SYNTHESIS OF THE ALLYLIC GONADAL STEROIDS, 3α-HYDROXY-4-PREGNEN-20-ONE AND 3α-HYDROXY-4-ANDROSTEN-17-ONE, AND OF 3α-HYDROXY-5α-PREGNAN-20-ONE

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ABSTRACT

A method for the convenient synthesis of the recently isolated allylic gonadal steroids, 3α-hydroxy-4-pregnen-20-one (3α-dihydroprogesterone; 3α-DHP) and 3α-hydroxy-4-androsten-17-one (3α-HA), was developed using 4-pregnene-3,20-dione (progesterone) and 4-androstene-3,17-dione as substrates and potassium trisiamylborohydride (KS-Selectride) as reducing agent. Similar reactions were also used for the reduction of 5α-pregnane-3,20-dione to 3α-hydroxy-5α-pregnan-20-one (3α-HP). The yields were about 15%, 50%, and >90% for 3α-DHP, 3α-HA and 3α-HP, respectively. Structures of the products, including the 3β-isomers and the 17α-epimer, formed in these reactions were determined by NMR and mass spectroscopic methods.

INTRODUCTION

Recently one of us reported (1) the isolation and identification of 3α-hydroxy-4-pregnen-20-one (3α-dihydroprogesterone; 3α-DHP) 2 as one of ten metabolites produced from progesterone 1 by Sertoli cells from rat testes. In addition, 3α-DHP has been found in cells from the uterus of rats, ovaries of chickens, and brain of humans and the allylic steroid, 3α-hydroxy-4-androsten-17-one (3α-HA) 7, has been identified as a product of testicular tissue (2). Both of these steroids appear to be produced in larger quantities during the period of sexual maturation. In connection with projected biological testing of these allylic steroids, reasonable amounts of the compounds were required. In this paper we report a convenient method for the synthesis of 3α-DHP and 3α-HA and

their 3β-hydroxy epimers and also of 3α-hydroxy-5α-pregnan-20-one **10** using the readily available Selectride reducing agents. The structure and stereochemistry of the compounds reported here were established using proton and carbon NMR along with infrared and mass spectrometry.

MATERIALS AND METHODS

Melting points were determined on a Reichert-Kofler microscope hot stage and are corrected. Infrared spectra were recorded on a Beckman Acculab 4 instrument with $CHCl_3$ solutions. ^1H NMR spectra were recorded on a Varian XL-200 spectrometer with $CDCl_3$ solutions containing tetramethylsilane; only relevant peaks from the ^1H NMR spectra are reported. The ^{13}C NMR spectra were obtained using $CDCl_3$ solutions with Varian XL-200 (50.3 MHz) and XL-300 (75.4 MHz) instruments. Comparison of the fully decoupled spectra with those obtained with either the APT (3) or DEPT (4) sequences served to identify the methyl, methylene, methine, and quaternary signals. The ^{13}C data are collected in Table 2. Optical rotations were measured with $CHCl_3$ solutions in 1-dm tube on a Rudolph Model 80 polarimeter. Exact masses were determined on a MAT 311A mass spectrometer. Capillary GC retention times and ion fragmentation patterns were determined on a Hewlett Packard 5790A GC/5970A MS. Camag DF-5 silica gel was used for thick- and thin-layer chromatography. Preparative plates (20x20 cm) contained 20 g of silica gel each. For the high performance liquid chromatography (HPLC) a Beckman Model 332 gradient liquid chromatograph with Altex Model 420 microprocessor and Model 155 variable wavelength detector was interfaced with a Hewlett-Packard 5840A terminal; a Whatman Partisil 10 (Magnum 9) ODS-3 preparative HPLC column was used for the purifications. Commonly, a liquid phase consisting of 70% methanol and 30% water was employed. A wavelength of 240 nm was employed for the detection of 4-ene-3-keto steroids and 206 nm or 210 nm for steroids with 5α- and/or 3-hydroxy configurations.

The following commercially available chemicals were used: progesterone (Sigma and Aldrich Chemical Co.), 4-androstene-3,17-dione (Sigma), 5α-pregnane-3,20-dione (Sigma), digitonin (Sigma), potassium tri-sec-butylborohydride (0.5M solution in THF; K-Selectride; Aldrich), and potassium trisiamylborohydride (1.0M solution in THF; KS-Selectride; Aldrich). Tetrahydrofuran (THF;Fisher reagent grade) was distilled from lithium aluminum hydride.

