EtOAc). The less polar component was identified as starting material on the basis of nmr evidence (side-chain olefinic proton δ 5.7, 17-acetate at δ 2.19) and tlc. Fractional crystallization from MeOH gave the more polar component **11**: yield 990 mg; mp 208–211°; uv max (EtOH) 216 mμ (ϵ 9150); ir ($CHCl_3$) 1650 cm^{-1}; nmr ($CDCl_3$) 2.02 (s, 3 H, acetate, C-3 H), 4.45 (m, 1 H, C-3 H), 5.40 (m, 1 H, C-5 olefinic H), 5.60 (m, 1 H, C-17 H), and 5.94 (m, 1 H, side-chain olefinic H, *cis*). (The preceding values are for the D_2O run, since the carboxyl proton overlapped the last three signals at δ 5.40.)

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.95; H, 7.96.

Hydrogenation of 3β,17β-Diacetoxy-5α-androst-1-en-2-ylacetic Acid (8).—A solution containing 503 mg of **8** and 50 mg of platinum oxide in 250 ml of EtOH was hydrogenated at 1 atm pressure until hydrogen uptake diminished. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ether to give 92 mg of recovered starting material. The mother liquors were concentrated, and the residue was recrystallized from ether to give 21 mg of a crystalline solid, mp 214–215°. The nmr spectrum of this compound showed angular methyl signals at 46 and 53 cps and two acetate singlets at δ 1.92 and 2.02. The C-3 and C-17 protons appeared at δ 4.92 and 4.10 (m), respectively.

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.32; H, 8.85.

Base-Catalyzed Isomerization of 8.—A solution containing 787 mg of **8** and 787 mg of NaOH in 100 ml of MeOH and 100 ml of H_2O was refluxed for 3 hr and then allowed to cool to room temperature. The solvent was evaporated to half its volume, 200 ml of H_2O was added, and the mixture was acidified with dilute HCl. The precipitate was collected and recrystallized from MeOH–Et_2O to give **12**: yield 483 mg; mp 217–219°; nmr ($CDCl_3$ –DMSO) δ 1.12 (s, 3 H, C-19 CH_3) and 3.63 (m, 1 H, C-17 H).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.12; H, 9.54.

17β-Hydroxy-5α-androstan-2α-ylacetic Acid 3-ξ-Methoxylactol (13).—A solution containing 400 mg of **12** and 30 mg of TsOH in 60 ml of MeOH was allowed to stand at room temperature. Tlc indicated that most of the starting material had been converted into a less polar product. The reaction mixture was poured into 300 ml of H_2O, extracted twice with 500 ml of Et_2O, and dried ($MgSO_4$). Evaporation of solvent and recrystallization from ether gave the crystalline solid **13**: yield 245 mg; mp 205–206°; ir ($CDCl_3$) 1770 cm^{-1}; nmr ($CDCl_3$) δ 0.72 (s, 3 H, C-18 CH_3), 0.84 (s, 3 H, C-19 CH_3), 3.32 (s, 3 H, OCH_3), and 3.6 (m, 1 H, C-17 H).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.71; H, 9.36.

Registry No.—**2**, 20712-22-5; **4**, 22287-21-4; **6**, 22287-22-5; **8**, 22287-23-6; **9**, 20708-74-1; **11**, 22287-06-5; **12**, 22287-07-6; **13**, 22287-08-7.

Acknowledgments.—The authors wish to acknowledge the fine technical assistance of Mr. Lawrence E. Patterson, Dr. William Hargrove and associates (physico-chemical data), Mr. George Maciak and associates (microanalyses), and Mrs. Nancy Cone for their help in preparation of this article.

The Structure of Damsinic Acid, a New Sesquiterpene from *Ambrosia ambrosioides* (Cav.) Payne[1]

RAYMOND W. DOSKOTCH AND CHARLES D. HUFFORD[2]

Division of Natural Products Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received July 14, 1969

The structure of a new sesquiterpene, damsinic acid, from *Ambrosia ambrosioides* (Cav.) Payne has been shown to be **2**. Pyrazoline derivatives of damsin (**1**) and damsinic acid were assigned structures based on CD and nmr studies.

We recently reported the isolation and identification of the pseudoguaianolide damsin (**1**)[3] as the cytotoxic principle of *Ambrosia ambrosioides* (Cav.) Payne. There was obtained in addition an inactive substance, mp 112–113°, which analyzed for $C_{15}H_{22}O_3$ and contained a carboxyl and carbonyl function, a secondary and tertiary methyl group, and an exocyclic methylene, as established by physical methods (uv, ir, nmr, and mass spectrum).[3] The structure of the compound, damsinic acid, has been determined as **2** from the following evidence. The nmr peaks for compounds reported in this paper are given in Table I.

