Increasing the period of reflux with base to 18 hr. gave 0.34 g. of product, m.p. 212–235°, from 0.40 g. of the acetyl lactone **11**. The entire product was acetylated, giving 0.33 g., m.p. 178–182°. The n.m.r. spectrum of this material showed no distinct peaks for the C-21α methyl, but only shoulders on the major peaks at 75 and 83 c.p.s. Recrystallization from cyclohexane gave readily the pure C-20β methyl compound identical in the n.m.r. and infrared with authentic **10b**.

2-(16β-Hydroxy-3-keto-13β-etiojervan-17β-yl)propanoic Acid Lactone (10c).—A slurry of 1.0 g. of hydroxy lactone **10a** in 50 ml. of acetone was treated with 1.0 ml. of 4 *N* chromic acid[29] in a water bath at 20°. The crystals dissolved immediately and a green gum precipitated. After a total of 4 min. the solution was diluted with 5 ml. of methanol followed by water. The resulting precipitate was collected on a filter and was recrystallized from acetone–petroleum ether to yield 0.75 g. of the pure ketolactone **10c**, m.p. 183–186°, λ_{max} 5.68 and 5.85 μ, $[\alpha]_D$ $-13°$.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.52; H, 9.34.

2-(16β-Hydroxy-3-keto-13β-etiojerv-1-en-17β-yl)propanoic Acid Lactone (13).—A solution of 0.40 g. of the ketolactone **10c** in 20 ml. of acetic acid was treated with a drop of hydrogen bromide in acetic acid and then with a solution of 1.0 mole equiv. of 0.23 *M* bromine in acetic acid solution. The bromine, added dropwise over a 3-min. period, was consumed immediately. The solution was diluted with water and the resulting crystalline precipitate was collected on a filter and washed with water, yielding 0.47 g. of crude bromide, m.p. 175–183°, λ_{max} 5.64 and 5.78 μ.

The bromo ketone (0.45 g.) was dissolved in 20 ml. of dimethyl formamide to which was added 10.0 g. of magnesium oxide. The mixture was heated at reflux for 90 min. and then cooled and diluted with excess aqueous hydrochloric acid. The mixture was extracted with benzene, washed three times with water dried, and concentrated to dryness. The residue, 0.37 g., was chromatographed on 30 g. of silica. Fractions eluted with 5% ethyl acetate in benzene were combined and recrystallized from acetone–petroleum ether to yield the unsaturated lactone **13** as an acetone solvate, m.p. 175–180°, λ_{max} 5.67 and 5.97 μ, λ_{max} 233 mμ (log ϵ 3.98).

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found : C, 75.28; H, 8.84.

Sesquiterpene Lactones. Coronopilic Acid

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Coronopilin, the sesquiterpenoid lactone of *Ambrosia psilostachya* DC., undergoes an acid-catalyzed dehydration–rearrangement that provides additional evidence for the structure assigned to it, and demonstrates the "abnormal" placement of the angular methyl group at C-5.

The structure of coronopilin (I), the major sesquiterpenoid constituent of *Ambrosia psilostachya* DC., has been established by Herz and Högenauer,[1] who showed that coronopilin is a dihydroparthenin. We had isolated coronopilin at about the same time from *A. psilostachya* and from *Franseria dumosa* Gray, and had reached the same conclusion regarding its structure, but on grounds that were quite different and which provide additional evidence concerning certain features of the chemistry of this compound.

In view of the results of Herz and Högenauer we need not describe the properties of coronopilin further than to say that a combination of analytical, spectrometric, and chemical diagnostic procedures established that coronopilin is a perhydroazulenic lactone that contains a cyclopentanone ring, an α,β-unsaturated γ-lactone with an exocyclic methylene group, and a hydroxyl group that is resistant to acylation and to chromic acid oxidation. The n.m.r. spectrum confirms the presence of a quaternary methyl group and a methyl group attached to a secondary carbon atom. The n.m.r. spectrum showed that the structure of coronopilin was that of the "abnormal" type typified by ambrosin.[2] These observations, coupled with reasonable inferences drawn from considerations of the numerous congeners of the type that are now known, left only the location of the hydroxyl and carbonyl groups in doubt, although their location as in I was regarded as likely.