Reaction of Progesterone with KS-Selectride

In a flame-dried 25 mL round bottom flask fitted with rubber septum and a condenser, were placed 1.0 g (3.2 mmol) of progesterone and 5.0 mL dry THF. The flask was cooled in an ice bath and to the stirred solution, under positive pressure of N_2, was slowly added 3.2 mL (3.2 mmol) of 1 M KS-Selectride solution in THF. The solution was brought to room temperature and the reaction allowed to continue for 4-5 hours, until 90% of the progesterone was converted (as monitored by TLC). The reaction was stopped by cooling the flask in an ice-bath and slowly

adding cold (0°C) water to the stirred solution. The contents of the flask were quickly transferred to a separatory funnel using additional ice-cold ether for the rinse. After a cold water wash, the organic layer was removed, dried, and concentrated. The resulting viscous liquid was dissolved in 50 mL ethanol and to it was added a warm solution of 1.0 g of digitonin in 25 mL ethanol and 15 mL water and the mixture was allowed to stand at 5°C for 12 hr. The precipitated digitonide was filtered and washed with ether. The filtrate was concentrated and the residue was taken up in ether. The mixture was filtered and the filtrate was concentrated to give a viscous deposit.

The viscous material was taken up in chloroform and chromatographed on 8 preparative plates using chloroform/ether (9:1) in 2 developments. The main band at R_f 0.59 was scraped and extracted, and when dried down, gave 250 mg of a colorless solid. The final purification on HPLC was carried out using methanol/water (69:31) at a flow rate rate of 3.7 mL/min and UV detection at 210 nm. The main peak with a retention time of about 35 min was collected, and when dried down in a rotary evaporator, yielded 165 mg of 3α-DHP **2** as colorless granules; the melting point and the spectroscopic characteristics of the 3α-DHP were determined (Tables 1, 2). The band at R_f 0.5 yielded 87 mg of 3α-hydroxy-17α-pregn-4-en-20-one **4** as a colorless viscous liquid, whose spectroscopic characteristics were determined (Tables 1,2). The most polar band at R_f 0.42 yielded 105 mg of crystalline solid. Two recrystallizations from acetone/hexane gave 52 mg of 4-pregnene-3α,20R(20β)-diol **5** as colorless needles whose melting point and spectroscopic characteristics were determined (Tables 1,2).

The digitonide from the above reaction was cleaved using the published procedure (5) and the crude steroidal material was chromatographed using preparative TLC plates (chloroform/ether, 95:5, two developments). The band at R_f 0.5 was removed, extracted with ether, and dried to give a colorless solid. Recrystallization from ether/petroleum ether and from acetone/hexane gave 3β-hydroxy-4-pregnen-20-one **3** as colorless plates whose melting point and spectroscopic characteristics were determined (Tables 1,2).

Reduction of 3α-hydroxy-4-pregnen-20-one **2** using $NaBH_4$

To a stirred solution of 2 mg of 3α-DHP in 0.3 mL CH_3OH was added 2 mg of $NaBH_4$ and the solution was stirred for 30 min at room temperature. After evaporating most of the CH_3OH under N_2, the residue was taken up in ether, washed with water, dried, and concentrated, resulting in 1.85 mg of viscous solid. On HPLC this substance was resolved as a 89:11 mixture of 3α,20β:3α,20α diols.

Epimerization of 17α-acetyl Isomer **4** to 3α-DHP **2**

To a stirred solution of sodium methoxide in methanol (10 mg Na and 1.0 ml dry CH_3OH) was added a solution of 10 mg of 3α-hydroxy-17α-pregn-4-en-20-one **4** in 0.5 mL CH_3OH and the solution was stirred for 2 days at room temperature. After evaporating most of the CH_3OH, the residue was taken up in ether, washed with water, dried, and concentrated, resulting in 8 mg of colorless oil. The TLC and NMR analyses indicated this substance to be mostly 3α-DHP **2**.

