Calcd for $C_{24}H_{29}ClN_2O_2$: C, 69.80; H, 7.08; N, 6.78; Cl, 8.58. Found: C, 70.03; H, 7.29; N, 6.77; Cl, 8.73.

Methyl 5-Ethyl-2-(3-indolyl)-4-piperidinecarboxylate (7). A solution of **6a** hydrochloride (240 mg, 0.58 mmol) in MeOH (25 mL) was hydrogenated over PtO_2 (50 mg) at 4 atm at room temperature for 16 h. The catalyst was filtered off and the solvent was evaporated. The resulting mixture was dissolved in aqueous 2 N NaOH solution and extracted with CH_2Cl_2. The organic extracts were dried and evaporated to give 160 mg (96%) of **7a** as a C_4-epimeric mixture: IR ($CHCl_3$) 3480 (NH), 1710 (CO) cm^{-1}; NMR δ 0.95 (br, 3 H, CH_2CH_3), 3.63 and 3.65 (2 s, 3 H, OCH_3), 3.83 (dd, J = 9, 2 Hz, 1 H, 2-H), 6.8–7.3 (m, 4 H, indole), 7.65 (m, 1 H, indole), 8.55 (br, 1 H, NH). For the hydrochloride: mp 218–220 °C (acetone–EtOH). Anal. Calcd for $C_{17}H_{23}ClN_2O_2$: C, 63.25; H, 7.18; N, 8.68; Cl, 10.98. Found: C, 63.59; H, 7.33; N, 8.65; Cl, 10.70.

A similar hydrogenation from **6b** hydrochloride (480 mg, 1.16 mmol) yielded 290 mg (87%) of **7b** as a C_4-epimeric mixture: IR ($CHCl_3$) 3480 (NH), 1720 (CO) cm^{-1}; NMR δ 0.92 (br, 3 H, CH_2CH_3), 3.28 (dd, J = 12, 4 Hz, 1 H, 6-Heq), 3.60 (s, 3 H, OCH_3), 3.90 (dd, J = 10, 3 Hz, 1 H, 2-H), 6.7–7.2 (m, 4 H, indole), 7.55 (m, 1 H, indole), 8.85 (br, 1 H, NH). For the hydrochloride: mp 238–240 °C (acetone). Anal. Calcd for $C_{17}H_{23}ClN_2O_2$: C, 63.25; H, 7.18; N, 8.68; Cl, 10.98. Found: C, 63.40; H, 7.29; N, 8.68; Cl, 11.19.

Isodasycarpidone (8a) and Epiisodasycarpidone (8b).[13,40] To a solution of the above mixture of **5a** and **5b** (1.7 g, 5.64 mmol) in EtOH (125 mL) was added aqueous 10% KOH solution (65 mL). After 5 h of refluxing, the mixture was cooled, neutralized with concentrated HCl, and evaporated to dryness. The residue was dried over P_2O_5 and digested several times with boiling absolute EtOH. The crude amino acid and excess of PPA were stirred vigorously under N_2 at 90–100 °C for 1 h 30 min. The mixture was cooled, poured into ice–water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. Evaporation of the extracts gave a syrup which was chromatographed. Elution with $CHCl_3$ gave epiisodasycarpidone (**8b**): 280 mg (18%); mp 203–204 °C (MeOH–Et_2O) (lit.[13] mp 201–202 °C); ^{13}C NMR δ 12.53 (q, CH_2CH_3), 23.99 (t, CH_2CH_3), 32.21 (t, 12-C), 39.62 (d, 4-C), 44.50 (d, 5-C), 45.57 (q, NCH_3), 49.98 (t, 3-C), 52.49 (d, 1-C), 112.86 (d, 8-C), 120.94 (d, 11-C), 122.03 (10- and 11b-C), 126.77 (9- and 11a-C), 132.78 (s, 6a-C), 138.17 (s, 7a-C), 194.95 (s, CO). Elution with 98:2 ($CHCl_3$–EtOH gave isodasycarpidone (**8a**): 270 mg (17%); mp 214–216 °C (MeOH) (lit.[13] mp 220–221 °C); ^{13}C NMR δ 11.58 (q, CH_2CH_3), 24.75 (t, CH_2CH_3), 38.14 (t, 12-C), 41.39 (d, 4-C), 43.96 (d, 5-C), 44.76 (q, NCH_3), 51.92 (t, 3-C), 52.58 (d, 1-C),

