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# Derivatives of bisnor-5-Cholenaldehyde

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In establishing the position of the double bond in the side chain of stigmasterol by ozonolysis of dibromostigmasteryl acetate, Fernholz,[1] using an excess of ozone, obtained ethylisopropylacetaldehyde and a 20% yield of 3-acetoxy-bisnor-5-cholenic acid.

We have found that 3-hydroxy-bisnor-5-cholenaldehyde (II), which has not been described previously, can be obtained also by this ozonization of dibromostigmasteryl acetate.

As indicated in Table I, the combined yield of bisnor-acid and aldehyde (II) was maximal when the amount of ozone passed into the reaction vessel was approximately 200% of theory. However, the aldehyde semicarbazone could be isolated at all levels if the derivative was made soon after the ozonolysis.

The fact that no aldehyde was found in the neutral fractions which had stood for any length of time was consistent with the difficulty encountered in trying to isolate pure aldehyde. Aldehyde fractions melting from 80 to 110° were isolated but these resinified on further manipulation.

By controlling and modifying conditions we have obtained up to 50% yields of 3-acetoxy-bisnor-5-cholenaldehyde semicarbazone (IV). We have also obtained this compound, as the semicarbazone, by a Rosenmund reduction of 3-acetoxy-bisnor-5-cholenyl chloride.

This aldehyde has been further characterized by the preparation of other derivatives and by its reaction product with phenyl and $\alpha$-naphthylmagnesium bromides. The melting points of 22-phenyl-3-hydroxy-bisnor-5-cholenol (VI) and its diacetate (VII) are in agreement with those of Butenandt and Fleischer,[2] who obtained this diol as a by-product of the reaction between methyl-3-hydroxy-bisnor-5-cholenate and phenylmagnesium bromide.

Riegel, Meyer and Beiswanger[3] suggested that yields of the bisnor-cholenic acid might be increased by ozonolysis of the *i*-ether (XIV) on the basis that 5,6 bromination is not completely selective. We have isolated 6-methoxy-bisnor-*i*-cholenaldehyde semicarbazone (XVI) in 30% yield. Work on this ozonization is in progress.

Other studies on the new 3-hydroxy-bisnor-5-cholenaldehyde and its derivatives will be reported in detail in the near future.

## Experimental

**Preparation of 3-Acetoxy-bisnor-5-cholenic Acid and 3-Acetoxy-bisnor-5-cholenaldehyde Semicarbazone (IV).**—The ozonolysis of dibromostigmasteryl acetate in chloroform at 0° yields more of the acid when ozone is used in excess and only the aldehyde when the amount passed through the solution approaches one equivalent. In the following experiments 6 g. of stigmasteryl acetate was dissolved in 200 ml. of chloroform at 0°; 2.12 g. of bromine in 100 ml. of chloroform was added and ozone passed through the solution at the rate of 0.02 g. per minute, and the total quantity used carefully controlled as reported in Table I.

The chloroform was removed from the ozonide *in vacuo*, below 30°, and the ozonide decomposed with zinc in acetic acid (or as otherwise reported). The solution of the products of ozonolysis was extracted with ether; 3-acetoxy-bisnor-5-cholenic acid was removed as insoluble sodium salt, and isolated as described by Fernholz.[1] Other acidic substances were extracted with 2 *N* sodium hydroxide solution. The dried ether solution of neutral products was taken to dryness and the residue recrystallized from a minimal volume of alcohol, whereupon a product consisting largely of unreacted stigmasteryl acetate was obtained (m. p. 125–130°).

The alcoholic filtrate from the sterol was treated in the usual manner with semicarbazide hydrochloride and sodium acetate and taken to dryness. The residue was washed with ether, with water, and crystallized from 95% alcohol. The semicarbazone of 3-acetoxy-bisnor-5-cholenaldehyde melts and decomposes at 210°. The yield of aldehyde was calculated from the semicarbazone (weight of semicarbazone × 0.867).

*Anal.* Calcd. for $C_{25}H_{39}N_3O_3$: N, 9.76. Found: N, 9.96, 10.02; $[\alpha]^{26}D$ $-41.9°$ (0.2842 g. made up to 20 ml. with chloroform, $[\alpha]^{26}D$ $-1.19°$; *l*, 2 dm.).

