A Convenient Method for the Formation of 16-Methylene-17-ketosteroids

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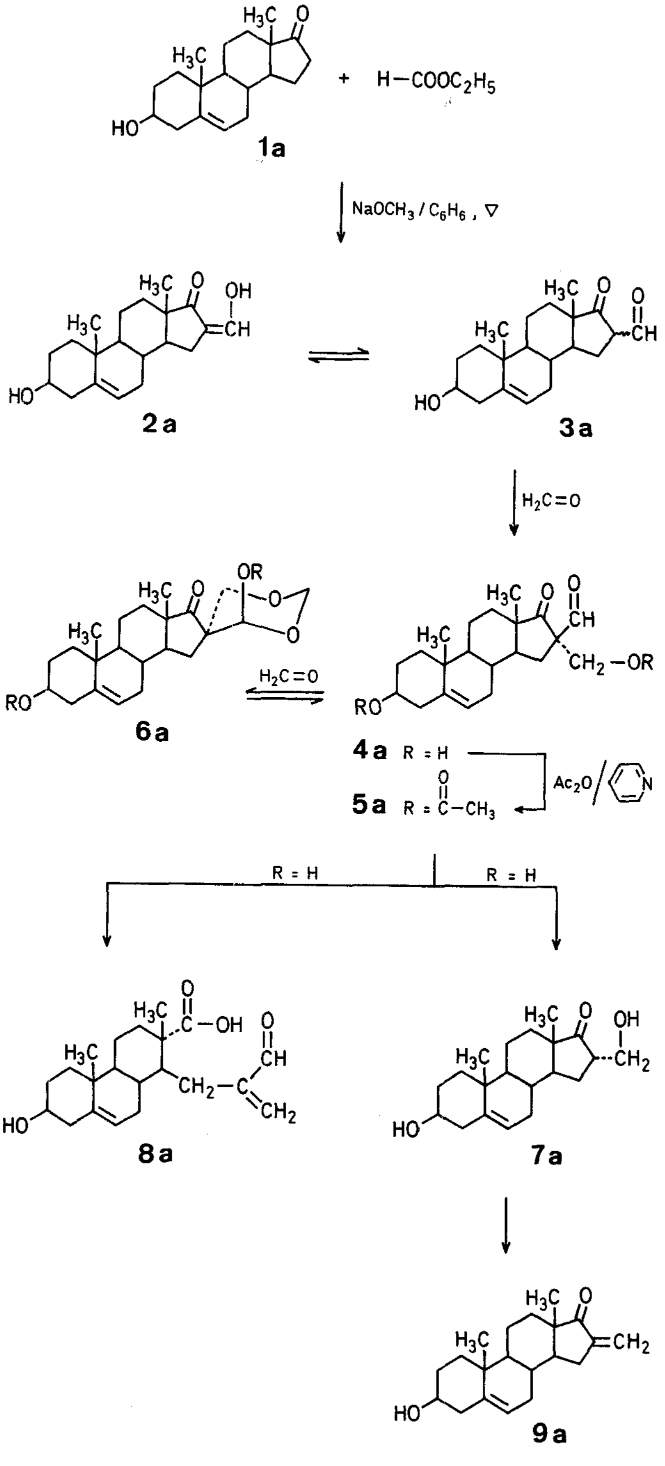
α-Methylene-ketosteroids are reactive compounds which can be prepared by several methods[1,2,3]. Recently, 16-hydroxymethylene-17-ketosteroids with various skeletons have been prepared by us in order to prepare exo-heterocyclic steroids[4]. The conversion of these compounds into the corresponding 16-methylene-17-ketosteroids has been attempted. In our method, the procedure suggested by Manson and Wood[5] was employed.

When a 16-hydroxymethylene-17-ketosteroid was mixed at room temperature with an excess of formaldehyde - either as formalin or paraformaldehyde - in solvents such as pyridine, triethylamine, acetone, or ethanol in the presence of potassium carbonate, the corresponding 16-methylene-17-ketosteroid was obtained in good yield.

The process seems formally to be a mixed Cannizzaro reaction. The hydroxymethylene group is reduced by formalin to hydroxymethyl, and the formalin itself oxidized to formic acid. This idea seems to be supported by the fact that the intermediate 16-hydroxymethyl-17-keto derivative could be isolated from the reaction mixture.

In the case of 16-hydroxymethyleneandrost-5-ene-3β-ol-17-one **(2a)**, the course of the reaction was monitored by thin layer chromatography. This procedure indicated a complicated reaction mechanism.

