nmr, 5.77 (4-H), 4.55 (20-H), 1.63, 1.53 (d, 21-$H_3$), 1.22 (19-$H_3$), 0.79 (18-$H_3$). *Anal.* ($C_{21}H_{31}NO_3$) C, H, N.

**20β-Nitropregn-4-ene-3,6-dione** (11).—An ice-cold solution of 0.2 g of **8** in 75 ml of acetone was allowed to react with excess 8 *N* $CrO_3$ solution for 45 min. The excess $CrO_3$ was destroyed by addition of *i*-PrOH, and the product was isolated by ether extraction. Purification by preparative tlc followed by recrystallization from MeOH gave 9 mg of yellow powder: mp 213–215°; nmr, 6.19 (4-H), 4.56 (20-H), 1.55, 1.45 (d, 21-$H_3$), 1.17 (19-$H_3$), 0.84 (18-$H_3$). *Anal.* ($C_{21}H_{29}NO_4$) C, H, N.

# The Solvolysis of 19-Hydroxy Steroid Derivatives[1]

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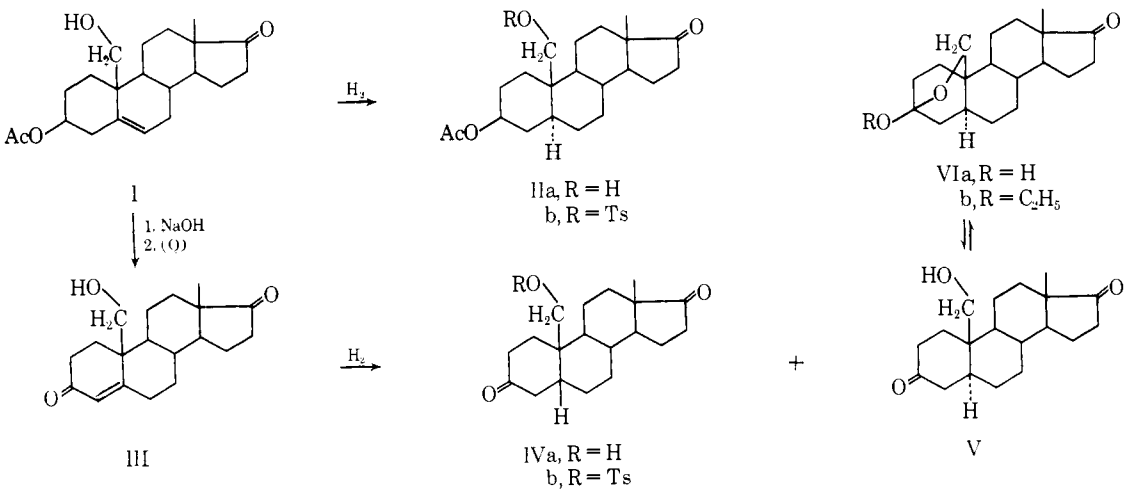
*Received September 2, 1967*

The 5α and 5β isomers IIa and IVa of 19-hydroxy steroids were prepared and their related *p*-toluenesulfonyl esters were solvolyzed in buffered acetic acid. In both series the predominant product was a $\Delta^{1(10)}$-19-nor-A-homoandrostene derivative VIIa or XIII. The structures of these solvolysis products were established by degradation.

The acetolysis of both *cis*- and *trans*-9-decalylcarbinyl *p*-toluenesulfonates[3,4] afforded mixtures of $\Delta^{1(7)}$-bicyclo[5.4.0]undecene and $\Delta^{1}$- and/or $\Delta^{1(11)}$-bicyclo[5.4.0]undecene in a ratio of about 7:3. These results, the absence of any bicyclo[4.4.1]undecane products, and a rate of reaction approximately equal to the rate of the similar neopentyl derivative can be rationalized by consideration of the formation of a classical carbonium ion followed by rearrangement to the most stable carbonium ion, the stability of which is related to the products.[5] The solvolysis results are to be contrasted with the results of the deamination of the corresponding *cis*- and *trans*-9-decalylcarbinylamines where bicyclo[4.4.1]undecane derivatives and tricyclo[4.4.1.-$0^{1,6}$]undecane were obtained.[4,6] These latter results have led to the suggestion that in the deamination reaction the geometry of the transition state closely resembles the conformation of the starting material and it is the steric arrangement of this latter species which controls the migratory aptitude of the groupings.

Since the products from the acetolysis of the decalylcarbinyl system appeared to be dependent upon the relative stability of the carbonium ions, it was of interest to know whether in an unsymmetrically substituted decalylcarbinyl system, where the conformational energies of the products would be different, the acetolysis would favor certain products over others. The recent availability of 19-hydroxy steroids (which are precursors of 19-nor steroids[7]) made this series of materials an attractive group of unsymmetrical decalylcarbinyl systems to study both from the viewpoint of solvolysis mechanisms and of the potential preparation of modified steroidal derivatives of the 19-nor-A- and the 19-nor-B-homo series.

