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 183–187°c; $\nu^{Nujol}$ 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.* ($C_{29}H_{32}O_5$) 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; $\nu^{Nujol}$ 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.* ($C_{29}H_{34}O_5$) 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°, $\nu^{Nujol}$ 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°; $\nu^{Nujol}$ 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-r hydrogen) and doublets ($J$ = 4 Hz) at 6.64 and 6.71. *Anal.* ($C_{23}H_{22}O_2F_6$) C,H.

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

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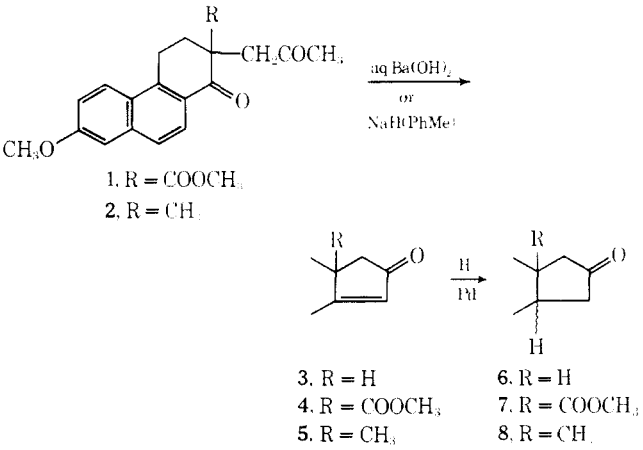
As part of a program concerned with the preparation of steroid analogs having hormone antagonist activity, some 16-keto steroids have been prepared and bioassayed. We were particularly interested in using synthetic methods previously developed[2] to prepare compounds having groups other than Me substituted 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-

(1) Supported, in part, by Grant CA-05057, National Cancer Institute, National Institutes of Health.

(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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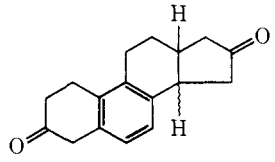
(4) (a) A. L. Wilds and T. L. Johnson, *J. Amer. Chem. Soc.*, **70**, 1186 (1948); (b) A. L. Wilds and W. J. Close, *ibid.*, **69**, 3079 (1947); (c) A. L. Wilds, L. W. Beck, and T. L. Johnson, *ibid.*, **68**, 2161 (1946); (d) A. L. Wilds and L. W. Beck, *ibid.*, **66**, 1688 (1944).

(5) A. L. Wilds, J. A. Johnson, and R. E. Sutton, *ibid.*, **72**, 5524 (1950).

(6) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *ibid.*, **64**, 1985 (1942).

(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).



9, *trans*
10, *cis*

ity. None of the compounds tested showed significant biological activity.

### Experimental Section[9]

**Methyl 2-Acetonyl-1,2,3,4-tetrahydro-7-methoxy-1-oxo-2-phenanthrenecarboxylate (1).**—Hydration of **12** in AcOH, HCOOH, and $H_2O$ catalyzed by $Hg^{2+}$ [2] produced **1** in a yield of 95%, mp 160–162°. *Anal.* ($C_{20}H_{20}O_5$) C, H.

**2-Acetonyl-3,4-dihydro-7-methoxy-2-methyl-1(2*H*)-phenanthrone (2).**—Alkylation of **11** (8.2 g) with propargyl bromide in Diglyme using NaH as catalyst, followed by hydration of the alkyne,[2] produced **13** (6.5 g, 66%), mp 79–81° (80–83°).[4b] *Anal.* ($C_{19}H_{20}O_3$) C, H.

**3-Methoxygona-1,3,5(10),6,8,14-hexaen-16-one (3).**—A mixture of **1** (12.0 g), $Ba(OH)_2 \cdot 8H_2O$ (45.0 g) in 120 ml $H_2O$ and 120 ml of methoxyethanol was refluxed for 4 hr. Recrystallization of the crude product from methoxyethanol gave 8.5 g (91%) of **3**, mp 177–179°. *Anal.* ($C_{18}H_{16}O_2$) C, H.

