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Structure of Helenium Lactone[1]

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A new guaianolide $C_{15}H_{20}O_3$, helenium lactone, has been isolated from the common sneezweed, *Helenium autumnale* (Compositae), cultivated in Japan. The structure of helenium lactone has been shown to be I by chemical and physico-chemical studies of it and its derivatives.

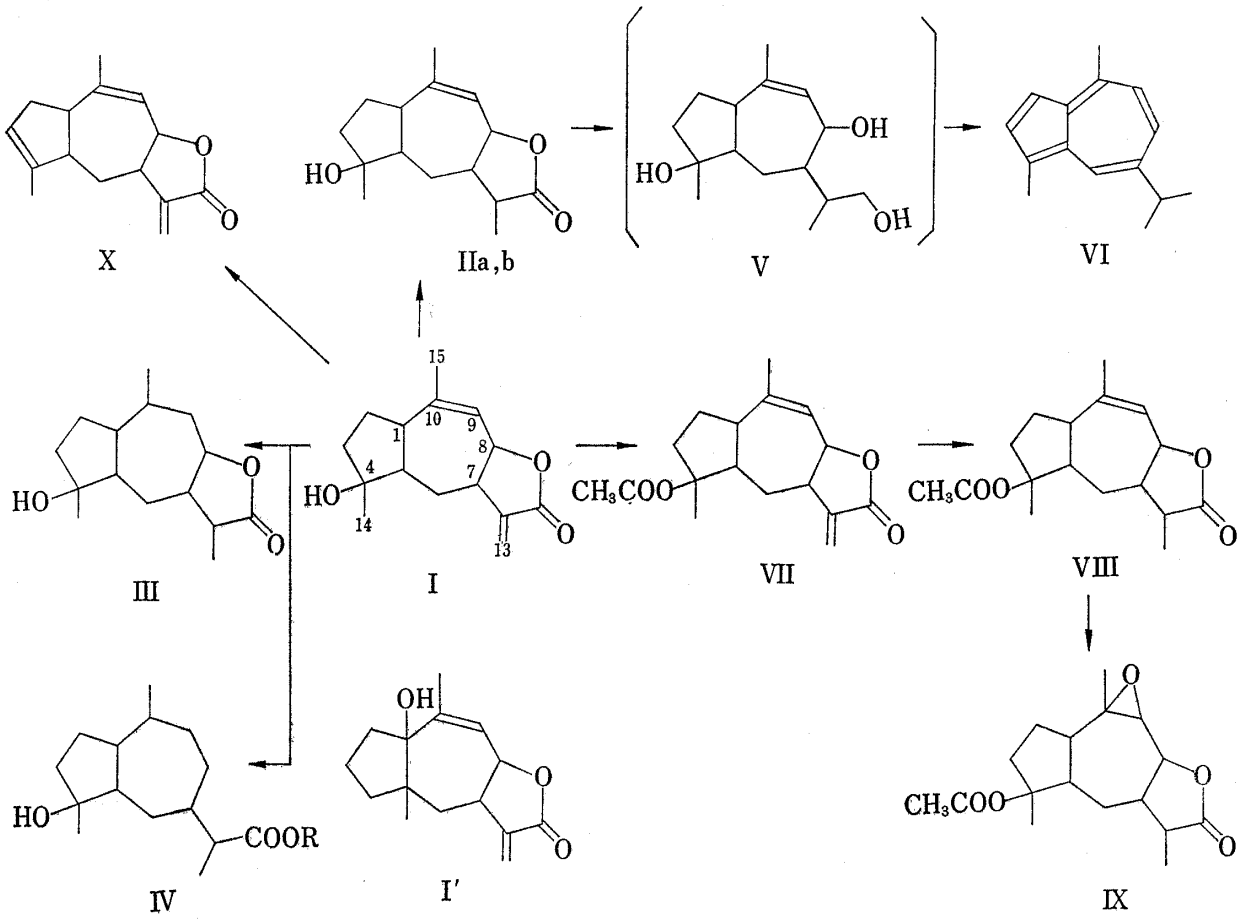
As part of our study on composite plants, we had occasion to investigate the herb of the common sneezweed, *Helenium autumnale* Linné, introduced into Japan from North America in old times and cultivated as an ornamental plant. The constituents of this plant harvested in the habitat were previously examined by Clark[3] and Lucas, *et al.*[4] who obtained a pseudoguaianolide, helenalin,[5] and a norguaianolide, dihydromexicanin E,[6] respectively. In our survey, we could isolate no modified guaianolides, but a new guaianolide which we have named helenium lactone. In the present communication, we show that the structure of this sesquiterpenoid is represented by formula I.

