of browniine, 107 mg (1.05 mmol) of (*S*)-(+)-2-methylbutyric acid ($[\alpha]^{22}_D$ +19.3° ($CH_2Cl_2$)), 217 mg (1.05 mmol) of DCC, and 32.1 mg (0.26 mmol) of DAP in 10 mL of dichloromethane was heated at reflux for 20 h. The usual workup procedure furnished 74 mg of crude product which was placed upon a column containing 15 g of alumina (activity III). The column was eluted with ethyl acetate to yield 62.2 mg (61%) of 14-(2-methylbutyryl)browniine (**10**), mp 110.5–111.5 °C. Recrystallization from hexane/acetone twice afforded **10** with a melting point of 113–118 °C and $[\alpha]^{17}_D$ +39.9° (*c*, 0.72, MeOH), in excellent agreement with the corresponding measurements for a sample of glaucedine isolated from the plant.

**Acknowledgment.** The initial phase of this work was supported in part by Grant CA 24180 from the National Cancer Institute, Department of Health, Education, and Welfare. We thank Mr. Courtney Pape for the mass spectra.

**Registry No.** 1, 6836-11-9; 2, 59989-92-3; 3, 78018-27-6; 3 perchlorate, 78018-28-7; 4, 78018-29-8; 5, 78018-30-1; 6, 75659-26-6; 6 perchlorate, 78018-31-2; 7, 50657-27-7; 8, 4829-56-5; 9, 5140-42-1; 9 perchlorate, 5005-20-9; 10, 78039-66-4; 11, 65601-04-9; 12, 21019-30-7; 13, 78018-32-3; 13 perchlorate, 78018-33-4; 15, 545-56-2; 16, 26000-17-9; 17, 22413-78-1; 18, 78018-34-5; 19, 58480-82-3; isobutyryl chloride, 79-30-1; 2-methylbutyryl chloride, 5856-79-1; benzoyl chloride, 98-88-4; (+)-α-methylbenzylamine, 3886-69-9; (*S*)-(+)-2-methylbutyric acid, 1730-91-2.

# Synthesis and Chemistry of a Stabilized Dehydrosecodine Model System[1]

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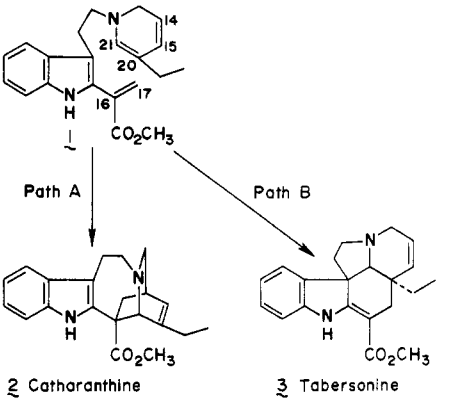
A stabilized dehydrosecodine analogue bearing carbomethoxy groups in the 3- and 5-positions of the dihydropyridine moiety has been prepared and its chemistry studied. Two novel procedures have been developed for this synthesis: (1) the Lewis acid assisted cleavage of an activated indole ether with trimethylsilyl cyanide to form a cyano alcohol and (2) the oxidation of 2-(α-substituted ethyl)indoles with *tert*-butyl hypochlorite to form the corresponding 2-vinylindole derivatives. Thermal decomposition of the dehydrosecodine analogue does not yield the desired intramolecular Diels–Alder adducts but instead seems to proceed by an intramolecular hydride transfer from the 1,2-dihydropyridine moiety to the vinylindole group.

Experimental evidence in support of the Thomas–Wenkert monoterpenoid hypothesis[2] for the biosynthesis of the indole alkaloids led Scott to propose a modified mechanistic scheme for the biosynthesis of the *Aspidosperma* and *Iboga* alkaloids (Scheme I).[3] The pivotal intermediate in this scheme, 14,21-dehydrosecodine (**1**),[4] might undergo an intramolecular Diels–Alder reaction in either of two ways (Scheme I): in path A, the dihydropyridine reacts as a diene leading to the formation of catharanthine (**2**); in path B, the dihydropyridine serves as the dienophile leading to the formation of tabersonine (**3**). Unfortunately, dehydrosecodine **1** or even dihydropyridines related to **1** have not been isolated or synthesized because of their propensity toward oxidation, dimerization, and polymerization.

Büchi and co-workers[5] used an *inter*molecular Diels–Alder reaction (path A type) between 1-benzyl-3-cyano-1,6-dihydropyridine and methyl vinyl ketone in their syntheses of ibogamine and ibogaine. Ziegler and Spitzner[6] used an *inter*molecular reaction (path B type) between methyl α-(*N*-methylindol-2-yl)acrylate and 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine in a biogenetically patterned synthesis of (±)-minovine. Kuehne and co-workers[7] subsequently reported the related *intra*molecular Diels–Alder reaction (path B type) of the biogenetically postulated secodine isomer (14,15-dihydro **1**) to give vincadifformine (14,15-dihydro **3**). Most recently, Fowler and co-workers[8] have elegantly demonstrated that the *inter*molecular Diels–Alder reaction between ethyl α-(*N*-methylindol-2-yl)acrylate and *N*-methyl-1,2-dihydropyridine does indeed proceed along both pathways A and B as depicted in Scheme I to give *Aspidosperma*- and *Iboga*-type products in a 2.3:1 ratio. Several other laboratories[9] have recently reported progress toward the syn-

Scheme I




(1) A preliminary account of this work was presented at the 179th National Meeting of the American Chemical Society, Houston, TX, Mar 24–28, 1980.

(2) (a) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98. (b) Thomas, R. *Tetrahedron Lett.* **1961**, 544.

(3) (a) Qureshi, A. A.; Scott, A. I. *Chem. Commun.* **1968**, 945, 947, 948. (b) Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151. (c) Scott, A. I. *Bioorg. Chem.* **1974**, *3*, 398. (d) Scott, A. I.; Qureshi, A. A. *Tetrahedron* **1974**, *30*, 2993. (e) Scott, A. I.; Wei, C. C. *Ibid.* **1974**, *30*, 3003. (f) Scott, A. I.; Cherry, P. C.; Wei, C. C. *Ibid.* **1974**, *30*, 3013.

(4) The numbering system for indole alkaloids was proposed by: Le-Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(5) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1966**, *88*, 3099.

(6) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146.

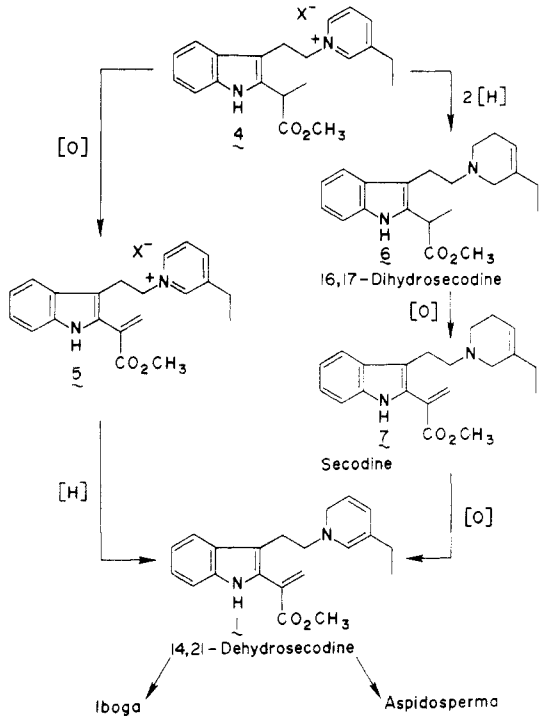
(7) (a) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705. (b) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. *Ibid.* **1979**, *44*, 1063.

(8) Weinstein, B.; Chang Lin, L.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1657.

(9) (a) Beeken, P.; Bonfiglio, J. N.; Hasan, H.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677. (b) Kutney, J. P.; Badger, R. A.; Beck, J. F.; Bosshardt, H.; Matough, F. S.; Ridaura-Sanz, V. E.; So, Y. H.; Sood, R. S.; Worth, B. R. *Can. J. Chem.* **1979**, *57*, 289.

0022-3263/81/1946-3293$01.25/0 

Scheme II




thesis of various α-(indol-2-yl)acrylates via the Claisen ortho ester rearrangement,[10] sulfoxide eliminations,[11] and alkylation[12] or acylation[13] of N-protected 2-lithioindoles.

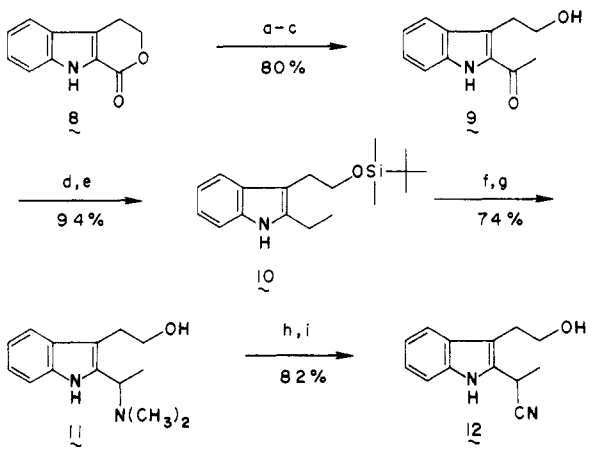
These papers have prompted us to report our results dealing with approaches to the synthesis of dehydrosecodine and its analogues. The synthetic framework upon which we have been concentrating our efforts is outlined in Scheme II. Dehydrosecodine **1** might be derived from the tryptophylpyridinium salt **4** by either of two routes, both of which involve an adjustment of the oxidation levels of the indole and pyridinium moieties. In the most direct approach the indole half might be oxidized one level to the 2-vinylindole **5** and the pyridinium half reduced one level to the dihydropyridine **1**. In an alternative, less direct, but perhaps more biosynthetically relevant approach, the pyridinium moiety could be reduced two levels to the tetrahydropyridine **6** (dihydrosecodine) followed by oxidation of the indole moiety one level to the 2-vinylindole **7** (secodine) and reoxidation of the tetrahydropyridine one level to the dihydropyridine **1**.

In the work reported here we have examined the more direct route using analogues of the (2-vinyltryptophyl)-pyridinium salt **5** bearing electron-withdrawing substituents on the pyridinium nucleus and studied the chemistry of the resulting stabilized derivatives of dehydrosecodine.

## Syntheses of (2-Vinyltryptophyl)pyridinium Salts

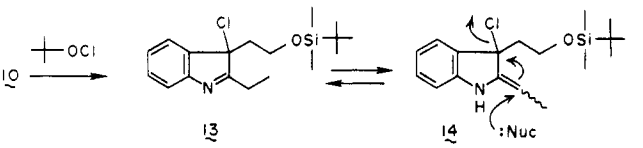
Our initial synthetic route to cyano alcohol **12**, the key intermediate for further elaboration to (2-vinyltryptophyl)pyridinium salts related to **5**, began with lactone **8** (Scheme III), prepared in four steps from γ-butyrolactone according to the procedure of Plieninger.[14] Hydrolysis of **8** followed by treatment of the resulting hydroxy acid[15] with excess methyllithium gave methyl ketone **9**. After Wolf–Kishner reduction of the ketone **9**, the alcohol was protected as the *tert*-butyldimethylsilyl ether[16] to give **10** in 74% overall yield from lactone **8**.

