Intramolecular Catalysis. III. Catalysis by Oxygen-Containing Groups in the Acetylation of Hydroxy Steroids[1,2]

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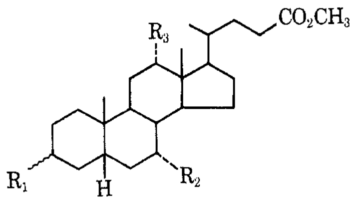
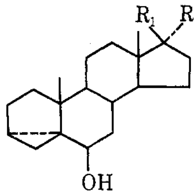
Methyl 7α-hydroxycholanate gives the same low yield on acetylation in the presence of methyl deoxycholate 3-acetate as in its absence; consequently the 3α-acetoxy and 12α-hydroxyl groups of methyl cholate 3-acetate act *intramolecularly*, enhancing acetylation of the 7-hydroxyl. The 6β-hydroxyl group is influenced somewhat it its reaction with acetic anhydride and pyridine by substituents at carbon 17. The 12α-hydroxyl group is also influenced by the side chain; in general, the larger the side chain the lower its reactivity toward acetylation. The 7α-hydroxyl acetylates similarly regardless of configuration of an enhancing 3-acetoxy group, in support of an inductive mechanism. Rates of acetylation of hydroxy steroids with acetic anhydride and pyridine were measured by glpc. Methyl lithiocholate, methyl 12α-hydroxycholanate, and methyl 7α-hydroxycholanate decreased in rate in that order. Methyl 7α,12α-dihydroxycholanate illustrates intramolecular catalysis by the 12-hydroxyl, its 7-hydroxyl undergoing acetylation 25 times as fast as in the absence of the 12-hydroxyl. Methyl cholate 3-*p*-nitrobenzoate (**1g**), prototype of uv-absorbing bile acid esters, was acetylated with acetic anhydride in pyridine. Aliquots were separated by tlc, recovered from absorbent, and analyzed spectrophotometrically. The 7-hydroxyl in **1g** is found to be much more reactive than in methyl 7α-hydroxycholanate.

One inhibiting and two enhancing effects were shown to be responsible for the selective acetylation of methyl 3α-acetoxy-7α,12α-dihydroxycholanate (methyl cholate 3-acetate, **1a**): (1) the 12α-hydroxyl group is deactivated by the side chain; (2) the 7 α-hydroxyl group is activated by the 3α-acetoxy group and (3) also by the 12α-hydroxyl group.[1] As part of an approach toward elucidating the mechanisms of intramolecular catalysis by the acetoxy and hydroxy (and possibly other) groups, we have compared a series of hydroxy steroids with respect to their ease of acetylation by acetic anhydride and pyridine.



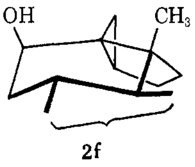
1a, $R_1 = AcO\text{---}$; $R_2 = R_3 = OH$
b, $R_1 = H$; $R_2 = OH$; $R_3 = H$
c, $R_1 = C_7H_7SO_3\text{---}$; $R_2 = R_3 = OH$
d, $R_1 = AcO\text{—}$ $R_2 = R_3 = OH$
e, $R_1 = HO\text{---}$; $R_2 = R_3 = H$
f, $R_1 = H$; $R_2 = R_3 = OH$
g, $R_1 = p\text{-}NO_2C_6H_4CO_2\text{---}$; $R_2 = R_3 = OH$
h, $R_1 = p\text{-}NO_2C_6H_4CO_2\text{---}$; $R_2 = OAc$; $R_3 = OH$
i, $R_1 = p\text{-}NO_2C_6H_4CO_2\text{---}$; $R_2 = R_3 = OAc$



2a, $R_1 = R_2 = H$
b, $R_1R_2 = {=}O$
c, $R_1R_2 = \text{-}OCH_2CH_2O\text{-}$
d, $R_1 = C_6H_5CO_2\text{-}$; $R_2 = H$
e, $R_1 = HO$; $R_2 = C{\equiv}CH$

The relatively low reactivity of the hydroxyl group in methyl 7α-hydroxycholanate (**1b**, 3–7% yield, Table I) is altered in the presence of the 3α-acetoxy group and the 12α-hydroxyl group (66–70% yield for **1a**). The 3 and 12 substituents conceivably could act on the 7α-hydroxyl *intermolecularly*. The acetylation of methyl 7α-hydroxycholanate (for which a new synthesis from methyl chenodeoxycholate is described in the Experimental Section) in only 4% yield in the presence of an equimolar amount of methyl deoxycholate 3-acetate, however, proves that the effect of the 3 and 12 substituents is *intramolecular* in methyl cholate 3-acetate.

In order to determine the effects of substituents at C-17 on the reactivity of the 6β-hydroxyl group, the series **2a–e** (prepared by rearrangement of the corresponding Δ^5-3β-tosylates) was treated with acetic anhydride and pyridine at room temperature for 24 hr. The yields of acetate isolated by chromatography are shown in Table I. The ethylenedioxy group in **2c** has no effect, but enhancement of 6β-hydroxyl reactivity is observed with the keto group of **2b**, the benzoyloxy group of **2d**, and the hydroxyl and ethynyl groups of **2e**. The 44–49% yield of acetate obtained with **2a** is at first surprising, as the 6β-hydroxyl might be assumed to encounter 1,3-diaxial nonbonded interaction with the C-18 methyl, as the 7α-hydroxyl apparently does with the C-4 methylene in **1b**, which acetylates in only 3–7% yield. Inspection of molecular models, however, shows that the bicyclo[3.1.0]hexane A ring distorts the B ring in such a way as to separate methyl and hydroxyl more than in the normal chair conformation (**2f**).



2f

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[1] For convenience in reference, we are now assigning to our earlier papers in the series Intramolecular Catalysis the following numbers: (a) I, R. T. Blickenstaff and B. Orwig, *J. Org. Chem.*, **32**, 815 (1967); (b) II, R. T. Blickenstaff and B. Orwig, *ibid.*, **34**, 1377 (1969).

[2] Taken in part from the M.S. thesis of Y. C. Kim, Indiana University, 1970. Supported in part by Public Health Service Grant No. GM 360-09.

