[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Degradation of 6-Methoxy-*bisnor-i*-cholenic Acid

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In a previous communication,[1] the preparation of 6-methoxy-*bisnor-i*-cholenic acid from stigmasterol was reported. This acid presents a new intermediate for side chain degradation by the Barbier–Wieland[2] procedure since it has been shown that the *i*-ether configuration is stable to the Grignard reagent.[3]

In the cholenic acid series, the critical step proved to be the dehydration of the *i*-ether-diphenylcarbinol. The elimination of water was accomplished with alumina in boiling xylene. However, this method failed in the present *bisnor*-cholenic acid series. The choice of a suitable dehydration reagent is considerably limited by the ease of rearrangement of the *i*-ether configuration under acidic conditions. Thus far all attempts to effect dehydration without damage to the *i*-ether structure have been unsuccessful.

6-Methoxy-*ternor-i*-cholenyldiphenylcarbinol (II) was prepared in two independent fashions: (a) by the reaction of methyl 6-methoxy-*bisnor-i*-cholenate (I) with phenylmagnesium bromide and (b) by the conversion of 3-*p*-toluenesulfonoxy-*ternor*-5-cholenyldiphenylcarbinol (III) into the *i*-ether. This diphenylcarbinol (II) is an interesting example of a levorotatory (−11°) *i*-ether; however, it has a much smaller levorotation than the normal methyl ether (IV, −84°). The carbinol (II) undergoes simultaneous dehydration and rearrangement of the *i*-ether structure when its acidified methanol solution is boiled. The product of this reaction, 3-methoxy-22,22-diphenyl-*bisnor*-5,20-choladiene (V), was also obtained from the *p*-toluenesulfonoxy-diphenylcarbinol (III) on treatment with methanol. The structure of the *bisnor*-choladiene (V) was further established by its synthesis from methyl 3-methoxy-*bisnor*-5-cholenate *via* the diphenylcarbinol (IV).

Since attempted dehydration of the diphenylcarbinol (II) was unsuccessful, the oxidative degradation of the corresponding diphenylethylene (VII) was studied. The *i*-ether-ethylene (VII) was readily obtained from the 3-*p*-toluenesulfonoxy derivative (VI) by reaction with methanol containing potassium acetate. The cleavage of the double bond of 1,1-diphenyl-2-methyl-2-(6-methoxy-*etio-i*-cholenyl)-ethylene was accomplished through ozonolysis; however, no attempt was made to isolate the intermediate 6-methoxy-*i*-pregnene-20-one[4] (VIII). By decomposition of the ozonide in methanol containing sulfuric acid, there resulted 3-methoxy-5-pregnene-20-one (IX) which was separated by chromatography of the crude reaction product. When 6-methoxy-*i*-pregnene-20-one (VIII) was heated in a solution of glacial acetic acid and zinc acetate it was converted into pregnenolone acetate (X).

Evidence indicates that the *i*-ether derivatives are not suitable for easy stepwise degradation of bile-acid side chains by the Barbier–Wieland method because of the difficulty in elimination of water from the *ternor*-cholenyl carbinols. This critical step is being further investigated. Nevertheless, the *i*-ether structure affords sufficient protection for the 3-hydroxyl group and the 5-6 double bond during the cleavage of side-chain double bonds such as that existing in the diphenylethylenes encountered in the Barbier–Wieland degradation process. This method of protection should have considerable merit in those instances where the nuclear double bond cannot be selectively brominated.

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Experimental[5]

