Tetrahedron Vol. 38, No. 12, pp. 1827 to 1829, 1982
Printed in Great Britain.

0040-4020/82/121827-03$03.00/0

SELECTIVE REDUCTION OF 3-KETO GROUP IN STEROIDAL KETOALDEHYDES

M. PAGLIALUNGA PARADISI* and G. PAGANI ZECCHINI
Centro di Studio per la Chimica del Farmaco del C.N.R., Istituto di Chimica Farmaceutica dell'Università, 00185 Rome, Italy

(*Received in the U.K. 3 November* 1981)

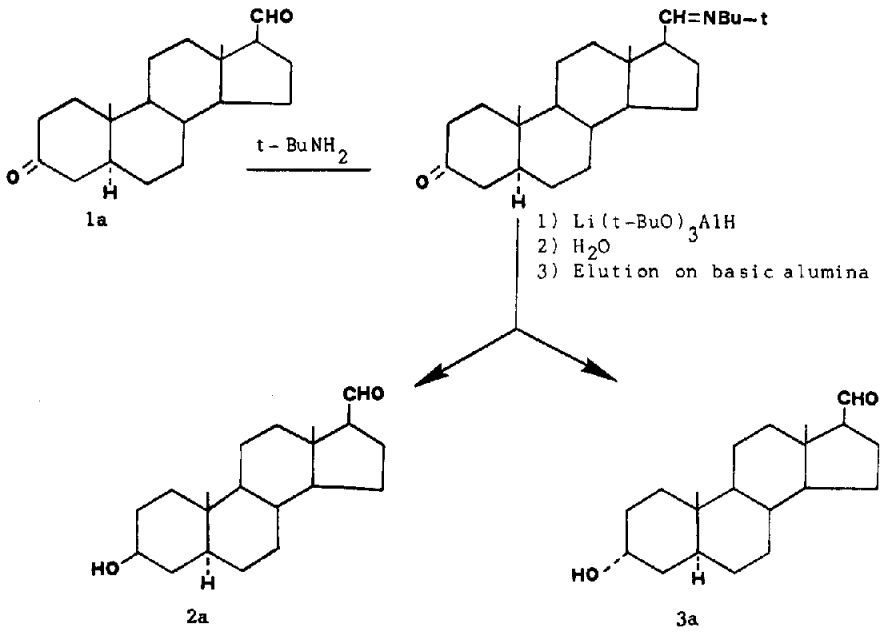
Abstract—Convenient preparation of some steroidal 3-hydroxyaldehydes from corresponding 3-ketoaldehydes was achieved by protection of the aldehyde group with t-butylamine followed by *in situ* reduction of the keto group with Li (*t*-BuO)$_3$AlH. Final cleavage of hydroxyaldimine was accomplished by eluting the reduction mixture on basic alumina.

3-Hydroxysteroids containing aldehyde groups in the side chain are of synthetic value.[1] Recently we developed an efficient one-pot method for the selective reduction of ketones in the presence of aldehydes, based on the preferential reaction of the aldehyde group with t-butylamine.[2]

As an extension of this simple three-step process we now report the preparation of 3-hydroxyaldehydes (e.g. **2a**), starting from the appropriate ketoaldehydes (e.g. **1a**).

However it must be pointed out that our method is not suitable for 3-keto-5-en aldehydes since it is well known that steroidal 3-keto-5-en derivatives undergo isomerization in acid or basic media.[4] The usual preliminary protection experiment with t-butylamine, carried out on 3-oxoandrost-5-ene-17β-carboxaldehyde, led indeed to a complex mixture which was not further reduced.