Methanol extract of the herbs of *Helenium autumnale*, cultivated in Sendai, was treated with benzene, and the water-insoluble portion of the benzene extract was chromatographed over alumina to furnish helenium lactone, $C_{15}H_{20}O_3$, mp 111—112°.

The ultraviolet(UV) (λ_{max} 218 mμ), infrared (IR) (ν_{max} 1745 and 1650 cm^{-1}), and nuclear magnetic resonance (NMR) spectrum (1H doublets at 5.48 and 6.16 ppm) indicate the presence of an exocyclic methylene group conjugated with the carbonyl group of a γ-lactone system. In consistent with this, reduction of helenium lactone with sodium borohydride saturated the exocyclic double bond to yield an epimeric mixture of the dihydro-derivatives (II), the NMR spectrum of each epimer showing the disappearance of the typical low field doublets of the exocyclic methylene protons and instead the formation of a doublet of secondary methyl protons. In the NMR spectrum of helenium lactone, a hydrogen on carbon carrying the lactonic oxygen is signaled by a broad peak at 5.20 ppm, the hydroxyl group involved in lactone formation being consequently secondary. The infrared absorption at 3560 cm^{-1} shown by helenium lactone demonstrates the presence of a hydroxyl group. The absence of an NMR signal in the low field (4.5—5.5 ppm) signifies that the hydroxyl group is tertiary. Two methyl groups are present in the helenium lactone structure and appear at the frequencies: singlet at 1.16 ppm and slightly splitting singlet at 1.71 ppm. The chemical shift and pattern of the former indicate that this signal may be generated by the methyl on the hydroxyl-bearing carbon atom. The latter is spin-coupled to an unresolved singlet at 5.22 ppm, an observation which shows the presence of a trisubstituted ethylenic linkage. That helenium lactone is doubly un-

1) This paper forms Part XXV in the series on Sesquiterpenoids. Preceding paper, Part XXIV: H. Hikino, K. Aota, Y. Tokuoka, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1088 (1968).
2) Location: *Kita-4-bancho, Sendai.*
3) E.P. Clark, *J. Amer. Chem. Soc.*, **58**, 1982 (1936).
4) R.A. Lucas, R.G. Smith, and L. Dorfman, *J. Org. Chem.*, **29**, 2101 (1964).
5) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Am. Chem. Soc.*, **85**, 19 (1963); M.T. Emerson, C.N. Caughlan, and W. Herz, *Tetrahedron Letters*, **1964**, 621.
6) A. Romo de Vivar, J. Romo, and W. Herz, *J. Am. Chem. Soc.*, **83**, 2326 (1961); J. Romo, A. Romo de Vivar, and W. Herz, *Tetrahedron*, **19**, 2317 (1963).

saturated was further confirmed by catalytic hydrogenation of helenium lactone with palladized charcoal in methanol which resulted in the uptake of over two mole equivalent of hydrogen to furnish the saturated tetrahydro-derivative (III), which, however, was a stereoisomeric mixture and difficult to separate, and a hydrogenolyzed product (IV), which will be discussed below.



The presence of these functional groups and the formula $C_{15}H_{20}O_3$ require that helenium lactone possesses a bicyclic carbon skeleton. Reductoin of the dihydro-derivatives (II) with lithium aluminum hydride followed by dehydrogenation with palladium-on-carbon formed S-guaiazulene (VI). Therefore, it is concluded that the carbon skeleton of helenium lactone is based on that of guaiane.

Acetylation of helenium lactone with refluxing acetic anhydride in the presence of sodium acetate afforded the acetate (VII) which was reduced with sodium borohydride to yield the dihydroacetate (VIII). Treatment of the dihydroacetate (VIII) with perbenzoic acid resulted in the formation of the epoxide (IX). In the NMR spectra of helenium lactone and its derivatives VII and VIII, the two signals originating from the vinyl hydrogen and the hydrogen on the carbon carrying the lactonic ether function occur closely and cannot be analyzed well. However, in the spectrum of the epoxide (IX), the two signals arising from the hydrogen on the epoxy ring and the hydrogen on the carbon attached to the lactonic oxygen are separated appearing at 2.70 and 4.19 ppm, and double resonance experiments revealed that both signals are spin-coupled with each other. Hence the lactone ring of helenium lactone must be closed to C-8 and the trisubstituted ethylenic linkage located at C-9: C-10 in the guaiane skeleton. This arrangement is supported by the previous observation that on catalytic hydrogenation helenium lactone gave the hydrogenolysis product, the hydroxy acid (IV; R=H), the infrared spectrum of which indicates the disappearance of the double bonds and

the γ-lactone system and the formation of a carboxyl grouping. This acid (IV: R=H) was characterized as the methyl ester (IV: R=CH_3). Occurence of the hydrogenolysis corroborates the lactone ring closure at the allylic position, *i.e.*, C-8.