6-Methoxy-*ternor-i*-cholenyldiphenylcarbinol (II).—A solution of 1.45 g. of methyl 6-methoxy-*bisnor-i*-cholenate[1] in 20 ml. of dry ether was added slowly, with agitation, to a solution of phenylmagnesium bromide prepared from 6.08 g. of bromobenzene and 0.94 g. of magnesium in 50 ml. of ether. After stirring for three hours, about 50 ml. of ether was removed by distillation and replaced with dry toluene. The opalescent mixture was warmed on a steam-bath for two hours and then decomposed with ice and ammonium chloride. The ethereal extract was washed free of acids and steam distilled. The residue, a yellow gum, was dissolved in ether. The orange sirup remaining after removal of solvent from the washed and dried ether solution crystallized upon addition of methanol to its acetone solution. By repeated crystallization from acetone, the product, 1.18 g. of solid melting at 150–157°, was freed of a small quantity of less soluble impurity which melted at 221–228°. The major fraction, of greater acetone solubility, yielded a white crystalline solid melting at 168–171°. This material showed no depression in melting point when mixed with the carbinol prepared from 3-*p*-toluenesulfonoxy-*ternor*-5-cholenyldiphenylcarbinol. It was later found that the crude carbinol can be purified readily by sublimation at 130–140° in a vacuum of 10^{-4} mm.

3-*p*-Toluenesulfonoxy-*ternor*-5-cholenyldiphenylcarbinol (III).—A mixture of 3.08 g. of 3-hydroxy-*ternor*-5-cholenyldiphenylcarbinol[6] and 2.0 g. of *p*-toluenesulfonyl chloride in 5.0 ml. of dry pyridine was warmed on a steam-bath to effect solution and allowed to stand overnight. The crystalline mass was taken up in ether and water, dilute hydrochloric acid added, and the mixture extracted with ether. The ether layer was washed successively with di-

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[1] B. Riegel, E. W. Meyer and J. Beiswanger, THIS JOURNAL, **65**, 325 (1943).

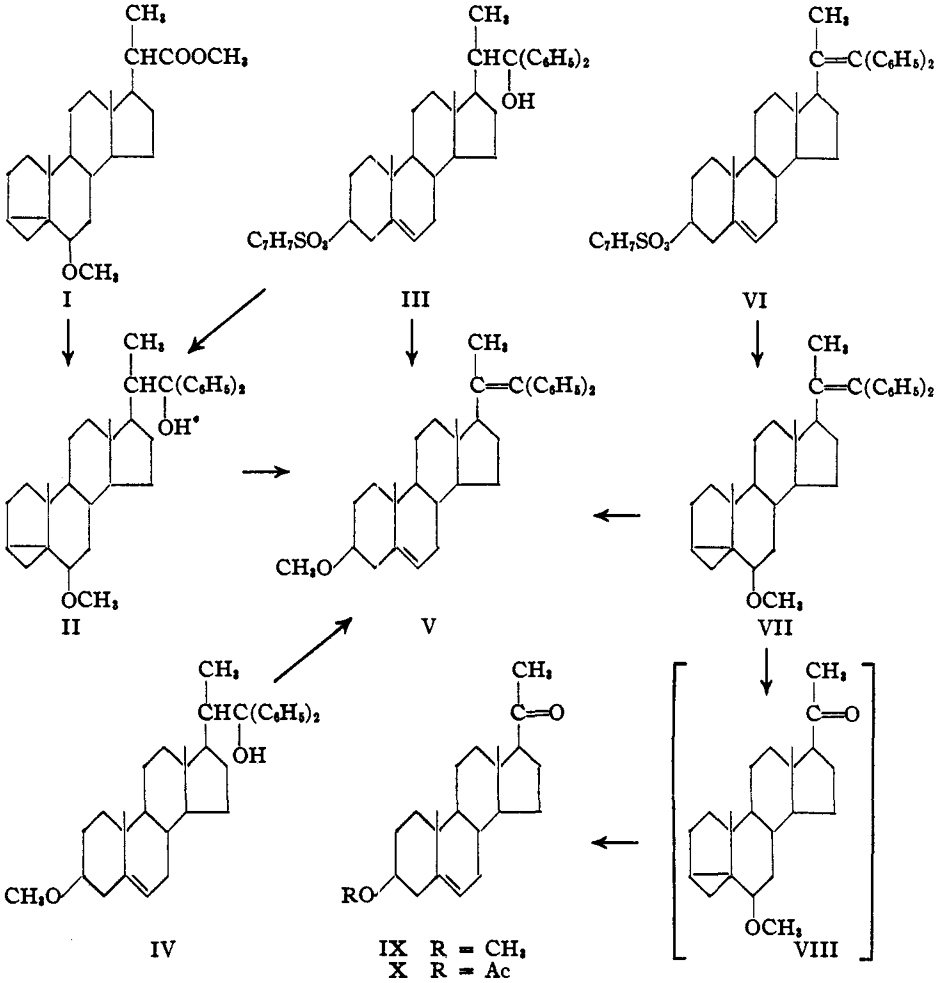
[2] B. Riegel, R. B. Moffett and A. V. McIntosh, "Organic Syntheses," **24**, 38, 41 (1944).

