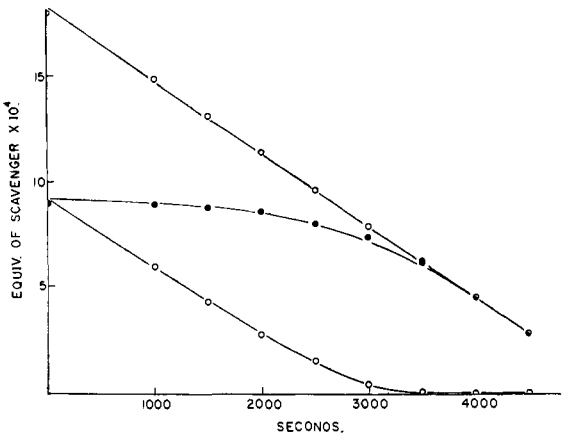

Fig. 2.—Behavior of galvinoxyl (lower curve) and iodine (middle curve) as competitive scavengers for cyanoisopropyl radicals: upper line, sum of lower two curves.

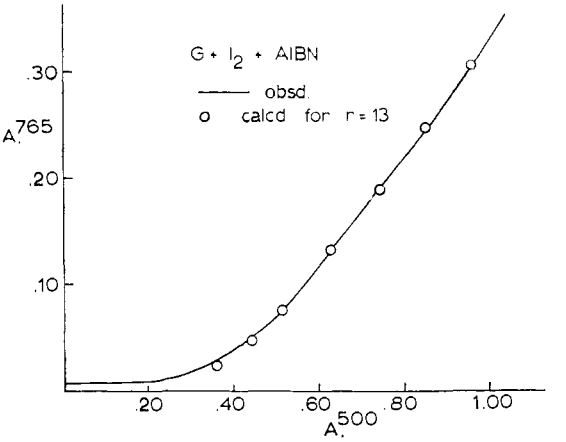

Fig. 3.—Optical densities at 500 and 765 mμ during competitive scavenging of radicals from azobis-isobutyronitrile by galvinoxyl and iodine.

tion of AIBN, the efficiency of radical production from this initiator is again found to be 62.2% at 61.65°.

When two scavengers at concentrations x and y are competing for the same reactive free radicals with the large rate constants k_x and k_y, their relative rates of disappearance are governed by the equations

$$\frac{dx}{dy} = \frac{k_x x}{k_y y}$$

so that

$$\log \frac{x_0}{x} = \frac{k_x}{k_y} \log \frac{y_0}{y} = r \log \frac{y_0}{y}$$

In the range of optical densities where these quantities can be determined with comparable precision (up to 92% consumption of galvinoxyl and 16% consumption of iodine) this function is reasonably linear, with a slope r of about 10. With all values of r higher than this, the experimental curve of a *vs.* b can be calculated within the experimental uncertainty (Fig. 3). Smaller values of r fail to fit the data.

An attempt to determine in the same way the relative efficiencies of galvinoxyl and iodine toward the *tert*-butoxy radical from di-*tert*-buty peroxyoxalate was unsuccessful. Analysis of the curves showed that scavenger was not disappearing as fast as radicals were being formed and that the rate of scavenger disappearance was constantly changing throughout the experiment. This is another instance of the unsuitability of iodine and iodides for quantitative work with peresters, on which we have commented previously.[10]

Toward the cyanoisopropyl radical, for which both galvinoxyl and iodine are satisfactory scavengers, galvinoxyl has reactivity to spare. If, with the 10-fold difference between these scavengers in mind, we examine the ends of the curves of disappearance of G and I_2 singly in the presence of AIBN, we see a consistent but small departure from linearity as the last few per cent. of iodine disappear, but no corresponding effect in the case of galvinoxyl. The normal mode of disappearance of free radicals in such a system must be slow compared to either of these scavenging processes.

Acknowledgment.—We thank the National Science Foundation for support of this work.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE FLORIDA STATE UNIVERSITY, TALLAHASSEE, FLA.]

The Structures of Parthenin and Ambrosin[1,2]

BY WERNER HERZ, HIROSHI WATANABE,[3] MAKOTO MIYAZAKI[3] AND YUKICHI KISHIDA

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Parthenin, the main constituent of *Parthenium hysterophorus* L., has been shown to be a sesquiterpene lactone and correlated with ambrosin, a constituent of *Ambrosia maritima* L. Structures for these substances have been established.

According to Arny,[4] extracts of *Parthenium hysterophorus* L., a bitter herb common in the Southeastern United States and the West Indies, have enjoyed some reputation as a folk remedy against various afflictions such as ulcerated sores, certain skin diseases, facial neuralgia, fever and

(1) For preliminary reports on part of this work, see (a) W. Herz, H. Watanabe and M. Miyazaki, *J. Am. Chem. Soc.*, **81**, 6088 (1959); (b) W. Herz, M. Miyazaki and Y. Kishida, *Tetrahedron Letters*, **No. 2**, 82 (1961).

(2) Supported in part by grants from the National Science Foundation (NSF-G 14396) and the United States Public Health Service (RG-5814).

(3) Recipients of Fulbright Travel Awards in 1958–1959 and 1959–1960, respectively.

(4) H. V. Arny, *J. Pharm.*, 121 (1890); 169 (1897). Earlier references to the medicinal use of *P. hysterophorus* L. are given in these papers.

anemia. By extracting the plant with dilute alcohol Arny was able to isolate an apparently non-alkaloidal, non-glycosidic substance of m.p. 168–169° which he named parthenin. Arny claimed to have determined the empirical formula, but in fact no formula was ever published.

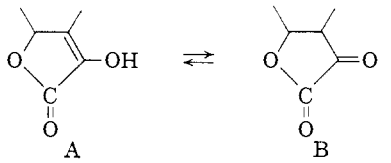
Subsequent references to this plant appear to be limited to a report[5] which states that extracts of *P. hysterophorus* L. gave positive tests with Wagner and Dithmar reagent but that the alkaloid content was very small and that the medicinal properties, if any, must be due to substances other than alkaloids.

We became interested in this problem because of the occurrence of the azulenogenic sesquiterpene alcohol partheniol, as the cinnamate ester, in the only other *Parthenium* species which had been investigated previously. This is *P. argentatum* Gray, more commonly known as guayule.[6] It seemed possible that the main constituent of *P. hysterophorus* was also a sesquiterpene derivative with a perhydroazulene skeleton. The identification of parthenin as a sesquiterpene lactone with an "abnormal" carbon skeleton and the correlation of parthenin with ambrosin, another naturally occurring sesquiterpene lactone, is the subject of this paper.

Extraction of *P. hysterophorus* gave a crystalline substance $C_{15}H_{18}O_4$, m.p. 163–166°, $[\alpha]^{25}D$ +7.02°, whose properties seemed to correspond to those of the material isolated by Arny[4,7] and for which we have therefore retained the name parthenin.[8]

The infrared spectrum of parthenin had bands at 1655 and 1592 cm.$^{-1}$ which disappeared on catalytic hydrogenation to tetrahydroparthenin (II) and which were therefore assigned to two double bonds. As in the case of helenalin[9] and balduilin,[10] the higher frequency arises from the presence of an exocyclic methylene group conjugated with a γ-lactone function (infrared bands at 1755 and 1408 cm.$^{-1}$).[11] This is supported by the following evidence.

Parthenin formed a pyrazoline[12] and had a near-infrared band at 1.64 μ[13] which disappeared on hydrogenation. Comparison of the C–methyl values and the methyl region of the n.m.r. spectra (see Table I) of parthenin and II indicated the presence of an additional C–methyl group in the latter. Ozonolysis of parthenin gave rise to formaldehyde. When the ozonolysis was carried out in methanol at −78°, there was also formed in good yield norparthenone (III), $C_{14}H_{16}O_5$, which contained the partial structure A. In accordance with the behavior of model compounds,[14] this α-ketobutyrolactone was completely enolized (titratable with



A B

dilute sodium hydroxide solution, ferric chloride test), exhibited the appropriate ultraviolet (λ_{max} 235 mμ, ϵ 12000)[15] and infrared maxima, could be further oxidized with the liberation of oxalic acid and furnished an enol benzoate.

The infrared band at 1592 cm.$^{-1}$ coupled with a strong carbonyl absorption at 1718 cm.$^{-1}$ suggested the presence of a cyclopentenone grouping in parthenin. The ultraviolet spectrum (λ_{max} 215 and 340 mμ, ϵ 15100 and 22, high intensity at 206–210 mμ) was similar to that of helenalin and balduilin and could be interpreted as arising from the overlap of α,β-unsaturated ketone and α,β-unsaturated γ-lactone chromophores. This hypothesis was strongly reinforced by the presence in the infrared spectrum of tetrahydroparthenin of two carbonyl maxima, one at 1760 cm.$^{-1}$ due to the γ-lactone and a second at 1742 cm.$^{-1}$ characteristic of a cyclopentanone, and by the ultraviolet absorption of II (λ_{max} 277 mμ, ϵ 71). A positive Zimmermann test and an infrared band at 1410 cm.$^{-1}$ indicated that the keto group of II was flanked by at least one methylene. Chemical evidence for the ketonic function was difficult to adduce, probably because of the ease with which dehydration occurred under the influence of acidic reagents, but the preparation of at least one crystalline derivative from a degradation product and the conversion to tetrahydroambrosin to be discussed in the sequel provided satisfactory proof.

