Preparation of Six 20-Deoxy Steroids in the 3α-Hydroxy-5β-pregnane Series and Their Use in Optical Rotation Studies[1]

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Received October 23, 1967

The synthesis of six 20-deoxy steroids derived from 3α-hydroxy-5β-pregnane is described. These compounds, three of which are new, were interrelated by a number of reactions. The 20-deoxy steroids and their derived acetates were used as compounds of reference in an extended study centering on the absolute contribution to optical rotatory activity of C-20 epimeric hydroxyl and acetoxyl groups. The influence of a variety of substituents at C-17 and C-21 on the qualitative and quantitative shifts in molecular rotation brought about by oxygen functions at C-20 is discussed.

As an approach to the more precise assessment of certain physical and chemical contributions of functional groups at or near C-20, it seemed essential to prepare a series of 20-deoxy steroids as compounds of reference. This paper describes the synthesis of 5β-pregnan-3α-ol, 5β-pregnane-3α,17-diol, 5β-pregnane-3α,21-diol, 5β-pregnane-3α,17,21-triol, methyl 3α-hydroxy-5β-pregnan-21-oate, and methyl 3α,17-dihydroxy-5β-pregnan-21-oate as well as a number of reactions which interrelate them. Also included is a detailed examination of the optical rotatory properties of these compounds and their 20-oxygenated analogs. Further use of these 20-deoxy steroids has been made in a separate study[2] to determine more exactly the contribution to paper chromatographic mobility of carbonyl and hydroxyl groups at C-20.

Reaction of pregnanolone acetate **1** (Scheme I) with ethanedithiol in the presence of boron trifluoride etherate[3] afforded 20-thioketal **3** in high yield. Reduction of the free thioketal **4** with Raney nickel gave 5β-pregnan-3α-ol **5** in 70% yield. A reaction sequence of this type was first described by Ruff and Reichstein[4] who prepared 11-keto-5β-pregnane from the 3,20-bisthioketal. The pregnanol **5** also was prepared directly in good yield by Wolff–Kishner reduction[5] of pregnanolone **2**. Marker [6] first prepared 5β-pregnan-3α-ol by Clemmensen reduction of pregnanolone. The melting points of the pregnanol **5** and its acetylation product **6** are in close agreement with his published constants.

The Wolff–Kishner reduction of 17-hydroxypregnanolone **7** (Scheme I) proved somewhat more complex. In addition to the desired 3α,17-diol **10**, which was obtained in only modest yield, a more mobile byproduct which gave a positive tetranitromethane test also was recovered. Its identity as the dehydration product 5β-pregn-16-en-3α-ol **8** was established by its catalytic reduction to the pregnanol **5**. The 3α,17-diol **10** also was prepared by lithium aluminum hydride reduction of both 17,20α-oxido-5β-pregnan-3α-ol (**12a**) and 17,20β-oxido-5β-pregnan-3α-ol (**12b**).[7] Both epoxides were reduced slowly even after prolonged refluxing in the presence of a large excess of reducing agent.

Preparation of 5β-pregnane-3α,17,21-triol (**13**) was accomplished by similar reduction of both 17,20α-oxido-5β-pregnane-3α,21-diol (**15a**) and its 20β epimer (**15b**).[7] It is interesting to note that, in contrast to the sluggish reduction of the 21-deoxy epoxides **12a** and **b**, the 21-hydroxy epoxides **15a** and **b** were rapidly and completely reduced to the 20-deoxy product. These results are in accord with the view of Rosowsky[8] that polar substituents adjacent to the oxide ring promote reductive fission of the C–O bond nearest them.

Treatment of the triol **13** with a limited amount of tosyl chloride afforded the 21-monotosylate **16**. Lithium aluminum hydride reduction of this product gave 5β-pregnane-3α,17-diol, thus linking the 3α,17-diol **10** and the triol **13**.

Partial hydrolysis of the diacetate **14** furnished the 3-monoacetate **17**. Oxidation of the latter with chromic anhydride followed by esterification with diazomethane of the saponified acidic fraction gave methyl 3α,17-dihydroxy-5β-pregnan-21-oate (**18**).

The 3α,21-diol **21** was obtained by lithium aluminum hydride reduction of the previously described diacetoxy tosylate **20**.[7] Marker[9] originally prepared the diol **21** by reduction of methyl 3α-hydroxy-5β-pregnan-21-oate with sodium in ethanol.

The reverse of Marker's synthesis was achieved by partial hydrolysis of the diacetate **22** to the 3-monoacetate **23** which, in a manner analogous to the preparation of **18** from **17**, was converted into methyl 3α-hydroxy-5β-pregnan-21-oate (**24**).

In order to show the relationship between the triol **13** and the 3α,21-diol **21**, elimination of the 17-hydroxyl group was attempted. Reaction of the triol 3,21-diacetate **14** with thionyl chloride in pyridine or boron trifluoride in acetic acid gave complex mixtures. However, treatment of the triol **13** with methanolic sulfuric acid afforded in low yield a more mobile product which gave a positive tetranitromethane test and formed a diacetate (**27**). Since the unsaturated diacetate was reduced catalytically to the saturated diacetate **22**, the dehydration product was formulated as 5β-pregn-16-ene-3α,21-diol (**26**).

A final correlation in this series was shown by conversion of the 3α,21-diol **21** into 5β-pregnan-3α-ol *via* the 21-tosylate **28** in a manner analogous to the preparation of **10** from **13** *via* **16**.

(1) This work was supported by a research grant (AM 01255) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(2) J. J. Schneider and M. L. Lewbart, submitted for publication.

(3) L. F. Fieser, *J. Amer. Chem. Soc.*, **76**, 1945 (1954).

(4) A. Ruff and T. Reichstein, *Helv. Chim. Acta*, **34**, 70 (1951).

(5) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

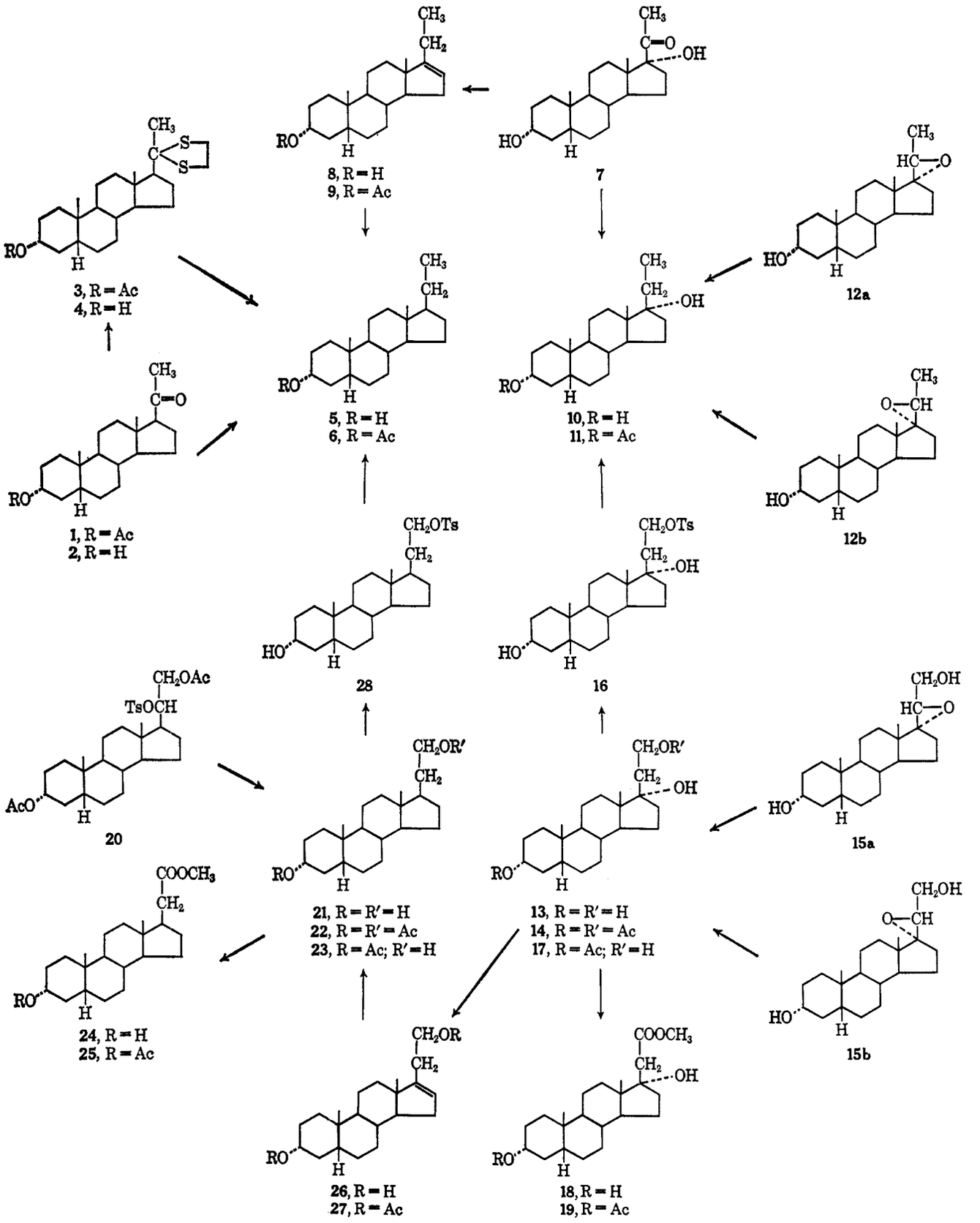
(6) R. E. Marker and E. J. Lawson, *J. Am. Chem. Soc.*, **60**, 2438 (1938).

