# Total Synthesis of Modified Steroids. II. 8β-Methyl-D-homoestranes[1]

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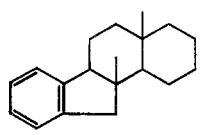
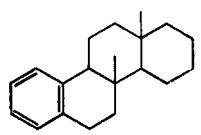
Synthetic methods have been developed for the preparation of 3-methoxy-8β-methyl-D-homoestra-1,3,5(10),-9(11),14-pentaen-17a-one by two routes. The first of these involved the alkylation of **3** with 2-bromo-3′-methoxyacetophenone, which could be converted into the key intermediate **24**, 3,7,8,8a-tetrahydro-5α-(*m*-methoxyphenethyl)-5β,8aβ-dimethyl-1,6(2H,5H)-naphthalenedione, by a variety of methods. The alternate route proceeded through the allyl derivative **16**, which was transformed into the aldehyde **18** in two steps. Reaction of **18** with *m*-methoxyphenylmagnesium bromide gave **10**, which on reduction and hydrolysis afforded the same intermediate **24**. Acid-catalyzed cyclization of **24** then yielded the D-homo steroid **26**.

The previous paper[1] in this series described the total synthesis of compounds related to 8β-methyl-D-homo-B-norestrane (**1**). Since these compounds are structurally further removed from the natural steroids than the corresponding homolog **2**, a synthesis of the latter system was developed utilizing intermediates already available from the preparation of **1**.

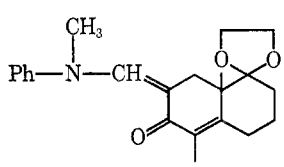


**1**

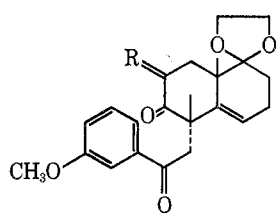


**2**

The synthesis of **1** was essentially completed when **3**[3,4] was successfully alkylated with *m*-methoxybenzyl chloride. A similar process for the preparation of **2** would require that **3** be alkylated with *m*-methoxyphenethyl bromide or some equivalent thereof. Although this reagent has been employed for the alkylation of several enolate anions,[5] the pronounced tendency for the bromine to undergo elimination to give the corresponding styrene rather than displacement has severely limited its use. Nevertheless the method, by virtue of its directness, was attractive and alkylation of **3** by *m*-methoxyphenethyl bromide was attempted. No evidence was obtained for the formation



**3**



**4**, R = CHN(CH$_3$)Ph
**5**, R = H$_2$

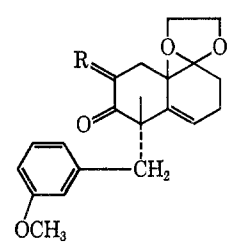
of even small amounts of the desired alkylation product under a wide variety of reaction conditions.

An obvious alternative to *m*-methoxyphenethyl bromide was the commercially available 2-bromo-3′-methoxyacetophenone. It was anticipated that the most serious side reaction in the use of this compound under strongly basic conditions would be that of self-condensation.[6] The anion of **3** prepared by

$$2PhCOCH_2Br \longrightarrow PhCOCH{=}CHCOPh$$

treatment with sodium hydride in dimethoxyethane is stable for extended periods. This fact allowed conditions to be defined under which self-condensation was minimized if not eliminated. Experimentally, it was found that both the temperature and rate of addition of the 2-bromo-3′-methoxyacetophenone were of prime importance. These are the factors which would be expected to effect the rate of self-condensation. By employing low temperatures (0–5°) and a slow rate of addition of the alkylating agent, an 80–90% yield of **4** could be realized. When the reaction was carried out on a large scale, the phenacyl bromide was conveniently added overnight in a cold room by means of an electric pump. It has been established[1] that alkylation of **3** with *m*-methoxybenzyl chloride occurs exclusively from the α side. It is therefore reasonable to assume that the product **4** has the relative stereochemistry shown.

Hydrolysis of **4** by a strong base[3] proved to be more difficult than that of the corresponding benzyl product **6**, which gave **7** in essentially quantitative



**6**, R = CHN(CH$_3$)Ph
**7**, R = H$_2$

yield. Under similar conditions **4** afforded a mixture which was readily separated into neutral and acidic fractions. The neutral product obtained in 60% yield was the desired ketone **5**, whereas the acidic material proved to be the β-keto aldehyde **8**. The nmr spectrum of **8** clearly showed the aldehydic proton at τ 0.62 as well as the enolic hydroxyl proton at τ −0.11. The increased stability of **8** to strong base over the

(1) Part I: D. J. France, J. J. Hand, and M. Los, *Tetrahedron*, **25**, 4011 (1969).

(2) To whom correspondence should be addressed.

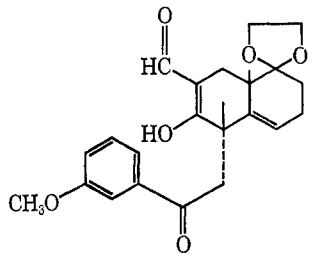
(3) Y. Kitahara, A. Yoshikoshi, and S. Oida, *Tetrahedron Lett.*, 1763 (1964).

