A-Subustituted 5β-Steroids. VI.[1] *trans*-S_N2' Reaction in Acylolysis of 4β-Bromo-3-keto-5β-steroids

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A new type of S_N2' reaction in which the nucleophile enters to the leaving group occurs in the acylolysis of 4β-bromo-3-keto-5β-steroids (**1**) to give 2α-acyloxy-3-keto-5β-steroids (**2**) as a product. This reaction pathway was observed by NMR and by tlc.

During the course of our studies on the chemistry of A-substituted 5β-steroids, we have found that the substitution reaction of 4β-bromo-3-keto-5β-steroid (**1a**) with potassium salts of organic acids under refluxing conditions is accompanied with a new rearrangement of a substituent from C_4 to C_2 resulting in the 2β-acyloxy-3-keto-derivative (**3a**) in good yield.[2] A rearrangement in the substitution reaction of steroidal α-halogenoketone has been investigated by several groups in recent years. For example, on acetolysis of 2α-bromo-5α-cholestan-3-one, Fieser and Romero[3] obtained 2α-acetoxy- and 4α-acetoxy-5α-cholestan-3-ones in a 1 to 1 ratio (40%). The fact that 4α-acetoxy-5α-cholestan-3-one was obtained proved that the rearrangement in the substitution reaction from C_2 to C_4 had partially taken place. Under the same condition, 2α-acetoxy-cholest-4-en-3-one was also obtained through the rearrangement from C_6 to C_2 in the substitution reaction of 6β-bromo-cholest-4-en-3-one in 17% yield.[3] Fieser and Romero suggested the following sequence as a possible mechanism for this rearrangement: enolization→allylic isomerization of the bromine atom→substitution with acetoxy-ion. This mechanism was also applied implicitly to the rearrangement from C_2 to C_4. Clarke *et al.* reported that when this reaction was carried out with 6β-bromotestosterone acetate as the reactant, the 2β-acetoxy-derivative was obtained, not the 2α-derivative.[4] They stated that the 2β-acetoxy-group epimerized to the α-acetoxy-derivative, which is a more stable form under the conditions. As a result, they concluded that the primary product was the 2β-acetoxy-derivative.

From the fact that halogeno-ketones as well as allylic halides undergo rearrangement in the substitution reaction, Newman suggested that the substitution reactions of a halogeno-ketone system also belong to the S_N2' reaction.[5] That is to say, these reactions are considered to involve nucleophilic substitution in the enolic form of the ketone; hence an allylic mechanism is reasonable. In these reactions the nucleophile has a *cis*-relationship to the leaving group when it attacks a γ-carbon (allylic position).[6] This consideration for the transition state seems consistent with the previous investigations of the S_N2' reactions in cyclic allylic compounds, in which only *cis*-substitutions have been investigated.[6] In the cases of the steroidal α-bromo-ketones,[3,4] mentioned above, the entering and the leaving groups are in *cis*-relationship to each other, also. In a recent communication, however, we reported a new type of S_N2' reaction in which the nucleophile enters *trans* to the leaving group.[7]

That is to say, when the 4β-bromo-3-keto-5β-steroid (**1a**) were treated with (a) potassium acetate–acetic acid, (b) potassium acetate–dioxane–water, (c) acetic acid–triethylamine and (d) potassium pivalate–dioxane–water at 90—95 °C, and with (e) tetramethylammonium acetate–dioxane at room temperature, the 2α-acyloxy-3-keto-derivatives (**2a**, **b**, **c**) was formed as a primary product.

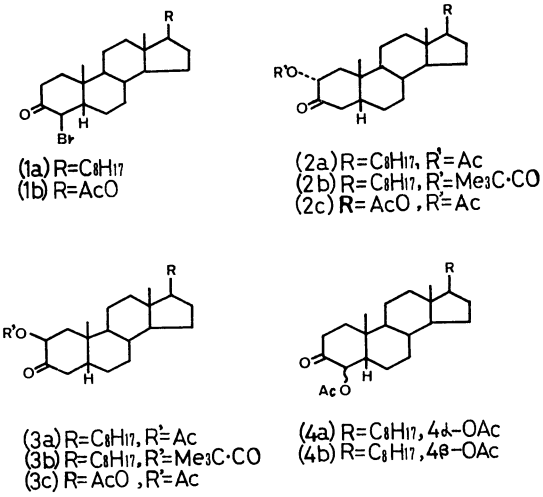

Fig. 1.

In the present paper, we wish to describe in full the details of the mechanism of the new reaction.

