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(18) The assumption[4] that the contribution of the C=O chromophore in acid does not differ significantly from that in alkaline medium does therefore not appear to be valid.
(19) The alternate suggestion that the greater intensity of the CD of reduced anaferine could be due to the effect of the newly generated asymmetric center does not seem valid since (a) the prochiral ketone **2** (C_2 symmetry) represents a trigonal system Yk_1k_2i in which the two faces of the carbonyl carbon are indistinguishable[20] as k_1 and k_2 are chemically and configurationally identical, (b) k_1 and k_2 are also identical in the reduced compound.
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Total Synthesis of Steroids. 12.[1] Final Evidence of the Configuration of the C-14 Hydroxyl Group in 3-Methoxy-14β-hydroxy-8α,9ξ-estra-1,3,5(10)-triene-11,17-dione

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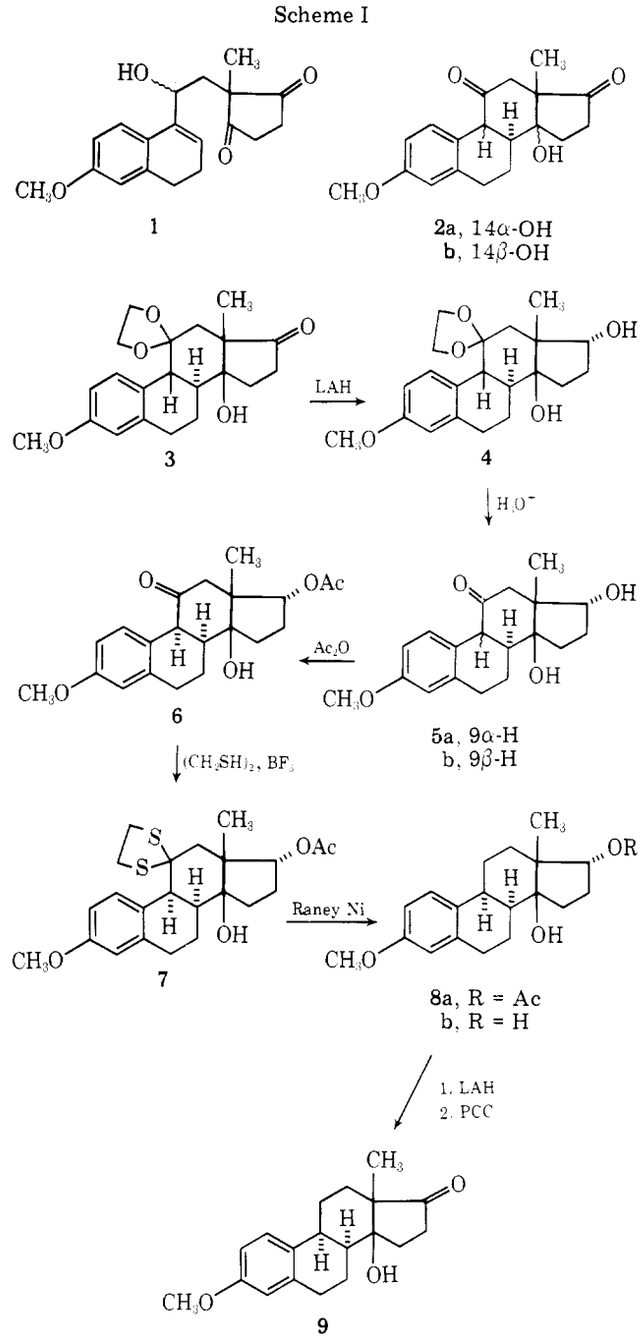
In one of the previous papers[2] of this series we described the synthesis of *rac*-3-methoxy-14α-hydroxy-8α,9ξ-estra-1,3,5(10)-triene-11,17-dione (**2a**) from the allylic alcohol **1** by cyclization with Meerwein reagents. The stereochemistry of compound **2a** at chiral carbon atoms 8, 9 and 13 was proved beyond any doubt. The configuration at C-14 was assumed to be α, on the basis of Sondheimer's observation[3] that either epoxidation or hydrogenation of the C-14 (15) double bond in nonaromatic steroids takes place from the β side of the molecule.

However, this assumption does not hold true for ring A aromatic steroids, and in fact the configuration of the 14-OH group in the cyclization product should be β, as in **2b.** This was demonstrated by the sequence of reactions shown in Scheme I.

The cyclization product **2b** was transformed into **3** as reported previously.[2] Reduction of the C-17 carbonyl group with lithium aluminum hydride led solely to the 17α-OH compound **4.** The configuration of the 17-OH group was proved to be α, because the hydrolysis products **5a** and **5b** and the acetyl derivative **6** obtained from **5a** were different in all respects from their epimers prepared previously[1] from optically active Torgov's secolone (with 17β-OH). Subsequently, compound **6** was converted by standard methods into *rac*-3-methoxy-14β-hydroxy-8α-estra-1,3,5(10)-trien-17-one (**9**). The latter compound had a MS spectrum identical with that reported by Wulfson et al.[4] Direct comparison of our sample **9** with the compound prepared by Zakharychev et al.[5] confirmed their identity.

