ALKALOIDS OF *PERIPENTADENIA MEARSII*. I. ISOLATION, STRUCTURAL DETERMINATION, AND SYNTHESIS OF PERIPENTADENINE

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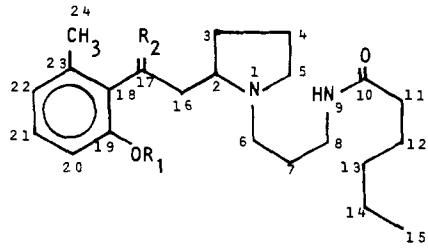
ABSTRACT.—Peripentadenine, the principal alkaloid of the elaeocarpaceous plant *Peripentadenia mearsii*, has been shown by spectroscopy, degradation, and synthesis to be *N*{3[2(2-hydroxy-6-methylbenzoylmethyl)pyrrolidin-1-yl]propyl}hexanamide (**1**).

Peripentadenia mearsii (C. T. White) L. S. Smith is a tree growing in rain forests of north Queensland. The genus concerned is monotypic and belongs to the family Elaeocarpaceae, from which a range of indolizidine (1) and indole (2) alkaloids has been reported. A previous examination of *P. mearsii* for alkaloids yielded tropane bases (3), but this finding could not be repeated subsequently, and the tropanes had evidently come from some other plant, so far unidentified (4). The present study has been carried out on authentic material that has been checked against herbarium voucher specimens. In addition to the major base peripentadenine (**1**), which is described here, a number of others have been isolated from leaf and bark extracts; the minor alkaloids will be treated in a subsequent report.

RESULTS AND DISCUSSION

Crude alkaloid extracts of bark and leaf material were made by standard procedures. The major base from both sources, peripentadenine (**1**), was separated and isolated by column chromatography as a light brown oil for which the formula $C_{22}H_{34}N_2O_3$ was derived by high resolution mass spectroscopy. Attempts to prepare crystalline derivatives were largely unsuccessful, but a borohydride reduction product (4A or 4B) was obtained as platelets which analyzed for $C_{22}H_{36}N_2O_3$. On hydrolysis under mild basic conditions or on prolonged storage



1 R_1 = H, R_2 = O

2 R_1 = CH_3, R_2 = O

3 R_1 = $COCH_3$, R_2 = O

4 A and B R_1 = H, R_2 = H, OH

5 A and B R_1 = CH_3, R_2 = H, OH

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in solvent, peripentadenine gave a complex mixture of basic compounds and 2-hydroxy-6-methylacetophenone (**6**). The presence of this acetophenone moiety in the original alkaloid could be deduced from the relevant absorptions in its ir and ^{13}C nmr (fig. 1) and from the characteristic aromatic proton pattern of resonances in its ^1H nmr spectrum (fig. 2) (5). Moreover, a low-field signal exchangeable with D_2O indicated a phenolic group, whose presence was confirmed by the formation of a monomethyl ether (**2**) with diazomethane, and a monoacetyl

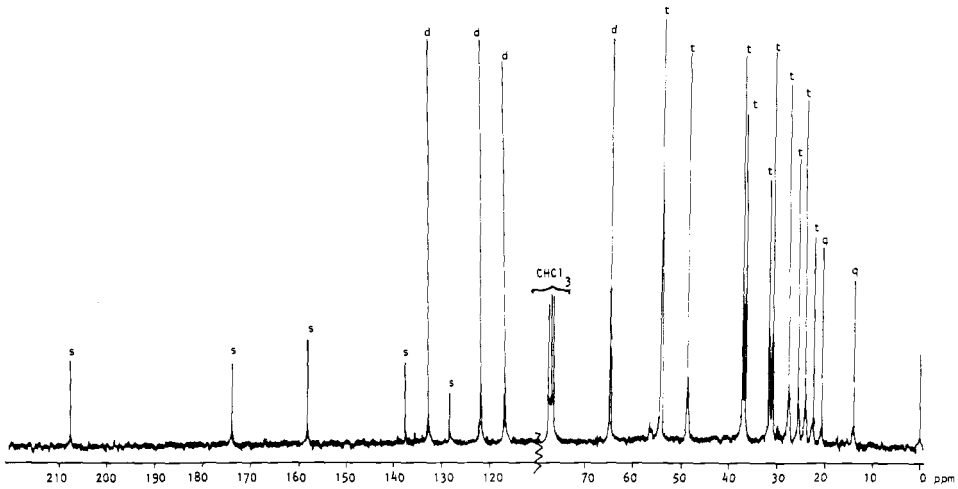


FIGURE 1.

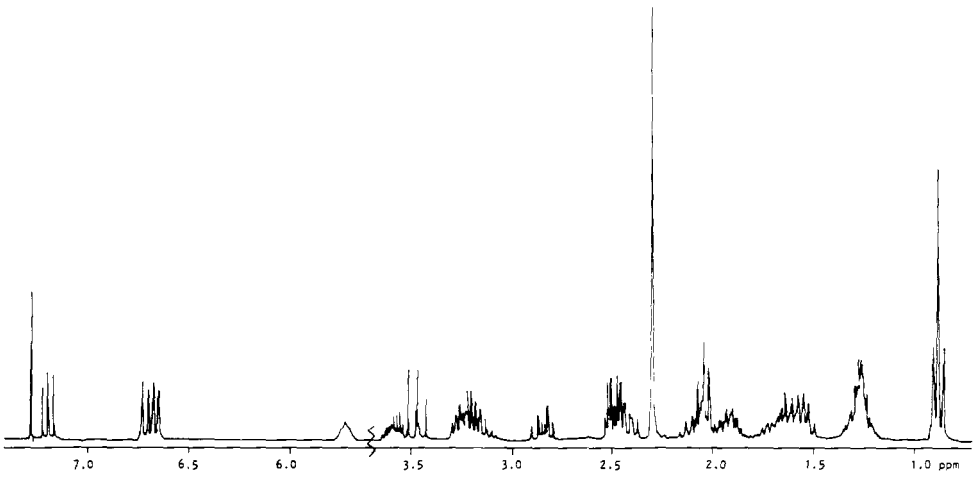
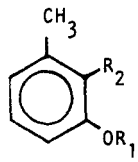


FIGURE 2.

derivative (**3**). These observations suggest that the acetophenone residue in (**1**) is linked to the rest of the molecule through the carbonyl side-chain and that the relative instability of peripentadenine may be due to the presence of a β-amino-ketone system.

The presence of an amide grouping in **1** was indicated by the appropriate absorptions in the ir and ^{13}C nmr spectra. The amide grouping could be extended to $-CH_2NHCO-$ by taking into consideration the ^1H nmr signals at 5.75 and 3.15 ppm; the latter collapsed to a triplet when the former was irradiated or exchanged with D_2O. Both signals were unaffected by treatment of peripentadenine with borohydride, but LAH reduction caused a shift to 6.9 and 2.7 ppm, respectively.



6 $R_1 = H$, $R_2 = COCH_3$

7 $R_1 = CH_3$, $R_2 = COCH_3$

8 $R_1 = H$, $R_2 = CH(OH)CH_3$

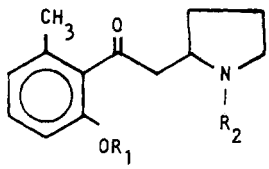
9 $R_1 = CH_3$, $R_2 = CH(OH)CH_3$

10 $R_1 = H$, $R_2 = CO_2H$

11 $R_1 = CH_3$, $R_2 = CO_2H$

An extended series of decoupling experiments indicated that the amide carbonyl is attached to a five-carbon paraffinic chain, and this inference was supported by prolonged acid hydrolysis of peripentadenine, which yielded an amine (**13**) and hexanoic acid.