Results and Discussion

In each case above, 2α-acyloxy-5β-cholestan-3-ones (**2a**, **b**) was produced first. Since the isomerization of the 2α-acyloxy- to the 2β-acyloxy-derivative (**3a**) is relatively fast for cases (a) and (c), it was impossible to isolate the intial product, 2α-acyloxy-5β-cholestan-3-one, in high yield, but the 2α-acyloxy-derivative was obtained almost stereospecifically in 5 hr by reaction (b) and in 5 days by reaction (e).

In order to examine the stereochemical pathway of this reaction, **1a** was treated with potassium acetate in acetic acid (reaction (a)). The progress of the reaction was followed by tlc at certain time intervals. It could be observed that only the initial product (**2a**) was formed during the first 0.5 hr; and then during the next 0.5 hr, this initial product began to isomerize to the **3a**. This isomerization gradually continued, and the ratio of **2a** to **3a** became 1 : 1 at 3 hr. After 6.5 hr,

the **2a** completely disappeared.

In reaction (d), the NMR spectrum of the reactant, terminated after 1 hr, had peaks at 5.20 ppm (t, J= 9.5 Hz, which probably is in a boat conformation due to the severe interaction of the 2α-pivaloyloxy group with C_9–H and C_9–C_{10} in the chair conformation) and 4.80 ppm (d, J=11.5 Hz) due to the 2β-H in the 2α-pivaloyloxy-derivative and the 4α-H in the starting material respectively. When the reaction, which had once been terminated, was continued for 8 hr, the NMR spectrum of the reactant showed peaks at 5.04 ppm (dd, J=6.0 and 14.5 Hz) and 5.20 ppm, due to the 2β- (**3b**) and 2α-pivaloyloxy-derivatives (**2b**), respectively. In the NMR spectrum of the reactant after 30 hr, the triplet at 5.20 ppm disappeared and the quartet at 5.04 ppm remained. This suggested that an α-side attack is also possible for such a bulky nucleophile as Me_3CCOO^-. These NMR spectra are shown in Fig. 2. Such a phenomenon was already observed in reaction (b) by using a 220 MHz spectrometer to observe the change in the signals due to the methyl protons of the 2α- and 2β-acetoxy groups.[7]

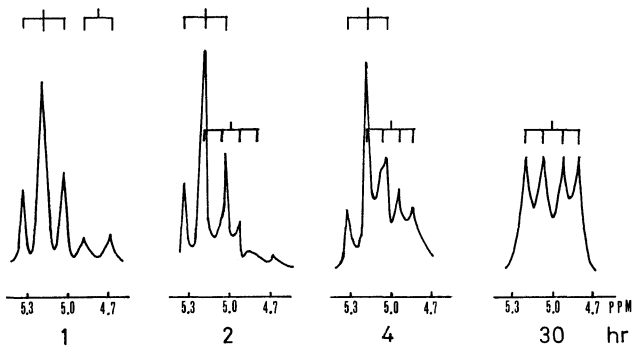

Fig. 2. 60 MHz NMR signals due to C_2H in the case of reaction (d) at intervals. Starting material: 4.80 ppm; α-Isomer: 5.20 ppm; β-Isomer: 5.04 ppm.

As the mechanism of the acylolysis, it is possible to consider that normal substitution occurs at C_4 with acyloxy-ion, and subsequently the acyloxy group formed rearranges to C_2.

Therefore, the 4α-acetoxy-derivative (**4a**) was synthesized from 5β-cholestan-3-one to find out whether or not the acetoxy-derivative changes to the 2α-acetoxy-isomer. Because this 4α-acetoxy-derivative contaminated with a trace of 4β-acetoxy-derivative, the crystallization of **4a** was unsuccessful. The structure of **4a** was confirmed by the comparison of NMR spectral data with the three other isomers (2α-, 2β-, and 4β-acetoxy-derivatives). When the 4α-acetoxy-derivative without further purification was treated with potassium acetate–acetic acid under the same conditions for the acetolysis described above, the 4β-acetoxy-derivative (**4b**) formed quantitatively. A parallel study[11] on 4α,17β-diacetoxy-5β-androstan-3-one found essentially the same behaviour. On the other hand, when the 4β-acetoxy-derivative was treated under the same conditions, the starting material was recovered.[8] From these results, it was ascertained that, in the acylolysis of 4β-bromo-5β-cholestan-3-one, the possibility of normal substitution products rearranging to give the 2-acyloxy-isomer is eliminated.