The main product in the hydrogenation of parthenin was not tetrahydroparthenin (II), but a substance IV resulting from the uptake of only two atoms of hydrogen, which was resistant to further hydrogenation. A double-strength carbonyl band in the infrared at 1745 cm.$^{-1}$ indicated that the cyclopentenone chromophore had been reduced, but a relatively strong band at 1668 cm.$^{-1}$ and the ultraviolet absorption (λ_{max} 220 and 261 mμ, ϵ 14000 and 70) pointed to the continued presence of conjugation. The formation of acetic acid and the absence of formaldehyde, coupled with the appearance of a new sharp signal at 1.80 p.p.m. in the n.m.r. spectrum,[16] intensity 3 protons, es-

(5) A. J. Loustalot and C. Pagan, *El Crisol*, **3**, no. 5, 3 (1949); *C. A.*, **44**, 2719 (1950).

(6) A. J. Haagen-Smit and C. T. O. Fong, *J. Am. Chem. Soc.*, **70**, 2075 (1948).

(7) As noted by Arny, the yield of crystalline material which seems to be concentrated in the leaves varies seasonally and seems to reach a peak in late summer. No attempt was made to put this on a quantitative basis and the yields 0.14%, given in the earlier reference,[15] and 0.33% reported in this paper refer to yields from whole plants collected at various times during the summers of 1957 and 1959, respectively.

(8) Parthenin should not be confused with a substance recently isolated from *Chrysanthemum parthenium* (L.) Bernh. by V. Herout, M. Souček and F. Šorm, *Chemistry & Industry*, 1069 (1959), and named by them parthenolide.

(9) (a) R. Adams and W. Herz, *J. Am. Chem. Soc.*, **71**, 2346, 2551, 2554 (1949); (b) G. Büchi and D. Rosenthal, *ibid.*, **78**, 3860 (1956).

(10) W. Herz, R. B. Mitra and P. Jayaraman, *ibid.*, **81**, 6061 (1959).

(11) M. Horák and J. Pliva, *Chemistry & Industry*, 102 (1960).

(12) P. G. Deuel and T. A. Geissman, *J. Am. Chem. Soc.*, **79**, 3778 (1957).

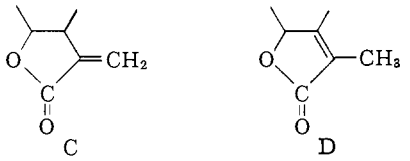
(13) W. H. Washburn and M. S. Mahoney, *ibid.*, **80**, 504 (1958).

(14) H. Schinz and M. Hinder, *Helv. Chim. Acta*, **30**, 1349 (1947). See also the ozonolysis product of iresin, C. Djerassi and W. Rittel, *J. Am. Chem. Soc.*, **79**, 3528 (1957), and an enolic ketolactone described by C. J. W. Brooks, G. Eglinton and D. S. Magrill, *J. Chem. Soc.*, 308 (1961).

(15) Reference 14 gives λ_{max} 232 mμ, log ϵ 4.1, for α-ketobutyrolactones. In the present instance the absorption is slightly modified by the cyclopentenone chromophore.

(16) Spectra were run by Mr. Fred Boerwinkle of our Department and Mr. L. F. Johnson of Varian Associates on a Varian HR-60 instrument in deuteriochloroform solution. Tetramethylsilane served as

tablished the presence of a methyl group on doubly-bonded carbon. We conclude that the catalyst effected isomerization of C to D in the manner



C D

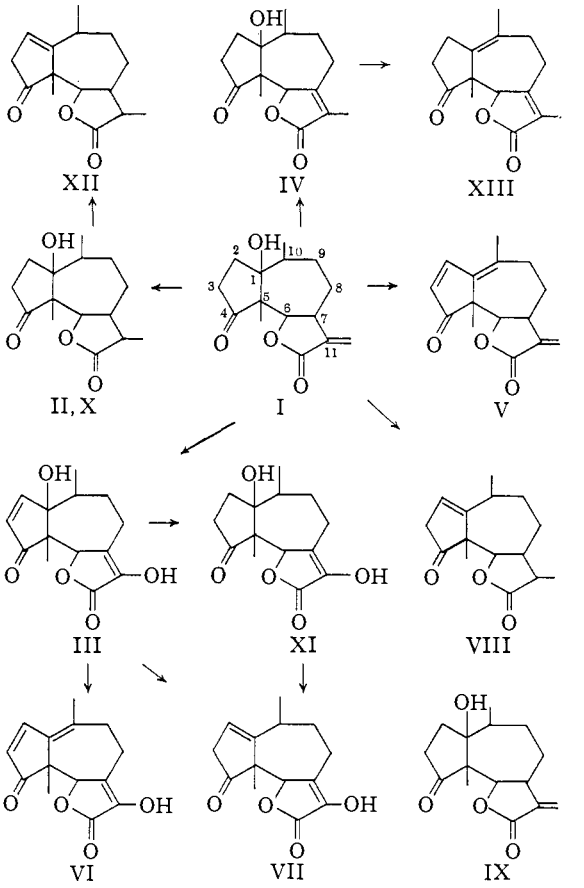
postulated as occurring during the hydrogenation of ambrosin[17] and name the new compound dihydroisoparthenin (IV) in accordance with established procedure.[9b,17,18]

The fourth oxygen atom of the parthenin formula derives from a hydroxyl group (infrared band at 3450 cm.$^{-1}$) which was assumed to be tertiary because II and IV could not be acetylated with acetic anhydride–pyridine and were not oxidized by chromium oxide at room temperature. The ease with which parthenin and its derivatives underwent dehydration supported this conclusion.

Treatment of parthenin with hot formic acid resulted in the formation of anhydroparthenin (V) which, from its ultraviolet spectrum (λ_{max} 210 and 296 mμ, ϵ 14300 and 12500), was clearly a conjugated dienone. Compound V retained the exocyclic methylene group of parthenin (formation of formaldehyde on ozonolysis, near infrared band at 1.64 μ), but had a new vinyl methyl group (singlet methyl proton signal at 2.03 p.p.m.). Norparthenone on treatment with formic acid formed an analogous anhydro derivative (VI) whose ultraviolet spectrum (λ_{max} 240 and 298 mμ, ϵ 9000 and 10900) showed that the dienone system was not conjugated with the enolic α-ketobutyrolactone chromophore. These observations indicate that the tertiary hydroxyl group occupies a position γ- or δ- to the α,β-unsaturated ketone system.

That the hydroxyl group is indeed at the γ-position was demonstrated by the facile deoxygenation of parthenin and norparthenone with zinc and acetic acid.[19] Analysis and ultraviolet spectrum (λ_{max} 295 mμ, ϵ 91) of the product (VIII) from parthenin showed that deoxygenation was accompanied by reduction of the conjugated lactone group. The remaining double bond was triply substituted (ϵ 1750 at 206 mμ) and resistant to hydrogenation. That the zinc–acetic acid reagent is capable of reducing the lactone system separately was also shown by the reduction of coronopilin (IX)[20] to a substance (X) isomeric with tetrahydroparthenin.[21]

The deoxygenation product VII of norparthenone could be obtained also by dehydration of dihydronorparthenone[20] (XI) with thionyl chloride–pyridine at room temperature, an observation which renders unlikely the possibility of an acid-catalyzed rearrangement during the conversion of I to VIII, and III to VII.



XII IV XIII

II, X I V

III XI VIII

VI VII IX

Other considerations necessary for the placement of the hydroxyl group on the carbon skeleton derive from the following observations. Parthenin, II and IV did not consume lead tetraacetate or periodic acid in neutral solution, thus excluding a possible α-ketol structure. In basic solution, II and IV were similarly unreactive toward periodic acid. Hence the tertiary hydroxyl group cannot be placed on a carbon atom vicinal to that carrying the lactone ether oxygen.[22]

It now remained to deduce the carbon skeleton by dehydrogenation, the usual practice in sesquiterpene chemistry. The presence of a cyclopentenone group suggested that parthenin, like parthenolide, was a perhydroazulene and a new member of the class of guaianolides. The dehydrogenation

internal standard and frequencies were calibrated by the side-band technique. We are grateful to Dr. M. T. Emerson and Mr. Johnson for assistance with the assignments. The spectrometer at Florida State University was purchased with funds provided by the Institute of Molecular Biophysics.

(17) (a) L. Bernardi and G. Büchi, *Experientia*, **13**, 466 (1957); (b) F. Šorm, M. Šuchý and V. Herout, *Coll. Czechoslov. Chem. Commun.*, **24**, 1548 (1959).