(7) M. L. Lewbart, *J. Org. Chem.*, **33**, 1965 (1968).

(8) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 216.

(9) R. E. Marker, R. B. Wagner, and E. L. Wittbecker, *J. Amer. Chem. Soc.*, **64**, 2093 (1942).

SCHEME I



The asymmetric nature of the monosubstituted 20 carbon atom in pregnanes has long been recognized. Marker[10] employed the arbitrary designations α and β to denote the respective configurations of natural and synthetic 20-ols. The subsequent important investigations of Fieser and Fieser[11] and of Sarett[12] established the basis for the determination of

(10) R. E. Marker, O. Kamm, E. L. Wittle, T. S. Oakwood, E. J. Lawson, and J. F. Laucius, *J. Amer. Chem. Soc.*, **59**, 2291 (1937).

(11) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); see also L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 612–622.

(12) L. H. Sarett, *J. Amer. Chem. Soc.*, **71**, 1165, 1175 (1949).

TABLE I

MOLECULAR ROTATIONS OF 3α-HYDROXY-5β-PREGNANES WITH SUBSTITUENTS AT C-17, C-20, AND C-21

Class	Pairs	C-3	C-17	C-20	C-21	20α epimer		20β epimer		$M_{365}^{20\alpha} - M_{365}^{20\beta}$	$M_D^{20\alpha} - M_D^{20\beta}$	Increments[a] Δ20α		Δ20β	
						M_{365}	M_D	M_{365}	M_D			365 mμ	D	365 mμ	D
A	1	α-OH	H	OH	H	+260	+92	+230	+64	+30	+28	...	...	...	...
	2	α-OH	H	OAc	H	+183	+75	+615	+208	−432	−133	−77	−17	+385	+144
	1	α-OH	H	OH	H	+260	+92	+230	+64	+30	+28	...	...	...	...
	3	α-OAc	H	OAc	H	+440	+163	+917	+305	−477	−142	−80	−14	+427	+156
	4	α-OAc	H	OH	H	+500	+174	+445	+159	+55	+15	...	...	...	...
	3	α-OAc	H	OAc	H	+440	+163	+917	+305	−477	−142	−60	−11	+472	+146
B	5	α-OH	H	OH	OH	+321	+110	+278	+100	+43	+10	...	...	...	...
	6	α-OAc	H	OAc	OAc	+395	+140	+1150	+385	−755	−245	−186	−55	+612	+200
	7	α-OAc	H	OH	OAc	+580	+202	+617	+212	−37	−10	...	...	...	...
	6	α-OAc	H	OAc	OAc	+395	+140	+1150	+385	−755	−245	−185	−62	+533	+173
	8	α-OAc	H	OH	OH	+548	+192	+540	+191	+8	+1	...	...	...	...
	9	α-OAc	H	OAc	OH	+350	+132	+1009	+336	−659	−204	−198	−60	+469	+145
C	10	α-OH	OH	OH	H	−37	−6	+40	+24	−77	−30	...	...	...	...
	11	α-OH	OH	OAc	H	−267	−80	+586	+200	−853	−280	−230	−74	+546	+176
	10	α-OH	OH	OH	H	−37	−6	+40	+24	−77	−30	...	...	...	...
	12	α-OAc	OH	OAc	H	−44	−4	+869	+291	−913	−295	−267	−83	+569	+182
	13	α-OAc	OH	OH	H	+229	+74	+287	+113	−58	−39	...	...	...	...
	12	α-OAc	OH	OAc	H	−44	−4	+869	+291	−913	−295	−273	−78	+582	+178
D	14	α-OH	OH	OH	OH	+51	+20	+152	+60	−101	−40	...	...	...	...
	15	α-OAc	OH	OAc	OAc	−251	−79	+1472	+488	−1723	−567	−402	−137	+905	+293
	16	α-OAc	OH	OH	OAc	+188	+68	+598	+206	−410	−138	...	...	...	...
	15	α-OAc	OH	OAc	OAc	−251	−79	+1472	+488	−1723	−567	−439	−147	+874	+282
	17	α-OAc	OH	OH	OH	+317	+109	+402	+141	−85	−32	...	...	...	...
	15	α-OAc	OH	OAc	OAc	−251	−79	+1472	+488	−1723	−567	−408	−141	+915	+297
	18	α-OH	OH	OH	OAc	−119	−32	+265	+99	−384	−131	...	...	...	...
	15	α-OAc	OH	OAc	OAc	−251	−79	+1472	+488	−1723	−567	−392	−132	+947	+304
	19	α-OH	OH	OH	Br	+70	+29	+598	+199	−528	−170	...	...	...	...
	20	α-OAc	OH	OAc	Br	−61	−9	+1428	+477	−1489	−486	−391	−123	+570	+193
	21	α-OH	OH	OH	Ts	−182	−58	+349	+139	−531	−197	...	...	...	...
	22	α-OAc	OH	OAc	Ts	−306	−99	+1140	+382	−1446	−481	−384	−126	+531	+158

[a] Corrected, where necessary, for acetylation at C-3 (all classes) and at C-21 (class D).

configuration at C-20 by utilizing changes in optical activity after acetylation. Fortuitously, their assignments of epimeric hydroxyl groups as α or β coincided with those of Marker and also with absolute configurations which later were fixed by Wieland and Miescher.[13] The Fieser–Sarett rule states that regardless of substituents elsewhere in the molecule (a) acetylation of a 20α-ol results in a weakly positive or negative shift in molecular rotation (M) while acetylation of a 20β-ol causes a strongly positive shift in M and (b) a 20β-acetate of any class is more dextrorotatory than its 20α epimer. In the intervening years this rule has proven extremely useful for configurational assignments in new 20-hydroxypregnanes from natural and synthetic sources. To our knowledge the rule has failed in 17β-pregnanes only in the case of 20-hydroxy-21-oic acids and esters.[14]

Although the Fieser–Sarett rule has been of great practical value, its application thus far has left unexplained certain more subtle aspects of rotatory behavior exhibited by 20-ols and 20-acetates, particularly those quantitative differences which are caused by vicinal effects. For this reason we undertook a detailed study in order more precisely to define these effects.

