served to separate the mixture of alcohols (9.2 mCi) from unchanged ketone (1.17 g, 77%). Actually isolated after repetitive tlc were (22*R*)-hydroxy-22-^{3}H-cholesteryl benzoate (11.3 mg, 0.24 mCi) and (22*S*)-hydroxy-22-^{3}H-cholesteryl benzoate (110 mg, 6.2 mCi), each shown to be radiochemically pure and free from the other.

Jones Oxidation of (22*S*)-Hydroxy-22-^{3}H-cholesteryl Benzoate.—An aliquot was cocrystallized with 45 mg of cold material (specific activity of first crop, 4.03×10^8 dpm/mmol; first crop recrystallized, 4.06×10^8 dpm/mmol). The alcohol (40 mg) was dissolved in acetone (5 ml) and was stirred at 15–20° for 25 min with 3 drops of Jones reagent. The resulting ketone was crystallized from ethyl acetate to constant specific activity (first crop, 1.74×10^6 dpm/mmol; first crop recrystallized, 1.16×10^6 dpm/mmol; first crop recrystallized twice, 1.20×10^6 dpm/mmol). Thus >99.6% of the tritium was at C-22 in the alcohol.

Jones Oxidation of (22*R*)-Hydroxy-22-^{3}H-cholesteryl Benzoate.—An aliquot was cocrystallized with 23 mg of cold material (specific activity of first crop, 5.33×10^6 dpm/mmol; first crop recrystallized, 5.36×10^6 dpm/mmol). Jones oxidation (20 mg of alcohol, 4 ml of acetone, 1 drop of Jones reagent, 20 min) gave 22-ketocholesteryl benzoate (first crop, 1.5×10^4 dpm/mmol; first crop recrystallized, 1.4×10^4 dpm/mmol). Thus >99.6% of the tritium was at C-22.

(22*S*)-^{3}H-Cholesterol.—To a cooled, stirred solution of (22*S*)-hydroxy-22-^{3}H-cholesteryl benzoate (66 mg, 3.7 mCi) in pyridine (1 ml) was added an excess (5 drops) of methanesulfonyl chloride. The mixture stood 16 hr at room temperature and then was cooled and stirred while water and ether were added. The aqueous layer was extracted with ether and the combined ether extracts were washed successively with 0.5 *N* hydrochloric acid, sodium bicarbonate solution and water, and dried. The methanesulfonate so obtained was stirred with excess lithium aluminum hydride in ether overnight. The mixture was cooled while water was added dropwise followed by sufficient 2 *N* sulfuric acid to dissolve the hydroxides. The ether layer was washed with dilute sodium carbonate solution and twice with saturated sodium chloride. (22*S*)-^{3}H-Cholesterol (1.3 mCi) was separated from the mixture of products by preparative tlc on silica gel. Its purity was demonstrated by tlc on silica gel–silver nitrate (19:1 benzene–methanol, single radioactive peak), and by cocrystallization with cold material which had been purified *via* the dibromide (first crop, 6.68×10^6 dpm/mmol; first crop recrystallized, 6.71×10^6 dpm/mmol).

(22*R*)-^{3}H-Cholesterol.—To a cooled stirred solution of (22*R*)-hydroxy-22-^{3}H-cholesteryl benzoate (11.3 mg, 0.24 mCi) in pyridine (0.5 ml) was added 3 drops of methanesulfonyl chloride. After standing 16 hr at room temperature the mixture was worked up as described above and the lithium aluminum hydride reduction and separation of the products were carried out in a similar manner. (22*R*)-^{3}H-Cholesterol (94 μCi) showed a single radioactive peak on tlc (silica gel–silver nitrate) and its purity was also demonstrated by cocrystallization with cold material (first crop, 4.21×10^6 dpm/mmol; first crop recrystallized, 4.23 dpm/mmol).[15]

Registry No.—**2a**, 17954-94-8; **2b**, 17954-95-9; **2a** (22-^{3}H), 17954-96-0; (**2b** (22-^{3}H), 17954-97-1; **3a**, 17954-98-2; **3b**, 17954-99-3; **3a** dibenzoate, 17955-00-9; **3b** dibenzoate, 17955-01-0; **5a**, 17955-02-1; **5b**, 17955-03-2; **6a**, 17955-04-3; **6b**, 17955-05-4; 22-ketocholesteryl benzoate, 17976-38-4; (22*S*)-^{3}H-cholesterol, 17955-06-5; (22*R*)-^{3}H cholesterol, 17955-07-6.

(15) NOTE ADDED IN PROOF.—While this paper was at the printers, Mori *et al.* [*Chem. Pharm. Bull. Jap.*, **16**, 1407 (1968)], had reversed their previous configurational assignment[3] from (22*S*)- to (22*R*)-hydroxycholesterol for the product isolated by Stabursvik.[7] This is in agreement with our conclusions, and provides added support for our results.

The Total Synthesis of Some (±)-18-Methyl-9β,10α-androstanes and (±)-18-Methyl-9β,10α-D-homoandrostanes

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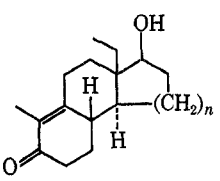
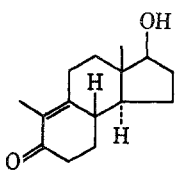
Received August 2, 1968

Synthetic methods developed for the preparation of retrotestosterone have been extended to the synthesis of its analog containing an 18-methyl group and to the 18-methyl-D-homo structure. The synthesis of the corresponding 17α-ethinyl and 17α-ethyl compounds is also described.

In 1966, the nonphotolytic partial synthesis of retrosteroids (*i.e.*, 9β,10α-steroids) of the pregnane series was reported[1] by workers in these laboratories. The synthesis used as the key intermediate a BCD tricyclic compound. More recently the total synthesis, in both racemic[2] and optically active modifications,[3] of such a tricyclic compound in the androstane series was described. As it is known that 18-methyl steroids of the normal series have interesting biological activities, it was decided to extend the synthetic methods that had been developed to the preparation of the title compounds. The initial targets in the present work were thus the tricyclic compounds **1** and **2** which correspond to the intermediate **3** used in the synthesis of retrotestosterone.



