2β,3β-epoxy steroids in the presence of BF_3 or $HClO_4$. This method has been extended for the purpose of the present synthesis.

The starting epoxide, 6α,7α-epoxy-16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-acetate (**3**), was prepared by selective saponification of the chlorodiacetate **4a**[7] with concomitant oxide formation. In a first experiment, the *trans* diaxial opening of the 6α,7α-epoxide ring by MeCN was effected with the aid of $SnCl_4$ as a Lewis acid. 6β-Acetamino-7α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione 17-acetate (**4c**), was obtained in 40% yield. In addition to this compound, we also isolated 10% of the 6β-chloro analog **4b**, which upon acetylation (Ac_2O) in pyridine, gave the corresponding acetate **4a**. Chlorhydrin **4b** most likely arose from the presence of HCl resulting from the partial hydrolysis of $SnCl_4$. Acetylation of **4c** led to the acetamino acetate **4d**. In order to obtain **4d** in one step, and simultaneously, to circumvent the formation of **4b**, the epoxide **3** was treated with a mixture of MeCN and Ac_2O in the presence of *p*-TSA at room temperature. The reaction was slower than that catalyzed by $SnCl_4$, but afforded **4d** smoothly, in 38% yield. When BF_3 etherate was used instead of *p*-TSA, no steroidal acetamide could be isolated. The assignment of configurations at C_6 and C_7 was made in accordance with the rule of diaxial opening of epoxides,[9] and is supported by nmr data, namely the lack of any noticeable coupling of the C_6 proton with the C_4 vinylic proton, and the small coupling (2 Hz), between the C_7 and C_8 protons. Elimination of the 7-acetate from **4d** was more facile than in the 6β-chloro analog **4a**. A comparative experiment showed that under identical reaction conditions (*p*-TSA in $CHCl_3$ at 60°), **4d** was transformed quantitatively to 6-acetamino-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**1b**), within 1 hr, whereas only 30% of **4a** was transformed to **1a** after 24 hr. This striking difference in reactivity is best explained by invoking the very favorable participation of the acetamino group in the acetate elimination, as represented by a possible intermediate species, such as **5**.

Experimental Section[10,11]

6α,7α-Epoxy-16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-Acetate (3).—To a solution of **4a** (5 g) in CH_2Cl_2 (62.5 ml) and MeOH (75 ml) was added a solution of NaOH (1.6 g) in H_2O (7.5 ml). The reaction mixture was left at 25° for 20 min. After the usual work-up ($CHCl_3$), crystallization from EtOAc–Et_2O afforded **3**: 2.45 g (57.3%); mp 250–254°; $[\alpha]D$ −104.7°; λ_{max} 240 mμ (ε 15,980); ν_{max} 1735, 1720, 1680, and 1625 cm^{-1}; nmr, δ 3.34 and 3.50 (J = 3.5 Hz, 6-H, 7-H) and 6.14 (s, 1, 4-H) ppm. *Anal.* ($C_{24}H_{30}O_5$) C, H.

6β-Acetamino-7α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione 17-Acetate (4c).—To a solution of **2** (398 mg) in CH_3CN (26 ml), $SnCl_4$ (1.1 ml) was added. After 15 min at 25°, the reaction mixture was worked up in the usual manner (CH_2Cl_2). Separation by preparative tlc afforded **4c**: 160 mg (41%); mp 230–231°; $[\alpha]D$ −36°; λ_{max} 239 mμ (ε 13,560); ν_{max} 3330, 3230, 1740, 1715, 1680, 1665, 1650, and 1635 cm^{-1}; nmr, δ 1.98 (s, 3, $NHCOCH_3$), 3.22 (7-OH), 4.58 (6-H), 6.00 (s, 1, 4-H), and 6.19 (m, 1, $NHCOCH_3$) ppm; *m/e* ($C_{26}H_{35}O_6N$) 457.

In addition to **4c**, chlorhydrin **4b**, 41 mg (10%) was isolated and characterized by comparison with an authentic sample.