Although Herz and his co-workers[3] record the failure of attempts to dehydrate coronopilin, treatment of the compound with acetic acid containing a small amount of sulfuric acid resulted in our hands in its smooth conversion in about 50% yield into a carboxylic acid with the composition of a monodehydration product of coronopilin. This compound, coronopilic acid, showed an intense ultraviolet absorption at 310 mμ (log ϵ 4.22) and formed a deep brown-red dinitrophenylhydrazone. It was clearly a dienone, showing that not only had the hydroxyl group of coronopilin been removed, but an additional double bond had been introduced with concomitant opening of the lactone ring. The new dienone system was isolated from the exocyclic methylene grouping of the lactone and of the acid, for the latter retained the characteristic absorption maximum of an α,β-unsaturated acid at 203 mμ (log ϵ 4.10) and could be converted into a pyrazoline (methyl ester) by the action of diazomethane. Ozonolysis of coronopilic acid yielded 35% of the theoretical amount of formaldehyde, and a Kuhn–Roth determination showed 1.74 C-linked methyl groups.

The unusual opening of the lactone ring under acidic conditions was taken as an indication that the hydroxyl group of coronopilin was located in such a position as to be uniquely involved in this reaction. Since this hydroxyl group was tertiary, and because the methyl group at C-10 was known (by n.m.r.) to be attached to a secondary carbon atom, only two positions for the hydroxyl group could be considered—C-1 and C-7—and, because the exocyclic methylene grouping of coronopilic acid was separate from the dienone system, position 7 was ruled out of consideration.

The first interpretation of the rearrangement that must have occurred during the dehydration reaction was that the opening of the lactone ring was accompanied by the migration of the methyl group from C-5 to C-6 (II), but it is now known that the structure of coronopilic acid is III.

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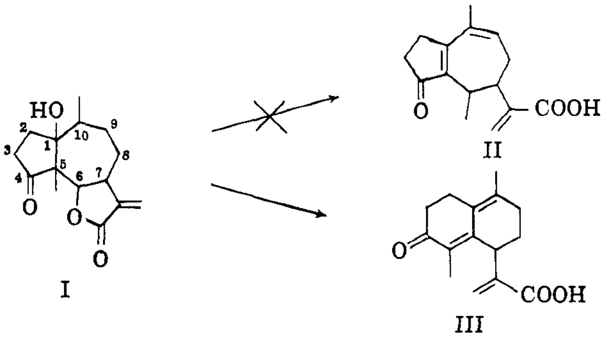
(1) W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).

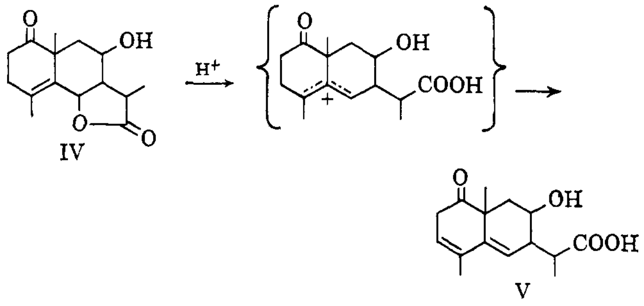
(2) W. Herz, M. Miyazaki, and Y. Kishida, *Tetrahedron Letters*, **No. 2**, 82 (1961).

(3) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).



I II III

The opening of a lactone ring in compounds of this class under acidic conditions is unusual. In the case of ψ-santonin (IV), which is converted by acid into ψ-santonic acid (V),[4] the reaction is understandable, for the intervention of the allylic carbonium ion provides the driving force for the eventual formation of the diene carboxylic acid.