Our investigation was made possible by the availability of a large series of closely related 3α-hydroxy-5β-pregnanes consisting of the 20-deoxy steroids described herein, the epimeric 20-oxygenated analogs from the previous paper,[7] and additional compounds prepared specifically for this project. Their utilization in the present study permitted a detailed appraisal of the absolute contributions to M of hydroxyl and acetoxyl groups at C-20 in the presence of a variety of different groups. In order to make comparisons more valid, all determinations were made in methanol solution under standard conditions of temperature and concentration in a Zeiss 0.005° photoelectric polarimeter. We chose to take readings both at 589 mμ (D line of sodium) and at 365 mμ since, as has been mentioned by Klyne,[15] differences in rotatory properties of epimers are exaggerated at lower wavelengths.

It was thought advisable first to present the data in the form employed by Fieser and Sarett. The values for a series of 20-oxygenated steroids are given in Table I. In following with some modification the nomenclature of Sarett, we have found it convenient to divide 20-hydroxypregnanes into four classes:

(13) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(14) (a) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1773, 1779 (1963); (b) M. L. Lewbart and J. J. Schneider, *ibid.*, **29**, 2559 (1964); (c) M. L. Lewbart and J. J. Schneider, *J. Biol. Chem.*, **241**, 5325 (1966).

(15) P. M. Jones and W. Klyne, *J. Chem. Soc.*, 871 (1960).

TABLE II

MOLECULAR ROTATIONS OF 3α-HYDROXY-5β-PREGNANES WITH OR WITHOUT OXYGEN FUNCTIONS AT C-20

Class	Group	C-3	C-17	C-20	C-21	M_{365}	MD	ΔM_{365}	ΔM_D
A	1	α-OH	H	H	H	+272	+98	...	...
		α-OH	H	α-OH	H	+260	+92	−12	−6
		α-OH	H	β-OH	H	+230	+64	−42	−34
	2	α-OAc	H	H	H	+516	+180	...	...
		α-OAc	H	α-OH	H	+500	+174	−16	−6
		α-OAc	H	β-OH	H	+445	+159	−71	−21
	3	α-OH	H	H	H	+272	+98	...	...
		α-OH	H	α-OAc	H	+183	+75	−89	−23
		α-OH	H	β-OAc	H	+615	+208	+343	+110
	4	α-OAc	H	H	H	+516	+180	...	...
		α-OAc	H	α-OAc	H	+440	+163	−76	−17
		α-OAc	H	β-OAc	H	+917	+305	+401	+125
B	5	α-OH	H	H	OH	+365	+134	...	...
		α-OH	H	α-OH	OH	+321	+110	−44	−24
		α-OH	H	β-OH	OH	+278	+100	−87	−34
	6	α-OAc	H	H	OH	+615	+216	...	...
		α-OAc	H	α-OH	OH	+548	+192	−67	−24
		α-OAc	H	β-OH	OH	+540	+191	−75	−25
	7	α-OAc	H	H	OAc	+594	+211	...	...
		α-OAc	H	α-OH	OAc	+580	+202	−14	−9
		α-OAc	H	β-OH	OAc	+617	+212	+23	+1
	8	α-OAc	H	H	OH	+615	+216	...	...
		α-OAc	H	α-OAc	OH	+350	+132	−265	−84
		α-OAc	H	β-OAc	OH	+1009	+336	+394	+120
	9	α-OAc	H	H	OAc	+594	+211	...	...
		α-OAc	H	α-OAc	OAc	+395	+140	−199	−71
		α-OAc	H	β-OAc	OAc	+1150	+385	+556	+174
C	10	α-OH	OH	H	H	−31	−2	...	...
		α-OH	OH	α-OH	H	−37	−6	−6	−4
		α-OH	OH	β-OH	H	+40	+24	+71	+26
	11	α-OAc	OH	H	H	+229	+82	...	...
		α-OAc	OH	α-OH	H	+229	+74	0	−8
		α-OAc	OH	β-OH	H	+287	+113	+58	+31
	12	α-OH	OH	H	H	−31	−2	...	...
		α-OH	OH	α-OAc	H	−267	−80	−236	−78
		α-OH	OH	β-OAc	H	+586	+200	+617	+202
	13	α-OAc	OH	H	H	+229	+82	...	...
		α-OAc	OH	α-OAc	H	−44	−4	−273	−86
		α-OAc	OH	β-OAc	H	+869	+291	+640	+209
D	14	α-OH	OH	H	OH	+7	+6	...	...
		α-OH	OH	α-OH	OH	+51	+20	+44	+14
		α-OH	OH	β-OH	OH	+152	+60	+145	+54
	15	α-OAc	OH	H	OH	+286	+104	...	...
		α-OAc	OH	α-OH	OH	+317	+109	+31	+5
		α-OAc	OH	β-OH	OH	+402	+145	+116	+41
	16	α-OAc	OH	H	OAc	+251	+90	...	...
		α-OAc	OH	α-OH	OAc	+188	+68	−63	−22
		α-OAc	OH	β-OH	OAc	+598	+206	+347	+116
	17	α-OAc	OH	H	OAc	+251	+90	...	...
		α-OAc	OH	α-OAc	OAc	−251	−79	−502	−169
		α-OAc	OH	β-OAc	OAc	+1472	+488	+1221	+398

class A (unsubstituted), class B (21 substituted), class C (17 substituted), and class D (17,21 disubstituted). Molecular rotation relationships of epimeric pairs of 20-ols and their derived acetates are expressed both as differences between epimers and as increments or decrements which occur after acetylation. In many of the examples acetylation at C-3 also occurred. The average increments calculated for acetylation at this position were +260 units at 365 mμ and +85 units at 589 mμ.[16] Sarett[12] gives an average value of +90 units at 589 mμ and cites values of +91 and +83 units at this wavelength. An increment of +82 units may be derived from the publications of Fieser and Fieser.[11]

In agreement with their findings, we have found no

(16) In close agreement with these values, the increments calculated for acetylation at C-3 for three pairs of epimeric epoxides were +262 ± 17 and +89 ± 9 units at the two wavelengths (see previous paper[7]).

TABLE III
EFFECT ON M OF INTRODUCING OXYGEN FUNCTIONS AT C-17 AND/OR C-21 IN THE PRESENCE OF VARIOUS SUBSTITUENTS AT C-20

				Group at C-20													
				—CH₂—		—C=O—		—α-OH—		—β-OH—		$\Delta^{M}_{CH_2}$		$\Delta^{M}_{C=O}$		$\Delta^{M}_{\alpha\text{-OH}}$		$\Delta^{M}_{\beta\text{-OH}}$	
Group	C-3	C-17	C-21	M_{365}	M_D	M_{365}	M_D	M_{365}	M_D	M_{365}	M_D	365	D	365	D	365	D	365	D
1	α-OH	H	H	+272	+98	+1850	+360	+260	+92	+230	+64	...	...	...	...	...	...	...	...
2	α-OH	H	OH	+365	+134	+1775	+357	+321	+110	+278	+100	+93	+36	−75	−3	+61	+18	+48	+36
3	α-OH	OH	H	−31	−2	+1280	+173	−37	−6	+40	+24	−303	−100	−570	−187	−297	−98	−190	−40
4	α-OH	OH	OH	+7	+6	+1560	+240	+51	+20	+152	+60	+265	−92	−290	−120	−209	−72	−78	−4
5	α-OAc	H	H	+516	+180	+2140	+446	+500	+174	+445	+159	...	...	...	...	...	...	...	...
6	α-OAc	H	OAc	+594	+211	+2340	+516	+580	+202	+617	+212	+78	+31	+200	+70	+80	+28	+172	+53
7	α-OAc	OH	H	+229	+82	+1560	+262	+229	+74	+287	+113	−287	−98	−580	−184	−271	−100	−158	−46
8	α-OAc	OH	OAc	+251	+90	+2150	+405	+188	+68	+598	+206	−265	−90	+10	−41	−312	−106	+153	+47

significant differences in the molecular rotation of 20-ols in classes A and B (pairs 1, 4, 5, 7, and 8), whereas 20β-ols of classes C and D are consistently, if slightly, more dextrorotatory than their 20α epimers (pairs 10, 13, 14, 16, 17, and 18). In addition we have observed that *the presence of a bulky substituent at C-21 such as tosylate or bromine (pairs 19 and 21) increases by a factor of four or five the differences in M between class D 20α- and 20β-ols.*

