Transformations of Steroidal Neopentyl Systems. VII. Mechanism of the Transformation of (19*R*)-Hydroxy-19a-methyl-(5α)-3-ones to 19-Keto-19a-methyl-(5α)-3α-hydroxy Analogs[1]

JERZY WICHA[2]

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

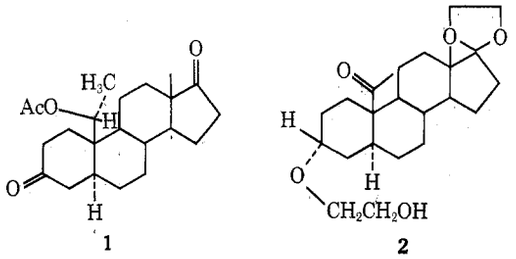
ELIAHU CASPI*

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Received October 17, 1972

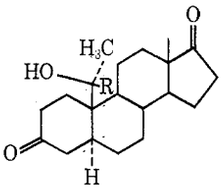
The synthesis of *19-d*-(19*R*)-19-hydroxy-19a-methyl-5α-androstane-3,17-dione is described. The product on treatment with base rearranged to *3β-d*-3α-hydroxy-19a-methyl-5α-androstane-17,19-dione without loss of deuterium. The results are in agreement with the hypothesis that the rearrangement involves an intramolecular hydride ion transfer. A mechanism for the rearrangement is proposed.

We have previously reported two cases[3,4] of the rearrangement of (19*R*)-hydroxy-19a-methyl-3 ketones to 3α-oxygenated 19a-methyl-19 ketones. This rearrangement was first noted when (19*R*)-acetoxy-19-methyl-5α-androstane-3,17-dione (**1**) was treated with ethylene glycol and *p*-toluenesulfonic acid in boiling benzene.[3] In addition to the expected 3,17 diketal, the 17,17-bisethylenedioxy-3α-(2-hydroxyethoxy)-19-methyl-5α-androstan-19-one (**2**) was obtained. Similarly, exposure of (19*R*)-hydroxy-19a-methyl-5α-androstane-3,17-dione (**3a**) to ethanolic potassium hydroxide[4] resulted in several compounds, among them 3α-hydroxy-19a-methyl-5α-androstane-17,19-dione (**4a**). On the basis of stereochemical considerations we have proposed a mechanism involving an intramolecular hydride ion transfer from C-19 to C-3β for this rearrangement.

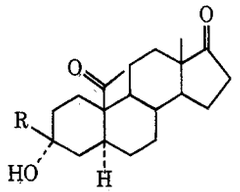


1

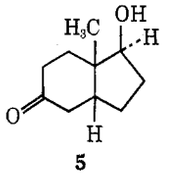
2



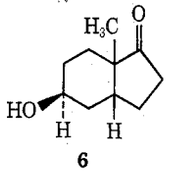
3a, R = H
b, R = D



4a, R = H
b, R = D



5



6

Several cases of similar rearrangements were previously reported. Acklin and Prelog[5] observed the transformation of hydrindanone (**5**) to product **6** on an alumina column. Dvornik and Edwards[6] treated the hydoxy ketone **7** with alcoholic potassium hydroxide and obtained **8**. Without providing experimental proof, these authors also assumed that the rearrangements involved an intramolecular hydride ion transfer.

It may be noted that the rearrangements observed by us and by others occurred in compounds in which the spatial orientation of the participating functions was essentially similar. Presumably relief from the steric compression is the driving force for the process. Since this appears to be a rather general reaction for the systems under consideration, we undertook to define the mechanism of the reaction.

We chose to study the rearrangement using *19-d*-(19*R*)-19-hydroxy-19-methyl-5α-androstane-3,17-dione **3b** as a model. From the loss or retention of deuterium in the derived 19 ketone **4** the mechanism of the reaction could then be deduced. With this in mind, the synthesis of the 19-deuterated alcohol **3b** was undertaken.

The 3β,17β-diacetoxyandrost-5-en-19-ol was treated with chromic acid in pyridine[7] and the resulting aldehyde **9a** was oxidized with potassium permanganate in pyridine[8] to yield the diacetoxy carboxylic acid[9] **9b**. Saponification of **9b** provided the dihydroxy acid[9] **9c**. The dihydroxy acid **9c** was treated with diazomethane and the obtained ester **9d** on exposure to dihydropyran and *p*-toluenesulfonic acid gave methyl 3β,17β-bis(2-tetrahydropyranyloxy)androst-5-en-10-carboxylic acid ester **9e**.

