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A SYNTHESIS OF DEETHYLVINCADIFFORMINE

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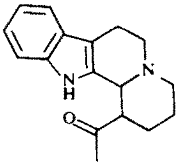
Abstract—The β-acylpyridine reduction-cyclization route has been applied to a short synthesis of the Aspidosperma alkaloid ring system. The resultant 20-deethyldehydroaspidospermidine has been transformed into 20-deethylvincadifformine by N_a-carbomethoxylation and photorearrangement.

For many years the two-reaction scheme of hydrogenation of 1-alkyl-3-acylpyridinium salts and cyclization of the resultant 2-piperideines has been the cornerstone of a general method of alkaloid synthesis.[2] Thus, for example, the two-step procedure of hydrogenation of 1-tryptophyl-3-acetylpyridinium bromide and acid-catalyzed cyclization of the resultant 1, 4, 5, 6-tetrahydropyridine **1a** leading to an indoloquinolizidine (**3**) had formed the basis for an early synthesis of the alkaloid eburnamonine[3] and constituted a model for subsequent syntheses of other tetrahydrocarboline-based indole akaloids.[2] Since the cyclization step, an apparent electrophilic substitution at the indole α-C site, was known to proceed by way of interaction at the indole β-C center, followed by Wagner–Meerwein rearrangement and deprotonation,[4] and since the intermediate indolenine (**2a**) seemed suited ideally for a second cyclization (via interaction of the enol of the acetyl group with the proximate indolenine imine), leading to the pentacyclic nucleus (**4**) of the Aspidosperma alkaloids, it had been of interest for a long time to exploit the general alkaloid synthesis scheme for the synthesis of Aspidosperma and related based. This task now has been accomplished and, as the ensuing discussion illustrates, a short, direct route to the angularly unsubstituted Aspidosperma skeleton has been introduced.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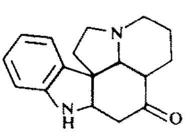
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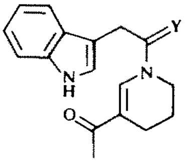
On the assumption of the enhancement of the lifetime of the cyclization intermediate (**2a**) increasing the competitiveness of the second ring closure over the skeletal rearrangement the starting vinylogous amide required structural modification, albeit without interference in the brevity and simplicity of the reaction scheme. As a consequence the cyclization tendency of the vinylogous imide **1b**, prepared readily by the N-acylation of 3-acetyl-1,4,5,6-tetrahydropyridine[5] with indoleacetic anhydride,[6] was investigated. The extra CO group was expected to increase the stability of the intermediate indolenine (**2b**) by the presence of the γ-lactam unit and/or decrease the rate of the Wagner–Meerwein rearrangement by diminution of the migratory aptitude of the rearranging moiety. The expectations were met, when it could be shown that treatment of the vinylogous imide **1b**, with boron trifluoride etherate at room temperature produced indolenine **2b** in the form of its hydration product **5**[7-9] in 72% yield. The same reaction at elevated temperature led to ketolactams **7a** and **8a** in 39 and 42% yield, respectively. Thus the pentacyclic nucleus of the Aspidosperma alkaloids became available in one step from a simple achiral precursor.[10-13]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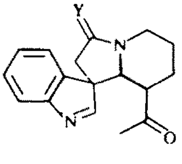
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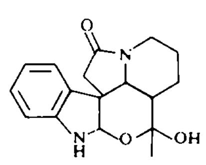
a, Y = H_2; **b**, Y = O

In order to transform ketolactams **7** into substances more representative of the Aspidosperma alkaloids, their keto groups had to be removed. For this purpose several reduction procedures were developed. Thus, for example, Wolff–Kishner reduction of either **7a** or **8a** yielded a mixture of lactams **7b** (5 and 7%, respectively) and **8b** (86 and 80%, respectively),[10] indicative of bridgehead isomerization during some stage of the reduction process. Lithium aluminum hydride (LAH) reduction of lactams **7b** and **8b** yielded deoxopentacycles **7c** (83%) and **8c** (86%)[10], respectively. Alternatively, reduction of ketolactams **7a** and **8a** with LAH and subsequent Oppenauer oxidation of the resultant alcohols (**7d** and **8d**, respectively) led to aminoketone **7e** (49 and 46%, respectively),[10] illustrative of a base-induced equilibration of ketones **7e** and **8e** during the latter oxidation process. Wolff-Kishner reduction of ketone



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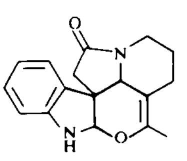

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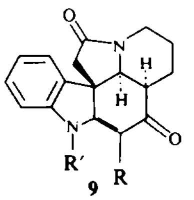

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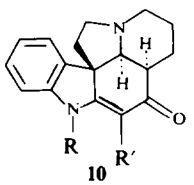

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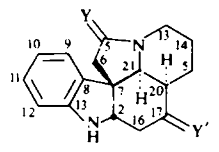
a, $R = R' = H$
b, $R = CO_2Me$, $R' = H$
c, $R = H$, $R' = CO_2Me$



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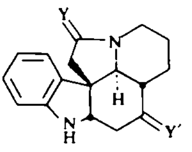

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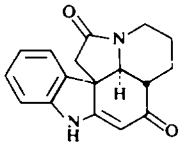
a, $Y = Y' = O$
b, $Y = O$, $Y' = H_2$
c, $Y = Y' = H_2$
d, $Y = H_2$, $Y' = H,OH$
e, $Y = H_2$, $Y' = O$



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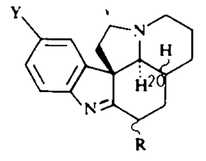

