[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE FLORIDA STATE UNIVERSITY]

Isolation and Structure of Coronopilin, a New Sesquiterpene Lactone[1]

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A new sesquiterpene lactone has been isolated from several *Ambrosia* species and its structure established as 1,2-dihydroparthenin. Two different samples of *Parthenium incanum* H.B.K. yielded coronopilin and ambrosin, respectively.

Parthenin (I), the bitter principle of *Parthenium hysterophorus* L., and ambrosin (II), the main constituent of *Ambrosia maritima* L., were correlated recently[2] and structures have been derived.[3]

The appearance of two closely related sesquiterpene lactones in these two species is of more than chemical interest, the position of *Ambrosia* and related genera in the general classification scheme of *Compositae* being a matter of some argument.[4] Certain authorities have elevated *Ambrosia* and seven other genera to separate family status (*Ambrosiaceae*).[5] Others[6] recognize a tribe *Ambrosieae* in the family *Compositae; Parthenium* belonging to the tribe *Heliantheae* by general agreement. Still others[4,7] absorb *Ambrosia* and its relatives in *Heliantheae* and assume a rather close affinity between them and *Parthenium* species.

For these reasons, we would like to report our work on the sesquiterpene lactones of several other *Ambrosia* and *Parthenium* species. This has led to the isolation of one new substance whose structure has been established. The results also indicate a rather close relationship between the two genera.

Extraction of *Ambrosia psilostachya* DC. var. *coronopifolia* (T. and G.) Farw., a weed rather widely distributed in the Great Plains region, furnished in 1.25% yield (based on leaves) a new substance $C_{15}H_{20}O_4$, m.p. 177–178°, $[\alpha]_D^{21}$ $-30.2°$ (ethanol), which we have named coronopilin. Coronopilin contained a hydroxyl group (infrared spectrum) which could not be acetylated and was therefore probably tertiary. The infrared spectrum also indicated the presence of a double bond (1655 cm.$^{-1}$) which was conjugated with a carbonyl group, probably a γ-lactone (double strength infrared band at 1750 cm.$^{-1}$, λ_{max} 213 mμ, ϵ 9800, formation of a pyrazoline). The fourth oxygen atom was assumed to be a cyclopentanone carbonyl because of the intensity of the 1750-cm.$^{-1}$ band and the presence in the ultraviolet spectrum of an absorption near 290 mμ.

These facts and inferences could be accommodated by structure III in which the hydroxyl and lactone groups were placed as indicated by analogy with parthenin and ambrosin. The NMR spectrum of coronopilin referred to earlier[3] was in agreement with this hypothesis. The correctness of the proposal was established by two reactions. Ozonolysis of coronopilin yielded formaldehyde and dihydronorparthenone (IV), a substance previously obtained by ozonolysis of parthenin[2] followed by hydrogenation. Attempted catalytic hydrogenation of coronopilin furnished dihydroisoparthenin (V)[2] by isomerization of the double bond. Coronopilin is therefore 1,2-dihydroparthenin.

Coronopilin was also isolated in 0.16% yield from the whole plant of *Ambrosia artemisiifolia* L. (common ragweed) collected in Tallahassee during the flowering period. This plant is highly variegated which may account for the fact that no crystalline material could be isolated from a sample of whole plant collected in Ohio in 1956. Previous workers[8] have reported the isolation of a sternutatory crystalline material of m.p. 208° and a bitter substance of m.p. 65–70°. No formulas were given but the analyses resembled that of coronopilin. A more recent communication[9] states that a crystalline nonalkaloidal substance of m.p. 160–164° and unspecified analysis was obtained from ragweed, presumably *A. artemisiifolia.*

We were not successful in our attempts to isolate crystalline sesquiterpene derivatives from extracts of *Ambrosia trifida* L. (giant ragweed) and *Ambrosia bidentata* Michx.

Of considerable interest was the isolation of coronopilin in 0.35% yield from a *Parthenium* species, *P. incanum* H.B.K. The occurrence of the same sesquiterpene lactone in two separate genera may well have a bearing on phylogenetic speculations previously based on morphological and cytological considerations. Further evidence for a possible connection between *Parthenium* and *Ambrosia* species is the isolation, in low yield, of ambrosin

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(1) Supported in part by grants from the United States Public Health Service (RG-5814) and the Eli Lilly Co.

(2) W. Herz and H. Watanabe, *J. Am. Chem. Soc.*, **81**, 6088 (1959).

(3) W. Herz, M. Miyazaki, and Y. Kishida, *Tetrahedron Letters*, 82 (1961).

(4) A. Cronquist, *Am. Midland Naturalist*, **53**, 478 (1955).