16-Hydroxymethyleneandrost-5-ene-3β-ol-17-one **(2a)** suspended in acetone dissolved on addition of aqueous formaldehyde. At room temperature 16α-hydroxymethyl-16β-formylandrost-5-ene-3β-ol-17-one **(4a)** separated in crystalline form. The mixture was then diluted with water and another com-



pound was isolated from the acetone solution, namely **6a** the 16-spirodioxane of **4a** formed with one mol of formaldehyde. Both compounds **4a** and **6a** decomposed in the manner characteristic for 1,3-dicarbonyl compounds in acetone solution with potassium carbonate. Cleavage occurred mainly at the C-16 formyl group and 16α-hydroxymethylandrost-5-ene-3β-ol-17-one (**7a**) was formed.

This intermediate **7a** could be isolated by chromatography. The compound is unstable in alkaline medium and eliminates water to form 16-methyleneandrost-5-ene-3β-ol-17-one (**9a**). The decomposition characteristic for 1,3-dicarbonyl compounds also took place at the C-17 keto group to a much lower extent, and yielded a seco-carbonic acid salt. The free acid **8a** could be obtained from the salt by the addition of dilute mineral acids.

The method is suitable for the conversion of 16-hydroxymethylene-17-ketosteroids **2a–f** into the corresponding 16-methylene-17-ketosteroids **9a–f** in high purities and in satisfactory yields.

Melting points were determined by using a Kofler block and are uncorrected. The specific rotation was measured with a Polamat-A polarimeter, the concentration being $c = 1$ in chloroform. The ^{1}H-N.M.R. spectra were obtained with a Jeol C-60 HL (60 MHz) instrument.

16-Hydroxymethylene-17-ketosteroids 2 from 17-Ketosteroids 1; General Procedure:

A suspension of dry sodium methoxide (10.8 g, 0.2 mol) in absolute benzene (200 ml) containing the starting 17-ketosteroid **1** (0.05 mol) is stirred and ethyl formate (122 ml, 1.5 mol) is added dropwise over a period of 2 h. The reaction mixture is subsequently stirred under reflux for 4 h (the completion of the reaction is indicated by the disappearance of the starting material), and then allowed to cool at ambient temperature. The mixture is diluted with water (1500 ml), the organic phase is separated, and the alkaline aqueous solution is neutralized with tartaric acid. The precipitate is filtered off, washed until neutral, and dried over phosphorus pentoxide in a vacuum desiccator. The product **2** can be used for the following reactions without further purification. A sample for analytical purposes is crystallized from a mixture of acetone and hexane (Table 1).

16-Methylene-17-ketosteroids 9 from 16-Hydroxymethylene-17-ketosteroids 2; General Procedures:

Method A: To a solution (in the case of **2d** and **2e**) or suspension (in the case of **2a**, **b**, **c**, and **f**) of 16-hydroxymethylene-17-ketosteroid (0.03 mol) in acetone (100 ml) or in ethanol (100 ml) formalin (10 ml; 0.12 mol formaldehyde) is added. The mixture is maintained at room temperature for 1 h. To the reaction mixture powdered sodium carbonate (10 g) is added and the mixture is vigorously stirred for 6 h. The mixture is then gradually diluted with saturated sodium chloride solution (300 ml) and extracted with dichloromethane (3 x 100 ml). The organic phase is washed neutral with water, then dried, and evaporated under vacuum. The residue is dissolved in chloroform or benzene and chromatographed over alumina with benzene/chloroform (3 : 1) (in the case of **9a**, **b**, or **c**) or with benzene (in the case of **9d**, **e**, or **f**).

Method B: To a solution of the 16-hydroxymethylene-17-ketosteroid **2** (0.03 mol) in pyridine or triethylamine (100 ml), formalin (10 ml, 0.12 mol formaldehyde) is added. After standing for 24 h, the solution is diluted with water (500 ml) and extracted with dichloromethane (3 x 100 ml). The organic phase is washed with water, then dried, and evaporated. The residue is chromatographed as in Method A (Table 2).

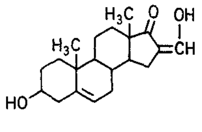
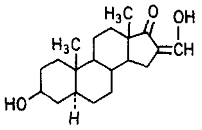
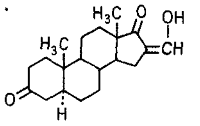
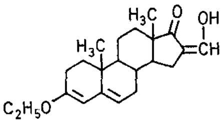
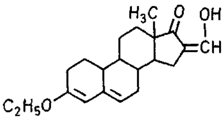
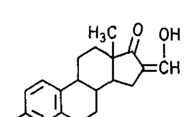
Reaction of 2a with Isolation of Intermediates:

A stirred suspension of 16-hydroxymethyleneandrost-5-ene-3β-ol-17-one (**2a**; 9.5 g, 0.03 mol) in acetone (100 ml) is treated dropwise with formalin (10 ml, 0.12 mol formaldehyde) at a rate that the temperature of the mixture is kept below 35 °C. The undissolved portion of the steroid goes into solution. After 1 h, crystals of **4a** separate from the solution; yield: 8.6 g (82%). On dilution of the mother liquor with water, a white precipitate separates, which is filtered off, and recrystallized from acetone/water to give **6a**; yield: 1.8 g (16%).

