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Steroid-hindered 17β-tertiary alcohol: Characterization of dehydrated compounds

Patrick Bydal, Kay-Mane Sam, and Donald Poirier

Medicinal Chemistry Division, Laboratory of Molecular Endocrinology, CHUL Research Center and Laval University, Ste-Foy, Quebec, Canada

Five dehydrated compounds obtained from a tert*-butyldimethylsilylchloride/imidazole or an aqueous hydrochloric acid treatment of 17α-butyl-3-*O*-methyl estradiol in refluxing solvent were purified and characterized. Three compounds were obtained from a direct vicinal proton elimination, the two others from a vicinal elimination after migration of methyl-18. Depending on the treatment, the proportions of dehydrated compounds are different. In addition, a general profile of experimental conditions providing a similar mixture of dehydrated compounds was also established for this steroid-hindered 17β-tertiary alcohol. (Steroids* **61**:349–353, 1996)

Keywords: tertiary alcohol; dehydration; 17α-butyl-3-*O*-methyl estradiol

Introduction

During our work related to the synthesis of antiestrogens and inhibitors of 17β-hydroxysteroid dehydrogenase, we introduced several types of side chains at position 17α of estradiol.[1–4] For these steroidal derivatives bearing a tertiary alcohol, we observed a relative instability in the acidic conditions that lead to the formation of a mixture of compounds. A similar mixture was also obtained when this family of compounds was submitted to an excess of *tert*-butyldimethylsilylchloride (TBDMS-Cl) and imidazole in refluxing dimethylformamide (DMF). Because it is generally necessary to pursue the functionalization of the 17α side chain or modification of the tertiary alcohol group, it is important to understand the chemical reaction involved in this process. In the present study, we report the purification and the characterization of compounds obtained during a TBDMS-Cl/imidazole or aqueous HCl treatment of 17α-butyl-3-*O*-methyl estradiol in refluxing solvent and the identification of some experimental conditions that cause the formation of this mixture of compounds.

Experimental

General procedure

Thin-layer chromatography (TLC) was performed on 0.20-mm silica gel $60F_{254}$ plates, and 230–400-mesh ASTM silica gel 60 was used for flash column chromatography. IR spectra were recorded on Perkin-Elmer 1600 (series FTIR) spectrophotometer and were expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded, respectively, at 300 and 75.47 MHz on a Bruker AC/F 300 and are reported in ppm (δ) downfield from residual $CHCl_3$ as reference (7.26 and 77.00 ppm). Carbon assignments were confirmed by homonuclear correlated spectroscopy (COSY), distortionless enhancement by polarization transfer (DEPT), heteronuclear shift correlation (HETCOR), correlation spectroscopy via long-range couplings (COLOC), and nuclear Overhauser effect (NOE) experiments.[5,6] However, assignments identified by an asterisk are uncertain. Mass spectra were recorded with a Hewlett-Packard spectrometer. Electron-impact high-resolution mass spectra (EI/HRMS) were recorded at the Centre Régional de Spectrométrie de Masse (Université de Montréal, Montréal, Canada). The high-performance liquid chromatography (HPLC) apparatus was a Waters associates unit including a model 600E pump controller, a model 991 photodiode array detector or a model 441 absorbance detector, and a reverse-phase column.

Synthesis of 17α-butyl-3-O-methyl estradiol (3)

To a solution of 300 mg (1.056 mmol) of 3-*O*-methyl estrone (**1**) dissolved in dry tetrahydrofuran (THF) (30 mL), 8.6 mL (13.76 mmol) of *n*-Buli (1.6 M) was added dropwise at −78°C, and the mixture was allowed to rise slowly to 4°C. After 20 h, the reaction mixture was cooled at −78°C, and 5.3 mL (5.3 mmol) of $LiAlH_4$ (1.0 M) was added. After 2.4 h, the excess $LiAlH_4$ was carefully destroyed with water before the addition of HCl (10%) and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography with hexane/EtOAc (90:10) as eluent to give 165 mg (55%) of 3-*O*-methyl estradiol (**2**) the re-duced form of the starting material) and 138