Reaction of 4-Androstene-3,17-dione **6** with K-Selectride

The reaction was similar to that with progesterone (above) using 0.5 g (1.8 mmol) of 4-androstene-3,17-dione, 3.0 mL dry THF and 3.6 mL (1.8 mmol) of 0.5 M K-Selectride in THF for 4.5 hr. The work up gave a viscous oil which was chromatographed on 4 preparative TLC plates (chloroform/ether, 9:1, three developments). The band at R_f 0.53 gave 127 mg of crystalline solid. Two recrystallizations from acetone/hexane yielded 90 mg of colorless needles which were analysed by melting point, NMR and mass spectrometry as 3α-hydroxy-4-androsten-17-one **7** (Tables 1,2). Spectral examination of the mother liquors of the 3α-alcohol **7** showed the presence of some α,β-unsaturated ketone, indicating reduction of the 17 ketone. No attempt was made to purify this material. The band at R_f 0.68 was extracted and yielded 144 mg of crystalline solid which was recrystallized from ether/petroleum ether and the crystals (110 mg) were analysed as 3β-hydroxy-4-androsten-17-one **8** (Tables 1 and 2).

Reaction of 5α-Pregnane-3,20-dione **9** with KS-Selectride

The reaction was carried out using 150 mg (0.48 mmol) of 5α-pregnane-3,20-dione **9**, 2.0 mL dry THF, and 0.48 mL (0.48 mmol) of 1 M KS-Selectride solution in THF for 18 h. The workup gave a viscous oily solid which was chromatographed on 2 preparative silica gel plates (benzene/ether, 76:24, three developments). The band at R_f 0.65 gave 80 mg of crystalline solid. One recrystallization from acetone/hexane resulted in 55 mg of colorless granules, identified by melting point and NMR and mass spectrometry as 3α-hydroxy-5α-pregnan-20-one **10** (Tables 1,2). The band at R_f 0.45 gave 20 mg of an oily solid which was not identified.

Capillary GC/MS Retention Times and Mass Spectra

To establish capillary GC retention times and fragmentation spectra, a Hewlett Packard 5790A GC/5970A MS was employed with a 12.5 m crosslinked methyl silicone capillary column. The conditions were as follows: splitless mode, 0.7 kg/cm^2 helium, 205°C injection temperature, column temperature 150°C (initial) to 220°C at 15°C/min, and scan speed of 690 amu/sec. Steroids were dissolved in methanol and 1 μL aliquots were injected. Under these conditions the retention times relative to progesterone (RT/RT progesterone) were 0.557 for 3α-hydroxy-4-androsten-17-one **7**, 0.562 for 3β-hydroxy-4-androsten-17-one **8**, 0.704 for 3α-hydroxy-17α-pregn-4-en-20-one **4**, 0.767 for 3α-hydroxy-4-pregnen-20-one **2**, and 0.786 for 3β-hydroxy-4-pregnen-20-one **3**. The GC conditions resulted in dehydration of 10-90% of the molecules; the dehydration fragments had short relative retention times (0.47 - 0.52). Trimethylsilyl ethers were prepared with N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA; Pierce Chem. Co.) and all showed mass of M + 72.

RESULTS AND DISCUSSION

Initial attempts to obtain 3α-DHP, using progesterone/sodium borohydride in isopropanol as reported (6), were not reproducible and our