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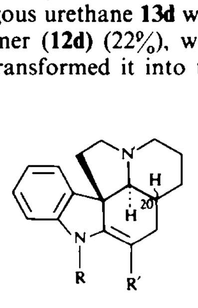
a, H(20α), $R = Y = H$
b, H(20β), $R = Y = H$
c, H(20β), $R = H$, $Y = OH$
d, H(20β), $R = CO_2Me$, $Y = H$

7e afforded a mixture of deoxopentacycles **7c** (28%) and **8c** (21%).[10] The aminoketone intermediate (**7e**) en route to the deoxygenated pentacycles could be obtained also by the reduction of the *p*-toluenesulfonylhydrazones of ketolactam **7a** or **8a** with LAH (60 and 26%, respectively). This unusual reduction, which in the latter case also yielded a minor quantity (9%) of deoxoamine **8c**, had been expected to produce exclusively deoxygenated compounds. The preponderant lack of removal of the ketone CO group by the hydride reduction of two sterically distinct tosylhydrazones and the recovery of only one ketone points to a reaction path involving α-imine H (i.e. H-20) abstraction, enamine N-aluminate formation, N–N bond reduction and, on aqueous work-up, H(20) reintroduction in a stereochemically unique manner and hydrolysis to ammonia and ketone **7e**.[14] Utilization of hydrides other than LAH in the reduction of hydrazones yielded deoxo products. Thus reduction of the tosylhydrazone of ketolactam **7a** with sodium cyanoborohydride and diborane produced lactam **7b** (20%) and amine **7c** (40%), respectively.

With the 20-deethyl derivative (**7c**) of the Aspidosperma alkaloid aspidospermidine[15] in hand[16] it became of interest to create access to 2-dehydro derivatives of the pentacycles. As a consequence several of the aforementioned synthetic intermediates were exposed to oxidation. Treatment of ketolactam **7a** and ketone **7e** with lead tetraacetate[17] yielded vinylogous amides **9a** (85%)[16] and **10a** (51%), respectively.[18] Whereas a similar oxidation of amine **8c** afforded indolenines **12b** (68%) and **c** (7%), deethylaspidospermidine (**7c**) was degraded by lead tetraacetate. However, its oxidation with potassium permanganate led to the 20-deethyl derivative (**12a**) (45%) of the Aspidosperma alkaloid dehydroaspidospermidine.[15]

Since many of the natural Aspidosperma bases are pentacyclic nuclei with 2,16-dehydro-16-carbomethoxy substituents, it was of interest to develop a scheme of introduction of this functionality. Hence N_a-carbomethoxylation of the above indolenines or their tautomers and photochemical rearrangement[19] of the resultant 2, 16-dehydrourethanes were undertaken. Whereas, in principle, the latter could be expected to undergo irradiation-induced carbomethoxy migration to either C(12) or C(16), it was hoped that the rearrangement involving the double bond would require less activation energy than that affecting the benzene ring. Treatment of indolenines **12a** and **b** and vinylogous amides **9a** and **10a** with sodium hydride and methyl chlorocarbonate yielded urethanes **13a** (63%), **13b** (72%), **9b** (77%) and **10b** (58%), respectively. Irradiation of enamides **13a** and **b** and urethanes **9b** and **10b** produced vinylogous urethanes **13c** (30%),[20] **13d** (15%), **9c**(15%) and **10c** (25%), respectively, and decarbomethoxylation products. Vinylogous urethane **13d** was accompanied also by its tautomer (**12d**) (22%), whose treatment with acetic acid transformed it into the conjugated form (**13d**).



13a, H(20α), $R = CO_2Me$, $R' = H$
b, H(20β), $R = CO_2Me$, $R' = H$
c, H(20α), $R = H$, $R' = CO_2Me$
d, H(20β), $R = H$, $R' = CO_2Me$

The above discussion has illustrated the application of the β-acylpyridine reduction-cyclization route in Aspidosperma alkaloid synthesis by the seven-step construction of 20-deethylvincadifformine (**13c**) in two segments, the prior synthesis of 20-deethyldehydroaspidospermidine (**12a**). (β-acetylpyridine→ 3 - acetyl - 1,4,5,6 - tetrahydropyridine→**1b**→**7a** → **7c**→**12a**), followed by a carbomethoxylation process (**12a**→**13a**→**13c**).

EXPERIMENTAL

Mp were determined on a Kofler micro hotstage and are uncorrected. IR spectra were recorded on Perkin–Elmer 137 and 257 spectrophotometers and UV spectra of 95% EtOH solns on Cary 14, Cary 17 and Unicam SP 1800 spectrophotometers. Mass spectra were obtained on Finnigan 3300, CEC 21–110B and AE1 MS902 spectrometers. ^{1}H NMR spectra of CDCl$_3$ solns with Me$_4$Si as internal standard ($\delta = 0$ ppm) were taken on Varian EM-390 and XL-100-15 spectrometers and on experimental 240 and 400 MHz instruments built at the the Institut d'Electronique Fondamentale, 91405 Orsay, France.[21] Photochemical experiments were carried out in a cooling quartz reactor with an immersion high-pressure mercury Hanau TQ 150 lamp assembly under argon.

