C-3 Substituted $\Delta^{1(10)}$-Steroids[1,2]

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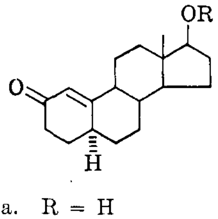
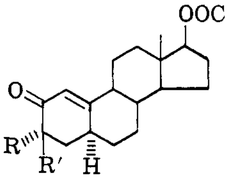
The synthesis of 17β-hydroxy-5α-estr-1(10)-en-3-one is described. The preparation of the corresponding 3α- and 3β-diols also is described. The isomerization of the $\Delta^{1(10)}$-3-ketone to the conjugated Δ^1-3-ketone is discussed.

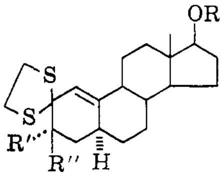
In extension of our previous work[3] on novel 19-norsteroids we wish to report the synthesis of other ring A double bond isomers of 19-nortestosterone, *i.e.*, the $\Delta^{1(10)}$ and Δ^1 compounds IVc and Va. The starting material employed was 17β hydroxy-5α-estr-1(10)-en-2-one (Ia), the preparation of which has been reported recently from this laboratory.[3] Lead tetraacetate oxidation of 17β acetoxy-5α-estr-1(10)-en-2-one (Ib) yielded a mixture of approximately equal amounts of the epimeric 3-acetoxy compounds IIa and IIb which were separated by chromatography on alumina. The 3α-acetoxy compound IIa, m.p. 147–9° $[\alpha]^{23}\text{D}$ −92, was eluted first, followed by the 3β-acetoxy compound IIb, m.p. 198–201° $[\alpha]^{23}\text{D}$ +5°. The orientation at C-3 of IIa follows from the epimerization of the axial 3α-acetoxy group with potassium acetate in refluxing glacial acetic acid[4] to give the more stable equatorial 3β-acetoxy compound IIb. The relative order of elution from the chromatogram was also consistent with these structures. With ethanedithiol in the presence of zinc chloride, the two epimeric ketol diacetates IIa and IIb gave the respective thioketal derivatives 2,2-ethylenedithio-5α-estr-1(10)-ene-3α,17β-diol diacetate (IIIa), m.p. 161–164°, and 2,2-ethylenedithio-5α-estr-1(10)-ene-3β,17β-diol diacetate (IIIb), m.p. 166–170°. The thioketal acetates IIIa and IIIb were hydrolyzed with methanolic alkali to give the 2-thioketal-3α,17β-diol IIIc, m.p. 104–110°, and 2-thioketal-3β,17β-diol IIId, m.p. 176–178°. Desulfurization of IIId with sodium in liquid ammonia[5] resulted also in the complete hydrogenolysis of the 3-hydroxyl group to give 5α-estr-1(10)-en-17β-ol (IVd), m.p. 107–110°, in excellent yield. The structure of this product was shown from its identity with the desulfurization product of 2,2-ethylenedithio-5α-estr-1(10)-en-17β-ol (IIIe). When, however, the desulfurization of the thioketal diols IIIc and IIId was effected with W2 Raney nickel in refluxing ethanol, no significant hydrogenolysis occurred and the unsaturated diols, 5α-estr-1(10)-ene-3α,17β-diol (IVa), m.p. 196–198°, and 5α-estr-1(10)-ene-3β,17β-diol (IVb), m.p. 208–211°, were obtained.



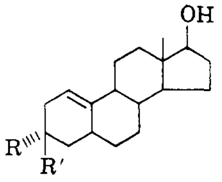
Ia. R = H
b. R = CH_3CO



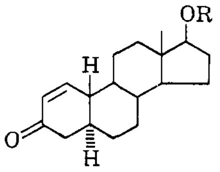
IIa. R = CH_3COO, R′ = H
b. R = H, R′ = CH_3COO



IIIa. R = CH_3CO, R′ = CH_3COO, R″ = H
b. R = CH_3CO, R′ = H, R″ = CH_3COO
c. R = R″ = 4, R′ = OH
d. R = R′ = H, R″ = OH
e. R = R′ = R″ = H



IVa. R = OH, R′ = H
b. R = H, R′ = OH
c. $\left.\begin{matrix}R\\R'\end{matrix}\right\rangle = O$
d. R = R′ = H



