16-SUBSTITUTED STEROIDS

XV. A NEW SYNTHETIC METHOD FOR 16-KETOSTEROIDS

By MAX N. HUFFMAN, MARY HARRIET LOTT, AND
ALBERT TILLOTSON

(From the Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma)

(Received for publication, February 4, 1955)

In 1941 (1) the senior author entered the field of 16-substituted steroids
with the view of preparing all of the three possible 16,17-epimers of nat-
ural estriol. Since that time two of these three epimers, 16-epiestriol (iso-
estriol-A) (2) and 17-epiestriol (3), have become available through our
efforts and those of the Swiss investigators. In 1952 the present authors
made an attempt to prepare the missing 1,3,5(10)-estratrien-3,16β,17α-
triotol by epimerization of 3-methoxy-1,3,5(10)-estratrien-16β,17β-diol-17
p-toluenesulfonate. However, much to our surprise, alkaline saponifica-
tion of the latter compound resulted in actual cleavage of p-toluenesul-
fonic acid from the molecule, yielding the 16-ketosteroid in very satisfying
yield.

This new synthetic approach to 16-ketosteroids is far superior to our orig-
inal method (4) which involved the Clemmensen reduction of the 16-keto-
17β-hydroxysteroid. The Clemmensen reduction always, rather strangely,
yields a mixture of 16-ketosteroid and 17-ketosteroid, and often this mix-
ture of 16- and 17-ketones is intractable. Furthermore, the Clemmensen
method is too drastic for some unsaturated compounds in the steroid series.

The present synthesis has wide applicability. We describe here its use
in the estrogen series, giving our original experiments along with later much
improved procedures. For instance, it is now possible to start with estrone
and operate through the seven synthetic steps of benzoylation, nitrosa-
tion, saponification, zinc-acetic acid reduction (5), ditosylation, sodium
borohydride reduction, and cleavage and to obtain pure estrone-16 in 54
per cent over-all yield.

In keeping with our other structural assignments at C₁₆ (6), we have des-
ignated the carbinol formed on the sodium borohydride reduction of 16-
ketoestradiol-3,17-di-p-toluenesulfonate as possessing the β configuration.

EXPERIMENTAL¹

Preparation of 3-Methoxyestra-1,3,5(10)-trien-17β-ol-16-one p-Toluenesul-
fonate—3-Methoxyestra-1,3,5(10)-trien-17β-ol-16-one (I), 1.90 gm.,

¹ All melting points are uncorrected. Microanalyses are by Dr. E. W. D. Huffman,
Denver.
melting at 167-168° (7), was esterified with p-toluenesulfonyl chloride by our usual procedure (6 gm. of tosyl chloride, 50 ml. of dry pyridine) at 0-5°. After 24 hours at room temperature the derivative was precipitated with 20 volumes of ice water. The yield was 2.60 gm. (III). A recrystallization from ethanolic acetone of a portion of this product gave tiny, fine needles melting at 179.5-180.5°, turning yellow.

Reduction of 3-Methoxyestra-1,3,5(10)-tri-en-17β-ol-16-one p-Toluenesulfonate by Lithium Aluminum Hydride—In 200 ml. of absolute ether were dissolved 1.95 gm. of the crude, unrecrystallized derivative in the preceding paragraph (III), and this solution, under nitrogen, was refluxed over 1.0 gm. of lithium aluminum hydride during 3 hours. The excess hydride was cautiously decomposed with water, and the reaction mixture was partitioned between ethyl ether and 1 N sulfuric acid. The separated ethereal phase was washed successively with dilute sulfuric acid, with dilute sodium hydroxide, and twice with water. Evaporation of the ether yielded an oily residue which again furnished an oil upon attempted crystallization from acetone-Skellysolve B. This oil (V) was therefore carefully dried and acetylated as usual with acetic anhydride and pyridine, whereupon it furnished an acetate from methanol, melting at 154-157°. Two more recrys-
tallizations from methanol (charcoal) yielded 0.53 gm. of the 3-methoxy-16β-acetoxyestra-1,3,5(10)-trien-17β-ol p-toluenesulfonate in the form of long, fine needles melting at 160-161°.

\[ \text{C}_{28}\text{H}_{31}\text{O}_{6}\text{S}. \text{Calculated. C}\ 67.44, \text{H}\ 6.87, \text{S}\ 6.43 \]
\[ \text{Found. C}\ 67.42, \text{H}\ 6.80, \text{S}\ 6.33 \]

**Saponification of 3-Methoxy-16β-acetoxyestra-1,3,5(10)-trien-17β-ol \- Toluenesulfonate**—Of the 17-tosylate in the preceding section, 104 mg. were dissolved in 20 ml. of warm 95 per cent ethanol, and an equal volume of 1 N potassium hydroxide added. After a 30 minute reflux period, 20 ml. of water were added, and the reaction mixture was distilled to turbidity; yield 57 mg. After two recrystallizations from aqueous methanol, 48 mg. of product melting at 124-124.5° were obtained.

\[ \text{C}_{18}\text{H}_{24}\text{O}_{2}. \text{Calculated, C}\ 80.24, \text{H}\ 8.51; \text{found, C}\ 80.34, \text{H}\ 8.49 \]

This product was identical with 3-methoxyestra-1,3,5(10)-trien-16-one (4) (VII).