The remaining carbons of **1**, apart from those in the acetophenone and hexanamide residues, are all aliphatic and comprise one methine and seven methylene carbons, as shown by the ^{13}C nmr spectrum (fig. 1). The second nitrogen is presumably present in a tertiary amine group since quaternization of peripentadenine with methyl iodide introduced only one methyl group. From these data it is evident that the amino group is in a heterocyclic ring. The ^{13}C nmr signal at 64.7 ppm for the methine carbon suggested that the ring is α-substituted; from the previous evidence, the substituent would appear to be the aroylmethyl group.



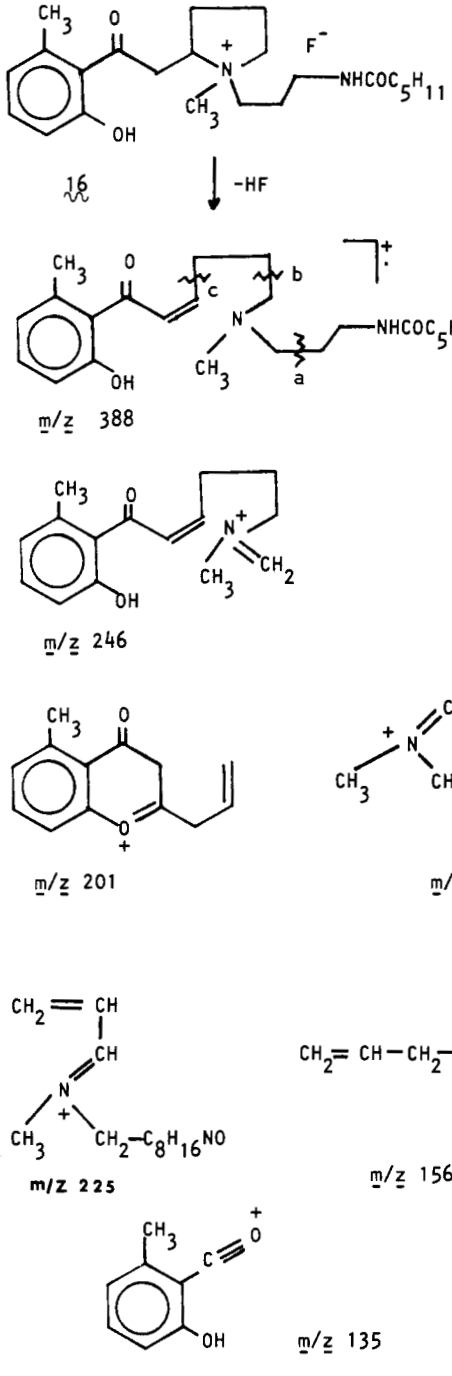
12 $R_1 = CH_3$, $R_2 = H$

13 $R_1 = H$, $R_2 = -(CH_2)_3NH_2$

14 $R_1 = CH_3$, $R_2 = -(CH_2)_3NH_2$

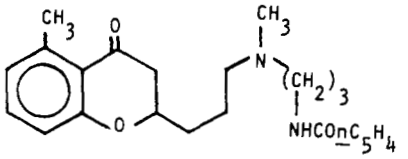
15 $R_1 = COCH_3$, $R_2 = -(CH_2)_3NHCOCH_3$

To gain an insight into the nature of the heterocyclic ring, a study was made of the ms fragmentation pattern of peripentadenine methofluoride (**16**) (scheme 1). The principal ions formed are consistent with the occurrence of a thermal Hofmann degradation (6) on a substituted pyrrolidine. When the methofluoride was subjected to pyrolysis in a kugelrohr, a single product, **17**, was formed without loss of carbon atoms. The absence of other products can be attributed to the directional effect of the carbonyl group in the β-aminoketone system. Spectroscopic and chemical evidence showed that **17** was non-phenolic and had no olefinic

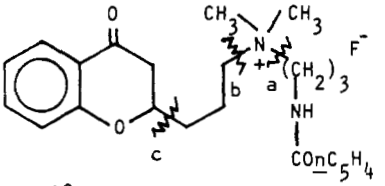


Scheme 1.

group. It could be inferred that the double bond initially formed by the Hofmann degradation had been involved in a cyclization with the hydroxyl to form a benzopyran ring. The properties of **17** were in accord with this conclusion; in



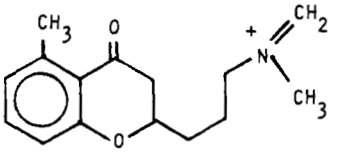
17



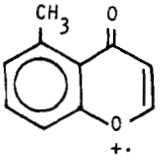
18

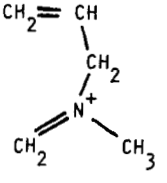
particular, the methine carbon signal at 64.7 ppm in the ^{13}C nmr spectrum of **1** had moved to 76.5 ppm in that of **17**, and new signals appeared at 4.42 (1H, ddt) and 2.65 ppm (2H, m) in the ^{1}H nmr spectrum of **17**. The methofluoride **18** formed by quaternization of **17** gave a mass spectrum consistent with the benzo-

From a: m/z 201, m/z 199 (cf. Scheme 1)

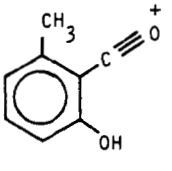
From b:  , m/z 156 (cf. Scheme 1)

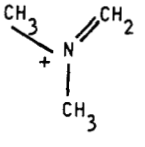
m/z 246

From c: 

m/z 160 , 

m/z 84

From a or b: 

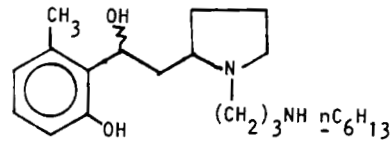
m/z 135 

m/z 58

Scheme 2.

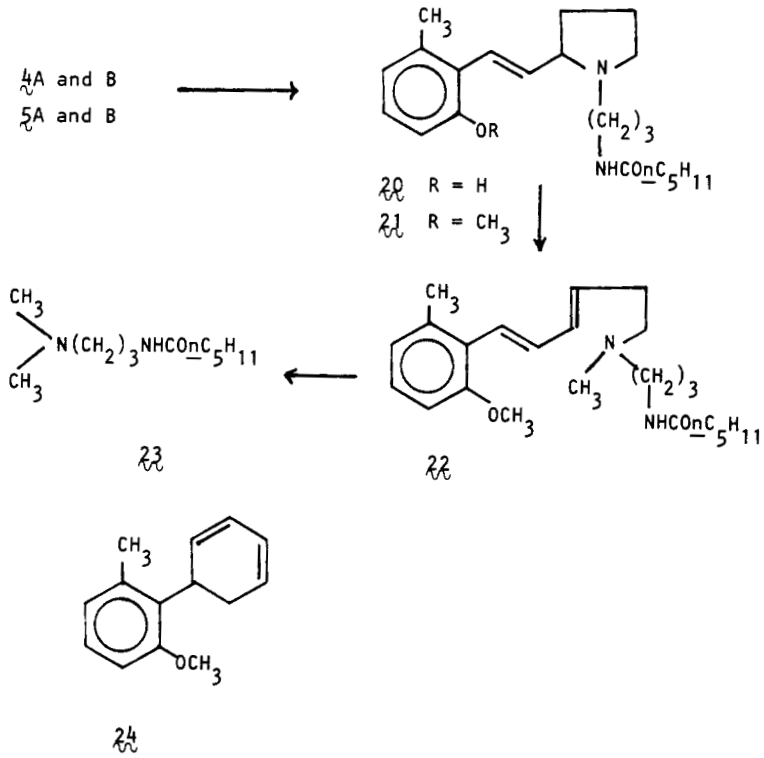
pyran structure proposed for **17** (scheme 2), but pyrolysis under similar conditions to those used for **16** gave a complex mixture from which no identifiable product could be isolated, evidently because the directional effect of the carbonyl group no longer applied. Presumably for the same reason, Hofmann degradation of **19A**, the LAH reduction product of **1** likewise gave a complicated mixture which could not be separated; Emde degradation also failed to give any useful result.

