sponds to the N–H stretching vibration. The uv spectrum has a maximum at 325 mμ with ε 12,060 in benzene.

Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.38; S, 13.02. Found: C, 58.4; H, 4.04; N, 11.5; S, 13.15.

Kinetics. The rate of reaction was followed at 350-mμ with a Durrum stopped-flow spectrophotometer.[19] The experimental infinity point was identical with that calculated from the extinction coefficient of the product sulfenamide. In two cases the whole spectrum of the solution at the infinity point was recorded with a Unicam recording spectrophotometer. The spectrum was identical with that of the sulfenamide at the same concentration.

Aniline and *p*-nitrobenzenesulfenyl chloride were kept in a dessicator, at 0° in the dark.

Due to the high lability of *p*-nitrobenzenesulfenyl chloride in the presence of traces of moisture, particular care was taken in the preparation of the solutions of the reagents. Benzene was distilled immediately before use and the solutions were prepared in a drybox and used immediately.

(19) For a description of the apparatus and treatment of the kinetic data see: G. Tomalin, M. Trifunac, and E. T. Kaiser, *J. Amer. Chem Soc.*, 91, 722 (1969).

Acknowledgment. This investigation was supported by C.N.R., Rome. Thanks are due to E. N. I., Rome, for the loan of a stopped-flow spectrophotometer.

Alkaloid Studies. LXIII.[1] The Constitution and Chemistry of Dichotine and 11-Methoxydichotine[2]

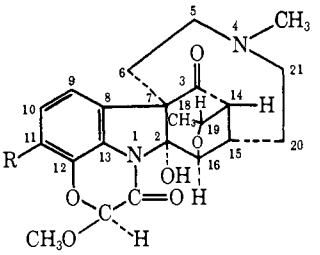
Nicholas C. Ling[3] and Carl Djerassi

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received March 16, 1970*

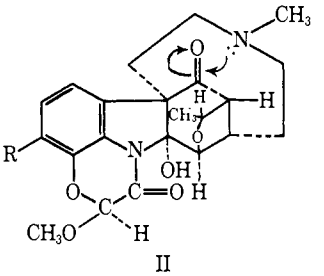
Abstract: The constitution of two closely related indole alkaloids, dichotine (Ia) and 11-methoxydichotine (Ib), isolated from the Peruvian *Apocynaceae*, *Vallesia dichotoma* Ruiz *et* Pav, was investigated with the help of infrared, ultraviolet, nuclear magnetic resonance, and mass spectroscopy as well as chemical degradations and isotopic labeling. During the course of the investigation, many new and interesting reactions were discovered. A theoretically plausible biogenetic route leading to these two unusual alkaloids is discussed.

The Peruvian plant, *Vallesia dichotoma*[4] Ruiz *et* Pav (family, *Apocynaceae*), is one of the richest sources of new indole alkaloids. This feature was documented in several papers published from our laboratories[5–10] starting in 1959. The latest paper[1] describes the X-ray crystallographic structure determination of two more novel indole alkaloids, dichotine and 11-methoxydichotine,[11] isolated from this plant. We should now like to report the structural investigation and interesting chemistry of these two alkaloids, which chronologically preceded the X-ray studies.[1]

(+)-Dichotine (Ia[12]) and (+)-11-methoxydichotine (Ib) are present in approximately 0.001% yield in the bark of *Vallesia dichotoma*. Both alkaloids have identical R_f values in many solvent systems but they were finally separated by tlc. A total of approximately 1.5 g of the alkaloid mixture was available for the structural work.



Ia, R = H
Ib, R = CH_3O



II

Microanalysis[8] and high-resolution mass spectrometric measurement showed molecular compositions of $C_{22}H_{26}N_2O_6$ and $C_{23}H_{28}N_2O_7$ for Ia and Ib, respectively, the difference being attributed to a methoxyl unit on the benzene ring of Ib, as evidenced by nmr and mass spectrometry.

The nmr spectrum (Figure 1) of dichotine (Ia) had the following characteristic features: a secondary methyl doublet (H^p) at δ 0.60 (J = 6.0 cps); a broad one-proton triplet at δ 1.76 (J = 14.0, 14.0 cps); a methyl singlet (H^1) at δ 2.02 which was assigned to an N-methyl signal because of its shift to δ 3.26 in trifluoroacetic acid; a complicated eight-proton signal between δ 2.10 and 3.02 with a distinct one-proton

(1) For paper LXII see N. C. Ling, C. Djerassi, and P. G. Simpson, *J. Amer. Chem. Soc.*, 92, 222 (1970).

(2) Taken from the Ph.D. Thesis (1969) of N. C. L. Financial support from the National Institutes of Health (Grant No. GM-11309) of the U. S. Public Health Service is gratefully acknowledged.

(3) Stauffer Predoctoral Fellow, 1965–1966.

(4) The plant material was collected by Mr. Juan A. Brissolese near Ica, Peru, at 300 m.

(5) J. E. S. Holker, M. Cais, F. A. Hochstein, and C. Djerassi, *J. Org. Chem.*, 24, 314 (1959).

(6) K. S. Brown, H. Budzikiewicz, and C. Djerassi, *Tetrahedron Lett.*, 1731 (1963).

(7) A. Walser and C. Djerassi, *Helv. Chim. Acta*, 47, 2072 (1964).

(8) A. Walser and C. Djerassi, *ibid.*, 48, 391 (1965).

(9) H. J. Monteiro, A. Walser, L. J. Durham, and C. Djerassi, *J. Amer. Chem. Soc.*, 88, 1792 (1966).

(10) S. H. Brown, C. Djerassi, and P. G. Simpson, *ibid.*, 90, 2445 (1968).

(11) Alkaloid 26 and 25, respectively, in ref 8.

(12) For numbering system see M. Hesse, "Indolalkaloid in Tabellen," Vol. I, Springer-Verlag, West Berlin and Heidelberg, 1964, p 41.

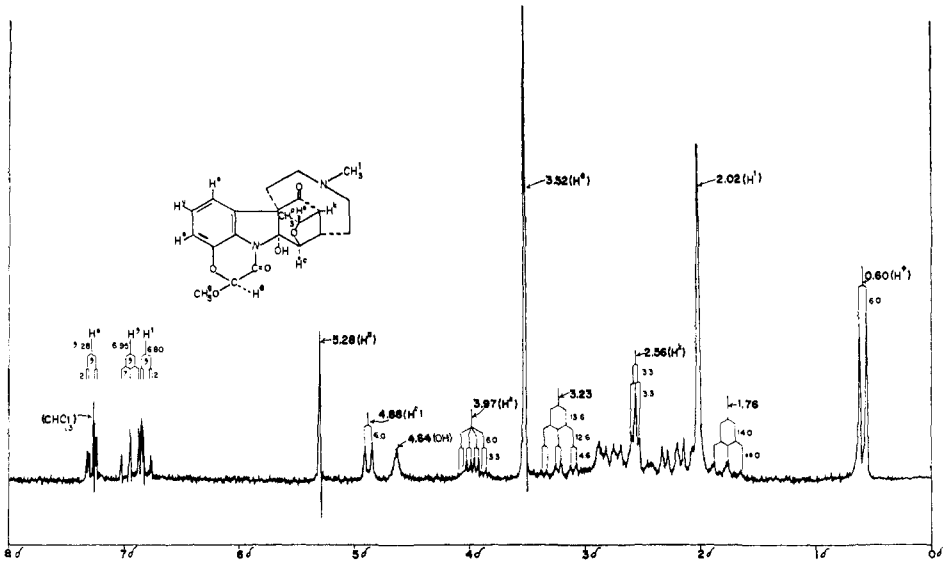


Figure 1. Nmr spectrum of dichotine (Ia).

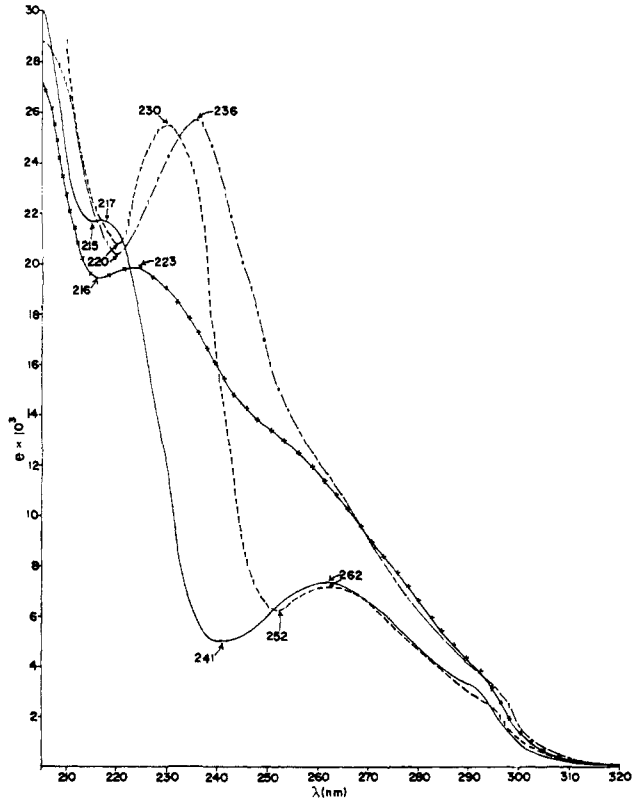
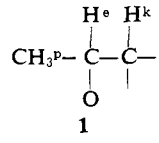


Figure 2. Uv spectra of dichotine (Ia, neutral, ×—×—×; acid, —) and 11-methoxydichotine (Ib, neutral, — · — · —; acid, – – –).

triplet (H^k) at δ 2.56 (J = 3.3, 3.3 cps); a one-proton sextet at δ 3.23 (J = 4.6, 12.6, 13.6 cps); a methoxy singlet (H^g) at δ 3.52; a one-proton octet (H^e) at δ 3.97 (J = 3.3, 6.0 cps) which was attributed to a hydrogen on a carbon bearing an oxygen; a hydroxyl proton at δ 4.64 (demonstrated by exchange with deuterium oxide); a one-proton doublet (H^c) at δ 4.88 (J = 6.0 cps) which was assigned to a proton on a carbon bonded to an oxygen; a sharp one-proton singlet (H^a) at δ 5.28 which was attributed to a proton on a carbon bearing two oxygens; and finally three aromatic protons (H^x, H^y, H^z) arranged in a 1,2,3 pattern on a benzene ring. The nmr spectrum of 11-methoxydichotine (Ib) was almost identical with that of dichotine, except it had only two aromatic protons appearing as a pair of doublets at δ 6.58 (J = 8.0 cps) and 7.20 (J = 8.0 cps) as well as an extra aromatic methoxyl signal at 3.88. Since the coupling constant of 8.0 cps belongs to an *ortho* coupling pattern, the methoxyl group and the two aromatic hydrogens must also be substituted in a 1,2,3 fashion on the benzene ring. Furthermore, the existence of structural unit **1** in both alkaloids was established because the proton (H^e) at δ 3.97 is coupled to the methyl doublet (H^p) at 0.60 and the triplet hydrogen (H^k) at 2.56 (see Figure 7).



1

In the ir spectra of dichotine and 11-methoxydichotine the presence of hydroxyl and carbonyl groups was inferred from the broad band between 3200 and 3500 cm^{-1} and the strong band at 1680 cm^{-1}.

The uv spectra (Figure 2) of dichotine and 11-methoxydichotine in neutral 95% ethanol were rather uncharacteristic, but on acidification new spectra resulted, typical of an N-acylindoline chromophore with one or more oxygens substituted on the benzene ring.[13] Basification regenerated the original spectrum, thus demonstrating the reversibility of this change. The "abnormal" ethanol spectrum is due to the fact that the two alkaloids exist as zwitterions (II) in their neutral form. The N_b nitrogen can come within bonding distance of the ketonic carbon and the resulting negatively charged oxygen (see arrows in II) interacts with the π electrons of the benzene ring to give the abnormal uv spectrum. Addition of acid protonates the carbonyl oxygen with concurrent formation of a full-

(13) N. Neuss, "Physical Data of Indole and Dihydroindole Alkaloids," Vol. I, II, and supplement, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind.

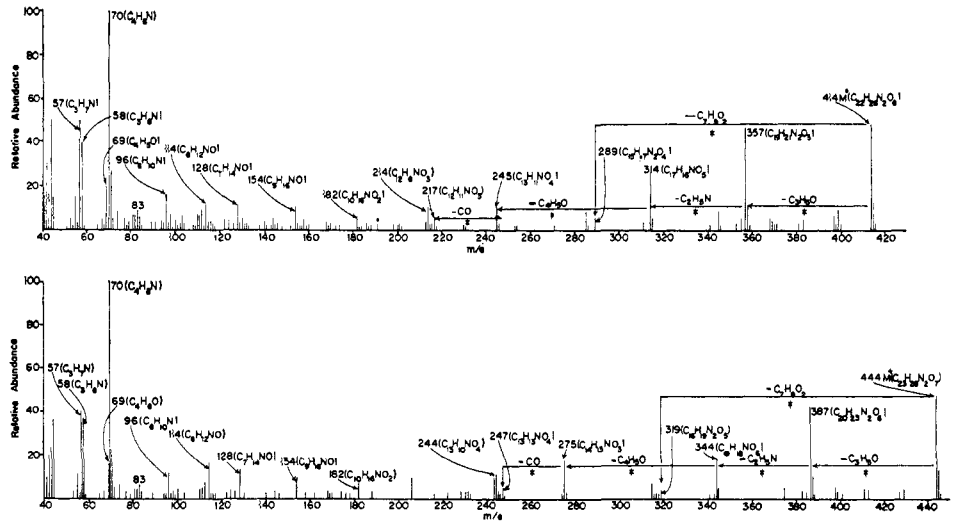


Figure 3. (a) Mass spectrum of dichotine (Ia) (top). (b) Mass spectrum of 11-methoxydichotine (Ib) (bottom).

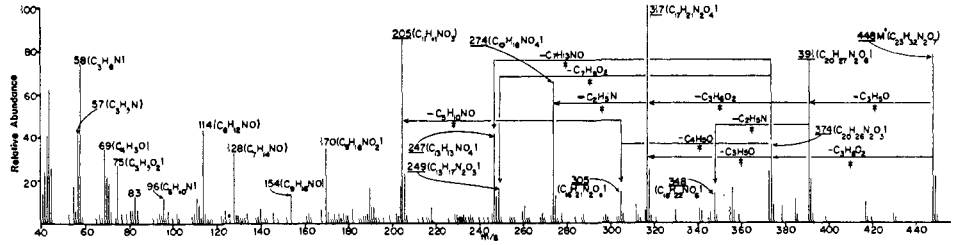


Figure 4. Mass spectrum of tetrahydro-11-methoxydichotine (IVb; the indole-containing peaks are underlined).

fledged carbon–nitrogen bond (see X-ray crystallographic structure determination of dichotine hydrobromide[1]), thus yielding a normal N-acylindoline uv spectrum. This unusual zwitterionic character has precedence in the Strychnos alkaloids such as vomicine,[14] novacine,[15] and icajine.[16]

The mass spectra[17] (Figures 3a and 3b) of dichotine (Ia) and 11-methoxydichotine (Ib) were of little diagnostic value because they did not resemble those of the known classes of indole alkaloids.[18] However, the indole-containing peaks were easily identified because of the appropriate 30 mass unit shifts between Ia and Ib. In addition, high-resolution measurements and metastable peak detection[19] demonstrated the sequential loss of C_3H_5O, C_2H_5N, C_4H_5O, and CO units.

The presence of a hydroxyl group in dichotine and 11-methoxydichotine had already been demonstrated by ir and nmr. An independent chemical proof was obtained by monoacetylation (I → III), as evidenced by an increase of 42 mass units for its molecular ion and a new methyl singlet at δ 2.17 in its nmr spectrum. The tertiary nature of the acetate was demonstrated by the absence of any appreciable downfield shift of any proton in the nmr spectrum. The uv curves of dichotine and 11-methoxydichotine acetates (IIIa,b) were identical with those (Figure 2) of their parent alkaloids and exhibited the same reversible change in acid and base.