Lactam 5. A soln of 28.7 g (86 mmol) indoleacetic anhydride[6] and 9.56 g (86 mmol) freshly prepared 3-acetyl-1, 4, 5, 6-tetrahydropyridine[5] in 300 ml dry THF was stirred at room temp under N$_2$ for 24 hr and then evaporated. The CH$_2$Cl$_2$ soln of the residue was washed with 10% HCl and 5% NaHCO$_3$aq, dried (Na$_2$SO$_4$) and evaporated. Crystallization of the residue from MeOH gave 17.3 g (71%) of 1-[indole-3-acetyl] **1b**: mp 142–143°; spectra identical with those of an authentic sample.[10]

A soln of 1.00 g of **1b** in 15 ml BF$_3$-etherate, freshly distilled from calcium hydride, was stirred at room temp for 12 hr and poured into ice water. The mixture was washed with ether, basified with NH$_4$OH and extracted with CH$_2$Cl$_2$. The extract was dried (Na$_2$SO$_4$) and evaporated. Washing of the residue with ether yielded 770 mg (72%) of crystals whose crystallization from acetone led to colorless needles of **5**, : m.p. 167–168°; UV (EtOH)λ_{max} 244 nm (log ϵ 3.90), 297 (3.50); IR (Nujol) OH, NH 3400 (m), 3350 (m), C=O 1658 (s), C–C 1613 (w) cm^{-1}; m/e 300 (M$^+$, 27%), 282 (86), 240 (44), 239 (base), 130 (64), 129 (51). (Found: C, 68.07; H, 6.71; N, 9.24. Calc for C$_{17}$H$_{20}$O$_3$N$_2$: C, 67.98; H, 6.71; N, 9.33%).

Ketolactams 7a and 8a. A soln of 1.80 g of **1b** in 30 ml freshly distilled BF$_3$-etherate was heated at 85° for 10 min. Work-up as above and crystallization of the crude product from MeOH gave 200 mg crystalline **7a**: m.p. 205–207°; spectra identical with those of an authentic sample.[10] Thick-layer chromatography of the evaporated mother liquor on Brinkman PF-254 silica gel and development with 10:1:1 benzene–acetone–isopropyl alcohol led to 500 mg more of **7a** (combined yield: 700 mg, 39%) and 760 mg (42%) of crystals whose crystallization from MeOH-ether gave colorless needles of **8a**: m.p. 194–196°; UV (MeOH) λ_{max} 242 nm (log ϵ 3.87), 297 (3.45): IR (KBr) NH 3300 (m), C=O 1710 (s), 1675 (s), 1605 (m) cm^{-1}; ^{1}H NMR δ 1.0–2.9 (m, 10, methylenes, methines), 3.58 (d, 1, J = 12 Hz, H-21), 3.8–4.4 (m, 2, H–2, H–3), 6.5–7.3 (m, 4, aromatic Hs); m/e 282 (M$^+$, base), 130 (45%). (Found: 73.65; H, 7.09; N, 8.86. Calc for C$_{17}$H$_{18}$O$_2$N$_2$: C, 73.52; H, 7.14; N, 9.02%).

A soln of 100 mg of **1b** in 50 ml MeOH was irradiated for 1 hr and then evaporated. Chromatography of the residue on 5 g of Merck silica gel (activity II) and elution with 4:1 CH$_2$Cl$_2$–EtOAc yielded 20 mg (20%) of amorphous, solid **6**: UV(EtOH)λ_{max}240 nm (log ϵ 3.83), 294 (3.64); IR (film)NH 3290 (m), C=O 1670 (s), C–C 1615 (m) cm^{-1}; ^{1}H NMR δ 1.2–3.0 (m, 7, methylenes, H-3), 1.73 (s, 3, Me), 4.15 (s, 1, H-21), 4.31 (m, 1, H-3), 4.77 (s, 1, H-2), 6.7–7.4 (m, 4, aromatic Hs); m/e 282 (M$^+$, 21%), 131 (11), 130 (base), 110 (10).

A soln of 100 mg of **6** in 15 ml freshly distilled BF$_3$-etherate was heated at 95° for 15 min. Work-up as above led to 40 mg each of lactams **7a** and **8a**.

Lactams 7b and 8b. A soln of 1.00 g of **7a**, 5 g Na and 15 ml hydrazine hydrate in 150 ml freshly distilled ethylene glycol was heated at 160° for 1 hr, distillable material then removed at 170° and the remaining soln heated at 210° for 2 hr. The latter was poured into water and extracted with CH$_2$Cl$_2$. Evaporation of the extract and crystallization of the residue, 950 mg, from acetone yielded 740 mg crystalline **8b**: m.p. 203–204°; spectra identical with those of an authentic sample.[10] Silica gel chromatography of the mother liquor and elution with 2:1 cyclohexane–EtOAc led to 75 mg (total 86% yield) of **8b** and 50 mg (5%) of crystalline **7b**: m.p. 217–219°; UV (EtOH) λ_{max} 246 nm (log ϵ 3.85), 299 (3.40); IR (film) NH 3400 (m), C=O 1675 (s), C=C 1610 (m) cm^{-1}; ^{1}H NMR δ 1.1–1.9 (m, 9, methylenes, CH), 2.13, 2.20, 2.75, 2.83 (4-line AB, 2, 2 H-6), 2.71 (m, 1, H-3), 3.38 (dd, 1, J = 12, 6 Hz, H-2), 3.93 (d, 1, J = 3 Hz, H-21), 4.16 (dd, 1, J = 14, 4 Hz, H-3), 6.6–7.2 (m, 4, aromatic Hs). Exact mass: m/e 268.1570 (Calc for C$_{17}$H$_{20}$ON$_2$: m/e 268.1576).

Reduction of 1.00 g **8a** under the same Wolff-Kishner conditions and work-up as above yielded 765 mg (80%) of **8b** and 65 mg (7%) of **7b**.

A mixture of 200 mg of **7a**, 200 mg *p*-toluenesulfonylhydrazine and 100 mg *p*-toluenesulfonic acid in 10 ml EtOH was stirred under N$_2$ at room temp for 24 hr and then evaporated under vacuum. A mixture of the residue, 4 ml dimethylformamide and 4 ml sulfolane in 5 ml cyclohexane was heated under N$_2$ for 4 hr. The cyclohexane was removed by evaporation and the other solvents by distillation at 140°/0.001 Torr. A CH$_2$Cl$_2$ soln of the residue was washed with 5% NaOH soln, dried (Na$_2$SO$_4$) and evaporated. Chromatography of the residue on silica gel and elution with 1:1 CH$_2$Cl$_2$–EtOAc yielded 60 mg (32%) of **7b**.

