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STRUCTURE OF BAIKEINE, A VERATRUM ALKALOID

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Isolation of jervine, veratramine and zygacine from Veratrum grandiflorum LOESEN has already been reported (1). The basic fraction of the plant collected in Nagano Prefecture, Japan, has yielded, in addition to those three, two new alkaloids named baikeine (I) and baikeidine (II) after Japanese name of the original plant "baikeiso".

Baikeine (I), $C_{27}H_{45}O_3N$, (M^+ 431), m.p. 153-153.5°, $[\alpha]_D$ -97.9°, pKa' 9.65, ϵ_{220} 153, $\epsilon_{220}^{MeOH+HCl}$ 95, δ 3.47 (1H, m), 3.81 (1H, br.s), 4.21 (1H, m), 5.32 (1H, br.d) (2) [picrate m.p. 177.5-178°; HCl salt, m.p. 285°] afforded on acetylation in methanol N-acetylbaikeine (III), m.p. 141-143°, $[\alpha]_D$ -63.3°, ν 3425, 1616 cm^{-1} and in pyridine tetraacetylbaikeine (IV), m.p. 230-234°, ν 1738, 1648 cm^{-1}, δ 2.00 (6H, s), 2.07 (3H, s), 2.11 (3H, s). $LiAlH_4$ reduction of III yielded N-ethylbaikeine (V), M^+ 459, m.p. 267-271°, pKa' 9.55 [triacetyl derivative (VI), m.p. 201-202.5°] which gave the corresponding methiodide, m.p. 297° (decomp.). These observations revealed the presence of an imino group, three secondary hydroxyl groups and a trisubstituted double bond.

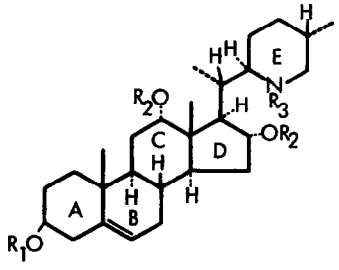
Baikeidine (II), though failed to be isolated pure, is O-acetylbaikeine because it gave, upon mild acetylation (MeOH), N-acetylbaikeidine (VII), m.p. 223.5-225°, $[\alpha]_D$ -103°, ν 3430, 1739, 1614 cm^{-1}, alkaline hydrolysis and acetylation (Py) of which afforded III and IV, respectively.

NMR spectrum of I exhibits four methyl signals; two singlets and two doublets (TABLE). This, when coupled with its molecular formula and its cooccurrence with the steroidal alkaloids, suggests I to have

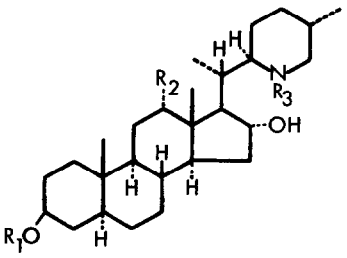
TABLE. NMR Methyl Signals of Baikeine Derivatives*

	19Me	18Me	21Me, 27Me		Ac-O	Ac-N
I	0.97	0.75	0.81 (6.2)	1.02 (7.5)		
III	0.98	0.77	0.98 (5.2)	0.99 (6.2)		2.12
IV	0.99	0.82	0.83 (6.0)	0.94 (6.2)	2.00, 2.00, 2.07	2.11
VI	1.01	0.90	0.86 (5.5)	0.92 (6.0)	2.03, 2.04, 2.11	
VII	0.97	0.80	0.97 (6.0)	0.99 (7.0)	1.97	2.10
VIII	0.77	0.77	0.96 (6.0)	0.97 (7.0)	1.97	2.10
IX	0.73	0.76	0.97 (5.7)	0.97 (5.7)		2.10
XI	1.09	1.09	0.83 (6.5)	0.96 (7.6)	1.96	2.06
XII	0.77	0.70	0.83 (5.6)	1.02 (6.2)		
XIII	0.76	0.68	0.93 (6.8)	0.96 (5.0)		2.10
XIV	0.78	0.81	0.95 (6.6)	1.01 (7.2)		2.10

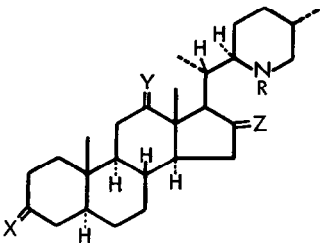
* Expressed in ppm from internal TMS. Numbers in parentheses are coupling constants.



I $R_1=R_2=R_3=H$
II $R_1=Ac$, $R_2=R_3=H$
III $R_1=R_2=H$, $R_3=Ac$
IV $R_1=R_2=R_3=Ac$
V $R_1=R_2=H$, $R_3=Et$
VI $R_1=R_2=Ac$, $R_3=Et$
VII $R_1=R_3=Ac$, $R_2=H$



VIII $R_1=R_3=Ac$, $R_2=OH$
IX $R_1=H$, $R_2=OH$, $R_3=Ac$
XII $R_1=R_2=R_3=H$
XIII $R_1=R_2=H$, $R_3=Ac$
XVI $R_1=R_2=H$, $R_3=Et$



X Δ^4, R=Et, X=Y=O, Z= 
XI R=Ac, X=, Y=O, Z=
XIV R=Ac, X=  , $Y=H_2$, Z=O
XV R=Et, X=  , $Y=H_2$, Z= 

a cholestane carbon skeleton (3).