[3] B. Riegel, M. F. W. Dunker and M. J. Thomas, THIS JOURNAL, **64**, 2115 (1942).

[4] A. Butenandt and W. Grosse, *Ber.*, **70**, 1446 (1937).

[5] Analyses by Dr. T. S. Ma, University of Chicago and The Arlington Laboratories, Fairfax, Virginia.

[6] M. Steiger and T. Reichstein, *Helv. chim. acta*, **20**, 1040 (1937).



lute hydrochloric acid, dilute alkali, and water. The white solid remaining after removal of solvent from the dried ether solution was crystallized from acetone–petroleum ether (b. p. 30–60°) yielding 3.04 g. of silky, white needles, melting at 129–133° (dec.). Two recrystallizations from acetone–petroleum ether and one from acetone raised the melting point to 134–134.6° (dec.); $[\alpha]^{24}_{\mathrm{D}}$ −74.64° (28.3 made to 2 ml. with chloroform, α^{24}_{D} −1.06°, l, 1 dm.) The ease of dehydration probably accounts for the high carbon analyses.

Anal. Calcd. for $C_{41}H_{50}O_4S$: C, 77.07; H, 7.88. Found: C, 77.85, 77.98; H, 7.92, 8.20.

6-Methoxy-*ternor*-*i*-cholenyldiphenylcarbinol (II) from the *p*-Tosylate (III).—The *p*-toluenesulfonoxy-carbinol (2.54 g.) was dissolved in 200 ml. of dry methanol containing 2.0 g. of freshly-fused potassium acetate and the solution was refluxed for three and one-half hours. After removing the major portion of the alcohol by distillation, the residue was diluted with water and extracted with ether. The ether extract was washed with water; dilute sodium bicarbonate solution, water and dried. The solution contained 1.94 g. of a white solid which on crystallization from acetone yielded 1.61 g. (81.7%) of material melting at 163–168°. Several recrystallizations from acetone gave clusters of stout needles melting at 171.5–172.5°; $[\alpha]^{26}_{\mathrm{D}}$ −10.97° (21.5 mg. made up to 2 ml. with chloroform, α^{26}_{D} −0.118°, l, 1 dm.).

Anal. Calcd. for $C_{35}H_{46}O_2$: C, 84.28; H, 9.30. Found: C, 84.66; H, 9.53.

3-Methoxy-*ternor*-5-cholenyldiphenylcarbinol (IV).—A solution of 1.60 g. of methyl 3-methoxy-*bisnor*-5-cholenate[1] in 25 ml. of dry ether was added dropwise with stirring to an ether solution (50 ml.) of phenylmagnesium bromide prepared from 6.72 g. of bromobenzene and 1.04 g. of magnesium. After stirring for one hour, the solution was concentrated to 20 ml. by distillation, 50 ml. of dry toluene was added, and then warmed on the steam-bath for one hour. The opalescent mixture was decomposed with ice and dilute hydrochloric acid and extracted with ether. The ether layer was washed with water, dilute sodium hydroxide solution and water; then it was steam distilled to rid it of biphenyl. The remaining yellow gum was taken up in ether, the ether solution washed as before and dried over anhydrous sodium sulfate. The yellow sirup remaining after the removal of solvent crystallized upon the addition of methanol to its acetone solution. The solid weighed 1.80 g. (85%) and melted at 150–156°. After treatment with charcoal and crystallizing five times from acetone–methanol, the product, long, white needles, melted at 164.5–166.5°; $[\alpha]^{26}_{\mathrm{D}}$ −84.31 (34.8 mg. made up to 2 ml. with chloroform, α^{26}_{D} −1.467°, l, 1 dm.).

