lenyl isoamyl ketone as 4 g. of sirup, dried two hours under high vacuum; $[\alpha]^{25}D$ +49° (216 mg. made up to 10 ml. with chloroform gave α +2.15°; l = 2 dm.).

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.04; H, 10.42.

This substance showed no luteoid activity in 25 mg. dose.[8]

3-Acetoxy-5-ternorcholenyl Mesityl Ketone.—To a Grignard solution made from 3 g. of magnesium, 28 g. of bromomesitylene and 60 ml. of ether was added 11 g. of dried cadmium chloride powder; then, after thirty minutes, a toluene solution of 6 g. of acetoxy-bisnorcholenic acid chloride was added. After stirring for one hour at room temperature then twenty hours in an oil-bath at 110° (the ether being distilled), the product was hydrolyzed, steam distilled and extracted with ether in the usual manner. Crystallization of the product from ether gave 3.3 g. of white crystals (m. p. 140–150°) plus several grams of brown sirup. Recrystallization from acetone gave the mesityl ketone as white needles, m. p. 169–170°; $[\alpha]^{29}D$ −54° (51.7 mg. made up to 6 ml. with chloroform gave α − 0.47°; l = 1 dm.).

Anal. Calcd. for $C_{33}H_{46}O_3$: C, 80.77; H, 9.45. Found: C, 80.31; H, 9.46.

When the mesityl ketone is melted then cooled, the melt displays a transient blue fluorescence while crystallizing. Solutions of the crystals and of the melt are colorless and non-fluorescent.

The same mesityl ketone has been obtained in 40% yield by the action of ten equivalents of mesitylmagnesium bromide on 3-acetoxybisnorcholenic acid chloride followed by acetylation of the product. That is, the Grignard reaction stops at the ketone stage. The reaction yields sirupy by-products, part of which results from the action of the Grignard reagent on the acetoxy group.

3-Hydroxy-5-ternorcholenyl Mesityl Ketone.—One gram of the acetate was hydrolyzed with 1 g. of sodium carbonate, 5 ml. of water and 80 ml. of methanol by refluxing for four hours. Crystallizing the product from acetone gave white needles, m. p. 211–212°; $[\alpha]^{28}D$ −62° (39.7 mg. made up to 6 ml. with chloroform gave α −0.41°; l = dm.).

Anal. Calcd. for $C_{31}H_{22}O_2$: C, 82.98; H, 9.88. Found: C, 83.34; H, 9.93.

Warming with acetic anhydride converted the hydroxy ketone into the original acetate, m. p. 169–170°.

Attempts to Prepare Enol-Esters of the Mesityl Ketone.—The acetoxy ketone was recovered unchanged after one hour in boiling acetic anhydride and after five hours of refluxing with acetic anhydride–sodium acetate mixture, hence it is not a stable enol such as described by Fuson, Corse and McKeever.[16]

To a solution of 0.09 mole of ethylmagnesium bromide in 60 ml. of ether was added an ether solution of 1.3 g. of the acetoxyternorcholenyl mesityl ketone. No gas or precipitate was formed. After ten hours of gentle refluxing, the solution was cooled in an ice-bath, then 12 g. of benzoyl chloride was added in portions and allowed to stand for six hours. The washed neutral product was concentrated under vacuum to a wax, which crystallized slowly from ethanol, yielding 0.6 g., m. p. 154–156°. The analysis indicates that only the **3-mono-benzoate** of the hydroxy ketone was formed.

Anal. Calcd. for $C_{38}H_{48}O_3$: C, 82.41; H, 8.74. Found: C, 82.70; H, 8.60.

Summary

1. The behavior of certain stereoisomeric steroids differing in configuration at C_{20} has been studied.

2. The 22-keto-steroids derived from 3-acetoxy-5-bisnorcholenic acid, selected as starting material for this study, have been obtained in stereoisomeric forms. The interconversion of these isomers by alkali demonstrates the mobility of the hydrogen atom at C_{20} and poses the question as to the configuration of the natural steroids at this position.

3. The carbonyl group at C_{22} is sufficiently hindered by the bulky ternorcholenyl group that the isoamyl and phenyl ketones do not react with ketone reagents. The methyl ketone shows normal reactivity, but the ethyl ketone reacts only sluggishly with semicarbazide.

4. Several homologs of progesterone are described and shown to have no progestational activity.

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(16) Fuson, Corse and McKeever, THIS JOURNAL, **62**, 3250 (1940).

CHICAGO, ILLINOIS RECEIVED APRIL 2, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. II. Unsaturation at the C_{22}-Position and the Behavior of C_{20}-Isomeric Carbinols

BY PERCY L. JULIAN, WAYNE COLE, EDWIN W. MEYER AND R. A. HERNESS

The investigations recorded in this paper are part of a general program dealing with unsaturated groupings at the C_{22}-position of the sterol side chain. In a previous communication[1] steroid ketones isomeric about the C_{20}-atom were described for the first time. The availability of these ketones (which seemed to be moderately hindered by the proximity of the bulky ternorcholenyl group) made possible a study of the influence of the spatial configuration at C_{20} of the steroid molecule upon reactions involving functional groups at the C_{22}-position and upon the degree of hindrance at this position. This paper reports the formation of the isomeric dimethylcarbinols and the nature of their dehydration products.

A change in configuration at C_{20} seemingly has no influence upon the behavior of the ketones toward methylmagnesium bromide or upon the mode of dehydration of the resulting tertiary carbinol, but does alter the reactivity of the resulting propenes. Curiously, each dimethylcarbinol gave as its principal dehydration product a substance having the side-chain double bond in the terminal position, without influencing the asymmetry at C_{20}.

