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

Sterols. I. A Study of the 22-Ketosteroids[1]

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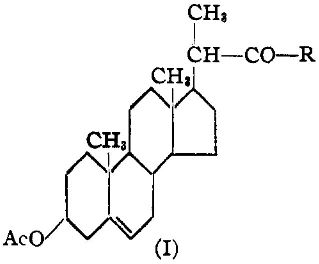
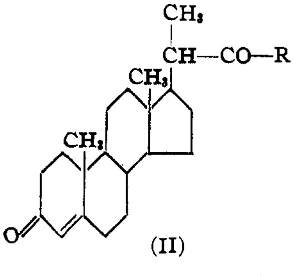
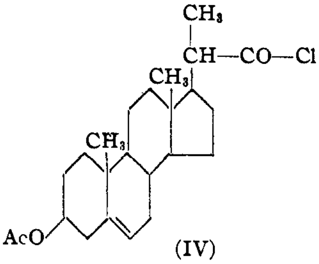
This investigation constituted part of a general program, one purpose of which was to provide more economical methods for degrading the side-chains of sterols. In its first phase the specific center of interest was the unsaturation at C$_{22}$ of stigmasterol. The interesting behavior of the double bond at this position of the sterol molecule led us to a study of other unsaturated groupings at the C$_{22}$-position. Thus the preparation and study of the 22-ketosteroids (I) became the immediate objective. These ketones offered several interesting avenues of investigation. First, they were readily converted into the corresponding 3,22-diketones of formula (II), certain of which are interesting homologs of progesterone (III). Second, it was thought that introduction of a group like the mesityl group (formula I, R = mesityl) might give rise to ketones readily convertible into enol esters[2] which might prove to be easily oxidizable to ketones like (III) and thus offer a simpler degradation procedure than the now classical Barbier–Wieland method.[3] Although no such enol esters have yet been obtained, the behavior of certain of the ketones clearly indicated enolization of the hydrogen atom at C$_{20}$, and this behavior has made possible a study of an isomerism at C$_{20}$ of the sterol molecule. Investigation of the reactivities of groups attached to the 20-carbon atom has contributed to an elucidation of the peculiar chemistry associated with the short-side-chain steroids.



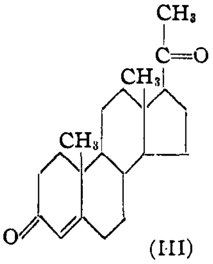
(I)



(II)



(IV)



(III)

Thus although the bisnor acid (formula I, R = OH) has an alpha hydrogen atom, the carboxyl group is definitely hindered as is the case in trimethylacetic acid. Replacement of the hydrogen atom at C$_{20}$ by other groups has not been accomplished, and its elimination during the introduction of a double bond is accompanied by peculiarities which will be described in a following communication.

The most suitable method for preparing these ketones (I) has been the coupling of 3-acetoxybisnorcholenic acid chloride (IV) with organometallic compounds. The crystalline acid chloride, prepared by the interaction of the acid and thionyl chloride in ether at room temperature, reacts slowly but cleanly with diphenylcadmium or with phenylzinc chloride to yield 3-acetoxy-5-ternorcholenyl phenyl ketone (I, R = phenyl). The reactions of the phenyl ketone show normal behavior for the acetate group and the 5,6-double bond, but the carbonyl group is quite hindered. Thus the ketone fails to yield a semicarbazone or an oxime when treated in the usual manner or by the pyridine method of Bachmann and Boatner.[4] It reacts, however, normally with phenylmagnesium bromide to yield a tertiary carbinol, which is dehydrated easily to the known diphenylethylene (VII).

The hydroxy ketone corresponding to V is partly isomerized at C-20 by heating with potassium hydroxide in methanol solution, but sodium carbonate does not effect such a change. More favorable conditions for studying this isomerization at C-20 were discovered in the methyl ketone series described below.

Hydrolysis and oxidation of the phenyl ketone (V) gave the diketone (VI) identical with that obtained by Butenandt and Fleischer[5] by the oxidation of the corresponding 3,22-diol, a by-product from the reaction of phenylmagnesium bromide with the methyl ester of 3-hydroxybisnorcholenic acid. Reduction of the hydroxy ketone corresponding to V with sodium and alcohol gave a mixture of diols, one of which is identi-

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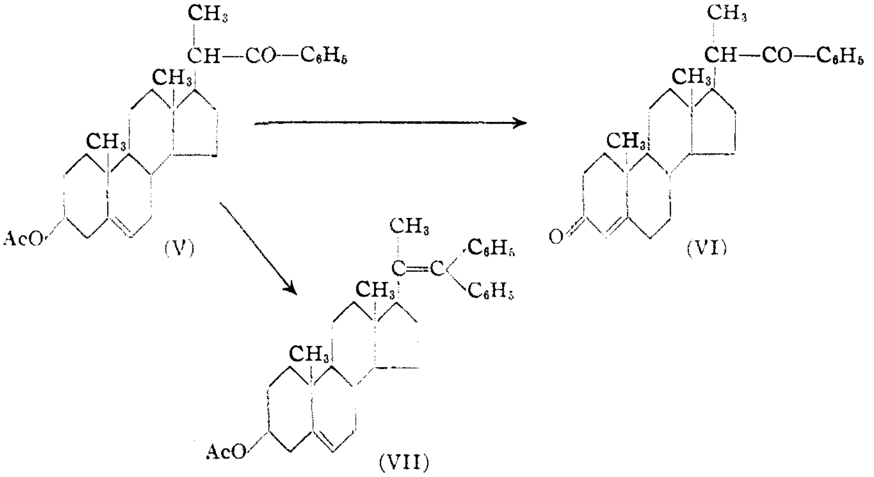
[1] Presented in part before the Organic Division of the American Chemical Society at Atlantic City, September, 1941.

