Tetrahedron Letters Vol. 22, pp 541 - 544 0040-4039/81/0201-0541$02.00/0

THE QUETTAMINES: A NEW CLASS OF ISOQUINOLINE ALKALOIDS

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Three quettamine type alkaloids, which incorporate either a benzofuran or a dihydrobenzofuran moiety within the molecular framework, have been obtained from Berberis baluchistanica. These are dihydrosecoquettamine (1), secoquettamine (2), and quettamine chloride (3). Alkaloids 1 and 3 are racemates. Hofmann degradation of quettamine (3) provides secoquettamine (2) and the styrene 4 which has a trans relationship between the hydrogens at C-1 and C-α, thus indicating the identical stereochemistry in quettamine. Emde reduction of quettamine leads to dihydrosecoquettamine (1) and the stilbene 5. Two other polar alkaloids in the plant are (+)-armepavine methochloride (6) and oblongine chloride (7). An oblongine type alkaloid must be the biogenetic precursor for the quettamines. Arguments are presented favoring direct oxidative coupling in the biogenesis of the cularine alkaloids.

We wish to describe a new class of isoquinoline alkaloids, the quettamines, which incorporate either a benzofuran or a dihydrobenzofuran moiety within the molecular skeleton.

Work-up of the polar alkaloid fraction from 15 kg of Berberis baluchistanica Ahrendt (Berberidaceae), collected in the highlands in the vicinity of Quetta, the provincial capital of Baluchistan, in western Pakistan, yielded 55 mg of amorphous racemic dihydrosecoquettamine (1), analyzing for $C_{19}H_{23}O_3N$. The uv spectrum of dihydrosecoquettamine evidences a bathochromic shift in base due to the presence of a phenolic function, λ_{max} 275 and 300 sh nm (log ε 3.51 and 2.72), $\lambda_{max}^{MeOH-OH^-}$ 242, 282 and 330 nm (log ε 4.13, 3.56 and 2.60). Of particular significance in the nmr spectrum of 1 are two quartets centered at δ2.97 and 3.36, and a triplet at δ5.64, representing the three aliphatic hydrogens of the substituted dihydrobenzofuran system (Table). The mass spectrum shows a base peak m/e 58 $(CH_2NMe_2)^+$, characteristic of a dimethylaminoethyl side chain, and peak m/e 107 for the $(CHC_6H_4OH + H)^+$ ion.

Acetylation of 1 using acetic anhydride in pyridine at room temperature, provided monoacetate 1a, $C_{21}H_{25}O_4N$, whose nmr spectrum (Table) shows a distinct downfield shift for H-2', H-3', H-5' and H-6', indicating the presence of the phenolic function at C-4' in compound 1.

Another alkaloid found is the optically inactive secoquettamine (2) (26 mg), $C_{19}H_{21}O_3N$, which is slightly fluorescent under uv light, and which was obtained as colorless needles, mp 171-172° C (MeOH), λ_{max} 205, 250, 300, 308 and 323 sh nm (log ε 4.19, 3.75, 4.12, 4.11 and 3.85), $\lambda_{max}^{MeOH-OH^-}$ 220, 250 and 324 nm (log ε 4.08, 3.50 and 4.17). A salient feature in the nmr spectrum is the one proton singlet at δ6.80 representing the C-1 furanyl hydrogen. As with dihydrosecoquettamine, the mass spectrum of 2 has a base peak m/e 58. The monoacetate derivative 2a, $C_{21}H_{23}O_4N$, was prepared, and its nmr spectrum shows the furanyl singlet proton located further downfield at δ7.07.

Quettamine (3), the third new alkaloid obtained, was isolated as an amorphous quaternary chloride salt (186 mg), $C_{19}H_{22}O_3NCl$. It displays near zero specific rotation at the sodium D line. The uv spectrum exhibits a pattern somewhat related to that for dihydrosecoquettamine, with λ_{max} 223 sh and 280 nm (log ε 3.89 and 3.16), $\lambda_{max}^{MeOH-OH^-}$ 248 and 283 nm (log ε 3.83 and 3.32). The nmr spectrum in TFA-d incorporates a doublet at δ5.47 and another at 5.94, each with J_{vic} = 9.8 Hz, representing

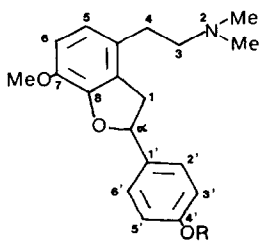
H-1 and H-α respectively. In the mass spectrum (Table), the base peak is once again m/e 58. Acetylation of quettamine yielded monoacetate 3a chloride.