The nmr spectrum of damsinic acid indicated an α-substituted acrylic acid side chain which was confirmed by (a) the spectral changes observed on hydrogenation to the dihydro acid **3**, (b) the formation of the methyl ester **4** with 1 mol of diazomethane and two isomeric pyrazoline esters **5a** and **5b** with excess reagent,[4] and (c) the liberation of acid **6** and formaldehyde on ozonolysis. The nature of the bicyclic system was established by dehydration followed by dehydrogenation of the diol **7** to chamazulene (**8**). The azulene product was not consonant with the requirement of one tertiary methyl group in the starting materials. Apparently a 1,2-methyl shift had occurred during aromatization, a migration already reported for other pseudoguaianolides.[5,6]

The location of the ketone group in the five-membered ring was suggested by the ir band at 1735 cm^{-1}. The C-4 position was preferred, in keeping with the previously isolated pseudoguaianolides from *Ambrosia*.[7] The incorporation of two deuterium atoms into the dihydro acid **3** according to the conditions of Komae and Nigam[8] established the assignment.

(1) Antitumor Agents. III. Previous paper: R. W. Doskotch and F. S. El-Feraly, *J. Pharm. Sci.*, in press. This investigation was supported by Public Health Service Research Grants CA-08133 from the National Cancer Institute and FR-00328 from Special Research Resources for purchase of the nmr spectrometer (Varian A-60A).

(2) National Institutes of Health Predoctoral Fellow, 1967–1968.

(3) R. W. Doskotch and C. D. Hufford, *J. Pharm. Sci.*, **58**, 186 (1969).

(4) P. G. Deuel and T. A. Geissman, *J. Amer. Chem. Soc.*, **79**, 3778 (1957); T. A. Geissman and R. Mukherjee, *J. Org. Chem.*, **33**, 656 (1968).

(5) (a) H. Abu-Shady and T. O. Soine, *J. Amer. Pharm. Assoc.*, **42**, 387 (1953); (b) L. Bernardi and G. Büchi, *Experientia*, **13**, 466 (1967).

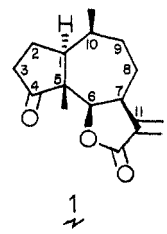
(6) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Amer. Chem. Soc.*, **84**, 2601 (1962).

(7) (a) W. Herz in "Recent Advances in Phytochemistry," T. J. Mabry, Ed., Appleton-Century-Crofts, New York, N. Y., 1968, p 229; (b) J. Romo and A. Romo de Vivar in "Progress in the Chemistry of Organic Natural Products," Vol. 25, L. Zechmeister, Ed., Springer-Verlag, New York, N. Y., 1967, pp 90–130.

(8) H. Komae and I. C. Nigam, *J. Org. Chem.*, **33**, 1771 (1968).

TABLE I

NMR PEAKS OF DAMSINIC ACID AND ITS DERIVATIVES[a]



1

Compd	C-5 CH_3	C-10 CH_3	C-11 CH_3	H-6	H-7	C-11 $=CH_2$	Miscellaneous
2	1.06	1.05 d (7.0)			2.83 m	5.63 6.27	11.23 (COOH)
3	1.01	1.02 d (6.6)	1.18 d (6.7)				10.47 (COOH)
4	1.04	1.05 d (7.0)				5.51 6.08	3.74 ($COOCH_3$)
5a	0.99	1.03 d (7)			2.9 m		3.77 ($COOCH_3$) 4.6 m[b] (CH_2CH_2N)
5b	1.02	1.03 d (7)			2.6 m		3.77 ($COOCH_3$) 4.5 m[b] (CH_2CH_2N)
6	1.01	1.02 d (6.3)			2.73 m		9.91 (COOH)
7	0.88	0.83 d (7)[c]	0.93 d (7)[c]				2.1 m[d] (OH)
9	1.17	1.16 d (6.8)	1.11 d (7.2)	4.54 d (5.4)			2.88 dq (7.2, 8.0,[e] H_{11})
11	1.12	1.09 d (6.8)[c]	1.24 d (6.7)[c]	4.44 d (8.2)			
12	0.98	0.95 d (7)[c]	0.97 d (7)[c]				3.4 m[d] (OH)
13	1.07	1.05 d (6.4)					3.15 d (4.8,[f] NCH_3) 7.4 m[d] (NH)
14	1.03	1.04 d (6.2)					2.78 d (4.7,[f] NCH_3) 5.51 m[d] (NH)
15a	1.27	1.15 d (7.3)		5.45 d (6.2)			4.75 m[b] (CH_2CH_2N)
15b	1.47	1.15 d (7.1)		4.79 d (9.1)	2.96 m		4.7 m[b] (CH_2CH_2N)

[a] Chemical shifts (δ, parts per million) were taken in $CDCl_3$ on Varian A-60A or HA100 instruments with TMS as internal standard; singlets are unmarked, d = doublet, m = multiplet with center given, q = quartet; coupling constants are given in parentheses in hertz. [b] The value recorded is the center of the multiplet of overlapping peaks for the four protons. [c] Values in row may be interchanged. [d] Lost in D_2O. [e] Two overlapping quartets forming five peaks are clearly visible in the 100-MHz spectrum. [f] Collapses to a singlet in D_2O.

