with authentic 1,1-dimethyl-4β-isopropyl-*trans*(10β-H)-2-decalone prepared as described below.

A stirred solution of 604 mg of the decalone mixture **12** and **18** in 15 ml of acetic acid was treated with 0.70 ml of 3.88 *M* bromine in acetic acid over 4 min. After stirring an additional 2 min, 70 ml of water was added. The product (795 mg, 97%), a colorless oil, was isolated with ether and hexane.

A mixture of 788 mg of this bromo ketone mixture, 0.80 g of calcium carbonate, and 30 ml of N,N-dimethylacetamide was heated at reflux for 0.5 hr, and the octalone **14** (538 mg, 93%) was isolated as previously described: bp 115° (bath temperature) at 0.3 mm; λ_{max}^{film} 5.99 (C=O), 6.14 (C=C), 7.11, 7.20, 8.54, and 11.26 μ; $\delta_{TMS}^{CCl_4}$ = 5.76 (H-3), 1.19 (1.5 H), 1.14 (1.5 H), 1.05 (6 H), and 0.90 ppm (3 H). These latter peaks must be due to the C-1 *gem*-dimethyl and the nonequivalent methyl groups of the C-4 isopropyl group. Vpc analysis (column C, 220°, 102 cc/min) indicated that the octalone was homogeneous (t_R' 12.3 min).

The **oxime derivative**, mp 131–132.5°, was prepared according to the method of Shriner and Fuson[22] and sublimed (85°, 0.1 mm) after recrystallization from methanol.

Anal. Calcd for $C_{15}H_{25}NO$: C, 76.54; H, 10.71; N, 5.95. Found: C, 76.5; H, 10.7; N, 6.1.

1,1-Dimethyl-4β-isopropyl-*trans*(10β-H)-2-decalone (18).—A 360-mg sample of octalone **14** was stirred with palladium on carbon in 10 ml of absolute ethanol under an atmosphere of hydrogen until the theoretical uptake was complete (1 hr). The product (354 mg) was obtained after the solvent was removed from the filtered reaction mixture. Vpc analysis (column C, 220°, 102 cc/min) revealed peaks at t_R' 7.0 (1%), 8.3 (92%, **18**), 10.2 (2%), and 12.3 min (5% starting octalone **14**). Evaporative distillation removed some of the impurities, affording a sample judged to be 96% decalone **18**: λ_{max}^{film} 5.85 (C=O), 7.11, 7.20, 8.82, 11.48, 12.8, and 13.8 μ.

The **oxime derivative** displayed mp 156.5–157° upon recrystallization from methanol.

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.89; H, 11.47; N, 5.90. Found: C, 75.8; H, 11.6; N, 5.9.

1,1-Dimethyl-4β-phenyl-*trans*(10β-H)-2-decalone (19). A. Addition to 7a.—This reaction was performed using 0.80 g of octalone **7a**, 0.22 g of cupric acetate, and 26.5 ml of 0.68 *M* phenylmagnesium bromide in tetrahydrofuran in the manner described above to give, after evaporative distillation, 1.35 g of partially crystalline material. A small portion of this material was dissolved in benzene for vpc analysis (column C, 220°, 102 cc/min): t_R' 5.2 (3%), 6.0 (14%, biphenyl), and 52 min (83%).

The semicrystalline mass was triturated with heptane and the resulting crystals were dried on adsorbent filter paper. This afforded 537 mg (47%) of decalone **19**: mp 90–98°; $\lambda_{max}^{CCl_4}$ 5.84 (C=O), 6.23 (C=C), 7.20, 7.29, 8.84, and 14.3 μ. Vpc analysis of this material indicated a purity of 99.2%. A 791-mg portion of the mother liquor was chromatographed on 100 g of alumina (Merck). The later benzene fractions afforded an additional 475 mg (41%) of decalone **19**: mp 96–99°; $\delta_{TMS}^{CCl_4}$ = 7.3 (phenyl group), 2.2–2.9 (a complex pattern owing to three hydrogens), 1.08, and 1.15 ppm (C-1 *gem*-dimethyl, two singlets).

The alcoholic material obtained on elution with ether–benzene was not investigated.

An analytical sample, mp 100.5–102°, was obtained by recrystallization from ethyl acetate: λ_{max}^{KBr} 5.90 (CO), 6.23 (C=C), 7.29, 8.83, 9.33, 12.66, 13.16, and 14.21 μ.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.2; H, 9.55.