The two products **4a** and **6a** are suspended in acetone (100 ml) and powdered sodium carbonate (10 g) is added. The slurry is stirred at room temperature for 2 h. Carefull addition of water first dissolves the solid sodium carbonate, then precipitates the product. The white precipitate is filtered off, dissolved in chloroform, and, after drying, subjected to chromatography over alumina. Compound **7a** is eluted with benzene; yield: 1.25 g (12%). Continued elution with a mixture of benzene and chloroform (3 : 1) gives pure **9a**; yield: 6.5 g (59%). The chromatography column is washed with methanol, which elutes **8a**; yield: 1.9 g (20%).

The acetates **5a**, **6a′**, or **7a′** are prepared by treating **4a**, **6a**, or **7a** (0.001 mol) with acetic anhydride (2 ml) and pyridine (2 ml) for 24 h at room temperature. The reaction is then diluted with water. The precipitate which separates is filtered off, washed with water, dried, and recrystallized from methanol (Table 3).

Table 1. 16-Hydroxymethylene-17-ketosteroids **2a-f** prepared

Product	Yield [%]	m.p. [°C]	$[\alpha]_D$ (c 1)	Molecular Formula[a] or Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
2a 	93	236-238°	−58° (C_2H_5OH)	238-239°[6]	0.88 (s, 3 H); 1.03 (s, 3 H); 3.4 (m, 1 H); 5.25 (s, 1 H); 7.35 (m, 1 H)
2b 	96	224-226°	+12° (C_2H_5OH)	223.5-225.5°[6]	0.85 (s, 6 H); 3.4 (m, 1 H); 4.00 (s, 2 H); 7.4 (m, 1 H)
2c 	78[b]	203-205°	+53° ($CHCl_3$)	$C_{20}H_{28}O_3$ (316.4)	0.95 (s, 3 H); 1.05 (s, 3 H); 7.05 (s, 1 H)
2d 	72	142-144°	−105° ($CHCl_3$)	$C_{22}H_{30}O_3$ (342.5)	1.00 (s, 6 H); 1.30 (t, 3 H, $J=7$ Hz); 3.73 (q, 2 H, $J=7$ Hz); 5.06 (s, 1 H); 5.1 (m, 1 H); 7.05 (s, 1 H)
2e 	70	162-165°	−96° ($CHCl_3$)	$C_{21}H_{28}O_3$ (328.5)	1.00 (s, 3 H); 1.32 (t, 3 H, $J=7$ Hz); 2.20 (s, 1 H); 3.80 (q, 2 H, $J=7$ Hz); 5.25 (s, 1 H); 5.3 (m, 1 H); 7.15 (s, 1 H)
2f 	96	169-171°	+137° ($CHCl_3$)	170-172°[7]	0.98 (s, 3 H); 3.73 (s, 3 H); 7.22 (s, 1 H); 9.85 (s, 1 H)

[a] Satisfactory microanalyses obtained: C ±0.21, H ±0.09.

[b] The corresponding 3-enol ethyl ether was used as starting material (see Ref.[10]).