The ether wash of the semicarbazone was a viscous oil which was kept for later examination.

Using quantities of stigmasteryl acetate which varied from 6 to 18 g., the experiments in Table I were repeated many times with identical results. The widest variation was found in the yields of acid. The average yield with a large excess of ozone (250%) is 20%, in agreement with the results of Fernholz. However, the recovery of a crystalline neutral fraction which was mostly stigmasteryl acetate would raise the yield to approximately 30% of the acid. In an attempt to explain this recovery, experiments were tried in which the ozonide was decomposed with hydrogen peroxide and sulfuric acid, making possible the isolation of any stigmasteryl acetate tetrabromide. From the ozonolysis of 6 g. of stigmasteryl acetate, 0.04 g. of tetrabromide was isolated. While indicating a lack of total selectivity in the bromine addition it does not account for the large amount of stigmasteryl acetate recovered.

**Examination of the Crystalline Neutral Fraction.**—The crystalline neutral fraction (7.1 g.) which had been obtained from the ozonolysis of 22 g. of the sterol acetate was hydrolyzed and two crystalline crops of slightly impure stigmasterol separated. These were separated into ketonic and non-ketonic fractions by the method of Girard.[4] The material proved almost entirely non-ketonic and upon concentration of the dried ether solution a top fraction (3.5 g.) separated. Upon one more crystallization almost pure stigmasterol (m. p. 159–161°; $[\alpha]^{26}D$ $-43.8°$) resulted. Further concentration of the ether mother liquor gave a second fraction (1.6 g.) which melted at 144–148°, while a third crop (1.6 g.) melted at 132–134° and $[\alpha]^{26}D$ $-38.1°$. The third crop proved to be approximately 50% stigmasterol when assayed gravimetrically by conversion into the tetrabromo acetate. When fraction III was converted into the acetate, the

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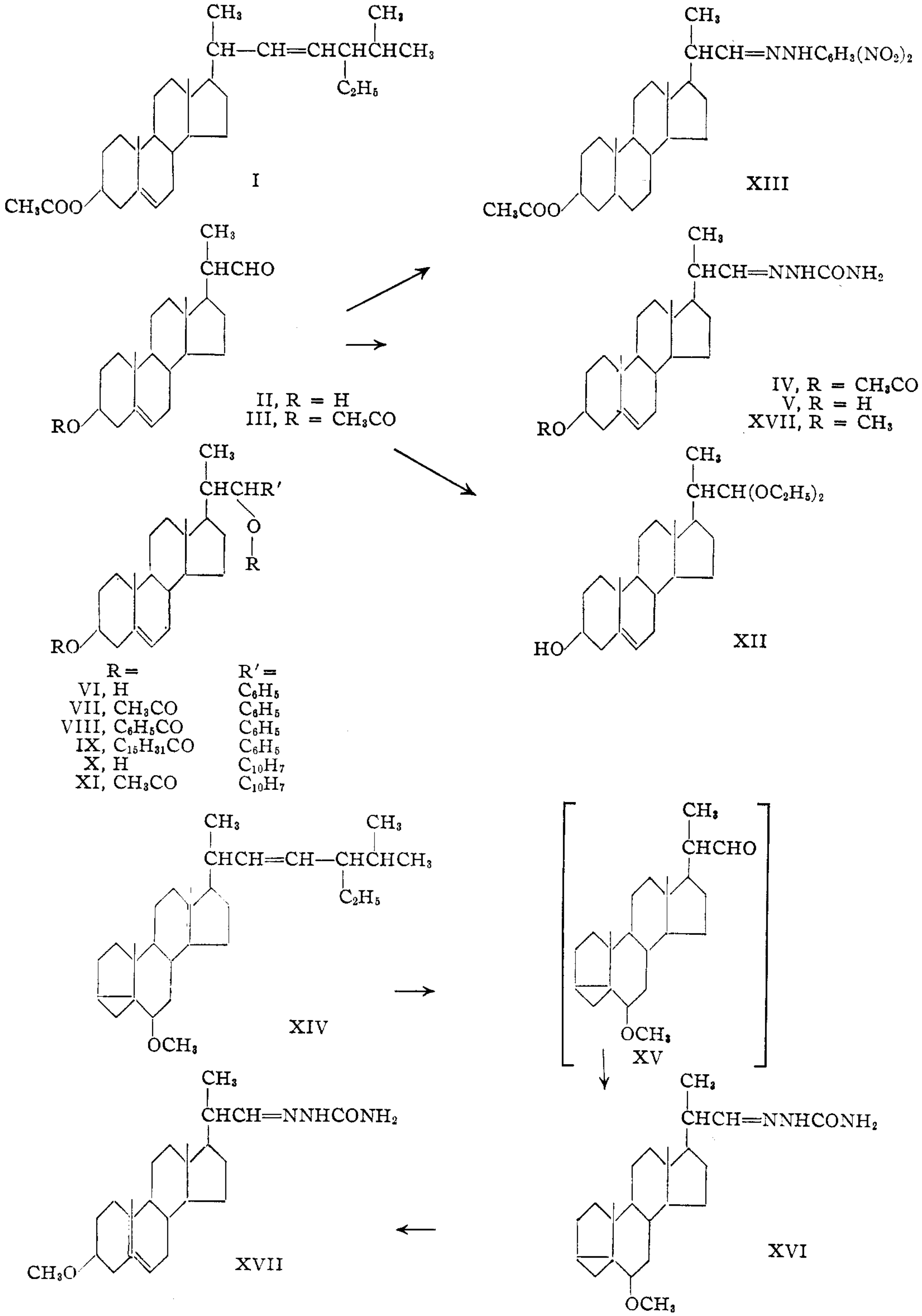
[1] Fernholz, *Ann.*, **507**, 132 (1933).