In order to provide an alternative orienting effect for a two-stage Hofmann



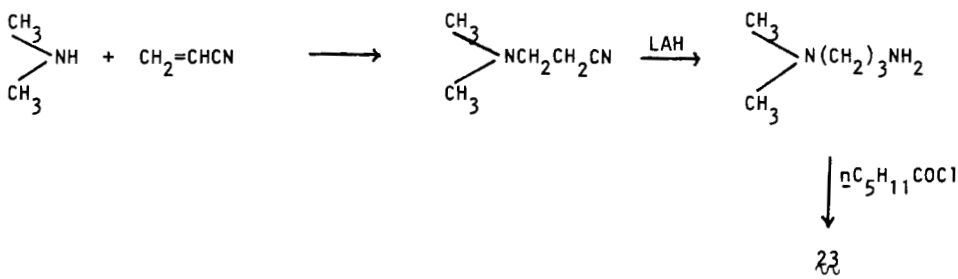
19A and B

degradation, the sequence of reactions shown in scheme 3 was carried out. Borohydride reduction of **1** gave a pair of diastereomeric secondary alcohols, **4A** and **4B**, which could be dehydrated to a single product, **20**. Formation of a heterocyclic Hofmann degradation product was prevented by use of the corresponding *O*-methylether **21** prepared from **2** through the alcohols **5A** and **5B**. Pyrolysis of

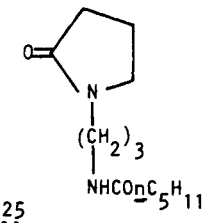


Scheme 3.

the methofluoride of **21** gave the diene **22**, and a second Hofmann degradation on this compound under similar conditions afforded a long-chain aminoamide, **23**, whose structure was proved by synthesis (scheme 4). The complementary

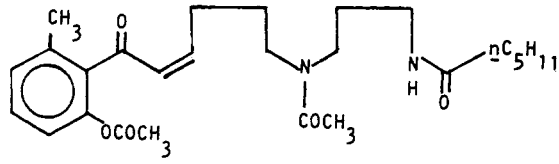


Scheme 4.



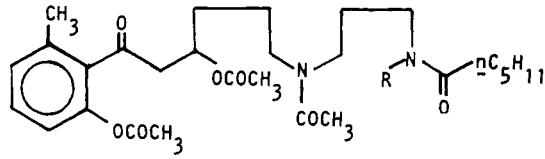
25

neutral fragment cyclized under the conditions used and was isolated as **24**. The degradations indicated the presence of a pyrrolidine ring in **1** and showed that the heterocyclic nitrogen bears a C_3 unit, as in the case of the indolizidine alkaloids isolated from *Elaeocarpus* spp. (1). Evidence for the pyrrolidine ring in peripentadenine came also from the isolation of the 2-pyrrolidone (**25**) on permanganate oxidation of **1**.



26

The above-mentioned monoacetyl derivative (**3**) of peripentadenine is formed on room-temperature acetylation; but when the reaction is carried out at 100°, a number of other products are formed. Three of these, (**26**, **27** and **28**), appear to be produced by opening of the pyrrolidine ring, while a fourth, **15**, proved to be a transacyl product derived from **3**.

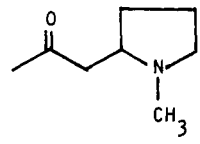


27 R = H

28 R = $COCH_3$

The structure deduced for peripentadenine has a chiral center, but the base as isolated from the plant material has a negligibly small specific rotation. The chiral center in hygrine (**29**), which presents some structural analogy to **1**, is known (7) to be readily racemized under basic conditions such as occur during the usual extraction procedures.

The structure of peripentadenine was finally confirmed by synthesis. 2-Methoxy-6-methylbenzoic acid (**11**) (8) was converted into the intermediate **12** (9), which was then reacted with acrylonitrile. Catalytic hydrogenation of the product gave the diamine (**14**), which on acylation with n-hexanoyl chloride



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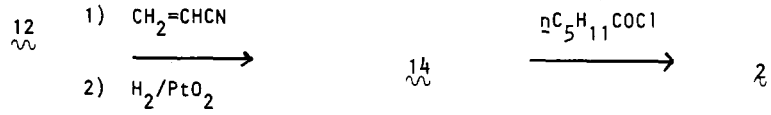
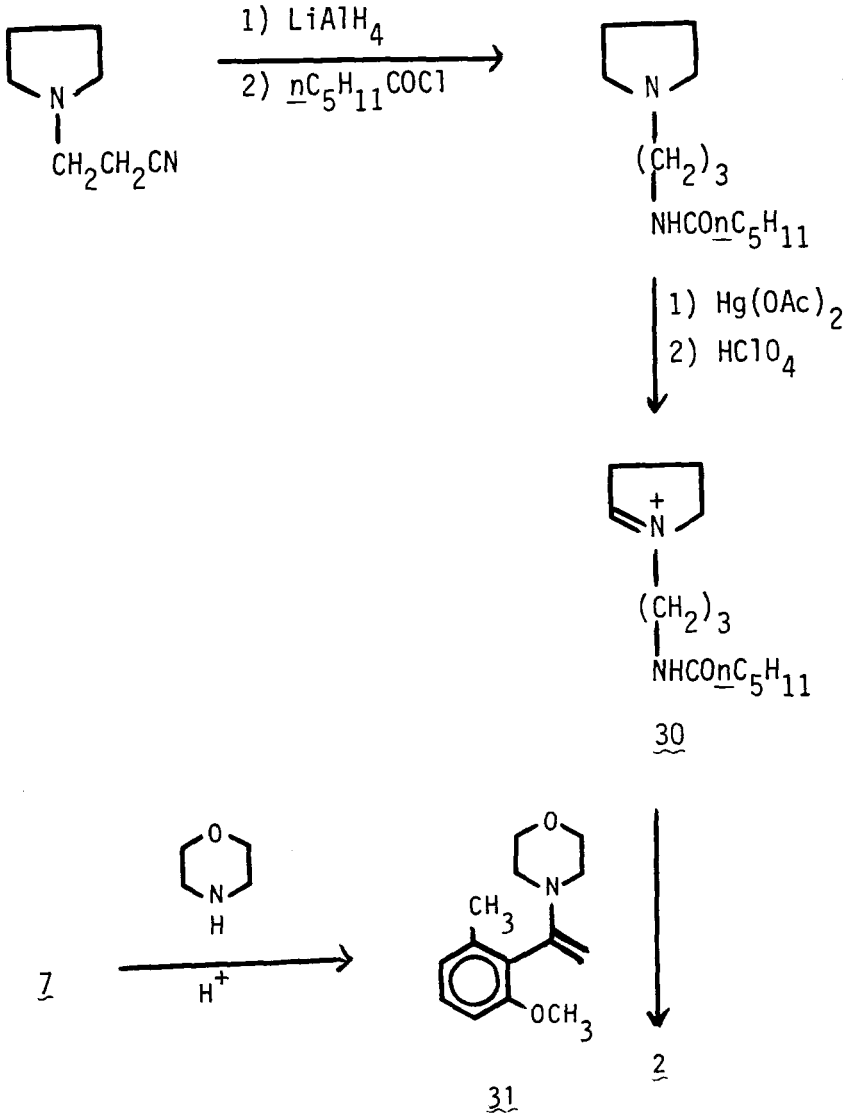


Scheme 5.

yielded **2** (scheme 5). A second approach involved the condensation of 2-methoxy-6-methylacetophenone (**7**) with the iminium salt (**30**); this reaction would correspond to a reversal of the above-mentioned hydrolytic cleavage of **1** which yields **6**. However, the condensation could not be carried out directly by basic catalysis owing to the instability of the iminium salt under these conditions. Instead the enamine (**31**) derived from **7** was prepared and immediately reacted with **30** under conditions of acid catalysis (scheme 6); subsequent work-up gave **2** in 32% yield.



