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

The Formation of Five- and Six-membered Rings by the Acyloin Condensation. V. A Novel Conversion of 16-Ketoestradiol-3-methyl Ether to Estrone

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Estrone has been obtained in high over-all yield by a new two-step route from 16-keto-17β-estradiol-3-methyl ether (II), readily prepared from dimethyl marrianolate methyl ether (I) by an acyloin condensation in homogeneous medium. The ketol II is reduced by sodium borohydride to a mixture of epimeric glycols, from which estrone was produced directly by treatment with pyridine hydrochloride. The *cis* and the *trans* forms of the individual glycols (16-epiestriol-3-methyl ether and estriol-3-methyl ether) both gave estrone in yields of 87 and 81%, respectively.

In order to avoid the essentially wasteful homologation and degradation steps required for closure of the D ring *via* the Arndt–Eistert and Dieckmann reactions as commonly featured in the published methods[3–6] leading to the total synthesis of estrone, the direct ring closure of dimethyl marrianolate methyl ether (I) has been investigated in this Laboratory. In the preceding publication in this series[7] there was reported the formation of 16-keto-17β-estradiol-3-methyl ether (II) in excellent yield by subjection of the diester I to the acyloin condensation in a homogeneous liquid ammonia–ether medium. The intermediate II was converted to the estrogenic steroids, estrone, estradiol and estriol 3-methyl ether.

We now wish to report a new and efficient transformation of 16-ketoestradiol-3-methyl ether (II) to estrone (VI). The acyloin II was reduced by means of sodium borohydride to a mixture of the epimeric glycols III, estriol-3-methyl ether (IV) and epiestriol-3-methyl ether (V). Dehydration of this mixture by fusion with pyridine hydrochloride at 200–220° gave estrone as the only product in 90% over-all yield. We previously reported[7] reduction of II by lithium aluminum hydride with essentially the same results.

In order to investigate the dehydration more thoroughly, the isomeric estriols were isolated from the mixture and their individual dehydrations studied. The *cis*-glycol, epiestriol-3-methyl ether, was isolated as the acetonide VII in 64% yield. Acid hydrolysis of this derivative afforded pure 16-epiestriol methyl ether (V). The *trans*-glycol, estriol-3-methyl ether (IV), was isolated in 8% yield. Fusion of 16-epiestriol acetonide 3-methyl ether (VII), 16-epiestriol 3-methyl ether (V) and estriol 3-methyl ether (IV) produced estrone (VI) in 81–87% yield. It is interesting that both the *trans*-glycol IV and the *cis*-glycol V give a good yield of the same ketone (estrone) on dehydration.

The synthesis of estrone from dimethyl marrianolate methyl ether by means of an acyloin condensation followed by reduction to the epimeric glycols and dehydration to estrone proves to be a simple and efficient operation. This procedure receives added interest in light of the recent isolation of 16-ketoestradiol and 16-epiestriol from urine by Prof. G. K. Marrian and his group. These estrogens had previously not been isolated from natural sources. Furthermore, M. N. Huffman and A. Katzberg have recently reported that 16-keto-estradiol-3-methyl ether is effective in hindering normal mitosis in chick embryo fibroblast, and hence may exhibit anticarcinogenic properties.[8]

Thus, using conventional methods for the total synthesis of estrone up to dimethyl marrianolate methyl ether, the acyloin condensation can be effectively employed to complete a total synthesis of these two important estrogens.

The authors are grateful to the Schering Corporation for generously supplying the estrone used for the preparation of dimethyl marrianolate methyl ether.

Experimental[9]

16-Keto-17β-estradiol-3-methyl ether (II).—The method of Sheehan, Coderre and Cruickshank[7] was followed for the preparation of 16-ketoestradiol. From 3.60 g. of dimethyl marrianolate methyl ether[7] added to a solution of 0.93 g. (0.04 g.-atom) of sodium in 200 ml. of dry ether and 300 ml. of anhydrous liquid ammonia, there was obtained 2.71 g. (91%) of 16-keto-17β-estradiol-3-methyl ether, m.p. 163–165°.

