

and the mixture allowed to stand for one hour at room temperature. The solution was poured slowly with stirring into 50 cc. of ice-water. The precipitate was filtered off and washed with water; yield, 280 mg. or 92.5%; m. p. 138°. Recrystallization from alcohol-water raised the melting point to 144°. A mixed m. p. with 2-bromo-3,5-dicarbethoxy-4-methylpyrrole showed no depression.

**Experiments upon the Formation of Dipyrrolymethane VII.**—(a) In a 25-cc. Erlenmeyer flask fitted with a reflux condenser is placed 450 mg. of 2,4-dicarbethoxy-3-methylpyrrole, 4 cc. of glacial acetic acid, 0.70 cc. of concentrated hydrochloric acid and 1 cc. of 36% formaldehyde solution. The solution is refluxed for ninety minutes. After fifteen minutes, 0.5 cc. of formaldehyde is added. At the end of the refluxing period, 0.5 cc. of water is added and the solution allowed to cool slowly to room temperature. After standing in the ice-box overnight, the crystals which separate out are filtered off and washed with 5 cc. of 50% acetic acid. Recrystallization from alcohol-water gives 210 mg. (23%) of a material melting at 135°. Mixed m. p. with dipyrrolymethane VII showed no depression.

(b) In a 25-cc. Erlenmeyer flask with a condenser is placed 255 mg. of 2-hydroxymethyl-3,5-dicarbethoxy-4-methylpyrrole, 2 cc. of glacial acetic acid, 0.3 cc. of concentrated hydrochloric acid and 0.2 cc. of distilled water. The reaction is treated exactly as described under (a); yield, 127 mg. or 55%.

(c) One hundred twenty-eight milligrams of 2-hydroxymethyl-3,5-dicarbethoxy-4-methylpyrrole and 113 mg. of 2,4-dicarbethoxy-3-methylpyrrole are treated exactly as described under (b); yield, 90 mg. Since the yield from this amount of the 2-hydroxymethylpyrrole alone would be 63–64 mg., the remaining 26–27 mg. is the amount which cannot be formed from this reaction and is the minimum amount to be ascribed to the cross-reaction between the two pyrroles.

### Summary

1. A method for the determination of the bridge structure of certain dipyrrolymethanes is described.

2. A pyrrole derivative is reported whose NH is more acidic than an OH in the same molecule.

3. Three dipyrrolymethanes which exhibit an anomalous melting point behavior are described.

4. 2-Carboxyl-3,5-dicarbethoxy-4-methylpyrrole has been prepared.

5. The catalytic debromination of a number of pyrrole derivatives has been accomplished.

6. A reaction sequence for the conversion of pyrrolyl carbinols to dipyrrolymethanes is proposed.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

## Sterols. CXLII. 17-Methyl-pregnan-3( $\beta$ )-ol-20-one and Related Compounds\*

BY RUSSELL E. MARKER AND R. B. WAGNER

Recently,<sup>1</sup> we have described the rearrangement of 17-bromo-pregnan-3( $\beta$ )-ol-20-one into the methyl ester of 3( $\beta$ )-hydroxy-17-methyl-*etio*-cholic acid. This readily available material led to the preparation of 17-methyl compounds of the hormone series.

Treatment of the methyl ester of 3( $\beta$ )-hydroxy-17-methyl-*etio*-cholic acid (I) with excess methyl Grignard reagent gave an unsaturated compound, C<sub>23</sub>H<sub>38</sub>O. It is very likely that this substance resulted from the dehydration of an intermediate tertiary carbinol. Similar observation of a simultaneous addition and dehydration to give an unsaturated compound has been made by Brown, Heilbron and Spring.<sup>2</sup> They obtained 7-methylene-cholesterol from 7-keto-cholesteryl acetate. The analogous compound in our reaction would be 20-methylene-17-methyl-pregnan-3( $\beta$ )-ol (II).

Catalytic hydrogenation of 20-methylene-17-

methyl-pregnan-3( $\beta$ )-ol (II) gave the corresponding saturated compound (III). Oxidation of the acetylated unsaturated compound (II) either by ozonolysis or with chromic anhydride in acetic acid gave 17-methyl-pregnan-3( $\beta$ )-ol-20-one (VI) isolated as the free hydroxy ketone.