In further correspondence with the data of Fieser and Sarett, acetylation increments for 20β-ols of all classes were moderately to strongly positive while acetylation increments for 20α-ols were weakly to moderately negative. Moreover, all 20β-acetates were consistently more dextrorotatory than their C-20 epimeric counterparts. The magnitude of the acetylation increments (ΔM_D) for 20β-ols of classes A, B, and C (+145 to +200 units) is somewhat greater than the +110 to +130 units found by Fieser, but the differences in M_D between epimeric 20-acetates of these classes (+142 to +245 units) are in close agreement with the range of +140 to +220 units given by Fieser.

It was noted that *acetylation at C-21 of class D 20-ols also results uniformly in equal but opposite shifts in M depending upon the configuration at C-20.* This effect is evident when comparison is made between M values for pairs 14/18 and 16/17. The average shift at the D line after acetylation at C-21 is −47 units for 20α-ols and +50 units for 20β-ols.

With regard to the rather heterogeneous group of compounds which he studied, Fieser reported a positive shift of from +240 to +410 units after acetylation of 20β-ols, but did not have a sufficient number of 20α-ols to establish a range of decrement values. In the present study the values, corrected for acetylation at C-3 and C-21, ranged from +282 to +304 units for 20β-ols and from −132 to −147 units for 20α-ols. As a check on the validity of our assigned shifts in molecular rotation due to acetylation at C-3, C-20, and C-21, we noted that the M_D value (−79 units) for the 20α-triacetate of pair 15 is in close agreement with the algebraic sum of the values for the free tetrol of pair 14 (+20) plus the individual contributions due to acetylation at C-3 (+85), at C-20 (−140), and at C-21 (−47), namely −82 units. A similar comparison of the observed value for the 20β-triacetate (+488 units) with the sum of the values for the free tetrol (+60) plus that due to acetylation at C-3 (+85), at C-20 (+293), and at C-21 (+50) shows exact correspondence.

It is apparent from a general examination of Table I that shifts after acetylation of the 17,21-disubstituted class D 20-ols are roughly the sum of the values for the corresponding monosubstituted 20-ols of classes B and C. It can therefore be concluded that *the presence of a single oxygen function in either position adjacent to a 20-hydroxyl group has no effect on the magnitude of the acetylation increment or decrement, but that the presence of oxygen functions at both adjacent positions results in a doubling of the Δ values.*

Changes in molecular rotation after acetylation at C-20 of the 21-bromides and 21-tosylates, while qualitatively similar to those obtained for simple class D compounds, are of a lesser magnitude, with the damping effect proportionately greater on the 20β-ols.

In Table II is shown the effect of introducing hydroxyl or acetoxyl groups at C-20 using the appropriate 20-deoxy steroid as the stem compound for each group. Because of the similarity in M values between 20-unsubstituted and the corresponding 20-ols, the shifts in M are of the same sign and order of magnitude as was noted in Table I for acetylation of 20-ols. With reference to the introduction of hydroxyl groups, it will be seen that *the direction of the shift in M, however slight, is determined by the nature and location of adjacent substituents.* Thus in classes A and B pregnanes (groups 1, 2, 5, 6, and 7) insertion of either α- or β-oriented hydroxyl groups at C-20 results generally in a weakly negative shift. Introduction of a 20α-hydroxyl group in class C pregnanes (groups 10 and 11) also causes a weakly negative shift, while insertion of a 20β-hydroxyl group results in a weakly positive shift. In simple class D pregnanes (groups 14 and 15) introduction of a hydroxyl group in either orientation results in a weakly positive shift which is somewhat greater for 20β-ols, but, if an acetoxyl function is present at C-21 (group 16), the difference between epimeric 20-ols is greatly exaggerated. However where a hydroxyl group is lacking at C-17 (group 7, class B), this effect is not noted. These results represent another expression of the effect of acetylation at C-21 noted above.

The magnitude of the negative shift in M after introduction of a 20α-acetoxyl group varies directly with the degree of substitution at C-17 and C-21: weak for class A (groups 3 and 4), moderate for class B (groups 8 and 9) and class C (groups 12 and 13), and strong (roughly the sum of the decrements for the latter two classes) for class D pregnanes (group 17). Similarly, *the magnitude of the positive shift after introduction of a 20β-acetoxyl group increases with increasing substitution of the adjacent positions.* As in the case of the 20α epimers, the value of M for class D pregnanes represents the sum of the singly substituted analogs.

The effect of introducing oxygen functions either singly or jointly at C-17 and C-21 in the presence of a variety of groupings at C-20 is shown in Table III

TABLE IV

MOLECULAR ROTATIONS OF METHYL 3α-HYDROXY-5β-PREGNAN-21-OATES WITH OR WITHOUT OXYGEN FUNCTIONS AT C-20

Class	Group	C-3	C-17	C-20	C-21	M_{365}	M_D	ΔM_{365}	ΔM_D
B	1	α-OH	H	H	$COOCH_3$	+226	+89	...	...
		α-OH	H	α-OH	$COOCH_3$	+253	+102	+27	+13
		α-OH	H	β-OH	$COOCH_3$	+61	+35	−165	−54
	2	α-OAc	H	H	$COOCH_3$	+484	+173	...	...
		α-OAc	H	α-OAc	$COOCH_3$	+865	+307	+381	+134
		α-OAc	H	β-OAc	$COOCH_3$	+425	+144	−59	−29
D	3	α-OH	OH	H	$COOCH_3$	−73	−16	...	...
		α-OH	OH	α-OH	$COOCH_3$	−50	+3	+23	+19
		α-OH	OH	β-OH	$COOCH_3$	+81	+22	+154	+38
	4	α-OAc	OH	H	$COOCH_3$	+192	+67	...	...
		α-OAc	OH	α-OAc	$COOCH_3$	+531	+199	+339	+132
		α-OAc	OH	β-OAc	$COOCH_3$	+529	+162	+337	+95

Insertion of a hydroxyl group or acetoxyl group at C-21 in simple pregnanes ($\Delta^M_{CH_2}$, groups 2 and 6) and 20-hydroxypregnanes ($\Delta^M_{\alpha\text{-OH}} + \Delta^M_{\beta\text{-OH}}$) causes a weakly positive shift in M. Introduction of a hydroxyl group at C-17 ($\Delta^M_{CH_2}$, groups 3, 4, 7, and 8) results in a moderately negative shift of the same magnitude regardless of the nature of the substituent at C-21.

The effect of inserting a hydroxyl group at C-17 in 20-hydroxypregnanes is greatly dependent upon the configuration at C-20. In general, the magnitude of the shift in M for 20α-hydroxypregnanes ($\Delta^M_{\alpha\text{-OH}}$, groups 3, 4, 7, and 8) is of about the same order noted for their 20-deoxy counterparts. In contrast, the magnitude of the negative shift in M for 20β-hydroxypregnanes is greatly reduced in C-21-unsubstituted pregnanes ($\Delta^M_{\beta\text{-OH}}$, groups 3 and 7). Where a hydroxyl group is present at C-21 ($\Delta^M_{\beta\text{-OH}}$, group 4), the size of the negative shift is further reduced and, in the presence of an acetoxyl group at C-21 ($\Delta^M_{\beta\text{-OH}}$, group 8), there is actually a small positive shift in M.

