2-ACYLINDOLE ALKALOIDS

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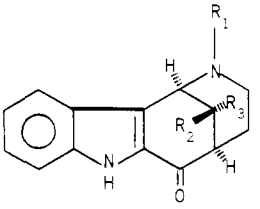
ABSTRACT.—The occurrence, structures, chemistry, and biosynthesis of the 2-acylindole alkaloids are discussed, and a glossary of the presently known members of this class is presented.

INTRODUCTION.—The 2-acylindole alkaloids comprise a relatively small but important class of alkaloids which are important not only in their own right but also as constituents of a large class of bis-indole alkaloids. Since the publication of the last reviews of these alkaloids (1–5) a number of new members of the class with different carbon skeletons have been discovered, and the stereochemistry of some members has been clarified. In this review the literature has been covered to the end of 1979, with some additional coverage of later publications where possible. Earlier work which is covered adequately in the reviews cited is not discussed further, and primary attention is given to the more recent developments in the field.

OCCURRENCE.—The 2-acylindole alkaloids occur in a variety of apocynaceous plants and have been obtained from many genera of the subtribe *Tabernaemontinae*. The predominant genera to date have been *Voacanga*, *Peschiera*, *Gabunia*, *Ochrosia*, *Tabernaemontana* = *Ervatamia*, *Hazunta*, and *Hunteria*.

STRUCTURE AND STEREOCHEMISTRY.—The 2-acylindole alkaloids can be classified on the basis of the size of ring containing both the carbonyl group and the non-indolic nitrogen atom. On this basis, the smallest ring is the eight-membered ring of the dasicarpidone skeleton (**1**), while the alkaloid ervitsine (**2**) is the sole current representative of 2-acylindole alkaloids with a nine-membered ring.



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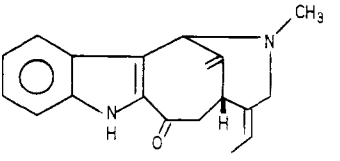

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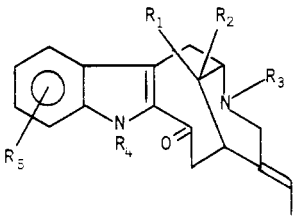
Alkaloids with a ten-membered ring are relatively common, and vobasine, the first 2-acylindole alkaloid to be investigated extensively, belongs to this class, having the general structure **3**. In some alkaloids of this class the compound exists largely or exclusively as the carbinolamine form **4**, while dihydro-derivatives have the structure **5**. Two unusual members of this series are picraphylline (**6**, R = H) and its dimethoxy derivative, and burnamicine (**7**).



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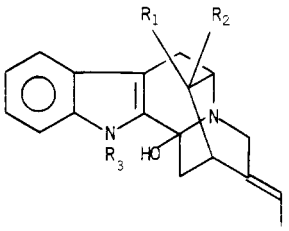

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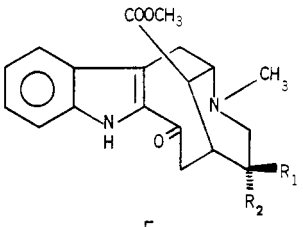

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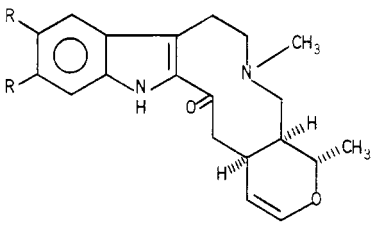

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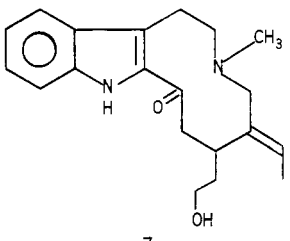

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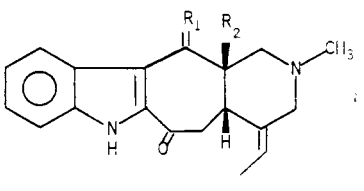
The fourth major group of 2-acylindole alkaloids was discovered more recently and consists of compounds in which the non-indolic nitrogen and the carbonyl group are both part of an eleven-membered ring. The first member of this group to have its structure elucidated was ervatamine, and the ervatamine alkaloids have the general structures **8** and **9**.



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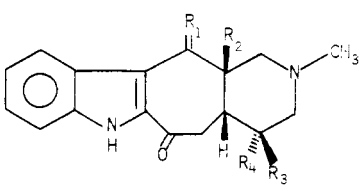

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The following tabulation lists the currently known 2-acylindole alkaloids and provides details of their occurrence, structures, and spectra. All uv data are in nm, and log ϵ values are quoted between parentheses. Ir frequencies are in cm^{-1}. Within each class, the compounds are arranged according to their molecular formulae. Unless otherwise stated, uv spectra were obtained in 95% ethanol, infrared spectra in chloroform, and proton magnetic resonance spectra in deutero-chloroform. The notation (N.S.) indicates that the conditions were not stated in the original reference. Spectroscopic data were obtained from the first reference cited for each compound unless otherwise stated.

The second table lists the plants from which 2-acylindole alkaloids have been obtained, together with their contained alkaloids.

TABLE 1. 2-Acylindole alkaloids.

I DASICARPIDONE CLASS

1A N-DEMETHYLDASICARPIDONE

$C_{16}H_{18}N_2O$: 254
STRUCTURE: **1**, R_1=H, R_2=CH_2CH_3, R_3=H (74,76)
MP: 208–210° ($CHCl_3$) (74)
UV: 238(4.15), 317(4.23)
IR: 3450, 3280, 1647
MS: 254(M^+), 225, 211, 197, 184, 169, 157, 130
SOURCE: *Aspidosperma dasycarpon* (74)

1B DASICARPIDONE

$C_{17}H_{20}N_2O$: 268
STRUCTURE: **1**, R_1=CH_3, R_2=CH_2CH_3, R_3=H (74,76)
MP: amorph.
$[\alpha]_D$: +64.7 (c=1.02, $CHCl_3$)
UV: 237(4.15), 316(4.29)
IR: 3410, 1640
^{1}H NMR: 10.3(1H,bd,s), 7.00–7.90(4H,m), 4.25(1H,d), 2.34(3H,s), 0.88 (3H,t).
MS: 268(M^+), 239, 225, 211, 198, 183 (75)
SOURCE: *Aspidosperma dasycarpon* (74)

1C 3-EPIDASICARPIDONE

$C_{17}H_{20}N_2O$: 268
STRUCTURE: **1**, R_1=CH_3, R_2=H, R_3=CH_2CH_3 (76)
MP: amorph.
UV: 237, 316
IR: 3380, 1640
^{1}H NMR (N.S.): 1.08(3H,t)
MS: identical with that of dasicarpidone
SOURCE: *Aspidosperma subincanum* (76)

II ERVITSINE CLASS

2 ERVITSINE

$C_{19}H_{20}N_2O$: 292
STRUCTURE: **2**, (57)
MP: 176–177° (MeOH)
$[\alpha]_D$: −160°, (c=1%, $CHCl_3$)
UV: 236(4.34), 318(4.44)
IR (NS): 1630
^{1}H NMR (NS): 9.27(bd,s), 5.30(1H,q), 5.17(1H,s), 5.16(1H,s), 5.03(1H,s), 2.30 (3H,s), 1.63(3H,d)
MS: 292(M^+)
SOURCE: *Pandaca boiteaui* (57,55)