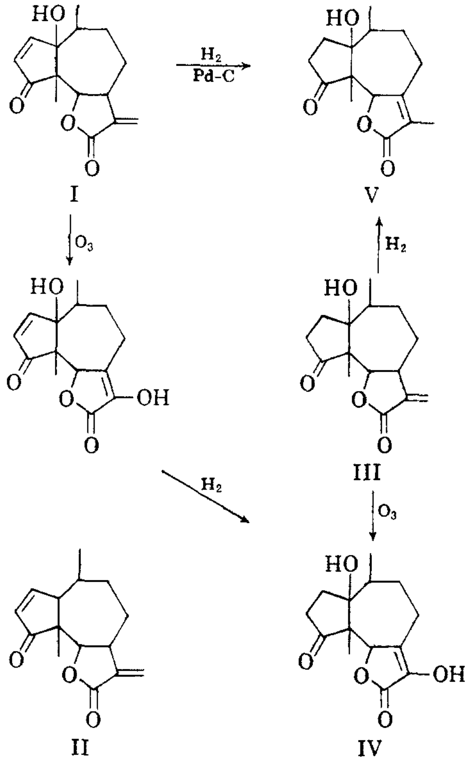
(5) J. K. Small, *Manual of the Southeastern Flora*, University of North Carolina Press, Chapel Hill, 1933.

(6) See, for example, A. Gray, *Synoptical Flora of North America*, Smithsonian Institution, Washington, D. C., 1888.

(7) M. L. Fernald, *Gray's Manual of Botany*, 8th ed., American Book Company, 1950.

(8) B. E. Nelson and G. W. Crawford, *J. Am. Chem. Soc.*, **36**, 2536 (1914).

(9) J. R. Brown, *Texas Repts. Biol. and Med.*, **7**, 3 (1949); *C.A.*, **44**, 2598 (1949).



from another sample of *P. incanum* which, however, did not yield any coronopilin. Whether this difference in lactone content is due to local conditions or to biogenetic changes during the growth cycle of *P. incanum* cannot be stated at present.

EXPERIMENTAL[10]

Isolation of coronopilin. Powdered leaves and small stems of *Ambrosia psilostachya* DC. var. *coronopifolia* (T. and G.) Farw., 960 g., collected by Dr. B. H. Braun in the vicinity of Ellis, Kansas in late August 1959, were extracted with chloroform in two large Soxhlet extractors for 2 days. Chloroform was removed. The residue was taken up in 250 ml. of hot ethanol, mixed with 275 ml. of hot water containing 10 g. of lead acetate and 5 ml. of acetic acid, and allowed to stand overnight. The clear filtrate was concentrated to small volume on the water pump and extracted thoroughly with chloroform. The chloroform extract was dried and evaporated *in vacuo*. The residual gum, wt. 47 g., was dissolved in 60 ml. of chloroform and chromatographed over 400 g. of alumina (Alcoa F-20). Benzene (2 l.) and chloroform (3 l.) eluted a total of 23 g. of crude coronopilin. Recrystallization of the various fractions from acetone–diisopropyl ether and working up the mother liquors gave a total of 11.9 g. (1.25%) of coronopilin, m.p. 165–170°. Further recrystallization from the same solvent mixture raised the m.p. to 177–178°; $[\alpha]^{21}_{D}$ $-30.2°$ (c 4.2,e thanol), $-2°$ (c 3.7, chloroform), λ_{ma} 213 mμ, ϵ 9800, shoulder near 290 mμ, ϵ 29, infrared bands 3600 and 3400 cm.$^{-1}$ (—OH), 1750 (double strength, cyclopentanone and γ-lactone), 1655 (double bond), and 1408 cm.$^{-1}$ (combination of —$CH_2C{=}O$ and methylene conjugated with lactone).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.35; H, 7.73.

Coronopilin gave a positive Zimmermann test. It was not acetylated by acetic anhydride in pyridine solution. The pyrazoline was prepared by mixing a solution of 0.18 g. of coronopilin in 200 ml. of ether with excess diazomethane in ether and by allowing it to stand for 4 days. The solvent was removed, and the residue recrystallized from ethyl acetate and acetone-isooctane, m.p. 145° dec.

Anal. Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 63.27; H, 7.08; N, 9.82.

Hydrogenation of coronopilin. A solution of 1.0 g. of coronopilin in 50 ml. of ethanol was hydrogenated in a Parr shaker with 0.1 g. of 5% palladium charcoal, filtered, and concentrated to dryness *in vacuo*. The residual gum crystallized on stirring with benzene–petroleum ether. One recrystallization from acetone–petroleum ether (b.p. 60–90°) gave 0.43 g. of crystals, m.p. 195–197°, raised to 200–201° by one further recrystallization. The mixed melting point with authentic dihydroisoparthenin[11] was undepressed and the infrared spectra were completely superimposable.