Sodium borohydride reduction of 11-methoxydichotine (Ib) gave in good yield a new compound (IVb), whose ir spectrum showed a broad O–H at 3350 cm,$^{-1}$, a sharp N–H absorption at 3570 cm^{-1}, and the "abnormal" weak carbonyl band[20] at 1635 cm^{-1}. The uv curve in acid corresponded to that of a dihydroindole with alkoxyl groups substituted on the benzene ring.[13] From the ir and uv data, we concluded that the amide group of the N-acylindoline moiety was cleaved by sodium borohydride.

When the nmr spectrum (see Figure 1) of 11-methoxydichotine (Ib) was compared with that of its borohydride reduction product (IVb), the following changes could be noticed: shifting of the one-proton doublet (H^c) from δ 4.88 (J = 6.0 cps) to 3.98 (J = 6.0 cps); disappearance of the sharp one-proton singlet (H^a) at δ 5.38; and appearance of a new one-proton triplet at 4.90 (J = 5.2, 5.2 cps), a very broad one-proton signal at 5.42 which was eliminated by addition of deuterium oxide, and a two-proton multiplet at 3.61–3.74.

In the mass spectrum (Figure 4) of IVb the molecular ion showed an increase of four mass units from the original alkaloid but still lost the elements of C_3H_5O, C_2H_5N, and C_4H_5O. However, there was an inde-

(14) H. Wieland and G. Oertel, *Justus Liebigs Ann. Chem.*, **469**, 193 (1929); R. Hüisgen, H. Eder, L. Blazejewicz, and Z. Mergenthaler, *ibid.*, **573**, 121 (1951).

(15) W. F. Martin, H. R. Bentley, J. A. Henry, and F. S. Spring, *J. Chem. Soc.*, 3603 (1952).

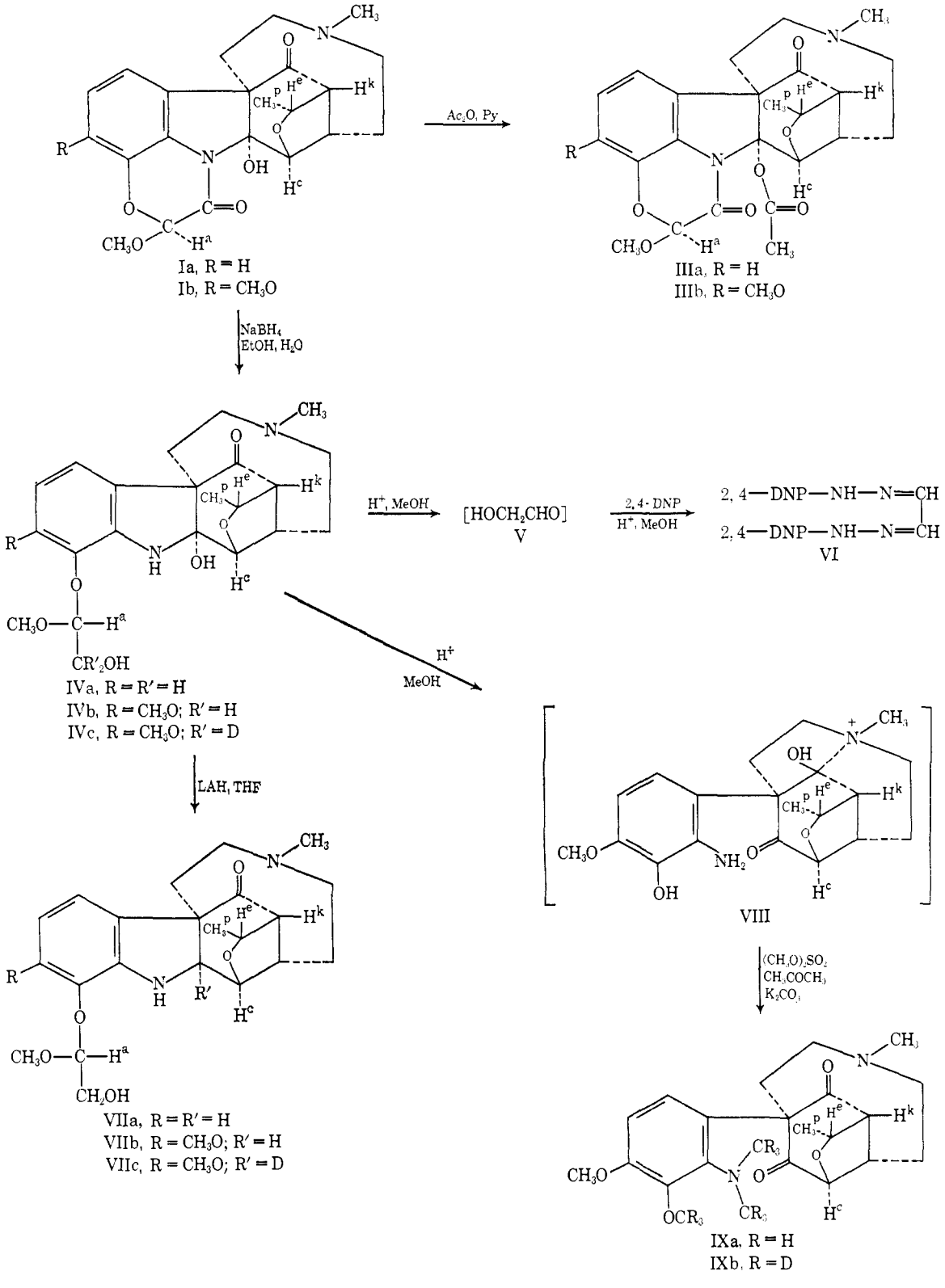
(16) H. Bisset, *C. R. Acad. Sci.*, **261**, 5237 (1965).

(17) Empirical formulas are marked for those peaks where the composition was established by high-resolution mass measurements.

(18) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, San Francisco, Calif., 1964.

(19) K. Biemann, "Mass Spectrometry—Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 43, 153–157, 166.

(20) N. J. Leonard, *Rec. Chem. Progr.*, 17, 242 (1956).



pendent neutral species $C_3H_6O_2$ which also was ejected at an early stage (see Figure 4). Furthermore, all the aliphatic peaks, with the exception of $C_9H_{16}NO_2$ (*m/e* 170) and $C_3H_7O_2$ (*m/e* 75), were also present in the parent alkaloid. (The indole-containing and aliphatic peaks were identified by noting the presence or absence of 30 mass unit shifts as compared to the spectrum of the corresponding tetrahydrodichotine (IVa).) This observation indicates that the molecular change accompanying sodium borohydride reduction occurred in the indoline moiety.

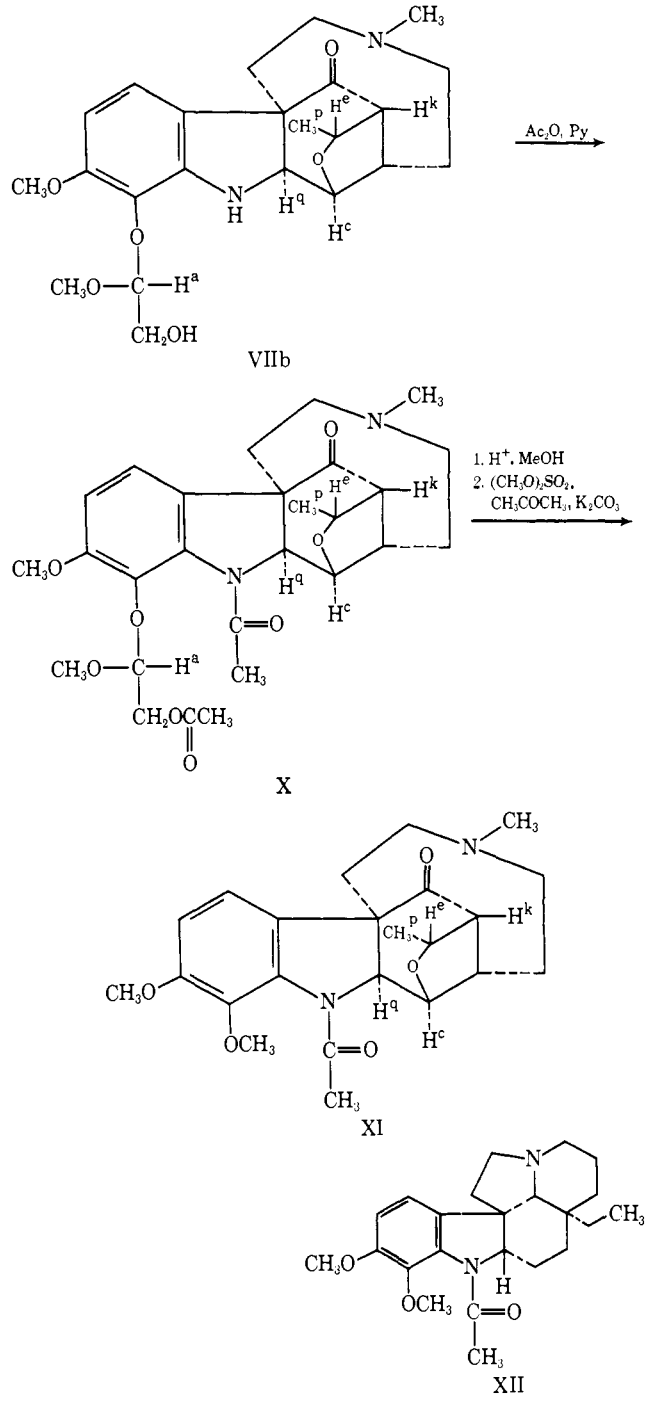
Reduction of 11-methoxydichotine (Ib) with sodium borodeuteride gave a dideuterio derivative (IVc) of tetrahydro-11-methoxydichotine, implying that two of the four hydrogen atoms introduced during the sodium borohydride reduction are labile. The fragmentation pattern of this d_2 derivative IVc was the same as that (Figure 4) of tetrahydro-11-methoxydichotine, except

that both deuterium atoms were lost in the $C_3H_6O_2$ species and retained in the $C_3H_7O_2$ fragment (now $C_3H_5D_2O_2$). The nmr spectrum of IVc differed from that of its nondeuterated analog IVb only by having a one-proton singlet at δ 4.90 instead of the triplet and the disappearance of the two-proton multiplet at 3.61–3.74.

All these data can be explained by assuming that sodium borohydride reduction of dichotine and 11-methoxydichotine opens the amide group of I to a primary alcohol and a secondary amine (see IV), resulting in the addition of four hydrogens, two of which are labile. The sharp one-proton singlet (H_a) at δ 5.38 becomes a triplet at 4.90 because it is split by the two added hydrogens of the primary alcohol group, the upfield shift of this signal being due to the elimination of the carbonyl group. Substitution of the two hydrogens of the primary alcohol IVb by deuterium (IVc) results in the collapse of the triplet to a singlet and disappearance of the two-proton multiplet at 3.61–3.74. Electron impact induced cleavage between the phenoxy oxygen and the carbon bearing H^a in IVb with charge retention on the acetal unit rationalizes the appearance of the charged species $C_3H_7O_2$ (*m/e* 75) in Figure 4. Rupture of the same bond but with the positive charge located on the indoline portion of the molecule and a hydrogen transfer from the glycolic aldehyde methyl acetal unit to the indoline ring results in the neutral fragment $C_3H_6O_2$ and the charged species $C_{20}H_{26}N_2O_5$ (*m/e* 374). The existence of the glycolic aldehyde methyl acetal unit was demonstrated by mild acidic hydrolysis of IVb, followed by trapping of the resulting glycolic aldehyde (V) as glyoxal osazone (VI).

Lithium aluminum hydride reduction of tetrahydro-11-methoxydichotine (IVb) afforded a small amount of a less polar compound to which structure VIIb was assigned. Its ir spectrum displayed a broad O–H band at 3200–3600 cm^{-1} and the weak "abnormal" carbonyl signal[20,21] at 1640 cm^{-1}. The nmr spectrum of VIIb was superimposable upon that of tetrahydro-11-methoxydichotine (IVb) except for an extra one proton singlet at δ 4.03, and its uv spectrum was identical with that of tetrahydro-11-methoxydichotine (IVb).

However, its mass spectrum was quite different from that (Figure 4) of the starting material. High-resolution mass spectrometric determination gave the molecular composition as $C_{23}H_{32}N_2O_6$ (*m/e* 432), *i.e.*, a difference of one oxygen atom compared to IVb, thus leading to the trivial name deoxytetrahydro-11-methoxydichotine (VIIb). The familiar loss (see Figure 4) of $C_3H_6O_2$ from the molecular ion with an appropriate metastable peak[19] was still encountered but no expulsion of either C_3H_5O or C_2H_5N. The lowest indole-containing fragment, $C_{11}H_{12}NO_2$ (*m/e* 190), was identified by making the corresponding deoxy compound (VIIa) from tetrahydrodichotine (IVa) and noting the shift to *m/e* 160. Replacing lithium aluminum hydride with the deuteride in the reduction step resulted in the incorporation of only one deuterium atom (VIIc). This deuterium atom must be located very close to the indoline nucleus because the *m/e* 190 peak is shifted 1 mass unit higher.



Since only an oxygen atom was eliminated from this reaction, it must originate from a carbinolamine hydroxyl group. Furthermore, from the mass spectrometric data of the labeled deoxytetrahydro-11-methoxydichotine (VIIc), the hydroxyl group can only be placed at the α position of the indoline ring. The resulting carbinolamine structure (IV) is easy to demonstrate because, upon treating tetrahydro-11-methoxydichotine (IVb) with acid, the glycolic aldehyde methyl acetal unit was cleaved and the carbinolamine moiety opened to give an *o*-hydroxyaniline derivative (VIII), which was then methylated with dimethyl sulfate. The uv spectrum of the methylation product IXa in acid was similar to that of *o*-methoxyaniline. Its

(21) The presence of the "abnormal" carbonyl group was actually not known until the X-ray diffraction analysis of dichotine hydrobromide was completed. The lack of reduction by lithium aluminum hydride had convinced us that there was no additional carbonyl group present in the two alkaloids aside from the N_a-amide grouping.

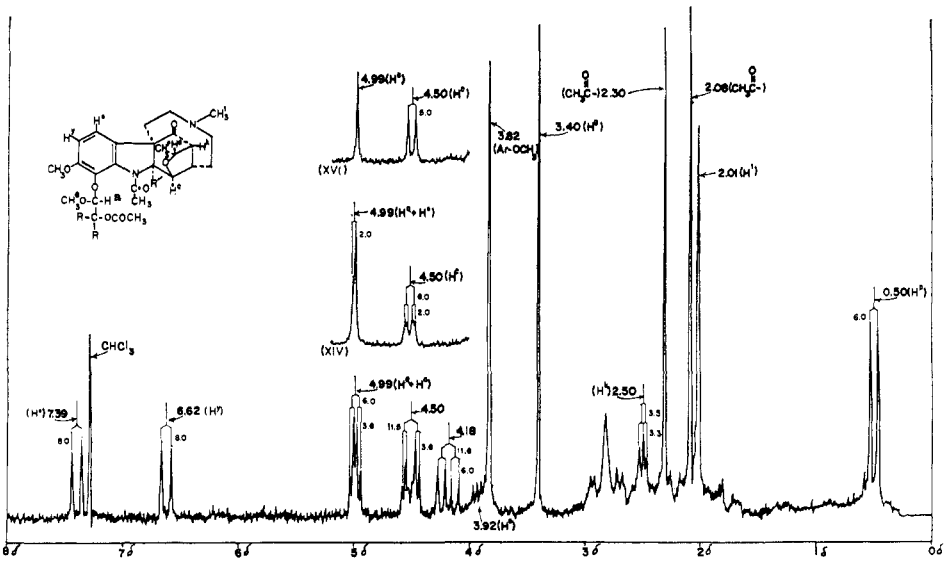


Figure 5. Nmr spectra of deoxytetrahydro-11-methoxydichotine diacetate (X, R = H; R′ = H^q), deoxy-d_2-tetrahydro-11-methoxydichotine diacetate (XIV, R = D; R′ = H^q), and deoxy-d_2-tetrahydro-11-methoxydichotine-d_1 diacetate (XVI, R = R′ = D).