[2] Butenandt and Fleischer, *Ber.*, **70**, 96 (1937).

[3] Riegel, Meyer and Beiswanger, THIS JOURNAL, **65**, 325 (1943).

[4] Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).



melting point of the latter was 129–131° while the melting point of the acetate of Fraction I was 137–138°. The acetyl numbers of both fractions were practically identical and correspond closely to that required for stigmasteryl acetate.

*Anal.* Calcd. for $C_{29}H_{47}O{\cdot}COCH_3$: $CH_3CO$, 9.5%. Fraction I. 0.5458 g. required 12.3 ml. of 0.1 *N* alkali. Found: 9.7% $CH_3CO$. Fraction III. 0.4300 g. required 9.75 ml. of 0.1 *N* alkali. Found: 9.75% $CH_3CO$.

The ketonic fraction weighed but 80 milligrams. It was dissolved in ethanol and warmed with 0.2 g. of semicarbazide hydrochloride and an equal amount of sodium acetate. After isolating a semicarbazone and washing with hexane and ether the product was redissolved in

TABLE I

OZONOLYSIS OF 6 G. OF STIGMASTERYL ACETATE IN 300 ML. OF CHLOROFORM[a]

| Ozone,[b] % | 3-Acetoxy-bisnor-5-cholenic acid, g. | % | Total neutral fraction, g. | 3-Acetoxy-bisnor-5-cholenaldehyde, g. | % | Sterol recovered, g. |
|---|---|---|---|---|---|---|
| 258 | 1.2 | 23.4 | 3.60 | 0.66 | 13.5 | 1.0 |
| 206 | 1.05 | 20.5 | 3.85 | .94 | 19.1 | 1.25 |
| 174 | 0.2 | 3.9 | .. | 1.02 | 20.7 | 1.72 |
| 106 | .0 | 0.0 | 5.66 | 0.96 | 19.6 | 2.2 |

[a] Blank determinations showed that approximately 35% of the ozone was destroyed when passing through this amount of chloroform. [b] The ozone was formed by passing dry oxygen through a commercial ozonizer (U. S. Air). The oxygen–ozone mixture was led into the ozonization cylinder through a three-way stopcock which permitted periodic sampling to determine the ozone content. It also afforded a convenient trap for the pre-ozonization warm-up period (twenty–forty minutes) necessary to reach a constant level of ozone. A potassium iodide trap placed behind the ozonization chamber was titrated to give the amount of unchanged ozone passing through the reaction mixture. Sampling during the ozonization showed that a uniform amount of ozone could be maintained for two to three hours at the rate of 0.02 g. per minute.

alcohol and reprecipitated by the cautious addition of water. It decomposed at 250–260° and upon analysis showed a possible composition of the semicarbazone of pregnenolone.