(4) Structural formulas containing one or more asymmetric carbon atoms depict one diastereomer but refer to racemic compounds throughout. Each racemate is arbitrarily represented by the diastereomer having the C-13 methyl group (steroid numbering) in the β configuration.

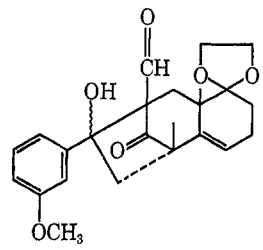
(5) See, *e.g.*, G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. T. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963), and references cited therein.

(6) B. M. Bogoslovskii, *J. Gen. Chem. USSR*; **14**, 993 (1944); *Chem. Abstr.*, **39**, 4600 (1945).

corresponding benzyl analog must be attributed to the presence of the phenacyl carbonyl group. It has been established[7] that under basic conditions **8** is in equilibrium with **9**, with the result that β-diketone cleavage is retarded.

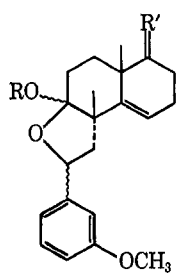


**8**



**9**

When **5** was catalytically reduced in methanol at 60°, 1 equiv of hydrogen was absorbed and two products were isolated in varying amounts. These proved to be the hemiketal **10** and the mixed ketal **11**. On one occasion **11** was the sole product. The variation in the ratio of products **10** and **11** is undoubtedly due



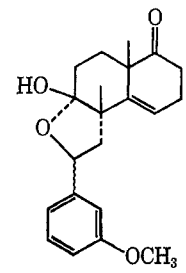
**10**, R = H; R′ = $OCH_2CH_2O$
**11**, R = $CH_3$; R′ = $OCH_2CH_2O$
**12**, R = $C_2H_5$; R′ = $OCH_2CH_2O$
**13**, R = H; R′ = O

to traces of acid in the reaction medium. Similar reduction of **5** in ethanol gave the corresponding ethyl ketal **12**. Treatment of **10** with methanol or ethanol containing a trace of acetic acid resulted in complete conversion into the mixed ketals **11** and **12**, respectively.

That these compounds are mixtures of isomers is indicated by broad melting point range and variable ir and nmr spectra. Thus, two sets of signals are visible at τ 4.0–5.5 for the benzylic and vinyl protons in the nmr spectra. It is noteworthy that this method for the preparation of compounds **10–12** is highly stereoselective in that the crude product is predominantly one isomer which can be obtained pure, whereas **10** synthesized by the alternate route described below yields essentially equal amounts of two isomers.

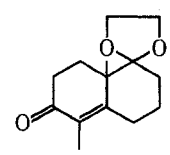
Hydrolysis of **10** or **11** or mixtures of these compounds with aqueous acetic acid yielded the ketone **13**. In this case a complete separation of the two isomers was achieved. It is reasonable to assume that the asymmetric center involving the hemiketal function is the same in both cases, since they were subjected to equilibrating conditions. Further, it would be expected that the hydroxyl group would adopt the β configuration to give a relatively strainless *cis*-fused furan ring. If, then, these compounds differ only in the configuration of the phenyl group, they should be distinguishable by variable-temperature nmr. The isomer in which the phenyl group is β (*cis* to the methyl groups) should cause a shift in the position of the furan ring methyl resonance as the rate of rotation of the phenyl group is decreased. In contrast, a shift would not be expected in the other isomer.

The nmr spectrum of the major isomer of **13** at 40° showed the methyl groups as two cleanly separated peaks. At −30° one of these peaks was shifted so that the methyl groups resonated at essentially the same place. The spectrum of the minor isomer of **13**, on the other hand, showed the methyl groups as a singlet at 40° unchanged by lowering the temperature. Based on this evidence, structure **14** is tentatively assigned to the major isomer.

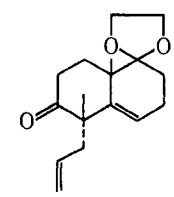


**14**

An alternative route to **10** was developed which avoided the use of the blocked ketone **3** and thus eliminated the hydrolysis step. Although direct alkylation of **15** with phenacyl bromide was unsuccessful, good yields of the alkylated product **16** were ob-

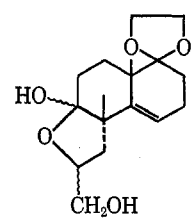


**15**

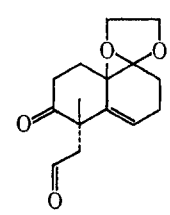


**16**

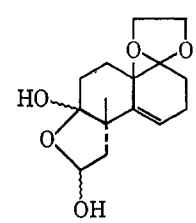
tained with allyl bromide.[8] Reaction of **16** with sodium chlorate in the presence of catalytic amounts of osmium tetroxide[9] resulted in complete conversion into a hydroxylated product to which structure **17** was assigned, since its ir spectrum was devoid of



**17**



**18**



**19**

carbonyl absorption bands. That **17** was also a mixture was indicated by wide melting point range and variable ir and nmr spectra. Oxidation of this mixture by sodium metaperiodate[9] gave a quantitative yield of the aldehyde **18**. Frequently, **18** was accompanied by a much more polar compound whose ir spectrum showed strong OH but no carbonyl bands. Formulation of this material as the hydrate **19** is

(7) J. J. Hand and M. Los, *Chem. Commun.*, 673 (1969).