1, $n=1$
2, $n=2$



3

The method used to prepare compound **1** (Scheme I) closely paralleled the procedures of the previous workers.[2,4] The known 2-ethylcyclopentane-1,3-dione[5] **4** was converted into the indanone **5** by Michael addition of methyl vinyl ketone and cyclization of the resultant adduct with *p*-toluenesulfonic acid. The bicyclo[3.2.1]octane derivative **6** was isolated as a very minor by-product of this reaction and was characterized by analytical and spectral data. It was not possible to ascertain if **6** was a single stereoisomer because, while it appeared to be homogeneous on thin

(1) M. Uskokovic, J. Iacobelli, R. Philion, and T. Williams, *J. Amer. Chem. Soc.*, **88**, 4538 (1966).

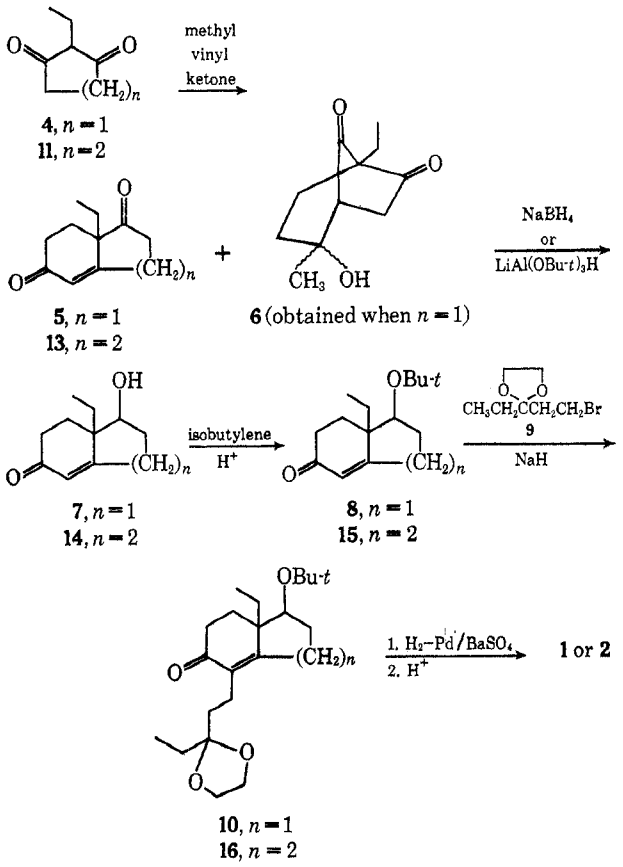
(2) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967).

(3) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron*, **24**, 2039 (1968).

(4) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2022 (1959).

(5) H. Smith, *et al.*, *ibid.*, 4472 (1964).

SCHEME I

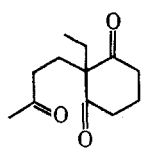


layer chromatograms, it decomposed on attempted gas chromatography (gc).

Reduction of **5** with sodium borohydride at −10°, or with lithium aluminum tri(*t*-butoxy)hydride at ambient temperature, led to the indanolone **7** in high yield. There was little detectable difference between the products from the two methods of reduction, crude **7** being obtained as a somewhat unstable oil of 85–90% purity, which yielded a crystalline 2,4-dinitrophenylhydrazone.

The unpurified oil was converted into the *t*-butyl ether **8** which was purified either by crystallization or, on a large scale, by molecular distillation. Alkylation of **8** with the bromo ketal **9** and chromatography of the crude product gave a gum in 50% yield which contained 80–85% of **10**. This material was hydrogenated over palladium on barium sulfate and then treated with mineral acid to give **1** in 40–45% yield by direct crystallization.

The preparation of **2** started by Michael addition of methyl vinyl ketone to 2-ethylcyclohexane-1,3-dione[6] (**11**). The resultant adduct **12** upon cyclization with



12

pyrrolidine in benzene gave the dione **13** in 54% yield. The problems involved in such a cyclization have been discussed by various workers.[7] Initially, when the process used to prepare the analogous compound containing an angular methyl group[8] was employed, **13** was obtained only in poor yield. It was concluded eventually that the concentration of pyrrolidine used for the cyclization is critical and that provision must be made to hold it constant while ensuring an adequate reaction time. This conclusion is in conflict with a preparation of **13** which has appeared recently in the patent literature.[9] The author reports the cyclization of **12** using pyrrolidine in benzene under reflux without any special precautions to give **13** in 49% yield. Reduction of **13** to the crystalline alcohol **14** was accomplished with lithium aluminum tri(*t*-butoxy)-hydride, although in the light of our experience with the reduction of **5** and of a recent report,[9] sodium borohydride at a low temperature should be equally satisfactory. Crude **14** was converted into the *t*-butyl ether **15** which was used without further purification in the next step of the synthesis.

The alkylation of **15** with the bromo ketal **9** proved unexpectedly troublesome. Despite variations in the solvent (dimethyl sulfoxide, dimethylformamide, triglyme), the base (sodium hydride, potassium hydride), the reaction temperature (25 and 50°), and the proportions of the reactants, the ratio of **16** to **15** in the product was never better than 3:2. A highly purified sample of **16** was obtained by arduous chromatography of such a mixture but on a large scale it was more convenient to effect some separation of **15** and **16** by molecular distillation, although even this was complicated by the relatively high melting point of **15**. Using this technique, about 50% of the starting material (**15**) was recoverable and could be reused, although it contained up to 30% of **16** and other impurities. The product fractions contained 55–60% of **16** and 5–10% of **15**, but the weight obtained was only *ca.* 50% of the weight of **15** put into the alkylation. This material was satisfactory for conversion to **2**.