Aminoketone 7e. A suspension of 800 mg LAH and 1.00 g of **7a** in 200 ml anhyd THF was refluxed under N$_2$ for 2 hr and then acidified with 5% HClaq. Evaporation of the organic solvent, treatment of the remaining soln with a sat K$_2$CO$_3$aq, sodium tartrate and then aqueous ammonia extraction with CH$_2$Cl$_2$ and evaporation of the dried (Na$_2$SO$_4$) extract led to a solid, whose crystallization from MeOH yielded 780 mg (81%) crystalline **7d**: m.p. 203–205°; m/e 270 (M$^+$, 71%), 252 (23), 178 (46), 130 (99), 122 (98), 98 (base).

A soln of 700 mg of **7d**, 433 mg of t-BuOK and 695 mg fluorenone in 200 ml dry benzene was refluxed under N$_2$ for 2 hr. The mixture was poured onto ice and a 5% HCLaq added. It was washed with ether for the removal of the fluorenone, basified with aqueous ammonia and extracted with CH$_2$Cl$_2$. The extract was dried (Na$_2$SO$_4$) and evaporated. Chromatography of the residue, 620 mg, on 60 g of Merck silica gel (activity II) and elution with 3:1 cyclohexane–EtOAc yielded 420 mg (60%) of **7e**: m.p. 115–117°; spectra identical with those of an authentic sample.[10]

A suspension of 2.00 g **8a** and 1.50 g LAH in 500 ml anhyd THF was refluxed under N$_2$ for 5 hr. Work-up as above gave 1.00 g (52%) amorphous solid **8d.** Oppenauer oxidation of the latter, 850 mg, under the above conditions and work-up yielded 750 mg (88%) of **7e**.[10]

Ketolactam **7a**, 1.20 g, was converted into its tosylhydrazone by the above procedure. A suspension of 800 mg LAH and the hydrazone in 250 ml anhyd THF was refluxed under N$_2$ for 4 hr. Work-up as above yielded 684 mg (60%) of **7e**.[10]

Ketolactam **8a**, 800 mg, was converted into tosylhydrazone by the above procedure for preparation of **7a** tosylhydrazone. (The hydrazones of **7a** and **8a**, while not isolated, were shown to be different substances by TLC.) A suspension of 800 mg LAH and the hydrazone in 250 ml anhyd THF was refluxed under N$_2$ for 4 hr. Work-up as above yielded 200 mg (26%) of **7e**[10] and 63 mg (9%) crystalline **8c**,[10] m.p. 104–106°; spectra identical with those of an authentic sample.[10]

20-Deethylaspidospermidine (**7c**). A THF soln of diborane, 2.1 ml of 1 M, was added dropwise over a 0.5 hr period to a soln of **7a** tosylhydrazone, prepared from 200 mg of **7a** by the above procedure, in 100 ml dry THF under N$_2$ at 0°. After stirring at this temp for 1 hr the mixture was refluxed for 1 hr, poured into sat NaOAc and refluxed for 0.5 hr. It then was acidified with 5% HClaq, heated under vacuum for the removal of THF, made basic with aqueous ammonia and extracted with CH$_2$Cl$_2$. The extract was dried (Na$_2$SO$_4$)

and evaporated. Chromatography of the residue on 20 g silica gel (activity II), and elution with 20:1 cyclohexane-EtOAc led to 70 mg (40%) of solid, whose crystallization in MeOH afforded crystalline **7c**: m.p. 101–103°; UV (EtOH) λ_{max} 245 nm (log ϵ 3.82), 297 (3.45); IR (KBr) NH 3300 (m), C=C 1610 (m) cm^{-1}; ^{1}H NMR δ 1.1–2.3 (m, 11, methylenes, CH), 2.50 (br.s, H-21), 3.16 (m, 4, N-methylenes), 3.50 (m, 1, H-2), 6.68 (d, 1, J = 8 Hz, H-12), 6.78 (t, 1, J = 8 Hz, H-10), 7.07 (t, 1, J = 8 Hz, H-11), 7.16 (d, 1, J = 8 Hz, H-9); *m/e* 254 (M$^+$, 76%), 253 (45), 226 (26), 162 (26), 96 (base). Exact mass: *m/e* 254.1793 (Calc for $C_{17}H_{22}N_2$: *m/e* 254.1783).

A suspension of 100 mg LAH and 100 mg of **7b** in 100 ml anhyd THF was refluxed for 4 hr. Work-up as above, chromatography of the crude product on 5 g of Merck alumina (activity I) and elution with cyclohexane yielded 78 mg (83%) of **7c**.

A soln of 600 mg of **7e** and 15 ml hydrazine hydrate in 2 ml ethylene glycol was refluxed for 1.5 hr. Water and excess hydrazine was removed by distillation, a soln of 2 g Na in 50 ml ethylene glycol was added and the mixture heated at 200° for 1 hr. Work-up as in the above Wolff-Kishner reduction, chromatography of the crude product on alumina (activity I) and elution with 20:1 cyclohexane-EtOAc yielded 120 mg (21%) of **8c**[10] and then 160 mg (28%) of **7c**.