Ozonolysis of coronopilin.[12] A solution of 0.3 g. of coronopilin in 50 ml. of chloroform was ozonized at 78° for 2 hr. The solution was steam distilled into a solution of dimedone in alcohol. This solution was again steam distilled; the residue deposited 40 mg. of the dimedone derivative of formaldehyde. The residue from the first steam distillation was concentrated to 2 ml. *in vacuo* and filtered. The product, 0.11 g., was recrystallized from acetone, m.p. 232–234°, mixed m.p. with dihydronorparthenone 231–233°. The infrared spectra of the two samples were indistinguishable.

Dihydronorparthenone. A solution of 500 mg. of norparthenone[2] in 25 ml. of ethanol was hydrogenated at atmospheric pressure with 5% palladium charcoal catalyst. The solution was filtered and concentrated. The residue solidified on standing and was recrystallized several times from acetone and acetone–petroleum ether (b.p. 30–50°), 330 mg. yield, m.p. 325° dec., $[\alpha]^{24}_{D}$ $-29.5°$ (c 1.97, chloroform), λ_{max} 240 mμ (ϵ 8500), shoulder near 280 mμ, infrared bands (potassium bromide disk) at 3600 and 3200 (—OH), 1750 (double strength, cyclopentanone and lactone), and 1660 cm.$^{-1}$ (double bond). The substance was acidic and gave a positive ferric chloride test.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.13; H, 6.86.

Extraction of Ambrosia artemisiifolia L. Ground whole plant of the above, collected at the flowering state on the outskirts of Tallahassee in September 1959, was extracted with chloroform in a large Lloyd extractor and worked in the usual manner. From a total of 94.5 lbs. of dried material there was obtained, after precipitation of coloring materials and tannins, 370 g. of crude gum which could not be induced to crystallize.

A 16-g. portion was dissolved in 25 ml. of benzene and chromatographed over 200 g. of alumina. Elution with benzene-chloroform (1:1, five 400-ml. fractions) and chloroform (three 400-ml. fractions) gave gum in fraction 2 and crystalline material in fractions 3–7. Crystallization from benzene of fractions 3–7 gave 2.9 g. of coronopilin. Additional material was obtained by rechromatographing fraction 2 and the mother liquors. Crystallization from acetone–diisopropyl ether raised the m.p. to 178–180°; infrared spectrum superimposable on that of coronopilin, $[\alpha]^{24}_{D}$ 35.3° (c 3.42, ethanol), $[\alpha]^{22}_{D}$ $-2.9°$ (c 6.66, chloroform), pyrazoline m.p. 150–151°. Paper chromatography of coronopilin and the material from *A. artemisiifolia* gave an R_f value of 0.74, using Whatman No. 4 filter paper impregnated with a 10% solution of octanol in acetone and a mixture of 30 ml. of

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(10) Melting points are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Dr. F. Pascher, Bonn, Germany. Ultraviolet spectra were run in 95% ethanol solution on a Cary Model 14 spectrophotometer, infrared spectra in chloroform solution, unless otherwise specified, on a Perkin-Elmer Infracord spectrophotometer.

(11) The melting point of dihydroisoparthenin was erroneously given as 142–144° in ref. 2. It should be 201–202°.

(12) This experiment and the following one were performed by Dr. M. Miyazaki.

methanol and 70 ml. of water saturated with octanol. Spots were detected by spraying with a saturated solution of antimony trichloride in chloroform and 20% thionyl chloride. Ozonolysis yielded dihydronorparthenone, m.p. 220°. Hydrogenation gave dihydroisoparthenin, m.p. 200–202°.

A sample of leaves and petioles identified as *Ambrosia artemisiifolia* L. var *elatior*, collected by Dr. B. H. Braun in the vicinity of Cincinnati, Ohio, in 1956, was extracted in the same manner but did not furnish crystalline material.

Two samples of *Ambrosia trifida* L. were extracted. One of leaves and petioles only, collected by Dr. B. H. Braun near Cincinnati in 1956, 1000 g., yielded 2.1 g. of gum which gave no crystalline fractions on chromatography. A second, large sample, 40 kg., collected in September 1959, on the outskirts of Tallahassee during the flowering period, gave 55 g. of gum which could not be separated into crystalline fractions.

A 600-g. sample of *Ambrosia bidentata* Michx., collected by Dr. B. H. Braun near Lamar, Missouri, in August 1959, gave 28 g. of gum which appeared to be quite polar. Chromatography over alumina failed to yield crystalline material.