Such dehydration of tertiary carbinols bearing

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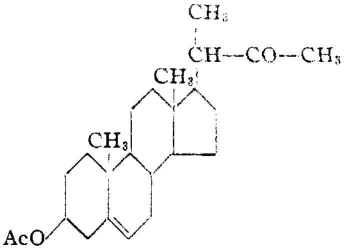
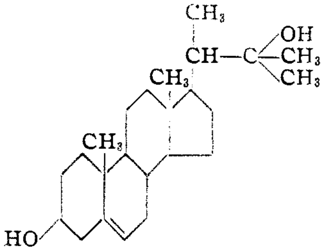
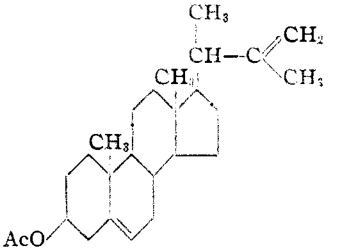
(1) Cole and Julian, THIS JOURNAL, **67**, 1369 (1945).

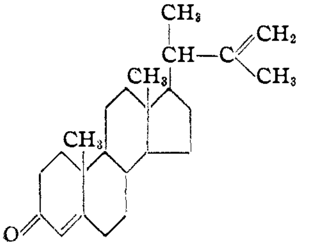
two methyl groups is well known. For example, Reindel and Niederlander[2] showed that the dimethylcarbinol obtained from 3-hydroxy-5-cholenic acid formed a methylene compound upon dehydration, and Wieland[3] revealed that the dimethylcarbinol formed from bisnorcholanic acid must have dehydrated to form a methylene compound, since oxidation converted it again into a bisnor-acid. Recently Jacobsen[4] observed that a dimethylcarbinol obtained during the degradation of the neoergosterol side chain gave a substituted propene (analogous to III) on dehydration.

The addition of methylmagnesium bromide to the "normal" methyl ketone (Ia) produced the tertiary carbinol (IIa) which led to the acetoxyternorcholenyl-propene (IIIa) on dehydration with acetic acid–acetic anhydride mixture or when treated with sulfuric acid and acetic anhydride.

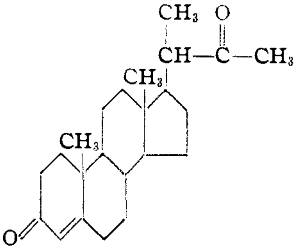

Ia (normal)
Ib (20-iso)


IIa (normal)
IIb (20-iso)


IIIa (normal)
IIIb (20-iso)

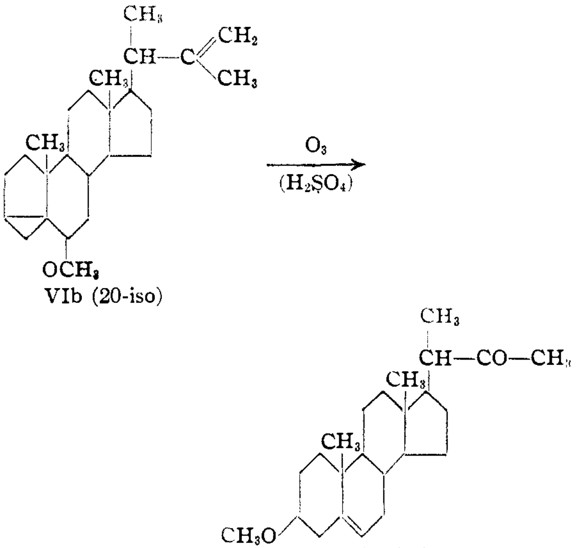

IVa (normal)
IVb (20-iso)

Hydrolysis and oxidation yielded the ketone (IVa). In this doubly-unsaturated ketone the 22–23 double bond is considerably more reactive than the 4–5 double bond, since mild ozonization led to a 70% yield of the diketone (Va). Together with the fact that ozonization of IIIa gave formaldehyde as the only volatile product, this formation of the diketone adequately proves the position of the double bond.


Va (normal)

Similar reactions with the 20-iso-ketone (Ib) led to the 20-iso-acetate (IIIb) and to the 20-isoketone (IVb). This ketone (IVb) of the C_{20}-iso series reacted sluggishly with ozone, making preferential ozonization of the side-chain double bond difficult and demonstrating that the 22–23 double bond in the C_{20}-iso series is more hindered than it is in the normal series. It was surprising that a change in configuration at C_{20} should alter the rate of ozonization to such an extent. Furthermore, the ozonide of the iso-ketone (IVb) was more difficult to hydrolyze than that of the normal ketone (IVa).

Since preferential ozonization of the side chain in the ketone (IVb) was not satisfactory, the acetate (IIIb) was studied; but each of the ace-



VIb (20-iso)
VIIb (20-iso)

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(2) Reindel and Niederlander, *Ann.*, **522**, 218 (1936).

(3) Wieland, Schlichting and Jacobi, *Z. physiol. Chem.*, **161**, 80 (1926).

(4) Jacobsen, THIS JOURNAL, **65**, 1789 (1943).

tates (IIIa and IIIb) took up four atoms of bromine readily, making difficult the protection of the nuclear double bond while attempting to operate on the side-chain double bond. Therefore, the *i*-ether (VIb) was prepared and studied. The ether (VIb) was cleaved by ozonolysis and the *i*-steroid ketone rearranged[5] to 3-methoxy-20-isoternorcholenyl methyl ketone (VIIb), which was made directly from the ketone (Ib) for comparison.

Thus despite its different reactivity, the side-chain double bond in the 20-iso-propene (IIIb) is, like that of its isomer (IIIa), in the terminal position. This fact was further demonstrated by the formation of formaldehyde as the only volatile ozonolysis product.

Table I lists the molecular rotations of the two groups of steroids, those derived from the normal ketone (3-hydroxy-5-ternorcholenyl methyl ketone) and those derived from its isomer (3-hydroxy-20-iso-5-ternorcholenyl methyl ketone). The molecular rotation remains fairly constant as the normal methyl ketone is converted into the dimethylcarbinol and dehydrated to the propene. Similarly, no change in molecular rotation occurs when the iso-ketone is converted into its dimethylcarbinol; however, dehydration causes a large change in rotation, indicating some abnormality in the propene side chain. This abnormality seems to be related to the peculiar reactivity of the double bond (*e. g.*, the sluggish reaction with ozone), but there is no other chemical evidence which aids in explaining why a shift in molecular rotation should occur in the C_{20}-iso series but not in the normal series.