6β-Acetamino-7α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione 7,17-Diacetate (4d). A. From 3.—Epoxide **3** (2.45 g) was added to a solution of *p*-TSA (2.4 g) in Ac_2O (60 ml) and MeCN (120 ml). The reaction mixture was kept at room temperature for 3.5 hr. After work-up in the usual way ($CHCl_3$), crystallization in Et_2O afforded the acetamino acetate **4d**: 1.16 g (38%); mp 238–241°; $[\alpha]D$ −82.7°; λ_{max} 237 mμ (ε 13,100); ν_{max} 3350, 1745, 1720, 1680, 1660, and 1520 cm^{-1}; nmr, δ 1.95 (s, 3, $NHCOCH_3$), 4.50 (6-H), 5.00 (7-H) ppm; *m/e* ($C_{28}H_{37}O_7N$) 499.

B. From 4c.—To a solution of **4c** (80 mg) in pyridine (2 ml), Ac_2O (0.4 ml) was added. After 2 days at room temperature, extraction with CH_2Cl_2 afforded 89 mg of crude material, which upon recrystallization in *i*-Pr_2O yielded pure **4d** (50 mg).

6-Acetamino-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (1b).—A solution of **4d** (1.0 g) and *p*-TSA (20 mg) in $CHCl_3$ previously shaken with $CaCl_2$ (30 ml), was kept at 60° for 1 hr. The solution was then washed ($NaHCO_3$), dried, and evaporated to a residue. Crystallization from EtOAc–Et_2O, afforded **1b**, 783 mg (89%). One more crystallization, MeOH, gave the analytical sample: mp 191–193°; $[\alpha]D$ −124.9°; λ_{max} 288 mμ (ε 16,950); ν_{max} 3350, 1720, 1705, 1665, 1645, 1595 and 1520 cm^{-1}; nmr, δ 2.10 (s, 3, $NHCOCH_3$), 6.00 (s, 1, 4-H), 6.45 (d, 1, 7-H), 7.03 (m, 1, $NHCOCH_3$). *Anal.* ($C_{25}H_{33}O_5N$) C, H, N, *m/e* (439).

Biological Data.[12]—In the progestational assay carried out by the method of McPhail,[13] **1b** was found to have less activity than progesterone, whereas **1a** is 77 times as active as progesterone. In the intact rat antiandrogenic screen[14] **1b** was also inactive.

Acknowledgments.—We are grateful to Mr. M. Yudis and Mrs. H. Marigliano for the interpretation of the nmr spectra, and to Dr. T. Traubel for the mass spectra.

(9) A. Furst and Pl.A. Plattner, Abstracts of Papers, 12th International Congress Pure and Applied Chemistry, New York, N. Y., 1951, p 409.

(10) All melting points are uncorrected. Rotations are in dioxane at 26°, uv spectra are of MeOH solutions and ir spectra are in Nujol. Nmr spectra were recorded in $CDCl_3$, using Me_4Si as internal standard. Mass spectra were determined on a CEC 21-103 spectrometer using a heated inlet at a temperature of 230–240°; elemental analyses were by the Physical Organic Chemistry Department of the Schering Corporation. Where analyses are indicated only by symbols, analytical results obtained for these elements were within ±0.4% of the theoretical values. Although all other physical data are in excellent agreement with the proposed structures of the acetamino conpounds, C analyses were consistently low. This phenomenon was also observed in other N-containing steroids, *i.e.*, D. Cheron and F. Winternitz, Thesis of D. Cheron, Montpellier, France, 1965.

(11) The term "usual work-up" denotes: the reaction mixture was poured into H_2O, extracted with either CH_2Cl_2 or $CHCl_3$ (as indicated in parentheses). The organic layer was washed with dilute acid or base, as the case may be, dried ($MgSO_4$), and taken to dryness.

(12) The authors express their appreciation to Dr. R. Neri and staff for carrying out the biological tests.

(13) M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1934).

(14) R. O. Neri, M. D. Monahan, J. G. Meyer, B. A. Afonso, and I. A. Tabachnick, *Eur. J. Pharmacol.*, **1**, 438 (1967).