The stereochemistry of the ring junction in damsinic acid was assigned as *trans* in keeping with other pseudoguaianolides[7b] on the basis of comparison of its ORD and CD curves with those of damsin. Both gave positive Cotton-effect curves with the first extremum at 315 mμ (a 37.7°) and 327 mμ (a 39.9°), respectively. The assignment for damsin derivatives was originally based on ORD studies[6] in comparison with appropriate steroid models.[9] The absolute stereochemistry follows from ambrosin (2,3-dehydrodamsin), whose 3-bromo derivative was subjected to X-ray analysis.[10]

Attempts to convert both damsin (**1**) and damsinic acid (**2**) into a common product, such as pseudoguaiane, for determining the configuration at C-7 and C-10 failed, but our findings are of interest to be recorded. Catalytic hydrogenation of damsin (**1**) under both heterogeneous[3,5] (Pd on charcoal) and homogeneous[11] [tris(triphenylphosphine)rhodium chloride] conditions results in poor yields of dihydrodamsin (**9**); the main product is dihydroisoambrosin (isodamsin, **10**). However, catalytic heterogeneous hydrogenation under alkaline conditions in which the lactone is opened gave no isodamsin, but instead gave dihydrodamsin (**9**) and 11-epidihydrodamsin (**11**).[12] The latter substance was prepared by Romo, *et al.*,[13] by Raney nickel desulfurization of the addition product of damsin and toluenethiol. Lithium aluminum hydride reduction of dihydrodamsin (**9**) gave the triol **12**, whose mesylate on reduction with the same reagent gave products of S–O bond cleavage. Similar products were obtained from the mesylate and tosylate of the diol **7**. Complete replacement of the tosylate by iodide in diol **7** ditosylate was likewise unsuccessful.

The stereochemistry at C-7 was established by CD studies.[14] In particular the curves of N-methyl thionamides have been shown to be related to the asymmetry at the α carbon,[16] and the corresponding derivative **13** of bisnordamsinic acid (**6**) was prepared *via* the amide **14**. The CD curve of **13** showed a weak negative band at 338 mμ ([θ] −200°) for the n → π^* absorption, the "optically active" band of the thione group. Since a negative Cotton effect in these deriva-

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

(10) M. T. Emerson, W. Herz, C. N. Caughlan and R. W. Witters, *Tetrahedron Lett.*, 6151 (1966).

(11) J. F. Biellman and M. J. Jung, *J. Amer. Chem. Soc.*, **90**, 1673 (1968).

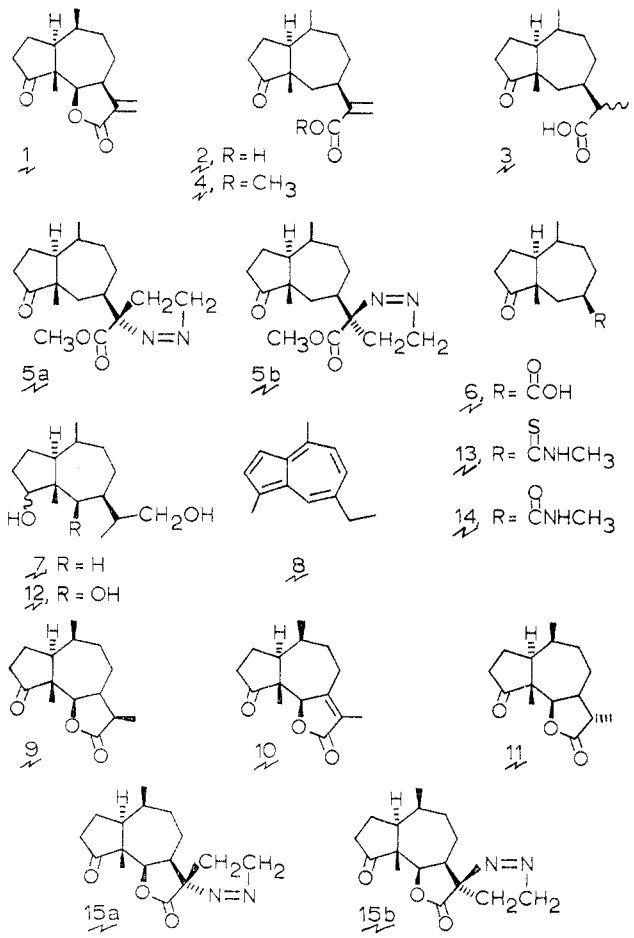
(12) Undoubtedly, dihydrodamsinic acid (**3**) is a mixture of the two C-11 epimers, but these are not separated by the paper chromatographic systems employed.

