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## Reaction of 21-Bromo-17 $\alpha$ -methoxy-20-ketopregnenes with Sodium Methoxide or Potassium Acetate

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The reaction of 21-bromo-3 $\beta$ -hydroxy-17 $\alpha$ -methoxypregn-5-en-20-one (**5**) with NaOCH<sub>3</sub> 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<sub>3</sub>COO<sup>-</sup>.

**Keywords**—21-bromo-17 $\alpha$ -methoxy-20-ketopregnene; 21-hydroxy-17 $\alpha$ -methoxy-20-ketopregnene; 21-acetoxy-17 $\alpha$ -methoxy-20-ketopregnene; 3 $\beta$ -hydroxy-20-methoxypregna-5,17(20)-dien-21-al; acetolysis

Recently we<sup>1)</sup> prepared the synthetic corticoid analogue **12**, which has a 17 $\alpha$ -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<sub>2</sub> 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<sup>1b)</sup> 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.<sup>2)</sup>

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<sub>3</sub>-MeOH. Acetolysis of compounds **5** and **11** is also described.

### Results and Discussion

3 $\beta$ -Hydroxy-17 $\alpha$ -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<sub>2</sub> in MeOH.<sup>1)</sup> The  $\alpha$ -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 17 $\alpha$ -hydroxypregnenolone acetate (**4**) with CH<sub>3</sub>I-Ag<sub>2</sub>O. Proton nuclear magnetic resonance (<sup>1</sup>H-NMR) analysis of the crude products obtained from compound **1** by the reaction with CuBr<sub>2</sub> according to the previous report<sup>1b)</sup> indicated the formation of the 17 $\beta$ -methoxy derivative **14** along with the 17 $\alpha$ -isomer **2**.<sup>3)</sup> Bromination of a 20-keto steroid with Br<sub>2</sub><sup>4)</sup> or CuBr<sub>2</sub><sup>5)</sup> gives the 17 $\alpha$ -bromo derivative. Considering this, we suggest that attack of OMe<sup>-</sup> 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<sub>N</sub>1 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<sup>1b)</sup> previously reported that the reaction of the 21-bromo-17 $\alpha$ -methoxides **5** and **11** with an excess amount of NaOCH<sub>3</sub> in MeOH at room temperature gave the corresponding