Anal. Calcd. for $C_{35}H_{46}O_2$: C, 84.28; H, 9.30. Found: C, 84.19; H, 9.33.

3-Methoxy-22,22-diphenyl-*bisnor*-5,20-choladiene (V): (a) By Dehydration of the Carbinol (IV).—A solution of 500 mg. of the 3-methoxycarbinol in 10 ml. of glacial acetic acid was refluxed for three hours. The crystalline precipitate which formed upon slow addition of water to the chilled solution was filtered, washed with water and dried. The product, 480 mg. (99%) of material melting at 175–182°, after four crystallizations from acetone–chloroform yielded long, white needles melting at 188–189.5°;

$[\alpha]^{25}\mathrm{D}$ +212.2° (27.9 mg. made up to 2 ml. with chloroform, $\alpha^{25}\mathrm{D}$ + 2.907°, *l*, 1 dm.).

Anal. Calcd. for $C_{35}H_{44}O \cdot {}^1/_2H_2O$: C, 85.33; H, 9.27. Found: C, 86.03, 86.26; H, 9.40, 9.27.

More rigorous drying *in vacuo* over boiling toluene produced an anhydrous product.

Anal. Calcd. for $C_{35}H_{44}O$: C, 87.44; H, 9.23. Found: C, 87.80; H, 9.55.

(b) **From 3-*p*-Toluenesulfonoxy-*ternor*-5-cholenyldiphenylcarbinol (III).**—A mixture of 200 mg. of the *p*-toluenesulfonate and 35 ml. of anhydrous methanol was refluxed for six hours. The solid dissolved slowly. Upon cooling, fine white needles formed. The mass was diluted with water, filtered, and washed with water yielding 120 mg. of dry material melting at 182–186°. One recrystallization from acetone raised the melting point to 185–187.5°. A melting point of a mixture with the material described above showed no depression.

(c) **From 6-Methoxy-*ternor*-*i*-cholenyldiphenylcarbinol (II).**—A suspension of 500 mg. of the *i*-ether carbinol (II) in 50 ml. of dry methanol containing five drops of concd. sulfuric acid was refluxed for five hours. The carbinol was not overly soluble, but was soon replaced by less soluble, finely divided substance. After cooling, water was added slowly. The precipitated material was filtered, washed with water and dried yielding 460 mg. of material melting at 175–185°. Two crystallizations from acetone–chloroform gave clusters of white needles at 185.5–187°. A melting point of a mixture with authentic ethylene (188–189.5°) gave no indication of depression.

3-*p*-Toluenesulfonoxy-22,22-diphenyl-*bisnor*-5,20-choladiene (VI).—A mixture of 2.06 g. of 3-hydroxy-22,22-diphenyl-*bisnor*-5,20-choladiene, 2.0 g. of *p*-toluenesulfonyl chloride and 3 ml. of dry pyridine was warmed on a steam-bath to effect solution and allowed to stand at room temperature for twenty-four hours. The crystalline mass was taken up in ether and water and the ether layer extracted with dilute hydrochloric acid, dilute sodium carbonate solution and water. After drying the solution and removing the solvent, a yellow sirup remained. On crystallization from acetone–methanol there was obtained 2.24 g. (84%) of white crystalline material melting at 130–140° (dec.). Three recrystallizations from the same solvents yielded white, tapering rods melting at 137–137.5° (dec.) $[\alpha]^{26}\mathrm{D}$ + 194.4° (50.5 mg. made up to 2 ml. with carbon tetrachloride, $\alpha^{26}\mathrm{D}$ + 4.91°, l, 1 dm.). The sample for analysis was dried *in vacuo* at room temperature to prevent decomposition.

Anal. Calcd. for $C_{41}H_{48}O_3S$: C, 79.31; H, 7.79. Found: C, 79.79; H, 7.94.