(13) J. Romo, A. Romo de Vivar, A. Velez, and E. Urbina, *Can. J. Chem.*, **46**, 1535 (1968).

(14) Damsinic acid (**2**) shows a weak Cotton-effect peak at 245 mμ ([θ] +300°) in addition to that for the ketone at 295 mμ ([θ] +3750°). This weak peak has been ascribed to the n → π^* transition of the carbonyl of α,β-unsaturated carboxylic acids by U. Weiss and H. Ziffer [*J. Org. Chem.*, **28**, 1248 (1963)], but no example of acids with exocyclic methylenes were studied. Damsin (**1**) likewise exhibits a weak peak at 240 mμ ([θ] +420°); the n → π^* absorption of the lactone carbonyl and its sign is a function not only of the C-7 configuration but also depends on the ring fusion (*cis* or *trans*) and the position of ring closure (C-6 or C-8).[15] Conclusions reached in the case of **2** would reflect the rotomer population distribution and not simply the stereochemistry at C-7.

(15) T. G. Waddell, W. Stocklin, and T. A. Geissman, *Tetrahedron Lett.*, 1313 (1969).

(16) J. V. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 51 (1965).



tives where only hydrocarbon substituents are at the asymmetric center corresponds to an *R* configuration,[17] the substituent at C-7 in damsinic acid can be said to have the β designation. The asymmetry at C-7 in damsinic acid and damsin is therefore the same. Two additional Cotton-effect peaks of high intensity were observed at 296 (n $\rightarrow$ π^* of the ketone) and 259 mμ ($\pi \rightarrow \pi^*$ of the thione).

The configuration at C-10 remained to be determined, and paucity of starting material prevented an extended study. However, on biogenetic grounds the methyl group very likely is β, since all of the sesquiterpenes isolated to date from *Ambrosia* spp. have this configuration.[7a]

Paper chromatographic examination of the reaction mixture from damsinic acid and diazomethane revealed the presence of two pyrazoline esters, **5a** and **5b**, which were purified by partition column chromatography. Both exhibit spectral properties (ir, nmr) consistent with C-11 epimeric structures. Their CD curves are shown in Figure 1, and the stereochemical assignment was made with the aid of the CD results from the pyrazolines of damsin.

The major pyrazoline (**15a**) of damsin readily crystallizes from the reaction mixture, but the minor isomer **15b** was obtained only after partition chromatography of the mother liquor residue. The product ratio was *ca.* 17:1, with the major isomer taken to be that formed by 1,3-dipolar addition of diazomethane from the sterically less hindered α side. The structure assignments were supported by the following spectroscopic data.

(17) R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

The chemical-shift differences of the C-5 methyl and the H-6 and H-7 protons in the nmr spectra of the two substances were primary evidence for the choices. Dreiding models of the two isomers indicated that, in **15a**, H-6 is situated along the longitudinal axis of the diazene (–N=N–) group. By analogy with an ethylene group, a deshielding would be expected along that axis. The H-6 proton was found in **15a** at δ 5.45, while in **15b** it appeared at δ 4.79. A similar but less intense deshielding exists for the H-7 proton (δ 2.69) in **15a** but not in **15b** (δ 2.96). If the diazene group is responsible for these chemical-shift differences, a similar effect should be observed for the C-5 methyl, but not for the reverse isomers. This indeed is the case, for one finds the peak at δ 1.47 in **15b** and at δ 1.27 in **15a**. Both isomers gave identical mass spectra.

The CD curves for the damsin pyrazolines are shown in Figure 1. It was therefore possible to make the stereochemical assignment for the methyl damsinate pyrazolines on the basis of these curves.[18]

Experimental Section

Melting points taken in capillaries were determined with a Thomas–Hoover apparatus and are uncorrected. Elemental analyses were performed by Mr. Joseph F. Alicino. Infrared spectra were taken in chloroform on a Perkin-Elmer Model 237 or 257 spectrophotometer, and ultraviolet spectra were obtained in methanol on a Cary Model 15 spectrophotometer. The nmr spectra were measured in deuteriochloroform on a Varian A-60A instrument with TMS as internal standard; chemical shifts are reported in δ (parts per million) units. The ORD, CD, and optical rotation values were determined in methanol on a Jasco Model ORD/UV-5 spectropolarimeter. Gas chromatography (glpc) was performed with an F & M Model 500 instrument equipped with a flame-ionization detector on 10% silicone gum rubber (SE-30) on Chromosorb W (80–100 mesh). Mass spectra were obtained on an AEI MS-9 double-focusing instrument and samples were introduced *via* the direct inlet probe.