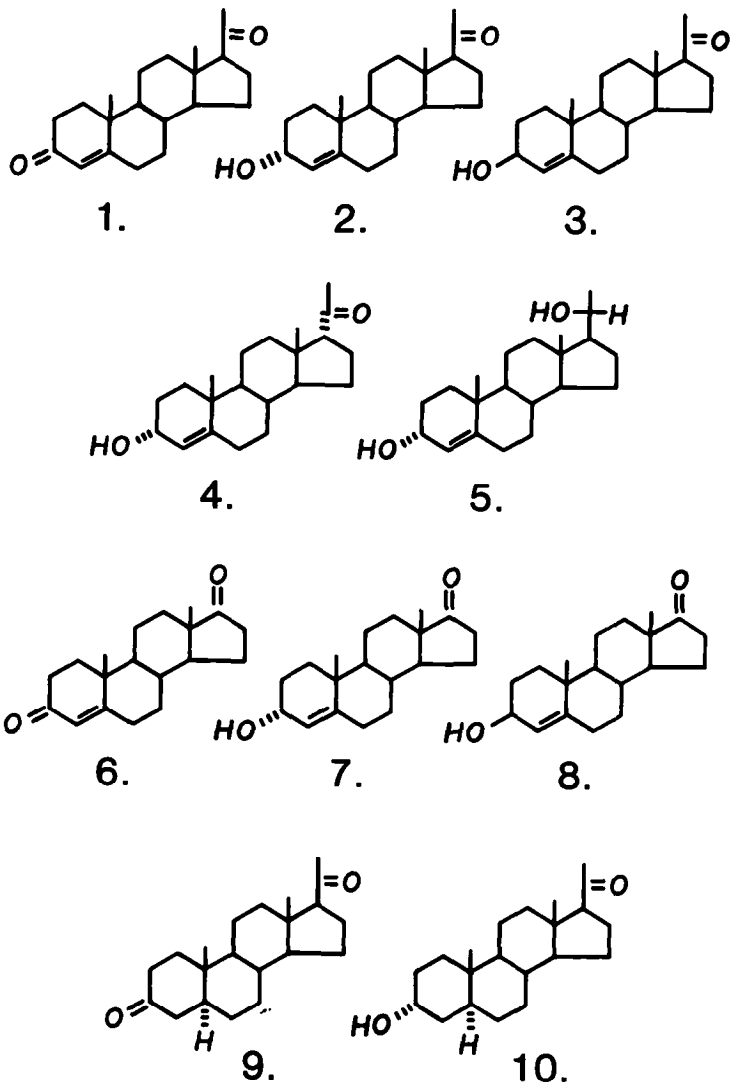

FIGURE 1. Steroidal ketones and their reduction products.

1. 4-pregnene-3,20-dione (progesterone)
2. 3α-hydroxy-4-pregnen-20-one
3. 3β-hydroxy-4-pregnen-20-one
4. 3α-hydroxy-17α-pregn-4-en-20-one
5. 4-pregnene-3α,20R-diol
6. 4-androstene-3,17-dione
7. 3α-hydroxy-4-androsten-17-one
8. 3β-hydroxy-4-androsten-17-one
9. 5α-pregnane-3,20-dione
10. 3α-hydroxy-5α-pregnan-20-one

TABLE 1. Physical constants and spectral characteristics of Selectride reduction products.

Compound[a]	M.P. °C	$[\alpha]_D$	IR cm^{-1}	δ (ppm)[b]					Mass Spec. m/e		Ref
				18-CH_3	19-CH_3	-$COCH_3$	3-H	4-H	Found	Calc	
2	127-129	+231° (26°,c,1.80)	3600, 1700	0.64	0.98	2.11	4.08	5.47	316.2401	316.2402 $C_{21}H_{32}O_2$	1, 13
3	153-155	+130 (27°,c,1.34)	3600, 1700	0.63	1.05	2.11	4.16	5.29	316.2398	316.2402 $C_{21}H_{32}O_2$	13
4	oil	-	3600, 1700	0.93	0.96	2.11	4.04	5.45	316.2407	316.2402 $C_{21}H_{32}O_2$	--
5	155-158	+114° (23°,c,1.15)	3600	0.77	0.98	c	4.06	5.45	318.2558	318.2558 $C_{21}H_{34}O_2$	--
7	195-198	+230° (26°,c,1.27)	3600, 1730	0.89	1.01	-	4.08	5.49	288.2093	288.2089 $C_{19}H_{28}O_2$	13
8	132-134	+157° (27°,c,1.67)	3600, 1730	0.89	1.07	-	3.99	5.31	288.2093	288.2089 $C_{19}H_{28}O_2$	13
10	168-170	-	3600, 1695	0.60	0.78	2.11	4.07	-	318.2558	318.2558 $C_{21}H_{34}O_2$	17

[a] Numbers refer to the compounds in Figure 1.

[b] The signal for 4-H in 3α-hydroxy-Δ^4- steroids appear as doublet of doublets with J=5.0;1.85 Hz and for 3β-hydroxy-Δ^4- steroids appear as a quartet with J=1.6 Hz, while the 3-H resonance of both appear as a broad multiplet.