TABLE I

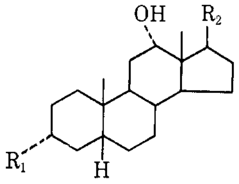
ACETYLATION OF HYDROXY STEROIDS WITH ACETIC ANHYDRIDE AND PYRIDINE

No.	Compd	Yield of acetate, %: Standard conditions[a]	Yield of acetate, %: Pyridine replacing benzene
1a	Methyl cholate 3-acetate	66–70	55–62[b]
1b	Methyl 7α-hydroxycholanate	3–7	
1b	Methyl 7α-hydroxycholanate with an equimolar amount of methyl deoxycholate 3-acetate	4	
1d	Methyl 3β-acetoxy-7α,12α-dihydroxycholanate		55–57
2a	3α,5-Cycloandrostan-6β-ol	44–49	
2b	3α,5-Cycloandrostan-6β-ol-17-one	59–61	
2c	17,17-Ethylenedioxy-3α,5-cycloandrostan-6β-ol	47	
2d	17β-Benzoyloxy-3α,5-cycloandrostan-6β-ol	57	
2e	17α-Ethynyl-3α,5-cycloandrostane-6β,17β-diol	58–63	
3a	Methyl 12α-hydroxycholanate	5–8	
3b	Methyl deoxycholate 3-acetate	11–13	
3c	5β-Pregnan-12α-ol-20-one	18–21	
3d	3α-Acetoxy-5β-pregnan-12α-ol-20-one	32–36	
3e	3α-Tosyloxy-5β-pregnan-12α-ol-20-one	31–39	
3f	24-Methyl-24-homocholane-12α,24-diol	10–12	
3g	Cholan-12α-ol	5–10	
3h	5β-Pregnan-12α-ol	45–50	
4a	20-Methyl-5β-pregna-3-ene-12α,20-diol		<1
4b	Methyl 12α-hydroxy-3-cholenate	4	8

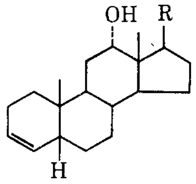
[a] Steroid (0.37 mmol), Ac_2O (0.1 ml), pyridine (0.1 ml), and benzene (0.84 ml), room temperature, 24 hr. [b] Average of three runs, 57%.

The slight enhancing effect of the 3α-acetoxy group on 12α-hydroxyl reactivity is shown (Table I) by comparing the 5–8% yield previously obtained with methyl 12α-hydroxycholanate (**3a**) with the 11–13% yield obtained with the 3-acetate (**3b**) of methyl deoxycholate. This is verified in the pregnane series by comparing the 18–21% yield obtained previously with 5β-pregnan-12α-ol-20-one (**3c**) with the yield obtained with the 3-acetate (**3d**); in addition, the tosylate group of 5β-pregnane-3α,12α-diol-20-one 3-tosylate (**3e**) is similarly enhancing.

A series of 12α-hydroxyl compounds was compared to assess the influence of the side chain on 12-hydroxyl group reactivity. In addition to those compounds already described,[1b] two derivatives (**3f** and **4a**) containing *tert*-hydroxyl groups in the side chain were prepared by Grignard reactions on methyl 12α-hydroxycholanate and on 5β-pregna-3-en-12α-ol-20-one, respectively. The series **3h**, **3c**, **3a**, **3g**, and **3f** illustrates that 12α-hydroxyl group reactivity decreases as the side chain increases in size. 20-Methyl-5β-pregna-3-ene-12α,20-diol (**4a**) does not fit neatly in the series as it gives less than a 1% yield of acetate. Such low reactivity is not the result of its being tested in pyridine (it is insoluble in the standard benzene mixture), because methyl 12α-hydroxy-3-cholanate (**4b**) gives the same or higher yield in pyridine compared to the benzene medium. Neither is it due to the ring-A unsaturation, as methyl 12α-hydroxycholanate (**3a**) and the Δ^3 analog (**4b**) do not differ significantly. It may be noted that the two hydroxyls of **4a** are close enough for strong H bonding, and that Wall, *et al.*,[3] found this to inhibit acetylation of a 12β-hydroxyl.



3a, $R_1 = H; R_2 = CH(CH_3)CH_2CH_2CO_2CH_3$
b, $R_1 = AcO; R_2 = CH(CH_3)CH_2CH_2CO_2CH_3$
c, $R_1 = H; R_2 = COCH_3$
d, $R_1 = AcO; R_2 = COCH_3$
e, $R_1 = C_7H_7SO_3; R_2 = COCH_3$
f, $R_1 = H; R_2 = CH(CH_3)CH_2CH_2C(CH_3)_2OH$
g, $R_1 = H; R_2 = CH(CH_3)CH_2CH_2CH_3$
h, $R_1 = H; R_2 = C_2H_5$



4a, $R = C(CH_3)_2OH$
b, $R = CH(CH_3)CH_2CH_2CO_2CH_3$

We have suggested[1b] intramolecular general acid–general base catalysis for the mechanism of action of the 3α-acetoxy and 12α-hydroxyl groups of methyl cholate 3-acetate (**1a**) in its reaction with the acetylpyridinium ion, the existence of which has now been verified experimentally.[4] On the other hand, it is necessary also to consider inductive effects, even though they are generally thought to drop off very fast as the length of saturated carbon chain between substituent group and reaction center increases. Recently several groups have reported long-distance inductive effects. The rate of addition of bromine to a Δ^5 double bond is shown to be influenced by substituents not only at C-3, but also those at C-17.[5] Acetolysis rates of 11α-tosylates are influenced by the type of substitution in ring A in the sapogenin series.[6] Solvolysis rates of 3-tosylates are decreased by electronegative substituents at C-17, *across the entire steroid nucleus.*[7] We have examined this question in a preliminary fashion by comparing the behavior of methyl cholate 3-acetate (**1a**) with methyl 3β-acetoxy-7α,12α-dihydroxycholanate

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(3) M. E. Wall, F. I. Carroll, and G. S. Abernethy, *J. Org. Chem.*, **29**, 604 (1964).

(4) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 2125 (1969); G. A. Olah and P. J. Szilagyi, *ibid.*, **91**, 2949 (1969).

(5) V. Schwarz and S. Hermanek, *Collect. Czech. Chem. Commun.*, **29**, 2360 (1964).

(6) K. Takeda, K. Tanida, and K. Horiki, *J. Org. Chem.*, **31**, 734 (1966).

(7) P. E. Peterson, unpublished results. We are grateful to Dr. Peterson for providing a prepublication copy of his manuscript and for calling our attention to this phenomenon. An alternative explanation is offered by Kogan, *et al.*, for some long-range effects in 17-substituted 4-androsten-3-ones (G. A. Kogan, V. N. Leonov, S. N. Ananchenko, and I. V. Torgov, 7th International Symposium on the Chemistry of Natural Products, Riga, June 1970, p 406). They interpret alterations of ORD curves of the ring-A chromophore in terms of ring-D distortions caused by type and configuration of substituents and transmitted to ring A by the Barton effect.

