ON STEROIDS. CLV.*

REACTIONS OF STEROIDAL β-OXO CYCLOPROPANES WITH JACQUES' REAGENT

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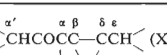
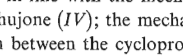
Bromination of ketones of the type  (X = H) was investigated.

If initial bromination is directed into the α-position (X = Br), the bromide anion is split off and the cyclopropane ring opens to form an α,β-unsaturated keto system. The nature of the product depends on the fate of the reaction center at the δ-position: elimination of the (γ- or ε-) proton may lead to a (γ,δ- or δ,ε) double bond formation, or a substitution process may result in a δ-bromo substituted derivative.

In our preceding paper[1] we demonstrated that treatment of 4α,5-cyclo-A-homo-5α-cholestan-2-one (*I*) with phenyltrimethylammonium perbromide (Jacques'reagent)[2-4] leads to opening of the cyclopropane ring and formation of the keto derivatives *II* and *III*. This result is in linè with the mechanism postulated by King and deMayo[5] for bromination of thujone (*IV*); the mechanism assumes initial bromination into the activated position between the cyclopropane ring and the keto group. The unstable (and not isolated) intermediary bromo derivative splits off one molecule of hydrogen bromide. This reaction course is indicated for the compound *I* in the reaction scheme (*I* → *II*, *III*).

It seemed of interest whether or not such a reaction pathway is of general validity for structures of the type



Therefore, we investigated the action of Jacques' reagent upon several steroidal models of this structural type; the formulae of the compounds examined are *X*, *XV*,

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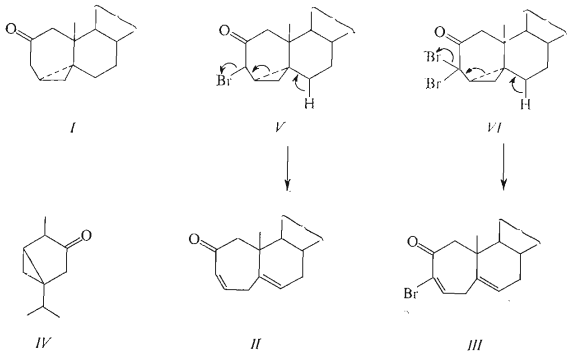
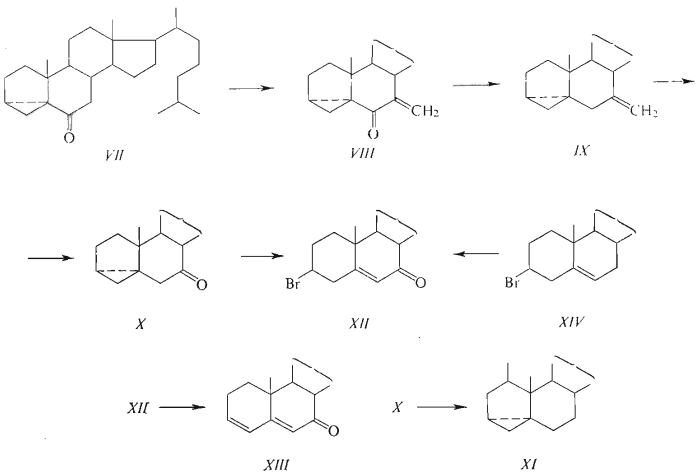
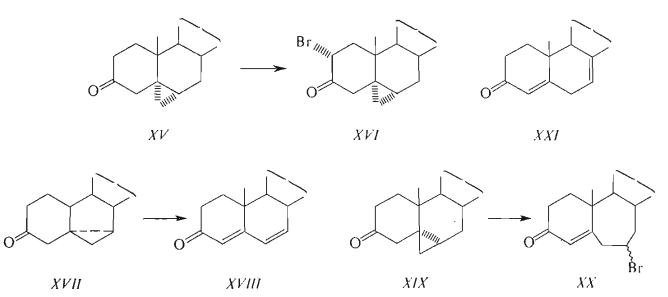


