SHORT PAPER

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Bromination of steroidal 3-keto-4,6-diene†

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The bromination reaction on 3-keto-4,6-diene steroids, via an epoxide intermediate, with hydrobromic acid in acetic acid medium gives the corresponding 6-bromo derivative. On the other hand, bromination with molecular bromine and subsequent dehydrobromination in an aprotic solvent and basic media afforded the unexpected 4-bromo derivative. In this work we suggest an alternative mechanism for explaining the bromine transposition from C6 to C4.

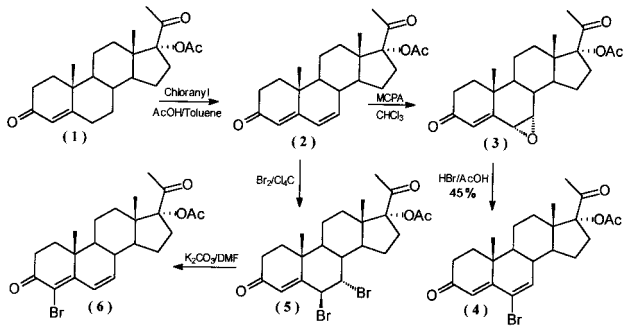
Keywords: bromination

Antiandrogens are of interest for the treatment of androgen-dependent prostate cancer, acne, seborrhea and hirsutism. Cyproterone acetate is widely used as antiandrogen but this compound also has progestational activity.[1]

Inhibitors of steroidal 5α-reductase are not only important tools for the study of physiological role of testosterone and 5α-dihydrotestosterone but may also be of use for the treatment of benign prostatic hyperplasia and prostatic cancer. Many compounds competitively inhibit 5α-reductase for example of 6-halo-16β-methylpregnane derivatives.[2–4]

Studies on the synthesis of halogenated steroids displayings biological activity have shown that the presence of a bromine atom in position 6 of the molecule increases the androgenic activity, with 73, 46 and 31 % of antiandrogenic activity in the series Br, Cl, F, respectively.[5]

In the present work, we have examined the synthetic route for brominated compounds using two different methods.



Scheme 1

17α-Acetoxy-progesterone **(1)** was chosen as starting material. It was converted with chloranil into the 4,6-diene **(2)** in satisfactory yield. Epoxidation of **2** with metachloroperbenzoic acid (MCPA) gave the 6α,7α-epoxide **(3)** in low yield. Treatment of compound **3** with a solution of hydrobromic acid in acetic acid gave the corresponding 17α-acetoxy-6-bromo-4,6-pregnadien-3,20-dione **(4)** in moderate yield. On the other hand, bromination of 3-keto-4,6-diene derivative **2** with molecular bromine gave the addition product **5**, as a crystalline solid. Dehydrobromination of 6β,7α-dibromo compound **(5)** with potassium carbonate in DMF gave the 4-bromo-3-keto-4,6-diene derivative **(6)** instead of the expected 6-bromo derivative.

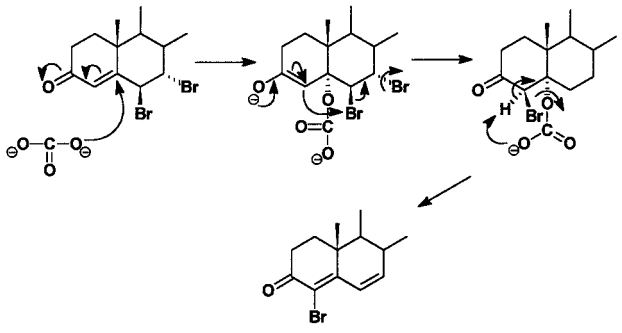
The rearrangement of the bromine in compound **6** was demonstrated by the disappearance of the signal at δ 5,71 assigned to olefinic proton H4 in compound **5**.

The presence of the olefinic double bond in C6–C7 was demonstrated by the appearance of signals at δ 6.80 and δ 6.30 in the ^{1}H NMR spectra of compound **6** with coupling constants $J_{6,7}$ = 10 Hz, $J_{6,8}$ = 2,1 Hz and $J_{7,8}$ = 2,85 Hz.

The ^{13}C NMR spectra of **6** contained a signal of quaternary carbon at δ 121.6 corresponding to C4. This spectrum also showed the signals of C6 and C7 at δ 127.8 and 143.1, respectively.

The ^{1}H^{1}H COSY spectra revealed allylic and homoallylic interactions between H7 and H6 with H8. The latter appeared to 2.29 ppm.