(**1d**). The latter was synthesized by the action of tetrabutylammonium acetate on methyl cholate 3-tosylate (**1c**). It was too insoluble to be tested in the benzene mixture, but in pyridine both epimers, **1a** and **1d**, evidenced the same amount of 7-acetylation. This result, to be expected if the 3-acetoxy groups exert an inductive effect on the 7-hydroxyl, requires reexamination of the proposed mechanism.[1b]

The first approximations of relative reactivity based on yield comparisons in this work are confirmed for several of these compounds (**1b**, **1e**, **1f**, and **3a**) whose rates of acetylation have been measured by a glpc method. The acetylation with acetic anhydride and pyridine was carried out in benzene solution under conditions shown to be responsive to intramolecular influences.[1] Aliquots were quenched in methanol, then examined by glpc directly, rather than undergoing conversion to trimethylsilyl ethers.[8] Inasmuch as ratios of the two peaks of each aliquot are determined, these transfers need not be quantitative. Peak areas (except for methyl 7α,12α-dihydroxycholanate (**1f**), for which peak heights are used) were converted to mole ratios by means of standard curves prepared from known mixtures of hydroxy steroid and acetate.

The method was developed with methyl lithocholate, methyl 7α-hydroxycholanate, and methyl 12α-hydroxycholanate representing the three hydroxyl groups of methyl cholate, and with methyl 7α,12α-dihydroxycholanate. As Eliel and Lukach had found alicyclic alcohols to follow second-order kinetics,[9] rate constants for the steroid acetylations were calculated from the standard expression

$$k = \frac{2.303}{t(b - a)} \log \frac{a(b - x)}{b(a - x)}$$

where a = starting concentration of steroid, b = starting concentration of acetic anhydride, and x = concentration of each having reacted at time t. It was assumed that no side reactions took place, and x values were calculated from the glpc measurements.[10] Typical values for methyl lithocholate are given in Table II. By varying the concentrations of reactants, the reaction was clearly shown to be first order in methyl lithocholate and in acetic anhydride, and (at these concentrations) zero order in pyridine (Table III).[11]

TABLE II

TYPICAL KINETIC RUN IN THE REACTION OF METHYL LITHOCHOLATE WITH ACETIC ANHYDRIDE AND PYRIDINE

Time, hr	$x/(a - x)$	x	$a - x$	$b - x$	k	Reaction, %
1.0	0.225	0.067	0.302	0.998	0.192	18.1
1.5	0.343	0.094	0.275	0.971	0.191	25.4
2.0	0.462	0.116	0.253	0.949	0.187	31.4
3.17	0.766	0.160	0.209	0.905	0.183	43.3
3.5	0.985	0.182	0.187	0.883	0.201	49.1
4.0	1.133	0.195	0.174	0.871	0.197	52.7
5.0	2.095	0.249	0.129	0.816	0.225	67.3
7.83	3.617	0.289	0.080	0.776	0.222	78.1
					Av 0.200 ± 0.015	

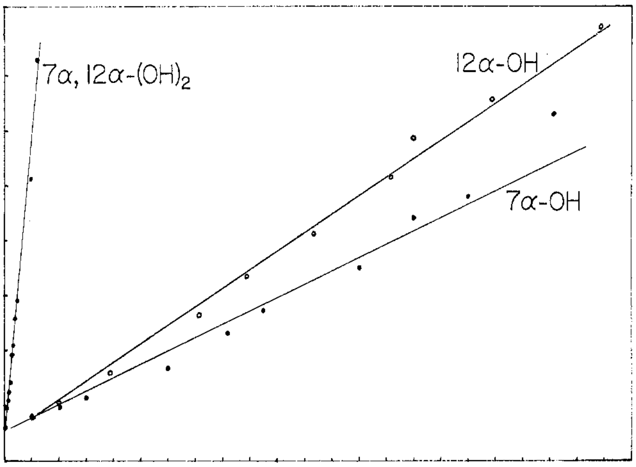

Figure 1.—Second-order rate plots for the acetylation of methyl 7α,12α-dihydroxycholanate, methyl 12α-hydroxycholanate, and methyl 7α-hydroxycholanate.

TABLE III

ACETYLATION OF METHYL LITHOCHOLATE WITH ACETIC ANHYDRIDE AND PYRIDINE IN BENZENE

Initial concentration (M)			Time	Product	
Steroid	Ac_2O	C_5H_5N	(min)	ROAc	
0.369	1.065	1.24	30	0.0335	
0.369	1.065	1.24	40	0.0445	
0.369	1.065	1.24	60	0.067	
0.035	1.065	1.24	30	0.0038	$m^a = 0.924$
0.360	0.533	1.24	40	0.023	$n^a = 0.957$
0.369	1.065	0.62	30	0.0317	$j^a = 0.078$

[a] From $(\Delta X/\Delta T_1)/(\Delta X/\Delta T_2) = k(\text{steroid})_1{}^m(Ac_2O)_1{}^n(C_5H_5N)_1{}^j/k(\text{steroid})_2{}^m(Ac_2O)_2{}^n(C_5H_5N)_2{}^j$; see ref 11.

Second-order plots for the other two monohydroxy steroids are shown in Figure 1. The rate constants given in Table IV clearly indicate the large difference in the reactivity of the 3α-hydroxyl compared with the 7α- and 12α-hydroxyls. The rate constants for the latter two verify our observation[1b] that in the absence of other nuclear substituents the 12α-hydroxyl is the more reactive. When both the 7α- and 12α-hydroxyls are present in the same molecule, however, the 7-hydroxyl is the more reactive; methyl 7α,12α-dihydroxycholanate (**1f**) had been converted in 56% yield to methyl 7α-acetoxy-12α-hydroxycholanate.[1b] In the present work methyl 7α,12α-dihydroxycholanate was found to acetylate (presumably at the 7-OH) at a rate 25 times that of methyl 7α-hydroxycholanate, verifying the

TABLE IV

RATES OF ACETYLATION WITH ACETIC ANHYDRIDE AND PYRIDINE IN BENZENE AT ROOM TEMPERATURE

Compound	k, M^{-1} sec^{-1}	Ratio of rates
Methyl lithocholate	$55.6 \pm 4.2 \times 10^{-6}$	68.5
Methyl 7α-hydroxycholanate	$0.81 \pm 0.15 \times 10^{-6}$	1
Methyl 12α-hydroxycholanate	$1.12 \pm 0.19 \times 10^{-6}$	1.4
Methyl 7α,12α-dihydroxycholanate	$20.5 \pm 4.5 \times 10^{-6}$	25.3

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(8) The 7α- and 12α-hydroxyl groups are known to undergo silylation very slowly [T. Briggs and S. R. Lipsky, *Biochim Biophys. Acta*, **97**, 579 (1965)], a factor which would greatly complicate analysis of aliquots from methyl 7α- and 12α-hydroxycholanates.