(38) Kinoshita, N.; Hamana, M.; Kawasaki, T. *Chem. Pharm. Bull.* **1962**, *10*, 753; *Chem. Abstr.* **1963**, *37*, 6785.
(39) Grob, C. A.; Renk, E. *Helv. Chim. Acta* **1954**, *37*, 1672.
(40) Systematic names: (1*RS*,4*RS*,5*RS*)- and (1*RS*,4*SR*,5*RS*)-4-ethyl-2-methyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]-indole, respectively.

112.75 (d, 8-C), 120.97 (d, 11-C), 121.81 (s, 11b-C), 121.89 (d, 10-C), 126.72 (9- and 11a-C), 133.55 (s, 6a-C), 137.98 (s, 7a-C), 192.64 (s, CO).

***N*-Demethylisodasycarpidone (9a).** The ester **7a** (160 mg, 0.56 mmol) was exposed to the same reaction sequence to give **9a** (50 mg, 34%) after column chromatography (97:3 $CHCl_3$–MeOH as eluent): mp 237–238 °C (MeOH–Et_2O); IR (KBr) 3360 (indole NH), 1640 (CO), cm^{-1}; NMR δ 1.05 (br s, 3 H, CH_2CH_3), 0.9–1.3 (m, 2 H, CH_2CH_3), 1.5–2.2 (m, 3 H, 12-H and 4-Hax), 2.2–3.0 (m, 4 H, 3-H, 5-Heq, and piperidine NH), 4.60 (apparent t, 1 H, 1-Heq), 6.8–7.7 (m, 4 H, indole), 11.10 (br, 1 H, indole NH). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.41; H, 7.04; N, 11.26.

***N*-Demethylepiisodasycarpidone (9b).** The reaction and workup from **7b** (670 mg, 2.3 mmol) were carried out according to the above directions. The crude product was chromatographed (99:1 $CHCl_3$–MeOH as eluent) to give **9b**: 210 mg (35%); mp 223–225 °C (MeOH–Et_2O); IR ($CHCl_3$) 3460 (indole NH), 1680 (CO) cm^{-1}; NMR δ 0.97 (t, 3 H, CH_2CH_3), 1.4–2.2 (m, 5 H, CH_3CH_2, 12-H, 4-Heq), 2.2–3.0 (m, 4 H, 3-H, 5-Heq, piperidine NH), 4.55 (br s, 1 H, 1-Heq), 6.8–7.3 (m, 4 H, indole), 10.80 (br, 1 H, indole NH). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.48; H, 7.09; N, 11.21.

Methyl 2-Cyano-1-methyl-1,2,3,6-tetrahydropyridine-4-acetate (11). Hydrochloric acid (6 N, 24 mL) was added dropwise to a stirred solution of NaCN (17 g, 0.35 mol) in H_2O (250 mL), layered with Et_2O (450 mL), and kept below 15 °C. To this mixture were added 4-[(methoxycarbonyl)methyl]-1-methylpyridinium iodide[41] (**10**, 24 g, 82 mmol) and then $NaBH_4$ (3.6 g, 95 mmol) portionwise. The mixture was stirred at room temperature for 4 h. The ethereal solution was decanted and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous 1 N HCl solution, dried, and evaporated. Purification by column chromatography (7:3 benzene–$CHCl_3$ as eluent) gave 0.98 g (7 %) of **4-[(methoxycarbonyl)methyl]-1-methyl-1,2,3,6-tetrahydropyridine–borane (12)**: mp 74–75 °C (hexane); IR (KBr) 2350 (BH), 1725 (CO), 1640 (C=C) cm^{-1}; NMR δ 2.50 (s, 3 H, NCH_3), 3.00 (s, 2 H, $COCH_2$), 3.60 (s, 3 H, OCH_3), 5.40 (br, 1 H, =CH). Anal. Calcd for $C_9H_{18}BNO_2$: C, 59.05; H, 9.91; N, 7.65. Found: C, 59.08; H, 9.93; N, 7.55. The acidic aqueous phase was basified with aqueous K_2CO_3 solution and extracted with CH_2Cl_2. The extracts were dried and evaporated to give 9.33 g (60%) of cyanotetrahydropyridine **11**. An analytical sample was obtained by column chromatography with $CHCl_3$ as the eluent: IR (NaCl) 2210 (CN), 1725 (CO) cm^{-1}; NMR δ 2.30 (s, 3 H, NCH_3), 2.95 (s, 2 H, $COCH_2$), 3.55 (s, 3 H, OCH_3), 3.75 (dd, J = 2, 6 Hz, 1 H, 2-H), 5.50 (br s, 1 H, =CH); MS, m/e (relative intensity) 194 (M^+), 27), 166 (37), 135 (24), 121 (63), 108 (45), 94 (69), 68 (43), 65 (39), 59 (47), 42 (100), 41 (61). For the hydrochloride: mp 136–137 °C (acetone–Et_2O). Anal. Calcd for $C_{10}H_{15}ClN_2O_2$: C, 52.06; H, 6.56; N, 12.14; Cl, 15.37. Found: C, 52.08; H, 6.60; N, 12.03; Cl, 15.58.