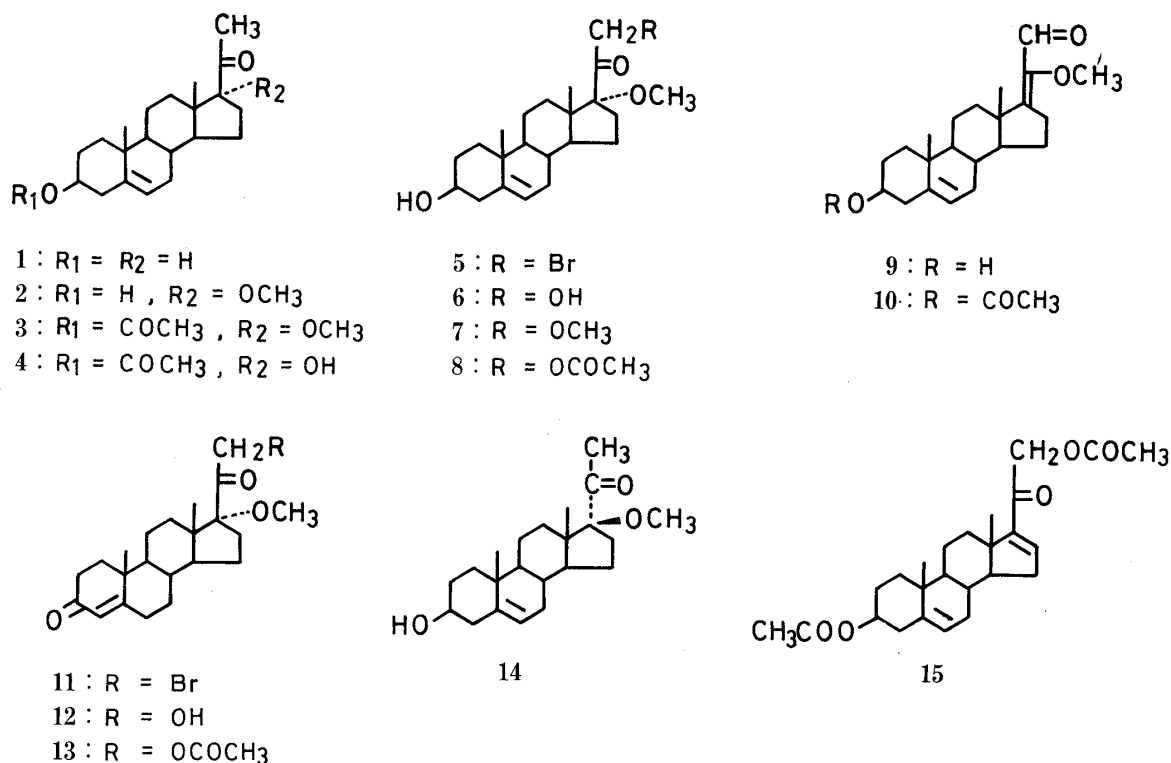


Chart 1

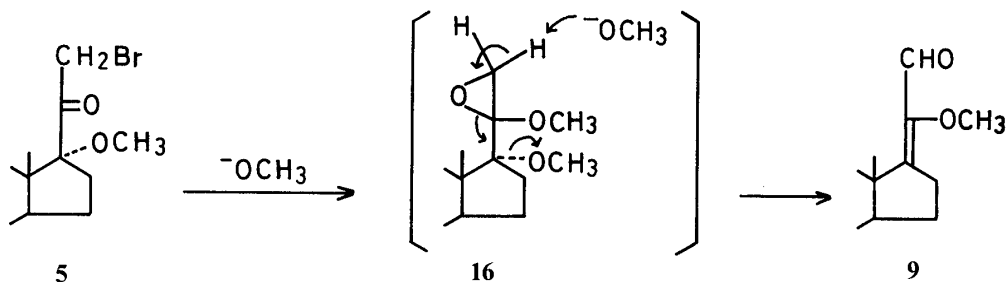


Fig. 1

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-17 $\alpha$ -methoxide **6** (10%) and the 17 $\alpha$ , 21-dimethoxide **7** (ca. 10%). The structure of compound **9** was determined by analysis of the  $^1H$ -NMR (3.62 ppm, 20- $OCH_3$ ; 9.63 ppm, 21-CHO), infrared (IR) ( $1678\text{ cm}^{-1}$ , 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**<sup>6)</sup> initially produced from compound **5**, forming the 21-aldehyde **9** (Fig. 1). When the 21-bromo derivatives **5** and **11** were treated with AcOK<sup>7)</sup> 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-17 $\alpha$ -hydroxy-20-one,<sup>7)</sup> was needed. The difference in acetolysis behavior between 17 $\alpha$ -methoxy and 17 $\alpha$ -hydroxy steroids might be due to steric hindrance by the bulky 17 $\alpha$ -methoxy group, which interferes with attack of the acetoxo ion at the C-21 position. Treatment of compound **5** with AcOK in AcOH<sup>8)</sup> 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<sup>1)</sup> have clarified the unique reactivity of a 21-bromo-17 $\alpha$ -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.  $^1\text{H}$ -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.

**3 $\beta$ -Hydroxy-17 $\alpha$ -methoxypregn-5-en-20-one (2)**—Compound **2** was synthesized according to the method previously reported by us.<sup>1)</sup> The  $^1\text{H}$ -NMR spectrum of the crude product showed the formation of the 17 $\beta$ -isomer **14** (**2**: **14** = 9:1). However, **14** could not be isolated in pure form. **14**:  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.73 (3H, s, 18- $\text{CH}_3$ ), 1.00 (3H, s, 19- $\text{CH}_3$ ), 2.13 (3H, s, 21- $\text{CH}_3$ ), 3.12 (3H, s, 17 $\beta$ - $\text{OCH}_3$ ), 3.42 (1H, br m, 3 $\alpha$ -H), 5.35 (1H, m, 6-H).