*Anal.* Calcd. for $C_{22}H_{35}N_3O_2$: N, 11.25. Found: N, 11.79.

From the recovered crystalline neutral sterol fraction consisting largely of stigmasteryl acetate, ozonolysis, as expected, yielded 3-acetoxy-bisnor-5-cholenic acid to the extent of approximately 20%.

**Ozonolysis of Dibromostigmasteryl Acetate in the Presence of Pyridine.**—Observation of an acid reaction after ozonization led to the use of pyridine (5 ml. per 300 ml. of chloroform) during ozonolysis, and washing the base out before taking off the chloroform. This increased the average yield of semicarbazone to 50%, as shown in Table II.

TABLE II

OZONOLYSIS OF DIBROMOSTIGMASTERYL ACETATE IN CHLOROFORM AND PYRIDINE

| Amount stigmasteryl acetate, g. | Ozone, % | 3-Acetoxy-bisnor-5-cholenic acid, g. | 3-Acetoxy-bisnor-5-cholenaldehyde, g. | % | Sterol recovered, g. |
|---|---|---|---|---|---|
| 4.54 | 205 | 0.06 | 1.67 | 44 | 1.4 |
| 4.54 | 200 | .14 | 1.52 | 41 | 1.4 |
| 9.08 | 200 | .47 | 4.6 | 61 | 2.4 |

**3-Acetoxy-bisnor-5-cholenaldehyde Semicarbazone (IV) from the Acid Chloride.**—Three and four-tenths grams of 3-acetoxy-bisnor-5-cholenyl chloride was dissolved in 75 ml. of xylene. This was reduced by the use of 0.2 g. of palladium–barium sulfate catalyst and 0.2 ml. of a quinoline sulfur mixture[5] at the boiling point. The hydrochloric acid evolved neutralized 34 ml. of 0.2 *N* alkali, equivalent to 81%. However, this required two further additions of the catalyst. After one hour 9 ml. of the alkali had been neutralized and a second addition of the catalyst induced a further evolution of hydrochloric acid. At the end of the second hour 16 ml. of alkali had been neutralized. A third charge of catalyst and another one and one-quarter hours brought the total acid evolved equivalent to 34 ml. of 0.2 *N* alkali.

The catalyst was removed by filtration and washed with ether. The combined filtrates were shaken with dilute sodium carbonate solution and then with water and dried over anhydrous sodium sulfate. The solvents were removed and the residue boiled with 95% alcohol, cooled and filtered from the insoluble material (m. p. 218–220°).

The alcoholic filtrate made up to 100 ml. and refluxed with semicarbazide hydrochloride and sodium acetate and then distilled to dryness. The residue, after washing many times with water and ether, weighed 0.5 g. and melted at 209°. Recrystallization left the melting point unchanged and a mixed melting point with the semicarbazone isolated from ozonolysis showed no depression (yield 14%).

*Anal.* Calcd. for $C_{25}H_{39}N_3O_3$: C, 69.89; H, 9.15; N, 9.76. Found: C, 69.60; H, 8.80; N, 9.98.

The alcohol insoluble fraction was boiled with acetic anhydride and filtered hot. On cooling, a substance separated which after recrystallization from a mixture of acetic acid and ethyl acetate melted at 220–225°. Analysis indicated it might be the diacetate of 3-hydroxybisnor-5-cholenol.

*Anal.* Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.67; $CH_3CO$, 20.6. Found: C, 74.73; H, 9.89; $CH_3CO$, 18.8

The free alcohol recovered from the acetyl analysis melted at 275–280°.[6]

***i*-Stigmasteryl Methyl Ether (XIV)** was prepared by the method of Fernholz.[7] Ten and one-half grams of stigmasteryl *p*-tosylate ($[\alpha]^{27}\text{D}$ −46.15°) was refluxed with an equal weight of fused sodium acetate and 600 ml. of absolute methanol for three hours and the crude *i*-methyl ether was separated in the usual manner. It weighed 8.35 g. The oil was dissolved in Skellysolve B and chromatographed over a column of 100 g. of alumina (Brockmann) with the results shown in Table III, using 200-ml. portions of the solvent.

