Tetrahedron Vol. 37, pp. 1015 to 1018
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0040-4020/81/051015-04$02.00/0

REACTIONS OF 5-HYDROXY-6-OXO STEROIDS—III

ACID-CATALYSED REACTIONS OF 3β-ACETOXY-5-HYDROXY-5α-CHOLESTAN-6-ONE†

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(*Received in UK 27 May 1980*)

Abstract—Aromatization of the title compound with selected acidic catalysts has been investigated. It has been established that depending upon the reaction conditions trienone 2, 1-methyltrienone 3, dienone 4, diacetoxyketone 5 or dione 6 are formed as the major products. Dienone 4 and dione 6 are the main compounds of the reactions of tosyloxyketone 10 with $KHSO_4$ and HBr_{aq}, respectively. The reaction of acetoxyketone 8 with HBr_{aq} furnishes epimeric 3-bromoketones 12 and 13 in the ratio about 1:1.

We have recently shown that 3β - acetoxy - 5α - hydroxy - 6 - oxo steroids ("difunctional" compounds) treated with hydrobromic acid or aqueous trichloroacetic acid in boiling acetic acid in the presence of oxygen led to A-aromatic-6-oxo derivatives of the type 2 and 3, while no aromatization was observed when perchloric acid was used under similar conditions.[1]

In order to shed some light on the influence of an acidic catalyst, water and solvent on the aromatization process, we examined the reactions of hydroxyketone 1 with some selected catalysts (Table 1). In general the experiments were carried out in boiling acetic acid under an argon atmosphere.

†Part of this material was presented at the Jubilee Scientific Convention of Polish Chemical Society, Wrocław, September 1979 and at the VIII Symposium on Natural Products, Prague, September 1979.

Trifluoroacetic, chloroacetic, trichloroacetic and tribromoacetic acids, however, were used without the solvent. The isolated products were identified on the basis of their PMR data and R_f values in comparison with authentic samples.[1,2]

The results summarised in Table 1 clearly show the complexity of the processes which occurred in the reactions. On the basis of the experiments it has been established that aromatization leading to trienone 2 occurs selectively with acids containing chlorine except hydrochloric and perchloric acids. The efficiency of acid decreases as follows: $CCl_3COOH > ClCH_2COOH > p$-TsCl/HOAc > CCl_3COOH/HOAc. The second aromatic product, 1-methyltrienone 3, was formed when tribromoacetic, hydrobromic or sulphuric acid was used as catalyst. However, when aromatization in anhydrous medium was not observed or this process was very slow, the formation of dienone 4 and/or diacetoxyketone 5

Table 1. Results of the reactions of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (1) with acidic catalysts (the yields in parentheses are calculated upon consumed substrate)

No	Catalyst	Time [min]	Products [%] 2	3	4	5	6	others	substrate
1	CCl_3COOH a/	5	43.4	-	-	-	-		-
2	$ClCH_2COOH$ a/	20	25.2	-	12.1	-	-		-
3	p-TsCl	120	7.5 /7.8/	-	24.7 /25.6/	25.6 /26.6/	-		3.6
4	CCl_3COOH	180	2.9 /7.0/	-	1.4 /3.4/	21.2 /51.3/	-	7, 4.5 /10.9/	58.7
5	CBr_3COOH b/	20	-	33.3	-	-	-		-
6	HBr_{aq}	20	-	14.1	3.2	-	32.4	8, 18.3	-
7	H_2SO_4	20	-	5.3	7.7	-	10.5		-
8	CBr_3COOH	60	-	-	15.9 /20.1/	25.3 /32.0/	-		20.9
9	$ZnCl_2$	120	-	-	53.8 /56.5/	10.2 /10.7/	-	9, 12.3 /12.9/	4.8
10	$BF_3.Et_2O$	20	-	-	55.8	7.8	-		-
11	p-TsOH.H_2O	20	-	-	33.1	2.7	29.0		-
12	$KHSO_4$	120	-	-	20.1 /22.5/	23.7 /26.5/	-	7, 3.2 /3.6/	10.5
13	$HClO_4$	20	-	-	2.8	-	49.8		-
14	HCl_{aq}	60	-	-	1.5	-	39.1		-
15	HBF_4 aq	60	-	-	0.9	6.6	43.1		-
16	$Ph_3C^{\oplus}BF_4^{\ominus}$	20	-	-	-	9.9 /10.3/	13.5 /14.1/		4.3
17	CF_3COOH a/	100	-	-	-	-	-		66.9
18	CF_3COOH	120	-	-	-	-	-		80.0

a/ Without HOAc as a solvent, at reflux b/ Without HOAc as a solvent, at ca. 140°