Scheme III[a]

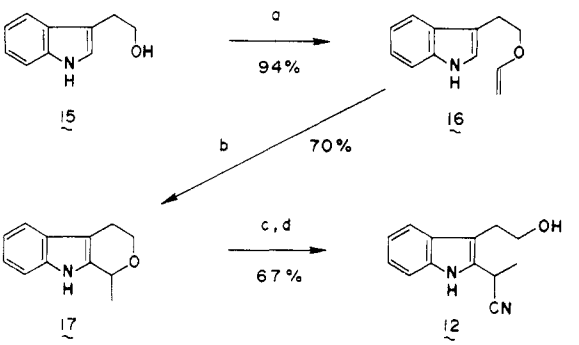



[a] (a) LiOH, $CH_3OH$; (b) HCl, $H_2O$; (c) $CH_3Li$, THF; (d) $H_2NNH_2$, $H_2O$, KOH, diethylene glycol, 200 °C; (e) *t*-$Bu(CH_3)_2SiCl$, imidazole, DMF; (f) *t*-BuOCl, $CH_2Cl_2$, $Et_3N$; (g) $HN(CH_3)_2$, $CH_3OH$; (h) $CH_3I$, EtOAc; (i) KCN, 18-crown-6, $CH_3CN$.

Scheme IV




Scheme V[a]




[a] (a) Ethyl vinyl ether, $Hg(OAc)_2$; (b) $CF_3CO_2H$, $CH_2Cl_2$, 15–18 °C; (c) $Me_3SiCN$, $ZnCl_2$, 105 °C, 72 h; (d) KF, HOAc, THF, $H_2O$.

(10) (a) Raucher, S.; Hwang, K; Macdonald, J. E. *Tetrahedron Lett.* **1979**, 3057. (b) Raucher, S.; Macdonald, J. E.; Lawrence, R. F. "Abstracts of Papers", Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 25–29, 1980; American Chemical Society: Washington, DC; ORGN 249. (c) Raucher, S; Lawrence, R. F.; Macdonald, J. E. *Ibid.* ORGN 342.

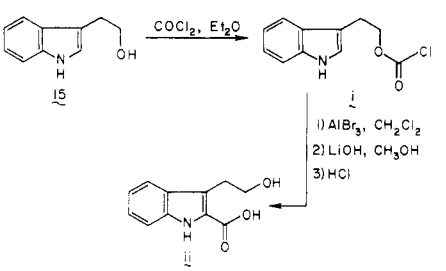
(11) (a) Marazano, C.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1977**, 742. (b) Marazano, C.; Fourrey, J.-L.; Das, B. C. *Ibid.* **1981**, 37.

(12) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382.

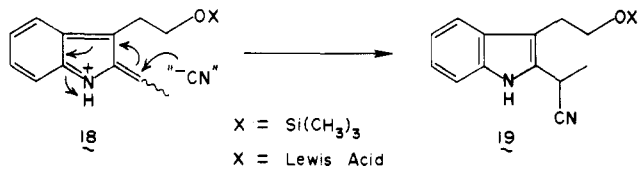
(13) Hasan, I.; Marinelli, E. R.; Chang Lin, L.-C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.

(14) Plieninger, H. *Chem. Ber.* **1950**, *83*, 271.

(15) We were subsequently able to prepare hydroxy acid ii in 45% yield (unoptimized) from the $AlBr_3$-catalyzed cyclization of 2-(1*H*-indol-3-yl)ethyl chloroformate (i) to lactone **8** followed by hydrolysis.



Scheme VI




Silyl ether **10** was then oxidized to the 3-chloroindolenine derivative **13** with *tert*-butyl hypochlorite (Scheme IV). Previous workers[17] have shown that compounds similar to **13** undergo nucleophilic attack at the $\alpha$-carbon of the enamine tautomer as indicated in Scheme IV. However, the direct introduction of the desired nitrile functional group into the side chain of **10** via **14** was not successful under a variety of conditions such as treatment of **13**/**14** with KCN/18-crown-6 or with $Et_2AlCN$. This difficulty was circumvented by treatment of the equilibrium mixture of **13**/**14** with dimethylamine in methanol to give, after acid hydrolysis of the silyl protecting group, the amino alcohol **11** in 74% yield. Conversion of **11** to the quaternary methiodide and displacement[18] in acetonitrile with KCN/18-crown-6 gave the desired cyano alcohol **12** in 82% yield.

Although this route did provide the requisite cyano alcohol **12**, it employed only conventional methods and involved so many steps that synthetically useful quantities of **12** could only be obtained with great effort and expense. Therefore, alternative approaches were sought. A particularly intriguing route was the cleavage of cyclic ether **17** (Scheme V) with trimethylsilyl cyanide ($Me_3SiCN$) to give **12** as the corresponding trimethylsilyl ether. Thus, tryptophol (**15**) was converted to its vinyl ether **16** by $Hg(OAc)_2$-catalyzed exchange with ethyl vinyl ether;[19] treatment of **15** with three portions of freshly distilled ethyl vinyl ether gave a 79% yield of **16** (94% based upon recovered tryptophol). Cyclization of **16** with 7 mol % of trifluoroacetic acid (TFA) in methylene chloride at 15–18 °C provided cyclic ether **17** in 70% yield. Heating of **17** with powdered anhydrous $ZnCl_2$ in *neat* $Me_3SiCN$ (12 mL of $Me_3SiCN$/g of **17**) at 105 °C for 3 days gave, after removal of the *O*-silyl group with KF, cyano alcohol **12** in 67–73% yield. Lewis acids such as $ZnI_2$ and $TiCl_4$ were found to catalyze the cleavage rapidly at room temperature, but in yields of only 22% and 26%, respectively. Treatment of **17** with $Me_3SiCN$ and $AlCl_3$ at 65 °C for several hours was also effective in promoting cleavage, but the time of reaction, amount of catalyst required, and yields (45–70%) were more variable.

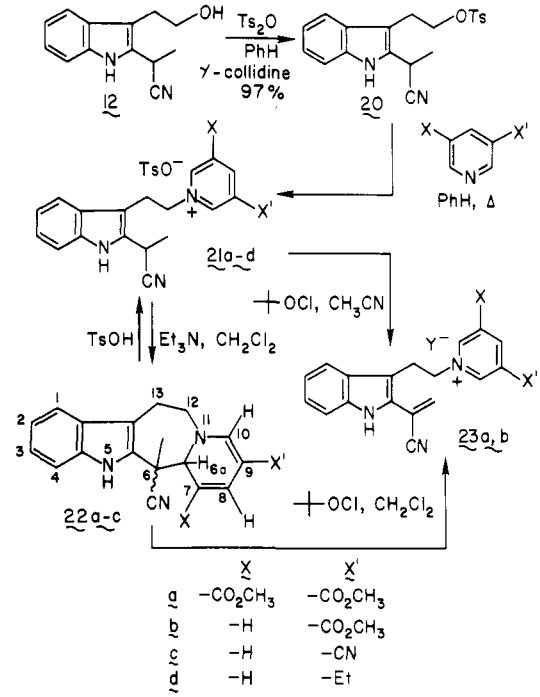
Although the precise mechanism of this reaction is not known, it is believed to proceed by initial formation of carbenium ion **18** (Scheme VI) to which cyanide adds to form **19**. Preliminary results for the analogous Lewis acid/$Me_3SiCN$ cleavage of 2-methyltetrahydrofuran indicated very poor nitrile yields. Therefore, this reaction may be limited to special cases in which a very stable carbenium ion such as **18** is an intermediate.

The overall yields of **12** via the two different synthetic routes to **12** are comparable: 46% via Scheme III vs. 44% via Scheme V. However, the greatest savings in utilizing the latter route are in time and expense: multigram quantities of **12** are readily available via Scheme V in about one-tenth the time required via Scheme III.

Table I. Yield of Intermediates in Scheme VII

| | % isolated yield (based on starting material no.) | | | |
|---|---|---|---|---|
| product | a | b | c | d |
| **21** | 80 (**12**) | 89 (**12**) | 80 (**12**) | 93 (**12**) |
| **22** | 85 (**21a**) | 96 (**21b**) | 50 (**12**) | |
| **23** (Y = Cl) | 88 (**22a**) | 0 (**22b**) | | |
| **23** (Y = TsO) | | 40 (**21b**) | | |

Scheme VII

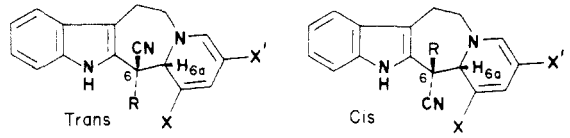



Cyano alcohol **12** was converted next to the corresponding tosylate **20** (Scheme VII and Table I) with *p*-toluenesulfonic acid anhydride[20] and $\gamma$-collidine in dry benzene at 25 °C for 30 min. The tosylate was normally not isolated, but the solution was concentrated and the residual oil rapidly filtered through a short silica gel column eluted with methylene chloride to remove the collidinium hydrotosylate and any excess collidine. The crude tosylate was then dissolved in a small volume of dry benzene and heated at 45–55 °C for 1–2 days with various substituted pyridines to give pyridinium salts **21a–d**.

Pyridinium salts **21a–c** were cyclized with triethylamine in methylene chloride to afford a mixture of epimeric seven-membered-ring dihydropyridines **22a–c** as the only cyclization products. In each case, the less polar epimer in which the 6-methyl and 6a-hydrogen are trans was formed as the major product. It had been observed previously[21] that for the dihydropyridines lacking the methyl group in the 6-position, **24** and **25**, the relative stereochemistry of the two epimers could be assigned on the basis of the chemical shift and coupling constant data for $H_{6a}$ (Table II). In *cis*-**24**, $H_{6a}$ appeared as a doublet ($J$ = 2.3 Hz) at $\delta$ 5.23 ($CDCl_3$), while in *trans*-**24**, $H_{6a}$ appeared as a doublet ($J$ = 10 Hz) at $\delta$ 5.52. The relative downfield chemical shift for $H_{6a}$ in the trans epimer can be attributed to the deshielding effect of the adjacent nitrile. If one can apply this same reasoning to the 6-methyldihydropyridines

(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(17) (a) Harley-Mason, J.; Atta-ur-Rahman *Chem. Commun.* **1967**, 208. (b) Dolby, L. J.; Gribble, G. W. *J. Org. Chem.* **1967**, *32*, 1391.
(18) Wenkert, E.; Dave, K. G.; Gnewuch, C. T.; Sprague, P. W. *J. Am. Chem. Soc.* **1968**, *90*, 5251.
(19) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.
(20) Field, L.; McFarland, J. W. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 940.
(21) (a) DiNinno, F., Jr.; Heckle, W. L., Jr.; Rehse, D. K.; Wilson, R. M. *Tetrahedron Lett.* **1972**, 2639. (b) Rehse, D. K. Ph.D. Dissertation, University of Cincinnati, 1979.

