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VESTOLIDE, A GUAIANOLIDE FROM *VICOA VESTITA**

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Key Word Index—*Vicoa vestita*, Asteraceae, guaianolide, vestolide

Abstract—A new sesquiterpene lactone, vestolide, of the guaiane series was isolated from the aerial parts of *Vicoa vestita* Its structure was established on the basis of chemical and spectral evidence

INTRODUCTION

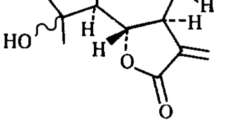
Vicoa vestita (Wall ex DC) Benth ex Hook f (syn *Inula vestita* Wall ex DC) is a woolly herb distributed all over India The alcoholic extract of the aerial parts of the plant was found to possess oxytocic activity when tested at this Institute The activity was later confirmed in its *n*-butanol-soluble fraction The chemical investigation of the *n*-butanol fraction carried out to trace the biologically active principle led to the isolation of vestolide (**1**), which, however, was inactive The present paper is concerned with the structural elucidation of the latter

RESULTS AND DISCUSSION

Vestolide ($[M]^+$ m/z 282) displayed IR bands at 3400, 3325 (H-bonded hydroxyl groups), 1740 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone) The presence of an exocyclic methylene group conjugated with the lactone was inferred from its UV maximum at 212 nm (ε12 408)

Since compound **1** was associated with another lactone of the same polarity only a small quantity could be isolated The two lactones were therefore resolved as their acetates The monoacetate of **1** ($[M]^+$ m/z 324) (**2**) was obtained as the major acetylated product The IR spectrum (KBr) of **2** also showed an intense band at 3425 cm^{-1} revealing the presence of hindered hydroxyl functions

The ^1H NMR spectrum of **2** exhibited two characteristic low-field doublets at δ5 34 (J = 3 Hz) and 6 14 (J = 3 5 Hz) corresponding to the protons of the exocyclic methylene γ-lactone Their J-values suggested *trans*-fusion of the lactone ring [1] The ^1H NMR spectrum also displayed two 3H singlets at δ1 22 and 1 45 corresponding to the two methyl groups present on carbons bearing hydroxyl groups The fact that **2** did not display any signal for a methyl group at the ring junction along with the requirement of a bicyclic nucleus suggested that it belonged to the guaianolide series The proton on the carbon bearing the oxygen of the lactone was responsible for a



R
1 H
2 Ac

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double-doublet ($J = 9$ and 12 Hz) centred at δ4 31 The large J-values of this signal also suggested *trans*-fusion of the lactone ring The trans-ring junction coupled with the observation of a negative Cotton effect at 252 nm ($\theta = -1737$) indicated that the lactone ring is closed towards C-6 in accordance with the Stocklin–Waddell–Geissman rule [2] The proton under the lactone, H-7, resonated as a multiplet at δ3 78 To account for the unusual downfield shift of this signal, the hydroxyl group at C-10 was assigned on α-configuration [3] The proton of the secondary acetoxyl group gave a triplet of doublets ($J = 7$ and 3 5 Hz) centred at δ5 54 A 3H singlet at δ1 96 was unambiguously assigned to the acetate protons

Intensive decoupling experiments led to the establishment of the position of the acetoxyl group as well as the stereochemical refinements of the molecule Irradiation at the frequency of H-7 led to the collapse of not only the H-13a and H-13b doublets to singlets but also simplified the triplet of doublets to a triplet ($J = 7$ Hz) at δ5 54 This showed that H-7 coupled with the carbinolic proton by 3 5 Hz thus having a *cis*-relationship with this vicinal proton present at C-8 Thus the acetoxy group was placed at C-8 In this irradiation experiment, the decoupling of H-6 could not be observed due to its proximity to H-7 Subsequent irradiation of H-6 signal changed the double-doublet ($J = 8$ and 12 Hz) at δ2 22 to a doublet ($J = 8$ Hz) This double-doublet was therefore assigned to H-5 The disappearance of its large coupling of 12 Hz suggested that it had a *trans*-diaxial relationship with H-6, and obviously its second coupling of 8 Hz was due to its coupling interaction with H-1 The magnitude of the J-value (8 Hz) indicated a *cis*-fusion of five- and seven-membered rings Similarly, when the H-5 signal at δ2 22 was irradiated, the H-6 double-doublet collapsed into a doublet with a J-value of 9 Hz, apparently due to its coupling with H-7 on the other side This coupling of 9 Hz required a *trans*-diaxial disposition of H-6 and H-7 which conforms with the interference drawn earlier