B. Hydrogenation of 1,1-Dimethyl-4-phenyl-*trans*-3-octal-2-one (15).—A mixture of 110 mg of bromo ketone **20**, 6.0 ml of N,N-dimethylacetamide, and 150 mg of calcium carbonate was heated at reflux for 0.6 hr.[9] The octalone **15** [λ_{max}^{film} 6.00 (C=O), 6.19, 6.34 (C=C), 8.59, 11.25, 12.98, and 14.29 μ] was obtained by extraction with heptane. Hydrogenation over palladium on carbon in ethanol afforded the crude ketone **19** which was treated with chromium trioxide reagent in acetone[23] to oxidize a small amount of alcoholic impurity. Sublimation of the material thus obtained gave 54 mg (64%) of the decalone **19**, mp 93–97°. Vpc analysis (column C, 220°, 102 cc/min) revealed only one peak (t_R' 52.0 min). The infrared spectrum was identical with that of the material prepared according to part A.

3α-Bromo-1,1-dimethyl-4β-phenyl-*trans*(10β-H)-2-decalone (20).—A stirred solution of 212 mg of decalone **19** (mp 90–98°) in 5 ml of acetic acid was treated with 0.22 ml of 3.88 *M* bromine in acetic acid over 4 min. After 1 min, 20 ml of water was added. The bromo ketone was isolated with ether[18c] and 251 mg (91%) of a white solid, mp 129–136°, was obtained after trituration with a small amount of hexane. This material was recrystallized from heptane–ethyl acetate, affording 204 mg (74%) of bromo ketone: mp 134–137.5°; $\delta_{TMS}^{CDCl_3}$ = 7.3–7.5 (phenyl group), 5.28 (H-3, doublet, $J_{3a,4a}$ = 12.6 cps), 2.78 (H-4, four lines, $J_{4a,3a}$ = 12.6 cps, $J_{4a,10a}$ = 11.0 cps), 1.27, and 1.24 ppm (C-1 *gem*-dimethyl, two singlets); λ_{max}^{KBr} 5.80 (C=O), 6.23 (C=C), 6.69, 6.90, 7.20, 8.52, 9.37, 9.56, 9.76, 11.30, 12.45 13.29, 13.75, 13.95, and 14.21 μ.

Recrystallization from heptane–ethyl acetate gave colorless flat needles, mp 140–141°.

Anal. Calcd for $C_{18}H_{23}BrO$: C, 64.48; H, 6.91; Br, 23.83. Found: C, 64.4; H, 6.8; Br, 24.0.

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Structure of Hysterin, a New Sesquiterpene Lactone[1,2]

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Hysterin, a new sesquiterpene lactone, has been isolated from *Parthenium hysterophorus* L. together with some ambrosin. The structure of hysterin is shown to be Ia.

In continuation of our search for *Compositae* whose sesquiterpene lactone composition varies with the geographical location[3] we have investigated *Parthenium hysterophorus* L.,[4] a common weed growing in the West Indies and the sourthern part of North America. The material growing in Florida has previously been studied by Herz, *et al.*,[5] who isolated parthenin, a member of the class of pseudoguaianolides. The plant growing in the Valley of Mexico has now yielded a different pseudoguaianolide, which we have named hysterin, as well as some ambrosin.

Hysterin, $C_{17}H_{24}O_5$, mp 168°, $[\alpha]D$ −80° (*c* 1.0, chloroform), has a free hydroxyl group as shown by the infrared absorption at 3620 cm^{-1} and by the formation

(1) Contribution No. 216 from the Instituto de Química de la Universidad Nacional Autónoma de México.

(2) Taken in part from a D.Sc. thesis to be submitted by E. A. Bratoeff to the Universidad Nacional Autónoma de México.

(3) A. Romo de Vivar and H. Jiménez, *Tetrahedron*, **21**, 1741 (1965).

(4) Identified by the late Dr. Faustino Miranda from the botanical department of the Universidad Nacional Autónoma de México with a herbarium number 9138.

