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STRICTANOL AND STRICTANINE—TWO NEW INDOLE ALKALOIDS FROM THE FRUITS OF *RHAZYA STRICTA*

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Key Word Index—*Rhazya stricta*; Apocynaceae; hydroxyindolenine, dihydroindole.

Abstract—Strictanol and a trace alkaloid strictanine have been isolated from the fruits of *Rhazya stricta*. Their structures were assigned on the basis of spectral studies.

INTRODUCTION

Rhazya stricta Decsne is an indigenous medicinal plant widely distributed through Western Asia and abundantly found in Pakistan [1, 2]. It has long been used in the indigenous system of medicine for the treatment of various diseases [1–5]. The anticancer activity of some of the indole alkaloids of the plant is also reported [6, 7].

As a result of our continuing studies [8, 9] on the chemical constituents of the fruits of *R. stricta* we have isolated two new alkaloids, strictanol (**1**) and strictanine (**2**). The identity of each alkaloid was established from extensive NMR studies.

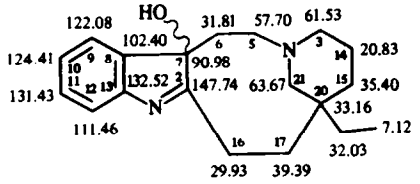
RESULTS AND DISCUSSION

The crude alkaloidal extract of the fruits (without seeds) was subjected to selective extractions with chloroform at different pH values according to their differential basicities [8]. The fractions obtained at pH 6.7–7.3 were combined and subjected to prep. TLC resulting in the isolation of strictanol and a trace alkaloid strictanine.

The UV spectrum of strictanol (**1**) was reminiscent of a hydroxyindolenine system showing λ_{max} at 227, 282 sh and 290 nm. The IR spectrum indicated the presence of O–H and C=N stretching vibrations at 3180 and 1658 cm^{-1}, respectively. Its EI mass spectrum afforded a $[M]^+$ at *m/z* 298 which was confirmed by FD and FAB. The HR mass spectrum indicated the $[M]^+$ at *m/z* 298.2031, leading to the molecular formula $C_{19}H_{26}N_2O$. The base peak occurred at *m/z* 281.2021 ($C_{19}H_{25}N_2$) from the loss of an hydroxyl group. A prominent fragment at *m/z* 269.1712 ($C_{17}H_{21}N_2O$), resulted from the loss of ethyl group from the $[M]^+$, a common feature in Aspidosperma alkaloids [10, 11]. Other fragments of alkaloid (**1**) which occurred at *m/z* 210, 157, 156, 144, 143, 138, 125, 124, 110 and 96 were also consistent with the presence of an Aspidosperma skeleton [10, 11].

In the ^1H NMR spectrum of **1** (CD_3OD, 300 MHz), the methyl (C-18H) of the ethylidine side chain appeared as a triplet at δ0.93 ($J_{18,19}$ = 7.56 Hz). The adjacent methylene protons (C-19H) resonated as a quartet at δ1.38 ($J_{19,18}$ = 7.56 Hz). The C-21 protons resonated as doublets at δ 3.12 and 3.63 with the same coupling constant (J_{gem} = 12.12 Hz). These two protons, as indicated by a COSY-45 spectrum and homo-decoupling results, were coupled to each other only without being coupled to any other proton. The signal at δ3.12 may be attributed to the C-21α proton while the signal at δ3.62 may be assigned to the C-21β proton. The four aromatic protons of the benzene moiety were identified individually (see Experimental).

The ^{13}C NMR spectrum (CD_3OD, 75.4 MHz) of **1** indicated the presence of 19 carbons and the multiplicity of each carbon atom was established by carrying out multipulse ID DEPT experiments with the last polarization pulse angle θ = 45, 90 and 135°. The possibility that the substance was quebrachamine *N*-oxide could be ruled out because of its non-indolic UV and its differing



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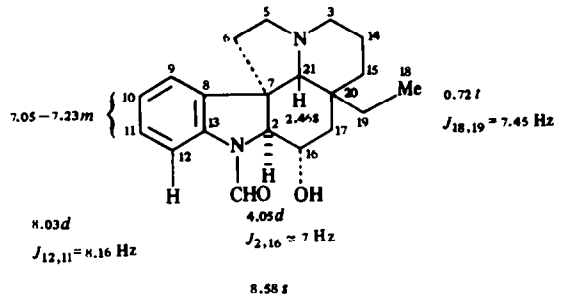