The hydrogenation of **16** over 10% palladium on barium sulfate and subsequent cyclization with acid to **2** was first examined using material of high purity. The hydrogenation product was shown by gc to be a complex mixture and the pattern of the chromatogram was not altered by attempted equilibration with sodium methoxide. Surprisingly, the crude cyclization product appeared to have a purity of 84% when assayed by gc, but on crystallization only 41% of **2** could be isolated. These results are comparable to those obtained in the preparation of **1** and suggest that the hydrogenation causes considerable by-product formation, and that, after treatment with acid to effect cyclization, gc failed to resolve all the materials present.

Compounds **1** and **2** were converted into their respective acetates and these were hydrogenated over rhodium on alumina in ethanol–hydrochloric acid.[1,10] Saponification of the crude products and crystallization gave the saturated tricyclic keto alcohols **17** and **18**. These on reaction with methyl vinyl ketone under

(6) H. Smith, *J. Chem. Soc.*, 803 (1953).

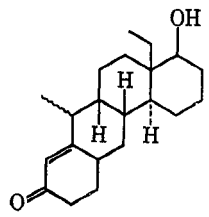
(7) (a) T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 3785 (1963); (b) N. L. Wendler, H. L. Slates, and M. Tishler, *ibid.*, **73**, 3816 (1951).

(8) S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961).

(9) M. Los, U. S. Patent 3,321,488 (1967).

(10) R. A. Micheli, J. N. Gardner, R. Dubuis, and P. Buchschacher, *J. Org. Chem.*, in press.

carefully controlled conditions[11] gave the testosterone analogs **19** and **20** in 25–30% yield, allowance being made for recovery of 40–50% of the starting tricyclic compounds. Both **19** and **20** were rather soluble compounds and purification was wasteful of material. Fortunately, the diones **21** and **22**, obtained by oxidation with Jones reagent,[12] were relatively insoluble and could be obtained in good purity and yield from impure samples of **19** and **20**. The anthrasteroid **23** was isolated, because of its insolubility, as a by-product of the preparation of **19** and was characterized by analyt-



23

ical and spectral data, the presence of a doublet at 1.08 ppm in the nmr spectrum, assignable to the 7ζ-methyl group, being especially significant.

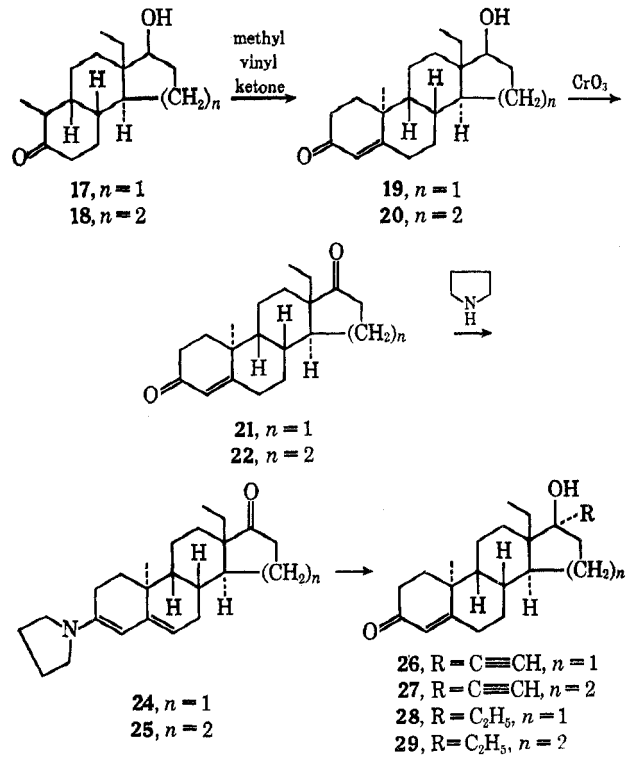
The diones **21** and **22** were converted into the enamines **24** and **25** by reaction with pyrrolidine. The preparation of **24** was investigated first and until a technique which gave a crystalline product was discovered no **24** could be isolated. The same method of preparation was then successful for **25**. Both **24** and **25** reacted slowly with lithium acetylide–ethylenediamine complex[13] and **24** would not react with methylmagnesium iodide. These results are not unexpected.[14] Selective hydrogenation of **26** and **27** then led to the 17α-ethyl compounds **28** and **29**.

No mention has been made of the stereochemistry of the initial tetracyclic products **19** and **20**. Analogy with the synthesis[1,2] of retrotestosterone leads to the configurations shown (Scheme II) at the 8, 9, 10, and 14 positions. There is no reason to suppose that this analogy is incorrect, and the available data support it. Comparison of the nmr spectra of the compounds reported in this paper with those obtained for the corresponding intermediates in the synthesis of retrotestosterone reveals no inconsistencies, and in some cases (*e.g.*, **17**) there is remarkably close correspondence in the fine structure. The hydrogenation of compounds **1** and **2** and their derivatives is discussed in more detail elsewhere,[10] but it may be mentioned that the stereochemistry assigned to **17** and **18** is supported by the fact that the crude hydrogenation products upon gc give elution patterns closely related to those obtained from the hydrogenation products of **3**.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope. Except where noted to the contrary, infrared and ultraviolet data refer to solutions in $CHCl_3$ and C_2H_5OH, respectively, and nmr spectra to solutions in $CDCl_3$ with $Si(CH_3)_4$ as internal standard. Unless otherwise stated, all products were isolated by extraction with an organic solvent, the extract being washed

SCHEME II



with brine and dried over anhydrous $MgSO_4$. Gas chromatography was performed on an F & M Model 810 using a hydrogen flame detector. The column was constructed from 6 ft × 0.25 in. aluminum tubing and employed 60–70 mesh Anakrom ABS as the support with 1% polyethylene glycol monosterate as the stationary phase. The carrier gas was nitrogen (100 ml/min) and the temperature was programmed from 100 to 260° at 8°/min. The adsorbent for tlc was silica gel.

