STEREOSELECTIVE REDUCTION OF THE DOUBLE BOND IN Δ^5-3-OXO-4-AZASTEROIDS

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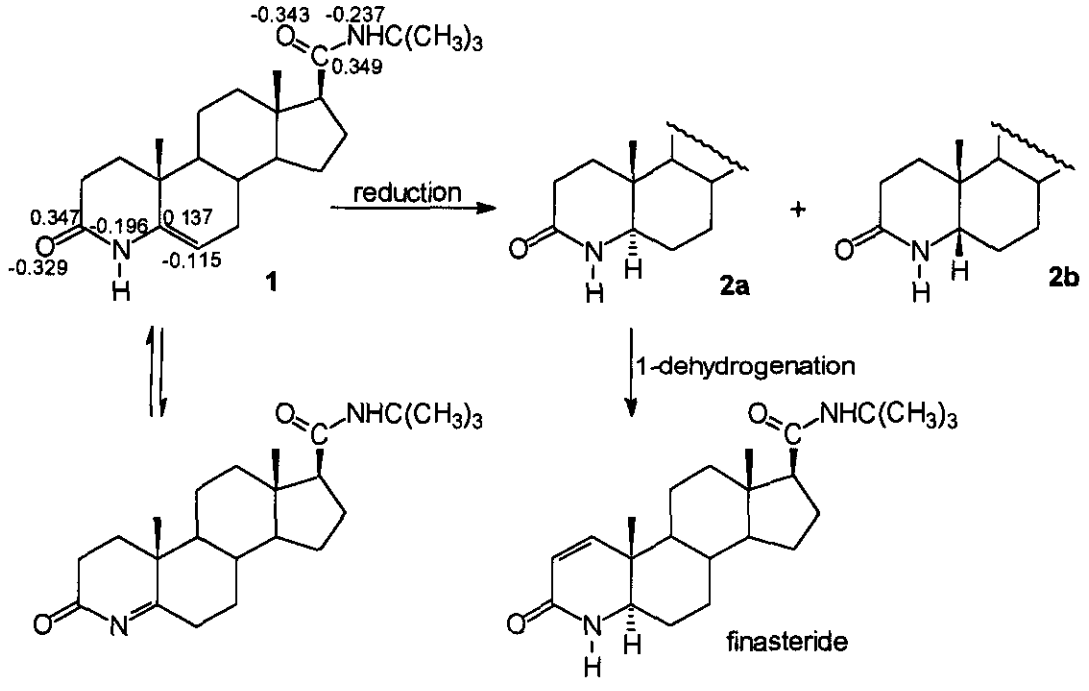
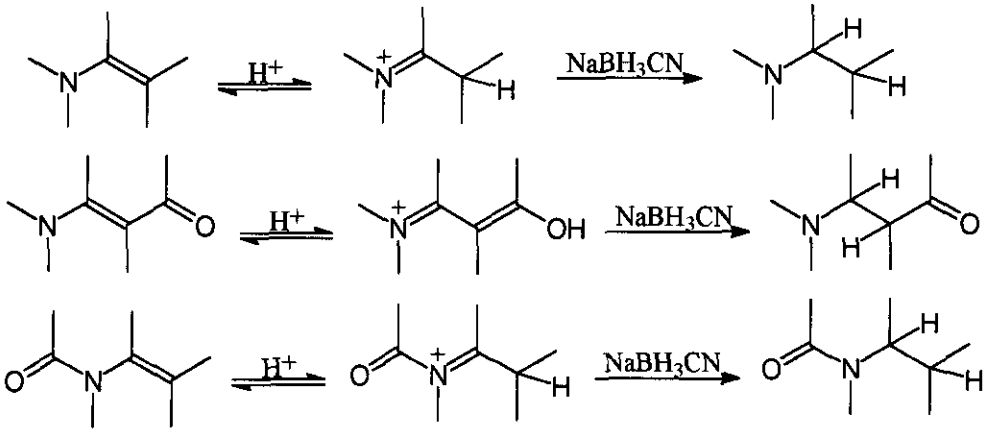
Abstract - The stereoselective borohydride/H^+ reduction of the $C_{(5)}$-$C_{(6)}$ double bond in Δ^5-3-oxo-4-azasteroids has been studied. The intermediate acylimine is preferentially attacked by borohydride from the α side. The optimization with respect to the type of borohydride, solvent, catalyst and temperature has been carried out.