[2] Fuson, Fisher, Ullyot and Fugate, *J. Org. Chem.*, **4**, 111 (1939).

[3] Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1240.

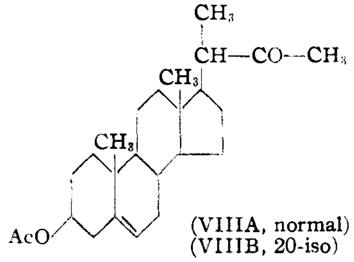
[4] Bachmann and Boatner, THIS JOURNAL, **58**, 2097 (1936).

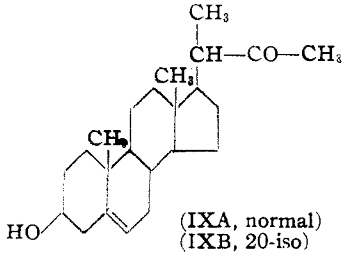
[5] Butenandt and Fleischer, *Ber.*, **70**, 99 (1937).



cal with that obtained as a by-product from the Grignard reaction mentioned above.

Dimethylcadmium in ether converts the acid chloride (IV) into the methyl ketone (VIII) in yields varying from 75 to 95% of the theoretical depending upon the excess of dimethylcadmium employed. It is of particular interest to note that whereas an excess of reagent might be expected to be harmful through further action on the acetate group or the ketone group, actually the best yields were obtained when several times the theoretical amount of dimethylcadmium was used. The reaction is two phase—the dimethylcadmium separating as an oil which is only slightly soluble in the ether[6]—which, together with the fact that we are using the chloride of a hindered acid, accounts for the slow ketone formation. Dimethylzinc likewise converted the acid chloride into the methyl ketone, but the yield was lower than that obtained from the dimethylcadmium reaction.


(VIIIA, normal)
(VIIIB, 20-iso)


(IXA, normal)
(IXB, 20-iso)

Although the acetoxy ketone (VIIIA) melting at 176° is the sole product from the reaction of the acid chloride with dimethylcadmium, a second form of the ketone (Acetate VIIIB) melting at 205° has been secured by isomerization in benzene with sodium methylate. This isomer has also been obtained by hydrolysis with potassium hydroxide followed by reacetylation. The hydrolysis and accompanying isomerization are illustrated by the scheme

$$\begin{tikzcd}
\text{Acetate VIIIA, m. p. }176^\circ \arrow[r, shift left, "\mathrm{Na_2CO_3}"] \arrow[d, shift right] \arrow[dr, "\mathrm{KOH}"] & \text{Hydroxy-ketone IXA, m. p. }175^\circ \arrow[l, shift left, "\mathrm{Ac_2O}"] \arrow[d, shift right] \\
\text{Acetate VIIIB, m. p. }205^\circ \arrow[u, shift right, "\mathrm{NaOCH_3}"'] & \text{Hydroxy-ketone IXB, m. p. }188^\circ \arrow[l, "\mathrm{Ac_2O}"] \arrow[u, shift right, "\mathrm{KOH}"']
\end{tikzcd}$$

By using the proper procedure the acetate (VIIIA) may be hydrolyzed in good yield to either hydroxy ketone (IXA) or hydroxy ketone (IXB), although by standard procedures a mixture of the two hydroxy ketones is secured. Thus treatment with sodium carbonate in moist methanol yields almost pure hydroxy ketone A. Potassium hydroxide, however, in methanol yields a mixture, which if allowed to crystallize slowly from the warm alkaline solution, continues to deposit crystals of the pure hydroxy ketone B (which is slightly less soluble) until practically all of the material has crystallized—the isomerization apparently continuing during the crystallization. If the alkali is removed or neutralized before the crystallization of the product, a mixture is obtained. Both hydroxy ketones give precipitates with digitonin; however, they show different optical rotations and yield different acetates, and, therefore, cannot be polymorphic modifications of the same substance. The most logical explanation of the isomerism is that the two ketones are diastereoisomers differing in configuration at C-20, the inversion being brought about through enolization in the presence of alkali.

The above isomeric 3-hydroxy-ternorcholenyl methyl ketones yield different isomers (XA and XB) of 3-keto-4-ternorcholenyl methyl ketone. One of these (XA) has been prepared recently in a similar manner by Wettstein,[7] who apparently did not encounter isomerism at C-20. We have confirmed Wettstein's observation that the di-

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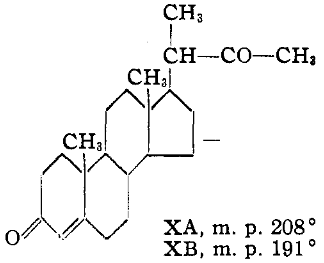
(6) *Cf.* deMahler, *Bull. soc. chim.*, **31**, 125 (1922).

