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ISOLATION AND STRUCTURE OF A NEW ALKALOID FROM RAUWOLFIA SERPENTINA BENTH

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Abstract — A new dihydroindole alkaloid sandwicolidine has been isolated from Rauwolfia serpentina and its structure elucidated through chemical and spectroscopic studies.

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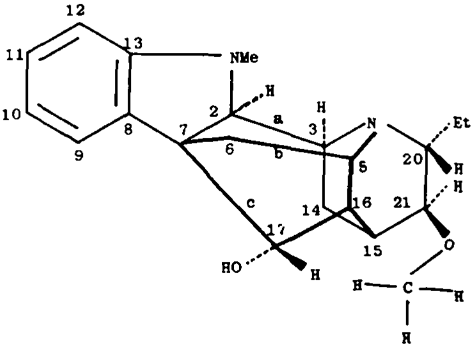
The isolation and structural elucidation of a new alkaloid has recently been communicated from Rauwolfia serpentina by Siddiqui, etal.[1] As a result of continued studies on the fresh undried roots collected in winter from Khatmandoo, a new dihydroindole base sandwicolidine has been isolated by employing mild isolation procedure as described in the experimental. The novel feature of the alkaloid is the presence of OCH_3 group at C-21 as determined through NMR (^1H and ^{13}C) spectral studies.

Sandwicolidine (I) m.p. 213-214° has molecular formula $C_{21}H_{28}N_2O_2$ (high resolution mass M^+ 340.2135). The U.V. spectrum maxima at 245 and 290 nm which is characteristic for dihydroindole alkaloids. The I.R. spectrum showed O-H stretching at 3400 cm^{-1} and peaks between 2850-3000 cm^{-1} due to C=C stretching, prominent bands at 1610, 1460 cm^{-1} and other peaks at lower frequency region between 800-960 cm^{-1} provided evidence of aromaticity. Band at 1270 cm^{-1} corresponded to OCH_3 while no peak was observed in the carbonyl region.



(I)

The mass spectrum showed prominent peaks at m/e 312.2209 and m/e 269.1649 for the fragments of composition $(C_{20}H_{28}N_2O)^+$ and $(C_{17}H_{21}N_2O)^+$ corresponding to

M^+-CO and M^+-C_4H_7O respectively. The base peak at m/e 196.1335 is due to the ion $(C_{11}H_{18}NO_2)^+$ resulting from the cleavage of bond a,b and c. Further loss of carbonyl group gives another prominent peak at m/e 168.1395 while the peak at m/e 144.0820 is due to the fragment of $(C_{10}H_{10}N)^{+\cdot}$. The ^{1}H NMR of sandwicolidine showed a four-protons multiplet extending from δ 7.25-6.67 attributed to aromatic protons; and two three-protons sharp singlets due to OCH_3 and N_1-CH_3 at δ 3.06 and 2.80 respectively. The signals for H-3 and H-5 appeared at δ 3.35 while a two-protons multiplet and a three-protons triplet at δ 1.27 and δ 0.95 have been attributed to H-19 and H-18 respectively. A one-proton multiplet at δ 2.74 has been assigned to H-20 and a one-proton doublet at δ 4.8 for the carbinylic proton, suggesting that the second oxygen is present as a hydroxyl function located at C-17, which was supported by the formation of its monoacetyl derivative and the shift of the proton at δ 5.70 in the latter. The coupling constant of H-17 (9Hz) conclusively showed that the orientation of the hydroxyl group in I is same as observed in sandwicine[2,3] that is α. The NMR (^{1}H and ^{13}C) spectra further showed that the position of the ethyl side chain is different in I, as normally observed in ajmaline and sandwicine series of alkaloids. Thus the ^{1}H NMR showed a one-proton doublet of doublet at δ 3.74 for H-21 which is only possible if the proton geminal to the methoxy group is coupled to two protons and led to the location of OCH_3 at C-21 ($J_{21,15}$ = 4.5Hz, $J_{21,20}$ = 1.0Hz). Moreover in the ^{13}C NMR spectrum, two carbons were observed at δ 70.8 and 78.7, the former of which was assigned to C-17 in analogy to that observed in sandwicine for this carbon (δ 70.8), whereas the chemical shift for the other carbon i.e. δ 78.7 is quite upfield as compared to that in ajmaline/sandwicine[4-6] (δ 88.1) and can be accounted for C-21 in structure I. These observations, collectively led to the assignment of structure I for sandwicolidine.

The position and configuration of the ethyl side chain and OCH_3 group have been conclusively determined through two-dimensional NOE spectroscopy (NOESY) which exhibited the connectivities of OCH_3 with H-17 as well as with H-20; and H-3 with H-21 showing that OCH_3 and H-20 are β-oriented since the β-disposition of H-17 has already been shown by its coupling constant. The inspection of Drieding model further showed that the connectivity of OCH_3 with H-17 is only possible if the former is β and located at C-21; thus the ethyl side chain at C-20 is α oriented. The structure of sandwicolidine is interesting from the biosynthetic point of view, since this is the first example of the location of the ethyl side chain at C-20 (ie carbon α to nitrogen).