Fractions 1 and 2 yielded 6.52 g. of *i*-stigmasteryl methyl ether or 82% of the calculated amount. It was dissolved in warm acetone from which it separated as an oil which eventually crystallized in blocks upon standing in the ice chest. It melted at 47–50°; $[\alpha]^{26}\text{D}$ +35.0.

Fractions 5, 6 and 7 were crystalline and melted at 115–118°. Recrystallized from ether–alcohol the melting point was 122°.

*Anal.* Calcd. for $C_{29}H_{47}OCH_3$: C, 84.44; H, 11.81. Found: C, 84.10; H, 12.30.

It appears that an appreciable amount of the normal 3-methyl ether corresponding to at least 10% of the product results from this reaction.

**Ozonolysis of *i*-Stigmasteryl Methyl Ether (XIV).**—A solution of 3.2 g. of *i*-stigmasteryl methyl ether in 150 ml. of ethyl acetate was ozonized at 0° with various amounts of ozone. The ozonide was decomposed catalytically

TABLE III

*i*-STIGMASTERYL METHYL ETHER CHROMATOGRAM

| Fraction no. | Solvent | Weight, g. |
|---|---|---|
| 1 | Skellysolve B | 3.235 |
| 2 | Skellysolve B | 3.285 |
| 3 | Skellysolve B | 0.23 |
| 4 | Skellysolve B | .04 |
| 5 | Skellysolve B + 10% benzene | .22 |
| 6 | Skellysolve B + 10% benzene | .24 |
| 7 | Skellysolve B + 20% benzene | .21 |
| 8 | Skellysolve B + 20% benzene | .06 |
| 9 | Skellysolve B + 50% benzene | .04 |
| 10 | Skellysolve B + 50% benzene | .08 |

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(5) Rosenmund and Zetzsche, *Ber.*, **54**, 436 (1921); "Organic Syntheses," Vol. XXI, p. 87.

(6) Johannessohn and Hatzig, U. S. Patent 2,259,698, indicated an alcohol of this composition melting at 202–206°.

(7) Fernholz and Ruigh, THIS JOURNAL, **62**, 3347 (1940).

using palladium on calcium carbonate and hydrogen at atmospheric pressure.[8] To the filtrate from the catalyst 1.5 g. each of semicarbazide hydrochloride and sodium acetate and 2 ml. of water was added and after refluxing for one hour the reaction mixture was concentrated to a small volume. The semicarbazone (XVI) of 6-methoxy-bisnor-*i*-cholenaldehyde was extracted with ether and the solution washed with alkali, water, and dried over anhydrous sodium sulfate. A viscous residue, obtained after evaporation of the ether, was twice refluxed with hexane leaving a colorless solid weighing 0.9 g. that melted at 182–185°. Recrystallized from dilute alcohol it melted at 188–190°; yield 30%.

*Anal.* Calcd. for $C_{24}H_{39}N_3O_2$: N, 10.45. Found: N, 10.26; $[\alpha]^{26}\text{D}$ +213° (0.314 g. made up to 10 cc. with chloroform, $[\alpha]^{26}\text{D}$ +0.67°, *l*, 1 dm.)

**3-Methoxy-bisnor-5-cholenaldehyde Semicarbazone (XVII).**—6-Methoxy-bisnor-*i*-cholenaldehyde semicarbazone (XVI), 475 mg., was dissolved in 25 ml. of warm methanol, 2 drops of hydrochloric acid added and the solution refluxed thirty minutes. After adding 2 drops of water, the compound began to come out. The solution was cooled and filtered. The precipitate was washed well with ether and small amounts of methanol then recrystallized from methanol to give 3-methoxy-bisnor-5-cholenaldehyde semicarbazone, yield 200 mg., m. p. 204–206°.

*Anal.* Calcd. for $C_{24}H_{39}N_3O_2$: N, 10.45. Found: N, 10.17; $[\alpha]^{26}\text{D}$ −59.85° (0.0598 g. made up to 10 cc. with chloroform, $\alpha^{26}\text{D}$ −0.358°, *l*, 1 dm.).

