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SESQUITERPENE LACTONES. NEW LACTONES FROM *HYMENOCLEA SALSOLA* T. AND G.[1]

F. P. TORIBIO and T. A. GEISSMAN

Department of Chemistry, University of California, Los Angeles 90024

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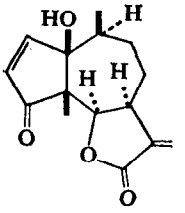
Abstract—Further examination of *Hymenoclea salsola* T. and G., from which four pseudoguaianolides and ilicic acid were previously isolated, has yielded three new compounds of the same class. These are hymenin (1-epiparthenin), hymenolin (11,13-dihydroparthenin), and salsolin (apoludin-2-acetate).

Hymenoclea salsola T. and G. (Compositae, tribe Ambrosieae) has been reported to contain the pseudoguaianolides ambrosin, neoambrosin, dihydrocoronopilin and coronopilin and ilicic acid.[2] The isolation of dihydrocoronopilin and its characterization as a pure compound was not completely satisfactory at that time because of the difficulties in separating it from its mixture with coronopilin. Dihydrocoronopilin has now been prepared in a pure state by treatment of the coronopilin–dihydrocoronopilin mixture with diazomethane, which converts coronopilin into the pyrazoline, easily separable from the dihydro compound. Pure dihydrocoronopilin from the natural source has m.p. 202–204° and was found to be identical with material prepared by zinc–acetic acid reduction of coronopilin.

Hymenin (I) has the composition $C_{15}H_{18}O_4$, m.p. 173–174°, $[\alpha]_D^{25}$ −88·7°. Its i.r. spectrum shows absorption at 3430 (hydroxyl), 1750 and 1650 (α-methylene-γ-lactone), and 1695 and

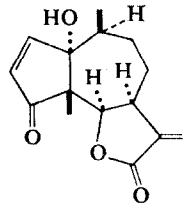


(I)

1596 cm^{-1} (cyclopentenone). The hydroxyl group of hymenin could not be acetylated with acetic anhydride-pyridine and was resistant to chromic acid oxidation. The mass spectrum of hymenin bears a striking resemblance to that of parthenin; it shows the expected molecular ion at *m/e* 262, and prominent peaks at *m/e* 244 (M-18), 229 (M-18-15), 216 (M-18-28) and 201 (M-18-15-28). Its NMR spectrum (Table 1) shows signals for two methyl groups at δ1·04 (singlet, 3H) and 1·10 (doublet, 3H, $J=7$ c/s), and for the two protons of the exocyclic

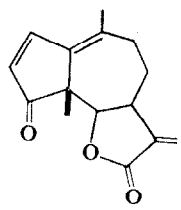
[1] Contribution No. 2230 from the Department of Chemistry, U.C.L.A.
[2] T. A. GEISSMAN and F. P. TORIBIO, *Phytochem.* **6**, 1563 (1967).

methylene group (1-H doublets at δ5·53 and 6·21, $J=3$ c/s). The C*H*—O proton of the lactone grouping appears as a doublet at δ4·84 (1H, $J=9$ c/s), which is characteristic of the proton at C-6 of the *cis*-fused lactones typified by coronopilin, parthenin and ambrosin. The two doublets, of one proton each, at δ6·13 and 7·66 ($J=6$ c/s) show the presence of cyclopentenone, and are closely similar in position and form to those of the C-2/C-3 protons of parthenin (II). Like those in parthenin, and unlike those in ambrosin, these doublets show



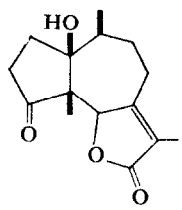
(II)

no additional splitting, an indication that they are adjacent to a substituent at C-1. The remarkable similarity between these properties of hymenin and those recorded for parthenin[3] suggested that the two compounds bore a close structural resemblance. Indeed, it was found that the two compounds differ only in the configuration at C-1, and hymenin is 1-epiparthenin.