(18) In the preliminary communication[18a] this substance was referred to as dihydroparthenin and the m.p. was erroneously given as 142–144°; the m.p. of IV is 200–201°.

(19) For a recent example of this type of reduction, see T. G. Halsall, W. J. Rodewald and D. Willis, *J. Chem. Soc.*, 2978 (1959).

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

(21) The reduction gave a relatively poor yield of crystalline material. Presumably II and X are epimeric at C_{11}, with X the thermodynamically more stable isomer. This conclusion is supported by the partial conversion of II to X on treatment with potassium carbonate in xylene.

(22) In basic solution, parthenin consumed one mole and norparthenone two moles of periodic acid. We ascribe this to the existence of the equilibrium

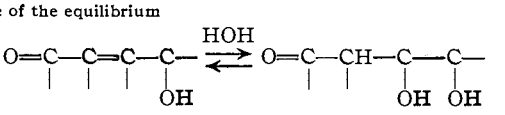


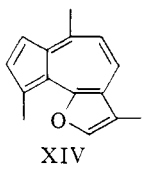
TABLE I

N.M.R. PEAKS OF PARTHENIN DERIVATIVES[a]

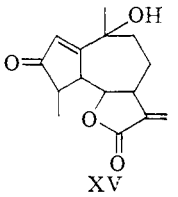
Compounds	H_3	H_2	H_6	CH_2	C_5–Me	C_{10}–Me	C_{11}–Me
I	7.55d(6)	6.18d(6)	5.08d(7)	5.59d(3) 6.29d(3)	1.28	1.11d(8)	
II			4.66d(5)		1.11	1.08, 1.11, 1.21 (comb. int. 6 protons)	
IV			5.50br		0.83	1.08d(7.5)	1.80
V	7.97d(6)	6.09d(6)	4.45d(6)	5.59d(3) 6.29d(3)	1.35	2.03	
VIII	5.96t	2.90d 3.04d	4.26d(8)		1.30	1.21d(7), 1.24d(6)	
IX			5.01d(7)	5.59d(3) 6.21d(3)	1.13	1.22d(7)	
XII	5.84t	2.90d 2.95d	4.66d(5.5)		1.41	1.18d(7), 1.25d(7)	
XIIIa[b]			4.69br		1.01	1.87(6 protons)	
XVII			4.33d(6)		1.37	1.07d(7)	1.86
XVIIIb			4.52d(5.5)		1.16	1.15d(8), 1.08d(8)	
XIX			4.66br		0.83	1.00d(6)	1.82
XXI	6.09t	2.90d 2.95d	4.59br		0.98	1.13d(8)	1.85
XXII	8.09d(6)	6.06d(6)	4.39d(6)		1.40	2.00	1.17d(7)
XXV	7.50q	6.14q	4.68d(9.2)	5.50d(2) 6.29d(2)	1.17	1.07d(6)	

[a] Values are given in p.p.m. relative to tetramethylsilane as reference. All signals in first four columns correspond to one H, all signals in last three columns to 3H, unless specified. Singlets are unmarked, multiplets are described as follows: d, doublet, t, triplet, q, quartet, br, somewhat broadened singlet. Numbers in parentheses denote coupling constants in c.p.s. [b] No signals corresponding to methylene and methinyl protons were present in the region 0–2 p.p.m., thus providing confirmation for the proposed structure.

results seemed to verify this hypothesis. Parthenin on reduction with lithium aluminum hydride followed by dehydrogenation with palladium–charcoal afforded artemazulene (XIV), albeit in low yield.[23] The properties of parthenin were therefore inter-



XIV



XV

preted[1a] on the basis of a guaiane skeleton in terms of formula XV which had the required orientation of the lactone ring toward C_6 and an allylic tertiary hydroxyl group not α to the ketone and lactone ether functions. The properties of parthenin and anhydroparthenin also removed from consideration formulas with the ketone orientation of lactucin[24] and matricarin.[25]

That formula XV could not be correct was first shown by the oxidative degradation of norparthenone. Potassium permanganate oxidation of III in acid solution furnished acidic material which, when liberated from its cyclohexylamine salt, gave a 25% yield of optically pure S-(+)-α-methylglutaric acid, m.p. 80–82°, $[\alpha]^{24}D$ +20°,[26] identical in every respect with an authentic sample.[27] It is obvious that dissection of XV cannot give rise to this six-carbon fragment.

High resolution n.m.r. spectra of parthenin and its derivatives (Table I) also eliminated formula XV and provided several alternatives which, when the chemical properties were considered, were uniquely reduced to I. In the vinyl proton region, parthenin and V displayed *two* low field doublets (intensity one proton each) associated with the cyclopentenone system (J = 6), the lack of further splitting indicating that the γ-carbon was fully substituted. A second pair of doublets, each representing one proton, was characteristic of the C_{11}–methylene conjugated with the lactone group present in I, V and related compounds, the chemical shift and magnitude of the coupling constant being typical of *gem*-vinyl protons. Coronopilin (1,2-dihydroparthenin, IX)[20] exhibited the second, but not the first, pair of doublets and all signals in this region disappeared on conversion of I to II and IV.

In the methyl region, parthenin exhibited a normal doublet due to $>CH-CH_3$ and a singlet at 1.28 p.p.m. In converting parthenin to V the singlet was retained; hence it cannot be ascribed to $R_2-\underset{\underset{OH}{|}}{C}-CH_3$. However, the doublet had disappeared and was replaced by a singlet at 2.03 p.p.m. characteristic of $=\underset{\underset{R}{|}}{C}-CH_3$.

(23) The isolation of a small amount of another unidentified azulene is also described in the Experimental section.

(24) D. H. R. Barton and C. R. Narayanan, *J. Chem. Soc.*, 963 (1958); L. Dolejš, M. Soucek, M. Horák, V. Herout and F. Šorm, *Coll. Czechoslov. Chem. Commun.*, **23**, 1295 (1958).

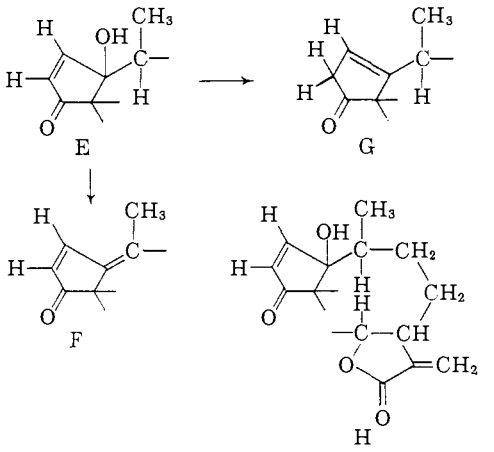
(25) Z. Čekan, V. Procházka, V. Herout and F. Šorm, *ibid.*, **24**, 1554 (1959); W. Herz and K. Ueda, *J. Am. Chem. Soc.*, **83**, 1139 (1961).

(26) A. Fredga, *Svensk. Kem. Tidskr.*, **67**, 343 (1955); *Arkiv. Kemi, Mineral. Geol.*, **24A**, No. 32 (1947).

(27) E. Berner and R. Leonardsen, *Ann.*, **538**, 1 (1939).

Deoxygenation of I to VIII resulted in retention of the methyl singlet and doublet, but the vinyl proton region was altered profoundly. Reduction of the C_{11}-methylene group was signaled by the expected changes (new methyl doublet, disappearance of the two narrowly split doublets at 5.61 and 6.26 p.p.m.) and the two vinyl protons of the cyclopentenone system also disappeared. Instead there was found one vinyl proton (triplet at 5.96 p.p.m.) and two sharply-defined doublets (intensity one proton each) at 2.90 and 3.04 p.p.m. This combination indicated the presence of an ABX system where $J_{AX} = J_{BX} = 2$, $J_{AB} = 5$.

The changes I → V and I → VIII can be interpreted only in terms of partial structures E, F and G. This is supported by the formation of XII on dehydration of II with thionyl chloride–pyridine. The dehydration was difficult, however. Treatment of IV with formic acid led to XIIIa, whose n.m.r. spectrum is in accord with this proposal (Table I). The dehydration of coronopilin (IX) could not be effected satisfactorily.