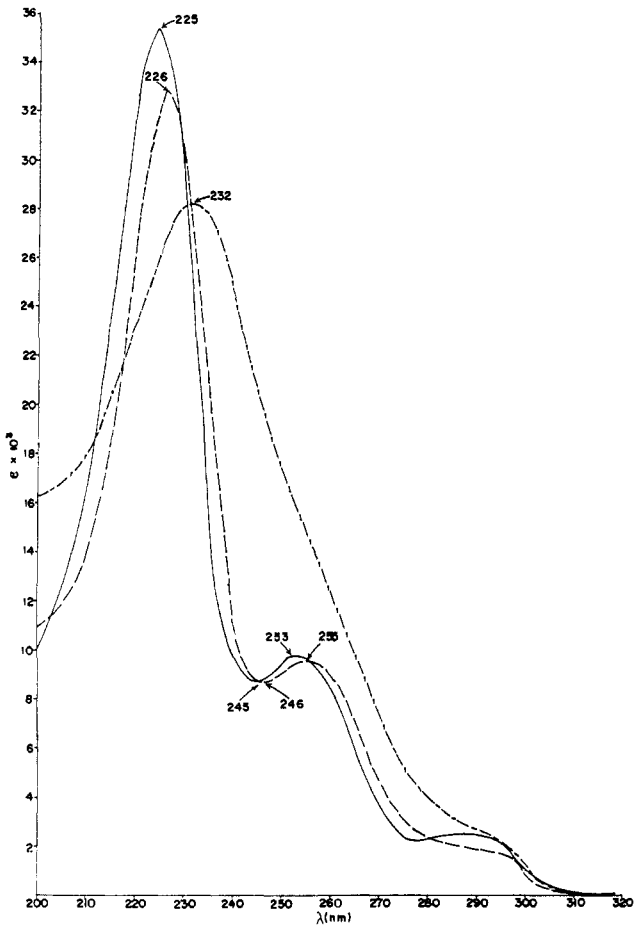


Figure 6. Uv spectra of methylation product XI (neutral, — · — · —; acid, – – – –) and (−)-pyrifolidine (XII, ——).

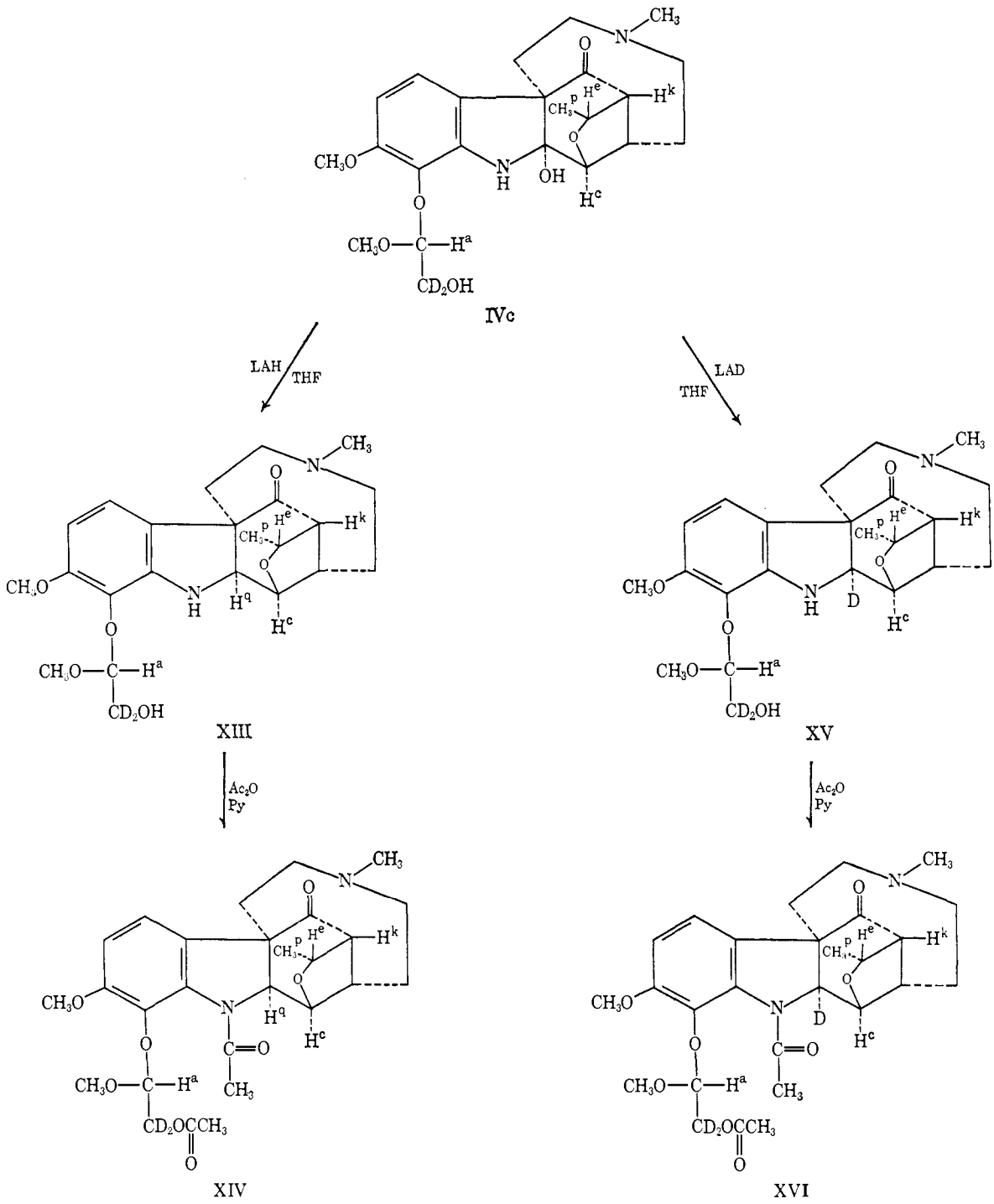
nmr spectrum showed three new methyl signals at δ 2.20, 2.86, and 3.87. The signal at δ 3.87 was assigned to the new aromatic methoxyl group while the other two must belong to the N,N-dimethyl moiety. The large chemical-shift difference between the two N_a-methyl groups is due to restricted rotation. The mass spectrum of IXa was consistent with a trimethylated product because the molecular ion appeared at *m/e* 416 ($C_{23}H_{32}N_2O_5$) as expected. Upon electron impact the molecule lost 44 mass units to give *m/e* 372 ($C_{21}H_{28}N_2O_4$ 55%, $C_{21}H_{26}NO_5$ 45%). Hence, the molecular ion actually loses either C_2H_4O (55%) or C_2H_6N (45%). Using dimethyl sulfate-d_6 for the methylation increased the molecular ion (IXb) by 9 mass units. Besides losing 44 mass units, the molecular ion also lost 50 mass units. This increase of 6 mass units is accounted for if the six hydrogens of C_2H_6N are replaced by deuterium. As a result, the C_2H_6N species must have come from the cleavage of the N,N-dimethyl group on the benzene ring.

The ir spectrum of IXa showed *no* O–H and N–H absorption but a very intense band at 1620 cm^{-1}, whose frequency is much too low for a saturated carbonyl group. Inspection of Dreiding models revealed that the N,N-dimethylamino nitrogen atom in IXa can come within bonding distance of the new ketonic group and thus destroy its carbonyl character (*cf.* II). Hence, the 1620-cm^{-1} band is probably associated with the dimethylaniline grouping.[22]

Since the carbinolamine hydroxyl group can be replaced by hydrogen, some useful information might be obtained if that hydrogen were located in the nmr spectrum. For this purpose deoxytetrahydro-11-methoxydichotine was N_a acetylated (VIIb → X) with acetic anhydride and pyridine, so as to shift the signal of the α proton on the indoline ring to lower field.[23] The mass spectrum of X demonstrated that a diacetate had been formed and that one of the acetate group was associated with the primary alcohol function because the base peak appeared at *m/e* 117 ($CH(OCH_3)$-CH_2OCOCH_3).

The nmr spectrum (Figure 5) of X showed the two acetyl methyl signals at δ 2.08 and 2.30. Besides the two aromatic hydrogens, there were five low-field proton signals beyond δ 4.00, three of which were quartets

(22) R. B. Barnes, U. Liddel, and V. Z. Williams, *Anal. Chem.*, 15, 659 (1943).
(23) B. Gilbert, *Alkaloids*, 8, 371 (1965).



at δ 4.18 (J = 6.0, 11.6 cps), 4.50 (J = 3.6, 11.6 cps), and 4.99 (J = 3.6, 6.0 cps). Each of the last two quartets was superimposed on another proton signal. From the coupling constants and chemical shifts, the quartets at δ 4.18 and 4.50 can be assigned to the methylene protons of the CH_2OCOCH_3 unit. They are being pulled downfield from δ 3.61-3.74 in the spectrum of tetrahydro-11-methoxydichotine (IVb) by the acetate group. The quartet at δ 4.99 is the acetal hydrogen (H^a) because it is being split by the two methylene protons.

In order to simplify the downfield region of the nmr spectrum (Figure 5), 11-methoxydichotine (Ib) was reduced with sodium borodeuteride (IVc) instead, followed by lithium aluminum hydride reduction (XIII) and acetylation (XIV). The spectrum (see Figure 5) of the dideuterio analog XIV had no signal at δ 4.18 and the signal at 4.50 (H^c) became a new quartet (J = 2.0, 6.0 cps) of only one proton. There was still a one proton singlet superimposed on another proton doublet (H^q, J = 2.0 cps) at δ 4.99. The superimposing singlet must be the H^a hydrogen because its splitting is being removed by the two deuterium atoms. Decoupling experiments (Figure 5) showed that the doublet (H^q) at δ 4.99 is coupled to the quartet (H^c) at 4.50. This doublet (H^q) is probably the α hydrogen introduced into the indoline ring when the carbinolamine hydroxyl group was removed by lithium aluminum hydride.

To test this proposition, the dideuterio-analog IVc

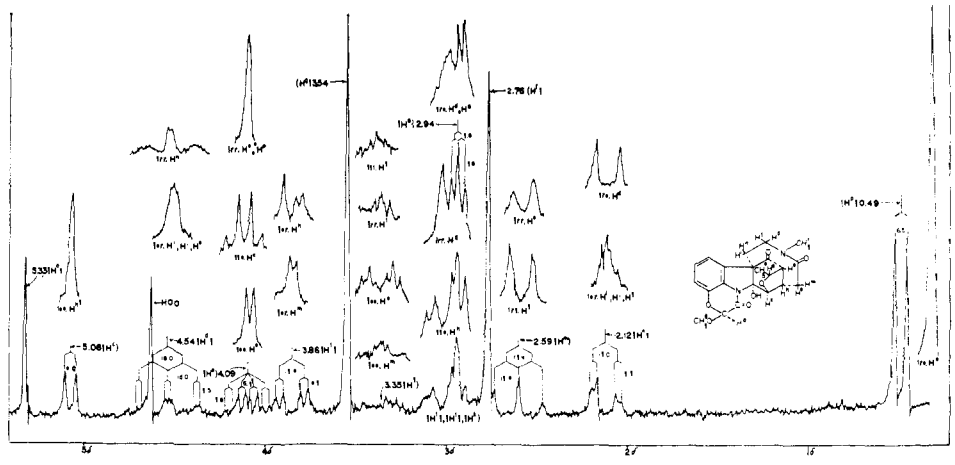
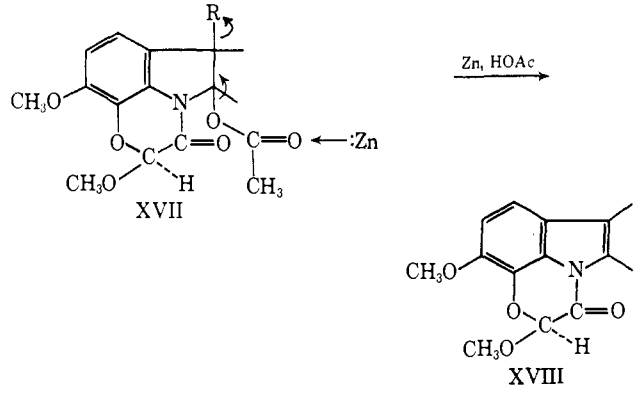


Figure 7. Nmr spectrum of dichotinamide (XXVIIa).

of tetrahydro-11-methoxydichotine was reduced with lithium aluminum deuteride (XV), followed by acetylation to yield XVI, which had only two low-field proton signals beyond δ 4.00 besides the two aromatic hydrogens in its nmr spectrum (see Figure 5). The doublet (H^q) at δ 4.99 (J = 2.0 cps) was gone, leaving only the sharp singlet (H^a). The quartet (H^c) at δ 4.50 collapsed to a doublet (J = 6.0 cps) because the small coupling of 2.0 cps was eliminated by the deuterium. This observation proves that the doublet (H^q) at δ 4.99 is the α hydrogen on the indoline ring, which is coupled to H^c at δ 4.50.