Methyl *trans*-2-Cyano-1-methylpiperidine-4-acetate (13). A solution of **11** (0.3 g, 1.54 mmol) in MeOH (30 mL) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C catalyst (100 mg). When the absorption ceased, the catalyst was filtered off and the clear solution evaporated to give 220 mg of an oil which was purified by column chromatography through aluminum oxide (FLUKA 507C). On elution with 3:7 hexane–benzene, nitrile **13** was obtained: 160 mg (53%); IR (NaCl) 2205 (CN), 1725 (CO) cm^{-1}; ^1H NMR (200 MHz) δ 1.30 (qd, J = 12.8, 4.5 Hz, 1 H, 5-Hax), 1.59 (td, J = 12.8, 4.5 Hz, 1 H, 3-Hax), 1.76 (dt, J = 12.8, 2.5 Hz, 1 H, 3-Heq), 1.99 (dq, J = 12.8, 2.5 Hz, 1 H, 5-Heq), 2.1–2.2 (m, 1 H, 4-Hax), 2.27 (AB, 2 H, CH_2CO), 2.38 (s, 3 H, NCH_3), 2.40 (td, J = 12.8, 2.5 Hz, 1 H, 6-Hax), 2.73 (dq, J = 12.8, 2.5, 1.6 Hz, 1 H, 6-Heq), 3.68 (s, 3 H, OCH_3), 3.85 (apparent t, J = 3.2 Hz, 1 H, 2-Heq); ^{13}C NMR δ 28.67 (d, 4-C), 31.17 (t, 5-C), 34.37 (t, 3-C), 40.37 (t, CH_2COO), 43.89 (q, NCH_3), 50.34 (q, OCH_3), 51.63 (t, 6-C), 54.46 (d, 2-C), 115.99 (s, CN), 172.14 (s, COO); MS, m/e (relative intensity) 196 (M^+, 6), 195 (4), 121 (14), 96 (46), 95 (17), 94 (11), 70 (25), 68 (19), 67 (18), 59 (15), 55 (26), 53 (15), 44 (17), 43 (33), 42 (100). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.43; H, 8.27; N, 14.30.

(41) Jones, R. A.; Katritzky, A. R. *Aust. J. Chem.* **1964**, *17*, 455.