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

TABLE I

NMR PEAKS OF HYSTERIN AND ITS DERIVATIVES[a]

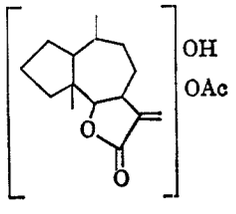
Compound	H-4	H-6	C-4 OAc	C-5 Me	C-10 CH_2OR	C-10 CH_2=	C-11 CH_2=	C-11 Me	Misc
Ia	5.12 tr	4.5 d (J = 9)	2.1	0.82	3.88 br	...	5.5 d (J = 3.5) 6.2 d (J = 3.5)	...	...
Ib	5.15 tr	4.5 d (J = 9)	2.08	0.85	4.35 br	...	5.5 d (J = 3.5) 6.15 d (J = 3.5)	...	...
II	5.12 tr	4.7	2.1	0.58	3.7 br	...	...	1.8	...
III	5 tr	4.5 d (J = 7)	2.1	0.9	3.7 br	...	...	1.15 d (J = 6.5)	...
IV	5.1 tr	4.34 d (J = 8)	2.1	0.92	3.88 br	...	...	1.18 d (J = 6.5)	...
V	5.24 tr	4.62 d (J = 6)	2.1	0.88	...	4.82 5.02	...	1.18 d (J = 6.5)	...
VI	5.12 tr	4.72 d (J = 5)	2.1	0.92	...	...	...	1.18 d (J = 6.5)	...
VII	5.2 tr	4.7	2.05	0.7	...	...	...	1.77	1.00 d (J = 7) (C-10 Me)
IX	5.3 tr	4.65 d (J = 9)	2.1	0.73	...	4.77 5.00	5.45 d (J = 3.5) 6.15 d (J = 3.5)	...	...
X	5.27 tr	4.53 d (J = 9)	2.12	0.88	...	...	5.5 d (J = 3.5) 6.2 d (J = 3.5)	...	10.1 (CHO)
XII	5.3 tr	4.78	2.08	0.75	...	...	...	1.80	1.08 d (J = 7) (C-10 Me)

[a] Spectra were determined by Mr. Eduardo Diaz on a Varian A-60 spectrometer in deuteriochloroform solution. Values are given in parts per million relative to tetramethylsilane as internal standard. Singlets are unmarked. Multiplets are described as follows: d, doublet; br, broadened singlet or ill-defined doublet; tr, ill-defined triplet. Coupling constants, J, are given in cycles per second.

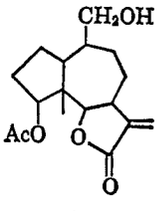
of a monoacetate (Ib). It contains one double bond (infrared band at 1660 cm^{-1}, uptake of 1 mole of hydrogen). The remaining four oxygen atoms are presumably present as a part of a γ-lactone (infrared band at 1758 cm^{-1}) conjugated with an exocyclic methylene group [ultraviolet absorption at 213 mμ (ϵ 10,000), infrared band at 885 cm^{-1}] and an acetoxy group (carbonyl band at 1728 cm^{-1} and C–O stretching band at 1245 cm^{-1}). Hysterin, on catalytic hydrogenation at 1 atm isomerizes to isohysterin [λ_{max} 222 mμ (ϵ 15,600)] which is resistant to further hydrogenation. This isomerization of the double bond is characteristic of many sesquiterpene lactones, such as ambrosin,[5,6] helenalin,[7] mexicanin A,[7] etc.

It now remained to deduce the fundamental skeleton of hysterin. We attempted first aromatization, the usual practice in sesquiterpene chemistry. However, dehydrogenation with selenium or palladium on charcoal under various conditions produced only a deep blue-greenish color and did not result in the formation of a crystalline adduct with 1,3,5-trinitrobenzene. In general, the dehydrogenation of pseudoguaianolides affords azulenes in very poor yield.

Since the *Parthenium* species studied until the present time have yielded only abnormal guaianolides[5,8] with the lactone ring closed to C-6; we adopted as a working hypothesis partial formula A.



A



B

The nmr spectra of hysterin and its devivatives (Table I) strongly confirmed the correctness of formula A and permitted us to establish the positions of the acetoxy and hydroxyl functions as in formula B.

The exocyclic methylene group conjugated with the lactone exhibits the characteristic two low-field doublets (one proton each) centered at 5.5 (J = 3.5 cps) and at 6.2 ppm (same J value) typical of *gem*-vinyl protons. These signals disappeared on conversion to the dihydro derivatives III and IV. The lactone group in hysterin should be closed to C-6 since the hydrogen on the carbon bearing the lactonic oxygen produces a sharp doublet centered at 4.5 ppm (J = 9 cps), intensity one proton. This doublet arises from the interaction with the single neighboring hydrogen at C-7.

In the methyl region hysterin exhibited a singlet at 0.82 ppm (3H) assigned to the methyl group at C-5, slightly shifted to higher field owing to shielding effect of the acetate carbonyl. The signal corresponding to the methyl group at C-10, which is present in the majority of the guaianolides studied so far, is absent, but there appeared a signal at 3.88 ppm (2H) which is shifted to lower field on acetylation or tosylation. We inferred that the methyl group is partially oxidized to a hydroxymethylene function.