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^{13}C NMR chemical shift values from those reported for quebrachamine [12, 13]. The other possibility that the isolated alkaloid might be the *N*-oxide of aspidospermidine was also ruled out on the basis of DEPT results and a UV spectrum. The three downfield methylene carbons at δ57.70, 61.53 and 63.67 were assigned to C-5, C-3 and C-21, respectively. The downfield signal at δ90.98 was assigned to C-7. The C-2 quaternary carbon was found to resonate at δ147.74. On the basis of these studies structure (1) is assigned to strictanol.

The minor alkaloid strictanine (2) possessed a UV spectrum typical of a dihydroindole chromophore [14, 15] with λ_{max} 212, 253, 260 sh, 280 and 290 nm. Its EI mass spectrum afforded the $[M]^+$ at *m/z* 326 which was also confirmed by FD and FAB. The HR mass spectrum contained the $[M]^+$ at *m/z* 326.1975 leading to the molecular formula $C_{20}H_{26}N_2O_2$. A fragment occurring at *m/z* 309.1685 ($C_{20}H_{25}N_2O$) corresponded to the loss of an hydroxyl group. Two different ions were formed with masses close to *m/z* 297 corresponding to the loss of two different fragments. The one at *m/z* 297.1954 ($C_{19}H_{25}N_2O$) indicated the loss of an aldehydic group while the other at *m/z* 297.1647 ($C_{18}H_{21}N_2O_2$) represented the loss of an ethyl group. This clearly showed the presence of an aldehydic as well as an ethyl group in the molecule. Other peaks occurring at *m/z* 153.1512 ($C_{10}H_{19}N$), 152.1442 ($C_{10}H_{18}N$), 144.0810 ($C_{10}H_{10}N$), 143.0730 ($C_{10}H_9N$), 138.1271 ($C_9H_{16}N$), 124.1137 ($C_8H_{14}N$), 122.0985 ($C_8H_{12}N$), 110.1003 ($C_7H_{12}N$), 109.0925 ($C_7H_{11}N$) and 96.0812 ($C_6H_{10}N$) were characteristic of the Aspidosperma skeleton [10, 11]. This type of mass fragmentation pattern is generally observed for Aspidosperma alkaloids such as limaspermine [16], spegazzinine and spegazzinidine [17]. The possibility for the substitution of the hydroxyl group at C-18 (as earlier observed in limaspermine [16]) was also ruled out by the presence of a peak at *m/z* 297.1647 in the mass spectrum which corresponded to the loss of an ethyl group.

The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of (2) clearly indicated the presence of a *N*-formyl group. The doublet for C-12H was shifted significantly downfield to δ8.03 ($J_{12,11}$ = 8.16 Hz) in comparison to the other aromatic protons C-10H (multiplet at δ7.06), C-11H (multiplet at δ7.14) and C-9H (multiplet at δ7.22) which was indicative of the substitution of a carbonyl group at the nitrogen of a dihydroindole nucleus [18]. The aldehydic proton resonated as a singlet at δ8.58. The C-2 proton appeared as a doublet at δ4.05 showing *trans* diaxial coupling with C-16H ($J_{2,16}$ = 7.03 Hz). This is characteristic of a C-2H in an α-disposition, *cis* to the adjacent hydroxyl group at C-16 [17]. A triplet appearing at δ0.72 ($J_{18,19}$ = 7.45 Hz) was assigned to the methyl (C-18H) of the ethyl side chain. The ^{13}C NMR spectrum of strictanine could not be recorded due to the paucity of sample. However, on the basis of the above spectroscopic studies structure (2) is assigned to strictanine.