Sodium Borohydride Reduction of 16-Keto-17β-estradiol-3-methyl Ether.—To 2.50 g. (0.066 mole) of sodium borohydride dissolved in 100 ml. of anhydrous methanol was added a solution of 3.81 g. (0.008 mole) of 16-keto-17β-estradiol-3-methyl ether in 125 ml. of methanol. After storage overnight, the mixture was heated for 20 minutes on a steam-bath, and then poured into 750 ml. of 5% hydrochloric acid solution to afford 3.21 g. (85%) of a colorless solid (III), m.p. 125–133°. In a separate experiment, employing more vigorous hydrolysis of the borate complex, a quantitative yield of mixed glycols was obtained.

16-Epiestriol-3-methyl Ether Acetonide (VII).—To 2.50 g. of the isomeric mixture of glycols III dissolved in 125 ml. of absolute acetone, was added 50 ml. of absolute acetone saturated with anhydrous hydrogen chloride. The mixture was swirled for 15 minutes, allowed to stand overnight, then poured into one l. of 3% potassium carbonate solution. After storage at 0–5° for 18 hours, 2.59 g. of crystalline material was obtained. Recrystallization from ethanol gave 1.81 g. (64%) of colorless needles, m.p. 153–155°. Repeated recrystallization from ethanol gave a constant m.p. 155–156.5, $[\alpha]^{25}D$ +110° (*c* 2 in chloroform).

16α,17β-Estriol-3-methyl Ether (IV).—After concentration of the mother liquors to dryness, the residue was dissolved in chloroform and passed through 10 g. of Brockman Grade III alumina using ether–ethyl acetate as eluent. There was obtained a small amount of the impure acetonide and 199 mg. (8%) of 16α,17β-estriol-3-methyl ether, m.p. 161–163° after recrystallization from ethanol. Recrystal-

(1) Union Carbide and Carbon Corporation Fellow, 1955–1956.

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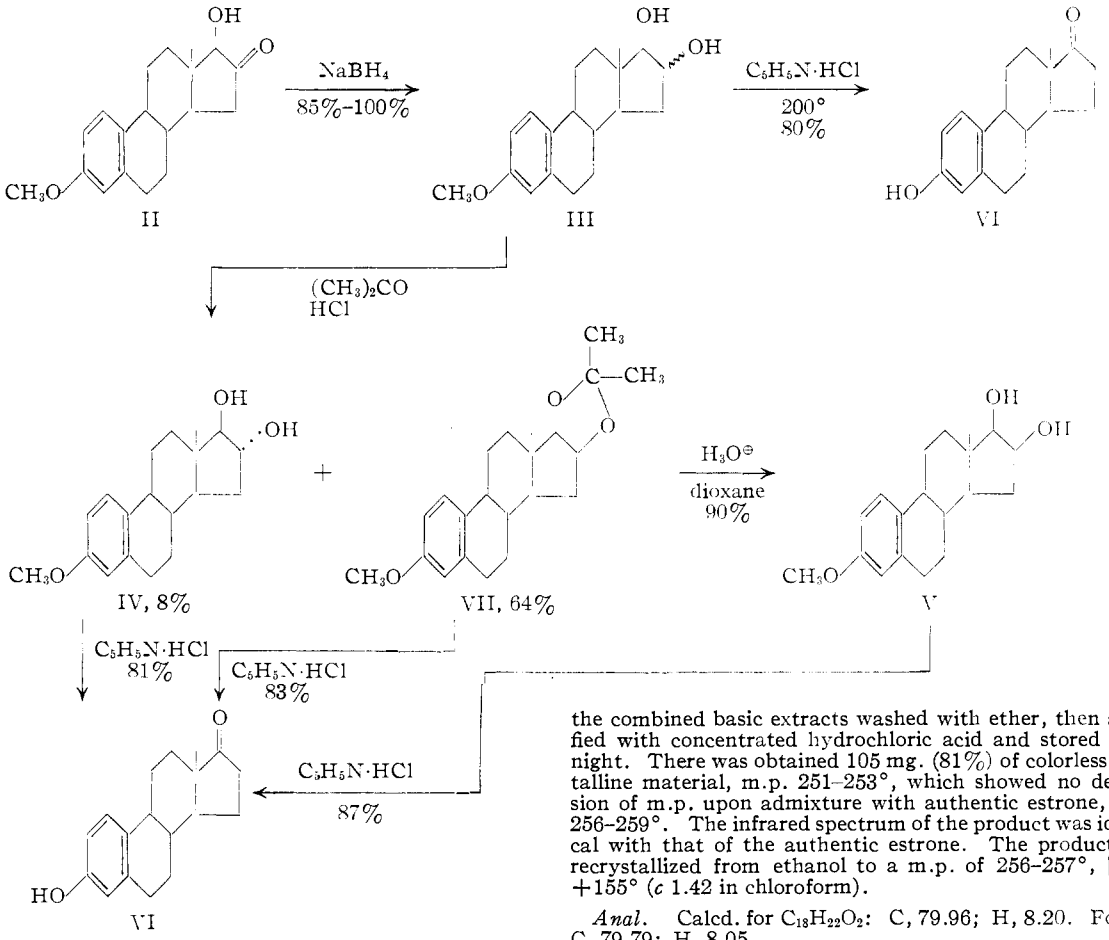
(6) W. S. Johnson and R. G. Christiansen, *ibid.*, **73**, 5511 (1951).