(7) Wettstein, *Helv. chim. acta*, **24**, 311 (1941). The properties of these ketones were discussed by one of us before the Chicago Section of the American Chemical Society, March 14, 1941.



XA, m. p. 208°
XB, m. p. 191°

ketone (XA) has no progestational activity, and further find that the isomeric diketone (XB) and the ethyl and isoamyl homologs are biologically inactive.[8]

Using the appropriate organo-cadmium compounds we have prepared the ketones of formula (I) in which R represents ethyl, isoamyl and mesityl. The ethyl ketone was isomerized by alkali and, although the isomers were closer together in melting point and optical rotation than the isomeric methyl ketones, they gave large melting point depression when mixed and gave different hydroxy ketones when mildly hydrolyzed. The isoamyl and mesityl ketones may well exist in isomeric forms, but only the normal forms have been obtained.

The mesityl ketone was obtained by the reaction of the acid chloride (IV) with mesitylcadmium chloride or with mesitylmagnesium bromide. A second mesityl group could not be introduced by means of the Grignard reaction. An enol ester of the mesityl ketone could not be obtained by acetylation or by treating the ketone with excess ethylmagnesium bromide followed by excess benzoyl chloride. The latter reaction gave merely 3-benzoxy-ternorcholenyl mesityl ketone.

A correlation of data on optical rotations indicates that the 3-acetoxy-5-bisnorcholenic acid secured by ozonization of stigmasteryl acetate,[9] and the ketones secured by the cadmium alkyls all have the same stereo-configuration, thus showing that no inversion at C-20 occurred prior to the isomerization by alkali. The accompanying table shows that the molecular rotations of these substances are more nearly uniform than could be expected if isomerism were involved, and that the rotations of the 20-iso ketones place them outside of the group. Curiously the rotation of the phenyl ketone does not agree with the others, although that of the mesityl ketone is in the group with the alkyl ketones.

TABLE I

OPTICAL ROTATIONS OF SUBSTANCES OF TYPE FORMULA (I)

	$[\alpha]_D$	$[M]_D$
3-Acetoxy-bisnorcholenic acid	−76	−29,500
3-Acetoxy-ternorcholenyl ketones		
Methyl	−80	−30,800
Ethyl	−67	−26,800
Isoamyl	−63	−27,900
Phenyl	−14	− 6,300
Mesityl	−54	−26,400
3-Acetoxy-20-iso-ternorcholenyl ketones		
Methyl	−50	−19,300
Ethyl	−53	−21,200
Phenyl	−43	−19,200

The fact that the preparations of the ketones give excellent yields of a single form and not an equilibrium mixture of two forms, such as is secured by the sodium methylate isomerization of the methyl ketone (VIIIA), further argues for the fact that no inversion at C-20 occurs during the preparations. Accordingly the normal ketones, such as VIIIA, correspond in configuration to the known 3-acetoxy-5-bisnorcholenic acid of melting point 235°. Although it is implied by the nomenclature used that this acid has the same configuration as cholesterol, there is at present no proof of this fact. It follows that the isoamyl ketone (I, R = isoamyl) may be 22-keto-cholesterol or the alternative 22-keto-20-isocholesterol. It was hoped that the isoamyl ketone could be reduced to cholesterol by the method of Wolff and Kishner, but this method did not give successful reduction. We have in progress further work designed to establish the stereochemical relationship between these ketones and cholesterol.

The 22-position in the sterol molecule is definitely a hindered position. Thus the methyl and ethyl ketones slowly form semicarbazones, but the isoamyl and phenyl ketones do not. The mesityl ketone shows no reactivity at the 22-position. This hindrance is also revealed in the case of the bisnor acids by extremely slow ester formation, and in the case of stigmasterol by slow addition of bromine to the 22,23-double bond.

Experimental Part[10]

3-Acetoxy-5-bisnorcholenic acid was prepared from stigmasteryl acetate according to the method of Fernholz.[11] Recrystallization from benzene gave plates melting at 235-236°; $[\alpha]^{29}_D$ −76° (273 mg. made up to 10 ml. with chloroform gave α −2.07°; l = 1 dm.).

3-Acetoxy-5-bisnorcholenic Acid Chloride (IV).—A mixture of 4 g. of the acid, 100 ml. of anhydrous ether, 1.8 ml. of freshly-distilled thionyl chloride and one drop of pyridine was allowed to stand at 25° for three hours with occasional swirling. The solvent was removed completely *in vacuo*, then 3 ml. of benzene was added and also removed *in vacuo* at 30°. The colorless crystalline residue was washed with 5 ml. of pentane, leaving 4.1–4.3 g. of acid chloride which was satisfactory for the following preparations. It may be recrystallized from 10 ml. of benzene, from which it separates as colorless stout needles melting at 130-131°; $[\alpha]^{25}_D$ −62° (134 mg. made up to 10 ml. with chloroform gave α −1.67°; l = 1 dm.).

Anal. Calcd. for $C_{24}H_{35}O_3Cl$: Cl, 8.71. Found: Cl, 8.94.

A small sample of the acid chloride was dissolved in hot methanol and the solution evaporated, yielding colorless

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[8] The bioassays were made by Mr. J. L. Gabby of this Laboratory, who employed the McPhail technique (*J. Physiol.*, **83**, 145 (1934)) giving doses up to 25 mg. of the substances being tested (five injections of 5 mg. each).

