A Synthesis of Aromatic Steroids

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Starting with the allyl derivative **2**, the diketo acid **1a** was prepared. Reaction of its acyl chloride **1c** with the enamines **4a** and **4b** furnished the tetrones **5a** and **5b**, respectively. Enol benzoylation followed by hydrogenation afforded the triones **7**, **8**, and **9**, which could be correlated with **10**, the key internediate in Torgov's total synthesis of steroids. Treatment of **9** with *p*-toluenesulfonic acid in boiling toluene led to a mixture of six crystalline compounds, the structure of four of which is presented. Two of these, **14a** and **15a**, are known tetracyclic structures having the 14β configuration.

Described herein is a relatively short synthesis of aromatic steroids, proceeding through the intermediates **2**, **1**, **5**, **6**, and **9**—connected by heavy arrows in Chart I—and leading, among others, to the known racemic 11-oxygenated compounds **14a** and **15a**.

The novelty of this synthesis stems from the use of the hitherto unknown diketo acid **1a**, which we obtained from 2-allylcyclopentane-1,3-dione (**2**)[1] by treatment with permanganate followed by scission with periodic acid. Some reactions of this eight-carbon fragment of rings C and D were next investigated. The methyl ester **1b** was unreactive in Claisen-type reactions: no condensation with α- or β-tetralone, or self-condensation, in the presence of sodium hydride, took place. Also the anhydride **3** and the chloride **1c** were unreactive in Friedel–Crafts condensations with aromatic compounds (naphthalene, 1,7-dimethoxynaphthalene) in the presence of aluminum chloride.

Synthetic uses of the pyrrolidine enamines **4a** and **4b** have been previously reported,[2,3] especially in conjunction with preparation of heterocyclic steroids.[4] We have now found that in the 3-deoxy series the acid chloride **1c** monoacylates the enamine **4a**, and after aqueous work-up the β-diketone **5a** could be obtained, exhibiting the expected positive ferric chloride color reaction. In the 3-methoxy series the acyl chloride **1c** reacted in an analogous manner with the enamine **4b** to give the β-diketone **5b**.

Further elaboration of the steroid skeleton required that the carbonyl oxygen at C_8 be removed from the β-diketone moiety. One approach suggested preferential enol thio ether formation at this site and subsequent treatment with deactivated Raney nickel.[5] However, selective attack of **5b** by methanethiol at position 8 could not be achieved. An alternative solution was sought by selective enol acylation at this position. With acetic anhydride the results were not encouraging, but the enol benzoate **6** could be satisfactorily obtained by the action of benzoyl chloride in pyridine.

The benzoate **6** was then subjected to hydrogenation in methanol in the presence of 5% palladium on charcoal and three compounds were obtained: (a) the known trione **7**, mp 113–116°, (b) its Δ^8 derivative **9**, mp 118–122°, and (c) the 8ξ-hydroxy derivative **8**, mp 142–144°, all of which were further interrelated as follows. Compound **8** (*m/e* 330) was dehydrated with *p*-toluenesulfonic acid in boiling benzene to the unsaturated ketone **9**, and this, in turn, could be readily hydrogenated to the triketone **7** (*m/e* 314). From the evidence at hand it is not clear whether the transformation of the enol benzoate **6** into the trione **7** proceeds only through the intermediates **8** and **9**, or if direct hydrogenolysis of **6** into **7** is also taking place.

At this stage we had occasion to confirm the identity of **7** by direct comparison with a sample which we prepared according to Zakharychev and collaborators,[6] and also Daniewski, *et al.*[7] The former treated **10** (Chart II), the key intermediate in the Torgov total synthesis of estrogens, with mercuric acetate, and the latter group used the more convenient peracid oxidation of **10**. In both cases the product was the hemiacetal **11b**, which in solution is in equilibrium with the tautomeric open-chain structure **11a**. The hemiacetal **11b** and its 14-acetate were converted[6,7] by *p*-toluenesulfonic acid in boiling benzene into the trione **7**. In a restudy of the epoxidation reaction of **10** with *m*-chloroperbenzoic acid, using slightly different experimental conditions, we were able to isolate not only **11b**, but also the alcohol **8**, which must be the product of further epoxidation of **11** followed by an acid-catalyzed rearrangement. We found the ketol **11** to be unreactive toward the Jones reagent and also perchloric acid at room temperature, but hydrogenation followed by Jones oxidation furnished the saturated trione **7**. Finally, treatment of **11** with *N*-bromosuccinimide and perchloric acid yielded the unsaturated triketone **9**, accompanied by small amounts of **7** and the known[8] naphthalenic trione **12**.