**Hydrolysis of 3-Acetoxy-bisnor-5-cholenaldehyde Semicarbazone (IV).**—One and six-tenths grams of the semicarbazone, 175 ml. of alcohol and 85 ml. of 5 *N* sulfuric acid were refluxed vigorously on the steam-bath for one hour. One hundred ml. of alcohol was removed by distillation and the reaction mixture on standing in the ice chest overnight became turbid. It was ether extracted. At the interface between the acid and ether layers material separated which decomposed at 234–235°. Recrystallized from alcohol it melted and decomposed at 241–242°. The ether solution was dried over anhydrous sodium sulfate and further quantities of this material flocked out. It was recovered by extracting the drying agent with chloroform and recrystallizing from alcohol. It is 3-hydroxybisnor-5-cholenaldehyde semicarbazone (V).

*Anal.* Calcd. for $C_{23}H_{37}N_3O_2$: N, 10.84. Found: N, 10.87.

The residue obtained upon evaporation of the dried ether extract was allowed to crystallize from a small volume of ether and 0.3 g. of unaltered starting material separated. The filtrate amounting to 5 ml. contained 0.55 g. of a substance which was not nitrogen-free. This material on further manipulation did not display the ether solubility which it had previously exhibited. It was dissolved in alcohol and precipitated in three fractions with water. Analysis of these indicated that they were mixtures which contained approximately 30% of the semicarbazone. (Found: C, 77.7; H, 10.0; N, 3.5).

**3-Acetoxy-bisnor-5-cholenaldehyde, 2,4-Dinitrophenylhydrazone (XIII).**—The crude aldehyde in methanol solution was refluxed with an excess of 2,4-dinitrophenylhydrazine. On cooling, the insoluble yellow hydrazone precipitated. The product was soluble in chloroform and was repeatedly crystallized from a mixture of boiling chloroform and methanol. It melted at 247–248°.

*Anal.* Calcd. for $C_{30}H_{40}N_4O_6$: N, 10.14. Found: N, 10.20; $[\alpha]^{28}\text{D}$ −25.9° (0.0231 g. made up to 10 cc. with chloroform, $\alpha^{28}\text{D}$ −0.06°, *l*, 1 dm.).

**Diethyl Acetal of 3-Hydroxy-bisnor-5-cholenaldehyde (XII).**—An ethereal solution of the neutral alcohol-soluble fraction from the ozonization containing the 3-acetoxy-bisnor-5-cholenaldehyde was diluted with benzene and distilled to remove the last traces of moisture; freshly distilled ethyl orthoformate and 2 drops of sulfuric acid was added. The volume of the solution was reduced during one hour by slow distillation. The solution was made alkaline, poured into water and extracted with ether. The 3-hydroxy acetal is separated best after saponification with 1% alcoholic potash, whereupon it is again precipitated with water and re-extracted with ether. Upon removal of the ether the diethyl acetal of 3-hydroxy-bisnor-5-cholenaldehyde was recrystallized repeatedly from hexane. It melts at about 175°, depending upon the rate of heating.

*Anal.* Calcd. for $C_{26}H_{44}O_3$: C, 77.20; H, 10.96. Found: C, 77.36; H, 10.69.

**22-Phenyl-3-hydroxy-bisnor-5-cholenol (VI).**[2]—The amount of aldehyde in an ether solution of the neutral fraction, obtained by ozonization of 9 g. of stigmasteryl acetate in the presence of pyridine as described, was determined by taking an aliquot and making the semicarbazone. The remaining solution (representing 8.1 g. of stigmasteryl acetate) was dissolved in toluene and most of the toluene distilled to remove any traces of moisture. The residual solution was dropped slowly into an ether solution of phenylmagnesium bromide (prepared from 3.7 g. of magnesium and 24 g. of bromobenzene). After all had been added, the ether was distilled and the reaction mixture heated for one hour on the steam-bath. The mixture was poured upon ice and ammonium chloride and extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid, dilute alkali and water. After removal of the solvent, the residue was steam distilled. A solid separated; the water was decanted and the dried residue was shaken with small volume of ether which left an insoluble crystalline residue which weighed 1.25 g. and melted at 236–237°. This substance can be crystallized readily from acetone, toluene, hexane, alcohol or ethyl acetate. It is soluble in cold chloroform. It separated from ethanol and chloroform in stout prisms that melted at 240°.

*Anal.* Calcd. for $C_{28}H_{40}O_2$: C, 82.30; H, 9.89. Found: C, 82.50; H, 9.90.

The yield amounts to 18% of the stigmasteryl acetate, 36% of the aldehyde employed.

