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ECHINOZOLINONE, AN ALKALOID FROM *ECHINOPS ECHINATUS**

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Key Word Index—*Echinops echinatus*; Compositae; alkaloids; echinopsine; echinozolinone; echinopsidine; ^{13}C NMR.

Abstract—In addition to echinopsine and echinopsidine, a new alkaloid, echinozolinone, has been identified in *Echinops echinatus* as 3(2-hydroxyethyl)-4(3H)-quinazolinone from its spectral data. This is the first report of alkaloids from this plant and the first occurrence of a 4-quinazolinone alkaloid in the Compositae.

Earlier work on the neutral part of the aerial parts of *E. echinatus* resulted in the isolation of flavone glycosides [1], and there is no chemical investigation on the alkaloidal part of this plant in the literature. The present investigation on the alkaloidal part of the plant led to the isolation of known alkaloids, echinopsine (**1**) and echinopsidine (**3**), and a new one, named echinozolinone (**2**), with a 4-quinazolinone skeleton.

Silica gel column chromatography of the basic chloroform extract afforded compound **1** from the chloroform–methanol (19:1) eluants whereas chloroform–methanol (9:1) eluants afforded the new compound **2**. The basic *n*-butanol extract afforded echinopsidine from the Al_2O_3 chromatogram as an amorphous base (**3**); hydrochloride (**3a**) (MeOH), mp 212° (d.)

Echinozolinone ($C_{10}H_{10}N_2O$, $[M]^+$ 190), mp 150°, has been assigned structure **2** from spectral evidence. Compound **2** was found to be homogeneous on TLC and by mass spectrometry. Its IR spectrum (KBr) showed bands at 1658 and 1610 cm^{-1} characteristic of a 4-quinazolinone system [2] and the UV spectral data at 230, 262, 270 and 319 nm were reminiscent of a 4(3H)-quinazolinone system [3]. The ^{1}H NMR spectrum (CD_3OD, 100 MHz) was also consistent with structure **2**, which was further substantiated by the mass fragmentation patterns (Scheme 1). Two 2H triplets each at δ4.12 (N-C$\underline{H}_2$) and 3.20 (C$\underline{H}_2$OH) of *J*-value 6 Hz were assigned to the methylene groups of the side chain attached to N-3. The downfield singlet at δ8.80 (H-2), unchanged in the D_2O exchange experiment, fitted well with the presence of a $\Delta^{1,2}$-double bond as the presence of a $\Delta^{2,3}$-double bond would have shifted the H-2 signal upfield at δ8.25 [4]. The one-proton doublet at δ8.00 (J = 9 Hz) was due to H-5 and the other aromatic protons appeared as a multiplet in the region δ7.4–7.65.

In its mass fragmentation pattern depicted in Scheme 1, the peak at *m/z* 172 due to loss of water showed the presence of a hydroxyl group in the side chain. The appearance of ion peaks at *m/z* 146, 119, 91 and the absence of ion peaks at *m/z* 163 and 145 (163 − H_2O), which would have appeared in the mass spectrum in the case of substitution on N-1 due to retro-Diels–Alder cleavage of the heterocyclic ring, confirmed the attachment of the side chain at N-3 and the absence of a hydroxyl group in the aromatic nucleus [5, 6].

Thus the structure of **2** was confirmed as 3(2-hydroxyethyl)-4(3H)-quinazolinone. During a literature study, compound **2** was found to be synthetically prepared [7] but due to the non-availability of the synthetic one, natural compound **2** could not be compared. The structures of echinopsine and echinopsidine were determined as **1** and **3**, respectively, from spectral data (see Experimental).

EXPERIMENTAL

NMR: Varian FT-80A, Jeol Fx-100; δ values; solvent DMSO-d_6 CD_3OD; TMS as internal standard; mps uncorr., MS on a Jeol JMS D × 300; silica gel, alumina (Brockmann Grade), BDH, India.

Extraction. Fresh aerial parts of *E. echinatus* (1.5 kg) were extracted and separated into C_6H_{12}, $CHCl_3$ and *n*-BuOH fractions as described earlier [1].

