A Convenient Method for the Preparation of 16,16-Bis[hydroxymethyl]-17-hydroxy-steroids and 16,16-Bis[hydroxymethyl]-17-oxo-steroids

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Bis-hydroxymethylation of steroids at the C-16 position greatly affects their chemical and biological properties and enhances their hydrophilic character. Furthermore, it provides a possibility for the preparation of steroids containing the 16-spiro heterocycle[1].

We describe here three different methods for annexing bis-hydroxymethyl groups at C-16 starting from 16-hydroxymethylene-17-oxosteroids **(1)**, 16-methylene-17-oxosteroids **(4)**, and 17-oxosteroids **(7)**.

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In an earlier paper[2], the conversion of 16-hydroxymethylene-17-oxosteroids **(1)** into 16α-hydroxymethyl-16β-formyl-17-oxosteroids **(2)** using aqueous formaldehyde in different solvents at room temperature was already described; the products then decomposed into 16-methylene-17-oxosteroids in alkaline media. When the conversion of **1** into 16α-hydroxymethyl-16β-formyl-17-oxosteroid **(2)** is carried out in ethanol, and the product is reduced with sodium borohydride without isolation, the corresponding 16,16-bis[hydroxymethyl]-17-hydroxysteroid **(3)** is obtained (Method A).

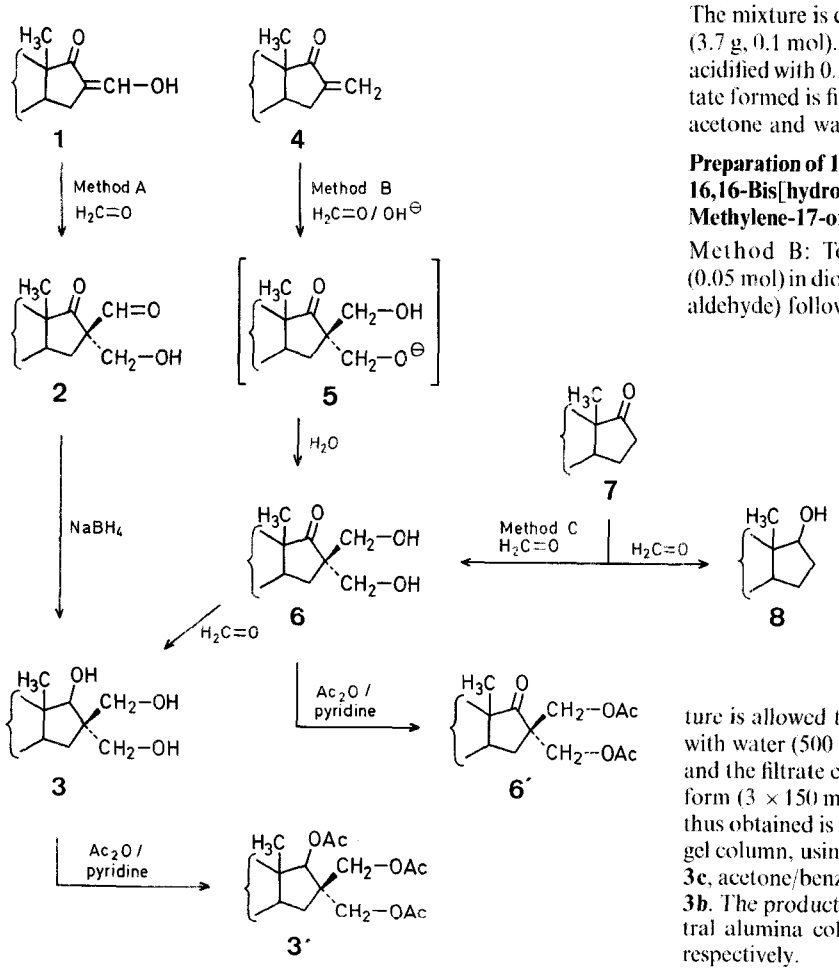
The 16-methylene-17-oxosteroids can be well used in Michael-type nucleophilic reactions. For example, 16-methyleneandrost-5-ene-3β-ol-17-one was converted to the corresponding 16-monosubstituted androst-5-ene-3β-ol-17-one[3], and also to 16α-hydroxymethyl-16β-ethoxymethyl-androst-5-ene-3β-17β-diol[4].

