A Biogenetically Modeled Synthesis *via* an Indole Acrylic Ester. A Total Synthesis of (±)-Minovine[1]

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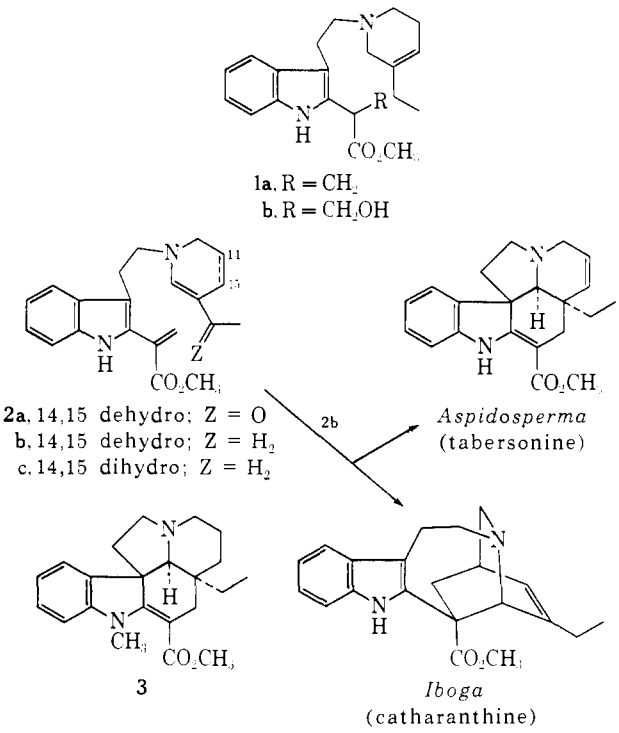
Abstract: The details of a total synthesis of (±)-minovine (**3**), patterned upon biogenetic considerations, are discussed.

In 1962 Wenkert[4] postulated that a protonated form of dihydropyridine acrylic ester **2a** might play an integral role in the biosynthesis of *Aspidosperma* and *Iboga* alkaloids. In recent years, *in vitro* experiments have been reported with alkaloids of these classes in an attempt to verify the intermediacy of the acrylic esters **2b**.[5] During this period secodine (**1a**) and 16,17-dihydrosecodin-17-ol (**1b**) have been isolated[6] and synthesized.[6c,7] Moreover, secodine has been shown to incorporate *in vivo* into the *Aspidosperma* nucleus.[7,8]

It was our intention to investigate the viability of the addition of an endocyclic enamine to a 2,2′-indole acrylic ester followed by a Mannich closure.[9] Although the ultimate test would have been the construction of acrylic ester **2b** or **2c**, prudence dictated that the manipulation of such a reactive functionality would be best accommodated by isolating the reactive moieties in separate substrates and only at the designated time to allow their chemical union.

Whereas an appropriate endocyclic enamine **4**[12] was already at hand from previous work, it was necessary to consider a suitable means of constructing a 2,2′-indole acrylic ester. Since it was known[13] that *N*-methylindole is capable of undergoing lithiation at the 2 position, it was an easily accessible method of appropriate functionalization of the indole nucleus which mandated that minovine (**3**) be a convenient test of the biogenetic-like sequence.



When ethyl oxalate was added dropwise to an ethereal solution of the lithioindole, only trace amounts of the desired ethyl 1-methyl-2-indole glyoxylic ester **5a** could be detected, the two major products being the diketone **6** and the hydroxy ketone **7**. Since it was apparent that the glyoxylic ester was undergoing further reactions, the situation was ameliorated by the slow addition of the lithium reagent to an excess of ethyl oxalate in ether. The major product from the inverse addition was the glyoxylate **5a** which was directly converted to its crystalline free acid **5b** by saponification of the reaction mixture, which served to allow facile chemical separation from both neutral species **6** and **7**. Treatment of the glyoxylic acid with ethereal diazomethane provided the methyl ester **5c** as a yellow oil whose nuclear magnetic resonance spectrum revealed two three-proton singlets at δ 3.95 and 3.99 (NCH_3 and

(1) For a preliminary account of this work, see F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, 92, 3492 (1970).

(2) National Institutes of Health Career Development Awardee, 1973–1978.

(3) National Institutes of Health Predoctoral Fellow, 1966–1969; taken in part from the Ph.D. Thesis of E. B. S., Yale University, 1970.