Va. R = H
b. R = CH_3CO

A recently described[6] minor oxidative side reaction during the desulfurization of similar compounds with deactivated Raney nickel suggested that with suitable modifications the side reaction might be enhanced to lead directly to a practical route to the desired β,γ-unsaturated ketone IVc. This indeed proved to be the case when the thioketal diol IIId was refluxed in acetone with Raney nickel which previously has been deactivated by boiling in acetone for twenty-four hours. The products consisted of a 20% yield of the 3β,17β-diol IVb, the normal desulfurization product, and a 50% yield of 17β-hydroxy-5α-estr-1(10)ene-3-one (IVc), m.p. 126–128° $[\alpha]^{24}\text{D}$ −36. This latter compound exhibited a single carbonyl in the infrared at 1723 cm.^{-1} in carbon tetrachloride, while the ultraviolet spectrum showed only end absorption. In a similar desulfurization of the epimeric diol IIIc a smaller proportion of the ketone IVc was obtained. This difference in yield could be due to the stereochemistry at C-3, or to the difficulty in duplicating the desulfurization conditions exactly. Reduction of the β,γ-unsaturated ketone IVc with lithium tri-*t*-butoxy aluminum hydride[7] led exclusively and in good yield to the equatorial 3β,17β-diol IVb which serves to confirm the structure of IVc as

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[1] This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

[2] Some of this work has appeared in a preliminary communication, J. Fishman, *Chem. Ind.* (London), 1467 (1962).

[3] J. Fishman, *ibid.*, 1556 (1958); J. Fishman and M. Tomasz, *J. Org. Chem.*, **27**, 365 (1962).

[4] R. L. Clarke, K. Dobriner, A. Mooradian, and C. M. Martini, *J. Am. Chem. Soc.*, **77**, 662 (1955).

[5] R. I. Ireland, T. I. Wrigley, and W. G. Young, *ibid.*, **80**, 4604 (1958); M. S. de Winter, C. M. Siegman, and S. A. Szpilvogel, *Chem. Ind.* (London), 905 (1959).

[6] P. Narasimha Rao and H. R. Gollberg, *ibid.*, 1317 (1961); *Tetrahedron*, **18**, 1251 (1962).

[7] O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958); J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

well as the correctness of the assigned configurations at C-3 in the original acetoxy compounds IIa and IIb.

The isomerization of the β,γ-unsaturated ketone IVc to the conjugated ketone Va with mineral acids at room temperature proved to be unusually slow. With 5% hydrochloric acid in methanol the isomerization reached its maximum only after five days at 25°. At reflux temperatures the isomerization was more rapid (two hours) but the yield was only about 50% as determined by absorption at 228 mμ and the product was difficult to isolate pure. This is in marked contrast to the isomerizations of the Δ^5- and $\Delta^{5(10)}$-3-ketones[8,9] under similar conditions since these proceed rapidly and give essentially single products in good yields. Although a new center of asymmetry is created at C-10 during the isomerization only the 10β compound Va, m.p. 147–149°, $\lambda_{\max}^{\text{EtOH}}$ 229 mμ (ε 10,000), was isolated.[10] On catalytic hydrogenation Va gave the known 17β-hydroxy-5α-estran-3-one.[11] Acetylation of Va gave the 17-acetate derivative Vb identical in all respects with that prepared by another route.[12,13] Hydrolysis of the 17-acetate in Vb by acid gave very poor yields of the ketone Va and the product was difficult to obtain in a pure state. This result together with the difficulty encountered in the isomerization of IVc suggest that the equilibrium between the β,γ-unsaturated ketone IVc and its α,β-unsaturated isomer Va does not favor the latter to the extent usual under such circumstances. Consequently, the 1(10)-double bond probably migrates to other positions in the molecule to yield a variety of isomers which may account for the low yield and difficulty in purification of the conjugated ketone Va.[14]

Among the most useful steroids in current clinical use are the 17α-ethynyl derivatives of 19-nortestosterone and its $\Delta^{5(10)}$ isomer. Both compounds are potent oral progestrogens[15,16] and have found wide acceptance as anovulatory agents. Although the physiological activities of these two double bond isomers are similar, significant differences do exist.[17] Since the new compounds reported in this paper represent further double bond isomers of the 19-nortestosterone structure, they or their derivatives may prove to be of biological significance.

