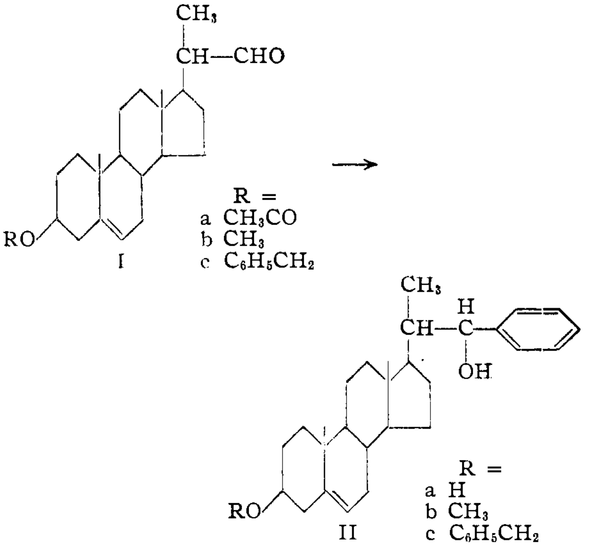
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY]

Derivatives of bisnor-5-Cholenaldehyde. II

BY A. P. CENTOLELLA, F. W. HEYL AND M. E. HERR

The ozonization of dibromostigmasteryl acetate to give 3-acetoxy-bisnor-5-cholenaldehyde (Ia), isolated as the semicarbazone, was reported recently.[1] The semicarbazone could not be hydrolyzed to give a pure aldehyde. We have now been able to obtain the aldehyde in the pure state by separating it as its bisulfite addition complex, and decomposing this product with either base or acid.

The reaction of the crystalline aldehyde (Ia) with phenylmagnesium bromide gave 22-phenyl-3,22-dihydroxy-bisnor-5-cholene (IIa)[1] in 73% yield. These reactions have been extended to the 3-methoxy and 3-benzyloxy ethers of stigmasterol giving the analogous aldehydes (Ib, Ic), and the respective 22-phenyl-3-alkoxy-22-hydroxy-bisnor-5-cholenes (IIb, IIc).



The 3-methyl, ethyl, *n*-butyl and benzyl ethers of stigmasterol were prepared by the method of Stoll.[2] Only the 3-methyl ether has been described previously.

i-Stigmasteryl *n*-butyl and benzyl ethers were prepared by the procedure of Fernholz and Ruigh[3] for *i*-stigmasteryl methyl ether. Although neither compound was obtained crystalline and both gave low carbon values, the positive rotation and the almost quantitative conversion of each to the 3-methyl ether of stigmasterol[4] indicated that the substances were the desired *i*-ethers.

i-Stigmastatriene, a possible by-product from the *i*-ether preparations, and one which would give the same reactions with alcohols as the *i*-ethers, was prepared for comparative purposes following the literature method for *i*-cholestadiene.[5] *i*-Stigmastatriene melted at 81–82° and had a negative rotation.

Experimental[6]

3-Substituted-bisnor-5-cholenaldehydes.—The ozonizations were conducted in the presence of pyridine as reported previously.[1] After the ozonolysis and decomposition of the ozonide, an addition to the procedure consisted of treating the neutral alcohol-soluble residue with hexane. This, in the case of the 3-acetoxy compound, gave, in yields up to 10%, a crystalline, hexane insoluble substance. This material, which has not been identified, melted at 120–121° after recrystallization. The ethers gave little or no analogous material.

3-Acetoxy-bisnor-5-cholenaldehyde.—After the ozonization and decomposition of the ozonide as reported previously,[1] the neutral alcoholic filtrate, from 9.08 g. of stigmasteryl acetate, was taken to dryness under reduced pressure and nitrogen. The residue was treated with 50 ml. of hexane producing a nicely crystalline hexane insoluble fraction which, after cooling, filtering, washing with cold hexane and recrystallizing from hot hexane, melted at 120–121° and weighed 1.05 g.

The hexane filtrate and washings were concentrated under reduced pressure and nitrogen. The residue was taken up in 50 ml. of methanol and shaken with 100 ml. of 40% sodium bisulfite solution for ten minutes. To the non-filtrable gel-like mixture was added 250 ml. of ether and the mixture shaken. Then ice water was added cautiously and the mixture separated into two layers with the addition compound at the interface. After drawing off most of the aqueous phase the mixture was centrifuged and the ether decanted. The solid was washed twice with ice water and twice with ether in the centrifuge cup, centrifuging each time and decanting the wash liquor. The solid bisulfite compound weighed 2.54 g. after drying in a desiccator.

To 60 ml. of 10% sodium carbonate in a separatory funnel, was added 1 g. of the finely ground bisulfite addition compound and 150 ml. of ether. Nitrogen was bubbled through until the addition compound disappeared. The aqueous layer was drawn off and extracted with ether and the combined ether solutions washed with water until neutral, then dried over sodium sulfate. The solvent was removed in the cold by passing nitrogen through the solution, leaving a nicely crystalline aldehyde weighing 0.79 g., melting at 116–117°, and giving the same semicarbazone previously reported.[1]

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.40; H, 9.74; CH_3CO, 11.5. Found: C, 76.85, 76.80; H, 9.50, 9.37; CH_3CO, 12.5, 12.6.