[c] 1.13 (doublet, J=6.2 Hz), 21-CH_3; 3.72 (multiplet), 20-H.

attention was directed to commercially available bulky trialkylborohydride reagents, viz. potassium tri-sec-butylborohydride (K-Selectride) and potassium trisiamylborohydride (KS-Selectride). These reagents are reported to be regioselective in the reduction of α,β-unsaturated ketones (7,8). Carrying out the reaction of progesterone with one equivalent of K-Selectride in dry THF at 25°C for 3 hours resulted in several products and 10-15% starting material (as determined by TLC). High performance liquid chromatography (HPLC) indicated that the reaction mixture consisted of two major products in a 40:60 ratio. Repeating the reaction with one equivalent of KS-Selectride resulted in a reversal of the ratio of the two major products to 60:40. All subsequent reactions were carried out using progesterone and one equivalent of KS-Selectride at room temperature for 3-5 hours.

Initially the workup was done using H_2O_2/NaOH at 0°C as recommended for Selectride reductions (7). However, spectral characteristics for some of the products isolated indicated them to be contaminated with products arising from H_2O_2 reactions with olefin(s) and also possible base-catalyzed epimerization of the acetyl group on C-17. To facilitate purification of products, KS-Selectride reactions were routinely worked up at 0-5°C without H_2O_2 and NaOH, the Selectride residue being removed in the subsequent chromatographic purification. The procedure of omitting the H_2O_2/NaOH following Selectride reductions has been employed by others (9).

The characteristics of the HPLC purified compound are indicated in Tables 1 and 2. While the infrared and proton NMR spectra indicated the presence of OH (3600 cm^{-1}) and $COCH_3$ (2.11 ppm) groups, confirmation of the presence of a 3-hydroxy-Δ^4- unit in this compound came from comparisons of the ^{13}C chemical shifts (δc) for C-3 (64.2), C-4 (120.9), and C-

TABLE 2. ^{13}C shieldings[a] of Selectride reduction products.

Carbon No.	Compound						
	2	3	4	5	7	8	10
C-1	31.7	35.4	31.7	31.7	31.5	35.4	32.2
C-2	27.9	29.5	27.8	27.9	27.8	29.4	29.0
C-3	64.2	67.9	64.1	64.2	64.1	67.8	66.5
C-4	120.9	123.6	121.0	120.8	121.3	124.0	35.8
C-5	149.9	147.2	149.7	150.1	149.3	146.7	39.1
C-6	32.7	33.0	33.0	32.8	32.1	(31.4)	28.4
C-7	32.3	32.1	32.3	32.4	31.6	(31.9)	32.0
C-8	35.8	35.9	36.0	35.7	35.3	35.5	35.5
C-9	53.9	54.3	53.3	54.1	54.1	54.5	54.2
C-10	37.5	37.3	37.4	37.6	37.6	37.4	36.1
C-11	21.5	21.0	21.5	21.4	20.8	20.3	20.8
C-12	39.0	38.9	35.2	40.0	31.7	(31.8)	39.1
C-13	44.2	44.1	45.7	42.5	47.7	47.7	44.3
C-14	56.3	56.4	49.9	55.6	51.1	51.1	56.8
C-15	24.4	24.4	(25.9)	24.5	21.8	21.8	24.4
C-16	22.8	22.8	(24.3)	25.6	35.8	35.8	22.8
C-17	63.7	63.7	61.2	58.5	221.1	221.1	63.8
C-18	13.4	13.4	20.8	12.5	13.7	13.7	13.5
C-19	18.1	18.9	18.1	18.1	18.1	18.9	11.2
C-20	209.6	209.6	212.7	70.5			209.8
C-21	31.5	31.5	32.8	23.6			31.6

[a] In ppm from internal TMS for $CDCl_3$ solution; similar values in parentheses may be interchanged.

5 (149.9) with the reported values (10) for the corresponding carbons in 4-cholesten-3α-ol (C-3, 64.2; C-4, 120.7; and C-5, 150.2) and in 4-cholesten-3β-ol (C-3, 67.9; C-4, 123.4; and C-5, 147.5). For comparison, chemical shifts (δc) for carbons 3, 5, and 6 of 5-cholesten-3α-ol are 67.2, 138.6, and 124.1 respectively (11). That the OH group is indeed a 3α-hydroxyl is apparent from the coupling of the olefinic 4-proton with the 3β-proton and with one of the 6-protons, the former showing a well-resolved doublet of doublets at 5.47 ppm with J=5.0, 1.85 Hz. Mass spectrometry indicated the same ion fragmentation pattern

(Figure 2) as reported for 3α-DHP from gonadal tissue (1). Under GC/MS conditions (220°C), H_2O was lost (m/e = 298) from about 70% of the applied material but the trimethylsilyl ether derivative was not dehydrated and had a m/e = 388 (316 + 72). These observations established the structure for the compound as 3α-hydroxy-4-pregnen-20-one (3α-dihydroprogesterone; 3α-DHP) **2**.