The presence of an acetoxy group is hysterin indicated by the infrared spectrum was confirmed by high-resolution nuclear magnetic resonance. The signal at 2.1 ppm (3H) is characteristic of an acetoxy methyl group. We assigned position C-4 to this acetoxy group on the following grounds. The hydrogen attached to C-4 shows a triplet centered at 5.12 ppm (1H) and, although caution is necessary in interpreting multiplicities, no other position for this group will give this signal. The two protons at C-3 are not equivalent and the two doublets which should probably be formed are superimposed, thus giving a triplet. The lack of further splitting indicates that the adjacent carbon atoms (C-5) is fully substituted.

Thus, formula B is completely in accord with the spectroscopic data. The structure and the stereo-

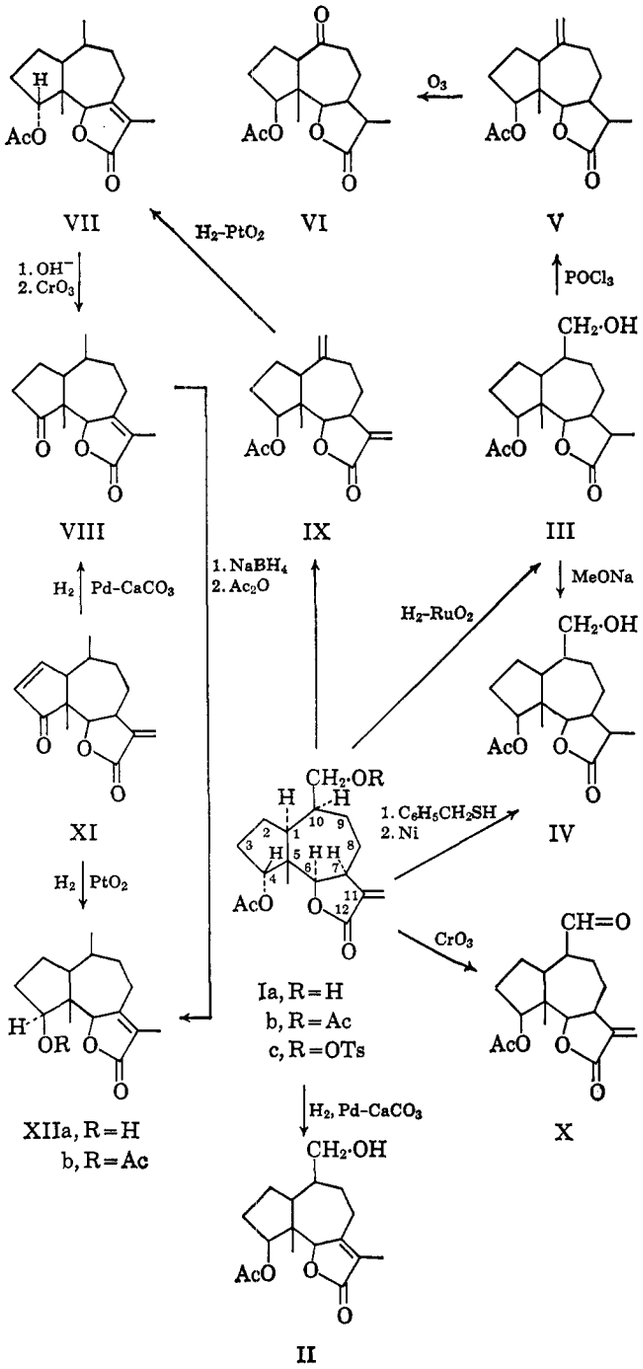
(6) F. Šorm, M. Suchy, and V. Herout, *Collection Czech. Chem. Commun.*, **24**, 1548 (1959).

(7) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Am. Chem. Soc.*, **85**, 19 (1963).

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

chemistry was established as in Ia on chemical grounds as follows (see Chart I). The primary nature of the hydroxyl group of hysterin was confirmed by oxidation to the aldehyde X. The nmr spectrum of X exhibited the same characteristin signals as those of hysterin; an additional signal at 10 ppm (1H) can be ascribed to the aldehyde proton and the signal at 3.88 ppm associated with the hydroxymethylene group had disappeared.