[9] Fernholz, *Ann.*, **507**, 128 (1933).

[10] Several of the analyses were made by Dr. T. S. Ma, University of Chicago.

[11] Fernholz, *Ann.*, **507**, 128 (1933).

crystals, m. p. 139°, of the methyl ester.[12] One gram of the acid chloride was dissolved in a mixture of 8 ml. of ethanol and 8 ml. of concentrated aqueous ammonia. The amide rapidly deposited as a crystalline powder (needles) which melted at 227–229°.

Anal. Calcd for $C_{24}H_{37}O_3N$: N, 3.63. Found: N, 3.56.

3-Acetoxy-5-ternorcholenyl Phenyl Ketone (V).—A Grignard reagent was prepared from 5.0 g. of magnesium, 250 ml. of ether and 32 g. of bromobenzene. The solution was cooled in an ice-bath and stirred slowly while 28 g. of powdered anhydrous cadmium chloride was added in portions during two minutes. The cadmium chloride had been dried one hour at 120°. After stirring for thirty minutes, the suspension of liquid diphenylcadmium in ether was treated with a solution of 18 g. of acetoxybisnorcholenic acid chloride in 100 ml. of benzene. Slow stirring was continued at room temperature for ten hours, during which a large amount of suspended crystalline solid formed. Ice and 100 ml. of 10% hydrochloric acid was added, stirred for about twenty minutes, then the whole mixture was filtered and the crystalline product washed with 5% hydrochloric acid, water, and methanol. After drying the product so obtained was 16.1 g. of grey-white crystals of the acetoxy ketone melting at 218–221°.

The small portion of the product which remained in the filtrates was extracted with ether, washed until neutral, steam distilled to remove biphenyl, then crystallized from 50 ml. of acetone, giving 3.3 g. of the acetoxy ketone melting at 216–218°. The ketone crystallized from acetone in colorless small bars which melt at 221°; $[\alpha]^{28}\mathrm{D}$ −14° (131 mg. made up to 10 ml. with chloroform gave α −0.19°; l = 1 dm.).

Anal. Calcd. for $C_{30}H_{40}O_3$: C, 80.32; H, 9.00. Found: C, 80.50; H, 9.41.

A similar preparation using an ether solution of anhydrous zinc chloride converted 10 g. of the acid chloride into 9.9 g. of the ketone melting at 215–218°. The ketone was recovered unchanged after refluxing with acetic anhydride.

A toluene solution of 5 g. of the phenyl ketone (m. p. 219–221°) was added to an ether solution of 0.15 mole of phenylmagnesium bromide, the ether was distilled, then the toluene solution was stirred and heated at 95° for eight hours. The crude carbinol so prepared was heated in a refluxing solution of 30 ml. of acetic anhydride and 30 ml. of acetic acid for two hours, then allowed to crystallize. The product, 1,1-diphenyl-2-methyl-2-(3-acetoxyetiocholenyl)-ethylene, m. p. 218–219°, gave no melting-point depression when mixed with the ethylene prepared by the procedure of Steiger and Reichstein.[13] A mixture of the ketone and the ethylene gave melting point depression to 195–200°. The ketone failed to yield a semicarbazone or an oxime by several of the usual methods of preparation.

3-Acetoxy-5,6-dibromoternorcholanyl Phenyl Ketone.—A solution of 0.224 g. (0.005 mole) of the phenyl ketone in 8 ml. of chloroform was titrated with 0.08 g. of bromine in 10 ml. of chloroform. Decolorization of the bromine was rapid. All of the solvent was removed *in vacuo* from the product, and the white residue (0.323 g.) was treated with 1 ml. of acetone, whereupon it crystallized completely in plates, m. p. 170–171°.

Anal. Calcd. for $C_{30}H_{40}O_3Br_2$: Br, 26.2. Found: Br, 24.6.

A sample of the dibromide in ether–acetic acid solution was treated with zinc dust for fifteen minutes at 40°. Washing out the salts and concentrating the ether solution gave plates of the unsaturated ketone.

3-Hydroxy-5-ternorcholenyl Phenyl Ketone.—A mixture of 8 g. of the acetate, 7 g. of sodium carbonate, 20 ml. of water, 150 ml. of methanol and 75 ml. of benzene was refluxed for three hours. Separating the product with ether and water gave 6.5 g. of the hydroxy ketone as prisms from benzene; m. p. 185–190°; after recrystallization, m. p. 192–193°; $[\alpha]^{29}\mathrm{D}$ −8° (448 mg. made up to 10 ml. with chloroform gave α −0.36°; l = 1 dm.).

Anal. Calcd. for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.39; H, 9.66.

A sample of the hydroxy ketone was heated with 2 ml. of acetic anhydride and 2 ml. of acetic acid at 110° for one hour. Cooling gave crystals of the original acetoxy ketone, m. p. 217–220°.