The bis-THP ether **9e** was reduced with $LiAlH_4$ to yield the alcohol **9f**, which was oxidized with chromium trioxide in pyridine[7] to the aldehyde **9g**. An analogous reduction of **9e** with $LiAlD_4$ gave *19-d*$_2$ alcohol **9h**, which was subsequently oxidized to the *19-d* aldehyde **9i**. The mass spectrum of the alcohol **9h** was devoid of a peak of *m/e* 474 but had a peak at *m/e* 476 indicating the presence of *two* atoms of deuterium at C-19. The mass spectrum of the aldehyde **9i** did not have a peak at *m/e* 472 and had a peak at *m/e*

(1) This work was supported by Grants CA 07137 and K3-16614 from the National Institutes of Health.

(2) Postdoctoral Fellow (1964–1966) on leave of absence from The Warsaw University, Warsaw, Poland.

(3) J. Wicha and E. Caspi, *J. Chem. Soc. C*, 1740 (1968).

(4) J. Wicha and E. Caspi, *Tetrahedron*, **25**, 3961 (1969).

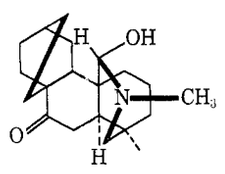
(5) W. Acklin and V. Prelog, *Helv. Chim. Acta*, **42**, 1239 (1959).

(6) D. Dvornik and J. O. E. Edwards, *Proc. Chem. Soc.*, 280 (1958).

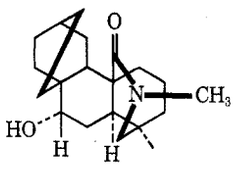
(7) G. I. Poos, G. E. Arth, E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(8) C. Djerassi and M. A. Kielczewski, *Steroids*, **2**, 125 (1963).

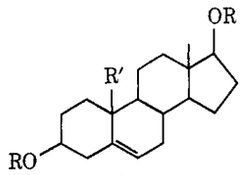
(9) B. Berkoz, E. Denot, and A. Bowers, *ibid.*, **1**, 251 (1963).



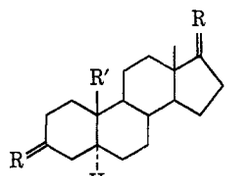
7



8



9



10

9a, R = Ac; R′ = CHO
b, R = Ac; R′ = COOH
c, R = H; R′ COOH
d, R = H; R′ = $COOCH_3$
e, R = THP; R′ = $COOCH_3$
f, R = THP; R′ = CH_2OH
g, R = THP; R′ = CHO
h, R = THP; R′ = CD_2OH
i, R = THP; R′ = CDO
j, R = THP; R′ = $CD(OH)CH_3$
k, R = THP; R′ = $CD(OAc)CH_3$
l, R = H; R′ = $CD(OAc)CH_3$

10a, R = β-OH, H; R′ = $CD(OAc)CH_3$
b, R = O; R′ = $CD(OAc)CH_3$
c, R = <O,O> ; R′ = $CD(OAc)CH_3$
d, R = <O,O> ; R′ = $CD(OH)CH_3$

473 as expected for monodeuterated product. Supporting evidence for the assigned structure of the d_2 alcohol **9h** and *d* aldehyde **9i** was provided by ir and nmr spectroscopy (see Experimental Section).

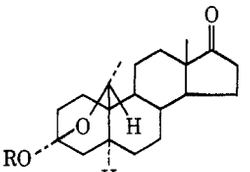
The *d* aldehyde **9i** was treated with methyllithium to yield the *19-d*-(19*R*)-hydroxy-19a-methylbis-THP ether[1] **9j**. The arguments for assigning the 19*R* configuration to the alcohol have been previously presented.[3,10] The crude **9j** was converted to the 19 acetate **9k**, which was not characterized and was hydrolyzed to yield *19-d*-(19*R*)-acetoxy-19a-methylandrost-5-ene-3β,17β-diol (**9l**). The mass spectrum of **9l** had a peak at *m/e* 363, but was lacking a peak at *m/e* 362, indicating the retention of a *whole atom* of deuterium at C-19. As could be expected, the **9l** nmr spectrum showed a singlet at τ 8.7 for the 19a-methyl.

