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SHORT COMMUNICATION

LUDALBIN, A NEW LACTONE FROM *ARTEMISIA LUDOVICIANA**

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Abstract—*Artemisia ludoviciana* Nutt. ssp. *albula* (Woot.) Keck, a member of the *vulgaris* complex, contains a sesquiterpene lactone, ludalbin, which is 8-α-acetoxydouglanine.

RESULTS AND DISCUSSION

PREVIOUS studies on a number of species of *Artemisia* (Compositae) belonging to a group that can be designated the *vulgaris* complex[1–4] have disclosed the presence in these allied taxa of a number of sesquiterpene lactones having many common structural features.

Examination of *A. ludoviciana* Nutt. ssp. *albula* (Woot.) Keck[5] has resulted in the isolation of a new lactone, ludalbin (I), which is 8-α-acetoxydouglanine. Douglanine itself has been found in *A. ludoviciana* Nutt. ssp. *mexicana*,[3] *A. douglasiana* Bess.[2] and *A. mexicana* Willd.,[6] all members of the *vulgaris* group. It is noteworthy that of the numerous eudesmanolides previously isolated from *vulgaris* species, none has been 8-hydroxylated. On the other hand, the co-occurrence of 8-hydroxy and the corresponding deoxy compound pairs in other cases is well known (e.g. matricarin and deacetoxymatricarin).

Ludalbin (I), $C_{17}H_{22}O_5$, m.p. 169–171°, $[\alpha]_D^{27}$ +227·6, shows IR absorption at 3600, 3430, 1765, 1730, 1650 and 1225 cm^{-1}, indicating that it is a hydroxy α-methylene-γ-lactone. The mass spectrum, with principal ion peaks at *m/e* 306 (M^+), 298 (M-18), 244 (M-60) and 228 (M-18-60), conforms with the results of the elemental analysis and the presence of one hydroxyl and one acetoxyl group.

The NMR spectrum was strikingly similar to those of douglanine (VII) and α-cyclotulipinolide (VIII),[7] differing from the former only in the additional signals for the 8-acetoxyl group and from the latter in the signals for the 1-hydroxyl group. The C-10 and C-4 methyl groups gave a sharp singlet (δ 0·91) and a doublet (δ 1·81, $J = 1{\cdot}3$ Hz), respectively. The methylene grouping (C-13) showed the characteristic doublets (δ 5·49, $J = 2{\cdot}9$ Hz;

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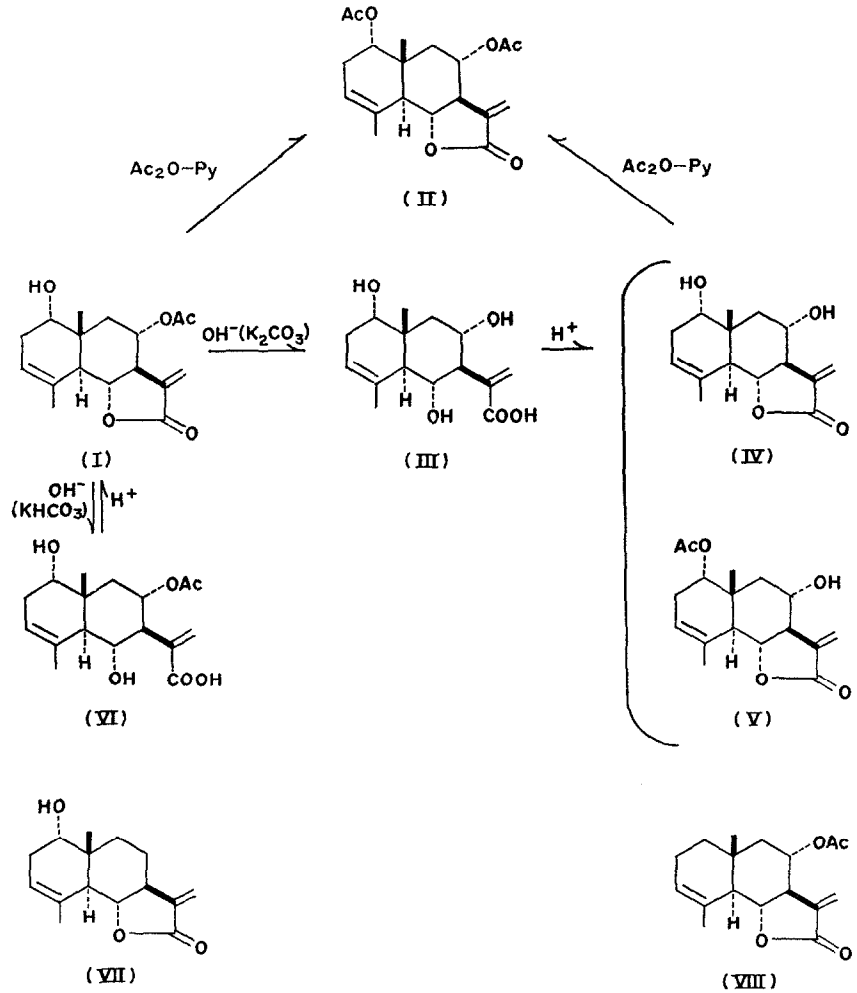
[1] T. A. GEISSMAN, *J. Org. Chem.* **31**, 2523 (1966).
[2] S. MATSUEDA and T. A. GEISSMAN, *Tetrahedron Letters* 2013, 2159 (1967).
[3] K. H. LEE and T. A. GEISSMAN, *Phytochem.* **9**, 403 (1970).
[4] T. A. GEISSMAN, *Phytochem.* **9**, 2377 (1970).
[5] One of a collection of several populations of *A. ludoviciana* and *A. ludoviciana* subspecies collected and identified by Professor James R. Estes, University of Oklahoma, Norman.
[6] J. ROMO, A. ROMO DE VIVAR, R. TREVIÑO, P. JOSEPH-NATHAN and E. DIAZ, *Phytochem.* **9**, 1615 (1970).
[7] R. W. DOSKOTCH and F. S. EL-FERALY, *J. Org. Chem.* **35**, 1928 (1970).