20-*Iso*-20-*deethylaspidospermidine* (**8c**). A suspension of 800 mg LAH and 1.20 g of **8b** in 300 ml dry THF was refluxed for 5 hr. Work-up as above, chromatography on 20 g Merck neutral alumina (activity I) and elution with 20:1 cyclohexane-EtOAc gave 978 mg (86%) of **8c**[10]: m.p. 104–106°; spectra identical with those of an authentic sample.[10]

Lead tetraacetate oxidations. A mixture of 500 mg of **7a** and 1.00 g lead tetraacetate in 25 ml $CHCl_3$ was refluxed under N_2 for 15 min and then filtered. The filtrate was washed with water, dried (Na_2SO_4) and evaporated. Chromatography of the residue on Merck silica gel (activity II) and elution with 1:1 cyclohexane–EtOAc led to the recovery of 20 mg starting ketone. Elution with EtOAc afforded 405 mg (85%) solid product whose crystallization in acetone yielded **9a**: m.p. 223–225°; UV (EtOH) λ_{max} 239 nm (log ϵ 4.16), 297 (3.90), 344 (4.23); IR (KBr) NH 3450 (m), C=O, C=C 1700 (s), 1685 (s), 1635 (s), 1605 (s); ^{1}H NMR δ 1.4–3.0 (m, 5, methylenes, CH), 2.83 (br.s, 2 H-6), 4.1–4.4 (m, 2, NCH_2), 4.41 (d, 1, J = 6 Hz, H-21), 5.56 (s, 1, H-16), 6.8–7.3 (m, 4, aromatic Hs), 8.70 (s, 1, NH); *m/e* 280 (M$^+$, base), 252 (24%), 224 (38), 170 (73), 110 (51). (Found: C, 72.75; H, 5.81; N, 9.86. Calc for $C_{17}H_{16}O_2N_2$: C, 72.84; H, 5.75; N, 9.99%).

A mixture of 450 mg of **7e** and 900 mg lead tetraacetate in 10 ml CH_2Cl_2 was refluxed under N_2 for 45 min. Work-up and chromatography as above and elution with 1:1 cyclohexane-EtOAc yielded 230 mg (51%) solid product whose crystallization from acetone gave **10a**: m.p. 146–148°; UV (EtOH) λ_{max} 240 nm (log ϵ 4.10), 295 (3.88), 345 (4.15); IR (KBr) NH 3140 (w), C=O, C=C 1625 (m), 1570 (s) cm^{-1}; IR (film)[22] NH 3250 (w), C=O 1720 (s), C=N 1625 (m), C=O, C–C 1600 (s), 1580 (s) cm^{-1}; ^{1}H NMR[22] δ 1.0–3.3 (m, 11, methylenes, CH), 2.78 (d, 1, J = 3 Hz, H-21), 3.41, 3.70, 3.78, 4.06 (4-line AB, 2, 2 H-16), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 266 (M$^+$, base), 265 (18%), 209 (71), 96 (63). Exact mass: *m/e* 266.1436 (Calc for $C_{17}H_{18}ON_2$: *m/e* 266.1419).

A mixture of 700 mg of **8c** and 1.50 g lead tetraacetate in 20 ml dry CH_2Cl_2 was refluxed under N_2 for 0.5 hr and then filtered. The filtrate was washed with sat $NaHCO_3$aq and evaporated. Crystallization of the residue from acetone yielded 350 mg crystals. Chromatography of the mother liquor on neutral Merck alumina (activity III) and elution with cyclohexane yielded 120 mg more (total 68%) of **12b**: m.p. 156–158°; UV (ETOH) λ_{max} 222 nm (log ϵ 4.18), 265 (3.73), IR (KBr) C=N 1575 (m) cm^{-1}; ^{1}H NMR δ 1.1–3.5 (m, 15, methylenes, CH), 2.40 (d, 1, J = 10 Hz, H-21), 7.1–7.7 (m, 4, aromatic Hs); *m/e* 252 (M$^+$, base), 110 (10%), 109 (81). Exact mass: *m/e* 252.1628 (Calc for $C_{17}H_{20}N_2$: *m/e* 252.1626).

Elution with EtOAc yielded 50 mg (7%) solid whose crystallization from EtOAc gave **12c**: m.p. 234–236°; UV (EtOH) λ_{max} 230 nm (log ϵ 3.80), 282 (3.58); (1N NaOH, EtOH) λ_{max} 236 nm (log ϵ 3.80), 3.07 (3.77), 340 (3.59); ^{1}H NMR δ 0.9–3.2 (m, 15, methylenes, CH), 2.20 (d, 1, J = 10 Hz, H-21), 6.62 (dd, 1, J = 9, 3 Hz, H-11), 6.96 (d, 1, J = 3 Hz, H-9), 7.17 (d, 1, J = 9 Hz, H-12); *m/e* 268 (M$^+$, base), 267 (26%), 212 (12), 211 (27), 109 (99). Exact mass: *m/e* 268.1581 (Calc for $C_{17}H_{20}ON_2$: *m/e* 268.1576).

20-*Deethyldehydroaspidosperidine* (**12a**). A mixture of 92 mg $KMnO_4$ and 154 mg 18-crown-6 ether in 2 ml dry benzene was stirred under N_2 at room temp for 15 min. After the addition of 100 mg of **7c** the mixture was stirred at room for 1 hr and then passed through 10 g alumina (activity I). Elution with 200:1 pentane–EtOAc yielded 41 mg (45%) amorphous, highly unstable **12a**: 260 nm UV absorption; *m/e* 252 (M$^+$, 98%), 209 (25), 208 (28), 195 (42), 182 (36), 180 (46), 109 (base), 96 (26). The compound was used immediately without purification in the next reaction.

N_a-*Carbomethoxylations.* An oil suspension (15 mg) of 50% NaH was added to a stirring soln of 65 mg of **12a** in 2 ml dry 1,2-dimethoxyethane at 0° under N_2 and the stirring continued for 5 min. Methyl chlorocarbonate, 40 μl, was added dropwise and the mixture stirred at 0° for 1.5 hr. It was then poured into icewater and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel and elution with 17:1 cyclohexane–EtOAc yielded 50 mg (63%) oily **13a** : IR (film) CH 2840 (w), 2770 (w), C=O 1715 (s), C=C 1600 (w) cm^{-1}; ^{1}H NMR δ 1.1–3.4 (m, 14, methylenes, methines), 3.91 (s, 3, OMe), 6.13 (br. d, 1, J = 10 Hz, olefinic H), 6.9–7.4 (m, 3, aromatic Hs), 7.78 (d, 1, J = 8 Hz, H-12). Exact mass: *m/e* 310.1684 (Calc for $C_{19}H_{22}O_2N_2$: *m/e* 310.1681).

