since 64% phenacyltriphenylphosphonium chloride is formed and no triphenylphosphine is left, but diphenylphosphine is left.

Attempts to Derivatize Bromo- or Chlorodiphenylphosphine from Dehalogenation Reactions.—Reaction of two equivalents of DPP with one equivalent of **1** led to acetophenone and diphenylphosphinic acid but no tetraphenyldiphosphine or the corresponding dioxide.[11b] In other experiments involving either bromodiphenylphosphine (from **1**) or chlorodiphenylphosphine (from **4**), addition of aniline or *t*-butylamine led to mixtures possibly containing anilino- or *t*-butylaminodiphenylphosphine. The products could not be purified to analytical purity and these experiments were abandoned.

The Reactions of α-Mesyloxy Ketones and Other Ketones with Diphenylphosphine.—The following serves as a general procedure with minor variations and other data given in Table IV. A mixture of α-mesyloxyacetophenone and DPP (0.0233 mol each) was heated at reflux in benzene for 240 hr under nitrogen and then left exposed to the air for 72 hr. Diphenylphosphinic acid, mp 193.0–196.0°, was removed by filtration and the residual solution was chromatographed through silica gel (20 g). Elution with benzene gave acetophenone (1.21 g, 0.0101 mol, 43%): ir (CH_2Cl_2) and nmr ($CDCl_3$) identical with a genuine sample's.

1-Hydroxy-1-diphenylphosphinoxy-2-mesyloxycyclohexane.—A mixture of α-mesyloxycyclohexanone (2.0 g, 0.010 mol) and DPP (2.32 g, 0.0125 mol) in benzene (5 ml) was stirred at room temperature for 168 hr. After removal of the solvent *in vacuo*, the resultant solid was dissolved in CH_2Cl_2 (25 ml) and washed with 5 *N* NaOH. The organic layer was dried and evaporated *in vacuo* to give 1-hydroxy-1-diphenylphosphinoxy-2-mesyloxycyclohexane (3.41 g, 0.00855 mol, 83.5%) after recrystallization from $CHCl_3$ (25 ml)–CH_3OH (3 drops): mp 147–148°; ir (CH_2Cl_2) 3.1–3.8 (broad), 7.3–7.7 (mesylate), 8.3–8.8 (mesylate), 10.2, 10.4, 10.7 μ.

Anal. Calcd for $C_{19}H_{23}O_5SP$: C, 57.85; H, 5.87; P, 7.85. Found: C, 57.60; H, 5.82; P, 7.93.

Registry No.—DPP, 829-85-6; **15**, 20187-69-3; **16**, 20187-70-6; **17**, 20187-71-7.

Acknowledgment.—We are indebted to Professors Donald and Dorothy Denney for ^{31}P nmr data and to Dr. Karl Untch, then at Mellon Institute, for mass spectral data. We wish to thank the National Science Foundation for grants towards the purchase of the Varian time averaging computer (at Yeshiva) and a Varian A-60 nmr spectrometer (at Lehigh).

Nor Steroids. VIII. Partial Synthesis and Chemical Studies of A-Nor Bile Acids[1,2]

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Methyl 3-keto-A-norcholanate (**6**) was reduced with several reagents to give the 3α- and 3β-hydroxy-A-nor compounds, with the former isomer predominating. The structural assignments were made on the basis of the nmr spectra and comparison with known model compounds. Similar studies were made with methyl 3,12-diketo-A-norcholanate (**12a**) to give A-nordeoxycholic acids. The benzilic acid rearrangement of methyl 3-hydroxy-4-keto-12α-acetoxy-5α-chol-2-enate (**16**) and lead tetraacetate cleavage of the product gave methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**).

Despite a considerable amount of interest in recent years in the partial synthesis of ring-nor steroids and their biological activity, little work has been reported in the bile acid series. Many years ago Windaus[4] pyrolyzed 2,3- and 3,4-secocholanic acid dioic acid to 2-keto- and 3-keto-A-norcholanic acid, respectively. He also[5] prepared 2,6-diketo-A-norcholanic acid by the pyrolysis of 2,3-seco-6-ketocholane-2,3,24-trioic acid. Wieland[6] obtained 2,12-diketo-A-norcholanic acid and 3,12-diketo-A-norcholanic acid by pyrolysis of the corresponding secodeoxycholic acids. No reports could be found of the reduction of any of these keto compounds to the corresponding A-nor bile acids. The present work was undertaken to accomplish this and to explore further the chemistry of the A-nor compounds.

In order to gain some understanding of the stereochemical behavior of several common reducing agents toward the cholanic acid molecule, lithium aluminum hydride and sodium borohydride were used to reduce the 3-carbonyl group of 3-ketocholanic acid (**1**) in the six-membered A-ring series. Lithium aluminum hydride gave 12% of 3β-hydroxycholan-24-ol (**2**)[7] and 88% of 3α-hydroxycholan-24-ol (**3**),[8] both previously prepared by different routes. Sodium borohydride gave, after esterification of the reduction product, 10% of methyl 3β-hydroxycholanate (**4**) and 90% of methyl 3α-hydroxycholanate (**5**). (The above percentages are relative figures, not yields.) The upper, or β side of the molecule must therefore be less hindered, allowing easier approach of the hydride to the carbonyl group.

Methyl 3-keto-A-norcholanate (**6**) was studied next. It is interesting to note that the A-nor ketone has a deshielding effect on the C-19 methyl protons, δ 1.16, compared to the six-membered keto compound, δ 1.03. Reduction of the A-nor ketone with sodium borohydride gave 75% of the 3α-hydroxy compound **7a** and 25% of the 3β isomer **8a**. Reduction with lithium aluminum hydride gave a ratio of 54% of 3α-hydroxy-A-norcholan-24-ol (**9**) to 46% of 3β-hydroxy-A-norcholan-24-ol (**10**). Reduction with lithium borohydride gave a ratio of 62% of the 3α-hydroxy compound **7a** and 38% of the 3β compound **8a**. Reduction with lithium in liquid ammonia gave a ratio of 51% of the 3α-hydroxy compound **7a** and 49% of the 3β compound **8a**.