The A/B-*cis* and A/B-*trans* isomers IVa and IIa, respectively, were prepared by slight modifications of published procedures,[8-11] and the synthetic sequences are outlined below. In the hydrogenation of 19-hydroxy-$\Delta^4$-androstene-3,17-dione (III) it had been reported[11] that the steric course of the reaction was




(1) This work was supported in part by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.

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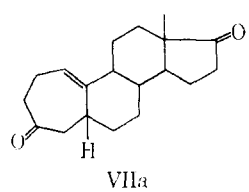
independent of the reaction conditions; however, it was found that only in neutral solution could pure IVa be obtained by direct recrystallization of the reaction mixture. Chromatography of the mother liquors yielded 28% of a mixture of isomers, 11% of pure *trans* V (in equilibrium with hemiketal VIa) and 2% of ethyl ketal VIb. The structure of VIb was established from its spectral properties, its conversion to V in aqueous acid solution, and its preparation on heating V under reflux with *p*-toluenesulfonic acid in absolute ethanol. It is of interest to note that no ketal was formed upon treatment of V with 10% palladium on strontium carbonate in ethanol under hydrogenation conditions. The 19-*p*-toluenesulfonyl ester IVb was prepared in the usual manner.

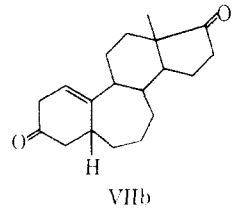
**Solvolysis.**—Acetolysis of the *cis*-tosylate IVb in refluxing acetic acid containing sodium acetate afforded a mixture of steroidal olefinic diones and tlc analysis indicated the presence of one major and one minor product plus trace amounts of other materials.. The reaction mixture was chromatographed on alumina to yield 22% of crystalline VII and 2% of crystalline VIII.

The major product VII analyzed for $C_{19}H_{26}O_2$ and had a molecular ion at *m/e* 286 in the mass spectrum. Its ir spectrum showed a cyclopentanone band (C-17) and a band indicative of a saturated six- or higher membered ring ketone. The intense end absorption in the uv spectrum indicated the presence of nonconjugated carbonyl groups as well as the presence of a highly substituted isolated double bond.[12] The presence of a single vinyl proton absorption at $\tau$ 4.32 (triplet, $J$ = 5–6 cps) in the nmr spectrum established the trisubstituted nature of the double bond.

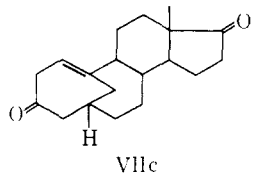
After consideration of the three possible *t*-amyl systems and the resulting nine olefinic products which could be formed from a single Wagner–Meerwein rearrangement of the starting tosylate, only the following three structures, VIIa, b, c, would fit the above data. The remaining six structures either would have a tetrasubstituted double bond or a trisubstituted double bond whose vinyl proton would only be a doublet. The structure VIIa was indicated by the stability of the solvolysis product to base, a feature expected of a $\gamma,\delta$



VIIa



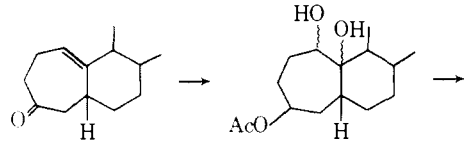
VIIb



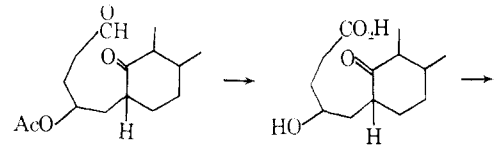
VIIc

but not of a $\beta,\gamma$-unsaturated ketone. For example, it has been reported that the $\beta,\gamma$-unsaturated ketone, A-homo-$\Delta^1$-5$\alpha$-androsten-3-on-17$\beta$-ol, was isomerized on base treatment to the related $\alpha,\beta$-unsaturated ketone.[13] The correctness of the assignment of structure VIIa was established by degradation.

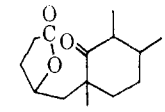
The solvolysis product VIIa was reduced to a diol with $LiAlH_4$, the diol was acetylated, and the resulting diacetate was allowed to react with $OsO_4$. The 1,10-diol IX was cleaved with periodic acid to X which was oxidized and saponified to the $\gamma$-hydroxy acid XI. The acid was heated with *p*-toluenesulfonic acid in benzene to form the $\gamma$-lactone XII which in the ir displayed two carbonyl bands: 1710 (six-ring ketone, C-10), and 1770 cm$^{-1}$ ($\gamma$-lactone). Structures VIIb and VIIc would have yielded a $\beta$-lactone ($\nu_{max}$ 1820–1840 cm$^{-1}$) or an unsaturated acid from this reaction sequence.