It follows that the tertiary hydroxyl group must be oriented at C-4, provided that helenium lactone has the normal guaianolide skeleton.

In order to examine the alternative possibility that helenium lactone possesses the pseudoguaianolide structure (I') which is, however, highly improbable from the biogenetic point of view, helenium lactone was subjected to treatment with phosphorus oxychloride in pyridine. On dehydration to the anhydro-derivative (X), the tertiary methyl signal moved lower field merging with the vinyl methyl signal, and a vinyl hydrogen signal appeared. This finding clearly excludes that helenium lactone is a member of the abnormal class of sesquiterpenic lactones, and verifies the correctness of the formulation as a normal guaianolide.

On the basis of the above evidence, helenium lactone is, therefore, expressed by formula I.

Helenium lactone is the second normally-constituted guaianolide isolated from *Helenium* species, the first being virginolide from *H. virginicum* Blake (=*H. autumnale* Linné?),[7] and further joins in the sesquiterpenoids with lactone ring closure to C-8 characteristic of substances isolated from *Helenium* and related genera.

That *H. autumnale* growing in Japan is of different composition than the plant growing in North America is not surprising. There are other examples in the literatures of certain Compositae species, such as *Helenium mexicanum*,[8,9] *Iva microcephala*,[10] and *Chrysanthemum parthenium*,[11,12] which give no reproducible results when collected in different places.

Experimental[13]

Isolation of Helenium Lactone——*Helenium autumnale* Linné (Compositae) was cultivated in the herbal garden of this School, and collected in September at the flowering stage. The air-dried flowers, leaves, and stems (6 kg) were extracted with hot MeOH. Removal of the solvent gave the residue (1.1 kg) which was treated with hot water. The water-insoluble portion was dissolved in benzene and chromatographed over alumina (1 kg). The benzene—AcOEt (2:1) eluate afforded an oil which could not be induced to crystallize cleanly and was rechromatographed over silica gel (0.7 kg). Elution with benzene—AcOEt (10:1) and crystallization from AcOEt gave helenium lactone (I) as colorless plates (7 g),[14] mp 111—112°, $[\alpha]_D$ −88.0° (c=2.5). *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.62; H, 8.37. UV λ_{max}^{EtOH} mμ (log ε): 218 (3.47), IR (KBr) cm^{-1}: 3550 (hydroxyl), 1743 (conjugated γ-lactone), 1665, 1650 (ethylene bonds), NMR ($CDCl_3$, 100 Mcps): 3H s at 1.16 ($C_{(14)}\underline{H}_3$), 3H s at 1.71 ($C_{(15)}\underline{H}_3$), 2H m at 3.06 ($C_{(1)}\underline{H}$ and $C_{(7)}\underline{H}$), 1H br at 5.20 ($C_{(8)}\underline{H}$), 1H s at 5.22 (unresolved, $C_{(9)}\underline{H}$), 1H d at 5.48 and 1H d at 6.16 (J=3, $C_{(13)}\underline{H}_2$).

Reduction of Helenium Lactone with Sodium Borohydride in Methanol——To helenium lactone (100 mg) in MeOH (5 ml) was added $NaBH_4$ (50 mg) and the mixture was stirred at room temperature for 2 hr. Upon isolation, the product gave two spots on thinlayer chromatography, and was chromatographed over silica gel (7 g).

Elution with benzene—AcOEt (10:1) afforded an isomer of the dihydro-derivatives (IIa) as an oil (43 mg), IR ($CHCl_3$) cm^{-1}: 3630, 3540 (hydroxyl), 1767 (γ-lactone), NMR ($CHCl_3$): 3H s at 1.17 ($C_{(14)}\underline{H}_3$), 3H d at 1.22 ($C_{(13)}\underline{H}_3$), 3H s at 1.75 ($C_{(15)}\underline{H}_3$), 1H br at 5.07 ($C_{(8)}\underline{H}$), 1H br at 5.20 ($C_{(9)}\underline{H}$).