As shown in the scheme, final cleavage of the aldimines was obtained eluting a benzenic solution of the



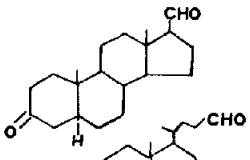
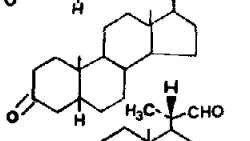
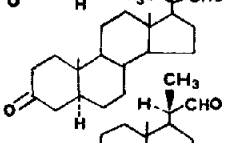
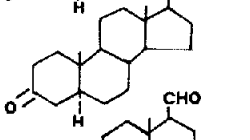
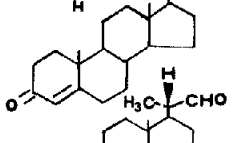
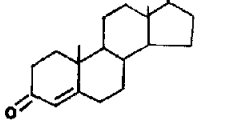
Scheme

The steroidal dicarbonyl compounds (**1a–f**) were prepared by oxidation of the corresponding diols with the Collins' reagent as previously described.[3]

The reduction results, summarized in Table 1, show that the reaction proceeded in high yields with remarkable site- and stereo-selectivity. In fact we have never been able to detect 3-ketoalcohols arising from a preferential hydride attack on the aldehydic group, and one of the two epimeric hydroxyaldehydes (e.g. **2a**) largely prevailed on the other (e.g. **3a**). Whereas the application to simple conjugated ketones failed,[2] the procedure can be successfully extended to steroidal 3-keto-4-en aldehydes (**1e** and **1f**) and no conjugated reduction occurs.

reduction mixture through a column of basic alumina. This procedure proved to be the most suitable in order to minimize epimerization at C-20 chiral centre. In fact use of aqueous HCl[2] in a preliminary deprotection experiment, carried out on (20*S*)-3-oxo-22,33-dinor-5α-cholan-24-al (**1c**), resulted in a poor yield of the partially isomerized **1c**. Silica gel, on other hand, caused isomerization more (~15%) than basic alumina (~8%) although the yield of the regenerated ketoaldehyde was a little better. The ratio of **1c** to **1d** could be estimated by comparing NMR spectra of reaction mixtures with those of mixtures of known composition. The 13-Me, 20-Me and CHO signals of 20*S*-compounds occur at slightly

Table 1. Product distribution (%)[a]

Entry	Ketoaldehyde 1	Time(h)[b]	3β-OH,CHO 2	3α-OH,CHO 3	Start. mat. recovered
a		3	83	6	
b		3	8	82	
c		14	81	8	
d		14	77	6	1.5
e		6	83.5	5	1.5
f		14	77	6.5	4

[a]Yields were calculated by NMR analysis of chromatographic fractions.

[b]Time required for the complete conversion of the aldehydic group to iminic one.[2]

lower field than those of corresponding 20*R* isomers (Table 2 and Ref. 3). Furthermore the coupling constant of the aldehydic doublet is, in the 20*R* series, larger (J = 4.5 Hz) than in the 20*S* one (J = 3.5 Hz). These NMR data allow a clear cut distinction to be made between 20*S* and 20*R* C-22 aldehydes.

Advantages of this first application of our one-pot procedure are the mild conditions required to cleave the intermediate aldimines.

EXPERIMENTAL

M.ps were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were taken at 20° with a Schmidt-Haensch polarimeter in a 1 dm cell (c 1.0 in $CHCl_3$). IR spectra (KBr discs) were recorded on a Perkin-Elmer 177 spectrophotometer. NMR spectra were measured with a Varian EM-390 spectrometer using $CDCl_3$ as the solvent; chemical shifts are given in ppm (δ) from Me_4Si as internal standard. Mass spectra were obtained using a Hewlett-Packard 5980A spectrometer operating at an ionizing energy of 70 eV. Woelm basic alumina (Brockmann IV) and silica Merck 60 (230–400 mesh) were used for column chromatography. Preparative layer chromatography (plc) was carried out with Merck F_{254} silica gel (layers 0.5 mm thick). Light petroleum refers to 40–60° b.p. fraction. The drying agent was sodium sulphate. All the reported reactions were performed under N_2.

