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CONSTITUTION OF FOUR NEW HASUBANAN ALKALOIDS FROM STEPHANIA JAPONICA MIERS

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From Stephania japonica Miers collected in Kagoshima Prefecture, we have isolated four new hasubanan alkaloids, stephamiersine (1), epistephamiersine(2), oxostephamiersine (3), and stephasunoline (4), and here we wish to report on the courses of structure elucidation of the bases.

Physical constants and spectral data of the bases (1 - 4) are tabulated as below. Mass spectra of 1 - 4 showed fragmentation patterns characteristic to hasubanan ketal alkaloids[1].

	Formula	mp	$[\alpha]_D(CHCl_3)$	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	UV λ_{max}^{EtOH} nm(ε)	MS(m/e) M^+, base peak
1	$C_{21}H_{27}NO_6$	165°	+33.0	1725	286 (2200)	389, 243
2	$C_{21}H_{27}NO_6$	98°	+64.1	1735	286 (2300)	389, 243
3	$C_{21}H_{25}NO_7$	290°	+88.3	1730, 1680	286 (2000)	403, 257
4	$C_{20}H_{27}NO_6$	233°	+121.4	3550	286 (2000)	377, 245

NMR signals, δ: ppm ($CDCl_3$), 60 MHz

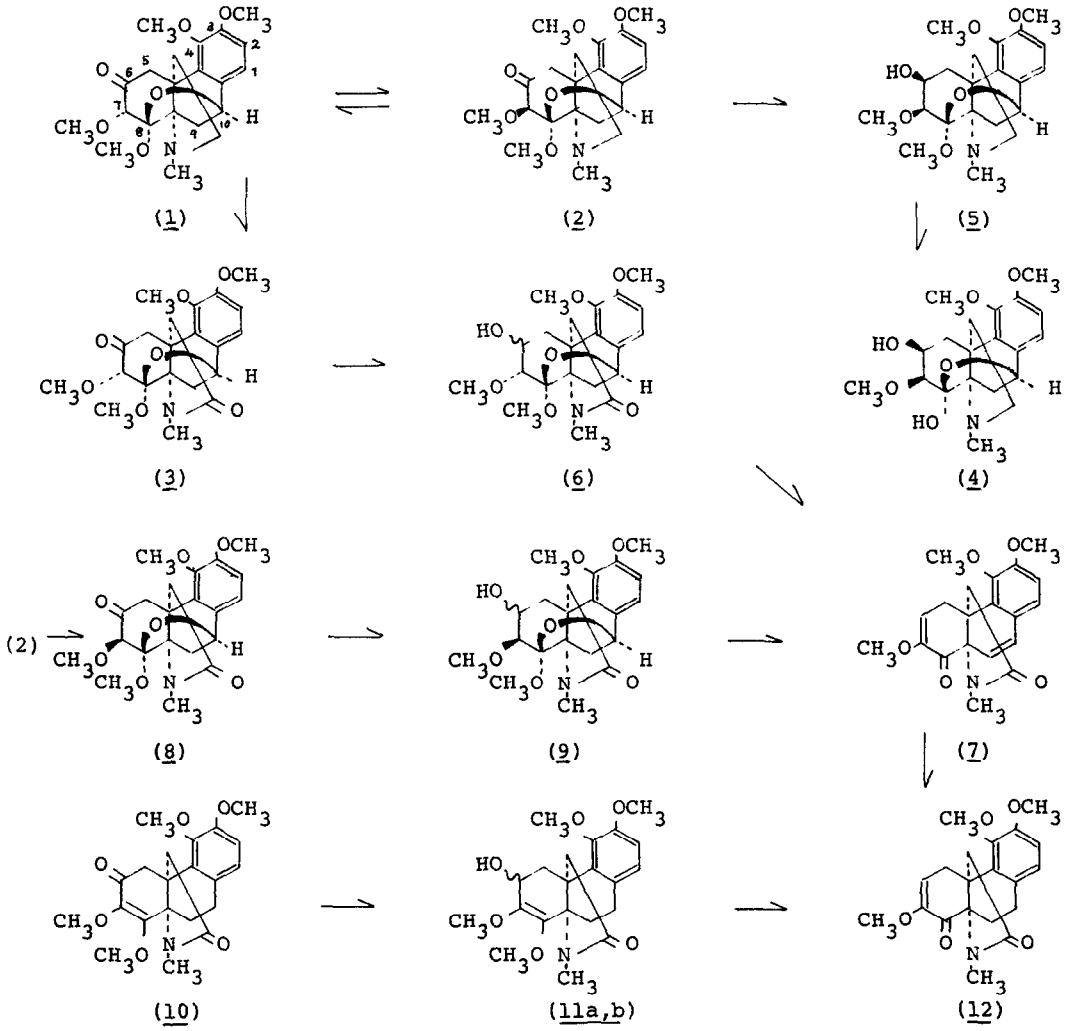
1 6.67 (2H), 3.52 (1H, d), 4.72 (1H, d), 3.92, 3.82, 3.34, 3.31 (each 3H, 4 x OCH_3) 2.64 (NCH_3)

2 6.66 (2H), 4.27 (1H, s), 4.82 (1H, d), 3.89, 3.76, 3.52, 3.45 (each 3H, 4 x OCH_3) 2.63 (NCH_3)