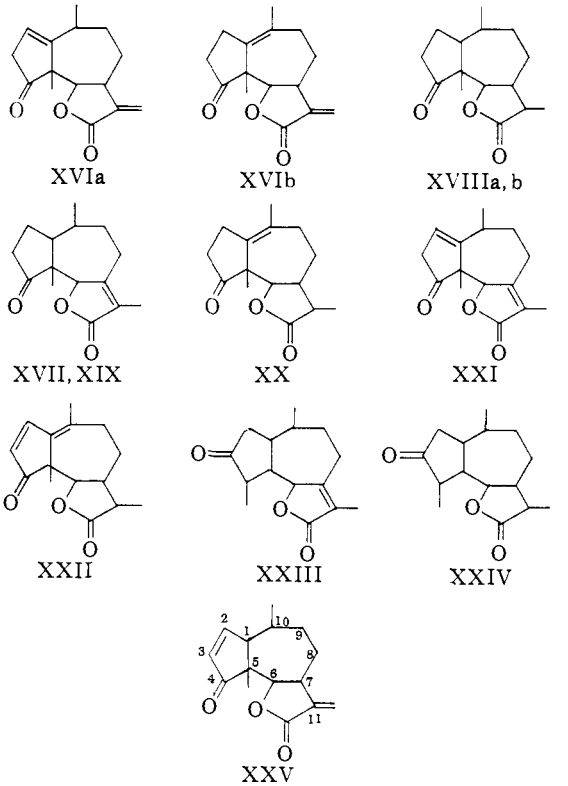
In expanding partial formula E, the following points must be borne in mind: (1) the presence of a singlet methyl signal in the n.m.r. spectra of parthenin and all of its derivatives, (2) the formation of α-methylglutaric acid on oxidation of norparthenone. The methyl group of this fragment must be identical with the methyl group already incorporated in E which therefore can be expanded to H.

The orientation of the lactone group in H is required by the formation of artemazulene which fixes the relative positions of the methyl and the potential isopropyl side chain. Moreover, the n.m.r. spectra of I, II, V, VIII, IX and many other compounds contain a sharp doublet ($J = 7$) near 4.5–5.2 p.p.m., intensity one proton. Its chemical shift is characteristic of hydrogen on carbon carrying lactone or ester oxygen.[28] The persistence of this doublet indicates that the two adjoining carbon atoms carry only one proton between them.[29] Now one proton must be placed on the carbon atom carrying the potential isopropyl side chain (enolic properties of III and VII) and although caution is necessary in interpreting multiplicities, the presence of two additional α-protons required by the reorientation of the lactone ring seems extremely unlikely. Ring closure to C_5 and placement of the tertiary methyl group at the same carbon atom necessarily follow, thus leading to expression I for parthenin.

Before we discuss the implications of this "abnormal" carbon skeleton, we would like to describe experiments which led to a correlation of parthenin with ambrosin, the major sesquiterpene lactone constituent of *Ambrosia maritima* L.[17,30]

Prior to elucidation of the actual structure of parthenin, the reduction of anhydroparthenin (V) appeared to offer excellent possibilities for correlating parthenin with substances then considered to be guaianolides. Treatment of V with zinc and acetic acid resulted in the formation of a new substance (XVI) in which the methylene group was retained (formation of formaldehyde on ozonolysis, λ_{max} 206 and 290–293 mμ, ε 15200 and 91). This may be XVIa, although the facile reduction to a dihydro derivative XVII[31] accompanied by the usual C → D isomerization suggested that the isolated double bond was perhaps located between C_9 and C_{10}, as in XVIb.[32]

Catalytic reduction of V resulted in the isolation of six new hydrogenation products—two dihydro



(28) The doublet is at the low field end of this range in compounds containing the hydroxyl group, but moves to higher field on dehydration and deoxygenation. This deshielding of the hydrogen atom by the hydroxyl group suggests that they are *cis* to each other.

(29) The assignment is supported by the shift of this signal, now a broad singlet (half-width 3 c.p.s.), to 5.53 p.p.m. in the n.m.r. spectrum of IV.

(30) H. Abu-Shady and T. D. Soine, *J. Am. Pharm. Assoc.*, **42**, 387 (1953); **43**, 365 (1954).

(31) Compare with the difficulty of reducing VIII.

(32) The insolubility of XVI in the common solvents used for this purpose precluded the determination of the n.m.r. spectrum.

derivatives, two tetrahydro derivatives and two hexahydro derivatives.

The two hexahydroanhydroparthenins were clearly formed by saturation of the three olefinic centers and should be represented by formula XVIII. Compound XVIIIa, obtained in very small amount only, had m.p. 104–106°, λ_{max} 293 mμ (ϵ 40); XVIIIb melted at 123–125°, $[\alpha]^{25}D$ +78°, λ_{max} 290 mμ (ϵ 93). Tetrahydroanhydroparthenin A, m.p. 161–162.5°, $[\alpha]^{24}D$ +23.2°, had a cyclopentanone ring and an α,β-unsaturated lactone system of the type found in dihydroisoparthenin (λ_{max} 218 and 300 mμ, ϵ 10500 and 31, infrared bands at 1755—double strength—and 1675 cm.$^{-1}$). We conclude that XIX (epimeric with XVII) is a satisfactory representation. This was confirmed by the n.m.r. spectrum which exhibited one methyl doublet, one methyl singlet at 0.833 and one vinylic methyl singlet at 1.82 p.p.m. Tetrahydroanhydroparthenin B, m.p. 80–82°, was obtained in one run only. Its ultraviolet and infrared spectrum indicated the absence of conjugation; hence formula XX is suggested.

Experiments using a limited amount of hydrogen yielded the isomeric dihydroanhydroparthenins XXI and XXII whose structure assignments are based on their spectral properties.

The properties of XVIIIb and XIX, the major reduction products, compared reasonably well with the properties of dihydroisoambrosin and tetrahydroambrosin[30] to which structures XXIII and XXIV had been assigned earlier.[17] A comparison of XVIIIb and tetrahydroambrosin, kindly carried out by Dr. V. Herout, showed that the two samples were identical in all respects. This of course necessitates a revision in the structure of ambrosin to XXV. Ambrosin is therefore not a guaianolide but a representative of a new class of sesquiterpene lactones to which parthenin also belongs.

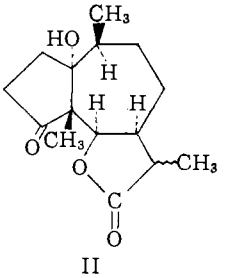
The fortuitous isolation of ambrosin from a collection of *Parthenium incanum* H. B. K.[20] allowed us to examine its n.m.r. spectrum. This was fully in accord with structure XXV. The two cyclopentenone vinyl proton signals at 6.14 and 7.50 p.p.m. were split into quadruplets by spin-coupling to each other and to the hydrogen atom at C_1 ($J_{H_2H_4}$ = 6.2, $J_{H_1H_3}$ = 3, $J_{H_1H_4}$ = 1.9), the methylene protons appeared at 5.51 and 6.29 p.p.m. (J = 3), H_6 was a sharp doublet centered at 4.69 ($J_{H_6H_7}$ = 9.2) and the methyl signals were at 1.17 (singlet) and 1.07 p.p.m. (doublet).[33]

The formation of artemazulene in small yield on dehydrogenation of parthenin and chamazulene[17a,30] and artemazulene[17b] from ambrosin is obviously due to a 1,2-methyl shift. The presence of the quaternary carbon atom accounts for the difficulty of dehydrogenation previously commented upon.[17b] However, it is surprising that azulenes resulting from loss of the angular methyl group have not been encountered in the course of this and earlier work. It is possible that this 1,2-methyl shift constitutes a reversal of a methyl migration occurring during biogenesis, although the parthenin skeleton may be dissected in such a way so as to allow for the irregular union of one C_5 with one C_{10} unit.

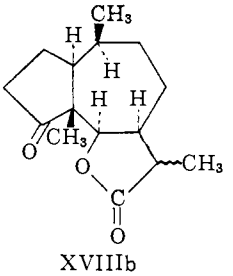
Ultraviolet spectra of ambrosin and similar compounds have previously been explained in terms of monoalkylsubstituted cyclopentenone structures which the n.m.r. spectra definitely exclude. Recent work[34] has shown, however, that ultraviolet absorption properties of complex cyclopentenones can vary considerably and that the spectra of parthenin and ambrosin present no particular abnormalities.

The isolation of *S*-(+)-α-methylglutaric acid of known absolute configuration establishes the absolute configuration of parthenin at C_{10} (methyl β). Bimolecular dehydration of compounds of the parthenin series is difficult and directed toward C_2, if successful. This suggests that the C_1-hydroxyl is *trans* to C_{10}-methyl, or α. Šorm and co-workers have deduced,[17b] by applying the modified Hudson–Klyne rule,[35] that the C_6-oxygen bond of ambrosin (and therefore of parthenin) is β.[36] The remaining centers of asymmetry are C_7 (side chain probably equatorial) and C_5.

In order to make tentative assignments for the absolute configuration of I and XXV at C_5, a comparison of rotatory dispersion curves with those of suitably-constituted model compounds is instructive. The rotatory dispersion curves of tetrahydroparthenin[37] and tetrahydroambrosin[38] (see Experimental) were remarkably similar in shape, amplitude and sign of Cotton effect to those of androstane-3β-14α-diol-17-one 3-monoacetate[34] and androstan-17-one,[39] respectively. Since the amplitudes of the 14β-analogs are considerably lower,[34] one is therefore tempted to ascribe to II and XVIIIb a *trans*-ring junction, with the C_5-methyl group β and the C_1-hydroxyl of II α, the latter orientation having already been deduced on chemical grounds. This argument is of course highly speculative because of the lack of reference lactones with well-documented



II



XVIIIb

stereochemistry and, more specifically, the unavailability of compounds epimeric with II and

(33) The n.m.r. spectra of helenalin, tenulin and balduilin and of other sesquiterpene lactones isolated from *Helenium* species also indicated the presence of two cyclopentenone vinyl protons split by hydrogen at C_1 and the presence of a tertiary methyl group. This leads to the conclusion that the carbon skeleton of these substances is that of parthenin and ambrosin; W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman and N. Viswanathan, *J. Am. Chem. Soc.*, in press.

