hydantoins, by means of the Bucherer method, from methyl styryl ketone, methyl cyclohexyl ketone, *p*-aminophenyl methyl ketone, Michler's ketone, diacetone alcohol and mesityl oxide, respectively.

AUSTIN, TEXAS RECEIVED AUGUST 17, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Oxidative Degradation of *i*-Stigmasteryl Methyl Ether

BY BYRON RIEGEL, EDWIN W. MEYER AND JOHN BEISWANGER

In an endeavor to make more readily available certain *bisnor*-cholenic acids for the synthesis of steroidal hormones, an investigation of the oxidative degradation of *i*-stigmasteryl methyl ether has been made. The classical method of ozonizing 5,6-dibromostigmasteryl acetate is not entirely satisfactory. The bromination of the 5–6 double bond of stigmasteryl acetate in preference to the 22–23 double bond may not be too selective and thus lead to a lower yield of 3-acetoxy-5-*bisnor*-cholenic acid. A truly selective method for the protection of the 5–6 double bond is based upon the formation of the so-called *i*-ether and furthermore this structure involves the simultaneous protection of the 3-hydroxyl group. The *i*-ether configuration which is sufficiently stable for many reactions, yet labile enough to be converted to desired structures, presents an unique arrangement for the oxidative degradation of the stigmasterol side-chain.

Crystalline *i*-stigmasteryl methyl ether[1] (I) can be prepared from pure stigmasterol in about a 77% over-all yield. Ozonolysis of this ether gave 6-methoxy-*i*-*bisnor*-cholenic acid (II) which crystallized with a molecule of water of hydration, melted at 174.8–176.3° and had a specific rotation of +17°. Because of the difficulty in obtaining the crystalline acid in good yield, conversion to other derivatives was investigated. All attempts to convert the *i*-ether configuration of the free acid to the normal configuration were only partly successful, hence attention was centered upon the methyl ester (III). Although all efforts to crystallize the methyl ester (III) prepared by oxidative degradation were unsuccessful, it underwent conversion to the normal configuration smoothly. The characteristic ease of rearrangement of *i*-methyl ethers to normal methyl ethers[2] upon treatment with methanol containing a trace of acid, receives added confirmation with the rearrangement of methyl 6-methoxy-*i*-*bisnor*-cholenate (III) to methyl 3-methoxy-5-*bisnor*-cholenate (IV). The normal methyl ether (IV) melted at 117–118° and had a specific rotation of −63.3°. Saponification of the ester (IV) gave 3-methoxy-5-*bisnor*-cholenic acid (VIII).

The *i*-ether-ester (III) was prepared by an unequivocal method for a comparison of its behavior with that of the ester obtained from the degradation of *i*-stigmasteryl methyl ether. A convenient starting material was 3-acetoxy-5-*bisnor*-cholenic acid. Saponification and esterification yielded the known methyl 3-hydroxy-5-*bisnor*-cholenate (VI). When treated with *p*-toluenesulfonyl chloride in pyridine, this ester (VI) gave methyl 3-*p*-toluenesulfonoxy-5-*bisnor*-cholenate (VII) melting at 139.8–140.5°. The *i*-ether-ester (III) was obtained by refluxing a methanol solution of the *p*-toluenesulfonate (VII) containing potassium acetate. The ester (III) prepared by this method did not crystallize readily; however, under proper conditions, it was obtained in the crystalline form. This ester (III) melted at 72.0–72.8° and possessed a specific rotation of +37.3°. The free acid obtained by saponification of the ester (III) melted at 168–171° and gave a specific rotation of +33°. A mixed melting point with the acid (II) prepared from *i*-stigmasteryl methyl ether gave a slight depression. By their methods of formation and their reactions these acids should be identical. The acids proved difficult to purify. This discrepancy in physical properties is being investigated. The *i*-ether-ester (III) prepared from the *p*-toluenesulfonate (VII) was easily converted either to the normal methyl ether (IV) or to the 3-acetoxy derivative (V). As a further check, the acid (II) prepared by saponification of the ester (III) was reconverted to the normal methyl ether-ester (IV). The identity of these derivatives and the corresponding ones above lends strong support to the assigned structures. Methyl 3-methoxy-5-*bisnor*-cholenate (IV)