Address reprint requests to Dr. Donald Poirier, Molecular Endocrinology Laboratory, CHUL Research Center, 2705 Laurier Boulevard, Ste-Foy, Quebec G1V 4G2, Canada.
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655 Avenue of the Americas, New York, NY 10010

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mg (38%) of 17α-butyl-17β-hydroxy-3-methoxy-estra-1,3,5(10)-triene (**3**). White solid; IR ν (film): 3475 (OH, alcohol), 2935 and 2870 (C–H, aliphatic), 1610, 1575w and 1500 (C=C, aromatic), 1465 (CH_2), 1255 (C–O, ether); ^{1}H NMR δ ($CDCl_3$): 0.90 (s, 3H, CH_3-18), 0.95 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.86 (m, 2H, CH_2-6), 3.78 (s, 3H, CH_3O), 6.63 (d, J = 2.7 Hz, 1H, CH-4), 6.71 (dd, J_1 = 2.7 Hz and J_2 = 8.7 Hz, 1H, CH-2), 7.21 (d, J = 8.7 Hz, 1H, CH-1); ^{13}C NMR δ ($CDCl_3$): 14.27 (C-4′), 14.33 (C-18), 23.38 and 23.59 (C-3′ and C-15), 25.83 (C-2′), 26.35 (C-11), 27.50 (C-7), 29.84 (C-6), 31.60 (C-12), 34.39 (C-16), 36.47 (C-1′), 39.66 (C-8), 43.78 (C-9), 46.63 (C-13), 49.46 (C-14), 55.16 (CH_3O), 83.40 (C-17), 111.41 (C-2), 113.78 (C-4), 126.26 (C-1), 132.71 (C-10), 137.97 (C-5), 157.42 (C-3); MS m/e (rel. intensity): 342 (M^+, 100), 324 (19), 295 (25), 267 (26), 242 (53), 227 (83); EI/HRMS: calculated for $C_{23}H_{34}O_2$ (M^+) 342.2559, found 342.2553.

Treatment of compound 3 with TBDMS-Cl-imidazole in refluxing DMF

To 62 mg (0.181 mmol) of 17α-butyl-3-*O*-methyl estradiol (**3**) dissolved in dry DMF (8 mL, HPLC grade), imidazole (123 mg, 1.809 mmol) and TBDMS-Cl (136 mg, 0.902 mmol) were added, and the mixture was heated to reflux. After 12 h, the same amounts of reagents were added. After a total of 28 h, the mixture was poured into diethylether, and the organic phase was washed five times with water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography with hexane/EtOAc (98:2 to 90:10) as eluent to give 36.4 mg (59%) of starting alcohol **3** (R_f = 0.13, hexane/EtOAc, 90:10) and 19.6 mg (33%) of dehydrated compounds **4–8** (R_f = 0.54, hexane/EtOAc, 90:10).

Treatment of compound 3 with 1N HCl in refluxing MeOH

To 40 mg (0.117 mmol) of 17α-butyl-3-*O*-methyl estradiol (**3**) dissolved in MeOH (10 mL), 1N HCl (2.4 mL) was added, and the solution was heated at reflux for 11 h. Water was then added, MeOH was evaporated under reduced pressure, and the residue was extracted with EtOAc. The organic phase was washed (water and brine), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography with hexane/EtOAc (95:5) as eluent to give 26.8 mg (71%) of dehydrated compounds **4–8** (R_f = 0.54, hexane/EtOAc, 90:10).

HPLC of dehydrated compounds 4–8

Analysis. The fractions of dehydrated compounds obtained by TBDMS-Cl and HCl treatments (one spot on silica gel TLC; hexane/EtOAc 90:10; R_f = 0.54) were analyzed by HPLC to afford chromatograms I and II of Figure 2. The equipment included a Waters apparatus, an ultraviolet detector (210 nM), and a C-18 NovaPak column (3.9 × 150 mm), with MeOH/H_2O/CH_3CN (30:15:55) as eluent at a flow rate of 1.0 mL/min.