TABLE I

MOLECULAR ROTATIONS OF 3-HYDROXY COMPOUNDS

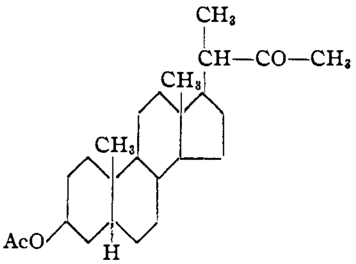
Ketone (Ia)	−24,100	iso-Ketone (Ib)	−17,500
Carbinol (IIa)	−24,300	iso-Carbinol (IIb)	−16,100
Propene (XIa)	−25,000	iso-Propene (XIb)	− 5,200

MOLECULAR ROTATIONS OF 3-ACETOXY COMPOUNDS

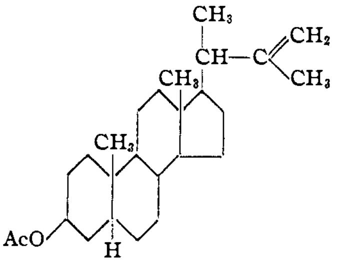
Ketone (Ia)	−29,700	iso-Ketone (Ib)	−19,300
Propene (IIIa)	−27,100	iso-Propene (IIIb)	− 7,200

The peculiar rotation of the dehydration product in the iso-series introduced an element of doubt as to its structure. Therefore, in an attempt to establish the validity of the determination of structure, we repeated the study of the influence of the configuration at C_{20} in an analogous series of compounds. The most suitable for our purpose was the 5,6-dihydro-series derived from 3-acetoxy-bisnor*allo*cholanic acid.

This study involved the preparation of the methyl ketone (VIIIa) by the action of dimethylcadmium on the acid chloride of 3-acetoxybisnor*allo*cholanic acid, and its isomerization by alkali to 3-acetoxy-20-isoternor*allo*cholanyl methyl ketone (VIIIb) using the procedure previously developed for the unsaturated series.[1]



VIIIa (normal)
VIIIb (20-iso)



Xa (normal)
Xb (20-iso)

The action of methylmagnesium bromide on each of the two isomeric ketones (VIIIa and VIIIb) yielded the isomeric carbinols (IXa and IXb). These carbinols upon dehydration with acetic acid–acetic anhydride gave two different propenes (Xa and Xb).

The analogy between the dihydro series and the unsaturated series was checked by a comparison of rotations and hydrogenation products of the four propenes. The propenes (IIIa and Xa) were shown to have the same side-chain configuration by virtue of the fact that each yielded the same hydrogenation product, which was different from the product derived from propenes (IIIb and Xb). The rotations of the compounds involved are listed in Table II.

TABLE II

MOLECULAR ROTATIONS OF 3-ACETOXY COMPOUNDS

	Normal series	Iso series
$\Delta^{5,6}$-Propene (III)	−27,100	− 7,200
allo-Ketone (VIII)	− 9,200	+ 4,500
allo-Propene (X)	− 6,800	+16,900
allo-Propane	+ 1,300	+ 4,600

In the *allo* series the same peculiarity in rotations is observed; namely, that little change in rotation occurs when the ketone of the normal series is converted into the corresponding propene; however, the similar conversion of the iso-ketone to the iso-propene is accompanied by a change in molecular rotation of the order of 12,000.

It is interesting to note that the difference in rotation of the isomeric propanes is of the same order of magnitude (but of different sign) as that reported by Plattner and Pataki[6] for the two 3(β)-hydroxynor*allo*cholanic acids isomeric at C_{20}.

The structure of the isomeric *allo*-propenes was confirmed by cleavage with ozone to formalde-

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(5) *Cf.* Riegel, Meyer and Beiswanger, THIS JOURNAL, **65**, 325 (1943).

(6) Plattner and Pataki, *Helv. Chim. Acta.*, **26**, 1241 (1943).

hyde and the corresponding methyl ketones (VIIIa and VIIIb).

Experimental Part[7]

Substances Related in Configuration to 3-Hydroxy-5-bisnorcholenic Acid

3-Hydroxy-5-ternorcholenyldimethylcarbinol (IIa). Five grams of 3-acetoxy-5-bisnorcholenic acid was converted into the acid chloride by two hours of treatment with 100 ml. of anhydrous ether, 3 ml. of thionyl chloride and one drop of pyridine, then concentrated under vacuum to a crystalline residue. A solution of the acid chloride in 120 ml. of toluene was added portionwise to the Grignard reagent prepared from 5 g. of magnesium, 21 g. of methyl bromide and 150 ml. of ether. After twenty minutes of stirring at room temperature, the ether was distilled and the toluene solution stirred and heated over a steam-bath for six hours. The product was diluted with ether and washed with cold ammonium sulfate solution. Washing the ether solution with 5% sodium hydroxide extracted no acids. Concentration and steam distillation left the crystalline carbinol, which after washing once with ether and drying, weighed 4.6 g. and melted at 194–200°. For analysis 0.5 g. of the carbinol in 35 ml. of warm toluene was adsorbed onto activated alumina and washed once with benzene. Elution with acetone gave 0.2 g. of plates, m. p. 209–210°; $[\alpha]^{25}$D −67° (90.6 mg. made up to 5 ml. with chloroform, α −1.22°, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{40}O_2$: C, 79.95; H, 11.17. Found: C, 80.03; H, 11.00.

A preparation using 5 g. of 3-acetoxy-5-ternorcholenyl methyl ketone (m. p. 171–174°), 4 g. of magnesium, 16 g. of methyl bromide and 150 ml. of ether gave 4.5 g. of the same dimethylcarbinol melting at 195–199°. The dimethylcarbinol has also been prepared by the action of methylmagnesium bromide on a toluene suspension of 3-hydroxy-5-bisnorcholenic acid.

