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Chemical Examination of the Roots of *Cissampelos pareira* Linn. Part V. Structure and Stereochemistry of Hayatidin

The structures of hayatinin and hayatin, two of the *bis*-benzyltetrahydroisoquinoline alkaloids isolated from the roots of *Cissampelos pareira* Linn. (Menispermaceae), were discussed earlier[1,2]. In the present communication, the structure and stereochemistry of another alkaloid – hayatidin[3], isolated from the same plant – are described.

Hayatidin, m.p. 179–180°; $[\alpha]_D$ – 109° (pyridine); $\lambda_{max} = 280$ nm (log $\varepsilon = 3.07$) (EtOH-H$_2$O, 4:1); $\lambda_{max} = 287$ nm (log $\varepsilon = 2.97$) (EtOH-N·NaOH, 4:1); corresponded to the molecular formula $C_{37}H_{40}N_2O_6$ (mol. weight = 608 by mass spectrometry). Its proton magnetic resonance (p.m.r.) spectrum showed that it had 10 aromatic protons including one at τ 4.12 characteristic of a C-8 proton highly shielded by the aromatic ring of a benzyl group[4], 3 of OMe and 2 of NMe groups.

The mass spectrum of hayatidin showed abundant ions at *m/e* 312, 298, 296, 191, 190, 174, 162, 148 and 145. There were small peaks at *m/e* 608 (M^+), 593, 501, 487, and a characteristic though much smaller peak at *m/e* 258.5 $[((M - 91)/2)^{++}]$[5].

Hayatidin was ethylated with triethylanilinium hydroxide. The ethyl ether which could not be crystallized gave only a single spot on thin layer chromatography (t.l.c.) (silica gel; system: benzene, ethyl acetate and diethylamine, 7:2:1), showed abundant ions at *m/e* 326, 312 and 296 in the mass spectrum and had an IR-spectrum identical with that of the *O*-ethyl derivative of (++)-4''-*O*-methylcurine. It was therefore apparent that hayatidin was a stereoisomer of (++)-4''-*O*-methylcurine isolated by HAYNES et al.[6] from *Cissampelos pareira* Linn. of Jamaican origin.

In order to study the stereochemistry at the 2 centres in this alkaloid, hayatidin ethyl ether was subjected to sodium and liquid ammonia reduction. The phenolic fragment, which was laevorotatory, could not be obtained in the crystalline form but had the same Rf on t.l.c. as *N*-

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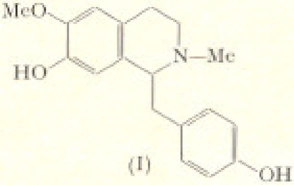
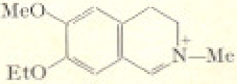
methylcoclaurine. Further, the IR-spectrum of *O,O′*-dimethyl methiodide of this compound, m.p. 131°, was identical with that of an authentic sample of the methiodide of *l*-*O,O′,N*-trimethylcoclaurine. This confirms the structure of the phenolic fragment as *l*-*N*-methylcoclaurine (I).

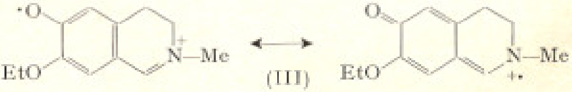
The non-phenolic fragment could also not be crystallized; it was purified by chromatography on alumina (neutral, activity I), gave a single spot on t.l.c. on silica gel and was dextrorotatory. Its p.m.r. spectrum was identical with that of the corresponding non-phenolic fragment obtained from hayatinin ethyl ether[1]. The absence of a signal at τ 6.40–6.50 indicated *O*-ethylation at the 7-position. This assignment was supported by (1) deuteration studies with hayatidin, which showed that there were no protons *ortho* or *para* to the phenolic group, as well as by (2) the mass spectrum, which showed intense peaks at *m/e* 220 and 206. The former corresponded to the ion (II) and the latter to (III) with a hydrogen transfer. The peaks for the other ions were at *m/e* 192, 190, 111, 97 and 91; the molecular ion peak was absent.



(I)



(II)



(III)

The methiodide of the non-phenolic fragment, m.p. 180°, was identical with that of the corresponding methiodide obtained from the non-phenolic fragment of hayatinin ethyl ether.

All this evidence led to the formulation of the non-phenolic fragment as *d*-1-*p*-methoxybenzyl-6-methoxy-7-ethoxy-2-methyl-tetrahydroisoquinoline (IV).

The assignment of the 2 fragments resulting from sodium and liquid ammonia reduction of hayatidin ethyl ether as (I) and (IV) respectively, clearly established the structure of hayatidin as (+−)-4″-*O*-methylbebeerine (V). Using the serine convention and the sequence rule,

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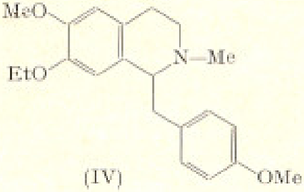
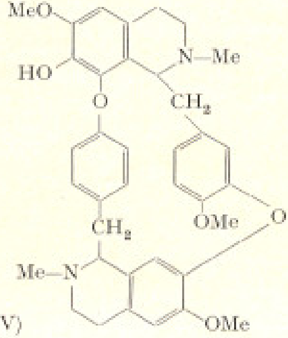
(+) = L = S and (−) = D = R, hayatidin then corresponds to the (S, R) absolute configuration[7,8].



(IV)



(V)

Zusammenfassung. Das Alkaloid Hayatidin, aus Wurzeln von *Cissampelos pareiras* Linn. isoliert, konnte nach Reduktion seines Äthyläthers und Identifikation der Fragmente durch die Darstellung passender Derivate mit protonmagnetischer Resonanz und weiteren Methoden als (+ −)-4″-*O*-Methylbebeerine charakterisiert werden.

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[8] The authors thank Prof. A. R. Battersby, Drs. M. L. Dhar and S. Bhattacharji for much useful advice, Dr. R. S. Kapil for mass spectral determinations and Dr. James Walker and Dr. E. J. Herbert for samples of the methiodide of *l-O,O′,N*-trimethylcoclaurine and *O*-ethyl derivative of (++)-4″-*O*-methylcurine respectively.