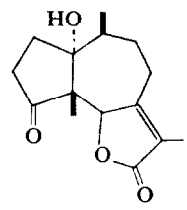


(III)

Although the dehydration of hymenin with formic acid affords a product (III) which is identical with anhydroparthenin,[3] its hydrogenation with platinum oxide at room temperature gives dihydroisohymenin (IV), different from dihydroisoparthenin (V).[3] These observations



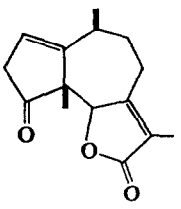
(IV)



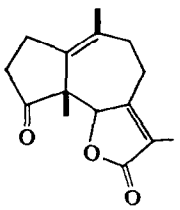
(V)

indicated that hymenin and parthenin are stereoisomers which differ in configuration at C-1 or C-10. Dehydration of dihydroisohymenin (IV) with thionyl chloride gave a mixture of the compounds VI and VII in a ratio of about 3:1. Both VI and VII have been described[3]

[3] W. HERZ, H. WATANABE, M. MIYAZAKI and Y. KISHIDA, *J. Am. Chem. Soc.* **84**, 2601 (1962).

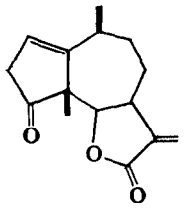


(VI)



(VII)

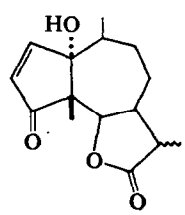
as derivatives of parthenin. Compound VI was obtained as one of the products of partial reduction of anhydroparthenin (III) and its structure assigned on the basis of its spectral properties; the configuration at C-10 was presumptive. We have confirmed the structure of VI by preparing it from neoambrosin (VIII) by catalytic isomerization of the 11/13 double bond.



(VIII)

Catalytic isomerization of the 11,13-double bond of coronopilin with palladium–barium sulfate yielded dihydroisoparthenin (V), previously prepared[3] by the reduction and isomerization of parthenin.

Hymenolin (IX) has the composition $C_{15}H_{20}O_4$, m.p. 186–188°. Its i.r. spectrum shows absorption at 3400, 1750, 1700 and 1580 cm^{-1}, indicating the presence of a γ-lactone and a cyclopentenone. The NMR spectrum showed signals for three methyl groups at δ1·28 (3H, singlet), 1·10 (3H, doublet, $J=7$ c/s) and 1·27 (3H, doublet, $J=7$ c/s); two vinyl protons (doublets at δ6·13 and 7·66, $J=6$ c/s), and the proton of the lactone grouping C*H*—O at δ5·05 (1H, doublet, $J=7{\cdot}5$ c/s). The mass spectrum of hymenolin shows the molecular ion at *m/e* 264, and peaks at 246 (M-18), 231 (M-18-15), 218 (M-18-28) and 203 (M-18-15-28). These data all pointed to the probability that hymenolin is 11,13-dihydroparthenin, and this was confirmed by the conversion of hymenolin into dihydrocoronopilin by catalytic reduction.

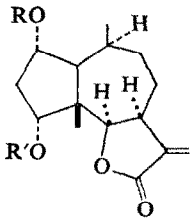


(IX)

Salsolin (X), $C_{17}H_{24}O_5$, m.p. 148–149°, was isolated in minute yield (0·004 per cent). Its i.r. spectrum reveals the presence of a hydroxyl group (3550 cm^{-1}), an α-methylene-γ-lactone (1755, 1650 cm^{-1}) and an acetoxy group (1720, 1240 cm^{-1}). Its NMR spectrum

confirms the presence of the acetate group (3H, singlet, δ2·14) and the α-methylene group of the lactone (1-H doublets at δ5·75 and 6·45), and shows two methyl groups (3H, singlet, δ1·12, and 3H, doublet, δ1·28, $J=7$ c/s). A one-proton doublet at δ4·66 ($J=10$ c/s) is characteristic of the C-6/C-7 *cis*-lactone. Two one-proton signals at δ4·13 (triplet) and δ5·46 (1H, quartet) indicate the presence of the groupings C*H*-OH and C*H*—OAc. The mass spectrum of salsolin shows peaks at *m/e* 308 (M^+), 290 (M-18), 248 (M-60), 230 (M-18-60), 220 (M-60-28), 215 (M-60-18-15) and 202 (M-60-28-18).