**Diacetate (VII).**[2]—When the above diol was allowed to stand overnight with an excess of acetic anhydride and pyridine, the corresponding diacetate which melts at 216–217° was formed quantitatively. It crystallizes in silky needles from ethanol.

*Anal.* Calcd. for $C_{32}H_{44}O_4$: C, 77.98; H, 9.00; $CH_3CO$, 17.4. Found: C, 77.74; H, 9.04; $CH_3CO$, 17.5.

The carbinol recovered from the determination of the acetyl value melted at 241°.

**Dibenzoate (VIII).**[9]—This was prepared quantitatively using benzoyl chloride in the presence of pyridine. It crystallized from alcohol and chloroform in needles that melted at 234–235°.

*Anal.* Calcd. for $C_{42}H_{48}O_4$: C, 81.78; H, 7.84; $C_6H_5CO$, 34.08. Found: C, 81.77; H, 7.78; $C_6H_5CO$, 34.7.

**Dipalmitate (IX).**—The dipalmitate could be prepared quantitatively from the diol, using palmityl chloride in pyridine. This waxy substance crystallized from acetone in crusts that became translucent at 45–50°.

*Anal.* Calcd. for $C_{60}H_{100}O_4$: $C_{15}H_{31}CO$, 54.1. Found: $C_{15}H_{31}CO$, 58.2.

**Mono-tosylate.**—One gram of diol was dissolved in 50 ml. of pyridine and treated with 0.935 g. (1 mole) toluene sulfonyl chloride. The reaction mixture was allowed to stand twenty hours when it was poured upon ice and sodium bicarbonate (1 g.). The white solid which separated when dried on a porous plate decomposed at 145–148°, showing signs of melting lower. It is a mixture of unaltered diol and the tosyl ester. The product was taken up in ether, thoroughly washed with acid, alkali and water, dried over sodium sulfate and upon concentration 0.82 g. of material separated. This was digested

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[8] Fischer, Düll and Ertel, *Ber.*, **68**, 1467 (1935).

[9] Cole and Julian, This Journal, **67**, 1372 (1945).

with an amount of ether insufficient to dissolve the entire fraction and from the insoluble part the diol was recovered. The ether solution was concentrated and after discarding the first crop of crystalline material a second crop, decomposing at 139–140°, analyzed for a mono-tosyl ester.

*Anal.* Calcd. for $C_{35}H_{46}O_4S$: S, 5.7; Found: S, 5.35.

**22-α-Naphthyl-3-hydroxy-bisnor-5-cholenol (X).**—This compound was made in the same manner as the phenyl analog using α-naphthylmagnesium bromide. After several recrystallizations from chloroform and toluene it sublimed at 245°.

*Anal.* Calcd. for $C_{32}H_{42}O_2$: C, 83.66; H, 9.22. Found: C, 83.84; H, 9.29.

**Diacetate (XI).**—This compound was made by the usual method of treating the diol with acetic anhydride in pyridine. After recrystallization from alcohol, it melted at 198–200°.

*Anal.* Calcd. for $C_{36}H_{46}O_4$: C, 79.56; H, 8.54; $CH_3CO$, 15.8. Found: C, 79.80; H, 8.50; $CH_3CO$, 14.2.

## Summary

1. A method is described for the preparation of 3-acetoxy-bisnor-5-cholenaldehyde semicarbazone (IV) in 50% yields, by the ozonolysis of dibromostigmasteryl acetate in the presence of pyridine.

2. The following compounds have been prepared: (a) 3-acetoxy-bisnor-5-cholenaldehyde semicarbazone (IV); (b) 3-hydroxy-bisnor-5-cholenaldehyde semicarbazone (V); (c) 3-acetoxy-bisnor-5-cholenaldehyde 2,4 dinitrophenylhydrazone (XIII); (d) the diethyl-acetal of 3-hydroxy-bisnor-5-cholenaldehyde (XII); (e) 22-phenyl-3-hydroxy-bisnor-5-cholenol (VI). From this diol (e) the following esters were prepared: (f) diacetate (VII); (g) dibenzoate (VIII); (h) dipalmitate (IX); (i) a mono-tosyl ester; (j) 22-α-naphthyl-3-hydroxy-bisnor-5-cholenol (X) and its diacetate (XI).