VIIa IX

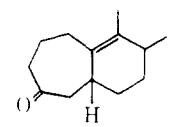


X XI

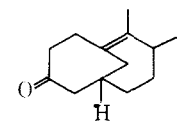


XII

The minor solvolysis product VIII was isomeric with VIIa (*m/e* 286), and the ir and uv spectra of the two products were almost identical. The nmr spectrum of VIII established the absence of any olefinic protons and of a cyclopropane ring. The material was not isomerized to an $\alpha,\beta$-unsaturated ketone with base. Again in considering the nine possible olefinic structures which could arise in the solvolysis, only VIIIa and VIIIb fit the data. Since in the simple decalyl series only bicyclo[5.4.0]undecanes were formed in the solvolysis



VIIIa



VIIIb

reaction,[3,4] VIIIa is tentatively assigned as the structure of the minor product. Insufficient material was obtained to permit establishment of its structure by degradation.

Acetolysis of the *trans* tosylate IIb yielded a mixture of monoolefinic products having a 17-keto and a 3-acetoxyl grouping. The mixture of materials gave a broad single spot on tlc analysis but the nmr spectrum showed the presence of two C-18 methyl groups (singlets at $\tau$ 9.03 and 9.13). The mixture upon chromatography on alumina gave 22% of a mixture of materials and then the major product XIII in 46% yield. XIII possessed

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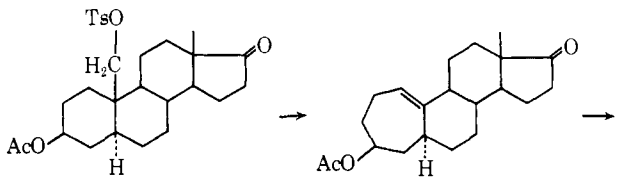
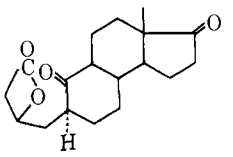



IIb




XIII




XIV

the composition of $C_{21}H_{30}O_3$, indicative of a product formed by rearrangement and loss of toluenesulfonic acid. The presence of a trisubstituted double bond was shown by a one-proton absorption at $\tau$ 4.55 (triplet, $J$ = 5.5 cps) in the nmr spectrum. Saponification and oxidation of XIII yielded a diketone which was stable to base. The similarity of the spectral and chemical properties of this material as compared with the solvolysis product VIIa from the *cis* isomer indicated structure XIII for the major product. The material was degraded as described earlier for VIIa and the $\lambda$-lactone XIV was obtained, establishing the correctness of structure XIII.

**Discussion.**—The over-all results of the acetolysis of the *trans* and *cis* tosylates IIb and IVb are in accord with the results obtained in the 9-decalylcarbinyl series, *i.e.*, only ring expansion to the bicyclo[5.4.0]undecane system occurred with no formation of a bicyclo[4.4.1]-undecane derivative. However, the exclusive expansion of ring A as well as the almost exclusive formation of a $\Delta^{1(10)}$ double bond in the steroidal system as contrasted to the predominant $\Delta^{1(7)}$ double bond formation in the decalylcarbinyl system distinguishes the former system from the latter. The exclusive formation of the bicyclo[5.4.0]undecane system fits well with the mechanistic concepts of an unassisted rate-determining step to form a classical carbonium ion which, in turn, rearranges to the most stable tertiary carbonium ion.[5,14] The relative energies of the three possible ions can be expected to be the same as the three possible products VIIa, b, c and, thus, the present results indicate the greater stability of the A-homo over the B-homo system, a feature not previously ascertained. Since this work was completed, the acid hydrolysis of 3$\alpha$,5-cyclo-6,19-dioxo steroids have been reported and also in this case only the A-homo ring system was formed.[15] Thus, solvolysis of 19-hydroxy steroids offers a convenient synthetic route to A-homo-19-nor steroid derivatives. Although it was desired to examine the deamination of a 19-carbinylamine, no facile synthesis from readily available starting materials could be developed.

The $\Delta^{1(10)}$-19-nor-A-homo-5$\alpha$-androsten-3$\beta$-ol-17-one 3-acetate XIII was tested for androgenic and myogenic activity using immature castrate male rats and a total dosage of 0.6–12 mg was given subcutaneously every other day; the material was found to possess less than 5% of that of testosterone.[16]

## Experimental Section

**Physical Measurements.**—All melting points are uncorrected. Column chromatography was done on neutral alumina (Woelm), activity III. Tlc analysis utilized silica gel G with mixtures of methylene chloride–acetone.