The 16-methylene-17-oxosteroids **(4)** were transformed into the corresponding 16,16-bis[hydroxymethyl]-17-oxosteroids **(3)** by reaction with aqueous formaldehyde in the presence of sodium carbonate at room temperature. In the course of the reaction, the intermediate **5** formed from the 16-methylene-17-oxosteroids **(4)** and formaldehyde is stabilized as the 16,16-bis[hydroxymethyl]-17-oxosteroid **(6)** in aqueous media. The conversion is completed by the formation of 16,16-bis[hydroxymethyl]-17-hydroxy-steroid **(3)**, owing to a mixed Cannizzaro reaction of the excess formaldehyde present in the reaction mixture (Method B).

Direct conversion of 17-oxosteroids **(7)** into 16,16-bis[hydroxymethyl]-17-oxosteroids was achieved by a modification of a suggested method[5]. Reaction of the 17-oxosteroid with formalin in the presence of sodium carbonate gave a 2 : 1 mixture of 16,16-bis[hydroxymethyl]-17-oxo- and -hydroxy-steroids (Method C). The formation of the 17-hydroxy derivative is again due to a mixed Cannizaro reaction caused by the excess formaldehyde present in the reaction mixture.

A disadvantage of this method is that the reduction of the starting 17-oxo-steroid **(7)** into the 17-hydroxy-steroid **(8)** also occurs. The products formed can be well separated by the chromatographic technique.

The above preparative methods for 16,16-bis[hydroxymethyl]-17-hydroxy-steroids **(3)** and 16,16-bis[hydroxymethyl]-17-oxosteroids **(6)** can generally be employed and yield the desired compounds in satisfactory yields (Table).



Melting points were measured on a Kofler block and are uncorrected. Specific rotation was measured with a POLAMAT-A polarimeter. T.L.C. were performed on Kieselgel-G (Merck) plates. The spots were detected by spraying with 50% aqueous phosphoric acid and subsequent heating at 100–120°C for 15 min. The R_f values were measured on the basis of the spots observed on illumination with UV light of a wavenumber of 365 nm. Neutral alumina with activity III–IV were used for column chromatography (50 g, 25 × 2 cm). Low pressure chromatography (0.2 atm) was done on Kieselgel-G (Merck) columns (30 g, 20 × 2.5 cm). The ^{1}H-N.M.R. spectra were recorded on a Jeol C-60 HL spectrometer (60 MHz).

Preparation of 16,16-Bis[hydroxymethyl]-17β-hydroxy-steroids (3a–e) from 16-Hydroxymethylene-17-oxosteroids (1a–e); General Procedure:

Method A: To a solution of the 16-hydroxymethylene-17-oxosteroid **1** (0.03 mol) in ethanol (100 ml) is added formalin (10 ml, 0.12 mol formaldehyde). The mixture is allowed to stand at room temperature for 2 h, during which time a clear solution is formed. The mixture is cooled to 0°C and treated with sodium borohydride (3.7 g, 0.1 mol). After 2 h the mixture is diluted with water (500 ml), acidified with 0.5 normal dilute sulfuric acid (100 ml) and the precipitate formed is filtered. The product is crystallized from a mixture of acetone and water.

Preparation of 16,16-Bis[hydroxymethyl]-17-oxosteroids (6a–e) and 16,16-Bis[hydroxymethyl]-17β-hydroxy-steroids (3a–e) from 16-Methylene-17-oxosteroids (4a–e); General Procedure:

Method B: To a solution of the 16-methylene-17-oxosteroid **4** (0.05 mol) in dioxan (40 ml) is added formalin (10 ml, 0.12 mol formaldehyde) followed by sodium carbonate (1 g, 0.01 mol). The mixture is allowed to stand at room temperature for 48 h, and diluted with water (500 ml). The crystalline product separated is filtered off and the filtrate containing the oily product is extracted with chloroform (3 × 150 ml) and the solvent is removed. The product mixture thus obtained is subjected to chromatographic separation on a silica gel column, using acetone/benzene (10 : 90) and (20 : 80) for **6c** and **3c**, acetone/benzene (20 : 80) for **6a** and **3a**, and acetone for **6b** and **3b**. The product mixtures **6d**/**3d** and **6e**/**3e** are separated on a neutral alumina column using chloroform/benzene (1 : 1) and (3 : 1), respectively.