Experimental[18]

17β-Acetoxy-5α-estr-1(10)-en-2-one (Ib).—A solution of 1 g. of 17β-hydroxy-5α-estr-1(10)-en-2-one (Ia) in 10 ml. of pyridine and 10 ml. of acetic anhydride was allowed to stand overnight at room temperature. After the usual work-up, the residue was crystallized from acetone–petroleum ether to give 940 mg. of the product Ib as white needles, m.p. 161–164°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.04; H, 9.15.

Lead Tetraacetate Oxidation of Ib.—To a solution of 7 g. of Ib in 100 ml. of glacial acetic acid was added 16 g. of lead tetraacetate in 275 ml. of glacial acetic acid. After heating on a steam bath for 4 hr., an additional 12 g. of lead tetraacetate was added, and the mixture was heated on a steam bath for another 20 hr. The acetic acid then was removed at reduced pressure and the residue was taken up in water and extracted four times with ether (800 ml.). The ether extract was washed with 5% sodium bicarbonate solution until basic and then with water. After drying, the ether was evaporated and the amber colored residue was taken up in 1:1 benzene–petroleum ether and chromatographed on 450 g. of acid-washed alumina. Elution with benzene gave 2.56 g. of crystals which were recrystallized from ether–petroleum ether to give **2-oxo-5α-estr-1(10)-ener-3α,-17β-diol diacetate (IIa)**, m.p. 140–145°. The analytical sample was obtained from the same solvents and melted at 147–149° $[\alpha]^{23}\text{D}$ −92°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.43; H, 8.07.

Further elution with benzene containing 10% ether gave 2.2 g. of crystals, which on recrystallization from ether–petroleum ether gave **2-oxo-5α-estr-1(10)-ene-3β,17β-diol diacetate (IIb)**, m.p. 195–200°. The analytical sample was obtained from the same solvents and melted at 198–201° $[\alpha]^{23}\text{D}$ +5°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.38; H, 8.28.

Epimerization of 2-oxo-5α-estr-(1(10)-ene-3α,17β-diol Diacetate (IIa).—A mixture of 10 mg. of IIa and 50 mg. of anhydrous potassium acetate in 3 ml. of glacial acetic acid was refluxed for 17 hr. On cooling, the reaction mixture was poured into water and extracted with ether which then was washed with dilute sodium bicarbonate solution and water. After drying and evaporating the ether, the residue was triturated with ether to give crystals, m.p. 194–200°, identical with the 3β,17β-diacetate IIb, by mixture melting point and infrared spectra comparison.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3α,17β-diol Diacetate (IIIa).—To a solution of 0.48 g. of IIa in 15 ml. of dioxane was added 6.3 g. of freshly fused zinc chloride, 6.3 g. of anhydrous sodium sulfate, and 1.5 ml. of ethanedithiol. After standing at room temperature overnight, the mixture was poured into cold dilute ammonium hydroxide and the white precipitate was filtered off and washed with water. The precipitate was dissolved in acetone, filtered, and the filtrate evaporated to dryness to give 0.60 g. of crude product, m.p. 154–160°. Recrystallization from ether gave the analytical sample of IIIa, m.p. 161–164° $[\alpha]^{21}\text{D}$ +30°.

Anal. Calcd. for $C_{24}H_{34}O_4S_2$: C, 63.96; H, 7.61; S, 14.23. Found: C, 64.11; H, 7.77; S, 14.62.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3β,17β-diol Diacetate (IIIb).—A 1-g. sample of IIb was converted to 1.3 g. of crude thioketal IIIb exactly as in the preceding procedure. The analytical sample obtained from ether melted at 166–171° $[\alpha]^{20}\text{D}$ −34°.

Anal. Calcd. for $C_{24}H_{34}O_4S_2$: C, 63.96; H, 7.61. Found: C, 63.65; H, 7.68.

2,2-Ethylenedithio-5α-estr-1(10)-en-17β-ol (IIIe).—A 0.1-g. sample of the unsaturated ketone Ia was converted to the thioketal IIIe by the same procedure. The product crystallized from petroleum ether–acetone to give needles (0.11 g.) which melted at 171–175° $[\alpha]^{21}\text{D}$ +10°.