(9) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

(10) Mole fractions calculated from peak areas of glc curves were used to calculate rate constants for the reaction of trimethylaluminum and benzophenone: E. C. Ashby and J. T. Laemmle, *J. Org. Chem.*, **33**, 3398 (1968).

(11) F. Daniels and R. A. Alberty, "Physical Chemistry," Wiley, New York, N. Y., 1955, p 330.

TABLE V

KINETIC RUN OF THE ACETYLATION OF METHYL CHOLATE 3-*p*-NITROBENZOATE WITH ACETIC ANHYDRIDE AND PYRIDINE

Time, hr	Acetate		Alcohol						
	Dilution	Absorbance	Dilution	Absorbance	$x/(a - x)$	x	$\text{Log}\ \frac{a(b-x)}{b(a-x)}$	k	% completion
1	10	0.530	50	0.610	0.174	0.0547	0.0453	0.145	14.8
2	10	0.958	50	0.589	0.321	0.0896	0.0828	0.137	24.3
3	20	0.637	50	0.532	0.479	0.120	0.117	0.129	32.5
5	25	0.872	50	0.538	0.810	0.165	0.185	0.122	44.7
7	25	0.718	50	0.280	1.28	0.207	0.263	0.124	56.1
9	25	0.759	20	0.516	1.84	0.239	0.342	0.126	64.8
11	50	0.695	20	0.595	2.92	0.275	0.464	0.140	74.5
13	50	0.440	25	0.400	2.20	0.254	0.387	0.099	68.8
16	50	0.450	25	0.304	2.92	0.276	0.467	0.097	74.8
24	50	0.395	10	0.345	5.72	0.314	0.676	0.093	85.1
39	100	0.168	10	0.200	8.40	0.330	0.813	0.093	89.4
34	100	0.317	10	0.206	15.4	0.347	1.05	0.102	94.0
39	50	0.338	5	0.171	19.8	0.351	1.14	0.097	95.1

Av $0.116 \pm 0.019\ M^{-1}\ \text{hr}^{-1}$

catalytic effect of the 12α-hydroxyl group on the 7α-hydroxyl.

Bile acids and their derivatives, like other steroids, absorb uv radiation when dissolved in concentrated sulfuric acid,[12] but in the usual spectral solvents they are transparent. Methyl cholate was made uv absorbing for the present work by converting it to the 3-*p*-nitrobenzoate ester (**1g**).[13] Its rate of acetylation by acetic anhydride and pyridine was determined by chromatographing aliquots of the reaction mixture on tlc plates, recovering starting material and product separately, and measuring them spectrophotometrically. The *p*-nitrobenzoate ester **1g** was not soluble in the benzene medium used previously; so the reaction was carried out in pyridine. The product formed initially is assumed to be the 7-monoacetate (**1h**) by analogy with the known conversion of methyl cholate 3-acetate to the 3,7-diacetate.[1b] Beginning with 4 hr, a third spot appeared on the tlc plate, which was always much weaker than the 7-acetate spot. It was shown to be the 7,12-diacetate (**1i**) of methyl cholate 3-*p*-nitrobenzoate by comparison with an authentic sample by tlc. Consequently, the two acetate spots were combined and measured together as representing total 7-acetate. Data for a typical run are given in Table V.[14]

The second-order rate constant of $31.3 \times 10^{-6}\ M^{-1}\ \text{sec}^{-1}$ is 39 times that for the acetylation of methyl 7α-hydroxycholanate by the glpc method. This implies that the 3α-*p*-nitrobenzoyloxy and/or 12α-hydroxyl groups catalyze acetylation of the 7α-hydroxyl, a result analogous to our earlier finding that the 7-hydroxyl of methyl cholate 3-acetate acetylates in much higher yield than that of methyl 7α-hydroxycholanate.

Experimental Section[15]

Methyl 7α-Hydroxycholanate (1b).—A solution of 4.44 g (11.3 mmol) of chenodeoxycholic acid in 50 ml of methanol containing 5 drops of concentrated HCl was refluxed 3.5 hr, cooled to room temperature, made turbid with aqueous $NaHCO_3$, and evaporated in an open dish. The oily residue was dissolved in ether and chromatographed on 133 g of Al_2O_3. The fraction eluted by ether–methanol (24:1 to 22:3), 4.75 g, an oil (containing a little solvent), was dried by azeotropic distillation of benzene, dissolved in 30 ml of pyridine (previously dried over KOH), and treated with 4.75 g (25 mmol) of *p*-toluenesulfonyl chloride. After standing overnight at room tempersture, the mixture was poured over crushed ice; the oil that separated gradually solidified. Filtering, washing with dilute HCl and H_2O, and then vacuum drying gave 6.36 g (quantitative yield) of crude methyl 7α-hydroxy-3α-tosyloxycholanate, crystallized twice from methanol: mp 128.5–129.0°; ir 2.76, 5.79, 6.22, 8.53 μ (SO_3).

Anal. Calcd for $C_{32}H_{48}O_6S$: C, 68.54; H, 8.63; S, 5.72. Found: C, 68.73; H, 8.61; S, 5.62.

A solution of 4.40 g (7.85 mmol) of the tosylate in 35 ml of freshly distilled collidine was refluxed 2.5 hr, cooled to room temperature, and poured into ice-cold, dilute H_2SO_4, causing an oil to separate. It was extracted into ether, washed with dilute acid and H_2O, dried over Na_2SO_4, and evaporated to give an oil, 2.495 g (82%), which slowly solidified. Crystallization from CH_3OH–H_2O, followed by three crystallizations from acetone–H_2O gave the analytical sample of methyl 7α-hydroxy-3-cholenate: slight melting at 112°, mp 117–120°; ir 2.73, 5.72, 6.03 (w, C=C), 8.58 μ (this is a strong band, but appreciably weaker than the 8.53-μ band of the tosylate).

Anal. Calcd for $C_{25}H_{40}O_3$: C, 77.28; H, 10.38. Found: C, 77.52; H, 10.31.

Hydrogenation of the olefin, 2.00 g, mp 101–112°, in absolute EtOH with 5% Pd/C at 50 psi for 22 hr gave 2.015 g of an oil, which was dissolved in benzene and chromatographed on 60 g of Al_2O_3. The fraction eluted by benzene–ether (4:1 to 2:3) and by ether (1.270 g) crystallized from acetone–H_2O to give 953 mg of methyl 7α-hydroxycholanate: mp 78.5–79.5° (lit.[1b] 78.5–80.0°); ir 2.73, 5.76, 9.08, 9.73, 9.87, 10.1 μ.