3. The ozonolysis of *i*-stigmasteryl methyl ether (XIV) yielded 30% of the 6-methoxy-bisnor-*i*-cholenaldehyde (XV), which was isolated as the semicarbazone (XVI), and this converted to 3-methoxy-bisnor-5-cholenaldehyde semicarbazone (XVII).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Derivatives of γ-Valerolactone, 1,4-Pentanediol and 1,4-Di-(β-cyanoethoxy)-pentane[1]

BY ROBERT V. CHRISTIAN, JR.,[2] HORACE D. BROWN AND R. M. HIXON

Catalytic reduction of levulinic acid to γ-valerolactone and 1,4-pentanediol was studied in the early war period as a source for pentadiene.[3] Availability of the diol led to the condensation with acrylonitrile and the catalytic reduction of the resulting cyanoethoxy derivative to the corresponding diamine. From the diamine a series of salts was prepared for investigation as possible linear polymer intermediates or surface active agents.

## Experimental[4]

**Materials.**—A technical grade of levulinic acid was used. It was found necessary to distil the acid *in vacuo* to free it from catalyst poisons (presumably mineral acids). Ethyl levulinate was prepared by the method of Ruzicka.[5] The acrylonitrile (Eastman Kodak Co. Practical grade) was used without further treatment. Raney nickel and copper–chromium oxide catalysts were prepared in the usual manner.[6] The acids used for the preparation of salts were either reagent grade or suitably purified practical or technical grades.

**Reduction Procedure.**—Hydrogenations were carried out in steel rocking bombs of standard design. Small runs (one mole or less of reactant) were made in a 500-ml. bomb. Production runs of γ-valerolactone were carried out in a copper-lined unit of 3.85 liters capacity.

**γ-Valerolactone.**[7]—The charge consisted of 580 g. (5 moles) of purified levulinic acid and 15 g. of Raney nickel. Hydrogen was introduced to an initial pressure of 700 p.s.i. The reduction started at about 100° and was complete after three hours. The maximum temperature reached was 220°. Separation of the catalyst and distillation of the reaction mixture gave 471 g. (94%) of γ-valerolactone; b. p. 87–90° (8–10 mm.).

**1,4-Pentanediol. A. From γ-Valerolactone.**—Using the method of Folkers and Adkins,[8] hydrogenations were made with 100 g. (1 mole) of γ-valerolactone, 6–8 g. of copper–chromium oxide catalyst and initial hydrogen pressures of 200 atmospheres. Yields of 1,4-pentanediol varied from 32 to 83%, the higher yields being obtained at a temperature of 240–260°. Reductions made at 270–290° gave low yields of diol and a low-boiling fraction (70–100°) from which a sample of α-methyltetrahydrofuran (b. p. 78–80°, $d^{20}_{4}$ 0.8548, $n^{20}_{D}$ 1.406[9]) was isolated.

**B. From Ethyl Levulinate.**—Hydrogenation of ethyl levulinate (0.7 mole, 8 g. copper–chromium oxide catalyst) without solvent at 250° and 200 atmospheres initial hydrogen pressure gave 72% of 1,4-pentanediol.

**C. From Levulinic Acid.**—The charge consisted of 92.8 g. (0.8 mole) of distilled levulinic acid and 8 g. of copper–chromium oxide catalyst with an initial hydrogen pressure of 200 atmospheres. Reduction, which began at 190° with a gage pressure of 267 atmospheres, took place

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(1) Taken in part from a thesis submitted by Robert V. Christian' Jr., to the Graduate Faculty of Iowa State College in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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(3) Unpublished studies by Horace D. Brown.

(4) All melting points and boiling points are uncorrected.

(5) Ruzicka, *Ber.*, **50**, 1367 (1917).

(6) Adkins, "Reactions of Hydrogen with Organic Compounds over Copper–Chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 20, 13.

(7) This method for the preparation of γ-valerolactone was developed during September, 1943. U. S. Patent 2,368,366 (*C. A.*, **39**, 4626 [1945]), which was granted January 30, 1945, describes essentially the same process.

(8) Folkers and Adkins, THIS JOURNAL, **54**, 1145 (1932).

(9) Compare Zelinskii and Shuikin, *Compt. rend. acad. sci. U. R. S. S.*, 60 (1933) [ *C. A.*, **28**, 2002 (1934)].