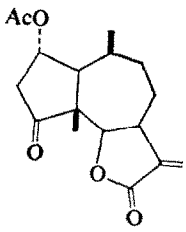
The structure of salsolin was established by its oxidation to the ketone XI, which is readily transformed into ambrosin (XII) by the loss of acetic acid. Acetylation of salsolin yields the diacetate (XIII), identical with the diacetate of apoludin (XIV), a lactone isolated from *Ambrosia dumosa* Gray.[4] Saponification of salsolin acetate yielded apoludin. Since other details of the stereochemistry of apoludin have been established,[4] that of salsolin is that represented in X.



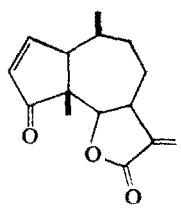
(X) R=Ac; R'=H

(XIII) R=R'=Ac

(XIV) R=R'=H



(XI)



(XII)

DISCUSSION

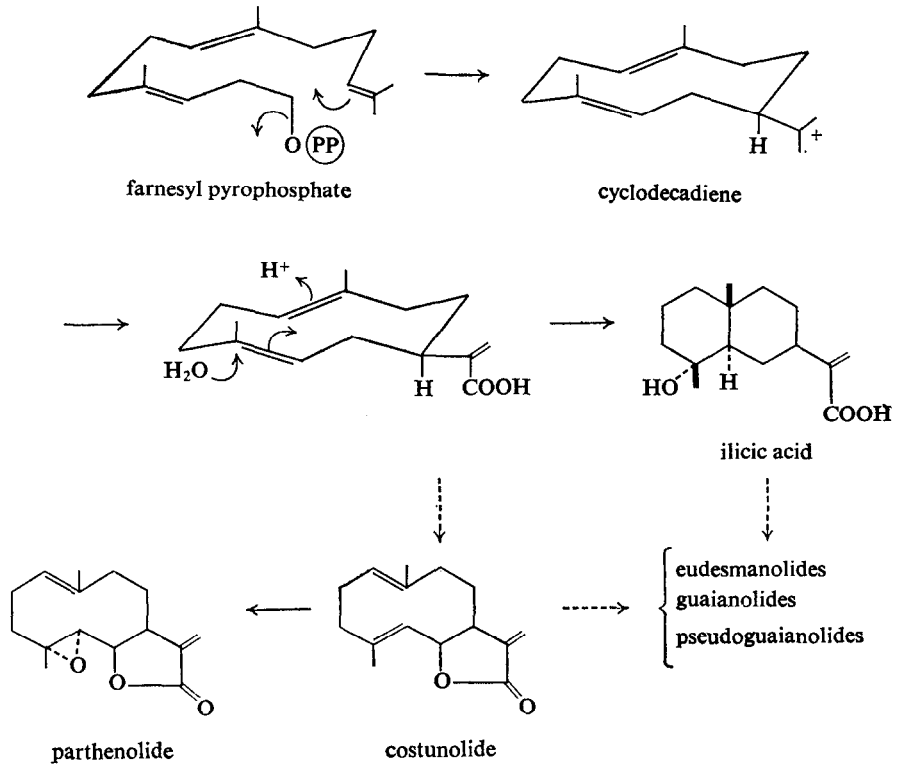
The structures of the eight sesquiterpenes of *Hymenoclea salsola* are in themselves unexceptional variations on what is now recognizable as a theme that is characteristic of many of the species within the tribe Ambrosieae. Two of the observations made in the course of these studies, do however, invite comment.

The presence of 1-epiparthenin and dihydroparthenin in the one species suggests that the hydroxyl group at C-1 is introduced at a late stage in the biosynthetic pathway, and is not present as a result of a process whose stereochemistry is controlled by what would be expected to be strict mechanistic requirements of reactions in which a progenitor containing a cyclodecadienolide ring undergoes ring closure to the [3:0:5] bicyclodecane ring system. Whether the 1-hydroxyl group is introduced by oxidation of a saturated (at C-1) precursor, or by hydration of a 1,2-unsaturated (as neoambrosin) precursor cannot be suggested on the basis of existing information.