III VOBASINE CLASS

3A PERIVINE

$C_{20}H_{22}N_2O_3$: 338
STRUCTURE: **3**, R_1=$COOCH_3$, R_2=R_3=R_4=R_5=H (9)
MP: 180–181° (7), 218–221° (CH_3OH) (8)
$[\alpha]_D$: −121.4° (c=1,$CHCl_3$) (8)
UV: 228(4.26), 238(4.19), 316(4.27) (4,6)
IR: 2940, 1725, 1650 (6)
^{1}H NMR: 7.7(1H,d), 7.4–6.7(3H,c), 5.38 (1H,q), 2.64(3H,s), 1.70(3H,d), (10,12)
MS: 338(M^+), 321, 295, 279, 237, 185, 184, 172, 166, 130 (10)
SOURCES: *Catharanthus roseus* (=Vinca rosea) (7,8), *Catharanthus lanceus* (6), *Gabunia eglandulosa* (11), *Voacanga thouarsii* (10)

3B 16-EPIVOBASINIC ACID

$C_{20}H_{22}N_2O_3$: 338
STRUCTURE: **3**, R_1=H, R_2=COOH, R_3=CH_3, R_4=R_5=H (64)
MP: 295° (dec.) (C_2H_5OH)
UV: 238(4.12), 316(4.30)
IR (KBr): 3105, 1650, 1610, 753
^{1}H NMR: 7.77–6.88(4H,m), 5.93(1H,q), 3.00(3H,s), 1.68(3H,d)
MS: 338(M^+), 293, 180, 166, 158, 122
SOURCE: *Tabernaemontana psychotrifolia* (64)

3C AFFININE

$C_{20}H_{24}N_2O_2$: 324
STRUCTURE: **3**, R_1=CH_2OH, R_2=H, R_3=CH_3, R_4=R_5=H (13,14)
MP: 265° (dec) (CH_3OH-$CH_3COOC_2H_5$)
$[\alpha]_D$ (HCl): −105.4° (c=0.5, MeOH)
UV: 238(4.18), 318(4.34)
IR (Nujol): 1645
SOURCE: *Pescheira affinis* (13,14)

3D 16-EPIAFFININE

$C_{20}H_{24}N_2O_2$: 324
STRUCTURE: **3**, R_1=H, R_2=CH_2OH, R_3=CH_3, R_4=R_5=H (15)
MP: 152–154° (ether-pentane)
$[\alpha]^{23}_D$: −190° (c=0.95,$CHCl_3$)
UV: 209(4.35), 238(4.19), 318(4.26)
IR: 3571, 3413, 3289, 2786, 1642

TABLE 1. *Continued.*

^{1}H NMR: 9.79, 7.64, 7.45–6.95(3H), 5.42 (1H,q), 3.93, 3.75–2.35, 2.47(3H,s), 1.85 (1H), 1.62(3H,d)
MS: 324(M^+), 306, 263, 172, 166, 152, 122
SOURCE: *Pleiocarpa talbotii* (15)

3E PERIFORMYLINE

$C_{21}H_{22}N_2O_4$: 366
STRUCTURE: **3**, R_1=$COOCH_3$, R_2=H, R_3=CHO, R_4=R_5=H (16,17)
MP: 206–209° (CH_3OH) (17)
UV: 240(4.22), 315(4.32) (17)
IR: 1650 (17)
^{1}H NMR: 9.4(1H), 8.2(1H,d), 2.65, 2.55 (3H), 1.72(3H,d) (12,16)
MS: 366(M^+), 194 (16,17)
SOURCE: *Catharanthus lanceus* (17)

3F VOBASINE

$C_{21}H_{24}N_2O_3$: 352
STRUCTURE: **3**, R_1=$COOCH_3$, R_2=H, R_3=CH_3, R_4=R_5=H (18,22)
MP: 111–113° (ether) (18)
[α]D: −158.8° (c=1,$CHCl_3$) (18); −148.3° (c=1,MeOH) (19)
UV (CH_3OH): 239(4.19), 315(4.27) (18)
IR (CH_2Cl_2): 3440, 2780, 1730, 1650 (18)
^{1}H NMR: 9.2(1H), 7.64(1H,d), 7.5–7.0 (3H,c), 5.44(1H,q), 2.68(3H,s), 2.64(3H,s), 1.78(3H,d) (10,12,20)
^{13}C NMR: (23)
MS: 352(M^+), 293, 194, 180, 158, 122 (18,21)
SOURCES: *Voacanga africana* (19), *Peschieira affinis* (13), *Gabunia eglandulosa* (11), *Pandaca minutiflora* (84), *Pagiantha cerifera* (86), *Peschiera laeta* (87), *Hazunta modesta* var. *modesta* subvar. *montana* (90), *H. modesta modesta* var. *brevituba* (91), *H. modesta modesta* var. *divaricata* (91), *Voacanga thouarsii* (10)

3G N-METHYL-16-EPIAFFININE

$C_{21}H_{26}N_2O_2$: 338
STRUCTURE: **3**, R_1=H, R_2=CH_2OH, R_3=R_4=CH_3, R_5=H (24)
MP: 208–210° (CH_3OH)
[α]D: −243° (c=0.05,$CHCl_3$)
UV (CH_3OH): 240(4.08), 317(4.07)
IR: 1635
^{1}H NMR: 7.72(1H,d), 7.48–7.05(3H,m), 5.49(1H,q), 4.07(3H,s), 2.57(3H,s), 1.72 (3H,dd)
MS: 338(M^+), 320, 152
SOURCE: *Tabernaemontana accedens* (24)

3H PELIRINE

$C_{21}H_{26}N_2O_3$: 354
STRUCTURE: **3**, R_1,R_2=H,CH_2OH, R_3=CH_3, R_4=H, R_5=OCH_3 (1) (tentative)
MP: 130–131° (CH_3OH–H_2O) (25)
[α]D: −121° (c=1.0,EtOH) (25)
UV: 328(4.33) (4)
IR: 1635 (1)
SOURCE: *Rauwolfia perakensis* (25)

3I OCHROPAMINE

$C_{22}H_{26}N_2O_3$: 366
STRUCTURE: **3**, R_1=$COOCH_3$, R_2=H, R_3=R_4=CH_3, R_5=H (26)
MP: 134° (CH_3OH–H_2O)
[α]D: −158° (c=1.0, CH_3COCH_3)
UV: 243(4.27), 315(4.25)
IR: 1730, 1647, 1623
^{1}H NMR (N.S.): 7.3(3H,c), 5.43(1H,q), 4.05(3H,s), 2.58(6H,s), 1.70(3H,d) (26,12)
^{13}C NMR: (23)
SOURCE: *Ochrosia poweri* (26)

3J VOACAFRICINE

$C_{22}H_{26}N_2O_4$: 382
STRUCTURE: **3**, R_1, R_2=$COOCH_3$, CH_2OH, R_3=CH_3, R_4=R_5=H (1)
MP: 196–198° (ether–CH_2Cl_2) (27)
UV (HCl in CH_3OH): 238(4.27), 315(4.35) (27)
IR (HCl in KBr): 3330, 1739, 1724, 1645, 1543, 1466, 1342, 752 (27)
SOURCE: *Voacanga africana* (27)

3K VINCADIFFINE

$C_{22}H_{26}N_2O_4$: 382
STRUCTURE: **3**, R_1=$COOCH_3$, R_2=CH_2OH, R_3=CH_3, R_4=R_5=H
MP: 230° (N.S.) (29); 193–197° (CH_3-$COOC_2H_5$) (28)
[α]D: −121° ($CHCl_3$) (29)
UV (N.S.): 242(4.17), 320(4.18) (2)
IR (N.S.): 1646, 1616, 1580, 1532 (29)
^{1}H NMR: 5.53(1H,q), 2.57(6H,s), 1.73 (3H,d) (28,29,12)
MS: 382(M^+), 364, 351, 180 (29)
SOURCE: *Vinca difformis* (28)

