was redissolved in hexane and filtered through alumina to give 0.051 g (41%) of **20**, identical with that described in part A.

19-Norabieta-8,11,13-trien-7-one (16).—The hydrocarbon was oxidized as described above in the preparation of the 18-norketone. From 0.50 g of starting material there was obtained 0.183 g (33%) of 7-one **16** as a colorless oil: $\lambda_{C=O}$ 5.96 μ; λ_{max} 254 mμ (log ε 4.04) and 302 (3.80); nmr 7.90 (br s, H-14), 1.16 (s, C-10 methyl), and 0.90 ppm (d, $J = 5$ Hz, C-4 methyl). For analysis, the dinitrophenylhydrazone, mp 204–295° from ethanol–ethyl acetate, was prepared.

Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 5.71; N, 12.44. Found: C, 66.42; H, 6.73; N, 12.29.

19-Norabieta-5,8,11,13-tetraen-7-one (23).—To a solution of 1.68 g of methyl 7-oxoabieta-5,8,11,13-tetraen-18-oate (**22**) in 10 ml of diethylene glycol was added 0.60 g of sodium hydroxide and a few drops of water. The reaction mixture was heated at reflux for 18 hr, cooled, diluted with water, and extracted with four portions of hexane. The hexane extracts were washed with water and diluted hydrochloric acid and dried, and the solvent was removed at reduced pressure to give 0.89 g of brown oil. Tlc (silica gel G–benzene) indicated the presence of two compounds, and the mixture was taken up in hexane–benzene (3:1) and chromatographed on alumina. Elution with hexane–benzene (2:1) gave 0.041 g of 19-nor-5β-abieta-8,11,13-trien-7-one (**17**), mp and mmp 100–102°. The more polar hexane–benzene fractions gave 0.173 g of **23** as off-white crystals: mp 65–67°; $\lambda_{C=O}$ 6.03 μ; λ_{max} 256 mμ (log ε 4.08), 266 (sh, 4.00), and 304 (3.34); nmr 8.03 (br s, H-14), 6.30 (d, $J = 1.5$ Hz, H-6), 1.48 (s, C-10 methyl), and 1.19 ppm (d, $J = 6$ Hz, C-4 methyl). This compound was too soluble in common solvents to be satisfactorily recrystallized, and was converted into the dinitrophenylhydrazone, mp 222–223° from ethyl acetate, for analysis. A mixture melting point with the derivative, mp 230–231°, of a ketone assigned this structure previously[3d] was 212–220°.

Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N 12.49. Found: C, 66.68; H, 6.12; N, 12.36.

19-Nor-5β-abieta-8,11,13-trien-7-one (17).—Catalytic hydrogenation (5% rhodium on alumina, methanol, 25 psi) of 0.056 g of **23** gave, after filtration and evaporation of solvent, 0.035 g of brown semisolid. The infrared spectrum of this material indicated that it was a mixture of ketone and alcohol, and tlc (silica gel G–benzene) confirmed this observation. The residue was taken up in hexane–benzene (3:1) and chromatographed on Merck acid-washed alumina. Elution with hexane–benzene (1:1) gave 0.009 g of **17** as white crystals, mp 99–101°, mmp 102–104° with the material obtained previously. Elution with

benzene–methylene chloride (1:1) gave 0.024 g of a mixture of alcohols, which was not investigated further.

Lead Tetraacetate Oxidation of Methyl Dehydroabietate.—The reaction with lead tetraacetate was carried out as described by DuPont.[24] From 2.00 g of ester there was obtained 0.172 g of methyl 7α-acetoxyabieta-8,11,13-trien-18-oate (**24**): mp 160–161° (lit. mp 167°); $\lambda_{C=O}$ 5.80 μ; nmr 5.89 (q, $W_{1/2} = 7$ Hz, H-7), 1.27 (s, C-4 methyl), and 1.18 ppm (s, C-10 methyl). Hydrolysis of this ester afforded the 7α-ol, mp 107–108° (lit.[24] mp 111°). The dark brown, gummy residue, 1.94 g, remaining after removing the crystalline α acetate was taken up in 200 ml of methanol to which was added 8.0 g of potassium hydroxide and 10 ml of water. The reaction mixture was heated at reflux for 2 hr, concentrated to a small volume, and diluted with ether, and the ether extracts were washed with water and dried. After removal of the solvent, there was obtained 0.531 g of a dark brown glass which was taken up in benzene and chromatographed on acid-washed alumina. Elution with benzene gave 0.183 g of colorless oil, which appeared to be a mixture of recovered starting material and elimination products. The methylene chloride fractions afforded 0.176 g of a mixture of 7β (**25**) and 7α-ols (**24**), which by integration of the nmr spectrum contained 63% β isomer. A sample of methyl 7β-hydroxyabieta-8,11,13-trien-18-oate (**25**), prepared by borohydride reduction of the 7 ketone, gave nmr signals at 4.82 (t, $J = 8$ Hz, H-7) and 1.28 ppm (s, C-10 methyl and C-4 methyl). The corresponding acetate has a similar spectrum with H-7 shifted to 6.08 ppm.

