STEROIDS 36: SYNTHESIS OF 16,16-DIMETHYL-17-KETOSTEROIDS AND 16,16-DIMETHYL-17β-HYDROXYSTEROIDS*

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ABSTRACT

Direct conversion of 17-ketosteroids (Ia-f) into 16,16-dimethyl-17β-hydroxysteroids (IIa-f) and 16,16-dimethyl-17-ketosteroids (IIIa-f) was achieved with methyl iodide in the presence of NaH.

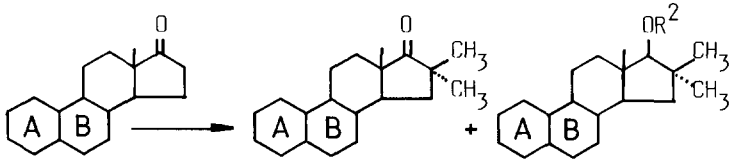
INTRODUCTION

In our previous paper we reported the conversion of 16-methylene-17-ketosteroids into the corresponding 16,16-dimethyl-17β-hydroxysteroids. This synthesis was extended to all 16-methylene-17-ketosteroids, where the reductive conversion leaves the other parts of the molecule unchanged (1). Although several patents describe other methods for the methylation of steroids at C-16, unfortunately, most of them do not contain physical data (2,3,4). For the purpose of comparative pharmacological examinations, the synthesis of 16,16-dimethyl-17-keto- and 16,16-dimethyl-17β-hydroxysteroids from 17-ketosteroids with dif-

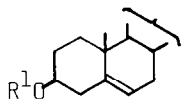
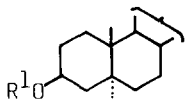
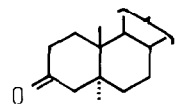
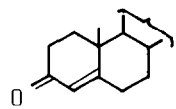
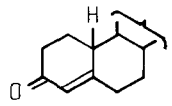
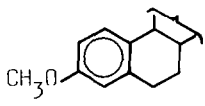
ferent fundamental skeletal structures was developed.

The 17-ketosteroids were allowed to react an excess of methyl iodide in the presence of NaH in tetrahydrofuran. The reaction was monitored by TLC. The 17-ketosteroids were quantitatively converted into a mixture (1:3) of the 16,16-dimethyl-17-ketosteroids and the 16,16-dimethyl-17β-hydroxysteroids. These could easily be separated on an Al_2O_3 column. According to our observations, when the excess NaH was decomposed with ethyl acetate instead of alcohol, a reacetylation reaction resulted in 16,16-dimethyl-17β-acetoxysteroids (Scheme).

The 17-ketosteroids containing a free hydroxyl group at C-3 were protected with tetrahydropyranyl ether, while an enol ether or dimethyl ketal form was employed for the protection of 3-ketosteroids. In the presence of a free hydroxyl or acetoxy group, the 3β-methoxy derivative of the 16,16-dimethylsteroid was formed. A similar ether formation reaction of the free hydroxyl group was also observed during the preparation of geminal dimethylsteroids effected with methylsulphinyl carbanion (5).



I.a-f

a	
b	
c	
d	
e	
f	

II.a-f

	R^1
a'	H
b'	Ac
c'	THP
d'	CH_3

III.a-f

	R^1	R^2
a"	H	H
b"	H	Ac
c"	Ac	Ac
d"	THP	H
e"	THP	Ac
f"	CH_3	H
g"	CH_3	Ac

Scheme I

EXPERIMENTAL

Melting points were determined with a Kofler plate apparatus and are uncorrected. Physical properties of the compounds are listed in Table 1. Specific rotation was measured with a Polamat-A polarimeter in $CHCl_3$ (c=1). TLC data: Kieselgel-G (Merck) (0.5 mm); developing solvents: methanol-benzene, UV detection (365 nm) after spraying with 50 % phosphoric acid and heating at 100-120°C for 15 minutes. Column chromatography: Al_2O_3 (Brockmann, activity III-IV) 50 g, column: 25 x 2 cm.

Preparation of 16,16-dimethyl-17-ketosteroids and 16,16-dimethyl-17β-hydroxysteroids

General Procedure. The 17-ketosteroid (Ia-f) (10 mmol) was dissolved in anhydrous tetrahydrofuran (60 mL) and NaH (2.39 g, 100 mmol) and methyl iodide (14.1 g, 100 mmol) were added to it; then the mixture was kept at the temperature of boiling. The conversion was monitored by TLC. The condensation reaction is complete practically in 3 h. For the decomposition of the excess NaH, ethanol was added to the cold reaction mixture; then it was poured onto ice (500 g). The aqueous reaction mixture was saturated with $(NH_4)_2SO_4$, the precipitate separated was filtered off and subjected to chromatographic separation on an Al_2O_3 column. Compounds (IIa'), (IIdb'), (IIc), (IId), (IIe) and (IIf) were eluted with benzene-petroleum ether (1:3) mixture, while benzene-petroleum ether (1:1) was used for (IIIaf''), (IIIbf''), (IIIca'') (1), (IIIda'') (1), (IIIea''), (IIIfa'') (1) (IIac') and (IIbc'). Compounds (IIIad'') and (IIIbd'') can be removed from the column with benzene.