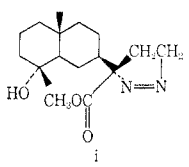
Damsinic Acid (**2**).—The detailed isolation procedure from *Ambrosia ambrosioides* and the physical properties are published.[3] The substance was obtained in a yield of 0.01% of the dried plant material. The nmr peaks are given in Table I.

Dihydrodamsinic Acid (**3**).—A solution of 500 mg of **2** in 5 ml of ethanol was added to 170 mg of 5% palladium on charcoal in 50 ml of ethanol. Hydrogen uptake at room temperature and 1-atm pressure ceased after 1 molar equiv was absorbed. The catalyst was removed by filtration and the residue from the filtrate was crystallized from hexane to give 250 mg of **3**: mp 108–109°; $[\alpha]^{25}D$ +121° (*c* 0.27, CH_3OH); uv max 290 mμ (ϵ 35); ir 1735 (cyclopentanone C=O) and 1700 cm^{-1} (carboxylic acid C=O).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.63.

Methyl Damsinate (**4**).—A solution of 38 mg of **2** in 2 ml of ether was treated with 1 equiv of ethereal diazomethane for 10

(18) After this study was completed, a report appeared by M. Suchy, L. Dolejs, V. Herout, F. Sorm, G. Snatzke, and J. Himmelreich, *Collect. Czech Chem. Commun.*, **34**, 229 (1969), and G. Snatzke, *Riechst. Aromen, Koerperpflegem.*, **19**, 1 (1969), on the CD properties of a number of sesquiterpene lactones and their pyrazolines, including that of the major damsin pyrazoline derivative **15a**. Of interest to us was that only one pyrazoline from methyl iliciate (i) was recorded. These authors indicate that the sign of the Cotton-effect curve at *ca.* 330 mμ for the pyrazoline may be used to assist in determining the stereochemistry of the lactone junctions (*e.g.*, jurineolide). In light of our findings, we would caution against the indiscriminate extension of this method to cases where one pyrazoline derivative does not constitute the predominant reaction product.



i

min. Removal of the ether and crystallization from aqueous ethanol gave 33 mg of **4**: mp 48–49°; $[\alpha]^{25}D$ +96° (*c* 0.32, CH_3OH); uv max 285 mμ (ε 50); ir 1740 (cyclopentanone C=O) and 1720 and 1626 cm^{-1} (α,β-unsaturated ester).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.60; H, 8.88.

Pyrazolines of Methyl Damsinate (5a and b).—A solution of 200 mg of **2** in 3 ml of ether was treated with a fourfold excess of ethereal diazomethane for 4 days at 5°. Removal of the solvent gave an amorphous residue that indicated two compounds (Zimmerman's reagent) on examination by paper chromatography [$HCONH_2$ and 5:1 C_6H_6–petroleum ether (bp 60–70°)], R_f 0.71 and 0.56.[19] The mixture was separated on a partition column (20 g of Celite 545[20]) employing the same solvent system. The fraction with R_f 0.71 (91 mg) crystallized from isopropyl ether to give 54 mg of **5a** as colorless needles: mp 130–131°; $[\alpha]^{25}D$ −6° (*c* 0.28, CH_3OH); uv max 324 mμ (ε 173); ir 1740 (double intensity, cyclopentanone and ester C=O) and 1560 cm^{-1} (N=N); ORD Φ_{400} −1240°, Φ_{335} −10,600° (trough), Φ_{327} 0°, Φ_{309} +14,200° (peak), Φ_{287} 0°, Φ_{250} −3420° (trough), Φ_{230} 0°, and Φ_{210} +1980° (last reading); CD Θ_{327} −15,600° (peak), Θ_{308} 0°, Θ_{295} +7300°, Θ_{260} +1340° (shoulder), Θ_{243} 0°, Θ_{234} −2080°, and Θ_{220} 0°; mass spectrum (70 eV) *m/e* (rel intensity) 278.1880 (25) [calcd for $C_{17}H_{26}O_3$ (M − N_2) 278.1882], 260 (16), 246 (17), 222 (15), 201 (14), 190 (15), 175 (17), 161 (24), 137 (44), and 121 (34).

Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.75; H, 8.26; N, 9.48.

The column fraction with R_f 0.56 (163 mg) contained compound **5b**, a colorless, viscous oil that resisted crystallization and had the following properties: $[\alpha]^{25}D$ +167° (*c* 0.32, CH_3OH); uv max 324 mμ (ε 199); ir 1740 (double intensity, cyclopentanone and ester C=O) and 1560 cm^{-1} (N=N); ORD Φ_{400} +2300°, Φ_{334} +13,500° (peak), Φ_{320} 0°, Φ_{308} −3370° (shoulder), Φ_{280} −5970° (trough), Φ_{240} −995° (peak), and Φ_{210} −7350° (last reading); CD Θ_{326} +15,000° (peak), Θ_{300} +7450° (shoulder), Θ_{260} +505° (shoulder), and Θ_{234} +3540° (peak); mass spectrum (70 eV) *m/e* (rel intensity) 278.1879 (20) [calcd for $C_{17}H_{26}O_3$ (M − N_2) 278.1882]. The rest of the spectrum was indistinguishable from that of **5a**.

