[Chem. Pharm. Bull. 11 (10) 1271 ~ 1275]

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204. Kyosuke Tsuda, Shigeo Nozoe,*1 and Yutaka Okada*2 : Stereochemistry of Steroids Containing Aromatic A-Ring. III.*3 Hydrogenation of 11β-Hydroxy-Δ8-dehydroestrone.

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The earlier paper[1] from this laboratory reported that the treatment of 11β-hydroxyandrosta-1,4,8-triene-3,17-dione (I) with zinc in dimethylformamide resulted in aromatization of the A-ring with the concomitant elimination of the C-19 angular methyl group to form 3,11β-dihydroxyestra-1,3,5(10),8-tetraen-17-one (II).

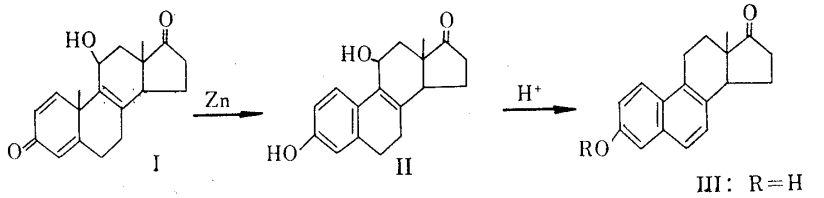

Chart 1.

This phenolic compound was converted to equilenin (3-hydroxyestra-1,3,5(10),6,8-pentaen-17-one) (III) on treatment with an acid and into equilenin methyl ether (IV) on methylation with dimethyl sulfate. Acetylation of II gave a monoacetate possessing no hydroxyl group and of an unknown structure.

In the present paper, reduction of the Δ8-tetrasubstituted double bond by catalytic hydrogenation and with lithium in liquid ammonia, will be described, along with the reference to the stereochemistry of the hydrogenated product.

Hydrogenation of 3,11β-dihydroxyestra-1,3,5(10),8-tetraen-17-one (II) over platinum catalyst in ethanol resulted in absorption of 1 mole of hydrogen to form a dihydro compound, m.p. 234~238°. From the intensity of its ultraviolet spectrum (λ_{max} 278 mμ (ε 16,200)) and the absence of absorption band in the carbonyl region of its infrared spectrum, this dihydro compound was shown to be 3,11β,17β-trihydroxy-1,3,5(10),8-tetraene compound (V) resulted by the reduction of only 17-oxo group. It was found that the double bond in 8-position of the compound (II) was resistant to reduction over platinum catalyst. The same catalytic hydrogenation was attempted in ethyl acetate, by which II absorbed 1.5 molar equivalents of hydrogen to form a tetrahydro compound (VI). The ultraviolet spectrum of this hydrogenation product showed absorption maximum at 280 mμ (ε 2,000) and the absorption for a five-membered ring ketone disappeared from its infrared spectrum, from which it wasconfirm ed that the product is an estratrienetriol (VI) with an unnatural conformation. During this hydrogenation, a compound with naphthol properties was obtained, being confirmed by the ultraviolet spectral analysis of the crude product.

Hydrogenation of II over palladium-on-charcoal in ethyl acetate afforded a mixture of two kinds of phenolic compounds. This product was purified by silica gel chromatography and elution of the column with methylene chloride gave a compound of m.p.

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*3 This paper constitutes Part XLV of the series entitled "Steroid Studies" by K. Tsuda. Part XLIV. This Bulletin, **11**, 1034 (1963).
1) K. Tsuda, S. Nozoe, Y. Okada : J. Org. Chem., **28**, 789 (1963).