Isomerization.—A solution of 2 g. of the hydroxy ketone (m. p. 192–193°) in 10 ml. of benzene and 40 ml. of methanol containing 2 g. of potassium hydroxide was refluxed for ten hours then cooled, extracted with ether and washed. Crystallization of the ether concentrate gave 1.9 g. of white powder, m. p. 172–177°; $[\alpha]^{30}\mathrm{D}$ −39°. Ten-hour hydrolysis of the original acetoxy ketone with potassium hydroxide likewise gave a hydroxy ketone which melted at 171–176°; $[\alpha]^{28}\mathrm{D}$ −34°. Neither of these products gave melting-point depression with the 192°-hydroxy ketone, but each, when repeatedly crystallized from acetone, yielded a small first crop (about 10% yield) of a new hydroxy ketone, **3-hydroxy-20-iso-5-ternorcholenyl phenyl** ketone, as white needles, m. p. 200–202°; $[\alpha]^{26}\mathrm{D}$ −47° (56 mg. made up to 5 ml. with chloroform gave α −0.53°; l = 1 dm.).

Anal. Calcd. for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.48; H, 9.56.

When 0.5 g. of the 200°-hydroxy ketone in 20 ml. of acetic anhydride solution was warmed on a steam-bath for one and one-half hours then treated with 4 ml. of water and allowed to crystallize, white needles of **3-acetoxy-20-iso-5-ternorcholenyl phenyl ketone** separated; m. p. 212–213°; $[\alpha]^{28}\mathrm{D}$ −43° (61 mg. made up to 5 ml. with chloroform gave α −0.52°; l = 1 dm.).

Anal. Calcd. for $C_{30}H_{40}O_3$: C, 80.31; H, 8.99. Found: C, 79.74; H, 9.04.

A mixture of the two acetates gave melting point depression to 193–200° A sample of the 212°-acetate was heated for twenty minutes at 100° in glacial acetic acid solution containing one drop of concd. hydrochloric acid, but no isomerization occurred. Mild sodium carbonate hydrolysis of the 212°-acetate gave the corresponding hydroxy ketone melting at 200–202°, but hydrolysis with potassium hydroxide gave material melting at 175–180°, and prolonged (8-hour) hydrolysis with sodium carbonate likewise gave a low-melting mixture.

3-Hydroxy-5-ternorcholenyl-phenyl-carbinol.—Five grams of the hydroxy ketone (m. p. 172–176°) was reduced with sodium slices (6 g.) and 100 ml. of propanol during one hour. The crude carbinol (4.5 g.) which crystallized from the ether concentrate melted at 185–205° and seemed to be a mixture of isomeric diols. The whole mixture was treated with benzoyl chloride in pyridine, then the mixed benzoates were recrystallized from benzene–ethanol, which yielded one isomer, m. p. 238–240°.

Anal. Calcd. for $C_{42}H_{48}O_4$: C, 81.78; H, 7.84, neut. equiv., 308. Found: C, 81.20; H, 8.16, neut. equiv., 314.

Hydrolysis with potassium hydroxide in methanol–benzene mixture gave the diol, m. p. 241–242°, as white crystals from methanol. This same diol was isolated in the manner described by Butenandt[6] as a by-product from the reaction of phenylmagnesium bromide with the methyl ester of 3-hydroxy-bisnorcholenic acid. The diol (m. p. 238–241°) obtained from the Grignard reaction gave no melting point depression when mixed with the diol from the dibenzoate described above.

3-Keto-4-ternorcholenyl Phenyl Ketone.—A mixture of 1 g. of the hydroxy ketone, 5 ml. of cyclohexanone, 1.5 g. of aluminum *t*-butoxide and 50 ml. of toluene was refluxed from an oil-bath at 125° for forty minutes, then worked up by hydrolysis and steam distillation. Two crystallizations from acetone gave 0.7 g. of colorless needles, m. p. 228–229°; $[\alpha]^{25}\mathrm{D}$ +90° (42 mg. made up to 5.6 ml. with chloroform gave α +0.67°; l = 1 dm.).

Anal. Calcd. for $C_{28}H_{36}O_2$: C, 83.12; H, 8,96. Found: C, 83.01; H, 8.52.

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[12] Fernholz and Stavely, THIS JOURNAL, **62**, 428 (1940).

[13] Steiger and Reichstein, *Helv. chim. acta*, **20**, 1040 (1934).

A sample of this same 3,22-diketone was prepared from the 3,22-diol as described by Butenandt.[5]

3-Acetoxy-5-ternorcholenyl Methyl Ketone (VIIIA).—A Grignard reagent was prepared from 1.3 g. of magnesium, 200 ml. of anhydrous ether and 9 g. of methyl iodide. The solution was cooled in an ice-bath, 5 g. of anhydrous cadmium chloride powder was added, rinsed in with 100 ml. of ether, and the mixture was stirred for one hour at 15°.[14] A solution of 4 g. of 3-acetoxybisnorcholenic acid chloride in 50 ml. of benzene was added, and the mixture stirred at room temperature for one hour then gently refluxed for three hours. Ice and 2% hydrochloric acid were added, then the ether layer was separated, washed with dilute acid, with alkali, then thoroughly with water. Evaporation of the ether gave the whole neutral product as 3.6 g. of white powdery crystals, m. p. 165–175°. Recrystallization from acetone gave prisms, which upon drying at 50° fractured, then melted sharply at 175–176°. High-vacuum sublimation gave a crystalline powder, m. p. 175–176°; $[\alpha]^{29}_{D}$ −80° (101 mg. made up to 5 ml. with chloroform gave α −1.62°; l = 1 dm.).

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.52; H, 10.00.