Ozonolysis of 2. A.—Compound **2** (200 mg) in 10 ml of methanol was treated with oxygen containing *ca.* 2% ozone at −78° for 15 min. The reaction mixture was steam distilled and the distillate was collected in a saturated alcoholic solution of dimedone. The solution deposited the dimedone derivative of formaldehyde, yield 18 mg, mp 189–190°, undepressed on admixture with an authentic sample.

B.—A solution of 100 mg of **2** in 10 ml of methanol was ozonized as before and the solvent was evaporated at reduced pressure. The ozonide was decomposed at room temperature by the addition of 2 ml of H_2O and occasionally stirred. After 1 hr the H_2O was removed by evaporation and the residue was chromatographed on a small partition column (20 g of Celite 545, $HCONH_2$ and C_6H_6 as solvents). Crystallization from C_6H_6–hexane yielded 49 mg of bisnordamsinic acid (**6**): mp 130–131°; $[\alpha]^{25}D$ +110° (*c* 0.27, CH_3OH); uv max 296 mμ (ε 30); ir 1735 (cyclopentanone C=O) and 1705 cm^{-1} (carboxylic acid C=O).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.98; H, 8.72.

$LiAlH_4$ Reduction of 3.—A solution of 500 mg of **3** in 20 ml of tetrahydrofuran was treated with 600 mg of $LiAlH_4$ under reflux for 24 hr. The reaction mixture was cooled, the excess $LiAlH_4$ was decomposed with ethyl acetate, and 3 ml of H_2O was added. The mixture was filtered, the gel was washed with $CHCl_3$, and the combined filtrate and wash were dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from C_6H_6–hexane gave 368 mg of the diol **7**: mp 119–120°; $[\alpha]^{25}D$ +54° (*c* 0.86, CH_3OH); ir 3600 and 3490 cm^{-1} (free and associated OH) and no carbonyl bands.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.73; H, 11.87.

The oily dimesylate was prepared in the usual manner. The ir spectrum showed no OH absorption, but peaks were present at 1350 and 1170 cm^{-1} (S=O stretching). An amorphous ditosylate was similarly prepared, ir 1595 (Ar) and 1355 and 1175 cm^{-1} (S=O stretching). Both derivatives were treated with $LiAlH_4$ in tetrahydrofuran under reflux for 24 hr, resulting in a mixture showing in the ir OH bands but no S=O stretching peaks. Heating the ditosylate with NaI in acetone at 100° in a sealed tube resulted in recovery of material with tosylate groups (ir).

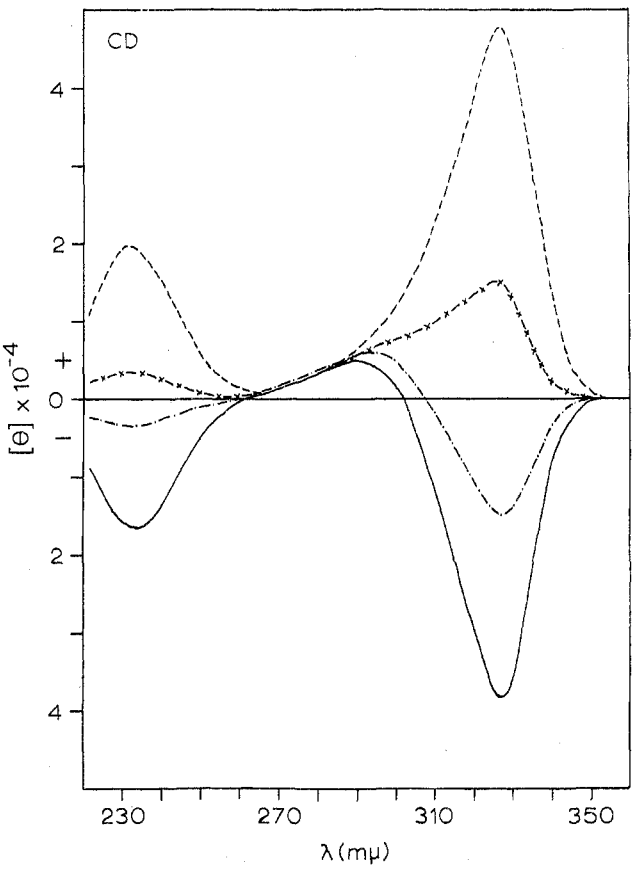


Figure 1.—Circular dichroism curves for methyl damsinate pyrazolines **5a** (-·-·-·-·-) and **5b** (-×-×-×-×) and damsin pyrazolines **15a** (——) and **15b** (- - - -).