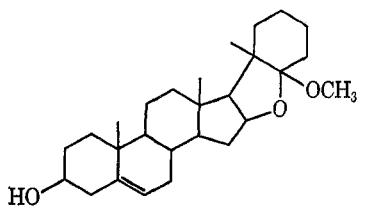
(8) Similarly, the compounds described in part I can be prepared by the direct alkylation of **15** with benzyl chloride.

(9) K. Wiesner, K. K. Chan, and C. Demerson, *Tetrahedron Lett.*, 2893 (1965).

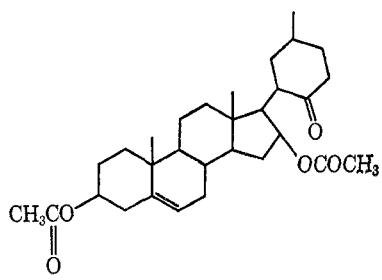
further supported by analytical data as well as the fact that it is quantitatively converted into the aldehyde **18** when passed through a short column of alumina in methylene chloride.

A study of the reaction between the aldehyde **18** and *m*-methoxyphenylmagnesium bromide was necessary to obtain satisfactory yields of the hemiketal **10**. This was somewhat surprising.[10] Titration of aldehyde **18** with the Grignard reagent at room temperature showed that 3 equiv were consumed before a positive Gilman test was obtained. These data are difficult to rationalize, since enolization of both carbonyl groups would require only 2 equiv and acceptable yields of **10** could be isolated from the reaction. It was found experimentally that, when a 20% excess of Grignard reagent was added all at once to **18** at −20°, a 76% yield of **10** could be isolated.

Uhle[11] recently reported the conversion of the ketal **20** into the keto acetate **21** by heating **20** with a mixture of acetic acid and acetic anhydride. When **13**

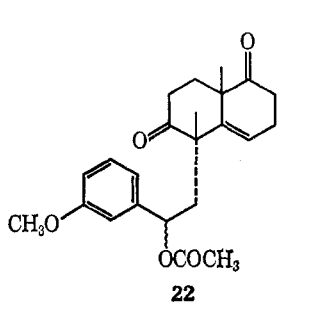


**20**

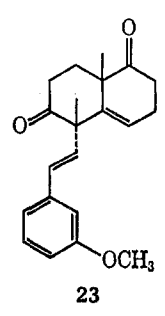


**21**

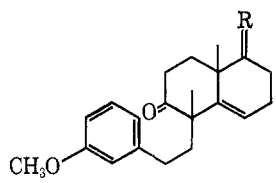
was subjected to these conditions, an oily product was formed whose ir spectrum indicated that a similar reaction had occurred to give **22**. An attempt to cyclodehydrate **22** to a tetracyclic compound by treatment with *p*-toluenesulfonic acid in benzene resulted instead in the elimination of the acetoxy group to form in moderate yield the styrene **23**. The nmr spectrum of **23** showed the styrene vinyl protons as a quartet with $J$ = 16 Hz, indicating a *trans* configuration about this double bond. Reduction of this double bond then gave **24**.



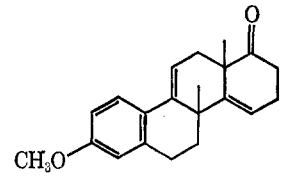
**22**



**23**



**24**, R = O
**25**, R = $OCH_2CH_2O$



**26**

Although all the compounds **10**–**12** could be efficiently converted into **24** through **25** by further catalytic reduction in acetic acid at 70° and 3 atm, the most direct route to **24** was that of direct reduction of **5** under the same conditions. Partial hydrolysis of the ketal group invariably occurred during the isolation of **25**, so that the crude product was acid hydrolyzed immediately to the dione **24**.

When the dione **24** was treated with concentrated hydrochloric acid in acetic acid overnight, the 8β-methyl-D-homoestrane **26** was obtained in essentially quantitative yield. The more commonly used reagents for effecting this type of cyclodehydration (polyphosphoric acid, hydrofluoric acid, hydrochloric acid in ethanol, and *p*-toluenesulfonic acid in benzene[5]) gave greatly reduced yields of **26**.