Methyl Cholate 3-Tosylate (1c).—Methyl cholate (4.33 g, 15 mmol) and *p*-toluenesulfonyl chloride (3.24 g, 17 mmol) were mixed in 50 ml of pyridine and the homogeneous solution was allowed to stand at 5–10°. After 3 hr it was poured onto crushed ice and acidified with concentrated HCl. Chloroform extraction and solvent removal *in vacuo* gave a viscous, yellow oil, thin layer chromatography of which indicated six to eight components. After numerous attempts at purification *via* various supports and solvent systems, it was found that benzene–methanol (99:1) on 225 g of Florisil (30–60 mesh) did a creditable (though not entirely satisfactory) job of separation. After initial elution of several unidentified components, the tosylate was found relatively pure in several succeeding cuts. Later fractions were contaminated with starting material. The nearly pure intermediate fractions were combined, the solvent was removed, and the resi-

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[12] L. L. Smith and S. Bernstein in "Physical Properties of the Steroid Hormones," L. L. Engle, Ed., Macmillan, New York, N. Y., 1963, p 321.

[13] Our first approch was the successful synthesis of phenacyl cholate, but we were unable to obtain pure 3-monoacetate and 3,7-diacetate derivatives of it.

[14] Preliminary experiments indicate that this procedure is applicable to some other uv-absorbing steroids. Testosterone, 11α-hydroxyprogesterone, and 11α-hydroxy-17α-methyltestosterone were run as described herein except that methanol–benzene mixtures (rather than $CHCl_3$–AcOH) were used in developing the tlc plates. The method failed, however, with cortisol and estrone; cortisol acetate crystallized out during the reaction and aliquots of the estrone acetylation did not separate adequately by tlc.

[15] The acetylation procedure and compounds not described in this section are described in ref 1b. Melting points were taken on a Unimelt apparatus and are uncorrected. Infrared spectra were determined as mineral oil mulls with an Infracrod. Ultraviolet spectra were determined with a Cary 15 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

due was recrystallized from methanol–water. There was obtained 1.693 g of the tosylate as small, white needles: mp 133–134°; ir 2.85 (OH), 5.80 (C=O), 7.42, 8.56 μ (SO_2–O).

Anal. Calcd for $C_{32}H_{48}O_7S$: C, 66.63; H, 8.36; S, 5.56. Found: C, 66.74; H, 8.36; S, 5.54.

Methyl 3β-Acetoxy-7α,12α-dihydroxycholanate (1d).—The 3α-tosylate (**1c**, 1.876 g, 3.25 mmol) and tetrabutylammonium acetate (2.355 g, 8.56 mmol)[16] were combined in 90 ml of acetone, and the resulting solution was refluxed under nitrogen for 29 hr and then allowed to stand at room temperature for 3 days. Ths solvent was allowed to evaporate and the residue chromatographed on 193 g of Florisil. Benzene–methanol (66:1) initially eluted the starting tosylate as well as some very minor components, then the 3β-acetate. Appropriate fractions were combined, the solvent was removed, and the residue was crystallized from methanol–water. The product (528 mg, 35%) was isolated as long needles: mp 191–193°; ir 2.87 (OH), 5.80 μ (C=O).

Anal. Calcd for $C_{27}H_{44}O_6$: C, 69.79; H, 9.55. Found: C, 69.68; H, 9.60.

The 7-acetate, **methyl 3β,7α-diacetoxy-12α-hydroxycholanate,** crystallized out of acetone–H_2O: mp 146–147°; ir 2.79, 5.79, 5.87, 7.91, 9.80 μ.

Anal. Calcd for $C_{29}H_{46}O_7$: C, 68.74; H, 9.15. Found: C, 68.50; H, 8.87.

Methyl Cholate 3-*p*-Nitrobenzoate (Methyl 7α,12α-Dihydroxy-3-*p*-nitrobenzoyloxycholanate (1g)).—Following the conditions used in the preparation of methyl cholate 3-benzoate,[17] a solution of methyl cholate (4.22 g, 10 mmol) in 30 ml of sodium-dried benzene was distilled to half volume, then cooled to room temperature. The solution was stirred while pyridine (1.25 ml) and then a solution of 1.85 g (10 mmol) of *p*-nitrobenzoyl chloride in 10 ml of benzene were added over a 20-min period. More benzene (30 ml) was added as the mixture thickened; stirring was continued at room temperature for 2 hr, after which the benzene layer was washed with three 20-ml portions of 0.5 *N* HCl, then 0.2 *N* HCl, and finally H_2O. The benzene solution was dried over Na_2SO_4 and evaporated under vacuum; a solution of the residue in 20 ml of benzene was diluted with 100 ml of ether and refrigerated overnight. A small amount of solid was filtered, mp 189–190°, and lacked an ir band in the OH region, but was not further characterized. The filtrate was concentrated to 10 ml, diluted with 100 ml of MeOH, and refrigerated overnight. The crystals were filtered, washed with cold MeOH, and dried: mp 216–218° (some preparations, mp 223–234°); ir 2.80, 5.83, 6.25, 6.54, 7.89, 8.29, 8.50, 9.05, 9.12, 10.38, 10.99, 11.39, 11.68, 13.92 μ.

Anal. Calcd for $C_{32}H_{45}O_8N$ (571.72): C, 67.23; H, 7.93; N, 2.45. Found: C, 67.15; H, 8.02; N, 2.36.

Methyl Chlolate 3-*p*-Nitrobenzoate 7-Acetate (Methyl 7α-Acetoxy-12α-hydroxy-3α-*p*-nitrobenzoyloxycholanate (1h)).—Acetic anhydride (0.5 ml) was added to a solution of **1g** (1.058 g, 1.70 mmol) in 4 ml of dry pyridine, and the solution was made up to a volume of 5.0 ml with pyridine. The solution stood 2 days in the drybox at room temperature and then was transferried in 15 ml of ether to a separatory funnel containing 10 ml of H_2O. The ethereal layer was washed with three 5-ml portions of H_2O and then evaporated to dryness under vacuum. A solution of the residue in 5 ml of acetone was diluted with 50 ml of petroleum ether (bp 30–60°) and refrigerated overnight. The crystalline product was filtered, washed with petroleum ether, and vacuum dried: mp 189–190°; ir 2.79, 5.84, 5.90, 6.27, 6.60, 7.89, 8.20, 9.00, 9.11, 9.91, 10.80, 12.00, 12.80, 13.99 μ.

Anal. Calcd for $C_{34}H_{47}O_9N$ (613.76): C, 66.54; H, 7.72; N, 2.28. Found: C, 66.36; H, 7.71; N, 2.07.