Conversion of 7 into Chamazulene (8).—A 49-mg sample of **7** in 1 ml of anhydrous pyridine was treated with 0.05 ml of $SOCl_2$ for 2 hr at room temperature. The reaction mixture was poured into 5 ml of water and extracted with ether. The ether extract was washed with 3 *N* HCl, 5% $NaHCO_3$, and water and dried (Na_2SO_4). The residue (46 mg) left after evaporation of solvent showed no OH bands in the ir and was thoroughly mixed with 35 mg of 10% palladium on charcoal in a hard-glass test tube. The tube was heated at 320–330° for 1 min and showed a blue vapor. The cooled reaction mixture was extracted with hexane and after removal of the hexane gave a blue-green residue (24 mg). Purification of the residue by preparative tlc (silica gel G, 9:1 *n*-hexane–C_6H_6) resulted in 2 mg of a blue oil which formed a 1,3,5-trinitrobenzene adduct, mp 129–131°. The uv spectrum was identical with that of an authentic sample of the TNB adduct of chamazulene (**8**).[21] The regenerated azulenes had superimposable uv spectra and identical R_f values (0.53) on tlc (silica gel G, 9:1 *n*-hexane–C_6H_6). In this system guaiazulene had R_f 0.60.

Deuterium Studies on 3.—Sodium metal (125 mg) was added to 1 ml of D_2O. After dissolution, 12 mg of **3** was added and the solution was refluxed for 10 hr. The cooled reaction mixture was acidified with D_2SO_4 and extracted with ether. The combined ether layer was evaporated to dryness, and the residue was dissolved in 2 ml of ethanol, evaporated again, and crystallized from *n*-hexane. The crystalline product (7 mg) was subjected to deuterium-exchange conditions and purification once again.

(19) Reference 3 gives procedures for the paper chromatographic and partition column separations.

(20) A diatomaceous earth from Johns-Manville Corp., New York, N. Y.

(21) Isolated from Chamomile Oil "German," a generous gift from Fritzsche Brothers, Inc., by adsorption chromatography on activity I neutral alumina with *n*-hexane as solvent. The blue band that was collected readily formed the TNB adduct, mp 129–130.5°.[22]

(22) E. Guenther and D. Althausen, "The Essential Oils," Vol. II, D. Van Nostrand Co., New York, N. Y., 1949, pp 132, 133.

The molecular ion of the deuterated product appeared at *m/e* 254, indicating an uptake of two deuterium atoms.

Hydrogenation of Damsin (1) under Alkaline Conditions.—A 546-mg sample of 1 was warmed in 15 ml of 0.1 *N* NaOH on a steam bath to affect lactone ring opening as evidenced by solution forming. The cooled solution was added to a suspension of 300 mg of 5% palladium on charcoal in 40 ml of ethanol containing 2 ml of 0.1 *N* NaOH and hydrogenated. After 10 hr at room temperature and atmospheric pressure, hydrogen uptake ceased. The catalyst was removed by filtration and the ethanol was evaporated from the filtrate at reduced pressure, diluted with 10 ml of H_2O, acidified with HCl, and extracted with $CHCl_3$. The dried (Na_2SO_4) $CHCl_3$-extract residue (550 mg), on paper chromatographic examination (2:1 C_6H_6–hexane and $HCONH_2$) showed two spots with R_f 0.60 and 0.45 (Zimmerman's reagent). A partition column[19] (100 g of Celite 545) employing the same solvent system separated the mixture. The R_f 0.60 band gave 276 mg of tetrahydroambrosin (dihydrodamsin, **9**) from *n*-hexane: mp 126–127° (lit.[5a] mp 128°); $[\alpha]^{25}D$ +66° (*c* 0.27, CH_3OH); ir 1770 (γ-lactone C=O) and 1740 cm^{-1} (cyclopentanone C=O).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.17; H, 9.14.

The band with R_f 0.45 gave from isopropyl ether 66 mg of 11-epitetrahydroambrosin (11-epidihydrodamsin, **11**): mp 116–117° (lit.[13] mp 115°); ir 1770 (γ-lactone C=O) and 1740 cm^{-1} (cyclopentanone C=O). The R_f of damsin in the solvent system employed is also 0.45.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.18; H, 9.08.