Scheme 6.

EXPERIMENTAL[1]

EXTRACTION AND FRACTIONATION.—Dried milled bark (14.5 kg) collected at Boonjie, north Queensland, was extracted by percolation with ethanol at 40°. The extract was concentrated under reduced pressure, diluted with water and acidified with dilute sulfuric acid, then filtered and made basic with ammonia. The crude alkaloids were extracted with chloroform, and the chloroform solution was repeatedly reextracted with aqueous sulfuric acid (2N) until no further base was removed. The alkaloids were then recovered by basifying the combined acid extracts with ammonia and re-extracting with chloroform. Evaporation of the chloroform solution gave an oily residue of crude alkaloids (90 g, 0.62%). This was separated into four fractions by column chromatography over silica gel. The fractions eluted with chloroform and chloroform-methanol (9:1) gave 2-hydroxy-6-methylacetophenone (**6**) (2.7%) and a minor alkaloid (0.8%), respectively. Elution with chloroform-methanol (17:3) gave the major alkaloid (18.3%) as a brown oil; elution with solvents of increasing polarity gave mixtures of minor alkaloids (24.5%).

PERIPENTADENINE (**1**).—The fraction eluted with chloroform-methanol (17:3) gave a chromatographically pure viscous brown oil, *Rf* 0.45 in methanol-chloroform (1:9) and 0.48 in triethylamine-chloroform (1:9). The physical properties remained unchanged after further purification by ptlc and dccc. The base could not be obtained crystalline, and attempts to prepare a crystalline derivative were likewise unsuccessful; uv λmax 228 nm (log ε 3.96), 253 (3.36), 283 (3.15), 309 (3.15); uv λmax (MeOH+OH^-) 210 (log ε 4.08), 234 (3.99); ir νmax (neat) 3250–3020 (br, NH and OH), 1690 (ArC=O), 1680 and 1650 (CONHR), 1630 cm^{-1} (ArC=O H-bonded to ortho OH); ^{1}H-nmr (270 MHz) δ 10.5 (1H, m, ArOH), 7.15 (1H, t, J=7.5 Hz) (C-21), 6.67 (1H, d, J=7.5 Hz), (C-20), 6.63 (1H, d, J=7.5 Hz) (C-22), 5.75 (1H, m) (CONH), 3.45 (1H, dm, J=7.5 Hz) (C-2), 3.15 (2H, dt, J=6.5 and 7.5 Hz) (C-8), 2.9 (1H, t, J=10 Hz) (C-5), 2.8 (1H, t, J=10 Hz) (C-5), 2.05 (2H, t, J=7.5 Hz) (C-11), 1.85 (2H, m) (C-7), 1.8–1.7 (4H, m) (C-3 and C-4), 1.6 (2H, m) (C-12), 1.35 (4H, m) (C-13 and C-14), 0.85 (3H, t, J=7.5 Hz) (C-15); on addition of D_2O the peaks at 10.5 and 5.75 were exchanged, and the multiplet at 3.15 collapsed to a triplet, J=7.15 Hz; on irradiation at 3.15, the peak at 5.75 collapsed to a singlet, and that at 1.85 to a triplet; ms m/z 374 (M^+, 10%); 359 (0.5), 283 (25), 224 (80), 150 (100), 135 (80); high resolution mass measurement: found 375.259, calcd. for $C_{22}H_{35}N_2O_3$ (MH^+) 375.269.

PREPARATION OF *O*-METHYLPERIPENTADENINE (**2**).—An ethanolic solution of peripentadenine (**1**) (0.108 g, 0.29 mmol) was treated with ethereal diazomethane (100 mg) and left overnight. On removal of solvents, **2** was obtained as a light brown gum (0.110 g); uv λmax 225 nm (log ε 4.05), 278 (3.35), 318 (5.24); ir νmax 3300 and 3080 (CONH), 1690 (ArC=O), 1650 (NHC=O); ^{1}H-nmr δ 7.15 (1H, t, J=7.5 Hz) (C-21), 6.67 (1H, d, J=7.5 Hz) (C-20), 6.63 (1H, d, J=7.5) (C-22), 6.15 (1H, m) (CONH), 3.8 (3H, s, OCH_3), 3.45 (1H, dm, J=7.5) (C-2), 3.15 (2H, dt, J=6.5 and 7.5) (C-8), 2.9 (1H, t, J=10) (C-5), 2.8 (1H, t, J=10) (C-5), 2.05 (2H, t, J=7.5) (C-11), 1.85 (2H, m) (C-2), 1.8–1.7 (4H, m) (C-3 and C-4), 1.6 (2H, m) (C-12), 1.35 (4H, m) (C-13 and C-14), 0.85 (3H, t, J=7.5) (C-15); ms m/z 388 (M^+, 10%), 373 (M–15, 8), 224 (80), 164 (25), 150 (100).

PREPARATION OF *O*-ACETYLPERIPENTADENINE (**3**).—Peripentadenine (**1**) (0.09 g, 0.24 mmol) was treated with acetic anhydride (0.5 ml) and pyridine (0.01 ml), and the mixture was left overnight at room temperature. The solvents were removed under vacuum at 40°, and the residue, purified by ptlc, was obtained as a brown gum (0.068 g, 68%) (**3**); uv λmax 215 nm (log ε 3.06), 305 (2.89); ir νmax 3300 (CONH), 1765 ($ArOCOCH_3$), 1680, 1655 (NHC=O), 1640, 1625 cm^{-1}; ^{1}H-nmr δ 6.8 (1H, brm, NHCO), 2.27 (3H, s, $COCH_3$), 2.21 (3H, s, $ArCH_3$); ms m/z 416 (M^+, 80%), 415 (75), 401 (20), 301 (56), 224 (10), 135 (100).

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[1]Thin-layer chromatography (tlc), preparative thin-layer chromatography (ptlc) and column chromatography were performed with Merck silica gel GF_{254} or Camag silica gel DSF-5. Chloroform-methanol (9:1) mixtures were used for the tlc and ptlc separations unless otherwise specified, and the compounds were visualised by spraying with iodoplatinate reagent or by examination under uv light. Droplet countercurrent chromatography (dccc) was carried out with mixtures of chloroform, methanol, and aqueous sulphuric acid (0.001 N). The distillation of high-boiling compounds was carried out from bulb to bulb on a kugelrohr apparatus. The melting points were recorded on a Yanagimoto Seisakusho micro-melting point apparatus and are uncorrected. Specified rotations were measured in methanol on a PEOPL 60 spectropolarimeter. Ultraviolet (uv) absorption spectra were recorded on methanol solutions with a Hitachi-Perkin-Elmer 124 spectrophotometer, and the logarithms of the extinction coefficients are given in parenthesis. Infrared spectra were recorded on chloroform solutions with a Beckman IR-33 spectrometer unless stated otherwise. Proton magnetic resonance (^{1}H-nmr) spectra were recorded on deuterochloroform solutions at 100 MHz with a Jeol JNM-4H-100 MHz spectrometer unless otherwise specified; the 270 MHz ^{1}H-nmr and 67.89 Hz ^{13}C-nmr were recorded with a Bruker HX-270 spectrometer. Tetramethylsilane was used as the internal standard. Chemical shifts are given in ppm and the coupling constants in hertz (Hz). Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q) or multiplets (m). Mass spectra were run on a Vacuum General Micromass 7070 F spectrometer by the direct insertion technique at 200° and 70 eV.