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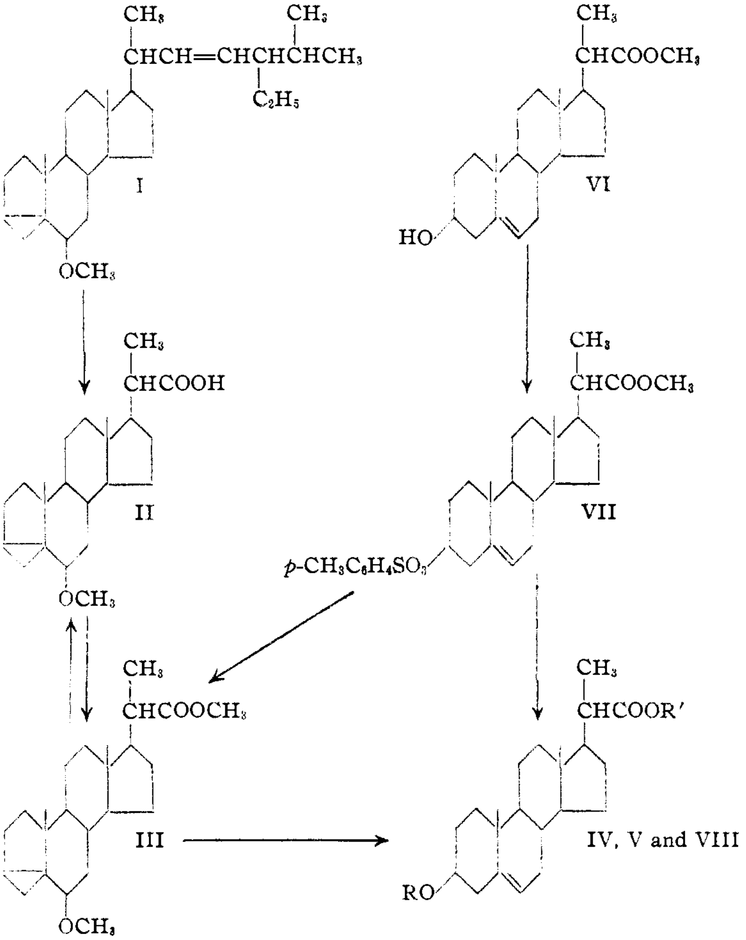
(1) E. Fernholz and W. L. Ruigh, THIS JOURNAL, **62**, 3346 (1940).

(2) T. Wagner-Jauregg and L. Werner, *Z. physiol. Chem.*, **213**, 119 (1932); B. Riegel, M. F. W. Dunker and M. J. Thomas, THIS JOURNAL, **64**, 2115 (1942).



IV R and R' = CH_3
V R = Ac and R' = CH_3
VIII R = CH_3 and R' = H

also was prepared directly from the *p*-toluenesulfonate (VII) by refluxing its methanol solution. Saponification of the normal methyl ether-ester (IV) gave the acid (VIII).

6-Methoxy-*i*-*bisnor*-cholenic acid (II) represents a novel starting material for the production of physiologically active steroids. Work in progress indicates that the *i*-ether structure offers sufficient protection for further degradative and synthetic reactions.

The authors wish to thank the Abbott Laboratories, the Glidden Company and the Upjohn Company for the financial aid and coöperation which made this work possible.

Experimental[3]

Preparations from *i*-Stigmasteryl Methyl Ether

6-Methoxy-*i*-*bisnor*-cholenic Acid (II).—From 1.1 g. of stigmasterol, m. p. 162–163°, 1.2 g. (79%) of stigmasteryl *p*-toluenesulfonate,[1] m. p. 147–148°, was prepared according to the method of Freudenberg and Hess.[4]

Following the method of Fernholz and Ruigh,[1] 8.49 g. (85%) of *i*-stigmasteryl methyl ether, m. p. 47–51°, was obtained from 13.3 g. of stigmasteryl *p*-toluenesulfonate. The yields on these two steps are not mentioned in the literature.

A solution of 3 g. of crystalline *i*-stigmasteryl methyl ether in 200 ml. of chloroform was cooled in an ice-bath and ozonized (5% ozone by volume at an oxygen rate of 3 liters per hour) for two hours. The solution was steam distilled after adding 10 ml. of 30% hydrogen peroxide. The yellow gum that separated during steam distillation was dissolved in ether. The ether solution was extracted several times with small quantities of cold 1 *N* sodium hydroxide. The combined alkaline extracts were extracted with ether, acidified with cold dilute hydrochloric acid and again extracted with ether. This cycle was repeated to insure the complete removal of the neutral material. The solution was dried with anhydrous sodium sulfate and upon removal of the ether 1.566 g. (62%) of a yellow viscous sirup remained The sirup crystallized slowly from an ethyl acetate–petroleum ether (b. p. 62–93°) solution on standing in a cold-room. A yield of 0.732 g. of gummy crystals was obtained. Several crystallizations from acetone-hexane and ethanol gave small white plates melting at 174.8–176.3°; $[\alpha]^{25}\text{D}$ +17° (18.2 mg. made up to 2.42 ml. with chloroform, $\alpha^{25}\text{D}$ +0.126°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{36}O_3 \cdot H_2O$: C, 72.97; H, 10.11. Found: C, 72.86; H, 9.54.