Since the diacetate X still contained the glycolic-aldehyde methyl acetal unit, it was hydrolyzed by dilute acid and the resulting phenolic hydroxyl group methylated with dimethyl sulfate (X → XI). The product XI had only one infrared carbonyl absorption at 1640 cm^{-1}, and all proton signals attributable to the $CH(OCH_3)CH_2OCOCH_3$ moiety were eliminated in its nmr spectrum. Instead, a new aromatic methoxyl singlet appeared at δ 3.70. The uv spectrum (Figure 6) of the methylation product XI taken in acid was almost superimposable upon that of (−)-pyrifolidine[24] (XII), thus showing that the two compounds must have the same chromophore in the indoline portion of the molecule. This finding proves that the two methoxyl groups of XI are located at the 11 and 12 position of the indoline ring.[12]



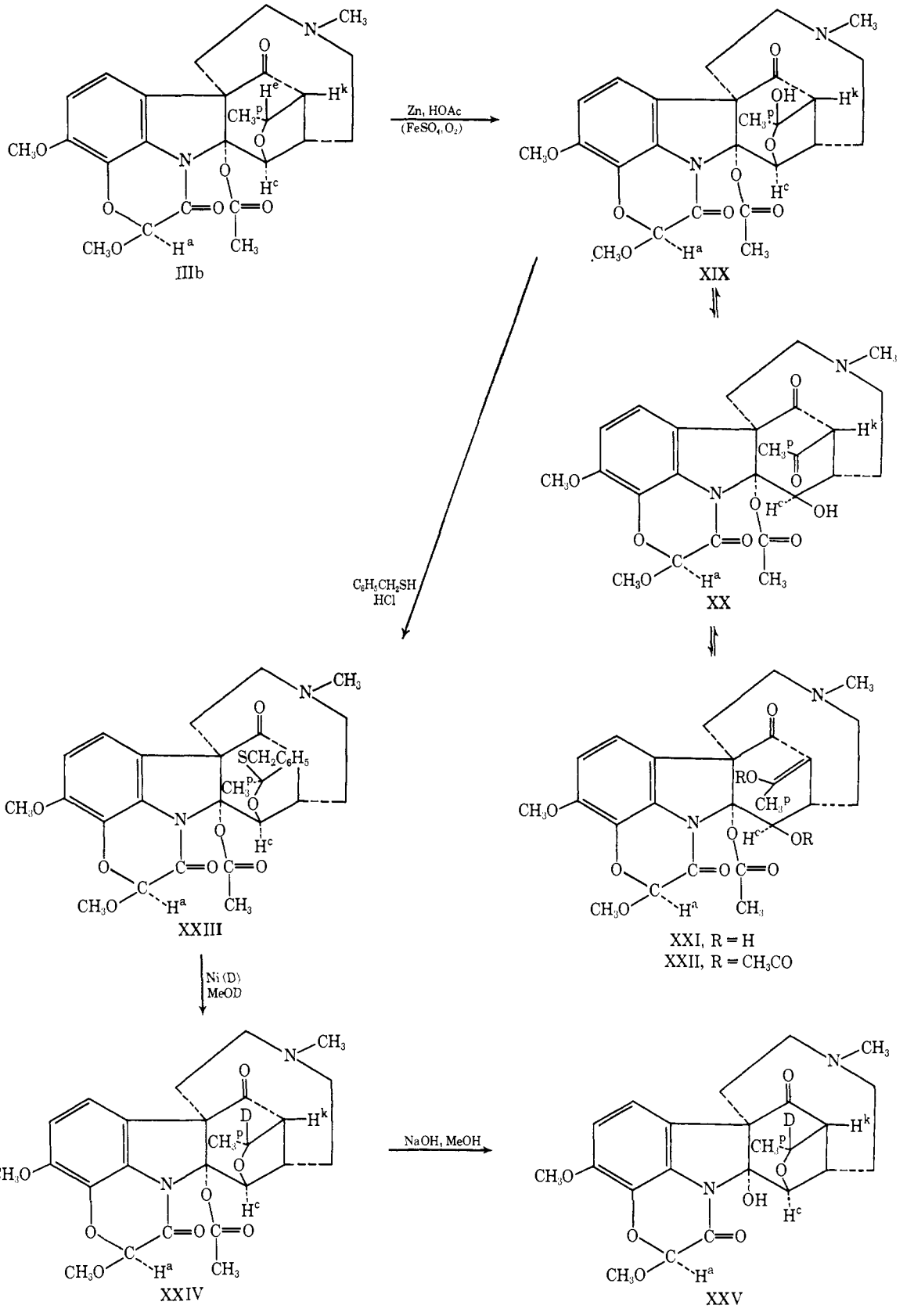
Because the ketonic oxygen was initially considered to be an ethereal oxygen bonded to the β-position of the indoline ring,[21] 11-methoxydichotine acetate (IIIb) was reduced with zinc in acetic acid, in the hope that the compound might undergo a transformation (XVII → XVIII) so as to yield an indole XVIII by analogy to aspidodasycarpine.[25] Although most of the product was recovered starting material (IIIb), a very small amount of a new product (XIX) was isolated, whose mass spectrum demonstrated that an oxygen atom had been introduced! A careful examination of the reagents revealed that the zinc used contained 0.004% iron as one of its impurities. Since ferrous ion is a reagent for producing free radicals,[26] it seemed to be implicated in the oxygenation. Indeed, an excellent yield of the oxygenation product XIX was obtained when the reaction was run under the same condition but in an oxygen atmosphere and with a few crystals of ferrous sulfate added to the reaction mixture.

The structure of oxy-11-methoxydichotine acetate (XIX) was deduced from its ir and nmr spectra. The ir spectrum displayed bands for a hydroxyl group at 3580 cm^{-1}, an acetate carbonyl at 1750 cm^{-1}, and an amide carbonyl at 1695 cm^{-1}. The nmr spectrum of XIX resembled that of its precursor IIIb with three exceptions. The methyl doublet (H^p) at δ 0.62 (J = 6.0 cps) in the spectrum of 11-methoxydichotine acetate (IIIb) became a singlet at 0.91 in XIX. The one-proton octet (H^e) at δ 4.00 (J = 3.3, 6.0 cps) in the starting material disappeared in the product. Instead of a one-proton triplet (H^k) at δ 2.62 (J = 3.3, 3.3 cps), there was a one-proton doublet at δ 2.72 (J = 3.6 cps). Since decoupling experiments had already established that the methyl doublet (H^p) at δ 0.62, the octet (H^e) at 4.00, and the triplet (H^k) at 2.62 belonged to partial structure **1** in 11-methoxydichotine acetate (IIIb), the collapse of the methyl doublet (H^p) to a singlet at δ 0.91 and the triplet (H^k) to a doublet at 2.72 plus the disappearance of the octet (H^e) as well as the addition of one oxygen atom and the presence of an O–H group in the oxygenation product XIX

(24) C. Djerassi, B. Gilbert, J. N. Shoolery, L. F. Johnson, and K. Biemann, *Experientia*, 17, 162 (1961); C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, and L. D. Antonaccio, *Tetrahedron*, 16, 212 (1961).

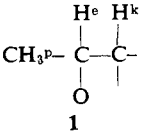
(25) M. Ohashi, J. A. Joule, and C. Djerassi, *Tetrahedron Lett.*, 3899 (1964); J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, 21, 1717 (1965).

(26) W. A. Waters, "Chemistry of Free Radicals," Clarendon Press, Oxford, 1948, pp 247–252.



suggest that oxy-11-methoxydichotine acetate (XIX) differs from 11-methoxydichotine acetate (IIIb) by having a hydroxyl group instead of H^e on the ethereal carbon in partial structure **1**.

Replacing H^e with a hydroxyl group in oxy-11-methoxydichotine acetate (XIX) leads to a hemiketal β to a carbonyl function; therefore, in addition to the hydroxyl proton, the doublet (H^k) at δ 2.72 (J = 3.6 cps) in the nmr spectrum was also eliminated by



1

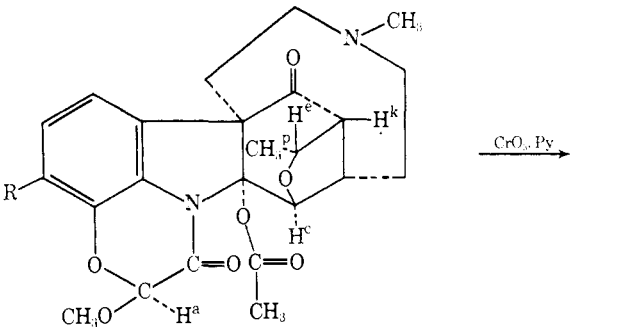
exchange with deuterium oxide. To explain this phenomenon one simply needs to envisage an equilibrium between the hemiketal (XIX) and its opened keto form (XX) which, in turn, is in equilibrium with its enol tautomer (XXI). As a result, both the hydroxyl proton and the H^k signal can be removed by deuterium oxide exchange. Acetylation of oxy-11-methoxydichotine acetate (XIX) with acetic anhydride and pyridine yielded a diacetate (XXII), which can again be explained by the opening of the hemiketal (XIX → XX), followed by enolization (XXI). Acetylation of both the alcoholic and enolic hydroxyl group would then rationalize the production of diacetate XXII.

Treatment of oxy-11-methoxydichotine acetate (XIX) with dry hydrogen chloride gas in benzyl mercaptan (XIX → XXIII) and desulfurization of the resulting benzyl mercaptoketal with Raney nickel (D) (XXIII → XXIV) should yield a compound XXIV which should differ from 11-methoxydichotine acetate (IIIb) only by replacement of H^e with a deuterium atom. Indeed, the major product (XXIV) of this reaction sequence exhibited an identical nmr spectrum to that of 11-methoxydichotine acetate (IIIb), except that H^k at δ 2.62 changed from a triplet (J = 3.3, 3.3 cps) to a doublet (J = 3,3 cps) and the methyl doublet (H^p) at δ 0.62 (J = 6.0 cps) to a singlet. This observation indicates that H^e was replaced by a deuterium atom. However, integration of the methyl singlet (H^p) at δ 0.62 showed that it corresponded only to 1.5 protons, thus proving that considerable scrambling of deuterium had occurred within the methyl group during the desulfurization. Such scrambling was supported by mass spectrometric analysis (d_0 3%, d_1 20%, d_2 20%, d_3 12%, d_4 26%, d_5 19%). The presence of a d_5 species confirms that there is only one hydrogen atom on the carbon bonded to H^k. If there were two, then the second hydrogen should also be exchanged with deuterium, resulting in a d_6 species.

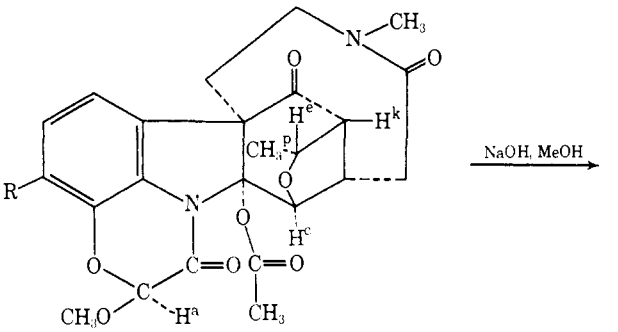
Hydrolysis of polydeuterio-11-methoxydichotine acetate (XXIV) with methanolic sodium hydroxide gave the corresponding polydeuterio-11-methoxydichotine (XXV). The deuterium content of the hydrolysis product XXV was the same as that of the starting acetate XXIV. The fragmentation pattern of XXV was identical with that (Figure 3b) of 11-methoxydichotine (Ib) and all of the deuterium atoms were lost in going from m/e 344 ($C_{18}H_{18}NO_6$) to 275 ($C_{14}H_{13}NO_5$). *Therefore, the neutral species C_4H_5O must include subunit* **1**.

Since loss of the neutral species C_2H_5N ($CH_3N{=}CH_2$) is observed in the mass spectra of dichotine (Ia), 11-methoxydichotine (Ib), and their tetrahydro derivatives (IVa,b), the N_b-methyl group must have at least one methylene group bonded to the same nitrogen atom. To provide chemical support for this conclusion, 11-methoxydichotine acetate (IIIb) was oxidized with chromium trioxide in pyridine to an amide, whose infrared, nmr, and mass spectra were fully consistent with structure XXVIb. The uv spectrum, however, was now that of a normal N-acylindoline[13] and was unchanged in acid. Clearly the reduced basicity of N_b did not permit any more interaction (I → II) with the ketonic carbonyl group.

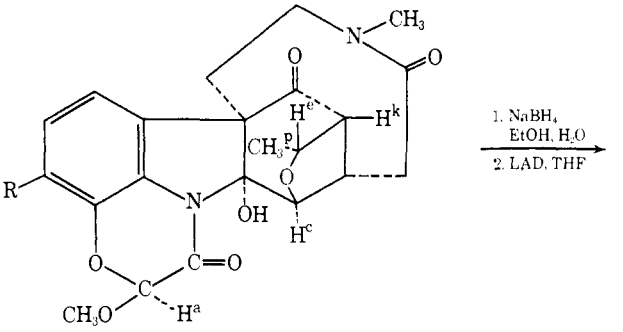
To ensure that no other changes had occurred during the chromium trioxide oxidation, the acetate XXVIb was hydrolyzed to 11-methoxydichotinamide (XXVIIb), followed by successive reduction with sodium borohydride and lithium aluminum deuteride. The resulting compound (XXVIII)[27] should have the same structure as tetrahydro-11-methoxydichotine (IVb), except for the substitution of two deuterium atoms at the site of the N_b-carbonyl carbon. Indeed, the product (XXVIII) of this reaction sequence had a mass



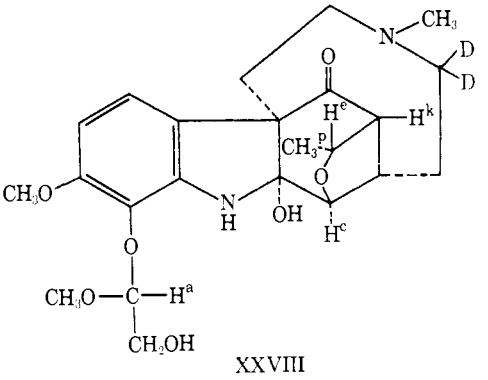
IIIa, R = H
IIIb, R = CH_3O



XXVIa, R = H
XXVIb, R = CH_3O



XXVIIa, R = H
XXVIIb, R = CH_3O

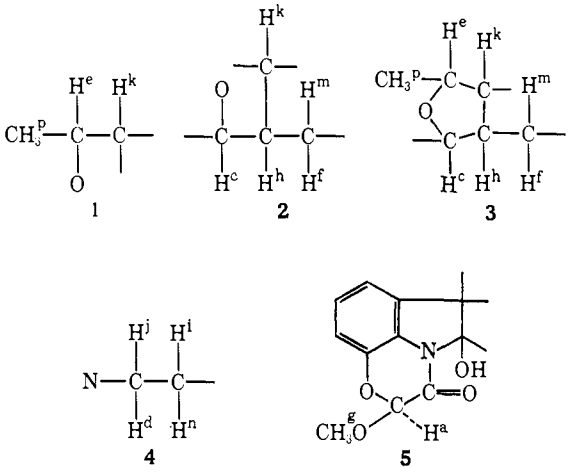


XXVIII

(27) Removal of the carbinolamine hydroxyl group in XXVIII by lithium aluminum deuteride requires higher temperature and longer refluxing time.

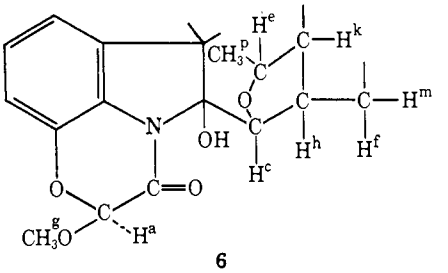
spectrum identical with that (Figure 4) of tetrahydro-11-methoxydichotine (IVb), except for the appropriate shift of the peaks which contained deuterium. Since both deuteriums were lost in the C_2H_5N species, this fragment must incorporate the methylene group bonded to the N_b nitrogen and the methyl group.

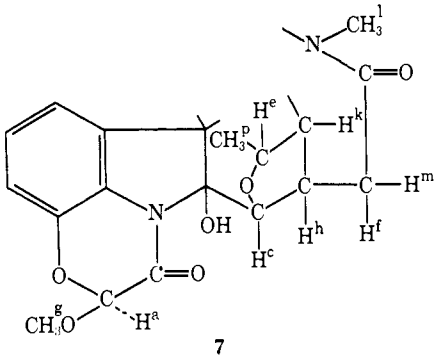
Dichotinamide (XXVIIa) appeared particularly suitable for nmr decoupling analysis, and a specimen was therefore prepared in an analogous fashion (IIIa → XXVIa → XXVIIa). With the exception of the hydroxyl and the aromatic protons, all other hydrogens in dichotinamide (XXVIIa) exhibit their signals clearly in the nmr spectrum (Figure 7). The signal for H^a at δ 5.33, the methoxyl singlet (H^g) at 3.54, and the N-methyl peak (H^l) at 2.76 are obvious and need no further comment. As expected H^e at δ 4.09 (J = 3.6, 6.5 cps) is coupled to H^k at 2.94 (J = 3.6, 3.6 cps) and H^p at 0.49 (J = 6.5 cps), forming the familiar subunit **1**. The large coupling (13.4 cps) of H^f at δ 3.86 goes with H^m at 2.59, while the small coupling (4.5 cps) of H^f and the other large coupling (13.4 cps) of H^m are associated with H^h at 3.35. H^h is also coupled to H^c at δ 5.08 through a coupling constant of 6.0 cps and to H^k by 3.6 cps. This coupling pattern is consistent with structural unit **2**. Since the two coupling constants of H^m are both 13.4 cps, they can only be explained in terms of a geminal coupling



to H^f and a vicinal axial axial coupling to H^h (see **2**). The vicinal axial equatorial coupling of H^f to H^h is in agreement with the small coupling of 4.5 cps. The coupling of H^h to H^c (6.0 cps) and H^h to H^k (3.6 cps) is also consistent with a vicinal coupling. Since H^c is at δ 5.08, it is either a vinyl proton or a proton bonded to a carbon bearing an oxygen. The latter alternative is favored in connection with the completely unsuccessful hydrogenation of dichotine (see below). Furthermore, since an oxygen and H^k are present in both subunits **1** and **2**, the two units can be tentatively joined together to give **3**. Irradiation of the H^i, H^j, H^k region causes H^d at δ 4.54 (J = 16.0, 16.0, 3.5 cps) to collapse from a broad triplet to a broad singlet. Therefore, H^d is coupled to H^i and H^j through two large coupling constants of 16.0 cps each. The small coupling of H^d (3.5 cps) goes with the small coupling of H^n at δ 2.12 (J = 13.0, 3.5 cps) and H^n, in turn, interacts with H^i through a large coupling of 13.0 cps. The coupling data of H^d, H^i, H^j, and H^n can be explained in terms of structural unit **4**. The geminal coupling of H^d with H^j and the vicinal axial–axial coupling of H^d with H are consistent with the two large coupling constants (16.0, 16.0 cps) of H^d (see **4**). The vicinal axial–equatorial coupling of H^d with H^n is in agreement with the small coupling (3.5 cps) of H^d. The large coupling of H^n (13.0 cps) is explainable in terms of a geminal coupling to H^i. However, no coupling is detected between H^n and H^j. This feature may be the result of a 90° dihedral angle between H^j and H^n. Since H^d is at δ 4.54, it has to be bonded to a carbon bearing either an oxygen or a nitrogen. Nitrogen is favored because the resulting structure **4** accounts for the tryptamine bridge which is present in nearly all indole alkaloids.[28] Also, H^d appears at such a low-field position only in the case of the amides (XXVIIa,b), which have a carbonyl group bonded to the N_b nitrogen. In all the other derivatives of dichotine and 11-methoxydichotine, H^d is located in the high-field region beyond δ 3.50.