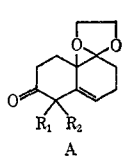
## Experimental Section[12]

**3′,7′,8′,8′a-Tetrahydro-5′α-(*m*-methoxyphenacyl)-5′β,8′aβ-dimethyl-7′-(N-methylanilinomethylene)spiro[1,3-dioxolane-2,1′-(2′H)-naphthalen]-6′(5′H)-one (4).**—To a solution containing 52.95 g (0.15 mol) of **3** in 600 ml of dry dimethoxyethane under nitrogen was added 8.5 g (0.27 mol) of sodium hydride as a 54% suspension in mineral oil. The mixture was heated under reflux with stirring for 2 hr and then cooled in an ice–water bath. A solution of 51.45 g (0.224 mol) of 2-bromo-3′-methoxyacetophenone in 500 ml of dry dimethoxyethane was added at ice-bath temperature during a 4.2-hr period. After the solution had stood overnight, water was added followed by excess 2.5 *M* sodium dihydrogen phosphate solution. The mixture was extracted twice with methylene chloride, and the combined extracts were washed twice with water and dried over sodium sulfate. Removal of the solvent left a crystalline residue which on recrystallization from acetone gave 63.9 g (85%) of **4**, mp 161–164.5°. Two further recrystallizations from acetone afforded an analytical sample: mp 169–170°; ir 1700, 1650, 1580, and 1540 $cm^{-1}$; nmr τ 4.58 (t, 1, C=CH), 6.20 (s, 3, $OCH_3$), 6.43 (s, 4 $OCH_2CH_2O$), 6.61 (s, 3, $NCH_3$), 8.59 (s, 3, $CCH_3$), and 8.86 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{31}H_{35}O_5N$: C, 74.23; H, 7.03; N, 2.79. Found: C, 74.39; H, 7.20; N, 2.36.

**3′,7′,8′,8′a-Tetrahydro-5′α-(*m*-methoxyphenacyl)-5′β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (5) and 3′,7′,8′,8′a-tetrahydro-7′-hydroxymethylene)-5′α-(*m*-methoxyphenacyl)-5′β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (8).**—To a solution containing 91.8 g of **4** in 610 ml of 2-ethoxyethanol was added 610 ml of water containing 258 g of potassium hydroxide. The solu-

(10) Compounds of type A, where $R_1$ and $R_2$ are alkyl groups, have been



A

found to be completely inert to Grignard and alkyllithium reagents (unpublished results from these laboratories).

(11) F. C. Uhle, *J. Org. Chem.*, **31**, 4193 (1966).

(12) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined as Nujol mulls or films using a Perkin-Elmer Infracord (Model 137). Proton nmr spectra were determined in deuteriochloroform solution with a Varian A-60A spectrometer with TMS as internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

tion was heated under reflux in a nitrogen atmosphere for 6 hr. After standing overnight, the solution was diluted with 2 l. of water and extracted twice with ether. The aqueous phase was retained. The extract was washed successively twice with water, once with cold 2 *N* hydrochloric acid, and three times with water. The organic phase was dried over sodium sulfate, the solvent was evaporated, and the residue was triturated with ether to give 43.7 g (62%) of the dione **5**, mp 104–118°. Two recrystallizations of this material from acetone–hexane gave the analytical sample: mp 121–122°; ir 1710, 1690 (C=O), 1650 (C=C), 1610, and 1580 $cm^{-1}$ (phenyl); nmr $\tau$ 4.61 (t, 1, C=CH), 6.04 (s, 4, $OCH_2CH_2O$), 6.22 (s, 3, $OCH_3$), and 8.68 (s, 6, 2 $CCH_3$).

*Anal.* Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.59; H, 7.34.

The aqueous phase from the original extraction was acidified with ice-cold 2 *N* hydrochloric acid and extracted three times with methylene chloride. The combined extract was washed twice with water and brine and dried over sodium sulfate. Evaporation of the solvent and trituration of the residue with ether gave the 13.8 g (18%) of the β-keto aldehyde **8**, mp 165–166°. Recrystallization from methanol gave an analytically pure sample: mp 157–160.5°; ir 1720, 1650, and 1590 $cm^{-1}$; nmr $\tau$ −0.11 (s, 1, enolic OH), 0.62 (s, 1, CHO), 4.26 (t, 1, C=CH), 6.01 (m, 4, $OCH_2CH_2O$), 6.21 (s, 3, $OCH_3$), 8.68 (s, 3, $CCH_3$), and 8.73 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.57; H, 6.89.

**2′,3′a,4′,5′,5′a,7′,8′,9′b-Octahydro-2′ξ-(*m*-methoxyphenyl)-5′aβ,9′bβ-dimethylspiro[1,3-dioxolane-2,6′(1′H)-naphtho[2,1-*b*]furan]-3′aξ-ol (10) and the Corresponding Methyl Ether 11 and Ethyl Ether 12.**—A solution of 10 g of **5** in 180 ml of methanol was reduced with hydrogen at 60° and 3 atm in the presence of 1.5 g of 5% palladium on carbon for 1 hr. The catalyst was removed by filtration and the solvent was evaporated. The residue was crystallized from acetone–hexane to give 5.4 g of the hemiketal **10**. The ir spectrum of this material varies with the sample in the fingerprint region. In all cases, however, no carbonyl band is evident but a strong OH band is present, sometimes as a doublet. Material recrystallized twice from methyl isobutyl ketone gave the following data: mp 153–159°; ir 3400 $cm^{-1}$ (OH); nmr $\tau$ 4.61 (t, 1, C=CH), 4.93 (t, 1, PhCH), 6.05 (s, 4, $OCH_2CH_2O$), 6.22 (s, 3, $OCH_3$), and 8.65 and 8.67 (d, 6, 2 $CCH_3$).