(20*R*) - 3 - *Oxo* - 22,23 - *dinor* - 5α - *cholan* - 24 - *al* **1d** *by treatment of* **1c** *with acid.* Following the procedure of Herr and Heyl[5] (20*S*) - 3 - oxo - 22,33 - dinor - 5α - cholan - 24 - al **1c** (0.65 g) was refluxed for 1 h in 32 ml ethanol, 3.2 ml conc H_2SO_4 and 3.2 ml water. The mixture was poured into ice and partitioned between sat aq Na_2CO_3 and ether in excess. The organic layers were washed with water, dried and evaporated. The residue was recrystallized from ether to give 0.32 g of **1d**, m.p. 143–147° (sample inserted into a Büchi oil bath at 130°); $[\alpha]_D$ + 51°; ν_{max} 2705 (w) and 1715 cm^{-1}; δ 0.68 (3H, s, 13-Me), 0.98 (3H, s, 10-Me), 1.02 (3H, d, J = 6.5 Hz, 20-Me), 9.58 (1H, d, J = 4.5 Hz, CHO); mass spectrum *m/e* 330 (M^+). (Found C, 79.58; H, 10.37. $C_{22}H_{34}O_2$ requires C, 79.95; H, 10.37%).

Reduction of methyl 3 - *oxoandrost* - 4 - *ene* - 17β - *carboxylate with* $LiAlH_4$. Methyl 3 - oxoandrost - 4 - ene - 17β - carboxylate[6] (3.15 g) was dissolved in dry THF (220 ml) and $LiAlH_4$ (2.15 g) was carefully added. After stirring at room temperature for 1 h the excess of the reagent was decomposed with the minimum amount of crushed ice, cooling at 0°. The THF solution was separated by filtration and the solid residue washed with the same solvent. The collected organic solutions were passed through a column of alumina (32 g), eluting with THF. The resulting solution was evaporated under reduced pressure to give a white foam (3.03 g), which was then oxidized[3] without further purification.

3 - *Oxoandrost* - 4 - *ene* - 17β - *carboxaldehyde* **1e**. Chromatographic purification of the residue (3 g) arising from oxidation of the above crude mixture of the diols (3.03 g), afforded pure **1e** (1.5 g), m.p. 145–148° (sample inserted into a Büchi oil bath at 128°) (from ether); $[\alpha]_D$ + 174° [lit. 7 mp 149–151°; $[\alpha]_D$ + 178°]; NMR and IR data in accord with those previously reported.[8]

Table 2. Analytical[a] and spectral data for 3-hydroxyaldehydes

Compound	M.p. °C (Solvent)[b]	$[\alpha]_D$	MS m/e(M^+)	IR (cm^{-1})	NMR (δ)
2d	154-156 E	+23°	332	2690,1730, 1710,1040	0.66 (3H,s,13-Me),0.78 (3H,s,10-Me), 0.99 (3H,d,J=6.5 Hz,20-Me),3.59 (1H, m,3α-H), 9.60 (1H,d,J=4.5 Hz,CHO)
3d	160 E	+21°	332	2705,1730, 1000	0.66 (3H,s,13-Me),0.76 (3H,s,10-Me), 1.00 (3H,d,J=6.5 Hz,20-Me),4.05 (1H, m,3ß-H),9.60 (1H,d,J=4.5 Hz,CHO)
2e	72-74[c] E-LP	+103°	302	2710,1720, 1660	0.77 (3H,s,13-Me),1.06 (3H,s,10-Me), 4.17 (1H,m,3α-H),5.3 (1H,m,4-H),9.82 (1H,d,J=1.5 Hz,CHO)
3e	126-127 E-LP	+172°	302	2730,1728, 1700,1660	0.77 (3H,s,13-Me),1.00 (3H,s,10-Me), 4.10 (1H,apparent d,3ß-H),5.50 (1H, br d,4H),9.84 (1H,d,J=1.5 Hz,CHO)
2f	130 E-LP	+39°	330	2718,1720, 1660	0.71 (3H,s,13-Me),1.03 (3H,s,10-Me), 1.09 (3H,d,J=6.5 Hz,20-Me),4.17 (1H, m,3α-H),5.31 (1H,br s, 4-H),9.63 (1H, d,J=3 Hz,CHO)
3f	Not isolated, detected on some chromatographic fractions on the basis of its characteristic vinyl doublet at 5.48 ppm.				