The presence of an acetoxyl group at C-20 has an even greater effect on the introduction of a hydroxyl group at C-17. Thus, from Table II, conversion of the class A diacetates (group 4) into class C diacetates (group 13) results in shifts of −167 and −14 units for 20α and 20β epimers, respectively. An even greater divergence is to be noted when M values for the class B (group 9) and class D (group 17) triacetates are compared: −219 units (20α) and +103 units (20β).

For 20-ketopregnanes (Table III), introduction of a hydroxyl group at C-21 ($\Delta^M_{C=O}$, group 2) is without significant effect, but insertion of an acetoxyl group at the same position ($\Delta^M_{C=O}$, group 6) results in a moderately positive shift in M. Introduction of a hydroxyl group at C-17 in 20-ketopregnanes ($\Delta^M_{C=O}$, groups 3 and 7) results in a negative shift of approximately twice the magnitude noted for simple pregnanes ($\Delta^M_{CH_2}$), but this effect is nullified largely if an acetoxyl group is present at C-21 ($\Delta^M_{C=O}$, group 8).

In view of our earlier demonstrations[14] that the configuration at C-20 of 20-hydroxy-21-oates cannot be determined by means of the Fieser–Sarett convention, it was of interest to examine additional members of this class in the 3α-hydroxy-5β-pregnane series. The $M^{20\alpha} - M^{20\beta}$ values for these new methyl esters are in close agreement with those obtained previously for analogous compounds. In Table IV, which is constructed in the manner of Table II, we have compared the M values of a series of 20-deoxy methyl esters with those of corresponding epimeric 20-hydroxy and 20-acetoxy derivatives. With the exception of the Δ values noted for the 17,20-dihydroxy methyl esters of group 3, the remaining values differ greatly from those obtained for the corresponding compounds containing substituents other than carbomethoxyl at C-21.

Introduction of an α-oriented hydroxyl (groups 1 and 3) or acetoxyl function (groups 2 and 4) at C-20 results, respectively, in weakly and strongly positive shifts in M. This effect is uninfluenced by the nature of the substituent at C-17. The Δ values in the 20β series also are anomalous. Insertion of either β-hydroxyl or β-acetoxyl groups at C-20 in class B methyl esters results in a negative shift which is more pronounced in the alcohol. Similar functionalization at C-20 of class D methyl esters is followed by a positive shift in M. We regard these effects as unusual and in contrast with the values appearing in Table II.

Glick and Hirschmann[17] have derived theoretical M values for simple pregnan-20-ols from a consideration of the most probable conformations of the side chain. However, the majority of the compounds described in the present study also bear substituents at C-17 and/or C-21 which greatly complicate conformational analysis because of the increased opportunities for interaction with neighboring groups. We have therefore limited our analysis of these data to an attempted correlation of observed optical rotatory changes with conformational possibilities as observed in Dreiding models and with our earlier observations on the steric requirements for boric acid complexing in steroidal glycols and glycerols.[18] It is assumed that deviations in Δ values from those obtained for the 20-deoxy stem compound reflect vicinal interaction(s) which lead to an altered, presumably more stable, conformation of the side chain and its attached groups. For example, introduction of oxygen functions either singly or jointly at C-20 and C-21 does not result in any appreciable change in M since free rotation between C-20 and C-21 does not permit the preponderance of a particular conformer. In contrast, insertion

(17) D. M. Glick and H. Hirschmann, *J. Org. Chem.*, **27**, 3212 (1962). For more recent studies bearing on conformational analysis of the 17β-pregnane side chain, see also J. C. Danilewicz and W. Klyne, [*J. Chem. Soc.*, 1306 (1965), and H. Lee, N. S. Bhacca, and M. E. Wolff, *J. Org. Chem.*, **31**, 2692 (1966).

(18) J. J. Schneider and M. L. Lewbart, *Tetrahedron*, **20**, 943 (1964).

of a hydroxyl group at C-17 in 20-ols and 20-acetates results in profound differences in Δ values since the stability conferred by coplanarity can occur only in the case of the 17,20β-diol system. Evidently the exaggeration of the M values observed for 17,20-diols with an acetoxyl, tosyloxyl, or bromine at C-21 is due to a preponderance of favored conformations which result from a further limitation on rotation around the C-17–C-20 bond.

Since bulky substituents at C-21 serve merely to increase the magnitude of the M values, the anomalous results in the case of the methyl esters cannot be ascribed solely to the size of the carbomethoxyl function. A more likely explanation of the aberrant optical rotatory behavior of the methyl esters may involve hydrogen bonding between substituents at C-20 and the carbonyl group of the carbomethoxy moiety such as is believed to account for anomalous rotatory values in the lactic acid series.[19]

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ± 1°. Infrared spectra were determined as KBr pellets with a Beckman IR-8 infrared spectrophotometer. Descriptions of the column, paper and thin layer (tlc) chromatographic techniques employed in this laboratory appear in papers cited previously.[7] Analyses were by E. Thommen, Basel, Switzerland, and August Peisker-Ritter, Brugg, Switzerland.

20-Ethylenedithio-5β-pregnan-3α-ol Acetate (3) from 1.—To a solution of 3α-acetoxy-5β-pregnan-20-one (1 g) in acetic acid (2 ml) was added 1 ml each of ethanedithiol (Matheson, Practical Grade) and boron trifluoride etherate. Crystals deposited slowly at room temperature, forming a solid mass in about 1 hr. After 2 hr the reaction mixture was partitioned between methylene chloride and water. The organic layer was washed successively with dilute sodium hydroxide solution and water, filtered through anhydrous sodium sulfate, and concentrated to dryness. Crystallization from methanol afforded 1175 mg of needles (mp 162.5–163°) in a yield of 97%. The analytical sample had mp 164.5–165°; $[\alpha]_{365}$ +116°, $[\alpha]_{436}$ +72.7°, $[\alpha]_{546}$ +41.1°, $[\alpha]_D$ +36.8° ($CHCl_3$).

Anal. Calcd for $C_{25}H_{40}O_2S_2$: C, 68.76; H, 9.23; S, 14.68. Found: C, 68.57; H, 9.27; S, 14.50.

20-Ethylenedithio-5β-pregnan-3α-ol (4) from 3.—Saponification of 20-ethylenedithio-5β-pregnan-3α-ol acetate with methanolic sodium hydroxide and crystallization of the product from methanol gave plates: mp 182.5–183°; $[\alpha]_{365}$ +63.8°, $[\alpha]_{436}$ +37.8°, $[\alpha]_{546}$ +22.1°, $[\alpha]_D$ +18.9° ($CHCl_3$).

Anal. Calcd for $C_{23}H_{38}OS_2$: C, 69.99; H, 9.71; S, 16.25. Found: C, 69.49; H, 9.80; S, 15.94; ash, 0.33.

5β-Pregnan-3α-ol (5) from 4.—A solution of 20-ethylenedithio-5β-pregnan-3α-ol (100 mg) in 10 ml of ethanol was refluxed for 18 hr with a suspension of freshly prepared Raney nickel W-2 catalyst. The recovered product was crystallized twice from acetone to give 54 mg (70%) of needles: mp 148–149°, lit.[6] mp 148°; $[\alpha]_{365}$ +89.3°, $[\alpha]_{436}$ +60.4°, $[\alpha]_{546}$ +36.4°, $[\alpha]_D$ +32.3°.

Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 82.72; H, 11.85.

5β-Pregnan-3α-ol Acetate (6).—Acetylation of 5β-pregnan-3α-ol with pyridine and acetic anhydride and crystallization from methanol gave plates: mp 105.5–106.5°, lit.[6] mp 106°; $[\alpha]_{365}$ +149°, $[\alpha]_{436}$ +98.4°, $[\alpha]_{546}$ +58.4°, $[\alpha]_D$ +52.0°.

Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.78; H, 11.10.

5β-Pregnan-3α-ol (5) from 2.—Reduction of 3α-hydroxy-5β-pregnan-20-one (300 mg) by the Barton[5] modification of the Wolff–Kishner procedure gave, following three crystallizations from aqueous methanol, 218 mg (76%) of needles, mp 146–147°. A mixture melting point with **5** prepared by catalytic desulfurization of **4** was 147–148° and their infrared spectra were identical.

5β-Pregn-16-en-3α-ol (8) and 5β-Pregnane-3α,17-diol (10) from 7.—3α,17-Dihydroxy-5β-pregnan-20-one (300 mg) was reduced by the modified Wolff–Kishner method. Paper chromatographic analysis of the crude product in toluene–isooctane–methanol–water (40:160:160:40, v/v) showed that no starting material (R_f 0.12) remained and that roughly equal amounts of two more mobile products (R_f 0.49 and 0.91) were present. The mixture was chromatographed in the same system on a 25 × 640 mm Celite column. Fractions of 6.5 ml were collected at 7.5-min intervals.

5β-Pregn-16-en-3α-ol. Fractions 22–35.—Crystallization from aqueous methanol gave 52 mg of needles which gave a yellow color with tetranitromethane. Recrystallization from methanol furnished the analytical sample: mp 172.5–173.5°; $[\alpha]_{365}$ +161°, $[\alpha]_{436}$ +107°, $[\alpha]_{546}$ +64.5°, $[\alpha]_D$ +56.4°; ν_{max} 3030 (sh) (C=C) and 1040 cm^{-1} (3α-hydroxyl); there was no absorption between 1500 and 1800 cm^{-1}.

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.88; H, 11.62.

5β-Pregn-16-en-3α-ol Acetate (9).—Acetylation of 5β-pregn-16-en-3α-ol in the usual fashion and crystallization from methanol gave plates: mp 101–104°; $[\alpha]_{365}$ +222°, $[\alpha]_{436}$ +143°, $[\alpha]_{546}$ +84.8°, $[\alpha]_D$ +75.7°.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53; CH_3CO, 12.49. Found: C, 80.33; H, 10.68; CH_3CO, 12.10.

Hydrogenation of a sample of **8** in the presence of 5% palladium on carbon followed by crystallization of the product from aqueous methanol gave needles, mp 149–150°, which had an infrared spectrum identical with that of **5β-pregnan-3α-ol**.

5β-Pregnane-3α,17-diol. Fractions 52–74.—Crystallization from ethyl acetate furnished 85 mg of small plates: mp 174–175°; $[\alpha]_{365}$ −9.82°, $[\alpha]_{436}$ −4.30°, $[\alpha]_{546}$ −1.23°, $[\alpha]_D$ −0.061°.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.55; H, 11.38.

5β-Pregnane-3α,17-diol 3-Acetate (11).—Acetylation of 5β-pregnane-3α,17-diol in the usual fashion followed by precipitation of the product with water from methanol solution gave a low-melting, filterable solid which was homogeneous (R_f 0.36) by tlc in the system isooctane–ethyl acetate (3:2, v/v): $[\alpha]_{365}$ +63.3°, $[\alpha]_{436}$ +42.5°, $[\alpha]_{546}$ +25.5°, $[\alpha]_D$ +22.7°.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57; CH_3CO, 11.87. Found: C, 75.90; H, 10.58; CH_3CO, 11.48.

5β-Pregnane-3α,17-diol (10) from 12a.—A solution of 17,20α-oxido-5β-pregnan-3α-ol[7] (50 mg) and lithium aluminum hydride (100 mg) in ether (40 ml) was refluxed for 4 hr. After inactivation of excess reducing agent by the successive addition of ethyl acetate and water, the mixture was diluted with an equal volume of ethyl acetate and washed with neutral brine. The organic layer was dried by filtration through anhydrous sodium sulfate and concentrated to dryness. Analysis of the crude product by paper chromatography in isooctane–methanol–water (200:170:30) showed a *ca.* 3:2 ratio of starting material (R_f 0.52) to a less mobile product (R_f 0.25). The mixture was re-treated with lithium aluminum hydride as above for an additional 24 hr at which point the ratio of starting material to product was approximately 1:3. The mixture was chromatographed on a 20 × 670 mm Celite column in the same system. Fractions (3 ml) were collected every 10 min. From fractions 82–105 there was obtained 7.8 mg of starting material as needles, mp 165–167°.

5β-Pregnane-3α,17-diol. Fractions 190–251.—Crystallization from ethyl acetate afforded platelets (33.5 mg, mp 174–175°; 4 mg, mp 173–175°) in a yield of 76%. The compound was identical in all respects with the less mobile product (**10**) from the Wolff–Kishner reduction of the diolone **7**.

5β-Pregnane-3α,17-diol (10) from 12b.—Reduction of 17,20β-oxido-5β-pregnan-3α-ol[7] (25 mg) with lithium aluminum hydride (100 mg) in ether was carried out for 4 hr as above. Since pc analysis of the crude product showed that only approximately 30% of the oxide had undergone reduction, the mixture was re-treated for an additional 24 hr as above. Analysis of the re-treated material showed that the amount of desired product had nearly doubled. The mixture was chromatographed on a 14 × 460 mm Celite column in the above system. Fractions (2 ml) were collected at 15-min intervals. The pooled residues from fractions 28–39 gave, from acetone, 6.5 mg of the 17,20β-oxide **12b**, mp 137–139°.

5β-Pregnane-3α,17-diol. Fractions 74–100.—Crystallization from ethyl acetate gave platelets (11.7 mg, mp 174–175°;

(19) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475 (1959).

1.2 mg, mp 172.5–173°) in a yield of 51%. The infrared spectrum was identical with that of the lithium aluminum hydride reduction product of **12a**.

5β-Pregnane-3α,17,21-triol (13) from 15a.—A solution of 17,20α-oxido-5β-pregnane-3α,21-diol[7] (100 mg) and lithium aluminum hydride (100 mg) in ether (75 ml) was refluxed for 3 hr. The product crystallized from acetone as plates (78 mg, mp 165–166°; 13 mg, mp 153–155°) in a yield of 91%. The analytical sample had mp 164–165°; $[\alpha]_{365}$ +2.21°, $[\alpha]_{436}$ +1.66°, $[\alpha]_{546}$ +1.66°, $[\alpha]_D$ +1.66°.

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.71; H, 10.78.

5β-Pregnane-3α,17,21-triol (13) from 15b.—Reduction of 17,20β-oxido-5β-pregnane-3α,21-diol[7] (7.6 mg) with lithium aluminum hydride (50 mg) in ether (20 ml) was carried out as in the preparation of **13** from **15a**. Crystallization of the product from acetone afforded plates (3.7 mg, mp 164.5–165.5°; 1.8 mg, mp 158–160°) in a yield of 80%. Comparison with the lithium aluminum hydride reduction product of **15a** in terms of mixture melting point and infrared spectra showed them to be identical.

5β-Pregnane-3α,17,21-triol 3,21-Diacetate (14).—Acetylation of 5β-pregnane-3α,17,21-triol in the usual fashion and crystallization of the product from aqueous acetone gave filamentous needles: mp 56–58°; $[\alpha]_{365}$ +52.5°, $[\alpha]_{436}$ +35.4°, $[\alpha]_{546}$ +21.0°, $[\alpha]_D$ +18.8°.

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Calcd for $C_{25}H_{40}O_5 \cdot CH_3COCH_3$: C, 70.26; H, 9.69. Found: C, 70.74; H, 9.75.

