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Reaction of 21-Bromo-17α-methoxy-20-ketopregnenes with Sodium Methoxide or Potassium Acetate

MITSUTERU NUMAZAWA* and MASAO NAGAOKA

Tohoku College of Pharmacy, 4–1 Komatsushima-4-chome, Sendai, Miyagi 983, Japan

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The reaction of 21-bromo-3β-hydroxy-17α-methoxypregn-5-en-20-one (**5**) with $NaOCH_3$ in MeOH under reflux gave the 21-aldehyde **9** in modest yield along with the 21-hydroxy derivative **6**. The 21-acetates **8** and **13** were obtained in good yields by prolonged reaction of the 21-bromides **5** and **11** with CH_3COO^-.

Keywords——21-bromo-17α-methoxy-20-ketopregnene; 21-hydroxy-17α-methoxy-20-ketopregnene; 21-acetoxy-17α-methoxy-20-ketopregnene; 3β-hydroxy-20-methoxypregna-5,17(20)-dien-21-al; acetolysis

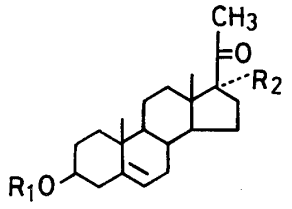
Recently we[1] prepared the synthetic corticoid analogue **12**, which has a 17α-methoxy substituent and can be expected to have interesting biological activity. The synthesis involved transformation of pregnen-20-ones to 21-bromo-17-methoxy compounds by reaction with $CuBr_2$ in MeOH followed by treatment of the bromides with NaOMe in MeOH. However, the configuration of the C-17 methoxy group has not been definitely determined. We[1b] previously reported that the 17-methoxy substituent caused a marked difference of reactivity in the nucleophilic displacement of the 21-bromine under controlled alkaline hydrolysis conditions.[2]

We report here an unambiguous determination of the configuration of the C-17 methoxy group of compound **2**, the precursor of compound **5**, and further studies on the reaction of compound **5** with $NaOCH_3$–MeOH. Acetolysis of compounds **5** and **11** is also described.

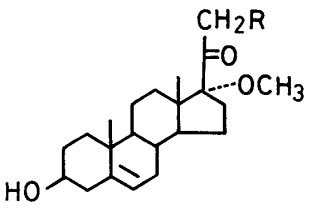
Results and Discussion

3β-Hydroxy-17α-methoxypregn-5-en-20-one (**2**) and its 21-bromo derivative **5** were obtained from the 20-ketopregnene **1** by reaction with 6 mol eq of $CuBr_2$ in MeOH.[1] The α-configuration of the 17-methoxy group of compounds **2** and **5** was determined by establishing the identity of the 3-acetate of **2** with the sample obtained by methylation of 17α-hydroxypregnenolone acetate (**4**) with CH_3I–Ag_2O. Proton nuclear magnetic resonance (^{1}H-NMR) analysis of the crude products obtained from compound **1** by the reaction with $CuBr_2$ according to the previous report[1b] indicated the formation of the 17β-methoxy derivative **14** along with the 17α-isomer **2**.[3] Bromination of a 20-keto steroid with Br_2[4] or $CuBr_2$[5] gives the 17α-bromo derivative. Considering this, we suggest that attack of OMe^- at C-17 of the 17-carbonium derivative produced during the reaction may result in the formation of both 17-methoxy derivatives **2** and **14** through an S_N1 type mechanism; the former would be produced preferentially over the latter mainly because of steric hindrance due to the C-18 angular methyl group.