dl-**7,7a-Dihydro-7a-ethyl-1,5(6H)-indandione (5).**—Methyl vinyl ketone (260 ml), *dry* 2-ethylcyclopentane-1,3-dione (**4**)[5,15] (240 g), and a solution of KOH (1 g) in CH_3OH (800 ml) were heated together under reflux for 7 hr. The CH_3OH was evaporated under reduced pressure and to the residue was added *p*-toluenesulfonic acid (16 g) in benzene (690 ml). The reaction solution was then heated under reflux using a Dean–Stark water separator, until no more water collected. After cooling, the solution was washed with saturated $NaHCO_3$ solution until free of acid and dried, and the solvent evaporated. The residue was distilled at 128° (0.12 mm) and the distillate, which crystallized, was recrystallized from acetone–hexane to yield **5** (168 g), mp 83–86.5°. A second crop (44 g) from ether had mp 85.5–87°; total yield 212 g (60%). Pure material obtained by crystallization from ether had mp 86–88°. The analytical sample was prepared by sublimation at 75° (35 μ): ir 1740 and 1660 cm^{-1}; uv max 239–240 mμ (ε 10,600). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.80; H, 8.29.

4ζ-Hydroxy-1-ethyl-4ζ-methylbicyclo[3.2.1]octane-7,8-dione (6).—On one occasion crystallization from ether of the mother liquors from the second crop of **5** resulted in the isolation of a small amount of **6**: mp 144–153° after crystallization from CH_3OH; ir (KBr) 3400, 1710 and 1670 cm^{-1}; nmr δ 1.42 ppm (s, 3, 4ζ-CH_3C). *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.50; H, 8.42.

dl-**7,7a-Dihydro-7aβ-ethyl-1β-hydroxy-5(6H)-indanone (7).**—Finely powdered **5** (211 g) as a suspension in C_2H_5OH (1000 ml) was agitated and cooled to −10°. A solution of $NaBH_4$ (13.2 g) in C_2H_5OH (1200 ml) was added over 30 min while the temperature was maintained at −5 to −10°. The mixture was stirred for 1 hr while warming to 5°. The clear solution was then cooled to −5 to −10° and 3 *N* HCl added until the pH was 5–7. The

(11) A. M. Krubiner, G. Saucy, and E. P. Oliveto, *J. Org. Chem.*, **33**, 3548 (1968).

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(13) G. C. Buzby, Jr., *et al.*, *J. Med. Chem.*, **9**, 339 (1966).

(14) K. Hiraga, *Chem. Pharm. Bull.* (Tokyo), **13**, 1289 (1965).

(15) 2-Ethylcyclopentane-1,3-dione undergoes slow decomposition on storage in the refrigerator. It develops a moist appearance. It is essential that the material used in this reaction be dry and pure. The presence of moisture results in lower yields, and on two occasions when material that had been stored for about 12 months was used, vigorous exothermic decomposition occurred during the heating with *p*-toluenesulfonic acid.

C_2H_5OH was evaporated under vacuum and the residue dissolved in EtOAc (500 ml). This solution was washed, dried and concentrated to leave **7** (214 g) as an oil of 85–90% purity as determined by gc. Purification by preparative tlc in the system $CHCl_3$–EtOAc (19:1) gave a sample of 91% purity: uv max 241 (ϵ 11,370); ir 3620 and 1660 cm^{-1}.

7 formed a 2,4-dinitrophenylhydrazone which crystallized from C_2H_5OH: mp 128–132°; uv max 286 (ϵ 27,800) and 256 (16,600). *Anal.* Calcd for $C_{17}H_{20}N_4O_5$: C, 56.64; H, 5.59; N, 15.54. Found: C, 56.39; H, 5.81; N, 15.24.

***dl*-1β-*t*-Butoxy-7,7a-dihydro-7aβ-ethyl-5(6H)-indanone (8).**—Compound **7** (214 g) in CH_2Cl_2 (1900 ml) was treated with boron trifluoride etherate (47% in ether; 97 ml) and H_3PO_4 (100%; 32 ml).[16] Isobutylene (liquefied by cooling; 375 g) was added over 1 hr. The excess isobutylene was then evaporated under vacuum and the reaction mixture brought to pH 7 by addition of 14% aqueous NH_4OH. The solvent was evaporated under vacuum and the residue taken up in EtOAc and washed with saturated $NaHCO_3$ solution. The residue (277 g), obtained after removal of the solvent, was diluted with corn oil and distilled at 44–80° (35–20 μ) in a centrifugal molecular still to yield crystalline **8** (233 g). An analytical sample obtained by crystallization from hexane had mp 53–54°; ir 1660 cm^{-1}; uv max 240–241 mμ (ϵ 12,900). *Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.11; H, 9.95.

***dl*-1β-*t*-Butoxy-7,7a-dihydro-7aβ-ethyl-4-(3′,3′-ethylenedioxypentyl)-5,6(H)-indanone (10).**—NaH (52% in mineral oil; 19.3 g) was washed with hexane by decantation and dissolved in DMSO (800 ml) by warming at 70° in an atmosphere of N_2. To this solution at 20° was added **8** (100 g) in DMSO (200 ml), the addition taking 30 min. 1-Bromo-3,3-ethylenedioxypentane (**9**)[2] (86.5 g) was then introduced and the mixture was stirred for 4 hr. Saturated NH_4Cl solution was added, while cooling at 20°, until the reaction mixture reached pH 7. The product was isolated by extraction with EtOAc and chromatographed on Florisil (1.4 kg) in hexane, fractions of volume 1.4 l. being collected. Elution with hexane (14 l.) and hexane–ether (4:1, 21 l.; 1:1, 14 l.) afforded **10** (76 g) as an oil in fractions 5–36, purity 80–85% by gc. An analytical sample (97% by gc) was obtained by preparative tlc in the system $CHCl_3$–EtOAc (19:1): ir 1660 cm^{-1}; uv max 250 mμ (ϵ 11,750). *Anal.* Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.69; H, 10.04.