Table II. Chemical Shift Data for *trans*- and *cis*-Dihydropyridine Epimers[a]




| compd | substituents R | X | X' | shift, δ *trans*-$H_{6a}$ | *cis*-$H_{6a}$ |
|---|---|---|---|---|---|
| **22a** | Me | $CO_2Me$ | $CO_2Me$ | 5.61 | 5.40 |
| **22b** | Me | H | $CO_2Me$ | 5.02[b] | 4.71[b] |
| **22c** | Me | H | CN | 4.96 | 4.67 |
| **24**[c,d] | H | $CO_2Me$ | $CO_2Me$ | 5.52 | 5.23 |
| **25**[c] | H | $CO_2Me$ | $CO_2Me$ | 5.68[e] | 5.28[f] |
| **27** | Me | Cl | $CO_2Me$ | 5.40[e] | 4.77 |

[a] Spectra acquired in $CDCl_3$ unless noted otherwise. [b] $CD_3COCD_3$ + $CDCl_3$. [c] Reference 21b. [d] 6-CN replaced by 6-$CO_2Me$. [e] $CD_3SOCD_3$ + $CDCl_3$. [f] $CD_3SOCD_3$.

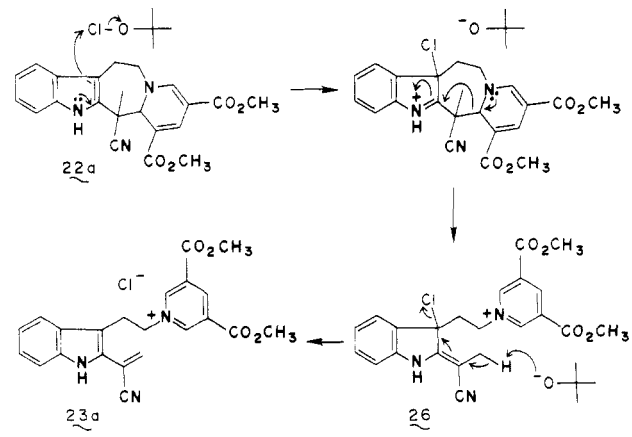
**22a–c** and **27**, then one can tentatively assign the trans stereochemistry to the major epimers, as in the NMR spectra of these epimers (*trans*-**22a–c** and *trans*-**27**) the signals for $H_{6a}$ are shifted downfield by 0.21–0.63 ppm relative to the signals for $H_{6a}$ in the minor epimers (*cis*-**22a-c** and *cis*-**27**). A variable ratio (7.5–13.1:1) of *trans*-/*cis*-**22a** was obtained, while for the carbomethoxy derivative **22b**, the trans isomer was formed almost exclusively. In contrast, *trans*-/*cis*-**22c** were formed in a 2:1 ratio. Whether these ratios reflect the relative thermodynamic stability of the two epimers or are merely a consequence of kinetic control in the cyclization is unknown at this time; however, it is interesting to note that the use of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) instead of triethylamine for the cyclization of **21b** afforded a 1.5:1 mixture of *trans*-/*cis*-**22b**. The separated epimers of dihydropyridines **22a–c** are stable only if they can be obtained in crystalline form, as they undergo equilibration in solution, slowly at room temperature and rapidly at 50 °C, to give mixtures of the trans and cis epimers. This interconversion makes purification of the individual epimers very difficult.

The assignment of **22b,c** as the 1,6-dihydropyridine isomers rather than the 1,2- or 1,4-dihydropyridine isomers is based on $^1H$ NMR data and analogy to previous results reported for the related compounds lacking the methyl group at the 6-position.[20a] For example, in *trans*-**22b**, $H_{6a}$ appears as a doublet (4.92 ppm, $J$ = 5 Hz), $H_7$ as a doublet of doublets (5.42 ppm, $J$ = 5 and 9 Hz), $H_8$ as a doublet (6.85 ppm, $J$ = 9 Hz), and $H_{10}$ as a singlet (7.60 ppm).

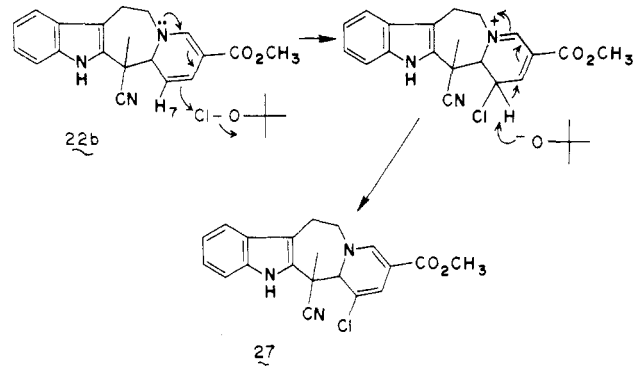
Finally, all of these condensations under basic conditions of the pyridinium salts to form the dihydropyridines can be reversed in the presence of strong acids (Scheme VII). Acid–base interconversions of this type can be quite useful in the isolation and purification of these pyridinium salts (**21a–c**) (see Experimental Section, preparation of **21a**).

The bis(carbomethoxy)dihydropyridine epimers **22a** were found to undergo a related and most interesting oxidative fragmentation (Schemes VII and VIII) with *tert*-butyl hypochlorite in methylene chloride to give the (2-vinyltryptophyl)pyridinium chloride **23a** which precipitated directly from the reaction mixture in 88% yield. The mechanism of this reaction is believed to involve initial chlorination at the 3-position of the indole nucleus[22,23] followed by fragmentation of the seven-membered ring

Scheme VIII




Scheme IX




facilitated by the lone pair of electrons on the nitrogen of the dihydropyridine.[24] The *tert*-butoxide generated in this process then might eliminate HCl from the intermediate **26** to give *tert*-butyl alcohol and the desired (2-vinyltryptophyl)pyridinium chloride **23a**.

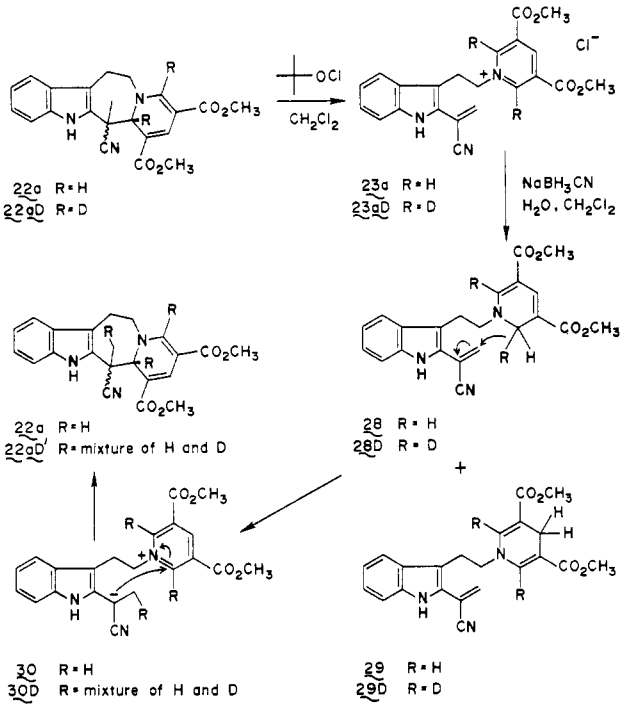
The oxidation of dihydropyridine **22b** with *tert*-butyl hypochlorite follows a different course (Scheme IX) to yield the chlorinated dihydropyridine epimers *trans*- and *cis*-**27** which were isolated in a 2.3:1 mixture, respectively. The molecular ions of these epimers indicated monochlorination, $m/e$ 367 and 369. For the more polar cis epimer, the $^1H$ NMR displayed singlets at δ 4.77 ($H_{6a}$) and 7.03 ($H_8$). The absence of $H_7$ was conspicuous. Apparently monsubstituted dihydropyridines such as **22b** undergo preferential electrophilic attack at the dihydropyridine rather than at the indole nucleus. A plausible mechanism that acounts for this observation is outlined in Scheme IX.

One can circumvent this problem by direct oxidation of pyridinium tosylate **21b** with *tert*-butyl hypochlorite in acetonitrile solution (Scheme VII) from which the (2-vinyltryptophyl)pyridinium tosylate **23b** precipitates as an orange powder in 40% yield. The actual yield of **23b** is much higher, as $^1H$ NMR analysis of the mother liquors indicated almost exclusive formation of the desired 2-vinyl derivative which exhibits two characteristic slightly broadened singlets in the NMR spectrum at δ 6.67 and 6.43 ($CD_3SOCD_3$) and an unsaturated nitrile peak at 2220 $cm^{-1}$ in the IR spectrum. However, concentrated solutions of this mother liquor undergo rapid decomposition to yield a black intractable tar.

Both of these crystalline (2-vinyltryptophyl)pyridinium salts **23a** and **23b** were quite stable. The instability of

(22) Godtfredson, W. O.; Vangedal, S. *Acta Chem. Scand.* **1956**, *10*, 1414.
(23) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871.
(24) Büchi observed the loss of chloride from the chloroindolenine obtained from ibogaine via a related fragmentation mechanism: Büchi, G.; Manning, R. E. *J. Am. Chem. Soc.* **1966**, *88*, 2532.

Scheme X




these substances in concentrated solutions of the crude reaction mixtures is not due to some intrinsic property of the 2-vinylindole moiety but rather to traces of *tert*-butyl hypochlorite or related substances which apparently initiate polymerization of the 2-vinylindole.[25] Thus, the oxidation of $\alpha$-substituted 2-ethylindoles to form 2-vinylindoles appears to be a general procedure which generates the desired 2-vinyl group in quite high yields in all cases examined to date.

## Preparation and Chemistry of a Stabilized 14,21-Dehydrosecodine Analogue

Reduction of **23a** with sodium cyanoborohydride in methylene chloride/water afforded a 1:2.3 mixture of dihydropyridines **28** and **29**, respectively (Scheme X). The $^1$H NMR spectrum of the mixture exhibited two singlets at 6.10 and 6.05 ppm for the vinylindole protons in both the 1,2- and 1,4-dihydropyridines, a singlet at 4.40 ppm for the 1,2-dihydropyridine protons at the 2-position, and a singlet at 3.18 ppm for the 1,4-dihydropyridine protons at the 4-position. This mixture could not be resolved by column chromatography on silica gel. However, the mixture was stable for months when stored as a dilute methylene chloride solution under nitrogen at −10 °C.

Only the 1,2-dihydropyridine **28** might function as a diene in the intramolecular Diels–Alder reaction to form the *Iboga* skeleton (Scheme I). In contrast, both the 1,2- and 1,4-dihydropyridines **28** and **29** might serve as dienophiles to form the *Aspidosperma* skeleton. With these considerations in mind, dilute solutions of this mixture were heated in an effort to induce the desired intramolecular Diels–Alder reaction. The only conditions which yielded a discrete product were refluxing a dilute methylene chloride solution of the mixture under an argon atmosphere for 5 days to give a 7–11% yield of **22a** (Scheme X). Apparently **28** undergoes an intramolecular hydride transfer to afford the betaine **30** which collapses to the

(25) In more recent work it has been observed that this problem can be eliminated by quenching the reaction mixture with $NaBH_3CN$ before concentration. Details of the procedure will be reported in a subsequent paper.

