silanes so obtained was then added to 76 g. (2 moles) of lithium aluminum hydride in 750 ml. of dry diglyme in a 3-neck flask equipped with a stirrer, condenser, and addition funnel. The reaction mixture was kept at 20–25°. The volatile vinylsilanes were then removed from the reaction mixture under vacuum and condensed in a Dry Ice trap. The volatile material (52 g.) was distilled on a Todd column. Eleven fractions were collected, but none of these gave an analytically pure sample of divinylsilane. Pure divinylsilane (n^{19}D 1.4180) was obtained from one of the fractions (b.p. 41–42°) by gas chromatography (16 ft. silicone oil column at room temperature).

Anal. Calcd. for C_4H_8Si: C, 57.06; H, 9.57. Found: C, 57.47; H, 9.67.

There was also isolated by gas chromatography a material which appeared to be ethylvinylsilane (probably caused by an ethyl halide impurity in the starting vinyl bromide).

The later fractions from the distillation proved to be trivinylsilane (b.p. 89.5°, n^{20}D 1.4475). See Table II for the n.m.r. spectrum of this compound.

Acknowledgment.—The authors are grateful to Dr. John Hooz and Dr. Garth M. Stanton for their technical assistance. We are also deeply indebted to Mr. William Baitinger for obtaining the n.m.r. spectra and to Dr. C. S. Yeh and her staff for all the microanalyses.

It was the financial assistance of the National Science Foundation which made this work possible.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

Alkaloid Studies. XLVI.[1] The Alkaloids of *Aspidosperma obscurinervium* Azembuja. A New Class of Heptacyclic Indole Alkaloids[2]

BY KEITH S. BROWN, JR.,[3] AND CARL DJERASSI

RECEIVED JANUARY 30, 1964

From *A. obscurinervium* bark extract there was isolated (+)-aspidocarpine (Ia), (+)-aspidolimine (Ib), a new alkaloid of the methoxyindole type, and four new alkaloids (dihydroobscurinervine, IIa; obscurinervine, IIb; dihydroobscurinervidine, IIc; and obscurinervidine, IId) representative of a new class of heptacyclic indole alkaloids. The structures were assigned on the basis of analysis, infrared, ultraviolet, n.m.r., and mass spectra of the parent alkaloids and of a variety of chemical transformation products. Dihydroobscurinervidinol (IIIu) and dihydroobscurinervinol (IIIt) were synthesized from depropionylaspidoalbine (IVb) by addition of iodopropanol and iodobutanol, respectively, followed by cyclization of the more polar isomer of each addition pair through its monobrosylate, and lithium aluminum hydride reduction of the ether linkage. Neblinine, an alkaloid isolated from *A. neblinae* Monachino, could be shown to be 15-demethoxyobscurinervidine (IIe). Dihydroneblininane (IIIz) and its C-22 epimer were synthesized from deacetylaspidocarpine (Ic) and the configuration of the natural isomer at position 22 established by n.m.r. measurements. The configuration at position 4 in the original series of alkaloids II–IIg was assigned by three independent and mutually consistent n.m.r. comparisons.

In connection with our investigation of the indole alkaloids of Brazilian *Aspidosperma* species,[4] the bark of *A. obscurinervium* Azembuja was extracted with ethanol[5] and the basic portion of the extract partitioned between benzene and dilute acetic acid. The latter fraction contained (+)-aspidocarpine (Ia)[6–8] in a very high yield (3.5% of the ethanol extract), (+)-aspidolimine (Ib, 0.025%),[7,9] and a new alkaloid of the methoxyindole type (0.5%) whose structure is currently under investigation. The former fraction (benzene-soluble acetates) contained four closely related bases: dihydroobscurinervine (IIa, 0.06%), obscurinervine (IIb, 0.07%), dihydroobscurinervidine (IIc, 0.01%), and obscurinervidine (IId, 0.03%). These were assigned the unusual heptacyclic constitutions on the basis of the evidence described below.

The four bases IIa–IId showed an ultraviolet spectrum very similar to that of O-methyl-N-ethylaspidoalbinol (VIb),[10] while the infrared spectrum indicated the presence of a strained carbonyl function (1750 cm.$^{-1}$). The mass spectra of the alkaloids (Fig. 1) showed a diagnostic and exceedingly simple pattern, with the only significant peaks arising from loss of methyl and carbon monoxide (from all four molecular ions) and ethyl (from the molecular ions of IIa and IIb only); small peaks were also present at *m/e* 244 (in all four spectra and unaffected by catalytic deuteration of the 6,7 double bond; ion a), 260 (IIa and IIb; ion f), and 246 (IIc and IId; ion c).[11,12a] The molecular ion peaks (IIa, *m/e* 440 = $C_{25}H_{32}N_2O_5$; IIb, *m/e* 438 = $C_{25}H_{30}N_2O_5$; IIc, *m/e* 426 = $C_{24}H_{30}N_2O_5$; IId, *m/e* 424 = $C_{24}H_{28}N_2O_5$) confirmed the formulas indicated by analysis, and led to a simplification of the picture confirmed by hydrogenation of IIb to IIa, and IId to IIc. Also implied in the mass spectra was the conclusion that the obscurinervine and obscurinervidine pairs differed only in the presence of an easily expelled ethyl group in the former, replaced by a methyl group in the latter, probably attached to the aromatic portion of the molecules.

(1) Part XLV: J. A. Joule and C. Djerassi, *J. Chem. Soc.*, in press.

(2) Partial support was provided by the National Institutes of Health (Grant No. GM-11309) of the U. S. Public Health Service.

(3) National Institutes of Health Postdoctorate Fellow, 1963.

(4) For most recent reference on this work, see J. M. Ferreira, B. Gilbert, R. J. Owellen, and C. Djerassi, *Experientia*, **19**, 585 (1963).

(5) We thank Dr. B. Gilbert, Universidade do Brasil, Rio de Janeiro, for the collection and initial extraction of the bark, which was collected 8 km. north of Manaus, Amazonas. Thanks are due to Dr. W. Rodrigues for locating this tree.

(6) S. McLean, K. Palmer, and L. Marion, *Can. J. Chem.*, **38**, 1547 (1960).

(7) Identity was established by infrared and ultraviolet spectra, optical rotation, and a mixture melting point with an authentic sample of the compound.

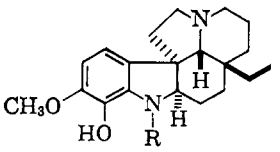
(8) The configurations of all compounds in this paper are relative and not absolute.

(9) H. Schmid and M. Pinar, *Helv. Chim. Acta*, **45**, 1283 (1962); B. Gilbert, J. A. Brissolese, J. M. Wilson, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Chem. Ind.* (London), 1949 (1962).

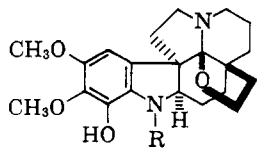
(10) C. Djerassi, L. D. Antonaccio, H. Budzikiewicz, J. M. Wilson, and B. Gilbert, *Tetrahedron Letters*, 1001 (1962).

(11) For reasons explained in H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, we are fixing the charge on nitrogen in molecular ions, followed by homolytic cleavages in all cases, to give ions in which the charge is also localized.

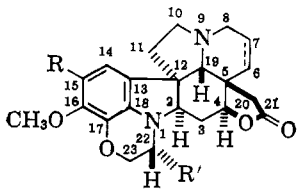
(12) (a) We thank Dr. H. Budzikiewicz and Mr. J. Smith for the mass spectral determinations. (b) We are indebted to Dr. L. Durham and Mr. T. Burkoth for the n.m.r. determinations.



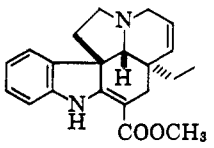
Ia, R = $COCH_3$
b, R = $COCH_2CH_3$
c, R = H
d, R = $CH(CH_3)CH_2OH$



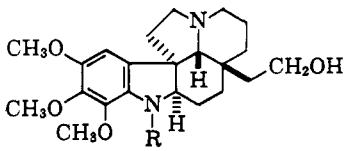
IVa, R = $COCH_2CH_3$
b, R = H
c, R = $CH(CH_3)CH_2OH$
d, R = $CH(CH_2CH_3)CH_2OH$



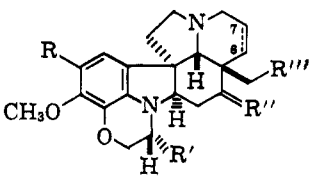
	R	R′	6,7-Double bond
IIa,	OCH_3	CH_2CH_3	Absent
b,	OCH_3	CH_2CH_3	Present
c,	OCH_3	CH_3	Absent
d,	OCH_3	CH_3	Present
e,	H	CH_3	Present
f,	H	CH_3	Absent
g,	H	CH_2CH_3	Present



V

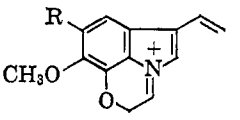


VIa, R = H
b, R = CH_2CH_3

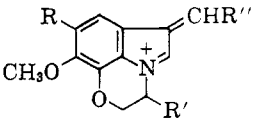


	R	R′	R″	R‴	6,7-Double bond
IIIa,	OCH_3	CH_2CH_3	H, OH	CH_2OH	Present
b,	OCH_3	CH_2CH_3	H, OH	CD_2OH	Present
c,	OCH_3	CH_2CH_3	H, OH	CH_2OH	Absent
d,	OCH_3	CH_3	H, OH	CH_2OH	Present
e,	OCH_3	CH_3	H, OH	CH_2OH	Absent
f,	H	CH_3	H, OH	CH_2OH	Present
g,	H	CH_3	H, OH	CH_2OH	Absent
h,	OCH_3	CH_2CH_3	H, $OCOCH_3$	CH_2OCOCH_3	Present
i,	OCH_3	CH_2CH_3	H, $OCOCH_3$	CH_2OCOCH_3	Absent
j,	OCH_3	CH_2CH_3	H, OH	CH_2OCOCH_3	Absent
k,	OCH_3	CH_3	H, OH	CH_2OCOCH_3	Present
m,	OCH_3	CH_3	H, OH	CH_3OCOCH_3	Absent
n,	H	CH_3	H, OH	CH_2OCOCH_3	Present
o,	H	CH_3	H, OH	CH_2OCOCH_3	Absent
p,	OCH_3	CH_2CH_3	O	CH_2OCOCH_3	Absent
q,	OCH_3	CH_3	O	CH_2OCOCH_3	Absent
r,	H	CH_3	O	CH_2OCOCH_3	Absent
s,	OCH_3	CH_2CH_3	O	CH_2OH	Absent
t,	OCH_3	CH_2CH_3	H_2	CH_2OH	Absent
u,	OCH_3	CH_3	H_2	CH_2OH	Absent
v,	H	CH_3	H_2	CH_2OH	Absent
w,	OCH_3	CH_2CH_3	H_2	CH_2OTs	Absent
x,	OCH_3	CH_2CH_3	H_2	CH_3	Absent
y,	H	CH_3	H_2	CH_2OTs	Absent
z,	H	CH_3	H_2	CH_3	Absent

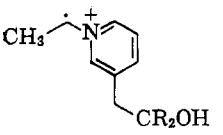
The n.m.r. spectra[12b] (for examples see Fig. 2) of the four alkaloids were completely compatible with this interpretation; a signal for a C-ethyl group in the spectra of IIa and IIb was replaced by one for a second-



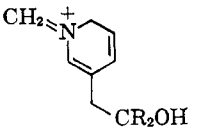
a (R = OCH_3), *m/e* 244
b (R = H), *m/e* 214



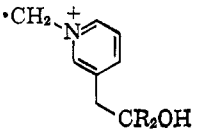
	R	R′	R″	*m/e*
c	OCH_3	CH_3	H	246
d	H	CH_3	H	216
e	OCH_3	CH_2CH_3	CH_3	274
f	OCH_3	CH_2CH_3	H	260
g	OCH_3	CH_3	CH_3	260
h	H	CH_3	CH_3	230



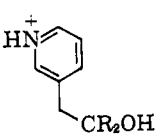
i (R = H), *m/e* 151
j (R = D), *m/e* 153



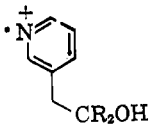
k (R = H), *m/e* 138
l (R = D), *m/e* 140



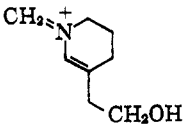
m (R = H), *m/e* 137
n (R = D), *m/e* 139



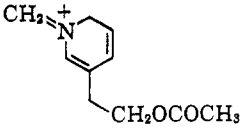
o (R = H), *m/e* 124
p (R = D), *m/e* 126



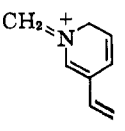
q (R = H), *m/e* 123
r (R = D), *m/e* 125



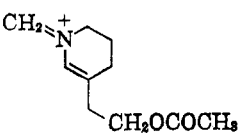
s, *m/e* 140



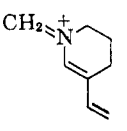
t, *m/e* 180



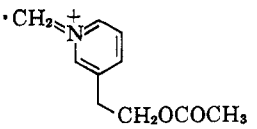
u, *m/e* 120



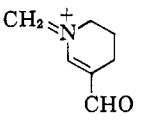
v, *m/e* 182



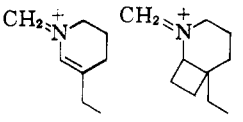
w, *m/e* 122



x, *m/e* 179



y, *m/e* 124



z, *m/e* 124 aa, *m/e* 152

ary C-methyl group in those of IIc and IId. The n.m.r. spectra of the four further defined the aromatic portion of the molecules in showing signals for a single aromatic proton (6.32 or 6.35 δ), two aromatic methoxyl groups (3.88–3.87 and 3.82–3.80 δ), and a methylene of a cyclic ether linkage (4.28 and 4.12 δ in IIa and b, collapsed to 4.18 δ in IIc and d); and also gave clear signals for the groupings $-CH_2-CH(O)-C$ (4.52 δ) and $C-CH_2-CO$ (1.78 and 2.62 δ in IIa) in the aliphatic portion. The vinyl protons in IIb and IId appeared in the n.m.r. as a single sharp peak (5.73 δ), much like that observed in the spectrum of tabersonine (V).[13]

Lithium aluminum hydride reduction of the lactones proceeded smoothly to give materials (IIIa–e) showing in the mass spectrum a gain of four mass units in molecular weight and a typical fragmentation pattern for

(13) M. Plat, J. LeMen, M.-M. Janot, J. M. Wilson, H. Budzikiewicz, L. J. Durham, Y. Nakagawa, and C. Djerassi, *Tetrahedron Letters*, 271 (1962).