The coupling constant of 9.8 Hz for H-1 and H-α in quettamine is not by itself sufficient evidence for the assignment of a trans configuration at these centers.[3] To establish conclusively the relative stereochemistry of quettamine chloride, as well as to ascertain further the above structural assignments, the alkaloid was subjected to Hofmann degradation using refluxing methanolic potassium hydroxide. Two products were obtained from this reaction, namely secoquettamine (2) (5%) and the oily methine base 4 (75%), $C_{19}H_{21}O_3N$. The nmr spectrum of 4 was particularly informative since it shows the coupling constant for the two adjacent dihydrofuranyl hydrogens to be 1.5 Hz, corresponding to a dihedral angle of $\sim 100^{\circ}$ in the molecule due to a trans stereochemistry. It follows that quettamine must also possess a trans relationship at C-1 and C-α. Alternatively, Emde reduction of quettamine using 5% sodium amalgam in water also supplied two products which proved to be dihydrosecoquettamine (1) (17%), and the stilbene 5, $C_{19}H_{23}O_3N$, (36%), λ_{max} 219, 232 sh, 292 and 312 sh nm (log ε 3.86, 3.62, 3.80 and 3.73).

Beside the above three quettamines, two polar alkaloids we have found in B. baluchistanica are the amorphous (+)-armepavine methochloride (6), $[\alpha]_D^{25}$ + 72° (c 0.50, MeOH), which had been previously recorded only in the racemic form,[4] and the known oblongine (7),[5] which we also obtained in the chloride form. The cd curves of oblongine chloride (7), dihydrosecoquettamine (1), and quettamine (3) are essentially flat and denote that the asymmetric centers in these three alkaloids are racemized.[6]

The quettamines must be derived biogenetically from the oxidation of an oblongine type benzylisoquinoline at C-α, followed by attack of the C-8 phenol at that center to form the dihydrofuran system as in quettamine (3) itself.

In the light of the above finding, one is warranted at this stage in reconsidering the central problem in the biogenesis of the cularine alkaloids. It is not known whether the cularines are formed by direct oxidative coupling of a 7,8,3',4'-tetraoxygenated tetrahydrobenzylisoquinoline of type 9 (Route A below), or through the intermediacy of a procularine which undergoes dienone-phenol rearrangement to the cularine skeleton (Route B). Although the evidence is still not conclusive, data presently available point to the probable validity of Route A, i.e. direct oxidative coupling. These data may be summarized as follows: (a) Oblongine type tetrahydrobenzylisoquinolines, which lack the C-3' phenolic function in the bottom ring required for direct phenolic oxidative coupling to a cularine base, are instead metabolized in plants to furnish quettamines through alternate benzylic oxidation at C-α, (b) todate, no procularines are known to occur in nature, (c) a synthetic diastereomeric mixture of procularines (8) was found not to rearrange in acid to cularine derivatives,[7] and (d) cularines monooxygenated in ring D are so far unknown. Such species would have been formed in nature by dienone-phenol rearrangement of a procularine derived from intramolecular oxidative coupling of an oblongine type tetrahydrobenzylisoquinoline precursor.



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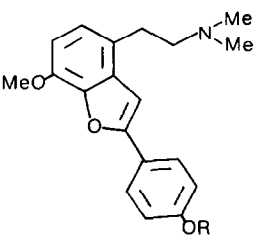
1a, R = Ac



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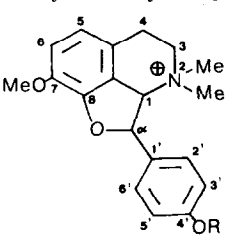

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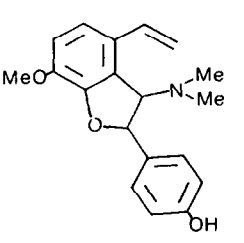

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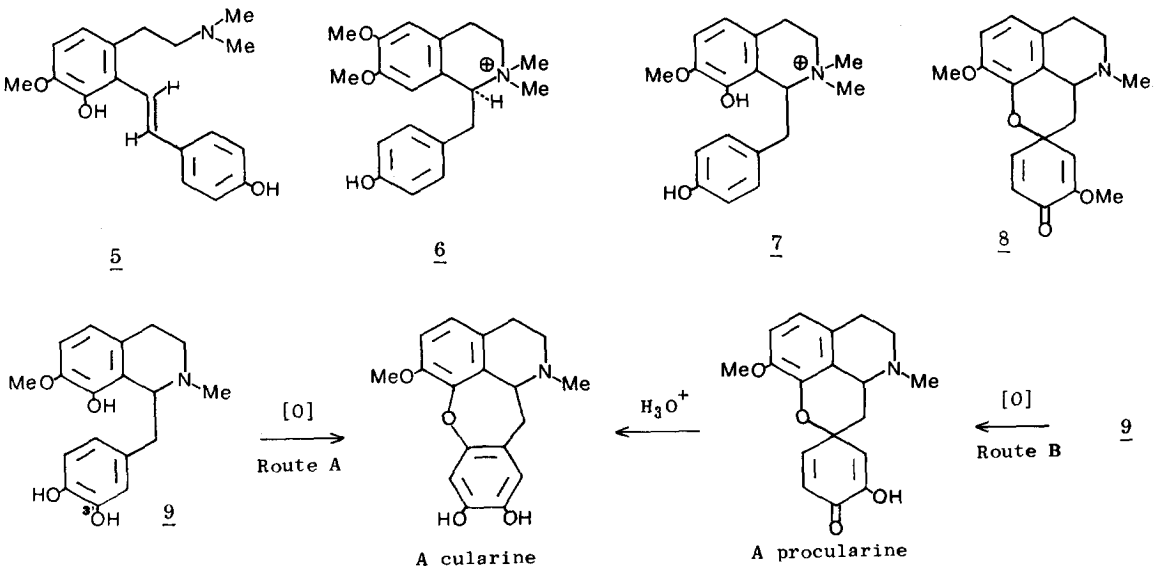