Owing to their non-crystalline nature, satisfactory elemental analyses could not be obtained for many of the compounds described. In such cases, high-resolution mass spectra were used to determine molecular formulae, and homogeneity on tlc was used as a criterion of purity.

ACID HYDROLYSIS OF PERIPENTADENINE (**1**).—A solution of peripentadenine (**1**) (0.3 g, 0.8 mmol) in methanol (10 ml) was treated with aqueous hydrochloric acid (10%, 90 ml). The mixture was heated under reflux until **1** could no longer be detected by tlc. The methanol was removed under vacuum, and the aqueous phase was extracted with chloroform (3 x 50 ml). The extract, when dried (Na_2SO_4) and evaporated gave a colorless gum (0.060 g, 64%); ir νmax 3000, 1760, 1710 cm^{-1}. An ethereal solution of the gum (0.06 g), treated with ethereal diazomethane overnight and then evaporated gave an oil (0.065 g) which was identified as methyl hexanoate by glc-ms comparison with an authentic sample. The aqueous phase was basified with ammonia and extracted with chloroform (3 x 50 ml); removal of solvents left a brown gum (0.16 g) which, when purified by tlc, gave **13** (0.074 g, 34%) as a yellow oil; uv λmax 225 nm (log ε 3.93), 255 (3.51), 315 (3.18); ir νmax 3400–3200 (NH, OH), 1690, 1680, 1650, 1640, 1600 and 1590 cm^{-1}; ^{1}H-nmr δ 7.15 (1H, dd, J=7.2), 6.8 (2H, dd, J=7.2), 3.5 (1H, m), 2.7 (2H, t, J=6.5), 2.6 (3H, s), 2.4–2.0 (4H, m), 1.8–1.6 (6H, m), 1.2 (2H, brm, exchanged with D_2O); ms m/z 276 (M^+, 2%), 246 (18), 218 (12), 185 (30), 150 (60), 136 (100); high resolution mass measurement: found 276.1876, calcd. for $C_{16}H_{24}N_2O_2$ 276.1852.

HOFMANN DEGRADATION OF PERIPENTADENINE (**1**).—An acetonitrile solution of **1** (0.5 g, 0.14 mmole in 10 ml) was heated to 100°, and methyl iodide was added at 10 hour intervals (5 x 1 ml). The solvent was removed under vacuum, and the methiodide salt, separated from unreacted **1** and purified by ptlc, was obtained as a yellow gum (0.170 g, 24.5%); high resolution mass measurement: found 389.2746, calcd. for $C_{23}H_{37}N_2O_3$ 389.2823. The methiodide was converted to the methofluoride (**16**) (0.11 g, 90%) by passing an aqueous methanol solution (1:1, 50 ml) through an Amberlite IRA 400 (F^- form, 20 g) column; ms m/z 388 (4%), 260 (6), 246 (95), 255 (18), 201 (24), 199 (100), 156 (13), 135 (5). A sample of **16** was pyrolysed in a kugelrohr at 220° and 6.3 x 10^{-1} Hg mm to give **17** as a colorless gum (0.085 g, 81%); uv λmax 222 nm (log ε 2.68), 258 (2.68), 320 (2.42); ir νmax 3340 (NH), 1710, 1680, 1650, 1600 cm^{-1}; ^{1}H-nmr δ 4.42 (1H, ddt, J=10.2, 5.1), 2.65 (1H, dd, J=10.2, 5), 2.63 (3H, s, H–CH_3); ^{13}C-nmr 193.7 (s), 173.1 (s), 162.5 (s), 142.1 (s), 134.6 (d), 126.2 (s), 124.5 (d), 115.7 (d), 76.5 (d), 57.5 (t), 56.6 (t), 44.5 (q), 41.6 (t), 39.0 (t), 36.9 (t), 32.6 (t), 31.5 (t), 25.9 (t), 25.5 (t), 22.7 (t), 22.5 (q), 22.4 (t), 13.9 (q); high resolution mass measurement: found 389.2794, calcd. for $C_{23}H_{37}N_2O_3$ (MH^+) 389.2804.

LAH REDUCTION OF PERIPENTADENINE.—A solution of peripentadenine (**1**) (0.374 g, 1 mmol) in dry dimethoxyethane (20 ml) was added dropwise to a stirred mixture of LAH (0.300 g, 7.9 mmol) in dimethoxyethane (30 ml) under anhydrous conditions. The mixture was stirred for 4 hours at room temperature, then treated successively with water (0.3 ml), aqueous sodium hydroxide (15%, 0.3 ml), and more water (1 ml). The white precipitate formed was filtered off and washed with methanol (50 ml), and the combined washings and filtrate were evaporated under vacuum to remove the organic solvents. The aqueous phase was diluted with water, basified with ammonia, and extracted with chloroform (3 x 30 ml). The extract was dried and evaporated to a gum (0.4 g) from which **19A** (0.085 g, 22%) and **19B** (0.076 g, 20%) were separated by ptlc; **19A**: uv λmax 235 nm (log ε 3.44), 303 (2.90); ir νmax 3300–3200 (NH and OH), 1590, 1460, 1380, 1260, 1050 cm^{-1}; ms m/z 362 (M^+, 85%), 344 (15), 291 (3), 233 (6), 230 (6), 225 (15), 220 (20), 211 (60), 210 (68), 209 (100), 202 (60), 182 (50), 149 (60). **19B**: uv λmax 230 nm (log ε 3.38), 310 (2.89); ir νmax 3400–3100, 1590, 1580, 1560, 1460, 1270, 1020 cm^{-1}; ms m/z 362 (M^+, 65%), 334 (6), 230 (15), 225 (45), 220 (30), 202 (40), 201 (65), 200 (85), 199 (100), 136 (85).

HOFMANN DEGRADATION OF **19A**.—The LAH reduction product, **19A**, (0.058 g, 0.16 mmol) was converted into its methofluoride as described for **1**; ms m/z 406 (6%), 392 (60), 369 (85), 242 (35), 221 (100), 199 (80), 152 (62), 150 (60), 129 (70). When the methofluoride was subjected to pyrolysis as described for **16**, a complex mixture was obtained from which no single product could be separated pure.

HOFMANN DEGRADATION OF **17**.—The first Hofmann product (**17**, 0.09 g, 0.23 mmol) from peripentadenine was converted to the methofluoride (**18**, 0.057 g, 58%) by the same procedure as for **1**; ms m/z 403 388 (5), 246 (47), 225 (2), 201 (24), 199 (44), 160 (10), 156 (65), 135 (28), 134 (10), 105 (11), 99 (18), 84 (12), 58 (100). When it was subjected to pyrolysis under similar conditions to **14**, a dark brown sublimate (0.03 g, 52%) was produced, which proved to be a complex mixture from which no pure substance could be isolated.