The presence of costunolide in *H. monogyra*[5] and of ilicic acid in *H. salsola* and *H. monogyra* supports the view, which is generally held,[6,7] that the sesquiterpene lactones of the Compositae owe their origin to an initial cyclization of farnesyl pyrophosphate to a cyclodecadiene, followed by the formation of the —C(COOH)=CH_2 side-chain and eventual

[4] S. MATSUEDA and T. A. GEISSMAN, manuscript submitted for publication.
[5] F. P. TORIBIO and T. A. GEISSMAN, unpublished results.
[6] J. B. HENDRICKSON, *Tetrahedron* **7**, 82 (1959).
[7] W. PARKER, J. S. ROBERTS and R. RAMAGE, *Quart. Rev. Chem. Soc.* **21**, 331 (1967).

lactonization after introduction of oxygen at an adjacent position (Fig. 1). Clearly, ilicic acid is close to the origin of this sequence, costunolide and parthenolide (present in *Ambrosia dumosa*[4]) following closely, and the more elaborate eudesmanolides, guaianolides and pseudoguaianolides being formed by later cyclizations to bicyclic ring systems:



EXPERIMENTAL

Melting points were taken in capillaries and are corrected. I.r. spectra were measured on a Perkin-Elmer Model 21 or a Model 237 spectrophotometer, and NMR spectra on a Varian A-60 instrument with TMS as an internal standard. The NMR data are collected in Table 1. TLC was carried out in the usual way.

Extraction and Isolation of Constituents of Hymenoclea salsola *T. and G.*

A collection of 5 kg of the dried aerial parts of *H. salsola*, collected near Mecca, California, in April 1967 was extracted in the manner previously described,[2] and the final $CHCl_3$ solution of the mixed constituents was washed with 5 per cent aqueous $NaHCO_3$ to remove ilicic acid (12 g; 0·24 per cent). Chromatography of the remaining mixture of lactones on silica gel gave the following compounds: neoambrosin (7 g; 0·14 per cent);[2] ambrosin (59 g; 1·18 per cent);[2] coronopilin/dihydrocoronopilin mixture (3 g; 0·06 per cent);[2] salsolin (200 mg; 0·004 per cent); and a mixture of hymenin and hymenolin (2·8 g; 0·056 per cent).

Dihydrocoronopilin

To a solution of 3·0 g of coronopilin/dihydrocoronopilin mixture in 50 ml of ether–methanol (80:20) was added a solution of CH_2N_2 (from 2 g of nitrosomethylurea) in ether. After 24 hr at 5° the solvents were evaporated and the residue recrystallized from ethyl acetate to yield pure dihydrocoronopilin, m.p. 203–205°, $[\alpha]_D^{25}$ +27·5° (*c* 2·44, $CHCl_3$). (Calc. for $C_{15}H_{22}O_4$: C, 67·67; H, 8·33. Found: C, 67·82; H, 8·21 per cent).

A mixed melting point with a sample of dihydrocoronopilin prepared by the zinc–acetic acid reduction of coronopilin (m.p. 202–203°, $[\alpha]_D^{25}$ +29·6°) showed no depression, and the i.r. and NMR spectra of the two specimens were identical.

TABLE 1. PRINCIPAL SIGNALS IN NMR SPECTRA OF *H. salsola* LACTONES AND DERIVATIVES

	H-2	H-3	H-6	$=CH_2$	$-CH_3$ (C-5)	$-CH_3$ (C-10)	$-CH_3$ (C-11)	Other
Hymenin (I)	7·66 d (6)	6·13 d (6)	4·84 d (9)	5·53 d (3) 6·21 d (3)	1·04 s	1·10 d (7)		
Hymenolin (IX)	7·66 d (6)	6·13 d (6)	5·05 d (7·5)		1·28 s	1·10 d (7)	1·27 d (7)	
Salsolin (X)	5·469		4·66 d (10)	5·75 d (4) 6·45 d (4)	1·12 s	1·28 d (7)		1·13 t (9)[1] 2·14 s[2]
Dihydroisohymenin (IV)			5·50 br		0·81 s	1·15 d (7)	1·74 d (1)	
Dihydrocoronopilin			4·97 d (7·5)		1·15 s	1·22 d (7)	1·20 d (7)	
4-Dehydro-salsolin (XI)	~5·57		4·53 d (10)	5·59 dl (4) 6·27 d (4)	1·34 s	1·22 d (7)		2·08 s[2]
Hymenin pyrazoline	7·61 d (6)	6·15 d (6)	5·22 d (10)		1·10 s	1·08 d (6)		

[1] Proton on C-4.
[2] 3H of acetate group. Values in parentheses are coupling constants, c/s.