Hydrogenation of **9l** over a 10% palladium on carbon catalyst provided the 5α-(H)-3,17-diol **10a**. We have previously proven that the hydrogenation product has indeed the critically important 5α configuration.[3] The diol **10a** was oxidized with Jones regent[11] to the 19-acetoxy-3,17-dione **10b**, which was converted in the conventional manner to the diketal acetate **10c**, *m/e* 449. The crude **10c** was first treated with $LiAlH_4$ and the resulting 19-hydroxy diketal **10d** was hydrolyzed to yield the required *19-d*-(19*R*)-19-hydroxy-19a-methyl-5α-androstane-3,17-dione (**3b**). The structure **3b** was confirmed by ir and nmr spectroscopy and its mass spectrum (*m/e* 319) confirmed the presence of a *whole atom* of deuterium at C-19.

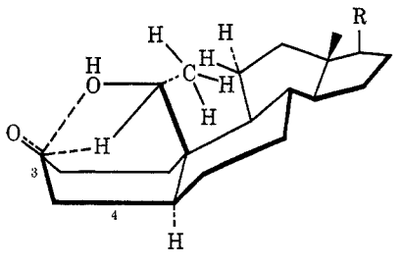
The obtained *19-d*-(19*R*)-19-hydroxy-19a-methyl-5α-androstane-3,17-dione (**3b**) was treated with aqueous methanolic potassium hydroxide. The resulting reaction mixture was fractionated by preparative thin layer chromatography on alumina. The less mobile product proved to be unchanged **3b**. The more mobile material had an R_f idendical with that of authentic (nondeuterated) **4a**. The nmr spectrum of **4b** had a signal at τ 7.80 for the 10-acetyl. The chemical shifts for the 10-acetyl and for the C-13 methyl in **4a** and **4b** were the same. Significantly, the narrow multiplet at τ 5.93 for the C-3 equatorial proton, present in **4a**, was absent in the deuterated **4b**. Finally, the mass spectrum of **4b** had a peak at *m/e* 319 for M^+ but was devoid of a peak at *m/e* 318.

It is evident that the transformation of **3b** to **4b** proceeded with complete retention of deuterium, which is consistent with intramolecular hydride ion transfer.

The observed reactions of 5α-steroidal (19*R*)-19-hydroxy-19a-methyl-3 ketones require comment. *A priori* it may be accepted that the reaction will occur when ring A assumes a boat form. It is feasible that the boat form could be stabilized by transannular interaction of the oxygen atom of the C-19 hydroxyl with the carbon of the C-3 carbonyl. Under acidic conditions both the C-19 to C-3 hydride ion transfer (*e.g.*, **2**, **4**) and 3β,19-oxide formation (*e.g.*, **11**) take



11a, R = H
b, R = CH_3



12

place,[3] while under alkaline conditions the β-face hydride ion transfer predominates.[4,10] For an intramolecular hydride ion transfer to occur, the C-19 hydrogen must approach and, in a sense, "bridge," the C-3 of the carbonyl. Similarly, a C-3,19 oxide formation is possible when the 19-hydroxyl is located in the proximity of the C-3 carbon. Hence the rearrangement can be viewed as occurring when either the 19-H or the 19-OH comes close to the C-3 electrophilic receptor.

An alternative interpretation based on the hypothesis of simultaneous positioning of the participating C-19 oxygen atom and 19-hydrogen atom in the proximity of C-3 of the carbonyl seems less plausible. In this instance the rearrangement would proceed through a four-centered transition state shown in **12**. The four-centered transition state **12** encompasses C-19, the 19-oxygen, 19-hydrogen, and C-3. Formation of the transition state requires rotation around the 10–19 bond and this could occur by flattening of ring C, which would minimize the interference of the 11β-hydrogen with the 19α-methyl. The high energy of the four-centered transition state would greatly favor either one of the observed reactions, as both would provide relief from the strain.

(10) J. Wicha and E. Caspi, *J. Chem. Soc. C*, 947 (1969).
(11) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

However, it should be noticed that a four-centered transition state cannot be formed in the case of **7** which is transformed to **8**. Also, we have previously indicated that, in the 19-hydroxy-19a-methyl steroids, the rotation around the C-10,19 bond is rather restricted.[3,10] Confirmation of this view is provided by the fact that, while the 19*R* alcohol **3a** readily gave the 3α-methoxy 3β,19-oxide **11b**, the 19*S* alcohol under similar conditions resisted oxide formation, and only starting material was recovered.[10] Thus the four-centered transition like **12** could possibly function only when products of both types **4** and **11** are formed.

