Anal. Calcd. for $C_{18}H_{25}ON \cdot 1/2\ H_2SO_4$: N, 4.37; S, 4.99. Found: N, 4.32; S, 5.10.

Hydrochloride of X.—A quantity of the free amine was converted to its hydrochloride and recrystallized from methanol–water three times. The salt was treated with active charcoal in methanol solution, filtered and again recrystallized. The product melted at 274° (evacuated capillary).

Anal. Calcd. for $C_{18}H_{25}ON \cdot HCl$: C, 70.22; H, 8.51; N, 4.55; Cl, 11.53. Found: C, 70.32; H, 8.58; N, 4.00; Cl, 11.61.

3-Acetamido-1,3,5(10)-estratriene-17β-ol-acetate (XI). From 19-Nortestosterone.—A solution of 19-nortestosterone (2.42 g.) in 30 ml. of methanol was treated with a solution of 1.86 g. of hydroxylamine hydrochloride and 5.0 g. of sodium acetate hydrate in 10 ml. of water. The mixture was boiled on the steam-bath for 3 hours and the concentration of methanol was adjusted to give a saturated solution. The solution was seeded and slowly cooled. The product, isolated by filtration and dried *in vacuo*, was 2.32 g. of crude 19-nortestosterone oxime.

The crude oxime was refluxed for 3 hours with 25 ml. of acetic anhydride and the reaction mixture was decomposed by pouring into 250 ml. of cold water. After one hour, with occasional agitation, the mixture was extracted with chloroform. The organic extract was washed with water and $KHCO_3$ solution, dried over Na_2SO_4 and evaporated. The residue could not be crystallized even when seeded, so it was chromatographed on 80 g. of neutral alumina (Woelm, activity III). The material was introduced onto the column in benzene solution and eluted with 500 ml. each of benzene, 10% chloroform–benzene and 30% chloroform–benzene; the eluate was collected in 250-ml. fractions which were distilled to dryness *in vacuo*. All the crystalline fractions were combined and dissolved in 30 ml. of hot benzene. Cyclohexane (30 ml.) was added and the solution was heated to boiling, although crystallization began almost at once. After cooling, the product was filtered, dried and recrystallized from absolute methanol. The product consisted of 1.47 g. (45% yield, based on 19-nortestosterone) of heavy platelets.

A sample was recrystallized three times from methanol for analysis. This material was found to contain 5.5% solvent of crystallization by drying at 100° *in vacuo*. The dried product showed a melting point of 207.5–209.8°; $\lambda_{max}^{CH_3OH}$ 249 mμ (15.000) (inflection at 273 mμ); $[\alpha]^{24}D$ + 15° (c 1.0, $CHCl_3$).

Anal. Calcd. for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.27; H, 8.29; N, 3.92.

From 3-Amino-1,3,5(10)-estratriene-17β-ol (X).—The free amino alcohol (10 mg.) was treated with 0.5 ml. of pyridine and 0.10 ml. of acetic anhydride, allowed to stand at room temperature for two hours and worked up in the usual way. The product was recrystallized from a small volume of methanol and dried at 100° in vacuum. This material, m.p. 210–214°, did not depress the melting point of the product from 19-nortestosterone. The infrared and ultraviolet spectra were also consistent with the identity of the two substances.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Nuclear Magnetic Resonance Studies on 6-Methyl Steroids

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Nuclear magnetic resonance spectra of representative 6-methyl steroids have been measured. The 6α- and 6β-methyl groups were differentiated readily. Some effects of interactions with other substituents are tabulated.

Shoolery and Rogers[1] have tabulated some useful correlations between the chemical shifts of the angular methyl groups of steroids with various functional groups on the molecule. Some 6α- and 6β-methyl steroids were studied in the present work, and it was found that the axial and equatorial conformations were readily distinguishable by nuclear magnetic resonance spectroscopy.

Methyl resonance frequencies were sensitive to configuration and to small changes in the geometry of the rings to which they were attached. It was apparent that changes which tended to increase crowding of the methyl group, by nearby axial hydrogens or other substituents, increased the

TABLE I

EFFECTS OF 6-METHYL GROUPS ON 19-METHYL RESONANCE FREQUENCIES, IN C.P.S.

	No 6-methyl	19-Methyl shift			
		For 6α-methyl subst.		For 6β-methyl subst.	
Compounds compared	H_0	H_0	Correction	H_0	Correction
11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate[a,b] *vs.*	130				
6-Methyl-11β,17α,21-trihydroxy-1,4-pregnadien-3,20-dione 21-acetate		130	0	..	..
Methyl 3,11-diketo-4,17(20)-[*cis*]-pregnadien-21-oate[c] *vs.*	131				
Methyl 3,11-diketo-6-methyl-4,17(20)-[*cis*]-pregnadien-21-oate		132	+1	128	−4
Methyl 3,11-diketo-4,17(20)-[*trans*]-pregnadien-21-oate[c] *vs.*	131				
Methyl 3,11-diketo-6-methyl-4,17(20)-[*trans*]-pregnadien-21-oate		130	−1	..	..
4-Pregnene-3,11,20-trione *vs.*	132				
6-Methyl-4-pregnene-3,11,20-trione		131	−1	128	−4
4-Pregnene-3,20-dione *vs.*	140				
6-Methyl-4-pregnene-3,20-dione		140	0	138	−2
5α-Pregnane-3,20-dione[d] *vs.*	147				
6-Methyl-5α-pregnane-3,20-dione		146	−1	144	−3

[a] J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, THIS JOURNAL, **77**, 4438 (1955). [b] These compounds were run in dimethyl sulfoxide solvent and the results have been corrected for the solvent shift. [c] J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, THIS JOURNAL, **77**, 4436 (1955). [d] W. J. Wechter, these laboratories.