More rigorous drying of the sample, *in vacuo* over boiling benzene, resulted in partial loss of the water of hydration.

Anal. Calcd. for $C_{23}H_{36}O_3 \cdot {}^1/_2H_2O$: C, 74.75; H, 10.09. Found: C, 74.43; H, 9.56.

Complete loss of water of hydration resulted on drying *in vacuo* over boiling toluene for thirty hours.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.61; H, 10.07. Found: C, 76.38; H, 9.44.

Attempts to rearrange the crude *i*-ether acid to 3-methoxy-5-*bisnor*-cholenic acid gave intractable resins. The conversion of the crude *i*-ether acid to 3-acetoxy-5-*bisnor*-cholenic acid was achieved in low yield.

The methyl ester of the crude *i*-ether acid was made by treatment with diazomethane. A solution of 1.66 g. of the methyl ester, a yellow sirup, in 50 ml. of dry methanol containing five drops of concd. sulfuric acid was refluxed for four hours. The solution was diluted with water and extracted with ether. The yellow ether solution was washed with water, dried and the ether removed. A solution of the product in methanol after treatment with Norit

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(3) All melting points are corrected. Analyses by Dr. T. S. Ma, University of Chicago.

(4) K. Freudenberg and H. Hess, *Ann.*, **448**, 128 (1926).

deposited a gummy solid upon standing in the cold-room. Sublimation of the gummy solid at 125–130° at 10^{-3} mm. gave 700 mg. of a white product melting at 100–110°. The product after crystallization from methanol melted at 115.1–117.6° and gave no melting point depression when mixed with an authentic sample of methyl 3-methoxy-5-*bisnor*-cholenate (m. p. 116.6–118.6°).

The ester saponified with difficulty to give an acid, m. p. 194–200°, which was identical with 3-methoxy-5-*bisnor*-cholenic acid described below.

Preparations from Methyl 3-Hydroxy-5-*bisnor*-cholenate

Methyl 3-*p*-Toluenesulfonoxy-5-*bisnor*-cholenate (VII).—Methyl 3-hydroxy-5-*bisnor*-cholenate (VI) was prepared by the method described by Fernholz.[5] A mixture of 1.647 g. of this methyl ester (VI) and 1.7 g. of *p*-toluenesulfonyl chloride in 4 ml. of dry pyridine was warmed until all solid material dissolved. After standing overnight the mixture was diluted with water, cooled to solidify the oil and filtered. The solid material was washed with 0.1 *N* sodium hydroxide, water and dried, yielding 2.313 g. (98%) of crude product. Crystallization from acetone gave 1.845 g. (78%) of material melting at 133–134°.

Anal. Calcd. for $C_{30}H_{42}O_5S$: C, 70.00; H, 8.22. Found: C, 70.11; H, 8.19.

Methyl 6-Methoxy-*i*-*bisnor*-cholenate (III).—A mixture of 1.296 g. of the previously described compound (VII) and 1.3 g. of fused potassium acetate in 50 ml. of anhydrous methanol was refluxed for three hours. Most of the methanol was removed and the residue dissolved in ether and water. The ether extract was washed with dilute alkali, water and dried over anhydrous potassium carbonate. After the ether was removed, 0.892 g. (98%) of light yellow oil was obtained. Molecular distillation of this oil at 140° and 10^{-4} mm. gave a colorless, viscous oil.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.63, 76.82; H, 9.96, 10.15.

On standing, the purified oil crystallized, after which it was relatively easy to obtain the crystalline material from methanol, m. p. 72.0–72.8°, $[\alpha]^{25}D$ + 37.3° (43.2 mg. made up to 5 ml. with chloroform, $\alpha^{25}D$ +0.332°, *l*, 1 dm.).

6-Methoxy-*i*-*bisnor*-cholenic Acid (II).—A 1.46-g. sample of the *i*-ether-ester (III) was saponified with methanolic potassium hydroxide. The reaction mixture was cooled, diluted with water and extracted with ether. The yellow aqueous layer was acidified and extracted with ether. This ether extract containing the acid was shaken several times with ice-cold 1 *N* sodium hydroxide. After acidifying the alkaline layer, the product was again taken up in ether. The ether layer was thoroughly washed with water, dried and the ether removed. The residue, 120 mg. of yellow sirup, crystallized upon evaporation of a hexane solution. Repeated crystallization from aqueous ethanol gave white platelets melting at 168–171°. A mixed melting point with the acid from the ozonolysis of *i*-stigmasteryl methyl ether (m. p. 175.3–177.3°) melted at 155–170°. The acid gave a specific rotation of +33° (12.9 mg. made up to 2 ml. with chloroform, $\alpha^{23}D$ +0.21°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.61; H, 10.07. Found: C, 76.76; H, 9.77.