(4) E. Wenkert, *J. Amer. Chem. Soc.*, **84**, 98 (1962).

(5) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 945, 947, 948 (1968); A. I. Scott, P. C. Cherry, and A. A. Qureshi, *J. Amer. Chem. Soc.*, **91**, 4932 (1969); A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970); R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, *Chem. Commun.*, 1475 (1969); R. T. Brown, J. S. Hill, G. F. Smith, and K. S. J. Stapleford, *Tetrahedron*, 27, 5217 (1971); A. I. Scott, *J. Amer. Chem. Soc.*, 94, 8262 (1972); and A. I. Scott and C. C. Wei, *ibid.*, **94**, 8263, 8264, 8266 (1972). A considerable amount of controversy has arisen over these results. We leave the reader to formulate his own opinions.

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(7) J. P. Kutney, J. F. Beck, C. Ehret, G. A. Poulton, R. S. Sood, and N. D. Wescott, *Bioorg. Chem.*, 1, 194 (1971).

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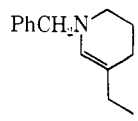
(9) The applicability of an intramolecular Mannich condensation in the indole alkaloid field was demonstrated by Schmid[10] and has been employed in the synthesis of indole alkaloids.[11]

(10) D. Schumann and Schmid, *Helv. Chim. Acta*, **46**, 1996 (1963).

(11) (a) B. W. Bycroft, D. Schumann, M. B. Patel, and H. Schmid, *ibid.*, **47**, 1147 (1964); (b) J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, and V. R. Nelson, *J. Amer. Chem. Soc.*, 90, 3891 (1968); (c) J. P. Kutney, E. Piers, and R. T. Brown, *ibid.*, **92**, 1700 (1970); (d) J. P. Kutney, W. J. Cretney, J. R. Hadfiled, E. S. Hall, and V. R. Nelson, *ibid.*, **92**, 1708 (1970); (e) G. C. Crawley and J. Harley-Mason, *Chem. Commun.*, 685 (1971); c and d are full papers relating to work communicated in 1964.

(12) F. E. Ziegler, J. A. Kloek, and P. A. Zoretic, *J. Amer. Chem. Soc.*, **91**, 2342 (1969); R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *Chem. Commun.*, 877 (1969).

(13) D. A. Shirley and P. A. Roussel, *J. Amer. Chem. Soc.*, 75, 375 (1953).



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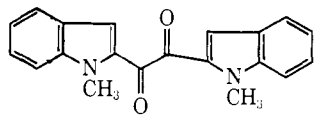

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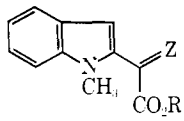
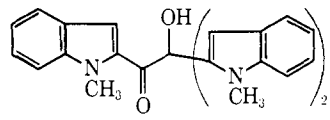


5a, R = C_2H_5; Z = O
b. R = H; Z = O
c. R = CH_3; Z = O
d. R = CH_3; Z = CH_2



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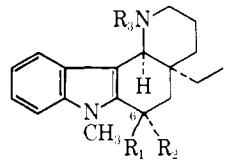
CO_2CH_3) and a one-proton singlet at δ 7.59 (indole β H). Treatment of glyoxylate **5c** with methylenetriphenylphosphorane provided the desired acrylate **5d**, which was readily characterized by the presence of two one-proton doublets (J = 2 Hz) at δ 5.93 and 6.58.

With the acrylic ester in hand, the critical condensation with 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine (**4**) was performed in refluxing methanol, which yielded two isomeric tetracyclics. Separation of the isomers was achieved by fractional crystallization to provide two isomers, mp 167–168 and 173–174°, which were shown (*vide infra*) to have the stereochemistry represented by structure **8a** and **8b**, respectively. Both isomers gave appropriate molecular ions (*m/e* 416) in their mass spectra in addition to indicating the facile loss of benzyl (*m/e* 325) and ethyl (*m/e* 387) fragments. In addition, the ultraviolet spectra revealed typical 2,3-substituted indole chromophores, while the infrared spectra displayed saturated ester absorption (1740 cm^{-1}).