Separation. The fractions of dehydrated compounds obtained in both treatments (TBDMS-Cl and HCl) were combined and submitted to preparative HPLC. The equipment included a Waters apparatus, an ultraviolet detector (280 nM), and a C-18 NovaPak 6 μm column (25 × 100 mm), with MeOH/H_2O/CH_3CN (30:15:55) as eluent at a flow rate of 15 mL/min. In a typical procedure, about 20 mg of dehydrated compounds was dissolved in eluents and injected into the column. The compounds corresponding to each peak (A–D) were recovered, and the solvents were evaporated under reduced pressure. After several injections, peaks A–D were combined and the corresponding compounds were characterized.

Peak A. (*Z*)-17-(Butenyl)-3-methoxy-estra-1,3,5(10)-triene (**4**). Colorless oil; IR ν (film): 2930 and 2855 (C–H, aliphatic), 1610, 1577w, and 1500 (C=C, aromatic), 1460 (CH_2), 1255 (C–O, ether); ^{1}H NMR δ ($CDCl_3$): 0.90 (s, 3H, CH_3-18), 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.86 (m, 2H, CH_2-6), 3.78 (s, 3H, CH_3O), 5.06 (t, J = 7.4 Hz, 1H, CH-1′), 6.63 (d, J = 2.7 Hz, 2H, CH-4), 6.71 (dd, J_1 = 2.7 Hz and J_2 = 8.6 Hz, 1H, CH-2), 7.21 (d, J = 8.6 Hz, 1H, CH-1); ^{13}C NMR δ ($CDCl_3$): 13.97 (C-4′), 17.46 (C-18), 23.87 (C-3′), 24.11 (C-15)*, 26.98 (C-11)*, 27.56 (C-7), 29.71 (C-16)*, 29.89 (C-6), 31.54 (C-2′), 37.41 (C-12)*, 38.43 (C-8), 43.81 (C-9), 44.51 (C-13), 55.21 (CH_3O), 55.26 (C-14), 111.46 (C-2), 113.77 (C-4), 120.09 (C-1′), 126.25 (C-1), 132.90 (C-10), 138.00 (C-5), 149.34 (C-17), 157.43 (C-3); MS m/e (rel. intensity): 324 (M^+, 100), 309 (8.8), 281 (59), 173 (100), 147 (91), 107 (43); EI/HRMS: calculated for $C_{23}H_{32}O$ (M^+) 324.2453, found 324.2448.

Peak B. (*E*)-17-(Butenyl)-3-methoxy-estra-1,3,5(10)-triene (**5**). Colorless oil; IR ν (film): 2925 and 2870 (C–H, aliphatic), 1610, 1575w, and 1500 (C=C, aromatic), 1465 (CH_2), 1255 (C–O, ether); ^{1}H NMR δ ($CDCl_3$): 0.79 (s, 3H, CH_3-18), 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.87 (m, 2H, CH_2-6), 3.78 (s, 3H, CH_3O), 5.02 (m, 1H, CH-1′), 6.64 (d, J = 2.6 Hz, 2H, CH-4), 6.72 (dd, J_1 = 2.7 Hz and J_2 = 8.6 Hz, 1H, CH-2), 7.23 (d, J = 8.6 Hz, 1H, CH-1); ^{13}C NMR δ ($CDCl_3$): 13.77 (C-4′), 19.12 (C-18), 22.87 (C-3′), 24.07 (C-15)*, 26.47 (C-16), 26.74 (C-11)*, 27.69 (C-7), 29.91 (C-6), 30.55 (C-2′), 36.24 (C-12), 38.72 (C-8), 43.90 (C-13), 44.26 (C-9), 53.72 (C-14), 55.19 (CH_3O), 111.42 (C-2), 113.81 (C-4), 116.27 (C-1′), 126.28 (C-1), 133.02 (C-10), 138.05 (C-5), 151.82 (C-17), 157.43 (C-3); MS m/e (rel. intensity): 324 (M^+, 100), 309 (14), 281 (69), 173 (63), 147 (41), 107 (26); EI/HRMS: calculated for $C_{23}H_{32}O$ (M^+) 324.2453, found 324.2449.