Table

Physical and Spectral Data for the Alkaloids and their Derivatives

Dihydrosecoquettamine (1): R_f 0.23 ($HNEt_2$-$CHCl_3$ 5:95); nmr δ2.43 (6H, s, NMe_2), 2.59-2.79 (4H, m, H-3 and 4), 2.97 and 3.36 (2H, 2q of AMX system, J_{AM} = 15.3 Hz, J_{AX} = 9.1 Hz and J_{MX} = 9.2 Hz, H-1), 3.83 (3H, s, OCH_3), 5.64 (1H, apparent t, X portion of AMX, H-α), 6.62 and 6.71 (2H, dd, J = 8.3 Hz, H-5 and 6), 6.74 and 7.18 (4H, dd, J = 8.5 Hz, H-2',3',5',6'); ms m/e 313 $(M)^+$ (3.2), 255 (0.1), 107 (0.6) and 58 (100).

Dihydrosecoquettamine acetate (1a): R_f 0.29 ($HNEt_2$-$CHCl_3$ 2:98); nmr δ2.30 (3H, s, $OCOCH_3$), 2.42 (6H, s, NMe_2), 3.20 and 3.63 (2H, 2q of AMX system, J_{AM} = 15.5 Hz, J_{AX} = 8.7 Hz and J_{MX} = 9.0 Hz, H-1), 3.88 (3H, s, OCH_3), 5.83 (1H, t, X portion of AMX, H-α), 6.69 and 6.75 (2H, dd, J = 8.3 Hz, H-5 and 6), 7.09 and 7.44 (4H, dd, J = 8.6 Hz, H-2',3',5',6'); ms m/e 355 $(M)^+$ (1.1), 235 (2.1), 234 (2.1), 192 (2.4), 150 (6.5), 84 (1.4), 58 (100), and 43 (5.5).

Secoquettamine (2): R_f 0.08 ($HNEt_2$-$CHCl_3$ 5:95); nmr δ2.45 (6H, s, NMe_2), 2.78 and 3.05 (2x2H, 2m, H-3 and 4), 3.99 (3H, s, OCH_3), 6.70 and 6.93 (2H, dd, J = 8.1 Hz, H-5 and 6), 6.80 (1H, s, H-1), 6.83 and 7.74 (4H, dd, J = 8.6 Hz, H-2',3',5',6'); ms m/e 311 $(M)^+$ (2.2), 253 (1.9), 238 (1.4), 181 (1.2), 165 (0.8), 84 (4.8), 58 (100), and 42 (2.3).

Secoquettamine acetate (2a): R_f 0.26 ($HNEt_2$-$CHCl_3$ 2:98); nmr δ2.33 (3H, s, $OCOCH_3$), 2.41 (6H, s, NMe_2), 4.03 (3H, s, OCH_3), 6.74 and 6.97 (2H, dd, J = 8.1 Hz, H-5 and 6), 7.07 (1H, s, H-1), 7.18 and 7.92 (4H, dd, J = 8.8 Hz, H-2',3',5',6'); ms m/e 353 $(M)^+$ (0.4), 253 (0.5), 238 (0.3), 181 (0.2), 86 (1.4), 84 (2.2), 59 (3.3), 58 (100), and 43 (3.3).

Quettamine chloride (3): R_f 0.38 ($MeOH$-$CHCl_3$-HCl_g 50:50:trace); nmr (TFA-d) δ3.14 and 3.17 (2x3H, 2xs, NMe_2), 4.05 (3H, s, OCH_3), 5.47 (1H, d, J = 9.8 Hz, H-1), 5.94 (1H, d, J = 9.8 Hz, H-α), 7.05 and 7.18 (2H, dd, J = 8.1 Hz, H-5 and 6), 7.22 and 7.62 (4H, dd, J = 8.3 Hz, H-2',3',5',6'); ms m/e 311 (0.9), 253 (0.7), 238 (0.5), 204 (0.9), 181 (0.4), 174 (1.6), 145 (0.7), 107 (0.4), 91 (0.5), 73 (2.3), 72 (1.3), 60 (1), 59 (3.6), and 58 (100).