**Improved Procedure for Preparation of 3-Methoxyestra-1,3,5(10)-trien-16-one**—Crude 3-methoxyestra-1,3,5(10)-trien-17β-ol p-toluenesulfonate (III) was prepared as indicated in the first experiment above. Of the crude product, 2.60 gm. were dissolved under reflux in a solution of 100 ml. of methanol plus 30 ml. of pyridine; the solution was cooled to 40° and then treated with 2 gm. of sodium borohydride dissolved in 25 ml. of methanol. After 45 minutes swirling, the excess sodium borohydride was decomposed with 25 ml. of acetone in 300 ml. of water, and the derivative was precipitated with 1 liter of ice water containing 25 ml. of concentrated hydrochloric acid and filtered after a day at 5°. The well washed product (damp) was dissolved under reflux in 250 ml. of 95 per cent ethanol, and during reflux 250 ml. of 1 N potassium hydroxide were slowly added. Refluxing was continued for 1 hour and the solution distilled to turbidity and very quickly filtered through glass wool (rinsing with 30 ml. of 50 per cent ethanol). After the addition of 150 ml. of water and a day at 5°, the 16-ketosteroid was filtered, washed thoroughly with water, and recrystallized from aqueous methanol (charcoal) to give 1.14 gm. of 3-methoxyestra-1,3,5(10)-trien-16-one (VII) in small plates melting at 123-123.5°. A mixed melting point with authentic 3-methoxyestra-1,3,5(10)-trien-16-one gave no depression.

**Preparation of Estrone-16 by New Procedure**—Estrone U. S. P. (5 gm.) was carried through the steps of benzylation, nitrosation, saponification, and zinc-acetic acid reduction as described in previous publications. The 16-ketoestradiol (II) thus obtained (approximately 3.7 gm.) was esterified at ice bath temperature, as previously described (pyridine, 100 ml.; p-toluenesulfonyl chloride, 15 gm.). After 24 hours at room temperature, the 3,17-ditosylate (IV) was precipitated with 20 volumes of ice water. The
well washed product was dried at 40° before reduction. (In another experiment crude 16-ketoestradiol-3,17-di-p-toluenesulfonate was recrystallized once from acetone-methanol and once from 95 per cent ethanol to give long needles melting at 159–159.5°.)

The ditosylate, approximately 6.8 gm., was dissolved under reflux in a mixture of 200 ml. of methanol and 60 ml. of pyridine. The solution was then cooled to 40°, and 4 gm. of sodium borohydride dissolved in 50 ml. of methanol were added. The reaction mixture was swirled frequently during the course of 45 minutes, at which time 500 ml. of water containing 50 ml. of acetone were mixed in and allowed to stand for 15 minutes. Then 2 liters of ice water containing 50 ml. of concentrated hydrochloric acid were added, and, after thorough agitation, the mixture was placed at 5° for a day. The reduced derivative was collected on a Büchner funnel and washed very thoroughly with water.

The crude 16-epiestriol ditosylate (VI) was dissolved under reflux in 540 ml. of 95 per cent ethanol, and 270 ml. of 1 N potassium hydroxide were added to the refluxing solution. After 30 minutes boiling, another 270 ml. portion of potassium hydroxide was added, followed by 30 minutes refluxing. The ethanol was then removed by distillation, 340 ml. of water were added, and after several hours at room temperature the alkaline solution was filtered through sintered glass (rinsing with 106 ml. of 0.1 N potassium hydroxide). The acidified solution after a day at 5° was filtered and the estrone-16 recrystallized from aqueous methanol (charcoal) to give 2.59 gm. (52 per cent over-all yield from estrone) melting at 243–244° (4) (VIII). Only one additional recrystallization from aqueous methanol was necessary to furnish a product of the highest purity.

**SUMMARY**

A new synthetic route to 16-ketosteroids is described, with examples in the estrogen series. This method takes advantage of the fact that 16-hydroxy-17β-toluenesulfonofxy steroids readily lose toluenesulfonic acid from the molecule upon mild saponification.

The authors are especially indebted to the Lasdon Foundation, Inc., Yonkers, New York, for financial assistance rendered during the course of this investigation.

**BIBLIOGRAPHY**

16-SUBSTITUTED STEROIDS: XV. A NEW SYNTHETIC METHOD FOR 16-KETOSTEROIDS
Max N. Huffman, Mary Harriet Lott and Albert Tillotson


Access the most updated version of this article at http://www.jbc.org/content/217/1/107.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/217/1/107.citation.full.html#ref-list-1