The next stage of the synthesis was concerned with attempts to cyclize the trione **9** to tetracyclic structures. Cyclodehydration with *p*-toluenesulfonic acid proceeded much more sluggishly than in the 11-deoxy series. In boiling toluene a complex mixture of air-sensitive compounds was obtained, some of which were products of disproportionation. Thus after a 6-hr reflux an oily mixture was obtained, which on careful chromatography yielded the trione **12**; after a 16-hr reflux five additional products were isolated. One was *rac*-11-keto-14-isoequilenin-3-methyl ether (**14a**), mp 158–160°, reported by Birch and Subba Rao.[9] Another identified cyclization product was *rac*-11-keto-8-dehydro-14-isoestrone-3-methyl ether (**15a**), mp 174–176°, identical with a sample obtained by Jones oxidation of the known 17β-ol analog **15b**.[10]

The structure of the next three isolated compounds is less certain. One, melting at 125–128° (*m/e* 294), contained three oxygen atoms and exhibited a single carbonyl maximum at 5.82 μ, but no hydroxyl absorption. A doublet centered at 6.0 ppm points to a H–C–O moiety, probably at position 11. These data, including maxima at 230 and 302 nm, are compatible with the oxido structure **13**. The two remaining compounds, mp 164–166 (*m/e* 294) and 192–193° (*m/e* 312), contain a hydroxyl group and are at present under investigation. See Table I for nmr spectra.

Mass Spectrometry. One of us has previously shown[11] that the mass spectral behavior of 8(14)-seco estrone de-

Chart I

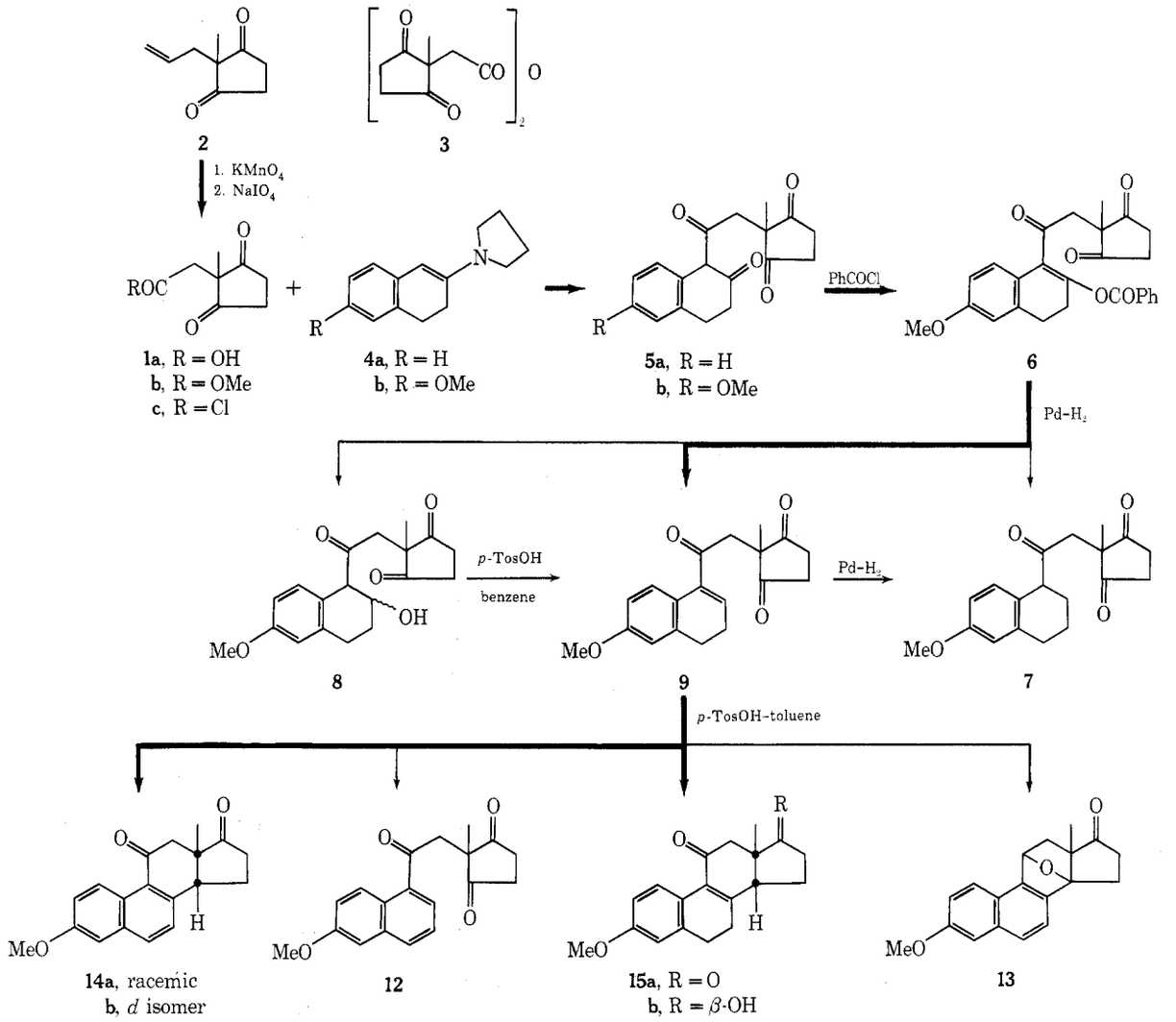
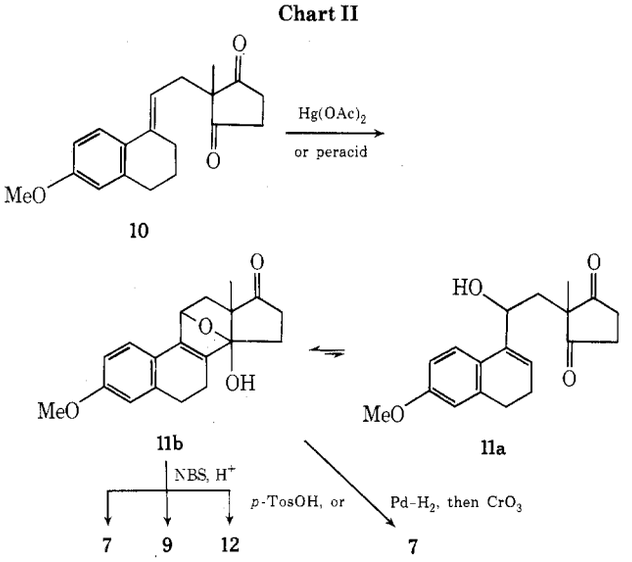