(1) For the previous paper in the series, see H. R. Nace and G. A. Crosby, *J. Org. Chem.*, **33**, 834 (1968).

(2) The major portion of this research was supported by the U. S. Public Health Service under Grant AM 05249-02. Grateful acknowledgment is hereby made.

(3) Abstracted from the Ph.D. Thesis of E. M. H., Brown University, 1966.

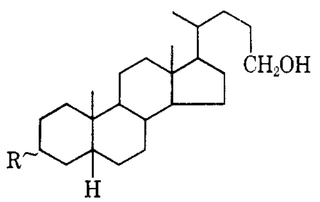
(4) A. Windaus, A. Bohne, and E. Schwartzkopf, *Z. Physiol. Chem.*, **140**, 177 (1924).

(5) A. Windaus and A. Bohne, *Ann.*, **442**, 7 (1925).

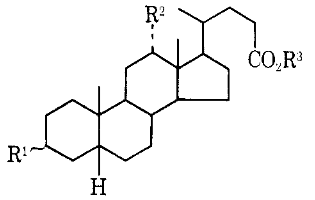
(6) H. Wieland and A. Kuhlenkampff, *Z. Physiol. Chem.*, **108**, 295 (1919).

(7) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2729 (1958).

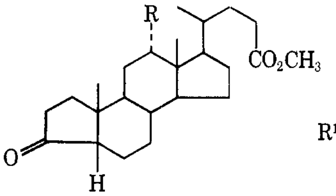
(8) L. F. Fieser and S. Rajagopalan, *ibid.*, **73**, 122 (1951).



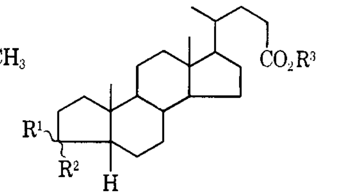
2, R = —OH
3, R = ···OH



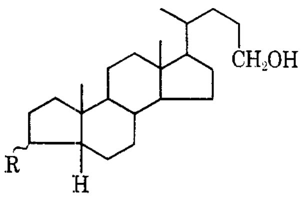
4, R^1 = —OH; R^2 = H; R^3 = CH_3
5, R^1 = ···OH; R^2 = H; R^3 = CH_3
11, R^1 = R^2 = ···OH; R^3 = H



6, R = H
15a, R = OH
15b, R = OAc

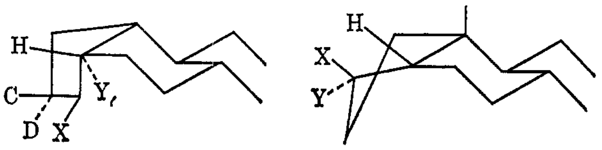


7a, R^1 = ···OH; R^2 = —H; R^3 = CH_3
b, R^1 = ···OH; R^2 = —D; R^3 = CH_3
c, R^1 = ···OAc; R^2 = —H; R^3 = CH_3
d, R^1 = ···OH; R^2 = R^3 = —H
8a, R^1 = —OH; R^2 = ···H; R^3 = CH_3
b, R^1 = —OH; R^2 = ···D; R^3 = CH_3
c, R^1 = —OAc; R^2 = ···H; R^3 = CH_3
d, R^1 = —OH; R^2 = ···H; R^3 = H



9, R = ···OH
10, R = —OH

The structural assignments for the reduction products are based on the characteristics of the nmr peaks for the hydrogens on the 3-carbon atom. Although the conformational analysis of a five-membered ring *cis*-fused to a six-membered ring is not completely understood, it appears that the two envelope models, A and B, represent the most stable conformations. Model A is preferred for two reasons. First, it explains



A B

the fact that whether a substituent at position 3 is α or β has essentially no effect on the field position of the C-19 methyl hydrogens. Normally a difference of 2 cps or more in the field position of these protons is seen with inversion of conformation of a substituent at any given position of the A or B rings, owing to an electronic effect transmitted through space. Table I shows that for pairs of isomeric 3-substituted A-nor compounds the field position of the C-19 methyl hydrogens is virtually unchanged.

The fact that the conformation of a 3 substituent has no effect on the C-19 methyl hydrogens indicates that the 3 position is held remote from the methyl group,

TABLE I
FIELD POSITION OF THE C-19 METHYL HYDROGENS OF THE 3-HYDROXY-A-NOR ISOMERS

Compound	C-19 resonance, cps
Methyl 3α-hydroxy-A-norcholanate (7a)	60.0
Methyl 3β-hydroxy-A-norcholanate (8a)	61.0
Methyl 3α-hydroxy-3β-deuterio-A-norcholanate (7b)	58.5
Methyl 3β-hydroxy-3α-deuterio-A-norcholanate (8b)	59.0
Methyl 3α-acetoxy-A-norcholanate (7c)	59.0
Methyl 3β-acetoxy-A-norcholanate (8c)	59.0
3α-Hydroxy-A-norcholan-24-ol (9)	61.5
3β-Hydroxy-A-norcholan-24-ol (10)	62.5

as in model A. Model A is also preferred because Barton models show that model B involves considerable deformation, and thus strain, of ring B.

Using structure A, application of the Karplus equation[9] provides a basis for assignment of conformation of the 3-substituted A-nor isomers. Using Barton models and measuring the angles between the H–C–C^1 and C–C^1–H^1 planes, the various coupling constants shown in Table II were calculated.