Anal. Calcd. for $C_{20}H_{30}OS_2$: C, 68.52; H, 8.63; S, 18.29. Found: C, 68.48; H, 8.59; S, 17.94.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3α,17β-diol (IIIc).—A solution of 0.25 g. of IIIa in 30 ml. of 5% methanolic potassium hydroxide was refluxed for 3 hr. The solution was diluted with water and extracted well with ether which was washed with 5% sulfuric acid solution and then with 5% sodium bicarbonate solution and water. After drying and evaporation of solvent, the residue was crystallized from acetone–petroleum ether to give 0.21 g. of IIIc, m.p. 100–110°. The analytical sample was ob-

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[8] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 50.

[9] A. J. Birch, *Quart. Rev.*, **4**, 49 (1950); A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

[10] This compound has been reported in the patent literature, however, without physical constants: U. S. Patent 3,007,947; *Chem. Abstr.*, **56**, 7393 (1962).

[11] A. Bowers, H. J. Ringold, and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958).

[12] R. Villotti, H. J. Ringold, and C. D'erassi, *ibid.*, **82**, 5693 (1960).

[13] U. S. Patent 3,007,947; *Chem. Abstr.*, **56**, 7393 (1962).

[14] In isomerization of a Δ^4-2-ketone to Δ^3-2-ketone, a comparable situation, no crystalline product is obtained and no yield is specified.[6] The authors explain their results as being due to the formation of 5α and 5β isomers. In our case the formation of two isomers at C-10 is not likely since the energetically unfavorable 10α *syn* structure would not be expected to result from the isomerization.

[15] D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958).

[16] F. J. Saunders and V. A. Drill, *Endocrinology*, **58**, 567 (1956).

[17] V. A. Drill, *Fed. Proc.*, **18**, 1040 (1959).

[18] Melting points were determined on a Kofler block and are corrected. Rotations were determined in chloroform unless specified otherwise. Microanalyses were determined by Spang Microanalytical Laboratories.

tained from the same solvents and melted at 104–110° $[\alpha]^{23}\mathrm{D}$ +8°.

Anal. Calcd. for $C_{20}H_{30}O_2S_2$: C, 65.24; H, 8.19. Found: C, 65.43; H, 8.49.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3β,17β-diol (IIId).—Hydrolysis of 1.2 g. of IIIb, by the same procedure, gave 0.90 g. of IIId, m.p. 166–170°. The analytical sample obtained from acetone–petroleum ether melted at 176–178° $[\alpha]^{23}\mathrm{D}$ +64°.

Anal. Calcd. for $C_{20}H_{30}O_2S_2$: C 65.42; H, 8.19; Found: C, 65.44; H, 8.12.

5α-Estr-1(10)-en-17β-ol (IVd). A. From IIId.—A solution of 0.10 g. of IIId in 20 ml. of tetrahydrofuran was added to 100 ml. of liquid ammonia. To the stirred solution, sodium ribbon was added portionwise until the blue color persisted. After 3 min. of stirring the blue color was discharged with ethanol and the ammonia was allowed to evaporate. The residue was taken up in water and extracted with ether. The ether was dried and evaporated and the residue crystallized from petroleum ether to give 58 mg. of IVd, m.p. 107–110°. The analytical sample showed an unchanged melting point $[\alpha]^{21}\mathrm{D}$ −30°.

Anal. Calcd. for $C_{18}H_{20}O$: C, 83.05; H, 10.8. Found: C, 83.20; H, 10.6.

B. From IIIe.—A 50-mg. sample of IIIe was desulfurized as above, to give 30 mg. of IVd, m.p. 106–110°, identical with that prepared before by mixture melting point and infrared spectra comparison.

5α-Estr-1(10)-ene-3α,17β-diol (IVa).—A solution of 80 mg. of the thioketal IIIc in 20 ml. of ethanol was refluxed with 2.5 g. of Raney nickel (W2) for 2 hr. The nickel was filtered off and washed well with ethanol. The filtrate was evaporated to dryness to give 60 mg. of crystals, m.p. 180–190°. Recrystallization from ether gave 47 mg. of the diol IVa, m.p. 194–197°. The analytical sample melted at 196–198° (with sublimation) $[\alpha]^{23}\mathrm{D}$ −68.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.2. Found: C, 78.16; H, 9.90.

5α-Estr-1(10)-ene-3β,17β-diol (IVb). A. By Desulfurization.—A 0.1-g. sample of the thioketal IIId was desulfurized with 3 g. of Raney nickel as described. The product was crystallized from dilute methanol to give 70 mg. of crystals, m.p. 194–198°. The analytical sample was obtained from ether, m.p. 208–211° (changes to prisms) $[\alpha]^{23}\mathrm{D}$ −4.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.2. Found: C, 78.27; H, 10.4.