Chart II



rivatives is characterized by the formation of the bicyclic ion a (Chart III), which gives rise to the base peak in the spectrum of 8(14)-seco-14-keto-D-homoestrone-3-methyl ether. The present study shows that the seco ketones **5**, **7**, **8**, and **9** undergo the same type of decomposition on electron bombardment, the most intense fragmentation reaction being the cleavage of the benzylic 9–11 bond and the formation of the ions a, b, c, and h, respectively. In triketones **7**, **8**, and **9** a simple cleavage of this bond takes place, whereas the formation of the ion h from the molecular ion of **5b** is accompanied by migration of a hydrogen

Chart III

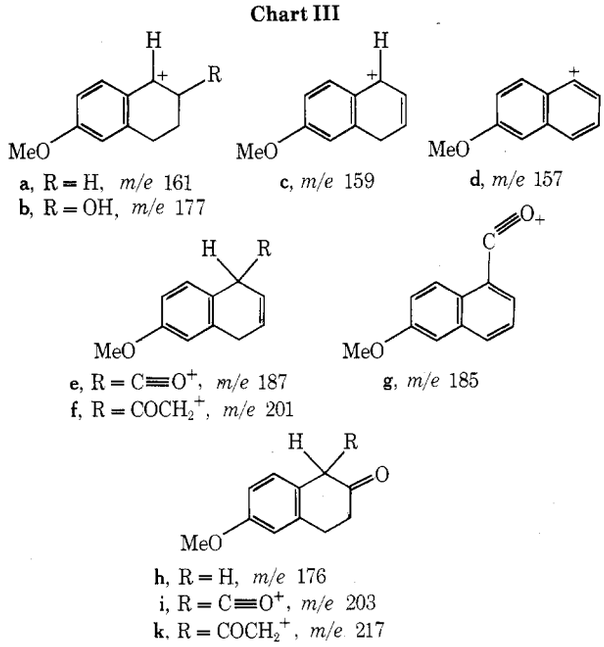
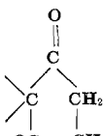


Table I
Nmr Spectra[a]