**Methylation of 3 $\beta$ -Acetoxy-17 $\alpha$ -hydroxypregn-5-en-20-one (4)**—A solution of **4** (100 mg, 0.27 mmol) in  $\text{CH}_3\text{I}$  (10 ml) containing  $\text{Ag}_2\text{O}$  (300 mg, 1.3 mmol) was heated under reflux for 50 h. The reaction mixture was diluted with  $\text{AcOEt}$  (200 ml) and the organic layer was washed with 5%  $\text{NaHCO}_3$  solution and  $\text{H}_2\text{O}$ , then evaporated to give an oil. The oil was chromatographed on silica gel. Elution with *n*-hexane- $\text{AcOEt}$  (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.<sup>5)</sup> 174–176 °C),  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.76 (3H, s, 18- $\text{CH}_3$ ), 1.00 (3H, s, 19- $\text{CH}_3$ ), 2.00 (3H, s, 3 $\beta$ - $\text{OCOCH}_3$ ), 2.13 (3H, s, 21- $\text{CH}_3$ ), 3.13 (3H, s, 17 $\alpha$ - $\text{OCH}_3$ ), 4.63 (1H, br m, 3 $\alpha$ -H), 5.40 (1H, m, 6-H). IR (KBr): 1738, 1710, 1258, 1042  $\text{cm}^{-1}$ .

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.

**3 $\beta$ -Hydroxy-20-methoxypregna-5,17(20)-dien-21-al (9)**—A solution of **5**<sup>1b)</sup> (1.0 g, 2.36 mmol) in 100 ml of dry  $\text{MeOH}$  was treated dropwise with 4.56 ml of a 28% methanolic solution of  $\text{NaOCH}_3$  with stirring under ice-cooling. The reaction mixture was heated under reflux for 30 min, then diluted with  $\text{AcOEt}$  (500 ml), and the organic layer was washed with 5%  $\text{HCl}$ , 5%  $\text{NaHCO}_3$  and  $\text{NaCl}$  solutions, and dried ( $\text{Na}_2\text{SO}_4$ ). After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with *n*-hexane- $\text{AcOEt}$  (5:1) gave a mixture of the 17 $\alpha$ ,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.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.98 (3H, s, 18- $\text{CH}_3$ ), 1.03 (3H, s, 19- $\text{CH}_3$ ), 2.05 (6H, s, acetone- $\text{CH}_3$ ), 3.43 (1H, br m, 3 $\alpha$ -H), 3.62 (3H, s, 20- $\text{OCH}_3$ ), 5.35 (1H, m, 6-H), 9.63 (1H, s, 21-CHO). IR (KBr): 3500, 1678, 1052  $\text{cm}^{-1}$ . UV  $\lambda_{\text{max}}^{95\% \text{ EtOH}}$  nm ( $\epsilon$ ): 245 (5400). Anal. Calcd for  $\text{C}_{22}\text{H}_{32}\text{O}_3 \cdot (\text{CH}_3)_2\text{CO}$ : 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%):  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.62 (3H, s, 18- $\text{CH}_3$ ), 1.03 (3H, s, 19- $\text{CH}_3$ ), 3.13 (3H, s, 17 $\alpha$ - $\text{OCH}_3$ ), 3.46 (3H, s, 21- $\text{OCH}_3$ ), 4.25 (2H, s, 21- $\text{CH}_2$ ), 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.<sup>1b)</sup> 191–193 °C).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.60 (3H, s, 18- $\text{CH}_3$ ), 1.02 (3H, s, 19- $\text{CH}_3$ ), 3.17 (3H, s, 17 $\alpha$ - $\text{OCH}_3$ ), 3.53 (1H, br m, 3 $\alpha$ -H), 4.17 and 4.53 (1H, d,  $J$  = 20 Hz, 21-H), 5.37 (1H, m, 6-H).

**3 $\beta$ -Acetoxy-20-methoxypregna-5,17(20)-dien-21-al (10)**—Compound **9** (60 mg, 0.15 mmol) was acetylated with pyridine- $\text{Ac}_2\text{O}$ . After usual work-up, the product was crystallized from acetone to give **10** (80%) as colorless prisms: mp 106–108 °C.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.97 (3H, s, 18- $\text{CH}_3$ ), 1.03 (3H, s, 19- $\text{CH}_3$ ), 2.00 (3H, s, 3 $\beta$ - $\text{OCOCH}_3$ ), 3.62 (3H, s, 20- $\text{OCH}_3$ ), 4.63 (1H, br m, 3 $\alpha$ -H), 5.40 (1H, m, 6-H), 9.63 (1H, s, 21-CHO). IR (KBr): 1733, 1682, 1245, 1040  $\text{cm}^{-1}$ . UV  $\lambda_{\text{max}}^{95\% \text{ EtOH}}$  nm ( $\epsilon$ ): 262 (8900). Anal. Calcd for  $\text{C}_{22}\text{H}_{34}\text{O}_4$ : C, 72.90; H, 9.45. Found: C, 72.70; H, 9.55.