Hydrolysis of the methyl ester (I) gave 3( $\beta$ )-hydroxy-17-methyl-*etio*-cholic acid previously described by us<sup>1</sup> which was acetylated and treated with thionyl chloride. The acid chloride (V) was not isolated but was immediately treated with dimethylzinc. Hydrolysis of this product gave the same 17-methyl-pregnan-3( $\beta$ )-ol-20-one (VI) previously obtained.

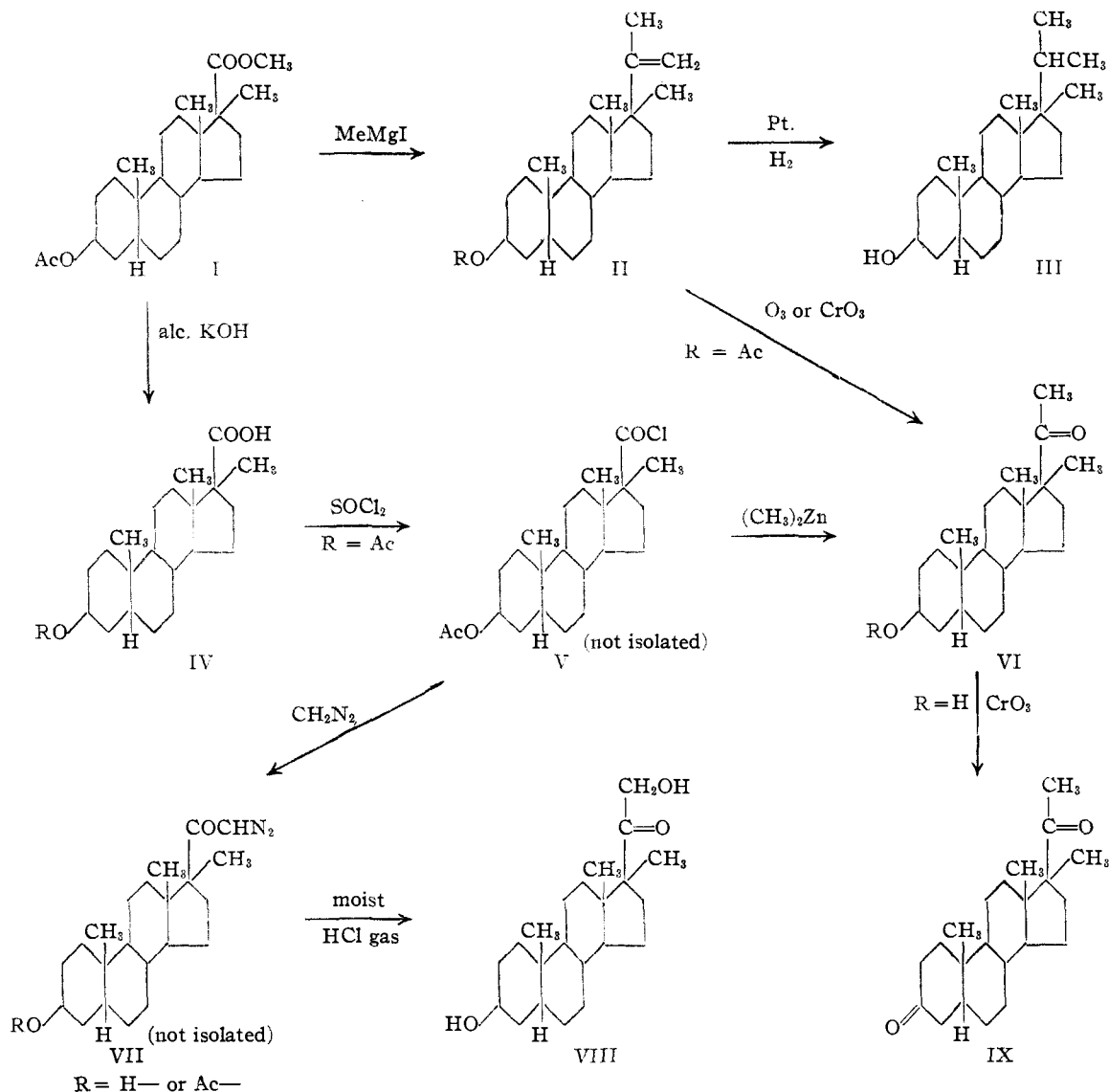
The acetylated acid chloride was treated with diazomethane to give (VII) and then with moist gaseous hydrochloric acid. Subsequent hydrolysis gave as the major product a substance, C<sub>22</sub>H<sub>36</sub>O<sub>3</sub>. By analogy this compound is considered to be 21-hydroxy-17-methyl-pregnan-3( $\beta$ )-ol-20-one (VIII), since Reichstein<sup>3</sup> similarly ob-

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(1) Marker and Wagner, *THIS JOURNAL*, **64**, 216 (1942).