238°, as the first fraction. From the ultraviolet spectrum of this compound and the melting points of its methyl ether and acetate, this product was proved to be equilenin (III).[2] Formation of equilenin by hydrogenation must be explained by a mechanism other than that for its formation by acid treatment. Equilenin was assumed to form by the hydrogenolysis of the allylic hydroxyl group in 11-position and dehydrogenation of the B-ring.[3]

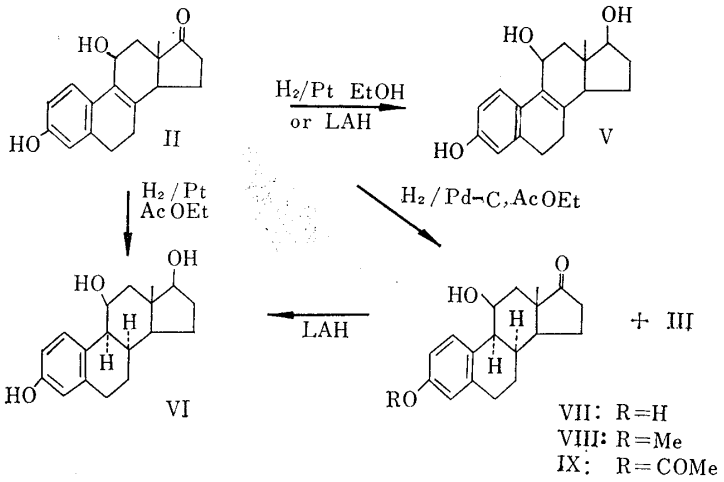

Chart 2.

A dihydro compound (VII), m.p. 227~230°, was obtained as the second fraction. Its ultraviolet spectrum was the same as that of VI and the presence of a five-membered ring ketone was indicated by its infrared spectrum. Reduction of VII with lithium aluminum hydride afforded the above VI. These results showed that VII is 3,11β-dihydrox yestra- 1,3,5 (10)-trien-17-one formed by the hydrogenation of the double bond alone. Both VI and VII possess B/C-*cis* juncture and should have *cis-syn-trans* conformation.

The dihydro compound (VII) formed methyl ether (VIII), m.p. 173~174°, by methylation with dimethyl sulfate and monoacetate (IX), m.p. 129.5~130.5°, by acetylation with acetic anhydride in pyridine. The fact that the hydroxyl group in 11-position was not acetylated by this acetylation seems to give a hint on the stereochemical assignment of this compound.

In general, the 11β-hydroxyl group in steroids with normal conformation is not acetylated with acetic anhydride in pyridine at room temperature due to the 1,3-diaxial interactions between the two methyl groups at 18-1 and 9-positions, but that in estra-1,3,5 (10)-triene skeleton as well as 19-norsteroids is acetylated under the same condition.[4]

The formulae (A) or (B) is possible as the structure for VII. In formula (A), the 7-8 bond as well as the 19-methyl group is in 1,3-diaxial relation to the 11β-hydroxyl group, whereas there is no corresponding hindrance in formula (B).

It is not unreasonable, therefore, to consider that the 11β-hydroxyl group in A conformation would be resistant to acetylation and compound (VII) assumably has the 8α,9α-configuration. In order to confirm this point, the methyl ether (VIII) was heated with methanesulfonyl chloride in dimethylformamide, in the presence of pyridine,[5] and derived to the corresponding dehydration product (X). This product had absorption maximum at 262 mμ in its ultraviolet spectrum and this maximum is the same as that of 9(11)-dehydroestrone methyl ether.[6]

2) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, C. Djerassi: J. Am. Chem. Soc., **72**, 4531 (1950).
3) W. Dirscherl, F. Hanusch: Z. Physiol., ¡233, 13 (1935); **236**, 131 (1935); W. Dirscherl: Angew. Chem., 48, 399 (1935).
4) B. J. Magerlein, J. A. Hogg: J. Am. Chem. Soc., **80**, 2220 (1958).

Chart 3.

The physical properties of the derivative having a natural conformation differ clearly from those of present compounds, as shown in Table I.

These experiments have shown that the hydrogen atom in 8-position has α-configuration.

TABLE I.

	m.p.	$[\alpha]_D$	λ_{max} (ε)
9(11)-dehydro-8-isoestrone 3-methyl ether (X)	119~120°	+129° *a)*	261.5 mμ (17, 300)
9(11)-dehydroestrone 3-methyl ether	142~144°	+289° *a)*	263 mμ (17, 300)

a) measured in $CHCl_3$.