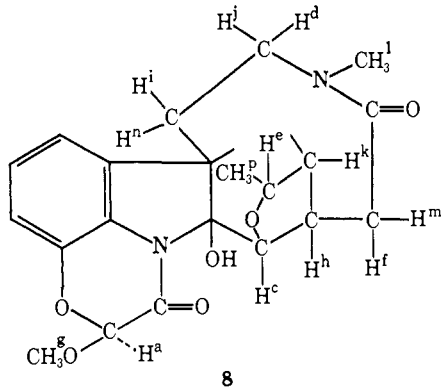
With structural units **3**, **4**, the CH_3^l—N—C=O fragment, the indoline moiety **5**, and the abnormal carbonyl group,[21] all the atoms in dichotinamide (XXVIIa) have been accounted for and it is only necessary to join them together in a manner that is consistent with all the data. One clue was supplied by the derivative, deoxy-d_2-tetrahydro-11-methoxydichotine diacetate (XIV), in which the carbinolamine hydroxyl group was replaced by a hydrogen atom (H^q). Since nmr decoupling showed that H^q is coupled to H^c, structural unit **3** can be joined with **5** to give **6**. Also, the chemical shift of H^m corresponds to a proton next to a carbonyl group and thus **6** can conceivably be extended to **7**. Incorporation of the tryptamine bridge





4 gives **8**. It only remains to fit the abnormal carbonyl group into this system. The ketonic carbonyl and the carbinolamine hydroxyl have to bear a *trans* relationship because this is the only way to join the molecule together so that the methyl group (CH_3^p) is directly above the benzene ring and, thus, accounts for its unusually high-field position. Structure **9** (Ia) for

(28) M. Hesse, "Indolalkaloide in Tabellen," Vol. I, Springer-Verlag, West and Heidelberg, Berlin, 1964; Vol. II, 1968.



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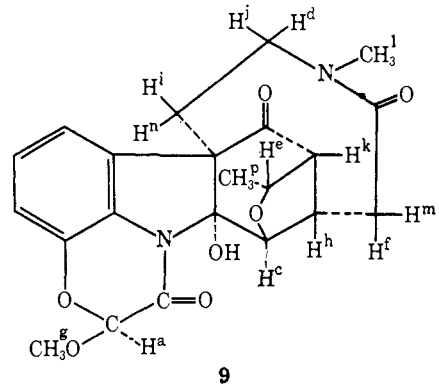


9

dichotine is consistent with all these observations and, as reported earlier,[1] has been established vigorously by X-ray analysis.

At an earlier stage of our investigation, in order to settle the question of whether the two parent alkaloids contained a double bond (the abnormal carbonyl band[20,21] at 1635 cm^{-1} in tetrahydrodichotine (IVa) and tetrahydro-11-methoxydichotine (IVb) was initially mistaken as a carbon–carbon bond vibration), dichotine (Ia) was hydrogenated with 10% palladium-on-carbon in absolute ethanol containing 10% acetic acid. Although most of the starting material was recovered from this hydrogenation, there was isolated a trace of a new product (XXIXa) whose mass spectrum showed it to be a dehydrodichotine (M^+, *m/e* 412, $C_{22}H_{24}N_2O_6$). Thus, instead of gaining any hydrogen, dichotine actually had lost two hydrogen atoms during the attempted hydrogenation process. In fact, when the hydrogen gas was omitted, an excellent yield of dehydrodichotine (XXIXa) was obtained when dichotine was stirred in an atmosphere of nitrogen with 10% palladium on carbon in absolute ethanol.

The uv spectrum of dehydrodichotine (XXIXa) was typical of an N-acylindoline chromophore[13] and was not altered in acid solution. Thus, aside from dichotine amide (XXVIIa), this is the only compound in this series whose uv spectrum is unaffected by the addition of acid. The ir spectrum showed no O–H or N–H absorption, but the N-acylindoline carbonyl band was still located at 1695 cm^{-1}. The nmr spectrum of this compound was quite different from that (Figure 1) of the starting dichotine, the most noticeable difference being the shift of the N-methyl signal (H^1) from δ 2.02 to 2.50 and the appearance of a new one-proton quartet at δ 4.96 (J = 4.0, 9.0 cps).

With the possibility that the new quartet at δ 4.96 (J = 4.0, 9.0 cps) might be a vinyl proton, the loss of two hydrogens in dichotine during the palladium dehydrogenation suggested the generation of a carbon–carbon double bond in dehydrodichotine. To test this hypothesis, dehydrodichotine (XXIXa) was hydrogenated with platinum oxide in absolute ethanol. The product, obtained in high yield, was identical with dichotine (Ia), thus confirming apparently the presence of a trisubstituted double bond in dehydrodichotine.

However, when dehydrodichotine (XXIXa) was hydrogenated with deuterium gas and platinum oxide in deuterioethanol, the resulting dichotine (XXX) contained only one deuterium atom. This result is not consistent with the presence of a carbon–carbon double bond in dehydrodichotine. Nevertheless, the mass spectrum of dichotine-d_1 (XXX) did offer a clue to the structure of dehydrodichotine because the deuterium was lost in the C_2H_5N species. Since the mass spectrum of tetrahydro-11-methoxydichotine-d_2 (XXVIII), derived from amide XXVIIb) had already shown that the C_2H_5N fragment is made up of the methylene group bonded to the basic nitrogen (N_b) and the N-methyl group, the deuterium in dichotine-d_1 is almost certainly located at the N-methylene carbon. Also, since dehydrodichotine lacked O–H absorption in its ir spectrum, formation of dehydrodichotine from dichotine probably involves the loss of the carbinolamine hydroxyl hydrogen plus one of the N-methylene hydrogens to give a carbinolamine ether linkage as shown in structure XXIX.

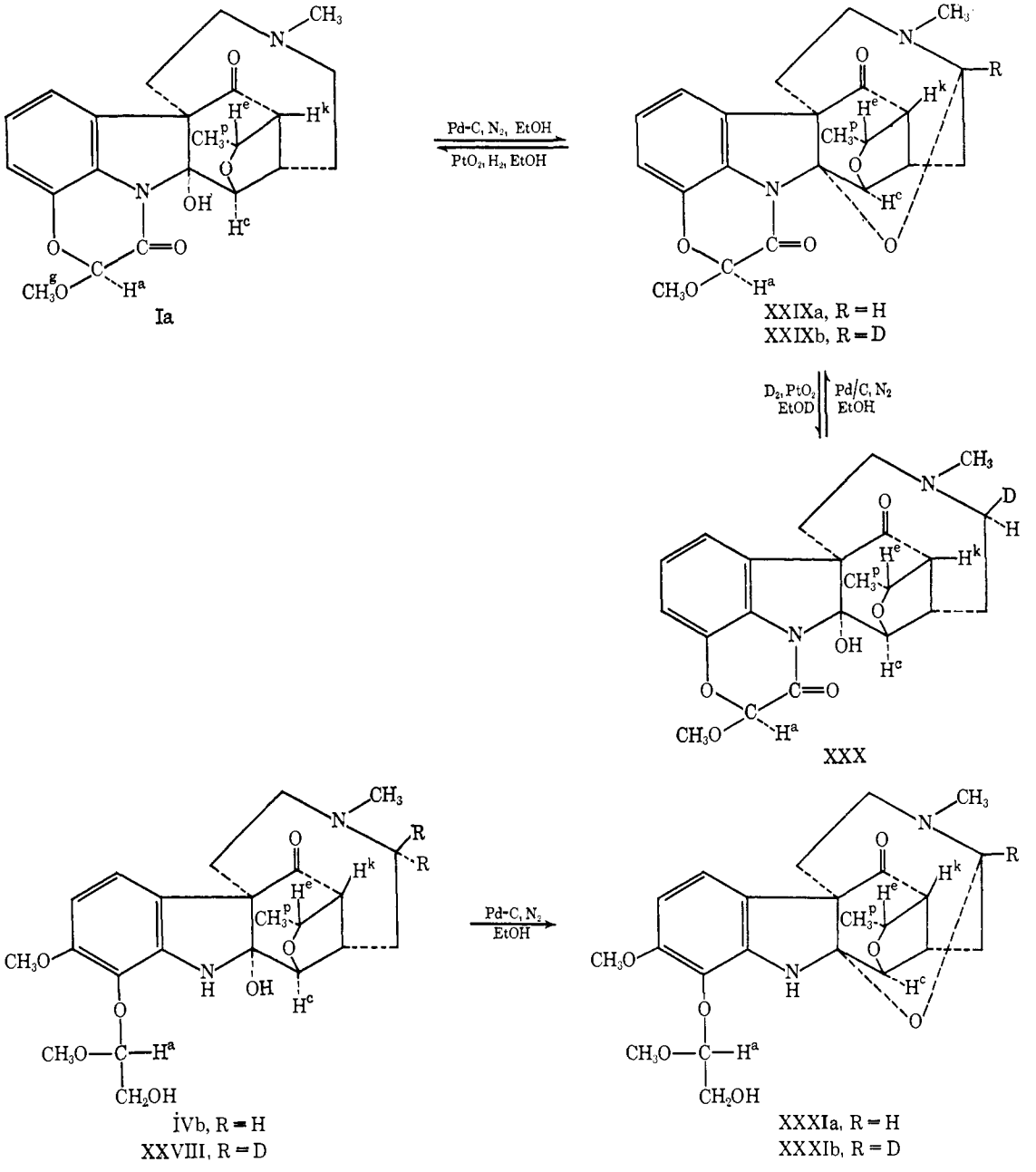
Structure XXIXa is in agreement with its nmr spectrum. The N-methyl signal (H^1) is pulled downfield to δ 2.50 by the carbinolamine ether oxygen. The quartet at δ 4.96 (J = 4.0, 9.0 cps) can be attributed to the hydrogen on the carbinolamine ether carbon because the alkaloid, picraline,[29] also has such a carbinolamine ether linkage and its corresponding hydrogen signal appears at δ 4.72.[30] Hydrogenation of dehydrodichotine (XXIXa) with platinum oxide cleaves the carbinolamine ether linkage[31] to regenerate the original N-methylene function and the hydroxyl group. If deuterium gas is used instead of hydrogen, only one deuterium atom will enter the molecule because the other one, being on a hydroxyl group, will be replaced by hydrogen during the work-up of the reaction.

Since tetrahydro-11-methoxydichotine (IVb) still possesses the carbinolamine hydroxyl group, it also yielded the corresponding dehydrogenation product XXXIa when stirred with 10% palladium-on-carbon. As expected, when the dideuterio analog XXVIII of tetrahydro-11-methoxydichotine (derived from the amide XXVIIb) was subjected to the dehydrogenation reaction, the corresponding dehydro compound XXXIb retained only one deuterium atom. This observation

(29) A. Z. Britten and G. F. Smith, *J. Chem. Soc.*, 3850 (1963); A. Z. Britten, G. F. Smith, and G. Spiteller, *Chem. Ind.* (London), 1492 (1963); L. Olivier, J. Lévy, J. LeMen, M.-M. Janot, C. Djerassi, H. Budzikiewicz, J. W. Wilson, and L. J. Durham, *Bull. Soc. Chim. Fr.*, 646 (1963); L. Olivier, J. Lévy, J. LeMen, M.-M. Janot, H. Budzikiewicz, and C. Djerassi, *ibid.*, 868 (1965); J. LeMen, *Lloydia*, 27, 456 (1964); A. Z. Britten, J. A. Joule, and G. F. Smith, *Tetrahedron*, 23, 1971 (1967).

(30) L. J. Durham, N. Bhacca, and H. Budzikiewicz, *Tetrahedron Lett.*, 5 (1965).

(31) Cleavage of a carbinolamine–ether linkage by platinum oxide hydrogenation has been reported in the chemistry of veatchine and garryine; see K. Wiesner and Z. Valenta, *Fortschr. Chem. Org. Naturst.*, 16, 26 (1958).



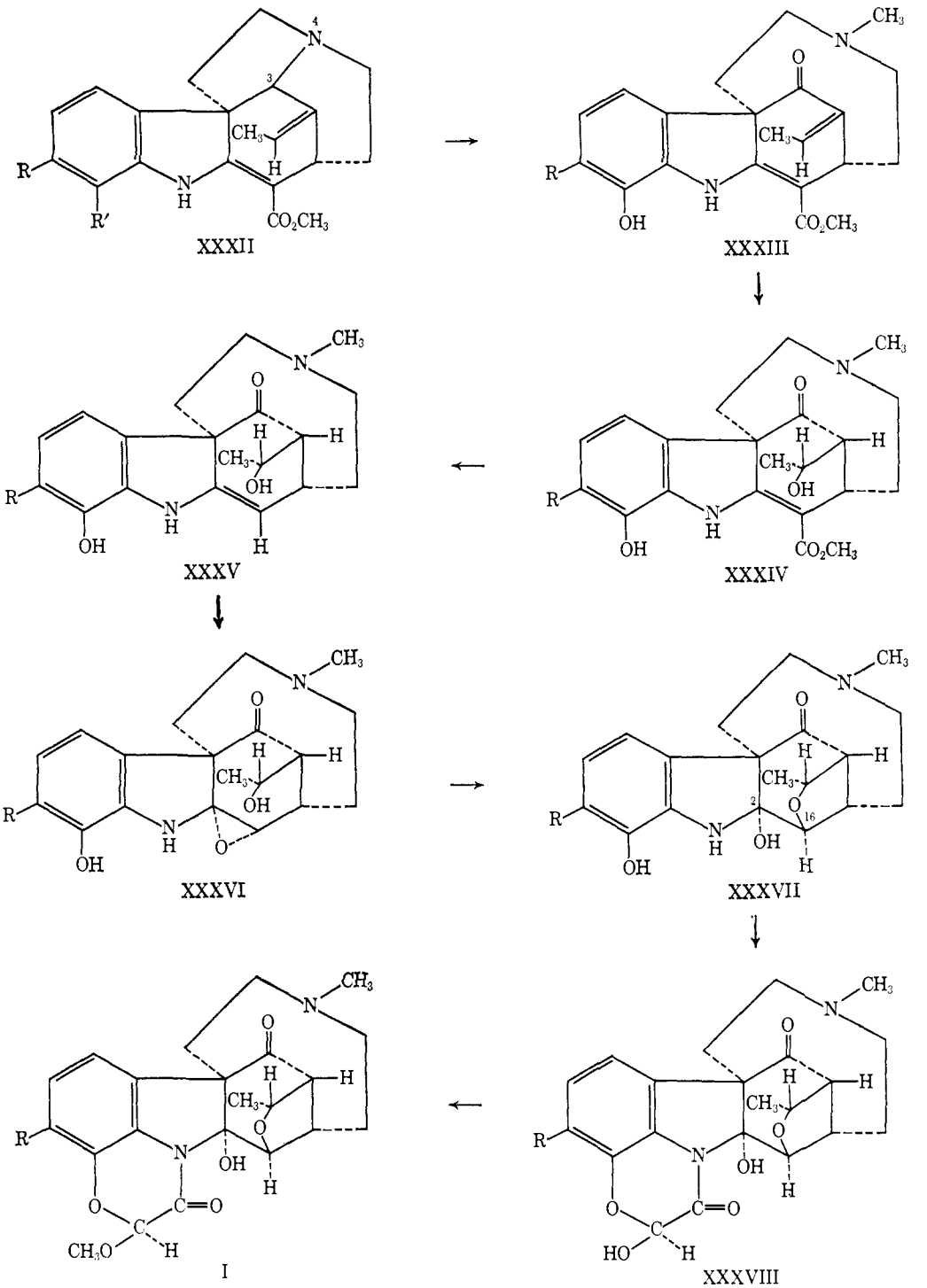
proves that the carbinolamine ether linkage involves the N-methylene carbon.