An oil suspension (30 mg) of 50% NaH was added to a stirring soln of 130 mg of **12b** in 3 ml dry 1,2-dimethoxyethane under N_2 at room temp and the stirring continued for 30 min. Methyl chlorocarbonate, 80 μl, was added dropwise and the stirring mixture heated at 60° for 30 min. Work-up as above and elution with 6:1 cyclohexane–EtOAc gave 114 mg (72%) solid, whose crystallization from MeOH yielded crystalline **13b**: m.p. 96–97°; UV (EtOH) λ_{max} 249 nm (log ϵ 3.97), 282 (3.06), 291 (3.01); IR (KBr) CH 2830 (m), C=O 1715 (s), C=C 1605 (w) cm^{-1}; ^{1}H NMR δ 1.1–3.4 (m, 14, methylenes, methines), 3.93 (s, 3, OMe), 5.90 (m, 1, H-16), 6.9–7.9 (m, 4, aromatic Hs); *m/e* 310 (M$^+$, 30%), 265 (14), 251 (4), 239 (7), 97 (11), 96 (base). Exact mass: *m/e* 310.1669 (Calc for $C_{19}H_{22}O_2N_2$: *m/e* 310.1681).

An oil suspension (100 mg) of 50% NaH was added to a stirring soln of 280 mg **9a** in 30 ml anhyd 1,2-dimethoxyethane under N_2 at room temp and the stirring continued for 30 min. Methyl chlorocarbonate, 188 mg, was added dropwise and the stirring continued at room temp for 1 hr. Work-up as above and crystallization from CH_2Cl_2-ether yielded 260 mg (77%) crystalline **9b**: m.p. 240–242°; UV (EtOH) λ_{max} 241 nm (log ϵ 4.17), 280 (3.67), 312 (3.75); IR (KBr) C=O 1740 (s), 1680 (s), 1665 (s), 1630 (s), C=C 1600 (m) cm^{-1}; ^{1}H NMR δ 1.4–1.8, 2.3–2.8, 3.9–4.5 (m, 9, methylenes, methines), 4.03 (s, 3, OMe), 4.48 (d, 1, J = 6 Hz, H-21), 6.67 (s, 1, H-16), 7.2–7.6 (m, 3, aromatic Hs), 7.97 (d, 1, J = 9 Hz, H-12); *m/e* 338 (M$^+$, 41%), 310 (6), 294 (6), 229 (15), 228 (base), 169 (10), 140 (5). Exact mass: *m/e* 338.1290. (Calc for $C_{19}H_{18}O_4N_2$: 338.1267).

A reaction of 106 mg **10a** with NaH and methyl chlorocarbonate as with **9a** above and an identical work-up gave crude product, whose chromatography on silica gel and elution with 4:1 cyclohexane–EtOAc yielded 75 mg (58%) solid. Crystallization of the latter from CH_2Cl_2-cyclohexane led to crystalline **10b**: m.p. 166–167° UV (EtOH) λ_{max} 241 nm (log ϵ 4.21), 278 (3.85), 305 (3.81);

IR (KBr) C=O 1730 (s), 1670(s), 1640(s), C=C 1600 (w) cm^{-1}; ^{1}H NMR δ 1.2–3.3 (m, 11, methylenes, methine), 3.13 (d, 1, J = 5 Hz, H-21), 3.98 (s, 3, OMe), 6.37 (s, 1, H-16), 7.0–7.4 (m, 3, aromatic Hs), 7.87 (d, 1, J = 9 Hz, H-12); *m/e* 324 (M$^+$, 17%), 167 (3), 154 (3), 97 (8), 96 (base). Exact mass: *m/e* 324.1469 (Calc for $C_{19}H_{20}O_3N_2$: *m/e* 324.1474).

20-*Deethylvincadifformine* (**13c**). A soln of 50 mg of **13a** in 50 ml cyclohexane, through which argon was being bubbled, was irradiated for 30 min and then evaporated to dryness. Chromatography of the residue on 3 g silica gel and elution with 1:1 cyclohexane–CH_2Cl_2 yielded 5 mg (12%) of **12a** and subsequently 15 mg (30%) amorphous **13c**: IR (film) NH 3370 (m), CH 2850 (m), 2780 (m), C=O 1675 (s), 1610 (s) cm^{-1}; ^{1}H NMR δ 1.1–3.1 (m, 14, methylenes, methines), 3.67 (s, 3, OMe), 6.7–7.2 (m, 4, aromatic Hs); *m/e* 310 (M$^+$, 14%), 96 (base). Exact mass: *m/e* 310.1684 (Calc for $C_{19}H_{22}O_2N_2$: *m/e* 310.1681).

20-*Deethyl*-20-*isovincadifformine* (**13d**). A soln of 220 mg of **13b** in 50 ml MeOH, through which argon was being bubbled, was irradiated for 1 hr and then evaporated. Chromatography of the residue on 15 g silica gel and elution with 4:1 cyclohexane–ether gave 33 mg (15%) solid, whose crystallization from hexane led to **13d**: m.p. 129–131°; UV (EtOH) λ_{max} 226 nm (log ϵ 4.11), 297 (4.05), 328 (4.19); IR (KBr) NH 3330 (m), CH 2840 (m), C=O 1675 (s), 1610 (s) cm^{-1}; ^{1}H NMR δ 1.2–3.3 (m, 13, methylenes, methine), 2.83 (d, 1, J = 10 Hz, H-21), 3.73 (s, 3, OMe), 6.7–7.6 (m, 4, aromatic Hs); *m/e* 310 (M$^+$, 24%), 96 (base). Exact mass: *m/e* 310.1693). (Calc for $C_{19}H_{22}O_2N_2$: *m/e* 310.1681).