2-(3-Acetoxy-5-ternorcholenyl)-propene (IIIa).—A mixture of 10 g. of the dimethylcarbinol (m. p. 195–199°), 15 ml. of acetic anhydride and 100 ml. of glacial acetic acid was refluxed four hours. The dark solution deposited white flakes (8 g.) of the acetoxy-propene melting at 192–195°. The product was purified by dissolving it in 80 ml. of hot benzene, concentrating to about 25 ml., then diluting with 40 ml. of glacial acetic acid and cooling. The pure acetoxy-propene (7.5 g.) melted at 197°; $[\alpha]^{25}$D −70° (96.2 mg. made up to 5 ml. with chloroform, α −1.36°; *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{40}O_2$: C, 81.20; H, 10.47. Found: C, 81.36; H, 10.15.

A cold chloroform solution of the acetoxy-propene rapidly decolorized two moles of bromine. No hydrogen bromide was evolved. Removal of the solvent and crystallization of the waxy product from ethyl acetate gave prisms of a tetrabromide melting at 144–146°.

2-(3-Hydroxy-5-ternorcholenyl)-propene (XIa).—Four grams of the acetoxy-propene in 20 ml. of warm benzene was hydrolyzed by refluxing for one hour with 4 g. of potassium hydroxide in 100 ml. of methanol. The hydrolysate was diluted with ether, washed three times with water, then concentrated and crystallized, giving 3.5 g. of the hydroxy-propene, m. p. 177–179°. Recrystallization from benzene–methanol gave white plates, m. p. 179°; $[\alpha]^{25}$D −73° (86.3 mg. made up to 5 ml. with chloroform, α −1.26°, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{38}O$: C, 84.13; H, 11.18. Found: C, 83.80; H, 10.96.

The same hydroxy-ternorcholenyl-propene was obtained when a solution of 3-hydroxy-5-ternorcholenyl-dimethylcarbinol in 50 ml. of anhydrous methanol containing 5 drops of sulfuric acid was refluxed for five hours.

Thirty minutes refluxing with acetic anhydride–acetic acid mixture (1:1) converted the hydroxy-propene into the 3-acetoxy-propene, m. p. 193–196°. Titration of a sample of the hydroxy-propene with perbenzoic acid in chloroform indicated 1.92 double bonds.

2-(3-Keto-4-ternorcholenyl)-propene (IVa).—A solution of 12 g. of the hydroxy-propene (m. p. 177–179°) in 200 ml. of toluene and 40 ml. of cyclohexanone was heated to 100°, then swirled under vacuum while about 10 ml. solvent was distilled in order to remove traces of moisture. A solution of 12 g. of aluminum *t*-butoxide in 400 ml. of warm toluene was added and the mixture heated for two hours over a steam bath. The cooled reaction mixture was separated with ether and cold 10% hydrochloric acid, and the washed neutral solution steam distilled. The residue was dried and crystallized from methanol, giving 8.0 g. of 1st crop ketone, m. p. 164–167°. Recrystallization from ethanol gave white plates, m. p. 170–171°; $[\alpha]^{28}$D +55° (318 mg. made up to 10 ml. with chloroform, α +1.74°, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{36}O$: C, 84.64; H, 10.65. Found: C, 84.56; H, 10.20.

Ozonization of 2-(3-Keto-4-ternorcholenyl)-propene.—Two grams of the ketone was dissolved in 60 ml. of chloroform, cooled in an ice-bath and ozonized for ten minutes at 0.5 l./min. with 5% ozone. Steam distillation left a residue, which was separated into 0.4 g. of acid and 1.5 g. of neutral white crystals melting at 170–190°. Several recrystallizations from acetone gave colorless needles (1.0 g.; m. p. 197–199°) of 3-keto-4-ternorcholenyl methyl ketone.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.00. Found: C, 80.82; H, 10.12.

These crystals showed no melting point depression when mixed with the 3-keto-4-ternorcholenyl methyl ketone (m. p. 205–206°) previously described.[1]

Ozonization of 2-(3-Acetoxy-5-ternorcholenyl)-propene.—A cooled solution of 1 g. of the acetoxy-propene in 40 ml. of glacial acetic acid was treated with ozone (5% by volume) for fifteen minutes at 0.5 l./min. After addition of 1 g. of zinc dust, 40 ml. of water and 2 drops of silver nitrate, the solution was slowly distilled. The first 15 ml. of distillate yielded a 2,4-dinitrophenylhydrazone (about 0.2 g., m. p. 162–165°) which gave no melting-point depression when mixed with the known formaldehyde 2,4-dinitrophenylhydrazone.

Substances Derived from 20-Iso-5-ternorcholenyl Methyl Ketone

3-Hydroxy-20-iso-5-ternorcholenyl Methyl Ketone. In following the preparation described in the previous communication,[1] it is imperative that the alkaline hydrolysis–isomerization solution cool sufficiently slowly that only the less soluble iso-ketone crystallizes. In working up large batches of the iso-ketone, it was found that more uniform results could be obtained by placing the flask containing the alkaline solution in a warm-water-bath and allowing the latter to approach room temperature slowly. Repeated recrystallizations of the crude iso ketone from acetone gave material melting at 188.5–189.5°.

3-Acetoxy-20-iso-5-ternorcholenyl Methyl Ketone. The acetate was prepared by refluxing for forty minutes a solution of 14.8 g. of the hydroxy-iso-ketone in 125 ml. of freshly-distilled acetic anhydride. The white solid which separated on chilling the solution was collected on a filter and washed with methanol, yielding 15.9 g. of the acetate melting at 203–205°.