Compd	CH_3-(C_{18})		CH_2-(C_{12})	OCH_3-(C_3)	Phenyl (H_1)	Phenyl ($H_2 + H_4$)		CH_2-$COOCH_3$	OCH_3
1b	1.08	2.90						2.97	3.63
5b	1.11	2.93	3.46	3.83	7.25	6.75			
6	1.00	2.91	3.50	3.81	6.8	6.9	Benzoate 7.6 and 8.1		
7	1.01	2.88	3.19, d J = 3 Hz	3.77	6.68	6.82			
8	1.03	2.93	3.18	3.80	6.7	6.82			
9	1.13	2.98, d J = 3 Hz	3.6	3.8	7.1	6.8	7.5, d J = 9 Hz		
11b (in DMSO)	0.97			3.70	6.5	6.7			
13	1.4	2.9		3.9	7.2, 7.7 (5 H, m), 6.0 (1 H, C_{11}, d, J = 16 Hz)				
mp 164°	2.5 (!)			3.72	6.5–7.8 [3 H, m, + vinyl proton (?)]				
mp 192°	1.26		3.73		6.8 (2 H, m, aromatic) 7.1 (1 H, m, aromatic)				

[a] In parts per million.

Table II
Relative Intensities of the Characteristic Peaks in the Mass Spectra of Compounds 5b, 7, 8, 9, and 12

Compd	M^+	a	b	c	d	e	f	g	h	i	k
					m/e (rel intensity)						
5b	328 (71)								176 (100)	203 (21)	217 (0.5)
7	314 (13)	161 (100)									
8	330 (1.1)		177 (100)	159 (4.3)		187 (1.4)	201 (1)				
9	312 (90)			159 (100)		187 (44)	201 (25)				
12	310 (43)				157 (34)			185 (100)			

atom to the charged fragment (Table II). Unlike ketones **7** and **8**, the seco compounds **9** and **12** containing the unsaturated ring B show intense formation of the ions e and g, respectively. Interestingly, in the tetrone **5b** there is a substantial peak at m/e 203 (ion i), also arising from the cleavage of the 11–12 bond. It is possible that at least partial enolization of the 8-CO group occurs under mass spectrometric conditions, leading to the formation of the 8-hydroxy analog of the trione **9** with an 8–9 double bond. Possibly this double bond hinders the vinylic cleavage of the 9–11 bond, and this, in turn, increases the probability of the competitive α-cleavage on the opposite side of the 11-keto group, in the order **5b** < **9** < **12**. Indeed, in the mass spectra of the ketones **5b** and **9** the relative intensities of the respective ions (i and e) are 21 and 44%, whereas in the equilenin derivative **12** the same cleavage of the 11–12 bond is even more intense: the respective ion g is the base peak of the spectrum.

Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian Associates A-60 instrument in $CDCl_3$, using TMS as internal standard. Mass spectra were determined at 70 eV and 120–130° on an Atlas CH4 spectrometer equipped with a TO-4 source, using a direct inlet system. Comparison of samples was done with aid of ir, uv, and nmr spectra, as well as the consistent use of tlc (Merck A.G. silica gel plates F-254, with benzene–ethyl acetate mixtures ranging from 6:1 to 1:1; visualization of spots with phosphomolybdic acid followed by sulfuric acid).

α-(1,3-Diketo-2-methylcyclopentane)acetic Acid (1a). A solution of 60 g of potassium permanganate in 516 ml of water and 2400 ml of acetone was added, over a 30-min period, into a mechanically stirred solution of 30 g of the allyl derivative **2**[1] in 900 ml of acetone containing 12 ml of acetic acid and cooled in an ice–salt bath. After stirring with continued cooling for an additional 30 min, a solution of 30 g of sodium metabisulfite in 300 ml of water was dropped in over a 10-min period. The mixture was filtered with suction through a large sintered glass funnel, the manganese dioxide was washed with acetone, and the combined filtrates were concentrated at 50° to a volume of 900 ml and treated with a solution of 90 g of sodium metaperiodate in 1620 ml of water. The following morning the fine red-brown precipitate was removed by filtration through a pad of Celite and the filtrate was continuously extracted for 40 hr with ethyl acetate. Evaporation of the solvent gave 17 g of a solid, which on recrystallization from ether afforded a total of 15 g of the acid **1a**: mp 180–182°; λ_{max} (KBr) 5.7 (w), 5.8–5.9, 6.86, 7.02, 7.13, 7.54, 7.65, 8.25, 8.63, 9.30, 9.95, 11.15, and 12.40 μ; m/e 170.

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C,56.71; H, 5.90.