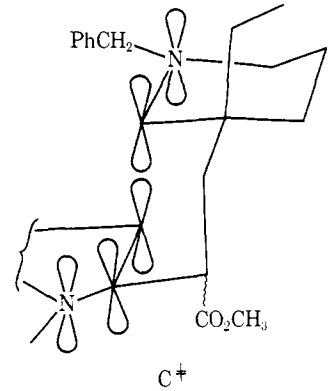
8a, $R_1 = CO_2CH_3$; R_2 = H; $R_3 = PhCH_2$
b, R_1 = H; $R_2 = CO_2CH_3$; $R_3 = PhCH_2$
c, $R_1 = CH_2OH$; R_2 = H; $R_3 = PhCH_2$
d, R_1 = H; $R_2 = CH_2OH$; $R_3 = PhCH_2$
e, $R_1 = CO_2CH_3$; R_2 = H; R_3 = H
f, R_1 = H; $R_2 = CO_2CH_3$; R_3 = H
g, $R_1 = CO_2CH_3$; R_2 = H; $R_3 = CH_2CH_2Br$
h, R_1 = H; $R_2 = CO_2CH_3$; $R_3 = CH_2CH_2Br$

A priori, four diastereomeric tetracyclics could have been formed. The appearance of only two isomers indicated that one was probably dealing with a mixture of epimeric esters having either a cis or a trans fused ring juncture. That this was indeed the case was confirmed by refluxing a solution of each isomer in methanol-d_1 containing sodium methoxide. Under these conditions the epimeric nature of the two isomers at the ester center was conclusively established since the ester **8a** was converted to ester **8b**, while the latter ester was recovered from its epimerization. In both instances, the thermodynamic ester **8b** contained a single deuterium (*m/e* 417), thereby dictating that both epimers had undergone deprotonation.

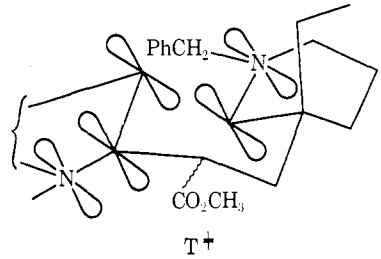
These data necessitated the conclusion that the epimers had the same ring juncture stereochemistry, the nature of which was elucidated spectroscopically. The 100-MHz nuclear magnetic resonance spectrum of ester **8a** revealed the α-ester proton (C-6 H) as a doublet of doublets (J = 7 and 10 Hz) centered at δ 3.98. On the other hand, the hydrochloride of ester **8a** displayed an extremely detailed spectrum which clearly revealed the same proton as a triplet (J = 9 Hz) centered at δ 3.98. Moreover, the nonequivalent protons at C-5 could each be easily recognized as a doublet of doublets (J = 9 and 14 Hz) centered at δ 2.62 and 2.12. Irradiation of the triplet signal caused the collapse of both upfield signals. The multiplicity of the C-6 proton requires ring C to undergo a conformational change from a half-chair in **8a** to a half-boat in **8a**·HCl. The latter's higher energy is maintained through strong hydrogen bonding between the protonated amine and the ester carbonyl. This effect was also observable as a −10-cm^{-1} shift in the carbonyl frequency of ester **8a**·HCl compared with either free bases **8a** or **8b**. These data clearly dictated a cis fused ring juncture since a trans fused ester having the ester group and the basic nitrogen cis to one another cannot become proximate to allow for the necessary hydrogen bonding.

Corroborative evidence for the stereochemical assignment was obtained from the alcohols **8c** and **8d** prepared by lithium aluminum hydride reduction of the esters **8a** and **8b**, respectively. The alcohol **8c** displayed concentration independent intramolecular hydrogen bonding while the isomeric alcohol **8d** revealed concentration dependent intermolecular hydrogen bonding in its solution infrared spectra.

The ring juncture results as a consequence of favorable orbital overlap during the Mannich closure. Thus, the transition state $C^{\mp}$ maintains complete orbital



$C^{\mp}$



$T^{\mp}$

overlap in the transition state, while the incipient ring B is in a chair-like conformation and ring D undergoes a half-chair to chair conversion. Moreover, transition state $T^{\mp}$, although capable of maintaining ring B in a chair conformation, necessitates ring D to be in a half-boat to obtain overlap and produces a

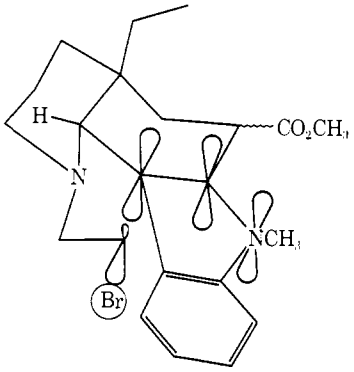
situation wherein the indole β H and the methylene of the ethyl group[14] create severe steric interactions.