Dehydrogenation of dichotine-d_1 (XXX) with palladium yielded dehydrodichotine-d_1 (XXIXb), which retained the deuterium as shown by its nmr and mass spectra. This result indicates that while the dehydrogenation with 10% palladium-on-carbon is taking place on one side of the N-methylene carbon, the hydrogenation with platinum oxide proceeds from the opposite side. Such an outcome is not surprising because, upon formation of the carbinolamine ether, the N_b nitrogen is folded down and away from the ketonic carbonyl group, thus exposing the opposite side of the N-methylene carbon to hydrogen or deuterium attack on platinum oxide. When dichotine-d_1 (XXX) is again subjected to dehydrogenation, the deuterium atom being on the opposite side is retained. Furthermore, folding down of the N_b nitrogen prevents the formation of the zwitterion II and dehydrodichotine, therefore, exhibits a normal N-acylindoline uv spectrum.

Biogenetically, dichotine and 11-methoxydichotine are based on an intriguing structure. Of the various hypothetical possibilities, a sequence starting with condylocarpine[32] (XXXII, R = H, R′ = H), which is also present in *Vallesia dichotma*,[8] or a related base (XXXII, R′ = OH) seems plausible and amenable to eventual experimental verification. The order of the steps is arbitrary, in that rupture of the 3,4 bond (XXXII → XXXIII) and generation of the unique acetamide ring (XXVII → XXXVIII) could occur at different stages than indicated. No biochemically plausible activating groups are indicated but an epoxide intermediate (XXXVI → XXXVII) seems attractive, since squalene epoxide[33]

(32) D. Stauffacher, *Helv. Chim. Acta*, **44**, 2006 (1961); A. Sandoval, F. Walls, J. N. Shoolery, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Tetrahedron Lett.*, 409 (1962); K. Biemann, A. L. Burlingame, and D. Stauffacher, *ibid.*, 527 (1962).

(33) R. B. Clayton, *Quart. Rev. Chem. Soc.*, **19**, 168 (1965).



offers a precedent, and the established[1] stereochemistry at positions 2 and 16 is consistent with *trans*-diaxial opening of an epoxide. Attention should also be called to the fact that the methyl ether formation (XXXVIII → I) is not an artifact of the isolation procedure, since the plant was subjected to ethanolic, rather than methanolic, extraction.

Experimental Section[34]

Isolation of Dichotine (Ia) and 11-Methoxydichotine (Ib). A 100-g aliquot of the concentrated ethanolic extract from the bark of *Vallesia dichotoma* Ruiz *et* Pav was dissolved in 95% ethanol (50 ml) and acetic acid (150 ml). The solution was then diluted to

(34) All melting points (uncorrected) were determined on the Kofler block. Ultraviolet spectra were measured in 95% ethanol with a Cary Model 14 spectrophotometer. Infrared spectra were determined with either a Perkin-Elmer Model 137 Infracord or a Perkin-Elmer Model 421 grating spectrophotometer. The band shape was abbreviated as s = strong, m = medium, w = weak. Nuclear magnetic resonance spectra were measured by Drs. L. Durham, T. Nishida, and Y. Kanasawa with a Varian HA-100 spectrometer and recorded in δ values with deuteriochloroform as solvent and tetramethylsilane as an internal reference standard unless otherwise specified. The proton signals were designated as s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, o = octet, m = multiplet. Mass spectra (70 eV, direct inlet system) were determined by Dr. A. Duffield, Mr. R. Ross, and Mr. C. Carroll with either an Atlas CH-4 or an A.E.I. MS-9 instrument, and high-resolution measurements were performed with the A.E.I MS-9 spectrometer. When the amount of substance available for a mass spectrum was too small to permit normal handling, the material was mixed with powdered graphite and the mixture introduced into the ionization chamber. Thin layer chromatography was performed on aluminum oxide GF_{254} (E.

10% acetic acid with water and stored in a refrigerator overnight. The resulting gummy suspension was filtered through Celite and the clear filtrate extracted with methylene chloride (2 l.), followed by neutralization to pH 7 with sodium bicarbonate and extraction with methylene chloride (2.5 l.). After drying, the pH 7 extract was evaporated at reduced pressure to give 3.25 g of residue. The residue dissolved in methylene chloride was first filtered through a 3-cm column of aluminum oxide (M. Woelm, Eschwege, Germany) to remove any polymeric material and then, after concentration, applied to a column of activity III aluminum oxide (30 times the weight of the residue) with a small amount of methylene chloride. Elution was performed with 2% methanol in benzene and 50-ml fractions were collected. Each fraction was compared with an authentic sample[8] of dichotine and 11-methoxydichotine. Those fractions which contained dichotine and 11-methoxydichotine were combined and further purified by preparative tlc on aluminum oxide GF_{254} with the upper layer of a mixture of acetone, hexane, and water (40:56:4) as the developing solvent. Fractional crystallization from acetone yielded 40 mg of dichotine and 70 mg of 11-methoxydichotine.

Dichotine (Ia) exhibited the following characteristics: $[\alpha]^{CHCl_3}D$ +88°; $pK_a^{CH_3CN}$ 7.20; mp 211–213°; ir $\nu_{max}^{CHCl_3}$ 3200–3500 (m), 1680 (s) cm^{-1}; uv, see Figure 2; nmr, see Figure 1; mass spectrum, see Figure 3a.

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.35; H, 6.19; N, 6.73.

11-Methoxydichotine (Ib) exhibited the following characteristics: $[\alpha]^{CHCl_3}D$ +11°; $pK_a^{CH_3CN}$ 7.20; mp 120–121°; ir $\nu_{max}^{CHCl_3}$ 3200–3500 (m), 1680 (s) cm^{-1}; uv, see Figure 2; nmr δ 0.63 (d, J = 6.0 cps; CH_3^p), 1.76 (t, J = 14.0, 14.0 cps, 1 H), 2.02 (s, NCH_3^l), 2.56 (t, J = 3.3, 3.3 cps, H^k), 3.23 (sex, J = 4.6, 12.6, 13.5 cps, 1 H), 3.60 (s, OCH_3^g), 2.88 (s, $ArOCH_3$), 3.97 (m, H^e), 4.30 (s, OH), 4.88 (d, J = 6.0 cps, H^c), 5.38 (s, H^a), 6.58 (d, J = 8.0 cps, H^y), 7.20 (d, J = 8.0 cps, H^x); mass spectrum, see Figure 3b.

Anal. Calcd for $C_{23}H_{28}N_2O_7$: C, 62.15; H, 6.35; N, 6.30. Found: C, 62.20; H, 6.55; N, 6.07.

11-Methoxydichotine Acetate (IIIb). 11-Methoxydichotine (Ib, 50 mg) was heated with acetic anhydrlde (1 ml) and pyridine (2 ml) at 100° in an oil bath for 8 hr. The resulting dark brown solution was evaporated at reduced pressure to yield a brown residue, which was purified by tlc (acetone–benzene, 25:75) to give 11-methoxydichotine acetate (IIIb, R_f 0.67, 42 mg) and 11-methoxydichotine (Ib, R_f 0.16, 8 mg). Crystallization from acetone yielded 36 mg of 11-methoxydichotine acetate: mp 189–190°; ir $\nu_{max}^{CHCl_3}$ 1755 (m), 1695 (s), 1650 (w) cm^{-1}; uv λ_{max} 236 (ε 24,700), λ_{min} 220 (ε 20,100), $\lambda_{max(acid)}$ 230 (ε 25,400), 262 (ε 7000), $\lambda_{min(acid)}$ 220 (ε 20,000), 252 nm (ε 6000); nmr δ 0.62 (d, J = 6.0 cps, CH_3^p), 2.03 (s, NCH_3^l), 2.17 (s, CH_3CO), 2.62 (t, J = 3.3, 3.3 cps, H^k), 3.55 (s, OCH_3^g), 3.88 (s, $ArOCH_3$), 4.00 (m, H^e), 5.10 (d, J = 6.0 cps, H^c), 5.30 (s, H^a), 6.60 (d, J = 8.0 cps, H^y), 7.14 (d, J = 8.0 cps, H^x); mass spectrum m/e 486 (M^+, 23%), 427 (100%).

Anal. Calcd mass for $C_{25}H_{30}N_2O_8$: 486. Found: 486.

Dichotine Acetate (IIIa). In the same manner, dichotine (Ia, 30 mg) was acetylated with acetic anhydride and pyridine. Crystallization from acetone yielded dichotine acetate (IIIa, 20 mg), mp 247–248°; ir $\nu_{max}^{CHCl_3}$ 1760 (m), 1700 (s), 1660 (w), cm^{-1}; uv λ_{max} 223 (ε 19,000), λ_{min} 216 (ε 20,000); $\lambda_{max(acid)}$ 217 (ε 22,000), 262 (ε 7000), $\lambda_{min(acid)}$ 215 (ε 21,000), 241 nm (ε 5000); nmr δ 0.60 (d, J = 6.0 cps, CH_3^p), 2.02 (s, NCH_3^l), 2.15 (s, CH_3CO), 3.50 (s, OCH_3^g), 4.00 (o, J = 3.3, 3.3 cps, H^e), 5.10 (d, J = 6.0 cps, H^c), 5.20 (s, H^a), 6.80 (q, J = 2.0, 7.0 cps, H^z), 6.95 (t, J = 7.0, 7.0 cps, H^y), 7.28 (q, J = 2.0, 7.0 cps, H^x); mass spectrum m/e 456 (M^+, 47%), 397 (100%).

Anal. Calcd for $C_{24}H_{28}N_2O_7$: 456. Found: 456.

Tetrahydro-11-methoxydichotine (IVb). 11-Methoxydichotine (Ib, 30 mg) was dissolved in 95% ethanol (1 ml) and water (0.25 ml). Sodium borohydride (30 mg) was added and the mixture stirred in an oil bath at 50° for 2 hr. The excess sodium borohydride was decomposed with acetic acid and 10% sodium bicarbonate (10 ml) was added. Extraction of the resulting solution with methylene chloride and evaporation of the extract at reduced pressure gave a slightly yellow residue. Purification of the residue by tlc (acetone–hexane–water, 51:45:4) yielded 18 mg of tetrahydro-11-methoxydichotine (IVb, R_f 0.35): mp 203–204° (from acetone–hexane); ir $\nu_{max}^{CHCl_3}$ 3350 (m), 3570 (m), 1635 (w) cm^{-1}; uv λ_{max} 214 (ε 29,900), 298 (ε 3600), λ_{min} 273 (ε 1700), $\lambda_{max(acid)}$ 216 (ε 37,100), 295 (ε 2800), $\lambda_{min(acid)}$ 266 n (ε 400); nmr δ 0.56 (d, J = 6.0 cps, CH_3^p), 2.00 (s, NCH_3^l), 3.50 (s, OCH_3^g), 3.61–3.74 (m CH_2OH), 3.78 (s, $ArOCH_3$), 3.95 (m, H^e), 3.98 (d, J = 6.0 cps H^c), 4.90 (t, J = 5.2, 5.2 cps, H^a), 5.42 (s, NH), 6.32 δ (d, J = 8.0 cps, H^y), 7.20 (d, J = 8.0 cps, H^x); mass spectrum, see Figure 4.

Anal. Calcd mass for $C_{23}H_{32}N_2O_7$: 448.22108. Found: 448.22090.

Tetrahydro-11-methoxydichotine-d_2 (IVc). Similarly 11-methoxydichotine (Ib, 16 mg) was reduced with sodium borodeuteride. Crystalline tetrahydro-11-methoxydichotine-d_2 (8 mg) (IVc) was obtained: mp 202–203°; nmr δ 0.56 (d, J = 6.0 cps, CH_3^p), 2.00 (s, NCH_3^l), 3.50 (s, OCH_3^g), 3.78 (s, $ArOCH_3$), 3.95 (m, H^e), 3.98 (d, J = 6.0 cps, H^c), 4.90 (s, H^a), 5.42 (s, NH), 6.32 (d, J = 8.0 cps, H^y), 7.20 (d, J = 8.0 cps, H^x); mass spectrum m/e 450 (M^+, 75%), 393 (89%), 374 (38%), 350 (14%), 317 (85%), 305 (12%), 274 (47%), 249 (17%), 247 (51%), 205 (96%), 170 (34%), 154 (20%), 128 (42%), 114 (58%), 96 (16%), 83 (19%), 77 (47%), 69 (48%), 58 (100%), 57 (60%).

Anal. Calcd mass for $C_{23}H_{30}D_2N_2O_7$: 450. Found: 450.

Tetrahydrodichotine (IVa). In the same manner, dichotine (Ia, 20 mg) was reduced with sodium borohydride to give tetrahydrodichotine (IVa, 16 mg): mp 158–160° (from acetone–hexane); mass spectrum m/e 418 (M^+, 42%), 361 (73%), 344 (9%), 318 (24%), 287 (44%), 275 (9%), 244 (45%), 219 (10%), 217 (30%), 175 (62%), 170 (21%), 154 (20%), 128 (31%), 114 (40%), 96 (14%), 83 (18%), 75 (57%), 69 (44%), 58 (100%), 57 (63%).

Anal. Calcd mass for $C_{22}H_{30}N_2O_6$: 418. Found: 418.

Acid Hydrolysis and 2,4-Dinitrophenylhydrazine Reaction of Tetrahydro-11-methoxydichotine (IVb → V → VI). Tetrahydro-11-methoxydichotine (IVb, 10 mg) was added to 0.15% concentrated hydrochloric acid in methanol containing saturated 2,4-dinitrophenylhydrazine (5 ml). After keeping the reaction mixture under nitrogen at room temperature for 4 days, some purple crystals (VI, 0.2 mg) appeared, which were collected by suction filtration and washed with cold methanol. The purple crystals did not melt but decomposed at 320°; mass spectrum m/e 418 (M^+ $C_{14}H_{10}N_8O_8$, 100%), 401 (12%), 236 (68%), 235 (27%), 219 (24%), 183 (64%), 122 (16%), 91 (31%), 90 (29%), 75 (57%), 63 (65%), 44 (29%).

Anal. Calcd mass for $C_{14}H_{10}N_8O_8$: 418.06215. Found: 418.06264.