Combustion analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley, mass spectral analyses by Miss Sherry Firth, Mass Spectral Laboratory, University of California, using a CEC Model 21-103C mass spectrometer. All rotations were taken in $CHCl_3$ and all nmr spectra were taken in $CDCl_3$ (TMS as internal standard). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

**3$\beta$,19-Dihydroxy-5$\alpha$-androstan-17-one 3-Acetate (IIa).**—A solution of 267 mg of 3$\beta$,19-dihydroxy-$\Delta^5$-androsten-17-one 3-acetate (I)[8] in 15 ml of absolute EtOH was hydrogenated at atmospheric pressure over 210 mg of 10% Pd–$SrCO_3$ for 7 hr. The catalyst was filtered, the filtrate was evaporated, and the resulting oil was triturated with pentane. The crude solid (245 mg) was recrystallized from 3% absolute EtOH in pentane and from ether–pentane to yield 102 mg (38%) of IIa, mp 163–165°. For analysis the product was recrystallized from absolute EtOH; mp 164.5–165.5°, $[\alpha]D$ +71°. *Anal.* ($C_{21}H_{32}O_4$) C, H.

A solution of 49 mg of IIa in aqueous methanolic $K_2CO_3$ was heated for 3 hr and processed in the usual fashion to yield 47 mg of crude 3$\beta$-hydroxy product which was recrystallized ($Me_2CO$); mp 227.5–229.0° (lit.[9] 237–238°, MeOH solvate; in the present work, when recrystallized from EtOAc, mp 228–230°); mmp 228–231° with authentic sample; tlc analysis showed one spot, identical with authentic sample.

**3$\beta$,19-Dihydroxy-5$\alpha$-androstan-17-one 3-Acetate 19-Tosylate (IIb).**—A solution of 2.31 g of IIa and 4.26 g of *p*-toluenesulfonyl chloride in 105 ml of anhydrous pyridine was prepared at 0° and allowed to stand for 10 days at room temperature; this length of time was required for reaction of all of the starting material. The mixture was poured into 150 ml of ice–water, and the mixture was extracted ($CHCl_3$, $Et_2O$). The combined organic extracts were washed (2 *N* $H_2SO_4$, 10% $NaHCO_3$, $H_2O$) and dried ($Na_2SO_4$). The solvent was evaporated and the crude product was chromatographed on 100 g of neutral alumina. The tosylate was eluted with $C_6H_6$–$Et_2O$ (95:5), yield 2.63 g (79%), mp 140–151°. For analysis, a sample was recrystallized from $Et_2O$; mp 153.5–154.5°, $[\alpha]D$ +31°, $\lambda_{max}^{MeOH}$ 228 m$\mu$ ($\epsilon$ 10,600). *Anal.* ($C_{28}H_{38}O_6S$) C, H.

**19-Hydroxy-$\Delta^4$-androstene-3,17-dione (III).**—Since the preparation of this material is only described briefly in patents,[10] a short detailed description is given. A mixture of 19 g of 3$\beta$,19-dihydroxy-$\Delta^5$-androsten-17-one,[10] 263 ml of toluene, and 60 ml of dry cyclohexanone was heated under reflux for 15 min, and 75 ml of solvent distilled. A solution of 5.7 g of aluminum isopropoxide in 57 ml of toluene and 14 ml of cyclohexanone was added to the hot solution and the refluxing was continued for 14 min. To the cooled mixture, 23 ml of AcOH was added, and most of the solvent was removed by steam distillation. The cooled residue was extracted ($CHCl_3$), and the organic extract was washed ($H_2O$) and dried. The solvent was evaporated and the yellow residue crystallized from acetone–hexane to yield 12.3 g (65%) of III, mp 165–167°. Recrystallization from absolute EtOH yielded III as prisms: mp 168.5–170.5°; $[\alpha]D$ +187°; $\lambda_{max}^{MeOH}$ 242 m$\mu$ ($\epsilon$ 15,400); $\nu_{max}$ 3310, 1740, 1656 $cm^{-1}$ (lit.[10,17] mp 170–171°, $[\alpha]D$ +190°).

The residue from evaporation of the recrystallization mother liquor was chromatographed on 490 g of neutral alumina, collecting 125-ml fractions. Fraction 20 ($C_6H_6$–$Et_2O$ 55:45) afforded 93 mg (0.5%) of $\Delta^4$-androstene-3,17-dion-19-al, mp 130–132°, $[\alpha]D$ +291°, $\lambda_{max}^{MeOH}$ 245 m$\mu$ ($\epsilon$ 12,400) (lit.[10,18] mp 129–133°, $[\alpha]D$ +269°).