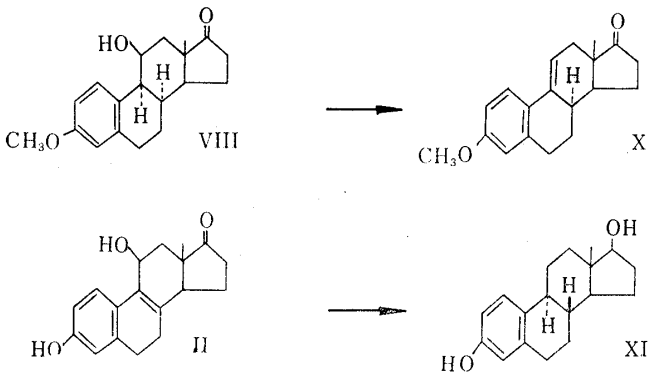

Chart 4.

Finally, reduction of II with lithium in liquid ammonia[7] afforded estradiol (XI) as the sole product, with or without addition of alcohol. This product was confirmed by admixture with the natural hormone and its diacetate, and by comparison of their infrared spectra. The formation of estradiol may be explained as the hydrogenolysis of the allylic hydroxyl group in 11-position, followed by the reduction of its double bond at 8-position. In this case, it became clear that the compound is reduced to B/C-*trans* juncture, *i.e.* to 8β,9α-configuration.

5) E.M. Chamberlin, E.W. Tristram, T. Utne, J.M. Chemerda : J. Org. Chem., **25**, 295 (1960).
6) K. Tsuda, E. Ohki, S. Nozoe *Ibid.*, **28**, 786 (1963).
7) W. Nagata, S. Hirai, T. Terasawa, K. Takeda : This Bulletin, **9**, 769 (1961).

Experimental[8)]

Estra-1,3,5(10),8-tetraene-3,11β,17β-triol (V)——i) A solution of 568 mg. of 3,11β-dihydroxyestra-1,3,5(10),8-tetraen-17-one (II) in 20 ml. of EtOH was shaken with 70 mg. of PtO_2 for 2 hr. under H_2. Filtration, evaporation and recrystallization from Me_2CO gave 480 mg. of V as a micro prisms, m.p. 220~223°(violet melt). Further recrystallization from Me_2CO afforded an analytically pure sample, m.p. 234~238°(brown melt). $[\alpha]_D$ +82°(c=0.62, dioxane). UV λ_{max} mμ (ε): 278 (16,200), 273 (shoulder). IR ν_{max} cm^{-1}: 3531, 3250 (broad), 1610, 1500, 839. *Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; O, 16.76. Found: C, 75.43; H, 7.74; O, 16.66.

ii) To a solution of 76 mg. of $LiAlH_4$ in 5 ml. of tetrahydrofuran was added a solution of 284 mg. of II in 10 ml. of tetrahydrofuran. The reaction mixture was allowed to stand overnight, and then few drops of Me_2CO was added to decompose the unreacted $LiAlH_4$. Dilution with H_2O, extraction with AcOEt and evaporation afforded 210 mg. of crude II, m.p. 194~200°. Recrystalllization from Me_2CO raised the melting point to 230~237° which exhibited the same absorption spectra and gave no depression in melting point on admixture with sample prepared from hydrogenation of II.

8α-Estra-1,3,5(10)-triene-3,11β,17β-triol (VI)——i) A solution of 120 mg. of II in 30 ml. of AcOE twas shaken with 30 mg. of PtO_2 for 2 hr. under H_2. Filtration, evaporation and crystallization from Me_2CO gave 80 mg. of crude product which was chromatographed over 20 g. of silica gel. The fraction eluted with CH_2Cl_2-EtOH (5%) afforded 40 mg. of VI as prisms, m.p. 245~250°. $[\alpha]_D$ +65°(c=0.92, dioxane). UV λ_{max} mμ (ε): 280 (1,950), 287 (shoulder). IR ν_{max} cm^{-1}: 3460, 3300 (broad), 1622, 1592, 1504, 835. *Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 75.03; H, 8.29; O, 16.60.

ii) To a solution of 40 mg. of $LiAlH_4$ in 3 ml. of tetrahydrofuran was added a solution of 140 mg. of VII (vide infra) in 5 ml. of tetrahydrofuran and the mixture allowed to stand for 20 hr. Isolation of the product was achieved by the procedure used for V. Recrystallization from Me_2CO gave an analytically pure sample of VI, m.p. 247~250°, which exhibited the same IR spectrum and gave no depression in melting point on admixture with the sample prepared by hydrogenation of II.