**21-Acetoxy-3-hydroxy-17 $\alpha$ -methoxypregn-5-en-20-one (8)**—A solution of **5**<sup>1b)</sup> (90 mg, 0.21 mmol),  $\text{AcOH}$  (300 mg, 5 mmol) and  $\text{KHCO}_3$  (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  $\text{AcOEt}$  ( $2 \times 150$  ml) were purified by thin layer chromatography (TLC) (*n*-hexane- $\text{AcOEt}$  = 2:1) and **8** was finally isolated in pure form by crystallization from acetone (colorless plates, 30 mg, 35%): mp 202–204 °C.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.65 (3H, s, 18- $\text{CH}_3$ ), 1.00 (3H, s, 19- $\text{CH}_3$ ), 2.20 (3H, s, 21- $\text{OCOCH}_3$ ), 3.27 (3H, s, 17 $\alpha$ - $\text{OCH}_3$ ), 4.88 (2H, s, 21- $\text{CH}_2$ -), 5.37 (1H, m, 6-H). IR (KBr): 3490, 1739, 1720, 1245, 1080  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{24}\text{H}_{36}\text{O}_5$ : C, 71.26; H, 8.97. Found: C, 70.98; H, 9.03.

**21-Acetoxy-17 $\alpha$ -methoxypregn-4-ene-3,20-dione (13)**—Compound **11**<sup>1b)</sup> (635 mg, 1.51 mmol) was similarly treated with  $\text{AcOH}$ - $\text{KHCO}_3$  (reaction time: 180 h) to give crude **13**, which was purified by column chromatography (silica gel, *n*-hexane- $\text{AcOEt}$ ) and then crystallized from acetone to yield pure **13** (402 mg, 66%) as colorless prisms: mp 194–195 °C.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.67 (3H, s, 18- $\text{CH}_3$ ), 1.18 (3H, s, 19- $\text{CH}_3$ ), 2.17 (3H, s, 21- $\text{OCOCH}_3$ ), 3.22 (3H, s, 17 $\alpha$ - $\text{OCH}_3$ ), 4.87 (2H, s, 21- $\text{CH}_2$ -), 5.73 (1H, s, 4-H). IR (KBr): 1738, 1720, 1670, 1608  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{24}\text{H}_{34}\text{O}_5$ : C, 71.62; H, 8.51. Found: C, 71.42; H, 8.46.

**3 $\beta$ ,21-Diacetoxypregna-5,16-dien-20-one (15)**— $\text{CH}_3\text{COOK}$  (240 mg, 2.45 mmol) was added to a solution of **5** (100 mg, 0.24 mmol) in 10 ml of  $\text{AcOH}$ , and the mixture was heated under reflux for 213 h, then poured into water (100 ml). The whole was extracted with  $\text{AcOEt}$  ( $2 \times 100$  ml). The residue, obtained after usual work-up of the organic layer, was subjected to TLC (*n*-hexane- $\text{AcOEt}$ , 2:1) to give two crude steroids. Crystallization of the more polar product from  $\text{MeOH}$  gave **15** (42 mg, 43%) as colorless needles: mp 151–152 °C (lit.<sup>5)</sup> mp 153–155 °C).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.93 (3H, s, 18- $\text{CH}_3$ ), 1.03 (3H, s, 19- $\text{CH}_3$ ), 2.03 (3H, s, 3 $\beta$ - $\text{OCOCH}_3$ ), 2.17 (3H, s, 21- $\text{OCOCH}_3$ ), 4.66 (1H, m, 3 $\alpha$ -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  $\text{cm}^{-1}$ .

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.<sup>5)</sup> 169—173 °C)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.95 (3H, s, 18- $\text{CH}_3$ ), 1.02 (3H, s, 19- $\text{CH}_3$ ), 2.00 (3H, s, 21- $\text{OCOCH}_3$ ), 3.17 (3H, s, 17 $\alpha$ - $\text{OCH}_3$ ), 4.03 and 4.28 (1H, d,  $J=14$  Hz, 21-CH), 4.55 (1H, m, 3 $\alpha$ -H), 5.42 (1H, m, 6-H). IR (KBr): 1715, 1702, 1242  $\text{cm}^{-1}$ .

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