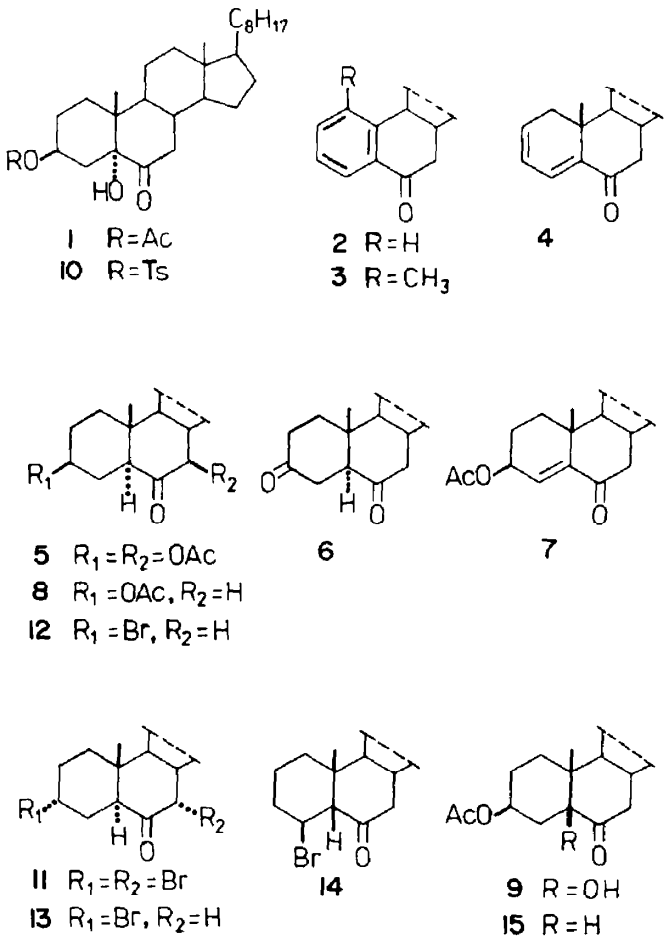

Fig. 1.

became predominant. If aqueous solutions of acids were used dione **6** was as the main product.

The anticipated acidic isomerisation[3] of hydroxyketone **1** to 5β-hydroxyketone **9** did not take place except in reaction with $ZnCl_2$. The isolated ketone **9** exhibited m.p. 143–144.5° (MeOH), $[\alpha]_D^{20} - 22°$ (reported[4] m.p. 142.5–144.5°, $[\alpha]_D - 22°$) and the PMR spectrum was almost identical with reported one.[5]

The formation of 7-acetoxy derivative **5** was explained on the basis of the literature data[6] (Fig. 2). It is fairly clear that the initially formed enol **1a** undergoes S_N2' reaction with acetic acid to give enol **5a** which in turn affords the more stable 5α-isomer of diacetoxyketone **5**. It seems possible that the reaction is catalysed by protonation of the 5α-OH group, which facilitates its leaving.

A number of pathways may be envisaged for the formation of aromatic products **2** and **3**, dienone **4** and dione **6**. On the basis of the investigation on aromatization of "trifunctional" 6-oxo steroids, Hanson proposed[7] that the 5α-OH group undergoes protonation and subsequent elimination as the last step in the formation of 1-methyl-A-aromatic compounds. This does not agree with the mechanism we propose. Protonation and elimination of the 3β-acetoxyl group prior to the OH group at C-5, seems unlikely. The presence of significant amounts of dione **6** (reactions: 15, 14, 13, 11 and 6) and enone **7** (by-product, reactions 4 and 12) strongly suggests that the first step of the process must be the simultaneous diaxial elimination of the 4β-proton and the 5α-OH group. Initiation of this step has to be induced by protonation of the substituent at C-5. This assumption is in a good agreement with the observed competitive formation of dienone **4** and diacetoxyketone **5** under the same conditions (anhydrous medium). The acetoxyenone **7** could react either via intermediate **7a** and fast isomerisation to dione **6** or by protonation and subsequent elimination of the acetoxy group to dienone **4**. It is also probable that intermediate enone **7a** could undergo protonation and elimination to dienone **4**. It seems highly possible that dienone **4** is the last intermediate in the pathway leading to aromatic products, but the expulsion or migration of the C-19 Me group depending on the used acid is not clear.