Peak C. (Major component, 85%): 17α-butyl-17β-methyl-3-methoxy-18-nor-estra-1,3,5(10),13(14)-tetraene (**7**). Colorless oil; IR ν (film): 2925 and 2855 (C–H, aliphatic), 1610, 1575w and 1500 (C=C, aromatic), 1458 (CH_2), 1255 (C–O, ether); ^{1}H NMR δ ($CDCl_3$): 0.89 (t, J = 7.1 Hz, 3H, CH_2CH_3), 0.99 (s, 3H, CH_3-18), 2.91 (m, 2H, CH_2-6), 3.78 (s, 3H, CH_3O), 6.66 (d, J = 2.5 Hz, 1H, CH-4), 6.72 (dd, J_1 = 2.6 Hz and J_2 = 8.5 Hz, 1H, CH-2), 7.26 (d, J = 8.5 Hz, 1H, CH-1); ^{13}C NMR δ ($CDCl_3$): 14.20 (C-4′), 22.32 (C-12)*, 23.55 (C-3′), 25.60 (C-18), 26.82 (C-11)*, 27.03 (C-2′), 27.29 (C-7), 30.07 (C-6), 30.47 (C-15)*, 36.01 (C-1′)*, 39.52 (C-16)*, 40.03 (C-8), 41.34 (C-9), 49.16 (C-17), 55.18 (CH_3O), 111.19 (C-2), 113.90 (C-4), 125.88 (C-1), 133.03 (C-10), 136.09 (C-14), 140.83 (C-13), 138.32 (C-5), 157.52 (C-3); MS m/e (rel. intensity): 324 (M^+, 100), 309 (14), 281 (67), 173 (62), 147 (41), 107 (26); EI/HRMS: calculated for $C_{23}H_{32}O$ (M^+) 324.2453, found 324.2450.

Peak C. (Minor component, 15%): "17α-butyl-17β-methyl-3-methoxy-18-nor-estra-1,3,5(10),12-tetraene" (**8**). ^{1}H NMR δ ($CDCl_3$): 0.89 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.02 (s, 3H, CH_3-18), 2.91 (m, 2H, CH_2-6), 3.78 (s, 3H, CH_3O), 5.37 (m, 1H, CH-12), 6.62 (d_{app}, 1H, CH-4), 6.72 (dd, J_1 = 2.6 Hz and J_2 = 8.5 Hz, 1H, CH-2), 7.19 (d, J = 8.6 Hz, 1H, CH-1); ^{13}C NMR δ ($CDCl_3$) (partial assignment): 14.20 (C-4′), 22.23, 23.55 (C-3′), 27.21 (C-7), 28.03, 28.77, 29.69 (C-6), 32.78, 38.47, 39.06 (C-8), 42.57, 43.14 (C-9), 44.08 (C-17), 48.26 (C-14), 55.18 (CH_3O), 111.94 (C-2), 113.38 (C-4), 115.06 (C-12)*, 127.62 (C-1), 132.77 (C-10), 138.09 (C-5), 152.57 (C-13)*, 157.23 (C-3).

Peak D. 17-Butyl-3-methoxy-estra-1,3,5(10),16-tetraene (**6**). Colorless oil; IR ν (film); 2926 and 2853 (C–H, aliphatic), 1610, 1575, 1500 (C=C, aromatic), 1464 (CH_2), 1255 (C–O, ether); ^{1}H NMR δ ($CDCl_3$): 0.78 (s, 3H, CH_3-18), 0.93 (t, J = 7.2 Hz, 1H, CH_2CH_3), 2.88 (m, 2H, CH_2-6), 3.78 (s, 3H, CH_3O), 5.31 (s_{app}, 1H, C-16), 6.64 (d, J = 2.6 Hz, 1H, CH-4), 6.71 (dd, J_1 = 2.7 Hz