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(1) J. N. Shoolery and M. T. Rogers, THIS JOURNAL, **80**, 5121 (1958).

TABLE II

CHEMICAL SHIFTS (δH_0) AND COUPLING CONSTANTS (J) FOR 6-METHYL STEROIDS IN C.P.S.

Compounds	6α-Methyl δH_0	J	6β-Methyl δH_0	J
6-Methyl-5α-pregnane-3,20-dione[a]	153, 156	3	147, 154	7
6,17α-Dimethyl-17β-hydroxy-5α-androstan-3-one[b]	153, 157	4	146, 152	6
5α,11α-Dihydroxy-6-methylpregnane-3,20-dione[d]	.....	..	140, 146	6
6-Methyl-4-pregnene-3,20-dione[c]	142, 148	6	135, 143	8
6-Methyl-4-pregnene-3,11,20-trione[d,e]	141, 148	7	134, 141	7
Methyl 3,11-diketo-6-methyl-4,17(20)-[*trans*]-pregnadien-21-oate[d,]	141, 147	6	.....	..
Methyl 3,11-diketo-6-methyl-4,17(20)-[*cis*]-pregnadien-21-oate[d,g]	142, 148	6	133, 141	8
6-Methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate[d,h]	141, 147	6	.....	..
6,17α-Dimethyl-5α-androstane-3β,17β-diol[i]	152, 155	3	149, 155	6
6,17α-Dimethylandrostane-3β,5α,17β-triol[b]	.....	..	144, 149	5
6,17α-Dimethylandrostane-3β,5α,17β-triol 3-acetate[b]	.....	..	144, 153	9
5α,11α-Dihydroxy-6-methylpregnane-3,20-dione 3,20-bisethylene ketal[d]	.....	..	143, 150	7
5α-Hydroxy-6-methylandrostane-3,17-dione 3-ethylene, ketal[b]	.....	..	144, 151	7

[a] P. F. Beal, M. A. Rebenstorf, J. E. Pike and J. A. Hogg, THIS JOURNAL, **81**, 1231 (1959). [b] J. A. Campbell, J. C. Babcock and J. A. Hogg, *ibid.*, **80**, 4714 (1958). [c] H. J. Ringold, E. Batres and G. Rosenkrauz, *J. Org. Chem.*, **22**, 99 (1957); sample provided by J. A. Pike, these laboratories. [d] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6218 (1956). [e] R. L. Pederson, these laboratories. [f] A. H. Nathan, these laboratories. [g] F. H. Lincoln, these laboratories. [h] These compounds were run in dimethyl sulfoxide solvent and the results have been corrected for the solvent shift. [i] J. A. Campbell, these laboratories.

magnitude of the second-order paramagnetic contribution[2] to the chemical shift. The result is that the methyl resonance occurs at a lower magnetic field. Thus the 6β-methyl was shown to lower the 19-methyl resonance by 2 to 4 c.p.s. while the 6α-methyl showed little or no effect (see Table I). Neither had any observed effect on the 18-methyl resonance frequency.

TABLE III

EFFECTS OF RING A SUBSTITUENTS ON 6-METHYL RESONANCE FREQUENCIES COMPARED TO 3β-HYDROXY-5α-HYDROGEN AS REFERENCE COMPOUND

Function	Correction in 6-methyl α	β
3β-OAC	..	0
3-Keto	+ 1	− 2
3-Ketal	..	0
Δ^4	−10	−12
Δ^2	0	..
5α-OH	..	− 6

Furthermore, the 6-methyl resonances, intense sharp doublets, were in general lower when the methyl group was β-oriented than when it was α, possibly due to 1,3-diaxial interactions with the 19-methyl group (see Table II). This observation points the way to a facile determination of the configuration of 6-methyl groups.

The results in Table II are in agreement with the work of Lemieux[3] where it was found that axial acetates showed a lower resonance frequency than equatorial acetates in various acetylated carbohydrates.

Shoolery and Rogers[1] also found that nearby polar substituents had marked effects on the 18- and 19-methyl resonances. The same was true for the 6-methyl resonance doublet. In addition to second-order paramagnetic effects, polar groups may cause shifts due to magnetic anisotropy associated with centers of high or low electron density. Since the 6-methyl group was most often encountered in steroids with a carbonyl at C-3, more data are available on these types but certain other functions also were observed (see Tables II and III).

Experimental

The spectra were measured with a Varian 4300-2 spectrometer at 40 mc. on solutions (0.3 molar or less, 0.3 ml.) of the steroids in deuteriochloroform. The spectra were calibrated against water in a precision external annular cell[4] using the audio frequency side band technique.[5]

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KALAMAZOO, MICH.

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[2] For leading references see E. R. Andrew, "Nuclear Magnetic Resonance," Cambridge University Press, 1956, p. 141.

[3] R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, THIS JOURNAL, **79**, 1005 (1957).

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[5] J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).