3L VOACAFRINE

$C_{22}H_{26}N_2O_4$: 382
STRUCTURE: **3**, R_1, R_2=$COOCH_3$, CH_2OH, R_3=CH_3, R_4=R_5=H (1)
MP: 135–137° (27)
[α]D (HCl): −107° (c=1%, MeOH) (27)
UV (HCl in CH_3OH): 240(4.23), 315(4.32) (27)
IR (HCl in KBr): 3330, 1724, 1645, 1538, 1466, 1342, 746 (27)
SOURCE: *Voacanga africana* (27)

3M OCHROPINE

$C_{23}H_{28}N_2O_4$: 396
STRUCTURE: **3**, R_1=$COOCH_3$, R_2=H, R_3=R_4=CH_3, R_5=11-OCH_3 (26)
MP: 140° (CH_3OH–H_2O)
[α]D: −229° (c=1, CH_3COCH_3)
UV: 236(4.16), 258(3.90), 337(4.35)
IR: 1730, 1647, 1626
^{1}H NMR (N.S.): 5.50(1H,q), 3.97(3H,s), 3.86(3H,s), 2.68(3H,s), 2.56(3H,s), 1.70 (3H,d) (26,12)
SOURCE: *Ochrosia poweri* (26)

TABLE 1. *Continued.*

IV VOBASINE CLASS: CARBINOLAMINE FORM

4A N-DEMETHYL-16-EPIACCEDINE

$C_{19}H_{22}N_2O_2$: 310
STRUCTURE: **4**, $R_1=CH_2OH$, $R_2=R_3=H$ (30)
MP: 170–172° (N.S.)
$[\alpha]_D$: +50° (c=0.06, $CHCl_3$)
UV (CH_3OH): 224(4.25), 282(3.86), 290 (3.79), 315(3.15)
^1H NMR: 9.56 and 9.37 (1H total)
MS: 310(M^+), 309, 293, 279, 185, 184
SOURCE: *Tabernaemontana accedens* (30)

4B ACCEDINE

$C_{20}H_{24}N_2O_2$: 324
STRUCTURE: **4**, $R_1=H$, $R_2=CH_2OH$, $R_3=CH_3$ (24)
MP: 148–149° (CH_3OH)
$[\alpha]_D$: +72° (c=0.096, $CHCl_3$)
UV (CH_3OH): 226(4.52), 284(3.85)
IR: 3600
^1H NMR: 7.1–6.6(3H,c), 6.65(1H,d), 5.29 (1H,q), 4.15(1H,bd d), 3.51(3H,s), 3.34 (2H,d), 3.02(1H,bd d), 2.43–2.77(3H,c), 2.21(1H,d), 1.79(2H,d), 1.53(3H,d)
MS: 324(M^+), 199, 198
SOURCE: *Tabernaemontana accedens* (24)

4C VOACARPINE

$C_{21}H_{24}N_2O_4$: 368
STRUCTURE: **4**, $R_1=COOCH_3$, $R_2=CH_2OH$, $R_3=H$ (31,32)
MP: 227–228° (31)
$[\alpha]_D$: +43.5° (c=0.4, CH_3OH) (31)
UV (CH_3OH): 225(4.50), 251(3.50), 282 (3.80), 292(3.71) (31)
IR (KBr): 1730, 735 (31)
^1H NMR (TFAA): 9.5(1H), 7.0(4H,m), 5.86(1H,q), 3.1(3H,s), 1.79(3H,d) (31)
MS: 368(M^-), 351, 337, 309, 265, 185, 184 (31)
SOURCES: *Voacanga chalotiana* (31), *Hazunta modesta modesta* var. *brevituba* (91)

4D 3-HYDROXYVOACHALOTINE

$C_{22}H_{26}N_2O_4$: 382
STRUCTURE: **4**, $R_1=CH_2OH$, $R_2=COOCH_3$, $R_3=CH_3$ (82)
MP: 247° ($CH_3COOC_2H_5$)
$[\alpha]_D$: +9° (c=1, $CHCl_3$)
UV (CH_3OH): 229(4.62), 286(3.88)
IR (KBr): 3450, 1740
^1H NMR: 7.4–6.4(4H,m), 5.24(1H,bq), 4.36 (1H,dd), 4.23(1H,bd), 3.61(3H,s), 3.32 (3H,s), 3.18(2H,s), 3.07(1H,dd), 2.96(1H, dd), 2.71(1H,dd), 1.86(1H,dd), 1.72(1H, dd), 1.54(3H,d)
MS: 382(M^+), 365, 351, 323, 279, 251, 199, 158, 144, 143
SOURCE: *Voacanga chalotiana* (82,83)

V DIHYDROVOBASINE CLASS

5A DREGAMINE

$C_{21}H_{26}N_2O_3$: 354
STRUCTURE: **5**, $R_1=H$, $R_2=CH_2CH_3$ 17,33,34)
MP: 186–205° (dec.) (35)
$[\alpha]_D$: −93.1° (c=1, $CHCl_3$) (35)
UV: 239(4.18), 316(4.27) (35)
IR (KBr): 1653, 1730, 1245 (35)
^1H NMR (C_6D_6): 10.01(1H,bd s), 6.96–7.68 (4H,m), 3.98(1H,dt), 2.56(3H,s), 2.34 (3H,s), 1.62(1H,m), 0.78(3H,t) (92)
^{13}C NMR: (23)
MS: 354(M^+), 322, 292, 279, 182, 164, 158, 152 (92)
SOURCES: *Voacanga dregei* (35), *Tabernaemontana coronaria* (36,37), *Ervatamia orientalis* (34), *Pandaca caducifolia* (38), *Pandaca calcarea* (80), *T. elegans* (85), *P. debrayi* (80), *Muntafara sessilifolia* (81), *Hazunta modesta* var. *modesta* subvar. *montana* (90), *H. modesta modesta* var *brevituba* (91), *H. modesta modesta* var. *divaricata* (91)

5B TABERNAEMONTANINE

$C_{21}H_{26}N_2O_3$: 354
STRUCTURE: **5**, $R_1=CH_2CH_3$, $R_2=H$ (18,33,34)
MP: 207–209° (ether), 217–219° (CH_3OH) (36)
$[\alpha]_D$: −57.5° (c=1, $CHCl_3$) (36)
UV: 236(4.21), 310(4.26) (39)
IR (KBr): 3300, 1724, 1637, 1253, 1205 (66)
^1H NMR: 2.58(3H,s), 2.53(3H,s), 0.96 (3H,t) (66)
^{13}C NMR: (23)
MS: 354(M^+), 322, 279, 196, 183, 182, 172, 164, 158, 152, 130, 122 (66)
SOURCES: *Tabernaemontana coronaria* (36, 37,41,42), *Tabernaemontana divaricata* (39), *Ervatamia orientalis* (34), *Ervatamia pandacaqui* (40), *T. elegans* (85), *Muntafara sessilifolia* (81), *Tabernaemontana mucronata* (43), *Hazunta modesta* var. *modesta* subvar. *montana* (90), *H. modesta modesta* var. *brevituba* (91), *H. modesta modesta* var. *divaricata* (91)

VI PICRAPHYLLINE CLASS

6A PICRAPHYLLINE

$C_{22}H_{26}N_2O_4$: 382
STRUCTURE: 6, R=H (45,46)
MP: 225° (45)
$[\alpha]_D$: −37° (45)
UV (N.S.): 238(4.14), 312(3.98) (46)
IR (N.S.): 3355, 1655, 1630, 755 (46)
^1H NMR (N.S.): 9.05(1H,bd), 7.55(1H,s), 3.72(3H,s), 2.00(3H,s), 1.30(3H,d) (46)
MS: 382(M^+), 284, 228, 224, 210, 209, 185, 184, 170, 169, 156, 154, 144, 143, 129, 115 (46)
SOURCE: *Picralina nitida* (45)