Experimental Section

Melting points were taken on a micro hot stage and are corrected. Infrared spectra were recorded on solids incorporated in KBr wafers. Ultraviolet spectra were taken on methanol solutions. Unless otherwise stated, deuteriochloroform was used for nmr spectra which were recorded at 60 MHz on a Varian HA-60 instrument, and are given in the τ scale. The mass spectra were taken on a Varian M66 instrument. Analyses were performed by I. Beetz, Kronach, Germany.

3β,17β-Acetoxyandrost-5-ene-10β-carboxylic Acid (9b).—To a stirred and cooled (in an ice–salt bath) solution of the aldehyde **9a** (10 g) in anhydrous pyridine (70 ml), a suspension of powdered potassium permanganate (10 g) in pyridine (100 ml) was added in several portions. The mixture was then stirred for 4 hr at ambient temperature and filtered, and the filtrate was diluted with ether (1 l.). The ether solution was washed sequentially with ice, cold 5% sulfuric acid, water, and a saline solution, dried over magnesium sulfate, and concentrated to a residue under reduced pressure. The residue was crystallized from a mixture of chloroform–ether to yield **9b** (8.5 g). The analytical specimen showed mp 211–214° (reported[9] mp 213–215°), ν_{max} (KBr) 1740, 1700, and 1250 cm^{-1}.

3β,17β-Dihydroxyandrost-5-ene-10β-carboxylic Acid (9c).—A mixture of the diacetate **9b** (8 g), methanol (500 ml), potassium hydroxide (10 g), and water (10 ml) was kept at room temperature for 16 hr. After the addition of water (100 ml), the solution was acidified with hydrochloric acid. The resulting crystalline acid **9c** was filtered, washed with aqueous methanol, and dried (6 g). A sample was sublimed at 190–200° (0.1 Torr), mp 320–322°, ν_{max} (KBr) 3400, 3180, and 1710 cm^{-1}. The physical constants agree with those previously reported.[9]

Methyl 3β,17β-Dihydroxyandrost-5-ene-10β-carboxylate (9d).—A suspension of the acid **9c** (6 g) in methanol (200 ml) was treated with an excess of an ethereal solution of diazomethane. Removal of the solvents and crystallization of the residue from acetone gave the ester **9d** (5.7 g), mp 172–174°. The analytical specimen showed mp 173–175°; ν_{max} (KBr) 3450, 1720, 1170 cm^{-1}; nmr ($CDCl_3$) τ 4.47 (1 H, 6-H), 6.3 (s, 3 H, 19-OCH_3), 9.3 (s, 3 H, 13-CH_3).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.0. Found: C, 72.10; H, 9.12.

Methyl 3β,17β-Bis(2-tetrahydropyranyloxy)androst-5-ene-10β-carboxylate (9e).—A mixture of **9d** (5 g), dihydropyran (3.2 g), *p*-toluenesulfonic acid (50 mg), and anhydrous chloroform (80 ml) was stored for 16 hr at ambient temperature. The reaction was terminated by the addition of powdered sodium hydrogen carbonate, and, after stirring for 10 min, the contents were poured into a saturated solution of sodium hydrogen carbonate. The chloroform phase was separated, washed, dried, and concentrated to a residue under reduced pressure. The crude bis-THP ether (7.4 g) was crystallized several times to yield plates, mp 108–113°, ν_{max} (KBr) 1720 and 1170 cm^{-1}.

Anal. Calcd for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.52; H, 9.13.

Reduction of 9e and Introduction of Deuterium at C-19. A.—A mixture of the ester **9e** (200 mg) and $LiAlH_4$ (200 mg) in dry ether (30 ml) was refluxed for 16 hr. The reaction was terminated by the addition of a saturated solution of sodium sulfate (cooling). The obtained solid was collected by filtration and washed with ether, and the combined filtrate was washed with water. Removal of the ether gave the crystalline **9f** (165 mg). A sample was crystallized several times: mp 161–167°; ν_{max} (KBr) 3430 cm^{-1}; nmr τ 4.42 (1 H, C-6 H), 6.07 (d), and 6.67 (d, 2 H, J = 19 Hz, C-19 H_2), 9.2 (s, 3 H, C-13 CH_3); *m/e* 474 (M^+).

