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# FRONT SIDE NEIGHBOURING GROUP PARTICIPATION IN THE 16-HYDROXYMETHYLANDROST-5-ENE-3, 17-DIOL SERIES[1,2]

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**Abstract**—The *cis* isomers of 16-hydroxymethylandrost-5-ene-3$\beta$, 17-diol (**1a** and **8a**) transform into 16-bromomethylandrost-5-ene-3$\beta$, 17 diacetate (**5** and **12**) on treatment with hydrogen bromide and acetic acid. The process is accompanied by the formation of some tri-acetate (**1d** and **8d**) and rearranged products (**6** and **13**). The *trans* isomers (**15a** and **16a**) yield, under similar experimental conditions, only triacetates (**15b** and **16b**).

It was found by Golding *et al.*[3] that *cis* and *trans* derivatives of vicinal diols show significant stereospecific behaviour towards acetic acid and hydrogen bromide. Thus, *cis*-cyclohexane-1, 2-diol transforms into *trans*-1-acetoxy-2-bromocyclohexane in satisfactory yield, while *trans*-cyclohexane-1, 2-diol was converted into the corresponding *trans*-diol diacetate. Other 1, 2-diol systems react in a similar manner. After the formation of the mono-acetate, a 1, 3-dioxolonium ion develops which yields *trans*-acetoxy bromide with the bromide ion.[4-6] The mechanism of the process can be interpreted by the front-side participation suggested by Boschan and Winstein.[7]

Stereospecificity of 1, 2-diols towards acetic acid in HBr was found also in 1, 3-diol systems developed on the sterane skeleton.

16 $\alpha$-Hydroxymethylandrost-5-ene-3$\beta$, 17$\alpha$-diol 3-acetate (**1a**) carrying a *cis* OH functions at the D ring in the sterane skeleton transforms a room temperature mainly into 16 $\alpha$-bromomethylandrost-5-ene-3$\beta$, 17 $\alpha$-diol 3, 17 diacetate (**5**) by acetic acid—HBr (2 equivts of HBr for 1 mole of steroid). The process is accompanied by the formation of some triacetate (**1d**) and 16 $\alpha$-acetoxymethyl-17 $\beta$-methyl-18-nor-5, 13 (14)-androstadiene-3$\beta$-ol 3-acetate (**6**) (Fig. 1).

Similarly, 16 $\beta$-hydroxymethylandrost-5-ene-3 $\beta$, 17 $\beta$-diol 3-acetate (**8a**) yielded the corresponding bromomethyl derivative (**12**). During the conversion, some triacetate (**8d**) and 16 $\beta$-acetoxymethyl-17 $\beta$-methyl-18-nor-5, 13(14)-androstadiene-3 $\beta$-ol 3-acetate (**13**) was also formed.

On the other hand, 16 $\alpha$-hydroxymethylandrost-5-ene-3 $\beta$, 17 $\beta$-diol 3-acetate (**15a**) and 16 $\beta$-hydroxymethylandrost-5-ene-3 $\beta$, 17 $\alpha$-diol 3-acetate (**16a**) carrying *trans* functional groups yield only triacetates (**15b** and **16b**) under the given experimental conditions (Fig. 2).

The stereospecific conversion was monitored by tlc methods in the case of **1a**. It was found that a significant amount of 16 $\alpha$-acetoxymethylandrost-5-ene-3 $\beta$, 17 $\alpha$-diol 3-acetate (**1b**) was formed at the beginning of the conversion, accompanied by 16 $\alpha$-hydroxymethylandrost-5-ene-3 $\beta$, 17 $\alpha$-diol 3, 17-diacetate (**1c**). The amount of both compounds (**1b** and **1c**) markedly decreased as the reaction proceeded. Presumably, **1b** cyclised into a mixture of ortho acid-ortho ester (**2a**) in the acid medium, which became stabilized either as **1c** or transformed via the ambident 2-methyl-1, 3-dioxonium ion (**3**) into **5**. Acetylation of the primary OH group in **1c** yielded **1d**. During formation of **5**, no change in configuration occurred, since ring cleavage in the ambident cation **3** takes place at the sterically favoured site $C_{16}$–$CH_2$–. The 16 $\alpha$, 17 $\alpha$ structure of **5** was supported by the H-NMR data. The coupling constant measured ($J_{16\beta H,17\beta H} = 5.5$ Hz) agreed well with the earlier observation.[8] Furthermore, compound **5** cyclised to 16$\alpha$, 17$\alpha$-epoxymethyl-eneandrost-5-ene-3$\beta$-ol (**7a**) of known structure in the presence of NaOMe in MeOH. The acetylated derivative (**7b**) was converted into **5** quantitatively with acetyl bromide.