Table 2. 16-Methylene-17-ketosteroids **9a-f** prepared

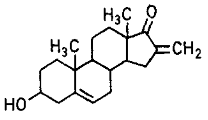
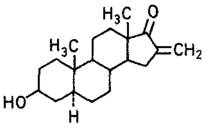
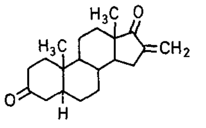
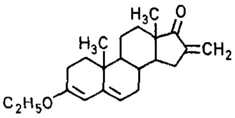
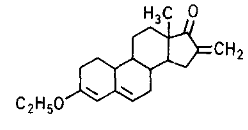
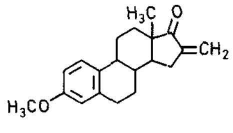
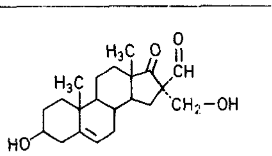
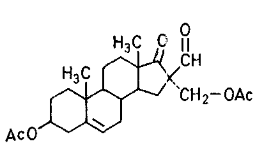
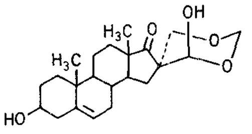
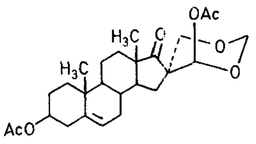
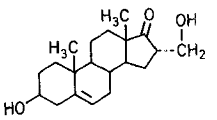
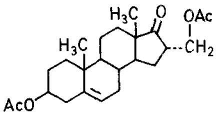
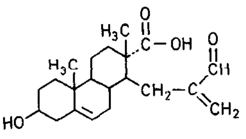
Product	Yield [%] Method		m.p. [°C]	$[\alpha]_D$ (c 1)	Molecular Formula[a] or Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
	A	B				
9a 	71	82	182-184°	−58° ($CHCl_3$)	183-184°[8]	0.94 (s, 3 H); 1.08 (s, 3 H); 1.80 (s, 1 H); 3.5 (m, 1 H); 5.3 (m, 1 H); 5.35 (m, 1 H); 6.05 (m, 1 H)
9b 	75	88	162-164°	+36° ($CHCl_3$)	$C_{20}H_{30}O_2$ (302.5)	0.85 (s, 3 H); 0.90 (s, 3 H); 1.90 (s, 1 H); 3.5 (m, 1 H); 5.35 (m, 1 H); 6.05 (m, 1 H)
9c 	68	—	166-169°	+47° ($CHCl_3$)	$C_{20}H_{28}O_2$ (300.4)	0.91 (s, 3 H); 1.06 (s, 3 H); 5.35 (m, 1 H); 6.05 (m, 1 H)
9d 	80	—	103-106°	−21° ($CHCl_3$)	$C_{22}H_{30}O_2$ (326.5)	0.95 (s, 3 H); 1.02 (s, 3 H); 1.30 (t, 3 H, $J=7$ Hz); 3.75 (q, 2 H, $J=7$ Hz); 5.10 (s, 1 H); 5.15 (s, 1 H); 5.35 (m, 1 H); 6.05 (m, 1 H)

Table 2. (Continued)

Product		Yield [%] Method A	B	m.p. [°C]	$[\alpha]_D$ (*c* 1)	Molecular Formula[a] or Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
9 e		82	—	132-134°	+37° ($CHCl_3$)	$C_{21}H_{28}O_2$ (312.5)	0.95 (s, 3H); 1.31 (t, 3H, *J*=7 Hz); 3.75 (q, 2H, *J*=7 Hz); 5.17 (s, 1H); 5.3 (m, 1H); 5.35 (m, 1H); 6.05 (m, 1H)
9 f		65	62	120-122°	+133° ($CHCl_3$)	121-123°[9]	0.94 (s, 3H); 3.70 (s, 3H); 5.36 (m, 1H); 6.05 (m, 1H)

[a] Satisfactory microanalyses obtained: C ±0.18, H ±0.15.

Table 3. Compounds Isolated from Reactions of **2a**

Product		Yield [%]	m.p. [°C]	$[\alpha]_D$ (*c* 1)	Molecular Formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4 a		82	230-235°	−20°	$C_{21}H_{30}O_4$ (346.5)	—
5 a		95	125-128°	+51°	$C_{25}H_{36}O_6$ (430.6)	0.86 (s, 3H); 1.17 (s, 3H); 2.06 (s, 6H); 4.29, 4.62 (dd, *J*=11 Hz, 2H); 9.62 (s, 1H)
6 a		16	130-132°	− 3°	$C_{22}H_{32}O_5$ (376.5)	—
6 a'		92	214-215°	+14°	$C_{26}H_{36}O_7$ (460.6)	0.91 (s, 3H); 1.08 (s, 3H); 2.06 (s, 6H); 5.89 (s, 4H); 4.85, 5.07 (dd, *J*=6.5 Hz, 2H); 3.90 (br. s, 2H)
7 a		12	192-194°	−19°	$C_{20}H_{30}O_3$ (318.5)	—
7 a'		96	144-145°	−29°	$C_{24}H_{34}O_5$ (402.5)	0.88 (s, 3H); 1.07 (s, 3H); 3.80 (d, *J*=2.5 Hz, 2H); 2.03, 2.06 (2s, 6H)
8 a		20	187-190°	−21°	$C_{21}H_{30}O_4$ (346.5)	0.96 (s, 3H); 1.16 (s, 3H); 5.90, 6.35 (2 br. s, 2H); 9.95 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.16, H ±0.14.

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