and J_2 = 8.5 Hz, 1H, CH-2), 7.20 (d, J = 8.6 Hz, 1H, CH-1); ^{13}C NMR δ ($CDCl_3$):14.05 (C-4′), 15.83 (C-18), 22.68 (C-3′), 26.55 (C-11), 26.79 (C-1′)*, 27.85 (C-7), 29.79 (C-2*), 29.86 (C-6), 30.85 (C-15), 34.73 (C-12)*, 37.51 (C-8), 44.47 (C-9), 46.90 (C-13), 55.20 (CH_3O), 56.40 (C-14), 111.37 (C-2), 113.87 (C-4), 120.92 (C-16), 125.99 (C-1), 133.20 (C-10), 138.10 (C-5), 156.16 (C.17), 157.42 (C-3); MS m/e (rel. intensity): 324 (M^+, 100), 309 (67), 267 (73), 173 (94), 147 (35), 135 (21), 107 (14); EI/HRMS: calculated for $C_{23}H_{32}O$ (M^+) 324.2453, found 324.2450.

Study of conditions giving dehydrated compounds

Microassays were performed to establish the experimental conditions that produce the mixture of dehydrated compounds. In a typical assay, about 10 mg of 17α-butyl-3-*O*-methyl estradiol (**3**) was dissolved in solvent (5–6 mL), and the reagent(s) (1 mL of solution or neat) were added (Table 1). The mixture was stirred at room temperature and, if no reaction was seen again, at reflux. TLC was performed in hexane/EtOAc (90:10) after 1, 4, and 18 h at each temperature, and products were correlated with starting alcohol **3** (R_f = 0.13) and the dehydrated mixture of compounds **4–8** (R_f = 0.54). The progression of reaction was indicated by the following letters: N (no reaction, only starting alcohol), P (partial reaction, both starting alcohol and dehydrated compounds), and T (total reaction, no starting alcohol).

Results and discussion

Characterization of compounds obtained during TBDMS-Cl/imidazole or HCl treatment

The first step in the characterization of compounds resulting from the instability of steroid-hindered 17β-tertiary alcohols was the synthesis of starting alcohol **3.** Thus, the butyl group was directly introduced to position 17 of 3-*O*-methyl estrone (**1**) using *n*-butyllithium in THF to give 17α-butyl-3-*O*-methyl estradiol (**3**) (Figure 1). To make the chromatographic separation of alcohol **3** from residual 3-*O*-methyl estrone (**1**) (very similar R_f on silica gel-TLC) easier, an additional reductive step ($LiAlH_4$) was performed, transforming **1** to the more polar 3-*O*-methyl estradiol (**2**) without affecting **3.**

When the tertiary alcohol **3** was submitted to TBDMS-Cl (5 eq), imidazole (10 eq) in DMF, no reaction occurred at room temperature. However, a less polar spot (on TLC) gradually appeared in the refluxing solvent. After 28 h, we obtained 33% of a mixture of dehydrated compounds and 59% of starting alcohol **3** (no TBDMS derivative was observed). HPLC analysis with a reverse-phase column of the less polar fraction (Figure 2, I) clearly showed four peaks (A: 4%, B: 49%, C: 24%, D: 23%). The same peaks (A–D) were obtained when alcohol **3** was submitted to aqueous HCl treatment. In this case the reaction was completed after refluxing 11 h and HPLC analysis (Figure 2, II) indicated different proportions of peaks (A: 1%, B: 21%, C: 73%, D: 5%) than others reported above.