(34) F. Sondheimer, S. Burstein and R. Mechoulam, *ibid.*, **82**, 3209 (1960).

(35) V. Sýkora and M. Romanuk, *Coll. Czechoslov. Chem. Commun.*, **22**, 1909 (1957).

(36) The evidence cited in footnote 28 supports their assignment.

(37) Kindly determined by Prof. Carl Djerassi and Dr. E. J. Eisenbraun at Wayne State University.

(38) We wish to thank Dr. M. O'Dwyer of this Department for determining this curve.

(39) C. Djerassi, R. Riniker and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

XVIIIb at C_1. If it and the previous suggestion are accepted for the moment, the structures shown above follow. The orientation of the C_{10}–methyl group of XVIIIb is based on the assumption that hydrogen adds *cis* to the C_1–C_{10} double bond of V.[39a]

The rotatory dispersion curves[38] of coronopilin (IX) and IV are quite similar to that of II, but have lower amplitudes, paralleling in this respect the relationship of dihydroambrosin[17b] and tetrahydroambrosin.

Because of the medicinal reputation of *P. hysterophorus* extracts, a sample of parthenin was submitted to the Lilly Research Laboratories for testing. Parthenin proved to be a central nervous system depressant and an adrenergic blocking agent, but its toxicity was too great to warrant further interest. It exhibited slight indications of antibacterial activity. Doses up to and including 100 mg./kg. produced no significant diuresis or saluresis in saline-loaded female rats. It was ineffective against P-1534 leukemia and the activity exhibited against adenocarcinoma 755 was not great enough to warrant further investigation.

Acknowledgment.—We are grateful to the Florida State University Research Council for funds toward the purchase of an extractor.

Experimental[40]

Isolation of Parthenin.—Air-dried *Parthenium hysterophorus* L., collected on vacant lots in Tallahassee and Quincy, Florida, in July and August, 1959, was shredded and extracted in 13–14 pound portions in a Lloyd extractor with warm chloroform for two days. Removal of the solvent yielded a black tarry mass. Each lot was taken up in 900 ml. of hot ethanol, mixed with 1000 ml. of hot water containing 35 g. of lead acetate and 6 ml. of acetic acid and allowed to stand overnight. The clarified solution was filtered and the filtrate concentration to 300–500 ml. on the water-pump. The residue was thoroughly extracted with chloroform. The chloroform layer was dried, filtered and concentrated *in vacuo;* yield of brown-green gum 515 g. (from 117 lb. of dried plant). The material crystallized on standing. A portion, wt. 150 g., was suspended in 50 ml. of ethyl acetate and 35 ml. of petroleum ether was added. There precipitated 55 g. of crude parthenin. The filtrate was concentrated *in vacuo* and chromatographed over 220 g. of alumina (Alcoa F-20). Benzene, benzene–chloroform and chloroform eluted 64.5 g. of gum which on treatment with acetone and petroleum ether yielded an additional 17 g. of crude parthenin. One recrystallization from water furnished material, m.p. 157–161°, which was sufficiently pure for further work; total yield 175 g. (0.33%). The average yield of material collected in the summer of 1957 was only 0.14%. Further recrystallizations from water raised the m.p. to 163–166°, $[\alpha]^{25}D$ + 7.02° (chloroform, *c*, 2.71); infrared bands at 3450, 1755, 1718, 1655 and 1592 cm.$^{-1}$; λ_{max} 215 and 340 mμ (ϵ 15100 and 22).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; mol. wt., 262. Found: C, 68.80; H, 7.13; C-methyl, 1.36 moles; mol. wt. (Rast), 270.

Parthenin, dihydroisoparthenin and tetrahydroparthenin did not consume periodic acid in neutral solution. A solution of 0.262 g. of parthenin in 50 ml. of warm water was treated with 10 ml. of 0.1 *N* sodium hydroxide solution and then with 10 ml. of 0.1 *N* sodium periodate. After 18 hours, there was consumed 9.8 ml. of periodic acid equivalent to one mole. Under similar circumstances, dihydroparthenin and tetrahydroparthenin did not consume any periodic acid, even after 3 days. Parthenin, dihydroisoparthenin and tetrahydroparthenin consumed no lead tetraacetate over a period of three days.

Parthenin, dihydroisoparthenin and tetrahydroparthenin were recovered when treated with acetic anhydride in pyridine. Chromic oxide treatment of dihydroisoparthenin and tetrahydroparthenin at room temperature resulted in recovery of starting material. Treatment of parthenin with *p*-toluenesulfonyl chloride in pyridine also resulted in recovery of starting material.

The pyrazoline of parthenin was prepared by treating a suspension of 130 mg. of parthenin in 100 ml. of absolute ether with diazomethane prepared from 350 mg. of nitrosomethyl urea. After 1 day, another portion of diazomethane was added. After 3 days in the refrigerator, the solvent was removed and the residue was triturated with ether. Crystallization from ether gave colorless crystals, m.p. 146–148°.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 62.85; H, 6.55; N, 9.43.

Hydrogenation of Parthenin.—A solution of 2.80 g. of parthenin in 100 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure with 5% palladium-on-charcoal. The hydrogen uptake corresponded to 1.2 moles. The solvent was removed and the residue crystallized from 30 ml. of benzene; yield 1.75 g. of dihydroisoparthenin, m.p. 192–194°. The m.p. was raised to 200–201° by further crystallization from acetone–petroleum ether or by chromatography, $[\alpha]^{25}D$ + 16.6 ($CHCl_3$, *c* 0.783), λ_{max} 220 and 261 mμ (ϵ 14000 and 70); infrared bands at 3450, 1745 (double strength) and 1668 cm.$^{-1}$. The substance gave a positive Zimmermann test.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.24; H, 7.24.

The benzene mother liquors were concentrated and chromatographed over alumina. Chloroform and chloroform–ether (20:1) yielded tetrahydroparthenin, wt. 0.78 g., m.p. 136–139°. The m.p. was raised to 142–144° by recrystallization from water; $[\alpha]^{25}D$ +78.4° ($CHCl_3$, *c* 0.651), λ_{max} 277 mμ (ϵ 71); infrared bands at 3450 and (in acetonitrile) 1760 and 1742 cm.$^{-1}$. The substance gave a positive Zimmermann test.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.44; H, 8.26; C-methyl, 2.53 moles.

Hydrogenation of 0.5 g. of parthenin with platinum oxide in acetic acid gave a gum which was chromatographed over alumina. Benzene–chloroform eluted 0.15 g. of a gum which could not be crystallized even after rechromatography. Chloroform eluted 0.32 g. of crude dihydroisoparthenin.

Dihydroisoparthenin was not reduced further at low pressure with platinum oxide or palladium.

Dihydroisoparthenin and tetrahydroparthenin gave crystalline derivatives with dinitrophenylhydrazine, but satisfactory analyses could not be obtained.

Ozonolysis of 263 mg. of dihydroparthenin in chloroform at room temperature followed by steam distillation gave 0.53 meq. of volatile acid. Color tests for formic acid were negative, for acetic acid positive. The latter was identified by preparation of the *p*-bromophenacyl ester.

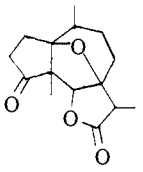
In an attempt to acetylate dihydroisoparthenin, a mixture of 0.2 g. (1.2 ml.) of acetic anhydride and 0.2 g. of anhydrous sodium acetate was refluxed for 6 hours, cooled, poured into ice-water and extracted with chloroform. Evaporation yielded in a gum which was taken up in benzene and chromatographed over alumina. Elution with benzene–chloroform (7:3) gave crystalline fractions, two of which melted sharply in the range 167–179°, wt. 25 mg. Recrystallization from ethyl acetate–petroleum ether gave plates, m.p. 169–171°, infrared bands at 1770 (γ-lactone) and 1740 cm.$^{-1}$ (cyclopentanone), but no –OH and double bond absorption. Since the ultraviolet spectrum had no high-intensity absorption and the substance was isomeric with dihydroisoparthenin, structure XXVI is a likely possibility.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.20; H, 7.47.

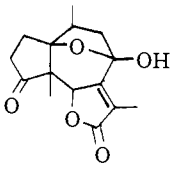
In an attempt to introduce an oxygen function at C_6, a solution of 0.264 g. of IV in 10 ml. of acetic acid containing 0.1 g. of sodium acetate was treated with 0.5 g. of chromium

(39a) The stereochemistry of II at C_{11} (less stable configuration) is left undefined at present, in view of the misleading argument concerning C_{11} in the santonin series based on conformational analysis, D. H. R. Barton, T. Miki, J. T. Pinhey and R. J. Wells, *Proc. Chem. Soc.*, 97 (1962); M. Nakazaki and H. Arakawa, *ibid.*, 151 (1962).