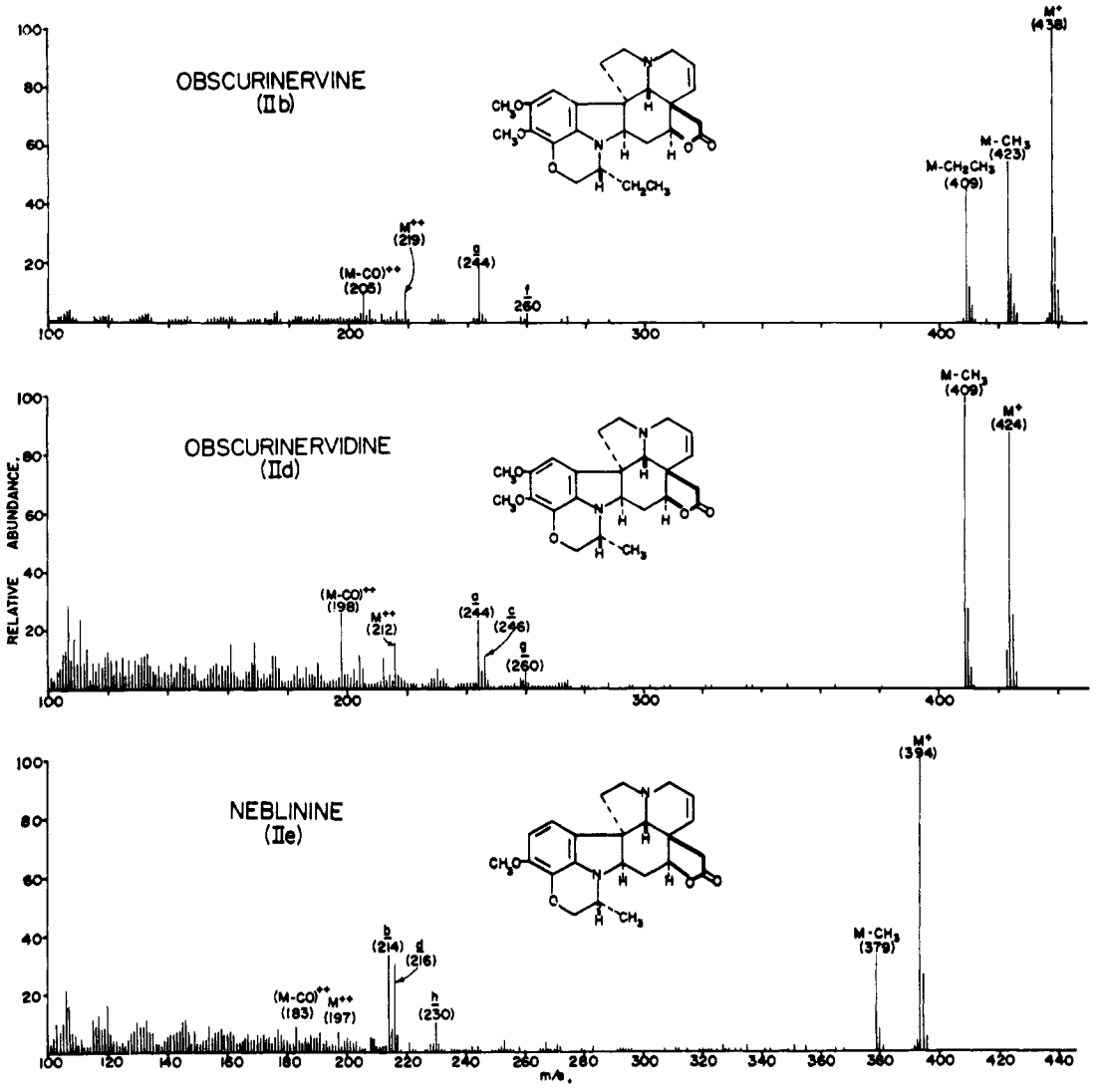


Fig. 1.—Mass spectra of obscurinervine (IIb), obscurinervidine (IId), and neblinine (IIe).

an aspidospermine-type ring system containing an alcohol in the ethyl side chain[10] and the double bond in ring E (base peaks, ions k, *m/e* 138 (IIIa, IIId) and s, *m/e* 140 (IIIc, IIIe)). The double-bond-containing alcohols IIIa and IIId also showed a series of ions having the piperidine ring aromatized (i, m, o, q); the structures assigned to these were best indicated by the two-unit shifts in the positions of all peaks in the spectrum (Fig. 3) of the deuteriated diol IIIb, produced by a reduction of obscurinervine (IIb) with lithium aluminum deuteride. The diol IIId showed a more normal ABX_2 splitting pattern[13,21b] for the n.m.r. signal corresponding to the vinyl protons, while the diacetate IIIh of diol IIIa exhibited (Fig. 4) n.m.r. signals for the two vinyl protons (ABX_2 splitting—see above; 5.70 and 5.58 δ), the group $-CH_2-CH(OAc)-C$ (5.23 δ, *J*'s 9 and 5 c.p.s.), and the group $-CH_2-CH_2-OAc$ (4.12 δ, *J* 8 c.p.s.).

Partial acetylation of the diols led to the primary monoacetates IIIj–m, which similarly showed a very diagnostic mass spectral fragmentation (Fig. 5) leading to ions t–x. Oxidation of the saturated monoacetates IIIj and IIIm with dicyclohexylcarbodiimide and phosphoric acid in dimethyl sulfoxide[14] gave the corresponding six-membered ketones IIIp and IIIq (ν_{max} 1705 cm.$^{-1}$), still showing ions v and w in the mass spectra. Base-catalyzed deuterium exchange on the derived keto alcohol IIIs gave at least partial introduction of two atoms of deuterium at position 3; shifts were observed in the mass spectral peaks corresponding to the molecular ion and the loss of water, methyl, and ethyl but no shifts were observed in the ions at *m/e* 124 (y), 140 (s), 260 (f), 274 (e), or 369 (loss of carbons 3, 4,[15] and 21 with their accompanying functions).

The ketoacetates IIIp and IIIq were reduced by a modified Wolff–Kishner method to the alcohols IIIt and IIIu; the former was also converted to the parent compound dihydroobscurinervinane (IIIx) by tosylation of the alcohol and displacement with lithium aluminum hydride. In none of these transformation products was there any change of the positions of the indole ions (c, e, f, g) in the mass spectra, indicating that all transformations were taking place in the aliphatic portion of the molecule.

Synthesis of dihydroobscurinervidinol (IIIu) from depropionylaspidoalbine (IVb)[10,16] proceeded by addition of 2-iodo-1-propanol to the indole nitrogen, followed by cyclization of the monobrosylate of the more polar of the alcohol epimers (IVc). Reduction of the

(14) J. G. Moffatt and K. E. Pfitzner, *J. Am. Chem. Soc.*, **85**, 3027 (1963).

(15) See K. Biemann, M. Spiteller-Friedmann, and G. Spiteller, *ibid.*, **85**, 631 (1963).

(16) We are grateful to Dr. L. Marion of the National Research Council, Ottawa, Ont., for a generous gift of aspidoalbine for these syntheses.

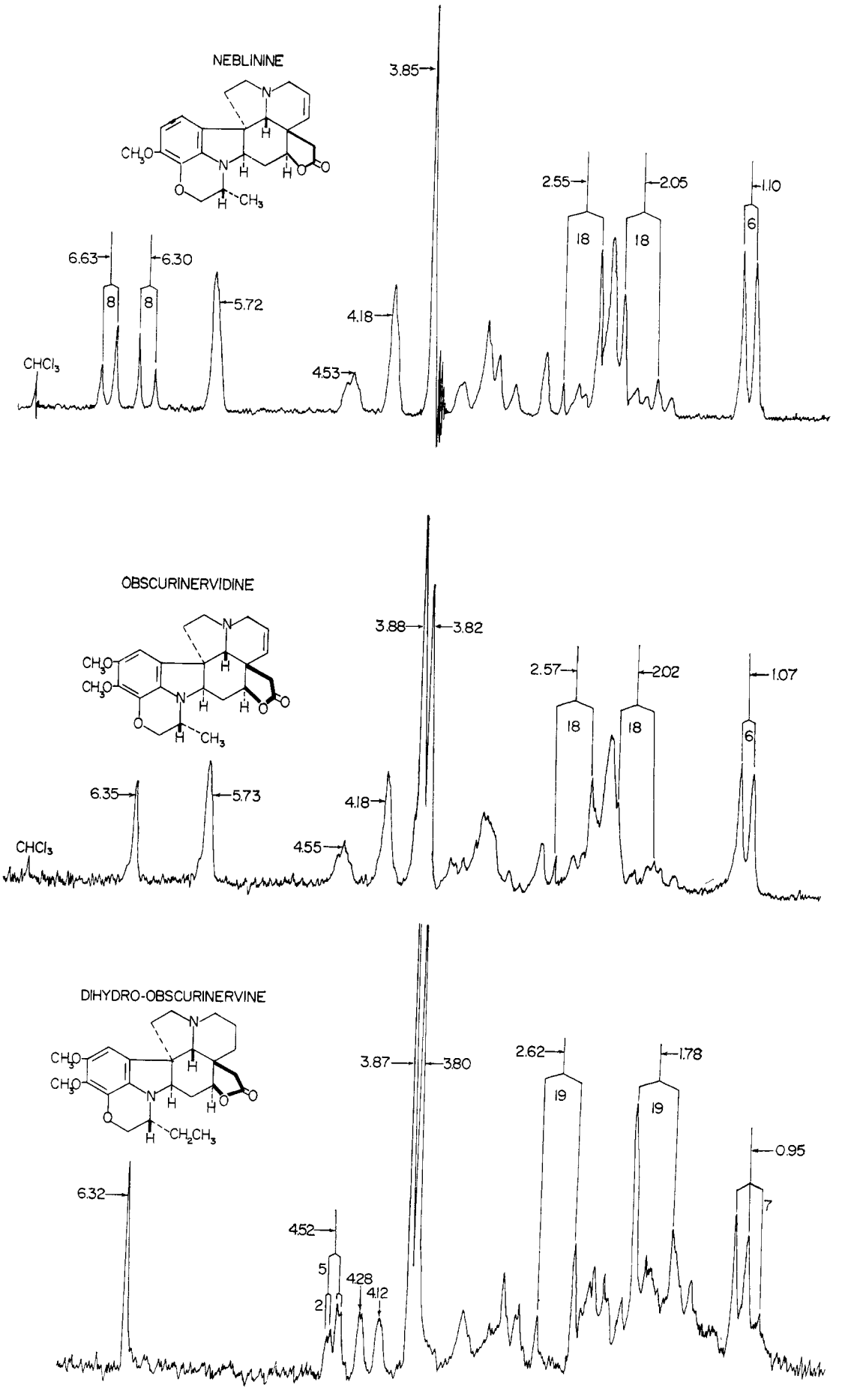


Fig. 2.—N.m.r. spectra of neblinine (IIe), obscurinervidine (IId), and dihydroobscurinervine (IIa).