There is a further possibility that the substitution reaction by acyloxy ion takes place after a rearrangement of the bromine from C_4 to C_2 in the 4β-bromo-3-keto-derivative (**1**). Recently, one of the authors reported the first example of rearrangement of a halogen in an α-halogeno-ketone from the α- to the α′-carbon in such acylolysis.[9] That is, in the acetolysis of 1β-halogeno-5β-cholestan-2-one with potassium acetate–acetic acid at 98 °C, 3-halogeno-ketones could be isolated along with the 3-acetoxy-2-keto-derivative. But in the case of the reaction of 4β-halogeno-3-keto-5β-steroids, the 2-halogeno-3-keto-derivatives were not obtained, nor could they be observed by following the reaction with NMR and tlc. The foregoing facts would suggest that the rearrangement of 4β-halogeno-3-keto-5β-steroids to 2-halogeno-derivatives does not occur under our conditions. This result was identical with Liston's observation that 2β- and 4β-bromo-17β-acetoxy-5β-androstan-3-ones are not interchanged or equilibrated.[10]

While this report was being prepared, Wareneboldt and Weiler reported that the reaction of 17β-acetoxy-4β-bromo-5β-androstan-3-one (**1b**) with sodium acetate–acetic acid gave 2β,17β-diacetoxy-5β-androstan-3-one (**3c**) under refluxing conditions.[11] They did not observe formation of the 2α-acetoxy-isomer (**2c**), but they discussed the mechanism of the acetolysis by reference to the possible pathways for the reaction of *cis*-S_N2' type catalogued by Bordwell.[12] That is to say, in the acetolysis of 17β-acetoxy-2β-bromo-5β-androstan-3-one, it is cleanly converted to the 2β-acetoxy derivative in refluxing acetic acid–sodium acetate at a rate comparable to the 4β-bromo-derivative. From this finding, they suggested a carbonium ion pathway for this reaction. Thus both bromoketones give the same intermediate. If the acetolysis proceeds by such a mechanism, it can be considered that, for acetoxy ion attack, the steric environment at C_2 is not so different from that at C_4. From the conception of "product development control",[13] moreover, a 4β-substituted product may be anticipated from the carbonium ion. However, Weiler's product was only the

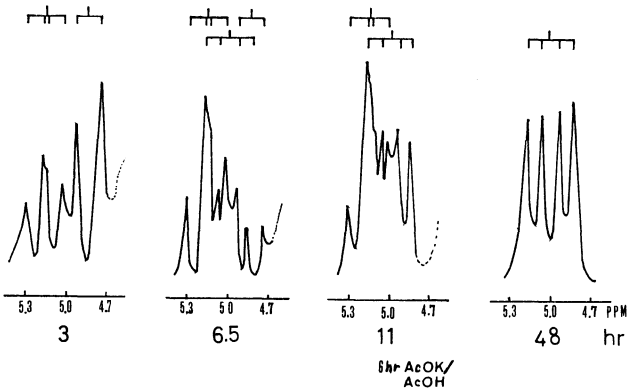

Fig. 3. 60 MHz NMR signals due to C_2H in the case of **1b**–potassium acetate–dioxane–water (100 mg/500 mg/7 ml/0.5 ml). Starting material: 4.80 ppm: α-Isomer: 5.14 ppm; β-Isomer: 5.02 ppm.

2β-acetoxy-derivative, not the 4-isomer. Therefore, we examined the acetolysis of 17β-acetoxy-4β-bromo-5β-androstan-3-one under our conditions. In both the case of reaction (a) and (b), the 2α-acetoxy-derivative (**2c**) was also formed as a primary product. In the former, however, the 2α-acetoxy-derivative was converted rapidly to the 2β-isomer (**3c**). In the latter case, it could be observed that the initial product was isomerized gradually to the 2β-isomer by the NMR spectra in each reaction step (Fig. 3).

According to these results, it is inferred that the acetolysis of 17β-acetoxy-4β-bromo-5β-androstan-3-one (**1b**) belongs to the *trans*-S_N2' reaction, and the primary product is the 2α-acetoxy-derivative (**2c**). Therefore, it does not seem reasonable that the carbonium ion pathway can be applied to the S_N2' reaction of the *trans* type. However, it seems reasonable that the acetolysis of 2α-bromo-5α-cholestan-3-one[3] proceeds by a carbonium ion pathway. To make sure that the reaction proceeded by such a pathway, the acetolysis of 2α-bromo-5α-cholestan-3-one was followed by taking NMR spectra at certain intervals. From these results, it turned out that 2α- and 4α-acetoxy-5α-cholestan-3-one in one to one proportion was already produced at an early stage. The ratio was retained during the acetolysis. The same results were also obtained in the case of 4α-bromo-5α-cholestan-3-one. Thus, it can be considered that with the 5α-series, this reaction proceeds by a carbonium ion pathway.