Methyl Cholate 3-*p*-Nitrobenzoate 7,12-Diacetate (Methyl 7α,12α-Diacetoxy-3α-*p*-nitrobenzoyloxycholanate (1i).—A solution of 423 mg (0.74 mmol) of **1g** and 0.2 ml of acetic anhydride in 1.8 ml of pyridine was refluxed 2 days, cooled to room temperature, and transferred in 10 ml of ether to a separatory funnel containing 2.5 ml of H_2O. The ethereal layer was washed with three 2.5-ml portions of H_2O and then evaporated to dryness under vacuum. All attempts to crystallize this product failed. Its solution in $HCCl_3$ was diluted with petroleum ether, causing an oil to separated. The supernatent was decanted and the residue was vacuum dried, leaving an amorphous solid: mp 87–88°, ir 5.92, 6.25, 6.59, 7.68, 7.78, 8.55, 10.7, 11.42, 13.99 μ.

Anal. Calcd for $C_{36}H_{49}O_{10}N$ (655.80): C, 65.93; H, 7.53; N, 2.14. Found: C, 65.99; H, 7.42; N, 2.07.

3α,5-Cycloandrostan-6β-ol (2a).—Androstenolone was reduced to 5-androsten-3β-ol according to Shoppee and Krueger.[18] Tosylation with *p*-toluenesulfonyl chloride and dry pyridine (KOH) at room temperture gave a 95% yield of crude tosylate, which crystallized from acetone to give fine needles: mp 129–130° (lit.[19] mp 136°); ir 6.21, 8.40, 8.50 μ (SO_3). The rearrangement was carried out similarly to that of Julia, *et al.*,[20] except for a shorter reaction time. The tosylate (3.218 g, 7.52 mmol) and potassium acetate (3.218 g, 32.8 mmol) were heated to reflux in a mixture of 520 ml of acetone and 120 ml of H_2O for 2.5 hr. Evaporation in an open dish left a residue, the organic portion of which was dissolved in $HCCl_3$ and dried over $CaCl_2$; evaporation of the $HCCl_3$ left 2.467 g of an oil, which was taken up in petroleum ether–benzene (4:1) and chromatographed on 74 g of Al_2O_3. Petroleum ether and mixtures of it with benzene (up to 40% benzene) eluted variable amounts of nonpolar compounds from which in one case was crystallized (out of ether–methanol) a solid, mp 188–190°, lacking hydroxyl and carbonyl absorption in the ir, with the formula $C_{19}H_{29}OC_{19}H_{29}$ indicated by analysis.

Anal. Calcd for $C_{38}H_{58}O$: C, 85.97; H, 11.01. Found: C, 85.79; H, 11.11.

After a small intermediate fraction, benzene eluted 107 mg of an oil with ir identical with the product obtained on acetylation of **2a**, but which was exceedingly difficult to crystallize. One sample out of methanol melted at 60–68°, and on a second crystallization out of methanol–H_2O melted at 72–81° (lit.[21] mp 59–60°; erroneously described as the 6α epimer). After an intermediate cut of 90 mg (mixture), benzene–ether (9:1 to 3:2) eluted 1.217 g (54% yield) of **3α,5-cycloandrostan-6β-ol:** after two crystallizations from methanol–H_2O, mp 69–71.8° (lit.[21] mp 52–53°, erroneously described as the 6α epimer[22]); ir 2.82, 9.50, 9.75 (OH), 9.82 μ (Δ). This material is a solvate (methanol) that is stable to vacuum drying at room temperature. For analysis it was vacuum dried above its melting point.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.34; H, 11.48.

Elution of the column with benzene–ether (2:3) gave an additional 174 mg of product (**2a**), slightly contaminated with the final fraction, most of which was eluted with ether, 396 mg of a solid material exhibiting OH and C=O absorption in the ir, but otherwise unidentified.

3α,5-Cycloandrostan-6β-ol-17-one (2b) was prepared similarly and crystallized from acetone–petroleum ether: mp 132–135° (lit.[19] mp 136–138°); ir 2.84, 5.85 (C=O), 9.51, 9.70, 9.75, 9.81 (Δ), 9.90 μ.

The **acetate** crystallized out of acetone–H_2O: mp 109–112° (lit.[19] mp 113–114°); ir 5.78 (C=O), 8.10, 9.80 μ (Δ).

17,17-Ethylenedioxy-3α,5-cycloandrostan-6β-ol (2c) was prepared similarly and crystallized from acetone: mp 141–143° (lit.[20] mp 142–144°); ir 2.79, 9.6 (OH), 9.81 μ (Δ).

The **acetate** crystallized out of acetone–H_2O: mp 109–110°, ir 5.82 (C=O), 9.81 μ (Δ).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.92; H, 8.82.

17β-Benzoyloxy-3α,5-cycloandrostan-6β-ol (2d).—17β-Benzoyloxy-5-androsten-3β-yl tosylate, mp 147–149° (lit.[23] mp 150.2–153.6°), was similarly subjected to *i*-steroid rearrangement; the product crystallized out of acetone: mp 105–106°; ir 2.79, 3.05, 5.90 (C=O), 9.35 (OH), 9.75 μ (Δ). Attempts to obtain this compound analytically pure were unsuccesful. Its identity is indicated by its method of preparation, its ir absorption curve, and its conversion to the acetate derivative.

The **acetate** crystallized out of acetone–H_2O: mp 98.2–99°; ir 5.81 (acetate C=O), 5.90 (benzoate C=O), 9.79 μ (Δ).

Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 76.83; H, 8.20.

17α-Ethynyl-3α,5-cycloandrostane-6β,17β-diol (2e).—17α-Ethynyl-5-androstene-3β,17β-diol was tosylated similarly to 5-

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(19) A. Butenant and L. Suranyi, *Ber.*, **75**, 591 (1942).

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(23) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 5029 (1961).

androsten-3β-ol to give an 84% yield of the **3-tosylate,** crystallized from methanol–H_2O: mp 139–140°; ir 2.98, 3.1, 6.26 (aromatic ring), 8.40, 8.51 (SO_3), 9.65 μ (OH).

Anal. Calcd for $C_{28}H_{36}SO_4$: C, 71.75; H, 7.74; S, 6.84. Found: C, 71.79; H, 7.52; S, 6.69.

i-Steroid rearrangement of the tosylate gave a crude product, which was chromatographed on silica gel. The fraction eluted by benzene–ether (4:1) and obtained in 62% yield was crystallized from methanol–H_2O, **17α-ethynyl-3α,5-cycloandrostane-6β,17β-diol:** mp 110–115°; ir 2.9, 3.0, 4.75 (C≡C, very weak), 9.56 (OH), 9.70 (OH), 9.82 μ (Δ).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.20; H, 9.61. Found: C, 80.06; H, 9.44.