The Photochemical Lactolization and Deconjugation of *trans*-Steroidal α,β-Unsaturated Acids

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The photoisomerization of 2-(*trans*-ylideneacetic acid)-17β-hydroxy-5α-androstan-3-one (**1**) was studied and was shown to give 3ξ,17β-dihydroxy-5′(2′H)-oxo-5α-androstano[3,2-*b*]furan (**2**). Irradiation of the corresponding 17-keto-16-(*trans*-ylideneacetic acid)androst-5(6)-en-3β-ol (**5**) gave only *trans–cis* isomerization of the side chain. A shift of the side-chain double bond in 2-(*trans*-ylideneacetic acid)-3β,17β-dihydroxy-5α-androstane diacetate (**7**) to the C-1(2) position was observed when the irradiation was carried out in acetone. This deconjugated acid **8** was characterized by the facile ketonization of its C-3 hydroxyl function in refluxing alkaline solution. Only *trans–cis* isomerization occurred when 16-(*trans*-ylideneacetic acid)-3β,17β-dihydroxyandrost-5(6)-ene diacetate (**10**) was similarly irradiated. Some aspects of the mechanisms of these transformations are discussed.

In the course of the study of general methods for the synthesis of ring-A fused heterocyclic steroids, we became interested in the chemistry of 2-(*trans*-ylideneacetic acid)-17β-hydroxy-5α-androstan-3-one (**1**).[1] The results of our study of the photochemical behavior of this system are reported here.

(1) M. Debono, R. M. Molloy, and L. Patterson, *J. Org. Chem.*, **34**, 3032 (1969).

Irradiation of **1** using ultraviolet light (3550 Å) for 3–4 hr in methanol gave a product with infrared, ultraviolet, and nmr spectra characteristic of the α,β-unsaturated lactol **2**. This compound was found to be identical with the lactol obtained from the acid-catalyzed cyclodehydration of **3**. The lactol was further characterized by its quantitative conversion into the pyridazone **4** with ethanolic hydrazine.[1]
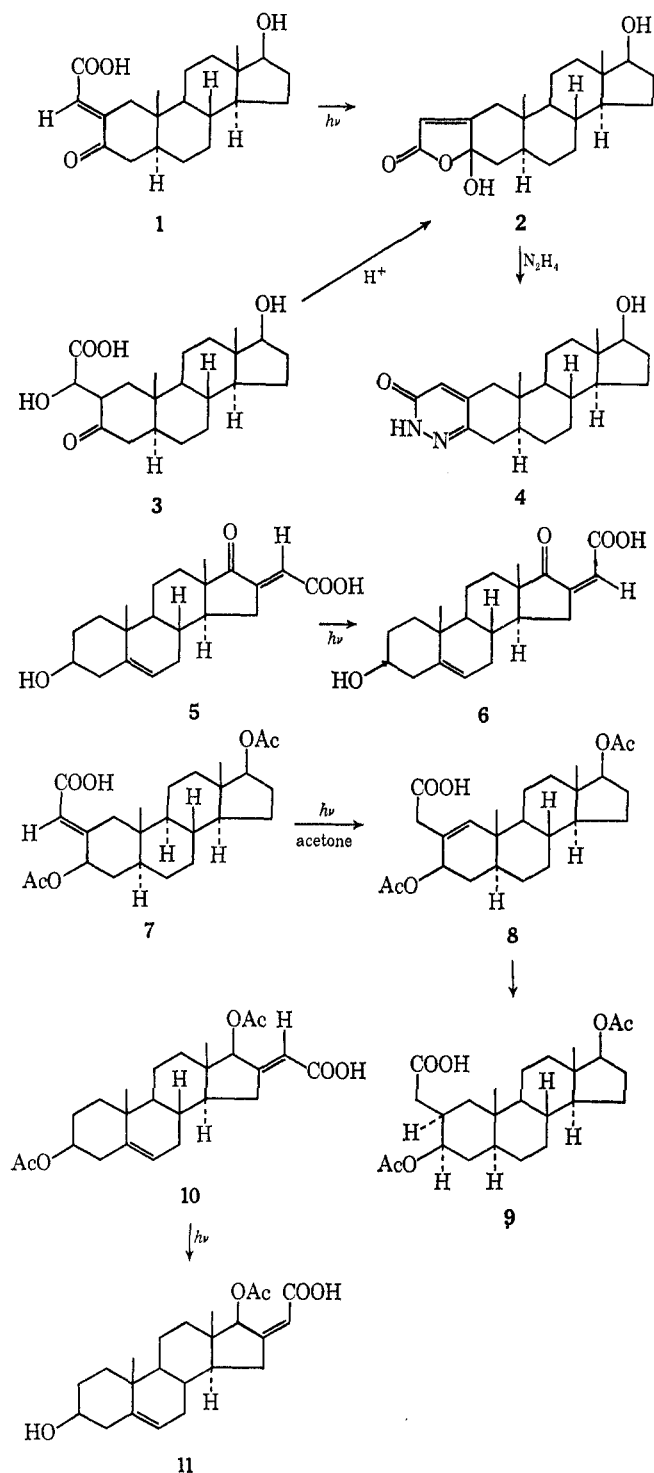
Previous study of the photochemistry of *v*-keto α,β-unsaturated acids has been limited to a report by Lutz concerning the lactolization of aroyl-α- (and β-) methylacrylic acids.[2] Lutz observed that the parent *trans*-benzoylacrylic acid did not cyclize upon irradiation with sunlight, but was isomerized to the open-chain *cis* isomer. Since 1 has alkyl substitution on the side-chain olefinic bond, it follows from Lutz's observation that the cyclic lactol form could be expected in the isomerization of 2.