1,1-Diphenyl-2-methyl-2-(6-methoxy-*etio*-*i*-cholenyl)-ethylene (VII).—A mixture of 790 mg. of the *p*-toluenesulfonate and 4.0 g. of fused potassium acetate in 40 ml. of dry methanol was refluxed for five hours. The *p*-toluenesulfonate went into solution slowly. Water was added and the precipitated solid filtered, washed with water and dried. Crystallization from acetone gave 510 mg. (83%) of small, white crystals melting at 173–178°. After repeated crystallization from acetone, the product, small clear cubes, melted at 180–181.4°, $[\alpha]^{23}\mathrm{D}$ + 329.8° (83.2 mg. made up to 2 ml. with chloroform, $\alpha^{23}\mathrm{D}$ + 13.72°, *l*, 1 dm.).

Anal. Calcd. for $C_{35}H_{44}O$: C, 87.43; H, 9.23. Found: C, 87.68; H, 9.45.

Rearrangement of 1,1-Diphenyl-2-methyl-2-(6-methoxy-*etio*-*i*-cholenyl)-ethylene (VII) to the Normal Ether (V).—A suspension of 370 mg. of the *i*-ether ethylene in 40 ml. of dry methanol containing four drops of concd. sulfuric acid was refluxed for three hours. A crystalline solid separated during the reflux period. The mixture was diluted with water and the solid filtered, washed with water and dried. The white solid weighed 350 mg. and melted at 182–185°. Several recrystallizations from acetone raised the melting point to 187–188°. This material showed no depression in melting point when mixed with an authentic sample of 3-methoxy-22,22-diphenyl-*bisnor*-5,20-choladiene.

Ozonization of 1,1-Diphenyl-2-methyl-2-(6-methoxy-*etio*-*i*-cholenyl)-ethylene (VII).—Ozone (3% O_3 by volume at 1 liter/min.) was bubbled through a solution of 3.0 g. of the *i*-ether in 100 ml. of carbon tetrachloride for 20 minutes at room temperature. After removal of the solvent *in vacuo*, the sirupy residue was dissolved in 100 ml. of dry methanol containing ten drops of concd. sulfuric acid, refluxed for two hours and diluted with water. An ether extract of the reaction mixture was washed with water, dilute alkali, water and dried. The residue, 1.9 g. of an orange sirup, remaining after removal of ether and treatment with charcoal in methanol was dissolved in 40 ml. of hexane and 10 ml. of benzene and chromatographed over an alumina column (1.5 cm. × 14.5 cm.). Elution with hexane–benzene (4:1) yielded an intermediate fraction of 0.5 g. which crystallized upon standing. One crystallization from aqueous methanol gave 0.35 g. of white solid melting at 115–120° after softening at 107°. A recrystallization from methanol raised the melting point to 120–124°. A sample when mixed with pregnenolone methyl ether[4] showed no depression in melting point.

Pregnenolone Acetate (X) from 6-Methoxy-*i*-pregnene-20-one (VIII).—A mixture of 340 mg. of the *i*-ether, 500 mg. of dry zinc acetate, 1.0 ml. of acetic anhydride and 25 ml. of glacial acetic acid was refluxed for two hours. The mixture was diluted with water, the solid filtered, washed with water and dried. The product, 300 mg. of slightly tan plates, was treated with charcoal and crystallized from methanol yielding 260 mg. of white, granular crystals melting at 146–149°. This material gave no depression in melting point when mixed with a sample of pregnenolone acetate.[7]

Summary

1. 6-Methoxy-*ternor*-*i*-cholenyldiphenylcarbinol was prepared by the reaction of methyl 6-methoxy-*bisnor*-*i*-cholenate with phenylmagnesium bromide and by the reaction of 3-*p*-toluenesulfonoxy-*ternor*-5-cholenyldiphenylcarbinol with methanol in the presence of potassium acetate.

2. Attempts to dehydrate this carbinol without destruction of the *i*-ether configuration were unsuccessful.

3. The preparation and ozonolysis of 1,1-diphenyl-2-methyl-2-(6-methoxy-*etio*-*i*-cholenyl)-ethylene are described.

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[7] R. E. Marker, H. M. Crooks, Jr., E. M. Jones and A. C. Shabica, THIS JOURNAL, **64**, 1276 (1942).