Having established the annelation sequence as a viable synthetic reaction capable of elaborating the correct ring juncture stereochemistry present in the *Aspidosperma* alkaloids, attention was now turned to the incorporation of the two-carbon tryptamine residue. The esters **8a** and **8b** could be cleanly debenzylated by catalytic hydrogenation over palladized charcoal in methanolic hydrogen chloride at room temperature providing the secondary amines **8e** and **8f**, respectively.

The introduction of the tryptamine residue was envisaged as proceeding through a double alkylation involving an initial alkylation of the secondary amine with subsequent β-indole alkylation on an appropriate 1,2-disubstituted electrophilic ethane. This scheme was realized when either secondary amine was treated with ethylene dibromide in refluxing dimethylformamide containing anhydrous sodium carbonate, producing (±)-minovine (**3**)[15] identical with a sample of natural origin[16] by comparison of solution infrared spectra, mass spectra, and thin layer chromatography.

Subjection of esters **8e** and **8f** to the reaction conditions in the absence of ethylene dibromide resulted in their recovery without epimerization, indicating that the alkylation at the β-indole position was occurring *via* the indole nucleus as opposed to alkylation through the γ position of the ester enolate.

The cis fusion present in β-bromoethyl amines **8g** and **8h** allows for efficient overlap in the transition state of the indole π system with the carbon–bromine σ bond (structure A). The resultant indolenine is subsequently deprotonated generating the β-amino acrylate chromophore.



A

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Microanalyses were performed by Galbraith (Knoxville) and Bernhardt (Hohenweg) Laboratories.

Infrared spectra were recorded on a Perkin-Elmer Model 421- or 237B spectrometer. Nuclear magnetic resonance spectra were obtained with Varian Model A-60, A-60A, and HA-100 instruments. Chemical shifts are reported in δ units using tetramethylsilane as an internal standard. Ultraviolet spectra were taken on a Bausch and Lomb Spectronic 505 or Cary 11S recording spectrometer. Mass spectra were recorded on a Hitachi RMU-6 or AE1-MS9 spectrometer.

Except where noted, solvents are reagent grade and were used without purification. Organic solutions were dried over anhydrous magnesium sulfate unless specified otherwise.

1-Methyl-2-indoleglyoxylic Acid (5b). To a stirred solution of 5.24 g (0.04 mol) of 1-methylindole[17] in 75 ml of dry ether maintained under a nitrogen atmosphere was added 30.0 ml (0.042 mol) of 1.4 *M* *n*-butyllithium in hexane *via* a syringe, after which the solution was refluxed for 5 hr. The cooled solution was in turn added dropwise over 40 min to a vigorously stirred solution of 25 g (0.17 mol) of ethyl oxalate in 100 ml of dry ether at 0°. After the addition was complete, the reaction mixture was stirred an additional hour at 0°, followed by decomposition with saturated sodium sulfate solution. The layers were separated, the aqueous portion was washed twice with ether, and the ether solutions were combined, dried, and concentrated *in vacuo* to remove ether and excess ethyl oxalate.

The residue was dissolved in 50 ml of methanol, treated with 50 ml of 25% potassium hydroxide in aqueous methanol (1:1), and allowed to stir at room temperatue overnight. After the addition of water and thorough extraction with methylene chloride, the aqueous phase was cooled in ice–water and cautiously acidified with concentrated hydrochloric acid. The acidified solution was extracted with methylene chloride, dried, and concentrated *in vacuo* to yield 4.76 g (59%) of an orange solid, mp 109–112°. Recrystallization from benzene provided orange crystals of the acid: mp 113.5–114°; ir ($CHCl_3$) 3310 (broad), 3300, 1785, 1750, and 1630 cm^{-1}; nmr ($CDCl_3$) δ 4.01 (3 H, s), 6.98–7.80 (4 H, m), 8.25 (1 H, s), and 9.86 (1 H, s).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.93; H, 4.52; N, 7.03.