SODIUM BOROHYDRIDE REDUCTION OF PERIPENTADENINE (**1**).—Peripentadenine (1.0 g, 0.02 mmol) was dissolved in aqueous methanol (30 ml), and sodium borohydride (0.4 g, 0.08 mmol) was added in small quantities with constant stirring. The mixture was left overnight, then diluted with water (120 ml), acidified with dilute sulfuric acid, and extracted with chloroform (2 x 50 ml). The extract, on evaporation, gave a colorless gum (0.021 g) which was not further examined. The aqueous phase on basification and extraction with chloroform (3 x 50 ml) gave a yellow gum (0.723 g), which on ptlc separation [chloroform-methanol (9:1)] yielded three products. The least polar fraction formed white crystals of dihydroperipentadenine (**4A**) (0.630 g, 63%), mp 78° (from acetone); $[\alpha]^{21}D$ 0° (in MeOH and in $CHCl_3$); uv λmax 217 nm (log ε 4.57), 276 (4.17); ir νmax 3300 (OH,NH), 1645 (CONH), 1600 cm^{-1}; ^{1}H-nmr (270 MHz) δ 5.95 (1H, t, J=7, NHCO), 5.53 (1H, dd, J=11.3, 2.5, C*H*OH); ms m/z 376 (M^+, 70%), 375 (100), 362 (10), 360 (75), 249 (8), 225 (90), 136 (40), 135 (50), 121 (80); found C 69.74, H 9.94, N 7.53; calcd. for $C_{22}H_{36}N_2O_3$, C 70.21, H 9.65, N 7.45%. The most polar fraction gave a colorless gum, (**4B**) (0.080 g, 8%); $[\alpha]^{21}D$ 0° (in MeOH and in $CHCl_3$); uv λmax 208 nm (log ε 4.22), 218 sh (4.06), 275 (3.53); ir νmax 3300 (NH, OH), 1645 (CONH), 1600 cm^{-1}; ^{1}H-nmr (270 MHz) δ 6.26 (1H, t, J=6.2, NHCO), 5.30 (1H, dd, J=10.9, 2.3, C*H*OH ms m/z 376 (M^+, 45%), 375 (58), 361 (40), 360 (45), 359 (60), 245 (10), 226 (20), 225 (100), 121 (70).

DEHYDRATION OF DIHYDROPERIPENTADENINE (**4A** and B).—A solution of **4A** (0.2 g), (0.53 mmol) in 10% aqueous oxalic acid (50 ml) was refluxed for 6 hours, allowed to cool, basified with ammonia, and extracted with chloroform (4 x 30 ml). The extract, on evaporation, gave **20** (0.182 g, 95%) as a yellow gum; uv λmax 217 nm (log ε 4.24), 255 (3.92), 297 (3.38); ir νmax 3300, 1650, 1600, 1590 cm^{-1}; ^{1}H-nmr (270 MHz) δ 6.95 (1H, m, CONH), 6.91 (1H, t, J=8), 6.6 (4H, m); ^{13}C-nmr 173.7 (s), 155.0 (s), 137.4 (s), 134.0 (d), 127.7 (d), 127.5 (s), 122.7 (s), 121.7 (d), 113.8 (d), 70.5 (d), 53.4 (t), 51.9 (t), 38.2 (t), 36.7 (t), 31.6 (t), 31.4 (t), 27.0 (t), 25.4 (t), 22.3 (t), 22.1 (t), 20.7 (q), 13.9 (q); ms m/z 359 (NH^+, 20%), 358 (M^+, 60), 342 (12), 315 (5), 280 (18), 231 (85), 226 (70), 202 (98), 185 (70), 155 (80), 149 (100).

A sample of **4B** (0.08 g, 0.21 mmol), when treated as for **4A**, gave **20** (0.068, 89%).

SODIUM BOROHYDRIDE REDUCTION OF *O*-METHYLPERIPENTADENINE (**2**).—A solution of **2** (2.547 g, 6.56 mmol) was reduced with borohydride, and the product was worked up under the same conditions as for **1**. The neutral fraction from ptlc gave 2-methoxy-6-methylacetophenone (**6**) (0.3 g, 27%); uv λmax 220 nm (log ε 4.85), 242 (3.63), 280 (3.56); ir νmax 1690 (CO), 1600, 1590 cm^{-1}; ^{1}H-nmr δ 7.2 (1H, dd, J=6.5), 6.8 (1H, d, J=6.25), 6.75 (1H, d, J=6.25), 3.8 (3H, s, OCH_3), 2.4 (3H, s, $COCH_3$), 2.25 (3H, s, $ArCH_3$); and 1 (2-methoxy-6-methylphenyl)ethanol (9) (0.042 g, 3.8%); uv λmax 220 nm (log ε 4.61), 275 (3.13), 280 (3.13); ir νmax 3300 (OH), 1600, 1590 cm^{-1}; ^{1}H-nmr δ 6.72 (1H, d, J=7.5), 5.25 (1H, q, J=7.5), 3.9 (3H, s, OCH_3), 2.19 (3H, s, $ArCH_3$), 1.45 (3H, d, $CHOHCH_3$). The basic fraction gave a brown gum (2.3 g) which, on ptlc, yielded **5A** (1.97 g, 79.8%); uv λmax 208 nm (log ε 3.78), 285 (3.00), 320 (2.79); ir νmax 3300, 1090, 1660, 1640 and 1600 cm^{-1}; ^{1}H-nmr δ 4.8 (1H, dd, J10, 3.=5, C*H*OH); ms m/z 390 (M^+); and **5B** (0.06 g, 2.3%); uv λmax 225 nm (log ε 3.80), 280 (2.97), 335 (2.77); ir νmax 3300, 1690, 1665, 1650, 1600 cm^{-1}; ^{1}H-nmr δ 5.1 (1H, dd, J=10, 3.5 C*H*OH); ms m/z 390 (M^+); also some highly polar material (0.36 g, 14%) which could not be satisfactorily purified.

DEHYDRATION OF *O*-METHYLDIHYDROPERIPENTADIENE (**5A**).—A solution of **5A** (1.97, 5.05 mmol) in aqueous oxalic acid (10%, 200 ml) was refluxed for 6 hours, and the product was worked up as for **20** and obtained as a yellow gum (**21**) (1.49 g, 80%) uv λmax 223 nm (log ε 3.90), 258 (3.62), 295 (3.23); ir νmax 3300, 1660, 1650, 1590 cm^{-1}; ^{1}H-nmr δ (1H, t, J=7.5); 6.8 (2H, dd, J=7.5), 6.78 (1H, d, J=16), 6.0 (1H, dd, J=16, 7.5), 3.8 (3H, s, OCH_3); ms m/e 372 (M^+, 28%), 357 (5), 244 (30), 226 (80), 225 (100), 216 (65), 201 (18), 200 (20), 185 (36), 156 (87), 135 (50).

HOFMANN DEGRADATION OF **21**.—The above-mentioned dehydration product, **21** (1.49, 4.01 mmol) was converted to the methiodide (1.51, 73.5%) and thence to the methofluoride (1.10 g, 92.5%) as described for **1**. Pyrolysis of the methofluoride at 160° and 6.3 x 10^{-4} Hg nm, and purification of the product by ptlc gave **22** as a yellow gum (0.695 g, 69%); uv λmax 218 nm (log ε 3.30), 308 (3.00); ir νmax 3300, 1660, 1650, 1575 cm^{-1}; ^{1}H-nmr (270 MHz) δ 7.1 (1H, dd, J=7), 6.8 (2H, dd, J=7), 6.78 (1H, d, J=14), 6.55 (1H, dd, J=16, 14), 6.25 (1H, dd, J=16, 7.5), 5.75 (1H, m), 3.83 (3H, s, OCH_3); ms m/z 386 (M^-, 2%), 384 (8), 372 (10), 341 (26), 244 (20), 230 (22), 216 (25), 200 (26), 199 (100), 156 (80).