*Anal.* Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.24; H, 7.97.

The mother liquors after removal of **10** were concentrated and the residue was crystallized from hexane to give 2.2 g of methyl ether **11**, mp 80–87°. Two further crystallizations from hexane gave an analytical sample: mp 88–92°; ir shows no OH or C=O bands; nmr $\tau$ 4.60 (m, 1, C=CH), 5.18 (t, 1, PhCH), 6.06 (s, 4, $OCH_2CH_2O$), 6.22 (s, 3, PhOCH$_3$), 6.71 (s, 3, $OCH_3$), and 8.68 (s, 6, 2$CCH_3$).

*Anal.* Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.93; H, 8.09.

A solution of 1 g of **10** in 25 ml of absolute methanol and 2 drops of glacial acetic acid was heated under reflux for 4 hr. The acid was neutralized by the addition of triethylamine and the mixture was poured into water. The solution was extracted with ether and the extract was washed with water and dried over sodium sulfate. Evaporation of the solvent and crystallization of the residue from hexane gave a quantitative yield of the methyl ether **11**.

Reduction of **5** in ethanol afforded the corresponding ethyl ether **12**: mp 93–94° (from hexane); nmr $\tau$ 4.68 (t, 1, C=CH) 5.13 (t, 1, PhCH), 6.04 (s, 4, $OCH_2CH_2O$), 6.21 (s, 3, $OCH_3$), 6.38 (q, 2, $CH_3CH_2$), 8.66 (s, 6, 2 $CCH_3$), and 8.81 (t, 3, $CH_3CH_2$).

*Anal.* Calcd for $C_{23}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.23; H, 8.42.

**1,2,3a,4,5,5a,9,9b-Octahydro-3aα-hydroxy-2ξ-(*m*-methoxyphenyl)-5aβ,9bβ-dimethylnaphtho[2,1-*b*]furan-6(7H)-one (13).**—Hydrolysis of the crude product from the reduction of 10 g of **5** in methanol with 25% aqueous acetic acid at 90° for 1 hr and isolation of the product by ether extraction gave a crude product which on crystallization from acetone–hexane afforded 6.1 g (69%) of one isomer of **13**, mp 131–138°. Three recrystallizations of this material from the same solvents gave an analytical sample: mp 135.5–138.5°; ir 3450 (OH) and 1700 $cm^{-1}$ (C=O); nmr $\tau$ 4.41 (m, 1, C=CH), 4.81 (m, 1, PhCH), 6.26 (s, 3, $OCH_3$), 8.63 (s, 3, $CCH_3$), and 8.68 (s, 3, $CCH_3$). When the nmr spectrum was recorded at −30° the methyl signals appeared as a singlet at $\tau$ 8.69.

*Anal.* Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.60; H, 7.59.

Concentration of the mother liquors gave the second crystalline isomer of **13**, mp 129–131°. The analytical sample was obtained from acetone–hexane: mp 132.5–133.5°; ir 3500 (OH) and 1700 $cm^{-1}$ (C=O); nmr $\tau$ 3.94 (m, 1, C=CH), 5.22 (m, 1, PhCH), 6.22 (s, 3, $OCH_3$), and 8.64 (s, 6, 2 $CCH_3$). The position of the methyl signal was unchanged when the spectrum was run at −30°.

*Anal.* Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.82; H, 7.36.

**5′α-Allyl-3′,7′,8′,8′a-tetrahydro-5′,β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (16).**—To a stirred solution of 4.7 g (20 mmol) of the ketone **15** in 100 ml of dry *t*-butyl alcohol under nitrogen was added 5.60 g (50 mmol) of potassium *t*-butoxide. The mixture was heated under reflux for 2 hr and cooled to room temperature, and 2.9 g (22 mmol) of allyl bromide was added. The solution was stirred for 0.5 hr, diluted with water, and extracted twice with ether. The combined extracts were washed twice with water and saturated brine and dried over sodium sulfate. Evaporation of the solvent gave an oil which was crystallized from a small volume of hexane, giving 3.3 g (60%) of the allyl compound **16**, mp 64–65.5°. Two recrystallizations from the same solvent gave an analytical sample: mp 67.5–68.5°; ir 1700 (C=O), 1650, and 1640 $cm^{-1}$ (C=C); nmr $\tau$ 3.9–5.3 (m, 4, vinyl H), 6.0 (s, 4, $OCH_2CH_2O$), 8.78 (s, 3, $CCH_3$), and 8.92 (s, 3, $CCH_3$).