The methyl ester **1b** (diazomethane) had mp 94–95° (petroleum ether); λ_{max} (KBr) 5.78 μ; m/e 184.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found C, 58.62; H, 6.37.

The anhydride **3** was prepared by treatment of a solution of 690 mg of the acid **1a** in 40 ml of dry ether with 515 mg of dicyclohexylcarbodiimide. The swirled solution rapidly deposited dicyclohexylurea, followed by **3**. After 48 hr the solid was filtered off and extracted with methylene chloride. Evaporation of solvent and trituration with dry benzene afforded a total of 537 mg of **3**: mp 162–165°; λ_{max} (KBr) 5.55 and 5.84 μ; m/e 322.

Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found C, 59.88; H, 5.55.

***rac*-8(14)-Seco-1,3,5(10)-estratriene-8,11,14,17-tetrone (5a).** The acid chloride **1c** was prepared by refluxing 2 g of **1a** with 40 ml of thionyl chloride for exactly 15 min and evaporation of the solvent *in vacuo*. Addition of 10 ml of dry benzene and evaporation *in vacuo* was carried out three times.

The residual oily **1c** was treated with a solution of 2 g of the enamine **4a**[3] in 60 ml of dry benzene and the mixture was refluxed with stirring for 1 hr. The resulting suspension was cooled

and worked up with ice–water and ether. The aqueous phase was allowed to stand at room temperature for 2 days (solution A). The organic phase was washed with water, evaporated, and chromatographed on a "dry" column of 190 g of silica gel ("Kieselgel 60," 70–230 mesh ASTM). Elution with cyclohexane–ethyl acetate (3:1) gave a total of 450 mg of **5a**: mp 117–119° (methylene chloride–ether); λ_{max} (KBr) 5.75 and 6.3 μ; m/e 298; λ_{max} (EtOH) 248 nm (ϵ 11,000), shifting on addition of alkali to 268 nm, followed by rapid decomposition; ferric chloride test, positive.

Solution A deposited 350 mg of a solid which upon crystallization from methylene chloride–ether yielded an additional 195 mg of **5a**, mp 117–119°.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found C, 72.59; H, 5.90.

***rac*-3-Methoxy-8(14)-seco-1,3,5(10)-estratriene-8,11,14,17-tetrone (5b).** The acid **1a** (8.5 g) was converted into its chloride **1c** as described above, and treated with a solution of 8.5 g of the enamine **4b**[3] in 170 ml of dry benzene. The mixture was refluxed with mechanical stirring for 1 hr, cooled in ice, and treated dropwise over a 10-min period with 80 ml of water. The aqueous phase was reextracted with benzene and ether, and after several days, when additional oily material has separated from it, with methylene chloride. The combined extracts were evaporated to a gum which was chromatographed on 600 g of "Kieselgel 60." Elution with petroleum ether furnished 2 g of 6-methoxy-2-tetralone, and with 10 and 30% ethyl acetate in petroleum ether 4.8 g of the tetrone **5b** was obtained. Recrystallization from ether yielded a total of 3.8 g: mp 140–143°; λ_{max} (KBr) 5.55 (w) and 5.8 μ; m/e 328; λ_{max} (EtOH) 246, 282, and 330 nm (ϵ 13,800, 7500, and 4300).

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.26; H, 6.30.

***rac*-8-Benzoyloxy-3-methoxy-8(14)-seco-1,3,5(10),8-estratetraene-11,14,17-trione (6).** To an ice-cooled solution of 5.24 g of **5b** in 52 ml of dry pyridine was added 12 ml of benzoyl chloride. The reaction mixture was allowed to stand overnight at room temperature, whereupon ice and water were added up to a volume of 250 ml and the mixture was then stirred for 2 hr. The aqueous layer was decanted from the half-solid, which was washed with water and treated with 20 ml of ether. The resulting benzoate weighed 4.54 g, mp 127–129°. Usual work-up of the aqueous phase with ethyl acetate and chromatography over Florisil (30% ethyl acetate in petroleum ether) furnished an additional 1.9 g of the same material. The pure sample had mp 128–130° (ether); λ_{max} (KBr) 5.77, 5.87, and 5.94 μ (w); m/e 432; λ_{max} (EtOH) 228 and 260 nm (ϵ 21,200 and 13,700).

Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.01; H, 5.33.