Ring-D-Bridged Steroid Analogs. VIII. Testosterone Analogs[1]

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Recently, there has been considerable interest in determining the details of the structural requirements

(1) (a) This investigation was supported, in part, by the National Institute of Arthritis and Metabolic Diseases under Grant AM-006900; (b) part VII: A. J. Solo, B. Singh, and J. N. Kapoor, *Tetrahedron*, **25**, 4579 (1969).

for androgenic and anabolic activity.[2] It seems well established that the presence of a 17α-Me groups is compatible with high androgenic and anabolic activity.[2a] While the presence of a 17α-Et group seems not to decrease myotropic response, its effect on androgenic activity is variable, and larger or more rigid 17α-alkyl groups appear to sharply decrease both activities.[2a,3] These effects have led several groups to postulate that androgens must complex with their receptors (at least in part) *via* the α face of the D-ring.[4]

An examination of molecular models reveals that 17α-alkyl groups should be preferentially oriented so as to extend the bulk of the group away from the under side of the D-ring. Rigid 17α-alkyl groups, such as ethinyl, of necessity project in just such a direction. Therefore, it would seem that the deleterious effect of bulky or rigid 17α-alkyl groups on anabolic or androgenic activity could be explained by a lack of bulk tolerance in the receptor either in a region directly below the D-ring,[4] or adjacent (in the vicinity of C-16 and -17) to the edge of the D-ring,[4c] or both. To distinguish between these possibilities, we decided to synthesize and assay 17α-alkyltestosterone derivatives in which the alkyl substituent was tied back to a position beneath the D-ring.

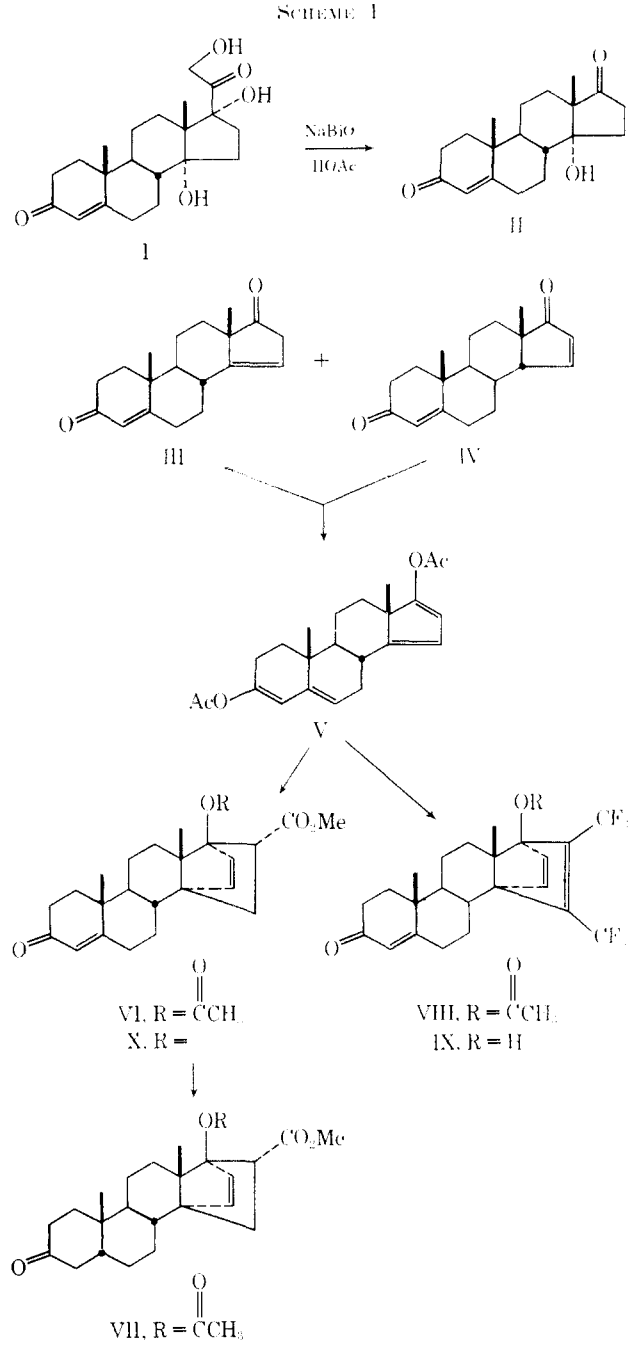
Introduction of a 14α,17α-propano bridge would appear to be an ideal approach to this problem since such a bridge would manifest its bulk almost exclusively in the area directly below the D-ring and would form a ring large enough to avoid causing angular deformation of C-17, or of other portions of the normal ring-D system. However, for reasons of synthetic simplicity, we decided to attempt initially the synthesis of 14α, 17α-ethenotestosterone derivatives and to reserve the option of later expanding the etheno bridge to a three carbon unit.