TABLE 1. *Continued.*

6B DIMETHOXYPICRAPHYLLINE
$C_{24}H_{30}N_2O_6$: 442
STRUCTURE: **6**, R=OCH_3 (77)
MP: 185° (ether)
$[\alpha]_D$: −50° (c=1, $CHCl_3$)
UV: 214(4.46), 342(4.20)
IR (N.S.): 1700, 1625
^1H NMR (N.S.): 7.45(1H,s), 6.90(1H,s), 6.76(1H,s), 3.91(6H,s), 3.69(3H,s), 2.03 (3H,s), 1.30(3H,d)
MS: 442(M^+), 224, 218, 210, 209, 204
SOURCE: *Ochrosia balansae* (77)

VII BURNAMICINE CLASS

7 BURNAMICINE
$C_{20}H_{26}N_2O_2$: 326
STRUCTURE: **7** (44)
MP: 198–200°
$[\alpha]_D$: −281°
UV (N.S.): 309–312 (4.16)
IR (KBr): 1630
^1H NMR: Signals for four aromatic protons, an ethylidene group, and an N-methyl group
MS: 326(M^+), 308, 210, 168, 144, 143, 130
SOURCE: *Hunteria eburnea* (44)

VIII DEHYDROERVATAMINE CLASS

8A 6-OXOMETHUENINE
$C_{19}H_{20}N_2O_3$: 308
STRUCTURE: **8**, R_1=O, R_2=H (47)
MP: >260°
$[\alpha]_D$: −15° (c=1, C_5H_5N)
UV: 227(4.31), 260(4.29), 336(4.15)
IR (Nujol): 1670, 1615
^1H NMR: 9.6(1H,bd s), 7.2–7.4(4H), 5.5 (1H,q), 1.7(3H,d)
MS: 308(M^+), 291, 171, 136, 122
SOURCE: *Hazunta modesta* var. *methuenii* (47)

8B METHUENINE
$C_{19}H_{22}N_2O$: 294
STRUCTURE: **8**, R_1=H_2, R_2=H (47)
MP: 205° (MeOH)
$[\alpha]_D$: +21° (c=1%, $CHCl_3$)
UV: 238(4.14), 314(4.29)
IR (Nujol): 1645, 3300
^1H NMR: 9.1(1H,bd s), 7–7.8(4H), 5.4 1H,d), 2.32(3H,s), 1.5(3H,d)
MS: 294(M^+), 136, 130, 122
SOURCES: *Hazunta coffeoides* (47), *H. costata* (47), *H. membranacea* (47), *H. membranacea* forma *pilifera* (47), *H. modesta* var. *methuenii* (47), *H. modesta* var. *modesta* (47), *H. silicicola* (47), *Pandaca boiteaui* (55), *H. modesta modesta* var. *brevituba* (91), *H. modesta modesta* var. *divariacata* (91), *H. modesta* var. *modesta* subvar. *montana* (90)

8C 16-EPIMETHUENINE
$C_{19}H_{22}N_2O$: 294
STRUCTURE: **8**, R_1=H_2, R_2=αH (91)
SOURCES: *Hazunta modesta modesta* var. *divaricata* (91), *H. modesta modesta* var. *brevituba* (91)

8D 19-DEHYDROERVATAMINE
$C_{21}H_{24}N_2O_3$: 352
STRUCTURE: **8**, R_1=H_2, R_2=$COOCH_3$ (48)
MP: 198–200° (dec) (ether) (49)
$[\alpha]_D$: +53° (c, 1.0) (48,49)
UV: 242(4.11), 315(4.28) (48,49)
IR (CS_2): 3450, 1740, 1650, 750 (48,49)
^1H NMR: 5.44(1H,q), 3.56(3H,s), 2.27 (3H,s), 1.58(3H,d) (48,49)
MS: 352(M^+), 337, 323, 293, 194, 180, 172, 166, 130 (48,49)
SOURCES: *Ervatamia orientalis* (49), *Pandaca boiteaui* (55)

IX ERVATAMINE CLASS

9A 6-OXOSILICINE
$C_{19}H_{22}N_2O_2$: 310
STRUCTURE: **9**, R_1=O, R_2=H, R_3=H, R_4=CH_2CH_3 (47,50–52)
MP: >260°
$[\alpha]_D$: −40° (c=1, C_5H_5N)
UV: 227(4.28), 260(4.25), 335(4.12)
IR (Nujol): 1670, 1615
^1H NMR (pyridine): 12.6(1H,bd s), 7.22 and 7.4(4H,c), 2.3(3H,s), 0.95(3H,t)
^{13}C NMR: (52)
MS: 310(M^+), 293, 171, 138, 124
SOURCES: *Hazunta silicicola* (47), *H. modesta* (52), *H. modesta* var. *modesta* subvar. *montana* (90), *H. modesta modesta* var. *divaricata* (91), *H. modesta modesta* var. *brevituba* (91)

9B 16-EPI-6-OXOSILICINE
$C_{19}H_{22}N_2O_2$: 310
STRUCTURE: **9**, R_1=O, R_2=αH, R_3=H, R_4=CH_2CH_3 (90)
SOURCES: *Hazunta modesta* var. *modesta* subvar. *montana* (90)

9C SILICINE
$C_{19}H_{24}N_2O$: 296
STRUCTURE: **9**, R_1=H_2, R_2=H, R_3=H, R_4=CH_2CH_3 (47,53)
MP: 112°(47), 99–100°(52) (MeOH)
$[\alpha]_D$: −18° (c=1%, $CHCl_3$) (47) −16° (c=0.5, $CHCl_3$) (52)
UV: 239(4.18), 314(4.35) (47)
IR (Nujol): 3300, 1645 (47)
^1H NMR: 9.1(1H,bd s), 2.25 (3H,s), 0.95 (3H,t) (47)
^{13}C NMR: (52)
MS: 296(M^+), 138, 130, 124 (47)
SOURCES: *Hazunta coffeoides* (47), *H. costata* (47), *H. membranacea* (47), *H. membranacea* forma *pilifera* (47), *H. modesta* var. *methuenii* subvar. *methuenii* (47), *H. modesta* var. *modesta* subvar. *modesta* (47), *H. modesta* var. *modesta*

TABLE 1. *Continued.*

subvar. *montana* (90), *H. silicicola* (47), *H. modesta* (52), *Rauwolfia discolor* (54), *H. modesta modesta* var. *brevituba* (91), *H. modesta modesta* var. *divaricata* (91)

9D 20-EPISILICINE
$C_{19}H_{24}N_2O$: 296
STRUCTURE: **9**, $R_1=H_2$, $R_2=H$, $R_3=CH_2CH_3$, $R_4=H$ (47,38)
MP: 190° (97), 153° (38) (MeOH)
$[\alpha]_D$: +20° ($CHCl_3$) (38)
UV: 239(4.23), 314 (4.33)
IR (Nujol): 3380, 1645, 1580, 1545 (38,47)
^1H NMR: 9.05(1H,bd s), 7.23–7.75(4H), 2.28(3H,s), 0.87(3H,t) (47)
MS: 296(M^+), 267, 253, 238, 224, 210, 197, 184, 168, 158, 138, 130, 124, 108, 98 (38)
SOURCES: *Pandaca caducifolia* (33), *Hazunta modesta* var. *methuenii* subvar. *methuenii* (47)

9E ERVATAMINE
$C_{21}H_{26}N_2O_3$: 354
STRUCTURE: **9**, $R_1=H_2$, $R_2=COOCH_3$, $R_3=CH_2CH_3$, $R_4=H$ (48,33,56)
MP: 92–98° (MeOH) (48,49)
$[\alpha]_D$: −3.7° (c=2.1) (48,49)
UV: 238(4.14), 312(4.18) (48,49)
IR (CS_2): 3450, 1730, 1640, 750 (48,49)
^1H NMR: 9.4(1H,bd s), 7.0–7.8(4H), 3.69 (2H,s), 3.48(3H,s), 2.28(3H,s) (48,49)
MS: 354(M^+), 322, 295, 224, 210, 196, 195, 182, 130 (48,49)
SOURCE: *Ervatamia orientalis* (49)