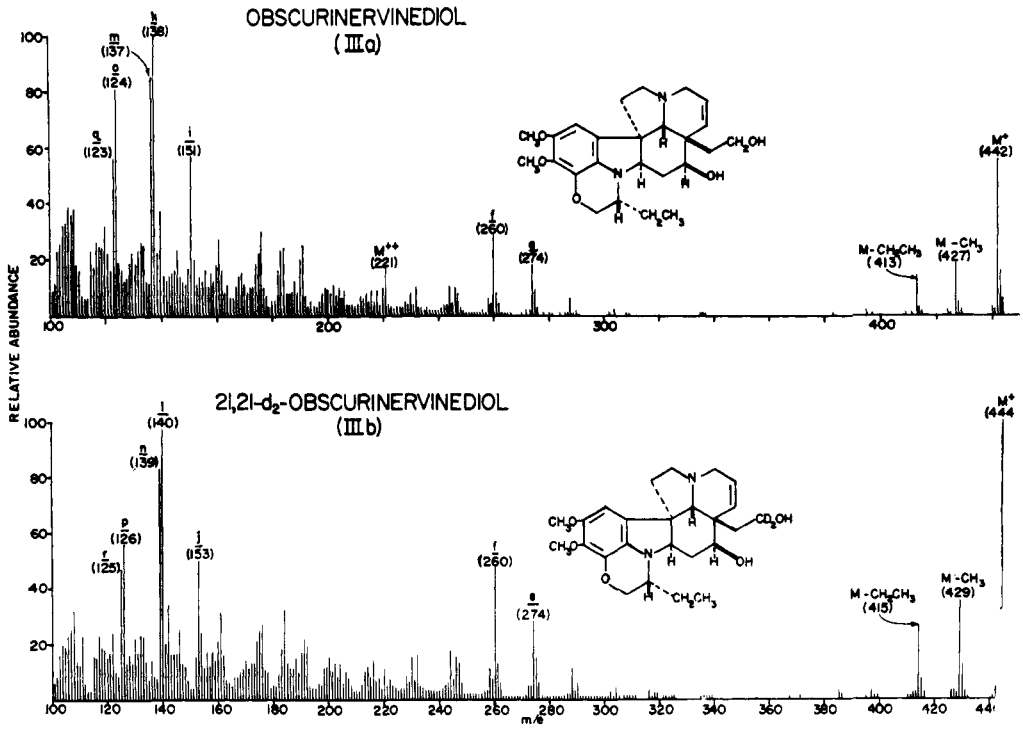


Fig. 3.—Mass spectra of obscurinervinediol (IIIa) and 21,21-d_2-obscurinervinediol (IIIb).

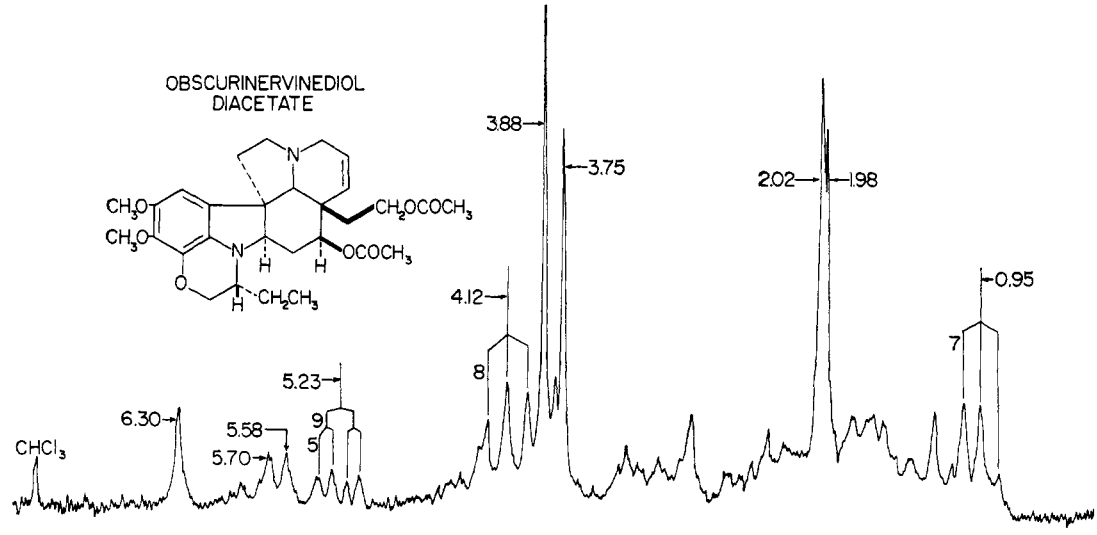


Fig. 4.—N.m.r. spectrum of obscurinervinediol diacetate (IIIh).

carbinolamine ether linkage of the product with lithium aluminum hydride[17] gave the desired substance, identical with natural material (IIIu) by behavior on thin-layer chromatography, optical rotation, and infrared and ultraviolet spectra. A similar synthesis, using 2-iodo-1-butanol, gave a small amount of dihydroobscurinervinol (IIIt), sufficient only for comparison with natural material by thin-layer chromatography, by which criterion the synthetic and natural specimens were identical. This conclusion was supported by infrared spectral measurements.

Those syntheses, while substantiating the proposed skeletal structures for the *obscurinervium* alkaloids, do not permit an assignment of configuration, since the latter has not been settled completely for the starting material (aspidoalbine[18] (IVa)). As seen below, the final evidence for constitutions IIa–IId came from a new direction.

Neblinine.—During the course of this work, there came to our attention an alkaloid isolated at Eli Lilly and Co. from *Aspidosperma neblinae* Monachino (collected in Venezuela), named *neblinine*. The mass spectrum of neblinine (Fig. 1) immediately suggested a demethoxyobscurinervidine; the only strong peak was due to loss of methyl from the molecular ion, weaker peaks

(17) In contrast to the interpretation reported previously (ref. 10), lithium aluminum hydride reduction of O-methyl-N-depropionylaspidoalbine (methyl ether of IVb) gives 90% of the natural (19β) isomer (VIa) and 10% of its 19α-epimer. These were differentiated by the mass spectrometric criterion described previously (K. S. Brown, Jr., H. Budzikiewicz, and C. Djerassi, *Tetrahedron Letters*, 1731 (1963)); the 19α-epimer gives a strong M − 1 peak for the loss of the 19-proton, and a much weaker normal fragmentation than that observed for the 19β-epimer, which shows no M − 1 peak. This new observation is in accord with other reports published recently on the opening of the carbinolamine ether linkage of aspidoalbine-type alkaloids with various reducing agents (M. P. Cava, S. K. Talapatra, K. Nomura, J. A. Weisbach, B. Douglas, and E. C. Shoop, *Chem. Ind.* (London), 1242 (1963), and M. P. Cava, K. Nomura, and S. K. Talapatra, *Tetrahedron*, in press).

(18) For the arguments in favor of structure IVa for aspidoalbine, see ref. 10.

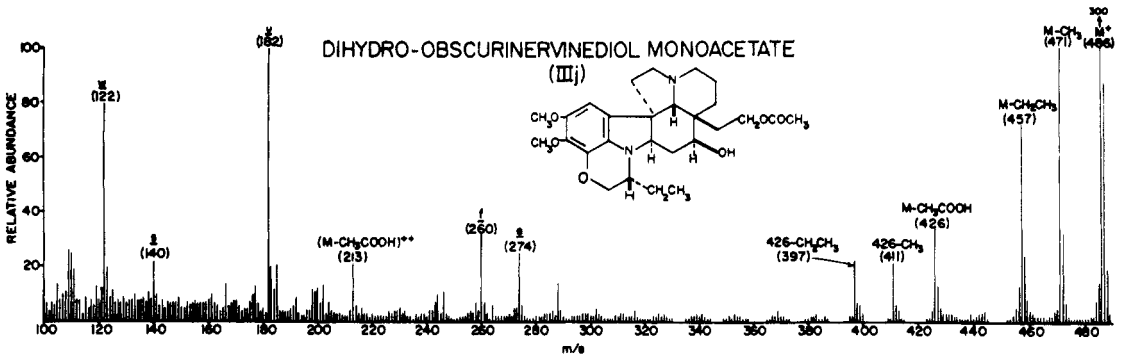


Fig. 5.—Mass spectrum of dihydroobscurinervinediol monoacetate (IIIj).

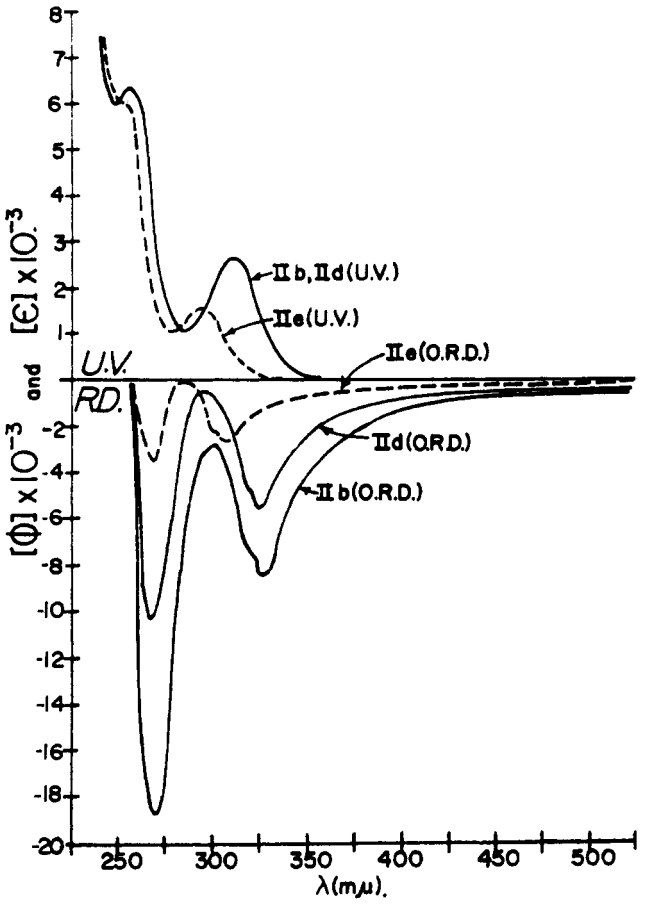


Fig. 6.—Optical rotatory dispersion and ultraviolet absorption spectra of neblinine (IIe), obscurinervine (IIb), and obscurinervidine (IId).

being present for loss of carbon monoxide and for the indole ions demethoxy-a (= b, *m/e* 214) and demethoxy-c (=d, *m/e* 216). The reported[19] infrared band of neblinine at 1750 cm.$^{-1}$ further suggested structure IIe, and when an n.m.r. spectrum of neblinine (Fig. 2) was procured,[19] it greatly supported this assignment; indeed, the spectra of neblinine (IIe) and obscurinervidine (IId) were essentially superimposable, except for the peaks corresponding to the substituent at 15 (H in neblinine, splitting the 14-H; OCH_3 in obscurinervidine). Complete stereochemical identity of the two was also indicated by the optical rotatory dispersion curves of neblinine and obscurinervidine, which were of completely the same type and sign through two Cotton effects (Fig. 6). Neblinine as received from Eli Lilly and Co. also contained about 4% of the 22-ethyl analog IIg, seen in the mass spectra and thin-layer chromatography of all derivatives; a small amount of this contaminant IIg was isolated by partition chromatography, and characterized by m.p. and mass spectrum; this further completed the analogy with the *obscurinervium* alkaloids.

Neblinine (IIe) was carried through the full sequence of transformations already performed on the *obscurinervium* alkaloids; all derivatives (dihydroneblinine, IIf; diols IIIf and IIIg; monoacetates IIIn and IIIo; ketoacetate IIIr; and alcohol IIIv) showed physical properties and mass spectra completely analogous to those of the corresponding compounds from obscurinervidine (IId). Finally, the alcohol IIIv was transformed to dihydroneblininane IIIz, which was synthesized in quantity, along with its 22-epimer, from deacetyl-(+)-aspidocarpine (Ic)[6] *via* the iodopropanol addition mixture Id; the more polar alcohol led to synthetic dihydroneblininane (IIIz), identical with natural material by infrared, ultraviolet, n.m.r., and mass spectra, optical rotation, and thin-layer chromatographic behavior. As the structure and relative configuration of (+)-aspidocarpine (Ia) are firmly established,[6] this synthesis not only provides conclusive evidence for the structure of neblinine (IIe) but also establishes the relative configuration at four of its six asymmetric centers (2, 5, 12, and 19) as being that of the normal (+)-aspidospermine series.[20] The relative configuration at position 22 was further indicated by the observation that dihydroneblininane (IIIz) showed an n.m.r. signal (Fig. 7) for the 22-methyl group at much higher field (1.10 δ) than that (1.44 δ) of its synthetic 22-epimer, indicating the methyl group to possess the α-configuration as shown (in which it lies preferentially nearly under the 17,18-bond; the β-methyl group, in contrast, can only lie in the plane of the aromatic ring, due to its interaction with the methylene groups at positions 3 and 4).

The n.m.r. spectrum (Fig. 7) of dihydroobscurinervidinol (IIIu) showed its very close relationship to dihydroneblininane (IIIz), the only substantial differences in the spectra being due to the differences of substitution at positions 15 and 21; in particular, the signals for the secondary methyl group at C-22 and the methylene group of the cyclic ether are essentially identical in the two spectra, confirming the same relative configurations at least at C-2 and C-22. The molecular rotations of the two compounds (IIIu and IIIz) were comparable in sign and magnitude (−128 and −154°, re-

(19) We are indebted to Dr. M. Gorman of the Eli Lilly Research Laboratories, Indianapolis, Ind., for physical data on neblinine and a 100-mg. sample of this rare alkaloid for the described degradations.