Glyoxal Osazone (VI). In the similar manner, glycolic aldehyde (3 mg) was treated with the 2,4-dinitrophenylhydrazine solution (10 ml) to give dark red glyoxal osazone (VI, 4 mg), decomposition point 320°, mass spectrum m/e 418 (M^+, 100%), 401 (11%), 236 (41%), 235 (21%), 219 (13%), 183 (46%), 122 (14%), 91 (27%), 90 (29%), 75 (43%), 63 (72%), 44 (57%).

Anal. Calcd mass for $C_{14}H_{10}N_8O_8$: 418. Found: 418.

Deoxytetrahydro-11-methoxydichotine (VIIb). Tetrahydro-11-methoxydichotine (IVb, 30 mg) was refluxed with lithium aluminum hydride (40 mg) in tetrahydrofuran (25 ml) for 1 day in a Soxhlet extractor. The excess lithium aluminum hydride was decomposed with water and the resulting pink emulsion extracted with methylene chloride. Drying and evaporation of the extract gave a pink residue which was purified by tlc (acetone–hexane–water, 51:45:4) to yield tetrahydro-11-methoxydichotine (IVb, R_f 0.35, 17 mg) and deoxytetrahydro-11-methoxydichotine (VIIb, R_f 0.54, 4.4 mg). Crystallization of deoxytetrahydro-11-methoxydichotine from acetone and hexane gave 3 mg of crystals: mp 182–184°; ir $\nu_{max}^{CHCl_3}$ 3200–3600 (m), 1640 (w) cm^{-1}; uv λ_{max} 217 (ε 24,800, 298 (ε 3200), λ_{min} 275 (ε 1700); $\lambda_{max(acid)}$ 217 (ε 28,900), 297 (ε 2700), $\lambda_{min(acid)}$ 269 nm (ε 800); nmr δ 0.68 (d, J = 6.0 cps, CH_3^p), 2.00 (s, NCH_3^l), 3.52 (s, OCH_3^g), 3.61–3.72 (m, CH_2OH), 3.76 (s, $ArOCH_3$), 4.03 (s, H^q), 3.90–4.15 (m, H^e, H^c), 4.90 (t, J = 5.2 cps, H^a), 6.23 (d, J = 8.0 cps, H^y), 7.18 (d, J = 8.0 cps, H^x); mass spectrum m/e 432 (M^+ $C_{23}H_{32}N_2O_6$, 33%), 358 ($C_{20}H_{26}N_2O_4$, 100%), 330 (11%), 299 ($C_1H_{17}NO_4$, 6%, $C_{18}H_{21}NO_3$, 2%), 190 ($C_{11}H_{12}NO_2$, 32%), 154 ($C_9H_{16}NO$, 8%), 126 ($C_8H_{16}N$, 18%).

Anal. Calcd mass for $C_{23}H_{32}N_2O_6$: 432.22602. Found: 432.22647.

Deoxytetrahydro-11-methoxydichotine-d_1 (VIIc). Similarly, tetrahydro-11-methoxydichotine (IVb, 30 mg) was reduced with lithium aluminum deuteride to give deoxytetrahydro-11-methoxydichotine-d_1 (VIIc, 3 mg) and tetrahydro-11-methoxydichotine (IVb, 19 mg). Deoxytetrahydro-11-methoxydichotine-d_1 showed: mp 183–185°; mass spectrum m/e 433 (M^+, 20%), 359 (100%), 331 (12%), 300 (4%), 299 (6%), 191 (38%), 154 (9%), 127 (19%).

Anal. Calcd for $C_{23}H_{31}DN_2O_6$: 433. Found: 433.

Deoxytetrahydrodichotine (VIIa). In the same manner, tetrahydrodichotine (IVa, 10 mg) was reduced with lithium aluminum

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Merck AG, Darmstadt, Germany) with single or multiplet development, and the spots were detected with either ceric sulfate spray, iodine vapor, or ultraviolet light. All solvents were dried with anhydrous sodium sulfate.

hydride to give deoxytetrahydrodichotine (VIIa, 1 mg) and tetrahydrodichotine (IVa, 6 mg). Deoxytetrahydrodichotine showed mass spectrum: *m/e* 402 (M^+, 30%), 328 (100%), 300 (8%), 269 (6%), 160 (34%), 154 (9%), 126 (18%).

Anal. Calcd mass for $C_{22}H_{30}N_2O_5$: 402. Found: 402.

Deoxy-d_2-tetrahydro-11-methoxydichotine (XIII). By a similar procedure, tetrahydro-11-methoxydichotine-d_2 (IVc, 45 mg) was reduced with lithium aluminum hydride to yield deoxy-d_2-tetrahydro-11-methoxydichotine (XIII, 4.6 mg, mp 182–184°) and tetrahydro-11-methoxydichotine (IVc, 24 mg).

Anal. Calcd mass for $C_{23}H_{30}D_2N_2O_6$: 434. Found: 434.

Deoxy-d_2-tetrahydro-11-methoxydichotine-d_1 (XV). Similarly, tetrahydro-11-methoxydichotine-d_2 (IVc, 38 mg) was reduced with lithium aluminum deuteride to give deoxy-d_2-tetrahydro-11-methoxydichotine-d_1 (XV, 5 mg, mp 183–185°) and tetrahydro-11-methoxydichotine-d_2 (IVc, 27 mg).

Anal. Calcd mass for $C_{23}H_{29}D_3N_2O_6$: 435. Found: 435.

Deoxytetrahydro-11-methoxydichotine Diacetate (X). Deoxytetrahydro-11-methoxydichotine (VIIb, 4.2 mg) was stirred with acetic anhydride (0.4 ml) and pyridine (0.8 ml) at room temperature under nitrogen for 1 day. The mixture was evaporated at reduced pressure and the residue taken up in methylene chloride (10 ml). After washing with 10% sodium bicarbonate and then water, the methylene chloride solution was dried and evaporated to give a residue which was found to contain only deoxytetrahydro-11-methoxydichotine diacetate (X, 5 mg) by tlc: ir $\nu_{max}^{CHCl_3}$ 1712 (s), 1620 (s) cm^{-1}; nmr, see Figure 5; mass spectrum *m/e* 516 (M^+, 6%), 400 (32%), 117 (100%), 43 (41%).

Anal. Calcd for $C_{27}H_{36}N_2O_8$: 516. Found: 516.

Deoxy-d_2-tetrahydro-11-methoxydichotine Diacetate (XIV). In the same manner, deoxy-d_2-tetrahydro-11-methoxydichotine (XIII, 4.6 mg) was acetylated to give deoxy-d_2-tetrahydro-11-methoxydichotine diacetate (XIV, 5 mg): nmr, see Figure 5.

Anal. Calcd mass for $C_{27}H_{34}D_2N_2O_8$: 518. Found: 518.

Deoxy-d_2-tetrahydro-11-methoxydichotine-d_1 Diacetate (XVI). Similarly, deoxy-d_2-tetrahydro-11-methoxydichotine-d_1 (XV, 5 mg) was acetylated to yield deoxy-d_2-tetrahydro-11-methoxydichotine-d_1 diacetate (XVI, 5.5 mg): nmr, see Figure 5.

Anal. Calcd mass for $C_{27}H_{33}D_3N_2O_8$: 519. Found: 519.

Acid Hydrolysis and Dimethyl Sulfate Methylation of Tetrahydro-11-methoxydichotine (IVb → IXa). Tetrahydro-11-methoxydichotine (IVb, 20 mg) was dissolved in 0.15% concentrated hydrochloric acid in methanol (5 ml) and kept under nitrogen for 1 day. The resulting yellow solution was evaporated at reduced pressure to give a green residue. The green residue was then refluxed under nitrogen with potassium carbonate (500 mg), dimethyl sulfate (150 mg), and acetone (10 ml, distilled over potassium carbonate) for 8 hr. After cooling to room temperature, the acetone solution was reduced to 2 ml at reduced pressure and then partitioned between water (10 ml) and methylene chloride (5 ml). The aqueous phase was further extracted with methylene chloride. The combined methylene chloride extract was evaporated at reduced pressure to give a yellow residue, which was purified by tlc (acetone–hexane–water, 26:70:4). The methylation product (4 mg) (XIa, R_f 0.45) was isolated: mp 147–148° (from acetone–hexane); ir $\nu_{max}^{CHCl_3}$ 1620 (s) cm^{-1}; uv λ_{max} 233 (ε 19,600), λ_{min} 223 (ε 18,700), $\lambda_{max(acid)}$ 238 (ε 9500), 282 (ε 1900), $\lambda_{min(acid)}$ 225 (ε 6500), 260 nm (ε 800); nmr δ 0.67 (d, J = 6.0 cps; CH_3^p), 1.98 (s, NCH_3^l), 2.12 (s, N_aCH_3), 2.86 (s, N_aCH_3), 3.85 (s, $ArOCH_3$), 3.87 (s, $ArOCH_3$), 4.08 (m, H^e), 4.32 (d, J = 7.0 cps, H^c), 6.78 (d, J = 8.0 cps, H^y), 7.85 (d, J = 8.0 cps, H^x); mass spectrum *m/e* 416 (M^+ $C_{23}H_{23}N_2O_5$, 41%), 372 ($C_{21}H_{26}NO_5$, 14%, $C_{21}H_{28}N_2O_4$, 17%), 248 ($C_{14}H_{18}NO_3$, 100%).

Anal. Calcd for $C_{23}H_{32}N_2O_5$: 416.23111. Found: 416.23162.

Acid Hydrolysis and Dimethyl Sulfate-d_6 Methylation of Tetrahydro-11-methoxydichotine (IVb → IXb). In a similar manner, tetrahydro-11-methoxydichotine (IVb, 20 mg) was hydrolyzed with hydrochloric acid and methylated with dimethyl sulfate-d_6. Crystalline methylation product d_9 (IXb) (2 mg) was obtained which melted at 149–150°: nmr δ 0.67 (d, J = 6.0 cps, CH_3^p), 1.98 (s, NCH_3^l), 3.91 (s, $ArOCH_3$), 4.08 (m, H^e), 4.32 (d, J = 7.0 cps, H^c), 6.78 (d, J = 8.0 cps, H^y), 7.85 (d, J = 8.0 cps, H^x); mass spectrum *m/e* 425 (M^+, 72%), 381 (11%), 375 (13%), 257 (100%).

Anal. Calcd mass for $C_{23}H_{23}D_9N_2O_5$: 425. Found: 425.

Acid Hydrolysis and Dimethyl Sulfate Methylation of Deoxytetrahydro-11-methoxydichotine Diacetate (X → XI). Deoxytetrahydro-11-methoxydichotine diacetate (X, 5 mg) was stirred with 1% concentrated hydrochloric acid in methanol (2 ml) for 2 hr. The acid solution was neutralized with 10% sodium bicarbonate (10 ml). Extraction with methylene chloride and evaporation of the extract left a residue, which was methylated with dimethyl sulfate by the same procedure used for the methylation of tetrahydro-11-methoxydichotine (IVb → IX). Crystalline methylation product (XI) (3 mg) was obtained: mp 172–173° (from acetone–hexane); ir $\nu_{max}^{CHCl_3}$ 1640 (s) cm^{-1}; uv, see Figure 5; nmr δ 0.48 (d, J = 6.0 cps, CH_3^p), 2.02 (s, NCH_3^l), 2.28 (s, CH_3CO), 3.70 (s, $ArOCH_3$), 3.86 (s, $ArOCH_3$), 3.94 (m, H^e), 4.56 (q, J = 2.0, 6.0 cps, H^c), 5.01 (d, J = 2.0 cps, H^q), 6.64 (d, J = 8.0 cps, H^y), 7.37 (d, J = 8.0 cps, H^x); mass spectrum *m/e* 414 (M^+ $C_{23}H_{30}N_2O_5$, 100%), 355 ($C_{20}H_{21}NO_5$, 8%, $C_{20}H_{23}N_2O_4$, 1%), 313 ($C_{18}H_{19}NO_4$, 15%), 285 ($C_{16}H_{15}NO_4$, 23%, $C_{17}H_{19}NO_3$, 4%), 243 ($C_{14}H_{13}NO_3$, 15%), 204 ($C_{12}H_{14}NO_2$, 38%).

Anal. Calcd mass for $C_{23}H_{30}N_2O_5$: 414.21546. Found: 414.21555.

Zinc Granule and Acetic Acid Reaction of 11-Methoxydichotine Acetate (IIIb → XIX). 11-Methoxydichotine acetate (IIIb, 10 mg) was stirred with zinc granule in acetic acid (2 ml) at room temperature for 6 hr. The reaction mixture was then poured into water (10 ml) and the zinc granule filtered. Sodium bicarbonate was added to neutralize the acetic acid and the product extracted with methylene chloride. Drying and evaporation of the extract left a residue which was purified by tlc (acetone–hexane–water, 47:50:3). 11-Methoxydichotine acetate (IIIb, R_f 0.54, 8 mg) and oxy-11-methoxydichotine acetate (XIX, R_f 0.40, 0.5 mg) were obtained.

Oxy-11-methoxydichotine Acetate (XIX). 11-Methoxydichotine acetate (IIIb, 193 mg) was stirred with zinc granule (50 g) and ferrous sulfate (3 mg) in acetic acid (100 ml) under a slightly positive pressure of oxygen for 20 hr. Work-up of the reaction was essentially the same as above. Oxy-11-methoxydichotine acetate (XIX, 48 mg) and 11-methoxydichotine acetate (IIIb, 20 mg) were obtained. Oxy-11-methoxydichotine acetate showed mp 135–137° (from acetone–hexane); ir $\nu_{max}^{CHCl_3}$ 3580 (w), 1750 (s), 1695 (s), 1648 (m) cm^{-1}; uv λ_{max} 236 (ε 19,900), λ_{min} 222 (ε 17,300), $\lambda_{max(acid)}$ 230 (ε 19,000), 263 (ε 5100), $\lambda_{min(acid)}$ 220 (ε 16,300), 254 (ε 4700), $\lambda_{max(base)}$ 296 (ε 9900), $\lambda_{min(base)}$ 256 nm (ε 8400); nmr δ 0.91 (s, CH_3^p), 2.02 (s, NCH_3^l), 2.17 (s, CH_3CO), 2.72 (d, J = 3.6 cps, H^k), 3.56 (s, OCH_3^g), 3.88 (s, $ArOCH_3$), 5.17 (d, J = 6.0 cps, H^c), 5.30 (s, H^a), 6.60 (d, J = 8.0 cps, H^y), 7.14 (d, J = 8.0 cps, H^x); mass spectrum *m/e* 502 (M^+ $C_{25}H_{30}N_2O_9$, 5%), 398 ($C_{22}H_{26}N_2O_5$, 57%), 355 ($C_{20}H_{23}N_2O_4$, 60%), 340 ($C_{19}H_{20}N_2O_4$, 100%), 251 ($C_{16}H_{15}N_2O$, 24%).

Anal. Calcd mass for $C_{25}H_{30}N_2O_9$: 502. Found: 502.

Oxy-11-methoxydichotine Triacetate (XXII). Oxy-11-methoxydichotine acetate (XIX, 7 mg) was stirred with acetic anhydride (0.5 ml) and pyridine (1 ml) at room temperature for 1 day. The solvent was removed at reduced pressure and the residue purified by tlc (acetone–hexane–water, 43:54:3). Oxy-11-methoxydichotine triacetate (XXII, R_f 0.70, 1.5 mg) and oxy-11-methoxydichotine acetate (XIX, R_f 0.42, 2 mg) were isolated: mass spectrum of oxy-11-methoxydichotine triacetate *m/e* 586 (M^+, 2%), 527 (91%), 485 (64%), 425 (24%), 43 (100%).

Anal. Calcd mass for $C_{29}H_{34}N_2O_{11}$: 586. Found: 586.