9F 20-EPIERVATAMINE
$C_{21}H_{26}N_2O_3$: 354
STRUCTURE: **9**, $R_1=H_2$, $R_2=COOCH_3$, $R_3=H$, $R_4=CH_2CH_3$ (48)
MP: 185–7° (dec) (ether–light petrol) (48,49)
$[\alpha]_D$: −22° (c=1.1) (48,49)
UV: 239(4.00), 318(4.11) (48,49)
IR (CS_2): 3445, 3280, 1735, 1655, 750 (48,49)
^1H NMR: 3.58(3H,s), 2.31(3H,s) (48,49)
MS: 354(M^+), 322, 295, 224, 210, 182, 180, 130 (48,49)
SOURCE: *Ervatamia orientalis* (49)

The chemical degradations leading to the assignment of structure **3F** to vobasine have been published (18) and summarized (1, 3) and will thus not be discussed further. The original assignments of configuration to the ethyl side chains of dregamine (**5A**) and tabernaemontanine (**5B**) have, however, been reversed. The original assignments were made on the basis of the alleged comparative facility with which the methoxycarbonyl groups underwent epimerization (18). A reinvestigation of this subject led to the conclusion that dregamine does

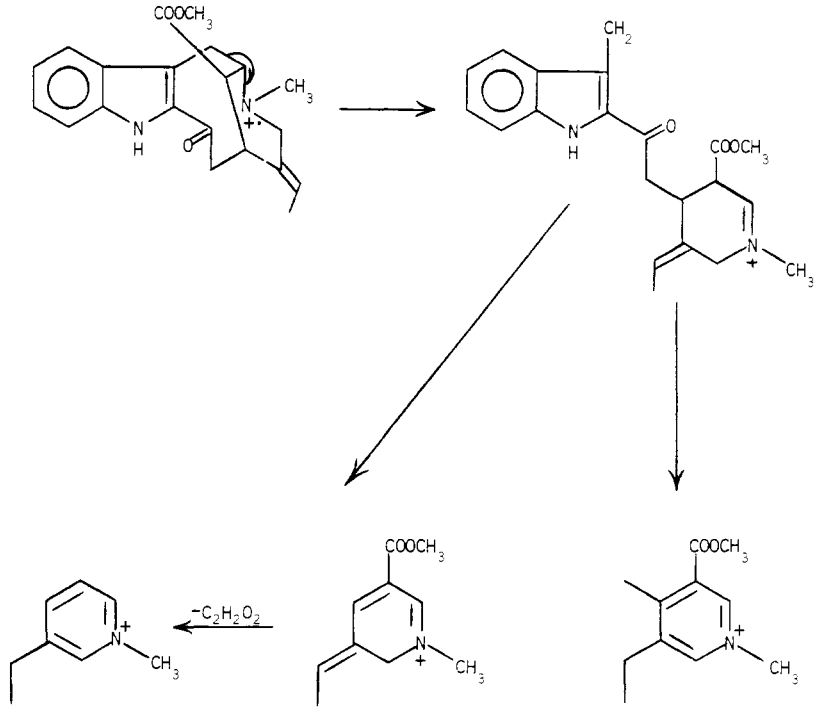
TABLE 2. Plant sources of 2-acylindole alkaloids.

Plant	*Alkaloids*	*Plant*	*Alkaloids*
Aspidosperma dasycarpon	1A, 1B	*P. caducifolia*	5A, 9D
A. subincanum	1C	*P. calcarea*	5A
Catharanthus lanceus	3A, 3E	*P. debrayi*	5A
C. roseus	3A	*P. minutiflora*	3F
Ervatamia orientalis	5A, 5B, 8D, 9E, 9F	*Pescheira affinis*	3C, 3F
		P. laeta	3F
E. pandacaqui	5B	*Picralina nitida*	6A
Gabunia eglandulosa	3A, 3F	*Pleiocarpa talbotii*	3D
H. coffeoides	9B, 9C	*Rauwolfia perakensis*	3F
H. costata	8B, 9C	*R. discolor*	9C
H. membranacea	8B, 9C	*Tabernaemontana accedens*	3G, 4A, 4B
Hazunta modesta	3F, 4C, 5A, 5B, 8A, 8B, 9A, 9B, 9C, 9D,	*T. coronaria*	5A, 5B
		T. divaricata	5B
		T. elegans	5A, 5B
H. silicicola	9B, 9A, 9C	*T. mucronata*	5B
Hunteria eburnea	7	*T. psychotrifolia*	3B
Muntafara sessilifolia	5A, 5B	*Vinca difformis*	3K
Ochrosia balansae	6B	*Voacanga africana*	3F, 3J, 3L
O. poweri	3I, 3M	*V. chalotiana*	4C, 4D
Pagiantha cerifera	3F	*V. dregei*	5A
Pandaca boiteaui	2, 8B, 8D	*V. thouarsii*	3A, 3F

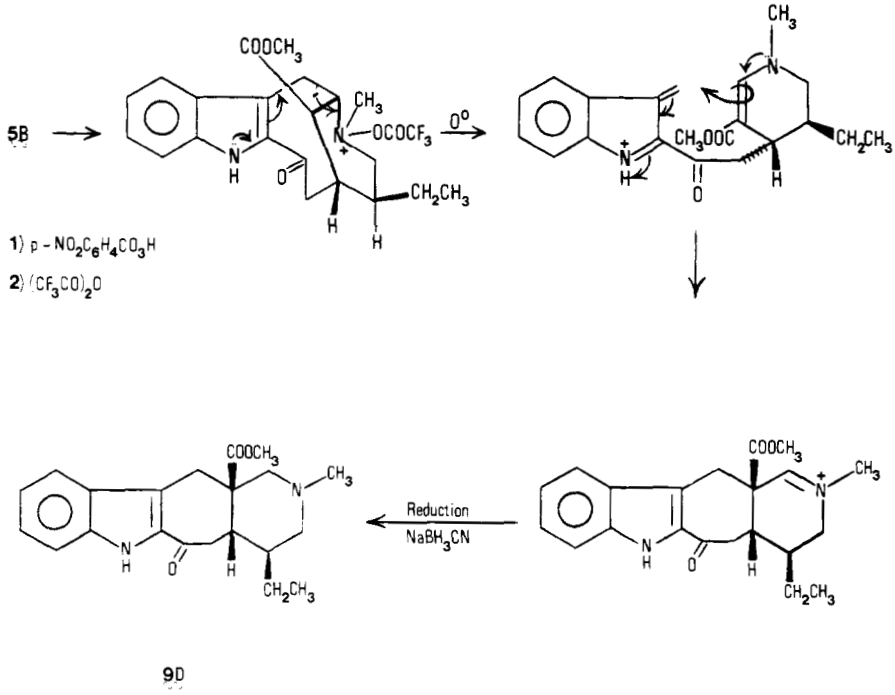
undergo major epimerization to 16-epidregamine on treatment with sodium methoxide, while tabernaemontanine yielded two epimeric lactams in addition to small amounts of epitabernaemontanine. Because of this finding and other evidence, the assignment of configurations of the ethyl side chains were reversed to those given in this review (34). In independent work, Potier's group showed that tabernaemontanine and dregamine can be converted to ervatamine and 20-epiervatamine, respectively, and also determined the structure of ervatamine by X-ray crystallography (33, 56).