**2′,3′a,4′,5′,5′a,7′,8′,9′b-Octahydro-3′aξ-hydroxy-5′aβ,9′bβ-dimethylspiro[1,3-dioxolane-2,6′(1′H)-naphtho[2,1-*b*]furan-2′ξ-methanol (17).**—To a solution containing 27.6 g (0.1 mol) of **16** in 450 ml of tetrahydrofuran was added a solution of 12.8 g (0.12 mol) of sodium chlorate in 200 ml of water. After 2 ml of a standard solution containing 1 mmol of osmium tetroxide in 5 ml of water was added, the mixture was stored in the dark for 64 hr. Two such reaction mixtures were combined and a solution of 575 g of sodium sulfite in 2.5 l. of water was added. The mixture was shaken thoroughly and extracted twice with methylene chloride. The combined extract was washed with saturated brine and dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from ether, giving 49.9 g of **17**, mp 122–136°. A second crop of **17** weighed 4.4 g (total yield, 87.5%). A sample was recrystallized twice from acetonitrile: mp 140–160° (with bubbling); ir 3450 $cm^{-1}$ (OH).

*Anal.* Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.73; H, 8.14.

**5′α-Formylmethyl-3′,7′,8′,8′a-tetrahydro-5′β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (18) and 2′,3′a,4′,5′,5′a,7′,8′,9′b-Octahydro-5′aβ,9′bβ-dimethylspiro-[1,3-dioxolane-2,1′(2′H)-naphtho[2,1-*b*]furan-2′,3′aξ-diol (19).**—To a stirred solution containing 49.9 g (0.18 mol) of **17** in 480 ml of tetrahydrofuran was added slowly 74.1 g (0.346 mol) of sodium periodate in 480 ml of water. An ice–water cooling bath was used to maintain a temperature of 18–20° during the addition. The mixture was stirred overnight and thoroughly shaken with a solution of 230 g of sodium sulfite in 800 ml of water, and the product was extracted into methylene chloride. The extract was washed with saturated brine and dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from ether–hexane to afford 39.2 g (87.5%) of the aldehyde **18**: mp 61–62.5°; ir 2750 (aldehyde CH), 1710, 1700 (C=O), and 1640 $cm^{-1}$ (C=C); nmr $\tau$ 0.43 (t, 1, CHO), 4.48 (t, 1, C=CH), 5.96 (s, 4, $OCH_2CH_2O$), and 8.62 (s, 6, 2 $CCH_3$).

*Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.75; H, 7.97.

From many preparations of the aldehyde, varying amounts of a compound less soluble in acetone–hexane than **18** were isolated. This product is formulated as the hydrate **19**. Two recrystallizations from acetone gave an analytical sample: mp 116–130°; ir 3500 and 3600 $cm^{-1}$ (OH), no carbonyl band; nmr showed *ca.* 30% dissociation to the free aldehyde **18** as determined by the intensity of the aldehyde CH band. The methyl groups appeared at $\tau$ 3.65 and 8.73.

*Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.85; H, 8.16. Found: C, 64.82; H, 8.23.

**Preparation of the Hemiketal 10 from the Aldehyde 18.**—A stirred solution containing 40.7 g (0.147 mol) of **18** in 500 ml of dry tetrahydrofuran under nitrogen was cooled to −20°. At

this temperature 194 ml of a 0.91 *M* solution of *m*-methoxyphenylmagnesium bromide in tetrahydrofuran was added in one portion. After 5 min, 150 ml of saturated aqueous sodium dihydrogen phosphate was added. Salts were removed by filtration and washed with tetrahydrofuran. The aqueous phase was separated, the organic phase was washed with saturated brine, and the solvent was evaporated. The residue was dissolved in ether, the ether was dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from ether–hexane to give 43.1 g (77.5%) of the hemiketal **10**, mp 133–143°. This product is a mixture of isomers. The analytical sample was obtained from acetone, mp 132–180°.

*Anal.* Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.97; H, 8.25.

The analytical sample of the ethyl ether **12** was prepared from the above hemiketal by treatment with ethanol and acetic acid, mp 112–126°.

*Anal.* Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.18; H, 8.30.

**3,7,8,8a-Tetrahydro-5α-(*m*-methoxystyryl)-5β,8aβ-dimethyl-1,6(2H,5H)-naphthalenedione (23).**—A solution of 5.0 g of the hemiketal **13** in 80 ml of acetic acid and 40 ml of acetic anhydride was heated under reflux for 1 hr. The solvents were removed, the residue was dissolved in toluene, and the solvent was again evaporated. The residue was an oil, consisting mainly of the acetate **22**, ir 1740 (acetate C=O) and 1710 $cm^{-1}$ (C=O).