**Methyl 3-Methoxy-16-oxoestra-1,3,5(10),6,8,14-hexaen-18-oate (4).**—The annelation reaction was carried out in refluxing PhMe, containing a small amount of *N*-methylpyrrolidone, using NaH as the base.[2] Starting with 1 (2.0 g) and NaH (0.4 g) and recrystallizing the crude product from $C_6H_6$, a yield of 1.1 g (57%) of **4** was obtained, mp 178–180°. *Anal.* ($C_{20}H_{18}O_4$) C, H.

**3-Methoxy-13-methylgona-1,3,5(10),6,8,14-hexaen-16-one (5).**—Starting with **2** (6.4 g) and using the procedure outlined for **3**, a yield of 4.8 g (80%) of **5** was obtained, mp 203–206° (205–206°).[2c]

**3-Methoxy-14β-gona-1,3,5(10),6,8-pentaen-16-one (*cis* Isomer) and 3-Methoxygona-1,3,5(10),6,8-pentaen-16-one (*trans* Isomer) (6).**—Hydrogenation of **3** in PhMe–DMA Csolution, using a Pd–C catalyst dried in refluxing PhMe produced a mixture of **6**(*cis* and *trans*) separated by fractional crystallization from $Me_2CO$ to produce **6**(*trans*): mp 155–157°; $\lambda_{max}^{alc}$ 231, 268 mμ; ν C=O 1739 $cm^{-1}$; **6**(*cis*), mp 138–140°; $\lambda_{max}^{alc}$ 229, 265 mμ; ν C=O 1734 $cm^{-1}$. *Anal.* ($C_{18}H_{18}O_2$) C, H.

***cis*- and *trans*-Methyl 3-Methoxy-16-oxoestra-1,3,5(10),6,8-pentaen-18-oate (7).**—Hydrogenation of **4** by the method outlined for **3** produced a mixture of isomers containing about 90% of the *trans* and 10% of the *cis* isomer. Fractional crystallization ($Me_2CO$) produced **7**(*trans*), mp 176–178°; $\lambda_{max}^{alc}$ 233, 269 mμ; ν C=O (ketone) 1732 $cm^{-1}$, and **7**(*cis*), mp 126–129°; $\lambda_{max}^{alc}$ 231, 267 mμ; ν C=O (ketone) 1730 $cm^{-1}$. *Anal.* ($C_{20}H_{20}O_4$) C, H.

**Conversion of 7(*trans*) into 8(*trans*). A. *trans*-Methyl 16,16-ethylenedioxy-3-methoxyestra-1,3,5(10),6,8-pentaen-18-oate (13).**—A solution of **7** (6.3 g) and excess $(CH_2OH)_2$ in $C_6H_6$ and Diglyme, with $MeSO_3H$ as catalyst, was refluxed using a Dean–Stark trap until evolution of $H_2O$ ceased. The product was recovered and recrystallized from $C_6H_6$ to give 3.8 g (82%) of **13**, mp 99–101°. *Anal.* ($C_{22}H_{24}O_5$) C, H.

**B. 16,16-Ethylenedioxy-13-hydroxymethyl-3-methoxygona-1,3,5(10),6,8-pentaene (14).**—Reduction of **13** by LAH in THF produced **14** in 79% yields, mp 212° dec. *Anal.* ($C_{21}H_{24}O_4$) C, H.

**C. 16,16-Ethylenedioxy-13-hydroxymethyl-3-methoxyestra-3,5(10),6,8-pentaene Methanesulfonate (15).**—Treatment of **14** with $MeSO_2Cl$ in $C_5H_5N$ produced **15** in 97% yields, mp 172–173°. *Anal.* ($C_{22}H_{26}O_6S$) C, H.