TABLE II
COUPLING CONSTANTS CALCULATED WITH THE KARPLUS EQUATION FOR THE 3-HYDROXY-A-NOR-5β STRUCTURE A

	Φ_{YH}	J_{YH}	Φ_{YD}	J_{YD}	Φ_{YC}	J_{YC}
3β-OH(3α-H)	180°	11 cps	30°	6 cps	135°	7 cps
	Φ_{XH}	J_{XH}	Φ_{XD}	J_{XD}	Φ_{XC}	J_{XC}
3α-OH(3β-H)	45°	4 cps	90°	0.5 cps	15°	7.5 cps

From the coupling constants in Table II it is obvious that a 3α hydrogen is subject to larger coupling constants than a 3β hydrogen, which subtends relatively smaller dihedral angles with its neighboring hydrogens. Thus the α hydrogens (β substituted) should give broader peaks than the isomers with the β hydrogen (α substituted). Table III shows the position and shape of the 3 protons and allows assignment of structure for the various isomers.

TABLE III
FIELD POSITION AND SHAPE OF THE 3-HYDROGEN NMR PEAK OF 3-HYDROXY-A-NOR COMPOUNDS

Compd	3-Hydrogen peak Position	Shape
Methyl 3α-hydroxy-A-norcholanate (7a)	257	Sharp
Methyl 3β-hydroxy-A-norcholanate (8a)	254	Broad
Methyl 3α-acetoxy-A-norcholanate (7c)	318	Sharp
Methyl 3β-acetoxy-A-norcholanate (8c)	310	Broad
3α-Hydroxy-A-norcholan-24-ol (9)	257	Sharp
3β-Hydroxy-A-norcholan-24-ol (10)	254	Broad

Based on the above structural assignments, all of the hydride reductions of the norketone gave a preponderance of the 3α-hydroxy compound, showing that the β or upper side of the A ring offers less hindrance to approach of the hydride, as was observed for the six-membered A ring.

The deoxycholic acid series was studied next. Deoxycholic acid (11) was oxidized with nitric acid to

(9) M. Karplus and D. H. Anderson, *J. Chem. Phys.*, **30**, 6 (1959); A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, **86**, 1221 (1964).

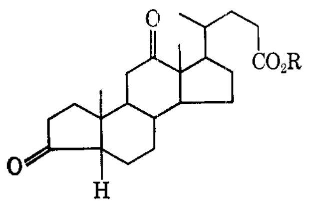
TABLE IV

NMR HYDROGEN ABSORPTIONS IN CYCLES PER SECOND OF THE ACETOXY-A-NOR COMPOUNDS[a]

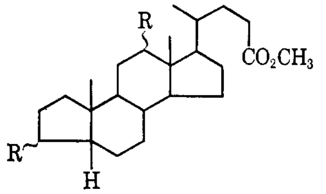
Compd	Hydrogen Configurations 3α	3β	12β
Methyl 3-keto-12α-acetoxy-A-norcholanate (**15b**)	...	...	304, sharp
Methyl-3α,12α-diacetoxy-A-norcholanate (**13b**)	...	...	305, sharp
Methyl-3α-acetoxy-A-norcholanate (**7c**)	...	318, sharp	...
Methyl 3β-acetoxy-A-norcholanate (**8c**)	310, broad	...	...
Methyl 3α,12α-diacetoxycholanate (from **11**)	...	...	305, sharp
Methyl 3-keto-12α-acetoxycholanate[b]	...	...	307, sharp

[a] Insufficient methyl 3β,12β-diacetoxy-A-norcholanate (**15b**) was available to obtain a spectrum. [b] Reference 22.

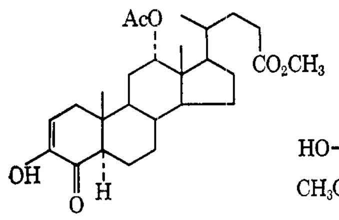
give the 12-keto-3,4-secoacid according to the procedure of Wieland and Kuhlenkampff,[6] and the seco acid was pyrolyzed to methyl 3,12-diketo-A-norcholanate (**12a**), after esterification of the pyrolysis product, in 14% yield. Again the field position of the C-19 methyl in the A-nor compound, δ 1.23, was shifted downfield from that of the C-19 methyl in methyl 3,12-diketocholanate, δ 1.12. Reduction of the 3,12-diketo-A-nor acid **12b** with excess sodium borohydride gave, after esterification, methyl 3β,12β-dihydroxy-A-norcholanate (**14a**) (6% yield), and methyl 3α,12α-dihydroxy-A-norcholanate (**13a**) (24% yield). If only one equivalent of hydride was used in the reduction, the major product, after esterification, was methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**), also formed in small amounts with excess hydride.



12a, R = CH_3
b, R = H



13a, R = ···OH
b, R = ···OAc
14a, R = —OH
b, R = —OAc



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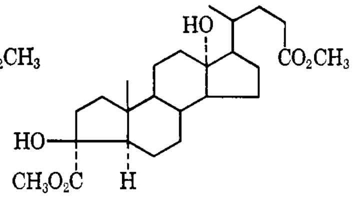

17

The structure of these three products was established in the following manner. The 3β,12β isomer **14a** showed infrared absorption at 1003 cm^{-1} and nmr absorption at 254 cps (broad). Chang, Wood, and Holton[10] in a study of the isomeric 3,12-dihydroxycholanic acids, found that only the 12β-hydroxy isomer absorbed near 1000 cm^{-1}, while the other isomers absorbed in the region 1018–1036 cm^{-1}. It has been shown above that a 3α hydrogen (3β-hydroxy) shows a broad nmr peak centered at 254 cps (Table III). The 3α,12α isomer **13a** showed infrared absorption in the 1013–1036-cm^{-1} range but none near 1000 cm^{-1}, and nmr absorption at 237 (sharp, 12β hydrogen) and 256 cps (sharp, 3β hydrogen). The 3-keto-12α-hydroxy compound **15a** showed the C-19 methyl resonance at 70 cps [*cf.* methyl 3α-hydroxy-12-ketocholanate (61.0), methyl 3,12-diketocholanate (67.0), and methyl 3-keto-A-norcholanate (69.5)], the 12β hydrogen at 239 cps, and infrared absorption at 1035 cm^{-1}, consistent with a 12α-hydroxyl group. Brown and Ichikawa[11] reported that cyclohexanone is more readily reduced with sodium borohydride than is cyclopentanone, and Dauben and Boswell[12] reported the selective reduction of the 6-keto group of A-norcoprostane-2,6-dione with sodium borohydride to give the 2-keto-6-hydroxy compounds. The formation of **15a** above is thus consistent with these results.