(40) M.p.'s are uncorrected. Ultraviolet spectra were determined by Mrs. M. Osmond on a Cary model 14 spectrophotometer in 95% ethanol solution. Analyses by Drs. Weiler and Strauss, Oxford, England, and Dr. F. Pascher, Bonn, Germany. Infrared spectra were run in chloroform solution, unless otherwise specified.



XXVI



XXVII

oxide at 56–58°. After 4 hours at this temperature, the excess oxidant was decomposed with methanol and water and the solvents were removed *in vacuo*. The residue was dissolved in water and extracted with ether and methylene dichloride. The combined organic layers were dried and concentrated. The residual oil was chromatographed on neutral alumina. Fractions 18–20 (20:1 chloroform–methanol) gave 20 mg. of white prisms, m.p. 210–213° from acetone–petroleum ether; infrared spectrum (KBr disk) 3400, 1745 (double strength) with shoulder at 1699 and 1655 cm.$^{-1}$, ultraviolet spectrum λ_{max} 219 and 282 mμ (ϵ 22,200 and 220). Structure XXVII, perhaps in equilibrium with the keto form, is suggested.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.63; H, 6.52; O, 28.75. Found: C, 64.43; H, 6.94; O, 28.14.

Dehydrogenation of Parthenin.—Parthenin, wt. 1.0 g., was reduced with 0.6 g. of lithium aluminum hydride in 400 ml. of ether by the Soxhlet method. Three days were required. Excess reagent was decomposed with wet ether and 50 ml. of saturated sodium sulfate solution was added to decompose the complex. The ether layer was dried and concentrated *in vacuo*. The residual oil, wt. 0.5 g., could not be induced to crystallize. Dehydrogenation of this material without solvent gave no azulenes. The gum resulting from a second run was suspended in a petroleum fraction, b.p. 300°, and dehydrogenated with 1 g. of 5% palladium-on-charcoal in a nitrogen atmosphere. The mixture was diluted with petroleum ether and extracted with 89% phosphoric acid. The acid extract was washed with petroleum ether and diluted with water (blue color). The azulenes were extracted with petroleum ether and chromatographed over 5 g. of alumina. Two fractions were obtained. The less polar azulene was blue-violet, wt. 3 mg., λ_{max} 530–535 mμ, trinitrobenzene complex m.p. 155–157°, mixed m.p. with linderazulene trinitrobenzene complex 130–143°.[41] The amount of purified material was insufficient for analysis. The more polar blue azulene, wt. 10 mg., had a visible spectrum identical with that of artemazulene, m.p. of trinitrobenzene complex 185–188°, mixed m.p. with an authentic sample[42] 187–190°. The infrared spectra were also identical.

Ozonolysis of Parthenin. (A).—A solution of 100 mg. of parthenin in 25 ml. of acetic acid was ozonized at 10° until a solution of potassium iodide became highly colored. Water was added and the mixture was steam distilled, the distillate being collected in two ice-cooled flasks containing a saturated solution of dimedone in water. There precipitated 41 mg. (37%) of the dimedone derivative of formaldehyde, m.p. 187–188°, undepressed on admixture of an authentic sample.

The water solution remaining in the distilling flask was thoroughly extracted with ether. The organic extract was shaken with sodium bicarbonate solution, the latter was neutralized, extracted with ether and the acid fraction dried. Removal of ether gave an oil which could not be induced to crystallize and did not give an iodoform test.

(B).—A solution of 7.0 g. of parthenin in 150 ml. of methanol was ozonized at −78° until a potassium iodide solution was deeply colored. A colorless solid precipitated, wt. 6.6 g. One recrystallization from acetone–ether gave 4.5 g. of norparthenone (III), m.p. 187–188° dec., $[\alpha]^{24}D$ −42.2° ($CHCl_3$, *c* 2.02); λ_{max} 35 mμ (ϵ 12000), infrared bands at 1760 and 1720 cm.$^{-1}$ (shoulder at 1700) (in acetonitrile), broad bonded -OH, 1735 (broad, consisting of at least two carbonyls, shoulder at 1700) and at 1670 cm.$^{-1}$. The Tollens test and ferric chloride tests were positive and a solution in hot water was acidic.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10; neut. equiv., 264. Found: C, 63.62; H, 5.88; neut. equiv., 262.

A solution of 0.142 g. of norparthenone in 10 ml. of 0.1 *N* periodic acid neutralized with sodium bicarbonate consumed 5.3 ml. of periodic acid, equivalent to 1.05 moles.

A solution of 0.142 g. of norparthenone in 10 ml. of 0.1 *N* sodium hydroxide solution was treated with 15 ml. of 0.1 *N* periodic acid solution neutralized with 15 ml. of 0.1 *N* sodium hydroxide. After 7 hours, the consumption of periodic acid was 11.1 ml., equivalent to 2.2 moles.

(C).—Ozonolysis of parthenin in methanol or in ethyl acetate at room temperature followed by catalytic reduction (palladium–charcoal), removal of solvent and trituration of the residue with ethyl acetate gave crystals, m.p. 99–102°, identified as oxalic acid dihydrate. The mother liquors were chromatographed over 25 g. of alumina. Benzene–acetone and acetone eluted an oil; acetone–ethanol and ethanol gave a solid, m.p. 139–142° after crystallization from benzene–acetone, λ_{max} 208 and 320 mμ, infrared bands at 3450 (strength indicative of at least two hydroxyls) and 1700 cm.$^{-1}$. The ferric chloride and iodoform tests were negative.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.34; H, 8.20. Found: C, 67.50; H, 7.73.

Oxalic acid was also obtained by further ozonolysis of norparthenone in acetic acid at room temperature.

Benzoylnorparthenone.—A solution of 0.1 g. of norparthenone in 1 ml. of pyridine was treated with 0.3 g. of benzoyl chloride. After 1 day at room temperature the mixture had solidified. It was decomposed with ice-water and extracted with ether. The ether extract was washed with dilute sodium bicarbonate solution and water, dried and concentrated. The residue crystallized; wt. 0.07 g. Crystallization from acetone–petroleum ether gave fine needles, m.p. 216–217°; infrared bands at 3700, 1770, 1750, 1710 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.09; H, 5.99. Found: C, 68.36; H, 6.06.

Oxidation of Norparthenone.—A solution of 9 g. of potassium permanganate in 450 ml. of water was added dropwise with stirring to 1.4 g. of norparthenone in 130 ml. of 5% sulfuric acid solution over a period of 5 hr. Manganese dioxide was reduced with sulfur dioxide and the clear solution concentrated to 70 ml. at reduced pressure, saturated with sodium sulfate and extracted with ether. The ether extract was washed with sodium sulfate solution, dried and concentrated. The residual oil, wt. 0.54 g., was chromatographed over acid-washed alumina. Fractions 1–5 (25 ml. of 9:1 benzene–methanol) eluted an oil which crystallized on standing. It was dissolved in acetone and treated with cyclohexylamine. The precipitate, wt. 1.07 g., m.p. 167–171°, was recrystallized from ethanol–acetone. Decomposition with dilute hydrochloric acid followed by extraction with ether, washing of the ether extract with sodium sulfate solution, drying and removal of solvent yielded 0.2 g. of *S*(+)-α-methyl glutaric acid which after two crystallizations from ethyl acetate–petroleum ether melted at 80–82°, $[\alpha]^{24}D$ +20° (95% ethanol, *c* 0.45), m.p. undepressed on admixture of an authentic sample of m.p. 78–80°, $[\alpha]^{24}D$ +18° (*c* 1.24), infrared spectra (KBr disk) undistinguishable.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.19; H, 6.92.

A solution of 180 mg. of dihydronorparthenone (XI) in 8 ml. of pyridine was treated with 3.5 ml. of thionyl chloride under cooling. The mixture was decomposed by pouring onto ice and extracted with chloroform. The chloroform extract was washed, dried and concentrated. The residual gum, wt. 0.08 g., solidified on standing and was recrystallized from ether–petroleum ether and benzene–petroleum ether. The product, m.p. 206–207°, gave a positive ferric chloride test, $[\alpha]^{24}D$ −91.9° ($CHCl_3$, *c* 0.62), λ_{max} 242 mμ (ϵ 10700), shoulder at 285 (ϵ 125), high intensity at 200 mμ (ϵ 7500); infrared bands at 3600 (OH), 1755 (γ-lactone and cyclopentanone) 1700 (double bond) and 1600 (weak, double band). There was a weak band at 905 cm.$^{-1}$, but not in the 880–895 cm.$^{-1}$ region.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.80; H, 6.83.

This compound was also obtained more simply by reduction of 0.5 g. of norparthenone with zinc and acetic acid. After removal of solvent at reduced pressure, the residue was taken up in benzene and chromatographed over alu-

(41) We wish to thank Dr. K. Takeda for an authentic sample of linderazulene.