3-Methoxy-bisnor-5-cholenaldehyde.—This was made in a manner similar to that described above, isolated as the bisulfite addition compound which gave the aldehyde melting at 104–105° after recrystallizing from hexane.

---

[1] Heyl, Centolella and Herr, THIS JOURNAL, **69**, 1957 (1947).

[2] Stoll, *Z. physiol. Chim.*, **207**, 151 (1932).

[3] Fernholz and Ruigh, THIS JOURNAL, **62**, 3347 (1940).

[4] McKennis, *ibid.*, **69**, 2565 (1947), has published a similar reaction of *i*-cholesteryl methyl ether in the presence of *p*-toluenesulfonic acid and *n*-propanol, obtaining the 3-*n*-propyl ether of cholesterol. We have observed that *i*-stigmasteryl methyl ether in the presence of sulfuric acid and ethanol is converted quantitatively to the 3-ethyl ether of stigmasterol.

[5] Riegel, Hager and Zenitz, *ibid.*, **68**, 2563 (1946). These authors showed that *i*-cholestadiene in the presence of sulfuric acid and methanol gave the 3-methyl ether of cholesterol.

[6] We are indebted for the microanalyses and rotations to the following members of our analytical department: H. Emerson, Wm. Struck, B. Fausnaugh, C. Triemstra, R. Shaw and R. Anderson. All melting points are uncorrected.

The yield of pure aldehyde was 30% as isolated from the reaction, or 41% allowing for recovered starting material. The semicarbazone gave no m. p. depression with that reported earlier.[1]

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.24; H, 10.53. Found: C, 80.35; H, 10.40.

2,4-Dinitrophenylhydrazone.—This was made in the usual fashion by refluxing 3-methoxy-bisnor-5-cholenaldehyde and an ethanolic hydrochloric acid solution of 2,4-dinitrophenylhydrazine. The hydrazone separated and was recrystallized from methanol and chloroform, m. p. 217°.

Anal. Calcd. for $C_{29}H_{40}O_5N_4$: N, 10.68. Found: N, 10.69.

3-Benzyloxy-bisnor-5-cholenaldehyde.—This was made in the manner described except that some of the aldehyde could be obtained directly by concentrating the neutral ether solution to a small volume. The remainder was isolated as bisulfite addition product. The aldehyde obtained by either method melted at 133–136° after recrystallizing from dilute acetone. The yield was 30% as isolated from the reaction, or 40% allowing for recovered starting material.

Anal. Calcd. for $C_{29}H_{40}O_2$: C, 82.81; H, 9.59. Found: C, 82.59, 82.48; H, 9.45, 9.43.

Semicarbazone of 3-Benzyloxy-bisnor-5-cholenaldehyde.—This compound was made in the usual way using semicarbazide hydrochloride, sodium acetate and the aldehyde. After recrystallizing from methanol and chloroform it melted at 244–245°.

Anal. Calcd. for $C_{30}H_{43}O_2N_3$: N, 8.80. Found: N, 8.80, 8.81.

22-Phenyl-3-alkoxy-22-hydroxy-bisnor-5-cholenes.—The reaction of the aldehydes with phenylmagnesium bromide was run in the manner described previously[1] except that a benzene solution of the pure aldehyde was used. This gave 70% yields of the carbinols.

22-Phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene.—This was recrystallized from methanol and chloroform and melted at 207–208° after being prepared in the same fashion.

Anal. Calcd. for $C_{29}H_{42}O_2$: C, 82.43; H, 10.02. Found: C, 82.36; H, 9.90; $[\alpha]^{25}\mathrm{D}$ −45.4 (0.0916 g. made up to 10 ml. with chloroform, $\alpha^{25}\mathrm{D}$ −0.416, *l*, 1 dm.).

22-Phenyl-3-benzyloxy-22-hydroxy-bisnor-5-cholene.—This was prepared by the Grignard reaction as described. After recrystallization from methanol and chloroform, it melted at 203–204°.

Anal. Calcd. for $C_{35}H_{46}O_2$: C, 84.28; H, 9.30. Found: C, 84.00, 84.34; H, 9.27, 9.47.

Ethers of Stigmasterol.—The 3-methyl,[2] ethyl, *n*-butyl and benzyl ethers of stigmasterol were prepared by the method of Stoll,[2] *e. g.*, heating stigmasteryl tosyl ester with the appropriate alcohol.

3-Ethyl Ether.—Stoll[7] had mentioned the reaction but gave no properties of stigmasteryl ethyl ether. The compound melted at 98–100° after recrystallizing from acetone.

Anal. Calcd. for $C_{31}H_{52}O$: C, 84.48; H, 11.90. Found: C, 84.49, 84.21; H, 11.60, 11.83; $[\alpha]^{28}\mathrm{D}$ −38.5 (0.0935 g. made up to 10 ml. with chloroform, $\alpha^{28}\mathrm{D}$ −0.36, *l*, 1 dm.).

3-*n*-Butyl Ether.—This was recrystallized from acetone and melted at 109–110°.