A repetition of the preparation using methyl bromide in place of methyl iodide gave similar results. The above preparation uses 2.5 moles of dimethylcadmium per mole of acid chloride. A preparation using 0.5 mole (the theoretical amount) of dimethylcadmium gave a 78% yield; one using 1.0 mole gave 91% yield; using 2.5 mole gave 95% yield. A preparation which employed 2.5 moles of dimethylzinc (in place of the dimethylcadmium) gave a 75% yield of the same methyl ketone.

Twenty minutes of boiling with acetic anhydride does not change the properties of the acetoxy ketone. Refluxing for two hours a solution of 1 g. of the ketone in 50 ml. of ethanol to which had been added 1 g. of semicarbazide hydrochloride and 1 g. of sodium acetate in 3 ml. of water gave a semicarbazone as white needles, m. p. 236–237° with dec.

Anal. Calcd. for $C_{26}H_{41}O_3N_3$: C, 70.39; H, 9.32. Found: C, 70.27; H, 9.60.

When 1.13 g. of the methyl ketone was treated with 0.48 g. of bromine then with 2 g. of chromic acid in 30 ml. of acetic acid for two days at 25°, then the material debrominated with zinc dust, a 12% yield of 3-acetoxy-bisnorcholenic acid, m. p. 232–235°, was obtained, but the major portion of the ketone was recovered unchanged.

3-Hydroxy-5-ternorcholenyl Methyl Ketone (IXA).—A mixture of 1 g. of sodium carbonate, 1 g. of the acetoxy ketone, 25 ml. of methanol and 3 ml. of water was refluxed for two hours. The product was separated with water and ether, and the washed ether solution was concentrated, whereupon plates (0.9 g., m. p. 143–146°) of a hydrate of the hydroxy ketone separated. Recrystallization from acetone gave colorless plates, m. p. 176–177°. (A mixture with the original acetate melted at 140–148°.) $[\alpha]^{25}_{D}$ −70° (131 mg. made up to 6.5 ml. with chloroform gave α −2.82°; l = 2 dm.).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.93; H, 10.51.

3-Hydroxy-20-iso-5-ternorcholenyl Methyl Ketone (IX-B).—A solution of 2 g. of 3-acetoxyternorcholenyl methyl ketone (m. p. 176°) in 40 ml. of methanol containing 2.5 g. of potassium hydroxide and 1 ml. of water was refluxed gently for two hours, then evaporated to about 18 ml. and let crystallize slowly. The crystallization must be slow enough that at least an hour is required for the crystallizate to cool to 25°. After eight hours the crystalline material was drained, washed with methanol and dried, yielding 1.5 g. of the iso-hydroxy ketone; m. p. 186–188°. Reworking the filtrates gave an additional 0.25 g. of the same material. Similar hydrolysis in which the potassium hydroxide was neutralized or washed out of the product before crystallization gave only mixtures; hence, slow crystallization from alkaline methanol is an essential step in the isomerization. Recrystallization from acetone gave heavy colorless plates which melted at 188–189°; $[\alpha]^{25}_{D}$ −51° (130 mg. made up to 6.8 ml. with chloroform gave α −1.96; l = 2 dm.).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.25; H, 10.45.

This hydroxy ketone, like its isomer, forms a precipitate in alcohol with digitonin. A mixture of the hydroxy ketone with its isomer gives melting-point depression to 155–165°.

3-Acetoxy-20-iso-5-ternorcholenyl Methyl Ketone (VIII-B):—A solution of 2 g. of the 3-hydroxy-20-iso-ternorcholenyl methyl ketone in 16 ml. of acetic anhydride was heated almost to boiling for thirty minutes then cooled and allowed to crystallize. The methanol-washed crystals were 1.8 g. of small white flakes; m. p. 202–204°. Recrystallization from glacial acetic acid raised the melting point to 205–206°; $[\alpha]^{29}_{D}$ −50° (129 mg. made up to 5.0 ml. with chloroform gave α −1.29°; l = 1 dm.).

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.67; H, 9.45.

This acetate has been obtained, although less cleanly, by the following isomerization. One gram of the acetoxyternorcholenyl methyl ketone was dissolved in 40 ml. of dry benzene, 0.5 ml. of 5% sodium methylate in methanol was added, 8 ml. of benzene was distilled at first to remove free methanol, then the mixture was refluxed for four hours. The cooled solution was washed with dilute acetic acid, then concentrated and the residue crystallized from acetic acid, giving 0.7 g. of material; m. p. 154–164°. By repeated crystallization from glacial acetic acid this material gave 0.05 g. of a little-soluble condensation product, m. p. 225–235° (which was not further investigated) and 0.10 g. of the iso-acetate melting at 202–204°. The material from the mother liquors melted at 167–170° and gave no depression in melting point when mixed with the starting material. When a sample of the pure iso-acetate was similarly treated with sodium methylate a mixture of isomers (m. p. 165–175°) was obtained.