(14) The results could equally well be rationalized utilizing the concept of a concerted mechanism. For a discussion of this latter mechanism, see J. R. Owen and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **88**, 5809 (1966); R. L. Heidke and W. H. Saunders, Jr., *ibid.*, **88**, 5816 (1966).

(15) R. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **15**, 38 (1967).

(16) These tests were kindly performed by The Endocrine Evaluation Branch, Cancer Chemotherapy National Service Center, Bethesda, Md.

(17) H. Ueberwasser, K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 344 (1963).

(18) A. S. Meyer, *Experientia*, **11**, 99 (1955); M. Nishikawa and H. Hagiwara, *Chem. Pharm. Bull.* (Tokyo), **6**, 226 (1958).

Fraction 36 ($Et_2O$–MeOH 9:1) gave 2.25 g of crude III which on recrystallization from acetone–hexane yielded 1.45 g (6%), mp 167–168°.

**19-Hydroxy-5β-androstane-3,17-dione (IVa).**—A solution of 13.46 g of 19-hydroxy-$\Delta^4$-androstene-3,17-dione (III)[9] in 385 ml of absolute EtOH and 1.05 g of 10% Pd-$SrCO_3$ was hydrogenated at atmospheric pressure 4.5 hr. The catalyst was filtered, the solvent was evaporated, and the crude product was recrystallized from absolute EtOH, yield 8.23 g (61%), mp 203–204°, single spot on tlc. An additional amount of IVa was obtained on chromatography of the mother liquors (see below). For analysis, a sample was recrystallized from absolute EtOH; mp 203–204° (lit.[11] 198–199°, 208–209°); $\nu_{max}$ 1710, 1740, 3400 $cm^{-1}$; $[\alpha]D$ +104° (lit.[11] $[\alpha]^{25}D$ +106°).

The mother liquor from the crystallization was evaporated and the residue was chromatographed on 500 g of neutral alumina. Elution with $C_6H_6$ yielded 265 mg (1.8%) of ethyl ketal VIb, mp 158–161°. For analysis, a sample was recrystallized from pentane; mp 163.5–165.5°, $[\alpha]D$ +115°, $\nu_{max}$ 1740 $cm^{-1}$, $\lambda_{max}^{EtOH}$ 298 mμ (ε 44). *Anal.* ($C_{21}H_{32}O_3$) C, H, *m/e*.

Elution with $C_6H_6$–$Et_2O$ (changing from 10:1 to 1:1) yielded 1.55 g (11.4%) of a mixture of the *trans*-ketone V and its hemiketal VIa. The material was recrystallized ($Et_2O$); mp 145–165° [lit.[8] mp 137–138° (hemiketal), 178–181° (dione)]. Continued elution with $C_6H_6$–$Et_2O$ (1:1 to 1:3) yielded a mixture highly enriched in *cis*-dione IVa and the material was recrystallized from absolute EtOH; yield 0.69 g (5%), mp 202–204°.

Catalytic hydrogenation of III in acidified EtOH over Pd-C yielded only IVa and V; no ethyl ketal VIb was detected. In methanolic KOH, the major product was IVa and the minor product was V while in dioxane about equal amounts of IVa and V were formed. These analyses were done by tlc.

**Interconversion of Dione V with Ethoxy Ketal VIb.**—A solution of 55 mg of dione V (mixed with its hemiketal VIa) and 24 mg of *p*-toluenesulfonic acid monohydrate in 2.5 ml of absolute EtOH was heated under reflux for 4 hr, ether was added, and the mixture was washed with 10% aqueous $Na_2CO_3$. The product was chromatographed on 15 g of silica gel, yield 44 mg of ketal VIb, mp 161–162°, spectral properties identical with authentic sample.

A solution of 24 mg of VIb in 2 ml of dioxane and 0.5 ml of 2 *N* $H_2SO_4$ was heated under reflux for 1 hr, $H_2O$ was added, and the mixture was extracted ($CH_2Cl_2$). After processing, 12 mg of a mixture of dione V and hemiketal VIa was obtained, mp 140–165°.

**19-Hydroxy-5β-androstane-3,17-dione 19-Tosylate (VIb).**—A solution of 1.14 g of IVa, 0.77 g of *p*-toluenesulfonyl chloride in 15 ml of dry pyridine was allowed to stand for 48 hr at room temperature and then processed as described for the *trans* isomer IIb (see above). The crude product was chromatographed on 250 g of alumina and elution with $C_6H_6$–$Et_2O$ (4:1 to 3:1) yielded 1.52 g of product which was recrystallized from EtOAc: yield 928 mg (54%), mp 186–188°, $[\alpha]D$ +72°, $\lambda_{max}^{MeOH}$ 229 mμ (ε 7200). *Anal.* ($C_{26}H_{34}O_5S$) C, H.