3-Hydroxy-20-iso-5-ternorcholenyldimethylcarbinol (IIb).—A methylmagnesium bromide solution was prepared from 21.8 g. of magnesium, 500 ml. of dry ether and 85 g. of methyl bromide (added as a benzene solution at 0.5 g./ml.). A solution of 23.2 g. of the acetoxy-iso-ternorcholenyl methyl ketone in 200 ml. of warm toluene was added rapidly with agitation. After stirring for one hour the ether was distilled and the residue diluted with 200 ml. of dry toluene. The solution was stirred over a steam-bath for five and one-half hours and then allowed to stand overnight. The product was hydrolyzed with

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(7) Certain of the carbon–hydrogen analyses in this paper were performed by Dr. T. S. Ma, University of Chicago.

ice and dilute hydrochloric acid, extracted with 1.5 liters of ether, washed with acid, alkali and water, then concentrated and steam distilled for three hours. The pale yellow residue was taken up in ether and again washed with dilute acid, dilute alkali and water until neutral. The dried solution was concentrated to 150 ml. (solid material separated), then diluted with 200 ml. of ether and cooled, giving 17.1 g. of carbinol melting at 175–178°. Several recrystallizations from acetone gave white platelets melting at 177–178°; $[\alpha]^{29}\mathrm{D}$ $-44.7°$ (209.8 mg. made up to 10 ml. with chloroform, α $-0.94°$, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{40}O_2$: C, 79.94; H, 11.17. Found: C, 79.71, 79.87; H, 10.62, 10.99.

Mixtures of the carbinol with 3-hydroxy-5-ternorcholenyl methyl ketone (m. p. 176°) and with 2-(3-hydroxy-5-ternorcholenyl)-propene (m. p. 179°) showed distinct depressions in melting points.

Several carbinol preparations were carried out with the hydroxy-iso-ketone; however, this procedure led to mixtures containing varying amounts of unchanged ketone, the difficulty very likely being due to the low solubility of the hydroxy-iso-ketone in ether and toluene. Methylmagnesium iodide may be used instead of methylmagnesium bromide.

An acetyl derivative of the carbinol was prepared in the known manner.[8] This material crystallized in colorless needles melting at 154–155°, $[\alpha]^{30}\mathrm{D}$ $-47.0°$ (75.5 mg. made up to 5 ml. with chloroform, α $-0.71°$, *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{42}O_3$: C, 77.57; H, 10.56. Found: C, 78.01; H, 10.11.

2-(3-Acetoxy-20-iso-5-ternorcholenyl)-propene (IIIb).—A solution of 12 g. of the iso-carbinol in 30 ml. of glacial acetic acid was refluxed for one hour, then 30 ml. of acetic anhydride was added and refluxing continued for two hours. The cooled crystalline product, after draining as well as possible on a filter and drying *in vacuo* at 100°, yielded 9.9 g. of the crude propene melting at 183–193°. Recrystallization from acetone gave glistening white plates, m. p. 195–198°; $[\alpha]^{29}\mathrm{D}$ $-18.7°$ (229.5 mg. made up to 10 ml. with chloroform, α $-0.43°$, *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48. Found: C, 81.04; H, 10.05.

The acetoxy-propene showed depression in melting point when mixed with 2-(3-acetoxy-5-ternorcholenyl)-propene of melting point 197°. Titration of the acetoxy-propene in chloroform solution with a chloroform solution of bromine indicated the presence of two double bonds. No clean end-point existed at one mole addition. Reaction of the propene with perbenzoic acid showed that 2.0 atomic equivalents of oxygen were used up. (As a standard cholesteryl acetate used up 1.0 atomic equivalent of oxygen.)

More of the acetoxy-propene may be obtained by dehydration of the lower-melting fraction separated during recrystallization of the carbinol.

2-(3-Hydroxy-20-iso-5-ternorcholenyl)-propene (XIb).—The acetoxy-propene was hydrolyzed by dissolving 5.0 g. in 50 ml. of benzene, adding a solution of 2.5 g. of potassium hydroxide in 50 ml. of ethanol, refluxing the solution for two hours, then diluting with water and extracting with ether. Concentration of the washed, dried ether solution gave a white solid, which crystallized from acetone in glistening plates (4.1 g.) melting at 164–165.5°; $[\alpha]^{28}\mathrm{D}$ $-15.1°$ (264.5 mg. made up to 10 ml. with chloroform, α $-0.40°$, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{38}O$: C, 84.13; H, 11.18. Found: C, 83.86; H, 11.39.

A solution of 5.0 g. of the carbinol in 100 ml. of methanol containing 10 drops of concd. sulfuric acid was refluxed for five hours. A solid separated during this period. Filtration of the chilled mixture yielded 2.3 g. of white platelets melting over the range 120–150° with frothing. Recrystallization from acetone gave 1.2 g. of material, m. p. 159–162.5°, which showed no depression in melting point when mixed with the 3-hydroxy-propene prepared by saponification of the acetoxy derivative. The lower-melting residual mixture was not further investigated. Re-acetylation of 1.0 g. of the hydroxy-propene with acetic anhydride in glacial acetic acid gave 1.1 g. of the acetate melting at 196–199°. This showed no depression in melting point when mixed with a sample of the acetoxy-propene derived from the carbinol.

2-(3-Keto-20-iso-4-ternorcholenyl)-propene (IVb).—Two grams of the hydroxy-propene in 100 ml. of dry toluene was treated with 15 ml. of freshly-distilled cyclohexanone and 4.0 g. of aluminum *t*-butoxide in 100 ml. of hot toluene. (The butoxide was crushed, dissolved in hot toluene, then centrifuged to remove a small quantity of aluminum hydroxide.) The solution was refluxed for one hour and allowed to stand at room temperature for one hour. The product was extracted with ether, washed, concentrated and steam distilled. The residue was taken up in ether, washed, dried, and concentrated to 2.0 g. of yellow solid, which yielded 1.4 g. of crystals (from methanol) melting at 130–135°. Several recrystallizations from methanol gave pale yellow prisms melting at 142–143°; $[\alpha]^{25}\mathrm{D}$ $+143.6°$ (143.4 mg. made up to 10 ml. with chloroform, α $+2.06°$, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{36}O$: C, 84.64; H, 10.66. Found: C, 84.91; H, 10.39.