Methyl 2-(3-Indolyl)-1-methyl-1,2,3,6-tetrahydropyridine-4-acetate (14). A solution of amino nitrile **11** (8.64 g, 40 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise under N_2 to a stirred solution of indolylmagnesium iodide (70 mmol) in an anhydrous 1:1 Et_2O–CH_2Cl_2 mixture (200 mL) maintained at 0 °C. The resulting mixture was stirred at room temperature for 4 h, poured into ice-cooled saturated NH_4Cl solution, made alkaline with concentrated NH_4OH, and extracted with CH_2Cl_2. The organic phase was extracted with aqueous 1 N HCl. The hydrochloric extracts were basified with aqueous Na_2CO_3 solution and extracted with $CHCl_3$. Evaporation left tetrahydropyridine **14** (10 g, 78%) as an oil which crystallized from acetone: mp 127–128 °C; IR ($CHCl_3$) 3460 (NH), 1725 (CO) cm^{-1}; NMR δ 2.05 (s, 3 H, NCH_3), 2.95 (s, 2 H, CH_2CO), 3.53 (s, 3 H, OCH_3), 3.6–3.9 (m, 1 H, 2-H), 5.53 (br, 1 H, =CH), 6.7–7.3 (m, 4 H, indole), 7.4–7.7 (m, 1 H, indole), 9.35 (br, 1 H, NH); MS, m/e (relative intensity) 284 (M^+, 65), 211 (35), 158 (96), 157 (79), 130 (68), 94 (38), 45 (35), 44 (38), 42 (100). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.76; H, 7.15; N, 9.83.

Methyl 2-(*m*-Methoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine-4-acetate (17). A solution of amino nitrile **11** (3 g, 15.4 mmol) in anhydrous THF (30 mL) was added dropwise under N_2 to the Grignard reagent prepared from magnesium (0.82 g, 33.7 mmol) and *m*-bromomethoxybenzene (5.76 g, 30.8 mmol) in anhydrous THF (15 mL). The resulting mixture was stirred at room temperature for 48 h and worked-up as above to give an oil which was chromatographed. On elution with 2:8 benzene–$CHCl_3$, pure **17** was obtained: 2.95 g (70%); IR (NaCl) 1725 (CO) cm^{-1}; ^1H NMR (200 MHz) δ 2.09 (s, 3 H, NCH_3), 2.93 (br d, J = 17 Hz, 1 H, 6-H), 3.03 (br s, 2 H, CH_2CO), 3.24 (dd, J = 9.5 and 4.5 Hz, 1 H, 2-Hax), 3.41 (br d, J = 17 Hz, 1 H, 6-H), 3.66 (s, 3 H, $COOCH_3$), 3.81 (s, 3 H, OCH_3), 5.68 (br, 1 H, =CH), 6.7–6.9 (m, 3 H, ArH), 7.24 (t, J = 8 Hz, 1 H, aromatic C^5H); ^{13}C NMR δ 38.31 (t, 3-C), 42.00 (t, CH_2CO), 43.01 (q, NCH_3), 51.79 (q, CO_2CH_3), 55.23 (q, OCH_3), 55.39 (t, 6-C), 65.75 (d, 2-C), 113.02 (d, aromatic C^2 and C^4), 120.34 (d, aromatic C^6), 123.34 (d, 5-C), 129.40 (d, aromatic C^5), 129.63 (s, 4-C), 144.36 (s, aromatic C^1), 159.82 (s, aromatic C^3), 171.67 (s, CO). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.68; N, 5.10. Found: C, 69.83; H, 7.69; N, 4.93. On elution with 1:1 benzene–$CHCl_3$, **1,1-bis(*m*-methoxyphenyl)-2-[2-(*m*-methoxyphenyl)-1-methyl-1,2,3,6-tetrahydro-4-pyridyl]ethanol (20**, 0.35 g, 8%) was obtained: IR (NaCl) 3400 (OH) cm^{-1}; NMR δ 1.92 (s, 3 H, NCH_3), 2.93 (br, 2 H, CH_2CO), 3.62 (s, 9 H, OCH_3), 5.33 (br, 1 H, =CH), 6.3–7.2 (m, 12 H, ArH). For the hydrochloride: mp 200–201 °C (Et_2O–acetone); IR (KBr) 3350 (OH) cm^{-1}; NMR δ 2.55 (s, 3 H, NCH_3), 3.65 (s, 9 H, OCH_3), 5.30 (br, 1 H, =CH), 6.4–7.2 (m, 12 H, ArH). Anal. Calcd for $C_{29}H_{34}ClNO_4$; C, 70.21; H, 6.92; N, 2.82. Found: C, 70.35; H, 6.53; N, 2.70.

