[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Formation of Five- and Six-membered Rings by the Acyloin Condensation. IV. The Natural Estrogenic Steroids

BY JOHN C. SHEEHAN, R. A. CODERRE[1] AND PHILIP A. CRUICKSHANK[2]

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By use of the acyloin reaction in homogeneous solution, dimethyl marrianolate methyl ether (I) has been cyclized stereospecifically in 96% yield to 16-keto-17β-estradiol-3-methyl ether (II), from which the major natural estrogenic steroids (estrone, estradiol, and estriol) may be derived. Conversion of II acetate to the trimethylenethioketal, followed by desulfurization, saponification and demethylation, afforded estradiol in good over-all yield. Estrone was obtained by oxidation and subsequent demethylation of β-estradiol-3-methyl ether. Estrane-3-methyl ether was produced by zinc–acid reduction of II. Lithium aluminum hydride reduction of II gave principally 16-epiestriol-3-methyl ether.

Published methods[3-6] leading to total syntheses of the natural female sex hormone estrone commonly feature a closure of the D ring *via* the Dieckmann condensation. In the most recent synthesis of estrone by Johnson,[6] as in the synthesis of Anner and Miescher,[4] a carbon atom is first added to the primary acid chain of dimethyl marrianolate methyl ether (I) and subsequently lost upon formation of ring D. A cyclization procedure directly applicable to the diester I would eliminate the essentially wasteful homologation steps required for closing the five-membered ring. Recent work[7] in this Laboratory on the formation of five- and six-membered rings *via* the acyloin condensation has pointed up the possibility of applying this reaction to the estrone series.

Dimethyl marrianolate methyl ether (I), subjected to the acyloin reaction in homogeneous medium, afforded stereospecifically in excellent yield the estrogenic steroid 16-keto-17β-estradiol-3-methyl ether (II), an intermediate from which the natural estrogens estradiol, estrone and estriol can be prepared readily.

Cyclization of dimethyl marrianolate methyl ether (I) was effected by addition of an ethereal solution of the diester to an excess of sodium dissolved in a medium containing 60% liquid ammonia and 40% anhydrous ether. The reaction is very rapid, with the rate of addition having little or no effect upon the yield. After complete evaporation of the ammonia and acidification of the residues, a 96% yield of acyloin II was obtained. A determination of the infrared spectra of this material showed all the characteristics of a highly enolic acyloin; a rather weak OH band at 2.80 μ, a strong carbonyl band at 5.75 μ, assigned to the cyclopentanone carbonyl, and a band of medium intensity at 6.18 μ attributed to a carbon–carbon double bond in a five-membered ring.

The acyloin II obtained from the cyclization was demonstrated to be 16-keto-17β-estradiol-3-methyl ether by comparison with an authentic sample pre-

(1) Bristol Laboratories Fellow, 1952.
(2) National Science Foundation Fellow, 1952–1953.
(3) W. E. Bachmann, S. Kushner and A. C. Stevenson, THIS JOURNAL, **64**, 974 (1942).
(4) G. Anner and K. Miescher, *Helv. Chim. Acta*, **31**, 2173 (1948).
(5) W. S. Johnson, *et al.*, THIS JOURNAL, **74**, 2832 (1952).
(6) W. S. Johnson and R. G. Christiansen, *ibid.*, **73**, 5511 (1951).
(7) J. C. Sheehan, R. C. O'Neill and M. A. White, *ibid.*, **72**, 3376 (1950); J. C. Sheehan and R. C. O'Neill, *ibid.*, **73**, 4614 (1950); J. C. Sheehan and R. A. Coderre, *ibid.*, **75**, 3997 (1953).

pared by the method of Huffman[8] and Butenandt.[9] No depression of melting point was observed upon admixture of the α-ketols or of their acetate derivatives. Specific rotation and infrared spectra also indicated that the α-ketols prepared by the different methods were identical. A 17β-hydroxyl group was thus shown to be present in the acyloin, not the α-epimer as was earlier reported[10] in a preliminary communication.

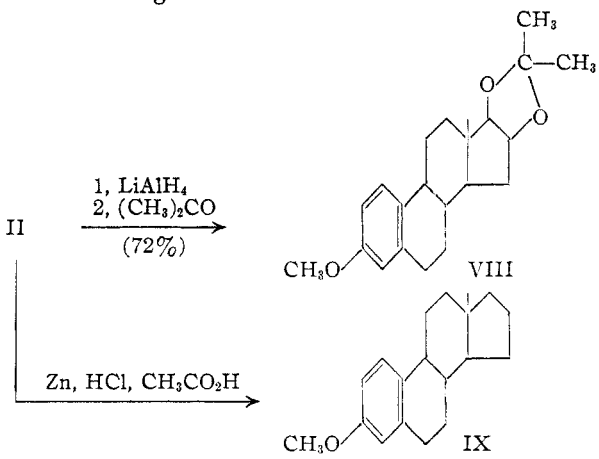
In contrast to this smooth reaction in homogeneous medium, the conventional heterogeneous reaction conditions of finely dispersed sodium in refluxing toluene yielded no detectable quantity of acyloin product from I. After high dilution addition of the diester during 6 hours, and a total heating period of 16 hours, the only substances isolated were 40% of the starting material and some insoluble, presumably polymeric material.