XVII and *XIX*. The first of these, the ketone *X*, was prepared from 3α,5-cyclo-5α-cholestan-6-one[6] (*VII*) *via* the methylene derivatives *VIII* and *IX*. The method used was identical with that applied previously for preparation of the corresponding androstane compounds[7]. The methylene derivative *VIII*, purified by chromato-



graphy, could not be obtained in crystalline condition and was used directly for the next step. Following the procedure of Burn and coworkers[7], the deoxo derivative *IX* was obtained by lithium aluminum hydride–aluminum chloride reduction. The crude reaction product was subjected to ozonolysis giving thus the required 7-ketone *X*. The structure of the latter compound follows from its IR-spectrum which discloses the presence of one cyclopropane ring and one keto group in a six-membered ring. Additional confirmation of the structure follows from the Huang-Minlon reduction of *X* yielding the known[8] 3α,5-cyclo-5α-cholestane (*XI*). Treatment of the ketone *X* with Jacques' reagent gave a complex reaction mixture from which an α,β-unsaturated ketone, containing one bromine atom, could be isolated. The structure *XII* for this compound was proved by two routes: first, by dehydrobromination with collidine leading to 3,5-cholestadien-7-one[9] (*XIII*). The second proof was presented by preparing the substance *XII* from 3β-bromo-5-cholestene[10] (*XIV*) by allylic oxidation with tert-butyl chromate. Thus, the compound *X* reacts analogously to the ketone *I* with the important difference that the ketone *XII* is a product of substitution arising from an attack by the bromide anion at the terminal position of the cyclopropane ring (type *c* $E \rightarrow F$).

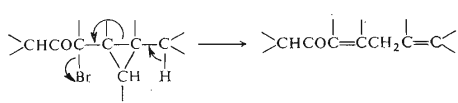
Opening of the cyclopropane ring resulting in the formation of an α,β-unsaturated ketone is also the characteristic reaction of a further model substance[11], *XVII*, furnishing the known[12] 4,6-cholestadien-3-one (*XVIII*). Formation of this substance is closely analogous to the reaction $I \rightarrow II$ and *III* differing in the degree of conjugation (linearly conjugated dienone *XVIII* versus α,β-unsaturated ketone *II* with the second double bond isolated). This difference appears to be related to different stabilities of the B-ring double bonds in *II* (or *III*) and *XVII*, respectively. Thus, it is known that some 4a,5-unsaturated A-homosteroids show lesser stability than their 5,6-unsaturated isomers[13,14]. On the other hand, the 4,6-dien-3-one constitutes the more stable structure than the 4,7-dien-3-one in the normal series. Reflection of this situation in the corresponding transition states may be responsible for the preferred



XV *XVI* *XXI*

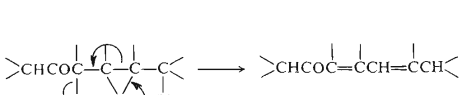
XVII *XVIII* *XIX* *XX*

a)



A B

b)



C D

c)

E F

formation of the respective dienone types. An alternative pathway for the formation of *XVIII* may be considered, *i.e.* initial formation of the dienone *XXI* followed by the shift of the 7,8-double bond into conjugation. This pathway appears to be unlikely since we found that the compound *XXI* was only slowly converted into *XVIII* on treatment with hydrogen bromide in tetrahydrofuran at a concentration corresponding to that present in the reaction medium.

When the compound[15] *XIX* was subjected to treatment with Jacques' reagent, the major component of the reaction mixture was isolated chromatographically but all attempts at obtaining it in crystalline condition failed. However, even in this case, the spectral and analytical data indicate a reaction course similar to that in the above cases (absence of the cyclopropane ring, presence of approximately one bromine atom) and suggest the presence of the compound *XX* in the reaction mixture.

An interesting behavior was observed with the ketone *XV*. In contrast to the foregoing examples, application of the Jacques'reagent converts *XV* into the 2-bromo ketone *XVI* without any change in the skeletal structure. The structure *XVI* is in agreement with the spectral data proving the equatorial conformation of the bromine atom (IR, UV); localization of the halogen in position 2 follows from NMR data, in particular from the characteristic quartet (δ 4·86) for the $C_{(2)}$-proton; besides, the spectrum also confirms the equatorial conformation of the bromine

atom ($J_{2\beta,1\alpha} = 11{\cdot}8$ Hz; $J_{2\beta,1\beta} = 6{\cdot}6$ Hz). The structure *XVI* was further confirmed by chemical transformations[16].

In the reactions resulting in the opening of the cyclopropane ring, the reaction products were isolated in relatively low yields. This is obviously due to the formation of strongly polar compounds which was observed in all cases investigated.

