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ALKALOIDS OF *Peripentadenia mearsii*. II[1]

MINOR BARK ALKALOIDS

I. RALPH C. BICK* and Y.A. GEEWANANDA P. GUNAWARDANA

Chemistry Department, University of Tasmania, Hobart, Tas., Australia 7005

and JOHN A. LAMBERTON

Division of Applied Organic Chemistry, CSIRO, GPO Box 4331, Melbourne, Vic., Australia 3001.

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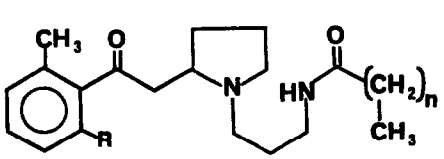
Abstract - The structures of the three minor alkaloids dinorperipentadenine, peripentamine and anhydroperipentamine have been established as 2, 5, and 6 respectively.

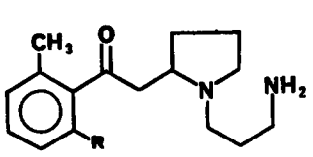
The elaeocarpaceous plant *Peripentadenia mearsii* (C.T. White) L.C. Smith, which grows in north Queensland rain forests, has proved to be a rich source of alkaloids both in quantity (0.62% of dry weight) and in structural diversity[1-3]. The major alkaloid of both bark and leaf extracts, peripentadenine, has been shown previously to have structure 1[1] from spectroscopic and degradative evidence and by synthesis.

RESULTS AND DISCUSSION

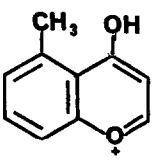
A number of minor alkaloids have been isolated from the bark, including dinorperipentadenine (2) which, like 1, was obtained as a yellow oil. Its molecular formula, established by high resolution ms, differs from that of peripentadenine by C_2H_4, and a comparison of the principal fragment ions from the two bases (Scheme 1) suggested that the difference lies in the amide side chains: when the latter are retained, corresponding ions differ by 28 amu, but otherwise the same ion fragments are observed; the S_N2-type cleavage products of the N[3-aminopropyl]amide grouping[4] are especially significant. The presumption of a shorter side-chain is supported by a comparison of the ^{13}C nmr spectra of 1 and 2 (Table 1), which match each other closely except for the absence



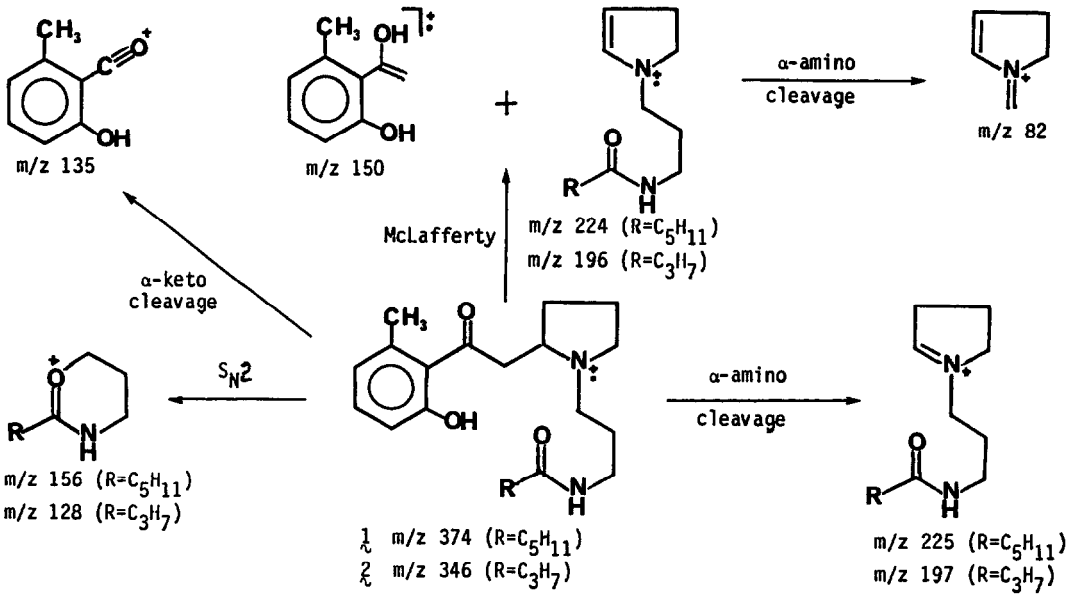
1 R=OH; n=4
2 R=OH; n=2
3 R=OMe; n=2



4 R=OMe



7 m/z 161



Scheme 1

from the latter spectrum of two methylene carbon signals in the paraffinic region. The ^1H spectra show corresponding differences in methylene proton signals, and decoupling experiments established that 2 is an amide of n-butanoic instead of n-hexanoic acid as for 1.