Scheme XI

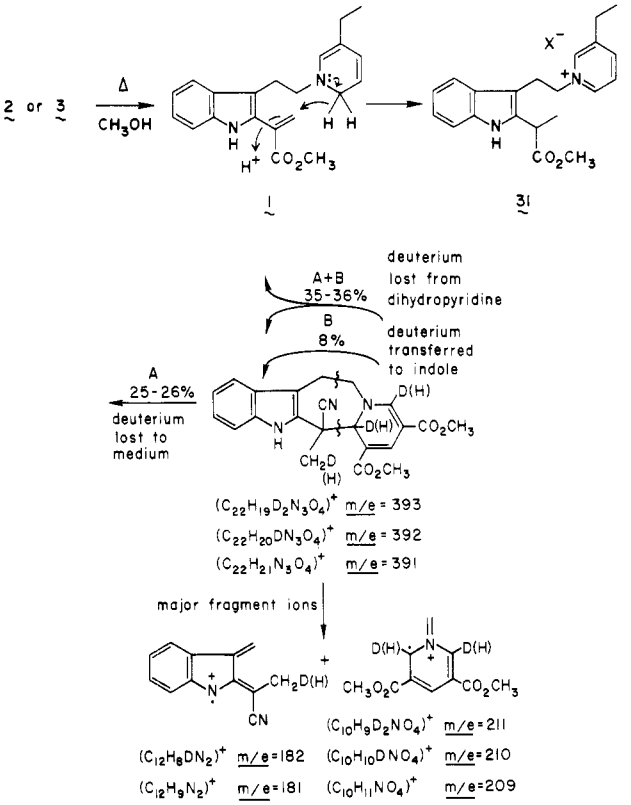



**Figure 1.** Fragmentation of **22aD'** in the mass spectrometer and the observed deuterium balance in the conversion of **22aD** to **22aD'** as outlined in Scheme X.

previously isolated cyclic dihydropyridine epimers **22a**. Scott[3f] reported the isolation of the pyridinium salt **31** (Scheme XI) from the thermal decomposition of either catharanthine (**2**) or tabersonine (**3**) in methanol. He proposed that **31** was formed from dehydrosecodine **1** via a similar hydride transfer from the 1,2-dihydropyridine to the acrylate double bond. Related intermolecular reductions of electron-deficient double bonds by dihydropyridines have been observed.[26]

In order to determine whether the double bond reduction in the dehydrosecodine analogues **28** and **29** was proceeding in an intramolecular mode involving only **28** or in an intermolecular mode involving both **28** and **29**, we prepared the 6a,10-dideuterio derivative **22aD** (Scheme X) in a manner analogous to the preparation of **22a**. A mixture of deuterated dihydropyridines **28D** and **29D** was prepared in the usual fashion, and the cyclic dihydropyridine epimers with the scrambled label (**22aD'**) were isolated from the thermal decomposition of **28D** and **29D**. The redistribution of deuterium label in the conversion of **22aD** to **28D'** is summarized in Figure 1. The deuterium lost by exchange with the medium[27] is determined to be 25–26% by comparison of the molecular ions ($m/e$ 393, 392, 391) for **22aD** and **22aD'**. The deuterium transferred to the indole moiety is determined to be 8% by comparison of the indole fragments ($m/e$ 182, 181) of **22aD** and **22aD'**. These values, (25–26%) + 8% = 33–34%, are in close agreement with the amount of deuterium lost by the dihydropyridine moiety which is determined to be 35–36% by comparison of the pyridinium

(26) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.

(27) Pyridinium salts can undergo proton exchange in the 2-position through zwitterionic species; see: (a) Zoltewicz, J. A.; Kauffman, G. M.; Smith, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 5939. (b) Ratts, K. W.; Howe, R. K.; Phillips, W. G. *Ibid.* **1969**, *91*, 6115.

fragments (*m/e* 211, 210, 209) of **22aD** and **22aD′**.

These values were compared with the theoretical amount of deuterium exchange for two possible mechanisms of vinyl group reduction: mechanism 1, intramolecular hydride transfer involving only **28D** (no product, **22aD′**, arising from **29D**); mechanism 2, all intramolecular or intermolecular hydride-transfer processes involving both **28D** and **29D**. Given that (1) the ratio of **28D** to **29D** is 1:2.3, (2) these substances are deuterated to the extent of 62% dideuterated and 22% monodeuterated, and (3) the deuterium isotope effect for reductions with dihydropyridines is $K_H/K_D = 4.5$,[28] and assuming that **28D** and **29D** react at the same rate in mechanism 2, the deuterium transfer via mechanism 1 is calculated to be about 8% and via mechanism 2 about 2.5%. The agreement of the observed percent exchange (8%) and that calculated for mechanism 1 (8%) is excellent and consistent with an intramolecular hydride transfer between the 1,2-dihydropyridine and the vinylindole moieties.

## Summary

Two methods for the preparation of α-cyano-2-ethyltryptophol (**12**) have been developed. The route proceeding through the unique cleavage of the ether **17** with trimethylsilyl cyanide (Scheme V) provides the most practical route to this strategic substance. Tryptophylpyridinium salts prepared from **12** are readily oxidized to (2-vinyltryptophyl)pyridinium salts with *tert*-butyl hypochlorite. One of these salts (**23a**) has been reduced to the dihydropyridines **28** and **29** and the chemistry of these substances studied as a model for the proposed biosynthesis of the indole alkaloids via dehydrosecodine. Instead of cyclizing through one of the desired Diels–Alder modes (Scheme I), **28** undergoes an intramolecular hydride transfer with oxidation of the dihydropyridine moiety and reduction of the vinyl group. Apparently the carbomethoxy substituents which serve to stabilize the dihydropyridine also greatly retard the Diels–Alder reaction to the extent that the hydride-transfer mode becomes dominant. Since this problem may not be as severe with dihydropyridines which more closely approximate the natural substances, we are continuing to explore approaches within the redox system outlined in Scheme II using the 3-ethylpyridinium salt **21d**.

## Experimental Section

**General Procedures.** Melting points and boiling points are uncorrected; melting points were determined on a Mettler FP-2 hot-stage apparatus with a polarizing microscope. $^1$H NMR spectra were recorded with a Varian Associates T-60 or A-60 spectrometer and are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. The abbreviations s, d, t, q, m, br m, and br s refer to singlet, doublet, triplet, quartet, multiplet, broad multiplet, and broad singlet, respectively. Infrared spectra were recorded on a Perkin-Elmer Model 337 or 599 spectrophotometer. Electronic absorption spectra were determined on a Cary Model 14 spectrometer. Mass spectra were recorded on a Hitachi RMU-7 spectrometer at 70 eV. Microanalyses were performed by Galbraith Laboratories, Inc.

Removal of solvent under reduced pressure was carried out by using a rotary evaporator with an aspirator vacuum. Preparative thin-layer chromatography was carried out by using plates prepared with Brinkmann ultraviolet sensitive silica gel 60 $PF_{254+366}$. Column chromatography was performed with Brinkmann silica gel (less than 0.063 mm).

**Preparation of 3-(2-Hydroxyethyl)-1*H*-indole-2-carboxylic Acid.** To 2.00 g (10.7 mmol) of lactone 8[14] suspended in 125 mL of methanol was added 0.275 g (11.4 mmol) of lithium hydroxide. The suspension was stirred for approximately 2 h and the resulting clear tan solution evaporated to dryness. The solid residue was dissolved in approximately 125 mL of distilled water, and 1.2 N hydrochloric acid was added until the resulting solution was slightly acidic. The white solid which precipitated was dissolved in ether (500 mL) and the ether layer dried ($MgSO_4$). The solvent was evaporated to give 1.98 g (9.66 mmol, 90%) of the hydroxy acid. This solid was used without further purification: mp 185.6–186.3 °C; NMR ($CD_3COCD_3$) δ 10.0 (br s, 1 H), 7.0 (br m, 4 H), 3.49 (t, $J$ = 6 Hz, 2 H), 3.01 (t, $J$ = 6 Hz, 2 H).

**Preparation of 2-Acetyl-3-(2-hydroxyethyl)-1*H*-indole (9).** To a solution of 0.433 g (2.11 mmol) of the aforementioned hydroxy acid dissolved in 25 mL of tetrahydrofuran (THF) (freshly distilled from calcium hydride) was added, with stirring under argon, a solution of methyllithium (22 mmol) in ether. The solution was stirred for 3 h and poured into 100 mL of a saturated solution of aqueous ammonium chloride with vigorous stirring. The THF was removed under reduced pressure, and the remaining aqueous suspension was extracted with 200–300 mL of ether. The ether layer was dried ($MgSO_4$) and the solvent removed. Preparative thin-layer chromatography (one elution with 3% methanol in chloroform) of the residue followed by recrystallization from acetone–chloroform yielded 0.381 g (1.88 mmol, 89%) of the ketone **9**: mp 128.0–128.7 °C; IR ($CHCl_3$) $\nu_{max}$ 3400, 3320, 1650 cm$^{-1}$; NMR ($CD_3COCD_3$) δ 9.5 (br s, 1 H), 7.8–7.0 (m, 4 H), 3.8 (t, $J$ = 6 Hz, 2 H), 3.4 (t, $J$ = 6 Hz, 2 H), 2.8 (s, 1 H), 2.6 (s, 3 H); mass spectrum, *m/e* 203 ($M^+$). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.93; H, 6.40; N, 6.81.

**Preparation of 2-Ethyl-3-(2-hydroxyethyl)-1*H*-indole.** To 1.00 g (4.93 mmol) of the ketone **9** dissolved in 50 mL of diethylene glycol was added 4.0 g (71.3 mmol) of potassium hydroxide and 8.0 mL of 95% hydrazine hydrate (156 mmol). The flask was fitted with a relfux condenser and heated at 100 °C for 2–3 h. The reflux condenser was replaced with a distillation apparatus and the solution heated to 200 °C for 4 h to remove water. The distillation apparatus was replaced with the reflux condenser after the addition of 6.0 mL (117 mmol) of 95% hydrazine hydrate. The solution was then heated at 100 °C overnight. As the mixture cooled, 40 mL of distilled water was added, and the reaction mixture was allowed to cool further. The solution was extracted with 125 mL of ether in three parts, and the combined ether layers were dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a viscous oil. Preparative thin-layer chromatography (one elution with 4% methanol in chloroform) yielded 0.89 g (4.71 mmol, 95%) of the 2-ethylindole derivative as a viscous oil: bp 194 °C (0.2 mm); IR ($CHCl_3$) $\nu_{max}$ 3515 cm$^{-1}$; NMR ($CDCl_3$) δ 8.1 (br s, 1 H), 7.7–7.1 (br m, 4 H), 3.8 (t, $J$ = 6 Hz, 2 H), 3.0 (t, $J$ = 6 Hz, 2 H), 2.75 (q, $J$ = 7 Hz, 2 H), 2.4 (br s, 1 H), 1.3 (t, $J$ = 7 Hz, 3 H); mass spectrum, *m/e* 189 ($M^+$). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.06; H, 7.99; N, 7.55.