An oxime of the 3-keto-propene was prepared using hydroxylamine hydrochloride and sodium acetate in aqueous ethanol. After several recrystallizations from ethanol it melted at 224–227° with dec. when placed in a melting point bath at 205°.

Anal. Calcd. for $C_{24}H_{37}ON$: C, 81.07; H, 10.49. Found: C, 80.82; H, 10.73.

2-(3-*p*-Toluenesulfonoxy-20-iso-5-ternorcholenyl)-propene.—The 3-hydroxy-propene (5 g.) was melted *in vacuo* to remove moisture and then dissolved in 20 ml. of hot carbon tetrachloride. To the solution, 20 ml. of pyridine and 9 g. of *p*-toluenesulfonyl chloride were added, then swirled to dissolve the chloride, whereupon a solid (water-soluble) began to separate. After standing overnight, the mixture was diluted with water, extracted with ether and benzene, and the extract washed, concentrated and crystallized from benzene–petroleum ether. The product was 6.4 g. of fine white needles melting at 148°, with dec. Recrystallization from benzene–petroleum ether gave crystals melting at 150°, dec.; $[\alpha]^{30}\mathrm{D}$ $-11.1°$ (98.7 mg. made up to 5 ml. with chloroform, α $-0.22°$, *l*, 1 dm.).

Anal. Calcd. for $C_{31}H_{44}O_3S$: C, 74.95; H, 8.93. Found: C, 75.09; H, 9.07.

2-(6-Methoxy-20-iso-*i*-ternorcholenyl)-propene (VI).—A mixture of 6.4 g. of the *p*-toluenesulfonate, 20 g. of fused potassium acetate, 25 ml. of benzene and 150 ml. of dry methanol was refluxed for four hours. The solution was diluted with water and extracted with ether, washed and concentrated. The sirupy residue, remaining after removal of all solvent *in vacuo*, was treated in 100 ml. of hexane with 4.0 g. of activated alumina. After fifteen minutes of swirling, the alumina was separated and washed with hexane. The combined hexane solution yielded a colorless sirup which crystallized from acetone–methanol as 3.9 g. of white solid melting at 62–70°. Several recrystallizations from acetone–methanol raised the melting point to 75–77°; $[\alpha]^{29}\mathrm{D}$ $+35.9°$ (167 mg. made up to 10 ml. with chloroform, α $+0.60°$, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{40}O$: C, 84.20; H, 11.30. Found: C, 84.72; H, 11.37.

2-(3-Methoxy-20-iso-5-ternorcholenyl)-propene.—A mixture of 300 mg. of the *i*-methyl ether and 25 ml. of methanol containing two drops of concd. sulfuric acid was refluxed for two hours. The solid *i*-ether was rapidly replaced by a less soluble solid. The white solid was separated and washed with cold methanol; 279 mg. melting at 152–153°. A recrystallization from methanol did not change the melting point of the plates; $[\alpha]^{29}\mathrm{D}$ $-10.9°$ (155.8 mg. made up to 10 ml. with chloroform, α $-0.17°$, *l*, 1 dm.).

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[8] *Cf.* Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1937).

Anal. Calcd. for $C_{25}H_{40}O$: C, 84.20; H, 11.30. Found: C, 84.54; H, 11.18.

Ozonization of 2-(6-Methoxy-20-iso-*i*-ternorcholenyl)-propene.—Ozone (3% by volume in oxygen) was passed through a solution of 3.0 g. of the *i*-ether in 100 ml. of carbon tetrachloride at ice-bath temperature for twenty minutes at the rate of one liter per minute. The sirup remaining after removal of carbon tetrachloride *in vacuo* was dissolved in 100 ml. of dry methanol containing fifteen drops of concd. sulfuric acid, and the solution was refluxed for two hours. It was then diluted with ether and washed with water and dilute sodium hydroxide followed by water. The orange gum remaining after steam distillation of the ethereal solution was taken up in ether and washed as before. After the addition of charcoal, the ether solution was filtered and dried. Upon removal of ether, 2.2 g. of a dark, orange sirup remained. This was dissolved in a mixture of 10 ml. of benzene and 40 ml. of hexane and chromatographed over an alumina column (1.5 × 17 cm.). A solution of hexane–benzene (4:1) was used for elution. There resulted an intermediate crystalline fraction weighing 0.5 g. Crystallization of this from aqueous methanol yielded 0.273 g. of white solid melting at 120–130° but softening lower. Three recrystallizations from methanal gave **3-methoxy-5-ternorcholenyl methyl ketone** as plates melting at 152–155°. A mixed melting point with the normal methyl ether of the propene showed depression.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.76; H, 10.46.

A semicarbazone prepared from a small quantity of the material melted at 195–200° dec.

For comparison the methoxy-ketone was synthesized from the known hydroxy-ketone as follows: A mixture of 2.2 g. of 3-hydroxy-20-iso-5-ternorcholenyl methyl ketone (m. p. 188°), 2.2 g. of *p*-toluenesulfonyl chloride and 5 ml. of anhydrous pyridine was gently warmed to 40° and let stand at room temperature for twelve hours. The toluenesulfonic ester was extracted with benzene, washed thoroughly with water, then concentrated and refluxed in anhydrous methanol (100 ml.) for ten hours. Concentrating to 40 ml. and chilling gave white flakes of the methyl ether melting at 144–146°. Two recrystallizations from hexane gave white plates of 3-methoxy-20-iso-5-ternorcholenyl methyl ketone melting at 152–153°; $[\alpha]^{29}\text{D}$ −52° (195.6 mg. made up to 10 ml. with chloroform, α −1.04°, *l*, 1 dm.). This gave no depression in melting point when mixed with the ozonization product described above.

The ketone gave a **semicarbazone** which recrystallized from methanol as a white crystalline powder melting at 208–210° with dec.

Anal. Calcd. for $C_{25}H_{41}O_2N_3$: C, 72:24; H, 9.94. Found: C, 72.56; H, 9.13.