Methyl 2-(3-Indolyl)-1-methylpiperidine-4-acetate (15). A solution of **14** (2.5 g, 8.8 mmol) in MeOH (100 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 (125 mg). When the absorption ceased, the catalyst was filtered off and the solution was evaporated to give a crude 1:1 mixture of *cis*-**15** and *trans*-**15** (2.6 g) which was purified by column chromatography ($CHCl_3$ as eluent). Each isomer was separated by preparative TLC. *cis*-**15** (higher R_f value): IR (NaCl) 3450 (NH), 1725 (CO) cm^{-1}; NMR (200 MHz) δ 2.17 (s, 3 H, NCH_3), 2.29 (AB, 2 H, CH_2COO), 3.26 (dt, J = 4, 12 H, 1 H, 6-Heq), 3.45 (dd, J = 4, 12 Hz, 1 H, 2-Hax), 3.63 (s, 3 H, OCH_3), 7.1–7.4 (m, 4 H, indole), 7.70 (dd, J = 6.9, 1.6 Hz, 1 H, indole), 9.27 (br, 1 H, NH). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.50; H, 7.74; N, 9.78. Found: C, 71.34; H, 7.66; N, 9.28. *trans*-**15** (lower R_f value): NMR (200 MHz) δ 2.23 (s, 3 H, NCH_3), 2.55 (AB, 2 H, CH_2CO), 2.95 (m, 1 H, 6-Heq), 3.67 (s, 3 H, OCH_3), 3.85 (dd, J = 4, 12 Hz, 1 H, 2-Hax), 7.0–7.4 (m, 4 H, indole), 7.69 (dd, J = 6.6, 1.6 Hz, 1 H, indole), 9.05 (br, 1 H, NH).

Methyl 1-Methyl-2-(*m*-methoxyphenyl)piperidine-4-acetate (18). Method A. Operating as above, from tetrahydropyridine **17** (0.39 g, 1.4 mmol) in CH_3OH (50 mL) and PtO_2 (20 mg), a 1:1 mixture (0.28 g, 72%) of *cis*-**18** and *trans*-**18** was obtained. Both isomers were separated by column chromatography (mixtures of benzene–$CHCl_3$ as eluent) followed by preparative TLC. *cis*-**18** (higher R_f value): IR (NaCl) 1725 (CO) cm^{-1}; ^1H NMR (200 MHz) δ 1.55 (qd, J = 3, 13 Hz, 1 H, 4-Hax), 1.78 (br d, J = 13 Hz, 1 H, 5-Heq), 2.02 (s, 3 H, NCH_3), 2.20 (AB, 2

H, CH_2CO), 2.82 (dd, J = 2.5, 12 Hz, 1 H, 2-Hax), 3.02 (m, 1 H, 6-Heq), 3.64 (s, 3 H, $COOCH_3$), 3.80 (s, 3 H, OCH_3), 6.76 (td, J = 8, 2, 1 Hz, 1 H, aromatic), 6.89 (m, 2 H, aromatic), 7.22 (t, J = 8 Hz, 1 H, aromatic C^5H); ^{13}C NMR δ 32.21 (t, 5-C), 33.48 (d, 4-C), 40.97 (t, 3-C), 41.82 (t, CH_2CO), 43.99 (q, NCH_3), 51.45 (q, $COOCH_3$), 55.22 (q, OCH_3), 56.72 (t, 6-C), 70.32 (d, 2-C), 112.72 and 112.84 (2 d, aromatic C^2 and C^4), 119.84 (d, aromatic C^6), 129.39 (d, aromatic C^2), 145.00 (s, aromatic C^1), 159.81 (s, aromatic C^3). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.13; H, 8.26; N, 5.03.