The diester I required for cyclization to the steroid acyloin can be prepared by the relatively short total synthesis reported by Johnson and Christiansen[6] starting from anisole. An alternative route to this starting material, employed in this work, involves the hypoiodite oxidation of estrone methyl ether.

Removal of the 16-keto group from the α-ketol II was effected by hydrogenolysis of the thioketal-acetate derivative IV, a method similar to that employed by Huffman and Lott[11] with 3,17-dihydroxy-16-keto-Δ^5-androstene. 16-Keto-17β-estradiol-17-acetate-3-methyl ether (III) was prepared in 86% yield from the unpurified acyloin by treatment with pyridine and acetic anhydride. Condensation of III with 1,3-propanedithiol afforded the trimethylene thioketal IV in 90% yield. Desulfurization of this derivative by heating for 18 hours with Raney nickel W-6 in dioxane led to an 88% yield of 17β-estradiol-3-methyl ether (V). Demethylation with pyridine hydrochloride gave 17β-estradiol (VII) in 90% yield. V and VII were identified by comparison with authentic 17β-estradiol and its 3-methyl ether prepared from estrone and estrone methyl ether, respectively, by sodium borohydride reduction.[12] Oxidation of V with chromic acid yielded estrone methyl ether (VI), identified by comparison with an authentic sample.

Attempts to condense 1,3-propanedithiol with the unprotected acyloin II led only to uncharacterized products, indicating that isomerization was occurring.

The α-ketol II has been employed previously as a precursor of estriol-16α,17β, the naturally occurring isomer. Butenandt and Shöffler[9] reported the use of sodium in isopropyl alcohol to effect the reduction of the 16-keto group to give a *trans*-glycol, and Huffman[13] effected the same reduction with sodium amalgam.



Lithium aluminum hydride treatment of II gave a mixture of products, from which the *cis*-glycol could be isolated as the acetonide VIII in 72% yield. Acid hydrolysis of this derivative afforded pure 16-epiestriol methyl ether.

A preliminary attempt to remove the hydroxyl group of the acyloin II to yield the methyl ether of estrone-16 was unsuccessful. Huffman,[14] working with the free phenol, succeeded in removing a 17β-hydroxy group from 16-keto-17β-estradiol by employing Clemmensen conditions. Treatment of II with zinc, acetic acid and concentrated hydrochloric acid, even for a relatively short time, removed all oxygen from ring D, yielding desoxoestrone methyl ether (IX).

Experimental[15]

Dimethyl Marrianolate Methyl Ether (I).—The method developed by Herr and Miescher[16] for the preparation of dimethyl marrianolate benzyl ether from 3-benzylestrone was employed. From 2.40 g. of estrone methyl ether, suspended in 300 ml. of prepurified methanol,[17] to which was added simultaneously solutions of 5.8 g. of iodine in 70 ml. of prepurified methanol and 10.5 g. of potassium hydroxide in 20 ml. of water and 50 ml. of prepurified methanol, there was obtained, after isolation and treatment with diazomethane, 2.0 g. (66%) of dimethyl marrianolate methyl ether, m.p. 73–74°.

16-Keto-17β-estradiol-3-methyl Ether (II).—To a 1-l. three-necked flask fitted with a Dry Ice condenser, stirrer, addition funnel, and nitrogen system was added 200 ml. of dry ether and 300 ml. of anhydrous liquid ammonia. In this liquid was dissolved 0.80 g. (0.0348 g.-atom) of freshly-cut sodium. The system was swept thoroughly with prepurified nitrogen and all subsequent operations up to the extractions were carried out under a slow stream of nitrogen. A solution of 1.82 g. (0.005 mole) of dimethyl marrianolate methyl ether (I) in 180 ml. of dry ether was added during 1.5 hours with efficient stirring, and the stirring was continued as the flask was allowed to come slowly to room temperature. After 4 hours only a trace of ammonia could be detected in the exit gases. To the white suspension of excess sodium and sodium enolate of acyloin in ether was added 2 ml. of methanol in 100 ml. of ether (to destroy excess sodium) and the mixture was acidified with 50 ml. of 5% hydrochloric acid. After partition and separation, the aqueous layer was ex-

(8) M. N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947).

(9) A. Butenandt and E. L. Schöffler, *Z. Naturforsh.*, **1**, 82 (1946).