The stereochemistry of vobasine has been shown to be as indicated by correlation with akuammidine (**4**, $R_1 = COOCH_3$, $R_2 = CH_2OH$, $R_3 = H$, HO group replaced by H) (8). Since the absolute stereochemistry of akuammidine is known from X-ray studies (58, 59), this work establishes the absolute configuration of vobasine and perivine. A more recent study compared the circular dichroism spectra of vobasine, dregamine, tabernaemontanine, perivine, periformyline, pelirine, ochropamine, and 16-epiochropamine and concluded that all these alkaloids have the same absolute configuration (60).

The proton nuclear magnetic resonance (^1H nmr) spectra of the vobasine alkaloids carrying a methoxycarbonyl group in the 16-position shows an interesting upfield shift of the methyl protons of the carbomethoxy group to approximately 2.6 ppm. This shift has been shown to be due to anisotropic shielding by the indole nucleus, and it is not observed in the epi-series (20). A second feature of

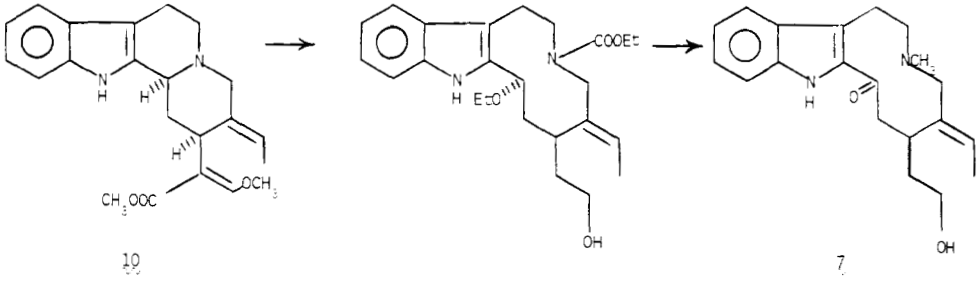


SCHEME 1



SCHEME 2

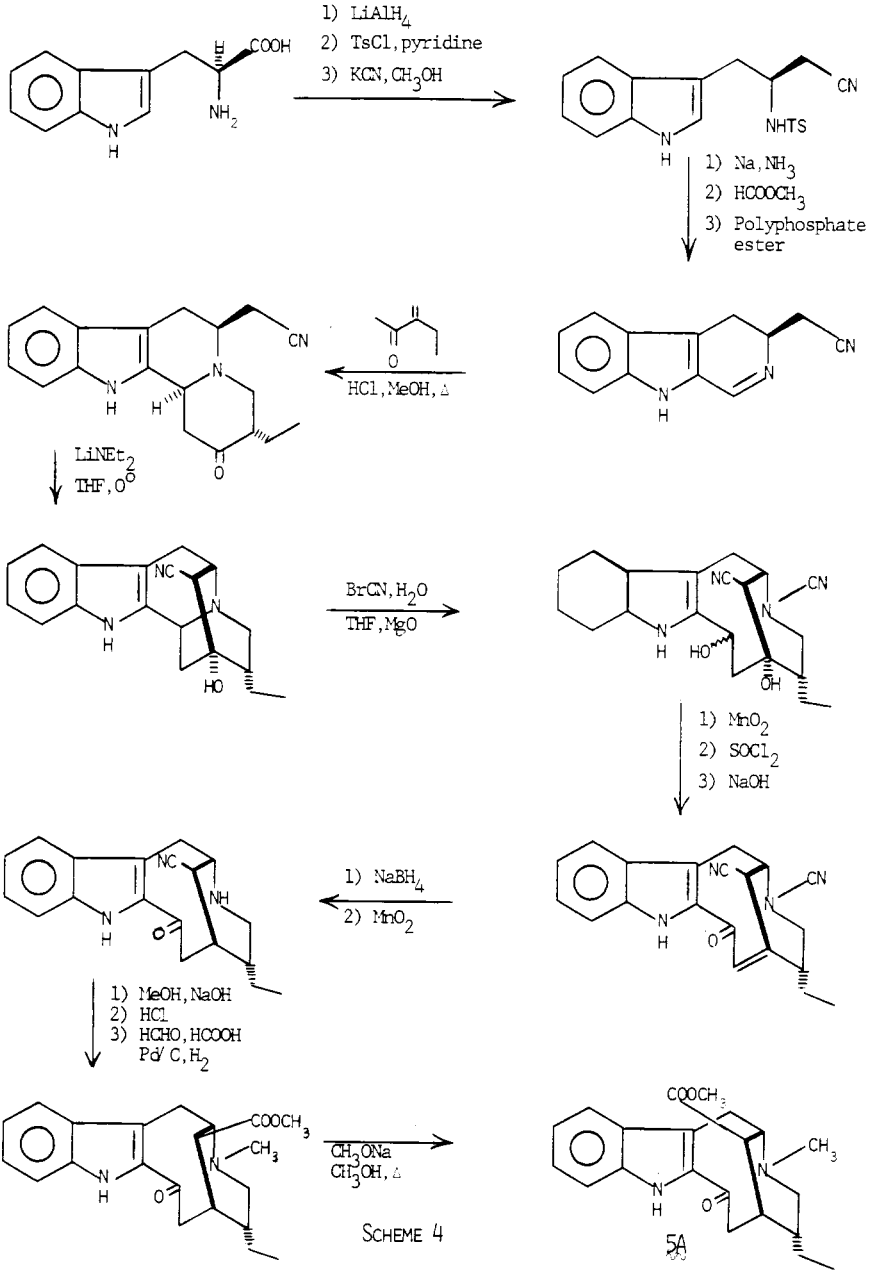
interest in the ^{1}H-nmr spectra of certain vobasine class alkaloids is that some expected singlet peaks can appear either as two distinct signals or can be entirely absent from the spectrum. This finding can be explained in terms of interconverting isomers, and it was shown that all of the alkaloids investigated did indeed give the expected sharp single peaks for methoxyl and *N*-methyl groups at 120°C (12). It is interesting to note that the ^{13}C-nmr spectrum of perivine shows signals for 34 carbons, presumably due to the existence of both acyl indole (**3**, R_1= $COOCH_3$, $R_2=R_3=R_4=R_5=H$) and carbinolamine (**4**, $R_1=COOCH_3$, $R_2=R_3=H$) forms in solution (61).



SCHEME 3

The mass spectra of the vobasine alkaloids have been discussed previously (59, 60). In vobasine itself it is postulated that the major ions at *m/z* 194, 180, and 122 are formed by the pathway of scheme 1 below (18), while analogous ions are formed from related compounds (16, 29, 54, 64–66).

The structure of the alkaloid pelirine (**3H**) is at present uncertain. A compound with structure **3** ($R_1=CH_2OH$, $R_2=H$, $R_3=CH_3$, $R_4=H$, $R_5=11\text{-}OCH_3$) has been synthesised from gardnerine and has been shown not to be identical