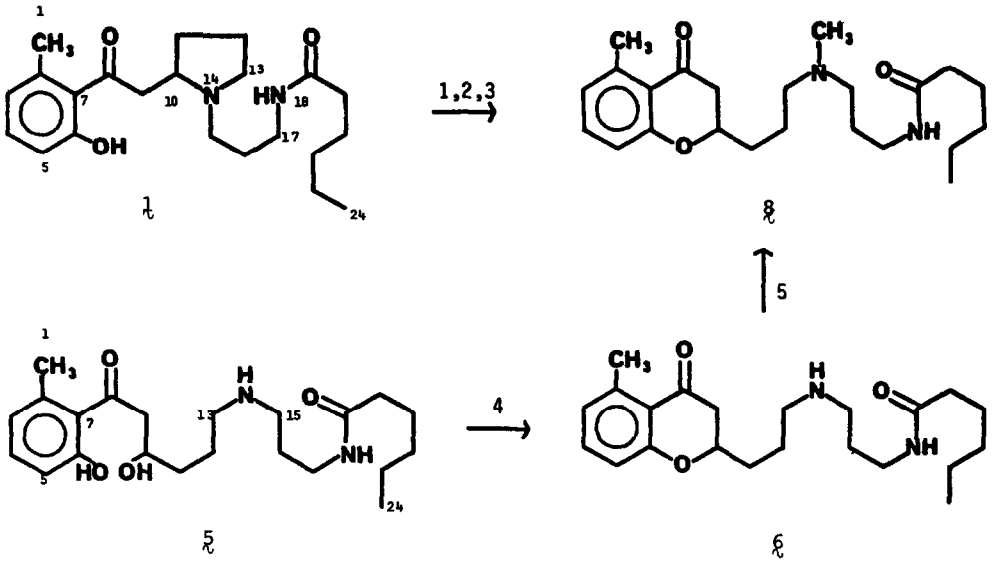
TABLE 1

^{13}C Nmr Spectra of Peripentadenia Alkaloids

Carbon	1	2	5	6[B]	8
1	20.6q	20.7q	22.5q	22.8q	22.5q
2	127.9s	127.9s	125.3s	119.7s	126.2s
3	121.5d	121.7d	122.9d	124.2d	124.5d
4	132.4d	132.4d	133.1d	134.9d	134.6d
5	116.5d	116.5d	115.6d	115.9d	115.7d
6	157.7s	157.7s	159.2s	162.4s	162.5s
7	137.2s	137.2s	137.9s	142.3s	142.1s
8	207.3s	207.1s	205.8s	193.4s	193.7s
9	48.4t	48.4t	49.2t	44.5t	41.6t
10	64.6d	64.6d	76.0d	76.2d	76.5d
11	30.8t	30.8t	30.1t	31.9t	32.6t
12	23.9t	23.9t	23.8t	22.2t	22.7t
13	54.2t[A]	54.2t[A]	56.6t[A]	45.5t[A]	57.6t[A]
15	53.9t[A]	53.9t[A]	57.6t[A]	48.2t[A]	56.6t[A]
16	25.7t	27.4t	25.9t	25.6t	25.9t
17	37.1t	38.6t	38.1t	36.2t	39.0t
19	173.6s	173.4s	173.4s	175.9s	173.1s
20	36.6t	37.1t	36.9t	36.5t	36.9t
21	27.4t	22.6t	25.6t	26.8t	25.5t
22	31.5t	13.8q	31.6t	31.6t	31.5t
23	22.4t	-	22.6t	22.5t	22.4t
24	13.9q	-	13.9q	13.9q	13.9q
14 NCH_3	-	-	-	-	44.5q

A: Assignments may be interchanged
B: Measured at 100.62 MHz

Structure 2 for dinorperipentadenine has finally been confirmed by synthesis: the diamine 4, prepared previously as an intermediate in the synthesis of O-methylperipentadenine[1], when treated with n-butanoyl chloride and base yielded O-methyldinorperipentadenine (3), identical with the methyl ether of 2.