The separation of dehydrated compounds (peaks A–D), which is not possible on normal phase flash silica gel chromatography, was performed by reverse-phase HPLC, and all peaks were analyzed by IR, ^1H NMR, ^{13}C NMR, and mass spectroscopy. Figure 1 shows the five dehydrated compounds with their corresponding peaks. The formation of compounds **4** (peak A) and **5** (peak B) can be explained by the elimination of a proton on the C-1′ of the butyl

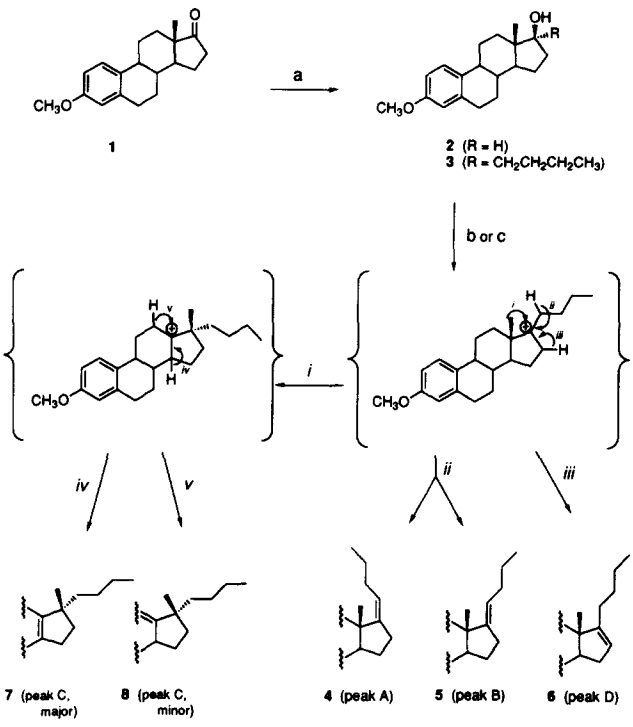

Figure 1 Synthesis of 17α-butyl-3-*O*-methyl estradiol (**3**) from 3-*O*-methyl estrone (**1**) and its transformation to dehydrated compounds **4–8.** The reagents and experimental conditions are: **(a)** 1. *n*-BuLi, THF; 2. $LiAlH_4$, THF; (b) TBDMS-Cl, imidazole, DMF, reflux; **(c)** 10% HCl (v/v), MeOH, reflux.

group. The lower energy *E*-configurated compound **5** (21% and 49% according to treatment) was favored, whereas a small amount (1% and 4%) of *Z*-isomer (compound **4**) was observed. The *E* and *Z* configurations were determined on the basis of NMR data of CH_3-18 and H-vinylic.[7–9] Thus, for 3β-acetoxypregna-5,17(20)-diene,[7] the chemical shifts of CH_3-18 and H-vinylic are 0.92, 5.13 ppm and 0.76, 5.06 ppm, respectively, for the *Z* and *E* isomers. According to these data, the peak A compound with signals at 0.90 and 5.06 ppm corresponds to the *Z* isomer, and the peak B compound with a signals at 0.79 and 5.02 ppm corresponds to the *E* isomer. Peak D contains only one compound, which corresponds to C-16 and C-17 unsaturated compound **6.** This compound results from the elimination of vicinal proton on steroidal backbone. Nuclear Overhauser effect difference experiments confirmed the structure of compound **6.** In these experiments, irradiation of vinylic signal (CH-16) showed three effects on 2′, 15α, and 15β protons.

Peak C showed two compounds by NMR (**7**: 85% and **8**:15%); these compounds resulted from the Wagner-Meerwein rearrangement of tertiary alcohol. After the formation of a carbocation at C-17, the vicinal methyl at C-13 underwent a migration to C-17, followed by elimination of a proton, giving **7** (major compound) and **8** (minor compound). Herein, the methyl shift is stereospecific, since the group migrates on the side of the ring system on which it is located (from 13β to 17β).[10] Such rearrangement is well known, and steroids similar to **7** were already reported, making the characterization easy.[11–25] The structure of compound **8** was not formally characterized but was suggested