(20) J. F. D. Mills and S. C. Nyburg, *J. Chem. Soc.*, 1458 (1960).

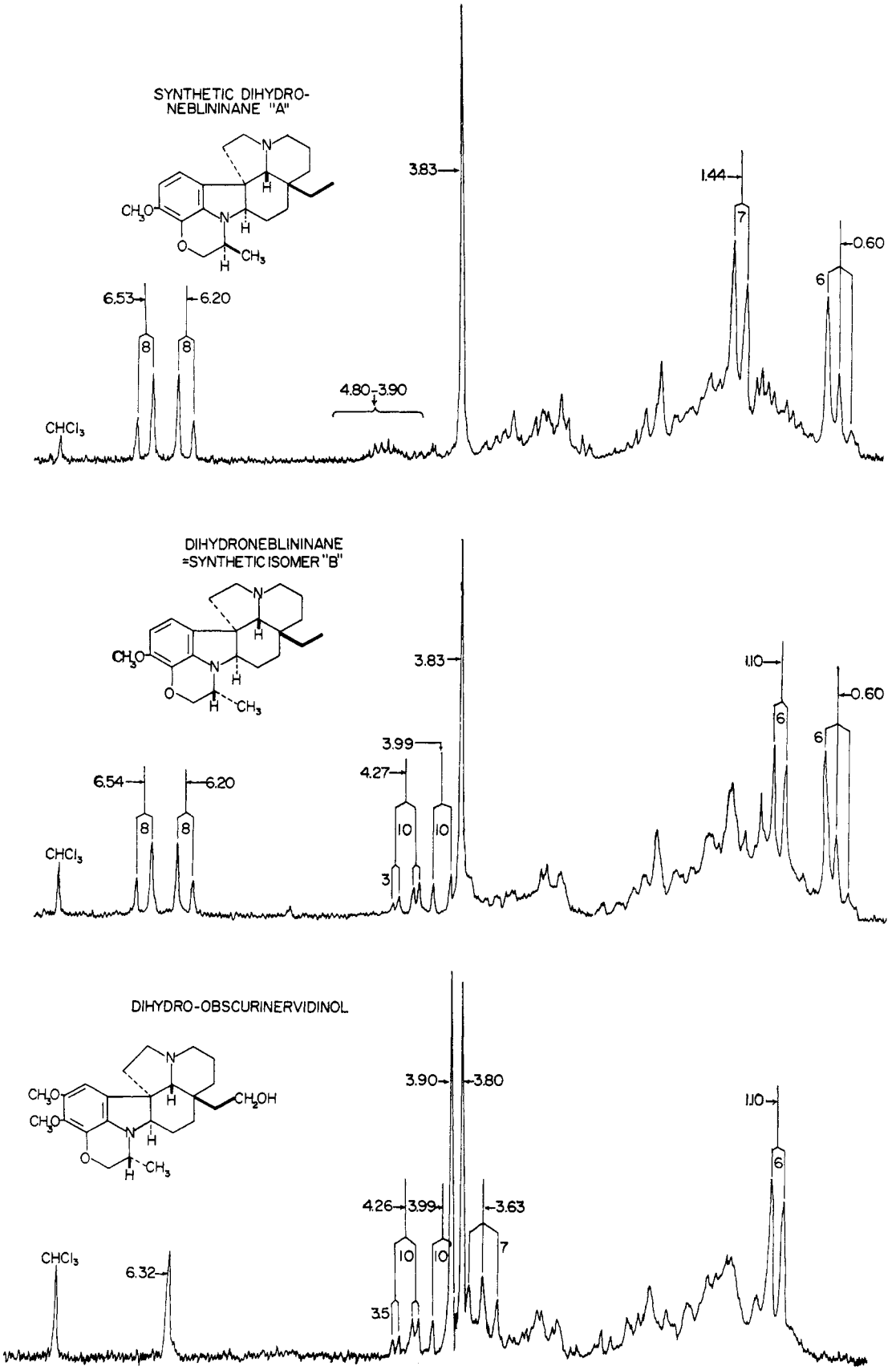
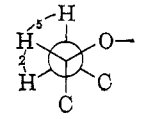
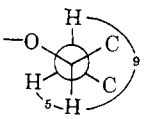


Fig. 7.—N.m.r. spectra of synthetic dihydroneblininanes A and B (IIIz) and dihydroobscurinervidinol (IIIu).

spectively). Thus, it can be assumed that the configurations of the *neblinae* and *obscurinervium* alkaloids are the same; the only point of ambiguity remaining is the configuration at position 4. Three independent and mutually consistent n.m.r. spectral comparisons (see Table I) give a picture of the configuration of the molecule at positions 4 and 5 which not only precludes a 4α-lactone terminus (the only possible conformation of rings C and E which permits such a *trans*-fused lactone also possesses a 4β-axial proton which would have to

TABLE I

N.m.r. features	Structural features	
Coupling constants for the proton on C-4 with the two protons on C-3	Lactone closed (Fig. 2): 5 and 2 c.p.s. (ring held rigidly, 4-H equatorial) 	Lactone open (Fig. 4): 9 and 5 c.p.s. (ring now flipped, acetate equat.) 
Position of high-field proton of methylene of lactone ring	Double bond absent (Fig. 2): 1.78 δ	Double bond present (Fig. 2): 2.02 δ (hence deshielded, in the plane of the double bond)
Position of 4α-proton in diacetate	Double bond absent: 5.65 δ	Double bond present (Fig. 4): 5 23 δ (hence shielded, above the plane of the double bond)

couple with the 3α-axial proton to the extent of at least 8 c.p.s.), but also is completely consistent with the relative configurations as indicated at positions 2, 12, and 19, the experimentally observed results (Table I) proving to be predictable from the most stable conformations of the various molecules. The assignment of constitutions IIa–IId to the *obscurinervium* alkaloids now provides excellent confirmation for the proposed (ref. 10) constitution of aspidoalbine (IVa).

The biogenesis of the unusual multifunctional heptacyclic system represented by IIa–IIg is straightforward (aspidospermine-type alkaloids have now been isolated with modifications at every possible position except 8 and 14[21]) with the exception of the formation of the cyclic ether, which could possibly arise through reductive condensation of formaldehyde with the carbonyl function of an aspidocarpine (Ia) or aspidolimine (Ib) type system, followed by a cyclization similar to that used in the syntheses above (possibly employing a 23-pyrophosphate).

Experimental[22]

General.—Basification of all acidic aqueous solutions was performed with concentrated ammonium hydroxide to pH 10; all methylene chloride, chloroform, and ether solutions of products were dried with anhydrous sodium sulfate and evaporated on a rotary evaporator at water-pump pressure and 65°, then pumped briefly under high vacuum.

In cases where lithium aluminum hydride reductions were carried out on compounds insoluble or sparingly soluble in ether, the material was first dissolved in a minimum amount of methylene chloride, and the ether was then added rapidly with swirling. In all reductions, the required amount of hydride was added as a solid to the solution of the compound to be reduced. Work-up of all lithium aluminum hydride reductions involved slow addition of saturated sodium sulfate solution to the cooled reaction mixture; the suspension was then refluxed until a clear solution was obtained over the white coagulated inorganics (about 30 min.) and filtered under vacuum through anhydrous sodium sulfate.

Chromatography.—Chromatography on "alumina" indicates Merck-Darmstadt active alumina (neutral) plus 6% water, which approximates activity III neutral alumina. The column length: diameter ratio was kept in the range 5–15 by the use of appropriately sized columns.

Partition chromatography was performed with the system hexane–ethylene dichloride–methanol–water (75:10:10:1) on two columns, dry-packed, and then run until fully wet before use[23]: (A), inside diameter 2.3 cm., 30 ml. lower phase on 45 g. of Celite 545, retention volume 70 ml.; and (B), inside diameter 4.0 cm., 150 ml. lower phase on 250 g. of Celite 545, retention volume 380 ml.

Analytical thin-layer chromatography (t.l.c.) was performed on 5 × 20 cm. plates uniformly covered with a 0.25-mm. layer of silica gel G, activated at 110°. Detection was accomplished with 2% ceric sulfate in 1 *M* sulfuric acid. The two systems used, methanol–benzene (1:9 and 1:6) gave approximately comparable results.

Isolation of Individual Alkaloids from *Aspidosperma obsurinervium* Azembuja.—Crude total ethanol extract (1130 g., from Dr. B. Gilbert, Universidade do Brasil, Rio de Janeiro) from *A. obscurinervium* bark was stirred vigorously for 6 hr. at room temperature with 10% aqueous acetic acid (3.0 l.). The solution was then decanted through Celite with the aid of suction; the filtrate was kept at 0° overnight, refiltered, and extracted with hexane (3 × 500 ml.). The extracts were backwashed with dilute ammonium hydroxide and evaporated to yield fraction A (110 mg.), which was discarded. The aqueous solution was then extracted with benzene (5 × 500 ml.); the benzene extracts were combined, evaporated to 200 ml., washed with 10% aqueous acetic acid (2 × 150 ml.) and dilute ammonium hydroxide, dried, and evaporated to yield fraction B (3.1 g.). The combined acetic acid washings yielded, upon basification and chloroform extraction, fraction B_1 (3.4 g.) which was further divided by dissolution in 10% aqueous acetic acid (30 ml.) and extraction with benzene (3 × 30 ml.); the benzene extracts were combined, concentrated to 30 ml., and backwashed with 10% acetic acid (3 × 30 ml.); finally these acetic acid washings were combined and washed with benzene (2 × 75 ml.). All of the benzene solutions (total 180 ml.) were combined, washed with dilute ammonium hydroxide, dried, and evaporated to give fraction B_1a (0.51 g.). The two acetic acid solutions (total 120 ml.) were combined, basified, and extracted with chloroform (2 × 50 ml.) to give fraction B_1b (2.9 g.).

The aqueous acetic acid solution from the first benzene extraction was then extracted with chloroform (3 × 500 ml.); the combined extracts were backwashed with dilute ammonium hydroxide and evaporated to give fraction C (52 g.). The aqueous solution was then neutralized to pH 7.5 with concentrated ammonium hydroxide (280 ml.) and further extracted with chloroform (3 × 500 ml.) to give fraction D (10.4 g.).

Analytical t.l.c. showed that fractions B and B_1a contained an homologous series of compounds (three easily separated, a fourth overlapping, all giving red spots), designated numbers 1, 2, 3, and 7; and B_1b, C, and D two compounds (well separated, ochre spots) designated numbers 4 and 5, and a slower-running compound (orange spot) designated number 6. Fractions B and B_1a were therefore combined as crude **amine fraction** (total 3.6 g. from 1130 g. of extract); fractions B_1b, C, and D were combined as crude **amide fraction** (65.3 g.).

(21) See, for example, the following alkaloids: (a) *vindoline* (substituents at 1, 3, 4, 6, 7, and 16): M. Gorman, N. Neuss, and K. Biemann, *J. Am. Chem. Soc.*, **84**, 1058 (1962); (b) *vindolinine* (substituents at 3, 6, 7, 11, and 20): C. Djerassi, S. E. Flores, H. Budzikiewicz, J. M. Wilson, L. J. Durham, J. LeMen, M.-M. Janot, M. Plat, M. Gorman, and N. Neuss, *Proc. Natl. Acad. Sci. U. S.*, **48**, 113 (1962), and unpublished work in this laboratory (M. Cereghetti); (c) *aspidoalbine* (substituents at 1, 15, 16, 17, 19, and 21): see ref. 10; (d) *pyrifoline* (substituents at 1, 2, 6, 17, and 21): B. Gilbert, J. M. Ferreira, R. J. Owellen, C. E. Swanholm, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Tetrahedron Letters*, 59 (1962); (e) *kopsine* (substituents at 2, 3, 11, and 21): T. R. Govindachari, B. R. Pai, S. Rajappa, N. Viswanathan, W. G. Kump, K. Nagarajan, and H. Schmid, *Helv. Chim. Acta*, **45**, 1146 (1962); and (f) *kopsinilam* (substituents at 2, 3, 10, and 21): C. Kump and H. Schmid, *ibid.*, **45**, 1090 (1962).

(22) Melting points were determined in an open capillary, corrected to the nearest degree. Rotations, all taken in chloroform, are rounded off to the nearest degree. Infrared spectra are in chloroform, at approximately 10% concentration; ultraviolet spectra are in 95% ethanol at appropriate concentrations. Nuclear magnetic resonance spectra, recorded by a Varian A 60 spectrometer, are in deuteriochloroform solution. We thank E. Meier and J. Consul of the Stanford Microanalytical Laboratory for microanalyses; all analytical samples were dried at least 12 hr. at 80° (0.1 mm.). Mass spectra were determined with a CEC Model 21-103C mass spectrometer using either an all-glass heated inlet system or a "direct inlet" technique (J. F. Lynch, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Experientia*, **19**, 211 (1963)). The optical rotatory dispersion curves, reproduced in Fig. 6, were obtained in methanol solution by Mrs. R. Records with a Bendix-Ericsson spectropolarimeter.

(23) K. S. Brown, Jr., and S. M. Kupchan, *J. Chromatography*, **9**, 71 (1962).