**D. 8(*trans*) from 15.**—Refluxing **15** with KI in DMAC, followed by hydrolysis of the ketal and hydrogenolysis of the iodide using the procedure previously outlined[2] converted **15** into **8**(*trans*) showing the original configuration of **7** was *trans*.

**3-Methoxy-13-methylgona-1,3,5(10),6,8-pentaen-16-one (8).**—Hydrogenation of **5** over Pd(C) followed by fractional crystallization of the crude product ($Me_2CO$) to give **8**, mp 162–165° (169.5–171°)[4b] identical with that obtained from **16**. *Anal.* ($C_{19}H_{20}O_2$) C, H.

**Gona-5(10),6,8-triene-3,16-dione (9).**—A solution of **16** (3.3 g) in 45 ml of *n*-BuOH was refluxed with Na (2.5 g) until all Na had reacted. The mixture was then hydrolyzed and the crude product allowed to stand 60 min in a mixture of AcOH, 15 ml of HCOOH, and 5 ml of $H_2O$. Addition of $H_2O$ followed by recrystallization of the crude product from $Me_2CO$ gave a yield of 1.7 g (63%), mp 134–137°. *Anal.* ($C_{17}H_{18}O_2$) C, H.

**14β-Gona-5(10),6,8-triene-3,16-dione (10).**—The procedure used to prepare **9** was followed. Starting with **17** (3.7 g), a yield of 1.9 g (63%) of **10** was obtained, mp 126–131°. *Anal.* ($C_{17}H_{18}O_2$) C, H.

**3,4-Dihydro-7-methoxy-2-methyl-1(2*H*)-phenanthrone (11).**—3,4-Dihydro-7-methoxy-1(2*H*)-phenanthrone was converted into **11** using the procedure previously outlined for the benz[*e*]indene analogs.[2] The overall yield of product was 83%, mp 104–106° (108°).[10]

**Methyl 1,2,3,4-Tetrahydro-7-methoxy-1-oxo-2-(2-propynyl)-2-phenanthrenecarboxylate (12).**—3,4-Dihydro-7-methoxy-1(2*H*)-phenanthrone was converted into **12** by successive condensations with $Me_2CO_3$ and propargyl bromide in DMAC using NaH as catalyst, as previously outlined.[2] The overall yield of product was 88%, mp 115–118°. *Anal.* ($C_{20}H_{18}O_4$) C, H.

**16,16-Ethylenedioxy-3-methoxygona-1,3,5(10),6,8-pentaene (16).**—The procedure used to prepare **13** was followed, **16** being obtained in a yield of 90%, mp 130–132°. *Anal.* ($C_{20}H_{22}O_3$) C, H.

**16,16-Ethylenedioxy-3-methoxy-14β-gona-1,3,5(10),6,8-pentaene (17).**—The procedure used to prepare **13** was followed, **17** being obtained in a yield of 92%, mp 135–138°. *Anal.* ($C_{20}H_{22}O_3$).

(10) G. Haberland and E. Blanke, *Ber.*, **70**, 169 (1937).

(9) All melting points are corrected. Ir spectra were obtained on a Beckman IR7 spectrophotometer. Where analyses are indicated only by symbols of the element, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were obtained on a Varian HA60 spectrophotometer. Spectral results agreed with the suggested structures routine.

## Potential Specific Inhibitors of the Lactose Transport System of *Escherichia coli*

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The membrane component of the lactose transport system of *Escherichia coli*, known as lactose permease,[2] contains an SH group which is essential for its activity.[3] Several galactosides protect this SH group from attack by SH reagents,[3] implying a close spatial relationship between the galactoside binding site and the SH group. The galactosides described here were designed as specific and irreversible inhibitors[4] of the permease—the D-galactose moiety enabling specific binding, while the *N*-bromoacetyl or *N*-(4-acetoxymercuri-3-methoxybutyryl) function could then react with the essential SH group. Analogs containing other carbohydrate moieties were prepared in order to test for specificity of inhibition. The unsubstituted gly-

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(4) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley & Sons, New York, N. Y., 1967.