Hymenin (I)

The fraction containing hymenin and hymenolin was chromatographed on silica gel impregnated with $AgNO_3$ with the use of benzene–ethyl acetate–acetone (80:15:5) as eluant. Fractions containing hymenin (by TLC) were combined and evaporated. Recrystallized from ethyl acetate, hymenin formed colorless leaflets, m.p. 173–174°, $[\alpha]_D^{25}$ −88·7° (*c* 2·11, $CHCl_3$). (Calc. for $C_{15}H_{18}O_4$: C, 68·68; H, 6·92. Found: C, 68·73; H, 7·00 per cent).

Hymenin Pyrazoline

Treatment of hymenin with diazomethane in the usual way converted it into the pyrazoline derivative. The compound showed dimorphism, crystallizing from ethyl acetate with m.p. 148° dec. and from acetone with m.p. 177° dec. It had $[\alpha]_D^{25}$ −215° (*c*, 0·70, methanol). (Calc. for $C_{16}H_{20}N_2O_4$: C, 63·14; H, 6·62; N, 9·21. Found: C, 63·25; 63·13; H, 6·57, 6·80; N, 9·15, 9·27 per cent.)

The mass spectrum of the pyrazoline showed a very weak molecular ion peak at *m/e* 304, and prominent ion peaks at *m/e* 276 (M-28); 258 (M-28-18); 243 (M-28-18-15); 230 (M-28-18-28); and 215 (M-28-18-15-28).

Anhydrohymenin (Anhydroparthenin) (III)

A solution of 60 mg of hymenin in 10 ml of anhydrous formic acid was refluxed for 16 hr. The solvent was removed *in vacuo* and the residue chromatographed over silica gel (benzene–acetone, 95:5). The purified product formed colorless crystals from ethyl acetate–hexane, m.p. 122–124°, $[\alpha]_D^{25}$ −120° (*c* 1·26, $CHCl_3$). Reported for anhydroparthenin,[3] m.p. 125–126°, $[\alpha]_D$ −121° (*c* 1·21, $CHCl_3$).

Dihydroisohymenin (IV)

Hymenin (120 mg) was hydrogenated in ethyl acetate in the presence of platinum oxide. After 15 min the hydrogen uptake corresponded to the absorption of 1 mole. The solvent was removed and the residue crystallized from ethyl acetate; m.p. 201–203°, $[\alpha]_D^{25}$ −139° (*c*, 1·20, $CHCl_3$). (Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63. Found: C, 68·22; H, 7·66 per cent.)

I.r. absorption was observed at 3430, 1740, 1710 and 1655 cm^{-1}. Dihydroisoparthenin is reported[3] to have m.p. 200–201°, $[\alpha]_D^{25}$ +16·6° (*c* 0·78, $CHCl_3$).

Dehydration of Dihydroisohymenin

To a cooled solution of 60 mg of dihydroisohymenin in 5 ml of pyridine was added 1 ml of thionyl chloride. After 10 min the solvents were removed and residue dissolved in $CHCl_3$ and passed through a short column of silica gel. Examination of the eluate by TLC showed that two compounds were present. Crystallization of a crude product from ethyl acetate afforded 21 mg of isoneoambrosin (VI), m.p. 147–149°, $[\alpha]_D^{25}$ −47·5° (*c* 2·09, $CHCl_3$). Reported[3] m.p. 143–145°, $[\alpha]_D^{25}$ −40·2° (*c* 0·27, $CHCl_3$). The NMR spectrum of the product was consistent with the structure assigned. (Calc. for $C_{15}H_{18}O_3$: C, 73·15; H, 7·37. Found: C, 73·17; H, 7·31 per cent.) The mother liquors from the crystallization of VI were shown by NMR analysis to contain a mixture of VI and VII.