[a] The microanalyses of the new 3ß-hydroxyaldehydes (2d and 2f) were in satisfactory agreement with the calculated values: C,±0.10; H,±0.19%.

[b] E= ether; LP= light petroleum

[c] Lit.[13] m.p. 55-57 °C as amorphous material

Reduction of methyl (20S) - 3 - *oxo* - 22,23 - *dinorchol* - 4 - *ene* - 24 - *carboxylate with* $LiAlH_4$. Methyl (20*S*) - 3 - oxo - 22,23 - dinorchol - 4 - ene - 24 - carboxylate[9] (2.29 g) was dissolved in dry THF (147 ml) and $LiAlH_4$ (1.44 g) was added. After above treatment the resulting solution was evaporated under reduced pressure to give a white powder (2.1 g), which was then oxidized.[3]

(20S) - 3 - *Oxo* - 22,23 - *dinorchol* - 4 - *en* - 24 - *al* **1f**. Usual chromatography of the residue (0.29 g) arising from oxidation of the above crude mixture (0.36 g), gave pure **1f** (0.15 g); $[\alpha]_D$ +85° [lit.[10] $[\alpha]_D$ + 82.5°]; δ 0.77 (3H, s, 13-Me), 1.19 (3H, s, 10-Me), 1.12 (3H, d, J = 6.5 Hz, 20-Me), 5.76 (1H, br s, 4-H), 9.64 (1H, d, J = 3.5 Hz, CHO); m.p. and IR data in accord with those previously reported.[10,11]

3 - *Oxoandrost* - 5 - *ene* - 17β - *carboxaldehyde*. Usual treatment of the residue (0.55 g) arising from oxidation[3] of 21 - norpregn - 5 - ene - 3β,20 - diol[12] (0.6 g) gave the title compound (0.29 g), m.p. 144–145° (sample inserted into a Büchi oil bath at 125°) (from ether); $[\alpha]_D$ + 36°; ν_{max} 2725 (w) and 1715 cm^{-1}; δ 0.79 (3H, s, 13-Me), 1.18 (3H, s, 10-Me), 5.37 (1H, m, 6-H), 9.87 (1H, d, J = 1.5 Hz, CHO); mass spectrum *m/e* 300 (M^+). (Found: C, 79.66; H, 9.45. $C_{20}H_{28}O_2$ requires: C, 79.95; H, 9.39%).

Isomerization of 3 - *oxoandrost* - 5 - *ene* - 17β - *carboxaldehyde in basic medium*. To a stirred solution of the title compound (1 mmol) in dry THF (2 ml), 4 Å molecular sieves (1 g) and dry *tert*-butylamine (0.42 ml) were added. The mixture was stirred for 6 hr at room temperature, filtered and evaporated under reduced pressure. The solid residue was purified by column chromatography (alumina, 20 g), eluting with benzene, to give starting material (0.075 g), **1e** (0.08 g) and a more polar complex mixture (0.075 g) which was not further analyzed.

General procedure for the selective reduction of steroidal ketoaldehydes. To a stirred mixture of ketoaldehyde (1 mmol) in dry THF (2 ml), 4 Å molecular sieves (1 g) and 0.42 ml of dry t-butylamine (0.21 ml in the case of **1a** and **1b**) were added. After the appropriate period of stirring at room temperature, lithium tri - t - butoxyaluminohydride (0.56 g) in dry THF (3 ml) was added and stirring was continued for 0.5 h. Excess hydride was destroyed at 0° with AcOEt and crushed ice. The solution was separated by filtration, washing the solid residue with AcOEt. The organic layers were washed with water, dried and evaporated under reduced pressure. The residue was passed through a column packed with alumina (20 g), eluting with benzene. Purification of products was achieved with further column chromatography on alumina and/or plc eluting with benzene and benzene/AcOEt (9:1). Purification of (20*S*) or (20*R*) compounds from their 20-epimers was accomplished by column chromatography on silica or plc (CH_2Cl_2-light petroleum (3:1) as eluent) and final crystallization. Compounds **2a–c** and **3a–c** were identified by comparison (IR and NMR) with autentical samples.[3]

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