As for the formation of **6**, the ambident cation **3** is assumed to isomerize into **4**, this undergoes a Wagner–Meerwein rearrangement to yield **6**.

In order to confirm the mechanism assumed for the formation of **5**, 16$\alpha$-acetoxymethylandrost-5-ene-3$\beta$,17$\alpha$-diol 3-acetate (**1b**), 16$\alpha$-hydroxymethyl-androst-5-ene-3$\beta$, 17$\alpha$-diol 3, 17-diacetate (**1c**) and the cyclic orthoester (**2b**) were allowed to react with acetic acid—HBr. Compounds **1b** and **2b** yielded **5** in high yield. Probably, **1b** was transisomerized into **2a**, which yielded **5** via **3**. In the case of **2b**, the ambident cation **3** was formed directly, which again yielded **5**. In the case of **1c**, a significant amount of triacetate (**1d**) was also formed, in addition to **5**. This was explained by partial isomerisation of **1c** in an equilibrium process into **2a**, this transformed into **5** via **3**, and the non-isomerized fraction became acetylated at the primary OH group to yield **1d**.

In the case of **8a** also carrying *cis* OH functions, **8b** would be formed on treatment with acetic acid–HBr, which then isomerised into **9a** and transformed into **12** via **10** while retaining the original configuration. The 16$\beta$, 17$\beta$ structure was confirmed by the coupling constant in the H-NMR spectrum ($J_{16\alpha H,17\alpha H} = 9.5$ Hz)[8]. Compound **12** cyclised into **14a** of known structure with NaOMe in MeOH,[11] the acetylated derivative of the product (**14b**) yielded **12** with acetyl bromide.

As for the formation of **13**, the ambident cation **10** was partly transformed into **11** and became stabilized as **13** after the Wagner–Meerwein rearrangement.

In order to verify the mechanism assumed, **12**, **8b**, **8c** and **9b** were allowed to react with acetic acid–HBr. Both **8b** and **9b** yielded **12** in satisfactory yield. In the conversion of **8c**, the formation of a signficant amount of **8d** was also observed.

Compounds **15a** and **16a** carrying *trans* functional groups are not suitable for the development of ambident cations, in accordance with the earlier statements.[9,12] Under the given experimental conditions, they suffer proton-catalysed acetylation (**15b** and **16b**) and do not transform into bromomethyl derivatives (Fig. 3).