CHART I



Dehydration of hysterin resulted in the formation of the anhydro compound IX, whose nmr spectrum exhibited a new methylene group as two singlets at 4.77 and 5 ppm (1H each). The singlet at 4.77 ppm was partially superimposed on the doublet centered at 4.65 ppm which is ascribed to the hydrogen at C-6.

As we mentioned before, aromatization of hysterin was not successful. However, since ambrosin had also been isolated from *P. hysterophorus*, an excellent possibility existed for correlating the structure of hysterin with that of ambrosin. For this purpose we prepared anhydrohysterin IX, which on hydrogenation produced desoxyisohysterin VII [λ_{max} 222 mμ (ϵ 16,000)]. An attempt to prepare this compound by catalytic hydrogenation of ambrosin (XI) with platinum oxide in acetic acid containing some perchloric acid afforded a mixture of XIIa and XIIb, the latter being an isomer of VII. Desoxyisohysterin VII and XIIb had almost identical nmr spectra exhibiting only very slight differences in the methyl-group region (Table I). The infrared spectra of both compounds were completely identical in the 3500–1300-cm^{-1} range, but very slight differences were observed in the fingerprint region. These results can be interpreted by assuming a difference in the stereochemistry of one or more asymmetric carbon atoms.

The only difference between VII and XIIb was the configuration at C-4 and this was demonstrated in the following manner. VII on hydrolysis and oxidation with chromic anhydride in acetic acid afforded VIII which was identical in all respects with an authentic sample of dihydroisoambrosin. This sequence of reactions, which led to a correlation of hysterin with ambrosin, definitely established the carbon skeleton of hysterin as being identical with that of ambrosin and also determined the configuration of the asymmetric centers C-1, C-5, C-6, and C-7 as being the same as those of ambrosin, the major sesqueterpene lactone constituent of *Ambrosia maritima* L.[6] The methyl group at C-5 in ambrosin is β oriented, and on catalytic hydrogenation of XI the hydrogen most likely should attack the molecule from the less-hindered back side, opposite to the C-5 β-methyl group, thus producing a β-hydroxyl group as formulated in XIIa. Acetylation of XIIa with acetic anhydride and pyridine afforded a white crystalline acetoxy derivative XIIb. $NaBH_4$ reduction of VIII resulted in the formation of the 4-hydroxy derivative XIIa which on acetylation afforded a crystalline product, identical in all respects with XIIb. The difference between VII and XIIb can be explained on stereochemical grounds. The orientation of the acetoxy group at C-4 in XIIb should be β, therefore compound VII should have the α configuration for the corresponding acetoxy group. We hope to investigate this in more detail, when additional supplies of ambrosin become available.

Hysterin itself furnished two epimeric dihydro derivatives III and IV depending on the method of reduction. As mentioned earlier, catalytic hydrogenation of hysterin Ia at ordinary pressure afforded isohysterin II whose infrared bands and ultraviolet absorption pointed to the continued presence of conjugation. Catalytic reduction of the exocyclic double bond was difficult under normal conditions but could be achieved readily with ruthenium dioxide at elevated temperature and pressure. The nmr spectrum of the resulting dihydrohysterin III exhibited the expected doublet for the new C-11 methyl group. Chemical reduction, achieved by conjugate addition of benzyl mercaptan followed by desulfuration with Raney nickel, afforded substance IV, possessing the more

stable configuration (thermodynamically more stable product). The same product was obtained on treatment of III with sodium methoxide, which epimerized the C-11 methyl group. This epimerization at C-11 is also observed with other sesquiterpene lactones. Tetrahydrohelenalin, having a β-oriented C-11 methyl group, on treatment with base epimerizes at this asymmetric center to the more stable α configuration in dihydromexicanin C.[9,10]

So far we have demonstrated that the carbon skeleton of hysterin and the stereochemistry at C-1, C-5, C-6, and C-7 are the same as those in ambrosin.

The chemical evidence presented so far has not allowed a determination of the configuration at the asymmetric center C-10. On biogenetical grounds, we can assign as the most probable stereochemistry for the C-10 methyl group the β configuration, the same as in ambrosin and in other pseudoguaianolides, such as parthenin and coronopilin, isolated from parthenium species. Therefore, the structure and the configuration of hysterin is represented by formula Ia.