The crude amide fraction from a total of 1730 g. of ethanol extract (95 g.), dissolved in benzene, was separated on alumina (1000 g.). The first 100 ml. of benzene eluate contained 16.6 g.; continued elution with benzene (1650 ml.) and ethyl acetate–benzene (1:49, 1:19, 1:9, and 1:3; 500 ml. each) gave another 44.2 g. Analytical t.l.c. showed that the 16.6 g. was a mixture of 4 and 5, while the 44.2 g. was pure 4. Continued elution with ethyl acetate–benzene (1:1, 250 ml.) gave 0.8 g. showing on t.l.c. a complex mixture of minor components; alkaloid 6 was then eluted with ethyl acetate–benzene (1:1, 750 ml., and 3:1, 500 ml.), a total of 8.5 g. of essentially homogeneous material being obtained.

Crystallization of the 16.6 g. from ethanol gave alkaloid 4 (12.3 g., homogeneous with no trace of 5 on t.l.c.), m.p. 166–169°; the mother liquor was treated as below. From the 44.2 g., another 37.8 g. of pure alkaloid 4, m.p. 168–169°, was obtained. Comparison of the infrared and ultraviolet spectra and rotation ($[\alpha]^{26}D$ +140°, *c* 1.16) of alkaloid 4 with those of (+)-**aspidocarpine** (**Ia**)[6] indicated that the two were identical; a mixture melting point with an authentic sample (167–169°) served as confirmation.

The mother liquor from the crystallization of the 16.6 g. (containing, by t.l.c., alkaloids 4 and 5) was rechromatographed in hexane–benzene (1:2) on alumina (100 g.). The first 20 ml. of eluate contained only alkaloid 5 (0.28 g.); the next 40 ml., alkaloids 4 and 5 (0.67 g.). Continued elution gave only alkaloid 4 (aspidocarpine, 2.18 g.). Similar rechromatography of the 0.67 g. on alumina (60 g.) gave alkaloid 5 (0.15 g.) and aspidocarpine (0.50 g.), clearly separated. The total alkaloid 5 (0.43 g.) gave upon crystallization from methanol 0.22 g., m.p. 147–150°; recrystallized material showed m.p. 150–152°, $[\alpha]^{25}D$ +139° (*c* 1.03), and infrared and ultraviolet spectra identical with those of (+)-**aspidolimine** (**Ib**).[9] A mixture melting point with authentic aspidolimine of m.p. 151–153° showed no depression, confirming the identification.

Purified **alkaloid 6** was amorphous, $[\alpha]^{27}D$ −168° (*c* 1.02); ν_{max} 3580 (m), 1735 (s), 1626 (s), 1590 (s) cm.$^{-1}$; λ_{max} 224 and 278 mμ, log ε 4.20, 3.90; λ_{min} 248 mμ, log ε 3.57; λ_{infl} 288 mμ, log ε 3.84; mass spec. *m/e* 382 (M^+), 351 ($M^+ - CH_2OH$), 323 ($M^+ - COOCH_3$), 279 ($M^+ - CH(CH_2OH)COOCH_3$), 140, 122, 121; n.m.r. 7.7–6.5 (3H, ABC pattern; 3 aromatic protons), 5.45 (1H, quartet, *J* 6.5 c.p.s.; C=C*H*CH$_3$), 4.52 (1H, doublet, *J* 4 c.p.s.), 3.83 and 3.80 (6H, two sharp peaks; aromatic OCH_3 and $COOCH_3$), and 1.62 δ (3H, doublet, *J* 6.5 c.p.s.; C=CH-CH_3).

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.81; H, 7.06; N, 7.05.

Alkaloid 6 picrate was prepared by mixing ethereal solutions of alkaloid 6 (840 mg.) and picric acid (575 mg.); the precipitated solid was washed repeatedly with warm ether, giving the picrate (950 mg.), m.p. >147° dec.

Anal. Calcd. for $C_{28}H_{29}N_5O_{11}$: C, 54.99; H, 4.78; N, 11.45. Found: C, 54.03; H, 5.11; N, 11.19.

The crude amine fraction from 1300 g. of ethanol extract (4.1 g.) was separated into its components in three portions on column B. Alkaloid 1 (**dihydroobscurinervine**—see below; total 1.02 g.) appeared at R_f 0.59–0.53; a small intermediate fraction, which also contained traces of aspidocarpine, was collected (0.13 g.) and rechromatographed; alkaloid 2 (**obscurinervine**) and alkaloid 7 (**dihydroobscurinervidine**—see below) appeared nearly together (total 1.38 g.) at R_f 0.49–0.43; a small intermediate fraction (0.10 g.) was followed by alkaloid 3 (**obscurinervidine**, total 0.50 g.) at R_f 0.38–0.34.

Crystallization of the crude **dihydroobscurinervine** (**IIa**, 1.02 g.) from acetone–hexane gave 638 mg., m.p. 182–184° dec.; pure material exhibited m.p. 184–185° dec., $[\alpha]^{26}D$ −61° (*c* 0.92); ν_{max} 2780 (m), 1750 (vs), 1610 (m) cm.$^{-1}$; λ_{max} 220, 256, and 313 mμ, log ε 4.46, 3.81, 3.43; λ_{min} 247 and 283 mμ, log ε 3.76, 2.91; spectrum unchanged in 4 *N* hydrochloric acid; mass spec. *m/e* 440 (M^+), 425, 411, 244 (ion a), 206 ($(M - CO)^{+2}$); n.m.r. (Fig. 2) 6.32 (1H, unsplit; lone aromatic proton), 4.52 (1H, quartet, *J*'s 5, 2 c.p.s.; CH_2CHOCO), 4.28 and 4.12 (2H, doublets, *J* 1.5 c.p.s.; CH_2 of cyclic ether), 3.87 and 3.80 (6H, two sharp peaks; two aromatic OCH_3), 2.62 and 1.78 (2H, doublets, *J* 19 c.p.s.; rigid C–CH_2–CO), and 0.95 δ (3H, triplet, *J* 7 c.p.s.; C–ethyl group).

Anal. Calcd. for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36; $2OCH_3$, 14.09. Found: C, 68.01; H, 7.21; N, 6.47; OCH_3, 14.16.

Crystallization of the crude **obscurinervine** (**IIb**, 1.38 g.) from acetone–hexane gave 878 mg., m.p. 203–204° dec.; pure material exhibited m.p. 203–205° dec., $[\alpha]^{27}D$ −54° (*c* 0.95); ν_{max} 2780 (m), 1750 (vs), 1605 (m) cm.$^{-1}$; λ_{max} 220, 253, and 312 mμ, log ε 4.49, 3.81, 3.43; λ_{min} 247 and 282 mμ, log ε 3.78, 2.99; mass spec. (Fig. 1) *m/e* 438 (M^+), 423, 409, 244 (ion a), 205 ($(M - CO)^{+2}$); n.m.r. 6.32 (1H, unsplit; lone aromatic proton), 5.71 (2H, sharp collapsed multiplet; vinyl protons), 4.52 (1H, quartet, *J* 5, 2 c.p.s.; CH_2CHOCO), 4.28 and 4.13 (2H, doublets, *J* 1.5 c.p.s.; CH_2 of cyclic ether), 3.87 and 3.80 (6H, two sharp peaks; two aromatic OCH_3), 2.57 and 2.02 (2H, doublets, *J* 18 c.p.s.; rigid C–CH_2–CO), and 0.97 δ (3H, triplet, *J* 6.5 c.p.s.; C–ethyl group).

Anal. Calcd. for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.28; H, 7.20; N, 6.45.

The mother liquor mixture from the above crystallization of obscurinervine (400 mg.) showed on t.l.c. two equal overlapping spots (obscurinervine and dihydroobscurinervidine) which were separated by hydrogenation of the mixture at atmospheric pressure with 10% palladium-on-charcoal (300 mg.) in ethyl acetate (50 ml.); the very rapid uptake of hydrogen amounted to 12.2 ml. (about 50% of the theoretical). Work-up by filtration, evaporation, and partition chromatography on column A gave dihydroobscurinervine (210 mg., R_f 0.58; crystallization from acetone–hexane gave 135 mg., m.p. 183–184° dec., identical with IIa by t.l.c.) and **dihydroobscurinervidine** (**IIc**, 145 mg., R_f 0.47; identical by t.l.c. to the overlapping alkaloid in the starting mixture, hence unchanged by hydrogenation). Crystallization of the latter from acetone–hexane gave 121 mg., m.p. 186–189° dec.; pure material exhibited m.p. 189–190° dec., $[\alpha]^{27}D$ −44° (*c* 0.85); ν_{max} 2780 (m), 1750 (vs), 1610 (m) cm.$^{-1}$; λ_{max} 219, 255, and 312 mμ, log ε 4.52, 3.80, 3.43; λ_{min} 247 and 282 mμ, log ε 3.77, 2.90; mass spec. *m/e* 426 (M^+), 411, 246 (ion c), 244 (ion a), 199 ($(M - CO)^{+2}$); n.m.r. 6.35 (1H, unsplit; lone aromatic proton), 4.53 (1H, quartet, *J* 5, 2 c.p.s.; CH_2CHOCO), 4.18 (2H, sharp collapsed multiplet; CH_2 of cyclic ether), 3.88 and 3.82 (6H, two sharp peaks; two aromatic OCH_3), 2.62 and 1.78 (2H, doublets, *J* 19 c.p.s.; rigid C–CH_2–CO), and 1.07 δ (3H, doublet, *J* 7 c.p.s.; N–CH–CH_3).

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.09; N, 6.57; $2OCH_3$, 14.55. Found: C, 67.51; H, 7.54; N, 6.73; OCH_3, 13.98.

Crystallization of the crude **obscurinervidine** (**IId**, 0.50 g.) from acetone–hexane gave 352 mg., m.p. 205–206° dec.; pure material exhibited m.p. 206–207° dec., $[\alpha]^{25}D$ −39° (*c* 0.62); ν_{max} 2780 (m), 1760 (vs), 1605 (m, doublet) cm.$^{-1}$; λ_{max} 219, 253, and 310 mμ, log ε 4.50, 3.77, 3.42; λ_{min} 247 and 282 mμ, log ε 3.74, 2.91; mass spec. (Fig. 1) *m/e* 424 (M^+), 409, 246 (ion c), 244 (ion a), 198 ($(M - CO)^{+2}$); n.m.r. (Fig. 2) 6.35 (1H, unsplit; lone aromatic proton), 5.73 (2H, sharp collapsed multiplet; vinyl protons), 4.55 (1H, broad; CH_2CHOCO), 4.18 (2H, sharp collapsed multiplet; CH_2 of cyclic ether), 3.88 and 3.82 (6H, two sharp peaks; two aromatic OCH_3), 2.57 and 2.02 (2H, doublets, *J* 18 c.p.s.; rigid C–CH_2–CO), and 1.07 δ (3H, doublet, *J* 6 c.p.s.; N–CH–CH_3).

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found: C, 68.09; H, 6.72; N, 6.64.

Hydrogenation of Obscurinervine (**IIb**).—Obscurinervine (30 mg.) was hydrogenated at atmospheric pressure with 10% palladium-on-charcoal (50 mg.) in ethyl acetate (10 ml.). A rapid uptake (10 min.) of 85% of the theoretical amount of hydrogen (2.1 ml.) was observed; the product was recovered by filtration and evaporation, purified by partition chromatography (column A, R_f 0.54), and crystallized from acetone–hexane to yield dihydroobscurinervine (IIa, 16 mg.), identical in m.p., infrared and ultraviolet spectra, and t.l.c. behavior with natural material; mixture m.p., 184–185° dec.

Catalytic Deuteration of Obscurinervine (**IIb**).—Similar reduction of obscurinervine (13 mg.) under deuterium gas, with partition chromatographic purification of the product, gave d_{1-3}-dihydroobscurinervine, m.p. 182–183° dec.; mass spec. *m/e* 443 (33%), 442 (47%), 441 (20%) (M^+ ions); similar shifts observed in the peaks at 427, 413, 207, and the range 100–150, but no shift in *m/e* 244 (ion a).

Hydrogenation of Obscurinervidine (**IId**).—Obscurinervidine (100 mg.) was hydrogenated as above; the uptake (5.5 ml. in 30 min.) was about 90% of the theoretical. Recovery of the crude product and direct crystallization from acetone–hexane gave dihydroobscurinervidine (IIc, 73 mg.), identical in m.p., infrared

spectrum, and t.l.c. behavior with natural material; mixture m.p. 188–189° dec.

Neblinine.[19]—Neblinine (IIe), as obtained from Dr. M. Gorman of Eli Lilly and Co. (isolated in 0.01% yield by direct crystallization of a hexane extract from *Aspidosperma neblinae* Monachino), exhibited m.p. 256–258° dec., $[\alpha]^{27}D$ −14° (*c* 1.19); ν_{max}[19] 2780 (m), 1750 (vs), 1618 (m), 1598 (m), 1492 (m) cm.$^{-1}$; λ_{max} 221, 256, and 295 mμ, log ε 4.57, 3.78, 3.20; λ_{min} 276 mμ, log ε 3.02; λ_{infl} 250 mμ, log ε 3.80; mass spec. (Fig. 1) *m/e* 394 (M^+), 379, 216 (ion d), 214 (ion b); n.m.r.[19] (Fig. 2) 6.63 and 6.30 (2H, doublets, *J* 8 c.p.s.; two adjacent aromatic protons), 5.72 (2H, sharp collapsed multiplet; vinyl protons), 4.53 (1H, broad; CH_2CHOCO), 4.18 (2H, sharp collapsed multiplet; CH_2 of cyclic ether), 3.85 (3H, unsplit; aromatic OCH_3), 2.55 and 2.05 (2H, doublets, *J* 18 c.p.s.; rigid $C-CH_2-CO$), and 1.10 δ (3H, doublet, *J* 6 c.p.s.; $N-CH-CH_3$); pK_a[19] (33% DMF), 4.88.

Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10[19]; OCH_3, 8.2.[19] Found: C, 69.92; H, 6.68; N, 7.08; OCH_3, 8.1.

Dihydroneblinine (IIf).—Neblinine (50 mg.) was hydrogenated as above; uptake of one equivalent of hydrogen was almost immediate. The product (60 mg.) was crystallized from acetone–hexane to give dihydroneblinine (IIf, 38 mg.), m.p. 230–233° dec., ν_{max} 1750 (vs) cm.$^{-1}$; mass spec. *m/e* 396 (M^+).

22-Ethyl-22-demethylneblinine (IIg).—Neblinine as obtained from Eli Lilly and Co.[19] (25 mg.) was separated on column A; pure neblinine (23.7 mg., m.p. upon crystallization 258–261° dec.) appeared at R_f 0.54–0.47; the ethyl analog (IIg, 1 mg., running s ightly faster than neblinine on t.l.c.), appearing at R_f 0.62–0.55, was crystallized from acetone–hexane to yield 0.5 mg., m.p. 263–265° dec., ν_{max} 1760 (vs), 1630 (m) cm.$^{-1}$; mass spec. *m/e* 408 (M^+), 379 ($M - C_2H_5$), 214 (ion b).

Some Attempted Reactions on Dihydroobscurinervine (IIa).—Dihydroobscurinervine (30 mg.) was hydrolyzed under nitrogen 3 hr. with refluxing 4 *N* hydrochloric acid (1.5 ml.). The product (30 mg.), recovered with water, ammonium hydroxide, and methylene chloride, showed an infrared spectrum and t.l.c. behavior identical with those of starting material.

Dihydroobscurinervine (10 mg.) was acetylated with acetic anhydride (1.0 ml.) in pyridine (0.5 ml.) at room temperature (2 hr.) and 70° (15 min.). Recovery of the product with water, ammonium hydroxide, and methylene chloride gave unchanged starting material (by infrared spectrum).

Obscurinervinediol (IIIa).—Obscurinervine (50 mg.) was reduced for 1 hr. with lithium aluminum hydride (100 mg.) in refluxing ether (20 ml.). Work-up gave impure product, purified on alumina (5 g.) by adding in benzene solution. Elution with ethyl acetate–benzene (1:1, 50 ml.) and ethyl acetate–methanol (49:1, 30 ml.) gave obscurinervinediol (IIIa, 40 mg.), crystallized from acetone–hexane to give 31 mg., m.p. 227–233° dec.; ν_{max} 3380 (s), no infrared maximum at 1750 cm.$^{-1}$; ultraviolet spectrum essentially unchanged from that of starting material; mass spec. (Fig. 3) *m/e* 442 (M^+), 427, 413, 288, 274 (ion e), 260 (ion f), 151 (ion i), 138 (ion k), 137 (ion m), 124 (ion o), and 123 (ion q).

Anal. Calcd. for $C_{25}H_{34}N_2O_5$: C, 67.85; H, 7.74. Found: C, 67.52; H, 7.94.

21,21-d_2-Obscurinervinediol (IIIb).—Obscurinervine (15 mg.) was reduced as above with lithium aluminum deuteride (50 mg.) in ether (10 ml.). The product was crystallized from acetone–hexane to give the deuterated alcohol IIIb (11 mg.), m.p. 226–229° dec.; mass spec. (Fig. 3) *m/e* 444 (M^+), 429, 415, 288, 274 (ion e), 260 (ion f), 153 (ion j), 140 (ion l), 139 (ion n), 126 (ion p), and 125 (ion r).

Dihydroobscurinervinediol (IIIc), produced in an analogous manner, was amorphous; ν_{max} 3380 (s) cm.$^{-1}$; mass spec. *m/e* 444 (M^+), 429, 415, 288, 274 (ion e), 260 (ion f), and 140 (ion s).

Obscurinervidinediol (IIId).—Obscurinervidine (50 mg.) was reduced as above with lithium aluminum hydride (50 mg.) in refluxing ether (20 ml.). The product was directly crystallized from acetone–isopropyl ether to give the diol IIId (40 mg.), m.p. 210–216° dec.; ν_{max} 3380 (s) cm.$^{-1}$; mass spec. *m/e* 428 (M^+), 413, 274, 260 (ion g), 246 (ion c), 151 (ion i), 138 (ion k), 137 (ion m), 124 (ion o), and 123 (ion q); n.m.r. 6.32 (1H, unsplit; lone aromatic proton), 6.22–5.50 (2H, AB of ABX_2 pattern; vinyl protons), 4.11 and 4.04 (2H, doublets, *J* 3 c.p.s.; CH_2 of cyclic ether), 3.88 and 3.78 (6H, two sharp peaks; two aromatic OCH_3), and 1.12 δ (3H, doublet, *J* 6 c.p.s.; $N-CH-CH_3$).

Anal. Calcd. for $C_{24}H_{32}N_2O_5$: C, 67.26; H, 7.53. Found: C, 67.60; H, 7.77.

Dihydroobscurinervidinediol (IIIe), prepared in like manner from dihydroobscurinervidine (IIc), was amorphous; ν_{max} 3380 (s) cm.$^{-1}$; mass spec. *m/e* 430 (M^+), 415, 260 (ion g), 246 (ion c), and 140 (ion s).

Neblininediol (IIIf).—Neblinine (30 mg.) was reduced for 1.5 hr. with lithium aluminum hydride (50 mg.) in refluxing ether (20 ml.). Work-up gave the crude diol IIIf (30 mg.), exceedingly poorly crystalline; ν_{max} 3380 (s) cm.$^{-1}$; mass spec. *m/e* 398 (M^+), 383, 380, 353, 335, 230 (ion h), 216 (ion d), 151 (ion i), 138 (ion k), 137 (ion m), 124 (ion o), and 123 (ion q).

Dihydroneblininediol (IIIg), prepared from dihydroneblinine (47 mg.) in like manner, showed ν_{max} 3380 (s) cm.$^{-1}$, mass spec. *m/e* 400 (M^+), 230 (ion h), 216 (ion d), and 140 (ion s).

Obscurinervinediol Diacetate (IIIh).—Obscurinervinediol (IIIa, 55 mg.) was acetylated with acetic anhydride (2 ml.) in pyridine (1 ml.) at room temperature (2 hr.) and 60° (15 min). The product, recovered with water, ammonium hydroxide, and methylene chloride, was placed as a benzene solution on alumina (5 g.). Elution with benzene (20 ml.) and ethyl acetate–benzene (1:19, 15 ml.) gave the pure amorphous diacetate IIIh (50 mg.), ν_{max} 1735 (vs) cm.$^{-1}$; ultraviolet spectrum essentially unchanged from that of starting material; mass spec. *m/e* 526 (M^+), 511, 497, 466 ($M^+ - HOAc$), 451, 180 (ion t), and 120 (ion u); n.m.r. (Fig. 4) 6.30 (1H, unsplit; lone aromatic proton), 6.00–5.32 (2H, AB of ABX_2 pattern; vinyl protons), 5.23 (1H, quartet, *J*'s 9, 5 c.p.s.; CH_2CHOAc), 4.42–3.75 (4H, complex; CH_2 of cyclic ether as well as CH_2CH_2OAc), 3.88 and 3.75 (6H, two sharp peaks; two aromatic OCH_3), 2.02 and 1.98 (6H, two sharp peaks; two $OCOCH_3$), and 0.95 δ (3H, triplet, *J* 7 c.p.s.; C–ethyl group).

Dihydroobscurinervinediol Diacetate (IIIi).—The analogous saturated compound IIIi was prepared by similar acetylation of dihydroobscurinervinediol (IIIc, 26 mg.). The chromatographically pure product (20 mg.) was similarly amorphous, ν_{max} 1735 (vs) cm.$^{-1}$; mass spec. *m/e* 528 (M^+), 513, 499, 468 ($M^+ - HOAc$), 453, 439, 408 ($M^+ - 2HOAc$), 393, 379, 182 (ion v), and 122 (ion w); n.m.r. 6.27 (1H, unsplit; lone aromatic proton), 5.65 (1H, quartet, *J* 9, 5 c.p.s.; CH_2CHOAc), 4.50–3.90 (4H, complex; CH_2 of cyclic ether and of CH_2CH_2OAc), 3.88 and 3.75 (6H, two sharp peaks; two aromatic OCH_3), 2.03 and 1.96 (6H, two sharp peaks; two $OCOCH_3$), and 0.95 δ (3H, triplet, *J* 7 c.p.s.; C–ethyl group).

Dihydroobscurinervinediol Monoacetate (IIIj).—Dihydroobscurinervinediol (IIIc, 100 mg.) was acetylated with acetyl chloride (20 mg.) and anhydrous potassium carbonate (1 g.), stirring 1 hr. at 0° in benzene (10 ml.). The benzene was removed under reduced pressure and the product (120 mg.), after recovery with water and methylene chloride, was placed as a benzene solution on alumina (10 g.). Elution with ethyl acetate–benzene (1:1, 50 ml.) gave the product IIIj (85 mg.), crystallized from acetone–hexane to yield 69 mg., m.p. 177–179° dec. Pure material showed m.p. 179–180° dec., $[\alpha]^{27}D$ −36° (*c* 0.54); ν_{max} 3380 (m), 1720 (s) cm.$^{-1}$; ultraviolet spectrum showing essentially no change from that of starting material; mass spec. (Fig. 5) *m/e* 486 (M^+), 471, 457, 426 ($M^+ - HOAc$), 411, 397, 288, 274 (ion e), 260 (ion f), 182 (ion v), 140 (ion s), and 122 (ion w).

Anal. Calcd. for $C_{27}H_{38}N_2O_6$: C, 66.64; H, 7.87. Found: C, 66.50; H, 7.94.

This compound (IIIj) was also prepared from obscurinervine (IIb, 200 mg.) without isolation of the intermediates IIa and IIIc; the yield was 175 mg. (79% over-all) of purified material.

Obscurinervidinediol Monoacetate (IIIk).—Similar treatment of obscurinervidinediol (IIId, 20 mg.) followed by chromatographic purification, gave crude monoacetate IIIk (10 mg.) which upon crystallization from acetone–hexane yielded 4 mg., m.p. 154–157°; mass spec. *m/e* 470 (M^+), 455, 410 ($M^+ - HOAc$), 395, 274, 260 (ion g), 246 (ion c), 180 (ion t), 179 (ion x), and 120 (ion u).

Dihydroobscurinervidinediol Monoacetate (IIIm).—Dihydroobscurinervidinediol (IIIe, 45 mg.) was monoacetylated and the product chromatographically purified in the same fashion; the product thus obtained (25 mg. after three purifications) gave upon crystallization from acetone–hexane the monoacetate IIIm (15 mg.), m.p. 155–156° dec.; ν_{max} 3380 (m), 1720 (s) cm.$^{-1}$; mass spec. *m/e* 472 (M^+), 457, 412 ($M^+ - HOAc$), 397, 260 (ion g), 246 (ion c), 182 (ion v), 140 (ion s), and 122 (ion w).

Anal. Calcd. for $C_{26}H_{36}N_2O_6$: C, 66.08; H, 7.68. Found: C, 66.21; H, 7.69.

Preparation of this monoacetate IIIm from obscurinervidine

(IId, 200 mg.) without isolation of the intermediates (IIc and IIIe) gave 175 mg. (79% over-all) of purified material.

Neblinine diol Monoacetate (IIIn).—Neblinine diol (IIIf, 27 mg.) was converted to the monoacetate in similar fashion; the crude product (30 mg.) was purified in benzene solution on alumina (5 g.). Elution with ethyl acetate–benzene (1:1, 25 ml.) gave 15 mg., very poorly crystalline (m.p. near 130°); ν_{max} 3380 (m), 1720 (s) cm.$^{-1}$; mass spec. *m/e* 440 (M^+), 425, 396, 380 (M^+ − HOAc), 365, 353, 335, 230 (ion h), 216 (ion d), 180 (ion t), 179 (ion x), and 120 (ion u).

Dihydroneblinine diol Monoacetate (IIIo).—Neblinine diol monoacetate (13 mg.) was hydrogenated at atmospheric pressure with equilibrated palladium-on-charcoal catalyst (25 mg.) in ethyl acetate (10 ml.); the product was purified on alumina (3 g.) to give the monoacetate IIIo (10 mg.), infrared spectrum very similar to that of the starting material; mass spec. *m/e* 442 (M^+), 427, 398, 382 (M^+ − HOAc), 367, 355, 230 (ion h), 216 (ion d), 182 (ion v), and 122 (ion w).