(42) Kindly supplied by Dr. V. Herout.

mina. Benzene–chloroform eluted a solid, wt. 0.2 g., which after crystallization from acetone–petroleum ether, benzene and ether–petroleum ether melted at 211–212° undepressed on admixture of the first sample. The infrared spectra were identical.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.69; H, 6.40.

Anhydroparthenin (V).—A solution of 7.0 g. of parthenin in 45 ml. of anhydrous formic acid was refluxed for 12 hours. The brown solution was diluted with water and thoroughly extracted with chloroform. Removal of solvent from the washed and dried chloroform extract gave a yellow oil which was dissolved in hot methyl acetate. A small amount of petroleum ether was added and the solution was set aside in the refrigerator. There precipitated 5.0 g. of anhydroparthenin, m.p. 122–124°. The filtrate was concentrated and the residue chromatographed over alumina. Benzene–chloroform (9:1) eluted 1.45 g. of solid which furnished an additional 0.65 g. of anhydroparthenin. Crystallization from benzene–petroleum ether raised the m.p. to 125–126°, $[\alpha]_D$ −121° ($CHCl_3$, *c* 1.21), λ_{max} 210 and 296 mμ (ε 14300 and 12500), shifted to 308 mμ (11500) in dilute alkali; infrared bands at 1758, 1700, 1650 and 1550 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 74.08; H, 6.74.

Ozonolysis of 100 mg. of anhydroparthenin in acetic acid at room temperature gave 50 mg. (41%) of the dimedone derivative of formaldehyde.

Anhydronorparthenone (VI).—Dehydration of 300 mg. of norparthenone with 10 ml. of formic acid in the usual manner gave, after recrystallization from benzene–acetone, 195 mg. of anhydronorparthenone, m.p. 258–260° dec., $[\alpha]^{24}D$ −99.2 ($CHCl_3$, *c* 0.34), λ_{max} 240 and 298 mμ (ε 9000 and 10900); infrared bands at 1755 (γ-lactone), 1695 (cyclopentenone), 1640 and 1560 cm.$^{-1}$ (double bonds), as well as −OH absorption.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.60; H, 5.82.

11-Epitetrahydroparthenin (X).—(a) A mixture of 2.0 g. of coronopilin (IX),[20] m.p. 171–176°, 12 g. of zinc and 100 ml. of acetic acid was refluxed for 24 hours with vigorous stirring. The filtered solution was concentrated to dryness *in vacuo*. The residue was recrystallized several times with severe losses from acetone–ether–petroleum ether, m.p. 189–191°, infrared bands (chloroform) at 3600 and 3480 cm.$^{-1}$ and, in acetonitrile, 1770 (γ-lactone) and 1743 cm.$^{-1}$ (cyclopentanone, $(\alpha)^{25}D$ +24.90° ($CHCl_3$, *C*, 2.294). The fingerprint region was different from that of tetrahydroparthenin.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.65; H, 8.37; O, 24.08.

(b) A mixture of 1.07 g. of II, 0.11 g. of potassium carbonate and 20 ml. of dry xylene was refluxed with stirring for 17 hours, cooled, diluted with water, and thoroughly extracted with ether. The organic extracts were washed with water and dried. Concentration at reduced pressure yielded 0.79 g. of gum (mainly X on the basis of its infrared spectrum) which was chromatographed over acid-washed alumina. Chloroform eluted 0.38 g. of crude X which after repeated crystallization melted at 186–190°, mixture m.p. with authentic X, 186–190°.

The aqueous layer and washings were combined, acidified, and extracted with ether. Evaporation yielded 0.17 g. of crude II which after recrystallization from ether–petroleum ether melted at 143–147°, mixture m.p. with authentic 143–145°.

Reduction of Parthenin with Zinc and Acetic Acid.—A solution of 2.0 g. of parthenin in 100 ml. of acetic acid was refluxed with 15 g. of zinc dust for 20 hours. The solution was cooled, filtered, evaporated *in vacuo*, taken up in benzene, washed thoroughly with water, dried and chromatographed over alumina. Fractions 1–3 (benzene and benzene containing 5 and 10% chloroform) eluted a solid which was recrystallized twice from acetone–petroleum ether, yield 0.4 g. of colorless needles (VIII), m.p. 141–143°. The analytical sample melted at 142–145°, $[\alpha]^{25}D$ −31.7 ($CHCl_3$, *c* 2.71), λ_{max} 295 mμ (ε 25), high intensity at 206 mμ (ε 1750); infrared bands at 1760 (combination of γ-lactone and β,γ-unsaturated cyclopentanone), 1610 (weak, double bond) and 1405 cm.$^{-1}$ $\left(\text{-CH}_2\text{-C(=O)-}\right)$.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 7.74.

The substance did not undergo isomerization on treatment with potassium carbonate in xylene. Attempts at catalytic hydrogenation at low pressure (palladium–charcoal in ethanol) were unsuccessful. The substance depressed the m.p. of XXI. Ozonolysis in chloroform at 0° followed by steam distillation furnished no volatile aldehyde or ketone.

In a subsequent run, the yield of crude product, m.p. 135–138°, from 2.0 g. or parthenin was 1.1 g.

Reduction of Anhydroparthenin with Zinc and Acetic Acid.—A solution of 1 g. of anhydroparthenin in 50 ml. of acetic acid was refluxed for 24 hours with 5 g. of zinc dust. The solid crude product was chromatographed over alumina, solvent and eluent chloroform–acetone (2:1). The first two fractions of 25 ml. each gave 0.4 g. of crystalline material (XVI) which was recrystallized from acetone–benzene; m.p. 258–262° dec. The analytical sample decomposed at 260–265°, $[\alpha]^{24}D$ −22.1° ($CHCl_3$, *c* 1.09), λ_{max} 206 and 290 mμ (ε 13600 and 45), infrared band at 1750 (double strength) and 1650 (rel. weak and broad, double bonds).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.83; H, 7.29.

Ozonolysis of 0.15 g. of this substance in chloroform at room temperature (without reductive work-up) gave a 23% yield of formaldehyde, isolated as the methone derivative.

A solution of 0.15 g. of the preceding compound in 30 ml. of dioxane was hydrogenated with 25 mg. of 10% palladium-on-charcoal. Hydrogen uptake corresponded to 1.2 moles. The solvent was removed and the residue was chromatographed over alumina (solvent and eluent chloroform). The eluate was concentrated and the residue (XVII), wt. 0.1 g., was recrystallized from acetone–petroleum ether, m.p. 287–289° dec., $[\alpha]^{23}D$ −86.1° ($CHCl_3$, *c* 0.99), λ_{max} 206 mμ (shoulder 295 mμ), ε 9400 (60), infrared bands at 1755 (combination of γ-lactone and cyclopentanone) and 1675 (double bond rel. strong).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.68; H, 7.84.

Hydrogenation of Anhydroparthenin. (A).—A solution of 2.5 g. of anhydroparthenin in 30 ml. of ethanol was reduced with 0.5 g. of 5% palladium-on-charcoal in a Parr hydrogenator at 4 atmospheres. After 4 hr. the solution was filtered, the solvent removed, the residue taken up in petroleum ether and benzene and chromatographed over alumina. Fractions 1–3 (50 ml. each of 15%, 20% and 30% benzene) were combined and recrystallized from petroleum ether; yield 20 mg. of hexahydroanhydroparthenin A (XVIIIa), m.p. 104–106°, λ_{max} 293 mμ (ε 40), infrared bands at 1760 (γ-lactone) and 1730 cm.$^{-1}$ (cyclopentanone).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 71.97; H, 8.86. Found: C, 72.26; H, 9.12.

Fraction 4 (40% benzene) was an oil. Fractions 5–11 (50 ml. each of 50%, 63% and 77% benzene, benzene, 2%, 5% and 10% chloroform), were combined; yield of crude tetrahydroambrosin (XVIIIb) 0.5 g. Recrystallization from acetone–petroleum ether gave crystals, m.p. 123–125°, $[\alpha]^{25}D$ + 78° ($CHCl_3$, *c* 0.705), λ_{max} 290 mμ (ε 93), infrared bands at 1755 and 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.03; H, 9.03.

A mixed m.p. determination with authentic tetrahydroambrosin (lit. m.p. 128°) and comparison of the infrared spectra showed that the two samples were identical.

Fractions 14–16 (50 ml. of 70% chloroform and two 50-ml. portions of chloroform) yielded 200 mg. of crude tetrahydroanhydroparthenin A (XIX) which was recrystallized from petroleum ether–acetone; m.p. 161–162.5°, $[\alpha]^{24}D$ +23.2° ($CHCl_3$, *c* 0.732), λ_{max} 218 and 300 mμ (ε 10500 and 31), infrared bonds at 1755 (combination of γ-lactone and cyclopentanone) and 1675 (double bond). This substance is undoubtedly identical with dihydroambrosin (lit. m.p. 165°).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.23.