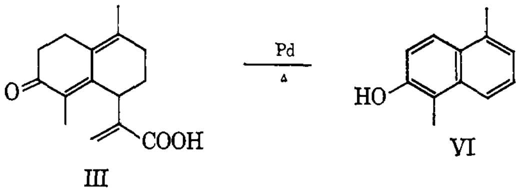
IV V

The properties of coronopilic acid were not, however, in agreement with any structure that could be written that contained the [5:3:0]bicyclodecane ring system. The ultraviolet absorption maxima of none of the numerous known dienones based on this skeleton correspond with the 310-mμ absorption of coronopilic acid. Those recorded are the 2,10-dien-4-one (296 mμ),[5] 4,10-dien-3-one (305,[6] 303,[7] and 299[7]), 4,6-dien-3-one (297),[8] 8,10-dien-2-one (301),[9] and 3,5-dien-2-one (281)[9] (numbering as in I).

On the other hand, the hydronaphthalenic dienone derived from ψ-santonic acid and containing the 4,6-dien-8-one system (305[10] and 310[4b] mμ) corresponds more nearly with coronopilic acid. The n.m.r. spectrum of coronopilic acid provided strong support for structure III. This showed two sharp three-proton singlets at 8.27 and 8.18 (all values in τ-units), two vinylic proton signals at 3.78 and 4.78 in the pattern characteristic of the $=CH_2$ grouping, a sharp one-proton singlet of the carboxyl group at −1.4, and the expected signals for the nine additional protons of the ring system of III, including a well-separated one-proton signal at 6.05 for the doubly allylic proton at C-5. No signals other than the two of the methylene group were seen in the region characteristic of vinyl protons.

Additional information confirmed the structural assignment. Sodium borohydride reduction of coronopilic acid gave an oily product which had an ultraviolet absorption maximum at 251 mμ (log ε 4.20), corresponding to the 4,4a–8,8a diene formed by reduction of the carbonyl group. Attempts to prepare pure, crystalline products by catalytic hydrogenation under a variety of conditions were unsuccessful. In one experiment, using a palladium catalyst and interrupting the hydrogenation after 1.1 mole equiv. of hydrogen had been absorbed, there was isolated a poorly characterized crystalline product that showed the characteristic absorption (248 mμ, log ε 4.08) of the cyclohexenone that would be produced from III by the addition of four hydrogen atoms, two of them at the 8,8a double bond.

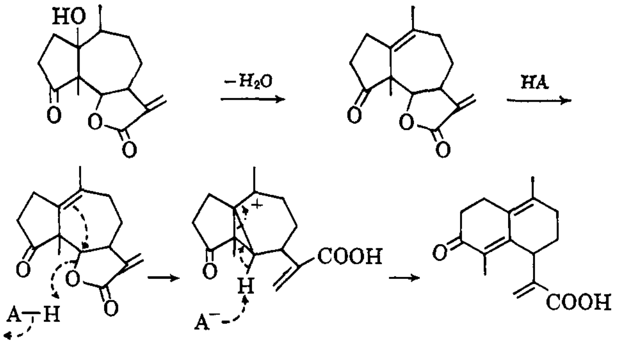
Final evidence in support of structure III was obtained by palladium-catalyzed dehydrogenation of coronopilic acid. The product was identified as 1,5-dimethyl-2-naphthol (VI),[11] characterized as its O-benzoate[12] and methyl ether[13] and by its n.m.r. spectrum. Although the possibility of structural alteration under the vigorous conditions of the dehydrogenation would minimize the value of this result considered alone, when coupled with the evidence adduced above it provides satisfactory confirmation of the structure (III) for coronopilic acid.