Method B. A solution of 2-cyanopiperidine **13** (0.95 g, 4.8 mmol) in anhydrous THF (50 mL) was added dropwise under N_2 to the Grignard reagent prepared from magnesium (0.23 g, 9.7 mmol) and *m*-bromomethoxybenzene (1.6 g, 8.7 mmol) in anhydrous THF (10 mL). The resulting mixture was stirred at room temperature for 48 h and worked-up as above for compound **15** to give *trans*-**18** (840 mg), which was purified by column chromatography with 3:7 benzene:$CHCl_3$ as eluent: IR (NaCl) 1725 (CO) cm^{-1}; ^1H NMR (200 MHz) δ 1.59 (dt, J = 3.2, 13.7 Hz, 1 H, 5-Heq), 2.04 (s, 3 H, NCH_3), 2.33 (td, J = 2.7, 12 Hz, 1 H, 6-Hax), 2.54 (AB, 2 H, CH_2CO), 2.83 (dq, J = 3.2, 4, 12 Hz, 1 H, 6-Heq), 2.99 (dd, J = 2.7, 12 Hz, 1 H, 2-Hax), 3.68 (s, 3 H, $COOCH_3$), 3.81 (s, 3 H, OCH_3), 6.76 (td, J = 8, 2.6, 1 H, 1 H, aromatic), 6.95 (m, 2 H, aromatic), 7.22 (t, J = 8 Hz, 1 H, aromatic C^5H); ^{13}C NMR δ 28.74 (d, 4-C), 29.41 (t, 5-C), 36.18 (t, CH_2COO), 39.45 (t, 3-C), 44.32 (q, NCH_3), 51.45 (q, $COOCH_3$), 51.53 (t, 6-C), 55.20 (q, OCH_3), 65.18 (d, 2-C), 112.68 (d, aromatic C^2 and C^4), 119.83 (d, aromatic C^6), 129.36 (d, aromatic C^5), 145.90 (s, aromatic C^1), 159.77 (s, aromatic C^3), 173.33 (s, CO).

2-Methyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (16). To a solution of the mixture of esters **15** (5.23 g, 18 mmol) in EtOH (100 mL) was added aqueous 10% KOH solution (50 mL). After 6 h of refluxing, the mixture was cooled, adjusted to pH 7 with 6 N HCl solution, and evaporated to dryness. The residue was dried over P_2O_5 and digested several times with boiling absolute EtOH. The solvent was removed, and the residue was dried over P_2O_5 to give 4.3 g of crude amino acid.

Method A. This amino acid (2 g) and PPA (100 g) were stirred under N_2 at 80 °C for 2 h. The cooled mixture was poured into ice–water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. Evaporation of the dried extracts left a solid which on column chromatography (95:5 $CHCl_3$–MeOH as eluent) afforded 100 mg (5% overall yield) of **16**: mp 260–261 °C (acetone; IR (KBr) 1650 (CO) cm^{-1}; NMR (200 MHz, CD_3OD) δ 1.94 (s, 3 H, NCH_3), 2.80 (dd, J = 17, 3.5 Hz, 1 H, 6-H), 3.04 (dd, J = 17, 5 Hz, 1 H, 6-H), 4.77 (dd, J = 5.6, 1.4 Hz, 1 H, 1-H), 7.12 (dd, J = 8, 7.5 Hz, 1 H, 11-H), 7.28 (dd, J = 8, 7.5 Hz, 1 H, 10-H), 7.44 (d, J = 8 Hz, 1 H, 9-H), 7.76 (d, J = 8 Hz, 12-H); ^{13}C NMR δ 27.63 (5-C), 31.06 (4-C), 34.12 (13-C), 44.43 (NCH_3), 46.58 (3-C), 50.05 (6-C), 55.25 (1-C), 113.89 (9-C), 121.66 (12b-C), 122.17 (11- and 12-C), 126.98 (12a-C), 127.42 (10-C), 136.95 (7a-C), 137.68 (8a-C), 199.47 (7-C). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.28; H, 7.20; N, 10.54.

Method B. The above amino acid (2 g) and methanesulfonic acid (20 mL) saturated with P_2O_5[42] were stirred under N_2 at 70 °C for 2 h. The cooled mixture was poured into ice–water, basified with aqueous Na_2CO_3 solution, and extracted with $CHCl_3$. Evaporation of the dried extracts gave a solid which was chromatographed. On elution with 98:2 $CHCl_3$–MeOH, pure **16** (60 mg) was obtained.