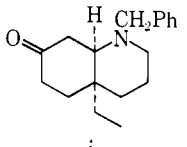
The dried and concentrated neutral fraction was chromatographed on Florisil providing 320 mg of 1-methylindole from the hexane eluent. Elution with benzene followed by crystallization from hexane–benzene gave 140 mg of yellow solid, mp 105–115°. Sublimation (125–135° (1 μ)) followed by crystallization from ether–petroleum ether gave 43 mg of yellow diketone **6**: mp 143–144°; ir ($CHCl_3$) 1650 cm^{-1}; nmr ($CDCl_3$) δ 4.18 (3 H, s), 7.32 (1 H, s), and 6.90–7.80 (4 H, m).

On another occasion the concentrated benzene eluent provided crystals from ether upon standing. Recrystallization from acetone gave pale yellow hydroxy ketone **6**: mp 253.5–255°; ir ($CHCl_3$) 3400, 2945, and 1645 cm^{-1}; nmr ($CDCl_3$) δ 3.78 (6 H, s), 4.18 (3 H, s), 5.52 (1 H, s), 6.35 (2 H, s), 6.83 (1 H, s), and 6.80–7.70 (12 H, m).

Methyl 1-Methyl-2-indoleglyoxylate (5c). To a stirred solution of 410 mg (2.0 mmol) of acid **5b** in 20 ml of methanol cooled in an ice–water bath was added an excess of ethereal diazomethane. After stirring 10 min, the excess diazomethane was destroyed with acetic acid and the ether solution washed with sodium bicarbonate solution, dried, and concentrated. Percolation of the residue through a short column of Florisil with 4:1 hexane–benzene gave 420 mg (96%) of the crude ester as an orange liquid, homogeneous by tlc: ir ($CHCl_3$) 1735 and 1650 cm^{-1}; nmr ($CDCl_3$) δ 3.95 (3 H, s), 3.99 (3 H, s), 7.59 (1 H, s), and 6.98–7.83 (4 H, m).

1-Methyl-2-(2′-carbomethoxyvinyl)indole (5d). In a dry 500-ml flask, fitted with a mechanical stirrer serum cap and reflux condenser, was placed, under nitrogen, 6.60 g (0.018 mol) of methyl triphenylphosphonium bromide in 200 ml of dry ether. To the stirred suspension was added *via* syringe 12.6 ml (0.018 mol) of 1.4 *M* butyllithium in hexane, and the mixtue was refluxed for 2 hr. After cooling to room temperature, a solution of 3.00 g (0.14 mol) of glyoxylate **5c** in 35 ml of dry ether was added as rapidly as possible with vigorous stirring, after which the mixture was refluxed for 40 min. The reaction mixture was cooled in an ice bath and decomposed with saturated sodium sulfate solution, and the ether

(14) These arguments also account for the formation of *cis*-amino ketone i[12] upon methyl vinyl ketone annelation of enamine **3**. See also



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(15) Racemic minovine has been previously synthesized (ref 11b).

(16) (a) We are grateful to Dr. J. Tomko, Institute of Chemistry, Bratislava, Czechoslovakia, for an authentic sample of minovine (*Vinca minor*): mp 79–81°, $[\alpha]D$ 0 ± 2°; (b) J. Mokry, L. Dubrakova, and Seflovic, *Experientia*, **18**, 564 (1962); (c) J. Mokry, I. Kompis, L. Dubrakova, and P. Sefcovic, *ibid.*, **19**, 311 (1963).

(17) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954); W. E. Noland, W. C. Kuryla, and R. F. Lange, *J. Amer. Chem. Soc.*, **81**, 6010 (1959).

layer was separated, washed twice with water, dried, and evaporated. Chromatography of the crude residue on a column of Florisil afforded from 5:1 hexane–benzene 2.27 g (73%) of the acrylate as a pale yellow oil, homogeneous by tlc: ir ($CHCl_3$) 1725 cm^{-1}; nmr ($CDCl_3$) δ 3.54 (3 H, S), 3.75 (3 H, S), 5.93 (1 H, d, J = 2 Hz), 6.49 (1 H, S), 6.58 (1 H, d, J = 2 Hz), and 6.85–7.70 (4 H, m); uv λ_{max} (MeOH) 295 nm (ϵ 5000), 283 (5000), 275 (5200), and 223 (27,400).