(10) J. C. Sheehan, R. A. Coderre, L. A. Cohen and R. C. O'Neill, THIS JOURNAL, **74**, 6155 (1952). The erroneous identification apparently was due to comparison with impure samples of 16-keto-17β-estradiol-3-methyl ether and the acetate prepared in this Laboratory by the method in ref. 8. Our assignment of the 17B-configuration has been confirmed by Dr. Mortimer Levitz (New York University) using essentially our procedures, which were made available to him in exact experimental detail prior to publication during his visit to our laboratory in September of 1952.

(11) M. N. Huffman and M. H. Lott, *ibid.*, **71**, 719 (1949).

(12) J. H. Biel, *ibid.*, **73**, 847 (1951).

(13) M. N. Huffman, *J. Biol. Chem.*, **169**, 167 (1947).

(14) M. N. Huffman and M. H. Lott, THIS JOURNAL, **73**, 878 (1951).

(15) All melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for the analyses and the infrared absorption measurements.

(16) J. Herr and K. Miescher, *Helv. Chim. Acta*, **28**, 160 (1945).

(17) H. H. Bater, J. M. Mullaly and H. Hartley, *J. Chem. Soc.*, **123**, 401 (1923).

tracted with an ether–methylene chloride mixture, and the combined organic solution was washed with dilute sodium bicarbonate and water. Removal of the solvents under reduced pressure afforded 1.44 g. (96%) of colorless crystalline product, m.p. 163–166°, $[\alpha]^{26}D$ −85° (*c* in ethanol). Treatment with charcoal and recrystallization gave silky needles of 16-keto-17β-estradiol-3-methyl ether (II), m.p. 169.5–171°, $[\alpha]^{27}D$ −87° (*c* 1 in ethanol).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.79; H, 8.09.

Upon admixture with a sample of 16-keto-17β-estradiol-3-methyl ether, m.p. 169–170.5°, $[\alpha]^{27}D$ −88° (*c* 1 in ethanol), prepared from 16-oximinoestrone methyl ether according to the method of Butenandt,[9] the m.p. was 169–170.5° (undepressed).

A sample of II prepared by the acyloin cyclization was converted to an oxime derivative. After three recrystallizations from ethanol the m.p. (dec., in bath at 194°) was 199.5–200°.

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 8.00. Found: C, 72.39; H, 8.21.

16-Keto-17β-estradiol-17-acetate-3-methyl Ether (III).—To 500 mg. (0.0016 mole) of α-ketol II, were added 5 ml. of dry pyridine and 2 ml. of acetic anhydride and the solutions stored at room temperature for 16 hours. The solution was diluted to about 35 ml. with water and neutralized with 11 ml. of 6 *N* hydrochloric acid. The crystals obtained were filtered, washed well with water, and recrystallized from ethanol to give 490 mg. (86%) of 16-keto-17β-estradiol-17-acetate-3-methyl ether, m.p. 151–151.5°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.87; H, 7.38. Found: C, 73.95; H, 7.68.

Upon admixture of this compound with the acetate of the α-ketol prepared by the method of Butenandt,[9] m.p. 150.2–151°, the m.p. was 150.2–151.5° (undepressed).

The Trimethylene Thioketal of 16-Keto-17β-estradiol-17-acetate-3-methyl Ether (IV).—To 440 mg. of the acyloin acetate III dissolved in 10 ml. of anhydrous benzene was added 500 mg. of freshly fused zinc chloride and 0.4 ml. of 1,3-propanedithiol. The benzene solution was saturated with anhydrous hydrogen chloride, and after 2 hours at room temperature, the solution was decanted from the zinc chloride. After washing successively with dilute sodium hydroxide and water and drying over sodium sulfate, the solvent was removed under reduced pressure and the residue crystallized from ethanol to give 500 mg. of the thioacetal IV, m.p. 158–159°.

Anal. Calcd. for $C_{24}H_{32}O_3S_2$: C, 66.62; H, 7.46. Found: C, 66.56; H, 7.62.

17β-Estradiol-3-methyl Ether (V).—A mixture of 325 mg. of the thioketal IV and 5 g. of Raney nickel W-6 in 50 ml. of dioxane (solvent pretreated with Raney nickel catalyst) was heated for 16 hours on a steam-bath. The catalyst was recovered by filtration and thoroughly washed with dioxane and ether. Removal of the solvents under reduced pressure and crystallization of the residues from aqueous methanol gave 190 mg. (88%) of 17β-estradiol-3-methyl ether (V), double m.p. of 96° and 119–119.5°, $[\alpha]^{27}D$ +73° (ethanol).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.67; H, 9.15. Found: C, 79.41; H, 9.32.