3 6.77 (2H), 3.63 (1H, s), 4.79 (1H, d), 3.92, 3.83, 3.33, 3.29 (each 3H, 4 x OCH_3) 3.12 (NCH_3)

4 6.67 (2H), 3.62 (1H, d), 4.88 (1H, d), 3.90, 3.82, 3.46 (each 3H, 3 x OCH_3), 2.57 (NCH_3)

The spectral data suggest that the bases are closely related compounds, and this was proved by following chemical correlations. (i) When heated in 1%



methanolic sodium hydroxide, both stephamiersine (1) and epistephamiersine (2) gave a separable mixture consisted of 1 and 2 in ca. 1:3 ratio, though they remained unchanged in absence of the alkali. Thus 1 and 2 must be epimeric with respect to the position adjacent to the ketonic function and 2 was assumed to be the thermodynamically stable isomer. (ii) Oxidation of stephamiersine (1) gave a lactam identical with oxostephamiersine (3). (iii) With borohydride, epistephamiersine (2) was reduced stereoselectively to give dihydroepistephamiersine (5) which on mild treatment with hydrochloric acid gave

a compound fully identical with stephasunoline (4).

Acetolysis[2] of 1 and 2 afforded 1,3-diacetoxy-2,5,6-trimethoxyphenanthrene and 1,2,3-triacetoxy-5,6-dimethoxyphenanthrene, respectively. On the other hand, acetolysis of 5 gave 1-acetoxy-2,5,6-trimethoxyphenanthrene. The results of the acetolyses coupled with the nmr data revealed the orientation of five oxygen functions out of six involved in the molecules of 1 and 2, and that of three methoxyls out of four. Therefore remnant one oxygen and one methoxyl should reasonably be assigned to ketal ether and ketal methoxyl, respectively. The conversion of 2 into 4 also presented a chemical support to this ketal methoxyl assignment.

Further, nmr spectra of 1 - 4 showed doublet signals at about δ 4.8 (J=6.5 Hz), and these were found to be attributable to C(10)-H. In case of epistephamiersine (2), an NOE (13%) was observed at this doublet (δ 4.82) by irradiating aromatic proton signal (δ 6.66), and the signals of $C(9)\text{-}H_2$ appeared at δ 1.47 (d, J=10.5 Hz), and δ 2.64 (dd, J=10.5, 6.5 Hz), respectively. From these assignments, it follows that the ketal ether bridge should be linked to C(10).

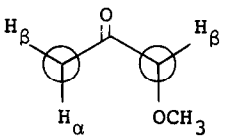
Though the two-dimensional formulae were given from the acetolyses products and the foregoing nmr assignments, the confirmation of the structures as well as the elucidation of the absolute stereostructures were accomplished by the following experiments.

Oxostephamiersine (3) was reduced with borohydride to 6, then 6 was treated with acetic anhydride-perchloric acid to afford the compound (7). Oxoepistephamiersine (8) derived from 2 by permanganate oxidation was reduced with borohydride to give 9, which on treatment with acetic anhydride-perchloric acid also afforded 7. On the other hand, 16-oxohasubanonine[3] (10) was reduced with borohydride to give epimeric alcohols (11a,b). Either of the alcohols gave conjugated ketone (12) when treated with 1% hydrobromic acid. Catalytic hydrogenation of 7 over palladized charcoal gave a compound identical with the conjugated ketone (12).

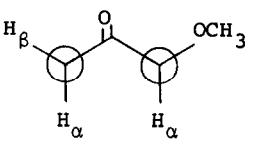
Configuration of C(7) was established by the nmr experiments. In the spectrum of 1, $C(5)\text{-}H_2$ signals occur at δ 2.86 (1H, dd, J=11.5, 1.5 Hz) and δ 3.67 (1H, d, J=11.5 Hz), and homonuclear INDOR spectra showed a long range

coupling between this higher field 1H and C(7)-H (δ 3.52, d, J=1.5 Hz). While, 2 showed C(5)-H_2 at δ 2.99, 3.18 as doublets with J=11.5 Hz, and an NOE signal enhancement (6.5%) of C(7)-H (δ 4.27, s) was observed by irradiating the lower field 1H, but no signal enhancement was observed between the higher field 1H and the C(7)-H upon irradiation.

These nmr findings together with the result of the equilibration reaction (i) disclosed the C(7) configuration of 1 and 2 as drawn in projections 1' and 2', respectively. Thus it has been shown that at C(7) 1 has α-axial methoxyl and 2 has β-equatorial one.



(1')



(2')

Configuration of C(6) of stephasunoline (4) follows from the nmr experiments. The nmr of 4 exhibited C(5)-H_2 signals at δ 2.46 (1H, dd, J=14.3, 2.4 Hz) and δ 2.82 (1H, dd, J=14.3, 3.8 Hz), and C(7)-H (δ 3.62, d, J=3.9 Hz) signal enhancement (12%) was observed upon irradiation of the higher field 1H. The NOE combined with analysis of coupling constant values of the signals for the four protons which situate at C(5,6, and 7), led to the conclusion that C(7)-OCH_3 should be β-equatorial, and C(6)-OH must be β-axial.

On the basis of the results stated above, the structures of stephamiersine (1), epistephamiersine (2), oxostephamiersine (3), and stephasunoline (4) were assigned as drawn in the formulae including their absolute stereochemistry.

References

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