In the course of the study of the halogenation reaction of steroidal 3-keto-1,4,6-trienes, Kocór *et al*.[6] found an analogous behaviour for the dehydrobromination with organic bases and proposed two different mechanisms for this reaction. Although both mechanisms may be involved, the formation of compound **6** is not straightforward. It can be accounted for by considering that the reaction occurs in an aprotic polar solvent which can strongly solvate cations. Under these reaction conditions, the carbonate anion is a good nucleophile which can be added to a β-olefinic carbon (Baylis-Hilman reaction[7]). This anion may facilitate the abstraction of the acidic hydrogen at C-4 to regenerate the 4(5) double bond (see Scheme 2).



Scheme 2

The elucidation of the structure of the novel compounds was carried out by analysis of ^{1}H and ^{13}C-NMR spectra. 2D experiments as H-H COSY, HMQC and HMBC as well as the data reported in the literature,[8,9] were used for the complete assignment of the proposed structures.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

17α-Acetoxy-4,6-pregnadien-3,20-dione **(2)**: A mixture of 1 g (2.7 mmol) of **1**, 7.72 ml (0.135 mol) of acetic acid, 0.68 g (2.8 mmol) of chloranyl in 29 ml toluene, was heated to boiling for 7 hours. The reaction was cooled at 0°C and the solid that precipitated was filtered and the mother liquors were added to sodium hydroxide solution. The main product was extracted and crystallised from methanol/methylene chloride. Yield 0.61 g (61 %). m.p. 225–227°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.16 (1H, d, H-7), 6.14 (1H, d, J_{67}=8.8Hz, H-6), 5.71 (1H, s, H-4), 3.02 (1H, broad t, H-16α) 2.15 (3H, s, CH_3CO); 2.06 (3H, s, CH_3-21); 1.15 (3H, s, CH_3-19); 0.72 (3H, s, CH_3-18). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.9 (C20), 199.4 (C3), 170.7 (C22), 163.2 (C5), 140.1 (C7), 128.3 (C6), 123.9 (C4), 96.4 (C17), 50.1 (C14), 48.9 (C9), 47.6 (C13), 37.5 (C8), 36.0 (C10), 33.9 (C2), 31.7 (C12), 30.2 (C16), 26.4 (C21), 23.4 (C15), 21.2 (C23), 20.3 (C11), 17.3 (19), 14.3 (C18). Found: C 74.70; H 8.36 %. $C_{23}H_{30}O_4$ requires C 74.55; H 8.17 %.

17α-Acetoxy-6α,7α-epoxy-4-pregnen-3,20-dione **(3)**: A mixture of 1 g (2.7 mmol) of **2** and 1.73 g (5.8 mmol) of metachloroperbenzoic acid (MCPA) in chloroform was stirred for 24 hours. After the reaction was completed, it was treated first with 10 % sodium sulfite solution and later with 10 % sodium bicarbonate. The organic layer was worked up as usual and a aqueous product (**3**) was obtained after crystallisation from methanol. Yield 0.32 g (31 %); m.p. 238–241°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.15 (1H, s, H-4), 3.52 (1H, d, H-6), 3.38 (1H, d, H-7), 3.01 (1H, t, H-16α), 2.22 (3H, s CH_3O), 2.05 (3H, s, CH_3-21), 1.11 (3H, s, CH_3-19); 0.72 (3H, s, CH_3-18). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.9 (C20), 198.2 (C3), 170.8 (C22), 162.1 (C5), 131.3 (C4), 96.2 (C17), 54.5 (C9), 52,6 (C14), 47.2 (C13), 46.9 (C7), 40.2 (C8), 35.5 (C10), 34.7 (C6), 34.0 (C1), 33.9 (C2), 30.5 (C12), 30.1 (C16), 26.3 (C21), 23.4 (C15), 21.3 (C23), 19.5 (C11), 17.2 (C19), 14.2 (C18). Found: C 71.62; H 7.95 %. $C_{23}H_{30}O_5$ requires C 71.46; H 7.83 %.