***dl*-1,2,3,3a,4,5,8,9,9aβ,9bα-Decahydro-3aβ-ethyl-3β-hydroxy-6-methyl-7H-benz[*e*]inden-7-one (1).**—A solution of **10** (76 g) in C_2H_5OH (700 ml) was agitated in an atmosphere of H_2 in the presence of 10% Pd–$BaSO_4$ (20 g) until uptake of H_2 ceased. The catalyst was removed by filtration and 3 *N* HCl (340 ml) added to the filtrate. The solution was heated at reflux for 2.5 hr, cooled and adjusted to pH 7 with 3 *N* NaOH. After concentration under reduced pressure, the product was isolated by extraction with EtOAc. After evaporation of the solvent, the residue was crystallized from CH_3OH to yield **1** (15.2 g), mp 148–158°. A second crop (7.5 g) from ether had mp 150–158°. Crystallization from acetone–hexane gave an analytical sample: mp 151–153°; ir 3620, 1660 and 1605 cm^{-1}; uv max 249 mμ (ϵ 15,800); nmr δ 1.80 ppm (s, 3, CH_3C). (Compound **1** appears to exhibit polymorphism. The initial samples melted at or below 153°, but in subsequent preparations crystals were present in the melt up to 158°. No other difference between the various samples could be detected.) *Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.57; H, 9.89

***dl*-1,2,3,3a,4,5,8,9,9aβ,9βα-Decahydro-3aβ-ethyl-3β-hydroxy-6-methyl-7H-benz[*e*]inden-7-one Acetate.**—Compound **1** (10 g) was acetylated in pyridine (20 ml) and Ac_2O (10 ml) at ambient temperature. The acetate (7.2 g) crystallized from aqueous CH_3OH, mp 72–83°. Recrystallization from the same solvent and then from hexane gave pure material: mp 83.5–85°; ir 1725, 1660, 1610 and 1250 cm^{-1}; uv max 248 mμ (ϵ 15,900). *Anal.* Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.35; H, 9.21.

***dl*-1,2,3,3a,4,5,5aβ,6,8,9,9aβ,9bα-Dodecahydro-3aβ-ethyl-3β-hydroxy-6β-methyl-7H-benz[*e*]inden-7-one (17).**—The aforegoing acetate (8.7 g) in C_2H_5OH (250 ml) and 3 *N* HCl (28 ml) was hydrogenated over 5% Rh–Al_2O_3 (2.7 g) until uptake of H_2 ceased. The catalyst was removed by filtration, 3 *N* NaOH was added to bring the solution to pH 7, and the solvent was evaporated under vacuum. After extraction with EtOAc and evaporation of solvent, the residue (8.9 g) was dissolved in CH_3OH (30 ml) and treated, under N_2, with KOH solution (13% in CH_3OH–H_2O 9:1; 15 ml). After 18 hr at room temperature the solution was neutralized with 3 *N* HCl, then concentrated under vacuum and the product isolated by extraction with EtOAc. Evaporation of the solvent and crystallization from ether gave **17** (4.5 g), mp 119–138°. A second crop (0.3 g) from the same solvent had mp 105–114°. Crystallization from aqueous CH_3OH gave pure material: mp 111–114°; ir 3610 and 1705 cm^{-1}; nmr δ 1.01 ppm (d, 3, J = 6.5 Hz, CH_3CH). (Melting points ranging from 107 to 140° were observed for different samples of **17**. Sometimes the melting point changed drastically on recrystallization. No inhomogeneity could be detected and the behavior is most likely due to polymorphism.) *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.61; H, 10.62.

***dl*-17β-Hydroxy-18-methyl-9β,10α-androst-4-en-3-one (19).**—NaOH (freshly powdered, 46 mg) was dissolved in *t*-butyl alcohol (75 ml) at 50° under N_2. Compound **17** (3.64 g) was added and followed for 40 min by methyl vinyl ketone (0.79 g) in benzene (8.5 ml). After a further 20 min, AcOH (0.65 ml) was added and the solvent was evaporated at 45° under vacuum. The residue in ether was filtered through alumina (neutral, activity I; 25 g), 1 l. of eluate being collected. After evaporation of the ether, the residue (4.3 g) in benzene (50 ml) was adsorbed on alumina (neutral, activity III; 350 g). The alumina was eluted with benzene (1.6 l.), benzene–ether (19:1, 3.5 l.; 9:1, 5 l.), fractions of volume 350 ml being collected. Fractions 8–16 afforded material (2.17 g) which was crystallized from acetone–hexane to yield recovered **17** (1.5 g), mp 107–135°. Crystallization from acetone–hexane of the material in fractions 19–30 gave **19** (631 mg), mp 145–147°. Repeated crystallization from the same solvent gave an analytical sample: mp 148–150°; ir 3650, 1660 and 1610 cm^{-1}; uv max 241–242 mμ (ϵ 16,200); nmr δ 1.34 ppm (s, 3, 10α-CH_3C). *Anal.* Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.07; H, 9.95.

***dl*-18-Methyl-9β,10α-androst-4-ene-3,17-dione (21).**—Compound **19** (0.99 g) in acetone (28 ml) was cooled on ice and stirred while 8 *N* CrO_3 in 12 *N* H_2SO_4 was added rapidly until an orange color persisted in the solution. After a total time of 2–3 min, the reaction was quenched by addition of 2-propanol, and the product precipitated with water. Crystallization from aqueous CH_3OH yielded **21** (819 mg): mp 208–216°, raised to 215–217° by repeated crystallization from acetone; ir 1730, 1665, and 1615 cm^{-1}; uv max 240 mμ (ϵ 16,400). *Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.04; H, 9.65.