This monoacetate IIIo was also prepared from dihydroneblinine diol (IIIg, 45 mg.) with acetyl chloride (20 mg.) and potassium carbonate (250 mg.), stirring 1.5 hr. at 0° in benzene (5 ml.). Recovery gave the crude product (55 mg.), which was placed in benzene on alumina (5 g.); ethyl acetate–benzene (1:3, 30 ml.) eluted the product (30 mg.), whose infrared spectrum was superimposable upon that of IIIo prepared as above.

Dihydroobscurinervinolone Acetate (IIIp).—Purified dihydroobscurinervinediol monoacetate (IIIj, 175 mg.) was dissolved in a mixture of dry dimethyl sulfoxide (1.8 ml.) and dry dimethyl sulfoxide 1 *M* in phosphoric acid (0.53 ml., 1.5 mole equivalents) and treated at room temperature for 35 hr. under nitrogen with dicyclohexylcarbodiimide (450 mg., freshly distilled).[14] At the end of this period, water was added, the suspension was filtered, and the solid dicyclohexylurea was washed well with water; the crude product was recovered from the filtrate with ammonium hydroxide and methylene chloride–ether, and purified on column A to give the oily ketoacetate IIIp (135 mg.), R_f 0.56; ν_{max} 1735 (s), 1705 (s) cm.$^{-1}$; mass spec. *m/e* 484 (M^+), 469, 455, 442 (M^+ − CH_2=C=O), 424 (M^+ − HOAc), 409, 395, 274 (ion e), 260 (ion f), 182 (ion v), and 122 (ion w).

Dihydroobscurinervidinolone Acetate (IIIq).—Purified dihydroobscurinervidinediol monoacetate (IIIm, 175 mg.) was oxidized[14] under exactly the same conditions as above; the oily product (135 mg., R_f 0.45 on column A) showed ν_{max} 1735 (s), 1705 (s) cm.$^{-1}$; mass spec *m/e* 470 (M^+), 455, 260 (ion g), 246 (ion c), 182 (ion v), and 122 (ion w).

Dihydroneblininolone Acetate (IIIr).—Dihydroneblinine diol monoacetate (IIIo, 30 mg.) was oxidized[14] as above (all quantities times 2/9); the amorphous product (22 mg.) appeared at R_f 0.55 on column A, ν_{max} 1735 (s) and 1705 (s) cm.$^{-1}$; mass spec. *m/e* 440 (M^+), 230 (ion h), 216 (ion d), 182 (ion v), and 122 (ion w).

Dihydroobscurinervinolone (IIIs).—The ketoacetate IIIp (20 mg.) was hydrolyzed for 15 min. with refluxing saturated methanolic potassium carbonate (5 ml.). Recovery with water and chloroform gave the keto alcohol IIIs (18 mg.), ν_{max} 3380 (m), 1705 (s) cm.$^{-1}$; mass spec. *m/e* 442 (M^+), 427, 424 (M^+ − H_2O), 413, 369 (M^+ − CH_2OH − CH_2=C=O), 274 (ion e), 260 (ion f), 140 (ion s), and 124 (ion y).

Deuterium Exchange of Dihydroobscurinervinolone.—The ketoalcohol IIIs (13 mg.) was deuterated by refluxing three times (15 min. each) with deuteriomethanol (1 ml.) and deuterium oxide (0.3 ml.) containing sodium (5 mg.), evaporating at the end of each time. The product (10 mg.), recovered with deuterium oxide (2 ml.) and chloroform (3 × 2 ml.) showed in the mass spectrum only partial dideuteration: *m/e* 444 (17%), 443 (33%), 442 (50%), 429, 428, 427, 426, 425, 424, 415, 414, 413, 369 (M^+ − CH_2OH − CD_2=C=O, not shifted), 274 (ion e), 260 (ion f), 140 (ion s), and 124 (ion y).

Dihydroobscurinervinol (IIIt).[24]—The ketoacetate IIIp (70 mg.) was refluxed (137°) under nitrogen for 3 hr. with diethylene glycol (10 ml.), 1-butanol (3 ml.), and anhydrous hydrazine (1.6 ml.). Then, the condenser was removed, powdered potassium hydroxide (100 mg.) was added, and the reaction mixture was distilled under a stream of nitrogen until the temperature of the mixture was about 205°; the solution was refluxed at this temperature for 1 hr. The total product (55 mg.) was recovered from the cooled reaction mixture with dilute hydrochloric acid, then ammonium hydroxide and methylene chloride. Remethylation of any phenols was accomplished by treatment overnight with dimethyl sulfate (0.1 ml.) and potassium carbonate (500 mg.) in refluxing acetone (10 ml.). The methylated product (40 mg.), recovered with water, evaporation of the acetone, and methylene chloride, showed only one spot on t.l.c., corresponding to purified alcohol IIIt. Chromatographically purified material (eluted from alumina with ethyl acetate–benzene (1:9)) was amorphous, ν_{max} 3380 (w) cm.$^{-1}$; mass spec. *m/e* 428 (M^+), 413, 399, 274 (ion e), 260 (ion f), 244 (ion a), and 140 (ion s).

The *p*-nitrobenzoate was prepared with *p*-nitrobenzoyl chloride and potassium carbonate in benzene, stirring 2 hr. at room temperature; pure material obtained from alumina with benzene and ethyl acetate–benzene (1:19) gave crystals from ether–hexane, m.p. 164–165°, ν_{max} 1735 (s) cm.$^{-1}$.

Dihydroobscurinervidinol (IIIu).—Similar reduction[24] of the ketoacetate IIIq (80 mg.), heating at 205° for only 30 min., gave crude product (90 mg.) which was directly purified in benzene solution on alumina (5 g.). Elution with ethyl acetate–benzene (1:19 and 1:9) gave the pure alcohol IIIu (20 mg.), amorphous, $[\alpha]^{27}D$ −31° (*c* 0.43); ν_{max} 3380 (w) cm.$^{-1}$; λ_{max} 219, 259, and 309 mμ, log ε 4.50, 3.77, 3.50; λ_{min} 247 and 283 mμ, log ε 3.71, 3.15; n.m.r. (see Fig. 7) 6.32 (1H, unsplit; lone aromatic proton), 4.60–3.85 (2H, AB of ABX pattern, *J*'s 10, 3.5 c.p.s.; CH_2 of cyclic ether), 3.90 and 3.80 (6H, two sharp peaks; two aromatic OCH_3), 3.63 (2H, triplet, *J* 7 c.p.s.; CH_2–CH_2–OH), and 1.10 δ (3H, doublet, *J* 6 c.p.s.; N–CH–CH_3); mass spec. *m/e* 414 (M^+), 399, 246 (ion c), and 140 (ion s).

Dihydroneblininol (IIIv).—Similar reduction[24] of the ketoacetate IIIr (20 mg.) gave, after purification on alumina (4 g.), pure alcohol IIIv (11 mg.), ν_{max} 3380 (w) cm.$^{-1}$.

Dihydroobscurinervinane (IIIx).—Dihydroobscurinervinol (8 mg.) was treated 14 hr. at room temperature with *p*-toluenesulfonyl chloride (5 mg.) in pyridine (1 ml.). Work-up with ice, ammonium hydroxide, and methylene chloride gave crude tosylate IIIw (10 mg.), purified by passage in benzene solution through alumina (3 g.). The later benzene eluates and first ethyl acetate–benzene (1:19) eluates contained pure product IIIw (4 mg.); ν_{max} 1370 (s), 1175 (s), 960 (s), no 3380 cm.$^{-1}$; the total amount was reduced for 1 hr. with lithium aluminum hydride (20 mg.) in refluxing ether (5 ml.). Work-up gave pure dihydroobscurinervinane (IIIx, 4 mg.), single spot on t.l.c., well-defined infrared spectrum (with no 3380 cm.$^{-1}$ band); mass spec. *m/e* 412 (M^+), 397, 383, 260 (ion f), with a very weak fragmentation pattern.

Dihydroneblininane (IIIz).—Dihydroneblininol (IIIb, 10 mg.) was treated at room temperature 10 hr. with *p*-toluenesulfonyl chloride (10 mg.) in pyridine (1 ml.). The total product IIIy (11 mg.), recovered with ice, ammonium hydroxide, and methylene chloride and showing a single spot on t.l.c. and ν_{max} 1360 (s), 1180 (s), and 960 (s), no 3380 cm.$^{-1}$, was reduced for 1 hr. with lithium aluminum hydride (20 mg.) in refluxing ether (5 ml.). Recovery gave crude product (6 mg.), which was purified by passage through alumina (3 g.) in benzene–hexane (1:3) solution. Elution with benzene–hexane (2:1) gave pure dihydroneblininane (IIIz, 5 mg.), $[\alpha]^{27}D$ −60° (*c* 0.15); well-defined infrared spectrum with no 3380 cm.$^{-1}$ band; λ_{max} 221, 261, and 296 mμ, log ε 4.48, 3.70, 3.23; λ_{min} 250 and 282 mμ, log ε 3.64, 3.15; mass spec. *m/e* 368 (M^+), 353, 340 (M^+ − CH_2=CH_2), 339, 216 (ion d), 124 (ion z),[15] with a weak fragmentation pattern; n.m.r. (Fig. 7) 6.54 and 6.20 (2H, doublets, *J* 8 c.p.s.; two adjacent aromatic protons), 4.65-3.80 (2H, AB of ABX pattern, *J*'s 10, 3 c.p.s.; CH_2 of cyclic ether), 3.83 (3H, unsplit; aromatic OCH_3), 1.10 (3H, doublet, *J* 6 c.p.s.; N–CH–CH_3), and 0.60 δ (3H, triplet, *J* 6 c.p.s.; C–ethyl group).

Iodoalcohols.—2-Iodo-1-propanol was prepared from ethyl α-bromopropionate (60 g.) by reduction with lithium aluminum hydride in ether at 0° (work-up with water and dilute sulfuric acid), followed by refluxing of the crude bromo alcohol with 1.02 mole equivalents of sodium iodide in acetone for 40 hr.[25]; the over all yield was 17.6 g.(29%), b.p. 65–73° (14 mm.).

2-Iodo-1-butanol was prepared from α-bromobutyric acid (67 g.) by exactly the same procedures; over-all yield 17.2 g. (21%), b.p. 47–49° (1.35 mm.).

Both of these iodides were stored at room temperature in the dark over a small coil of copper wire.

Depropionylaspidoalbine (IVb).—Aspidoalbine (IVa, 450 mg., m.p. 171–173°) was hydrolyzed 1 hr. under nitrogen with reflux-

(24) The reaction conditions are based on unpublished experiments by R. H. Shapiro of this laboratory.

(25) C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1259 (1954).

ing 4 *N* hydrochloric acid; recovery with ammonium hydroxide and chloroform gave the pure deacyl material (465 mg.), highly crystalline but saved as a froth for the following reactions. Crystallization of a sample from benzene afforded material showing m.p. 211–213° dec.; ν_{max} 3550 (sh), 3350 (w) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.62; H, 7.67; N, 7.70.

Iodopropanol Addition to Depropionylaspidoalbine. Alcohols A and B (IVc).—Depropionylaspidoalbine (100 mg.) was sealed into a nitrogen-filled 10-mm. Pyrex tube with 2-iodo-1-propanol (0.18 ml.) and heated 1 hr. in a steam bath (temperature 95°). The total crude product, recovered from the cooled and opened tube with ammonium hydroxide and methylene chloride, was added to alumina (5 g.) in benzene. Elution with benzene (50 ml.) gave only iodopropanol; ethyl acetate–benzene (1:9, 30 ml.) gave isomer A (40 mg.), and ethyl acetate–benzene (1:4, 30 ml. and 1:1, 20 ml.) isomer B (30 mg.) of IVc. The infrared spectra of the two products were essentially identical (ν_{max} 3550 (sh) cm.$^{-1}$), but they differed considerably in t.l.c. mobility (A moving faster).

Cyclization and Reduction. Dihydroobscurinervidinols A and B (22-Epi-IIIu and IIIu).—Isomer B (100 mg.) of the alcohol IVc was dissolved in pyridine (2 ml.) and treated for 1.5 hr. at room temperature with *p*-bromobenzenesulfonyl chloride (80 mg., 1.3 mole equivalents). The crude product (100 mg.), recovered with ice, ammonium hydroxide, and methylene chloride, was directly cyclized for 2 hr. with 1 *N* aqueous sodium hydroxide (1.5 ml.) in refluxing methanol (10 ml.). The crude cyclization product (60 mg.), recovered with dilute hydrochloric acid, evaporation of the methanol, ammonium hydroxide, and methylene chloride, was added to alumina (5 g.) in benzene; the later benzene eluates and first eluates of ethyl acetate–benzene (1:19) contained the crude product (5 mg.), showing only a single spot on t.l.c. This material was directly reduced for 1 hr. with lithium aluminum hydride (25 mg.) in refluxing ether (5 ml.); the product (5 mg.) was rigorously purified by two passes through alumina (3 g. each), eluting with ethyl acetate–benzene (1:1) and pure ethyl acetate. In this fashion there was obtained nearly pure dihydroobscurinervidinol B (IIIu, 1.3 mg.), identical by t.l.c. and color reaction (including a mixture) with natural dihydroobscurinervidinol (IIIu); $[\alpha]^{26}D$ −29° (*c* 0.087); ultraviolet and infrared spectra essentially identical with those of natural material.