Quettamine Acetate (3a): R_f 0.48 (MeOH-CH_2Cl_2-HCl_g 40:60:trace); nmr (TFA-d) δ2.50 (3H, s, $OCOCH_3$), 3.19 (6H, s, NMe_2), 4.07 (3H, s, OCH_3), 5.48 (1H, d, J = 9.7 Hz, H-1), 6.02 (1H, d, J = 9.7 Hz, H-α), 7.07 and 7.24 (2H, dd, J = 8.4 Hz, H-5 and 6), 7.36 and 7.76 (4H, dd, J = 8.3 Hz, H-2',3',5',6'); ms m/e 354 (5.7), 353 (16.6), 310 (7.4), 295 (11.5), 253 (33.8), 238 (31.5), 181 (20.6), 174 (20.8), 152 (22.3), 110 (25.8), 58 (100), and 43 (72.2).

Methine Base 4: R_f ($HNEt_2$-$CHCl_3$ 5:95); nmr δ2.34 (6H, s, NMe_2), 3.93 (3H, s, OCH_3), 4.52 (1H, d, J = 1.5 Hz, H-1), 5.20 (1H, q, J = 1.1 Hz, J' = 11.0 Hz, H-vinyl), 5.70 (1H, q, J = 1.1 Hz, J' = 17.7 Hz, H-vinyl), 5.79 (1H, d, J = 1.5 Hz, H-α), 6.76 and 7.12 (4H, dd, J = 8.4 Hz, H-2',3',5',6'), 6.89 and 7.15 (2H, dd, J = 8.5 Hz, H-5 and 6), and part of one H-vinyl overlap with ArH's; ms m/e 312 $(M+1)^+$ (11.6), 311 $(M)^+$ (55.5), 296 (12.6), 268 (35.4), 267 (100), 266 (32.1), 121 (33.2), 107 (11.8), 58 (18.9), and 43 (11.3).

Stilbene 5: R_f 0.15 ($HNEt_2$-$CHCl_3$ 5:95); nmr δ2.40 (3H, s, NMe_2), 3.90 (3H, s, OCH_3), 6.71 (2H, s, H-5 and 6), 6.73 and 7.34 (4H, dd, J = 8.5 Hz, H-2',3',5',6'), 6.96 (1H, d, J = 16.4 Hz, H-vinyl), 7.28 (1H, d, J = 16.4 Hz, H-vinyl); ms m/e 313 $(M)^+$(10.3), 107 (1.6), and 58 (100).

Acknowledgment:- This research was supported by NIH grant CA-11450, NCI, USPHS. We are grateful to Professor Paul L. Shiff, Jr., for a sample of oblongine iodide.

References and Footnotes[8,9]

1. On leave from the Department of Chemistry, University of Jordan, Amman, Jordan.
2. Department of Chemistry, Gomal University, Dera Ismail Khan, NWFP, Pakistan.
3. For a discussion of the nmr spectra of dihydrobenzofurans, see T.J. Batterham, "NMR Spectra of Simple Heterocycles", J. Wiley and Sons, New York (1973), pp. 375-377.
4. J. Wu, J.L. Beal, W.-N. Wu, and R.W. Doskotch, J. Nat. Prod., 43, 270 (1980).
5. A.N. Tackie, J.B. Reighard, M.M. El-Azizi, D.J. Slatkin, P.L. Schiff, Jr., and J.E. Knapp, Phytochem., 19, 1882 (1980).
6. It is worth noting that freshly resolved synthetic (-)-petaline, a 7,8,4'-trioxygenated tetrahydrobenzylisoquinoline alkaloid, shows a well defined circular dichroism curve, see G. Grethe, M. Uskoković, and A. Brossi, J. Org. Chem., 33, 2500 (1968).
7. T. Kametani, K. Fukumoto, and M. Fujihara, Chem. Commun., 352 (1971).
8. The numbering system adopted here for the quettamines corresponds to that for the benzylisoquinolines. All uv data were obtained in methanol. TLC was on Merck silica gel G F-254 glass plates, thickness 0.25 or 0.5 mm. NMR spectra are at 200 MHz (FT) in $CDCl_3$ with TMS as internal standard unless indicated otherwise.
9. To ensure that quettamine (3) is not an artefact of isolation, the attempted oxidation of oblongine chloride (7) with air in ethanol, or in a mixture of methanol-chloroform, in the presence of alumina (or silica gel), furnished no trace of 3. Additionally, treatment of quettamine chloride with ammonium hydroxide solution for five days at room temperature produced no secoquettamine (2).

(Received in USA 7 November 1980)