3-Keto-4-ternorcholenyl Methyl Ketone (XA).—A solution of 1 g. of the hydroxy ketone (m. p. 176°) in 8 ml. of cyclohexanone and 20 ml. of toluene was heated to refluxing, a centrifuged solution of 2 g. of aluminum *t*-butoxide in 40 ml. of hot toluene was added, and the mixture heated in an oil-bath at 120° for twenty minutes. The cooled mixture was shaken with ether and 2% sulfuric acid, and the washed neutral product was steam distilled. The crude product (0.85 g., m. p. 198–203°) was crystallized from a small volume of ether. Recrystallization from benzene gave prisms; m. p. 206–208°; $[\alpha]^{29}_{D}$ +54° (113 mg. made up to 6.5 ml. with chloroform gave α + 1.88°; l = 2 dm.).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.00. Found: C, 80.86; H, 9.66.

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

3-Keto-20-iso-4-ternorcholenyl Methyl Ketone (XB).—In a manner similar to the above preparation, 2 g. of 3-hydroxy-20-iso-ternorcholenyl methyl ketone (m. p. 188°) was converted into the diketone, which crystallized from moist acetone as 1.8 g. of crystals melting at 175–187°. Two forms were obtained. Recrystallization from dry acetone lowered the melting point, giving colorless plates, m. p. 165–166° (the liquid, when cooled then remelted, showed m. p. 180–188°). Crystallization from methanol gave prisms; m. p. 189–191°; $[\alpha]^{25}_{D}$ +67° (100 mg. made up to 3 ml. with chloroform gave α +2.22°; l = 1 dm.).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.70; H, 10.00. Found: C, 80.68; H, 10.31.

This diketone showed no luteoid activity in 25 mg. dose.[8] Mixtures of the dimorphic forms (m. p. 191° and m. p. 166°) melted intermediate. A mixture of equal parts of the two isomeric diketones (m. p. 191° and m. p. 207°) melted at 179–185°.

Coupling of 3-Keto-4-bisnorcholenic Acid Chloride with Dimethylzinc.—The keto-acid was prepared according to

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[14] *Cf* Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

the method of Butenandt and Mamoli.[15] One gram of the acid was converted into a waxy acid chloride by the procedure described for the acetoxy-acid. A benzene solution of the chloride was stirred for six hours at 35° with 0.1 mole of dimethylzinc. Working up the reaction mixture with 2% sulfuric acid and ether, and crystallizing the product from benzene gave prisms of 3-keto-ternorcholenyl methyl ketone, m. p. 202–204°.

3-Acetoxy-5-ternorcholenyl Ethyl Ketone.—In a manner similar to that described for the preparation of the methyl ketone, a benzene solution of 25 g. of the acid chloride was added to 600 ml. of cold ether solution containing 0.2 mole of di-ethylcadmium. Cooling in an ice-bath was necessary until twenty minutes after all of the acid chloride had been added. Recrystallizing the crude product (23 g., m. p. 167–169°) from acetone gave the ethyl ketone as prisms, m. p. 171–172°; $[\alpha]^{29}D$ −67° (201 mg. made up to 11.1 ml. with chloroform gave α −2.44°; l = 2 dm.).

Anal. Calcd. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.06. Found: C, 78.12; H, 9.89.

The acetoxy-ketone slowly formed a semicarbazone, m. p. 253–256°.

Anal. Calcd. for $C_{27}H_{43}O_3N_3$: C, 70.85; H, 9.47. Found: C, 71.10; H, 9.88.

3-Hydroxy-5-ternorcholenyl Ethyl Ketone.—A mixture of 6 g. of the acetate, 5 g. of sodium carbonate, 10 ml. of water and 150 ml. of methanol was refluxed for four hours, then diluted with water and extracted with ether. The product crystallized directly from the ether concentrate as 4.5 g. of white needles, m. p. 173–176°. Recrystallization from acetone gave stout needles, m. p. 175–176°; $[\alpha]^{29}D$ −66° (158.6 mg. made up to 10 ml. with chloroform gave α −1.05°; l = 1 dm.).

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.69; H, 10.32.

Boiling the hydroxy ketone with acetic anhydride for twenty minutes gave the original acetate, m. p. 172–173°. A mixture of equal parts of the hydroxy-ketone and its acetate melted at 148–156°.

3-Acetoxy-20-iso-5-ternorcholenyl Ethyl Ketone.—Twenty grams of the normal acetoxy ketone was hydrolyzed by refluxing for four hours with 8 g. of potassium hydroxide in 15 ml. of water and 200 ml. of methanol, giving 19 g. of a crystalline product (m. p. 138–148°) which was a mixture of the hydroxy ketone described above and its 20-epimer. Fractional crystallization did not lead to an easy separation. The whole product was re-acetylated by heating an acetic anhydride solution at 100° for one hour then removing all of the solvent under vacuum. The residue (m. p. 140–150°) was dissolved in 80 ml. of benzene and passed through a 2 × 40-cm. column of alumina (Aluminum Ore Co., minus 80 mesh) using about 200 ml. of benzene for washing through. The first 50 ml. of filtrate yielded 1.1 g. of white plates of the 20-iso-acetoxy ketone, m. p. 173–175° (crystallized from ethanol). Later fractions gave a low-melting mixture, which was re-hydrolyzed, reacetylated and again passed through alumina in order to obtain more of the same 20-iso-ketone. Recrystallization from ethanol gave the iso-ketone as colorless plates, m. p. 176–177°; $[\alpha]^{26}D$ −53° (118.1 mg. made up to 10.1 ml. with chloroform gave α −0.62°; l = 1 dm.).

Anal. Calcd. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.06. Found: C, 77.60; H, 9.91.

