[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY, MAYO FOUNDATION]

STUDIES ON STEROID α-KETOLS. II. A NEW PARTIAL SYNTHESIS OF 5-ANDROSTENE-3,16,17-TRIOL: AN INTERMEDIATE IN THE PREPARATION OF 16-HYDROXYTESTOSTERONE

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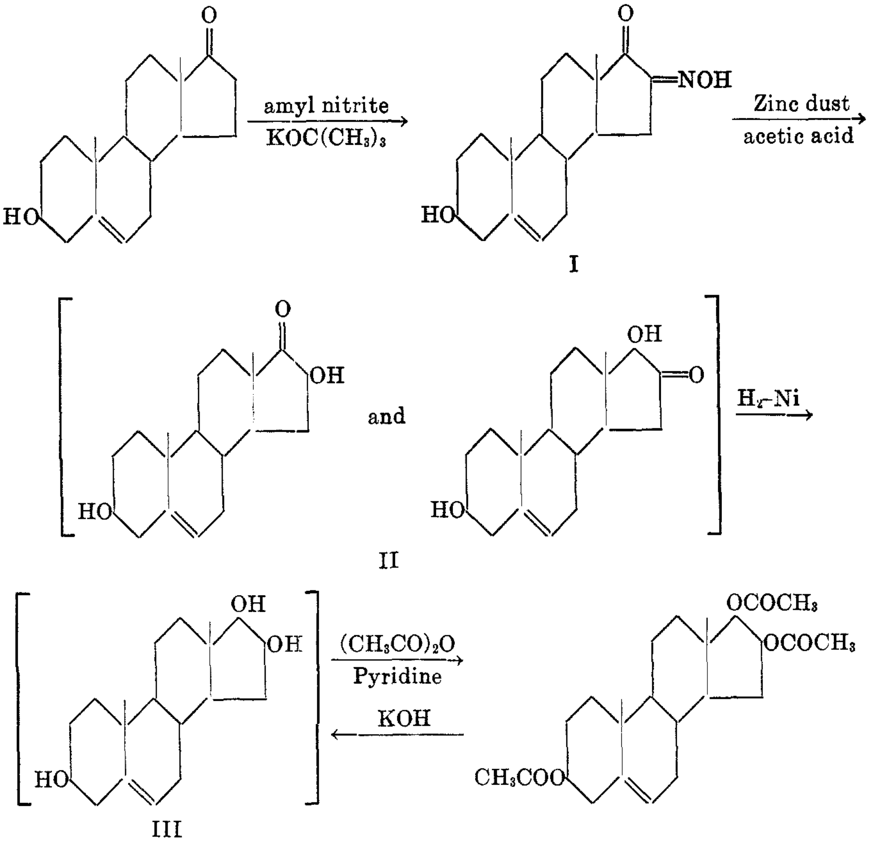
Received June 18, 1941

In 1939, Butenandt and co-workers (1) synthesized 16-hydroxytestosterone and investigated its sex hormone activity. Unfortunately the synthesis devised by these workers was long, laborious, and costly. Moreover the yields were so low that investigation of all the intermediate compounds was not possible. For these reasons we believe that any improvement in this synthesis would be welcomed by those who wish to prepare this compound for further study of its hormonal activity. We are able to report such an improvement as a result of synthetic work in this laboratory on steroid derivatives which have an α-ketol grouping in ring D. We have found that the 3,16,17-triol required in the synthesis by the method of Butenandt and co-workers can be prepared easily by a new method so satisfactory that the yield of 16-hydroxytestosterone can be increased almost ten-fold by its use.

The essential contribution of the new method involves the reduction of the isonitroso derivative of dehydroisoandrosterone with zinc dust and acetic acid. The reduction of the isonitroso group was attempted with the reasonable expectation that the α-amino ketone would be formed, since that type of compound results from the reduction of isonitrosocamphor (2). The fact that a neutral product was obtained suggested that formation of an α-ketol had taken place. This was confirmed by conversion of the ketol to a diacetate which agreed in melting point with that given by Butenandt and co-workers. For further confirmation the ketone group of the diacetate was reduced, and the resulting compound characterized as the triacetate. It appeared worth while, in view of the difficulties of the synthesis by the method of Butenandt and co-workers, to make use of this unusual reduction for the synthesis of the intermediate 5-androstene-3,16,17-triol required in the preparation of 16-hydroxytestosterone.

The following method was found most suitable:



The yield of the triol by our method was 24.7% compared with 2.50% by the method of Butenandt and co-workers. This reduction of an isonitroso ketone to an α-ketol provides a very satisfactory method for the introduction of a hydroxyl group next to a keto group in the steroid nucleus. The reaction is being studied further with other isonitroso ketones.

EXPERIMENTAL

All melting points are uncorrected.