We hoped initially to obtain the desired testosterone derivatives by degradation of the acetyl side chain of suitable 14α,17α-ethenoprogesterone derivatives. However, lack of success on attempted Baeyer–Villiger reaction of 3β-acetoxy-16α-carbomethoxy-14α, 17α-ethenopregn-5-en-20-one[5] and failure to effect satisfactory Beckmann rearrangement of the oxime of this compound caused us to abandon this approach.[6] We then decided to attempt the synthesis of these compounds by Diels–Alder addition to an enol ether or enol ester derived from a 14-dehydro-17-keto steroid.

Ring-D unsaturated 17-keto steroids have been prepared by bromination–dehydrobromination of derivatives of 17-keto steroids[7] and by dehydration of 14-hydroxy-17-keto steroids.[8] Because of the present availability of 14α-hydroxy steroids *via* microbiological oxidation, we chose the latter approach.[9]

Bismuthate oxidation of 3,20-dioxopregn-4-ene-14α-17α-21-triol (I) afforded 14α-hydroxyandrost-4-ene-3,17-dione (II).[8d,e] Dehydration of II gave mainly androsta-4,14-diene-3,17-dione (III) plus a small amount of 14β-androsta-4,15-diene-3,17-dione (IV).[8d] Since III and IV are interconvertable in the presence of acid,[7] the mixture was converted with isopropenyl acetate and TsOH[10] into 3,17-diacetoxyandrosta-3,5,-14,16-tetraene (V) (Scheme I). The latter compound,

SCHEME I



not unexpectedly, proved to be very labile. It was therefore not purified, but was characterized by spec-

(2) For a summary of recent theories see: (a) J. A. Vida, "Androgens and Anabolic Agents," Academic Press, New York, N. Y., 1969; (b) M. E. Wolff and G. Zanati, *J. Med. Chem.*, **12**, 629 (1969); (c) Z. Cekan and B. Pelc, *Steroids*, **8**, 209 (1966).

(3) The latter fact has been widely exploited in the use of 17α-alkyltestosterone derivatives as progestational agents.

(4) (a) H. J. Ringold in "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engel, Ed., Pergamon Press, Oxford, 1961, p 200; (b) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964); (c) Reference 2a, p 74.

(5) A. J. Solo and B. Singh, *ibid.*, **9**, 179 (1966).

(6) B. Singh and J. N. Kapoor, unpublished work in this laboratory.

(7) W. S. Johnson and W. F. Johns, *J. Amer. Chem. Soc.*, **79**, 2005 (1957).

(8) (a) A. F. St. Andre, H. B. MacPhillomy, J. A. Nelson, A. C. Shabica and C. R. Scholy, *ibid.*, **74**, 5506 (1952); (b) For a variant see: B. M. Bloom, A. J. Agnello, and G. D. Laubach, *Experientia*, **12**, 27 (1956); (c) S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh Osborn, A. Weintraub, L. M. Reineke, and R. C. Meeks, *J. Amer. Chem. Soc.*, **80**, 3382 (1958); (d) M. Tanabe and D. F. Crowe, *J. Org. Chem.*, **30**, 2776 (1965); (e) L. Mamlok, A. Horeau, and J. Jacques, *Bull. Soc. Chim. Fr.*, 2359 (1969).