1-Benzyl-4a-ethyl-6-carbomethoxy-7-methyl-1,2,3,4,4a,5,6,11c-octahydro-7*H*-pyrido[3,2-*c*]carbazole (8a and 8b). A solution of 1.51 g (7.03 mmol) of acrylate **5d** and 3.19 g (15.9 mmol) of enamine **4** in 15 ml of methanol was refluxed under nitrogen for 13 hr. The cooled solution was diluted with 25 ml of methanol, scratched to induce crystallization, and placed in a refrigerator overnight. After filtration, 1.51 g of a pale yellow solid (mp 152–163°) was obtained. The mother liquors were concentrated, taken up in chloroform, and washed with 1% hydrochloric acid until the washings, which were in turn reextracted with chloroform, were acid. The combined chloroform extracts were neutralized with solid sodium carbonate, washed with water, dried, and concentrated. The residue upon trituration provided 80 mg of pale yellow solid which was combined with the original solid.

The combined solids (1.59 g) were dissolved in chloroform and thoroughly washed with 1% hydrochloric acid. After back extracting the aqueous acid solution with chloroform, the organic layers were combined, dried, filtered, and concentrated. Trituration of the residue with methanol provided 607 mg of ester **8a** as a white crystalline solid. Recrystallization from acetone–methanol gave chunky white crystals: mp 167–168°; ir ($CHCl_3$) 1740 cm^{-1}; nmr (acetone-d_6) δ 3.10 (d, 1 H, J = 13 Hz, $-CH_2Ph$), 3.61 (3 H, S), 3,80 (3 H, S), 3.98 (1 H, dd, J = 7 and 10 Hz, C_6H), and 4.10 (1 H, d, J = 12 Hz); uv λ_{max} (MeOH) 286 nm (ϵ 8300) and 222 (38,200); mass spectrum (70 eV) *m/e* (rel intensity) 416 (52), 387 (60), 325 (54), 210 (37), 200 (28), 194 (36), 181 (45), 146 (46), 120 (88), 106 (100), and 91 (88).

Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73. Found: C, 78.06; H, 7.71; N, 6.68.

The filtrate was concentrated and the residue triturated with acetone to give 789 mg of a white solid (**8b**·HCl, mp 229–231°). Treatment with methanolic sodium methoxide in methanol precipitated isomer **8b** as white needles: mp 173–174°; ir ($CHCl_3$) 1740 cm^{-1}; nmr (acetone-d_6) δ 3.07 (1 H, d, J = 13 Hz, $-CH_2Ph$), 3.55 (3 H, S), 3.72 (3 H, S), 3.72 (3 H, S), and 3.99 (1 H, d, J = 13 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 416 (18), 387 (58), 325 (10), 210 (14), 194 (15), 181 (16), 146 (24), 120 (100), 106 (96), and 91 (39).

Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 774; N, 6.73. Found: C, 78.04; H, 7.80; N, 6.67.

Hydrochloride Salt of Ester 8a. To 0.5 ml of 0.1 *M* methanolic hydrochloric acid was added 25 mg of ester **8a**, and the mixture was shaken until solution was achieved. The solution was concentrated *in vacuo* and the residual oil triturated with ethyl acetate to give 43 mg of the hydrochloride: mp 158–158.5°; ir ($CHCl_3$) 2925, 2450 broad, and 1725 cm^{-1}; nmr (MeOH-d_4) δ 0.80 (3 H, t, J = 7 Hz), 1.17 (2 H, t, J = 7 Hz), 2.12 (1 H, dd, J = 9 and 14 Hz), 2.62 (1 H, dd, J = 9 and 14 Hz), 3.75 (3 H, S), 3.92 (3 H, S), 4.28 (1 H, t, J = 9 Hz), 4.37 (1 H, d, J = 13 Hz), 4.61 (1 H, d, J = 13 Hz), and 4.62 (1 H, S).

1-Benzyl-4aα-ethyl-6α-hydroxymethyl-7-methyl-1,2,3,4,4a,5,6,-11cα-octahydro-7*H*-pyrido[3,2-*c*]carbazole (8d). To a suspension of 76 mg (2.0 mmol) of lithium aluminum hydride in 5 ml of tetrahydrofuran was added a solution of 100 mg (0.23 mmol) of ester **8b** in 1 ml of tetrahydrofuran, and the mixture was refluxed for 45 min. The reaction mixture was cooled, carefully decomposed with saturated sodium sulfate solution, diluted with water, extracted with chloroform, dried, and concentrated giving 98 mg of clear oil. Crystallization from ethyl acetate–isopropyl ether gave 40 mg of alcohol **8d**: mp 163–164°; ir ($CHCl_3$) 3620 (shifts to 3695 on dilution) and 3450 cm^{-1} (broad, disappears on dilution); mass spectrum (70 eV) *m/e* (rel intensity) 388 (10), 370 (12), 329 (15), 210 (16), 201 (22), 194 (23), 181 (17), 147 (29), 146 (56), 120 (84), 106 (60), and 91 (100).