Reagents:- 1: CH_3I; 2: F^-; 3: Δ; 4: $(CO_2H)_2/H_2O$,Δ; 5: $HCHO/HCO_2H$

Scheme 2

Another minor alkaloid, peripentamine (5), likewise failed to crystallise. High-resolution ms indicated the molecular formula $C_{22}H_{36}N_2O_4$ by chemical ionisation, but electron impact resulted in the same formula as peripentadenine (1) through loss of a unit of water. A comparison of the ^1H and ^{13}C (Table 1) nmr spectra of 1, 2, and 5 showed that the peripentamine molecule has 2-hydroxy-6-methylbenzoyl and n-hexanamide moities as for 1. These account for one nitrogen and three oxygen functions, and also for two of the four exchangeable proton signals appearing in the ^1H nmr spectrum; that the remaining oxygen and nitrogen are in secondary alcohol and amino groupings was suggested by a one-proton multiplet at 4.38 ppm and a methine carbon signal at 76.0 ppm in the nmr spectra, and by the fact that quaternisation of peripentamine with methyl iodide added two methyl groups. The amino group evidently forms part of an N[3-aminopropyl]amide grouping similar to those of 1 and 2, since ions appear in the ms of both 5 and its methofluoride that correspond to the above-mentioned S_N2-type cleavage. The alcohol group must be located β to the keto group: when the signal referred to above at 4.38 ppm was irradiated, the multiplicities of two one-proton signals at 3.2 and 2.9 ppm were simplified; from their chemical shifts, these geminal protons are situated α to the keto group, and their irradiation in turn affects only the proton resonating at 4.38 ppm, which must thus be attached to the carbon bearing the hydroxyl.

Microanalysis of anhydroperipentamine (6), which was obtained as colourless needles, showed that it is an isomer of peripentadenine (1), and its ^{13}C (Table 1) and ^1H nmr spectra suggested that n-hexanamide and 2-oxy-6-methylbenzoyl residues are present as in 1 and 5. The remaining portions of the nmr spectra of 6 show a resemblance to those of peripentamine (5); in particular, signals appear at 76.2 ppm and at 4.47 ppm in the ^{13}C and ^1H nmr spectra respectively, similar to the above-mentioned peaks associated with the secondary alcohol group in 5. However, anhydroperi-

pentamine appears to have no hydroxyl groups, since it is not phenolic and has only two exchangeable proton signals in its ^{1}H nmr spectrum: the low-field peaks at 16.4 and 10.4 ppm ascribed to the hydroxyl protons in 5 are absent from the anhydroperipentamine spectrum. The evidence points to the benzopyran structure 6, which is in accord with the appearance of an ion at m/z 161 in its ms that can be represented as 7. Structure 6 is supported by the formation of anhydroperipentamine when 5 is dehydrated under mild acid conditions (Scheme 2); the structures of both 5 and 6 are confirmed by the conversion of the latter by N-methylation to the aminoamido-benzopyrone 8, identical with the Hofmann degradation product previously obtained[1] from peripentadenine (1, Scheme 2).

Although the three minor bases 2, 5, and 6 all have chiral centres, their specific rotations are negligible as in the case of 1[1], possibly as a result of racemisation during extraction and isolation.

EXPERIMENTAL

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, and the compounds were visualised by spraying with iodoplatinate reagent or by examination under uv light. The melting point (mp) was recorded on a Yanigimoto Seisakusho micro-melting point apparatus and is uncorrected. 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 with a Beckman IR-33 spectrometer. Proton magnetic resonance (^{1}H nmr) and carbon-13 magnetic resonance (^{13}C nmr) spectra were recorded on deuterochloroform solutions at 270 MHz and 67.89 MHz respectively unless otherwise specified, 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 unless otherwise specified. Intensities are given in parentheses as percentages of base peak intensity. Owing to their noncrystalline nature, satisfactory elemental analyses could not be obtained for most 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.

Isolation of Minor Alkaloids - The extraction of the plant material and separation of the crude alkaloid fraction have been described elsewhere[1]. Chromatography of the latter on a short column gave peripentamine (5) upon elution with a mixture of chloroform-methanol (9:1). A more polar mixture (17:3) yielded initially peripentadenine (1), but subsequent fractions contained dinorperipentadenine (2). Further elution with a 1:1 mixture of chloroform and methanol afforded anhydroperipentamine (6).