HOFMANN DEGRADATION OF **22**.—The above-mentioned Hofmann degradation product, **22**, (0.695 g, 1.8 mmol) was converted to the methofluoride (0.233 g, 30.8%) as before; pyrolysis under similar conditions gave a brown oil (0.211 g) which after ptlc yielded **24** (0.065 g, 30%): ur λmax 208 nm (log ε 4.06), 275 (3.62), 292 (3.62), 310 (3.57); ir νmax 1650, 1600, 1590 cm^{-1}; ^{1}H-nmr δ 7.1 (1H, m), 6.7 (2 I, m), 6.2 (2H, m), 5.6 (2H, m), 3.8 (3H, s), 2.35 (3H, m); ms m/z 201 (MH^+, 65%), 200 (25), 187 (12), 177 (36), 175 (28), 149 (60), 135 (100), 128 (80), 115 (95), 105 (56), 91 (72), 77 (68); and N-[3-(dimethylamino)propyl]hexanamide (**23**) (0.038 g, 18%), ir νmax 3450 and 3300 (CONH), 1665 (CONH), 1450, 1430, 1420, 1180, 1050 cm^{-1}; ^{1}H-nmr (270 MHz) δ 7.0 (1H, m, CONH), 3.34 (2H, dt, J=6.5, 6.5), 2.45 (2H, t, J=6.5), 2.28 (6H, s, NMe_2), 2.16 (2H, t, J=7.3), 1.69 (2H, tt, J=7.3, 7.3), 1.61 (2H, tt, J=6.5, 6.5), 1.29 (tq, J=7.3, 7.3), 1.25 (2H, tq, J=7.3, 7.3), 0.87 (3H, t, J=7.3, CH_3); ms m/z 200 (M^+, 20%), 199 (5), 149 (15), 142 (10), 85 (36), 72 (80), 59 (60), 58 (100); and some highly polar material which could not be purified.

SYNTHESIS OF N-[3-(DIMETHYLAMINO)PROPYL]HEXANAMIDE (**23**).—To a mixture of dimethylamine (20 ml, 25% w/v aq. soln., 5 g, 0.1 mol) and methanol (20 ml) at 0°, acrylonitrile (5 g, 0.09 mol) was added dropwise. The mixture was heated at 100° in a sealed tube for 3 hours, then acidified with dilute sulfuric acid; the methanol was removed under vacuum. The aqueous residue was basified and extracted with chloroform, and the extract was dried and evaporated. The residue, 3-(dimethylamino)propanenitrile (7.5 g, 85%), bp 68° [lit. 68° (10)] was reduced with LAH, and the product was worked up in the usual way and distilled to give 3-(dimethylamino)propylamine, bp 133–137°, in 81% yield. To a rapidly-stirred mixture of this base (1.02 g, 0.01 mol) in ether (10 ml) and aqueous sodium hydroxide (10%, 20 ml) at 0°, *n*-hexanoyl chloride (1.34 g, 0.01 mol) was added dropwise, and the mixture was allowed to stand overnight. The ether phase was washed, dried and evaporated to give **23** as a viscous oil (1.8 g, 90%), bp 114°, identical (co-tlc, ir, nmr) with the Hofmann degradation product **23**.

ACETYLATION OF PERIPENTADENINE (**1**) AT 100°.—Peripentadenine (0.850 g, 2.27 mmol) was heated on a waterbath with acetic anhydride (5 ml), glacial acetic acid (5 ml) and pyridine (0.5 ml) for 30 minutes. The mixture was poured into ice water (50 ml), made alkaline with ammonia, and extracted with chloroform (3 x 50 ml). The extract was dried (Na_2SO_4) and evaporated to dryness, and traces of pyridine were removed from the residue under vacuum over phosphorus pentoxide. The dark brown gum obtained (1.3 g) was separated by chromatography over silica gel (70 g) into five compounds:

Diacetate **26**: the least polar fraction gave a light brown oil **26** (0.27 g, 13.2%); ir νmax 3300, 1765, 1720, 1670, 1650 cm^{-1}; ^{1}H-nmr δ 6.8 (1H, m, NHCO), 6.4 (2H, m), 2.25 (3H, s,

$ArOCOCH_3$), 2.2 (3H, s, $ArCH_3$), 2.1 (3H, s, $NCOCH_3$); ms *m/z* 460 (M^+, 100%), 443 (26), 416 (70), 40 (15), 373 (5), 343 (20), 301 (18).

Triacetate **27**: The next fraction in order of polarity gave a brown gum (0.03 g, 2.3%); ir νmax 3300, 1765, 1760, 1745, 1700, 1655 cm^{-1}; ^{1}H-nmr ($CDCl_3$ æ 6.8 (1H, m, NHCO), 3.7 (1H, m), 2.35 (3H, s, $OCOCH_3$), 2.25 (3H, s, $ArOCOCH_3$), 2.2 (3H, s, $ArCH_3$); ms *m/z* 518 (M^+, 100%), 500 (40), 485 (10), 475 (32), 473 (15), 458 (80), 443 (25), 416 (70), 343 (20), 301 (20).

Monoacetate **3**: the next fraction gave the monoacetate previously obtained (0.740 g, 56.9%).

Tetraacetate **28**: the fourth fraction gave a dark brown gum (0.02 g, 1.5%); ir νmax 1770, 1765, 1745, 1700, 1650, 1640 cm^{-1}. ^{1}H-nmr δ 3.7 (1H, m), 2.35 (3H, s, $OCOCH_3$), 2.75 (3H, s, $ArOCOCH_3$), 2.2 (3H, s, $ArCH_3$), 2.15 (3H, s, $NCOCH_3$), 2.1 (3H, s, $NCOCH_3$); ms *m/z* 560 (M^+, 20%), 458 (45), 416 (40), 214 (100).

Transacetylated compound **15**: the fraction of highest polarity (0.066 g, 5.1%); ir νmax 3300, 1765, 1750, 1690, 1650, cm^{-1}; ^{1}H-nmr δ 6.8 (1H, m, NHCO), 2.25 (3H, s, $ArOCOCH_3$), 2.2 (3H, s, $ArCH_3$), 2.1 (3H, s, $NCOCH_3$); ms *m/z* 360 (M^+, 30%), 318 (10), 300 (8), 258 (12), 135 (100).

PERMANGANATE OXIDATION OF PERIPENTADENINE (**1**).—Peripentadenine (0.120 g, 0.3 mmol) was dissolved in acetone (5 ml) that had been freshly distilled over potassium permanganate. To this solution was added a freshly prepared solution of potassium permanganate in acetone (1%, 14 ml) until the purple color persisted for a few minutes. The precipitate was filtered and boiled with acetone (100 ml) for 30 minutes, then the suspension was filtered and the acetone solutions were combined and evaporated under vacuum. The gummy residue was dissolved in chloroform (50 ml) and the solution was extracted with aqueous sodium carbonate (10%, 3 x 25 ml). The extract was acidified and extracted with chloroform (3 x 10 ml).Evaporation of the solvent gave 2-hydroxy-6-methylbenzoic acid (0.026 g) (10) as white needles after recrystallization from benzene, mp 167° [lit. 167° (11)]. The chloroform solution from above after extraction with aqueous sodium carbonate was dried and evaporated. The residue (0.070 g) on ptlc gave a brown gum (**25**) (0.058 g, 72%); ir νmax 3300 (NHCO), 1660, 1640 cm^{-1}; ^{1}H-nmr δ 6.7 (1H, m, NHCO), 3.4 (2H, m), 3.2 (2H, td, J=6.5, NH-CH_2), 2.45 (2H, m), 2.3 (2H, m), 2.1 (2H, t), 1.9 (2.4 m), 1.7 (4H, m), 1.3 (4H, m), 0.8 (3H, t); ms *m/z* 240 (M^+, 5%), 198 (5), 184 (30), 112 (100), 99 (10), 98 (70), 97 (72), 85 (20), 84 (18), 57 (60), 43 (95), 42 (12), 41 (50).

2-METHOXY-6-METHYLBENZOYL CHLORIDE.—2-Methoxy-6-methylbenzoic acid (2.0 g, 12.05 mmol) in chloroform (20 ml) was refluxed for 12 hours with thionyl chloride (2.97 g, 24 mmol) and dimethylformamide (0.1 g) under anhydrous conditions. The solvents were removed under vacuum, and the yellow viscous oil remaining was distilled to obtain the acid chloride (1.56 g, 71%), bp 235–240°; ir νmax (neat) 1680 (CO), 1570, 1460, 1390, 1360, 1280 and 1250 cm^{-1}.