A 100-mg. sample of the crude acid was reconverted to the methyl ester with diazomethane. This reaction product was rearranged to its normal methyl ether by refluxing its methanol solution containing a few drops of concd. sulfuric acid. After chilling and diluting with water, a crystalline solid separated which was removed by filtration. A yield of 80 mg. of a product melting at 110–115° was obtained. Recrystallization from methanol gave glistening plates melting at 115–117°. They gave no mixed melting point depression when mixed with an authentic sample described below.

Methyl 3-Methoxy-5-*bisnor*-cholenate (IV).—(a) By Rearrangement of the *i*-Methyl Ether (III).—A solution of 520 mg. of the *i*-ether-ester (III) in 50 ml. of anhydrous methanol containing six drops of concd. sulfuric acid was refluxed for three and one-half hours. The reaction mixture was diluted with water and the product extracted with ether. The ether layer was washed with water, dilute sodium carbonate, water and dried. Upon removal of the solvent 510 mg. of white solid remained. Crystallization from methanol yielded 450 mg. (87%) of white plates melting at 115–117°. Further crystallizations from methanol raised the m. p. to 117–118°; $[\alpha]^{25}D$ −63.3° (42.2 mg. made up to 5 ml. with chloroform, $\alpha^{25}D$ −0.534°, *l*, 1 dm.).

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.95; H, 10.20. Found: C, 77.37; H, 10.38.

(b) Preparation from Methyl 3-*p*-Toluenesulfonoxy-5-*bisnor*-cholenate (VII).—A solution of 500 mg. of the *p*-toluenesulfonate in 25 ml. of anhydrous methanol was refluxed for four hours. Upon dilution with sufficient water, solid material separated which was removed by filtration and washed with water. After drying, 360 mg. (99%) of product was obtained, m. p. 114–117.5°. Crystallization from methanol gave plates melting at 116.5–117.5° which gave a m. p. of 116–118° when mixed with the rearranged product (m. p. 116.5–118°) from (a) above.

3-Methoxy-5-*bisnor*-cholenic Acid (VIII).—A 600-mg. sample of the previously described methyl ether-ester (IV) was saponified with methanolic potassium hydroxide. After refluxing eleven hours the potassium salt was isolated, washed with ether and converted to the free acid. Several crystallizations from methanol and from acetone gave needles or flat square crystals melting at 199–202°, $[\alpha]^{25}D$ −77.8° (88.2 mg. made up to 2 ml. with chloroform, $\alpha^{25}D$ −3.20°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.61; H, 10.07. Found: C, 76.98; H, 10.09.

Methyl 3-Acetoxy-5-*bisnor*-cholenate (VIII).—A mixture of 610 mg. of the *i*-ether-ester (III), 1 g. of fused zinc acetate, 2 ml. of acetic anhydride and 50 ml. of glacial acetic acid was refluxed for four hours. The reaction mixture was diluted with water and thoroughly extracted with ether. The ether extract was washed with water, dilute sodium carbonate, water and dried. The ether was removed and the residue crystallized from methanol yielding 480 mg. (72%) of product melting at 137–139°. One additional crystallization raised the m. p. to 139–141°. A mixed m. p. with an authentic sample of methyl 3-acetoxy-5-*bisnor*-cholenate (m. p. 139–141°) showed no depression.

Summary

1. 6-Methoxy-*i*-*bisnor*-cholenic acid has been prepared by the ozonolysis of *i*-stigmasteryl

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

methyl ether. This acid was also prepared from methyl 3-hydroxy-5-*bisnor*-cholenate.

2. Several rearrangement and conversion products of methyl 6-methoxy-*i*-*bisnor*-cholenate have been described.

EVANSTON, ILLINOIS RECEIVED DECEMBER 28, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

Studies on High Molecular Weight Aliphatic Amines and their Salts. X. Ionization Constants of Primary and Symmetrical Secondary Amines in Aqueous Solution

BY C. W. HOERR, M. R. McCORKLE AND A. W. RALSTON

The ionization constants of the lower amines in aqueous solution have been accurately determined by several methods.[1-7] However, no constants have yet been reported for the amines containing 6 or more carbon atoms. Studies upon other high molecular weight organic derivatives of ammonia[4] and upon the higher fatty acids[8] have demonstrated methods by which the relative strengths of compounds which have limited solubility in water can be evaluated indirectly.