Hydrogenation of the Enol Benzoate 6. A solution of 6 g of the benzoate **6** in 1 l. of methanol was hydrogenated for 10 hr at atmospheric pressure in the presence of 10 g of 5% palladium on charcoal. The oily product was carefully chromatographed on 300 g of Florisil. With 10% ether in benzene solid fractions were obtained, the first ones being pure ***rac*-3-methoxy-8(14)-seco-1,3,5(10)-estratriene-11,14,17-trione (7):** mp 113–116° (methanol); λ_{max} (KBr) 5.81, 5.87, 6.20, and 6.64 μ; λ_{max} (EtOH) 278 and 285 nm (ϵ 1900 and 1660) (reported mp 120–122°,[6] 116–117°[7]). Ir, mass, and nmr spectra were identical with those reported. Further elution with 10% ether in benzene gave solid mixtures containing **7** and ***rac*-3-methoxy-8(14)-seco-1,3,5(10),8-estratetraene-11,14,17-trione (9).** By means of laborious fractional crystallizations from methanol it was possible to separate **7** and **9**, the latter as a solvate having a characteristically wide melting point of about 76–86°, rising to 118–122° after drying *in vacuo* at 70°: λ_{max} (KBr) 5.80, 6.05, and 6.21 μ; m/e 312; λ_{max} (EtOH) 244 and 287 nm (ϵ 14,000 and 4300).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.79; H, 6.71.

The weights of pure **7** and **9** isolated were 1.27 and 1.26 g, respectively. Elution with 50% ether in benzene furnished a third crystalline substance. Its solution in ether was filtered to remove an accompanying high-melting impurity and then concentrated to afford a total of 0.45 g of ***rac*-8ξ-hydroxy-3-methoxy-8(14)-seco-1,3,5(10)-estratriene-11,14,17-trione (8):** mp 142.5–144° (ether); λ_{max} (KBr) 2.90, 5.70 (sh), 5.84, 6.23, and 6.65 μ; m/e 330; λ_{max} (EtOH) 275 and 282 nm (ϵ 1720 and 1610).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.80; H, 6.65.

Dehydration of the Ketol 8. A solution of 8 mg of **8** in 25 ml of benzene containing 200 mg of *p*-toluenesulfonic acid was refluxed for 30 min. The cooled solution was washed with water, bicarbonate, and water and then evaporated to furnish the tetraene **9**. Recrystallization from methanol gave 5 mg, mp 75–93°, identical with the solvated sample isolated from hydrogenation of **6**.

Hydrogenation of the Tetraene 9. A solution of 9 mg of **9** in 10 ml of ethyl acetate was hydrogenated for 3 hr at atmospheric pressure in the presence of 50 mg of 5% palladium on charcoal. The product was crystallized from methanol to give 7 mg of the trione **7**, mp 113–117°, identical with a sample isolated from hydrogenation of the benzoate **6**.

Treatment of *rac*-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (10) with *m*-Chloroperbenzoic Acid. A solution of 10.6 g of the tetraene **10**[12] in 125 ml of chloroform was treated at 0° with a cold solution of 7.8 g of *m*-chloroperbenzoic acid (80% pure) in 125 ml of chloroform. After standing overnight at room temperature the solution was washed with 5% potassium hydroxide solution and evaporated. The residue crystallized on addition of warm ether to furnish 4.84 g of ***rac*-14-hydroxy-3-methoxy-11,14-oxido-8(14)-seco-1,3,5(10),8-estratetraen-17-one (11b):** mp 154–155.5°; λ_{max} (KBr) 3.05, 5.75, 6.22, 6.40, and 6.70 μ; λ_{max} (EtOH) 268 nm (ϵ 13,000) [reported[7] mp 156–157°, λ_{max} (MeOH) 269 nm (ϵ 12,350)]. In most cases treatment of the main filtrate with perchloric acid–dioxane–water (0.6:25:3 ml) overnight at room temperature afforded additional amounts of the same compound. Chromatography of the residue on silica gel, using ethyl acetate–cyclohexane (1:1) as the eluting agent, furnished at first minute amounts of **11b**, followed by **8**. Recrystallization of the latter from methylene chloride–ether yielded 0.50 g, mp 140–141°, identical with a sample obtained from the hydrogenation of **6**.

Conversion of 11b into 7. A solution of 200 mg of **11b** in 10 ml of ethyl acetate was hydrogenated for 3 hr in the presence of 200 mg of 5% palladium on charcoal. The ultraviolet spectrum of the resulting gum showed that saturation of the 8–9 bond had taken place. A portion (40 mg) of this mixture of stereoisomeric alcohols was dissolved in 10 ml of acetone and treated at 0° with 0.3 ml of the Jones reagent. Usual work-up gave an oil which was chromatographed on Florisil. Elution with benzene and 2% ether in benzene afforded at first crystals of an unknown nature, mp 74–75°, followed by the trione **7** (10 mg).