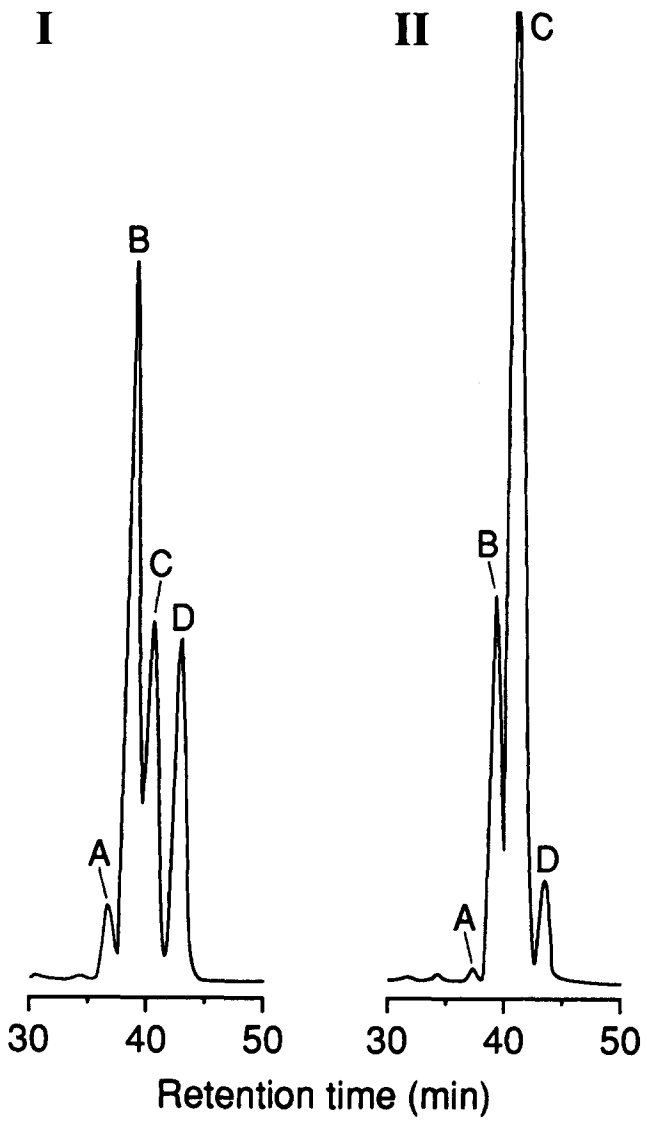

Figure 2 Chromatograms of dehydrated compounds obtained from 17α-butyl-3-*O*-methyl estradiol (**3**) by a TBDMS-Cl (I) or HCl (II) treatment. The retention times were 37, 39, 41, and 43 min, respectively, for peaks A–D. The proportions of peaks were 4% **(A)**, 49% **(B)**, 24% **(C)**, and 23% **(D)** in chromatogram I and 1% **(A)**, 21% **(B)**, 73% **(C)**, and 5% **(D)** in chromatogram II. See Experimental section for HPLC conditions.

by the proposed mechanism and the NMR data. To our knowledge, no observation of a compound similar to **8** (C-12 and C-13 unsaturated) has been reported under refluxing aqueous acid conditions, probably because it was a very small component of a major compound (C-13 and C-14 unsaturated). However, Schanzer et al.[11] have reported the formation of a similar C-12/C-13 unsaturated compound (less than 2%) by decomposition of 17β-sulfate-17α-methyl steroids.

The formation of dehydrated compounds represented in Figure 1 can be rationalized from the intermediate C-17 carbocation, which undergoes a methyl migration with elimination of a proton (**7** and **8**) or only a proton elimination (**4, 5,** and **6**).[11] Both conditions used herein give different distributions of dehydrated compounds. Aqueous HCl treatment led mainly to rearrangement compounds **7** and **8** (73% of total dehydrated compounds), whereas TBDMS-Cl treatment led to only 24% of **7** and **8.** However, in other, similar assays with aqueous HCl treatment, the percentage of peak C (compounds **7** and **8**) was higher than 73% (nearly 100% by NMR). We propose that a solvent effect can explain these results. Indeed, in TBDMS-Cl treatment, C-17 carbocation would be stabilized by DMF, decreasing the ability of methyl-18 to migrate (Wagner-Meerwein rearrangement) and promoting the direct elimination of a proton at C-16 or C-1′.