Isolation. The $CHCl_3$ concentrate showing a positive Dragendorff's test was extracted with 3% HCl soln and repeatedly extracted with $CHCl_3$ (4 × 500 ml), which was then dried (Na_2SO_4). The dried $CHCl_3$ soln on removal of solvent afforded the crude basic residue A (0.5 g). Similarly, the *n*-BuOH concentrate was treated to isolate the crude basic residue B (0.8 g).

Echinopsine (**1**). Residue A was chromatographed over silica gel and the column was eluted with C_6H_{12}, C_6H_6, C_6H_6–$CHCl_3$ (1:1), $CHCl_3$ and $CHCl_3$–MeOH of increasing polarities. The $CHCl_3$–MeOH (19:1) eluants gave a light-brown solid which was purified by prep. TLC (silica gel) using $CHCl_3$–MeOH (97:3) to afford echinopsine [8], crystallizing from C_6H_6–$CHCl_3$ as light-yellow needles, mp 152°, R_f 0.2 ($CHCl_3$–MeOH, 49:1). MS *m/z* (rel. int.): 159 $[M]^+$ (100), 133 (45), 105 (4); ^{1}H NMR ($CDCl_3$, 80 MHz): δ8.40 (2H, *d*, *J* = 9 Hz, H-2, H-5), 7.20–7.85 (3H, *br m*, H-6, H-7, H-8), 6.25 (1H, *d*, *J* = 8.2 Hz), 3.85 (3H, *s*, N–Me); ^{13}C NMR (20 MHz, $CDCl_3$): δ172.8 (C-4), 152.72 (C-2), 152.60 (C-8a), 135.10 (C-7), 128.44 (C-6), 124.20 (C-5), 121.18 (C-4a), 117.98 (C-8) 102.87 (C-3), 30.27 (N–Me). (Assignments followed from comparison with the ^{13}C NMR values of 4-quinazolone derivatives [6, 9].)

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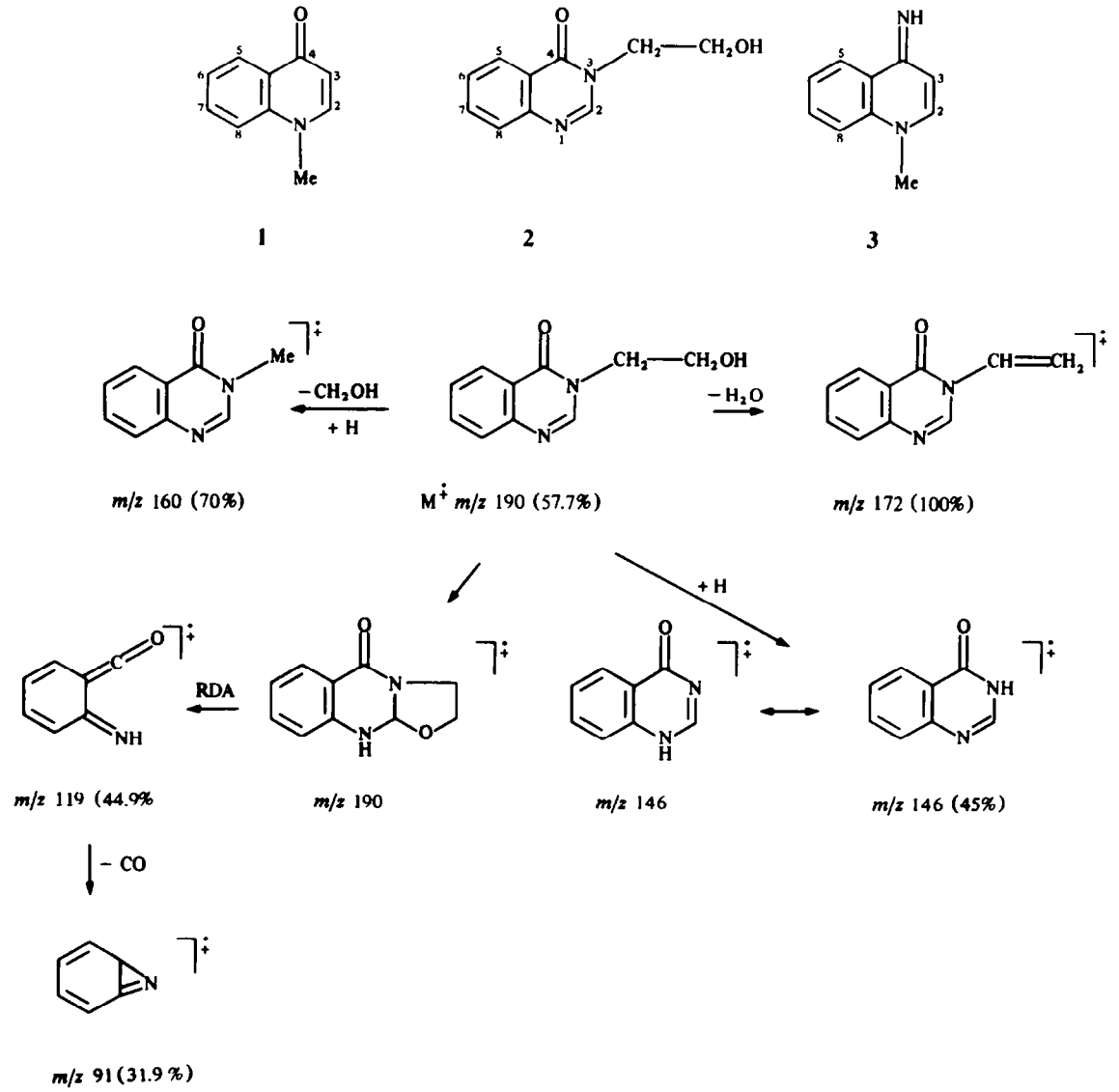