(2) Brown, Heilbron and Spring, *J. Chem. Soc.*, 1274 (1936).

(3) Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).



tained 21-hydroxy compounds from the corresponding diazo compound with dilute sulfuric acid.

The reactions are summarized as shown in the chart.

We wish to thank Parke, Davis and Company for their assistance.

#### Experimental

**20-Methylene-17-methyl-pregnan-3( $\beta$ )-ol (II).**—To a Grignard reagent prepared from 12 g. of magnesium, 73.6 g. of methyl iodide and 200 cc. of ether was added 5.0 g. of the methyl ester of 3( $\beta$ )-acetoxy-17-methyl-*etio*-cholanolic acid (I) in 200 cc. of ether. Most of the ether was distilled off and the residual liquid was refluxed thirty-six hours with 50 cc. of dry benzene. The mixture was decomposed with dilute hydrochloric acid and the solid was dissolved in ether. The product was crystallized from methanol to give white crystals, m. p. 167–168°; yield 2.0 g.

*Anal.* Calcd. for C<sub>29</sub>H<sub>48</sub>O: C, 83.6; H, 11.6. Found: C, 83.5; H, 11.4.

When treated with acetic anhydride in pyridine, this substance yielded the acetate which crystallized from methanol, m. p. 136–138°.

*Anal.* Calcd. for C<sub>26</sub>H<sub>40</sub>O<sub>2</sub>: C, 80.6; H, 10.8. Found: C, 81.0; H, 10.7.

The acetylated product was unaffected by refluxing with phosphorus oxychloride in pyridine at 135°.

**Catalytic Reduction of 20-Methylene-17-methyl-pregnan-3( $\beta$ )-ol (II).**—A solution of 100 mg. of 20-methylene-17-methyl-pregnan-3( $\beta$ )-ol (II) in 50 cc. of acetic acid was shaken with 100 mg. of Adams catalyst and hydrogen at 3 atm. and room temperature for two hours. The reaction mixture was filtered and the acetic acid removed *in vacuo*. The residue crystallized from methanol to give white crystals, m. p. 176–177°. This was 17,20-dimethyl-pregnan-3( $\beta$ )-ol (III).

*Anal.* Calcd. for  $C_{23}H_{40}O$ : C, 83.1; H, 12.1. Found: C, 82.7; H, 12.1.

**Ozonolysis of 20-Methylene-17-methyl-pregnan-3( $\beta$ )-ol (II).**—Through a solution of 1.0 g. of 20-methylene-17-methyl-pregnan-3( $\beta$ )-ol (II) in 200 cc. of dry chloroform was bubbled oxygen containing 7% ozone at the rate of 30 liters per hour for fifteen minutes. At the end of this time no more ozone was absorbed. The reaction mixture was poured into water and stirred for thirty minutes. The chloroform was removed by steam distillation. After cooling, the product was extracted with ether and the solution was washed several times with 10% potassium hydroxide. The ether was evaporated and the residue was crystallized from acetone to give white needles, m. p. 169–171°; yield 0.8 g. This substance is 17-methyl-pregnan-3( $\beta$ )-ol-20-one (VI).

*Anal.* Calcd. for  $C_{22}H_{38}O_2$ : C, 79.5; H, 10.9. Found: C, 79.5; H, 10.9.

**Oxidation of the Acetylated 20-Methylene-17-methyl-pregnan-3( $\beta$ )-ol (II).**—To a solution of 400 mg. of acetylated 20-methylene-17-methyl-pregnan-3( $\beta$ )-ol (II) in 20 cc. of acetic acid was added a solution of 400 mg. of chromic anhydride in 10 cc. of 90% acetic acid. The mixture was warmed on the steam-bath for one hour, cooled, and poured into water. The ethereal solution of the precipitated solid was washed with water and 10% potassium hydroxide. The acidified alkaline washings gave very little precipitate. The ether was evaporated and the residue hydrolyzed with 5% methanolic potassium hydroxide. The mixture was cooled, poured into water, and extracted with ether. The product was crystallized from acetone to give white fine needles, m. p. 184–187° which is a polymorphic form of the product (VI) from ozonolysis; mixed m. p. 174–179°.