Screening study of conditions giving dehydrated compounds

To determine the experimental conditions that produce dehydrated compounds **4–8,** many microassays were performed (Table 1). Any base (aqueous and others) leads to the formation of dehydrated compounds (results not shown). However, these dehydrated compounds were gradually obtained by aqueous HCl (entries 2–4) in refluxing methanol. On the other hand, Lewis acids easily transformed alcohol **3** at room temperature (entries 6–8) and reflux (entry 9). No transformation of alcohol **3** was observed with tetrabutylammoniumfluoride (TBAF) (entry 10).

As reported above, standard TBDMS protective conditions (entry 11) led to dehydrated compounds **4–8,** but the process was slower than aqueous HCl treatment, and starting alcohol was partially recovered. When imidazole in DMF (entry 13) or DMF alone (entry 14) was used, no reaction occurred. A partial reaction, however, was observed in refluxing DMF with TBDMS-Cl alone (entry 12) or pyridine · HCl and imidazole (entry 15), suggesting the formation of a C-17 carbocation, which is the key intermediate to dehydrated compounds **4–8** (Figure 1). Indeed, salts like pyridine · HCl, DMF · HCl, or imidazole · HCl will be in equilibrium with their protons, which will protonate the tertiary alcohol, leading to carbocation and dehydrated compounds. A high heating temperature (refluxing DMF, b.p. = 150°C) is essential to this process. Moreover, heating at lower temperature (refluxing THF, b.p. = 67°C) will not give any dehydrated compounds after 18 h (entry 16).

Conclusion

The formation of dehydrated compounds with methyl migration, similar to **7,** was well described for aqueous acid treatment (Wagner-Meerwein rearrangement).[11–25] However, to our knowledge, the formation of other compounds (**4, 5, 6,** and **8**) has not been confirmed, although their presence was suggested.[11,24] Herein five compounds were characterized, and a general profile of experimental conditions providing this mixture of dehydrated compounds was established. This additional information permits a better evaluation of the stability of steroidal 17β-tertiary alcohols regarding some of the currently used reagents.

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Table 1 Transformation of 17α-butyl-3-*O*-methyl estradiol (**3**) to a mixture of dehydrated compounds **4–8** under many experimental conditions[a]

Entry	Conditions		Room temp.			Reflux temp.		
	Reagents	Solvents	1 h	4 h	18 h	1 h	4 h	18 h
1	H_2O	Methanol	N	N	N	N	N	N
2	HCl (1N)	Methanol	N	N	N	P	P	T
3	HCl (0.1N)	Methanol	N	N	N	N	P	P
4	HCl (0.01N)	Methanol	N	N	N	N	N	P
5	AcOH (1N)	Methanol	N	N	N	N	N	N
Lewis acids								
6	$AlCl_3$ (10 eq)[b]	Benzene	T	—	—	—	—	—
7	$BF_3 \cdot OEt_2$ (10 eq)[b]	Benzene	T	—	—	—	—	—
8	ZnI_2 (10 eq)	Benzene	P	P	P	P	P	P
9	pTSA (10 eq)	Methanol	N	N	N	P	T	—
10	TBAF (5 eq)	Tetrahydrofuran	N	N	N	N	N	N
Others								
11	TBDMS-Cl (5 eq), imidazole (10 eq)	Dimethylformamide	N	N	N	N	P	P
12	TBDMS-Cl (5 eq)	Dimethylformamide	—	—	—	—	P	P
13	Imidazole (10 eq)	Dimethylformamide	—	—	—	—	N	N
14	None	Dimethylformamide	—	—	—	—	N	N
15	Pyr · HCl (5 eq), imidazole (10 eq)	Dimethylformamide	N	N	—	N	—	P
16	TBDMS-Cl (5 eq), imidazole (10 eq)	Tetrahydrofuran	N	N	N	N	N	N

[a]See experimental section for the description of microassays. N, no reaction; P, partial reaction; T, total reaction; –, no data available.
[b]A complex unresolved mixture was formed.

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