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Table. 16,16-Bis[hydroxymethyl]-steroids **3** and **6** (R = H) and their Acetates **3'** and **6'** (R = Ac) prepared

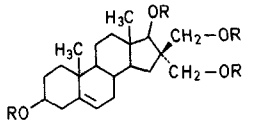
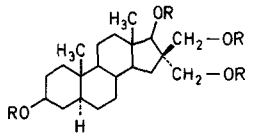
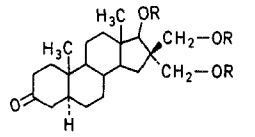
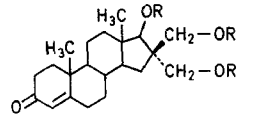
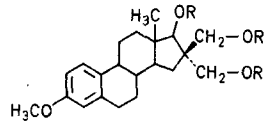
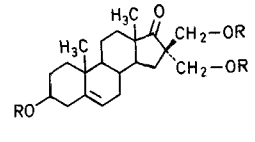
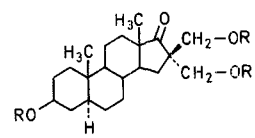
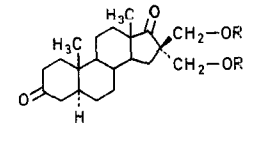
Product		Method	Yield [%]	R_f	m.p. [°C]	$[\alpha]_D$ (*c* 1, $CHCl_3$)	Molecular Formula or Lit. Data	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
	**3a**	A	85	0.10[c]	282–287°	−71°[6]	256–258°[4]	–
		B	12					
		C	15					
	3a'	–	96	0.80[d]	170–172°	−61°	$C_{29}H_{42}O_8$ (518.7)	0.90 (s, 3H); 1.05 (s, 3H); 2.03 (s, 12H); 4.00 (s, 2H); 3.9, 4.2 (dd each 2H, J = 12 Hz, J = 3 Hz, 6.5 Hz); 4.5 (m, 1H); 4.7 (s, 1H); 5.35 (m, 1H)
	**3b**	A	92	0.15[c]	285–290°	−10°[b]	$C_{21}H_{36}O_4$ (352.5)	–
		B	10					
		C	12					
	3b'	–	98	0.70[d]	113–116°	−22°	$C_{29}H_{44}O_8$ (520.7)	0.85 (s, 3H); 0.86 (s, 3H); 2.05, 2.07 (2s, 6H each); 4.00 (s, 2H); 3.9, 4.2 (dd each, 2H, J = 12 Hz, J = 3 Hz, 6 Hz); 4.68 (s, 1H)
	**3c**	A	78[e]	0.25[c]	222–226°	+ 9°	$C_{21}H_{34}O_4$ (350.5)	–
		B	10[e]					
		C	14[e]					
	3c'	–	96	0.50[d]	151–155°	– 2°	$C_{27}H_{40}O_7$ (476.6)	0.90 (s, 3H); 1.04 (s, 3H); 2.01, 2.03, 2.05 (3s, 3H each); 4.00 (s, 2H); 3.90, 4.25 (dd each, 2H, J = 12 Hz, J = 2.5 Hz, 7 Hz); 4.7 (s, 1H)
	**3d**	A	65[e]	0.25[c]	192–198°	+54°	$C_{21}H_{32}O_4$ (348.5)	–
		B	16[e]					
		C	10[e]					
	3d'	–	90	0.40[d]	132–135°	+41°	$C_{27}H_{38}O_7$ (474.6)	0.91 (s, 3H); 1.18 (s, 3H); 2.00, 2.02, 2.05 (3s, 3H each); 4.70 (s, 1H); 5.70 (s, 1H); 4.00 (s, 2H); 3.90, 4.20 (dd each, 2H, J = 12 Hz, J = 2 Hz, 6.5 Hz)
	**3e**	A	95	0.30[c]	164–167°	+56°	106–106.5°[6]	–
		B	14					
		C	18					
	3e'	–	95	0.90[d]	76–82°	+26°	$C_{27}H_{36}O_7$ (472.6)	0.90 (s, 3H); 2.01, 2.06 (2s, 3H each); 3.66 (s, 3H); 4.75 (s, 1H); 4.05 (s, 2H); 3.95, 4.20 (dd each, 2H, J = 12 Hz, J = 2 Hz, 6 Hz); 4.75 (s, 1H)
	**6a**	B	60	0.20[c]	202–205°	+14°	$C_{21}H_{32}O_4$ (348.5)	
		C	32					
	6a'	–	92	0.85[d]	130–134°	+ 3°	$C_{27}H_{38}O_7$ (474.6)	0.98 (s, 3H); 1.06 (s, 3H); 2.05, 2.07 (2s, 3H each); 4.04 (s, 2H); 4.12 (s, 2H); 4.50 (m, 1H); 5.35 (m, 1H)
	**6b**	E	65	0.25[c]	223–225°	+83°	$C_{21}H_{34}O_4$ (350.5)	–
		C	30					
	6b'	–	96	0.75[d]	148–151°	+49°	$C_{27}H_{40}O_7$ (476.6)	0.85 (s, 3H); 0.95 (s, 3H); 2.00, 2.02, 2.04 (3s, 3H each); 4.02 (s, 2H); 4.11 (s, 2H)
	**6c**	E	64[e]	0.40[c]	204–208°	+83°	$C_{21}H_{32}O_4$ (348.5)	–
		C	27[e]					
	6c'	–	92	0.55[d]	116–120°	+74°	$C_{25}H_{36}O_6$ (432.6)	1.00 (s, 3H); 1.07 (s, 3H); 2.06 (s, 6H); 4.05 (s, 2H)