The above structural assignments were confirmed by examination of the nmr spectra of the acetylated compounds, Table IV.

The synthesis of A-nordeoxycholic acid derivatives *via* the benzilic acid rearrangement of methyl 3-hydroxy-4-keto-12α-acetoxy-5α-chol-2-enate (**16**) was also studied. Oxygenation[13] of an alkaline solution of methyl 3-keto-12α-acetoxycholanate and esterification of the product gave the diosphenol **16** in 22% yield. It was assigned the structure shown and not the isomeric 3-keto-4-hydroxy-4-ene structure for two reasons. The ultraviolet spectrum showed λ_{max} 277.9 mμ (ε 24,000), and application of Woodward's rules for a conjugated system[14] gave a calculated value of 280 mμ for the structure shown, and a value of 297 mμ for the isomer. In addition, the nmr spectrum showed a vinyl proton at δ 6.0, in confirmation of the structure shown, and not possible for the isomer. The hydrogen at the 5-position was assigned the α configuration because of the greater stability of an A–B *trans* ring juncture for fused six-membered rings, and the ease of isomerization in a basic medium of a 4-keto compound.

The benzilic acid rearrangement was carried out by heating the diosphenol with potassium hydroxide in aqueous *n*-butanol and esterification of the rearrangement product to give methyl 3α-carbomethoxy-3β-hydroxy-12α-hydroxy-5α-A-norcholanate (**17**) in low yield (9%), and no other products from the reaction mixture could be characterized. The structure is assigned by analogy to the same reaction in the cholestane series[15] and is based on the assumption that the hydroxide addition intermediate[16] which is formed will be most stable when it involves the minimum

(10) F. C. Chang, N. F. Wood, and W. G. Holton, *J. Org. Chem.*, **30**, 1718 (1965).

(11) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).

(12) W. G. Dauben and G. A. Boswell, *J. Amer. Chem. Soc.*, **83**, 5003 (1961).

(13) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

(14) I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 58.

(15) H. R. Nace and M. Inaba, *J. Org. Chem.*, **27**, 4024 (1962).

(16) N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959).

repulsive forces owing to 1,3-diaxial interactions and oxygen–oxygen dipoles. This assignment is also supported by the position of the C-19 methyl resonance which is roughly in the same field position as in the other 3-hydroxy-A-nor compounds, namely at 58.8 cps. If the ester group at the 3 position had the β configuration, it would be expected to have a large effect on the field position of the C-19 methyl, especially with the A–B *trans* ring fusion.

The diester **17** could not be cleaved to the A-nor-3 ketone with lead tetraacetate, but after hydrolysis the diacid was cleaved with lead tetraacetate to give, after esterification, methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**) identical in melting point and infrared spectrum with the material described above.

Experimental Section

Melting points were determined with a Hershberg apparatus and Anschutz thermometers and are corrected. Microanalyses were done by Micro-Tech of Skokie, Illinois, and Schwarzkopf Microanalytical Laboratory, Woodside, New York, Deuterium analyses were done by Dr. Josef Nemeth, University of Illinois. The analytical samples were recrystallized to constant melting point. Ir spectra were determined with a Perkin-Elmer 141 spectrometer, ORD curves with a Cary 60 polarimeter, and uv spectra with a Bausch and Lomb 505 Spectrometer. Nmr spectra were determined in $CDCl_3$ with 30–35 mg of steroid per 0.6 ml of solvent, using TMS as an internal standard, and either a Varian HF-60 or a Varian A-60 spectrometer. The authors are indebted to Dr. G. O. Dudek and Dr. H. Janjagian and to Harvard University for the use of the latter instrument.

Acknowledgment is also made to the National Science Foundation for grants to the Chemistry Department for the purchase of the ir and uv spectrometers and the ord polarimeter.

Chromatographic separations were made using Baker Chromatographic Grade silica gel and Merck chromatographic grade alumina. The alumina was deactivated before use by allowing it to stand in the open air for 3 hr. The R_f values reported for tlc are travel distances on glass plates coated with a 500-μ thickness of Merck (Darmstadt) silica gel G, and refer to travel distances relative to a 10-cm solvent path. The solvent was 2:1 benzene–ether unless indicated otherwise. A solution of 2,4-dinitrophenylhydrazine in phosphoric acid and 95% ethanol was used for development, and the plates were baked at 70–90° for further development.

Reduction of 3-Ketocholanic Acid (1). **A. With Lithium Aluminum Hydride.**—To a solution of 250 mg (0.67 mmol) of the keto acid in 100 ml of a 1:1 mixture of benzene–petroleum ether was added 2 g of lithium aluminum hydride, and the mixture was stirred for 5 hr. Then an additional 1 g of hydride was added and the mixture was stirred overnight. After the addition of 100 ml of 30% sulfuric acid, the organic layer was washed with water, 10% $NaHCO_3$ solution, and water, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 1:1 benzene–ether gave, after recrystallization from aqueous methanol, 12.3 mg (5%) of 3β-hydroxycholan-24-ol (**2**), mp 146–148°; $[\alpha]_D$ 24.2° (*c* 1.9, $CHCl_3$); ir (KBr) 3333 cm^{-1}; R_f 0.35; formed a precipitate with digitonin; nmr δ 0.66 (18-CH_3), 0.96 (19-CH_3); lit.[7] mp 150–151.5°.