The **6-acetate** crystallized out of acetone–H_2O: mp 70–73°; ir 2.9 sh, 3.05, 5.85 (C=O), 9.56 (OH), 9.81 μ (Δ).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.98; H, 8.95.

Methyl deoxycholate 3-acetate (3b) was prepared by acetylation of methyl deoxycholate under conditions which convert methyl cholate to its 3-acetate.[24] The crude product was chromatographed twice on alumina and crystallized twice from methanol–H_2O to give the 3-acetate, mp 112–113° (lit.[25] mp 128–129.5°). Although the melting point could not be raised, the sample gave a single spot by tlc with R_f intermediate between methyl deoxycholate and its diacetate, so it was assumed to be pure.

3α-Acetoxy-5β-pregnan-12α-ol-20-one (3d) was prepared similarly, except that in this case the crude product was a mixture of diacetate (25%) and 3-monoacetate (75%) which was separated by chromatography on alumina. Benzene and ether eluted the diacetate and then ether–methanol (9:1) eluted **3d**, crystallized from acetone–H_2O, mp 143–145°. Another crystallization gave the analytical sample: mp 144–145.4°; ir 2.80, 5.85, 7.92, 9.70 μ.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.07; H, 9.31.

24-Methyl-24-homocholane-12α,24-diol (3f) was prepared by a Grignard reaction with methyl 12α-hydroxycholanate under conditions similar to the preparation of **4a** (below); the crude product, an oil, was chromatographed on Al_2O_3. The column was developed with benzene and with ether; then the product (no C=O in the ir) was eluted with 4% MeOH in ether, 85% yield, and crystallized from MeOH–H_2O, mp 65–70°. Crystallization from MeOH–H_2O gave the analytical sample: mp 68–70°; ir 2.9, 8.7, 9.7 μ.

Anal. Calcd for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87. Found: C, 79.56; H, 11.57.

20-Methyl-5β-pregna-3-ene-12α,20-diol (4a).—A solution of 3.16 g (10 mmol) of 5β-pregna-3-en-12α-ol-20-one[1b] in 50 ml of benzene was added slowly to a stirred solution of Grignard reagent (prepared from 28.4 g, 0.20 mol, of methy iodide and 4.88 g of Mg) in 50 ml of ether. The condenser was turned and the ether distilled out; the remaining solution was heated under reflux (benzene) for 12 hr. The cooled reaction mixture was diluted with benzene, washed with cold aqueous 25% NH_4Cl (containing a few drops of 50% H_2SO_4) and then with water, and dried over Na_2SO_4. Evaporation left a solid product, which was crystallized from methanol, 2.041 g (61.5% yield), mp 156–157°. A second crystallization from methanol gave the analytical sample: mp 173–174°; ir 2.82, 8.52, 9.29, 9.56, 9.62 μ.

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.50; H, 10.91. Found: C, 79.56; H, 10.94.

Methyl 12α-hydroxy-3-cholanate (4b) was prepared by dehydrotosylation of methyl deoxycholate 3-tosylate as described by Chang, *et al.*[26]

Kinetic Measurements by Glpc.—The steroid (0.37 mmol) was weighed diretly into a 1-ml volumetric flask. Pyridine (0.100 ml) and benzene (about 0.5 ml) were added to effect solution,[27] acetic anhydride (0.100 ml) was added to start the reaction, and the volume was quickly made up to 1 ml with benzene. The stoppered flask was kept in a drybox at room temperature (25 ± 1°) and unmeasured aliquots were withdrawn periodically with Pasteur pipets and transferred directly into methanol. Samples that had evaporated to dryness were redissolved in acetone for chromatography in a MicroTek 220 fitted with a flame ionization detector and a Disc integrator. Two or three separate injections of each aliquot were averaged. The samples were chromatographed on either a 6-ft 1% OV-17 on Chrom G column (methyl lithocholate, methyl 7α-hydroxycholanate, and methyl 7α,12α-dihydroxycholanate) or a 4-ft 3% polysulfone on Chrom Q column (methyl 12α-hydroxycholanate). Separations were satisfactory using a column temperature of 290° and a carrier gas (N_2) flow rate of 55 ml/min. Surprisingly, with methyl lithocholate the alcohol had a shorter retention time than the acetate, though with the other three the reverse was true.

For rate calculations, the value of *a* was taken as 0.370 mol/l. based on the sample of steroid weighed, and *b* was assumed to be 1.065 mol/l. based on the volume of Ac_2O pipetted. Reactions were followed to 78–87% of completion. This level was reached in 30 hr in the case of methyl 7α,12α-dihydroxycholanate; at 174 hr there was no starting material left and the product was a mixture of 71% 7-monoacetate and 29% diacetate.

Kinetic Runs by Uv.—Methyl cholate 3-*p*-nitrobenzoate (**1g**, 212 mg, 0.37 mmol) was weighed into a 1-ml volumetric flask and dissolved in about 0.6 ml of pyridine which had been dried over molecular sieve type 4A. When solution was complete, 0.10 ml (1.065 mmol) of acetic anhydride was added to start the reaction and immediately pyridine was added to the mark. The flask was stoppered tightly, swirled gently to mix the contents, and kept in a drybox at room temperature (25 ± 1°). In taking aliquots of the reaction mixture, Pasteur pipets were used to transfer about 10 μl of the solution to a test tube containing 0.2 ml of H_2O. The tube was capped, shaken briefly, and refrigerated until the next step was carried out.

Contents of the tubes were evaporated by warming in a wire rack on the hot plate, care being taken to avoid excessive heating of the residue. Drops of condensate which appeared on the walls of the tubes were removed with facial tissues, after which the tubes were dried in a vacuum desiccator. Chloroform (0.1 ml) was added to each tube and the solutions were spotted on thin layer plates coated with silica gel containing lead manganese-activated calcium silicate phosphor. The plates were developed in 4% acetic acid in $HCCl_3$ and observed in a uv view box. The two spots from each aliquot were scraped from the plate separately and transferred to volumetric flasks (chosen so as to give absorbances between 0.2 and 0.7). The flasks were filled to the mark with MeOH, and the contents were mixed and allowed to settle. A portion of each supernatant was centrifuged to ensure removal of the silical gel; a blank was prepared similarly by scraping an unused portion of the plate. Spectra exhibited a maximum at 259 mμ, whose absorbance was measured employing the absorbance at 400 mμ as a base line.

A standard curve was prepared with ten mixtures of **1g** and **1h** ranging in composition from a mole ration of **1h** to **1g** of 0.10 to 9.00. A plot of the ratio of acetate absorbance to alcohol absorbance *vs.* mole ratio gave a straight line with a slope of 1.00 (least mean squares). Consequently, the $x/(a - x)$ values in Table V are equivalent to the ratio of acetate absorbance to alcohol absorbance (corrected for dilution to 50 ml).