The m.p. of a mixture with 17β-estradiol-3-methyl ether, m.p. 119–119.8°, $[\alpha]^{27}D$ +75° (ethanol), prepared by sodium borohydride reduction[12] of estrone methyl ether, was 119–119.5° (undepressed).

Estrone Methyl Ether (VI).—To 200 mg. of 17β-estradiol-3-methyl ether dissolved in 5 ml. of glacial acetic acid in an ice-bath was added 60 mg. of chromic anhydride dissolved in 1 ml. of glacial acetic acid. After 20 minutes the flask was allowed to warm to room temperature. Water was added after 60 minutes and the cold green solution made alkaline by the slow addition of solid sodium carbonate. After extraction with ether, the ketonic product was obtained crystalline upon removal of the solvent. Recrystallization from ethanol gave 135 mg. of estrone methyl ether, m.p. 169–170°, $[\alpha]^{27}D$ +169°. Upon admixture with an authentic sample, m.p. 168–169°, the m.p. was 168–169° (undepressed).

17β-Estradiol (VII).—A mixture of 117 mg. of 17β-estradiol-3-methyl ether and 2 g. of anhydrous pyridine hydrochloride was heated at 200–220° for 40 minutes under an atmosphere of nitrogen.[18] After cooling, 5 ml. of dilute hydrochloric acid was added, and the product taken up in ether. Extraction with several portions of *N* potassium hydroxide, followed by acidification of the combined basic extracts, afforded 100 mg. (90%) of 17β-estradiol, m.p. 174–177° with previous softening. After recrystallization from aqueous methanol the m.p. was 176–177.5°, $[\alpha]^{27}D$ +80° (*c* 1, dioxane).

The m.p. of a mixture with an authentic sample of 17β-estradiol, m.p. 176.5–177.5°, $[\alpha]^{27}D$ +82.5° (*c* 1, dioxane), prepared by sodium borohydride reduction of estrone,[12] showed no depression (176–177.5°).

Lithium Aluminum Hydride Reduction of 16-Keto-17β-estradiol-3-methyl Ether.—To a stirred slurry of 150 mg. of lithium aluminum hydride in 40 ml. of dry tetrahydrofuran was added over a 10-minute period a solution of 312 mg. (0.001 mole) of the α-ketol II in 5 ml. of dry tetrahydrofuran. The mixture was heated at reflux for 50 minutes, cooled, and excess reagent was destroyed by adding 5 ml. of ethyl acetate. Twenty-five ml. of 5% hydrochloric acid was added and stirring continued for 10 minutes. The layers were separated, the acid layer extracted with ether, and the combined organic solution washed well with water, dried, and concentrated to yield 300 mg. (96%) of colorless crystals, m.p. 128–133° after recrystallization from methanol.

To 64 mg. of this isomeric mixture of glycols, dissolved in 10 ml. of absolute acetone, was added 2 ml. of absolute acetone saturated with anhydrous hydrogen chloride. The medium was swirled for 15 minutes, then poured into 100 ml. of 3% potassium carbonate solution. After storage at 0–5° for 16 hours, 52 mg. (72%) of the acetonide VIII of the *cis*-glycol, estriol-16β,17β,3-methyl ether, was obtained, m.p. 150–152° after recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.84. Found: C, 77.31; H, 8.76.

Twenty mg. of the acetonide VIII dissolved in 2 ml. of dioxane was refluxed for 2 hours with 2 ml. of 10% aqueous hydrochloric acid. Ten ml. of water was added, and after 16 hours at 0–5°, 15 mg. of 16-epiestriol was isolated. After recrystallization from aqueous methanol, the m.p. was 135.5–136.5° (reported[19] 141–142°).

Desoxoestrone Ether (IX).—To 50 mg. of α-ketol II, m.p. 163–166°, dissolved in 3 ml. of glacial acetic acid, were added 2.0 g. of zinc dust and 3 ml. of concentrated hydrochloric acid and the mixture was heated at reflux for 9.5 hours. An additional 3-ml. portion of concentrated hydrochloric acid was added 30 minutes after heating had begun. Water and ice were added and the solution extracted with ether. The ether layer was washed well with water, dilute sodium carbonate solution and again with water. After drying over sodium sulfate, the ether solution was evaporated to dryness, and the colorless oil remaining crystallized from methanol to give 30 mg. of desoxoestrone methyl ether. Recrystallization from aqueous acetone gave a sample of m.p. 77° (reported[20] 76.5°).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84,39; H, 9.69. Found: C, 84.80; H, 9.41.

CAMBRIDGE 39, MASSACHUSETTS

(18) The method of A. L. Wilds and W. McCormack, THIS JOURNAL, **70**, 4127 (1945).

(19) M. N. Huffman and H. H. Darby, *ibid.*, **66**, 150 (1944).

(20) A. Butenandt and U. Westphal, *Z. physiol. Chem.*, **223**, 147 (1934).