At this point mention should also be made of the possibility of a homolytic mechanism. This mechanism of Jacques' bromination has already been ruled out by Jacques' experiments[4]; however, we considered it desirable to present evidence in favor of an ionic mechanism for the type of bromination reactions studied in this paper: thus, the bromination of the ketone *I* in tetrahydrofuran, containing peroxides, was analyzed by thin-layer chromatography and compared with the reaction mixture obtained in peroxide-free tetrahydrofuran in the presence of hydroquinone. Both chromatograms were indistinguishable showing identical spots of the same intensity; this renders the homolytic pathway unlikely.

The above results permit the postulation of the following mechanistic views:

1. The reaction course is primarily controlled by the direction of enolization of the starting ketone under given conditions. If the enolization directs the bromine atom into the α′-position (and no shift of the bromine atom from the α′-into the α-position follows) no skeletal changes occur (*cf.* $XV \rightarrow XVI$).

2. If the direction of enolization forces the bromine atom to enter into the α-position, the unstable α-bromo ketone decomposes with opening of the cyclopropane ring and formation of an α,β-unsaturated ketonic moiety, the nature of the product being thereby determined by the fate of the terminal reaction center at the δ-position: *a*) splitting off of one proton from ε-carbon results in the formation of a diene with isolated double bonds ($A \rightarrow B$; *cf.* $I \rightarrow II$), or *b*) splitting off of one proton from the cyclopropane ring (γ-position) leads to a linearly conjugated dienone ($C \rightarrow D$; *cf.* $XVII \rightarrow XVIII$), or *c*) substitution with the bromide anion in the δ-position gives rise to a δ-bromo derivative ($E \rightarrow F$; *cf.* $X \rightarrow XII$). Which of the alternatives *a*, *b* or *c* is preferred in any particular case depends obviously on more subtle structural factors that have not been investigated in this paper.

EXPERIMENTAL

Melting points are determined on a Kofler block and are uncorrected. Unless stated otherwise, optical rotations are measured in chloroform. The infrared spectra were measured on a Zeiss UR 10 spectrophotometer, ultraviolet spectra on a CF 4 (Optica, Milano) spectrophotometer and ORD measurements on a Jasco Model ORD/UV-5 spectropolarimeter. Unless stated otherwise, the NMR-spectra were measured on a Varian-Ha-100 instrument in deuteriochloroform using tetramethylsilane as an internal reference. Chemical shifts are expressed in δ-scale with an accuracy of 0·01 p.p.m. Multiplicity of signals is recorded by the following symbols: s singlet, d doublet, dd doublet of doublets, t triplet, m multiplet, b broad, *W* width of a multiplet, $W_{1/2}$ half-width of a signal. The statement "worked up as usual" means: the solution was washed with water, 5% HCl, water, 5% $KHCO_3$ water, dried with magnesium sulfate and the solvent evaporated at 20—25°C *in vacuo*.

3α,5-Cyclo-5α-cholestan-7-one (*X*)

A mixture of the ketone *VII* (10 g), dimethylamine hydrochloride (4·8 g) and paraformaldehyde (1·8 g) was refluxed in dioxane (140 ml) for 4 h, then poured in water, extracted with ether and

worked up as usual. The oily residue was purified by chromatography on silica gel (200 g) using a petroleum ether–ether mixture (97 : 3) as eluant. Attempts at crystallization of the purified fraction (9 g) from acetone, methanol and diisopropyl ether were unsuccessful. IR-spectrum (tetrachloromethane): 1677, 1603 cm^{-1}. UV-spectrum (ethanol): λ_{max} 233 nm. The product was dissolved in ether (450 ml) and added while stirring in the course of 10 minutes to a solution of aluminum chloride (11 g) and lithium aluminum hydride (2 g) in ether (220 ml). The solution was then heated at reflux temperature for two hours, then poured upon ice–2% HCl, taken up in ether and worked up as usual. The non-polar product thus formed was separated by chromatography on silica gel (200 g) in light petroleum; it amounted to 5·4 g. This non-polar fraction (mainly *IX*) was dissolved in dichloromethane (200 ml), pyridine (3 ml) was added and a stream of ozonized oxygen passed through the solution at −70°C until a strong KI–starch reaction. The solution was then filtered through a small layer of neutral aluminum oxide (grade III). Chromatography on silica gel (150 g) in light petroleum separated non-polar components (387 mg); subsequent elution with light petroleum–ether (97 : 3) yielded the main component (2·5 g) which crystallized from acetone to give the product (2·16 g), m.p. 86–88°C. The analytical sample was obtained from acetone, m.p. 89–90°C, $[\alpha]_D$ +3° (*c* 1·21), mixed m.p. with *VII* 86–89°C, IR-spectrum (tetrachloromethane): 1717, 1430, 3060, 3020 cm^{-1}; the spectrum is not identical with that of *VII*. For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·45% C, 11·49% H.

