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VERBASKINE, A MACROCYCLIC SPERMINE ALKALOID OF A NOVEL TYPE FROM VERBASCUM pseudonobile STOJ. et STEF. (SCROPHULARIACEAE)[1]

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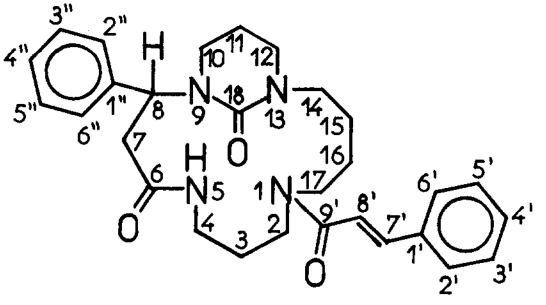
Summary: On the basis of chemical degradation and spectral data (UV, IR, NMR and MS) the structure 1 was deduced for the macrocyclic spermine alkaloid verbaskine from Verbascum pseudonobile Stoj. et Stef. of Bulgarian origin. (E)-Cinnamamide was also isolated from the same plant material.

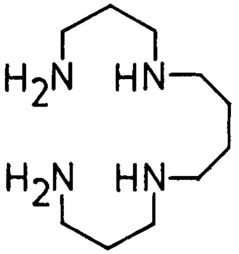
In the past few years, a number of macrocyclic alkaloids structurally derived from spermine have been found to occur in certain species of the families Acanthaceae, Ephedraceae, Fabaceae, Flacourtiaceae and Scrophulariaceae[2-7]. The very recent paper by Seifert, Johne and Hesse[8] on the structure of the spermine alkaloid verbascenine (ex Verbascum phoeniceum L. and V. nigrum L.) prompted us to report on the structure elucidation of another member of this group, verbaskine, which was earlier isolated[9] from Verbascum pseudonobile Stoj. et Stef.[10] grown in Bulgaria. The structure **1** was ascribed to this alkaloid on the basis of the following arguments.

Verbaskine[11] ($C_{29}H_{36}N_4O_3$ by high resolution MS) is optically active, possesses one active hydrogen and exhibits a UV spectrum which showed a close overall similarity to that of (E)-cinnamamide[12] which accompanies **1** in the same plant species. The actual presence of a cinnamyl residue in the molecule of **1** was shown by the formation of dihydroverbaskine **2** (H_2/10% Pd(C) in MeOH and AcOH, 100:1, 20h) and by the identification of cinnamic acid (m.p. 132 to 134 °C from benzene) along with spermine[13] **3** on acid hydrolysis (2M-HCl, 18h at 150 °C in sealed tube). In contrast to 1, dihydroverbaskine 2 afforded under similar conditions in addition to cinnamic acid also 3-phenylpropionic acid which was identified by GLC as methyl ester. Evidently, one molecule of cinnamic acid was present in 1 and 2 in a masked form.

The ^{13}C-NMR spectrum of 1 exhibits three distinct carbonyl signals (C-6, C-9′ and C-18), aromatic carbons, two sp^2 methines (C-7′, C-8′), one sp^3 methine (C-8), six methylenes α to nitrogen (C-2, C-4, C-10, C-12, C-14, C-17) and five aliphatic methylenes (C-3, C-7, C-11, C-15 and C-16). The spectrum is complicated by E,Z-isomerism of the amide groups so that most signals appear as doublets, the splitting being largest for the methylenes C-2, C-3, C-4, C-16 and C-17. At 90 °C the latter doublets disappear due to a near coalescence, while the remaining carbon signals appear as singlets. The low sensitivity of the ^{13}C-shifts of C-8, C-10, C-11, C-12 and C-15 to the amide isomerism points to a relatively rigid arrangement around the third carbonyl group (C-18). This is consistent with linking the N-9 and N-13 nitrogen atoms by the C-18 carbonyl to form the unusual hexahydropyrimidinone ring in 1.



1
2 : 7′,8′-dihydro



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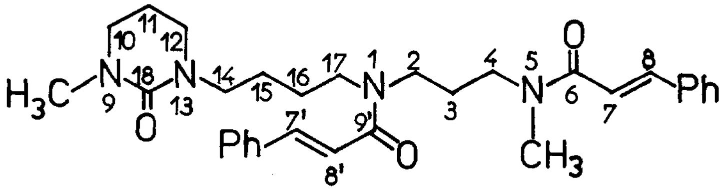
On alkylation with MeI in alkaline medium (NaH, dioxane, reflux 16 h) 1 afforded after chromatographic purification an amorphous, optically inactive product 4 ($C_{31}H_{40}N_4O_3$ by high resolution MS). The ^{13}C-NMR spectrum[14] of 4 shows three distinct carbonyl groups, two almost identical phenyl groups, four cinnamyl sp^2 methines, six sp^3 methylenes and two methyl groups bound to nitrogen, and four aliphatic methylenes. Except for the N-9 methyl, C-10, C-11, C-12, C-14, C-18 and the aromatic carbons, all signals appear as doublets due to the amide isomerism. The final evidence for the structure 4 followed from the fragmentation map, constructed on the basis of metastable transitions in the mass spectrum (Scheme 1). Following ionization, 4 loses either cinnamoyl fragment to form isomeric ions a_1 and a_2. The N-methylhexahydropyrimidinone moiety is eliminated from both a_1 and a_2 by the McLafferty rearrangement producing isomeric ions b_1 and b_2 which further eliminate C_4H_7N and C_5H_9N, respectively. This reaction sequence, together with other fragmentations of the spermine chain in a_1 and a_2 (Scheme 1) give evidence of the bonding sites of the cinnamoyl groups and exclude alternative structures.