Further elution gave 48 mg (22%) of solid, whose crystallization from ether–hexane led to crystalline **12d**: m.p. 103–105°; UV (EtOH) λ_{max} 222 nm (log ϵ 4.14), 266 (3.65); IR (KBr) CH 2890 (m), 2850 (m), C=O 1729 (s), cm^{-1}; ^{1}H NMR δ 1.0–3.4 (m, 14, methylenes, methines), 4.10 (d, 1, J = 5 Hz, H-16), 7.2–7.7 (m, 4, aromatic Hs); *m/e* 310 (M$^+$, 77%), 251 (27), 109 (37), 96 (base), 83 (12), 82 (13). A soln of the indolenine in 10 ml glacial AcOH was stirred at room temp for 15 min, then made basic with 10% NaOHaq and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. The residue, 40 mg (83%), was identical spectroscopically (UV, IR, ^{1}H NMR) and by TLC with **13d**.

Further elution gave 52 mg (29%) of indolenine **12d**.

20-*Deethyl*-5,17-*dioxovincadifformine* (**9c**). A soln of 200 mg of **9b** in 50 ml MeOH, through which argon was being bubbled, was irradiated for 2 hr and then evaporated. Crystallization of the residue from CH_2Cl_2 yielded 100 mg of **9a**. Chromatography of the residue from the mother liquor on silica gel and elution with 1:1 cyclohexane–EtOAc yielded 30 mg more **9a** (46% total yield) and in earlier fractions 30 mg (15%) of amorphous **9c**: UV (EtOH) λ_{max} 243 nm (log ϵ 4.09), 286 (3.54), 296 (3.63), 345 (4.08); IR (film) NH 3280 (br. m), C=O 1675 (s), 1580 (s) cm^{-1}; ^{1}H NMR δ 1.4–4.2 (m, 9, methylenes, methine), 3.85 (s, 3, OMe), 4.38 (d, 1, J = 6 Hz, H-21), 7.1–7.4 (m, 4, aromatic Hs); *m/e* 338 (M$^+$, 46%), 280 (32), 228 (base), 196 (20), 170 (27), 143 (13), 130 (16), 110 (20), 83 (27). Exact mass: *m/e* 338.1283 (Calc for $C_{19}H_{18}O_4N_2$: *m/e* 338.1267).

20-*Deethyl*-17-*oxovincadifformine* (**10c**). A soln of 140 mg of **10b** in 10 ml THF was added to 50 ml cyclohexane and the combined soln irradiated for 1 hr. Evaporation of the mixture, chromatography of the residue on 10 g of silica gel and elution with 1:1 cyclohexane–EtOAc gave 50 mg (44%) of **10a**. Earlier elution with 4:1 cyclohexane–EtOAc yielded 35 mg (25%) amorphous **10c**: UV (EtOH) λ_{max} 241 nm (log ϵ 4.05), 287 (3.51), 296 (3.57), 345 (4.06); IR (film) NH 3280 (br. m), C=O 1690 (s), 1645 (s), 1560 (s) cm^{-1}; ^{1}H NMR δ 1.2–3.6 (m, 12, methylenes, methines), 3.76 (s, 3, OMe), 6.8–7.4 (m, 4, aromatic Hs); *m/e* 324 (M$^+$, 6%), 86 (40), 84 (50), 51 (40), 49 (base). Exact mass: *m/e* 324.1471 (Calc for $C_{19}H_{20}O_3N_2$: *m/e* 324.1474).

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REFERENCES AND NOTES

[1] Present address: Department of Chemistry (D-006), University of California-San Diego, La Jolla, CA 92093, U.S.A.

[2] E. Wenkert, *Acc. Chem. Res.* **1**, 78 (1968). E. Wenkert, *The Recent Chemistry of Natural Products, Including Tobacco*, (Edited by N. J. Fina), pp. 15–28. *Proc. 2nd Philip Morris Science Symp.*, Richmond, Virginia. 30 Oct. (1975).

[3] E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.* **87**, 1580 (1965).

[4] A. H. Jackson and A. E. Smith, *Tetrahedron* **24**, 403 (1968).

[5] E. Wenkert, K. G. Dave, F. Haglid and R. G. Lewis, *J. Org. Chem.* **33**, 747 (1968).

[6] J. C. Hart, E. M. Matheson and O. Hutzinger, *Can. J. Chem.* **48**, 177 (1970).

[7] Neither the origin of the water of hydration nor the stereochemistry of the product were determined in view of their lack of relevance in the subsequent reactions.

[8] Whereas most previous cyclizations of vinylogous amides,[2] such as the **1a**→**3** transformation,[3] were executed under mineral acid catalysis in protic media, the ease of solvolysis of the vinylogous imides under these reaction conditions (e.g.: treatment of **1b** with methanolic HCl yielding exclusively methyl indoleacetate and 3-acetyl-1,4,5,6-tetrahydropyridine) restricted their cyclization to Lewis acid catalysis in non-protic media.

[9] An interesting, alternate route to the indolenine **2b**, albeit again in masked form, involved the photoisomerization of **1b**. BF_3-induced cyclization of the photoproduct (**6**) produced **7a** and **8a** (Experimental).

[10] For a preliminary communication on the preparation and reduction of **7a** see E. Wenkert, J. S. Bindra and B. Chauncy, *Synth. Commun.* **2**, 285 (1972).