Ozonolysis of 2-(3-Acetoxy-20-iso-5-ternorcholenyl)-propene.—Ozone (5% by volume) was passed through a suspension of 3.0 g. of the propene in 100 ml. of glacial acetic acid at the rate of 0.5 l./min. for a period of forty minutes (fifteen minutes after the propene had passed into solution). The effluent gas was bubbled through 50 ml. of water. The acetic acid solution and wash water were then combined and distilled until a sample of the distillate gave no test with 2,4-dinitrophenylhydrazine reagent. From the distillate, 0.164 g. of a yellow 2,4-dinitrophenylhydrazone, m. p. 137–150°, was obtained. Two recrystallizations from ethanol gave needles melting at 161–164°. This showed no depression in melting point when mixed with a sample of formaldehyde 2,4-dinitrophenylhydrazone.

Substances Derived from 3-Acetoxybisnor*allo*cholanic Acid

The *allo* acid was prepared by hydrogenation of 3-acetoxy-5-bisnorcholenic acid in ether–acetic acid using platinum oxide catalyst.[9] From 20 g. of the unsaturated acid there was obtained 16.0 g. of once-recrystallized dihydro-acid melting at 194–196°. A further recrystallization from acetone did not change the melting point.

3-Acetoxyternor*allo*cholanyl Methyl Ketone (VIIIa).—This ketone was prepared in a manner similar to that described for the preparation of the 5,6-unsaturated ketone.[1] Twenty-five grams of 3-acetoxybisnor*allo*cholanic acid, when converted into the acid chloride and treated with 0.3 mole of dimethylcadmium in ether, gave 24.7 g. of crude ketone melting at 162–164°. One crystallization from methanol raised the melting point to 167–168° (20 g.); $[\alpha]^{26}\text{D}$ −23.6° (245.8 mg. made up to 10 ml. with chloroform, α −0.58°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{40}O_3$: C, 77.27; H, 10.37. Found: C, 77.15, H, 10.45.

3-Hydroxyternor*allo*cholanyl Methyl Ketone.—A five-gram sample of the acetoxy-ketone was refluxed for two hours in 125 ml. of methanol with 5 g. of sodium carbonate in 15 ml. of water. The mixture was poured into water and extracted with 1 liter of ether. The washed and dried ether solution was concentrated to the point of crystallization. The product (4.0 g., m. p. 145–158°), after recrystallization from acetone, melted at 164–165°; $[\alpha]^{26}\text{D}$ −15.7° (230 mg. made up to 10 ml. with chloroform, α −0.36°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.73; H, 11.04.

3-Hydroxyternor*allo*cholanyldimethylcarbinol.—A Grignard reagent was prepared from 21.8 g. of magnesium, 85 g. of methyl bromide (previously diluted with benzene to 170 ml.) and 350 ml. of anhydrous ether. A solution of 23.2 g. of 3-acetoxyternor*allo*cholanyl methyl ketone in 150 ml. of toluene was added to the Grignard reagent and stirred for one hour. The major portion of the ether was distilled and replaced with an equal volume of toluene, and the reaction mixture was stirred and heated over a steam-bath for five hours. The cooled reaction mixture was treated with ice and hydrochloric acid, and an attempt made to extract the carbinol with ether, but much of the product remained as an insoluble solid which was filtered and washed with dilute acid, water and chloroform, giving 5.0 g. of white powder melting at 195–198°. Steam distillation of the residue from the ether filtrate gave 7.0 g. of white crystalline carbinol melting at 188–192°. Steam distillation of the residue from the chloroform washings gave 3.2 g. of carbinol melting at 193–196°. Melting points of mixtures showed that all three fractions were the same substance. The combined material after recrystallization from methanol melted at 196–199°; $[\alpha]^{31}\text{D}$ −3° (96 mg. made up to 10 ml. with chloroform, α −0.03°, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{42}O_2$: C, 79.49; H, 11.68. Found: C, 79.37; H, 11.71.

2-(3-Acetoxyternor*allo*cholanyl)-propene (Xa).—The above-described carbinol (8.0 g.) in 25 ml. of glacial acetic was refluxed for one hour and then for a period of two hours following the addition of 15 ml. of acetic anhydride. After cooling, the crystalline propene was separated and washed with cold methanol. The product, 7.1 g. melting at 155–158°, gave upon recrystallization from acetone 6.4 g. of the acetoxy-propene melting at 156–158°; $[\alpha]^{32}\text{D}$ −17.7° (209 mg. made up to 10 ml. with chloroform, α −0.37°, *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95. Found: C, 80.57; H, 10.93.

Ozonolysis of 2-(3-Acetoxyternor*allo*cholanyl)-propene.—Three grams of the propene was ozonized as described for the 5,6-unsaturated iso-propene. The acetic acid solution and wash water were combined and distilled in the presence of 1.0 g. of zinc dust which had previously been treated with silver nitrate solution. To the distillate, 90 ml., an excess of a solution of 2,4-dinitrophenylhydrazine in ethanol was added. The hydrazone which separated amounted to 1.2 g. and melted at 164–167°. It gave no depression in melting point when mixed with an authentic sample of formaldehyde 2,4-dinitrophenylhydrazone.

The distillation residue yielded an orange gum which

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(9) *Cf.* Gilman, "Organic Syntheses," Coll. Vol. II, p. 191.

crystallized from methanol. The product, 1.0 g. melting at 156–167°, was purified by crystallization and chromatography over an alumina column (9 × 76 mm.) in benzene–hexane (1:4) using anhydrous ether for elution. The 3-acetoxy-ternor*allo*cholanyl methyl ketone so obtained melted at 165–167° and gave no depression in melting point when mixed with a known sample.

3-Hydroxy-20-iso-ternor*allo*cholenyl Methyl Ketone.—Forty grams of 3-acetoxyternor*allo*cholanyl methyl ketone was added to a filtered solution of 51 g. of potassium hydroxide in 20 ml. of water and 530 ml. of methanol. The solution was refluxed for two hours and then crystallized in a gradually cooling water-bath. To ensure that crystals would separate properly from the hot solution, a few drops were removed, cooled, crystallized, then returned to the main solution as seed. After cooling to room temperature, the solid was separated, washed with cold methanol and dried. The product, 32.0 g. melting at 180–184°, after recrystallization from methanol melted at 185–186°; $[\alpha]^{26}\text{D}$ +12.0° (216.7 mg. made up to 10 ml. with chloroform, α +0.26°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.53; H, 10.92.