3α,5-Cyclo-5α-cholestane (*XI*)

The ketone *X* (200 mg) was heated at 140°C with 99% hydrazine hydrate (2 ml), NaOH (400 mg) in triethylene glycol (15 ml) for 30 min. The condenser was then removed until the temperature reached 200°C and the mixture maintained under reflux for 3 h. It was then cooled, poured upon ice–water, extracted with light petroleum, passed through a small layer of silica gel and worked up as usual. The crystalline residue (165 mg) was repeatedly crystallized from acetone to give the product *XI* (100 mg), m.p. and mixed m.p. 78–80°C. IR-spectrum (carbon disulphide): identical with that of the authentic sample. For $C_{27}H_{46}$ (370·6) calculated: 87·49% C, 12·51% H; found: 87·62% C, 12·57% H.

3β-Bromo-5-cholesten-7-one (*XII*)

a) The ketone *X* (400 mg) was dissolved in tetrahydrofuran (8 ml) and Jacques' reagent (630 mg) was added gradually in several portions. After 30 minutes, no starting material was present. The reaction mixture was poured in water, extracted in ether, washed with sodium hydrogen carbonate, sodium sulfite, sodium hydrogen carbonate and water. After being dried with magnesium sulfate, the solvent was removed under reduced pressure at room temperature and the oily residue (540 mg) chromatographed on silica gel (20 g) in light petroleum–ether (97 : 3). The first fractions removed non-polar impurities (60 mg) which were followed by the more polar component (64 mg). Crystallization from light petroleum at −70°C gave the product (44 mg), m.p. 85°C, $[\alpha]_D$ −52° (*c* 1·88). IR-spectrum (tetrachloromethane): 1679, 1633, 3030 cm^{-1}. For $C_{27}H_{43}BrO$ (463·5) calculated: 69·95% C, 9·35% H, 17·24% Br; found: 70·30% C, 9·50% H, 17·51% Br.

b) To the solution of the bromo derivative *XII* (220 mg) in tetrachloromethane (1·2 ml) there was added over a period of 5 min a solution of tert-butyl chromate[17] (2 ml) with acetic acid (0·6 ml) and acetic anhydride (0·2 ml). The reaction mixture was stirred at reflux temperature for 10 h, chilled with ice and a solution of oxalic acid (0·4 g) in water (4 ml) was added dropwise over a period of one hour at 0°C, then solid oxalic acid (0·25 g) and the stirring was continued

for 2 h. The organic layer was separated, washed with water, sodium hydrogen carbonate, water, dried with magnesium sulfate and the solvent removed *in vacuo*. The residue solidified after addition of an acetone–light petroleum mixture. The crude product was dissolved in light petroleum–ether (97 : 3) and passed through a layer of silica gel; evaporation of the solvent and crystallization of the residue from petroleum ether gave the product, m.p. 85°C, undepressed on admixture with the compound obtained from *X* and identical with it by the IR-spectrum, $[\alpha]_D$ −59° (*c* 1·58). For $C_{27}H_{43}BrO$ (463·5) calculated: 69·95% C, 9·35% H, 17·24% Br; found: 69·82% C, 9·23% H, 17·55% Br.

3,5-Cholestadien-7-one (*XIII*)

The ketone *XII* (100 mg was refluxed in s-collidine for 70 min, poured upon ice-hydrochloric acid, taken up in ether and worked up as usual. The residue (87 mg) was chromatographed on silica gel (8 g) in light petroleum–benzene (1 : 1) to give 80 mg of a product which was crystallized from methanol to give the dienone *XIII*, m.p. 113—115°C undepressed on admixture with an authentic sample of *XIII* and showing an identical IR-spectrum. $[\alpha]_D$ −290°, literature[18] reports m.p. 114·5°C, $[\alpha]_D$ −305°. For $C_{27}H_{42}O$ (382·6) calculated: 84·75% C, 11·07% H; found: 84·44% C, 11·18% H.