$LiAlH_4$ Reduction of 9.—A solution of 185 mg of **9** in 20 ml of tetrahydrofuran was treated with 300 mg of $LiAlH_4$ under reflux for 24 hr. After cooling, the excess reducing agent was decomposed with ethyl acetate followed by the addition of 2 ml of H_2O. The mixture was filtered, the gel was washed with $CHCl_3$, and the wash and filtrate were dried (Na_2SO_4). The residue from the $CHCl_3$ solution crystallized from isopropyl ether to give 100 mg of the triol **12**: mp 139–140°; $[\alpha]^{25}D$ +23° (*c* 0.33, CH_3OH); ir 3600 and 3350 cm^{-1} (OH).

Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.28; H, 10.69.

The trimesylate of the triol **12** was prepared in the usual manner, giving a heavy oil lacking OH absorption in the ir but showing peaks at 1330 and 1160 cm^{-1} (S=O stretching). Reduction of the trimesylate with $LiAlH_4$ under reflux for 24 hr in tetrahydrofuran gave a mixture that lacked the S=O absorption in the ir and showed peaks in the OH region.

N-Methylthionbisnordamsinamide (13).—A 30-mg sample of **6** was dissolved in 1 ml of dry C_6H_6, and 0.15 ml of $(COCl)_2$ was added. The reaction proceeded at room temperature for 8 hr and then the solvent and excess reagent were evaporated at reduced pressure. The oily acid chloride was redissolved in dry C_6H_6 and excess anhydrous CH_3NH_2 was bubbled in. After 10 min at room temperature the reaction solution was extracted with dilute base and H_2O. The dried (Na_2SO_4) C_6H_6 solution on evaporation yielded 16 mg of the amide **14** as an oil: homogeneous on tlc and paper chromatogaphic analysis; ir 3455 (NH), 1733 (ketone C=O), and 1665 and 1525 cm^{-1} (amide C=O).

The amide **14** (16 mg) in 1 ml of xylene was treated with 12 mg of sulfurated potash and 10 mg of phosphorus pentasulfide according to the method of Burakevich and Djerassi.[16] The reaction residue was purified twice by tlc (silica gel G, 4:1 C_6H_6–EtOAc), and the eluted band (R_f 0.20) gave the thioamide **13** (7 mg): homogeneous on further tlc and glpc;[23] the mass spectrum (70 eV) *m/e* (rel intensity) 253.1499 (51) (calcd for $C_{14}H_{23}NOS$ *m/e* 253.1500), 238 (15), 220 (28), 204 (12), and 102 (100, C_4H_8NS); CD Θ_{335} −206°, Θ_{297} +4000°, and Θ_{260} +6300°.

Pyrazolines of Damsin (15a and b).—To 329 mg of **1** dissolved in 20 ml of ether, excess ethereal diazomethane was added; the mixture was kept at 5° for 24 hr. The solvent and excess reagent were allowed to evaporate and the residue was crystallized from acetone–hexane to give 218 mg of pyrazoline **15a**: mp 133–135° dec; uv max 323 mμ (ε 204); ir 1770 (γ-lactone C=O), 1740 (cyclopentanone C=O), and 1560 cm^{-1} (N=N); mass spectrum (70 eV) *m/e* (rel intensity) 262.1550 (4) [calcd for $C_{16}H_{22}O_3$ (M − N_2) 262.1569], 247.1333 (100) (calcd for $C_{15}H_{19}O_3$ 247.1334), 229 (6), 205 (5), 137 (21), 109 (16), and 97 (32). The mother liquors showed on paper chromatography (C_6H_6–$HCONH_2$, Zimmerman's reagent) an additional substance at R_f 0.54. The major product had R_f 0.65. Employing the same solvent system in a partition column[19] gave the minor pyrazoline **15b**, which crystallized (15 mg) from acetone–hexane: mp 146–148° dec; uv max 327 mμ (ε 275); ir 1770 (γ-lactone C=O), 1740 (cyclopentane C=O), and 1555 cm^{-1} (N=N); mass spectrum (70 eV) *m/e* (rel intensity) 262.1564 (6) [calcd for $C_{16}H_{22}O_3$ (M − N_2) 262.1569], 247.1335 (100), 229 (6), 205 (5), 137 (24), 109 (20), and 97 (34). The mass spectra for the two isomers were indistinguishable.

Registry No.—**2**, 22844-19-5; **3**, 22922-35-6; **4**, 22844-20-8; **5a**, 22844-31-1; **5b**, 22844-21-9; **6**, 22844-22-0; **7**, 22844-23-1; **9**, 21848-56-6; **11**, 19908-71-5; **12**, 22844-26-4; **13**, 22844-27-5; **14**, 22844-28-6; **15a**, 22844-29-7; **15b**, 22844-30-0.

Acknowledgment.—We thank Dr. Rodger L. Foltz of Battelle Memorial Institute for the mass spectra.

(23) Less than 2% impurity was detected. On a 4 ft × 0.25 in. column at a temperature of 200° and carrier gas flow rate (He) at 45 ml/min, the retention time for the thionamide was 5.7 min.