Scheme 1. Mass fragmentation of compound 2.

Echinozolinone (2). The $CHCl_3$–MeOH (9:1) eluants during the isolation of echinopsine afforded a light-yellow compound, 2, which crystallized from $CHCl_3$–MeOH as pale-yellow needles, mp 150°. It gave a light-green fluorescence in UV, and a light-orange colour after spraying with Dragendorff's reagent followed by H_2SO_4 (50%). TLC (silica gel): 0.84 (EtOAc–EtOH–25% NH_3, 8:6:1), 0.33 ($CHCl_3$–MeOH, 9:1); (cellulose): 0.70 (C_6H_6–MeOH, 7:3); UV λ_{max}^{MeOH} nm: 230 (4.39), 265 (3.67), 270 (3.68), 319 (3.77); IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 2920, 2880, 1665 (C=O), 1620, 1572, 1555 (quinazolinone skeleton), 1495, 1212, 1050, 925, 840; MS *m/z*: 190 $[M]^+$. Elemental analyses: found: C, 63.10; H, 5.32; N, 14.62. $C_{10}H_{10}N_2O_2$ requires: C, 63.17; H, 5.25; N, 14.74%.

Echinopsidine (3). Residue B on chromatography over neutral Al_2O_3 afforded a light-brown solid from the $CHCl_3$–MeOH (1:2) eluants. Further purification through MeOH–Me_2CO washing gave an amorphous base 3, which showed an orange-coloured spot with Dragendorff's reagent. Compound 3 was made crystalline as its hydrochloride **3a**, mp 212° d (MeOH) (lit. mp 214–215° d [10]). TLC (silica gel): 0.12 (MeOH–$CHCl_3$, 1:1), 0.18 ($CHCl_3$–MeOH–Et_2NH, 1:1:0.1), 0.65 ($CHCl_3$–MeOH–HOAc, 1:1:0.01); (Al_2O_3): 0.60 (*n*-BuOH–HOAc–H_2O, 4:1:5); UV λ_{max}^{MeOH} nm: 228, 239, 262, (sh), 328, 340; IR ν_{max}^{KBr} cm^{-1}: 3420, 3300, 3120, 2916, 2845, 1645, 1620, 1565, 1545, 1375, 1240, 1136, 1045, 758; ^1H NMR (DMSO-d_6, 100 MHz): δ8.45 (1H, *dd*, J = 9.5 and 2 Hz, H-5), 8.4 (1H, *d*, J = 8 Hz, H-2), 8.00 (2H, *m*, H-6 and H-8), 7.75 (1H, *m*, H-7), 6.80 (1H, *d*, J = 8 Hz, H-3), 4.15 (3H, *s*, N-Me); ^{13}C NMR (DMSO-d_6, 20 MHz): δ158.01 (C-4), 134.70 (C-7), 147.00 (C-2), 139.0 (C-8a), 126.60 (C-6), 124.20 (C-5), 120.9 (C-4a), 101.07 (C-3), 42.00 (N-Me); MS *m/z* (rel. int.): 158 (100), 134 (61.09), 104 (4.10).