Dinorperipentadenine (2) - The crude base obtained by short column chromatography was purified by multiple elution ptlc using chloroform-methanol (9:1) for development. Dinorperipentadenine was isolated as a yellow gum, R_f 0.45 ($CHCl_3$-MeOH 9:1); λ_{max} 218 (4.01), 252 (3.15), 285 nm (3.15); ν_{max} (neat) 3250-3020 (br, NH and OH), 1690 (Ar C=O), 1680 and 1650 (CONHR), 1630 cm^{-1} (Ar C=O H-bonded to ortho OH); ^{1}H nmr δ 10.5 (1H, m, ArOH), 7.17 (1H, dd $J_{H4/H3} = J_{H4/H5} = 7.5$ Hz, H4), 6.72 (1H, d, $J_{H5/H4} = 7.5$ Hz, H5), 6.65 (1H, d, $J_{H3/H4} = 7.5$ Hz, H3), 6.05 (1H, br t, $J_{H18/2H17} = 6.0$ Hz, H18), 3.59 (1H, dddd, $J_{H10/H9a} = 10.0$, $J_{H10/H9b} = 5.0$, $J_{H10/H11a} = 8.3$, $J_{H10/H11b} = 5.0$ Hz, H10), 3.48 (1H, dd, $J_{H9a/H9b} = 12.75$ Hz, $J_{H9a/H10} = 10.0$ Hz, H9a), 3.27 (1H, ddd, $J_{H15a/H15b} = 10.5$, $J_{H15a/H16a} = 6.3$, $J_{H15a/H16b} = 4.5$ Hz, H15a), 3.25 (1H, dd, $J_{H17a/H17b} = 13.5$, $J_{H17a/H18} = 6.0$ Hz, H17a), 3.15 (1H, dddd, $J_{H17b/H17a} = 13.5$, $J_{H17b/H16a} = 8.25$, $J_{H17b,\ H16b} = 6.0$, $J_{H17b/H18} = 6.0$ Hz, H17b), 2.87 (1H, ddd, $J_{H13a/H13b} = 12.0$, $J_{H13a/H12a} = 7.5$, $J_{H13a/H12b} = 7.5$ Hz, H13a), 2.57 (1H, dd, $J_{H9b/H9a} = 12.75$, $J_{H9b/H10} = 5$ Hz, H9b), 2.52 (1H, dd, $J_{H13a/H13b} = 12$, $J_{H13a/H12b} = 3.5$ Hz, H13b), 2.46 (1H, ddd, $J_{H15a/H15b} = 10.5$, $J_{H15aH16a} = 8.5$, $J_{H15a/H16b} = 7.5$ Hz, H15a), 2.3 (3H, s, 3H1), 2.2 (1H, ddd, $J_{H11a/H11b} = 13.0$, $J_{H11a/H10} = 8.5$, $J_{H11a/H12a} = 12.0$ Hz, H11a), 2.07 (2H, t, $J_{20/21} = 7.5$ Hz, 2H20), 2.0 (1H, m, H11b), 1.95 (1H, m, H16a), 1.75 (1H, m, H16b), 1.67 (2H, m, 2H12), 1.55 (2H, tt, $J_{21/20} = J_{21/22} = 7.5$ Hz, 2H21), 0.9 (3H, t, $J_{22/21} = 7.5$ Hz, 3H22); ms m/z 346 (M^+,12), 197 (65), 196 (25), 150 (82), 135 (100), 128 (36), 82 (87). Found: 346.2267; calculated for $C_{20}H_{30}N_2O_3$: 346.2166.

O-Methyldinorperipentadenine (3) - A methanolic solution of dinorperipentadenine (0.03 g in 20 ml) was treated with an excess of ethereal diazomethane and left at room temperature overnight. Removal of the solvents gave O-methyl dinorperipentadenine as a light brown gum (0.03 g), R_f 0.45 ($CHCl_3$-MeOH 9:1); ^{1}H nmr: cf 2, an additional signal appeared at δ 3.8 (3H, s, OCH_3), and the broad signal at δ 10.5 disappeared; ms m/z 360 (M^+, 12), 345 (16), 197 (62), 164 (73), 135 (92), 128 (42), 82 (100).