EXPERIMENTAL

Melting points were recorded in glass capillary tubes and are uncorrected. I.R. (chloroform) and U.V. (methanol) spectra were measured on JASCO IRA-I spectrometer and Pye-Unicam SP-800 Spectrometer respectively. Mass spectra were recorded on Finnigan MAT 112 and MAT 312 double focussing mass spectrometer connected to PDP 11/34 computer system. ^1H and ^{13}C NMR (Broad band and Gated spin echo) spectra were recorded in $CDCl_3$ with T.M.S. as internal reference and NOESY experiments were carried out on 300 MHz instruments model, Bruker Aspect 3000 with pulse delay 2 sec and mixing time 0.5 sec. The purity of samples was checked on t.l.c. (silica gel S.I.F.-254) precoated aluminium cards.

Isolation: The aqueous extract of the undried roots was freez dried and divided into ethyl acetate soluble and insoluble fractions. The ethyl acetate insoluble fraction was dissolved in a little quantity of 5% acetic acid which was treated with dilute ammonia bringing up the pH to 9. The liberated bases were exhaustively extracted out with ethyl acetate, washed and dried over anhydrous sodium sulfate, concentrated in vacuum and triturated with petroleum ether. The clear solution was freed of the solvent in nitrogen atmosphere under reduced pressure and the cream coloured residue was subjected to thick layer chromatography (silica gel, chloroform-methanol 7:3). As a result, sandwicolidine was obtained as off-white crystallizate, which on recrystallization from ethanol-ethyl acetate (9:1) formed irregular plates m.p. 213-214°C $|\alpha|_D^{20} = 227$ ($CHCl_3$). EIMS m/e (rel.int. %) 340.2135 (M^+, calcd. for $C_{21}H_{28}N_2O_2)^+$ (4), 312.2209 $(C_{20}H_{28}N_2O)^+$ (10), 269.1642 $(C_{17}H_{21}N_2O)^+$ (6), 213.1379 $(C_{14}H_{17}N_2)^+$ (10), 196.1335 $(C_{11}H_{18}NO_2)^+$ (100), 168.1395 $(C_{10}H_{18}NO)^+$ (28) and 144.0820 $(C_{10}H_{10}N)^+$ (20). It analyzed for $C_{21}H_{28}N_2O_2$ (obs. C = 74.00, H = 8.26, N = 8.27, O = 9.47%; calcd. for $C_{21}H_{28}N_2O_2$ C = 74.11, H = 8.23, N = 8.23, O = 9.43%). I.R. ν_{max} (cm^{-1}) 3400 (O-H stretching), 1365 (O-H bending) 3000 and 1460 (aromatic vibrations) U.V. λ_{max} (n.m) 210, 245 and 290. ^1H NMR ($CDCl_3$) δ 6.67-7.25 (4H, m, aromatic protons), 4.8 (1H, d, J = 9Hz, H-17), 3.74 (1H, dd, $J_{21,15}$ = 4.5Hz, $J_{21,20}$ = 1Hz, H-21), 3.35 (2H, m, H-3, H-5), 3.06 (3H, s, $OC\underline{H}_3$), 2.80 (3H, s, N_1-$C\underline{H}_3$), 2.74 (1H, m, H-20), 1.27 (2H, m, H-19) and 0.95 (3H, t, H-18).

Table

^{13}C-NMR Chemical Shift

Carbon No.	δ	Carbon No.	δ
2	72.0	14	28.0
3	39.1	15	28.5
5	51.4	16	34.6
6	36.5	17	70.8
7	54.4	18	12.5
8	131.8	19	24.7
9	120.2	20	49.7
10	119.1	21	78.7
11	129.6	N_1-CH_3	36.0
12	109.2	O-CH_3	58.3
13	154.6		

Acetylation of I

To a solution of sandwicolidine (10 mg) in pyridine (0.5 ml), acetic anhydride (1 ml) was added and the reaction mixture kept overnight at room temperature. On usual work up 17-acetyl derivative of I was obtained as crystalline solid m.p. 241-242°C. EIMS m/e(rel.int. %) 382.2259 (M^+, calcd. for $C_{23}H_{30}N_2O_3$) (40). I.R. ν_{max}(cm^{-1}) 1715 (C=O stretching). ^{1}H-NMR ($CDCl_3$) δ : 6.67-7.25 (4H, m, aromatic protons), 5.70 (1H, d, J = 9Hz, H-17), 3.74 (1H, dd, $J_{21,15}$ = 4.5Hz, $J_{21,20}$ = 1Hz, H-21), 3.06 (3H, s, OCH_3), 2.80 (3H, s, N_1-CH_3), 2.74 (1H, m, H-20), 1.27 (2H, m, H-19) and 0.95 (3H, t, H-18).

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