10-Methoxy-2-methyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-2-benzazonine (19). To a solution of a 1:1 mixture of esters **18** (1 g, 3.6 mmol) in dioxane (50 mL) was added a saturated aqueous solution of $Ba(OH)_2$ (50 mL). The mixture was heated at 80 °C for 5 h, cooled, saturated with CO_2, and filtered. The resulting solution was evaporated to dryness. The residue (1.2 g) was vigorously stirred under N_2 in the presence of an excess of PPA (60 g) at 80 °C for 2 h. After cooling, the mixture was poured into ice–water, made alkaline with concentrated NH_4OH, and extracted with $CHCl_3$ containing some drops of MeOH. Evaporation of the dried extracts gave an oil (200 mg) which on preparative TLC provided pure benzazonine **19**: 120 mg (14%); IR ($CHCl_3$) 1650 (CO) cm^{-1}; NMR (200 MHz) δ 1.99 (s, 3 H, NCH_3), 2.86 (m, 2 H, $COCH_2$), 3.85 (s, 3 H, OCH_3), 3.98 (br d, J = 6 Hz, 1 H, 1-Heq), 6.66 (d, J = 2.6 Hz, 1 H, 11-H), 6.87 (dd, J = 2.6, 8.5 Hz, 1 H, 9-H), 7.75 (d, J = 8.5 Hz, 1 H, 8-H). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44, H, 7.81; N, 5.71. Found: C, 74.76; H, 7.91; N, 5.74.

Acknowledgment. This investigation was supported by the Comisión Asesora de Investigación Científica y Técnica, Spain.

Registry No. **1a**, 59097-06-2; **1a**·HCl, 52632-29-8; **1b**, 80845-58-5; **1b**·HCl, 95532-97-1; (±)-*cis*-**2a**, 95532-98-2; (±)-*cis*-**2a**·HCl, 95533-26-9; (±)-*trans*-**2a**, 95532-99-3; (±)-*trans*-**2a**·HCl, 95533-27-0; (±)-*cis*-**2b**, 95533-00-9; (±)-*cis*-**2b**·HCl, 95533-28-1; (±)-*trans*-**2b**, 95533-01-0; (±)-*trans*-**2b**·HCl, 95533-29-2; (±)-**3**, 80845-50-7; (±)-**4**, 80845-52-9; **5**, 95533-02-1; **6**, 95533-03-2; **6**·HCl, 95533-04-3; (±)-**7a** (isomer 1), 95533-05-4; (±)-**7a** (isomer 1)·HCl, 95533-06-5; (±)-**7a** (isomer 2), 95533-30-5; (±)-**7a** (isomer 2)·HCl, 95533-31-6; (±)-**7b** (isomer 1), 95533-07-6; (±)-**7b** (isomer 1)·HCl, 95533-08-7; (±)-**7b** (isomer 2), 95533-32-7; (±)-**7b** (isomer 2)·HCl, 95533-33-8; (±)-**8a**, 28192-70-3; (±)-**8b**, 28192-71-4; (±)-**9a**, 95533-09-8; (±)-**9b**, 95588-59-3; **10**, 39998-19-1; (±)-**11**, 95533-10-1; **12**, 95533-11-2; (±)-**13**, 95533-12-3; (±)-**14**, 95533-13-4; (±)-*cis*-**15**, 95533-16-7; (±)-*trans*-**15**, 95533-20-3; (±)-*cis*-**15** (acid), 95533-22-5; (±)-*trans*-**15** (acid), 95533-34-9; (±)-**16**, 95533-18-9; (±)-**17**, 95533-14-5; (±)-*cis*-**18**, 95533-17-8; (±)-*trans*-**18**, 95533-21-4; (±)-*cis*-**18** (acid), 95533-23-6; (±)-*trans*-**18** (acid), 95533-35-0; (±)-**19**, 95533-19-0; (±)-**20**, 95533-15-6; *m*-$CH_3OC_6H_4Br$, 2398-37-0; 1-methyl-4-(methoxycarbonyl)pyridinium iodide, 7030-02-6; 1-benzyl-4-(methoxycarbonyl)pyridinium iodide, 7630-02-6; 1-(1-benzyl-3-ethyl-4-piperidyl)-1-propanone, 95533-24-7; 3-indolyl iodide, 26340-47-6; methyl 1-methyl-4-piperidineacetate, 95533-25-8.

(42) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.