7) W. Herz and P.S. Santhanam, *J. Org. Chem.*, **32**, 507 (1967).
8) A. Romo de Vivar and J. Romo, *J. Am. Chem. Soc.*, **83**, 2326 (1961).
9) E. Dominguez and J. Romo, *Tetrahedron*, **19**, 1415 (1963).
10) W. Herz, G. Högenauer, and A. Romo de Vivar, *J. Org. Chem.*, **29**, 1700 (1964).
11) M. Soucek, V. Herout, and F. Šorm, *Coll. Czechoslov. Chem. Communs.*, **26**, 803 (1961).
12) A. Romo de Vivar and H. Jiménez, *Tetrahedron*, **21**, 1741 (1965).
13) Melting points are uncorrected. Specific rotations were determined in $CHCl_3$ solution. NMR spectra were recorded at 60 Mcps in CCl_4 solution unless otherwise stated. Chemical shifts are given in ppm from internal Me_4Si and coupling constants (J) in cps. Abbreviations: s=singlet, d=doublet, t=triplet, m=multiplet, and br=broad peak.
14) This substance was first isolated by Mr. Y. Inamori, this Laboratory, to whom thanks are due.

Further elution with the same solvent yielded the other isomer of the dihydro-derivatives (IIb) as an oil (29 mg), IR ($CHCl_3$) cm^{-1}: 3640, 3450 (hydroxyl), 1766 (γ-lactone), NMR ($CHCl_3$): 3H d at 1.25 (J=5, $C_{(13)}\underline{H}_3$), 3H s at 1.27 ($C_{(14)}\underline{H}_3$), 3H s at 1.70 ($C_{(15)}\underline{H}_3$), 1H br at 5.13 ($C_{(8)}\underline{H}$), 1H br at 5.36 ($C_{(9)}\underline{H}$).

Hydrogenation of Helenium Lactone over Palladium-on-carbon in Methanol——Helenium lactone (200 mg) in MeOH (10 ml) was hydrogenated at atmospheric pressure with Pd-C (5%, 30 mg) untill there was no further uptake of H_2 (about 2.5 moles). After work-up in the usual manner, the product was chromatographed over silica gel (3 g).

Elution with benzene gave an oil (90 mg) which was distilled under reduced pressure to yield a stereoisomeric mixture of tetrahydrohelenium lactone (III) as a colorless oil, *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.70; H, 9.21. IR (CCl_4) cm^{-1}: 3650, 3500 (hydroxyl), 1750 (γ-lactone).

Elution with benzene—AcOEt (10:1) afforded the crude acid (IV: R=H) as an oil (100 mg), IR (CCl_4) cm^{-1}: 3400—2600, 1710 (carboxyl).

The crude acid (IV: R=H) (50 mg) was treated with CH_2N_2 in ether. The residue obtained on evaporation was chromatographed over silica gel (1 g). Fractions eluted with benzene–AcOEt (10:1) gave an oil (40 mg) which on distillation under diminished pressure furnished the hydroxy-ester (IV; R=CH_3) as a colorless oil, $[\alpha]_D$ −9.7° (c=5.0). *Anal.* Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.94; H, 10.34, IR (CCl_4) cm^{-1}: 3650, 3500 (hydroxyl), 1735 (ester), NMR: 3H s at 1.06 ($C_{(14)}\underline{H}_3$), 3H d at 1.06 (J=7, $C_{(15)}\underline{H}_3$), 3H d at 1.18 (J=7, $C_{(13)}\underline{H}_3$), 3H s at 3.60 ($C_{(12)}OOC\underline{H}_3$).

Lithium Aluminum Hydride Reduction followed by Dehydrogenation of the Dihydrohelenium Lactones——The epimeric mixture of dihydrohelenium lactone (II) (500 mg) in ether (50 ml) was treated with $LiAlH_4$ (50 mg) and the reaction mixture was stirred at room temperature for 8 hr. Working up in the usual manner furnished an isomeric mixture of the triol (V) as a colorless oil (450 mg), IR (CCl_4) cm^{-1}: 3640, 3410 (hydroxyl).

This isomeric mixture of the triol (V) (50 mg) was heated with 10% Pd-C (25 mg) at a bath temperature of 320° for 3 min. The dark green light petroleum extract was filtered, chromatographed over alumina (3 g), and eluted with light petroleum. The eluate was treated with 1,3,5-trinitrobenzene in EtOH and crystallized from EtOH to give the 1,3,5-trinitrobenzene adduct of S-guaiazulene (VI) as dark maroon needles, mp 133—136°, UV λ_{max}^{EtOH} mμ: 244, 285, 289 (inflection), 305, 349, 364. Identification was carried out in the usual criteria.