Further elution with the same solvent gave, after recrystallization from aqueous methanol, 87 mg (36%) of 3α-hydroxy-cholan-24-ol (**3**), mp 175–176°; $[\alpha]_D$ 32.0° (*c* 2.2, $CHCl_3$); ir (KBr) 3333 cm^{-1}; R_f 0.2; gave no precipitate with digitonin; nmr δ 0.66 (18-CH_3), 0.93 (19-CH_3); lit.[8] mp 176–177°, $[\alpha]_D$ 44°.

Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.49; H, 11.68. Found: C, 79.37; H, 11.66.

B. With Sodium Borohydride.—To a solution of 696 mg (1.85 mmol) of the keto acid in 30 ml of absolute ethanol (made basic by the addition of 3 ml of 1 *N* NaOH) was added 20 mg (2.1 mmol) of sodium borohydride dissolved in basic ethanol, and the resulting solution was boiled under reflux overnight. Then the solution was cooled, acidified with concentrated hydrochloric acid, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated, and the residue was esterified by allowing it to stand overnight in 10% methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 10% ether–benzene gave, after recrystallization from aqueous methanol, 30.4 mg (7.8%) of methyl 3β-hydroxycholanate (**4**), mp 114–115° (lit.[17] mp 115–116°), R_f 0.6 (ether), gave a precipitate with digitonin.

Further elution with the same solvent gave, after recrystallization from aqueous methanol, 289 mg (74%) of methyl 3α-hydroxycholanate (**5**), mp 128–130°, $[\alpha]_D$ 28.3° (*c* 1.3, $CHCl_3$) [lit.[18] mp 130°, $[\alpha]_D$ 22° ($CHCl_3$)[19]], R_f 0.55 (ether), gave no precipitate with digitonin.

Methyl 3α- (7a) and 3β-Hydroxy-A-norcholanate (8a) by Sodium Borohydride Reduction of Methyl 3-Keto-A-norcholanate (6).—A solution of 270 mg (0.72 mmol) of **6** in 30 ml of ethanol was made basic with 1 *N* NaOH, a solution of 250 mg of sodium borohydride in the minimum amount of basic ethanol was added, and the resulting solution was boiled under reflux for 14 hr. Then the solution was acidified with concentrated hydrochloric acid, diluted with water, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), distilled, and the residue was esterified with 100 ml of 15% methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on alumina. Elution with 5% ether–benzene and recrystallization of the residue from aqueous MeOH gave 103 mg (38%) of methyl 3α-hydroxy-A-norcholanate (**7a**), mp 72–75°; $[\alpha]_D$ 28.0° (*c* 3.5, $CHCl_3$); ir (KBr) 3205, 1730 cm^{-1}; nmr δ 0.70 (18-CH_3), 1.00 (19-CH_3), 4.28 (sharp s, 1, 3β-H); (DMSO) 4.39 (s, 1, H on 3α-OH, disappears on the addition of D_2O); R_f 0.55

Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.83; H, 10.67.

Further elution with the same solvent gave several mixed fractions followed by methyl 3β-hydroxy-A-norcholanate (**8a**), yield 35 mg (13%) after recrystallization from aqueous MeOH; mp 84–87°; $[\alpha]_D$ 39.5° (*c* 2.7, $CHCl_3$); ir (KBr) 3200, 1730 cm^{-1}; nmr δ 0.68 (18-CH_3), 1.02 (19-CH_3), 4.23 (broad s, 1, 3α-H); (DMSO) 4.20 (s, 1, H on 3β-OH, disappears on the addition of D_2O); R_f 0.35.

Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.11; H, 10.65.

Reduction of Methyl 3-Keto-A-norcholanate (6) **with Lithium Aluminum Hydride.**—To a solution of 404 mg (1.08 mmol) of the norketone **6** in 200 ml of absolute ether was added 1 g of lithium aluminum hydride and the solution was boiled under reflux for 3 hr. Then 40 ml of 30% H_2SO_4 solution was added and the ether layer was removed, washed with water, $NaHCO_3$ solution, and water, dried ($MgSO_4$) and evaporated to give an oil. This was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 25% ether–benzene gave, after recrystallization from aqueous methanol, 174 mg (46%) of 3α-hydroxy-A-norcholan-24-ol (**9**), mp 155–157°; $[\alpha]_D$ 18° (*c* 2.0, $CHCl_3$); ir (KBr) 3257 cm^{-1}; R_f 0.25; nmr δ 0.70 (18-CH_3), 0.99 (19-CH_3), 4.30 (sharp s, 3β-H).

Anal. Calcd for $C_{23}H_{40}O_2$: C, 79.25; H, 11.57. Found: C, 79.45; H, 11.67.

Further elution with the same solvent gave, after recrystallization from aqueous methanol, 146 mg (39%) of 3β-hydroxy-A-norcholan-24-ol (**10**), mp 185–186°; $[\alpha]_D$ 52° (*c* 1.8, $CHCl_3$); ir (KBr) 3225 cm^{-1}; R_f 0.15; nmr δ 0.70 (18-CH_3), 1.00 (19-CH_3), 4.25 (broad s, 3α-H).

When the reduction was carried out at room temperature for only 5 min, tlc analysis showed the presence of starting keto ester **6**, 3α-, and 3β-hydroxy-A-nor esters **7a** and **8a**, and no cholan-24-ols.