Hydrogenation and Dehydrogenation of 3,11β-Dihyroxyestra-1,3,5(10)-8-tetraen-17-one (I) with Palladium-on-charcoal in Ethyl Acetate——A solution of 1 g. of II in 30 ml. of AcOEt was shaken with 1 g. of 10% Pd-C under the atmosphere of H_2. Filtration and evaporation gave 800 mg. of crude product. Chromatography on 25 g. of sillica gel and elution with CH_2Cl_2 afforded white powder, m.p. 211~220°, as a first eluate. Recrystallization from Me_2CO-Et_2O gave equilenin, m.p. 238~248°(red melt). UV λ_{max} mμ: 230, 259.5, 270, 281, 292.5, 327.5, 340. *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.12; H, 7.41.

Acetate, m.p. 157~158°; methyl ether, m.p. 194~196°. Further elution with CH_2Cl_2 afforded 320 mg. of 8-iso-3,11 β-dihydroxy-1,3,5(10)-trien-17-one(VII) as prisms, m.p. 224~226°. Recrystallization from Me_2CO-Et_2O afforded an analytically pure sample, m.p. 227~230°, $[\alpha]_D$ +109° (c=0.57, dioxane), UV λ_{max} mμ (ε): 280.5 (1,750), 286 (shoulder). IR ν_{max} cm^{-1}: 3570, 3400 (broad), 1717, 1610, 1583, 1498, 818. *Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.79; H, 7.70.

Methyl Ether of VII——To a solution of 50 mg. of VII in 5 ml. of MeOH and 0.6 ml. of H_2O containing 0.5 g. of KOH was added a total of 1 ml. of Me_2SO_4. When the reaction was completed, H_2O was added to the reaction mixture and warmed on water bath for 20 min. Extraction with Et_2O, evaporation, and crystallization of the residue from Me_2CO-Et_2O gave 38 mg. of methyl ether (VIII) as prisms, m.p. 173~174°. UV λ_{max} mμ (ε): 278 (2370), 286.6 (2320). IR ν_{max} cm^{-1}: 3510, 1730, 1611, 1590, 1504, 823. *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.09; H, 7.92.

3-Monoacetate of VII——A solution of 50 mg. of VII in 0.5 ml. of Ac_2O and 0.5 ml. of pyridine was allowed to stand at room temperature for 20 hr. The solution was poured into ice water and the crystals were collected by filtration to give 42 mg. of monoacetate (IX) as needles, m.p. 121~127°. Recrystallization from Et_2O furnished an analytical sample, m.p. 129~130.5°. $[\alpha]_D$ −95°(c=0.95). UV λ_{max} mμ (ε): 275 (1010), 267.5 (900), 261 (shoulder). IR ν_{max} cm^{-1}: 3530, 1769, 1733, 1615, 1586, 1496, 1200. *Anal.* Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.19; H, 7.54.

3-Methoxy-8α-estra-1,3,5(10),9(11)-tetraen-17-one (X)——To a solution of 80 mg. of methyl ether (VIII) in 2 ml. of dimethylformamide and 1.4 ml. of pyridine was added 0.2 ml. of methane sulfonyl chloride. After warming for 2 hr. at 80° in water bath, the dark reaction mixture was poured into cold dilute $NaHCO_3$ solution, and extracted with Et_2O. The Et_2O extracts were washed with H_2O and dried over Na_2SO_4. The residue obtained after evaporation of Et_2O, was crystallized from MeOH to afford 46 mg. of X. Recrystallization from MeOH gave prisms with a slight yellow tinge, m.p. 119~120°. UV λ_{max} mμ (ε): 261.5 (17,300), 294 (shoulder). IR ν_{max} cm^{-1}: 1763, 1600, 1495, 816. *Anal.* Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 81.28; H, 7.78.