Anal. Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.31; H, 9.59.

B.—A similar reduction of ester **9e** (5 g) with $LiAlD_4$ (4 g) in dry ether (600 ml) gave *19-d*$_2$ alcohol **9h** (4.2 g): mp 159–167°; ν_{max} (KBr) 3430 cm^{-1}; nmr τ 6.07 (s) and 6.67 (s); *m/e* 476 (M^+), 444 (M − 32), 426 (444 − 18), 392 (476 − 84), 374 (392 − 18), 360 (392 − 32).

***19-d*-3β,17β-Bis(2-tetrahydropyranyloxy)androst-5-en-19-al (9i).**—The deuterated alcohol *19-d*$_2$-**9h** (4 g) in pyridine (2 ml) was treated with a suspension of chromic acid (4 g) in pyridine (4 ml). After 6 hr at room temperature the mixture was diluted with ethyl acetate (300 ml) and the solid was removed by filtration. The filtrate was processed in the conventional manner and the obtained residue was crystallized from acetone to yield the aldehyde **9i**: ν_{max} (KBr) 1720 cm^{-1}; nmr ($CDCl_3$) τ 4.38 (1 H, C-6 H), 9.12 (s, 3 H, C-13 CH_3); *m/e* 473 (M^+), 455 (M − 18), 454 (M − 19), 389 (473 − 84, C_5H_8O), 371, 361, 359.

A nondeuterated sample (**9g**) was obtained by oxidation of 19 alcohol **9f** (100 mg) with chromic acid (100 mg) in pyridine (0.4 ml). The recovered aldehyde was crystallized several times from acetone: mp 115–116°; ν_{max} (KBr) 1720 cm^{-1}; nmr ($CDCl_3$) τ 0.3 (s, 1 H, C-19 H), 4.38 (1 H, C-6 H), 9.12 (s, 3 H, C-13 CH_3).

Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.40; H, 9.21.

***19-d*-(19*R*)-19-Acetoxy-19a-methylandrost-5-ene-3β,17β-diol (9l).**—To a solution of the aldehyde **9i** (3.3 g) in anhydrous ether (70 ml), a 1.6 *M* solution of methyllithium (10 ml) was added during 10 min. The mixture was refluxed for 30 min, then cooled, and the excess reagent was decomposed with water. The product **9j** was recovered with ether, washed with water, dried, and concentrated to a residue. The obtained **9j** (3.4 g) was dissolved in a mixture of acetic anhydride–pyridine (1:1, 40 ml) and the solution was stored for 20 hr at room temperature. The reaction mixture was poured on ice and HCl, and after 2 hr the product was recovered with ether. The ether extract was washed with 5% aqueous HCl, water, a saturated solution of sodium bicarbonate, and again with water, then dried and evaporated. Crystallization from ether gave the dihydroxy-19-monoacetate **9l** (1.1 g): mp 80–82°; ν_{max} (KBr) 3550, 1740, and 1245 cm^{-1}; nmr τ 4.53 (1 H, C-6 H), 8.0 (s, 3 H, 19-OAc), 8.70 (s, 3 H, 19a-CH_3), 9.18 (s, 3 H, C-13 CH_3); *m/e* 363 (M^+, less than 1%), 303 (M − 60, CH_3COOH, 90%), 285 (303 − H_2O, 42%), 275 (M − 88, CH_3-CDOAc, 100%).

***19-d*-(19*R*)-19-Acetoxy-19a-methyl-5α-androstane-3β,17β-diol (10a).**—A mixture of **9l** (520 mg), a 10% palladium on carbon catalyst (300 mg), and methanol (100 ml) was agitated under normal pressure in an atmosphere of hydrogen for 8 hr. The uptake of hydrogen was 32 ml. The catalyst was removed by filtration and the filtrate was concentrated to a residue. The saturated diol **10a** (490 mg) showed mp 92–97°; a mixture melting point of the deuterated material with an authentic ^{1}H sample[3] was not depressed; ν_{max} (KBr) 3550, 1730, and 1245 cm^{-1}; nmr τ 8.00 (s, 3 H, 19-OAc), 8.65 (s, 3 H, 19a-CH_3), 9.18 (s, 3 H, C-13 CH_3); *m/e* 365 (M^+, small), 305 (M^+ − 60), 287 (305 − 18), 277 (M − 88, CH_3CDOAc), 261, 259, 241.