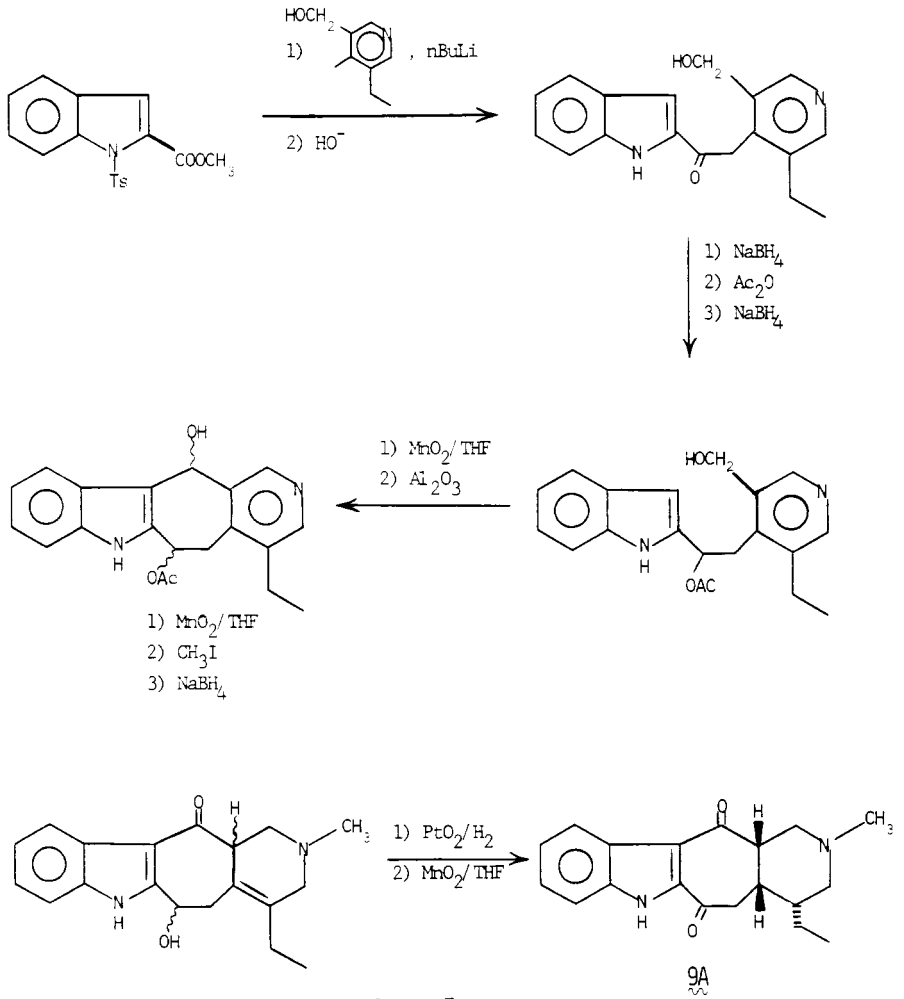
SCHEME 4

5A

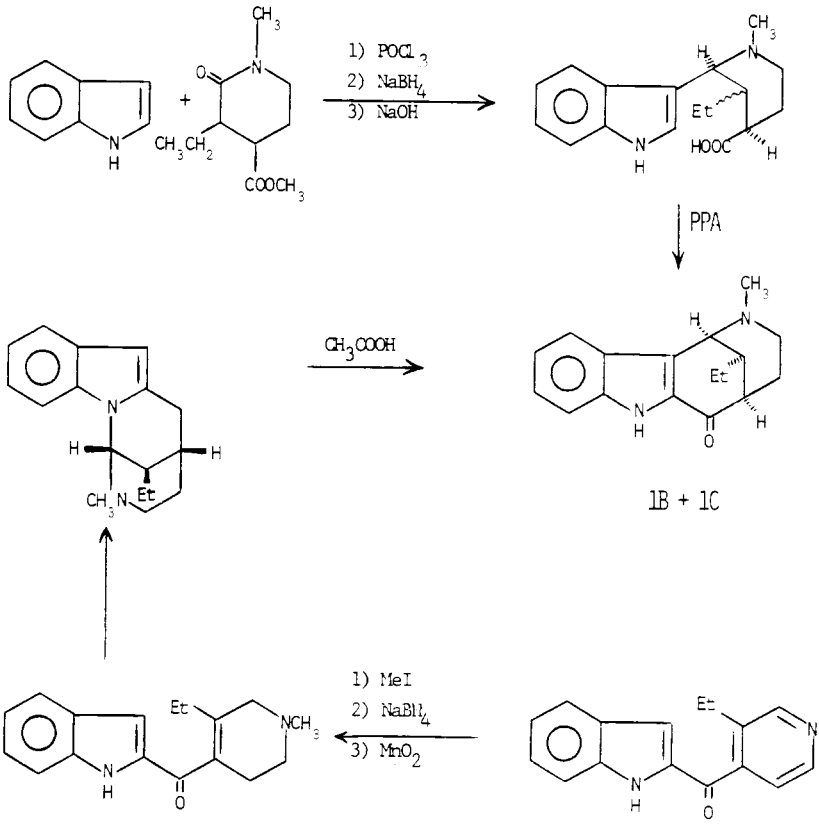
with pelirine (67); differences in the uv spectra of pelirine and the synthetic compound suggest that pelirine differs in the position of its methoxyl group, but the question is not yet settled.

The alkaloid voacafricine (**3J**) may well be identical with vincadiffine (**3K**) since it has very similar physical properties. Unfortunately the lack of a specific rotation and other data for voacafricine makes a definite conclusion impossible at this time.

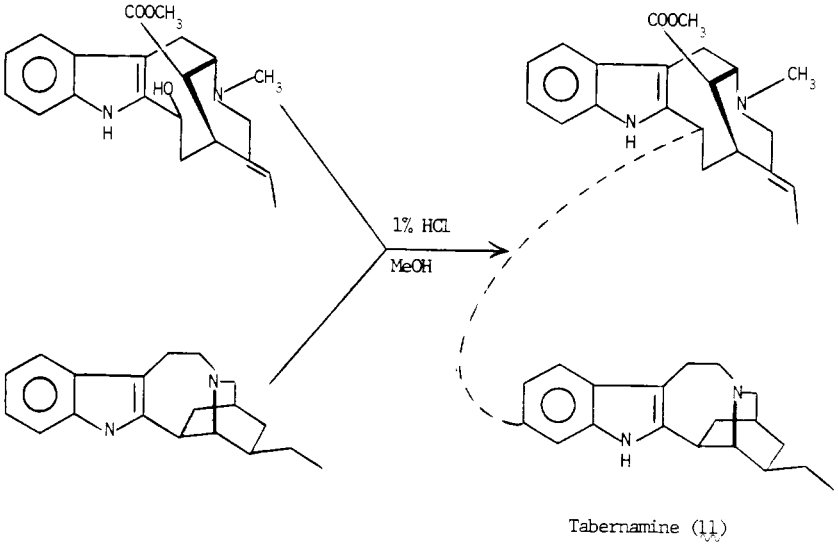
The structures of the alkaloids of the ervatamine series are on secure ground since they rest on X-ray structures of both ervatamine (33) and 16-descarbomethoxy-20-epiervatamine (53). The literature is somewhat confusing on the matter of the assignment of the side-chain configurations, but it is clear that the absolute stereochemistry of the ethyl side-chain in 16-descarbomethoxy-20-epiervatamine (which is stated to be identical with silicine (50)) is α (53) and that it has the R configuration. The structures given in the tabulation are correct, based on the identity of silicine with 16-descarbomethoxy-20-epiervat-