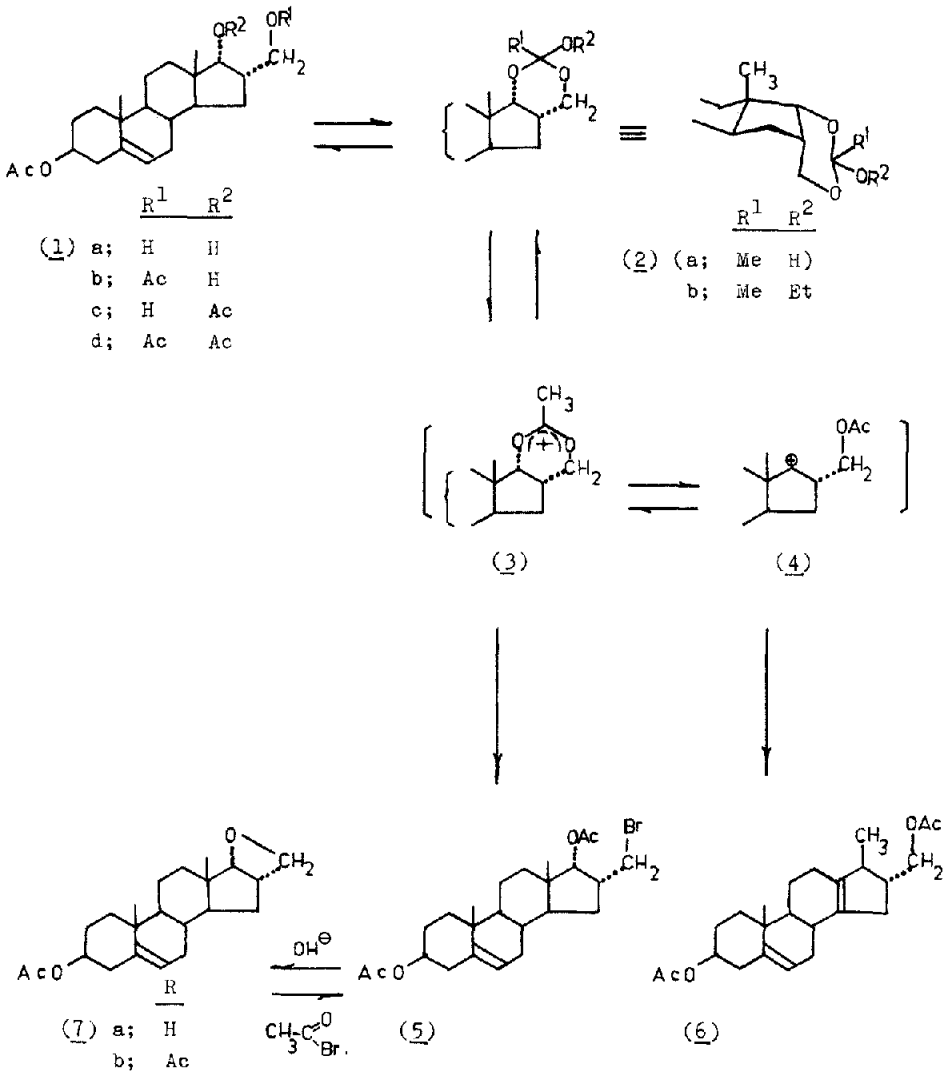


Fig. 1.

## EXPERIMENTAL

Mps were measured on a Kofler block and are uncorrected. Specific rotation was determined with a Polamat-A (Carl Zeiss, Jena) polarimeter. The limiting error of the rotation values given is ±2°. The H-NMR measurements were effected with a JEOL C-60 HL, Tokyo, (60 MHz) instrument, the spectra were recorded in $CDCl_3$ using TMS as the internal standard. The values are given on the $\delta$ scale in ppm. The IR spectra were recorded with a Unicam SP 200 instrument in KBr pellets. The thin-layer chromatograms were obtained in Kieselgel-G (Merck) layers of 0.5 mm thickness. The developing agent was MeOH–benzene (1 : 99). The spots were detected by spraying with 50% aqueous phosphoric acid followed by heating at 100–120° for 15 min. The $R_f$ values were determined in UV light of 365 nm wavelength. In the column chromatographic separation, $Al_2O_3$ packing of activity III–IV standardized by Brockmann was used. Dimensions of the chromatographic column were 25 cm length, 2 cm dia., the amount of the $Al_2O_3$ used was 50 g.

*Reaction of* **1a**, **1b**, **1c**, **2b**, **8a**, **8b**, **8c**, **9b**, **15a** *and* **16a** *with* HBr-AcOH

*General method* 1. Compounds **1a**, **1b**, **1c**, **2b**, **8a**, **8b**, **8c**, **9b**, **15a** and **16a** (0.01 mole) were dissolved in $CH_2Cl_2$ (10 mL) and 33% HBr–AcOH reagent (5 mL) was added at room temp. The mixture was allowed to stand for 8 hr, then diluted with water. The two phases were separated, washed with water and $NaHCO_3$ aq until free from acid, dried and evaporated to dryness.

The evaporation residue was dissolved in benzene and subjected to chromatographic separation on an $Al_2O_3$ column (activity III-IV). When using benzene–petroleum ether (10 : 90) mixture the bromomethyl derivative (**5** and **12**) could be isolated. Benzene–petroleum ether (15 : 85) eluted the rearranged product (**6** and **13**). The triacetate derivatives (**1d**, **8d**, **15b** and **16b**) were eluted with a benzene–petroleum ether (25 : 75) mixture (Table 1).