**Acetolysis of 19-Hydroxy-5β-androstane-3,17-dione 19-Tosylate (IVb).**—A solution of 1.91 g of IVb and 685 mg of anhydrous NaOAc in 116 ml of AcOH was heated under reflux for 72 hr. The cooled solution was poured into 150 ml of ice–water, NaCl was added, and the mixture was extracted ($CHCl_3$, $Et_2O$). The combined organic extracts were washed (2 *N* NaOH, NaCl solution), and dried ($Na_2SO_4$). The filtered solution was evaporated to yield 1.03 g of a brown oil. Tlc analysis indicated one major and one minor product.

The reaction mixture was chromatographed on 300 g of neutral alumina, collecting 125-ml fractions. Fractions 24–25 (pentane–$C_6H_6$, 25:75) yielded 65 mg (5.5%) of impure VIIa and fractions 26–29 (pentane–$C_6H_6$, 20:80 to 10:90) yielded 265 mg (22%) of pure VIIa, mp 92–95°. For analysis a sample of VIIa was recrystallized from pentane and ether–pentane to give VIIa as colorless plates: mp 97–98°; $[\alpha]D$ +19°; $\epsilon_{293}^{cyclohex}$ 10,500; $\lambda_{max}^{cyclohex}$ 293 mμ (ε 66); $\nu_{max}$ 1740, 1704 $cm^{-1}$; nmr, τ 4.32 (1 H, triplet, $J$ = 5–6 cps), 9.12 (3 H, singlet). *Anal.* ($C_{19}H_{26}O_2$) C, H, *m/e*.

Fractions 30–33 (pentane 1:9 to 100% $C_6H_6$) contained small amounts of mixtures of VIIa and VIIIa, the amount of VIIIa increasing in the higher fractions.

Fractions 34–36 ($C_6H_6$ to $C_6H_6$–$Et_2O$ 99:1) yield 20 mg (1.7%) of crude VIIIa which was rechromatographed on alumina and then recrystallized from pentane; mp 105.0–106.5°; mmp 75–97° with VIIa; tlc, $R_f$ value shorter than that of VIIa; $\nu_{max}$ 1740, 1705 $cm^{-1}$; nmr, τ 9.04 (3 H, singlet); *m/e* 286.

**Treatment of VIIa with Base. A.** A solution of 22 mg of VIIa and 48 mg of potassium *t*-butoxide in 1.4 ml of dry *t*-BuOH was stirred at room temperature for 3 hr. After work-up, only starting material was recovered as evidenced by the analysis and ir and uv spectra.

**B.**—A solution of 13 mg of VIIa in 0.5 ml of 95% EtOH containing 3 drops of 2 *N* NaOH was heated at 60° for 1 hr. After work-up, starting material was recovered.

**Degradation of VIIa to Lactone XII. A. Conversion of VIIa to IX.**—A solution of 179 mg of VIIa and 200 mg of $LiAlH_4$ in 18 ml of dry THF was heated under reflux for 3 hr, sodium potassium tartrate solution was added, and the mixture was evaporated. The residue was extracted ($Et_2O$, $CHCl_3$) and the combined organic layers were washed ($H_2O$) and dried ($Na_2SO_4$). The filtered solution was evaporated to yield 183 mg of a yellow semisolid. The $R_f$ values on tlc indicated the presence of two components, VIIa being absent; the ir spectrum indicated the absence of C=O absorption. The residue was dissolved in 2.4 ml of pyridine and 2.4 ml of $Ac_2O$, and the solution was allowed to stand at room temperature for 24 hr and then processed in the standard manner. The pale brown semisolid product possessed OAc bands but lacked OH bands in the ir. The material was dissolved in 4.5 ml of $CHCl_3$ and 4.5 ml of pyridine containing 360 mg of $OsO_4$ and the solution was allowed to stand 11 days at room temperature in the dark. The mixture was evaporated under reduced pressure, 25 ml of EtOH and 1 g of sodium thiosulfate in 5 ml of $H_2O$ were added, the mixture was heated under reflux for 1 hr and diluted with $Et_2O$ and EtOAc, and the organic phase separated. Evaporation of the dried solvent yielded 119 mg of IX as a greenish semisolid which on tlc showed the absence of previous products.