[11] E. Wenkert, *Pure Appl. Chem.* **53**, 1271 (1981).

[12] For a conceptually similar scheme of Aspidosperma alkaloid synthesis see G. Büchi, K. E. Matsumoto and H. Nishimura, *J. Am. Chem. Soc.* **93**, 3299 (1971), and subsequent papers.

[13] The minor products of cyclization, accompanying **7a** and **8a**, included Na-ethyl-**7a** [m.p. 208–209° (from ether-CH_2Cl_2); IR (Nujol) C=O 1713 (s), 1680 (s), C=C 1603 (m) cm^{-1}; UV (MeOH) λ_{max} 206 nm (ϵ 22,500), 250 (7,200), 307 (1,700); *m/e* 310 (M$^+$, base), 296 (10%), 295 (55), 159 (12), 158 (47), 138 (15); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3, J = 7 Hz, Me), 2.5 (m, 4, H-3, H-16, H-20), 2.51 (d, 1, J = 18 Hz, H-6), 2.77 (dd, 1, J = 10, 3 Hz, H-16), 3.12 (q, 1, J = 7 Hz, NCH_2), 3.20 (d, 1, J = 18 Hz, H-6), 3.59 (d, 1, J = 4 Hz, H-21), 3.73 (t, 1, J = 3 Hz, H-2), 4.09 (q, 1, J = 14, 5 Hz, H-3), 6.3–7.3 (m, 4, aromatic Hs)], N_a-ethyl-16,17-dehydro-17-deoxo-17-ethoxy-**7a** [m.p. 167–169° (from ether); IR (Nujol) C=O 1688 (s), C=C 1646 (s), 1606 (s) cm^{-1}; UV (MeOH) λ_{max} 206 nm (ϵ 33,600), 258 (8,200), 312 (1,900); *m/e* 338 (M$^+$, base), 323 (15%), 310 (19), 309 (54), 281 (14), 218 (24), 217 (22), 198 (13), 158 (20), 93 (25); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3, J = 7 Hz, Me of NEt), 1.30 (t, 3, J = 7 Hz, Me of OEt), 2.7 (m, 3, H-6, H-6, H-20), 3.15 (q, 2, J = 7 Hz, CH_2 of NEt), 3.61 (d, 1, J = 6 Hz, H-21), 3.75 (q, 2, J = 7 Hz, OCH_2), 4.00 (d, 1, J = 6 Hz, H-2), 4.80 (dd, 1, J = 6, 3 Hz, H-16), 6.3–7.3 (m, 4, aromatic Hs)] and N_a-ethyl-**8a** [m.p. 177–179° (from ether); IR (Nujol) C=O 1710 (s), 1670 (s), C=C 1600 (m) cm^{-1}; UV (MeOH) λ_{max} 208 nm (ϵ 21,800), 253 (8,700), 308 (1,600); *m/e* 310 (M$^+$, base), 295 (13%), 159 (11), 158 (55), 138 (7); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3, J = 7 Hz, Me), 2.20 (dd, 1, J = 16, 5 Hz, H-16), 2.54, 2.57 (s, 1 each, H-6), 2.8 (m, 2, H-3, H-16), 2.95 (q, 2, J = 7 Hz, NCH_2), 3.28 (d, 1, J = 12 Hz, H-21), 4.06 (q, 1, J = 7, 5 Hz, H-2), 4.25 (dd, 1, J = 10, 4 Hz, H-3), 6.3–7.3 (m, 4, aromatic Hs)].

[14] Were it possible to make this reaction a general process, a tosylhydrozone may serve as an excellent ketone masking group during LAH reductions.

[15] G. F. Smith and M. A. Wahid, *J. Chem. Soc.* 4002 (1963). K. Biemann, M. Friedmann-Spiteller and G. Spiteller, *Ibid.* **85**, 631 (1963).

[16] For an alternate synthesis of 3-oxo-**10a** and the N_a-acetyl derivatives of **7c** and **12a** see Y. Ban, T. Ohnuma, M. Nagai, Y. Sendo and T. Oishi, *Tetrahedron Letters* 5023 (1972).

[17] For early examples of the conversion of indoline alkaloids into indolenines or their 2-alkylideneindoline tautomers by lead tetraacetate oxidation see M. F. Bartlett, B. F. Lambert and W. I. Taylor, *J. Am. Chem. Soc.* **86**, 729 (1964).

[18] Lead tetraacetate oxidation of **8a** has yielded **11** (33%): UV (EtOH) λ_{max} 235 nm (log ϵ 4.05), 296 (3.86), 3.37 (4.10); ^{1}H NMR δ 1.0–3.2 (m, 6, methylenes, CH), 2.35, 2.53, 3.06, 3.26 (4-line AB, 2, 2 H-6), 3.73 (d, 1, J = 10 Hz, H-21), 4.23 (m, 1, H-3), 5.48 (s, 1, H-16), 6.6–7.3 (m, 4, aromatic Hs), 8.46 (br. s, 1, NH); *m/e* 280 (M^+, 50%), 171 (17), 170 (base), 144 (9), 143 (14), 130 (13), 115 (11).

[19] N. C. Yang and G. R. Lenz, *Tetrahedron Letters* 4897 (1967).

[20] M. E. Kuehne, C. L. Kirkemo, T. H. Matsko and J. C. Bohnert, *J. Org. Chem.* **45**, 3259 (1980).

[21] P. Gonord, S. K. Kan and M. J. Sauzade, *J. Magn. Res.* **24**, 457 (1976). S. K. Kan, P. Gonord, M. Fan, M. Sauzade and J. Courtieu, *Rev. Sci. Instrum.* **49**, 785 (1978).

[22] The major tautomer in $CHCl_3$ soln is 17-oxo-**12a**.