16, 17-*Epoxymethyleneandrost-5-ene-3β-ol* (**5a** *and* **11a**)

*General method* 2. Compound **5** or **12** (0.9535 g, 0.002 mole) was dissolved in MeOH (25 mL) and refluxed with NaOMe (0.45 g, 0.008 mole) for 6 hr. The mixture was then diluted with water. The soln was saturated with $(NH_4)_2SO_4$ and the ppt was filtered off. After drying it was recrystallized from benzene.

**7a**: 0.580 g (95.8%). (Ref. 11)

**14a**: 0.535 g (88.4%). (Ref. 11).

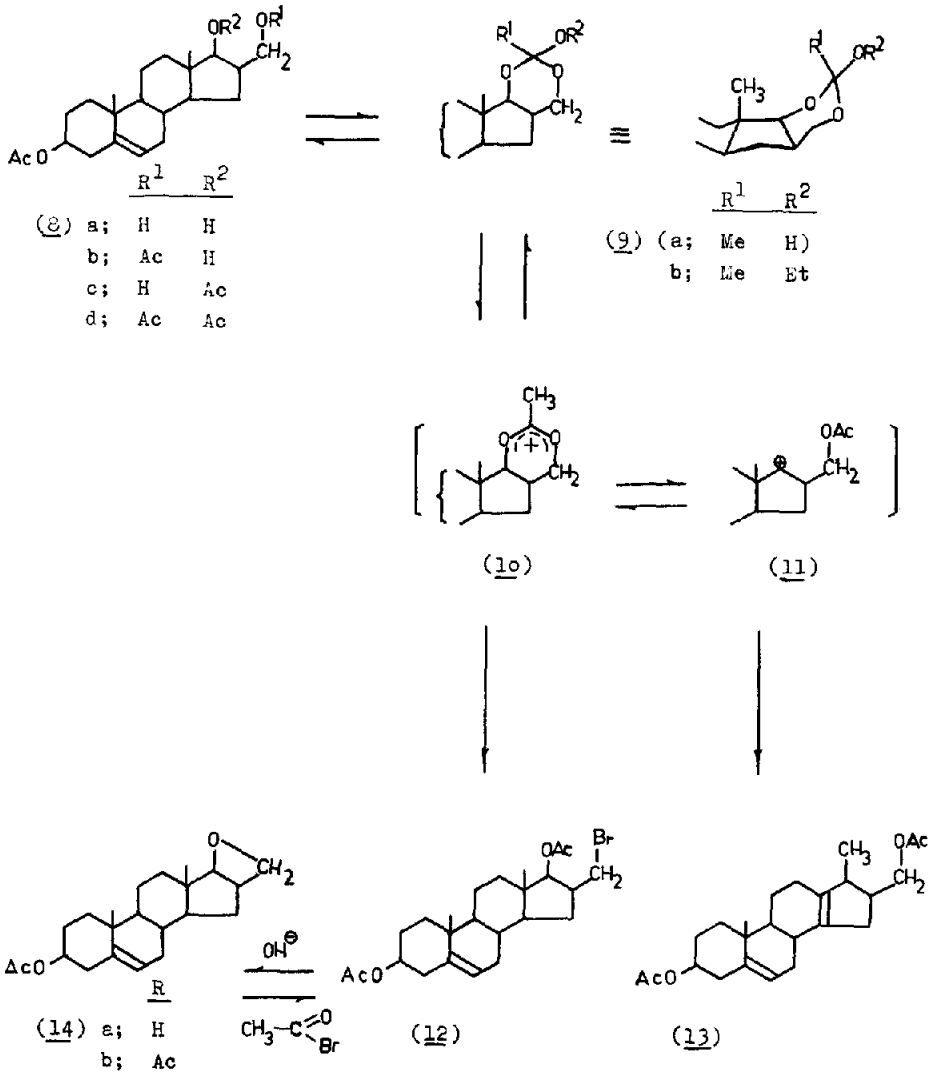


Fig. 2.