Enlargement of the prostate gland, medically termed benign prostatic hyperplasia, is a medical problem in the aging human male.[1,2] The discovery and development of potent and selective inhibitors of steroid 5α-reductase and pure androgen receptor antagonists are at present being pursued with an interest in the hope of procuring a nonsurgical treatment for this affliction.[3-7] One of the most potent *in vivo* 5α-reductase inhibitors appeared to be *N-tert*-butyl-3-oxo-4-aza-5α-androst-1-en-17β-carboxamide (finasteride).[8,9] The crucial step in its synthesis is reduction of the Δ^5 precursor (1). This process is usually accomplished by catalytic hydrogenation over platinum in acidic solvent (HOAc) at 60°C under pressure (45 psi). The forced conditions are necessary as this relatively polar double bond is resistant to hydrogenation under milder conditions. It is claimed that the stereoselectivity of this process is high but in our experiments the ratio (2a : 2b) was not better than 87 : 13. The reaction must be then followed by crystallization of the crude product in order to get rid of the undesirable 5β-product. Alternately the double bond in Δ^5-3-oxo-4-azasteroids may be reduced with formic acid in *N*-methylformamide (Leuckart-type reaction).[10] Although this reaction was reported to be superior to catalytic hydrogenation,

we found that it is even less satisfactory (the ratio 5α . 5β - 75 . 25). Moderate stereoselectivity of the existing methods and a high cost of a platinum catalyst prompted us to undertake search for a new method which would be more stereoselective and simple enough to be applicable in the pharmaceutical industry



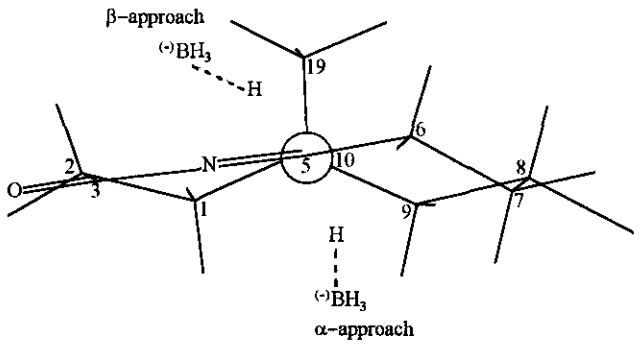


The most promising one seemed to be reduction with complex metal hydrides. It is known[11] that the highly reactive reagent, lithium aluminum hydride, reduces selectively the 3-carbonyl group in 4-azacholest-5-en-3-one while the carbon - carbon double bond remains intact. We found that the less potent reducing agent, sodium borohydride, reduces neither the carbonyl group nor the double bond in the absence of acid catalyst. Because of the well established[12] propensity for borohydrides to reduce iminium ions, the enamide

system appeared to be a likely candidate for reduction in acidic medium. In the case of the enamine group, rapid and reversible protonation of the β-carbon generates a readily reducible iminium salt [13] If the enamine is conjugated with a carbonyl group, the reduction becomes slower and more acid is required.[14] The studies on enamino-ketones have shown the carbonyl oxygen to be the basic site for protonation.[15] The reduction of enamide system due to its decreased basicity seemed to be still more difficult, but possible providing that a strong acid is added. It was found indeed that prior activation of the starting material by protonation is essential for successful reduction. There are five potential sites of protonation[16] in enamide (1)· all heteroatoms and carbon atom C-6. Of these, both oxygen atoms bear the highest negative charge but the most likely protonation preferentially occurs at C-6. The stabilized iminium ion thus formed has lower energy compared to cations formed by protonation at any of heteroatoms. Acid conditions allow for rapid equilibration between the Δ^5 and Δ^4 isomers. Molecular mechanics calculations show that the former compound in its preferred conformation is more stable by 6.5 kcal/mol.[15] This difference of energy corresponds to Δ^5 : Δ^4 ratio of 10000 : 1. The intermediate in the reduction process could be either a cation formed in acid medium or the Δ^4 isomer. The evidence that the latter is the actual species being trapped by hydride was provided by the experiment with the enamide 4-methyl derivative. This compound proved resistant to borohydride/H^+ reduction since it cannot isomerize by a double bond shift.