A mixture of this acetoxy ketone (m. p. 176–177°) and its isomer (m. p. 172°) gave melting-point depression to 150–162°. One hour of heating of the acetoxy-iso-ketone with alcoholic semicarbazide hydrochloride and sodium acetate gave back the ketone unchanged, but twelve hours of boiling of the same mixture gave a 50% yield of a semicarbazone, m. p. 256–258°, which gave no melting point depression when mixed with the semicarbazone of the normal acetoxy ketone. The twelve-hour heating also left some of the acetoxy-iso-ketone unchanged.

3-Hydroxy-20-iso-5-ternorcholenyl Ethyl Ketone.—Hydrolysis of the acetate with sodium carbonate in wet methanol gave the hydroxy ketone as plates, m. p. 158–160° (crystallized from methanol.)

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.38; H, 10.79.

This hydroxy ketone gave melting point depression with its acetate and with the isomeric hydroxy ketone. Acetylation gave the acetoxy-iso-ketone.

3-Keto-4-ternorcholenyl Ethyl Ketone.—Two grams of the normal 3-hydroxy ketone was oxidized by refluxing with 8 ml. of cyclohexanone, 75 ml. of toluene and 3.5 g. of aluminum *t*-butoxide for one hour, then working up as described for the methyl analog. The product crystallized from 10 ml. of wet acetone in flat prisms (bars), m. p. 157–160° (1.4 g. plus 0.4 g. of lower-melting product). Vacuum sublimation gave a crystalline powder melting at 158°; the melt resolidifies then remelts at 168–170°; $[\alpha]^{25}D$ +59° (88.3 mg. made up to 3 ml. with chloroform gave α +1.73°; l = 1 dm.).

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.84; H, 10.18. Found: C, 80.46; H, 10.06.

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

3-Acetoxy-5-ternorcholenyl Isoamyl Ketone.—A Grignard solution was prepared from 8 g. of magnesium, 60 ml. of isoamyl bromide and 600 ml. of ether, then cooled in an ice-bath and treated with 38 g. of powdered anhydrous cadmium chloride. After thirty minutes stirring, the di-isoamyl-cadmium solution (two liquid phases) was treated with a benzene solution (200 ml.) of the acid chloride prepared from 25 g. of acetoxy-bisnorcholenic acid. The mixture was stirred cold for one hour then at room temperature for twelve hours. Working up, including steam distillation to remove di-isoamyl, gave 26 g. of the ketone, m. p. 148–150°. Recrystallization from ethanol gave stout needles, m. p. 152°; $[\alpha]^{29}D$ −63° (271.1 mg. made up to 10 ml. with chloroform gave α −1.71°; l = 1 dm.).

Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.69; H, 10.47. Found: C, 78.68; H, 10.58.

This ketone is only moderately soluble in acetic acid and in alcohols, but is very soluble in acetone, ether, benzene or chloroform. With sulfuric acid it gives a bright red solution; with sulfuric acid–acetic anhydride mixture it gives a violet solution. Attempts to prepare a semicarbazone and an oxime in alcoholic solution failed. Ten hours of heating of a solution of the ketone and hydroxylamine hydrochloride in anhydrous pyridine gave an amorphous oxime which could not be purified.

3-Hydroxy-5-ternorcholenyl Isoamyl Ketone.—A mixture of 10 g. of the acetoxy ketone, 8 g. of sodium carbonate, 10 ml. of water and 200 ml. of methanol was refluxed from a hot water-bath for six hours then cooled and diluted with ether. The washed ether solution was concentrated, and the residue was diluted with acetone, from which the hydroxy ketone crystallized as white needles, m. p. 142–143°; $[\alpha]^{30}D$ −55° (303 mg. made up to 10 ml. with chloroform gave α −1.66°; l = 1 dm.).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.43; H, 11.01.

When recrystallized from acetone–water mixture or alcohol–water mixture, the hydroxy ketone separates in less soluble hydrated plates which melt at 123–125°. The hydroxy ketone is precipitated from alcoholic solution by digitonin. When the acetate was hydrolyzed by means of potassium hydroxide in methanol, a waxy hydroxy ketone, which probably contained both C-20 epimers, was obtained.

3-Keto-4-ternorcholenyl Isoamyl Ketone.—An Oppenauer oxidation was run for two hours at 100° using 6 g. of the hydroxy ketone (m. p. 140–142°), 20 ml. of cyclohexanone, 6 g. of aluminum *t*-butoxide and 300 ml. of toluene. The product could not be crystallized. After steam distillation to remove cyclohexanone and condensation products, the material was converted into a semicarbazone melting at 228–230°. This was assumed to be the 3-monosemicarbazone since the 22-keto group previously had failed to react. Hydrolysis with dilute sulfuric acid in ethanol gave the crude 3-keto-4-ternorcho-

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(15) Butenandt and Mamoli, *Ber.*, **68**, 1851 (1935).

lenyl isoamyl ketone as 4 g. of sirup, dried two hours under high vacuum; $[\alpha]^{25}\mathrm{D}$ +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°; $[\alpha]^{29}\mathrm{D}$ −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°; $[\alpha]^{28}\mathrm{D}$ −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.

(16) Fuson, Corse and McKeever, This Journal, **62**, 3250 (1940).

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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).