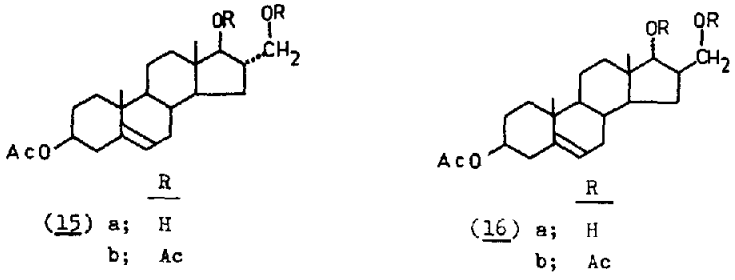


Fig. 3.

16-*Bromomethylandrost-5-ene-3β, 17-diol* 3, 17-*diacetate* (**5** *and* **12**)

*General method* 3. Compound **7b** or **14b** (Ref. 11) (0.688 g, 0.002 mole) was dissolved in $CH_2Cl_2$ (10 mL) and acetyl bromide (0.5 g, 0.004 mole) was added while cooling in ice. After standing for 1 hr, it was washed with water and $NaHCO_3$ aq until neutral and evaporated to dryness. An oil was obtained, this crystallized on the addition of MeOH.

**5**: 0.860 g, 92.0%. M.P. 186–187°, $[\alpha]_D = -25°$ (c = 1, chloroform), $R_f = 0.85$.

$C_{24}H_{35}O_4Br$ (467.45). Calc. for C 61. 67; H 7.54; Br 17.10. Found C 61.52; H 7.75; Br 16.90%.

IR: 1250, 1730 $cm^{-1}$ (OCO).

H-NMR ($CDCl_3$): $\delta$ 0.85 (s, 3H, $18CH_3$), 1.02 (s, 3H, $19CH_3$), 2.03 and 2.1 (each s, 3H, OAc), 5.25 (m, 1H, Δ6), 4.6 (m, 1H, 3αH), 5.02 (d, $J_{16,17} = 5.5$ Hz, 1H, 17βH), 3.48 and 3.3 (each m, 1H, $CH_2Br$) **12**: 0.900 g, 96.3%, m.p. 134–316°, $[\alpha]_D = -46°$ (c = 1, chloroform). $R_f = 0.85$.

$C_{24}H_{35}O_4Br$ (467.45). Calc. for C 61.67; H 7.54; Br 17.10. Found C 61.55; H 7.60; Br 17.30%.

Table 1. Per cent of component[a]

| Compound | 5 | 1d[d] | 6[d] | 12 | 8d[c] | 13[c] | 15b[c] | 16b[c] |
|---|---|---|---|---|---|---|---|---|
| 1a[e] | 84 | 7.5 | 6.5 | | | | | |
| 1b[e] | 87.8 | 5.5 | 6 | | | | | |
| 1c[e] | 76.5 | 19 | 4 | | | | | |
| 2b[b] | 93 | | 5.5 | | | | | |
| 8a[c] | | | | 80 | 11.5 | 7.5 | | |
| 8b[c] | | | | 89 | 5.5 | 4.5 | | |
| 8c[b,c] | | | | 78.5 | 15 | 5.5 | | |
| 9b[c] | | | | 91 | 3 | 4.5 | | |
| 15a[c] | | | | | | | 100 | |
| 16a[c] | | | | | | | | 99.5 |

[a] Products obtained in column chromatographic processing

[b] Ref.[2]

[c] Ref.[9]

[d] Ref.[10]

[e] Ref.[12]

IR: 1250, 1730 $cm^{-1}$ (OCO).

H-NMR ($CDCl_3$): $\delta$ 0.8 (s, 3H, $18CH_3$), 1.0 (s, 3H, $19CH_3$), 2.02 and 2.05 (each s, 3H, OAC), 5.4 (m, 1H, $\Delta$6H), 4.5 (m, 1H, 3$\alpha$H), 4.75 (d, $J_{16,17} = 9.5$ Hz, 1H, 17$\alpha$H), 3.15 and 3.4 (each m, 1H, $CH_2Br$).

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