Experimental Section[11]

Isolation of Hysterin (Ia).—Air-dried *Parthenium hysterophorus* L., 1.6 kg, collected in the vicinity of Mexico City in August and September, was ground to a fine powder and extracted in a Soxhlet extractor with chloroform for 24 hr. Removal of the solvent yielded a black tarry mass. The extract was dissolved in 1000 ml of ethanol and mixed with 1000 ml of hot water containing 20 g of lead acetate and 2 ml of acetic acid. The mixture was allowed to stand overnight. The clarified solution was filtered and the filtrate was concentrated to 300–500 ml under vacuum. Subsequent distillation with steam removed some essential oils. The residue was thoroughly extracted with chloroform. The chloroform layer was dried, filtered, and evaporated to dryness under vacuum, yielding a brown-black residue, 51.6 g. The residue was dissolved in 200 ml of benzene and chromatographed over 1 kg of alumina (Alcoa F-20) washed with ethyl acetate. Pure benzene eluted ambrosin[12] (2 g). Benzene–ethyl acetate eluted crude hysterin. Recrystallization from isopropyl ether afforded 7.6 g of white crystalline material (yield 0.4%): mp 166–168°; $[\alpha]_D$ −80° (*c* 1.0); infrared bands at 3620, 1758 1728, 1660, 1245, and 885 cm^{-1}; λ_{max} 213 mμ (ϵ 10,000).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84; O, 25.95. Found: C, 66.03; H, 7.92; O, 26.05.

Hysterin Acetate (Ib).—A solution of 0.1 g of hysterin in 1 ml of pyridine and 1 ml of acetic anhydride was heated on a steam bath for 1 hr. The reaction product was diluted with water and extracted with ether. The organic layer was washed, dried with sodium sulfate, and evaporated to dryness. Recrystallization from ethyl acetate–hexane afforded 70 mg of hysterin acetate: mp 115–117°; $[\alpha]_D$ −77.2° (*c* 1.0); infrared bands at 1758, 1728, 1660, 1245, and 885 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48; O, 27.40. Found: C, 64.95; H, 7.42; O, 27.64.

Hysterin Tosylate (Ic).—To a cold solution of hysterin (100 mg) in 2 ml of anhydrous pyridine was added *p*-toluenesulfonyl chloride (90 mg). The mixture was stirred for 2 hr and allowed to stand at room temperature for 42 hr. The reaction product was diluted with water and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated to dryness. Recrystallization from acetone–isopropyl ether afforded 110 mg of hysterin tosylate: mp 143°; $[\alpha]_D$ −72.2° (*c* 1.0); infrared bands at 1758, 1728, 1660, 1245, and 885 cm^{-1}.

Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.32; H, 6.54; O, 24.22; S, 6.92. Found: C, 62.22; H, 6.64; O, 24.06; S, 6.83.

Isohysterin (II).—A solution of 1000 mg of hysterin in 25 ml of ethanol was hydrogenated under normal conditions for 24 hr over 100 mg of Pd–$CaCO_3$. The catalyst was filtered and the solvent was evaporated to dryness. A white crystalline material was obtained with a melting point of 135°. Recrystallization from acetone–isopropyl ether raised the melting point to 146° (yield 800 mg): $[\alpha]_D$ −29° (*c* 0.97); λ_{max} 220 mμ (ϵ 15,600); infrared bands at 3620, 1748, 1660, and 1250 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84; O, 25.95. Found: C, 66.19; H, 7.87; O, 25.51.

Dihydrohysterin (III).—A solution of 5 g of hysterin in 100 ml of ethanol was hydrogenated at 40° under 1600 psi in the presence of 0.5 g of ruthenium dioxide. Filtration of the catalyst and removal of the solvent afforded an oily residue which crystallized from diethyl ether–hexane to yield 725 mg of dihydrohysterin, mp 99–100°. The mother liquors were concentrated and chromatographed over alumina, Alcoa F-20. Benzene–ether (80:20) eluted an additional 1.33 g of dihydrohysterin: mp 105°; $[\alpha]_D$ −27° (*c* 1.0); infrared bands at 3600, 1748, 1720, and 1250 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44; O, 25.78. Found: C, 65.55; H, 8.55; O, 25.54.

Epidihydrohysterin (IV).—A solution of hysterin (600 mg) in benzene (50 ml) was mixed with 2 ml of piperidine and 2 ml of benzyl mercaptan. The mixture was refluxed for 16 hr. The cold solution was washed, dried, and evaporated to dryness. The oily residue was dissolved in 60 ml of ethanol and to this solution was added Raney nickel (10 g). The mixture was refluxed for 17 hr, the catalyst was filtered, and the ethanol was evaporated to dryness. Crystallization from acetone–isopropyl ether afforded 260 mg of epidihydrohysterin: mp 142–143°; $[\alpha]_D$ −68° (*c* 1.0); infrared bands at 3620, 1748, 1720, and 1250 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}O_5$: D, 65.78; H, 8.44; O, 25.78. Found: C, 65.91; H, 8.27; O, 26.24.