A solution of 2.0 g of *p*-toluenesulfonic acid in 170 ml of benzene was heated under reflux under a Dean–Stark water separator for 20 min. The crude acetate prepared above in 40 ml of benzene was added and heating was continued for 1 hr. The cooled solution was diluted with ether, washed with saturated sodium bicarbonate solution, and dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from methanol, affording 1.8 g of the styrene **23**. Recrystallization from methanol gave 1.5 g of **23**, mp 89.5–92°. One further recrystallization gave an analytical sample: mp 91–92°; ir 1700 (C=O), 1640 (C=C), and 1600 $cm^{-1}$ (phenyl); nmr $\tau$ 3.52 (d, 1, $J$ = 16 Hz, PhCH=CH), 3.90 (d, 1, $J$ = 16 Hz, PhCH=CH), 4.04 (m, 1, C=CH), 6.18 (s, 3, $OCH_3$), 8.48 (s, 3, $CCH_3$), and 8.78 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.57; H, 7.51.

**3,7,8,8a-Tetrahydro-5α-(*m*-methoxyphenethyl)-5β,8aβ-dimethyl-1,6(2H,5H)-naphthalenedione (24). A.**—A solution containing 324 mg (1 mmol) of **23** in 15 ml of ethanol was reduced with hydrogen at room temperature and atmospheric pressure in the presence of 50 mg of 5% palladium on carbon. Reduction was complete in 4 min. The catalyst was removed and the solvent was evaporated. Crystallization of the residue from ether–hexane gave 283 mg of dione **24**: mp 69–71°; ir 1700 (C=O), 1650 (C=C), 1610, and 1580 $cm^{-1}$ (phenyl); nmr $\tau$ 4.11 (m, 1, C=CH), 6.23 (s, 3, $OCH_3$), 8.65 (s, 3, $CCH_3$), and 8.76 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.39; H, 7.93.

**B.**—A solution containing 20 g of **5** in 200 ml of acetic acid was reduced with hydrogen at 70° and 3 atm in the presence of 1.0 g of 5% palladium hydroxide on carbon. Reduction was complete in 3.5 hr. The catalyst was removed and the solvent was evaporated. The residue consisted mainly of the ketal **25** together with varying amounts of the dione **24**.

To the residue in 60 ml of tetrahydrofuran was added 48 ml of 2.6 *N* perchloric acid. After 0.5 hr the solution was diluted with water and extracted with ether. The extract was washed twice with water and dried over sodium sulfate. Evaporation of the solvent and crystallization of the residue from ether–hexane gave 16.6 g (96%) of dione **24**, mp 68–70°, identical with that prepared above.

**C.**—Reduction of the hemiketal **10** under the same conditions described in B followed by hydrolysis gave a similar yield of the dione **24**.

**3-Methoxy-8β-methyl-D-homoestra-1,3,5(10),9(11),14-pentaen-17a-one (26).**—To 21.5 g of the dione **24** in 170 ml of acetic acid was added 17 ml of concentrated hydrochloric acid. After standing overnight at room temperature, the mixture was poured into water and extracted with ether. The extract was washed twice with water followed by cold 1 *N* sodium hydroxide, water, and saturated brine, and dried over sodium sulfate. The solvent was evaporated to give 19.7 g (97%) of crystalline **26**, mp 89–95.5°. Two recrystallizations from 2-propanol gave an analytical sample: mp 97–97.5°; $\lambda_{max}^{MeOH}$ 257 mμ (ε 18,300) [3-methoxy-D-homoestra-1,3,5(10),9(11)-tetraen-17a-one is reported[5] to have $\lambda_{max}^{EtOH}$ 262 mμ (ε 18,700)]; ir 1710 (C=O), 1650, 1640 (C=C), 1610, and 1570 $cm^{-1}$ (phenyl); nmr $\tau$ 4.16 (m, 2, 2 C=CH), 6.23 (s, 3, $OCH_3$), 8.54 (s, C, $CCH_3$), and 8.78 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.70; H, 7.90.

**Registry No.**—**4,** 22430-84-8; **5,** 22430-85-9; **8,** 22430-86-0; **10,** 22430-87-1; **11,** 22430-88-2; **12,** 22487-51-0; **13,** 22430-89-3; **16,** 22430-90-6; **17,** 22430-91-7; **18,** 22430-92-8; **19,** 22430-93-9; **23,** 22430-94-0; **24,** 22430-95-1; **26,** 22430-96-2.

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# Studies on Resin Acids. IV. The Structure, Stereochemistry, and Reactions of Some Dihydroabietic Acids[1]