III VI

An important consequence of this study is that it provides a new proof of the "abnormal" position of the methyl group (at C-5) in coronopilin and thus in the compounds that have related to it.[3] No alternative arrangements of the substituents in the five-membered ring would allow the formation of coronopilic acid under the conditions used.

The course of the rearrangement of coronopilin into coronopilic acid remains to be considered. There is little doubt that the position of the hydroxyl group at C-1 is a factor in the reaction. There is also ample



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[4] (a) W. G. Dauben, P. D. Hance, and W. K. Hayes, *J. Am. Chem. Soc.*, **77**, 4609 (1955); (b) N. M. Chopra, W. Cocker, J. T. Edward, T. B. H. McMurry, and E. R. Stuart, *J. Chem. Soc.*, 1828 (1956).

[5] W. Herz, H. Watanabe, and M. Miyazaki, *J. Am. Chem. Soc.*, **81**, 6088 (1959).

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[7] D. H. R. Barton and J. T. Pinhey, *Proc. Chem. Soc.*, 279 (1960).

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[9] D. H. R. Barton and C. R. Narayanan, *ibid.*, 963 (1958).

[10] D. H. R. Barton, O. C. Bockman, and P. deMayo, *ibid.*, 2263 (1960); D. H. R. Barton and P. deMayo, *ibid.*, 150 (1957).

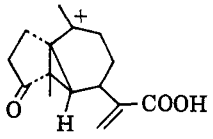
[11] R. Schuyzer, H. G. Biswas, and P. Karrer, *Helv. Chim. Acta*, **34**, 652 (1951).

[12] C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan, and J. Herran, *J. Am. Chem. Soc.*, **76**, 6410 (1954).

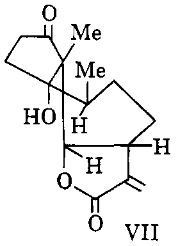
[13] L. Ruzicka and E. Rey, *Helv. Chim. Acta*, **26**, 2136 (1943).

precedent for the view that at no stage in the course of events leading to III does carbonium ion character develop at C-5, adjacent to the carbonyl group. The most satisfactory explanation for the rearrangement is that it proceeds by way of a cyclopropane intermediate that is formed subsequent to an initial C-1–C-10 dehydration.

If an intermediate cyclopropane were assumed, some of the stereochemical features of coronopilin are suggested. It is clear that the original configurations of C-1 and C-10 are lost in the course of the reaction outlined above. The cyclopropane must hold two *cis*-fused rings.



As the lactone ring is probably opened with inversion at C-6, the configurations at C-5 and C-6 are as shown in VII, in which the known[3] configuration of C-10 is included. These structural requirements (along with the arbitrary assumption of a *cis* attachment of the lactone ring and the suggested[3] orientation of the C-1 OH) are accommodated in the following formula (VII) for coronopilin.



VII

Experimental

Coronopilin was isolated substantially as described by Herz and Högenauer[1]; the yield from *Ambrosia psilostachya* DC. (Western Ragweed) was often as high as 3% of the pure lactone (dry weight basis). In a typical experiment, 820 g. of dried plant material gave 21.4 g. of coronopilin (2.6%). The properties of coronopilin corresponded with those recorded.[1]

Coronopilic Acid (III).—A solution of 20 g. of coronopilin in 50 ml. of glacial acetic acid containing 5 ml. of concentrated sulfuric acid was warmed on the steam bath, with stirring, for 1 hr. The solution became red-brown in color. After cooling, the mixture was diluted with water and extracted thoroughly with ethyl acetate. The organic layers were combined and washed thoroughly with water and then extracted with 10% aqueous sodium bicarbonate. The bicarbonate extract was washed with ether and acidified and extracted with ethyl acetate, and the organic layer was dried and evaporated to give a crystalline residue. The yield of crude, crystalline bicarbonate-soluble material varied from 60 to 80%; the yield decreased with prolonged heating of the original reaction mixture. Repeated recrystallization from ethyl acetate gave coronopilic acid, m.p. 168–169°. The ultraviolet absorption spectrum showed maxima at 310 mμ (ϵ 16,300) and 203 mμ (ϵ 12,600).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.00; H, 7.29.