1-Benzyl-4aα-ethyl-6β-hydroxymethyl-7-methyl-1,2,3,4,4a,5,6,-11cα-octahydro-7*H*-pyrido[3,2-*c*]carbazole (8c). In a similar fashion as described (*vide supra*), **8a** was converted to **8c**: mp 173–174°; ir ($CHCl_3$) 3430–2400 (no shift upon dilution); mass spectrum (70 eV) *m/e* (rel intensity) 388 (7), 370 (44), 357 (41), 330 (30), 329 (96?), 210 (40), 194 (30), 182 (37), 181 (34), 146 (50), 120 (100), 106 (87), and 91 (100).

4aα-Ethyl-6β-carbomethoxy-7-methyl-1,2,3,4,4a,5,6,11cα-octahydro-7*H*-pyrido[3,2-*c*]carbazole (8f). To a solution of 250 mg (0.6 mmol) of ester **8b** in 25 ml of methanol was added a sufficient amount of saturated methanolic hydrogen chloride to adjust the solution to pH 1. The resultant solution was hydrogenated over 25 mg of 10% palladium on charcoal at atmospheric pressure until gas uptake ceased. After removal of the catalyst, the solution was concentrated, partitioned between water and chloroform, and neutralized with 5% aqueous potassium hydroxide solution. The layers were separated and the organic phase extracted twice with chloroform. The combined organic extracts were dried and concentrated to give a clear oil. Trituration with hexane afforded 144 mg of white solid which upon recrystallization afforded clear prisms: mp 103–104° (hexane); ir ($CHCl_3$) 3420 and 1730 cm^{-1}; uv λ_{max} (MeOH) 291 sh nm (ϵ 5700), 282 (6900), 277 (ϵ 6700), and 221 nm (ϵ 31,000).

Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03; N, 8.58. Found: C, 73.78; H, 7.99; N, 8.55.

4aα-Ethyl-6α-carbomethoxy-7-methyl-1,2,3,4,4a,5,6,11cα-octahydro-7*H*-pyrido[3,2-*c*]carbazole (8e). In the same manner as described for the preparation of **8f** (*vide supra*), ester **8a** provided secondary amine **8e**: mp 96–96.5° (hexane); ir ($CHCl_3$) 3420 and 1730 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03; N, 8.58. Found: C, 73.47; H, 7.89; N, 8.48.

(±)-Minovine (3). A mixture of 192 mg (0.59 mmol) of amine **8e**, 132 mg (0.70 mmol) of ethylene dibromide, and 240 mg (2.4 mmol) of anhydrous sodium carbonate in 3 ml of freshly distilled dimethylformamide was refluxed under nitrogen for 14 hr. The reaction mixture was cooled, diluted with water, extracted with chloroform, backwashed with water, dried, and concentrated *in vacuo* (the remaining dimethylformamide being removed with a vacuum pump) leaving 172 mg of an orange gum. Chromatography on Florisil with benzene (redistilled) removed considerable nonpolar material. Subsequent elution with 99:1, 95:5, 90:10, and 75:25 benzene–ether provided fractions containing minovine. The combined fractions were rechromatographed in the same fashion again providing four fractions, the first three of which were rechromatographed using 80:20 and 50:50 benzene–hexane to remove the remaining nonpolar material. Further elution with benzene and 99:1 and 90:10 benzene–ether provided oils, each of which was homogeneous by thin layer chromatography (3:1 benzene–ethyl acetate and 9:1 benzene–acetone), in a combined yield of 20% (9% from **8f**). Attempts to crystallize these samples met with repeated failure. The major fraction (99:1) was identical with a sample from natural sources[16] by comparison of their solution infrared, ultraviolet, and mass spectra. In addition, all samples of minovine produced the same blue color upon spraying the chromatograms with 1% ceric ammonium nitrate in 85% phosphoric acid.

Acknowledgment. Financial support for this work was provided by the National Cancer Institute, National Institutes of Health (CA-08869), the National Science Foundation (GP-5828), and Eli Lilly and Company. We thank Professor A. I. Scott for many stimulating discussions and Dr. G. Bennett for recording numerable 100-MHz nmr spectra.