An identical cyclization and reduction performed on isomer A (105 mg.) of the alcohol IVc gave dihydroobscurinervidinol A (22-epi-IIIu, 1 mg.), with an infrared spectrum quite different from that of the natural material or of the synthetic isomer B (IIIu).

Iodobutanol Addition to Depropionylaspidoalbine. Alcohols A and B (IVd).—Depropionylaspidoalbine (3 × 100 mg.) was sealed into nitrogen-filled 10-mm. Pyrex tubes with 2-iodo-1-butanol (3 × 0.2 ml.) and heated 2 hr. in a steam bath (temperature 95°). The reaction mixtures were removed from the cooled and opened tubes with ammonium hydroxide and methylene chloride, and the product recovered from the organic layers; the total was added to alumina (30 g.) in benzene. Elution with benzene (300 ml.) gave only iodobutanol; ethyl acetate–benzene (1:19, 300 ml., and 1:9, 50 ml.) gave isomer A (100 mg.) of IVd; further elution with ethyl acetate–benzene (1:9, 250 ml., and 1:4, 100 ml.) yielded isomer B (40 mg.) of IVd. The infrared spectra of the two isomers were essentially identical (ν_{max} 3550 (sh) cm.$^{-1}$).

Cyclization and Reduction. Dihydroobscurinervinol B (IIIt).—Alcohol IVd, isomer B (40 mg.), was dissolved in pyridine (2 ml.), cooled to 0°, and treated with *p*-bromobenzenesulfonyl chloride (30 mg.) in cold pyridine (1 ml.); after standing at 0° for 10 hr., the reaction mixture was poured onto ice and the product (35 mg.) recovered with ammonium hydroxide and methylene chloride. This was directly cyclized for 2 hr. with 1 *N* aqueous sodium hydroxide (0.5 ml.) in refluxing methanol (5 ml.); the crude total product (25 mg.), recovered with water and methylene chloride, was placed in benzene solution on alumina (5 g.). Benzene and ethyl acetate–benzene (1:19) eluted crude product (4 mg.), which was directly reduced 1 hr. with lithium aluminum hydride (25 mg.) in refluxing ether (5 ml.). The product (4 mg.) was rigorously purified on alumina (3 g.); elution with ethyl acetate–benzene (1:1) and ethyl acetate gave fairly pure dihydroobscurinervinol B (IIIt, less than 1 mg.), identical by thin-layer chromatography and color reaction (including a mixture) with natural dihydroobscurinervinol (IIIt); the infrared spectrum was very similar to that of natural material.

Deacetylaspidocarpine (Ic).—Aspidocarpine (Ia, 3.0 g., m.p. 167–169°) was hydrolyzed 2 hr. under nitrogen with refluxing 4 *N* hydrochloric acid (75 ml.); the product (Ic, 3.0 g.), recovered with ammonium hydroxide and methylene chloride, was amorphous, single spot on t.l.c.; ν_{max} 3550 (sh), 3350 (w) cm.$^{-1}$.

Iodopropanol Addition to Deacetylaspidocarpine. Alcohols A and B (Id).—Deacetylaspidocarpine (4 portions of 250 mg. of froth each) was sealed into nitrogen-filled 10-mm. Pyrex tubes with 2-iodo-1-propanol (4 × 0.45 ml.) and heated 2.5 hr. in a steam bath (temperature 95°). The reaction mixtures were removed from the cooled and opened tubes with ammonium hydroxide and methylene chloride, combined, and washed with dilute sodium bisulfite solution; the total product, obtained by evaporation of the methylene chloride solution (and containing some iodopropanol even after pumping at 0.5 mm.), was added to alumina (50 g.) in benzene. The first 20 ml. of benzene eluate contained iodopropanol (500 mg.); further elution with benzene (300 ml.) gave the pure isomer A (335 mg.) of Id. Elution with ethyl acetate–benzene (1:19, 500 ml., and 1:9, 200 ml.) gave isomer B (525 mg.) of Id, contaminated with considerable amounts of isomer A; ethyl acetate–benzene (1:2, 150 ml.) gave starting deacetylaspidocarpine (115 mg.).

The impure isomer B (525 mg.) was repurified on alumina (25 g.). Elution with benzene (150 ml.) gave isomer A (125 mg.), added to the above A (total 460 mg., 44% based on recovered starting material). Further elution with benzene (150 ml.) and ethyl acetate–benzene (1:3, 150 ml.) gave nearly pure isomer B (330 mg., 32% based on recovered starting material). The total yield of desired products was 790 mg. (76%); the infrared spectra of the two isomers were essentially superimposable (ν_{max} 3550 (sh) cm.$^{-1}$), but they were easily distinguished on t.l.c. (A, faster-running, brown spot; B, slower-running, yellow spot); the mass spectra differed only in peak intensities: *m/e* 386 (M^+) and base peak at *m/e* 124 (ion z).

The diacetate of the product Id mixture, prepared with acetic anhydride in pyridine, showed ν_{max} 1770 (s), 1735 (s) cm.$^{-1}$.

Cyclization. Dihydroneblininanes A and B (22-Epi-IIIz and IIIz).—Isomer A (460 mg.) of alcohol Id was dissolved in pyridine (5 ml.), cooled to 0°, and treated with *p*-bromobenzenesulfonyl chloride (395 mg., 1.3 mole equivalents) in cold pyridine (3 ml.). After 2.5 hr. at 0°, the reaction was complete (as judged by t.l.c.). Work-up with ice, ammonium hydroxide, and methylene chloride gave the crude brosylate A (680 mg., ν_{max} 3550 (sh), 1380 (s), 1175 (s), 1010 (s) cm.$^{-1}$; monoacetate (acetic anhydride–pyridine), ν_{max} 1780 (s), no 3550 cm.$^{-1}$), which was treated for 2 hr. under nitrogen with 1 *N* aqueous sodium hydroxide (4.8 ml.) in refluxing methanol (20 ml.). Recovery with dilute hydrochloric acid and evaporation of the methanol, ammonium hydroxide, and methylene chloride gave very crude product (565 mg.), which was added as a benzene solution to alumina (25 g.). The first benzene eluates (30 ml.) contained purified dihydroneblininane A (22-epi-IIIz, 50 mg.), followed by starting brosylate (30 mg.) in the next 30 ml. This product A could be rigorously purified by the use of alumina, adding the substance in hexane–benzene (3:1) and removing the product with hexane–benzene (1:2). The pure material was oily, but exhibited a well-defined infrared spectrum; λ_{max} 222, 258, and 297 mμ, log ε 4.52, 3.80, 3.30; λ_{min} 249 and 282 mμ, log ε 3.78, 3.17; mass spec. *m/e* 368 (M^+), 353, 340 ($M^+ - CH_2CH_2$), 339, 325, 230 (ion h), 216 (ion d), 152 (ion aa),[15] and 124 (ion z),[15] with a strong fragmentation pattern; n.m.r. (see Fig. 7) 6.53 and 6.20 (2H, doublets, *J* 8 c.p.s.; two adjacent aromatic protons), 4.80–3.90 (2H, very broad and low with no discernible splitting; CH_2 of cyclic ether), 3.83 (3H, unsplit; aromatic OCH_3), 1.44 (3H, doublet, *J* 7 c.p.s.; N–CH–CH_3), and 0.60 δ (3H, triplet, *J* 6 c.p.s.; C–ethyl group).

Isomer B of Id was similarly treated with *p*-bromobenzenesulfonyl chloride (285 mg.) in cold pyridine (10 ml.); the crude brosylate B (525 mg., infrared spectrum practically identical with that of the crude brosylate A) was cyclized for 2 hr. under nitrogen with 1 *N* aqueous sodium hydroxide (3.7 ml.) in refluxing methanol (20 ml.). A benzene solution of the crude product (430 mg.) was added to alumina (25 g.). The first benzene eluates (50 ml.) contained purified dihydroneblininane B (IIIz, 50 mg.); further eluates (75 ml.) contained starting brosylate (35 mg.). Rigorous purification of the product was performed exactly as above; the pure synthetic dihydroneblininane B was oily, $[\alpha]^{27}D$ −42° (*c* 1.03); infrared spectrum superimposable upon that of natural dihydroneblininane (IIIz); ultraviolet,

n.m.r., and mass spectra, t.l.c. behavior, and color reaction essentially identical with those of the material obtained by degradation of neblinine (IIe).

Lithium Aluminum Hydride Reduction of O-Methyl-N-depropionylaspidoalbine.[17]—O-Methyl-N-depropionylaspidoalbine (60 mg., m.p. 147–148°) was reduced 1.5 hr. with lithium aluminum hydride (50 mg.) in refluxing ether (10 ml.); the product (65 mg.) was purified on a 22-mm. dry-packed partition column containing 30 ml. of the lower phase of the system hexane–ethylene dichloride–methanol–water (40:20:8:1) on 45 g. of Celite 545. Product A (19-epi-VIa, 6 mg., amorphous) appeared at R_f 0.50; product B (VIa, 52 mg.) appeared at R_f 0.40, and was crystallized from acetone–isopropyl ether to give 24 mg., m.p. 154–155°; mass spec. *m/e* 388 (M^+), 370 ($M^+ - H_2O$), 360 ($M^+ - CH_2{=}CH_2$), 140 (ion s).

Product isomer A showed mass spec. *m/e* 388 (M^+), 387 ($M^+ - 1$) while the above-mentioned peaks occurred at much lower intensity.[17]

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Steroids Containing Ring A Aromatic. VIII. Mechanism of Dienone–Phenol Rearrangement[1]

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Conclusive proof is provided for the mechanism of dienone–phenol rearrangements of steroids. Formation of I proceeds through the migration of the 19-methyl from C-10 to C-1. The route to phenols II is initiated by the rupture of the C-9(10) bond, followed by formation of intermediate III. Subsequently, migration and attachment of C-9 to the C-4 of the dienone occurs.

The versatility[3] and biosynthetic implications[4] are probably the reasons for the continuous interest in the chemistry of the dienone–phenol rearrangements. By varying reaction conditions, acid catalysts, or substituents on the substrate, either phenols of type I or II are obtained as predominant products[5] from the rearrangement of steroidal 1,4-dien-3-ones. It is usually assumed that *meta* derivatives I are formed by a shift of the C-10 methyl to C-1 and *para* derivatives II through intermediate III. Though a large body of indirect evidence supporting these assumptions was accumulated in recent years, unequivocal proof was lacking. It was therefore considered relevant to establish conclusively the pathways of the rearrangement. The approach we chose was to rearrange 4-C^{14}-labeled steroidal dienones, degrade the appropriate ring A phenols, and locate the tracer.

In considering possible pathways leading from dienones to 3-hydroxy-1-methyl-1,3,5(10)-trienes, an alternative route[6] can be visualized in addition to a C-10 to C-1 shift of the angular methyl. If the 19-methyl migrates to C-5 after the initial protonation of the carbonyl, formation of intermediate IV could occur. Subsequent migration of the C-6 bond rather than the C-9 would yield phenol I, which would contain the tracer at C-2. Should the C-10 to C-1 shift of the methyl occur, the distribution of ring A atoms in both the dienone and the phenol would remain the same. Obviously by utilizing a 4-C^{14}-dienone, the problem lends itself to a facile solution. All that is required is to locate the tracer in the *m*-phenol I. Since the 3-hydroxy-1-methyl-1,3,5(10)-trienes can be obtained from both the 1,4-dien-3-one and 1,4,6-trien-3-one, it was deemed necessary to investigate the mechanism in both cases.

For the present studies 4-C^{14}-testosterone acetate (Va) was dehydrogenated[7,8] to yield the 1,4-dienone Vb. Saponification of Vb gave Vc which was oxidized to Vd. The dienedione Vd was treated with aqueous acetic acid–hydrochloric acid[9] giving a mixture of *p*-(1,4) and *m*-(1,3) phenols from which Ia was obtained after saponification. Alternatively, 4-C^{14}-testosterone acetate (Va) was converted in two steps[8,10] to the 1,4,6-trien-3-one Ve which was saponified and oxidized to Vf. The trienedione Vf was rearranged with acetic anhydride–*p*-toluenesulfonic acid.[11] The obtained methylphenol acetate Ib was reduced catalytically, then saponified to provide Ia. The phenols Ia, obtained through the two routes, were converted *via* Birch reduction of their methyl ethers to 17β-hydroxy-1α-methylestr-4-en-3-one[12] (VIa). Ozonolysis of the acetates VIb provided formic acid[13,14] derived from C-4. Subsequently, the formic acid was oxidized to carbon dioxide, which was isolated as barium carbonate. From the nonvolatile ozonization residue the lactol[15] VII was recovered. The distribution of radioactivity in the products is summarized in Table I.

It is apparent that in both cases the radioactivity was located at C-4 of 17β-acetoxy-1α-methylestr-4-en-3-one(VI), independent of whether it was derived from dienone Vd or trienone Vf. Thus, it can be concluded with certainty that in both cases the rear-

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