It should be noted that previous reports of the synthesis of 3α-DHP by other methods failed to provide thorough structural proof or yield. The formation of 3α-DHP from progesterone using sodium borohydride in isopropyl alcohol has been reported (5); however, the yield was not specified and no proof for the presence of the allylic alcohol grouping was presented. Similarly, the complex of zinc bis-tetrahydroborate/dimethyl formamide [$Zn(BH_4)_2$1.5DMF] in acetonitrile is reported (12) to react with progesterone to give a 20% yield of 3-hydroxy-4-pregnen-20-one of unknown C-3 hydroxyl stereochemistry (12). The reduction of progesterone using poly(N-isopropyliminoalane) in benzene has been reported to give 3α-DHP in 7% yield (13).

Synthesis and Identification of 3β-Hydroxy-4-pregnen-20-one (3β-DHP) **3**

The digitonide from the above reaction was decomposed using a published procedures (5) and the product was purified by TLC and recrystallization. The infrared (OH, 3600 and CO, 1700 cm^{-1}), carbon NMR (C-3, 67.9; C-4, 123.6; C-5, 147.2) and proton NMR (3β-OH-Δ^4-) spectra (Tables 1 & 2) confirmed this steroid to be 3β-hydroxy-4-pregnen-20-one **3**. Mass spectrometric analysis indicated a fragmentation pattern similar to that of **2**, but significant differences were noted in the m/e 213/203 ratios (Figure 2).