The reaction of acetoxyketone **8** with hydrobromic acid in boiling acetic acid exhibited the low reactivity of the 3β-acetoxyl group in the absence of the 5α-OH group and this is additional proof for the proposed mechanism. Bromoketone **12** and its 3α-epimer **13** were formed as the main products of this reaction. Both compounds were identified on the basis of PMR spectra and physical constants.[8,9] Moreover, bromoketone **12** and acetoxyketone **15** were isolated as the minor products. The structure of 4β-bromoketone **14** was established from its IR and PMR spectra. The C=O frequency (1707 cm^{-1}) as for ketone **15** and the chemic

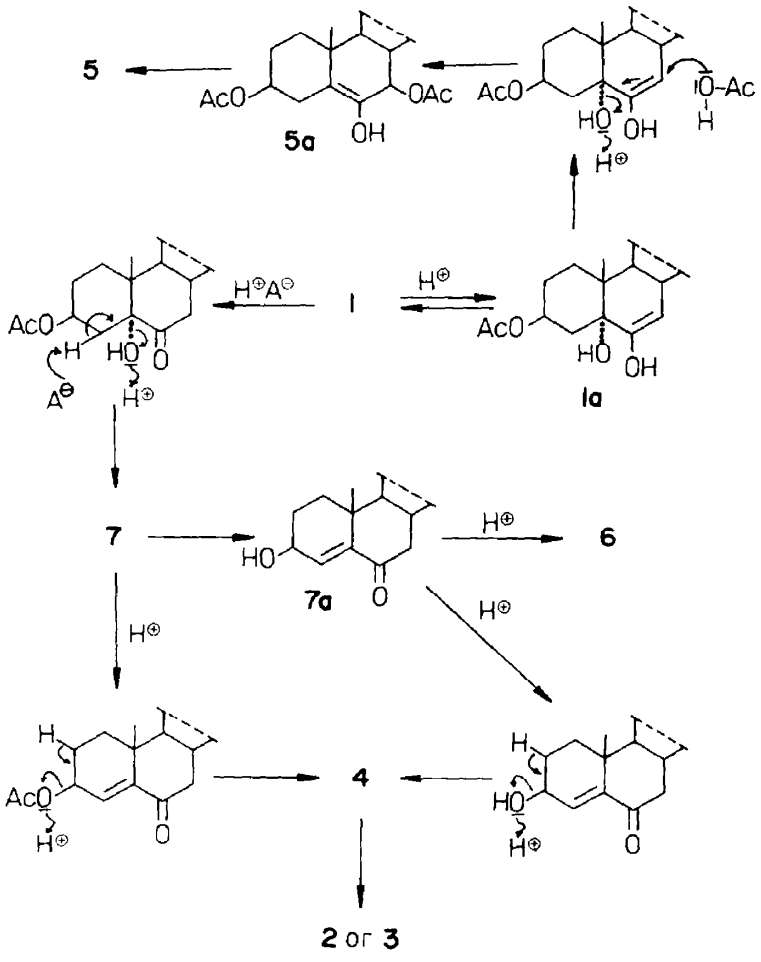

Fig. 2.

shift of the C-19 protons (δ 0.89) indicated the *cis*-fusion of A/B rings. The chemical shift of the proton linked to the C atom substituted by bromine (δ 4.18) as well as the magnitudes of the coupling constants proved its 4α-position.

Considering the known solvolytic ability of the tosyloxy group we have examined reactions of hydroxyketone **10** with hydrobromic acid and potassium hydrogen sulphate in boiling acetic acid. Dione **6**, bromoketone **12** and dibromoketone **11** were obtained as the main products of the reaction of **10** with HBr_{aq}. The structure of compound **11** was deduced from its PMR spectrum in which the characteristic signals of 3β-H and 7β-H protons at δ 4.76 and 4.18, respectively, were present. Additional proof for this structure was the signal of 5α-H proton (δ 3.89) strongly deshielded by two axial Br atoms. Traces of 1-methyltrienone **3** and dienone **4** were isolated as by-products. Dienone **4**, however, was the main product of the reaction of **10** with $KHSO_4$, whereas diacetoxyketone **5** and dione **6** were only the minor products. The above results are in good agreement with our previous conclusions and proposed mechanisms.

EXPERIMENTAL

For general experimental directions see Ref. [2]. The results of the reactions of **1** with acidic catalysts are summarised in the table.

(a) *In acetic acid.* To a soln of **1** (1.382 g, 0.003 mole) heated under reflux in AcOH (30 ml) 0.015 mole of catalyst was added rapidly and the heating was continued. After a definite time, the mixture was cooled, diluted with water and extracted twice with 100 ml portions of benzene. Usual work-up gave a crude product which was chromatographed on a silica column.

The used quantities of catalysts: *p*-TsCl 2.86 g, CCl_3COOH 2.45 g, HBr_{aq} (40%) 2.2 ml, H_2SO_4 (96%) 0.85 ml, CBr_3COOH 4.45 g, $ZnCl_2$ (anhyd) 2.04 g, $BF_3{\cdot}Et_2O$ (freshly distilled) 2.55 ml, *p*-TsOH·H_2O 2.85 g, $KHSO_4$ (anhyd) 2.04 g, $HClO_4$ (60%) 1.65 ml, HCl_{aq} (36%) 1.3 ml, $HBF_{4\,aq}$ (*d* 1.31) 3 ml, $Ph_3C^{\oplus}BF_4^{\ominus}$ 4.95 g and CF_3COOH 1.15 ml.