Photolysis of the 16-ylideneacetic acid 17-keto steroid 5 did not result in lactol formation, but a *trans–*

(2) R. E. Lutz, P. S. Bailey, C. Dien, and J. W. Rinker, *J. Amer. Chem. Soc.*, **75**, 5039 (1953).

cis isomerization of the side chain occurred to give a keto acid, **6**, as evidenced by the shift of the nmr signal for the olefinic proton of **6** from δ 6.3 to 6.1 ppm.[2] This shift corresponds to the removal of the side-chain olefinic proton from the deshielding region about the C-17 carbonyl group. The reaction appeared to reach equilibrium rapidly, and the ratio of *cis* to *trans* isomers approached 1:1 within 6 hr. The factors
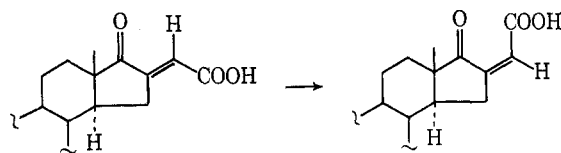
which determine whether the keto group will interact with the side-chain carboxyl group to form a lactol remain obscure. Undoubtedly a number of steric and electronic factors are operative in this transformation.

Conversion of the C-3 carbonyl group of 1 into a 3β-acetoxyl group by reduction and acetylation gave **7**, which was expectedly inert to the irradiation conditions which isomerized 1.[3] However, irradiation of **7** in acetone caused disappearance of the uv and ir bands characteristic of α,β-unsaturated acid (217 mμ and 1650 cm⁻¹, respectively).

The product showed an upfield shift of the olefinic proton signal from δ 5.9 to 5.62 (isolated double bond), where it is partially superimposed on the broad multiplet at δ 5.42 (allylic C-3 proton). In addition, the doublet at δ 4.2, which corresponds to the signal for the equatorial C-1 proton, is no longer present.[4] These data are consistent with the structural assignment **8**, which results from the deconjugation of the olefinic bond to the C-1 position. Shift of the double bond in α,β-unsaturated acids to the β,γ position upon photolysis has been observed by Kropp[5,6] with crotonic acid, while others have observed this with acyclic α,β-unsaturated aldehydes and ketones.[7] This structural assignment was confirmed by hydrogenation to **9**, which had also been obtained from the hydrogenation of **7**.[1] The 2β configuration of the side chain of **9** was assigned on the basis of steric hindrance of the β side favoring hydrogenation from the α side.

The acid **8** was further characterized by its novel behavior under basic conditions.

When a methanolic solution of **8** containing excess base was refluxed for 3 hr, a keto acid was formed. Its nmr spectrum showed disappearance of the olefinic proton, the loss of one proton on carbon bearing oxygen, and a shift of the C-19 methyl from δ 0.78 to 1.12,[8] while the carboxylic proton was still evident (δ 10.13, which disappeared with D₂O). Treatment of **12** with methanolic *p*-toluenesulfonic acid at room temperature

(3) (a) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961); (b) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *ibid.*, **23**, 1832 (1958).