Anal. Calcd. for $C_{33}H_{56}O$: C, 84.55; H, 12.03. Found: C, 84.13, 84.39; H, 12.25, 12.36; $[\alpha]^{26.5}\mathrm{D}$ −47.4 (0.0780 g. made up to 10 ml. with chloroform, $\alpha^{26.5}\mathrm{D}$ −0.37, *l*, 1 dm.).

3-Benzyl Ether.—This was recrystallized from acetone and melted to a clear melt at 99–100°, resolidified while heating was slowly continued, and then melted at 118–119°.

Anal. Calcd. for $C_{36}H_{54}O$: C, 86.00; H, 10.72. Found: C, 86.51, 86.27; H, 11.00, 10.91; $[\alpha]^{26}\mathrm{D}$ −39.5 (0.2098 g. made up to 10 ml. with chloroform, $\alpha^{26}\mathrm{D}$ −0.83, *l*, 1 dm.).

***i*-Stigmasteryl *n*-butyl ether** was prepared from 5.0 g. of stigmasteryl *p*-tosylate by the method of Fernholz and Ruigh.[3] In this reaction part of the tosylate was converted to the normal ether. These were separated by chromatography over alumina (Fisher adsorption). The mixture was adsorbed from a 1:10 benzene–hexane solution and eluted with hexane followed by ether. The hexane fractions contained the *i*-ether which was obtained as a colorless oil in 60% yield.

Anal. Calcd. for $C_{33}H_{56}O$: C, 84.55; H, 12.03. Found: C, 83.87, 83.67; H, 11.83, 11.83; $[\alpha]^{28}\mathrm{D}$ +29.1 (0.1340 g. made up to 10 ml. with chloroform, $\alpha^{28}\mathrm{D}$ +0.39, *l*, 1 dm.).

The ether eluate contained 1.10 g. of crystalline normal *n*-butyl ether of stigmasterol, which upon recrystallization from acetone melted at 109–110° and gave no melting point depression with the 3-*n*-butyl ether described above.

When 185 mg. of the *i*-ether was refluxed in 20 ml. of methanol and 4 drops of concentrated sulfuric acid for twenty minutes, the normal methyl ether of stigmasterol precipitated from the reaction mixture. After cooling this was filtered off and washed with a little methanol to give 150 mg. of crystals, m. p. 121–122°. A mixture melting point with an authentic sample of 3-methyl ether of stigmasterol showed no depression.

***i*-Stigmasteryl benzyl ether** was prepared as above. This compound also proved to be a colorless oil which gave the same reaction with methanol and sulfuric acid to yield the 3-methyl ether of stigmasterol.

Anal. Calcd. for $C_{36}H_{54}O$: C, 86.00; H, 10.82. Found: C, 84.95, 85.14; H, 10.65, 10.52; $[\alpha]^{25}\mathrm{D}$ +37.0 (0.0185 g. made up to 10 ml. with chloroform, $\alpha^{28}\mathrm{D}$ +0.39, *l*, 1 dm.).

***i*-Stigmastatriene.**—This compound was made by the method of Riegel, Hager and Zenitz[6] by refluxing 2.0 g. of *i*-stigmasteryl methyl ether in 350 ml. of dry xylene with 32 g. of activated alumina (Fisher adsorption) for four hours. After removing the alumina by filtration and washing it several times with solvent, the filtrate and washings were distilled under reduced pressure. The residual oil was taken up in 40 ml. of hexane and 4 ml. of benzene and passed through a 40-g. column of activated alumina. On elution with hexane the first five 40-ml. fractions gave 1.0 g. (54%) of colorless crystals which, on recrystallization from acetone, gave stout rods, m. p. 81–82°.

Anal. Calcd. for $C_{29}H_{46}$: C, 88.3; H, 11.70. Found: C, 88.15, 88.06; H, 11.59, 11.65; $[\alpha]^{28}\mathrm{D}$ −67.5 (0.1038 g. made up to 10 ml. with chloroform, $\alpha^{28}\mathrm{D}$ −0.70, *l*, 1 dm.).

Summary

The ozonization of dibromostigmasteryl derivatives to produce bisnor-5-cholenaldehyde has been extended to the 3-methyl and benzyl ethers.

The pure aldehydes—3-methoxy-bisnor-5-cholenaldehyde, m.p. 104–105°, dinitrophenylhydrazone, m.p. 217°, 3-benzyloxy-bisnor-5-cholenaldehyde, m.p. 133–136°, semicarbazone, m.p. 244–245°, and 3-acetoxy-bisnor-5-cholenaldehyde, m.p. 116–117°—were isolated from the ozonization of the appropriate dibromostigmasteryl derivative.

The use of the pure aldehydes in the reaction with phenylmagnesium bromide has given excellent yields and the new compounds, 22-phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene, m.p. 207–208°, and 22-phenyl-3-benzyloxy-22-hydroxy-bisnor-5-cholene, m.p. 203–204°, were prepared.

KALAMAZOO, MICHIGAN RECEIVED APRIL 20, 1948

---

[7] Stoll, *Z. physiol. Chem.*, **246**, 8 (1937).