Mass spectra of I, V and VII exhibit strong peaks corresponding to methylpiperidine moiety (4), i.e. m/e 98 (100%), 99 (75%), m/e 126 (100%), 127 (60%) and m/e 140 (93%), respectively. Catalytic hydrogenation (PtO_2/AcOH) of VII gave the dihydro compound (VIII), m.p. 131-132°, $[\alpha]_D$ -39.4°, alkaline hydrolysis of which yielded N-acetyldihydrobaikeine (IX), m.p. 220-222°, $[\alpha]_D$ +10.3°. Effects of the double bond on molecular rotation [$\Delta[M]_D$ (VII-VIII)= -329°] (5) and on chemical shift of 18- and 19-methyl signals (cf. VII and VIII, and III and IX in TABLE)(6) strongly suggest the double bond at C_5 position. Jones' oxidation of V yielded N-ethylbaikeindione (X), m.p. 275° (decomp.), ν^{CHCl_3} 3430, 1710, 1665, 1605 cm^{-1}, λmax 237 nm (ϵ 10000). Formation of α,β-unsaturated ketone here as well as the positive Lieberman-Burchard reaction for I locates a hydroxyl group at C_3. The molecular rotation changes ($\Delta[M]_D$ -253, -233) on acetylation (IX→VIII and III→VII, respectively) suggest β-orientation for the hydroxyl group (5). Therefore, baikeidine (II) is 3-acetylbaikeine.

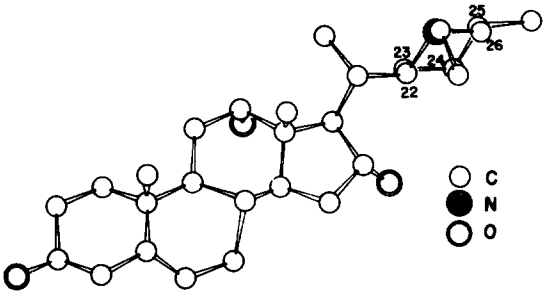
Similar oxidation of VIII gave the corresponding 6-membered ring ketone (XI), m.p. 258-261°, ν 3450, 1730, 1708, 1625 cm^{-1}. $[\phi]_{309}^{peak}$+3500, $[\phi]_{263}^{trough}$ -5900. Sign of the Cotton effect in XI suggests the carbonyl group at C_{11} or C_{12} of the 14α-cholestane; the latter more preferred from the position of the extrema (7). Whereas $NaBH_4$ reduction of XI gave only VIII suggesting β-orientation of the hydroxyl group, dehydration of VIII via its mesylate yielded mainly the Δ^{11} compound, amorphous, ν^{CHCl_3} 3420, 1728, 1620 cm^{-1}, δ 5.42, 6.05 (each 1H, br.d, J=10.0), implying the hydroxyl be axial orientations. These informations suggest 11β-axial hydroxyl group in VIII. However, the chemical shift changes of 18- and 19-methyl signals on going from VIII to XI (TABLE) are not explicable by 11β-hydroxyl but rather by 12α-hydroxyl group (6).

The third hydroxyl group is on the D ring: Huang-Minlon reduction of XI afforded deoxydihydrobaikeine (XII), m.p. 155-157°, [N-acetate (XIII), m.p. 234.5-235°, ν^{CHCl_3} 3370, 1610 cm^{-1}]. CrO_3 oxidation of XIII yielded the corresponding 5-membered ring ketone (XIV), m.p. 177-179°, ν^{CHCl_3} 3400, 1748, 1632 cm^{-1}, $[\phi]_{337}^{trough}$ -7700, $[\phi]_{290}^{peak}$ +13500. The large negative Cotton effect suggests 14α-16-one structure (8). $LiAlH_4$ reduction of XIV yielded N-ethyl diol (XV), amorphous, which was not identical with the N-ethyl diol (XVI), m.p. 215-218°, obtained by ethylation of XII. Furthermore, XII was not identical with any of tetrahydrosolasodines and dihydrotomatidines (9).

As the amount of I isolated prevented the further chemical study to establish the nature of 2nd and

3rd hydroxyl groups as well as the stereochemistry of the carbon skeleton, X-ray crystallographic analysis was undertaken. The derivative used for this purpose is N-ethylbaikeine hydrobromide monohydrate (from aq. methanol), m.p. $>350^{\circ}$, which belongs to the monoclinic system, space group $P2_1$ with two molecules in a unit cell of dimensions a=17.612 Å, b=7.837 Å, c=10.597 Å and $\beta=91.6^{\circ}$.

Three dimensional intensity data were collected on an automatic diffractometer with ω-2θ scanning technique using MoKa radiation. A total of 1640 independent structure factors was evaluated. The structure was solved by several cycles of Fourier and difference Fourier synthesis and refined by least-squares calculations. At the final stage of refinement the discrepancy factor (R) is 10.3%. The molecular structure viewed along the C axis is shown.



Although the structure of I was established as (22R:25S)-22,26-epiminocholest-5-ene-3β,12α,16α-triol, the rather unusual behavior of XI toward $NaBH_4$, described above, is not obvious. This may be due to the stereoelectronic effect of the E ring.

Thanks are due to Miss Ryoko Kikuchi for her preliminary X-ray investigation.

References and Footnotes

1) B. Shimizu and R. Hayashi, Yakugaku Zasshi, 79, 615 (1959).

2) All compounds described gave correct elemental analyses. UV (and ORD) and IR spectra were referred to methanol and Nujol or KBr, respectively, unless otherwise stated. $[\alpha]_D$s and pKa were measured in chloroform and 66.7% EtOH, respectively. NMR spectra were recorded for $CDCl_3$ solution.

3) The functional groups and methyl groups (TABLE) can not be accommodated in the other modified C_{27} steroidal skeletons hitherto known.

4) Cf. H. Budzikiewicz, Tetrahedron, 20, 2267 (1964).

5) Cf. W. Klyne in "Determination of Organic Structures by Physical Methods", E.A. Braude and F.C. Nachod, Ed., Vol. 1, p. 108. Academic Press, New York (1955).

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