Acetylation of Helenium Lactone——Helenium lactone (300 mg) in Ac_2O (3 ml) was heated under reflux in the presence of AcONa (300 mg) for 3 hr. Upon isolation in the customary manner, the product was chromatographed over silica gel (20 g). Elution with light petroleum–benzene (1:1) and crystallization from light petroleum–AcOEt (1:1) afforded helenium lactone acetate (VII) as colorless needles, mp 151—152°, $[\alpha]_D$ −41.5° (c=3.3). *Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.09; H, 7.96. IR (KBr) cm^{-1}: 1760 (γ-lactone), 1735, 1251 (acetoxyl), 1660 (ethylene bond), NMR: 3H s at 1.36 ($C_{(14)}\underline{H}_3$), 3H s at 1.73 ($C_{(15)}\underline{H}_3$), 3H s at 1.92 ($C_{(4)}OCOC\underline{H}_3$), 1H br at 5.08 ($C_{(8)}\underline{H}$), 1H br at 5.29 ($C_{(9)}\underline{H}$), 1H d at 5.47, 1H d at 6.15 (J=4, $C_{(13)}\underline{H}_2$).

Reduction of Helenium Lactone Acetate with Sodium Borohydride——Helenium lactone acetate (VII) (530 mg) in MeOH (60 ml) was stirred with $NaBH_4$ (130 mg) at room temperature for 20 min. The product was isolated in the usual manner and chromatographed over silica gel (20 g). Elution with light petroleum–benzene (1:1) and crystallization from benzene gave dihydrohelenium lactone acetate (VIII) as colorless needles (316 mg), mp 84—85°, $[\alpha]_D$ −56.7° (c=3.0). *Anal.* Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.17; H, 8.54. IR (KBr) cm^{-1}: 1783 (γ-lactone), 1729, 1260 (acetoxyl), NMR: 3H d at 1.18 (J=7, $C_{(13)}\underline{H}_3$), 3H s at 1.36 ($C_{(14)}\underline{H}_3$), 3H s at 1.73 ($C_{(15)}\underline{H}_3$), 3H s at 1.92 ($C_{(4)}OCOC\underline{H}_3$), 1H br at 5.0 ($C_{(8)}\underline{H}$), 1H br at 5.32 ($C_{(9)}\underline{H}$).

Oxidation of Dihydrohelenium Lactone Acetate with Perbenzoic Acid——Dihydrohelenium lactone acetate (VIII) (70 mg) and BzO_2H (50 mg) in $CHCl_3$ (10 ml) were set aside at room temperature for 1 hr. After isolation in the customary way, the product was crystallized from light petroleum to give dihydrohelenium lactone acetate epoxide (IX) as colorless plates, mp 171—172°, $[\alpha]_D$ +14.7° (c=2.7). *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.04; H, 7.75, IR (KBr) cm^{-1}: 1784 (γ-lactone), 1730, 1240. (acetoxyl), NMR: 3H s at 1.23 ($C_{(15)}\underline{H}_3$), 3H d at 1.28 (J=5, $C_{(13)}\underline{H}_3$), 3H s at 1.38 ($C_{(14)}\underline{H}_3$), 3H s at 1.92 ($C_{(4)}OCOC\underline{H}_3$), 1H d at 2.69 ($J$=7, $C_{(9)}\underline{H}$), 1H t at 4.16 (J=7, $C_{(8)}\underline{H}$).

Dehydration of Helenium Lactone with Phosphorus Oxychloride in Pyridine——Helenium lactone (50 mg) in pyridine (0.5 ml) was treated with $POCl_3$ (0.05 ml) at 0° for 1.5 hr. The mixture was poured on crushed ice and the deposited crystals were collected, dried, and crystallized from AcOEt to give anhydrohelenium lactone (X) as colorless plates (45 mg), mp 124—126°, $[\alpha]_D$ −54.8° (c=0.11). *Anal.* Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.18; H, 7.87. UV λ_{max}^{EtOH} mμ (log ε): 218 (4.15), IR (KBr) cm^{-1}: 1760 (conjugated γ-lactone), 1655 (ethylene bond), NMR: 6H s at 1.68 ($C_{(14)}\underline{H}_3$, $C_{(15)}\underline{H}_3$), 2H m at 5.30 ($C_{(3)}\underline{H}$, $C_{(9)}\underline{H}$), 1H d at 5.41, 1H d at 6.11 (J=4, $C_{(12)}\underline{H}_2$).

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