(7) John C. Sheehan, R. A. Coderre and Philip A. Cruickshank, *ibid.*, **75**, 6231 (1953).

(8) Address before the Division of Biological Chemistry, American Chemical Society Meeting, Dallas, Texas, April, 1956.

(9) All melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for the microanalyses, and to Dr. N. A. Nelson and his associates for the infrared and ultraviolet spectra.



lization from benzene–petroleum ether, followed by repeated recrystallization from aqueous ethanol gave a m.p. of 167–168°.

16-Epiestriol-3-methyl Ether (V).—The acetonide VII (305 mg.) was dissolved in 20 ml. of dioxane and the solution refluxed for 2.5 hours with 20 ml. of 5% hydrochloric acid solution. The hot solution was added to 100 ml. of water, the mixture allowed to stand overnight, and the precipitate collected. Charcoal decolorization and recrystallization from methanol afforded 0.275 g. (90%) of colorless plates, m.p. 135–137°. Recrystallization from benzene–petroleum ether followed by repeated recrystallization from aqueous methanol gave a constant m.p. of 138.5–139.5°.

Dehydration of Estriols to Estrone by Pyridine Hydrochloride Fusion.—In all cases the same general procedure for the pyridine hydrochloride fusion was carried out. The dehydration of the acetonide of 16-epiestriol-3-methyl ether is described in detail.

Dehydration of 16-Epiestriol-3-methyl Ether Acetonide (VII).—The acetonide VII (0.1656 g.) was fused with 7.05 g. of anhydrous pyridine hydrochloride at 200–220° for one hour under nitrogen. After cooling, the fused mass was crushed in 15 ml. of 5% hydrochloric acid solution and the mixture extracted with ether. The ethereal solution was washed with water, extracted with *N* potassium hydroxide, the combined basic extracts washed with ether, then acidified with concentrated hydrochloric acid and stored overnight. There was obtained 105 mg. (81%) of colorless crystalline material, m.p. 251–253°, which showed no depression of m.p. upon admixture with authentic estrone, m.p. 256–259°. The infrared spectrum of the product was identical with that of the authentic estrone. The product was recrystallized from ethanol to a m.p. of 256–257°, $[\alpha]^{25}D$ +155° (*c* 1.42 in chloroform).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.79; H, 8.05.

Dehydration of 16-Epiestriol-3-methyl Ether (V).—From 150 mg. of 16-epiestriol-3-methyl ether there was obtained 121 mg. (87%) of estrone, m.p. 253–255° after recrystallization from ethanol. The mixture m.p. of the product with authentic estrone, m.p. 256–259°, gave no depression. The product was recrystallized from ethanol to a constant m.p. of 255–256°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.91; H, 8.15.

Dehydration of 16α,17β-Estriol-3-methyl Ether (IV).—From 75 mg. of 16α,17β-estriol-3-methyl ether, m.p. 161–163°, there was obtained 55.6 mg. (83%) of estrone, m.p. 250–253°. The product was recrystallized from ethanol to a constant m.p. of 255–257°, undepressed upon admixture with a sample of authentic estrone.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.03; H, 8.31.

Dehydration of the Epimeric Mixture of Glycols III.—From 40 mg. of the glycol mixture III there was obtained 30 mg. of estrone, m.p. 252–253°, undepressed when mixed with authentic estrone.

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