Extraction of Parthenium incanum H.B.K. A 2380-g. sample of the above, collected by Dr. H. F. L. Rock in July 1960, near El Paso, Texas, was ground and extracted with chloroform for 2 days. The extract was concentrated; the residue taken up in 200 ml. of hot ethanol, 300 ml. of hot water containing 15 g. of lead acetate, and a few ml. of acetic acid. After 1 day the mixture was filtered, the filtrate concentrated *in vacuo*, extracted with chloroform, and dried. Removal of chloroform gave 45 g. of gum which was dissolved in 35 ml. of chloroform, diluted with 80 ml. of benzene, and chromatographed over 400 g. of alumina. The first fractions (benzene-chloroform 4:1) eluted some gum. This was followed by 14 g. of crystalline material in the benzene-chloroform and chloroform fractions. Recrystallization from acetone–diisopropyl ether gave 8.3 g. of colorless crystals, m.p. 175–178°, raised to 178–180° by further purification, $[\alpha]_D^{24}$ −32.5° (*c* 4.3, ethanol), $[\alpha]_D^{22}$ −5.7°(*c* 5.1, chloroform). The substance was indistinguishable from coronopilin in infrared spectrum and paper chromatography.

A finely ground sample of the same plant, wt. 1420 g., collected by Mr. R. J. Barr in September 1960, near Portal, Cochise County, Arizona, was extracted with chloroform. The usual work-up gave 32 g. of an orange-yellow gum which was taken up in 30 ml. of chloroform and diluted with 70 ml. of benzene. Chromatography over 350 g. of alumina with benzene (eight 100-ml. fractions), benzene-chloroform (10 fractions, 10:1), chloroform (21 fractions) and chloroform-methanol (20 fractions, 50:1) gave no crystalline material. The second benzene fraction was taken up in benzene and diluted with ligroin to incipient cloudiness. Some benzene was added to clear the solution. On standing there precipitated 0.15 g. of crystalline material which was recrystallized from benzene-ligroin. The colorless needles melted at 145–146°, $[\alpha]_D^{20}$ −15.4° (*c*, 0.925, chloroform), ultraviolet maxima at 218 mμ, ϵ 13,900, and 325 mμ, ϵ 38. The infrared spectrum exhibited bands at 1770 cm.$^{-1}$ (γ-lactone), 1718 (cyclopentenone), 1660 (double bond conjugated with lactone), and 1595 cm.$^{-1}$ (cyclopentenone double bond). The NMR spectrum reported previously[3] confirmed the assignments. These properties suggested that the material was ambrosin which was confirmed by comparison with an authentic sample.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37; O, 19.49. Found: C, 72.84; H, 7.57; O, 19.29.

Rechromatography of the gummy fractions did not result in crystalline material.

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[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL MEDICINE, NEW YORK UNIVERSITY MEDICAL CENTER]

Chemistry of Edulin, Neorautone, and Related Compounds from *Neorautanenia edulis C.A. Sm.*

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Four of the compounds isolated in an earlier study from *N. edulis* were subjected to chemical and spectroscopic examination. A structure is proposed for edulin and a partial structure is derived for neorautone. One new compound, substance vii, was isolated from extracts of the tuber of this plant and examined in this work. Substance vii and edulin are structurally closely related to the reduced isoflavanes pterocarpin and homopterocarpin and to the angular rotenoids pachyrrhizone and pachyrrhizine.

In a previous report[1] the isolation of six new substances from the tuber of *Neorautanenia edulis C.A. Sm.* was described. A study of the chemical constituents of the tuber of this plant became of interest in view of the use of the tuber as a fish poison by natives in the Northern Transvaal region of Southern Africa.[2] Of the six compounds isolated, two were found to be toxic to goldfish.[3] On the basis of elemental analyses and molecular weight determinations molecular formulas were assigned to the six compounds[1] but chemical studies were not described. The present report gives the results of chemical studies on some of these compounds of which larger quantities were available for investigation.

In the isolation of these compounds from the tuber[1] large amounts of dark brown resins were obtained; these resins were examined with the purpose of improving the yields of the compounds obtained from the tuber. Three of the compounds

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(1) B. L. Van Duuren and P. W. G. Groenewoud, *J. S. African Chem. Inst.*, **3**, (2), 29 (1950).

(2) J. M. Watt and M. G. Breyer-Brandwijk, *Medical and Poisonous Plants of Southern Africa*, Livingstone, Edinburgh, 1932, p. 77.

(3) B. L. Van Duuren and P. W. G. Groenewoud, *J. S. Afr. Chem. Inst.*, **3**, (2), 35 (1950).