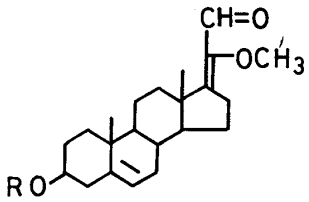
We[1b] previously reported that the reaction of the 21-bromo-17α-methoxides **5** and **11** with an excess amount of $NaOCH_3$ in MeOH at room temperature gave the corresponding



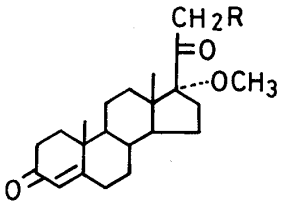
1 : $R_1 = R_2 = H$
2 : $R_1 = H$, $R_2 = OCH_3$
3 : $R_1 = COCH_3$, $R_2 = OCH_3$
4 : $R_1 = COCH_3$, $R_2 = OH$



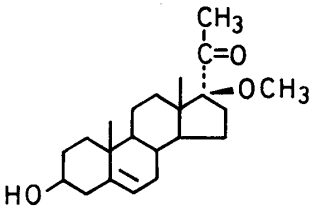
5 : R = Br
6 : R = OH
7 : R = OCH_3
8 : R = $OCOCH_3$



9 : R = H
10 : R = $COCH_3$



11 : R = Br
12 : R = OH
13 : R = $OCOCH_3$



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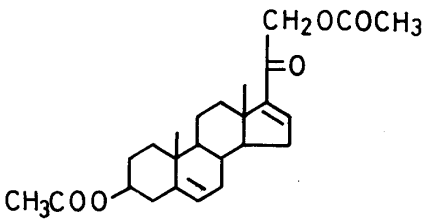

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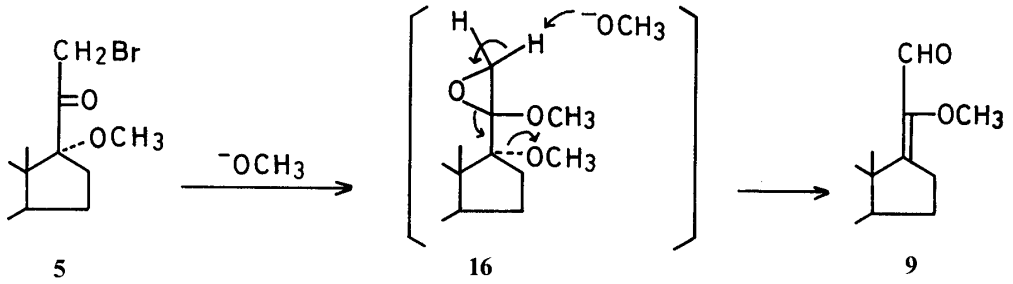
Chart 1



5 16 9

Fig. 1

21-hydroxyderivatives **6** and **12**, respectively, in modest yields. However, when compound **5** was subjected to the same reaction under heating, the 21-aldehyde derivative **9** was obtained in 26% yield along with the 21-hydroxy-17α-methoxide **6** (10%) and the 17α, 21-dimethoxide **7** (*ca.* 10%). The structure of compound **9** was determined by analysis of the ^{1}H-NMR (3.62 ppm, 20-OCH_3; 9.63 ppm, 21-CHO), infrared (IR) (1678 cm^{-1}, conjugated carbonyl group) and mass (M^+ *m/z* 344) spectra, and elemental analysis. The 21-aldehyde **9** may be produced by way of deprotonation at C-21 of the 20,21-oxide **16**[6] initially produced from compound **5**, forming the 21-aldehyde **9** (Fig. 1). When the 21-bromo derivatives **5** and **11** were treated with AcOK[7] in acetone for 104 h under reflux, the corresponding 21-acetates **8** and **13** were produced in modest yields; a longer reaction time, compared to that (*ca.* 12 h) reported previously in the acetolysis of the 21-bromo-17α-hydroxy-20-one,[7] was needed. The difference in acetolysis behavior between 17α-methoxy and 17α-hydroxy steroids might be due to steric hindrance by the bulky 17α-methoxy group, which interferes with attack of the acetoxy ion at the C-21 position. Treatment of compound **5** with AcOK in AcOH[8] unexpectedly gave the 21-acetoxy-16-en-20-oxo derivative **15** instead of the 21-acetate **8**.

The present results together with the previous data[1] have clarified the unique reactivity of a 21-bromo-17α-methoxy-20-oxo steroid with nucleophiles (OH^- and OMe^-).

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were obtained with a Shimadzu IR 430 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV 300 spectrometer. ^{1}H-NMR spectra were obtained on a JEOL PMX 60 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra were measured on Hitachi RMU-7 spectrometer.