***19-d*-(19*R*)-19-Acetoxy-19a-methyl-5α-androstane-3,17-dione (10b).**—The diol **10a** was dissolved in acetone (70 ml) and treated with Jones reagent.[9] After the usual processing of the reaction mixture, the diketone **10b** (350 mg) was obtained: mp and mmp with authentic unlabeled product 145–150°; ν_{max} (KBr) 1740, 1710, and 1220 cm^{-1}; nmr τ 7.93 (s, 3 H, 19-OAc), 8.60 (s, 3 H, 19a-CH_3), 9.05 (s, 3 H, C-13 CH_3); *m/e* 361 (M^+, 90%), 301 (M − 60, 100%), 318 (M − 43, CH_3CO), 273 (M − 88, CH_3·CD-OAc, 98%).

***19-d*-(19*R*)-19-Hydroxy-19a-methyl-5α-androstane-3,17-dione (3b).**—A mixture of the diketone **10b** (340 mg), ethylene glycol (10 ml), and *p*-toluenesulfonic acid (5 mg) was distilled at 0.05 Torr in an atmosphere of nitrogen. The distillation was continued for 2 hr at 80°, during which time 5 ml of distillate was collected.

The mixture was cooled, pyridine (0.4 ml) was added, and the product was recovered with ether in the usual manner. The diketal **10c** (280 mg) showed mp 97–100°; *m/e* 449 (M^+), 405 (M − 44), 390 (405 − 15), 377 (405 − 28), 361 (M − 88), 125, 112, 99.

The crude diketal **10c** was dissolved in anhydrous ether (50 ml), $LiAlH_4$ (400 mg) was added, and the mixture was refluxed for 16 hr. After work-up the hydroxy diketal **10d** (220 mg) was obtained as a colorless syrup, *m/e* 407 (M^+).

To a solution of the above diketal **10d** in dioxane (10 ml), 2 *N* hydrochloric acid (1 ml) was added and the mixture was stored for 20 hr at the ambient temperature. The hydroxy diketone **3b** (110 mg) was recovered with ether. The product **3b** showed mp 167–170°. A mixture melting point with authentic[1] unlabeled material (**3a**) was not depressed; ν_{max} (KBr) 3400, 1740, 1712 cm^{-1}; *m/e* 319 (M^+), 304 (M − 15), 274 (M − 45, $CH_3 \cdot CDO$), 256 (274 − 18).

Rearrangement of *19-d*-(19*R*)-19-Hydroxy-19a-methyl-5α-androstane-3,17-dione (3b) to *3β-d*-3α-Hydroxy-19a-methyl-5α-androstane-17,19-dione (4b).—A solution of the deuterated **3b** (100 mg) in methanol (50 ml) containing potassium hydroxide (100 mg) and water (0.5 ml) was refluxed for 3 hr in an atmosphere of nitrogen. The mixture was cooled, diluted with water, and neutralized with acetic acid. The product was recovered with ethyl acetate in the usual manner. The obtained residue (103 mg) was fractionated by thin layer chromatography on neutral alumina (purchased from Woelm A.G.). The plates were developed with ethyl acetate. The two major products were recovered with ethyl acetate and were identified as starting material **3b** (12 mg) and the deuterated alcohol **4b** (46 mg).

The 3α-hydroxy-*3β-d* product (**4b**), mp 170–171°, showed ν_{max} (KBr) 3550, 1730, and 1680 cm^{-1}; nmr ($CDCl_3$) τ 7.8 (s, 3 H, 19a-CH_3), 9.21 (s, 3 H, 13-CH_3); *m/e* 319 (M^+), 301 (M − 18), 276 (M − 43), 258 (276 − 18), 240 (258 − 18).

Registry No.—**3b**, 38308-99-5; **4b**, 38309-00-1; **9a**, 2951-52-2; **9b**, 14413-29-7; **9c**, 14413-27-5; **9d**, 38431-64-0; **9e**, 38309-04-5; **9f**, 38309-05-6; **9g**, 38309-06-7; **9h**, 38309-07-8; **9i**, 38309-08-9; **9j**, 38309-09-0; **9l**, 38309-10-3; **10a**, 38309-11-4; **10b**, 38312-19-5; **10c**, 38312-20-8; **10d**, 38312-21-9.