(9) F. Sondheimer, W. McCrae, W. G. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969).

(10) G. A. Hughes and H. Smith, *Steroids*, **8**, 547 (1966).

TABLE I

Compd	Dose, μg/day	No. of rats	Mean body weight (g) Initial	Mean body weight (g) Final	Mean wt, levator ani, mg ± std dev	Mean wt, seminal vesicles, mg ± std dev	Mean wt, ventral prostate, mg ± std dev
Controls		14	59.9	93.5	21.4 ± 5.7	11.7 ± 2.7	15.1 ± 2.9
Testosterone	10	14	61.0	98.7	28.7 ± 4.5[a]	16.1 ± 1.9[a]	28.4 ± 8.3[a]
VI	1000	10	59.7	96.1	23.9 ± 4.5	12.3 ± 2.5	16.1 ± 2.1
Testosterone	10	8	62.6	99.0	27.5 ± 3.0[a]	16.8 ± 3.3[a]	33.3 ± 7.8[a]
VI	1000						

[a] $P < 0.05$, significance of difference between treated animals and oil-treated controls.

TABLE II

Compd	Dose, μg/day	No. of rats	Mean body weight (g) Initial	Mean body weight (g) Final	Mean wt, levator ani, mg ± std dev	Mean wt, seminal vesicles, mg ± std dev	Mean wt, ventral prostate, mg ± std dev
Control		12	53	92	21.5 ± 2.7	10.3 ± 0.8	10.3 ± 1.4
Testosterone	50	12	52	92	27.6 ± 2.4[a]	22.3 ± 3.6[a]	36.7 ± 8.1[a]
	10	12	53	94	26.0 ± 4.1[b]	14.9 ± 1.4[a]	21.0 ± 5.3[a]
VIII	1000	5	54	94	21.8 ± 4.3	11.4 ± 1.6	12.0 ± 1.9
IX	1000	12	54	93	22.3 ± 2.0	10.8 ± 1.7	11.4 ± 2.7
	100	12	54	91	23.3 ± 3.8	10.7 ± 1.2	10.0 ± 1.6
	50	12	52	90	23.0 ± 3.1	10.5 ± 1.3	12.3 ± 1.8
Testosterone	50	6	57	94	25.5 ± 1.3[a]	19.9 ± 2.2[a]	33.3 ± 3.0[a]
IX+	1000						

[a] $P < 0.001$; significance of difference between treated animals and oil-treated controls. [b] $P < 0.01$.

troscopic methods, and it was then used directly in the Diels–Alder reaction. Methyl acrylate and hexafluorobutyne-2 were each found to add to V to form adducts VI and VIII in yields of 34 and 28%, respectively. The stereochemistry of adducts VI and VIII is assigned by analogy to the proven structure of the products resulting from Diels–Alder addition of methyl acrylate to 3β-acetoxypregn-5,14,16-trien-20-one.[11] Mild base hydrolysis of VIII produced 17-hydroxy compound IX, but similar treatment of VI resulted in a complex mixture, presumably caused, at least in part, by a retro-aldol type of ring opening.

Biological Results.—Compound VI, the first of this series to be synthesized, was tested by the method of Hershberger.[12] It was found to be devoid of anabolic, androgenic, antiandrogenic, and antianabolic activity under the conditions specified in Table I. It has been hypothesized that androgens must have free 17β-hydroxyl groups, *in vivo*, in order to exert their activity.[13] To test the possibility that the lack of activity of VI was mainly the result of an abnormally slow *in vivo* rate of hydrolysis of VI to the corresponding 17-alcohol, an attempt was made to synthesize and test the alcohol. However, all attempts to convert VI into the alcohol failed, because of ring-opening of the intermediate anion X *via* a retro-aldol reaction.