(b) *Without solvent.* The mixture of **1** (1.382 g) and 20 g of CCl_3COOH (or $ClCH_2COOH$ or CBr_3COOH) or 20 ml of CF_3COOH was heated as shown in Table 1. Further isolation of products as in point (a).

Reaction of 3β-acetoxy-5α-cholestan-6-one (**8**) *with hydrobromic acid*

To a soln of **8** (6.67 g) heated under reflux in AcOH (150 ml) HBr_{aq} (8.3 ml) was added and boiling was continued for 4 hr. After usual work-up and chromatography on a silica column the following compounds were obtained, in order of their elution:

(1) Compound **12** (2.488 g; 35.6%), m.p. 128.5–129° (Me_2CO); IR 1721 cm^{-1}, 718 (C-Br_{eq}) cm^{-1}; PMR δ 0.67 (18-H), 0.81 (19-H) and 3.94 (m, w/2 = 25 Hz, 3α-H); lit.[8] m.p. 123° (HOAc).

(2) Compound **13** (2.415 g; 34.6%), m.p. 176.5–178° (Me_2CO); IR 1718 cm^{-1}; PMR δ 0.67 (18-H), 0.73 (19-H), 2.83 (dd, J = 10 and 5 Hz, 5α-H) and 4.77 (m, w/2 = 9 Hz, 3β-H); lit.[9] m.p. 176° (Me_2CO).

(3) Compound **14** (0.22 g; 3.2%), m.p. 146–148° (Me_2CO); $[\alpha]_D^{20}$ −79.0° (*c* = 0.047, CH_2Cl_2); IR 1707 cm^{-1} and 721 (C-Br_{eq}) cm^{-1}; PMR δ 0.65 (18-H), 0.89 (19-H) and 4.18 (td, $J_1 = J_2 = 10$ Hz

and $J_3 = 3$ Hz, 4α-H). (Found: C, 69.61; H, 9.70. Calc. for $C_{27}H_{45}BrO$: C, 69.66; H, 9.74%).

(4) Substrate **8** (1.1 g; 16.5%).

(5) Compound **15** (0.259 g; 2.9%), identical with authentic sample.[2]

*Reaction of 3β - tosyloxy - 5 - hydroxy - 5α - cholestan - 6 - one (**10**) with hydrobromic acid*

To a soln of **10** (1.718 g) heated under reflux in AcOH (30 ml) HBr_{aq} (2.2 ml) was added rapidly and boiling was continued for 20 min. Work-up gave the crude product which was separated by column chromatography to yield:

(1) Compound **11** (0.19 g; 11.6%), m.p. 129–131° (Me_2CO); $[\alpha]_D^{20} + 31.6°$ ($c = 0.008$, CH_2Cl_2); IR 1720 cm^{-1}; PMR δ 0.69 (18-H), 0.74 (19-H), 3.89 (dd, J = 8.7 and 6.6 Hz, 5α-H), 4.18 (d, J = 1.8 Hz, 7β-H) and 4.76 (m, w/2 = 7 Hz, 3β-H). (Found: C, 59.50: H, 8.11. Calc. for $C_{27}H_{44}Br_2O$: C, 59.56; H, 8.14%).

(2) Bromoketone **12** (0.161 g; 11.5%), identical (m.p., IR, PMR) with the substance obtained in the preceding experiment.

(3) Some traces of **3**, identical (R_f, IR and PMR) with the compound previously described.[2]

(4) Compound **4** (0.028 g; 2.4%), m.p. 127–130° (EtOH), identical with authentic sample[1]

(5) Compound **6** (0.278 g; 23.1%), m.p. 171–173° (MeOH), identical with authentic sample.[2]

*Reaction of hydroxyketone **10** with potassium hydrogen sulphate*

A mixture of **10** (1.718 g) and anhyd $KHSO_4$ (2.04 g) in AcOH (30 ml) was heated under reflux for 45 min. The usual work-up yielded:

(1) Dienone **4** 0.399 g (34.8%), m.p. 128–130° (EtOH), identical (m.p., R_f, IR and PMR) with the substance obtained in the preceding experiment.

(2) Compound **5** 0.08 g (5.3%), oil, identical (R_f, IR and PMR) with an authentic sample.[1]

(3) Dione **6** 0.08 g (6.7%), m.p. 170–172° (MeOH), identical (m.p., R_f, IR and PMR) with the compound obtained in the preceding experiment.

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