Isonitrosodehydroisoandrosterone (*I*). The method of Litvan and Robinson (3) was used. Potassium (0.50 g. or 0.0128 atom) was dissolved in 20 cc. of *tert.* butyl alcohol and 2.00 g. (0.00693 mole) of dehydroisoandrosterone was added. Nitrogen was passed over the well-stirred solution for one hour and then 1.90 cc. (0.0138 mole) of freshly prepared *n*-amyl nitrite was added dropwise. A precipitate appeared in less than a minute and the solution became red. After the solution had been stirred for two hours under nitrogen the reaction mixture was kept overnight at room temperature. It was then diluted with water and extracted twice with ether. The aqueous layer was separated, acidified with acetic acid, and extracted with chloroform. The chloroform extract was shaken once with a dilute solution of potassium carbonate to remove impurities. It was then extracted repeatedly with 0.1 *N* sodium hydroxide solution until the alkaline extracts were no longer yellow. Acidification of the combined aqueous extracts gave 1.51 g. of pale yellow crystals (65.5% yield) sufficiently pure for the reduction with zinc in acetic acid. The compound was difficultly soluble in alcohol or chloroform but easily soluble in chloroform which contained a little alcohol. For analysis a sample was crystallized from isopropyl alcohol in the form of almost colorless needles. The compound sinters at 240° and melts at 248–249° with evolution of gas.

Anal. Calc'd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41.
Found: C, 72.14; H, 8.82; N, 4.37.

3-Acetoxyisonitrosodehydroisoandrosterone. One hundred milligrams of the isonitroso ketone (I) was dissolved in 5 cc. of pyridine and 1.5 cc. of acetic anhydride and kept at room temperature for two days. From this reaction mixture 109 mg. of a crystalline white solid was isolated. Recrystallization from acetone-water gave long needles which melted at 183–184°.

Anal. Calc'd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90.
Found: C, 70.02; H, 8.29; N, 4.15.

Reduction of the isonitroso ketone (I). The isonitroso ketone (1.50 g.) was suspended in 50 cc. of acetic acid and 3 cc. of water. Four grams of zinc dust was added in small portions while the temperature of the solution was kept at 40–45°. The compound soon dissolved and the solution became yellow. After the addition of 20 cc. of water, the solution was refluxed for one hour during which time it became colorless. It was then cooled and filtered to remove zinc dust. To the filtrate sufficient strong potassium carbonate solution was added to neutralize about 90% of the remaining acetic acid. The acid solution was extracted five times with chloroform. The combined chloroform extracts were shaken first with 50 cc. of 1 *N* sulfuric acid to remove a small amount of amine. After an extraction with dilute potassium hydroxide, the chloroform solution was thoroughly washed with water and concentrated in a vacuum to a white powder which consisted of a mixture of α-ketols (II) and weighed 1.38 g. (95.9% conversion).

Reduction of the ketols (II) to the triol (III). The mixture of ketols (1.00 g.) was hydrogenated in alcohol in the presence of Raney nickel catalyst until no more hydrogen was absorbed. The reduction product was dissolved in acetic anhydride and pyridine and kept at room temperature for twenty-four hours. From this acetylation mixture was obtained 651 mg. of crude triacetate (m.p. 209–213°) which was saponified by refluxing with alcoholic potassium hydroxide for thirty minutes. The triol was isolated and crystallized from an alcohol-water-pyridine mixture in the form of blocks; m.p. 273–275°. The melting point reported by Butenandt and co-workers was 273–275°. The yield was 395 mg. (39.2%).

Acetylation of the ketol mixture (II). The ketol mixture (II) was dissolved in 5 cc. of pyridine and 3 cc. of acetic anhydride and kept at room temperature for twenty-four hours. The diacetate was isolated and crystallized from dilute alcohol in the form of needles. The yield was 285 mg. (59.9%); m.p. 124–125°. Butenandt and co-workers report the melting point 123°. This compound is either 3,16-diacetoxy-5-androstene-17-one or 3,17-diacetoxy-5-androstene-16-one.

Anal. Calc'd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30.
Found: C, 70.78; H, 8.13.

Reduction of the diacetate. The diacetate (100 mg.) was hydrogenated in alcohol for four hours in the presence of Raney nickel catalyst. Acetylation of the reduction product gave 66 mg. of triacetate which was crystallized from methyl alcohol in large plates. Repeated recrystallization did not raise the melting point of 214–215° although the value given by Butenandt and co-workers is 224–226°.

Anal. Calc'd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39.
Found: C, 69.27; H, 8.56.

SUMMARY

A new method is described for the preparation of 5-androstene-3,16,17-triol from isonitrosodehydroandrosterone. By the use of this method it is now possible to obtain 16-hydroxytestosterone in a yield ten times that previously reported.

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REFERENCES

(1) Butenandt, Schmidt-Thomé, and Weiss, *Ber.*, **72,** **417** (1939).
(2) Claisen and Manasse, *Ann.*, **274,** 90 (1893).
(3) Litvan and Robinson, *J. Chem. Soc.*, **1938,** 1997.