(4) (a) H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965); (b) R. L. Clarke, S. J. Daum, P. E. Shaw, and R. K. Kullnig, *J. Amer. Chem. Soc.*, **88**, 5865 (1966).

(5) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967).

(6) For a recent study on the photoisomerization of ethyl crotonate, see R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968).

(7) For a representative summary of examples, see R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 29.

(8) This chemical-shift position for the C-19 methyl group could be estimated from Zurcher's rules, which are summarized in N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 19.

for 0.5 hr gave methoxylactol **13**. Its infrared spectrum showed a carbonyl band at 1770 cm^{-1}, and its nmr had a signal at δ 3.32 (s, 3 H, CH$_3$O-). The isolation of **13** indicates that the base treatment of **8** resulted in ketonization of the C-3 oxygen function.
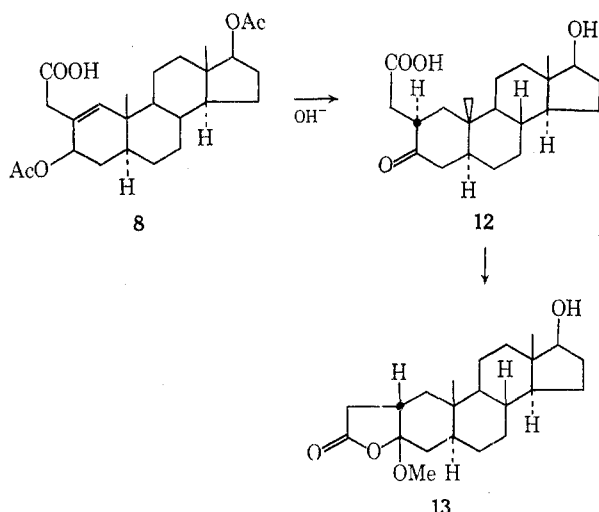
The general features of this transformation are analogous to the work of Elderfield on the transformation of the $\Delta^{\alpha,\beta}$-lactol ring of strophanthidin into the lactolic side chain in isostrophantidin.[9] When the steroidal acid **7** was subjected to base treatment under conditions which isomerized **8**, no ketonization occurred, indicating that β,γ unsaturation, rather than α,β unsaturation, was necessary and that it was unlikely that isomerization of **8** to **7** occurred prior to formation of **12**.

The reaction can be formally represented as a base-catalyzed isomerization of a Δ^1 to a Δ^2 double bond, as shown in the following scheme.
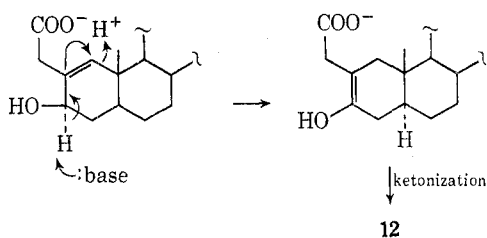
Irradiation of the corresponding 16-*trans*-ylideneacetic acid 3β,17β-dihydroxyandrost-5-ene-3,17-diacetate (**10**) in acetone did not result in deconjugation but resulted solely in the *trans–cis* isomerization of C-16 side chain to give **11**. The product of this transformation retained the ultraviolet chromophore at 217 mμ and the nmr signal for the olefinic proton at δ 5.92, which corresponds to a downfield shift of δ 0.22 from the corresponding signal for the *trans* isomer at δ 5.7.

The difference between the photolyses of **7** and **10** in acetone deserves further comment. Reports concerning the conversion of α,β-unsaturated to β,γ-unsaturated carbonyl compounds propose that γ-hydrogen abstraction occurs through a six-membered transition state, a variation of the Norrish type II

reaction.[10,11] Without speculating about the triplet or singlet character of the excited states involved, it seems reasonable that factors which assist the formation of a six-membered transition state will favor the deconjugation.[12] Models of **7** show that the C-2 side chain and the C-1 equatorial proton can achieve coplanarity, and close approach of the carboxyl carbonyl to the C-1 equatorial proton is possible without much conformational deformation of ring A. These factors would tend to facilitate ν-hydrogen abstraction and isomerization by the mechanism described above. Analogous discussion of the steric factors in **10** leads to the conclusion that the C-15 protons and the C-16 ylideneacetic acid side chain can not achieve coplanarity; therefore, an increased carboxyl–C-15 proton distance results, making abstraction of C-15 protons difficult.