Elution of the column with chloroform–ethanol gave no residue. The column was extracted with 1% sodium bicarbonate solution, the extract washed with chloroform, acidified and extracted again with chloroform. Evaporation of the chloroform followed by recrystallization from petroleum, ether–acetone yielded an additional 110 mg. of hexahydroanhydroparthenin A, m.p. 98–104°.

In one early run, there was obtained in the early eluates, an isomeric tetrahydroanhydroparthenin (XIX), m.p. 80–82°, infrared bands at 1735 (broad, shoulder near 1730), shoulder at 285 mμ in the ultraviolet.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.66; H, 8.46.

Subsequent fractions eluted dihydroisoambrosin and tetrahydroambrosin.

(B).—A solution of 485 mg. of anhydroparthenin in 100 ml. of ethanol was reduced with 40 mg. of 5% palladium-on-charcoal at atmospheric pressure in a semi-micro hydrogenation apparatus. The hydrogen uptake corresponded to 1.5 moles. The solution was filtered and evaporated and the residue chromatographed over 18 g. of alumina. Fractions 1–6 (25 ml. of petroleum ether containing increasing proportions of benzene) yielded no residue or ill-defined solids, fractions 7–10 (benzene and benzene containing 5 and 10% chloroform) gave dihydroanhydroparthenin A (XXI), m.p. 143–145° from petroleum ether–acetone, $[\alpha]^{25}D$ −40.2° ($CHCl_3$, *c* 0.274), λ_{max} 218 and 288 mμ (ε 13200 and 86), infrared bands at 1750 (combination of γ-lactone and cyclopentanone) and 1670 (double bond) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.18; H, 7.33.

Further elution of the column with benzene-chloroform (20–100%) gave dihydroisoambrosin.

In a subsequent run using 0.4 g. of anhydroparthenin in 40 ml. of ethanol the reduction was stopped after the absorption of 1 mole of hydrogen. The solution was filtered and evaporated. The residue was chromatographed over acid-washed alumina. Fractions 1–3 (25 ml. each of benzene–petroleum ether 7:3) yielded a gum whch crystallized on standing. Several recrystallizations from ether–petroleum ether furnished 25 mg. of α-hydroanhydroparthenin A, m.p. 142–144°. Fractions 4–6 (same eluent) did not crystallize. Fraction 7 (25 ml. of benzene) and fractions 8–11 (chloroform–benzene, 3:7) and chloroform gave a gum which solidified and was recrystallized several times from ether–petroleum ether and acetone–petroleum ether; yield 0.11 g., m.p. 187–188°, $[\alpha]^{26}D$ −231.5° ($CHCl_3$, *c* 0.549); infrared bands at 1770 (γ-lactone), 1695 (cyclopentenone), 1645 and 1600 (double bonds); λ_{max} 298 and 205 mμ (13000 and 8700), shoulder near 220 mμ (ε 6100). Analysis and spectrum showed this to be dihydroanhydroparthenin B (XXII).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.35. Found: C, 72.66; H, 7.34.

Anhydrotetrahydroparthenin (XII).—A solution of 200 mg. of tetrahydroparthenin in pyridine was mixed, under cooling, with 4 ml. of thionyl chloride. After 15 minutes the mixture was decomposed with ice. The precipitate was filtered (wt. 35 mg.) and recrystallized from ligroin; m.p. 112–113.5°, $[\alpha]^{25}D$ +36.5° ($CHCl_3$, *c* 2.90), λ_{max} 285 mμ (ε 40), high intensity at 208 mμ (ε 1260) indicative of a trisubstituted double bond, infrared bands at 1765 and 1750 cm.$^{-1}$ (γ-lactone and β,γ-unsaturated cyclopentanone).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.48; H, 8.24.

Dehydration of tetrahydroparthenin with formic acid gave a poorer yield of the anhydro derivative.

Anhydrodihydroisoparthenin (XIIIa) and (XIIIb).—A solution of 1 g. of dihydroisoparthenin in 20 ml. of formic acid was refluxed for 11 hours and worked up in the usual manner. The product (XIIIa) was recrystallized from acetone–petroleum ether; yield 0.4 g., m.p. 154–156°, $[\alpha]^{25}D$ +7.17° ($CHCl_3$, *c* 1.256), λ_{max} 217 mμ (ε 11100) with a shoulder hear 295 mμ (ε 104). The intensity at 200 mμ (13000) corresponded to the presence of an additional highly-substituted double bond. The infrared spectrum had bands at 1752 (γ-lactone and cyclopentanone) and 1675 cm.$^{-1}$ (conjugated double bond).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.22; H, 7.70.

Dehydration of dihydroisoparthenin, wt. 0.4 g., with thionyl chloride in pyridine, followed by the usual work-up, gave an oil which solidified. This material was chromatographed over alumina; the benzene–chloroform (8-2) eluate crystallized but did not melt sharply. Another chromatographic purification gave a solid which was recrystallized from ether–petroleum ether; m.p. 152–155°, wt. 0.05 g., infrared spectrum superimposable on that of the material obtained with formic acid; no depression of mixed m.p. Two attempted acetylations of dihydroisoparthenin in acetic anhydride with a few drops of boron trifluoride etherate gave a complex mixture from which a 10% yield of XIIIa was isolated by chromatography. In another run, however, using 0.2 g. of dihydroisoparthenin, 4 ml. of acetic anhydride and 4 drops of catalyst, the first three fractions (benzene–chloroform 1:1) yielded 100 mg. of a solid which after recrystallization from ethyl acetate–petroleum ether melted at 132–134° and had the properties of an isomeric anhydrodihydroisoparthenin (XIIIb), infrared bands at 1750 (double strength) and 1660 cm.$^{-1}$ (double bonds). (Note, however, the formation of XXVI in a run using acetic anhydride–sodium acetate.)

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.17; H, 7.33.

Hydrogenation of Anhydronorparthenone.—A solution of 0.6 g. of anhydronorparthenone (VI) in 30 ml. of ethanol was reduced catalytically (5% palladium-on-charcoal) at atmospheric pressure. The hydrogen uptake corresponded to 2.0 moles. Filtration and evaporation at reduced pressure yielded a gum which solidified on standing. It was taken up in benzene–chloroform (1:3) and chromatographed over acid-washed alumina. Fractions 4–11 (eluent 1:3 benzene-chloroform, 30-ml. portions) gave crystals of tetrahydroanhydronorparthenone melting in the range 160–175°, wt. 0.09 g., which were recrystallized from acetone–petroleum ether and ethyl acetate and then melted at 182–184°, $[\alpha]^{24}D$ 66.4° ($CHCl_3$, *c* 0.80), pos. ferric chloride test, λ_{max} 240 mμ (ε 10600), shoulder at 285 mμ (ε 120), high intensity at 205 mμ.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.77; H, 6.82.

Fractions 12–23 (four 30-ml. portions of 3:1 chloroform–benzene, five 30-ml. portions of 9:1 chloroform-benzene and two 30-ml. portions of chloroform) yielded 0.265 g. of gum containing crystals. These were recrystallized from acetone–ether, washed with a little ether to remove gum and again crystallized from ether–petroleum ether; m.p. of tetrahydroanhydronorparthenone B 199–201°, $[\alpha]^{24}D$ −39° ($CHCl_3$, *c* 0.51), pos. ferric chloride test, λ_{max} 241 mμ (ε 11000); infrared bands at 36000, 1755 and 1700.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.10; H, 6.92.

Tetrahydronorparthenone A (0.2 g. crude) gave a thioketal which was obtained in solid form after chromatography over alumina. The oily acetone–acetic acid eluates were dissolved in ethanol and diluted with water. The white solid was recrystallized from acetone–petroleum ether; m.p. 202°.

Anal. Calcd. for $C_{16}H_{22}O_3S_2$: C, 58.84; H, 6.79. Found: C, 58.75; H, 6.75.

Rotatory Dispersion Curves.—Dihydroisoparthenin[37] (in dioxane, *c* 0.125): $(\alpha)_{700}$ + 16, $(\alpha)_{589}$ + 21°, $(\alpha)_{325}$ + 615°, $(\alpha)_{290}$ − 565°, $(\alpha)_{280}$ − 400° (best reading).

Tetrahydroparthenin[37] (in dioxane, *c* 0.2135): $(\alpha)_{700}$ +47°, $(\alpha)_{589}$ + 96°, $(\alpha)_{315}$ + 1725°, $(\alpha)_{300}$ +873° (best reading).

Coronopilin[38] (in dioxane, *c* 1.204): $(\alpha)_{700}$ −17°, $(\alpha)_{589}$ −17°, $(\alpha)_{317}$ + 1070, $(\alpha)_{260}$ −1678° (no minimum).

Tetrahydroambrosin[36] (in dioxane, *c* 1.355): $(\alpha)_{700}$ + 181°, $(\alpha)_{589}$ + 225°, $(\alpha)_{370}$ + 3650, $(\alpha)_{276}$ −3940°, $(\alpha)_{250}$ − 3590°, $(\alpha)_{235}$ − 4490°.