5β-Pregnane-3α,17,21-triol 3-Acetate (17) from 14.—To a solution of 5β-pregnane-3α,17,21-triol 3,21 diacetate (111 mg) in methanol (25 ml) was added 25 μl of 1 N sodium hydroxide. After 19 hr at room temperature excess acetic acid was added. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and water. The material recovered from the organic layer was chromatographed on a 20 × 700 mm silica gel column in ethyl acetate–isooctane (2:1). Fractions (4 ml) were collected at interfals of 10 min. The residue from fractions 136–181 weighed 72.4 mg (72%) and crystallized from acetone–*n* hexane as fine needles: 60 mg; mp 125.5°; $[\alpha]_{365}$ +75.8°, $[\alpha]_{436}$ +51.7°, $[\alpha]_{546}$ +31.0°, $[\alpha]_D$ +27.6°; ν_{max} 3420 (hydroxyl), 1735, 1240, and 1030 cm^{-1} (3α-acetoxyl).

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.14; H, 10.20.

Methyl 3α,17-Dihydroxy-5β-pregnan-21-oate (18) from 17.—To a solution of 5β-pregnane-3α,17,21-triol 3-acetate (60 mg) in acetic acid (2.85 ml) was added a solution of chromic anhydride (60 mg) in water (0.15 ml). After 21 hr at room temperature methanol was added and the solvents were blown off with a stream of nitrogen. The crude acetoxy acid was recovered by extraction with ethyl acetate and saponified with methanolic sodium hydroxide. The acidic fraction (46 mg) was recovered and treated with ethereal diazomethane. The reaction mixture was chromatographed on a 16 × 840 mm silica gel column in ethyl acetate–isooctane (3:2). Fractions (2 ml) were collected every 10 min. Crystallization from acetone–*n*-hexane of the residue from fractions 126–166 (15.9 mg) provided needles: mp 123–125°; $[\alpha]_{365}$ −20.0°, $[\alpha]_{436}$ −11.2°, $[\alpha]_{546}$ −6.69°, $[\alpha]_D$ −4.46°; ν_{max} 3440 (hydroxyl), 1720, 1202, and 1170 cm^{-1} (carbomethoxyl).

Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.40; H, 9.99.

Methyl 3α-Acetoxy-17-hydroxy-5β-pregnan-21-oate (19).—A sample of methy 3α,17-dihydroxy-5β-pregnan-21-oate was acetylated in the usual manner. The product crystallized as needles from methanol–water: mp 113–113.5°; $[\alpha]_{365}$ +47.3°, $[\alpha]_{436}$ +30.8°, $[\alpha]_{546}$ +18.9°, $[\alpha]_D$ +16.6°.

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.00; H, 9.48.

21-Tosyloxy-5β-pregnane-3α,17-diol (16) from 13.—A solution of 5β-pregnane-3α,17,21-triol (100 mg, 0.298 mm) and tosyl chloride (65 mg, 0.342 mm) in pyridine (1 ml) stood for 23 hr at 5°. The recovered crude product was chromatographed on a 20 × 470 mm silica gel column in ethyl acetate–isooctane (1:1). Fractions (3 ml) were collected at a rate of six per hour. The contents of fractions 162–225 were dissolved in methanol, charcoaled, and crystallized from the same solvent as prisms (52 mg, mp 82–85°; 3 mg, mp 81–84°). Recrystallization from methanol gave the analytical sample: mp 82–85°; $[\alpha]_{365}$ −10.7°, $[\alpha]_{436}$ −5.36°, $[\alpha]_{546}$ −2.30°, $[\alpha]_D$ −1.53°; ν_{max} 1595, 1490, 1360, 1185, 1170, 1094, 810, 662 (tosylate),[7] and 1036 cm^{-1} (3α-hydroxyl).

Anal. Calcd for $C_{28}H_{42}O_5S \cdot 0.5H_2O$: C, 67.30; H, 8.67. Found: C, 67.04; H, 8.54.

Lithium aluminum hydride reduction of the tosylate **16** (15 mg) as in the earlier examples, followed by crystallization from ethyl acetate gave **5β-pregnane-3α,17-diol (10)** as plates (7.9 mg, mp 174–175°; 1.6 mg, mp 171–172°) in a yield of 94%.

5β-Pregnane-3α,21-diol (21) from 20.—A solution of 20β-tosyloxy-5β-pregnane-3α,21-diol diacetate[7] (1 g) and lithium aluminum hydride (500 mg) in ether (250 ml) was refluxed for 3.5 hr. Crystallization of the product from methanol gave plates (294 mg, mp 207–209°; 77 mg, mp 206–207.5°; 28 mg, mp 201–202.5°) in a yield of 70%. The analytical sample had mp 206.5–208°, lit.[9] mp 205–206°; $[\alpha]_{365}$ +114°, $[\alpha]_{436}$ +77.9°, $[\alpha]_{546}$ +45.6°, $[\alpha]_D$ +41.8°.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 79.00; H, 11.25.

5β-Pregnane-3α,21-diol Diacetate (22).—Acetylation of 5β-pregnane-3α,21-diol in the usual manner and crystallization from methanol afforded needles: mp 73–75°; $[\alpha]_{365}$ +147°, $[\alpha]_{436}$ +97.2°, $[\alpha]_{546}$ +57.4°, $[\alpha]_D$ +52.2°.

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.08; H, 9.88.

5β-Pregnane-3α,21-diol 3-Acetate (23) from 22.—To a solution of 5β-pregnane-3α,21-diol diacetate (240 mg) in methanol (60 ml) was added 0.60 ml of 0.1 N aqueous sodium hydroxide. After 22 hr at room temperature acetic acid (0.3 ml) was added and the solution was concentrated to dryness. The crude product was chromatographed on a 25 × 750 mm silica gel column in isooctane–ethyl acetate (3:2). Fractions (5 ml) were collected every 12 min. From fractions 22–40 was obtained 16.3 mg of starting material.

5β-Pregnane-3α,21-diol 3-Acetate. Fractions 71–110.—Crystallization from methanol gave 129 mg (60%) of rectangular plates: mp 55–65°; $[\alpha]_{365}$ +170°, $[\alpha]_{436}$ +112°, $[\alpha]_{546}$ + 67.0°, $[\alpha]_D$ +59.5°; ν_{max} 3500 (hydroxyl), 1735, 1240, and 1028 cm^{-1} (3α-acetoxyl).

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56. Found: C, 76.10; H, 10.48.

Methyl 3α-Hydroxy-5β-pregnan-21-oate (24) from 23.—To a solution of 5β-pregnane-3α,21-diol 3-acetate (50 mg) in acetic acid (2.85 ml) was added a solution of chromic anhydride (50 mg) in water (0.15 ml). After 19 hr at room temperature, methanol was added and the solvents were removed with a current of nitrogen. The residue was partitioned between ethyl acetate and water and, after evaporation of the organic layer, the crude acetoxy acid was saponified and the liberated acid was treated with diazomethane as in the previous example. The methyl ester **24** (44 mg) crystallized as needles from ether: mp 117.5–118.5°, lit.[9] mp 118–119°; $[\alpha]_{365}$ +56.1°, $[\alpha]_{436}$ +41.4°, $[\alpha]_{546}$ +27.4°, $[\alpha]_D$ +25.7°; ν_{max} 3290 (hydroxyl), 1735, 1192, and 1165 cm^{-1} (carbomethoxyl).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 76.06; H, 10.39.

Methyl 3α-Acetoxy-5β-pregnan-21-oate (25).—Acetylation of methyl 3α-hydroxy-5β-pregnan-21-oate (25 mg) with acetic anhydride and pyridine and crystallization of the product from *n*-hexane gave 20 mg of platelets: mp 109–111°, lit.[9] mp 85–87°; $[\alpha]_{365}$ +124°, $[\alpha]_{436}$ +82.4°, $[\alpha]_{546}$ +49.4°, $[\alpha]_D$ +44.4°.

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.64; H, 9.89.