3-Acetoxy-20-iso-ternor*allo*cholanyl Methyl Ketone (VIIIb).—A solution of 21.5 of the hydroxy-iso-ketone in 180 ml. of acetic anhydride was refluxed for forty-five minutes and then chilled. The plate-like crystals were separated, washed several times with cold methanol and dried *in vacuo* over a steam-bath. There remained 23.5 g. of ketone melting at 178–180°. One recrystallization from methanol gave 20.2 g. melting at 180–181°; $[\alpha]^{26}\text{D}$ +11.6° (283.7 mg. made up to 10 ml. with chloroform, α +0.33°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{40}O_3$: C, 77.27; H, 10.37. Found: C, 77.03; H, 10.45.

3-Hydroxy-20-iso-ternor*allo*cholanyldimethylcarbinol (IXb).—To a solution of Grignard reagent prepared from 21.8 g. of magnesium and 85 g. of methyl bromide (used as benzene solution containing 0.5 g./ml.) in 350 ml. of ether, 23.2 g. of the acetoxy-iso-*allo*-ketone in 150 ml. of dry toluene was added and stirred for one hour. The ether was distilled and replaced with toluene. After heating the reaction mixture at steam-bath temperature for five hours, it was decomposed with ice and dilute hydrochloric acid, extracted with ether–benzene and washed. The solid carbinol, which remained after steam distillation, yielded 21.3 g. of dry material, m. p. 167–182°. Recrystallization from acetone raised the melting point to 184–186°; $[\alpha]^{30}\text{D}$ +25.1° (215 mg. made up to 10 ml. with chloroform, α +0.54°, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{42}O_2$: C, 79.49; H, 11.68. Found: C, 79.01; H, 11.63.

2-(3-Acetoxy-20-iso-ternor*allo*cholanyl)-propene (Xb).—Ten grams of the hydroxy-iso-dimethylcarbinol was dissolved in 25 ml. of glacial acetic acid. This solution was refluxed for one hour and then for two hours following the addition of 15 ml. of acetic anhydride. The solid was separated from the chilled mixture and dried *in vacuo* over a steam-bath. The dried product, 6.4 g. melting at 158–165°, was crystallized from acetone to yield 4.5 g. melting at 168.5–169°; $[\alpha]^{30}\text{D}$ +43.8° (228.4 mg. made up to 10 ml. with chloroform, α +1.00°, *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95. Found: C, 80.8; H, 11.01.

Ozonolysis of 2-(3-Acetoxy-20-iso-ternor*allo*cholanyl)-propene.—Three grams of the propene was ozonized in the same manner as that described for the isomer. From the volatile fraction there was obtained 0.65 g. of formaldehyde 2,4-dinitrophenylhydrazone melting at 165–167°.

The residue of distillation was taken up in ether and washed successively with several portions of water, dilute sodium bicarbonate solution and water. The neutral, orange gum remaining after removal of solvent from the dried ether solution crystallized from methanol as 0.46 g. of white solid melting at 147–164°. Several crystallizations from methanol and chromatography gave material melting at 175–178°. This showed no depression in melting point when mixed with 3-acetoxy-20-iso-ternor*allo*cholanyl methyl ketone.

Hydrogenation of the 20-Normal Propenes.—A one-gram sample of 2-(3-acetoxy-5-ternorcholenyl)-propene in 20 ml. of absolute ether and 40 ml. of glacial acetic acid was hydrogenated over 0.1 g. of Adams platinum oxide catalyst at room temperature and three atmospheres pressure. The product, 0.8 g., crystallized from acetone in colorless prisms melting at 150.5–152°. Although this material when mixed with 2-(3-acetoxyternor*allo*cholanyl)-propene (m. p. 156–158°) showed no depression in melting point, it must be the saturated compound, **2-(3-acetoxyternor*allo*cholanyl)-propane,** since it will not decolorize a solution of bromine in chloroform; $[\alpha]^{31}\text{D}$ +3.4° (103.9 mg. made up to 5 ml. with chloroform, α +0.07°, *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{44}O_2$: C, 80.34; H, 11.42. Found: C, 80.42; H, 11.55.

The same hydrogenation product was obtained from 2-(3-acetoxyternor*allo*cholanyl)-propene.

Hydrogenation of the 20-Isopropenes.—In a manner similar to that described above, 1.0 g. of 2-(3-acetoxy-20-iso-5-ternorcholenyl)-propene was hydrogenated. The reduction product crystallized from acetone in large, colorless plates melting at 171–172°. This material gave no depression in melting point when mixed with a sample of 2-(3-acetoxy-20-iso-ternor*allo*cholanyl)-propene (169°); however, unlike the propene, it did not decolorize a solution of bromine in chloroform. Therefore it must be **2-(3-acetoxy-20-iso-ternor*allo*cholanyl)-propane;** $(\alpha)^{31}\text{D}$ +11.9° (113.2 mg. made up to 5 ml. with chloroform, α +0.27°, *l*, 1 dm.).

Anal. Calcd. for $C_{26}H_{44}O_2$: C, 80.34; H, 11.42. Found: C, 80.37; H, 11.34.

The same hydrogenation product was obtained from 2-(3-acetoxy-20-iso-ternor*allo*cholanyl)-propene.

Summary

In a study of the dehydration of dimethylternorcholenylcarbinols, it is shown that the configuration of the adjacent carbon atom does not influence the course of the dehydration, but does affect the reactivity of the resulting propene. In each instance the C-20 configuration was retained and a terminal double bond was formed This behavior was demonstrated for both the $\Delta^{5,6}$-steroids and for the 5,6-dihydro-steroids.

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