6·08, $J = 3{\cdot}2$ Hz) for this structural unit. Although geminal coupling was absent in the 8-acetoxy compound, I, and was not prominent in deacetylludalbin (IV), the NMR spectrum of the latter in deuteropyridine showed the two protons at C-13 at nearly the same chemical shift, as a doublet at δ 6·19.[8]

The stereochemistry of the C-5/C-6/C-7 positions is clear from the appearance of a triplet for H-6 (δ 4·03), in which coupling to H-5 (11 Hz) and H-7 (11 Hz) show the all-*trans*-axial disposition of the protons at these centers. Douglanine and its several congeners possess the same stereochemistry. The vinylic proton at C-3 gave a broad multiplet at δ 5·20, partially obscured by the signal for the CH–OAc proton at C-8. The proton of CH–OH at C-1 gave a broad doublet (δ 3·40, $J = 3$ Hz) which shifted downfield to δ 4·66 on acetylation. The signal for the proton at C-8 of ludalbin, overlapped with that of H-3 in the spectra of ludalbin and ludalbin acetate (II), was clearly separated in the spectrum of deacetylludalbin, appearing as a sextet at δ 4·30 ($J_{7,8} = J_{8,9ax} = 10{\cdot}4$ Hz; $J_{8,9eq} = 4{\cdot}4$ Hz).

[8] T. A. GEISSMAN and M. A. IRWIN, unpublished observations; also H. YOSHIOKA, T. J. MABRY, M. A. IRWIN, T. A. GEISSMAN and Z. SAMEK, *Tetrahedron*, in press.

These observations indicated that the disposition of the 8-hydroxyl group was α-, a conclusion substantiated by the NMR spectrum of deacetylludalbin in deuteropyridine, alluded to above. The α-disposition for the 1-hydroxyl group is deduced from the coupling constants of H-1, and from the fact that its NMR signal is nearly identical with that of H-1 of douglanine. Douglanine has been shown to be the 1-α-hydroxy compound.[9]

When ludalbin was heated with aqueous potassium carbonate, deacetylation and opening of the lactone ring occurred, with the formation of deacetylludalbinic acid (III). When potassium bicarbonate was used only lactone hydrolysis occurred, with the formation of ludalbinic acid (VI). Relactonization of deacetylludalbinic acid with glacial acetic acid gave deacetylludalbin (IV), acetylation of which gave ludalbin acetate (II). The C-4 methyl groups of ludalbinic acid (VI) and deacetylludalbinic acid (III) appear at unusually low chemical shifts (δ 2·23 and 2·32, respectively). Models show the proximity of the C-4 methyl group and the 6-α-hydroxyl group, a relationship that can account for the downfield shift observed.

It is of interest to note that while the acids derived from germacranolides, possessing C-6-α and C-8-α hydroxyl groups, close at C-8 upon relactonization,[10] ludalbinic acid, also C-6-α-OH and C-8-α-OH, relactonizes at C-6 to reform the original lactone.

EXPERIMENTAL

Isolation of ludalbin (I). A 470-g sample of *Artemisia ludoviciana* ssp. *albula*[11] was extracted with $CHCl_3$, yielding 31 g of crude extract. This was extracted with two portions (300 and 150 ml) of EtOH–H_2O (1:2), and the clarified aqueous solution extracted with $CHCl_3$. Removal of the solvent left 7 g of a yellow–brown oil.