Since in guaianolides H-7 has conventionally an α-configuration, the protons located at C-5, C-6 and C-8 will possess α, β and α-configurations, respectively

When the carbionolic proton was irradiated, the doublets of doublet at δ2 20 and 1 90 (each $J = 7$ and 15 Hz) changed to doublets (each $J = 15$ Hz, geminal coupling), therefore these doublets of doublet were assigned to C-9 methylenic protons The multiplet of H-7 at δ3 78 also experienced a slight change

Thus structure **2** followed from above discussion for the monoacetate, and thereby structure **1** for the lactone This structure was also substantiated by the mass fragmentation pattern of the lactone

EXPERIMENTAL

UV and CD spectra were recorded in MeOH and IR spectra in KBr A mixture of $CDCl_3$ and DMSO-d_6 with TMS as int standard was used for recording ^{1}H NMR TLC solvent systems used were (1) $CHCl_3$–MeOH (9 1), and (2) C_6H_6–MeOH (19 0 1)

Extraction and isolation The air-dried plant material (20 kg), collected from Lucknow (a voucher specimen has been deposited at CDRI), was extracted with EtOH The EtOH extract was fractionated into *n*-hexane, $CHCl_3$, *n*-BuOH and H_2O-soluble fractions The *n*-BuOH fraction contained mainly three compounds provisionally designated M, M′ and N CC of this fraction over silica gel using EtOAc (satd with H_2O)–MeOH in increasing order of polarity initially resulted in the isolation of a small quantity of compound M (**1**) Later, this compound was always associated with compound M′ which had identical R_f in different TLC systems to the former All efforts to resolve this mixture failed The mixture was therefore acetylated with Ac_2O–pyridine and the acetate of compound M (**2**) was obtained by CC of the acetylated products over silica gel using *n*-hexane–Me_2CO mixtures of increasing polarity

Vestolide **1** TLC in solvent system 1, IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1} 3400, 3325 (H bonded –OH), 1740 and 1660 (α,β-unsatd-γ-lactone), UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm 212 (ε12 408), CD λ^{MeOH} nm 252 ($\theta = -1737$), MS m/z (rel int) 282 $[M]^+$ (26), 267 $[M-Me]^+$ (20), 263 $[M-H-H_2O]^+$ (10), 251 (43), 246 $[M-2H_2O]^+$ (21), 231 (14), 203 (28), 188 (38), 178 (54), 175 (29), 161 (25), 131 (28), 121 (50), 117 (33), 107 (44), 105 (42), 91 (100), 71 (50)

Vestolide acetate (**2**) was crystallized from *n*-hexane–Me_2CO, mp 234°, TLC in solvent system 2, IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1} 3425, 2920, 1735 and 1660, for ^{1}H NMR see text, MS m/z (rel int) 324 $[M]^+$ (8), 309 $[M-Me]^+$ (1), 306 $[M-H_2O]^+$ (1), 279 (14), 267 $[M-CH_2-CH_2{=}C{=}O]^+$ (2), 264 $[M-H_2O-CH_2{=}C{=}O]^+$ (3), 246 $[M-2H_2O-CH_2{=}C{=}O]^+$ (1), 228 $[M-3H_2O-CH_2{=}C{=}O]^+$ (13), 203 $[M-Me-3H_2O-CH_2{=}C{=}O]^+$ (9), 188 (29), 175 (9), 167 (42), 149 (100) (Found C, 61 15, H, 7 34 Calcd for $C_{17}H_{24}O_6 \frac{1}{2} H_2O$ C, 61 21, H, 7 55%)

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