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STRICTANOL AND STRICTANINE—TWO NEW INDOLE ALKALOIDS FROM THE FRUITS OF *RHAZYA STRICTA*

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Key Word Index—*Rhazya stricta*; Apocynaceae; hydroxyindolenine, dihydroindole.

Abstract—Strictanol and a trace alkaloid strictanine have been isolated from the fruits of *Rhazya stricta*. Their structures were assigned on the basis of spectral studies.

INTRODUCTION

Rhazya stricta Decsne is an indigenous medicinal plant widely distributed through Western Asia and abundantly found in Pakistan [1, 2]. It has long been used in the indigenous system of medicine for the treatment of various diseases [1–5]. The anticancer activity of some of the indole alkaloids of the plant is also reported [6, 7].

As a result of our continuing studies [8, 9] on the chemical constituents of the fruits of *R. stricta* we have isolated two new alkaloids, strictanol (**1**) and strictanine (**2**). The identity of each alkaloid was established from extensive NMR studies.

RESULTS AND DISCUSSION

The crude alkaloidal extract of the fruits (without seeds) was subjected to selective extractions with chloroform at different pH values according to their differential basicities [8]. The fractions obtained at pH 6.7–7.3 were combined and subjected to prep. TLC resulting in the isolation of strictanol and a trace alkaloid strictanine.

The UV spectrum of strictanol (**1**) was reminiscent of a hydroxyindolenine system showing λ_{max} at 227, 282 sh and 290 nm. The IR spectrum indicated the presence of O–H and C=N stretching vibrations at 3180 and 1658 cm^{-1}, respectively. Its EI mass spectrum afforded a $[M]^+$ at *m/z* 298 which was confirmed by FD and FAB. The HR mass spectrum indicated the $[M]^+$ at *m/z* 298.2031, leading to the molecular formula $C_{19}H_{26}N_2O$. The base peak occurred at *m/z* 281.2021 ($C_{19}H_{25}N_2$) from the loss of an hydroxyl group. A prominent fragment at *m/z* 269.1712 ($C_{17}H_{21}N_2O$), resulted from the loss of ethyl group from the $[M]^+$, a common feature in Aspidosperma alkaloids [10, 11]. Other fragments of alkaloid (**1**) which occurred at *m/z* 210, 157, 156, 144, 143, 138, 125, 124, 110 and 96 were also consistent with the presence of an Aspidosperma skeleton [10, 11].

In the ^1H NMR spectrum of **1** (CD_3OD, 300 MHz), the methyl (C-18H) of the ethylidine side chain appeared as a triplet at δ0.93 ($J_{18,19}$ = 7.56 Hz). The adjacent methylene protons (C-19H) resonated as a quartet at δ1.38 ($J_{19,18}$ = 7.56 Hz). The C-21 protons resonated as doublets at δ 3.12 and 3.63 with the same coupling constant (J_{gem} = 12.12 Hz). These two protons, as indicated by a COSY-45 spectrum and homo-decoupling results, were coupled to each other only without being coupled to any other proton. The signal at δ3.12 may be attributed to the C-21α proton while the signal at δ3.62 may be assigned to the C-21β proton. The four aromatic protons of the benzene moiety were identified individually (see Experimental).

The ^{13}C NMR spectrum (CD_3OD, 75.4 MHz) of **1** indicated the presence of 19 carbons and the multiplicity of each carbon atom was established by carrying out multipulse ID DEPT experiments with the last polarization pulse angle θ = 45, 90 and 135°. The possibility that the substance was quebrachamine *N*-oxide could be ruled out because of its non-indolic UV and its differing