Reduction of the Keto Ester 6 with Lithium Aluminum Deuteride.—To an ether solution of 1.0 g (2.67 mmol) of the keto ester **6** was added 198 mg of lithium aluminum deuteride. After 1 min of stirring, 100 ml of 10% hydrochloric acid was added and the ether layer was removed, washed with 10% Na_2CO_3 solution, and water, dried ($MgSO_4$), evaporated, and the residue taken up in benzene and chromatographed on 60 g of alumina. Elution with benzene gave 20 mg of starting material, 42 mg of mixed material, and then, after recrystallization from aqueous methanol, 281 mg (28%) of methyl 3α-hydroxy-3β-deuterio-A-norcholanate

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(**7b**), mp 84–85°; [α] D 9.9° (*c* 2.1, $CHCl_3$); ir (KBr) 3300, 2150, 1748 cm^{-1}; R_f 0.5; nmr δ 0.68 (18-CH_3), 0.98 (19-CH_3).

Anal. Calcd for $C_{24}H_{39}O_3D$: 2.50 atom % deuterium. Found: 2.48 atom % deuterium.

We are unable to explain the differences in melting point and [α] D between the deuterated and undeuterated material.

Further elution with benzene gave 387 mg of mixed material, and then, after recrystallization from aqueous methanol, 61 mg (6%) of methyl 3β-hydroxy-3α-deuterio-A-norcholanate (**8b**), mp 85–86°; [α] D 46° (*c* 1.8, $CHCl_3$); ir (KBr) 3400, 2150, 1745 cm^{-1}; R_f 0.3; nmr δ 0.66 (18-CH_3), 0.98 (19-CH_3).

Anal. Calcd for $C_{24}H_{39}O_3D$: 2.50 atom % deuterium. Found: 2.03 atom % deuterium.

Reduction of the Keto Ester 6 with Lithium Borohydride.—To a solution of 1.0 g (2.67 mmol) of the keto ester in 500 ml of ether was added 114 mg of lithium borohydride. After 1 min of stirring, 100 ml of 10% hydrochloric acid was added and the ether layer was removed, washed with water, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on 60 g of alumina. Elution with benzene gave 133 mg of starting material, 35 mg of mixed material, and then, after recrystallization from aqueous methanol, 341 mg (34%) of the α-hydroxy-A-nor ester **7a**, mp 84–85°; [α] D 28° (*c* 3.2, $CHCl_3$); R_f 0.55.

Further elution with benzene gave 154 mg of mixed material, and then, after recrystallization from aqueous methanol, 213 mg (21%) of the 3β-hydroxy-A-norester **8a**, mp 84–85°; [α] D 39.5° (*c* 2.5, $CHCl_3$); R_f 0.35.

Reduction of 3-Keto-A-norcholanic Acid with Lithium–Ammonia.—To a solution of 300 mg (0.83 mmol) of the nor acid (from **6**) in 12 ml of anhydrous ether, 6 ml of anhydrous methanol, and 50 ml of ammonia was added 1 g of lithium over a period of 30 min. The mixture was stirred under reflux for 15 min, the ammonia was then allowed to evaporate, and water was added. The mixture was acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water, dried ($MgSO_4$), evaporated, and the residue was esterified by boiling under reflux for 3 hr with 15% methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on 20 g of silica gel. Elution with benzene gave 50 mg of methylated starting material. Elution with 10% ether–benzene gave 132 mg (43%) of the 3α-hydroxy ester **7a**, followed by 124 mg (40%) of the 3β-hydroxy ester **8a**.

3α-Hydroxy-A-norcholanic Acid (7d).—A solution of 450 mg (1.2 mmol) of the 3α-hydroxy-A-nor ester **7a** in methanolic potassium hydroxide was allowed to stand overnight. Then acidification with hydrochloric acid gave 411 mg of the 3α-hydroxy acid **7d**, mp 135–137°; [α] D 27.0° (*c* 2.7, MeOH); ir (KBr) 1709 cm^{-1}; R_f 0.0.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.56. Found: C, 75.53; H, 10.30.

3β-Hydroxy-A-norcholanic Acid (8d).—Treatment as above of 100 mg (0.265 mmol) of the 3β-hydroxy-A-norester **8a** gave 89 mg of the 3β-hydroxy acid **8d**, mp 223–224°; [α]D 42° (*c* 1.2, MeOH); ir (KBr) 1709 cm^{-1}; R_f 0.0.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.56. Found: C, 75.22; H, 10.35.

A satisfactory analysis could not be obtained for this compound.

Methyl 3α-Acetoxy-A-norcholanate (7c).—A solution of 200 mg (0.53 mmol) of the 3α-hydroxy ester **7a** in 10 ml of acetic anhydride and 10 ml of anhydrous pyridine was boiled under reflux for 3 hr, cooled, diluted with water, and extracted with ether. The extract was washed with water, 10% sodium carbonate solution, and water, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on 20 g of alumina to give 117 mg of colorless oil which crystallized on standing neat in a refrigerator. Recrystallization from aqueous methanol gave the 3α-acetoxy-A-nor ester **7c**, mp 59–60°; [α]D 20° (*c* 1.6, $CHCl_3$); ir (KBr) 1745, 1730 cm^{-1}; R_f 0.7; nmr δ 0.68 (18-CH_3), 0.98 (19-CH_3), 5.30 (sharp s, 3β-H).

Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.61; H, 10.09.

Methyl 3β-Acetoxy-A-norcholanate (8c).—Treatment of the 3β-hydroxy ester **8a** as above gave the 3β-acetoxy-A-nor ester **8c**, mp 63–65°; [α] D 61° (*c* 0.8, $CHCl_3$); ir (KBr) 1745, 1740 cm^{-1}; R_f 0.7; nmr δ 0.65 (18-CH_3), 0.98 (19-CH_3), 5.17 (broad, 3α-H).

Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.64; H, 10.04.