Thus, the position of the C-14 hydroxyl group in compound **2** obtained by cyclization of **1** was proved to be β (as in **2b**) but not α (compound **2a**), contrary to the previous report.[2] This means that epoxidation of the C-14 (15) double bond in ring A aromatic 8-isosteroids takes place in a manner opposite, i.e., from the α side, to that observed during hydrogenation of the same double bond.

Scheme I



Consequently, the configuration at C-14 of all compounds with the 14-OH group described in our previous papers,[1,2,6] as well as in compounds **15, 16, 22,** and **24–28** reported in Part 7 of this series,[7] should be reversed.

If we assume that the π orbitals must overlap in the transition state for the cyclization **1** → **2**, reexamination of Dreiding models indicates that the preferred geometry of the product at C-8 and C-14 should be trans with a cis C/D ring junction.

Experimental Section[8]

3-Methoxy-11,11-ethylenedioxy-8α,9β-estra-1,3,5(10)-triene-14β,17α-diol (4). To a solution of **3** (1.0 g, 2.79 mmol) in THF (100 mL) was added 0.2 g of LAH, and the mixture was stirred at room temperature for ca. 10 min. The reaction was quenched with aqueous $(NH_4)_2SO_4$ and after standard workup a quantitative yield of **4** was obtained: mp 185–186.5 °C (from C_6H_6); IR no CO band, 3450 cm^{-1}; ^1H NMR δ 1.28 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 4.18 (t, 1, H-17), 6.58–6.73 (m, 2, H-2 and H-4), 7.32 ppm (d, 1, H-1).

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Anal. Calcd for $C_{21}H_{28}O_5$: C, 70.00; H, 7.78. Found: C, 70.08; H, 7.71.

3-Methoxy-14β,17α-dihydroxy-8α-estra-1,3,5(10)-trien-11-one (5a) and 3-Methoxy-14β,17α-dihydroxy-8α,9β-estra-1,3,5(10)-trien-11-one (5b). The solution of **4** (1.0 g, 2.77 mmol) in 100 mL of MeOH and 10 mL of 10% aqueous HCl was left at room temperature for 2 h. Methanol was evaporated in vacuo and the residue was extracted with $CHCl_3$. The extracts were washed with saturated aqueous $NaHCO_3$ and dried with anhydrous $MgSO_4$. Chromatography on 30 g of silica gel using hexane–ethyl acetate (95:5) as eluent afforded **5a** (0.71 g, 81%) and **5b** (0.04 g, 4.6%). The second run of the same reaction gave only compound **5a.**

5a: mp 109–112 °C (from C_6H_6); IR 1710 cm^{-1}; ^1H NMR δ 1.11 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 3.95 (d, 1, $J_{9,8}$ = 6.25 Hz, H-9), 4.22 (t, 1, H-17), 6.58–6.80 (m, 2, H-2 and H-4), 6.82 ppm (d, 1, H-1).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.15; H, 7.59. Found: C, 72.10; H, 7.52.

5b: ^1H NMR δ 1.08 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 3.98 (d, 1, $J_{9,8}$ = 12.5 Hz, H-9), 4.35 (q, 1, H-17), 6.58–6.88 (m, 2, H-2 and H-4), 7.25 ppm (d, 1, H-1).

However, the regeneration of **5b** from the ^1H NMR sample gave a mixture of both epimers **5a** and **5b**; therefore, we are not giving further analytical data of **5b.**

3-Methoxy-14β-hydroxy-17α-acetoxy-8α-estra-1,3,5(10)-trien-11-one (6). The solution of **5a** (0.60 g, 1.89 mmol) in acetic anhydride (2 mL) and pyridine (4 mL) was left at room temperature for 12 h. Evaporation of pyridine and of excess of Ac_2O in vacuo followed by crystallization from methanol afforded **6** (0.62 g, 92%): mp 207–211 °C (from MeOH): IR 1710 and 1725 cm^{-1}; ^1H NMR δ 1.12 (s, 3, CH_3), 2.08 (s, 3, CH_3COO), 3.80 (s, 3, OCH_3), 3.95 (d, 1, $J_{9,8}$ = 6.25 Hz, H-9), 5.15 (t, 1, H-17), 6.68–6.80 (m, 2, H-2 and H-4), 6.85 ppm (d, 1, H-1).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.20; H, 7.25.

11-Thioketal of 3-Methoxy-14β-hydroxy-17α-acetoxy-8α-estra-1,3,5(10)-trien-11-one (7). To the solution of **6** (0.50 g, 1.39 mmol) in ethanedithiol (2 mL), BF_3-Et_2O (0.1 mL) was added and the mixture was stirred at room temperature for ca. 20 min until a clear solution was obtained. The reaction was then diluted with 10 mL of aqueous $NaHCO_3$ and extracted with benzene. Further standard workup gave the crude product **7**, which after recrystallization from Et_2O yielded pure **7** (0.48 g, 80%): mp 213–217 °C (from Et_2O): IR 1715 cm^{-1}; ^1H NMR δ 1.42 (s, 3, CH_3), 2.12 (s, 3, CH_3COO), 3.50 (d, 1, $J_{9,8}$ = 5 Hz, H-9), 3.85 (s, 3, OCH_3), 5.12 (t, 1, H-17), 6.55–6.72 (m, 2, H-2 and H-4), 7.80 ppm (d, 1, H-1).