5β-Pregn-16-ene-3,21-diol (26) from 13.—To a solution of 5β-pregnane-3α,17,21-triol (300 mg) in methanol (75 ml) was added concentrated sulfuric acid (0.75 ml).[20] After 24 hr at room temperature the reaction mixture was added to 200 ml of methylene chloride and the solution was washed twice with water. Examination of the crude product (263 mg) by tlc in ethyl acetate showed that in addition to starting material and several very mobile by-products, two substances were present which had mobilities close to that of the saturated 3α,21-diol **21**. The mixture was chromatographed on a 25 × 720 mm silica gel column in ethyl acetate–isooctane (3:2). Fractions (6 ml) were collected every 12 min. The contents of fractions 187–238 were pooled to give 39.4 mg of crude diol. Crystallization from acetone gave rhomboidal prisms (35.6 mg, mp 165–165.5°). The compound gave a light yellow color with tetranitromethane. Recrystallization from acetone provided the analytical sample: mp 166–

(20) L. O. Smith, M. Marx, H. Mendelsohn, T. Foell, and J. J. Goodman, *J. Amer. Chem. Soc.*, **84**, 1265 (1962).

166.5°; $[\alpha]_{365}$ +104°, $[\alpha]_{436}$ +67.3°, $[\alpha]_{546}$ +39.7°, $[\alpha]_D$ +36.7°; ν_{max} 3050 and 1620 cm^{-1} (C=C).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.03; H, 10.84.

5β-Pregn-16-ene-3α,21-diol Diacetate (27).—Acetylation of 5β-pregn-16-ene-3α,21-diol in the usual fashion gave an amorphous product which was homogeneous (R_f 0.20) by tlc in isooctane–ethyl acetate (6:1): $[\alpha]_{365}$ +144°, $[\alpha]_{436}$ +93.6°, $[\alpha]_{546}$ +55.0°, $[\alpha]_D$ +47.7°.

Hydrogenation of a sample of **27** as in the reduction of **8** to **5** and purification of the product on a small silica gel column afforded prismatic needles from methanol, mp 73–75°. This compound was identical in all respects with the lithium aluminum hydride reduction product (**22**) of the diacetate tosylate **20**.

21-Tosyloxy-5β-pregnan-3α-ol (18) from 21.—A solution of 5β-pregnane-3α,21-diol (100 mg) and tosyl chloride (70 mg) in pyridine (1 ml) stood for 18 hr at room temperature. The crude product was chromatographed on a 20 × 705 mm silica gel column in isooctane–ethyl acetate (3:2). Fractions (3 ml) were collected at 10-min intervals. The residue from fractions 141–180 weighed 39.1 mg and, although homogeneous (R_f 0.14) by tlc in the same system, could not be obtained in crystalline form: ν_{max} 1598, 1493, 1357, 1188, 1173, 1095, 810, 660 (tosylate), and 1035 cm^{-1} (3α-hydroxyl).

Lithium aluminum hyride reduction of the tosylate **28** (23.5 mg) in the usual fashion and crystallization of the product from acetone gave needles (8.8 mg, mp 148.5–150°; 4 mg, mp 144.5–146.5°). On admixture with a sample of **5β-pregnan-3α-ol** derived from **1**, the melting point was unaltered and their infrared spectra were identical. In addition, acetylation afforded a crystalline product which had the same infrared spectrum as that obtained from **6**.

Registry No.—**3**, 16054-71-0; **4**, 16054-58-3; **5**, 4352-07-2; **6**, 16054-60-7; **8**, 16109-75-4; **9**, 16054-61-8; **10**, 16109-76-5; **11**, 16109-77-6; **13**, 16054-62-9; **14**, 16054-63-0; **16**, 16054-64-1; **17**, 16054-65-2; **18**, 16109-78-7; **19**, 16054-66-3; **21**, 16109-79-8; **22**, 16054-67-4; **23**, 16109-80-1; **24**, 16054-68-5; **25**, 16054-69-6; **26**, 16054-70-9.

Studies in the 21-Methyl Steroid Series. Organoborane Rearrangements and a Novel Synthesis of 21-Methyl-19-nor Steroids

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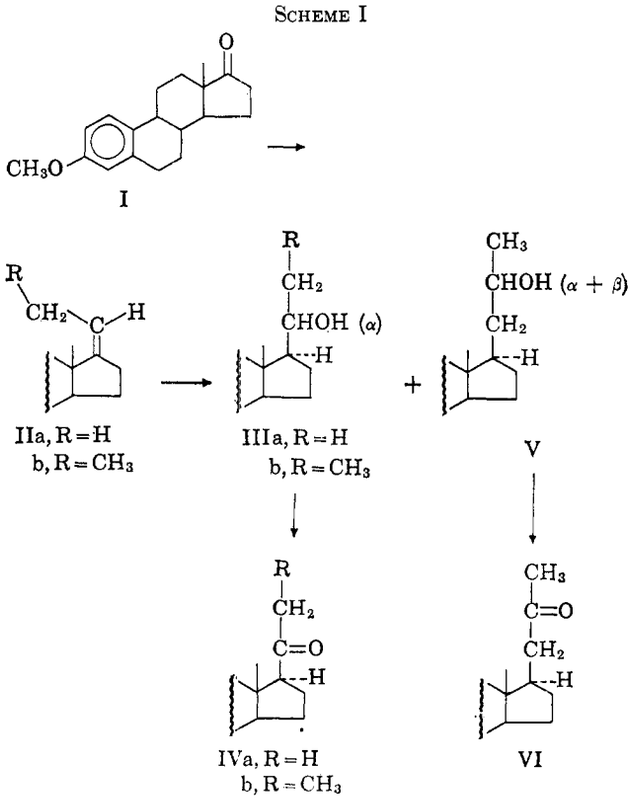
Received January 2, 1968

The Wittig reaction of estrone methyl ether (I) with propylidenetriphenylphosphorane gave the 17-propylidene derivative (IIb). Hydroboration at room temperature produced a mixture of C-20 and C-21 alcohols (IIIb and V). At higher temperatures mostly V was formed, whereas at low temperatures predominantly IIIb was obtained. Further conversions into 21-methyl-19-nor steroids X, XI, and XIIIa, b, and c are described.

The addition of a two-carbon pregnane (17β acetyl) side chain to a 17-keto steroid by a Wittig–hydroboration–oxidation sequence (*e.g.* I → IIa → IIIa → IVa) has been previously described[1] (see Scheme I).

Scheme I



We would now like to report the results of our studies directed toward the synthesis of 21-methylpregnanes, *i.e.*, introduction of a three-carbon side chain by the same sequence. Surprisingly, the addition of one more carbon atom to the side chain led us to some fascinating and unexpected new chemistry. For all studies estrone methyl ether (I) was used as a starting 17-keto steroid.

Reaction of I with *n*-propylidenetriphenylphosphorane under identical conditions as those used for the preparation of IIa led to *ca.* 80% of crude, semicrystalline product. This material, when analyzed by vapor phase chromatography (vpc), proved to be a mixture of 90% of the expected geometrically isomeric olefins (ratio 96:4) and 10% of impurities. The major product was obtained pure by recrystallization in an over-all yield of 50–55%. Since the major geometrical isomer (92%) from the two-carbon Wittig reaction (IIa) was shown to be *cis*,[1] we have by analogy assigned the identical configuration to IIb. In addition, the nmr spectra are in agreement. The C-18 methyl resonance of IIa is at δ 0.90 (relative to TMS) and that of its *trans* isomer is at 0.77, consistent with the deshielding effect of the 21-methyl group. The C-18 methyl resonance of IIb also occurred at δ 0.90 being compatible with the above stereochemical assignment. Hydroboration of IIb with excess 1 *M* borane–tetrahydrofuran reagent[2] at room temperature for 2 hr, followed by the usual oxidative work-up, afforded a mixture of alcohols separated by careful column chromatography into two components. The major alcohol isolated in 40% yield after chromatography proved to

(1) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).

(2) Available from Metal Hydrides, Inc., Beverly, Mass.