Methyl 3,12-Diketo-A-norcholanate (12a).—Deoxycholic acid (**11**) (2.0 g, 5.1 mmol) was added to nitric acid in portions while the temperature was kept below 50° by ice-bath cooling. After the violent fuming stopped, water was added and the resulting precipitate was collected, yield 1.2 g. A 1.14-g sample of this material was heated in a sublimer at 290° (0.6 mm) to give 730 mg of material which was esterified by boiling under reflux for 3 hr with 15% methanolic HCl. Tlc of the product showed three spots, R_f 0.9, 0.5, and 0.45. The material was taken up in benzene and chromatographed on 60 g of alumina. Elution with benzene gave 22 mg of oil, R_f 0.8, whose ir spectrum showed unsaturation. Elution with 5% ether–benzene gave, after recrystallization from aqueous methanol, 261 mg (14%) of the 3,12-diketo-A-nor ester **12a** mp 143–145° (lit.[6] mp 149°); [α] D 180° (*c* 3.6, $CHCl_3$); ir (KBr) 1740, 1700 cm^{-1}; R_f 0.5; nmr δ 1.03 (18-CH_3), 1.23 (19-CH_3) [For methyl 3,12-diketocholanate, nmr δ 1.07 (18-CH_3), 1.12 (19-CH_3).]; ORD (*c* 0.9, MeOH) $[\Phi]_{450}$ 5.5°, $[\Phi]_{320}$ 151.6°, $[\Phi]_{309}$ 162.6°, $[\Phi]_{272}$ −93.4°, $[\Phi]_{250}$ −22.0°.

3,12-Diketo-A-norcholanic Acid (12b).—A solution of 500 mg (1.28 mmol) of the 3,12-diketo ester **12a** in 200 ml of methanol and 10 ml of 1 *N* methanolic KOH was boiled under reflux for 2 hr, then neutralized with hydrochloric acid, diluted with water, and the resulting precipitate collected and recrystallized from aqueous methanol. The 3,12-diketo acid **12b** had mp 170–175°; [α] D 167.8° (*c* 2.2, MeOH); R_f 0.0 (lit.[6] mp 197–198°). Despite repeated recrystallizations, the melting point could not be raised.

Reduction of 3,12-Diketo-A-norcholanic Acid (12b) with Sodium Borohydride.—To a solution of 1.2 g (3.2 mmol) of the acid in 100 ml of anhydrous methanol was added slowly 1 g of sodium borohydride, and then the solution was boiled under reflux for 1 hr. After cooling and acidification with dilute hydrochloric acid, the solution was extracted with ether and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was esterified by boiling under reflux for 1 hr with 15% methanolic HCl. After removal of the solvent the residue was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 5% ether–benzene gave 122 mg of unsaturated materials, R_f 0.65 and 0.6. Elution with 15% ether–benzene gave 75 mg (6%) of methyl 3β,12β-dihydroxy-A-norcholanate (**14a**) mp after recrystallization from aqueous methanol, 128–130°; [α] D 27.6° (*c* 1.0, MeOH); ir (KBr) 3400, 3350, 1735 cm^{-1}; R_f 0.3; nmr δ 0.77 (18-CH_3), 1.08 (19-CH_3), 4.32 (broad, 3α-H).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.19.

Further elution with the same solvent gave some mixed material, followed by 300 mg (24%) of methyl 3α,12α-dihydroxy-A-norcholanate (**13a**), mp after recrystallization from aqueous methanol, 145–147°; [α] D 37.8° (*c* 0.9, MeOH); R_f 0.1; nmr δ 0.77 (18-CH_3), 1.00 (19-CH_3), 3.95 (sharp, 12β-H), 4.27 (sharp, 3β-H).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.23.

It was found that if the reduction was carried out with only one equivalent of borohydride, the major product was methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**), mp after recrystallization from aqueous methanol, 169–170°; [α] D 145° (*c* 0.7, MeOH); ir (KBr) 1740, 1710 cm^{-1}; R_f 0.2; nmr δ 0.75 (18-CH_3), 1.17 (19-CH_3), 3.98 (sharp, 12β-H).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.36; H, 9.94.

Methyl 3α,12α-Diacetoxy-A-norcholanate (13b).—A solution of 90.5 mg of the dihydroxyester **13a** in 10 ml of acetic anhydride and 10 ml of anhydrous pyridine was boiled under reflux for 3 hr, cooled, poured into water, and extracted with ether. The extract was washed with water and 10% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on silica gel to give, after recrystallization from aqueous methanol, 39.5 mg of the diacetoxy compound **13b**, mp 109–110°; [α] D 82.6° (*c* 1.2, $CHCl_3$); ir (KBr) 1735 cm^{-1}; nmr δ 0.77 (18-CH_3), 0.98 (19-CH_3), 5.28 (sharp, 3β-H).

Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.36; H, 9.34.

Similar treatment of the 3-keto-12α-hydroxy ester **15a** also gave an oil which could not be recrystallized, but which was homogeneous to tlc, R_f 0.3; nmr δ 0.78 (18-CH_3), 1.00 (19-CH_3), 5.16 (12β-H).

Methyl 3α-Hydroxy-12-ketocholanate.—A solution of 700 mg (1.86 mmol) of 3α-hydroxy-12-ketocholanic acid[20] in 15% methanolic HCl was allowed to stand overnight, then the solvent was

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removed and the residue was recrystallized from aqueous methanol to give 250 mg (34%) of the ester, mp 114–116°; $[\alpha]_D$ 95.6° (c 2.8 MeOH) (lit. mp 110–111°; $[\alpha]_D$ 96.5°);[21] ir (KBr) 1735, 1700 cm^{-1}; R_f 0–0.1; nmr δ 1.02 (18- and 19-CH_3), 2.29 (broad, 3β-H); ORD (c 1.12, MeOH) $[\Phi]_{400}$ 133°, $[\Phi]_{350}$ 223°, $[\Phi]_{304}$ 580°, $[\Phi]_{255}$ 223°, $[\Phi]_{230}$ 534°.