This was chromatographed over 100 g of silica gel (Baker) with collection of 45 25-ml fractions. Evaporation of the 11th to 15th fractions left a residue which crystallized when rubbed with Et_2O–light petroleum. Recrystallized from EtOAc–light petroleum, the compound, ludalbin, formed stout, colorless prisms, m.p. 169–171°; 370 mg.

Rechromatography of fractions 1–8 afforded an additional 80 mg, to give a total yield of 450 mg. (Calc. for $C_{17}H_{22}O_5$: C, 66·65; H, 7·24. Found: C, 66·79; H, 7·18%.)

The compound had $[\alpha]_D^{25}$ +227·6° (c = 1·0, $CHCl_3$). Its IR spectrum ($CHCl_3$) showed absorption at 3600, 3430, 1765, 1730, 1650 and 1225 cm^{-1}. The mass spectrum showed the molecular ion at *m/e* 306 and principal ions at *m/e* 288 (M–H_2O), 246 (M–HOAc), 228 (M–H_2O–HOAc) and 213 (M–CH_3–H_2O–HOAc).

Ludalbin acetate (II). Acetylation of ludalbin with Ac_2O–pyridine afforded the acetate, which resisted attempts to crystallize it. Its IR spectrum showed no absorption in the hydroxyl region, and peaks at 1773, 1735 and 1235 cm^{-1}. Its NMR spectrum is described in the text.

Deacetylludalbinic acid (III). To a solution of 150 mg of K_2CO_3 in 3 ml H_2O was added 110 mg of ludalbin. The mixture was heated on a steam bath for 2 hr, the ludalbin dissolving during this time. The cooled solution was washed with ether, then acidified with HCl and extracted with *n*-BuOH (ether extraction removed but a trace of ludalbinic acid). After removal of the butanol *in vacuo* the residue was crystallized from EtOAc to give 63 mg of deacetylludalbinic acid, m.p. 180–181°. It had IR absorption at 3450, 3300 (broad), 1705 and 1625 cm^{-1}. The mass spectrum did not show the molecular ion, but a prominent peak was observed at *m/e* 246 (M–$2H_2O$). (Calc. for $C_{15}H_{22}O_5$: C, 63·81; H, 7·85. Found: C, 63·79; H, 7·69%.)

Deacetylludalbin (IV) *and isoludalbin* (*V*). A solution of deacetylludalbinic acid (50 mg) in 2 ml HOAc was refluxed for 90 min. The solvent was removed *in vacuo* and the residue chromatographed over silica gel.

Deacetylludalbin, the major product (16 mg) was recrystallized from EtOAc–light petroleum, m.p. 228–229. Its mass spectrum showed the molecular ion at *m/e* 264. (Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63. Found: C, 68·24; H, 7·77%.)

Isoludalbin (1-*O*-acetyl-8-α-hydroxydouglanine) had m.p. 174–175° (from EtOAc–light petroleum); the yield was 3·2 mg. It was not investigated further than to characterize it by means of its NMR spectrum, which was in accord with structure V. Traces (by TLC) of ludalbin and ludalbin acetate were also recognized in the products of the chromatographic separation.

[9] M. UL-HAQUE, C. N. CAUGHAN, M. T. EMERSON, S. MATSUEDA and T. A. GEISSMAN, *J. Chem. Soc.* B, 598 (1970).

[10] H. YOSHIOKA, W. RENOLD and T. J. MABRY, *Chem. Commun.* 148 (1970).

[11] Collection No. 880, by Dr. J. R. Estes, University of Oklahoma.

Deacetylludalbin acetate (=*ludalbin acetate*). Acetylation of deacetylludalbin (IV) in the usual way afforded ludalbin acetate, identified by IR, TLC and NMR, all of which were identical with those of ludalbin acetate prepared from ludalbin.

Ludalbinic acid (VI). Ludalbin (70 mg) was added to a solution of 120 mg of $KHCO_3$ in 5 ml H_2O. The mixture was heated on the steam bath for 2 hr, cooled, and extracted with Et_2O (which removed a negligible amount of starting material). After acidification, ether extraction afforded 37 mg of ludalbinic acid, m.p. 219–220° (from EtOAc). The IR spectrum showed peaks at 3530, 3200 (broad), 1715, 1703, 1635, 1200 cm^{-1}. The mass spectrum did not show the molecular ion, but gave a prominent peak at *m/e* 264 (M–HOAc). The elemental analysis was unsatisfactory, a high value (0·8%) for carbon probably being attributable to partial lactonization on keeping and drying.

Ludalbin from ludalbinic acid. Lactonization of ludalbinic acid (50 mg) in hot HOAc afforded 37 mg of ludalbin, characterized by direct comparison with the natural material (IR, TLC, NMR, m.p. and m.m.p.).

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Key Word Index—*Artemisia ludoviciana* ssp. *albula*; Compositae; sesquiterpene lactones; ludalbin; 8-α-acetoxy douglanine.