Treatment of 11b with *N*-Bromosuccinimide and Acid. A warm solution of 4.74 g of the hemiketal **11b** in 150 ml of acetone was concentrated to 80 ml, cooled in an ice–salt bath, and treated with 2.62 g of *N*-bromosuccinimide, followed by 8.5 ml of 10% perchloric acid. After the solution was allowed to stand at 0° for 2 hr, several milliliters of aqueous bisulfite solution was added, followed by water and methylene chloride. The organic phase was washed with bicarbonate solution and evaporated to an oil which was dissolved in 40 ml of hot methanol and seeded with the ketone **9**. There was obtained 2.1 g of the solvated product having the characteristically wide melting point of 78–92°, identical with that of authentic material. The concentrated filtrate deposited on storage at room temperature for 3 days a crop of 0.55 g of the saturated trione **7**, mp 113–114°. Chromatography of the residue on silica gel furnished, with benzene–ethyl acetate (4:1), 0.2 g of ***rac*-3-methoxy-8(14)-seco-1,3,5(10),6,8-estrapentaene-11,14,17-trione (12),** mp 110–112° (ether or methanol), identical in all respects with an authentic sample prepared by treatment of **7** with DDQ, for which mp 115° was reported.[8]

Treatment of 9 with *p*-Toluenesulfonic Acid in Toluene. A. A solution of 1 g of **9** and 1.5 g of *p*-toluenesulfonic acid monohydrate in 100 ml of toluene was refluxed for 6 hr, using a Dean-Stark water collector. The cooled reaction mixture was washed with water and bicarbonate, and the gum obtained after evaporation of the solvent was chromatographed on 50 g of Florisil. With 1% ether in benzene there was obtained 100 mg of a soft solid, which after two recrystallizations from ether melted at 110–112°; it was identical with the naphthalenic trione **12** obtained above. Elution with more polar solvents gave mixtures of materials described below.

B. A solution of 2.8 g of **9** and 5.3 g of *p*-toluenesulfonic acid in 280 ml of toluene was refluxed for 15 hr. The oily product was chromatographed on 140 g of Florisil. With 1% ether in benzene there was obtained 10 mg of a product assumed to be ***rac*-11,14-oxidoequilenin-3-methyl ether (13):** mp 125–128° (methanol); λ_{max} (KBr) 5.82 μ; m/e 294; λ_{max} (EtOH) 230 and 302 nm (ϵ 24,000 and 6100).

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.59; H, 6.30.

Continued elution with 1% ether in benzene furnished a solid which after crystallization from methanol afforded 50 mg of *rac*-

11-keto-14-isoequilenin-3-methyl ether (14a), mp 158–160°,[13] *m/e* 294, whose identity was confirmed by comparison of its ir in potassium bromide with that of the optically active form **14b**, mp 187–189°, obtained by methylation of 11-keto-14-isoequilenin[14,15] with diazomethane.[18]

Elution with 5% ether in benzene yielded a solid which after recrystallization from methanol and then ether furnished 52 mg of a material, mp 164–166°, *m/e* 294. Its spectrum exhibited a hydroxyl and a peak at 5.90 μ, λ_{max} (EtOH) 222, 254, and 327 nm (ϵ 35,000, 13,000, and 3500), shifting on addition of alkali to 244 and 380 nm (ϵ 29,000 and 4000), reversible on acidification to the original wavelengths. The location of the methyl peak at 2.5 ppm shows unsaturation at the adjacent carbon atom.

Further elution with 5% ether in benzene furnished a mixture of solids, which on recrystallization from ethanol deposited 25 mg of ***rac*-11-keto-8-dehydro-14-isoestrone-3-methyl ether (15a)**: mp 174–176°; *m/e* 296; λ_{max} (KBr) 5.75 and 6.05 μ; λ_{max} (EtOH) 245, 295, and 315 nm (ϵ 17,000, 4800, and 4810). The identity of this compound was established by the Jones oxidation of an authentic sample of the corresponding 17β-ol analog **15b**,[10] and direct comparison of the product with our sample. The nonidentity with its 14α epimer, mp 161–163°, was confirmed by direct comparison with a sample of the latter.[17]

The next crop from crystallization of **15a** provided yet another material. Recrystallization furnished 53 mg, mp 192–193°, *m/e* 312, exhibiting a hydroxyl absorption and a carbonyl at 5.75 μ, λ_{max} (EtOH) 275 and 281 nm (ϵ 1500 and 1400), and a peak at 3.73 ppm.