**Preparation of 2-Ethyl-3-[2-(*tert*-butyldimethylsiloxy)ethyl]-1*H*-indole (10).** To 0.7586 g (4.01 mmol) of 2-ethyl-3-(2-hydroxyethyl)-1*H*-indole dissolved in 7 mL of dimethylformamide were added 0.980 g (6.51 mmol) of *tert*-butyldimethylchlorosilane and 1.159 g (17.0 mmol) of imidazole, and the solution was stirred for 7 days. To the resulting solution was added 75 mL of water saturated with sodium chloride and the mixture extracted with 125 mL of cyclohexane in three portions. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Preparative thin-layer chromatography (one elution with 1–2% methanol in chloroform) of the residue yielded 1.198 g (3.95 mmol, 98.5%) of **10** as a thick oil: bp 155–160 °C (0.3 mm); IR (neat) $\nu_{max}$ 3430 cm$^{-1}$; NMR ($CDCl_3$) δ 9.0 (br s, 1 H), 8.0–7.0 (m, 4 H), 3.90 (t, $J$ = 8 Hz, 2 H), 3.05 (t, $J$ = 8 Hz, 2 H), 2.85 (q, $J$ = 7 Hz, 2 H), 1.30 (t, $J$ = 7 Hz, 3 H), 0.95 (s, 9 H), 0.06 (s, 6 H); mass spectrum, *m/e* 303 ($M^+$). Anal. Calcd for $C_{18}H_{29}NOSi$: C, 71.28; H, 9.63; N, 4.61. Found: C, 71.14; H, 9.66; N, 4.53.

**Preparation of 2-[1-(Dimethylamino)ethyl]-3-(2-hydroxyethyl)-1*H*-indole (11).** To 1.144 g (3.78 mmol) of the silylated alcohol **10** dissolved in 100 mL of methylene chloride were added at −78 °C 0.40 g (3.90 mmol) of triethylamine and 0.41 g (3.78 mmol) of *tert*-butyl hypochlorite. The solution was stirred for 1 h, after which time 25–50 mL of methanol was added

(28) Mauzerall, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2261.

and dimethylamine bubbled through the solution for 30 min. The resulting solution was allowed to stir for 5 days. The solvent was removed under reduced pressure and the solid residue dissolved in water. Treatment of this solution with 1.2 N hydrochloric acid was followed by extraction with ether. The aqueous layer was then neutralized with concentrated potassium hydroxide solution and extracted with ether. The ether layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting solid was recrystallized from ethyl acetate to yield 0.653 g (2.81 mmol, 74%) of **11** as a white solid: mp 142.5–142.8 °C; IR (KBr) $\nu_{max}$ 3400, 3175 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.55 (br s, 1 H), 7.6–6.9 (m, 4 H), 4.0 (s, 1 H), 3.80 (t, $J$ = 6 Hz, 2 H), 3.65 (q, $J$ = 8 Hz, 1 H), 2.95 (t, $J$ = 6 Hz, 2 H), 2.15 (s, 6 H), 1.35 (d, $J$ = 8 Hz, 3 H); mass spectrum, $m/e$ 232 ($M^+$). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.53; H, 8.79; N, 11.90.

**Preparation of [1-[3-(2-Hydroxyethyl)-1*H*-indol-2-yl]-ethyl]trimethylammonium Iodide.** To 0.1024 g (0.44 mmol) of the amine **11** dissolved in 50 mL of ethyl acetate was added 0.131 g (0.93 mmol) of methyl iodide, and the solution was stirred at room temperature for 3–4 h. The precipitate was collected to yield 0.148 g (0.395 mmol, 90%) of the quaternary ammonium iodide which was used without further purification; mp 133.6–134.6 °C. An analytical sample was obtained by recrystallization from acetone–water–benzene–ethyl acetate. This unusual solvent system was necessary in order to separate the product from small amounts of tetramethylammonium iodide which were present as a contaminant. The recrystallization was performed at room temperature to avoid further contamination due to decomposition: IR (KBr) $\nu_{max}$ 3370, 3200 $cm^{-1}$; NMR ($D_2O$, $CD_3COCD_3$) $\delta$ 9.0 (s, 1 H), 7.6–6.9 (m, 4 H), 5.15 (q, $J$ = 8 Hz, 1 H), 3.65 (t, $J$ = 6 Hz, 2H), 3.10 (s, 9 H), 2.85 (t, $J$ = 6 Hz, 2 H), 1.80 (d, $J$ = 8 Hz, 3 H); mass spectrum, $m/e$ 374 ($M^+$). Anal. Calcd for $C_{15}H_{23}N_2OI$: C, 48.14; H, 6.19; N, 7.48. Found: C, 48.13; H, 6.23; N, 7.40.

**Preparation of 2-(1-Cyanoethyl)-3-(2-hydroxyethyl)-1*H*-indole (12) via the Route in Scheme III.** A solution of 0.369 g (0.99 mmol) of the aforementioned quaternary ammonium iodide, 0.439 g (6.74 mmol) of potassium cyanide, and 0.255 g (0.85 mmol) of 18-crown-6 in 50 mL of distilled acetonitrile (from $P_2O_5$) was stirred at 60 °C under argon for 2 days. The solution was filtered to remove the insoluble salts and condensed to less than one-third of its original volume under reduced pressure. The concentrated solution was diluted to 50 mL with water and extracted with 125 mL of methylene chloride in three parts. The combined methylene chloride layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Preparative thin-layer chromatography (one elution with 3% methanol in chloroform) of the residue followed by recrystallization from acetone–chloroform–hexane yielded 0.192 g (0.897 mmol, 91%) of **12** as a white solid: mp 125.1–125.3 °C; IR ($CHCl_3$) $\nu_{max}$ 3430, 3320, 2245 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.73 (br s, 1 H), 7.7–7.0 (br m, 4 H), 4.20 (q, $J$ = 7 Hz, 1 H), 3.80 (t, $J$ = 6 Hz, 2 H), 2.90 (t, $J$ = 6 Hz, 2 H), 2.20 (br s, 1 H), 1.58 (d, $J$ = 7 Hz, 3 H); mass spectrum, $m/e$ 214 ($M^+$). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.95; H, 6.56; N, 13.15.

**Preparation of 3-(3-Oxa-4-pentenyl)-1*H*-indole (16).** To a stirred suspension of 7.50 g (46.5 mmol) of tryptophol (**15**) in 75 mL of freshly distilled ethyl vinyl ether was added 0.415 g (1.30 mmol, 2.8 mol%) of mercuric acetate. After several minutes the reaction mixture became homogeneous. The solution was stirred at 25 °C for 23 h and then concentrated in vacuo. Freshly distilled ethyl vinyl ether (65 mL) was added and again the solution was stirred at 25 °C for 23 h. This was repeated once more. After the third cycle was complete, the reaction was quenched by the addition of triethylamine. The reaction mixture was partitioned between ether and dilute aqueous $K_2CO_3$. The organic layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo. Filtration through a 37-g silica gel column eluted with 3:1 methylene chloride/cyclohexane gave 6.825 g (36.5 mmol, 78%) of **16** as a light yellow oil. In a similar experiment, further elution of the column with 3% methanol in methylene chloride gave 17% of recovered tryptophol in addition to 75.7% of **16** (94% based on recovered starting material).

Kugelrohr distillation gave analytically pure **16** as a colorless oil: bp 144–148 °C (0.16 mm); IR (neat) $\nu_{max}$ 3420, 1640, 1625, 1201 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.0–6.83 (m, 6 H), 6.47 (m, 1 H), 4.30–3.90 (m, 2 H), 3.93 (t, $J$ = 7 Hz, 2 H), 3.10 (t, $J$ = 7 Hz, 2 H). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.11; H, 6.99; N, 7.41.

**Preparation of 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (17).** To a stirred solution of 6.228 g (33.26 mmol) of **16** in 600 mL of methylene chloride (freshly distilled from $P_2O_5$) at 15–18 °C under nitrogen was added 0.175 mL (2.27 mmol, 6.8 mol %) of trifluoroacetic acid dropwise with a syringe. The solution was maintained at 15–18 °C for 2.25 h before being quenched by addition of triethylamine and $K_2CO_3$. After several minutes, the mixture was filtered and the filtrate concentrated in vacuo. Chromatography of the residue on 110 g of silica gel eluted with methylene chloride gave 4.35 g (23.3 mmol, 70%) of **17** as a very pale yellow solid. An analytical sample was obtained by chromatography on silica gel with 4:1 methylene chloride/cyclohexane followed by recrystallization from cyclohexane to give **17** as colorless crystals: mp 111.5–113.1 °C; IR (KBr) $\nu_{max}$ 3375, 1455, 1102 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.87 (br s, 1 H), 7.6–6.97 (m, 4 H), 4.8 (m, 1 H), 4.4–3.57 (m, 2 H), 3.2–2.2 (m, 2 H), 1.4 (d, $J$ = 7 Hz, 3 H); mass spectrum, $m/e$ (relative intensity) 187 ($M^+$, 100), 172 (100), 157 (62), 154 (33), 144 (89), 115 (33). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.62; H, 7.02; N, 7.45.

**Preparation of 2-(1-Cyanoethyl)-3-(2-hydroxyethyl)-1*H*-indole (12) via the Route in Scheme V.** A mixture of 1.99 g (10.6 mmol) of **17** and 0.425 g (3.12 mmol, 0.29 equiv) of powdered anhydrous $ZnCl_2$ in 25 mL of trimethylsilyl cyanide ($Me_3SiCN$) was heated at 105 °C with stirring under nitrogen for 3 days. The mixture was cooled and concentrated at or below room temperature under high vacuum with a dry ice/acetone trap to collect the excess $Me_3SiCN$ for later reuse. The residue was partitioned between water and ether. The organic layer was concentrated and dissolved in a mixture of 70 mL of THF and 20 mL of water under nitrogen. Excess KF, a small amount of $NH_4Cl$, and 1 mL of acetic acid were added. The resulting two-phase mixture was neutralized after 2 h with $NaHCO_3$, and stirring was continued for an additional 36 h. Dilution with water followed by extraction with ether gave, after drying ($MgSO_4$) of the organic extracts, crude **12** which was purified by chromatography on silica gel (2.5% methanol/methylene chloride) and recrystallized from cyclohexane/chloroform/acetone to give 1.520 g (7.10 mmol, 67%) of **12** as pale yellow needles: mp 124.0–125.2 °C; identical by NMR and TLC with previously prepared **12** (Scheme III).

**Preparation of 2-[2-(1-Cyanoethyl)-1*H*-indol-3-yl]ethyl *p*-Toluenesulfonate (20).** To a stirred solution of 3.31 g (10.1 mmol) of TsOTs[20] and 1.40 mL (10.5 mmol) of $\gamma$-collidine (distilled from BaO) in 65 mL of dry benzene (stored over sodium ribbon) under nitrogen was added 1.217 g (5.69 mmol) of **12**. The solution was gently warmed with vigorous stirring to facilitate dissolution of the alcohol **12**. Oily $\gamma$-collidinium hydrotosylate began separating within minutes. The mixture was stirred at 25 °C for 1 h and then concentrated in vacuo. The resulting oil was rapidly eluted through a column of silica gel (26 g) with methylene chloride. The eluate was concentrated in vacuo to give the oily tosylate **20**: NMR ($CDCl_3$) $\delta$ 9.2 (br s, 1 H), 7.60–6.65 (m, 8 H), 4.15 (t, $J$ = 6.5 Hz, 2 H), 4.10 (q, $J$ = 7 Hz, 1 H), 3.05 (t, $J$ = 6.5 Hz, 2 H), 2.25 (s, 3 H), 1.55 (d, $J$ = 7 Hz, 3 H).