Formation of VI by the Isomerization of Neoambrosin

A solution 1·0 g of neoambrosin in 50 ml of ethyl acetate containing 50 mg of 5 per cent palladium–barium sulfate was refluxed for 5 hr. After removal of the solvent the residue was recrystallized from ethyl acetate to give VI, m.p. 148–150°, $[\alpha]_D^{25}$ −48·1° (*c* 2·3, $CHCl_3$), which did not depress the melting point of the material prepared from dihydroisohymenin.

Isomerization of Coronopilin

Coronopilin was isomerized with palladium in ethyl acetate in the manner described for neoambrosin. The product had m.p. 203–205°, $[\alpha]_D^{25}$ +4·5° (*c* 4·2, $CHCl_3$). Reported[3] for dihydroisoparthenin, m.p. 200–201°, $[\alpha]_D^{25}$ +16·6 (*c* 0·78, $CHCl_3$). (Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63. Found: C, 68·04; H, 7·75 per cent.)

Hymenolin (IX)

The fraction containing a mixture of hymenin and hymenolin was treated with diazomethane, as described for the coronopilin–dihydrocoronopilin mixture. The crude product from 2 g of the mixture was treated with $CHCl_3$, in which the pyrazoline of the unsaturated lactone is only slightly soluble, and the hymenolin, isolated from the chloroform solution, was crystallized from ethyl acetate. Hymenolin had m.p. 186–188°, $[\alpha]_D^{25}$ +47° (*c*, 2·49, $CHCl_3$). (Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63. Found: C, 68·24; H, 7·69 per cent.)

Dihydrohymenolin (Dihydrocoronopilin)

Hydrogenation of 100 mg of hymenolin over Pt_2O yielded 85 mg of dihydrocoronopilin, m.p. 202–204°, $[\alpha]_D^{25}$ +28° (*c* 1·46, $CHCl_3$), identical with the natural product and that prepared by reduction of coronopilin. (Calc. for $C_{15}H_{22}O_4$: C, 67·67; H, 8·33. Found: C, 67·63; H, 8·48 per cent.)

Oxidation of Salsolin (X)

Salsolin (m.p. 148–149°, $[\alpha]_D^{25}$ −72·5 (*c* 202, $CHCl_3$)), 140 mg in 10 ml of acetone, was treated with sufficient chromic acid (26·7 mg of CrO_3 and 23 ml conc. H_2SO_4 in water to make 100 ml) to oxidize one secondary hydroxyl group. After 15 min the mixture was diluted with water and extracted with $CHCl_3$. Evaporation of the solvent yielded a crystalline residue which proved (TLC) to be a mixture of two compounds. These were separated by chromatography on silica gel (benzene–ethyl acetate, 90:10) into (*a*) *ambrosin*, m.p. 148–149°, identified by comparison with an authentic sample; and (*b*) 4-*dehydrosalsolin* (2-α-acetoxydamsin) (XI), m.p. 146–148°. (Calc. for $C_{17}H_{22}O_5$: C, 66·64; H, 7·24. Found: C, 66·77; H, 7·55 per cent.) I.r.: 1750, 1720, 1650, 1240 cm^{-1}. 4-Dehydrosalsolin was readily converted into ambrosin (XII) by treatment with acid.

Salsolin Acetate (Apoludin Diacetate) (XIII)

Acetylation of salsolin with acetic anhydride–pyridine yielded a compound whose R_f (TLC), m.p., and i.r. and NMR spectra were identical with those of the diacetate of apoludin.[4]

Apoludin (Deacetylsalsolin) (XIV)

A solution of salsolin acetate in aqueous ethanol (10 ml) containing 100 mg of K_2CO_3 was refluxed for 2 hr. Inspection of thin-layer chromatograms during the course of the hydrolysis showed that two compounds appeared: one was salsolin, formed by deacylation of the hydroxyl group at C-2; the other was apoludin (deacetylsalsolin). Hydrolysis was completed by the addition of a few drops of 6 N potassium hydroxide, and the product isolated in the usual way. There was obtained 30 mg of a crystalline product, m.p. 133–135°, identical (m.p., i.r., NMR) with an authentic specimen of apoludin. (Calc. for $C_{15}H_{22}O_4$: C, 67·67; H, 8·33. Found: C, 67·39; H, 8·45 per cent.)

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