During the acetylation, beginning with 5 hr three spots appeared on the thin layer plates. The fastest moving spot was found to have the same R_f as an authentic sample of the 7,12-diacetate (**1i**). It was assumed to arise from the 7-monoacetate (**1h**); consequently both spots were measured together representing total 7-acetate.

A duplicate run to that in Table V gave an average *k* of 0.115 ± 0.016 M^{-1} hr^{-1}.

Registry No.—**1b**, 28050-19-3; **1c**, 28192-77-0; **1d**, 28192-78-1; **1g**, 28192-79-2; **1h**, 28192-80-5; **1i**, 28192-81-6; **2a**, 2574-55-2; **2b**, 663-39-8; **2c**, 28192-84-9; **2c** acetate, 1624-79-9; **2d**, 28192-86-1; **2d** acetate, 28192-87-2; **2e**, 7253-33-0; **2e** 6-acetate, 28192-89-4; **3d**, 28192-90-7; **3f**, 28192-91-8; **4a**, 28192-92-9; methyl 7α-hydroxy-3α-tosyloxycholanate, 28192-93-0; methyl 7α-hydroxy-3-cholenate, 28192-94-1; methyl 3β,7α-diacetoxy-12α-hydroxycholanate, 28192-95-2; 17α-ethynyl-5-androstene-3β,17β-diol 3-tosylate, 28192-96-3.

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[24] R. Grand and T. Reichstein, *Helv. Chim. Acta*, **28**, 347 (1945).

[25] T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, 162, 521 (1946).

[26] F. C. Chang, A. Feldstein, J. R. Gray, G. S. McCaleb, and C. H. Sprunt, *J. Amer. Chem. Soc.*, **79**, 2167 (1957).

[27] In the case of methyl 7α,12α-dihydroxycholanate it was necessary to raise the proportion of pyridine to 0.3 ml (replacing benzene) to keep it in solution, but this change is believed to have no significant influence on the rate.

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Studies of the Synthesis of the B, C, and D Rings of Gibberellic Acid[1]

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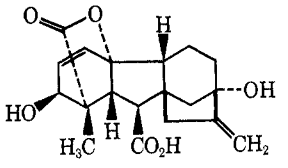
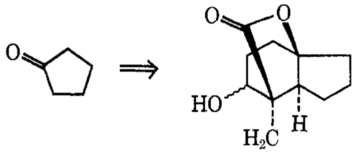
Cyclopentenones **3** and **7** have been condensed with butadiene to give the tetrahydroindene **4** and tetrahydro-1-indanone **8** derivatives, respectively. The tetrahydroindene **4** results from condensation on the enolic double bond of the enol form of **3** and is of no use for the synthesis of gibberellic acid. The tetrahydro-1-indanone **8** was saponified and subjected to iodolactonization to give iodolactone **10**. Removal of the iodine gave keto lactone **16** which was condensed with the anion of dimethyl sulfone to give the β-keto sulfone **17**. Oxidation of **17** afforded the triketone **18** which cyclized smoothly with base to give the tricyclic sulfone **19** possessing the skeleton of the B, C, and D rings of gibberellic acid. Attempts to remove the extraneous D ring keto group from sulfone met with failure. An alternative elaboration of **17** was carried out. The extraneous keto group of the β-keto sulfone moiety was removed by a six-step sequence to give the diketo sulfone **29**. However, cyclization of **29** failed to give tricyclic material and the corresponding methyl ester, **32**, cyclized to an undesired β-keto sulfone **33**.

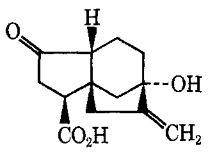
The total synthesis of the gibberellins has attracted a great deal of attention in the past several years. In considering the problem, it is attractive to construct the A ring in the final stages of the synthesis because of its great chemical sensitivity. Our earlier model studies provided an attractive approach for assembling the A ring as illustrated by the elaboration of cyclopentanone into the AB ring system of gibberellic acid.[5]



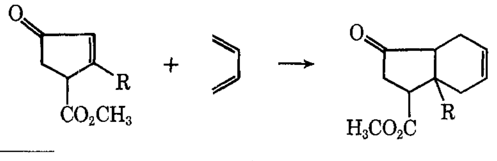
gibberellic acid

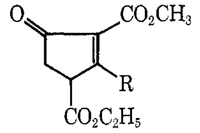


Therefore, our synthetic target is the tricyclic compound **1**.[6] Our general approach to this problem is to begin with a substituted cyclopentenone and generate the BC rings by means of a Diels–Alder reaction. Our first effort involved the condensation of cyclopentenone **2** with 2-methoxybutadiene, a reaction which gives a monocyclic product.[7] In a further attempt, the condensation of butadiene with the more easily obtained cyclopentenone **3** was examined. A simple adduct was obtained in good yields, but the material proved to have structure **4** rather than the expected structure **5**. This result appears to be another manifestation of the enolic character of **2** and **3**.

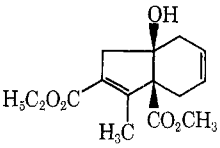


1

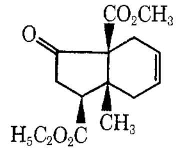




2, $R = CH_2CH_2CN$
3, $R = CH_3$



4



5

The structure follows from both spectroscopic examination and chemical transformations. The ultraviolet spectrum shows λ_{max}^{EtOH} 231 nm (ϵ 6550) as found for similar compounds.[7] The infrared spectrum shows hydroxyl absorption, and the material did not form a 2,4-dinitrophenylhydrazone. The pmr spectrum shows the methyl group as a triplet (J = 2 Hz) owing to homoallylic coupling as previously observed in related compounds.[7] Saponification affords the corresponding dibasic acid and catalytic hydrogenation readily reduces the disubstituted double bond. Reduction of the dihydro derivative with potassium in liquid ammonia affords the saturated dibasic acid. Treatment of **4** with a

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[3] National Institutes of Health Postdoctoral Fellow, Fellowship 1-F2-GM-39,115-01.

[4] NDEA Predoctoral Fellow, 1966–1969.

[5] L. J. Dolby and R. J. Milligan, *J. Amer. Chem. Soc.*, **88**, 4536 (1966).

[6] All asymmetric synthetic products described are racemic mixtures. Only one enantiomorph for each is drawn for convenience of representation and discussion. Nomenclature is for the enantiomorph indicated.

[7] L. J. Dolby, C. A. Elliger, S. Esfandiari, and K. S. Marshall, *J. Org. Chem.*, **33**, 4508 (1968).