The tosylate **20** must be chromatographed rapidly and not heated in order to avoid the loss of toluenesulfonic acid and the associated formation of the spirocyclopropane at the 3-position of the indole nucleus. Due to the propensity of **20** to cyclize in this fashion, it was always used immediately without further purification. Some TsOTs was usually present in this material, but it did not interfere with the next step.

**General Procedure for the Synthesis of Pyridinium Tosylates 21a–d.** The tosylate **20** was dissolved in a small amount of dry benzene (stored over sodium), typically 1.5–4 mL of benzene/g of **20**, and 1–2 equiv of the substituted pyridine was added. The solution was heated at 45–80 °C for 18–48 h. The salts **21a–d** separated either as oils or solids; the benzene layer was decanted and the residual oil/solid washed with dry benzene.

***N*-[2-[2-(1-Cyanoethyl)-1*H*-indol-3-yl]ethyl]-3,5-bis(carbomethoxy)pyridinium *p*-toluenesulfonate (21a)** was obtained as a reddish orange oil in 80% yield. All attempts to induce crystallization of this oil failed. Therefore, an analytical sample was obtained by first cyclizing **21a**, as the oil, to the readily crystallized *trans*-dihydropyridine **22a** (vide infra), purifying **22a**

by recrystallization, and regenerating crystalline **21a** as follows. To a solution of recrystallized *trans*-dihydropyridine **22a** (39.1 mg, 0.10 mmol) in 12 mL of ethyl acetate was added a solution of anhydrous *p*-TsOH in 8 mL of benzene [prepared by the azeotropic removal of water by boiling a mixture of 19.0 mg (0.10 mmol) of *p*-TsOH·$H_2O$ in benzene until a homogeneous solution was obtained]. This solution was refluxed under nitrogen for 24 h. The bright yellow crystalline solid which separated in nearly quantitative yield was collected, washed with ethyl acetate, and dried. This material was analyzed directly and had the following: mp 185.4–186.3 °C; IR ($CH_2Cl_2$) $\nu_{max}$ 3160, 2300, 1740 $cm^{-1}$; NMR ($CDCl_3$, $CD_3CN$) $\delta$ 10.0 (br s, 1 H), 8.95 (s, 2 H), 7.8–6.95 (m, 9 H), 5.1 (t, $J$ = 6 Hz, 2 H), 4.3 (q, $J$ = 7 Hz, 1 H), 3.90 (s, 6 H), 3.5 (t, $J$ = 6 Hz, 2 H), 2.35 (s, 3 H), 1.55 (d, $J$ = 7 Hz, 3 H); mass spectrum, $m/e$ 391 (M − 172). Anal. Calcd for $C_{29}H_{29}N_3O_7S$: C, 61.80; H, 5.19; N, 7.46. Found: C, 61.65; H, 5.32; N, 7.30.

***N*-[2-[2-(1-Cyanoethyl)-1*H*-indol-3-yl]ethyl]-3-(carbomethoxy)pyridinium *p*-toluenesulfonate hemihydrate (21b)** was obtained in 89% yield as a bright yellow powder. Three recrystallizations from acetonitrile gave bright yellow crystals: mp 145.7–146.6 °C; IR (KBr) $\nu_{max}$ 1735, 1190, 1125, 1035, 1012, 680 $cm^{-1}$; NMR ($CD_3SOCD_3$) $\delta$ 11.5 (br s, 1 H), 9.37 (s, 1 H), 9.2 (d, $J$ = 6 Hz, 1 H), 8.87 (d, $J$ = 7 Hz, 1 H), 8.13 (t, $J$ = 7 Hz, 1 H), 7.66–6.83 (m, 8 H), 5.13–4.43 (m, 3 H), 3.93 (s, 3 H), 3.7–3.2 (m, $H_2O$ present), 2.26 (s, 3 H), 1.58 (d, $J$ = 7 Hz, 3 H). Anal. Calcd for $(C_{27}H_{27}N_3O_5S)_2{\cdot}H_2O$: C, 63.02; H, 5.48; N, 8.17. Found: C, 63.07, H, 5.59; N, 8.14.

***N*-[2-[2-(1-Cyanoethyl)-1*H*-indol-3-yl]ethyl]-3-cyanopyridinium *p*-toluenesulfonate hemihydrate (21c)** was obtained in greater than 80% yield and recrystallized four times from acetonitrile to give bright yellow crystals: mp 138.2–138.8 °C; IR (KBr) $\nu_{max}$ 3435, 2240, 1460, 1185, 1122, 1032, 1013, 683, 571 $cm^{-1}$; NMR ($CD_3SOCD_3$) $\delta$ 11.55 (s, 1 H), 9.83 (s, 1 H), 9.28 (d, $J$ = 6 Hz, 1 H), 9.07 (d, $J$ = 8 Hz, 1 H), 8.32 (dd, $J$ = 6, 8 Hz, 1 H), 7.83–6.90 (m, 8 H), 5.13–4.55 (m, 3 H), 3.50 (distorted t, $J$ = 7.5 Hz, 3 H, $H_2O$ peak present), 2.30 (s, 3 H), 1.65 (d, $J$ = 7 Hz, 3 H). Anal. Calcd for $(C_{26}H_{24}N_4O_3S)_2{\cdot}H_2O$: C, 64.85; H, 5.23; N, 11.63. Found: C, 64.45; H, 5.39; N, 11.45.

***N*-[2-[2-(1-Cyanoethyl)-1*H*-indol-3-yl]ethyl]-3-ethylpyridinium *p*-toluenesulfonate hemihydrate (21d)** was obtained in 83–93% yield as a partially crystalline yellow material by using only 1.1 equiv of 3-ethylpyridine. Three recrystallizations from chloroform/acetonitrile gave shiny colorless flakes: mp 95.1–96.8 °C; IR (KBr) $\nu_{max}$ 3160, 3060, 2240, 1460, 1205, 1188, 1127, 1035, 1012, 682, 570 $cm^{-1}$; NMR ($CD_3CN$) $\delta$ 10.97 (br s, 1 H), 8.33–6.6 (m, 12 H), 4.68 (t, $J$ = 6.5 Hz, 2 H), 4.30 (q, $J$ = 7 Hz, 1 H), 3.35 (t, $J$ = 6.5 Hz, 2 H), 2.48 (q, $J$ = 8.5 Hz, 2 H), 2.27 (s, 3 H), 1.48 (d, $J$ = 7 Hz, 3 H), 0.88 (t, $J$ = 8.5 Hz, 3 H). Anal. Calcd for $(C_{27}H_{29}N_3O_3S)_2{\cdot}H_2O$: C, 66.92; H, 6.24; N, 8.67. Found: C, 67.00; H, 6.16; N, 8.64.

**Preparation of Dimethyl 6-Cyano-6-methyl-6,6a,12,13-tetrahydro-5*H*-pyrido[1′,2′:1,2]azepino[4,5-*b*]indole-7,9-dicarboxylate (22a).** To 0.300 g (0.533 mmol) of pyridinium salt **21a** dissolved in methylene chloride was added 0.150 g (1.495 mmol) of triethylamine, and the resulting mixture was stirred for 15 min. The solvent was removed under reduced pressure and preparative thin-layer chromatography (three elutions with 2% methanol in chloroform) yielded 0.153 g of the less polar isomer (73%) and 0.013 g of the more polar isomer (6%) of **22a**.

**Less Polar Trans Isomer of 22a**: After two recrystallizations from chloroform/hexane: mp 171.8–172.2 °C; IR (KBr) $\nu_{max}$ 3330, 1690, 1620 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 9.0 (br s, 1 H), 7.93 (s, 1 H), 7.85 (br s, 1 H), 7.53–6.97 (m, 4 H), 5.61 (s, 1 H), 4.23–2.29 (m, 4 H), 3.77 (s, 6 H), 1.63 (s, 3 H); mass spectrum, $m/e$ 391 ($M^+$). Anal. Calcd for $C_{22}H_{21}N_3O_4{\cdot}^2/_3CHCl_3$: C, 57.75; H, 4.70; N, 8.91. Found: C, 57.87; H, 4.55; N, 9.11. NMR analysis of the analytical sample indicated that it was solvated with chloroform which could not be removed even under high vacuum. Recrystallization from other solvents always lead to solvated crystals.

**More Polar Cis Isomer of 22a**: NMR ($CDCl_3$) $\delta$ 8.8 (br s, 1 H), 8.15 (s, 1 H), 7.8 (s, 1H), 7.65–7.00 (m, 4 H), 5.4 (s, 1 H), 3.85 (s, 3 H), 3.80 (t, $J$ = 6 Hz, 2 H), 3.78 (s, 3 H), 3.25 (t, $J$ = 6 Hz, 2 H), 1.65 (s, 3 H); mass spectrum, $m/e$ 391($M^+$). Analysis of the more polar isomer was not attempted due to the rapid equilibration of this isomer to a mixture with the thermodynamically more stable less polar isomer.

**Preparation of Methyl 6-Cyano-6-methyl-6,6a,12,13-tetrahydro-5*H*-pyrido[1′,2′:1,2]azepino[4,5-*b*]indole-9-carboxylate (22b).** A suspension of 133 mg (0.263 mmol) of **21b** in 20 mL of methylene chloride containing 2 mL of triethylamine was stirred under nitrogen for 5 h, after which time the mixture became homogeneous. The solution was washed twice with aqueous $NaHCO_3$, dried ($Na_2SO_4$), and concentrated in vacuo to give 86 mg (98%) of **22b** as a pink solid which consisted solely of the trans epimer. Three recrystallizations from ether/methylene chloride gave fine colorless crystals of **22b**: mp 193.1–194.8 °C dec; IR (KBr) $\nu_{max}$ 3230, 2235, 1650, 1610, 1560, 1425, 1300, 1190, 735 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.58 (br s, 1 H), 7.65–7.03 (m, 5 H), 6.85 (d, $J$ = 9 Hz, 1 H), 5.42 (dd, $J$ = 5 and 9 Hz, 1 H), 4.92 (d, $J$ = 5 Hz, 1 H), 4.07–3.05 (m, 4 H), 3.72 (s, 3 H), 1.7 (s, 3 H); mass spectrum, $m/e$ (relative intensity) 333 ($M^+$, 33), 196 (100), 195 (53), 193 (20), 181 (81), 168 (29), 154 (25), 151 (93), 137 (55), 106 (85), 78 (41). Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.95; H, 5.89; N, 12.57.

When the cyclization was conducted with 2.0 equiv of DBN in methylene chloride, **21b** dissolved almost immediately. After 10 min, the reaction mixture was poured into ether and washed with three portions of water and saturated sodium chloride solution and dried ($Na_2SO_4$). Concentration in vacuo gave a bright yellow solid which consisted of a 3:2 mixture of *trans*- and *cis*-**22b**, respectively: NMR ($CDCl_3/CD_3COCD_3$) for *cis*-**22b** $\delta$ 4.71 (d, $J$ = 5 Hz, $H_{6a}$).