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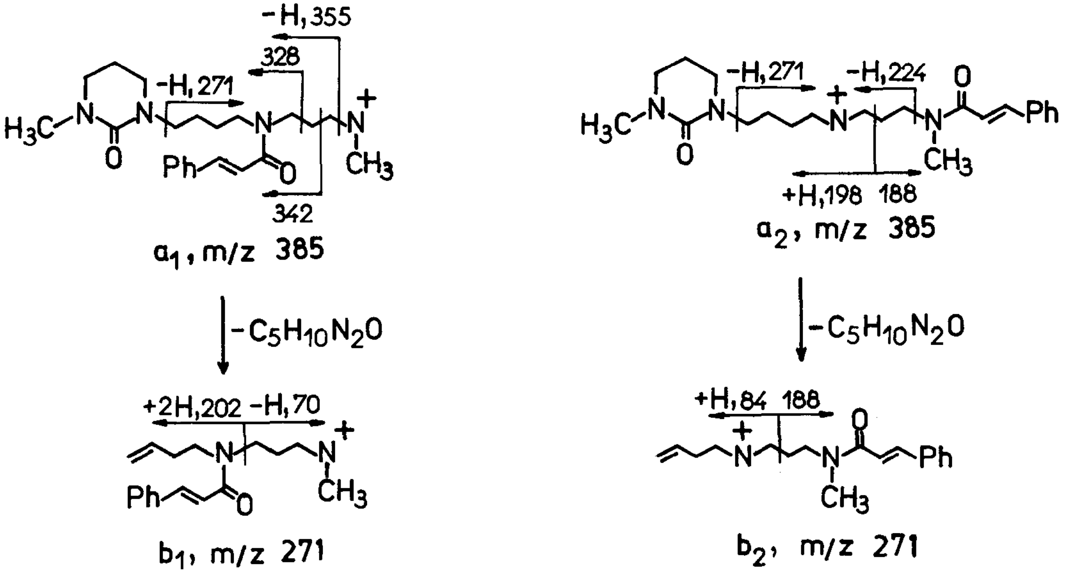
Scheme 1



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10. This species was earlier considered as synonymous with *Verbascum* nobile Vel.; later it has been recognized as an independent taxon (Stefanova B., Ninova P.: Farmatsiya (Sofia) 23, 39 (1973)).
11. M.p. 120-123 °C (acetone); $[\alpha]_D^{20}$ -26° ($CHCl_3$); UV (EtOH), λ_{max}(log ε): 219(4.16), 225(4.05), 284 nm(4.20); IR (KBr): 3500, 3300(NH), 1610,1590 (aromatic), 1660, 1645(amide); ^{1}H-NMR (DMSO-d_6, 23 °C) δ: 8.16(m, 1H), 7.68(m, 2H), 7.50+7.48(d, J = 15.3 Hz, 1H), 7.32(m, 8H), 7.08(d, J = 15.3 Hz, 1H), 6.17(dd, J = 10.3, 7.1 Hz, 1H), 4.21(dd, J = 12, 10.9 Hz, 1H), 3.54, 3.36, 3.18, 3.00, 2.68(m, 12H), 1.79, 1.68, 1.47(m, 9H); ^{13}C-NMR ($CDCl_3$, 23 °C) δ: 170.57+170.34s, 166.14+165.99s, 157.21+157.09s, 142.61+142.33s, 139.16+139.01d, 135.42+135.31s, 129.54, 129.46, 128.70, 127.84, 127.77, 127.41, 127.31d, 117.63+117.30d, 52.80+52.69d, 47.63+45.52t, 45.23+44.33t, 44.99+44.11t, 43.99+43.70t, 39.92t, 37.44t, 37.14+36.59t, 29.02+27.08t, 24.85+22.90t, 22.71+22.37t, 21.86t.
12. M.p. 149-150 °C (sublim.); For C_9H_9NO (147.2) calculated: 73.45 %C, 6.16 %H, 9.52 %N; found: 73.78 %C, 6.56 %H, 9.36 %N. UV (EtOH) λ_{max}(log ε): 217(4.22), 222(4.17), 274 nm(4.22).
13. M.p. of tetrahydrochloride 303-305 °C (dec.)(from 85% EtOH); tetrapicrate 250-252 °C (dec.)(from water). Satisfactory combustion analyses were obtained for both derivatives.
14. ^{13}C-NMR ($CDCl_3$, 23 °C) δ: 166.44+166.30s, 166.19+165.95s, 156.31s, 142.97d, 142.43d, 135.30s(2C), 129.48d (2C), 128.72d (4C), 127.80d (4C), 117.68+117.16d, 48.02t, 47.77t, 47.65+47.20t, 46.92+46.36t, 45.74t, 44.58+44.23t, 35.62q, 35.41+34.08q, 29.62+29.29t, 27.75+26.74t, 25.53+25.28t, 25.13t, 22.25t.

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