**B. Conversion of IX to XI.**—A solution of 119 mg of IX and 304 mg of $HIO_4$ in 6 ml of MeOH and 1 ml of $H_2O$ was kept at room temperature in the dark for 26 hr. The reaction mixture was worked-up in the usual fashion to yield 119 mg of product which showed ir absorption for an aldehyde group and for a trace of a carboxy group. The crude product was dissolved in 10 ml of $Me_2CO$ and oxidized with 2.5 ml of Jones reagent[19] at −15 to −5° for 18 min and 1.2 ml of *i*-PrOH added; after 10 min the supernatant layer was decanted and the residue was washed ($Et_2O$). The organic layers were combined and extracted (10% $Na_2CO_3$). The alkaline solution was acidified and extracted ($Et_2O$) and the solvent was evaporated to yield 58 mg of a crude acid: $\nu_{max}$ 3500–3100, 1735 $cm^{-1}$. A solution of 58 mg of the crude acid in 2.5 ml of aqueous MeOH containing 0.12 g of $K_2CO_3$ was heated under reflux for 75 min. The solution was concentrated, the residue was acidified, the material was extracted ($Et_2O$), and the ether was evaporated to yield 42 mg of crude hydroxy acid XI.

**C. Conversion of XI to XII.**—The 42 mg of crude XI was dissolved in 1 ml of $CHCl_3$ and 10 ml of $C_6H_6$ and 19 mg of *p*-toluenesulfonic acid added. The solution was heated under reflux for 1 hr and diluted with ether, and the solution was extracted with 10% $Na_2CO_3$. The organic layer was washed (saturated NaCl) and dried, the solvent evaporated, and 30 mg of crude XII was obtained: $\nu_{max}$ 1710, 1770 $cm^{-1}$. The material was chromatographed on 8.5 g of alumina. Elution ($C_6H_6$–$Et_2O$, 7:3) yielded 6 mg of pure XII which was recrystallized from pentane; mp 176–180°, *m/e* 320.

**Acetolysis of 3β,18-Dihydroxy-5α-androstan-17-one 3-Acetate 19-Tosylate (IIb).**—A solution of 2.67 g of IIb and 1.28 g of anhydrous NaOAc in 190 ml of AcOH was heated under reflux for 50 hr. The solution was processed as described above for IVb to yield 1.39 g of a brown crystalline solid. The material was chromatographed on 740 g of neutral alumina and elution with pentane through $C_6H_6$ gave a total of 380 mg of a mixture of materials, none of which could be obtained in a pure form. Elution ($C_6H_6$–$Et_2O$, 99:1 to 97:1) yielded 800 mg (46%) of crude colorless crystalline XIII. The solid was recrystallized ($Et_2O$); mp 132.5–133.5°; $[\alpha]D$ −8.5°; $\lambda_{max}^{cyclohex}$ 200 mμ (ε 10,300); $\lambda_{max}^{MeOH}$ 289 mμ (ε 59); $\nu_{max}$ 1740 $cm^{-1}$ (broad); nmr, τ 4.55 (1 H, triplet, $J$ = 5.5 cps), 4.97 (1 H, multiplet), 8.00 (3 H, singlet), 9.13 (3 H, singlet). *Anal.* ($C_{21}H_{30}O_3$) C, H, *m/e*.

**Degradation of XIII to Lactone XIV.**—Following the same general procedure described for the degradation of VIIa to XII, 75 mg of XIII was allowed to react with $OsO_4$, the resulting diol

(19) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

was cleaved with $HIO_4$, the aldehyde was oxidized with Jones reagent, the acetoxyl group was saponified, and the hydroxy acid was converted to the lactone XIV, yield 21 mg of crude product; $\nu_{max}$ 1712, 1738, 1770 $cm^{-1}$. The material was purified by preparative tlc and the pure material which could not be obtained crystalline possessed the identical spectral properties of the crude material. The spectral and chromatographic properties of the oil were different from those of lactone XII; the difference in products could be due to the stereochemistry of the lactone and/or the configuration of C-5.

**Acknowledgment.**—The authors are indebted to the Syntex Corp. for their generous contribution of the starting 19-hydroxy steroids used in this study.

# Synthesis of Hormone Analogs Containing the *p*-Hydroxybenzyl Group

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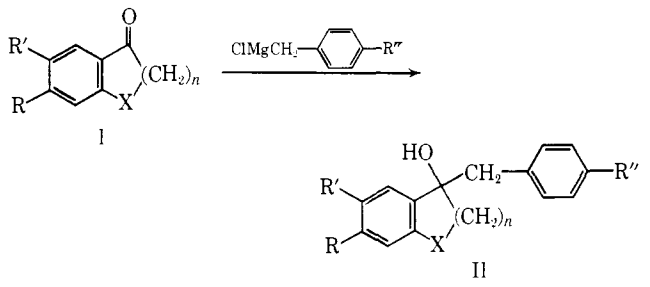
*Received August 11, 1967*

A series of 1-(*p*-hydroxybenzyl)naphthalene, 1-(*p*-hydroxybenzyl)indan, and 4-(*p*-hydroxybenzyl)chroman derivatives was made for study as endocrine agents. These compounds were synthesized by reaction of substituted benzylmagnesium chlorides with appropriate methoxy or acetoxy ketones followed by transformations of the functional groups. Several of the compounds which contained two hydroxy or acetoxy groups were antigonadotropic and weakly estrogenic.