***dl*-18-Methyl-3-(pyrrolid-1-yl)-9β,10α-androsta-3,5-dien-17-one (24).**—Dione **21** (797 mg) was dissolved in CH_3OH (40 ml) at reflux under N_2. Pyrrolidine (2 ml) was added to the hot solution and heating was continued for 20 min. The condenser was then set for distillation and the solution was distilled down to a volume of 5–10 ml. On cooling, **24** separated as pale yellow crystals (828 mg): mp 113–120°; uv max (CH_3OH) 277 mμ (ϵ 23,350). On attempted recrystallization from CH_3OH containing a trace of pyridine, **24** decomposed.

***dl*-17α-Ethinyl-17β-hydroxy-18-methyl-9β,10α-androst-4-en-3-one (26).**—Enamine **24** (1.06 g) in dimethylacetamide (40 ml) was stirred and cooled to 10°. A stream of acetylene was passed through the solution and lithium acetylide–ethylenediamine complex (1.38 g) was added. The reaction mixture was allowed to warm to ambient temperature, the acetylene stream was discontinued, and the reaction vessel was stoppered. After a total time of 6 hr, the reaction solution was poured into a vigorously stirred mixture of ice and saturated brine. The orange precipitate (1.1 g) was isolated by filtration, dried, and dissolved in C_2H_5OH (50 ml) and water (5 ml). This solution was heated under reflux for 45 min, then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and the solution mixed with alumina (neutral, activity III; 25 g). The solvent was evaporated and the residue was placed on top of a column of the same alumina (75 g) in benzene. Elution with benzene–ether (19:1; 1 l.), evaporation of the solvent, and crystallization of the residue from acetone gave **26** (471 mg): mp 202–208°, raised to 206–209° by further crystallization from the same solvent; ir 3610, 3300, 1665 and 1615 cm^{-1}; uv max 241 (ϵ 16,400). *Anal.* Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.17; H, 9.47.

***dl*-17α-Ethyl-17β-hydroxy-18-methylandrost-4-en-3-one (28).**—Compound **26** (719 mg) was hydrogenated in toluene (200 ml) over 5% Pd–$CaCO_3$ (240 mg), the reaction being stopped when 2.12 mol equiv of H_2 had been consumed. The catalyst was removed by filtration and the residue, after removal of the sol-

(16) H. C. Beyerman and G. J. Heiszwolf, *Rec. Trav. Chim. Pays-Bas*, **84**, 203 (1965).

vent, was crystallized from aqueous CH_3OH to yield **28** (575 mg), mp 143–146°. Three crysallizations from ether–petroleum ether (bp 30–60°) gave pure **28**: mp 146–147°; ir 1665 and 1615 cm^{-1}; uv max 242 mμ (ε 16,200), nmr δ 0.97 ppm (t, 6, CH_3CH_2). *Anal.* Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.27; H, 10.46.

dl-**8a-Ethyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione (13)**.—2-Ethylcyclohexane-1,3-dione (**11**)[6] (112 g), methyl vinyl ketone (84 g), and KOH in CH_3OH (400 ml; 1 mg/ml) were heated together under reflux for 2.5 hr. The solvent was evaporated under vacuum, and a solution of pyrrolidine in benzene (6% v/v; 200 ml) was then added. The mixture was heated to boiling and distilled at a rate of 150 ml/hr while fresh pyrrolidine in benzene solution was added at the same rate. At the end of 3 hr the distillate contained 17 ml of water (theory 14.5 ml). The reaction was cooled, diluted with EtOAc, washed free of pyrrolidine with 3 *N* HCl, washed with brine, and the solvents were evaporated. The residue (144 g) was distilled at 112–117° (0.05 mm), the distillate being a crystalline mass (107 g). Crystallization from ether gave **13** (84 g, 54%), mp 64–67°. Repeated crystallization from ether gave a sample mp 68–69°; ir 1710, 1660 and 1615 cm^{-1}; uv max 245 mμ (ε 12,980) (lit.[9] mp 67.5–68.5°). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.01; H, 8.19.

dl-**4aβ-Ethyl-5β-hydroxy-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (14)**.—Diketone **13** (159 g) in THF (430 ml) was stirred while a solution of lithium aluminum tri(*t*-butoxy)hydride (314 g) in THF (1350 ml) was added, cooling being used to maintain the temperature at 20–25°. On completion of the addition the solution was brought to pH 7 by means of 3 *N* HCl, the temperature being held in the same range. The mixture was filtered, the filtrate concentrated, and **14** isolated with EtOAc. This material (154 g, 95%) was sufficiently pure for further reactions. Crystallization from acetone–hexane gave a pure sample: mp 89–90°; ir 3620, 1660 and 1620 cm^{-1}; uv max 242 mμ (ε 13,950) (lit.[9] mp 88–89.5°). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.51; H, 9.49.

dl-**5β-*t*-Butoxy-4aβ-ethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (15)**.—Compound **14** (84 g) in CH_2Cl_2 (840 ml) was treated with boron trifluoride etherate (47% in ether; 42 ml) and H_3PO_4 (100%; 14 ml).[16] This solution was treated with isobutylene (638 g) and the product isolated as described for **8**. The brown solid thus obtained (107 g, 98%), assay 97% (gc), was converted into **16** without purification. An analytical sample was obtained by crystallization from DMSO, then from hexane and finally from CH_3OH: mp 83–85°; ir 1660 and 1615 cm^{-1}; uv max 245–246 mμ (ε 12,000). *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.45; H, 10.74.