Compounds VIII and IX were found to be devoid of androgenic and anabolic activity and IX was also found to lack antiandrogenic and antianabolic activity under the conditions shown in Table II.[14] These additional data appear to indicate that the inactivity of VI, VIII, IX arises either from the presence of the extraneous polar function(s) at position 16 (and 15) or from the presence of the **14α,17α**-etheno bridge. Attempts to distinguish between these possibilities by synthesizing and testing analogs lacking the extraneous polar substituents are currently in progress.

(11) A. J. Solo, B. Singh, E. Shefter, and A. Cooper, *Steroids*, **11**, 637 (1968).

(12) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, **83**, 175–180 (1953).

(13) J. van der Vies, *Acta Endocrinol.*, **49**, 271 (1965).

(14) Compounds VII and IX were also tested in the Clauberg assay (subcutaneous administration) and were found to be inactive at a total dose level of 2.0 mg.[15] This result was as expected in view of the known inactivity of 14α, 17α-etheno-15,16-di(trifluoromethyl)pregna-4,15-dien-3,20-dione under virtually identical conditions.[16]

(15) This assay was performed at the Endocrine Laboratory, Madison, Wis.

(16) A. J. Solo and B. Singh, *J. Med. Chem.*, **10**, 1048 (1967).

Experimental Section[17]

14α-Hydroxyandrost-4-ene-3,17-dione (II).—To a solution of 10.0 g of I in 170 ml of HOAc and 30 ml of H_2O was added 20 g of sodium bismuthate. The mixture was stirred 26 hr at room temp and then diluted to 300 ml by addition of ice. The cold mixture was partly neutralized by the addition of a cold solution of 104 g of KOH in 200 ml of H_2O. Extensive extraction with C_6H_6 afforded 6.0 g of II which crystallized from MeOH as rods: mp 250–254° (lit. mp 257–260°,[8a] 242–245.5°,[8c,d] 261–263°,[8e] 256–259°[9]); ν^{CHCl_3} 3470, 1740, and 1660 cm^{-1}; δ 0.99 (s, C-18-H's), 1.22 (s, C-19—H's) and 5.74 (m, C-4 vinyl H). *Anal.* ($C_{19}H_{26}O_3$) C,H.

3,17-Diacetoxyandrosta-3,5,14,16-tetraene (V). A.—A solution of 370 mg of II, 200 mg of *p*-TsOH, and 15 ml of C_6H_6 was heated under reflux for 3 hr. Standard work-up afforded 315 mg of a material which appeared by tlc and spectroscopic criteria to consist mainly of androsta-4,-14-diene-3,17-dione (III) plus a small amount of androsta-4,15-diene-3,17-dione (IV).

A solution of 406 mg of the crude mixture of III and IV and 250 mg of *p*-TsOH in 15 ml of isopropenyl acetate was heated under reflux for 24 hr. Then approx 5 ml of distillate was removed over 1 hr. The residue was diluted with 50 ml of Et_2O, washed with cold $NaHCO_3$ and then with cold H_2O. After being dried ($MgSO_4$) and filtered, the Et_2O solution was evapd to dryness to give 509 mg of a residue which gave one major spot on tlc. This substance appeared to decompose on attempted crystallization or purification. On the basis of its transformation products and of the following spectroscopic data, the material is assumed to be crude V: ν^{CCl_4} 1745 (broad), 1665, 1612 and 1365 cm^{-1}; λ_{max}^{EtOH} 234, 267 (sh). The nmr had a 6 H singlet at δ 1.08 (C-18 and C-19-H's) 3-H$^+$ singlets at 2.09 and 2.17 (acetate-H's) and 1-H$^+$ multiplets at 5.48, 5.70, 5.83, and 6.15 (vinyl H's).

B.—A solution of 1.13 g of II and 700 mg of *p*-TsOH in 25 ml of isopropenyl acetate was heated under reflux for 18 hr. Then 10

(17) Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Nmr spectra were determined on a Varian A-60 and are reported in ppm downfield from a TMS internal standard. The solvent designated as hexane is redistilled Fisher "hexanes." All analyses reported were within ± 0.3% of the theoretical values and are designated by the symbols of the elements analyzed for.

ml of distillate was removed over 3 hr. Work-up afforded a residue which appeared to contain V but which gave 4 spots on tlc and appeared to be far less pure by nmr than was the V prepared as in A.