Methyl 3-Hydroxy-4-keto-12α-acetoxy-5α-chol-2-enate (16).—To a solution of 447 mg (1.0 mmol) of methyl 3-keto-12α-acetoxy cholanate[22] in 100 ml of t-butyl alcohol (freshly distilled from calcium hydride) was added a solution of 1.12 g (10.0 mmol) of potassium t-butoxide in 80 ml of t-butyl alcohol. The resulting solution was stirred under 1 atm of oxygen until 11.2 ml (1.0 mmol) had been taken up, then it was acidified with hydrochloric acid, diluted with water, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), evaporated, and the residue was esterified by boiling under reflux for 3 hr in a 15% solution of methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on 20 g of silica gel. Elution with 5% ether–benzene gave the diosphenol **16** which was recrystallized from aqueous methanol to give 100 mg (22%), mp 160–162°; $[\alpha]_D$ 111° (c 3.9, MeOH); ir (KBr) 1730, 1725, 1660, 1625 cm^{-1}; R_f 0.45; uv λ_{max} (MeOH) 277.9 mμ (ε 24,000); nmr δ 1.96 (12-$OCOCH_3$), 5.08 (12β-H), 6.00 (t, 2-H).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 69.75; H, 8.78.

Methyl 3α-Carbomethoxy-3β,12α-dihydroxy-A-nor-5α-cholanate (17).—To a solution of 1.95 g (4.2 mmol) of the diosphenol **16** in 100 ml of n-butyl alcohol was added a solution of 14 g of KOH and 10 ml of water, and the resulting solution was boiled under reflux for 3 days. After acidification with hydrochloric acid and dilution with water, the reaction mixture was extracted with ether and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was esterified by boiling under reflux for 3 hr with 15% methanolic HCl, the solvent was evaporated, and the residue was taken up in benzene and chromatographed on silica gel. Benzene eluted an oil which was crystallized from aqueous methanol to give 178 mg (9.4%) of the A-norhydroxy ester **17**, mp 53–54°; $[\alpha]_D$ 36° (c 1.7, MeOH); ir (KBr) 1730, 1720, 1018–1036 cm^{-1}; nmr δ 0.98 (19-CH_3), 3.58, 3.68 ($OCOCH_3$), 3.95 (12β-H).

Anal. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 70.33; H, 9.51.

Methyl 3-Keto-12α-hydroxy-A-norcholanate (15a).—The diester **17**, 86 mg, was first hydrolyzed to the dihydroxy diacid in quantitative yield by warming in a solution of methanolic potassium hydroxide. Acidification with hydrochloric acid and dilution with water gave the crystalline diacid, mp 96–98°, which was dissolved in 5 ml of acetic acid and 2 ml of acetic anhydride. Lead oxide (Pb_3O_4), 287 mg, was added and the mixture was warmed on a steam bath until the red color disappeared, stirred overnight, diluted with water, and extracted with ether. The extract was washed with water, several times with 10% $NaHCO_3$ solution, and water, dried ($MgSO_4$), and evaporated. The residue was esterified by boiling under reflux for 3 hr with 15% methanolic HCl. Removal of the solvent and recrystallization of the residue gave 30 mg of the 3-keto-A-nor ester **15a**, identical in melting point and ir spectrum with the material described above.

The oxidation did not take place if the diester was used instead of the hydrolyzed material.

Registry No.—**2**, 20414-15-7; **3**, 20414-16-8; **6**, 20445-42-5; **7a**, 20414-17-9; **7b**, 20414-18-0; **7c**, 20414-19-1; **7d**, 20414-20-4; **8a**, 20414-21-5; **8b**, 20414-22-6; **8c**, 20414-23-7; **8d**, 20414-24-8; **9**, 20445-43-6; **10**, 20445-44-7; **13a**, 20414-25-9; **13b**, 20414-26-0; **14a**, 20414-27-1; **15a**, 20414-28-2; **16**, 20414-29-3; **17**, 20414-30-6.

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Further Stereochemical Studies of the Catalytic Reduction of $\Delta^{1,4}$-3-Keto Steroids with Tritium[1a]

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The stereochemical distribution of label resulting from reduction of $\Delta^{1,4}$-steroids at C-1,2 with tritium gas using palladium-charcoal was studied. The tritium distribution at C-1 in 11β-hydroxyandrost-4-ene-3,17-dione and 11β,17,21-trihydroxypregn-4-ene-3,20-dione (cortisol) obtained from the corresponding Δ^1 compounds was analyzed using stereospecific chemical and enzymatic reactions. The distribution was found to be 76% β and 24% α. This is in general agreement with results obtained previously after reduction of a compound without an 11β-hydroxyl group. Analysis of testosterone-1,2-t using the C-1,2-dehydrogenase of *B. sphaericus* and the ring A aromatase (estrogen forming) enzyme system from human placenta indicated that the tritium distribution at C-2 was in a ratio of 1.4:1 (β:α), considerably less than that at C-1, 3.4:1 (β:α). A mechanism of reduction involving 1,4 addition to the enone system is discussed. The results are in agreement with our previous finding that estrogen formation in placenta involves *cis* elimination at C-1,2 (1β,2β).

Catalytic reduction of carbon–carbon double bonds with carrier-free tritium gas is a facile method for preparing pure radioactive compounds of high specific activity at relatively low cost. However, the distribution and orientation of tritium in the product is often not apparent. Owing to the instability of highly tritiated molecules and the dangers of contamination, physical measurements used for deuterated compounds are not made routinely on tritiated species. Instead, stereospecific reactions with diluted material and extrapolation of results obtained with deuterium often are used to determine the position labeled.[2] In previous publications, methods were discussed which enabled us to determine the distribution of tritium at positions 1,[3] 6, 7,[4,5] 11, and 12[6,7] of the steroid nucleus. The study of

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