dl-**5β-*t*-Butoxy-4aβ-ethyl-1-(3′,3′-ethylenedioxypentyl)-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (16)**.—NaH (52% in mineral oil; 16.6 g) was washed with hexane by decantation and covered with DMF (400 ml). The mixture was stirred and a solution of **15** (85.5 g) in DMF (400 ml) was added slowly while cooling to maintain the temperature at 20°. After agitation for 1 hr, **9** (74.2 g) was added and stirring was continued for a further 4 hr. Saturated NH_4Cl solution (1000 ml) was introduced while cooling the mixture at 35°. The product was isolated by extraction with three 900-ml portions of EtOAc, and, after evaporation of the solvent, the residue (117 g) was degassed at 100° (0.05 mm). This material was diluted with corn oil (23 g) and distilled in a falling film molecular still. Three passes at 100° (5–25 μ) afforded a crystalline material (35 g) containing **15** and **16** in the ratio 2:1. One pass at 112° (10–25 μ) gave material (14 g) containing **15** and **16** in the ratio 1:2.5, while six passes at 139° (10–60 μ) yielded **16** (45 g). The **16** obtained in this way assayed at 55–60% (gc) and contained 5–10% of **15**. It was used without further purification to prepare **2**. Analytically pure **16** was obtained as a gum by preparative tlc in the system $CHCl_3$–EtOAc 19:1 and assayed at 94% (gc): ir 1660 and 1600 cm^{-1}; uv max 255–256 mμ (ε 12,280). *Anal.* Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 72.79; H, 10.27.

dl-**4,4aβ,4bα,5,6,7,8,8a,9,10-Decahydro-8aβ-ethyl-8-hydroxy-1-methylphenanthren-2(3H)-one (2)**.—Compound **16** [55.9 g; assay 60% (gc)] was hydrogenated in C_2H_5OH (450 ml) over 10% Pd–$BaSO_4$ (16 g), and the product treated with acid as described for the preparation of **1**. The resultant gum (36 g) was crystallized from ether to yield **2** (7.4 g), mp 120–135°. Recrystallization from acetone–hexane and then from aqueous 2-propanol gave a pure sample: mp 142–144°; ir 3625, 1660 and 1610 cm^{-1}; uv max 250 mμ (ε 16,900); nmr δ 1.80 ppm (s, 3, CH_3C=). *Anal.* Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.88; H, 10.03.

dl-**4,4aβ,4bα,5,6,7,8,8a,9,10-Decahydro-8aβ-ethyl-8-hydroxy-1-methylphenanthren-2(3H)-one Acetate**.—Compound **2** (12.2 g) was acetylated in pyridine (23 ml) and Ac_2O (23 ml) at ambient temperature. The acetate (13.2 g), isolated by precipitation with water, crystallized from acetone–hexane, mp 121–129°. The analytical sample, from aqueous CH_3OH, had mp 127.5–129°; ir 1720, 1660, 1605 and 1250 cm^{-1}; uv max 249–250 mμ (ε 16,100). *Anal.* Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.10; H, 9.33.

dl-**3,4,4aβ,4bα,5,6,7,8,8a,9,10,10aβ-Dodecahydro-8aβ-ethyl-8-hydroxy-1β-methylphenanthren-2(1H)-one (18)**.—Hydrogenation and subsequent hydrolysis of the aforegoing acetate (7.05 g) in the manner described for the preparation of **17**, and crystallization of the product from ether gave **18** (3.6 g), mp 98–102°. This material was used without purification for the preparation of **20**. A pure sample was obtained by repeated crystallization from ether–hexane: mp 102.5–104°; ir 3620 and 1700 cm^{-1}; nmr δ 1.01 (d, 3, J = 6 Hz, CH_3CH). *Anal.* Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.54; H, 10.80.

dl-**17aβ-Hydroxy-18-methyl-9β,10α-D-homoandrost-4-en-3-one (20)**.—Compound **18** (9.85 g) reacted with methyl vinyl ketone to yield **20**, employing the procedure used in the preparation of **19**. Unreacted **18** (5.7 g) was recovered, mp 87–100°. The crude **20** (1.69 g) obtained from the chromatogram was triturated with ether and afforded an insoluble portion (154 mg), mp 114–212°. The ether solution on concentration gave crystals (524 mg), mp 94–114°. Repeated crystallization from ether–hexane and acetone–hexane, following treatment of the solution in acetone with charcoal, gave **20**: mp 136–138°; ir 3630, 1660 and 1620 cm^{-1}; uv max 243 mμ (ε 16,300). *Anal.* Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.40; H, 9.99.

dl-**4aβ-Ethyl-4β-hydroxy-2,3,4,4a,5,6,6a,7,10,11,11a,12,12a,-12b-tetradecahydro-7-methyl-6aβ,12aβ,12bα-benz[*a*]anthracen-9-(1H)-one (23)**.—The ether-insoluble material (mp 114–212°) obtained during the isolation of **20** was crystallized repeatedly from CH_2Cl_2–acetone to yield **23**: mp 210–218°; ir 3620, 1665 and 1615 cm^{-1}; uv max 242–243 mμ (ε 17,950); nmr δ 1.08 ppm (d, 3, J = 8 Hz, CH_3CH). *Anal.* Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.64; H, 9.83.

dl-**18-Methyl-9β,10α-D-homoandrost-4-ene-3,17a-dione (22)**.—Prepared from crude **20** (1.83 g) as described for the preparation of **21**, **22** (690 mg) had mp 200–217° after crystallization from CH_2Cl_2–acetone. Recrystallization from acetone gave material: mp 213.5–218°; ir 1705, 1660 and 1620 cm^{-1}; uv max 240 mμ (ε 17,000). *Anal.* Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.22; H, 9.58.

dl-**18-Methyl-3-(pyrrolid-1-yl)-9β,10α-D-homoandrosta-3,5-dien-17a-one (25)**.—The dione **22** (690 mg) was converted into the enamine **25** (715 mg) as described for the preparation of **24**, uv max 276–277 mμ (ε 25,100).