Experimental Section

Melting points are uncorrected. Uv spectra were recorded on a Cary 15 spectrophotometer. Ir spectra were determined on a Perkin-Elmer 21. Nmr spectra were obtained on a Varian HR-60 with TMS as an internal standard. Irradiations were carried out in a Rayonet–Srinivasan–Griffin photochemical reactor under purified nitrogen at 35–40°, using quartz vessels.

Irradiation of 17β-Hydroxy-3-oxo-5α-androstane-$\Delta^{2,\alpha}$-acetic Acid (1).—Irradiation of 1.0 g of **1** in 450 ml of methanol was carried out in a Rayonet Chamber reactor equipped with 3550-Å ultraviolet sources under a stream of nitrogen for 3–4 hr.[1] The reaction mixture was evaporated to dryness under reduced pressure. The residue **2** was recrystallized from EtOH: yield 0.5 g; mp 256–260°; uv max (EtOH) 214 mμ (ϵ 30,000); ir (CHCl$_3$) 1760 and 1640 cm^{-1}; nmr δ 5.86 (br s, 1 H).

The compound was identical in all respects with the compound prepared from **3** by acid dehydration.[1]

Conversion of 3ξ,17β-Dihydroxy-5'(2'H)-oxo-5α-androstano-[3,2-b]furan (2) into the Pyridazone 4.—The lactol **2** (0.30 g) in 10 ml of EtOH was treated with 0.25 ml of hydrazine hydrate and refluxed for 6 hr.[1] Evaporation of solvent and recrystallization of the product from EtOH gave 200 mg, mp 268–270°.

Anal. Calcd for C$_{21}$H$_{30}$N$_2$O$_2$·^{1}/$_2$C$_2$H$_5$OH: C, 72.29; H, 9.10; N, 7.67. Found: C, 72.54; H, 8.84; N, 8.11.

Irradiation of 3β-Hydroxy-17-oxo-androst-5-en-16-ylideneacetic Acid (5).—A solution of 1.00 g of **5** in 500 ml of MeOH was irradiated by the above procedure for 3 hr.[3a] The solvent was removed under reduced pressure, and the product was collected, yield 501 mg. The nmr spectrum showed a 1:1 mixture of *cis* and *trans* keto acids. The *cis* acid could be fractionally crystallized from MeOH: yield 55 mg; mp 180–185°; nmr (CDCl$_3$ and 0.3 ml of DMSO) δ 6.20 (m, 1 H, >C=CHCOOH) and 1.07 and 1.01 (s, 3 H each, 2 angular CH$_3$).

Anal. Calcd for C$_{21}$H$_{28}$O$_4$: C, 73.22; H, 8.19. Found: C, 73.10; H, 8.00.

Photoisomerization of 3β,17β-Diacetoxy-5α-androstan-2-ylideneacetic Acid (7).—The irradiation of **7** (2.5 g) was performed in 500 ml of Me$_2$CO, using the method described above, for 18 hr.[1] The solvent was removed under reduced pressure, and the residue was recrystallized from Et$_2$O–Me$_2$CO mixtures to give **8**: yield 1.35 g (54%); mp 211–213°; nmr (CDCl$_3$) δ 0.8 (s, 3 H, angular CH$_3$), 2.03 (s, 6 H, acetate), 4.6 (br t, 1 H, C-17 H), 5.5 (m, 1 H, C-3 H), 5.6 (s, 1 H, C-1 H), and 10.1 (m, 1 H, COOH).

Anal. Calcd for C$_{25}$H$_{36}$O$_6$: C, 69.42; H, 8.39. Found: C, 69.20; H, 8.42.

When this irradiation was carried out in MeOH, no significant amount of deconjugation occurred, and only starting material was isolated.

Photoisomerization of 3β,17β-Diacetoxyandrost-5-en-16-ylideneacetic Acid (10).—A solution of 2.0 g of **10** in 500 ml of Me$_2$CO was irradiated with 3550-Å ultraviolet light for 6 hr[3a] using the procedures outlined above. Evaporation of solvent gave a mixture which showed two components on tlc (silica gel,

(9) (a) W. D. Paist, E. R. Blout, F. C. Uhle, and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941). (b) For a review of the examples of this phenomenon in the strophanthidin series, see L. F. Fieser and M. Feiser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p 736.

(10) See ref 7, p 73.

(11) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968).

(12) M. J. Jorgenson and L. Gundel, *ibid.*, 4991 (1968).

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$_2$O 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-yl-acetic 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$_2$O 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$_2$O was added, and the mixture was acidified with dilute HCl. The precipitate was collected and recrystallized from

MeOH–Et$_2$O 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-Methoxy-lactol (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$_2$O, extracted twice with 500 ml of Et$_2$O, 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.

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

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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 formalde-

hyde 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.

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(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).

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(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).