The *trans*-S_N2' reaction proceeded perfectly without allowing the normal substitution to take place, that is, the reaction of 4β-bromo-3-keto-5β-steroids with nucleophilic reagents gave 2-substituted 3-keto-5β-steroids only. Therefore, the acetoxy-ion present at high concentration in the reaction system is likely to attack the C_2-position directly by the S_N2' reaction mechanism. On the α-side attack at C_2, the enolization of the 3-keto group by acylolysis of **1** allows ring A to be a relatively flat with respect to ring B.[7] This conformation provides a favorable environment for nucleophile to attack at C_2. Furthermore, α-attack occurs more readily than β-attack at this position, because of the steric effect of the 10-methyl group. The 2α-acyloxy-derivative (**2**) was, therefore, formed as the product of the *trans*-S_N2' reaction and then was isomerized to the more stable 2β-isomer. Whether the nucleophile enters *trans* or *cis* to the leaving group depends on the stereochemistry of the reactant.

On the basis of these results, we conclude that in the S_N2' reaction of the α-halogeno-ketone, the entering group is not always *cis* to the leaving group.

Experimental

Thin-layer chromatography was carried out on Wakogel B-5 (Wako Pure Chemical Industries Ltd.), and detected by sulfuric acid. IR spectra were measured (KBr) with a Hitachi model 215 infrared spectrophotometer. ORD spectra were obtained in dioxane with JASCO model ORD/UV-5 instrument. NMR spectra were recorded in carbon tetrachloride with tetramethylsilane as an internal standard using a Hitachi-Perkin Elmer R-20A and Varian HR-220 instruments.

Acetoxylation of 5β-Cholestan-3-one. The synthesis was carried out following the procedure of Henbest *et al.*[14] for the synthesis of 2α-acetoxy-5α-cholestan-3-one from 5α-cholestan-3-one. A solution of 5β-cholestan-3-one (5 g) and lead tetraacetate (6.4 g) in benzene (150 ml) containing boron trifluoride–ether complex (1 ml) was stirred at room temperature in a nitrogen atmosphere for 4 hr. The reaction mixture was washed with water, dried and evaporated. The resultant oily product was chromatographed on silica gel and elution with benzene–light petroleum (2: 3) gave 4β-acetoxy-5β-cholestan-3-one (**4b**) (1.7 g), which crystallized from ethanol as needles, mp 104—106 °C, IR: ν_{max} 1745, 1725, and 1225 cm^{-1}; ORD (*c* 0.4, dioxane) at 21 °C: $[\alpha]_{389}$ +67.5°, $[\alpha]_{321}$ +247.5°, $[\alpha]_{306}$ +170°, $[\alpha]_{301}$ +185°, $[\alpha]_{299}$ +170°, and $[\alpha]_{280}$ +450; NMR: 5.33 ppm (d, J=12 Hz, 1H); Found: C, 78.27; H, 10.92, $C_{29}H_{48}O_3$ requires C, 78.37; H, 10.88%.

Reaction of 4β-Acetoxy-5β-cholestan-3-one (4b) with Potassium Acetate–Acetic Acid. A mixture of **4b** (22 mg), potassium acetate (20 mg) and acetic acid (2 ml) was refluxed for 6 hr. After the usual work-up, the starting material was recovered from the reaction mixture.

3β,4β-Oxido-3α-acetoxy-5β-cholestane. The synthesis was carried out following the procedure of Williamson and Johnson.[15] A solution of 3-acetoxy-5β-cholest-3-ene (4.5 g) in dichloromethane (70 ml) was treated with *m*-chloroperbenzoic acid (3.0 g) at room temperature for 24 hr. The reaction mixture was poured into water and the dichloromethane layer was worked up in the usual manner. Crystallization of the resulting oil from acetone gave 3β,4β-oxido-3α-acetoxy-5β-cholestane (844 mg), mp 135—138 °C, IR cm^{-1}: ν_{max} 1745, 1225, and 1052; NMR: 2.86 ppm (s, 1H); Found: C, 78.33; H, 10.88, $C_{29}H_{48}O_3$ requires C, 78.26; H, 10.97%.