dl-**17aα-Ethinyl-17aβ-hydroxy-18-methyl-9β,10α-D-homoandrost-4-en-3-one (27)**.—The enamine **25** (1.18 g) was converted into **27** as described for the preparation of **26**. The crude **27** (672 mg) from the chromatogram on crystallization from CH_2Cl_2–acetone gave a first crop of 370 mg (mp 198–207°), and a second crop of 135 mg (mp 177–202°). Repeated recrystallization gave pure **27**: mp 206–208°; ir 3620, 3300, 1665 and 1620 cm^{-1}; uv max 241–242 mμ (ε 16,900). *Anal.* Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.31; H, 9.53.

dl-**17aα-Ethyl-17aβ-hydroxy-18-methyl-9β,10α-D-homoandrost-4-en-3-one (29)**.—The ethinyl compound **27** (100 mg) in toluene (30 ml) was hydrogenated over 5% Pd–$CaCO_3$ (45 mg) as described for the preparation of **28**. Crystallization of the product from ether gave **29** (36 mg), mp 128–134°. Three further crystallizations from ether–petroleum ether gave material: mp 133–136°; ir 1655 and 1610 cm^{-1}. *Anal.* Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.20; H, 10.54.

Registry No.—**1**, 18267-52-2; **1** acetate, 18267-53-3; **2**, 18267-50-0; **2** acetate, 18267-51-1; **5**, 18267-54-4; **6**, 18267-44-2; **7** (2,4 dinitrophenylhydrazone), 18267-55-5; **8**, 18267-56-6; **10**, 18267-57-7; **13**, 17506-53-5; **14**, 17506-54-6; **15**, 18267-60-2; **16**, 18267-61-3; **17**, 18267-62-4; **18**, 18267-63-5; **19**, 18267-64-6; **20**,

18267-65-7; **21**, 18267-66-8; **22**, 18267-67-9; **23**, 18267-68-0; **24**, 18267-69-1; **26**, 18267-70-4; **27**, 18267-71-5; **28**, 18267-72-6; **29**, 18267-73-7.

Acknowledgments.—The authors are indebted to Dr. V. Toome, Dr. F. Vane, Dr. T. Williams, and Mr. S. Traiman for the measurement and interpretation of spectra. They also wish to thank Mr. H. Jenney and Dr. A. Steyermark for determination of gas chromatographic and microanalytical data.

Oxidation of Steroidal Ketones. VII. Cleavage of Steroidal Conjugated Ketones with Ruthenium Tetroxide[1,2]

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Received June 4, 1968

Ruthenium tetroxide has been utilized for the cleavage of conjugated and cross-conjugated steroidal ketones. In some instances the yields have been superior to those found for ozone. The unexpected formation of enediones has been observed in the oxidation of 1,4-diene-3,11-diones.

An important step in the partial synthesis of steroid analogs having one or several atoms replaced with heteroatoms is the synthesis of appropriate intermediates. The intermediates are usually prepared by the cleavage and removal of a portion of the steroid nucleus. Subsequently, the removed carbons are replaced with other atoms, and the ring system is reconstructed. A convenient route for the synthesis of the intermediates is the oxidative cleavage of conjugated olefins and particularly of the readily available conjugated ketones. Unfortunately, reagents[5,6] such as chromium trioxide, permanganate, ozone, hypohalites, etc., used for the cleavage of such entities are not easy to control and frequently overoxidation and/or low yields occur. Our work[7] with ruthenium tetroxide as an oxidant for ring A aromatic steroids prompted us to explore the possibilities of this rarely used and versatile reagent with the steroidal ketone system. The reagent appeared to provide the advantage of attacking double bonds and hydroxyl groups without further oxidation[8] of the products. Although no attempts were made to optimize the conditions, the yields were in most instances considerably better than those obtained by other methods. Of particular interest was its applicability to the 5β-9(11)-en-12-one system which has been reported as being unusually resistant to oxidative cleavage by other methods.[9]

As with the aromatic steroids the oxidation conditions involved the use of acetone–water mixtures. The ruthenium tetroxide was initially generated *in situ* from ruthenium dioxide and sodium periodate and was then regenerated throughout the reaction by the addition of a sodium periodate solution. The progress of the reaction was followed visually since the dioxide was black and the tetroxide yellow.

The oxidation of ring A or ring C α,β-unsaturated ketones gave the expected products in very good yield. Testosterone acetate easily provided the known[10,11] keto acid **1** in an 80% yield. Cleavage of another ring A enone, 17β-acetoxy-3-oxo-5α-androst-1-ene, gave diacid **2** in an 85% yield. Application of the ruthenium tetroxide procedure to the hindered ring C conjugated ketone **3** resulted in an 80% yield of the keto acid **4**. In the latter two cases the structure of the products followed from their elemental analyses and spectroscopic data.

Ruthenium tetroxide was also found to be a good oxidant for conjugated systems where the double bond was exocyclic to the ring containing the ketone, as exemplified by the diacetate[12] **7**. In this instance the 5α-16,17-diacid **8** results. Again, elemental analyses and spectroscopic data were used to establish the structure of the products.

Rather unexpectedly oxidation of 3β-acetoxy-5β-pregnan-16-en-20-one (**5**) did not proceed to completion, and instead of the anticipated 16,17-diacid the seco-17,20-diketo-16-carboxylic acid **6** was formed. Elemental analysis indicated the $C_{21}H_{32}O_5$ composition. The mass spectrum was devoid of the molecular ion peak (M^+ 364), but had fragments at *m/e* 321 (M − CH_3CO), 293 (M − CH_3COCO), 275 [M − (CH_3CO-CO + H_2O)], 257 (275 − H_2O), and 215 (257 − C_2H_2O). The results are in full agreement with the proposed structure **6**.

We next turned our attention to more complex cross-conjugated systems. It was expected that by utilizing systems with extended conjugation, we should be able to eliminate from two to three carbons from the nucleus.[13] This phase of the study began with the known[10] compound **9**. Oxidation of this cross-conjugated system

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(2) This work was supported by Public Health Service Grants A-5326 and CA-07137.

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