**Preparation of 6,9-Dicyano-6-methyl-6,6a,12,13-tetrahydro-5*H*-pyrido[1′,2′:1,2]azepino[4,5-*b*]indole (22c).** Crude **21c** was dissolved in a solution of 20 mL of methylene chloride, 5 mL of methanol, and 1.5 mL of triethylamine, and the mixture was stirred at 25 °C for 3 days. The aforementioned aqueous $NaHCO_3$ isolation procedure gave partially crystalline orange material which was chromatographed on a silica gel column eluted first with 80/20 methylene chloride/cyclohexane to give 172 mg (34% overall yield based on starting with 364 mg of **12**) of **22c** as colorless crystals. Further elution with 0.4% methanol/methylene chloride gave 83 mg (16%) of the other epimer of **22c** as pale yellow crystals.

**Less Polar Trans Isomer of 22c.** This isomer was recrystallized three times from chloroform/methanol to give fine colorless platelets: mp 217.2–218.1 °C dec; IR (KBr) $\nu_{max}$ 3330, 2200, 1638, 1570, 750 $cm^{-1}$; NMR ($CDCl_3$, $CD_3OD$) $\delta$ 7.53–7.0 (m, 5 H), 6.33 (dd, $J$ = 1.5, 9 Hz, 1 H), 5.4 (dd, $J$ = 5, 9 Hz, 1 H), 5.0 (br d, $J$ = 5 Hz, 1 H), 3.86–3.0 (m, 4 H), 1.73 (s, 3 H); mass spectrum, $m/e$ (relative intensity) 300 ($M^+$, 59), 195 (100), 181 (68), 167 (11), 156 (13), 154 (16), 118 (35), 104 (11). Anal. Calcd for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 75.62; H, 5.60; N, 18.67.

**More Polar Cis Isomer of 22c.** This isomer was recrystallized three times from chloroform/methanol/cyclohexane to give light yellow cubes: mp 204.2–205.3 °C dec; IR ($CHCl_3$) $\nu_{max}$ 3000, 2200, 1640, 1570, 1050, 1027 $cm^{-1}$; NMR ($CD_3SOCD_3$) $\delta$ 9.4 (br s, 1 H), 7.52–6.85 (m, 5 H), 6.27 (dd, $J$ = 1.5, 9 Hz, 1 H), 5.18 (dd, $J$ = 5.5, 9 Hz, 1 H), 4.78 (dd, $J$ = 1.5, 5.5 Hz, 1 H), 4.08–2.95 (m, 4 H), 1.68 (s, 3 H); mass spectrum, $m/e$ (relative intensity) 300 ($M^+$, 25), 196 (65), 182 (29), 181 (62), 154 (22), 118 (41), 104 (100), 77 (66), 76 (21). Anal. Calcd for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 75.74; H, 5,56; N, 18.40.

**Preparation of *N*-[2-[2-(1-Cyanoethenyl)-1*H*-indol-3-yl]ethyl]-3,5-bis(carbomethoxy)pyridinium Chloride (23a).** To a solution of 260 mg (0.665 mmol) of *cis*- and *trans*-**22a** dissolved in 10 mL of methylene chloride was added dropwise with a syringe 80 μL (0.67 mmol) of *tert*-butyl hypochlorite, and the mixture was stirred at room temperature for 20 min. Care must be taken not to add an excess of *tert*-butyl hypochlorite in order to avoid further oxidation of the product. The mixture was concentrated in vacuo and the resulting yellow-orange solid washed with ether to give, after drying, 250 mg (0.588 mmol, 88%) of **23a**. This solid was used in subsequent reactions without further purification. Recrystallization can be accomplished by using methanol/methylene chloride to yield a yellow powder: mp 176–177 °C; IR (KBr) $\nu_{max}$ 3380, 2220, 1740 $cm^{-1}$; NMR ($CD_3CN$, $D_2O$) $\delta$ 9.1 (t, $J$ = 1.5 Hz, 1 H), 9.0 (d, $J$ = 1.5 Hz, 2 H), 7.7–7.0 (m, 4 H), 6.5 (s, 1 H), 6.3 (s, 1 H), 5.15 (t, $J$ = 6 Hz, 2 H), 4.05 (s, 6 H), 3.80 (t, $J$ = 6 Hz, 2 H). Anal. Calcd for $C_{22}H_{20}N_3O_4Cl{\cdot}^1/_3CH_2Cl_2$: C, 57.75; H, 4.70; N, 8.91. Found: C, 57.87; H, 4.55; N, 9.11. NMR analysis of the analytical sample indicated the presence of

methylene chloride that could not be removed under high vacuum.

**Preparation of 7-Chloro-6-cyano-6-methyl-6,6a,12,13-tetrahydro-5*H*-pyrido[1′,2′:1,2]azepino[4,5-*b*]indole-9-carboxylate (27).** To a solution of 154 mg (0.46 mmol) of **22b** in 30 mL of methylene chloride under nitrogen was added dropwise with a syringe 60 μL (0.50 mmol) of *tert*-butyl hypochlorite. An orange solid soon began to separate. After 30 min, 0.5 mL of triethylamine was added and stirring continued for 26 h. The solution was partitioned between methylene chloride/ether and dilute aqueous $NaHCO_3$. The organic layer was dried and concentrated in vacuo to give 0.16 g (0.435 mmol, 95%) of **27** as an orange semicrystalline foam consisting of a mixture of epimers. Separation of the epimers was achieved by column chromatography on silica gel eluted with 1% methanol/methylene chloride to give 66 mg (39%) of the less polar *trans*-**27** and 28 mg (16%) of the more polar *cis*-**27**.

**Less Polar Trans Isomer of 27.** This isomer was recrystallized three times from cyclohexane/chloroform/acetone to give pale yellow crystals: mp 204.6–205.4 °C dec; (KBr) $\nu_{max}$ 3290, 1660, 1615, 1610, 1560, 1425, 1305, 1245, 1185, 1165, 745 $cm^{-1}$; NMR ($CD_3COCD_3$, $CDCl_3$) δ 7.6–6.96 (m, 5 H), 5.4 (s, 1 H), 4.0–3.1 (m, 4 H), 3.66 (s, 3 H), 1.8 (s, 3 H); mass spectrum, *m/e* (relative intensity) 369 (M + 2, 20), 367 ($M^+$, 50), 196 (100), 195 (86), 185 (74), 182 (68), 181 (100), 169 (45), 140 (54), 69 (56). Anal. Calcd for $C_{20}H_{18}ClN_3O_2$: C, 65.31; H, 4.93; N, 11.42. Found: C, 65.32; H, 5.03; N, 11.36.

**More Polar Cis Isomer of 27.** This isomer was isolated as a yellow foam: IR ($CHCl_3$) $\nu_{max}$ 3450, 3330, 3010, 2235, 1685, 1625, 1565, 1430, 1300, 1250, 1190, 1155 $cm^{-1}$; NMR ($CDCl_3$) δ 8.53 (br s, 1 H), 7.60–7.03 (m, 6 H), 4.77 (s, 1 H), 3.97–3.60 (m, 2 H), 3.70 (s, 3 H), 3.33–3.00 (m, 2 H), 1.91 (s, 3 H); mass spectrum, *m/e* (relative intensity) 369 (M + 2, 9), 367 ($M^+$, 23), 196 (99), 185 (41), 182 (47), 181 (100), 171 (55), 154 (35), 142 (34), 140 (96), 112 (65), 76 (30).

**Preparation of *N*-[2-[2-(1-Cyanoethenyl)-1*H*-indol-3-yl]-ethyl]-3-(carbomethoxy)pyridinium *p*-Toluenesulfonate Monohydrate (23b).** To a solution of 76 mg (0.15 mmol) of **21b** in 5.5 mL of acetonitrile (distilled from $P_2O_5$) under nitrogen was added dropwise with a syringe 19 μL (0.16 mmol) of *tert*-butyl hypochlorite. A yellow solid soon began to separate. After 30 min, the mixture was filtered and the solid washed with cold acetonitrile. The salt (30 mg, 0.06 mmol, 40%) was hygroscopic and became orange upon standing. Recrystallization from acetonitrile gave orange crystals: mp 220.2–221.5 °C; IR (KBr) $\nu_{max}$ 3420, 3060, 2220, 1730, 1300, 1220, 1180, 1120, 1030, 1010, 745, 685, 570, 565 $cm^{-1}$; NMR ($CD_3SOCD_3$) δ 11.82 (br s, 1 H), 9.57–9.3 (m, 1 H), 9.3–8.88 (m, 2 H), 8.43–8.10 (m, 1 H), 7.73–7.0 (m, 8 H), 6.67 (br s, 1 H), 6.43 (br s, 1 H), 5.12 (t, $J$ = 6.5 Hz, 2 H), 4.20–3.37 (m, 7 H, $H_2O$ present, $OCH_3$ at 4.02), 2.32 (s, 3 H). Anal. Calcd for $C_{27}H_{25}N_3O_5S \cdot H_2O$: C, 62.17; H, 5.22; N, 8.06. Found: C, 62.48; H, 5.03; N, 8.35.

In an identical experiment the entire crude reaction mixture was concentrated in vacuo. The $^1H$ NMR spectrum showed only **23b** and a trace of residual **21b**.

**Preparation of Dihydropyridines 28 and 29 and the Conversion of 28 to 22a.** To a solution of 0.052 g (0.122 mmol) of the salt **23a** in 30 mL of water were added 24 mL of methylene chloride and 0.0087 g (0.122 mmol) of sodium cyanoborohydride, and the mixture was shaken vigorously. The methylene chloride layer was dried ($MgSO_4$) and evaporated to 15 mL. The concentrated solution containing **28** and **29** was placed under argon and heated at 50 °C for 5 days at which time the dihydropyridines had been consumed as judged by thin-layer chromatography. The solvent was removed under reduced pressure and preparative thin-layer chromatography (two elutions with 3% methanol in chloroform) yielded 0.003 g (7%) of the cyclization product **22a** as shown by comparison with an authentic sample by means of thin-layer chromatography and NMR spectroscopy.

Dihydropyridines **28** and **29** can be purified but not separated by chromatography on silica gel (1.5% methanol/methylene chloride). Upon removal of the solvent in vacuo, **28** and **29** were obtained as a yellow glass: IR ($CHCl_3$) $\nu_{max}$ 3330, 3030, 3020, 1705–1675, 1595, 1440, 1410, 1335, 1250, 1235, 1180, 1085, 765 $cm^{-1}$; NMR ($CDCl_3$) δ 6.80 (s, relative intensity = 2, **29**, NCH=), 6.10 and 6.05 (2 s, 3, **28** and **29** C=$CH_2$), 4.40 (s, 1, **28**, $NCH_2$), 3.18 (s, 2, **29**, =$CCH_2$C=) (these chemical shift assignments are based upon the model 1,2- and 1,4-dihydropyridines in which the C=$CH_2$ of **28** and **29** is replaced by $CH_2$; these model compounds have been isolated in pure form and completely characterized[21b]); mass spectrum, *m/e* (relative intensity) 391 ($M^+$, 10), 196 (100), 195 (90), 181 (71), 164 (46).