8) All melting points are uncorrected and unless noted otherwise, all rotations were measured in chloroform solution at 25°. Methanol was used for the ultraviolet spectra and nujol paste for the infrared spectra.

Reduction of II with Lithium in Liquid Ammonia to Estradiol (XI)——To a solution of 140 mg. of Li in 30 ml. of liquid NH_3 cooled in a dry ice Me_2CO-bath was added a solution of 284 mg. of II in 12 ml. of tetrahydrofuran and 6 ml. of EtOH over a period of 10 min. and the mixture was further stirred for 15 min. at −70°. H_2O was added after evaporation of NH_3 and the product was extracted with Et_2O. The residue obtained on evaporation of the solvent was recrystallized from MeOH to give estradiol, m.p. 176~177°, which on acetylation gave diacetate, m.p. 127~128°. Both compounds showed no melting point depression when mixed with authentic specimens of natural estradiol and its diacetate.

The authors are indebted to Dr. S. Akagi, of Sankyo Co., Ltd. for his helpful discussion and to Misses H. Yamanouchi and K. Hayashi for elemental analyses and to Misses N. Satō, N. Tōhata and K. Arimoto for infrared spectra measurements.

Summary

Reduction of the Δ^8-double bond in 3,11β-dihydroxyestra-1,3,5(10),8-tetraen-17-one (II) was carried out. Catalytic hydrogenation of II occurred from rear side and afforded the compound having 8α,9α-configuration, which was assigned in consideration of its resistance to acetylation and by leading to 9(11)-dehydro-8-isoestrone methyl ether, whereas reduction of II with lithium in liquid ammonia afforded estradiol.

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205. Hiroko Hasegawa, Yoshihiro Sato, und Kyosuke Tsuda : Untersuchungen über Steroide. XLVI.[1] Über die vier Isomere des zum Progesteron gehörigen 14,15-Diols.*1

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Bei der Behandlung des Pregna-4,14-dien-3,20-dions (I)[2] mit Benzopersäure ergab sich ein Epoxid, dem auf Grund der folgenden Versuche die Formel (II) mit 14α,15α-Epoxylgruppe zukommen : durch reduktive Ringaufspaltung der Epoxylgruppe mit Lithiumalminiumhydrid*3 und anschließende Oxydation der neugebildeten sekundären Alkoholgruppen mit Chromtrioxid in Pyridin entstand ein Hydroxyprogesteron vom Schmelzpunkt 190~195°, das sich nach Infrarot Spektrum und dem Misch-Schmelzpunkt als identisch mit dem bekannten 14-Hydroxypregn-4-en-3,20-dion (III)*4 erwies.

Bei Umsetzung des Epoxids (II) mit Perchlorsäure in Aceton ergab sich ein Rohprodukt, aus dem sich durch Umkristallisieren und darauffolgendem Chromatographieren drei kristalline Stoffe isolieren ließen. Nach Infrarot Spektrum und der Elementaranalysen

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*1 Die Zusammenfassung dieser Arbeit ist bereits als Communication veröffenlicht worden; dieses Bull., **9**, 409 (1961).

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*3 Bei der Lithiumalminiumhydrid-Reduktion einer Epoxylgruppe der tertiären und sekundären Kohlenstoffatomen ergibt sich im allgemeinen ein tertiäres Alkohol, vgl. R.E. Parker, N.S. Isaacs, Chem. Review, **59**, 739 (1959); A.S. Hallsworth, H.B. Henbest, J. Chem. Soc., **1957**, 4607.

*4 Wir danken Herrn Dr. K. Tanabe, Takamine Laboratorium, hier bestens für die Überlassung des genannten Präparates, vgl. K. Tanabe, R. Hayashi, R. Takasaki, M. Shirasaka : Dieses Bulletin, **7**, 811 (1959).

1) XLV Mitteil. : Dieses Bulletin, im Drucke (1963).

2) H. Hasegawa, Y. Sato, T. Tanaka, K. Tsuda : *Ibid.*, **9**, 740 (1961).