Synthesis of O-Methyldinorperipentadenine (3) - To a rapidly-stirred mixture of ethereal 3[2(2-methoxy-6-methylbenzoylmethyl)pyrrolidin-1-yl]propylamine (0.05 g, 18.5 mmol, 20 ml) and aqueous sodium hydroxide (10%, 20 ml) at 0°, n-butanoyl chloride (0.025 g, 24 mmol) in ether (20 ml) was added dropwise, then the solution was stirred for a further 2 hrs at room temperature. The aqueous phase was separated and extracted with chloroform (2 x 20 mol), and the extract was combined with the ether layer, dried and evaporated. The yellow gum obtained after purification of the residue by ptlc (0.035 g, 53%), was found to be identical with the methyl ether 3 of the natural product (tlc, ir and ^{1}H nmr).

Peripentamine (5) - Further ptlc purification of the base obtained by column chromatography afforded peripentamine as a yellow viscous oil, R_f 0.75 ($CHCl_3$-MeOH 9:1); λ_{max} 218 (4.26), 245 (3.98), 250 (3.94), 256 (3.93), 263 (3.81), 300 nm (3.63); λ_{max} (+NaOH) 225 (4.46), 245 (4.24), 252 nm (4.16); ν_{max} ($CHCl_3$) 3300 (NH, OH), 1690 (Ar C=O), 1680 and 1655 (RNHCO), 1640 and 1630 cm^{-1}; ^{1}H nmr δ 16.4 (1H, br m, OH), 10.4 (1H, br m, ArOH) (both exchanged on addition of D_2O), 7.15 (1H, dd, $J_{H4/H3} = J_{H4/H5}$ = 7.5 Hz, H4), 6.8 (1H, d, $J_{H5/H4}$ = 7.5 Hz, H5), 6.69 (1H, d, $J_{H3/H4}$ = 7.5 Hz, H3), 6.65 (1H, br t, exchanged with D_2O, -NHCO-, H18), 4.38 (1H, m, H10), 3.37 (2H, ddd, $J_{H17a/H17b}$ = 12, $J_{H17/H16a}$ = 7, $J_{H17/H18}$ = 6 Hz, 2H17), 3.2 (1H, dm, $J_{H9a/H9b}$ = 16 Hz, H9a), 2.95 (1H, dd, $J_{H9a/H9b}$ = 16, $J_{H9a/H10}$ = 5 Hz, H9b), 2.87 (1H, dt, $J_{H13a/H13b}$ = 12, $J_{H13a/H12}$ = 5 Hz, H13a), 2.6 (2H, m, 2H15), 2.44 (1H, dd, $J_{H13b/H13a}$ = 12, $J_{H13b/H12}$ = 4 Hz, H13b), 2.4 (3H, s, 3H1), 2.4 (1H, br, exchanged with D_2O, H14), 2.2 (2H, t, $J_{H20/H21}$ = 7.5 Hz, 2H20), 1.85-1.5 (8H, unresolved m, 2H11, 2H12, 2H16, 2H21), 1.3 (4H, m, 2H22, 2H23), 0.9 (3H, t, $J_{H24/H23}$ = 7.5 Hz, 3H24); ms (ci) m/z 392 (M^+, 9), 391 (50), 375 (100), 373 (36), 305 (11), 225 (93), 224 (12), 201 (22), 173 (66), 156 (29), 151 (57), 116 (57). Found: 392.2464; calculated for $C_{22}H_{36}N_2O_4$: 392.2587.