When the excess NaH was decomposed with ethyl acetate, the 16,16-dimethyl-17β-acetoxysteroids (IIIag''), (IIIae''), (IIIbg''), (IIIbe''), (IIIcb'') (1), (IIIdb'') (1), (IIIeb'') and (IIIfb'') (1) were formed, which can be eluted with petroleum ether from the 16,16-dimethyl-17-ketosteroids.

Acid hydrolysis of 16,16-dimethyl-17-ketosteroids-3-tetrahydropyranyl ether (IIac') and (IIbc'), 16,16-dimethyl-17β-hydroxysteroid-3-tetrahydropyranyl

ether (IIIad'') and (IIIbd'')and 16,16-dimethyl-17β-acetoxysteroid-3-tetrahydropyranyl ether (IIIac'') and (IIIbc'')

General Procedure. The 16,16-dimethylsteroid-3-tetrahydropyranyl ether (5 mmol) was dissolved in ethanol (100 mL) and 10 drops of concentrated HCl were added to it. The reaction mixture was allowed to stand for 6 h then it was diluted with water. The precipitate separated was filtered off, the 3β-hydroxysteroids formed (IIaa'), (IIba'), (IIIaa'') (1), (IIIba'') (1), (IIIab'') (1) and (IIIbb'') (1) were crystallized from a mixture of acetone and water.

Acetylation of 16,16-dimethyl-3β-hydroxy-17-ketosteroids and 16,16-dimethyl-3β,17β-dihydroxysteroids

General Procedure. The 16,16-dimethyl-3β-hydroxy-17-ketosteroid (IIaa') and (IIba') or 16,16-dimethyl-3β,17β-dihydroxysteroid (IIIaa'') and (IIIba'') (5 mmol) was dissolved in a mixture of pyridine (5 mL) and acetic anhydride (5 mL) and the mixture was allowed to stand for 24 h at room temperature. It was then diluted with water, the acetates separated (IIab'), (IIbb'), (IIIac'') (1) and (IIIbc'') (1) were filtered off and recrystallized from a mixture of methanol and water.

Table 1

No	Formula[a,b]	Mol.wt.	m.p. (°C)	$(\alpha)_D$	R_F	yield %
(IIaa')	$C_{21}H_{32}O_2$	316.48	183-186	- 4	0.55[c]	24
(IIab')	$C_{23}H_{34}O_3$	358.52	175-178	- 9	0.55[d]	98
(IIac')	$C_{26}H_{40}O_3$	400.61	158-161	- 12	0.65[d]	24
(IIad')	$C_{22}H_{34}O_2$	330.51	118-120	- 5	0.65[d]	27
(IIba')	$C_{21}H_{34}O_2$	318.50	186-187	+ 76	0.55[c]	12
(IIbb')	$C_{23}H_{36}O_3$	360.53	143-146	+ 56	0.50[d]	97
(IIbc')	$C_{26}H_{42}O_3$	402.62	136-140	+ 3	0.70[d]	12
(IIbd')	$C_{22}H_{36}O_2$	332.52	100-102	+ 75	0.50[d]	20
(IIc)	$C_{21}H_{32}O_2$	316.48	132-133 (135-137)[e]	+ 104	0.25[d]	20

continued

Table					(continued)	
(IId)	$C_{21}H_{30}O_2$	314.47	163-165 (164-165)[e]	+ 168	0.30[d]	21
(IIe)	$C_{20}H_{28}O_2$	300.44	145-148	+ 107	0.30[d]	17
(IIf)	$C_{21}H_{28}O_2$	312.45	93-95	+ 147	0.80[d]	19
(IIIad'')	$C_{26}H_{42}O_3$	402.62	128-131	- 85	0.75[c]	68
(IIIae'')	$C_{28}H_{44}O_4$	444.66	194-196	- 74	0.60[d]	71
(IIIaf'')	$C_{22}H_{36}O_2$	332.52	146-147	- 68	0.75[c]	62
(IIIag'')	$C_{24}H_{38}O_3$	374.56	168-170	- 62	0.80[d]	96
(IIIbd'')	$C_{26}H_{44}O_3$	404.64	152-159	- 54	0.75[c]	80
(IIIbe'')	$C_{28}H_{46}O_4$	446.67	161-165	- 42	0.60[d]	86
(IIIbf'')	$C_{22}H_{30}O_2$	334.54	171-174	- 3	0.75[c]	68
(IIIbg'')	$C_{24}H_{40}O_3$	376.58	98-101	+ 4	0.55[d]	65
(IIIea'')	$C_{20}H_{30}O_2$	302.46	171-175 (167-175)[g]	+ 13	0.25[c]	45
(IIIeb'')	$C_{22}H_{32}O_3$	344.49	115-119	+ 32	0.35[d]	38

[a]Satisfactory microanalysis obtained: C± 0.25, H±0.28;

[b]Structures were[d] confirmed by ^{1}H-NMR; [c]methanol-benzene (2:98); [d]methanol-benzene (0.5:99.5);

[e]Ref. 2; [f]Ref. 3; [g]Ref. 4.

ACKNOWLEDGMENTS

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NOTES

[x]Part 35 of this series: Schneider, Gy., Wölfling, J., Meskó, E., and Dombi, Gy., STEROIDS (preceding).

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