4α-Acetoxy-5β-cholestan-3-one (4a). A sample of 3β,4β-oxido-3α-acetoxy-5β-cholestane (636 mg), mp 135—138 °C, was placed in a 20 ml Erlenmeyer flask which was immersed for 5 min in an oil bath maintained at 160 °C. The resulting oil which failed to crystallize; IR: ν_{max} 1750, 1727, and 1235 cm^{-1}; NMR: 5.25 ppm (d, J=8.6 Hz, 1H). The synthesis was carried out following the procedure of Williamson and Johnson.[15]

Reaction of 4α-Acetoxy-5β-cholestan-3-one (4a) with Potassium Acetate–Acetic Acid. A mixture of (**4a**, oil) (22 mg), potassium acetate (20 mg) and acetic acid (2 ml) was refluxed for 6 hr. The NMR indicated that 4α-acetoxyderivative completely isomerized to the corresponding 4β-acetoxy-derivative (**4b**).

Acetolysis of 1a with Tetramethylammonium Acetate in Dioxane. A mixture consisting of **1a** (50 mg), tetramethylammonium acetate (210 mg) and dioxane (2.5 ml) was stirred at room temperature. After 5 days, the reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water, dried and evaporated. Crystallization of the residue from ethanol gave (**2a**) (23 mg) as needles, mp 138—139 °C. The product was identical in infrared spectrum with authentic 2α-acetoxy-5β-cholestan-3-one.[2]

2β-Trimethylacetoxy-5β-cholestan-3-one (3b). A solution of **1a** (100 mg) in dioxane (5 ml) was stirred with pivalic acid (521 mg), potassium hydroxide (286 mg), and water (1 ml) at refluxing temperature. After 18 hr, the reaction mixture was poured into water, and extracted with ether. After the usual work up, crystallization from ethanol afforded needles (258 mg), mp 125—126 °C, IR: ν_{max} 1746, 1728, and 1158 cm^{-1}; ORD (*c* 0.96, dioxane) at 25 °C: $[\alpha]_{330}$ −31.3°, $[\alpha]_{310}$ −146°, $[\alpha]_{275}$ +407°; NMR: 5.04 ppm (q, J=6.0 and 13.5 Hz, 1H); Found: C, 79.19; H, 11.23, $C_{32}H_{54}O_3$ requires C, 78.96; H, 11.18%.

Followings of the Progress in Acylolysis of 1a. Each

amount (100 mg) of 4β-bromo-5β-cholestan-3-one (**1a**) was treated with (a) potassium acetate–acetic acid (500 mg/6 ml), (b) potassium acetate–dioxane–water (500 mg/7 ml/0.5 ml), (c) triethyl amine–acetic acid (3 ml/7 ml), (d) pivalic acid–potassium hydroxide–dioxane–water (521 mg/286 mg/5 ml/1 ml) at 90—95 °C, and (e) tetramethylammonium acetate–dioxane (420 mg/5 ml) at room temperature. Each reaction was stopped at certain time intervals. After the usual work up, the progress of the reaction was followed by tlc and by using NMR spectrometer. R_f values of the starting material (**1a**) and the resultant α-acyloxy-ketones in benzene–ether system (19: 1) are as follows; 4β-bromo- (**1a**): 0.77, 2α-acetoxy- (**2a**): 0.46, 2β-acetoxy- (**3a**): 0.61, 2α-pivaloxy- (**2b**): 0.45, and 2β-pivaloyloxy-5β-cholestan-3-one (**3b**): 0.64. The NMR spectra of method (b), as an example for the acetolysis, and method (d) are shown in Figs. 3 and 2, respectively.

Epimerization of 2α-Acetoxy-5β-cholestan-3-one. (i) A solution of **2a** (50 mg) in acetic acid (2 ml) was refluxed with potassium acetate (35 mg) for 3 hr. The tlc indicated that the 2α-acetoxy-derivative (**2a**) completely epimerized to the corresponding 2β-acetoxy-isomer (**3a**). (ii) Instead of using acetic acid as a solvent, dioxane was used. The epimerization was completed in 6 hr refluxing conditions.

*Acetolysis of 17β-Acetoxy-4β-bromo-5β-androstan-3-one (**1b**).* This method was identical with reaction (b), described above. 2α,17β-Diacetoxy- and 2β,17β-diacetoxy-5β-androstan-3-one formed could not be identified on the tlc. The NMR spectra of the reaction mixture at certain time intervals are shown in Fig. 3.

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