2-(2-METHOXY-6-METHYLBENZOYLMETHYL)PYRROLIDINE (**12**).—The acid chloride from above (1.54 g, 8.47 mmol) in ether (50 ml) was added dropwise to a stirred mixture of alcohol-free anhydrous diazomethane (1.12 g, 25 mmol) in ether (85 ml) and dry triethylamine (0.5 g, 8.5 mmol) under anhydrous conditions at 0°. The mixture was stored overnight at 0°, and the separated salt was then filtered off. The solvents were removed under vacuum, and the diazoketone thus obtained was dissolved in dry chloroform (50 ml) and added dropwise to a magnetically-stirred mixture of pyrrole (1.7 g, 25 mmol), freshly prepared and dried copper powder (2 g), and benzene (30 ml) under anhydrous conditions. The temperature of the mixture was maintained at 55–60° for 5 hours, then the solvents were removed and the black syrup was chromatographed on a silica gel column with chloroform-methanol mixtures of increasing polarity. The fraction eluted with a 4:1 mixture gave the pyrrolylmethyl ketone (0.52 g, 26%), mp 93° [lit. 93° (9)]; ir νmax 3400, 1685, 1620 cm^{-1}; ^{1}H-nmr δ 2.2 (3H, s, $ArCH_3$), 3.85 (3H, s, OCH_3), 4.12 (2H, s, $COCH_2$), 6.2–7 (6H, m). This ketone was hydrogenated in glacial acetic acid (8 ml) over PtO_2 (0.3 g) at room temperature and atmospheric pressure. After the usual work-up, pyrrolidinyl methyl ketone (**12**) (0.315 g, 62%) was obtained as a yellow oil; ir νmax (neat) 3400, 1685, 1620, 1590 cm^{-1}; ms *m/z* 233 (M^+, 5%); ^{1}H-nmr δ 7.1 (1H, t, J=7), 6.8/2H, dd, J=7), 3.1 (1H, m, NCH), 2.9 (2H, m, CH_2CO), 2.5 (2H, m, NCH_2), 1.6–1.8 (4H, m).

3[2(2-METHOXY-6-METHYLBENZOYLMETHYL)PYRROLIDIN-1-YL]PROPYLAMINE (**14**).—The pyrrolidine derivative (**12**) (0.300 g, 1.28 mmol), acetonitrile (20 ml), acrylonitrile (0.150 g, 2.8 mmol) and a drop of glacial acetic acid were heated under reflux for 6 hours. The solvents were removed under vacuum, and the crude nitrile thus obtained (0.305 g), ir νmax 2250 cm^{-1} (C≡N), was hydrogenated over PtO_2 (0.3 g) in glacial acetic acid (10 ml) at atmospheric pressure. The acid solution was filtered, diluted with water, basified with ammonia, and extracted with chloroform (3 x 50 ml). The brown gum obtained on evaporation of the chloroform was purified by ptlc to yield **14** as a brown viscous oil (0.22 g, 62%); uv λmax 225 nm (log ε 3.16), 245 (2.71), 280 (2.47); ir νmax 3350 (NH_2), 1680 (C=O), 1640, 1580, 1565 cm^{-1}; ^{1}H-nmr δ 7.1 (1H, t, J=7), 6.7 (1H, d, J=7), 6.65 (1H, d, J=7), 5.2 (2H, m, NH_2), 3.85 (3H, s, OCH_3), 3.15 (1H, m), 2.2 (3H, s, $ArCH_3$); ms *m/z* 291 (MH^+, 1%), 290 (3), 226 (8), 232 (11), 164 (14), 149 (72), 127 (34), 126 (18), 125 (15), 96 (25), 91 (44), 84 (100).

N{3[2(2-METHOXY-6-METHYLBENZOYLMETHYL)PYRROLIDIN-1-YL]PROPYL}HEXANAMIDE (**2**).—To a rapidly-stirred mixture of **14** (0.05 g, 0.17 mmol) and aq. sodium hydroxide (10 ml of 10%) at 0°, n-hexanoyl chloride (0.03 g, 0.22 mmol) in ether (10 ml) was added dropwise and the solution was stirred for another 2 hours at room temperature. The ether layer was separated, the aqueous phase was extracted with chloroform (2 x 20 ml), combined with the ether layer, and evaporated. The gum obtained, when purified by ptlc, gave **2** (0.06 g, 89%), identical (tlc, ir, ^{1}H-nmr) with O-methylperipentadenine.

2-METHOXY-6-METHYLACETOPHENONE (**6**).—The method employed for the preparation of the acid **11** was followed; acetylacetone was used instead of ethyl acetoacetate to give **6**, bp 98° at 2 mm Hg, in 20% yield c.f. acetylacetone.

N[3-(PYRROLIDIN-1-YL)PROPYL]HEXANAMIDE (**30**).—*n* Hexanoyl chloride (5 g, 3.2 mmol) in ether was added to the magnetically-stirred mixture of 3-(pyrrolidin-1-yl)propylamine (5 g, 4 mmol) prepared by LAH reduction of 3-(pyrrolidin-1-yl)propanenitrile, and aqueous sodium hydroxide (10%, 50 ml) at 0°. The mixture was left at room temperature for 6 hours; the ether layer, when dried and distilled, gave **30** (8 g, 96%), bp_{10mm} 148°; ir νmax (neat) 3300, 3100 (NHCO), 1660 cm^{-1}; ^{1}H-nmr δ 7.2 (1H, m, CONH), 3.35 (2H, dt, J=6.5, CH_2–NH), 2.65 (2H, t, J=2.5, N–CH_2), 2.5 (2H, m), 2.15 (3H, t, J=7.5, $COCH_3$), 1.85 (2H, m), 1.8 (2H, m), 1.7 (2H, m), 1.3 (4H, m), 0.9 (3H, t, J=2.5).

IMINIUM SALT OF **30**.—The hexanamide **30** (1.12 g, 0.01 mmol) in aqueous acetic acid (5%, 50 ml) and mercuric acetate (9.56 g, 0.03 mol) were heated on a water bath for 2 hours. The mixture was cooled, then filtered to remove mercurous salts; hydrogen sulfide was passed through the filtrate until no more mercuric sulfide was precipitated. The mixture was centrifuged, and the precipitate was washed with dilute acetic acid. The combined washings and filtrate were evaporated to dryness under vacuum at 45°. The residue, dried under vacuum and dissolved in absolute ethanol (10 ml), was treated with perchloric acid (0.5 ml) and stored overnight at 0°. The perchlorate salt separated as a yellow gum, which was dried under vacuum for several days (1.48 g). Attempts to crystallize the salt were not successful.

SYNTHESIS OF O-METHYLPERIPENTADENINE (**2**).—2-Methoxy-6-methyl-acetophenone (**6**) (0.5 g, 3 mmol), morpholine (0.5 ml, 5.6 mmol) and *p*-toluenesulphonic acid (0.1 g) in toluene (30 ml) were refluxed for 4 hours in a flask fitted with a Dean and Stark separator and a dropping funnel. The iminium salt of **30** (1.0 g, 3 mmol) in diglyme (20 ml) was added slowly, and the mixture was refluxed for a further 5 hours, then the solvents were removed under vacuum and the residue was dissolved in dilute sulfuric acid (50 ml). The solution was washed with chloroform (50 ml), basified with ammonia, and extracted with chloroform (3 x 25 ml). The chloroform extract was dried and evaporated; the brown gum obtained (1.2 g), when separated by ptlc, gave (**2**) (0.375 g, 32%), identical (tlc, ir, ^{1}H-nmr) with *O*-methylperipentadenine.

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