The method adopted for this investigation was the measurement of the conductance of the amines in various dilutions of alcohol. It has been shown that when the apparent strength in alcohol is plotted in logarithmic units against the alcohol content, the form of the curve obtained is always such as to permit satisfactory extrapolation to the strength in pure water.[9] Hence, for the amines whose limited solubility in water precluded direct measurement, the conductivity was determined in various dilutions of ethanol, the log of their equivalent conductance was plotted against the volume percentage of ethanol, and the ionization constants were calculated from the extrapolated values obtained.

The amines used in this investigation, with the exception of the butyl- and amylamines, were prepared by hydrogenation of the corresponding nitriles.[10] The primary amines were separated from the secondary amines by vacuum distillation. The secondary amines were purified by crystallization from ethanol with the exception of dihexyl- and dioctylamines which were distilled. Normal and isobutylamine and normal and isoamylamine were commercial products purified by distillation. All of the amines were protected from the atmosphere to minimize absorption of carbon dioxide.

The conductivity apparatus employed and the preparation of the conductivity water have been described elsewhere.[11] The specific conductance

TABLE I

IONIZATION CONSTANTS OF THE ALIPHATIC AMINES IN WATER AT 25°

Amine	Λ_0	Concn. range investigated, moles/liter	$K_B \times 10^{-4}$
Butyl[a]	235	0.0004–0.073	4.1
Isobutyl[b]	235	.0008– .057	2.7
Amyl[c]	232	.0008– .049	4.3
Isoamyl[d]	232	.0008– .040	4.0
Hexyl	229	.0008– .046	4.4
Dihexyl	214	.0008– .030	10.2
Heptyl	226	.0008– .022	4.6
Octyl	223	.0008– .016	4.5
Dioctyl	208	.0008– .014	10.2
Nonyl	220	.0008– .015	4.4
Decyl	217	.0008– .012	4.4
Undecyl	214	.0008– .011	4.3
Dodecyl	211	.0008– .011	4.3
Didodecyl	197	.0008– .011	9.9
Tridecyl	208	.0008– .011	4.3
Ditridecyl	193	.0008– .008	9.9
Tetradecyl	205	.0008– .008	4.2
Pentadecyl	202	.0008– .008	4.1
Dipentadecyl	187	.0008– .008	10.0
Hexadecyl	199	.0008– .008	4.1
Heptadecyl	196	.0008– .008	4.0
Octadecyl	193	.0008– .008	4.0
Dioctadecyl	180	.0008– .008	9.9
Docosyl	180	.0008– .008	4.0

[a] Hall, *et al.*,[4] $K_B = 4.1 \times 10^{-4}$. [b] Bredig,[1] $\Lambda_0 = 235$, $K_B = 2.6 \times 10^{-4}$; Hall, *et al.*,[4] $K_B = 2.6 \times 10^{-4}$; Marcinkow, *et al.*,[7] $K_B = 3.1 \times 10^{-4}$. [c] Hall, *et al.*,[4] $K_B = 4.4 \times 10^{-4}$. [d] Bredig,[1] $\Lambda_0 = 232$, $K_B = 4.0 \times 10^{-4}$; Hall, *et al.*,[4] $K_B = 4.4 \times 10^{-4}$; Marcinkow, *et al.*,[7] $K_B = 5.10 \times 10^{-4}$.

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(1) Bredig, *Z. physik. Chem.*, **13**, 191 (1894).

(2) Moore and Winmill, *J. Chem. Soc.*, **101**, 1635 (1912).

(3) Harned and Owen, THIS JOURNAL, **52**, 5079 (1930).

(4) Hall and Sprinkle, *ibid.*, **54**, 3469 (1932).

(5) Britton and Williams, *J. Chem. Soc.*, 796 (1935).

(6) Damsgaard-Sörensen and Unmack, *Z. physik. Chem.*, **A172**, 389 (1935).

(7) Marcinkow and Plazek, *Roczniki Chem.*, **16**, 395 (1936); *cf.* *Chem. Abst.*, **31**, 1776 (1937).

(8) Halford, THIS JOURNAL, **53**, 2944 (1931).

(9) Michaelis and Mizutani, *Z. physik. Chem.*, **116**, 135 (1925); **118**, 318, 327 (1925).

(10) Ralston, Selby, Pool and Potts, *Ind. Eng. Chem.*, **32**, 1093 (1940).

(11) Ralston, Hoerr and Hoffman, THIS JOURNAL, **64**, 97 (1942).