3β-Hydroxy-17α-mehoxypregn-5-en-20-one (2)——Compound **2** was synthesized according to the method previously reported by us.[1)] The ^{1}H-NMR spectrum of the crude product showed the formation of the 17β-isomer **14** (**2**:**14**=9:1). However, **14** could not be isolated in pure form. **14**: ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 2.13 (3H, s, 21-CH_3), 3.12 (3H, s, 17β-OCH_3), 3.42 (1H, br m, 3α-H), 5.35 (1H, m, 6-H).

Methylation of 3β-Acetoxy-17α-hydroxypregn-5-en-20-one (4)——A solution of **4** (100 mg, 0.27 mmol) in CH_3I (10 ml) containing Ag_2O (300 mg, 1.3 mmol) was heated under reflux for 50 h. The reaction mixture was diluted with AcOEt (200 ml) and the organic layer was washed with 5% $NaHCO_3$ solution and H_2O, then evaporated to give an oil. The oil was chromatographed on silica gel. Elution with *n*-hexane–AcOEt (5:1) afforded a solid, which, after crystallization from *n*-hexane–acetone, gave **3** (20 mg, 19%) as colorless plates: mp 174—175.5 °C (lit.[5)] 174—176 °C), ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 2.00 (3H, s, 3β-$OCOCH_3$), 2.13 (3H, s, 21-CH_3), 3.13 (3H, s, 17α-OCH_3), 4.63 (1H, br m, 3α-H), 5.40 (1H, m, 6-H). IR (KBr): 1738, 1710, 1258, 1042 cm^{-1}.

Identity with the material obtained by acetylation of **2** was established through the absence of any depression in melting point on admixture and by IR comparison.

3β-Hydroxy-20-methoxypregna-5,17(20)-dien-21-al (9)——A solution of **5**[1b)] (1.0 g, 2.36 mmol) in 100 ml of dry MeOH was treated dropwise with 4.56 ml of a 28% methanolic solution of $NaOCH_3$ with stirring under ice-cooling. The reaction mixture was heated under reflux for 30 min, then diluted with AcOEt (500 ml), and the organic layer was washed with 5% HCl, 5% $NaHCO_3$ and NaCl solutions, and dried (Na_2SO_4). After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with *n*-hexane–AcOEt (5:1) gave a mixture of the 17α,21-dimethoxy compound **7** and the 21-aldehyde **9**. Recrystallization of the crude fraction from acetone gave **9** (26%) as colorless needles: mp 165—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 2.05 (6H, s, acetone-CH_3), 3.43 (1H, br m, 3α-H), 3.62 (3H, s, 20-OCH_3), 5.35 (1H, m, 6-H), 9.63 (1H, s, 21-CHO). IR (KBr): 3500, 1678, 1052 cm^{-1}. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 245 (5400). *Anal.* Calcd for $C_{22}H_{32}O_3 \cdot (CH_3)_2CO$: C, 74.59; H, 9.51. Found: C, 74.20; H, 9.34. Compound **7** could not be isolated in pure form from the mother liquor because of partial decomposition during the isolation procedure. **7** (*ca.* 10%): ^{1}H-NMR ($CDCl_3$) δ: 0.62 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 3.13 (3H, s, 17α-OCH_3), 3.46 (3H, s, 21-OCH_3), 4.25 (2H, s, 21-CH_2), 5.33 (1H, m, 6-H). Recrystallization of the more polar fraction from acetone gave compound **6** (10%) as colorless needles: mp 190—193 °C (lit.[1b)] 191—193 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.60 (3H, s, 18-CH_3), 1.02 (3H, s, 19-CH_3), 3.17 (3H, s, 17α-OCH_3), 3.53 (1H, br m, 3α-H), 4.17 and 4.53 (1H, d, J=20 Hz, 21-H), 5.37 (1H, m, 6-H).