*Anal.* Calcd. for  $C_{22}H_{38}O_2$ : C, 79.5; H, 10.9. Found: C, 78.9; H, 10.7.

**Oxidation of 17-Methyl-pregnan-3( $\beta$ )-ol-20-one (VI).**—A solution of 300 mg. of 17-methyl-pregnan-3( $\beta$ )-ol-20-one (VI) in 10 cc. of acetic acid was treated with a solution of 0.3 g. of chromic anhydride in 10 cc. of 90% acetic acid at room temperature for one hour. The reaction mixture was poured into water and the precipitated solid was extracted with ether. The ethereal solution was washed with water and 10% potassium hydroxide and evaporated. The residue crystallized from methanol to give white crystals, m. p. 131–134°. This is 17-methylpregnenedione-3,20 (IX).

*Anal.* Calcd. for  $C_{22}H_{34}O_2$ : C, 79.9; H, 10.4. Found: C, 79.9; H, 10.3.

**21-Hydroxy-17-methyl-pregnan-3( $\beta$ )-ol-20-one (VIII).**—To 5 cc. of thionyl chloride at 0° was added 3( $\beta$ )-acetoxy-17-methyl-*etio*-cholic acid (IV) obtained from

the hydrolysis and subsequent acetylation (pyridine method) of one gram of the methyl ester (I). The solution was allowed to stand at 5° for sixteen hours and then repeatedly evaporated to dryness *in vacuo* with several cc. of dry benzene. The residue was dissolved in 20 cc. of anhydrous ether and was treated with a cold, dry ethereal solution of diazomethane. The mixture was allowed to stand at room temperature for sixteen hours, then filtered and evaporated. Through a moist ethereal solution of the residue was bubbled gaseous hydrochloric acid for thirty minutes. The reaction mixture was evaporated to dryness and the residue crystallized from methanol to give white crystals, m. p. 140–142°; yield 0.3 g. This material gave a negative Beilstein test for halogen.

*Anal.* Calcd. for  $C_{22}H_{38}O_3$ : C, 75.8; H, 10.4. Found: C, 76.0; H, 10.4.

**Reaction of Dimethylzinc with 3( $\beta$ )-Acetoxy-17-methyl-*etio*-cholic Acid Chloride (V).**—A solution of 1.3 g. of 3( $\beta$ )-acetoxy-17-methyl-*etio*-cholic acid (IV) in 10 cc. of thionyl chloride at 0° was treated as described above to obtain the crude acid chloride. To a solution of 2 g. of dimethylzinc in 50 cc. of tetralin contained in a flask continuously swept out with nitrogen was added the acid chloride dissolved in 50 cc. of tetralin. The mixture was allowed to stand sixteen hours at room temperature and was then warmed for one hour on the steam-bath. The mixture was cooled and decomposed with dilute hydrochloric acid. The solid was extracted with ether and the solvent removed. After hydrolysis with 5% methanolic potassium hydroxide the product was crystallized from acetone to give fine white needles, m. p. 171–179°, which gave no depression with previously obtained polymorphic forms of 17-methyl-pregnan-3( $\beta$ )-ol-20-one (VI). This is a mixture of the two polymorphic forms.

*Anal.* Calcd. for  $C_{22}H_{38}O_2$ : C, 79.5; H, 10.9. Found: C, 79.3; H, 10.9.

### Summary

1. Reaction of the methyl ester of 3( $\beta$ )-hydroxy-17-methyl-*etio*-cholic acid (I) with excess Grignard reagent gave 20-methylene-17-methyl-pregnan-3( $\beta$ )-ol (II) which was converted into 17-methyl-pregnan-3( $\beta$ )-ol-20-one (VI).

2. The corresponding acid (IV) from the hydrolysis of the above ester (I) was converted into 21-hydroxy-17-methyl-pregnan-3( $\beta$ )-ol-20-one (VIII) as well as 17-methyl-pregnan-3( $\beta$ )-ol-20-one (VI).

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