Introduction of a 2′,3′ Double Bond into 1-(5′-*O*-Benzoyl-β-D-lyxofuranosyl)uracil by Selective Elimination Reactions. A Facile Synthesis of 5′-*O*-Benzoyl-3′-deoxy-2′-ketouridine

TADASHI SASAKI,* KATSUMARO MINAMOTO, AND KANEAKI HATTORI

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

Received October 20, 1972

For the purpose of synthesizing 2′,3′-didehydrouracil nucleosides from 1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**1**) by base-induced elimination reactions, **1** was monotosylated to 1-(5′-*O*-benzoyl-2′-*O*-tosyl-β-D-lyxofuranosyl)-uracil (**2**) and 1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**3**). Mesylation of **2** and **3** gave isomers **4** and **7**, respectively. Dimesylation of **1** gave 2′,3′-di-*O*-mesyl analog **9**. Elimination reactions on **4**, **7**, and **9** gave 5′-*O*-benzoyl-3′-deoxy-2′-ketouridine (**6**). The intermediary 2′-*O*-tosyl-2′,3′-didehydro nucleoside (**5**) was isolated and characterized. Action of alcoholic ammonia on **4** gave 1-(2′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**10**) *via* debenzoylation and demesylation.

In a previous paper,[1] the results of some base-catalyzed elimination reactions on 2′,3′-di- and 2′,3′,5′-tri-*O*-mesyl derivatives of 3-benzyluridine were described. One of the important features of these results was the selective 2′-hydrogen abstraction in the trans-elimination reactions regardless of the size of the 5′-*O* substituent. However, there was a known drawback in that the 3-benzyl group in the uracil skeleton cannot be removed by hydrogenolysis.[2,3]

This report describes the results of similar elimination reactions on 2′,3′-di-*O*-mesyl, 3′-*O*-mesyl-2′-*O*-tosyl, and 2′-*O*-mesyl-3′-*O*-tosyl derivatives of 1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**1**),[4] in which both the leaving groups are syn with respect to the base moiety, thus precluding cyclonucleoside formation. Further interesting situations foreseen for this series of compounds are that the sugar protons $H_{1'}$–$H_{4'}$, are all in β and trans relation to one of the leaving groups, suggesting various possible directions in β elimination, and that basic catalysts must attack, advantageously, from the less hindered bottom side of the nucleoside derivatives.

1-(5′-*O*-Benzoyl-β-D-lyxofuranosyl)uracil (**1**) was treated with 2 molar equiv of tosyl chloride to give the monotosylated compounds, 1-(5′-*O*-benzoyl-2′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**2**) and 1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**3**) in 41 and 6% yield, respectively, presumably for steric reasons. Compounds **2** and **3** were crystals which included one molecule of methanol and acetone, respectively. In the nmr spectrum of **2** free of solvent, the signal of the anomeric proton appeared at δ 6.25 as a doublet with $J_{1',2'}$ = 6.8 Hz, while the resonance of $H_{2'}$ occurred at δ 5.3 as a doublet of doublets with $J_{1',2'}$ = 6.8 Hz and $J_{2',3'}$ = 4.7 Hz. The assignment of $H_{2'}$ was self-evident on the basis of a strong deshielding effect by the tosyl group, but was also confirmed by spin decoupling, since irradiation at δ 6.25 collapsed the signal at δ 5.3 to a doublet with a splitting of 4.7 Hz. Thus, the structure of **2** and therefore that of **3** was established.

The monotosylation of **1** is useful for elucidating the structure of the elimination products when another different leaving group is introduced into **2** or **3**. Hence, **2** was converted to 1-(5′-*O*-benzoyl-3′-*O*-mesyl-2′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**4**) using the less bulky mesyl chloride. On treatment with excess sodium benzoate under relatively mild reaction conditions **4** gave the expected 1-(5′-*O*-benzoyl-3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)uracil (**5**) as the sole product in 20% yield, 43% of the starting material being recovered. Some degree of resinification was also observed. The nmr spectrum of **5** is shown in Figure 1. The resonance pattern is quite similar to that of 1-(3′-deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil.[1] The

(1) T. Sasaki, K. Minamoto, and H. Suzuki, *J. Org. Chem.*, **38**, 598 (1973).
(2) N. Imura, T. Tsuruo, and T. Ukita, *Chem. Pharm. Bull.*, **16**, 1105 (1968).
(3) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3478 (1971).
(4) R. Fecher, J. F. Codington, and J. J. Fox, *ibid.*, **83**, 1889 (1961).