Anhydroperipentamine (6) - The column fraction eluted with an equal mixture of chloroform and methanol was further separated by ptlc, and the least polar component finally crystallised as white needles from aqueous acetone, mp 96°; R_f 0.31 ($CHCl_3$-MeOH 9:1); λ_{max} 214 (4.5), 250 (3.64), 285 (3.42), 320 nm (3.44); ν_{max} ($CHCl_3$) 3300 (NH), 1695 (Ar C=O), 1680, 1650 cm^{-1}; ^{1}H nmr δ (400 MHz) 7.35 (1H, dd, $J_{H4/H3} = J_{H4/H5}$ = 7.5 Hz,H4), 7.24 (1H, t, $J_{H18/H17}$ = 6 Hz, H18), 6.88 (1H, d, $J_{H5/H4}$ = 7.5 Hz, H5), 6.83 (1H, d, $J_{H3/H4}$ = 7.5 Hz, H3), 4.47 (1H, m, H10), 3.58 (2H, dt, $J_{H17/H18}$ = 6, $J_{H17/H16}$ = 6 Hz, 2H17), 3.03 (2H, t, $J_{H13/H14}$ = 6 Hz, 2H13), 2.98 (2H, t, $J_{H15/H16}$ = 6 Hz, 2H15), 2.69 (2H, m, 2H9), 2.64 (3H, s, 3H1), 2.28 (2H, t, $J_{H20/H21}$ = 7.5 Hz, 2H21), 2.16 (2H, m, 2H16), 1.95-1.89 (4H, m, 2H11, 2H12), 1.62 (2H, tt, $J_{H21/H20} = J_{H21/H22}$ = 7.5 Hz, 2H20), 1.29 (4H, m, 2H22, 2H23), 0.89 (3H, t, $H_{24/H23}$ = 7.5 Hz, 3H24); ms m/z 374 (M^+, 12), 232 (31), 225 (18), 218 (11), 211 (14), 202 (16), 185 (100), 161 (16), 156 (56), 135 (46). Found: 374.2501; calculated for $C_{22}H_{34}N_2O_3$: 374.2569. Found: C 63.37, H 9.03, N 6.55; calculated for $C_{22}H_{34}N_2O_3.2^1/_2H_2O$: C 62.96, H 9.37, N 6.68%.

Dehydration of Peripentamine - Peripentamine (5, 0.052 g, 0.13 mmol) was refluxed with aqueous oxalic acid (10%, 30 ml) for 12 hrs. The solution was cooled, basified with ammonia, and extracted with chloroform. The gum obtained on evaporation of the chloroform extract contained three compounds; the one of intermediate R_f, when purified by ptlc (0.018 g, 36%) proved identical with anhydroperipentamine (6) (tlc, uv, ir, and ^{1}H nmr).

N-Methylation of anhydroperipentamine - Anhydroperipentamine (6, 0.035 g, 0.094 mmol) was dissolved in ice-cold formic acid (98%, 0.5 ml, 13 mmol), and formaldehyde (37%, 1 ml, 12 mmol) was added. The mixture was heated on a water bath for 8 hrs, then diluted with ice-cold water (10 ml), basified with ammonia, and extracted with chloroform. Removal of solvents gave N-methylanhydroperipentamine (8, 0.027 g, 77%) as a brown gum; λ_{max} 222 (2.68), 258 (2.68), 320 nm (2.42); ν_{max} ($CHCl_3$) 3340 (CONH), 1710 (Ar C=O), 1680, 1650, 1600 cm^{-1}; ^{1}H nmr δ 7.3 (1H, dd, $J_{H21/H20} = J_{H21/H22}$ = 7.5 Hz, H21), 7.0 (1H, t, $J_{H18/H17}$ = 6 Hz, H18), 6.8 (2H, m, H20, H23), 4.4 (1H, m, H10), 3.35 (2H, dt, $J_{H17/H18}$ = 6, $J_{H17/H16}$ = 7 Hz, 2H17), 2.69 (2H, m, 2H9), 2.62 (3H, s, 3H25), 2.51 (2H, t, $J_{H15/H16}$ = 7 Hz, 2H15), 2.48 (2H, t, $J_{H13/H12}$ = 7 Hz, 2H13), 2.28 (3H, s, 3H1), 2.15 (2H, t, $J_{H20/H21}$ = 7.5 Hz, 2H20), 1.81 (4H, m, 2H11, 2H12), 1.73 (2H, tt, $J_{H16/H15} = J_{H16/H17}$ = 7.5 Hz, H16), 1.61 (2H, tt, $J_{H21/H20} = J_{H21/H22}$ = 7.5 Hz, 2H21), 1.28 (4H, m, 2H22, 2H23), 0.88(3H, t, $J_{H24/H23}$ = 7.5 Hz, 3H24); ms m/z 388 (M^+, 11), 246 (64), 323 (14), 201 (22), 200 (16), 199 (100), 186 (13), 156 (35), 135 (43). The compound 8 was found to be identical with the Hofmann degradation product[1] of peripentadenineethofluoride (tlc, uv, ir, ms, and ^{1}H nmr).

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