The **methyl ester**, prepared with 1 equiv. of diazomethane, was an oil which was characterized as the deep red 2,4-dinitrophenylhydrazone, m.p. 163–165°.

Anal. Calcd. for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.98; H, 5.70; N, 12.84.

The **p-bromophenacyl ester** of coronopilic acid formed light yellow crystals, m.p. 118.5–120°.

Anal. Calcd. for $C_{23}H_{23}BrO_4$: C, 62.31; H, 5.23. Found: C, 62.53; H, 5.29.

Monopyrazoline of Methyl Coronopilate.—An ether solution of diazomethane prepared from 1.8 g. of nitrosomethylurea was added to a solution of 0.5 g. of coronopilic acid in 20 ml. of ether. The excess diazomethane and ether were removed by evaporation, and the residue was recrystallized from aqueous methanol. The compound had m.p. 113–14° (gas evolution) and λ_{max} 309 mμ (ϵ 15,500).

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.69, H, 7.56; N, 9.40.

Ozonolysis of Coronopilic Acid.—Ozonized oxygen was passed for 1 hr. through a solution of 107 mg. of coronopilic acid in 25 ml. of methylene chloride maintained at Dry Ice temperature. The solution was steam distilled and the distillate was treated with a saturated aqueous solution of dimedone. The formaldimedone that crystallized (45 mg.; 35%) was identical (mixture melting point) with an authentic specimen.

Sodium Borohydride Reduction of Coronopilic Acid.—To a solution of 0.5 g. of coronopilic acid in 5% aqueous sodium hydroxide was added a solution of 100 mg. of sodium borohydride in 5 ml. of water. After 3 hrs. at ice-bath temperature, the solution was acidified and extracted with ether. Removel of the solvent left a colorless gum which could not be induced to crystallize. It showed infrared absorption at 1619, 1705, and 3570 cm.$^{-1}$, and had λ_{max} 251 mμ (ϵ 15,800).

Catalytic Hydrogenation of Coronopilic Acid.—Numerous attempts to prepare characterizable hydrogenation products with the use of platinum or palladium catalysts led to no useful results.

In one experiment the hydrogenation of 1.0 g. of coronopilic acid in ethanol over 5% palladium–charcoal was interrupted after the absorption of 1.1 mole equiv. of hydrogen. Manipulation of the residue left after removal of the solvent yielded 0.16 g. of material melting over the range 171–183°. After several recrystallizations the melting point was improved to 179–184°. The material had λ_{max} 248 (ϵ 12,000, calcd. for a tetrahydro compound). The compound was not sufficiently pure for a meaningful carbon–hydrogen analysis and was not characterized further.

Dehydrogenation of Coronopilic Acid.—A mixture of 3.5 g. of coronopilic acid and 2 g. of 10% palladium–charcoal was heated at 325° for 6 hr. The solid mass that resulted was triturated with ether and the filtrate was washed first with 10% aqueous sodium bicarbonate and then with 10% aqueous sodium hydroxide. The sodium hydroxide extract was acidified and extracted with ether. After removal of the ether, the residue was steam distilled to give 150 mg. of crystalline material. Recrystallized from carbon tetrachloride, it formed white needles, m.p. 162–163. Its ultraviolet absorption spectrum was identical with that recorded for 1,5-dimethyl-2-naphthol, lit.[11] m.p. 161.5–163°.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.52; H, 7.15.

The compound was characterized as the O-benzoate and the methyl ether.

The **O-benzoate** had m.p. 152–153° (lit.[12] m.p. 151.5–153°).

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.55; H, 6.03.

The **methyl ester** had m.p. 93–94° (lit.[13] m.p. 92–93°).

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.62; H, 7.67.