17α-Acetoxy-6-bromo-4,6-pregnadien-3,20-dione **(4)**: 2.46 ml (4.4 mmol) of 45% solution of hydrobromic acid in acetic acid was added slowly to a solution of 0.5 g (1.3 mmol) of **3** in chilled acetic acid. The solution was stirred for 2 hours and then allowed to reach room temperature and stirred for additional 2 hours. The reaction mixture was neutralised with 10 % sodium hydroxide and the product was extracted as usual with ethyl acetate to yield 0.3 g (52 %) and a sample was purified by preparative chromatography (0.25 mm width and $CHCl_3$-CH_3OH 9.8:0.2) for analysis; m.p 158–161°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.56 (1H, d, H-7), 6.32 (1H, s, H-4), 3.00 (1H, t, H-16α), 2.11 (3H, s, CH_3O), 2.06 (3H, s, CH_3-21), 1.17 (3H, s, CH_3-19), 0.75 (3H, s, CH_3-18). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.9 (C20), 194.2 (C3), 170.7 (C22), 159.4 (C5), 142.7 (C7), 126.7 (C4), 121.5 (C6), 96.2 (C17), 49.5 (C14), 48.5 (C9), 47.5 (C13), 40.1 (C8), 38.4 (C10), 34.2 (C1), 33.8 (C2), 30.9 (C12), 30.3 (C16), 26.4 (C21), 23.3 (C15), 21.2 (C23), 20.2 (C11), 16.4 (C19), 14.2 (C18). Found: C 61.62; H 6.64 %. $C_{23}H_{29}O_4Br$ requires C 61.59; H 6.52 %.

17α-acetoxy-6β,7α-dibromo-4-pregnen-3,20-dione **(5)**: 0.15 ml (2.8 mmol) of bromine was added slowly to a soluton of 1 g (2.7 mmol) of **2** in carbon tetrachloride between 0 and 5°C. The reaction mixture was treated with 5 % sodium hydroxide solution. The layers were separated and the organic layer was worked up as usual, to yield 1.4 g (97 %). A sample of the crude product was purified by preparative chromatography (0.25 mm width and *n*-hexane:ethyl acetate 3:2) for analysis; m.p. 140–145°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.00 (1H, s, H-4), 5.12 (1H, d, H-6), 4.57 (1H, t, H-7), 3.00 (1H, broad t, H-16α), 2.25 (3H, s, CH_3O), 2.08 (3H, s, CH_3-21), 2.05 (1H, m, H-9), 1.60 (1H, m, H-14), 1.55 (3H, s,CH_3-19), 0.78 (3H, s, CH_3-18). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.6 (C20), 198.6 (C3), 170.6 (C22), 160.8 (C5), 130.3 (C4), 96.3 (C17), 59.4 (C7), 52.1 (C6), 48.3 (C9), 46.7 (C13), 44.6 (C14), 38.0 (C10), 37.4 (C1), 34.1 (C8), 34.1 (C12), 30.4 (C2), 30.1 (C16), 26.4 (C21), 23.4 (C19), 22.7 (C15), 21.2 (C23), 20.3 (C11), 14.8 (C18). Found: C 52.45; H 5.90 %. $C_{23}H_{30}O_4Br_2$ requires C 52.27; H 5.73 %.

17α-Acetoxy-4-bromo-4,6-pregnadien-3,20-diona **(6)**: A mixture of 1 g (1.9 mmol) of **5** and 0.52 g (3.8 mmol) of potasium carbonate in 6.5 ml dimethyformamide was heated between 50 and 60°C for 3 hours. When the reaction was finished, it was cooled to room temperature, added into water and the pH adjusted with hydrochloric acid. The precipitate which formed was filtered and dried to vacuum. The yield of (**6**) was 1.28 g (89 %) and a sample was purified by preparative chromatography (0.25 mm width and $CHCl_3$-CH_3OH 9.8:0.2) for analysis; m.p. 224–226°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (1H, dd, H-6), 6.30 (1H, dd, H-7), 3.00 (1H, broad t, H-16α), 2.11 (3H, s, CH_3O), 2.07 (3H, s, CH_3-21), 1.17 (3H, s, CH_3-19), 0.75 (3H, s, CH_3-18); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.8 (C20), 190.7 (C3), 159.4 (C5), 143.1 (C7), 127.8 (C6), 121.6 (C4), 170.6 (C22), 96.2 (C17), 50.3 (C9), 48.5 (C14), 47.5 (C13), 39.8 (C10), 37.5 (C8), 33.9 (C2), 32.8 (C1), 31.0 (C12), 30.3 (C16), 26.4 (C21), 23.2 (C15), 21.1 (C23), 20.3 (C11), 16.0 (C19), 14.2 (C18). Found: C 61.68; H 6.68 %. $C_{23}H_{29}O_4Br$ requires C 61.59; H 6.52 %.

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