Epimerization of Dihydrohysterin (III).—A solution of 500 mg of dihydrohysterin (III) in 5 ml of methanol was refluxed with 0.2 g of sodium for 1 hr. The reaction mixture was diluted with water, acidified with acetic acid, and extracted with chloroform. The organic layer was washed, dried, and evaporated to dryness. Crystallization from isopropyl ether afforded 135 mg of white crystals, mp 139–142°. This compound did not give a depression in mixture melting point with epidihydrohysterin (IV) and the infrared spectra were identical.

Anhydrodihydrohysterin (V).—To a solution of dihydrohysterin (III) (30 mg) in anhydrous pyridine (5 ml) was added freshly distilled phosphorus oxychloride (0.5 ml). The mixture was heated on the steam bath for 6 hr, poured over ice–water, and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated to dryness. Crystallization from ether–hexane afforded 165 mg of anhydrodihydrohysterin: mp 110–111°; $[\alpha]_D$ −24° (*c* 1.0); infrared bands at 1725, 1720, 1640 1225, and 895 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; O, 21.89. Found: C, 69.64; H, 8.39; O, 22.23.

Ozonolysis of Anhydrodihydrohysterin (V).—A solution of 110 mg of anhydrodihydrohysterin (V) in 20 ml of methanol was ozonized at −70°. The solution was transferred to a hydrogenator and the ozonide was decomposed catalytically over 50 mg of Pd–$CaCO_3$. The catalyst was filtered and the solution was evaporated to dryness. The residue was crystallized from acetone–isopropyl ether: yield 75 mg; mp 175–177°; $[\alpha]_D$ −73.5° (*c* 1.0); infrared bands at 1760, 1720, 1700, and 1225 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.54; O, 27.17. Found: C, 65.01; H, 7.41; O, 26.98.

Anhydrohysterin (IX).—To a solution of hysterin (900 mg) in anhydrous pyridine (15 ml) was added freshly distilled phosphorus oxychloride (1.4 ml). The mixture was heated on the steam bath for 6 hr, poured over ice–water, and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated to dryness. Crystallization from ether–hexane afforded 615 mg of anhydrohysterin: mp 96–97°; $[\alpha]_D$ −100.0° (*c* 1.0); infrared bands at 1660, 1245, and 885 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64; O, 22.04. Found: C, 70.01; H, 7.48; O, 21.92.

Desoxyisohysterin (VII).—A solution of 720 mg of anhydrohysterin in 30 ml of acetic acid was hydrogenated under normal

(9) A. Romo de Vivar and J. Romo, *Chem. Ind.* (London), 882 (1959).

(10) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963).

(11) Melting points were determined on the Kofler block and are uncorrected; infrared spectra were run on a Perkin-Elmer Model 21 spectrophotometer in chloroform, ultraviolet spectra with a Beckman DK-2 spectrophotometer in ethanol solution. Microanalyses were determined by Dr. Franz Pascher, Bonn, Germany. Rotations were taken in chloroform.

(12) We thank Dr. Werner Herz for the comparison of our material with an authentic sample of ambrosin.

conditions for 5 hr over 70 mg of platinum dioxide. The catalyst was filtered and the solvent was concentrated to a small volume. A solution of sodium bicarbonate was added and the neutral mixture was extracted with ethyl acetate. The organic layer was dried and evaporated to dryness, yielding 410 mg of desoxyisohysterin, mp 91–92°. Recrystallization from isopropyl ether–hexane raised the melting point to 103–104°: $[\alpha]_D$ −15.6° (*c* 1.0); λ_{max} 222 mμ (ε 16,000); infrared bands at 1748, 1660, and 1225 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; O, 21.89. Found: C, 69.80; H, 8.30; O, 21.83.

Dihydroisoambrosin from Hysterin (VIII).—A solution of 100 mg of desoxyisohysterin and 100 mg of potassium bicarbonate in 20 ml of methanol was refluxed for 45 min. The methanol was removed under vacuum and the residue was acidified with acetic acid. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated to dryness affording an oily product which did not crystallize. This alcohol without further purification was dissolved in 6 ml of acetic acid and to this solution was added dropwise with stirring a solution of 100 mg of chromic oxide in 2 ml of water. Stirring was continued for 3 hr. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated to dryness. Crystallization from ethyl acetate–isopropyl ether afforded 20 mg of dihydroisoambrosin: mp 165°; $[\alpha]_D$ −9.3° (*c* 1.0). This compound was compared with an authentic sample of dihydroisoambrosin and was found to be identical in all respects.