The present work is intended to provide a series of compounds which retain the approximate molecular size and functional group spacing of known estrogens but differ in conformation and flexibility. Although work toward this goal has been reported,[2,3] structures which meet the requirement by having a *p*-hydroxybenzyl group bonded to the 1 position of a bicyclic nucleus such as I have remained unavailable.

The desired compounds were synthesized by condensing substituted benzyl Grignard reagents with appropriate indanones, tetralones,[4] and chromanones as shown in Scheme I, followed by dehydration and hydrogenation. Precautions were taken in the preparation of the Grignard reagents to prevent coupling;

SCHEME I




namely, high dilution and slow addition of the halide to a large excess of magnesium having a large surface area.[5]

In only two cases (IIa and IIb) could the tertiary alcohols (II) be purified. They were obtained by mild decomposition of the Grignard complex with ice water. The tertiary alcohols readily dehydrated to give the unsaturated compounds III (Table I). In the six-membered ring compounds a mixture of *exo* and *endo* double-bond isomers was obtained. In one instance (IIIg) only the exocyclic isomer was isolated; however, an nmr spectrum on crude material from the mother liquor revealed the presence of some of the *endo* isomer. In the case of IIIe a pure sample of the *exo* isomer was obtained by fractional crystallization.

Identification of the isomers was based in part on their different vinyl hydrogen absorptions in the nmr spectra. The endocyclic isomers of the hydronaphthalene compounds have vinyl hydrogen signals at about 340 cps with a side-chain methylene signal at about 224 cps that is partly hidden by aromatic methoxy signals. The vinyl hydrogens of the exocyclic isomers appear at or above 400 cps.

The nmr spectrum of 7-methoxy-4-(*p*-methoxybenzylidene)chroman (IIIg) was studied further because of the questionable assignment of two protons which absorbed in the region of 380–400 cps. The overlap of signals in this region gave rise to an apparently inconsistent coupling pattern. In order to assign these protons and to verify the low-field absorption of the vinyl proton, a spectrum at 100 Mc was obtained. This spectrum clearly indicated that the 380–400-cps absorption at 60 Mc was due to the $C_6$ and $C_8$ aromatic hydrogens. The $C_6$-H is coupled ($J_o$ = 8.5 cps) with the $C_5$-H (which is centered at 452 cps at 60 Mc) and also with the $C_8$-H ($J_m$ = 2.5 cps). The remaining absorption in the aromatic region is the vinyl hydrogen absorption at about 414 cps (60 Mc), which is split ($J$ = 1.5 cps) by the allylic methylene group, and the $A_2B_2$ pattern of the aromatic hydrogens of the *p*-methoxybenzylidene group. The absence of endocyclic vinyl hydrogen absorption (at about 313 cps on the 60-Mc spectrum) and the presence of two $CH_2$ triplets (centered at 172 and 249 cps, $J$ = 5.5 cps; 60-Mc spectrum) definitely confirm the exocyclic structure for IIIg.

In contrast with the six-membered ring cases, the indanones gave isolable products (IIIa and IIIb) in which the double bond is exocyclic.[6,7] The nmr spectra

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(2) *Cf.* J. Grundy, *Chem. Rev.*, **57**, 281 (1957); R. E. Juday, D. P. Page, and G. A. Du Vall, *J. Med. Chem.*, **7**, 519 (1964); J. Bascoul and A. C. De Paulet, *Compt. Rend.*, **C264**, 629 (1967).

(3) D. M. Lynch and W. Cole, *J. Org. Chem.*, **31**, 3337 (1966).

(4) For a paper dealing with the condensation of benzylmagnesium chloride with tetralones see H. A. Fahim, A. M. Fleifel, and F. Fahim, *ibid.*, **25**, 1040 (1960).

(5) M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, *J. Am. Chem. Soc.*, **70**, 2296 (1948). When the Grignard reaction started at the onset of addition of the halide, no coupling product was detected.

(6) One nmr spectrum of IIIb taken in $CDCl_3$ showed some endocyclic isomer (vinyl hydrogen, 363 cps). This was shown to be due to isomerization caused by acid in the $CDCl_3$, since a spectrum of IIIb taken in $CDCl_3$ stored over $Na_2CO_3$ showed no trace of the *endo* isomer. For this reason $Na_2CO_3$-treated $CDCl_3$ has been used to record the nmr spectra reported in this paper.

(7) The condensation of γ-picoline with indanones also gave products having the exocyclic double bond, while the condensation of γ-picoline with tetralones gave products containing both double-bond isomers. See ref 3.