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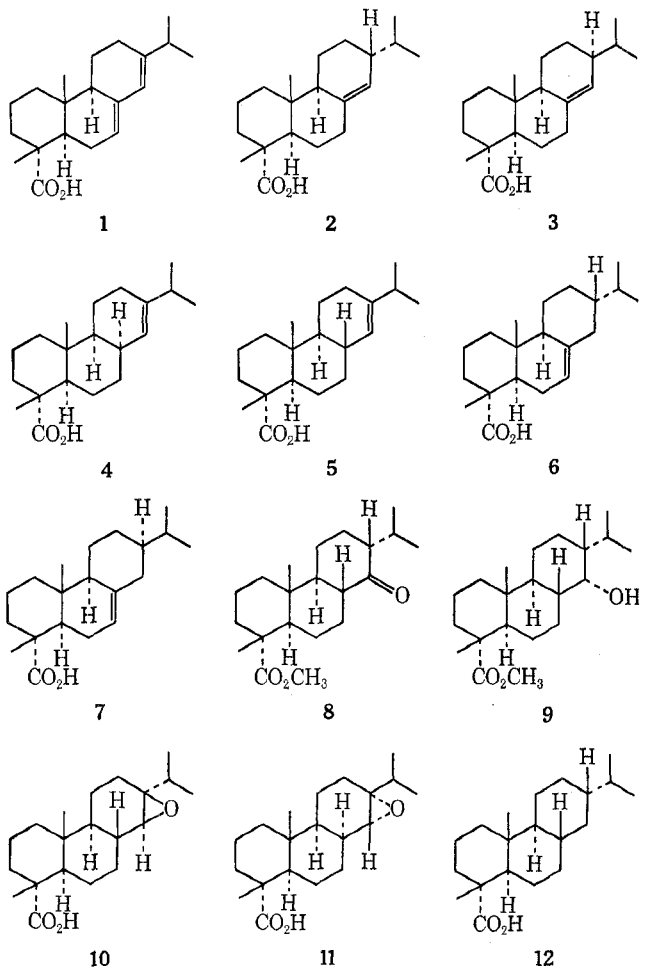
Unequivocal syntheses of 8α-abiet-13-en-18-oic (**4**), abiet-13-en-18-oic (**5**), and abiet-7-en-18-oic acids (**6**) are described. The stereochemical course of various reactions of these compounds as well as those of the two abiet-8-(14)-en-18-oic acids (**2** and **3**) are discussed.

Direct reduction of abietic acid (**1**) by either chemical or catalytic methods may, in theory, give rise to six different dihydro acids (**2**–**7**). At the time this work was initiated, the structure and stereochemistry of only one of these acids (**2**) was known with certainty,[1,3] although a number of other dihydroabietic acids had been prepared and characterized.[4] Following the initiation of this work, we learned that acids **3**, **5**, and **6** had been obtained and identified in addition to **2** from the lithium–ammonia reduction of abietic acid,[5] and structure **7** had been assigned to one of the acids obtained by Velluz, *et al.*[4b] In earlier work in this laboratory, structure **4** had been assigned to the $\Delta^{13}$-dihydro acid, which is present to the extent of *ca.* 15% in most samples of **2** prepared by reduction of abietic acid;[1] however, Burgstahler, Marx, and Zinkel[5] present rather convincing evidence that this impurity is in fact **5**. The earlier assignment of stereochemistry was based on the course of the rearrangement of an epoxide obtained in low yield from the oxidation of a sample of **2** obtained in the usual manner.[1] In order to reconcile this discrepancy, and also to confirm the structural and stereochemical assignments made by Burgstahler, *et al*,[5] the preparation of acids **4**–**6** by unambiguous routes has been carried out.




The synthesis of **5** was accomplished by first reducing the known[1,5] methyl 14-oxoabietan-18-oate (**8**) with sodium borohydride to give the 14α (axial) alcohol (**9**) contaminated with a small quantity of another alcohol, presumably the 14β-ol. The nmr spectrum of **9** was in accord with that expected for an axial alcohol, with H-14 appearing as a broadened singlet at δ 3.72 and the C-10 methyl peak at relatively high field (δ 0.84) as expected for a compound with a *trans* B,C-ring fusion.[1] Dehydration of this alcohol with phosphorus oxychloride–pyridine and hydrolysis of the esters afforded a mixture of the corresponding acids, from which **5** contaminated with a few per cent of **2** could be obtained. The nmr spectrum of **5** was in agreement with the assigned structure, showing the C-10 methyl signal at δ 0.86. Reaction of **5** with *m*-chloroperbenzoic acid gave epoxide **10**, which was markedly different from that reported earlier and assigned structure **11**.[1] By analogy with the hydrogenation of **5**, which affords almost exclusively abietan-18-oic acid (**12**),[1,5] and hydroboration of the methyl ester of **5**, which gives methyl 14β-hydroxyabietan-18-oate (**13**), it is assumed that **10** is the β oxide.

While this work was in progress, Cross and Myers obtained a glycol from the osmylation of the usual mixture of **2** and **4** or **5**[6] to which they assigned structure **14**; however, when acid **5** was treated with osmium tetroxide, a glycol was obtained which was identical with that prepared by Cross and Myers.[7] The nmr spectrum of this glycol showed H-14 as a doublet with a coupling constant of 9 Hz, indicating a *trans*-diaxial relationship between H-8 and H-14, and on

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(5) (a) J. N. Marx, Ph.D. Dissertation, University of Kansas, Sept 1965. (b) A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, **34**, 1550 (1969). We would like to thank Professor Burgstahler for sending us a copy of this manuscript prior to its publication.

(6) B. E. Cross and P. L. Myers, *J. Chem. Soc.*, *C*, 471 (1968).

(7) We would like to thank Professor Cross for a sample of this compound.