Benzyl Mercaptoketal of Oxy-11-methoxydichotine Acetate (XXIII). Oxy-11-methoxydichotine acetate (XIX, 32 mg) was stirred with benzyl mercaptan (2 ml) containing a trace of dry hydrogen chloride gas at room temperature under nitrogen for 1 day. The solvent was removed by reduced pressure and the residue dissolved in methylene chloride (10 ml) and washed with 1 *N* sodium hydroxide. Drying and evaporation of the methylene chloride solution left a residue which was purified by tlc (acetone–hexane–water, 23:75:2). The benzyl mercaptoketal of oxy-11-methoxydichotine acetate (XXIII, R_f 0.41, 25 mg) was isolated: mass spectrum *m/e* 608 (M^+, 1%), 485 (38%), 469 (100%), 425 (45%), 391 (19%), 313 (23%), 259 (13%), 197 (33%), 188 (21%), 149 (25%), 124 (20%), 91 (76%).

Anal. Calcd mass for $C_{32}H_{36}N_2O_8S$: 608. Found: 608.

Polydeuterio-11-methoxydichotine Acetate (XXIV). Deuterio Raney nickel was prepared by adding, portionwise, Raney nickel alloy (600 mg) to D_2O (5 ml) containing dissolved sodium metal (500 mg) over a period of 20 min. When the foaming stopped, the supernatant solution was decanted and the residue washed successfully with three 3-ml portions of D_2O and three 3-ml portions of deuteriomethanol. To the washed deuterio Raney nickel catalyst was added mercaptoketal XXIII (24 mg) in deuteriomethanol (5 ml) and the mixture refluxed under nitrogen for 6 hr. The catalyst was filtered and washed with methanol. Evaporation of the methanol solution left a residue which was purified by tlc (acetone–hexane–water, 40:58:2). Polydeuterio-11-methoxydichotine acetate (XXIV, R_f 0.65, 10 mg) was isolated. Polydeuterio-11-meth-

oxydichotine acetate showed: mp 189–190° (from acetone–hexane); nmr δ 0.62 (s, 1.5 H, CH_3^p), 2.03 (s, NCH_3^l), 2.17 (s, CH_3CO), 2.62 (d, J = 3.3 cps, H^k), 3.55 (s, OCH_3^g), 3.88 (s, $ArOCH_3$), 5.10 (d, J = 6.0 cps, H^e), 5.30 (s, H^a), 6.60 (d, J = 8.0 cps, H^y), 7.14 (d, J = 8.0 cps, H^x); mass spectrum *m/e* 491 (M^+, 22%), 490 (M^+, 22%), 489 (M^+, 16%), 488 (M^+, 20%), 487 (M^+, 15%), 486 (M^+, 3%), 432 (88%), 431 (100%), 430 (61%), 429 (86%), 428 (69%), 427 (12%).

Anal. Calcd mass for $C_{25}H_{25}D_5N_2O_8$: 491. Found: 491.

Polydeuterio-11-methoxydichotine (XXV). Polydeuterio-11-methoxydichotine acetate (XXIV, 8 mg) was stirred with 1% sodium hydroxide in methanol (2 ml) at room temperature for 3 hr. The resulting solution was partitioned between methylene chloride (10 ml) and water (10 ml). The aqueous phase was further extracted with methylene chloride. The combined methylene chloride extract was evaporated and the residue crystallized from acetone and hexane to yield polydeuterio-11-methoxydichotine (XXV, 5.8 mg), mp 121–122°; mass spectrum *m/e* 449 (M^+, 23%), 448 (M^+, 27%), 447 (M^+, 17%), 446 (M^+, 23%), 445 (M^+, 18%), 444 (M^+, 3%), 392 (22%), 391 (28%), 390 (18%), 389 (26%), 388 (22%), 349 (4%), 348 (20%), 347 (10%), 346 (7%), 345 (19%), 320 (7%), 319 (7%), 275 (31%), 247 (11%), 187 (4%), 186 (4%), 185 (3%), 184 (4%), 183 (3%), 159 (4%), 158 (6%), 157 (4%), 156 (6%), 155 (5%), 129 (12%), 128 (12%), 115 (19%), 114 (18%), 97 (21%), 96 (21%), 84 (15%), 83 (15%), 73 (12%), 72 (21%), 71 (100%), 70 (87%), 59 (40%), 58 (73%), 57 (43%).

Anal. Calcd mass for $C_{23}H_{23}D_5N_2O_7$: 449. Found: 449.

11-Methoxydichotinamide Acetate (XXVIb). Chromium trioxide (200 mg) was added, portionwise, to pyridine (2 ml) followed by 11-methoxydichotine acetate (IIIb, 33.6 mg). The mixture was stirred at room temperature for 5 hr and then poured into ice water (100 ml), followed by extraction with chloroform (300 ml). The chloroform extract was washed with 3 *N* sulfuric acid (3 × 20 ml). Drying and evaporation of the chloroform solution left a residue which was purified by tlc (acetone–benzene, 40:60). The acetylated 11-methoxydichotinamide (XXVIb, R_f 0.29, 8 mg) was isolated: mp 159–160° (from acetone–hexane); uv (unchanged in acid) λ_{max} 205 (ε 27,000), 248 (ε 8700), λ_{min} 237 nm (ε 7700); ir $\nu_{max}^{CHCl_3}$ 1760 (m), 1700 (s), 1635 (s) cm^{-1}; nmr δ 0.51 (d, J = 6.0 cps, CH_3^p), 2.18 (s, CH_3CO), 2.75 (s, NCH_3^l), 3.54 (s, OCH_3^g), 3.87 (s, $ArOCH_3$), 5.25 (d, J = 6.0 cps, H^e), 5.30 (s, H^a), 6.60 (d, J = 8.0 cps, H^y), 7.02 (d, J = 8.0 cps, H^x); mass spectrum *m/e* 500 (M^+ $C_{25}H_{28}N_2O_9$, 43%), 441 ($C_{23}H_{25}N_2O_7$, 100%), 397 ($C_{21}H_{21}N_2O_6$, 2%, $C_{22}H_{25}N_2O_5$, 6%).

Anal. Calcd mass for $C_{25}H_{28}N_2O_9$: 500.17946. Found: 500.17948.

11-Methoxydichotinamide (XXVIIb). The acetylated 11-methoxydichotinamide (XXVIb, 18 mg) was stirred with 2.5% sodium hydroxide in methanol for 2 hr. The solution was then neutralized with 3 *N* sulfuric acid and extracted with methylene chloride. Drying and evaporation of the extract gave a residue which was crystallized from acetone to give 11-methoxydichotinamide. (XXVIIb, 10 mg): mp 240–241°; ir $\nu_{max}^{CHCl_3}$ 3510 (w), 1685 (s), 1630 (s) cm^{-1}; uv (unchanged in acid) λ_{max} 205 (ε 27,000), 247 (ε 9000), λ_{min} 237 nm (ε 8000); nmr δ 0.51 (d, J = 6.0 cps, CH_3^p), 2.12 (q, J = 3.5, 13.0 cps, H^n), 2.58 (t, J = 13.4, 13.4 cps, H^m), 2.75 (s, NCH_3^l), 2.82–3.14 (m, H^i, H^i, H^k), 3.35 (m, H^b), 3.56 (s, OCH_3^g), 3.86 (m, H^f), 3.87 (s, $ArOCH_3$), 4.08 (o, J = 3.6, 6.0 cps, H^e), 4.54 (sex, J = 3.5, 16.0, 16.0 cps, H^d), 5.08 (d, J = 6.0 cps, H^e), 5.35 (s, H^a), 5.51 (s, OH), 6.58 (d, J = 8.0 cps, H^y), 7.03 (d, J = 8.0 cps, H^x); mass spectrum *m/e* 458 (M^+ $C_{23}H_{26}N_2O_8$, 100%), 414 ($C_{22}H_{26}N_2O_6$, 20%), 304 ($C_{16}H_{20}N_2O_4$, 65%).

Anal. Calcd mass for $C_{23}H_{26}N_2O_8$: 458. Found: 458.

Dichotinamide (XXVIIa). Likewise, dichotine acetate (IIIa, 158 mg) was oxidized with chromium trioxide and pyridine, followed by hydrolysis with methanolic sodium hydroxide. Dichotinamide (XXVIIa, 22 mg) was obtained which melted at 244–245° (from chloroform): uv (unchanged in acid) λ_{max} 261 (ε 7900), λ_{min} 246 nm (ε 7700); ir $\nu_{max}^{CHCl_3}$ 3510 (w), 1683 (s), 1630 (s) cm^{-1}; nmr, see Figure 7; mass spectrum *m/e* 428 (M^+, 100%), 384 (11%), 274 (38%).

Anal. Calcd mass for $C_{22}H_{24}N_2O_7$: 428. Found: 428.

Tetrahydro-11-methoxydichotine-d_2 (XXVIII). 11-Methoxydichotinamide (XXVIIb, 30 mg) was reduced with sodium borohydride by the same procedure used in the preparation of tetrahydro-11-methoxydichotine (IVb). The tetrahydro-11-methoxydichotinamide (10 mg) thus obtained was refluxed with lithium aluminum deuteride (10 mg) in diethyl ether (3 ml) for 5 hr. The excess lithium aluminum deuteride was decomposed with water and the product extracted with methylene chloride. Drying and evaporation of the extract left a residue which was purified by tlc (acetone–hexane–water, 51:45:4). Tetrahydro-11-methoxydichotine-d_2 (XXVIII, R_f 0.43, 3 mg) was isolated, mp 203–204° (from acetone–hexane); mass spectrum *m/e* 450 (M^+, 52%), 393 (70%), 376 (35%), 348 (25%), 319 (100%), 307 (14%), 251 (16%), 247 (44%), 205 (81%), 172 (33%), 156 (13%), 130 (27%), 116 (37%), 98 (11%), 85 (13%), 83 (9%), 75 (22%), 69 (30%), 60 (63%), 59 (40%).

Anal. Calcd mass for $C_{23}H_{30}D_2N_2O_7$: 450. Found: 450.

Palladium-on-Carbon "Hydrogenation" of Dichotine in Absolute Ethanol Containing 10% Acetic Acid. Dichotine (Ia, 1 mg) was "hydrogenated" with 10% palladium-on-carbon (100 mg) in absolute ethanol containing 10% acetic acid (5 ml) at atmospheric pressure and room temperature for 1 hr. The catalyst was filtered and washed with ethanol. The ethanol solution was then concentrated to a volume of 2 ml. Sodium bicarbonate was added to neutralize the acetic acid and the resulting solution partitioned between water (5 ml) and methylene chloride (5 ml). The aqueous phase was further extracted with methylene chloride. Drying and evaporation of the extract left a residue, which was purified by tlc (acetone–hexane–water, 42:55:3). Dichotine (Ia, R_f 0.49) and dehydrodichotine (XXIXa, R_f 0.56) were isolated.

Dehydrodichotine (XXIXa). Dichotine (Ia, 50 mg) was stirred with 10% palladium-on-carbon (300 mg) in absolute ethanol (5 ml) under nitrogen at room temperature for 2 hr. The catalyst was filtered and washed with ethanol. Evaporation of the ethanol solution left a residue which was purified by tlc (acetone–hexane–water, 30:68:2). Dehydrodichotine (XXIXa, R_f 0.46, 32 mg) and dichotine (Ia, R_f 0.37, 3 mg) were isolated. Dehydrodichotine showed: mp 194–196° (from acetone–hexane); ir $\nu_{max}^{CHCl_3}$ 1695 (s) cm^{-1}; uv (unchanged in acid) λ_{max} 258 (ε 7100), λ_{min} 242 nm (ε 6400); nmr δ 0.76 (d, J = 6.0 cps, CH_3^p), 2.50 (s, NCH_3^l), 3.56 (s, OCH_3^g), 4.16 (o, J = 3.6, 6.0 cps, H^e), 4.96 (q, J = 4.0, 9.0 cps, 1 H), 5.12 (d, J = 6.0 cps, H^e), 5.34 (s, H^a), 6.80–7.00 (m, 3Ar*H*); mass spectrum *m/e* 412 (M^+ $C_{22}H_{24}N_2O_6$, 35%), 355 ($C_{19}H_{17}NO_6$, 7%), 302 ($C_{16}H_{18}N_2O_4$, 42%), 245 ($C_{13}H_{11}NO_4$, 7%), 83 (C_5H_7O, 40%), 71 (C_4H_9N, 100%).

Anal. Calcd mass for $C_{22}H_{24}N_2O_6$: 412.16342. Found: 412.16463.

Dehydrodichotine-d_1 (XXIXb). In the same manner, dichotine-d_1 (XXX, 17.6 mg) was dehydrogenated with palladium-on-carbon. Dehydrodichotine-d_1 (XXIXb, 9.7 mg) was obtained: mp 195–196°; nmr δ 0.77 (d, J = 6.5 cps, CH_3^p), 2.50 (s, NCH_3^l), 3.56 (s, OCH_3^g), 4.16 (o, J = 3.6, 6.5 cps, H^e), 5.14 (d, J = 6.0 cps, H^e), 5.34 (s, H^a), 6.80–7.00 (m, 3Ar*H*); mass spectrum *m/e* 413 (M^+, 29%), 412 (M^+, 8%), 355 (8%), 303 (43%), 302 (16%), 245 (7%), 83 (48%), 72 (100%).

Anal. Calcd mass for $C_{22}H_{23}DN_2O_6$: 413. Found: 413.

Dehydrotetrahydro-11-methoxydichotine (XXXIa). Tetrahydro-11-methoxydichotine (IVb, 10 mg) was dehydrogenated as above to give dehydrotetrahydro-11-methoxydichotine (XXXIa, 5.5 mg): uv (unchanged in acid) λ_{max} 213 (ε 24,000), 295 (ε 2000), λ_{min} 275 nm (ε 1600); mass spectrum *m/e* 446 (M^+, 11%), 372 (58%), 315 (15%), 262 (45%), 205 (28%), 71 (100%).

Anal. Calcd mass for $C_{23}H_{30}N_2O_7$: 446. Found: 446.

Dehydrotetrahydro-11-methoxydichotine-d_1 (XXXIb). Similarly, tetrahydro-11-methoxydichotine-d_2 (XXVIII, 0.1 mg) was dehydrogenated with 10% palladium-on-carbon to give dehydrotetrahydro-11-methoxydichotine-d_1 (XXIXb, 0.02 mg): mass spectrum *m/e* 447 (M^+, 8%), 373 (30%), 315 (50%), 263 (19%), 205 (25%).

Anal. Calcd mass for $_{23}H_{29}DN_2O_7$: 447. Found: 447.

Platinum Oxide Hydrogenation of Dehydrodichotine (XXIXa → Ia). Platinum oxide (20 mg) was hydrogenated in absolute ethanol (5 ml) at room temperature and atmospheric pressure for 30 min. Then dehydrodichotine (XXIXa, 5 mg) dissolved in absolute ethanol (1 ml) was added and the hydrogenation continued for another 3 hr. The catalyst was filtered and washed with ethanol. Evaporation of the ethanol solution left a residue which was purified by tlc (acetone–hexane–water, 42:55:3) to give dichotine (Ia, R_f 0.53, 3 mg).

Dichotine-d_1 (XXX). In the similar manner, dehydrodichotine (XXIXa, 27.3 mg) was deuterated with deuterium gas in 95% deuterioethanol to yield dichotine-d_1 (XXX, 23.2 mg): mp 212–213° (from acetone–hexane); mass spectrum *m/e* 415 (M^+, 71%), 358 (75%), 314 (53%), 290 (10%), 245 (23%), 217 (11%), 183 (8%), 155 (12%), 129 (12%), 115 (12%), 97 (15%), 84 (7%), 83 (10%), 71 (100%), 69 (29%), 59 (46%), 58 (60%).

Anal. Calcd mass for $C_{23}H_{25}DN_2O_6$: 415. Found: 415.