14α,17α-Etheno-16α-carbomethoxyandrost-4-en-17-ol-3-one Acetate (VI).—A mixture of 418 mg of crude V, 1 ml of methyl acrylate, and 5 mg of hydroquinone was sealed in a glass tube under reduced pressure, and then heated to 120° for 116 hr. The mixture was then evapd to dryness under reduced pressure. The residue was warmed in Me_2CO containing 1 drop of aq HCl for 10 min and then again taken to dryness. The residue was chromatographed over 50 g of acid-washed alumina. Elution with C_6H_6–EtOAc mixtures afforded material which crystallized from Et_2O–hexane to afford VI, in a yield of 160 mg (34%) as white needles: mp 183–185°c; ν^{Nujol} 1745 (sh) 1730 (broad) and 1675 cm^{-1}. The nmr had 3-H$^+$ singlets at δ 1.00 (C-18-H's), 1.17 (C-19-H's), 2.11 (acetate), and 3.65 (OMe), and a 1-H$^+$ multiplet at 5.8 and 1-H$^+$ doublets at 6.11 and 6.34 (J = 6 Hz). *Anal.* ($C_{24}H_{32}O_5$) C,H.

14α,17α-Etheno-16α-carbomethoxy-5α-androstan-17-ol-3-one Acetate (VII).—A solution of 100 mg of VI in 25 ml of MeOH was hydrogenated over 10 mg of 10% Pd–C at 3.6 kg cm^2 for 19 hr at room temperature. Standard work-up yielded VII, which crystallized from Et_2O–hexane, in a yield of 98.5 mg, as small needles: mp 182.5–184° c; ν^{Nujol} 1740, 1720, 1710 (sh) cm^{-1}. The nmr spectrum had a 6-H$^+$ singlet at δ 0.99, 3-H$^+$ singlets at 2.10 and 3.62, a 1-H$^+$ doublet at 6.17 and 6.32 (J = 5.47 Hz for both). *Anal.* ($C_{25}H_{34}O_5$) C,H.

14α,17α-Etheno-15,16-di(trifluoromethyl)androsta-4,15-dien-17-ol-3-one Acetate (VIII).—A mixture of 2.90 g of V, 5 mg of hydroquinone, and an excess of hexafluorobutyne-2 was kept at 120° for 132 hr in a steel bomb fitted with a glass liner. The reaction was worked up essentially as described for VI to afford VIII in a yield of 1.00 g (28%), as needles from Me_2CO–hexane: mp 246.5–248°, ν^{Nujol} 1750, 1678 cm^{-1}. The nmr showed strong singlets at δ 1.23 (18 and 19-H's), 2.13 (acetate), a multiplet at 5.77 and doublets at 6.73 and 7.03 (J = 6 Hz). *Anal.* ($C_{25}H_{26}O_3F_6$) C,H.

14α,17α-Etheno-15,16-di(trifluoromethyl)androsta-4,15-dien-17-ol-3-one (IX).—A mixture of 190 mg of VIII, 45 gm of KOH, 15 ml of MeOH, and 1 ml of H_2O was stirred at room temp for 24 hr. A standard work-up gave IX as rods from CH_2Cl_2–hexane, in a yield of 160 mg; mp 262.5–264.5°; ν^{Nujol} 3370, 1655 cm^{-1}. The nmr has singlets at δ 1.21 (C-18 and C-19-H's), a multiplet at 5.77 (C-4 hydrogen) and doublets (J = 4 Hz) at 6.64 and 6.71. *Anal.* ($C_{23}H_{25}O_2F_6$) C,H.

Acknowledgment.—We are indebted to the Koninklijke Nederlandsche Gist-en Spiritusfabriek N. V. (Delft) for a most generous supply of I. We wish to thank Miss Carole A. Hayden for most able technical assistance.