SCHEME 5



SCHEME 6

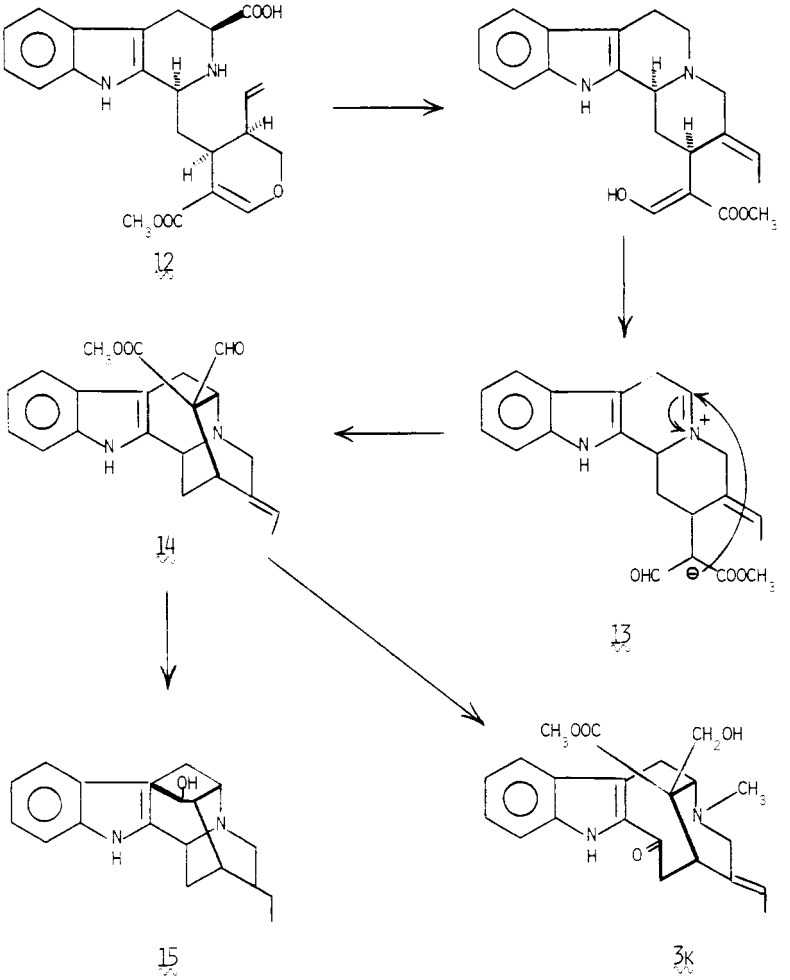


SCHEME 7

amine, and a manuscript correcting some incorrect assignments (47, 53) is in preparation (93).

SYNTHESIS.—Several synthetic studies on the 2-acylindole alkaloids have appeared in the last few years. The conversion of vobasine alkaloids to ervatamine alkaloids has already been referred to. Vobasine itself was converted to dehydroervatamine, dregamine to 20-epiervatamine, and tabernaemontanine to ervatamine (33). The pathway for the last of these conversions is shown in scheme 2 below, and it has an obvious implication for the biosynthesis of the ervatamine alkaloids. The key step of the Polonovski reaction in this conversion has been studied with dregamine with various acylating agents, and it was found that a trifluoroacetate leaving group is required for conversion to the ervatamine series to occur (68). Various other interconversions leading to 2-acylindole alkaloids are summarized in a recent review (67). Thus geissoschizine methyl ether (**10**) has been converted to burnamicine (**7**) (scheme 3), and the partial synthesis of one of the possible structures for pelirine has been noted.

The total synthesis of vobasine, ervatamine, and dasicarpidone alkaloids has

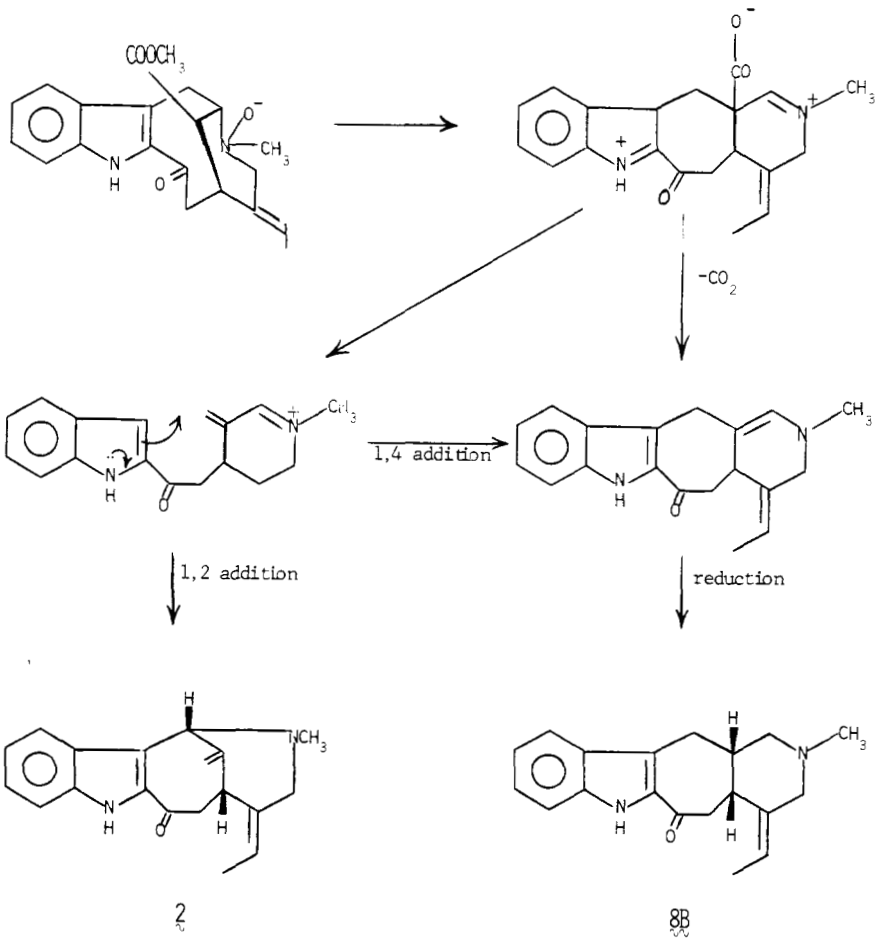


SCHEME 8

also been achieved. In the vobasine area, dregamine and epidregamine have been synthesized from L-tryptophan by the pathway summarized in scheme 4 (69, 70); 16-desmethoxycarbonylvobasine (3, $R_1=R_2=H$, $R_3=CH_3$, $R_4=R_5=H$) has also been synthesized (72a). In the ervatamine series the alkaloids (±)-6-oxosilicine, (±)-desethylervatamine, (±)-15,20-dehydroervatamine, and (±)-16,20 epi-Nα-methylervatamine have been synthesized (50, 71, 72b). The pathway to 6-oxosilicine (**9A**) is summarized in scheme 5. Two approaches to (±)-dasicarpidone and its 3-epimer have been published (78, 79), and are summarized in scheme 6.

The conversion of ervitsine (**2**) into a hydrogenation product of methuenine (**8B**) furnished evidence for the structure of the former alkaloid.

Finally, it should be noted that the 2-acylindole alkaloids supply a portion of the molecule for the important bisindole alkaloids of the voacamine class. The synthesis of these alkaloids can be effected from the 2-acylindoles and an appropriate second substrate; an example is the synthesis of the cytotoxic alkaloid tabernamine (**11**) from vobasinol and ibogamine (scheme 7) (73).



SCHEME 9

BIOSYNTHESIS.—In spite of the widespread occurrence and importance of the 2-acylindole alkaloids, no biosynthetic studies on them have been reported to date. The biosynthesis of ajmaline, which is clearly structurally related to alkaloids of the vobasine class, has been studied, however, and this work has been reviewed (88). It has been proposed that ajmaline (**15**) is biosynthesized from 5α-carboxystrictosidine (**12**) via an electrophilic imine **13** which cyclizes to a sarpagine-type alkaloid **14**. This alkaloid is then suggested to undergo further cyclization to ajmaline (**15**), but it could also undergo oxidative ring cleavage to a vobasine alkaloid such as vincadiffine (**3K**) (scheme 8).

The rearrangement of the vobasine alkaloids to the ervatamine alkaloids previously mentioned provides a logical biosynthetic pathway to the latter alkaloids and makes less likely an earlier suggestion for their biosynthesis (88). A plausible pathway that incorporates both ervitsine (**2**) and the ervatamine alkaloid methuenine (**88**) from the same precursor (vobasine) is shown as scheme 9 (57).

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