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Registry No.—**1a**, 51270-51-0; **1b**, 51270-52-1; **1c**, 51270-53-2; **2**, 26828-48-8; **3**, 51270-54-3; **4a**, 21403-95-2; **4b**, 20915-80-4; **5a**, 51270-55-4; **5b**, 51270-56-5; **6**, 51270-57-6; **7**, 51270-58-7; **8**, 51270-59-8; **9**, 51270-60-1; **10**, 899-79-6; **11b**, 24421-61-2; **12**, 41021-02-7; **13**, 51270-61-2; **14a**, 26584-94-1; **15a**, 26435-94-9; **16**, 51270-62-3; *m*-chloroperbenzoic acid, 937-14-4.

References and Notes

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(14) "Inactive 11-oxoequilenin" described[15] is in fact 11-keto-14-isoequilenin, for hydrogenolysis of its 3-methyl ether for 4 hr at room temperature in acetic acid solution, in the presence of 5% palladium on charcoal and perchloric acid, afforded 14-isoequilenin-3-methyl ether, mp 116–118° (lit.[16] mp 119° and, for equilenin-3-methyl ether, mp 193–194°). Furthermore, the above methyl ether, mp 187–189°, was not changed by heating with hydrochloric acid–acetic acid (1:4) for 1 hr at 100°, treatment which might be expected to cause isomerization of 11-ketoequilenin-3-methyl ether to **14b**.
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(18) Note Added in Proof. We have now prepared **14a** also by polyphosphoric acid cyclization of the pure "unnatural" stereoisomer of *rac*-5-(6-methoxy-2-naphthyl)-1-methyl-2-oxocyclopentane-1-acetic acid, mp 151–153° [E. G. Brain, F. Cassidy, M. F. Constantine, J. C. Hanson and D. J. D. Tidy, *J. Chem. Soc. C*, 3846 (1971)], kindly provided by Dr. Brain of the Beecham Laboratories. The product, mp 158–159°, was identical with **14a** described above.

Nonbenzenoid Aromatic Systems. X.[1a] Formation, Nuclear Magnetic Resonance Spectral Identification, and Reactions of Both Meisenheimer Type and Methyleneazulenate Anions

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The reaction products from azulene and certain methylazulenes with several nucleophilic strong bases have been observed and identified by nmr spectroscopy. With azulene, lithium dicyclohexylamide (**3**) and tritylsodium (**18**) yield exclusively products of nucleophilic addition to the ring 6 position, 6-X-6*H*-azulenate anions, while, with lithium dimethylamide (**15**), methyllithium (**23**), and sodium methylsulfinylmethide (**27**), products derived from nucleophilic addition to both the azulene ring 4 (predominant) and 6 positions are observed. The Meisenheimer type of addition complexes formed with the amide nucleophiles (**3** and **15**) and azulene were shown to thermally equilibrate while those complexes resulting from ring addition by the carbon nucleophiles (**18**, **23**, and **27**) were thermally stable. Competitive nucleophilic addition and methyl group proton abstraction reactions were examined with some of these nucleophilic bases and 4,6,8-trimethylazulene (**31**). Exclusive proton abstraction was observed in the reaction of sodium *N*-methylanilide, **18**, or **27** with **31** to yield mixtures of the methyleneazulenate anions **32** and **33**. However, amide **15** reacted with **31** by nucleophilic addition to the 4 and 6 positions, the initially formed mixture being thermally equilibrated. Carbonation of lithium 6-dicyclohexylamino-6*H*-azulenate (**20**) yields a mixture of azulene mono- (1 and 2), di- (1,2 and 1,3), and tricarboxylic (1,2,3) acids. Carbonation of a mixture of lithium 6-dimethylamino-6*H*-azulenate and its 4 isomer yields only azulene. Other related reactions are presented, and discussions of the involved processes are given.

Our investigations of the effects of the five nonequivalent azulene ring positions on the solvolysis of β-azulylethyl arenesulfonates have thus far dealt with the ethyl side chain attached to the azulene 1,[2] 4,[3] and 6 positions.[3] 2-(1-Azulyl)ethanol was synthesized by electrophilic substitution of azulene.[4] The 2-(4- (**2**) and 2-(6-azulyl)ethanol