4-Epidesoxyisohysterin (XIIb).—A solution of 200 mg of ambrosin in 15 ml of acetic acid and 2 drops of perchloric acid was hydrogenated under normal conditions for 24 hr in the presence of 20 mg of platinum dioxide. The reaction mixture was filtered, neutralized with sodium bicarbonate solution, and extracted with ethyl acetate. The oily residue was acetylated in the usual manner, yielding 85 mg of 4-epidesoxyisohysterin, mp 93–95°. The mother liquors (90 mg) contained approximately 70% of 4-epidesoxyisohysterin (tlc).

Dehydrohysterin (X).—To an ice-cold solution of 310 mg of hysterin in 10 ml of pyridine was added dropwise with stirring a solution of 210 mg of chromic oxide in 15 ml of pyridine. Stirring was continued for 6 hr at 37°. The excess of chromic oxide was destroyed with 10 ml of methanol and the solvents were evaporated to dryness. The oily residue was extracted with ethyl acetate and the organic layer was washed with water, dried, and evaporated to dryness. Recrystallization from isopropyl ether afforded 95 mg of dehydrohysterin (X): mp 154–155°; $[\alpha]_D$ −65.5° (*c* 1.0); λ_{max} 213 mμ (ε 10,000); infrared bands at 2860, 1710, 1245, 1045, and 885 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 65.94; H, 7.26; O, 26.93.

4-Epidesoxyisohysterin (XIIb) from Dihydroisoambrosin (VIII).—To a solution of 280 mg of dihydroisoambrosin in 15 ml of methanol was added 250 mg of $NaBH_4$. The mixture was refluxed for 2 hr. The reaction product was acidified with acetic acid and the solvent was evaporated under vacuum to dryness. The residue was extracted with ether. The organic layer was washed, dried, and evaporated to dryness. The oily residue was acetylated in the usual manner. The resulting product was chromatographed over alumina (Alcoa F-20) yielding 180 mg of 4-epidesoxyisohysterin (XIIb). This compound was compared with a sample of 4-epidesoxyisohysterin obtained by catalytic hydrogenation of ambrosin and was found to be identical in all respects.

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Synthesis of Simple Hydrazones of Carbonyl Compounds by an Exchange Reaction

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Simple N-unsubstituted hydrazones of most aldehydes or ketones, usually difficult to obtain in good yields and high purity, may be so prepared from the corresponding N,N-dimethylhydrazones by exchange with anhydrous hydrazine. Since azine formation is nil under these conditions, the reaction can be followed by observing loss of color. Hydrazones prepared in this manner are stable for long periods when stored as crystalline solids. The N,N-dimethylhydrazones used as reagents are prepared in high yields directly from aldehydes or ketones and *unsym*-dimethylhydrazine. Exceptions to this occur only if the carbonyl compound is sterically hindered or possesses a labile group (toward nucleophilic substitution) *ortho* to the carbonyl function on an aromatic ring. In the latter instance, derivatives of 1H-indazole are formed.

Preparation in good yield of pure unsubstituted hydrazones of the more reactive aldehydes and ketones has been generally reported as difficult. Azine formation, hard to prevent during direct reactions between hydrazine and the carbonyl compounds (particularly aliphatic aldehydes and ketones or mixed alkaryls), is catalyzed by acids or is the principle reaction when the system is not quenched.[3-5] The hydrazones themselves may spontaneously decompose to tars[6] or azines with water or catalysts.[5,7]

In contrast, the few reported reactions of aldehydes or ketones with N-alkyl- and N,N-dialkylhydrazines to give the corresponding hydrazones indicate that these are uncomplicated by side reactions.[7c,8-10] The product N-substituted hydrazones are variously reported as oils of high refractive index obtained in yields from 20 to 80%. The most extensive preparative investigations of these compounds are those of Wiley and coworkers,[11] who prepared N-methyl- and N,N-dimethylhydrazones of a number of aldehydes and ketones as potential tumor growth retardants. Dialkylhydrazones have also been prepared from geminal dihalides instead of the corresponding carbonyl compounds.[12]

Preliminary to a study of subsequent reactions of pure aldehyde and ketone hydrazones now underway

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