3β-Acetoxy-20-methoxypregna-5,17(20)-dien-21-al (10)——Compound **9** (60 mg, 0.15 mmol) was acetylated with pyridine–Ac_2O. After usual work-up, the product was crystallized from acetone to give **10** (80%) as colorless prisms: mp 106—108 °C. ^{1}H-NMR ($CDCl_3$) δ:0.97 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 2.00 (3H, s, 3β-$OCOCH_3$), 3.62 (3H, s, 20-OCH_3), 4.63 (1H, br m, 3α-H), 5.40 (1H, m, 6-H), 9.63 (1H, s, 21-CHO). IR (KBr): 1733, 1682, 1245, 1040 cm^{-1}. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 262 (8900). *Anal.* Calcd for $C_{22}H_{34}O_4$: C, 72.90; H, 9.45. Found: C, 72.70; H, 9.55.

21-Acetoxy-3-hydroxy-17α-methoxypregn-5-en-20-one (8)——A solution of **5**[1b)] (90 mg, 0.21 mmol), AcOH (300 mg, 5 mmol) and $KHCO_3$ (423 mg, 4.25 mmol) in acetone (30 ml) was heated under reflux for 104 h, then poured into water (150 ml). Products obtained by extraction with AcOEt (2×150 ml) were purified by thin layer chromatography (TLC) (*n*-hexane–AcOEt=2:1) and **8** was finally isolated in pure form by crystallization from acetone (colorless plates, 30 mg, 35%): mp 202—204 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 2.20 (3H, s, 21-$OCOCH_3$), 3.27 (3H, s, 17α-OCH_3), 4.88 (2H, s, 21-CH_2-), 5.37 (1H, m, 6-H). IR (KBr): 3490, 1739, 1720, 1245, 1080 cm^{-1}. *Anal.* Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 70.98; H, 9.03.

21-Acetoxy-17α-methoxypregn-4-ene-3,20-dione (13)——Compound **11**[1b)] (635 mg, 1.51 mmol) was similarly treated with AcOH–$KHCO_3$ (reaction time: 180 h) to give crude **13**, which was purified by column chromatography (slica gel, *n*-hexane–AcOEt) and then crystallized from acetone to yield pure **13** (402 mg, 66%) as colorless prisms: mp 194—195 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, s, 18-CH_3), 1.18 (3H, s, 19-CH_3), 2.17 (3H, s, 21-$OCOCH_3$), 3.22 (3H, s, 17α-OCH_3), 4.87 (2H, s, 21-CH_2-), 5.73 (1H, s, 4-H). IR (KBr): 1738, 1720, 1670, 1608 cm^{-1}. *Anal.* Calcd for $C_{24}H_{34}O_5$: C, 71.62; H, 8.51. Found: C, 71.42; H, 8.46.

3β,21-Diacetoxypregna-5,16-dien-20-one (15)——CH_3COOK (240 mg, 2.45 mmol) was added to a solution of **5** (100 mg, 0.24 mmol) in 10 ml of AcOH, and the mixture was heated under reflux for 213 h, then poured into water (100 ml). The whole was extracted with AcOEt (2×100 ml). The residue, obtained after usual work-up of the organic layer, was subjected to TLC (*n*-hexane–AcOEt, 2:1) to give two crude steroids. Crystallization of the more polar product from MeOH gave **15** (42 mg, 43%) as colorless needles: mp 151—152 °C (lit.[5)] mp 153—155 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 2.03 (3H, s, 3β-$OCOCH_3$), 2.17 (3H, s, 21-$OCOCH_3$), 4.66 (1H, m, 3α-H), 4.73 and 5.10 (1H, d, J=18 Hz, 21-H), 5.38 (1H, m, 6-H), 6.72 (1H, m, 6-H). IR (KBr): 1740, 1728,

1682, 1242 cm^{-1}.

Crystallization of the less polar product from acetone gave the 3-acetate of **5** (56 mg, 51%) as colorless prisms: mp 179—180 °C (lit.[5] 169—173 °C) ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s, 18-CH_3), 1.02 (3H, s, 19-CH_3), 2.00 (3H, s, 21-$OCOCH_3$), 3.17 (3H, s, 17α-OCH_3), 4.03 and 4.28 (1H, d, J=14 Hz, 21-CH), 4.55 (1H, m, 3α-H), 5.42 (1H, m, 6-H). IR (KBr): 1715, 1702, 1242 cm^{-1}.

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References and Notes

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