EXPERIMENTAL

Isolation of strictanol (1). Plant material was collected from Thana Bula Khan, 90 km from Karachi and was identified by Prof. S. I. Ali at the Botany Department of Karachi University where a voucher specimen is deposited. Air dried fruits (without seeds) (10 kg) were soaked in EtOH, ground, filtered and concd. This resulted in the sepn of a brown gummy material which was filtered off. The filtrate was concd and the soln acidified with 5% HCl, filtered and basified with conc. NH_3 to pH ~ 9. The resulting soln was extd with $CHCl_3$, dried (Na_2SO_4), filtered and evapd to dryness (120 g). The crude alkaloidal extract thus obtained was dissolved in 10% HOAc and subjected to selective pH sepns after stepwise basification with conc. NH_3. This produced a number of fractions. Fractions obtained at pH 6.7 and 7.3 were combined (16 g) and a portion (4 g) was subjected to prep. TLC using precoated 2 mm thick silica gel plates (GF-254, Merck) and development with $CHCl_3$–MeOH (3:2). This afforded a major band (R_f = 0.69). The material thus obtained was again subjected to prep. TLC using precoated 0.2 mm thick silica gel plates with $CHCl_3$–EtOAc–MeOH (3:1:1) resulting in the sepn of an amorphous compound (R_f = 0.16) (21 mg, 0.0008% yield), $[\alpha]_D^{23}$ – 57.9° (MeOH); IR ($CHCl_3$) ν_{max} cm^{-1} 3180, 2970–2860, 1658, 1618, 1465 and 758; UV (CH_3OH) λ_{max} nm 227, 282 sh and 290, λ_{min} 270; ^{1}H NMR 300 MHz (CD_3OD) δ0.93 (*t*, 3H, $J_{18,19}$ = 7.56 Hz, C-18H), 1.38 (*q*, 2H, $J_{19,18}$ = 7.56 Hz, C-19H), 3.12 (*d*, 1H, $J_{21\alpha,21\beta}$ = 12.12 Hz, C-21αH), 3.63 (*d*, 1H, $J_{21\beta,21\alpha}$ = 12.12 Hz, C-21βH), 6.73 (*d*, 1H, $J_{12,11}$ = 7.86 Hz, C-12H), 6.88 (*dd*, 1H $J_{10,9}$ = 7.59, $J_{10,11}$ = 7.36 Hz, C-10H), 7.18 (*dd*, 1H, $J_{11,12}$ = 7.86, $J_{11,10}$ = 7.36 Hz, C-11H), 7.28 (*d*, 1H, $J_{9,10}$ = 7.59 Hz, C-9H); ^{13}C NMR 75 MHz (CD_3OD) (see formula 1). HRMS *m/z* (rel. int.), 298.2031 ($[M]^+$, calcd. 298.2045 for $C_{19}H_{26}N_2O$, 8), 297.1978 ($C_{19}H_{25}N_2O$, 2), 282.2098 ($C_{19}H_{26}N_2$, 25), 281.2012 ($C_{19}H_{25}N_2$, 100), 280.1930 ($C_{19}H_{24}N_2$, 4), 251.1536 ($C_{17}H_{19}N_2$, 15), 210.1278 ($C_{15}H_{16}N$, 12), 156.0821 ($C_{11}H_{10}N$, 17), 138.1285 ($C_9H_{16}N$, 16), 124.1133 ($C_8H_{14}N$, 97), 110.0962 ($C_7H_{12}N$, 24).

Isolation of strictanine (2). The major band (R_f = 0.69) which resulted from prep. TLC of the combined fractions of pH 6.7 and 7.3 (as described above for strictanol) was subjected to a second prep. TLC in $CHCl_3$–EtOAc–MeOH (7:1.5:1). This afforded an alkaloid (R_f = 0.67) (3 mg, 0.0001% yield), UV (MeOH) λ_{max} nm 212, 253, 260 sh, 280 and 290 nm, λ_{min} 228, 277 and 287; ^{1}H NMR 300 MHz ($CDCl_3$) δ0.72 (*t*, 3H, $J_{18,19}$ = 7.45 Hz, C-18H), 2.46 (*s*, 1H, C-21 H), 4.05 (*d*, 1H, $J_{2,16}$ = 7.03 Hz, C-2H), 7.06 (*m*, 1H, C-10H), 7.14 (*m*, 1H, C-11H), 7.22 (*m*, 1H, C-9H), 8.03 (*d*, 1H, $J_{12,11}$

= 8.16 Hz, C-12H), 8.58 (*s*, 1H, –CHO); HRMS *m/z* (rel. int.), 326.1975 ([M]$^+$, calcd. 326.1994 for $C_{20}H_{26}N_2O_2$, 50).

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