Table III. Deuterium Content of Dihydropyridines 22aD and 22aD′

| ion formula | peak, *m/e* | % 22aD[a] | % 22aD′[a] | total deuterium lost from ion, % |
|---|---|---|---|---|
| $C_{22}H_{19}D_2N_3O_4$ | 393 | 79 | 62 | 17 |
| $C_{22}H_{20}DN_3O_4$ | 392 | 14 | 22 | 8–9 |
| $C_{22}H_{21}N_3O_4$ | 391 | 7 | 15 | (25–26) |
| $C_{10}H_9D_2NO_4$ | 211 | 84 | 58 | 26 |
| $C_{10}H_{10}DNO_4$ | 210 | 12 | 30 | 9–10 |
| $C_{10}H_{11}NO_4$ | 209 | 3 | 12 | (35–36) |
| $C_{12}H_8DN_2$ | 182 | 11 | 19 | 8 |
| $C_{12}H_9N_2$ | 181 | 89 | 81 | (8) |

[a] Raw data corrected for natural isotope abundance.

**Preparation of Dimethyl 2,6-Dideuteriopyridine-3,5-dicarboxylate and Its Conversion to 22aD′.** A sealed tube containing 1.00 g (5.98 mmol) of 3,5-pyridinedicarboxylic acid dissolved in 10 mL of $D_2O$ was heated to 205 °C for 24 h. After cooling, the solvent was removed under reduced pressure and the resultant solid dried under vacuum. The residue was checked by NMR to determine the percentage of deuteration. This procedure was repeated five times to yield 97% deuteration at the 2- and 6-positions.

The deuterated pyridine was treated with 6 mL of concentrated sulfuric acid and 15 mL of methanol at 0 °C for 30 min. The solution was refluxed for 1.5 h at 110 °C. The resulting solution was cooled, neutralized with an aqueous slurry of sodium carbonate, and extracted with ether. The ethereal layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The solid residue was recrystallized from ether/methanol to yield 0.400 g (33.9% overall) of dimethyl 2,6-dideuteriopyridine-3,5-dicarboxylate as a colorless solid: mp 84.8–85.1 °C. This esterification procedure resulted in negligible exchange of the deuteriums as judged by NMR.

A solution of 0.2265 g (0.615 mmol) of the tosylate **20** and 0.13 g (0.659 mmol) of the dideuterated diester in dry benzene was heated overnight at 90 °C under argon. The solvent was removed, and the remaining reddish oil was dried under vacuum to yield 0.2922 g (84.3%) of the pyridinium salt; mass spectrum, *m/e* 393 (M − 172).

A solution of 0.29 g (0.513 mmol) of the pyridinium salt dissolved in 20 mL of methylene chloride was treated with 1.0 g (9.88 mmol) of triethylamine, and the resulting solution was stirred for 1 h. The solvent was removed under reduced pressure, and preparative thin-layer chromatography of the resulting oil (two elutions with 3-4% methanol in chloroform) yielded a yellow oil. Recrystalliation from chloroform/hexane yielded 0.090 g (44.6%) of a yellow solid, **22aD**, mass spectrum, *m/e* 393 ($M^+$).

The cyclized product, **22aD** (0.083 g, 0.226 mmol), was dissolved in 4–5 mL of methylene chloride, and 0.0227 g (0.226 mmol) of *tert*-butyl hypochlorite was added. The solution was stirred at room temperature for 10 min. The reaction mixture was centrifuged and the solvent decanted from the precipitate. The remaining solid **23aD** was dried under vacuum to yield 0.0592 g (61.3%) of dry product.

The vinylpyridinium salt **23aD** (0.0592 g, 0.138 mmol) was dissolved in 30 mL of water, and 25 mL of methylene chloride was added. To this solution was added 0.0087 g (0.138 mmol) of sodium cyanoborohydride, and the resulting solution was shaken vigorously until the yellow color was extracted from the water into the methylene chloride layer. The organic layer was dried ($MgSO_4$) and evaporated to half of its original volume, and the resulting solution was heated at 50 °C under argon for 5 days. Removal of the solvent under reduced pressure yielded an oil which upon preparative thin-layer chromatography (six elutions with chloroform) yielded 0.0057 g (11.4%) of the cyclized product

22aD'. The deuterium content of both **22aD** and **22aD'** and the deuterium redistribution upon going from **22aD** to **22aD'** are outlined in Table III.

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**Registry No.** **8**, 6250-88-0; **9**, 20321-71-5; **10**, 77903-71-0; **11**, 77924-76-6; **12**, 77903-72-1; **15**, 526-55-6; **16**, 77903-73-2; **17**, 77903-74-3; **20**, 77903-75-4; **21a**, 77903-77-6; **21b**, 77903-79-8; **21c**, 77903-81-2; **21d**, 77903-83-4; *cis*-**22a**, 77903-84-5; *trans*-**22a**, 77903-85-6; *cis*-**22b**, 77903-86-7; *trans*-**22b**, 77903-87-8; *cis*-**22c**, 77903-88-9; *trans*-**22c**, 77903-89-0; **23a**, 77903-90-3; **23b**, 77903-92-5; *cis*-**27**, 77903-93-6; *trans*-**27**, 77903-94-7; **28**, 77924-77-7; **29**, 77924-77-7; **22aD**, 77924-78-8; **23aD**, 77903-95-8; 3-(2-hydroxyethyl)-1*H*-indole-2-carboxylic acid, 77903-96-9; 2-ethyl-3-(2-hydroxyethyl)-1*H*-indole, 76507-86-3; [1-[3-(2-hydroxyethyl)-1*H*-indol-2-yl)ethyl]trimethylammonium iodide, 77903-97-0; dimethyl 2,6-dideuteriopyridine-3,5-dicarboxylate, 77903-98-1; dimethyl 3,5-pyridinedicarboxylate, 4591-55-3; methyl 3-pyridinecarboxylate, 93-60-7; 3-cyanopyridine, 100-54-9; 3-ethylpyridine, 536-78-7.

# Structure of Nepetalic Acid in the Solid State and in Solution by X-ray Diffraction and Nuclear Magnetic Resonance Analysis

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Single-crystal X-ray analysis of nepetalic acid (**1c**, mp 75 °C) from *Nepeta cataria* shows that the six-membered ring adopts a half-boat conformation with near planarity of the lactone (C–C(O)O–C) moiety, the absolute configuration of the chiral centers being 3*S*, 4*R*, 4a*R*, 7*S*, and 7a*R* as determined by the Bijvoet method. The crystals are monoclinic: $P2_1$, $a$ = 6.625 (3) Å, $b$ = 8.885 (3) Å, $c$ = 8.408 (3) Å, $\beta$ = 95.06 (3)°. The structure was solved by direct methods and refined by block-diagonal least-squares methods to an $R$ value of 0.030 for 1073 reflections. Solution studies by $^1$H and $^{13}$C NMR established the presence of two epimers at C(3) (CHOH) with axial and equatorial OH, respectively, in a ratio of (77 ± 3):(23 ± 3) in the −15 to −25 °C temperature range and (79 ± 2):(21 ± 2) in the −40 to −70 °C temperature range ($\Delta G°$ = 0.60 ± 0.05 kcal/mol). The coalescence temperatures of the pertinent signals in $^{13}$C NMR lead to an activation energy of 14.8 kcal/mol for interconversion of the epimers.

(+)-Nepetalic acid (**1a–c**; mp 75 °C) and nepetalactone (**2**) were the first of the methylcyclopentane monoterpenoids to have their constitution[2a-c] and their absolute configuration[3a] elucidated. The structures of **1** and **2** are correlated as shown in Scheme I. Because of its biological activity as a feline attractant, **2** is usually the focus of attention.[2e] However, **1** is chemically more significant since it was the source of the intermediate nepetalinic acids[2a] (**5** is one example), the nepetonic acids,[2a,c] and the nepetic acids[2c,d] which served as important reference compounds for constitution and configurational correlation to the iridomyrmecins[2g] and other iridoids,[4,5a,b] the methylcyclopentane sesquiterpenes,[6a] and the skytanthine related methylcyclopentane monoterpenoid alkaloids as they were discovered.[5c,6b,c] These earlier studies established, through chemical correlation to (+)-pulegone, the absolute configuration[3a] of C(7) of **1a** and **2** and the relative configuration at other centers with the exception of C(3) of **1**. Recent $^1$H and $^{13}$C NMR studies have confirmed these earlier relative configurational assignments[3b] to **2**.

The tautomeric relationship of **1a–c** was known,[2a] and the reactions of Scheme I along with formation of carbonyl derivatives of **1b** support the aldehydo acid structure **1b**. However, nepetalic acid also displays chemical evidence of the lactol structures **1a**/**1c**: formation of an acetate,[2e] conversion to nepetalic anhydride, a diether,[2e,f] and thermal dehydration[2a,e,f] as well as remarkable resistance to air oxidation, in contrast to rapid air oxidation once the lactol structure is disrupted, as shown in the facile conversion[2a] of **3** to **4**. Unfortunately, these observations do not reveal whether the aldehydo acid (**1b**) or lactol (**1a,c**) structure predominates since any of the reactions may occur through miniscule amounts of a minor tautomer, nor do they allow assignment of configuration (**1a** or **1c**) to the lactol, if nepetalic acid is, in fact, partially or entirely in the lactol

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(2) (a) McElvain, S. M.; Eisenbraun, E. J. *J. Am. Chem. Soc.* **1955**, *77*, 1599. (b) Meinwald, J. *Ibid.* **1954**, *76*, 4571. (c) Bates, R. B.; Eisenbraun, E. J.; McElvain, S. M. *Ibid.* **1958**, *80*, 3420. (d) Eisenbraun, E. J.; Adolphen, G. H.; Schorno, K. S.; Morris, R. N. *J. Org. Chem.* **1971**, *36*, 414. (e) McElvain, S. M.; Bright, R. D.; Johnson, P. R. *J. Am. Chem. Soc.* **1941**, *63*, 1558. (f) McElvain, S. M.; Walters, P. M.; Bright, R. D. *Ibid.* **1942**, *64*, 1828. (g) McElvain, S. M.; Eisenbraun, E. J. *J. Org. Chem.* **1957**, *22*, 971.

(3) (a) Eisenbraun, E. J.; McElvain, S. M. *J. Am. Chem. Soc.* **1955**, *77*, 3383. (b) Eisenbraun, E. J.; Browne, C. E.; Irvin-Willis, R. L.; McGurk, D. J.; Eliel, E. L.; Harris, D. L. *J. Org. Chem.* **1980**, *45*, 3811.

(4) Djerassi, C.; Nakano, T.; James, A. N.; Zalkow, L. H.; Eisenbraun, E. J.; Shoolery, J. N. *J. Org. Chem.* **1961**, *26*, 1192.

(5) (a) Bobbitt, J. M.; Segebarth, K. P. In "Cyclopentanoid Terpene Derivatives"; Taylor, W. I.; Battersby, A. R., Eds.; Marcel Dekker: New York, 1969; Chapter 1. (b) Cavill, G. W. K. *Ibid.*, Chapter 3. (c) Wildman, W. C.; LeMen, J.; Wiesner, K. *Ibid.*, Chapter 4.

(6) (a) Eisenbraun, E. J.; George, T.; Riniker, B.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 3648. (b) Eisenbraun, E. J.; Bright, A.; Appel, H. H. *Chem. Ind. (London)* **1962**, 1242. (c) Cordell, G. A. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1977; Vol XVI, Chapter 8, pp 432–502. (d) Eisenbraun, E. J. Ph.D. Thesis, University of Wisconsin, 1955.

0022-3263/81/1946-3302$01.25/0 