2α-Bromo-B-homo-5,7β-cyclo-5β-cholestan-3-one (*XVI*)

The ketone *XV*[15] (200 mg) in tetrahydrofuran (4 ml) was treated with Jacques' reagent (186 mg) for 5 min. The mixture was then poured in water, taken up in ether and the solution worked up as usual. The colorless and solid residue (255 mg) was crystallized from light petroleum at −50°C to give 121 mg of the product, m.p. 122—127°C; the analytical sample was prepared by crystallization from aqueous acetone, m.p. 128—129°C, $[\alpha]_D$ +8° (*c* 1·78). IR-spectrum (tetrachloromethane): ν(CO) 1731 (as compared with ν(CO) of *XV* 1715), 1430, 3065 cm^{-1}. UV-spectrum (ethanol): λ_{max} 288 nm (as compared with λ_{max} of *XV* at 288 nm). NMR-spectrum: 1·56 (d, $C_{4\beta}$—H, $J_{4\beta,4\alpha}$ = 14·0 Hz), 1·96 (t, $C_{1\alpha}$—H, $J_{1\alpha,1\beta}$ = 12·6 Hz, $J_{1\alpha,2\beta}$ = 11·8 Hz), 2·61 (q, $C_{1\beta}$—H, $J_{1\beta,1\alpha}$ = 12·6 Hz, $J_{1\beta,2\beta}$ = 6·6 Hz), 3·12 (broad d, $C_{4\alpha}$—H, $J_{4\alpha,4\beta}$ = 14·0 Hz, $J_{4\alpha,2\beta}$ = 0, $J_{4\alpha,\text{cyclopropane}-H}$ = 0), 4·86 (q, $C_{2\beta}$—H, $J_{2\beta,1\alpha}$ = 11·8 Hz, $J_{2\beta,1\beta}$ = 6·6 Hz, $J_{2\beta,4\alpha}$ = 0). ORD (*c* 0·081, 26°C, chloroform): Φ_{270} −13750°, Φ_{275} −13050°, Φ_{300} ±0°, Φ_{313} +7350°, Φ_{375} +750°. For $C_{28}H_{47}BrO$ (477·6) calculated: 70·41% C, 9·50% 16·73% Br; found: 70·19% C, 9·56% H, 16·60% Br.

4,6-Cholestadien-3-one (*XVIII*)

The Jacques' reagent (105 mg) was added in several portions to a solution of the ketone *XVII* over a period of c. 1 min. The solution decolorized quickly, the reaction was finished after 2 min. The reaction mixture was poured in water, extracted with ether, washed with water ten times, dried with magnesium sulfate and the solvent evaporated under reduced pressure. Chromatography in light petroleum–ether (97 : 3 on silica gel separated 12 mg of the starting material (8 mg from acetone, m.p. and mixture m.p. 77—78°C) from 51 mg of the crystalline main component. Recrystallization of the latter from aqueous acetone gave pure *XVIII* (43 mg), m.p. 79·5—81°C, undepressed on admixture with the authentic sample, $[\alpha]_D$ +36° (*c* 1·3 . Literature[19] reports m.p. 79·5—81°C, $[\alpha]_D$ +35° (chloroform). IR-spectrum (tetrachloromethane) of *XVIII* is identical with that of the authentic sample. UV-spectrum (ethanol): λ_{max} 286 nm (log ε 4·36); authentic 4,6-cholestadien-3-one: λ_{max} 286 nm, (log ε 4·39 . For $C_{27}H_{42}O$ (382·6) calculated: 84·75% C, 11·07% H; found: 85·19% C, 11·23% H.

Action of Jacques'Reagent upon *XIX*

The ketone[15] *XIX* (200 mg) in tetrahydrofurane (4 ml) was treated with Jacques'reagent (190 mg) in several portions. After standing 5 min it was worked up by pouring in water, extraction in ether, washing with water, drying with magnesium sulfate and evaporating the solvent *in vacuo* at 20°C. Chromatography on silica gel (15 g) in benzene–light petroleum (1 : 1) gave an oily main component (25 mg). IR-spectrum (tetrachloromethane): 1680, 1611 cm^{-1}, no cyclopropane ring. UV-spectrum (ethanol): λ_{max} 246 nm. For $C_{28}H_{45}Br$ (477·6 calculated: 16·73% Br; found: 15·53% Br.

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