Analogs of Steroid Hormones. IV. 16-Keto Steroid Derivatives[1,2]

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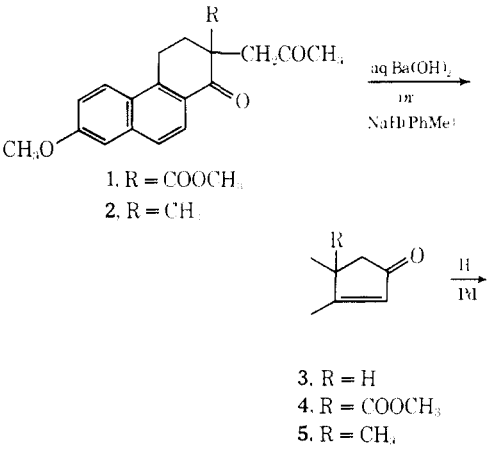
As part of a program concerned with the preparation of steroid analogs having hormone antagonist activity, some 16-keto steroids have been prepared and bioassayed. We were particularly interested in using synthetic methods previously developed[2] to prepare compounds having groups other than Me substituted at C-13. 16-Keto steroids have previously been synthesized by Wilds and coworkers[4] from suitably substituted 2-acetonyl-1-phenanthrones. We used this approach but followed the new scheme[2] for preparing the acetonylphenanthrones and the annelation reactions (Scheme I).

SCHEME I



In contrast to the results obtained from the benz[*e*]-indene analog, hydrogenation of **3** gave both isomers of **6**. As the bulk of R increased from Me to carbomethoxy, the *trans* isomer became predominant. The stereochemistry of the reduction is thus probably determined by the orientation of the adsorbed substrate on the catalyst.[2,5,6]

The configuration of **7**(*trans*) was confirmed by converting **7** into **8**(*trans*) using the method previously outlined.[2] The *cis* and *trans* isomers of **6, 7,** and **8** can be distinguished by differences in both their ir and uv spectra. The ν C=O band frequencies of the presumed *trans* isomers were higher by 3–4 cm^{-1} as had been previously observed for the benz[*e*]indene derivatives.[2] Wilds had noted that the uv maxima of **8**(*trans*) showed a bathochromic shift of about 2 mμ over those of **8**(*cis*). This also proved true for the presumed *trans* isomers of **6** and **7**.[7]

Reduction of the ethylene ketal derivatives of **6** with Na–*n*-C_4H_9OH followed by hydrolysis of the enol ether produced **9** and **10** which were tested[8] for androgen, antiandrogen, and antigonadotropic activity. In addition, **3, 6**(*trans*), **6**(*cis*), and **7**(*trans*) were tested for estrogen, antiestrogen, and antogonadotropic activ-

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(2) For paper III, see R. E. Juday, B. Bukwa, K. Kaiser, and G. Webb, *J. Med. Chem.*, **13**, 314 (1970).

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(4) (a) A. L. Wilds and T. L. Johnson, *J. Amer. Chem. Soc.*, **70**, 1166 (1948); (b) A. L. Wilds and W. J. Close, *ibid.*, **69**, 3079 (1947); (c) A. L. Wilds, L. W. Beck, and T. L. Johnson, *ibid.*, **68**, 2161 (1946); (d) A. L. Wilds and L. W. Beck, *ibid.*, **66**, 1688 (1944).

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(7) This phenomenon is probably caused by the higher energy of the ground state of the more strained *trans* isomers compared with the *cis*. Since the excited states possess more single bond character, there is less difference between them resulting in a smaller gap between the two states for the *trans* isomers. The isomers of **6** show a hypsochromic shift of 2 mμ compared with the corresponding isomers of **7** and **8**, indicating that the compounds with bulkier angular groups are more strained. Note that the chromophore of all these compounds is the methoxynaphthalene moiety. The maxima of the uv spectrum of 2-methoxynaphthalene show a 1–2 mμ blue shift compared with **6**(*cis*). See H. H. Jaffe and Milton Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, N. Y., 1962, p 203.

(8) R. E. Juday, L. Cubbage, J. Mazur, and B. Bukwa, *J. Med. Chem.*, **11**, 872 (1968).