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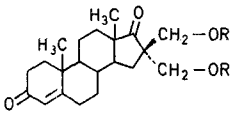
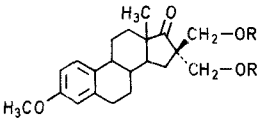
Table. (continued)

Product		Method	Yield [%]	R_f	m.p. [°C]	$[\alpha]_D$ (c1, $CHCl_3$)	Molecular Formula or Lit. Data	^{1}H-N.M.R. ($CDCl_3$/TMS) δ[ppm]
	**6d**	B	28[e]	0.4[c]	220–225°	+69°	$C_{21}H_{30}O_4$ (346.5)	–
		C	25[e]					
	6d′	–	90	0.45[d]	94–97°	+64	$C_{25}H_{34}O_6$ (430.6)	1.00 (s, 3H); 1.21 (s, 3H); 2.04 (s, 6H); 4.03 (s, 2H); 4.12 (s, 2H); 5.70 (s, 1H)
	**6e**	B	52	0.40[c]	179–182°	+136°	148–151°[6]	–
		C	34					
	6e′	–	92	0.95[d]	84–87°	+116°	$C_{25}H_{32}O_6$ (428.5)	1.00 (s, 3H); 2.05 (s, 6H); 3.72 (s, 3H); 4.06 (s, 2H); 4.15 (s, 2H)

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.28.
[b] Measured in pyridine.
[c] Eluent: acetone/benzene/petroleum ether (30 : 35 : 35).
[d] Eluent: methanol/benzene (2 : 98).
[e] The corresponding 3-ethyl enol ether was used as starting material (see Ref. [7]).

Preparation of 16,16-Bis[hydroxymethyl]-17-oxosteroids (6a–e) and 16,16-Bis[hydroxymethyl]-17β-hydroxy-steroids (3a–e) from 17-oxosteroids (7a–e); General Procedure:

Method C: To a solution of the 17-oxosteroid **7** (0.05 mol) in dioxan (40 ml) is added formalin (25 ml, 0.3 mol formaldehyde) followed by sodium carbonate (1 g, 0.01 mol). The mixture is allowed to stand at 45°C for 6 h, then diluted with water (500 ml) and the product mixture obtained is worked-up and separated as given in Method B.

The acetates **3a′–e′** and **6a′–e′** are prepared by treating **3a–e** and **6a–e** (1 mmol) with acetic anhydride (2 ml) and pyridine (2 ml) for 24 h at room temperature. The mixture is then diluted with water, the crystals separated are filtered off, washed with water, and recrystallized from a mixture of methanol and water (Table).

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[1] G. Schneider, I. Vincze, A. Polák, A. Vass, L. Dömök, C. Mészáros, L. Szporny, *Hungarian Patent* 171658 (1974); *C.A.* **85**, 46946 (1976).
[2] G. Schneider, I. Vincze, L. Hackler, G. Dombi, *Synthesis* **1983**, 665.
[3] K. Brückner, K. Irmscher, F. Werder, K. Bork, H. Metz, *Chem. Ber.* **94**, 2897 (1961).
[4] I. Weisz-Vincze, Ö.K.J. Kovács, A. Deák, *Eur. J. Steroids* **2**, 139 (1967).
[5] C. Mannich, K. Schulte, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **276**, 593 (1938).
[6] I. Weisz-Vincze, Ö.K.J. Kovács, L. Dömök, Á. Rauscher, *Eur. J. Steroids* **2**, 157 (1967).
[7] A. Serini, H. Köster, *Chem. Ber.* **71**, 1766 (1938).

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