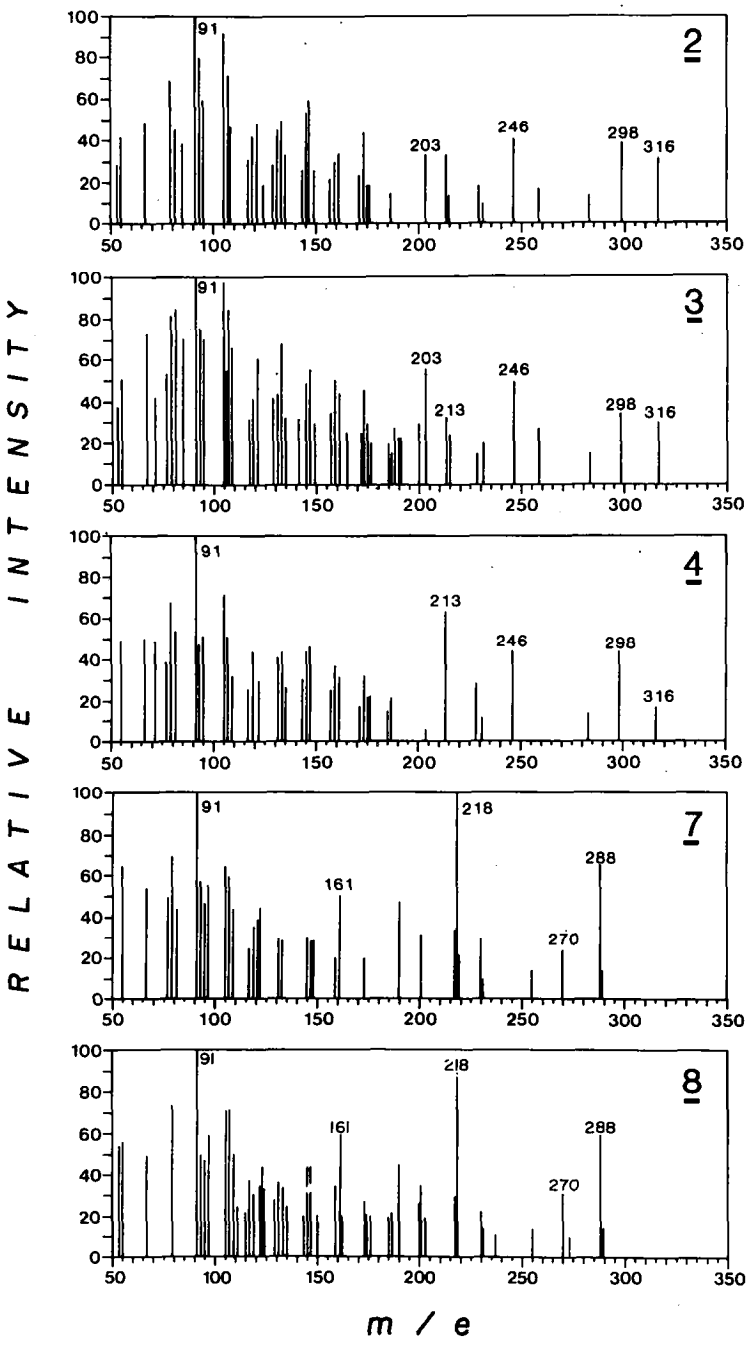

FIGURE 2. Mass spectra of 3α-hydroxy-4-pregnen-20-one (2), 3β-hydroxy-4-pregnen-20-one (3), 3α-hydroxy-17α-pregn-4 en-20-one (4), 3α-hydroxy-4-androsten-17-one (7), and 3β-hydroxy-4-androsten-17-one (8).

Epimerization of 3α-DHP to 3α-Hydroxy-17α-pregn-4-en-20-one 4

The band slightly more polar than 3α-DHP on the preparative plates gave a colorless liquid which mass spectrometry indicated to be isomeric with 3α-DHP. The IR, proton and carbon NMR indicated the presence of an acetyl group and a 3α-hydroxy-Δ^4- unit. That this compound is 3α-hydroxy-17α-pregn-4-en-20-one 4 was proved by its epimerization to 3α-DHP 2, using sodium methoxide in methanol. The MS fragmentation pattern is similar to that of 2 and 3 (Figure 2) with a notable exception in the m/e 213/203 ratio. The compound appears to be formed by epimerization of the 17β-acetyl group in 3α-DHP during the aqueous workup.

Formation of 4-pregnene-3α,20(R)-diol 5

The most polar compound isolated was a crystalline solid. Mass spectrometry indicated this compound to be a diol. Carbon NMR showed the presence of a 3-hydroxy-Δ^4- unit and the proton spectrum contained olefinic proton absorption at 5.45 ppm, similar to the olefinic pattern for 3α-DHP (Table 1) indicating the compound to be 4-pregnene-3α,20-diol. Although unequivocal assignment of the stereochemistry for the hydroxyl group on C-20 was not possible using proton and carbon NMR, an indication that the compound may have a 20R(20β) hydroxy grouping came from product analysis of 3α-DHP/sodium borohydride reaction in methanol. This reaction gave a 89:11 mixture of the two diols, 5 and its 20S (20α) epimer, separable on HPLC; the major peak (89%) from this mixture had the same retention time on HPLC as the diol 5 produced from progesterone with KS-Selectride. That the major product (89%) from the 3α-DHP/sodium borohydride reaction has a 20R(20β) configuration follows from the analogous reaction of progesterone/sodium borohydride where the ratio of 20R:20S (20β:20α) was reported to be 88:12 (14). Based on these obser-

vations we tentatively assign the structure of 4-pregnene-3α,20R-diol 5 to this product.

Synthesis of Allylic Androstenols

Unlike the reaction of progesterone with Selectrides, the reaction of 4-androstene-3,17-dione 6 with K-Selectride resulted in only two products in about equal amounts. The more polar compound had spectral characteristics similar to those of 3α-DHP (Tables 1 and 2) and is concluded to be 3α-hydroxy-4-androsten-17-one 7. Similarly, the less polar compound was proved to be 3β-hydroxy-4-androsten-17-one 8. The MS ion fragmentation patterns for 7 and 8 are shown in Figure 2; prominent peaks occur at M-18 and M-70.

Synthesis of 3α-hydroxy-5α-pregnan-20-one 10

In contrast to 3-keto-Δ^4- steroids, saturated 3-keto steroids react with Selectride reducing agents to give axial alcohols as essentially the only product (15). The reaction of 5α-pregnane-3,20-dione 9 with K-Selectride has been reported and ratios of alcohols formed under different conditions have been determined (9). The reaction of KS-Selectride with 5α-pregnane-3,20-dione 9 under the conditions used in the present work for the α,β-unsaturated ketones gave a single product (>90% yield). Spectral characteristics indicated this to be 3α-hydroxy-5α-pregnan-20-one 10.

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