B. By Reduction of IVc.—A 25-mg. sample of unsaturated ketone IVc was allowed to stand with lithium tri-*t*-butoxy aluminum hydride in tetrahydrofuran at room temperature for 1 hr. After the usual work-up, 20 mg. of crystals was obtained from ether, m.p. 205–210°. This was identical with the product of method A by mixture melting point and infrared spectra comparison.

17β-Hydroxy-5α-estr-1(10)-en-3-one (IVc).—A suspension of 20 g. of Raney nickel in 400 ml. of acetone was refluxed for 20 hr. To this suspension, a solution of 0.8 g. of the thioketal diol IIId in 50 ml. of acetone was added, and the mixture was refluxed for 4 hr. After filtration the solvent was evaporated and the residue taken up in benzene and chromatographed on 50 g. of acid washed alumina. Elution with benzene gave first 45 mg. of recovered starting material IIId. Further elution with benzene gave 310 mg. of the ketone IVc, which on recrystallization from acetone–petroleum ether melted at 121–125°. The analytical sample obtained from the same solvents melted at 124–126°, $[\alpha]^{23}\mathrm{D}$ −36. Carbonyl band absorption in the infrared was at 1723 $\mathrm{cm.}^{-1}$ in carbon tetrachloride; only end absorption was observed in the ultraviolet.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.68; H, 9.57.

Subsequent elution of the column with ether and ether–chloroform mixtures gave 113 mg. of the 3β,17β diol IVb.

A similar desulfurization on 0.4 g. of the thioketol diol IIIc gave 45 mg. of the ketone IVc and 0.1 g. of the 3α,17β-diol IVa plus 0.11 g. of recovered starting material.

17β-Hydroxy-5α-estr-1-en-3-one (Va). A. Isomerization of IVc.—A small sample of IVc (10 mg.) was dissolved in 3 ml. of methanol and 1 ml. of 3 *N* hydrochloric acid was added. The solution was allowed to stand at room temperature with aliquots being withdrawn to measure ultraviolet absorption at 229 mμ. Only after 5 days did the absorption at 229 mμ reach a maximum. Longer standing resulted in a decrease in the absorption. A similar study at steam bath temperatures indicated that 2 hr. was the optimum time.

A solution of 80 mg. of the unsaturated ketone IVc in 25 ml. of ethanol and 5 ml. of 3 *N* hydrochloric acid was refluxed on a steam bath for 2 hr. After the usual work-up the residue was subjected to quantitative thin layer chromatography on silica gel containing a zinc phosphor. The main ultraviolet absorbing zone was eluted to give 16 mg. of an oil which crystallized slowly from acetone–petroleum ether to give 10 mg. of the conjugated ketone Va, m.p. 145–147° $[\alpha]^{21}\mathrm{D}$ +100 (ethanol), $\lambda_{\max}^{\mathrm{EtOH}}$ 229 mμ (ε 10,000).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.56; H, 9.19.

A less polar, nonultraviolet absorbing zone contained 22 mg. of the starting material, IVc. There were also present four other zones which yielded small amounts of intractable oils.

B. Hydrolysis of Vb.—A solution of 80 mg. of Vb in 10 ml. of methanol and 5 ml. of 5% sulfuric acid was refluxed overnight. After the usual work-up the oily residue was chromatographed on a thin layer silica plate. Six different zones were obtained, one of which on elution gave 10 mg. of oil, the infrared spectrum of which was identical with 17β-hydroxy-5α-estr-1-en-3-one (Va).

Acetylation of Va.—A 4-mg. sample of Va was acetylated in the usual manner. On work-up, crystalline material was obtained, which on recrystallization from petroleum ether melted at 132–136°, identical with 17β-acetoxy-5α-estr-1-en-3-one (Vb) by mixture melting point and infrared spectra comparison.

Hydrogenation of Va.—An 8-mg. sample of Va was hydrogenated in ethanol over 10% palladized charcoal. The crystalline product showed no specific ultraviolet absorption and after a Girard T separation the ketonic material, 4 mg., m.p. 124–128°, proved to be identical with 19-nordihydrotestosterone by mixture melting point and infrared spectra comparison.

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