Anal. Calcd for $C_{23}H_{30}O_4S_2$: C, 63.60; H, 6.92. Found: C, 63.65; H, 6.91.

3-Methoxy-8α-estra-1,3,5(10)-trien-14β,17α-diol 17-Acetate (8a). Freshly prepared Raney nickel (from 5 g of alloy) was added to the solution of the thioketal **7** (0.35 g, 0.80 mmol) in a mixture of methanol and benzene (1:1, 50 mL) and it was stirred at room temperature for ca. 3 h. Nickel was then filtered off and the solvent was evaporated in vacuo. The residue was crystallized from methanol giving **8a** (0.25 g, 91%): mp 178–188 °C (from MeOH): IR 1720 cm^{-1}; ^1H NMR δ 1.10 (s, 3, CH_3), 2.10 (s, 3, CH_3COO), 3.82 (s, 3, OCH_3), 5.20 (t, 1, H-17), 6.58–6.85 (m, 2, H-2 and H-4), 7.05 ppm (d, 1, H-1).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.25; H, 8.13. Found: C, 73.26; H, 8.20.

3-Methoxy-14β-hydroxy-8α-estra-1,3,5(10)-trien-17-one (9). To a solution of **8a** (0.20 g, 0.58 mmol) in THF (10 mL) was added 0.05 g of LAH, and the mixture was stirred at room temperature for ca. 10 min. The reaction was quenched with aqueous $(NH_4)_2SO_4$, and after standard workup the oily diol **8b** (0.15 g, 91%) was obtained. It was dissolved in dry methylene chloride (25 mL) and oxidized with pyridinium chlorochromate (PCC)[9] (0.20 g). The compound **9** was isolated by short-column chromatography and crystallized from hexane–acetone (2:1) solution yielding pure **9** (0.13 g, 86%): mp 174–176 °C (from hexane–acetone): IR 1730 cm^{-1}; ^1H NMR δ 1.18 (s, 3, CH_3), 3.82 (s, 3, OCH_3), 6.62–6.85 (m, 2, H-2 and H-4), 7.05 ppm (d, 1, H-1); MS *m/e* 300.

Registry No.—**3,** 64069-77-8; **4,** 64035-53-6; **5a,** 64069-78-9; **5b,** 64069-79-0; **6,** 64069-80-3; **7,** 64035-54-7; **8a,** 64069-81-4; **9,** 10003-00-6; acetic anhydide, 108-24-7; ethanedithiol, 540-63-6.

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Base-Catalyzed Disproportionation Reactions of 3′,5′-Di-*O*-aroyl Derivatives of 1-β-D-Arabinofuranosyluracil

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In a recent publication,[1] we reported that 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-arabinofuranosyl)uracil (iii) forms as a by-product in the synthesis of 1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (ii) from 1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (i) and sodium benzoate in hot DMF and that the immediate precursor of iii is compound ii. The unusual formation of iii has posed the question of whether the 2′-*O*-benzoyl group in iii originates from the external benzoate anion of benzoic acid, or if iii forms by an intramolecular disproportionation reaction of ii. Another possibility that it results by an intramolocular benzoyl rearrangement with concomitant introduction of a second benzoyl unit from outside can not be ruled out immediately. To solve this problem, we designed a synthetic study using analogues of i and ii with different aroyl groups and sodium salts of substituted benzoic acids as basic catalysts. This report deals with some mechanistic evidences to support a disproportionation reaction in the formation of iii, the first observed example of such reactions in the nucleoside field.

Treatment of 2′,3′,5′-tri-*O*-mesyluridine (**1**)[2] with sodium *p*-chlorobenzoate by the known method[2] gave 2,2′-anhydro-(5′-*O*-*p*-chlorobenzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-uracil (**2**) in an excellent yield. Acidic hydrolysis of **2** yielded the desired substance, 1-(5′-*O*-*p*-chlorobenzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**3**). The structures of **2** and **3** were based on the analysis and spectroscopic data described in the Experimental Section.

The first reaction of sodium *p*-methylbenzoate on **3** was focused on the separation of two possible isomers, 1-(5′-*O*-*p*-chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)uracil (**4a**) and 1-(5′-*O*-*p*-chlorobenzoyl-2′-*O*-*p*-methylbenzoyl-β-D-xylofuranosyl)uracil (**5**), to evaluate the approximate yields of these isomers, reducing the formations of other products as far as possible. Thus, a short-time reaction using a rather more dilute mixture of the reactants (method A) permitted isolation of **4a** and **5** in 44 and 8% yield, respectively. TLC on the reaction mixture also revealed the formation of a trace amount of a faster running substance corresponding to a triaroyl derivative like iii, but it was neglected. The structures of **4a** and **5** could be easily assigned largely on the basis of NMR data (Table I): in the spectrum of **4a,** the anomeric proton signal appeared at 6.28 ppm as a

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