We have carried out detailed studies on reduction of a finasteride precursor with $NaBH_4$ or $NaBH_3CN$ in acidic medium. The addition of small amounts of a strong acid to the $NaBH_4$ or $NaBH_3CN$ solutions results in incomplete hydrolysis with the formation of borane or cyanoborane complexes with solvent. The hydrolysis takes place in both cases although it is considerably slower for sodium cyanoborohydride Various aggregates exist in alcohols, ethers, and in other solvents There was no much research done on the stereochemistry of the acylimine reductions but its stereochemical course seems to be similar to the metal hydride reduction of cyclic ketones.[17] In all reactions performed, the 5α-product prevailed. It is interesting that molecular mechanics calculations[16] show for 4-aza-5α-steroid lactam a higher energy than for its 5β-isomer, indicating clearly that there is no product development control in the reduction process. The transition state for reduction is suggested to resemble the reactants in geometry. The reduction stereochemistry is then determined by a combination of steric interference and torsional strain in the transition state. The approach of the reducing agent along the quasi-axial direction leading to the 5α-product is hindered by the axial hydrogen atoms at C-7 and C-9 only. The alternative

β-approach (quasi-equatorial) suffers from torsional strain involving bonds to the entering nucleophile and the axial C-19 methyl group.



The results (Table 1 and Table 2) show that all experimental parameters (type of hydride, acid catalyst, solvent, temperature, and even reagent concentration) are important for the stereochemical outcome of reduction. Although it is difficult to draw precise conclusions, it can be noticed that more of undesired 5β-product is produced in a more polar medium. It is known that the borohydride ion is heavily solvated in

Table 1. Reduction of the double bond in compound (1) (0.1 mmol) with borohydrides (4 mmol) and acid catalyst (0.4 mmol) in various solvents (4 ml), reaction time 1.5 h, room temperature

	$NaBH_4$		$NaBH_3CN$	
Solvent, acid	Conversion (%)	**2a** : **2b** ratio	Conversion (%)	**2a** : **2b** ratio
i-PrOH; aq HCl	100	73:27	100	80:20
i-PrOH; *p*-TsOH	45	84:16	15	65:35
i-PrOH, TFA	0		22	89.11
DMF; *p*-TsOH	20	56:44	100	81:19
THF; aq HCl	100	67.33	100	77:23
THF; *p*-TsOH	100	87:13	13	80.20
dioxane; aq HCl	100	74:26	100	78:22
dioxane; *p*-TsOH	59	78.22	86	81:19
formic acid	100	68:32	100	76:24
acetic acid	42	78:22	54	81:19

Table 2. Reduction of the double bond in compound (1) (0.1 mmol) with borohydrides (4 mmol) and acid catalyst in cyclic ethers

Hydride	Acid (mmol)	Solvent (ml)	Time (h)	Temp (°C)	Conversion (%)	**2a** : **2b** ratio
$NaBH_4$	*p*-TsOH (0.2)	THF (4)	1	40	23	82:18
$NaBH_4$	*p*-TsOH (0.2)	THF (4)	1	25	32	84:16
$NaBH_4$	*p*-TsOH (0.2)	THF (4)	2	10	42	86:14
$NaBH_4$	*p*-TsOH (0 2)	THF (4)	24	0	100	88:12
$NaBH_4$	*p*-TsOH (0.4)	THF (4)	24	0	100	87:13
$NaBH_4$	*p*-TsOH (0 2)	THF (4)	24	-78	0	
$NaBH_4$	*p*-TsOH (0.2)	THF (2)	24	0	100	83·17
$NaBH_4$	*p*-TsOH (0.2)	THF (8)	24	0	77	89.11
$NaBH_4$	TFA (0.8)	dioxane (4)	3	20	81	86:14
$NaBH_3CN$	TFA (0.2)	dioxane (4)	2	20	100	91 9

polar solvents whereas it is effectively small in ethers because of the weak anion-solvating power of these solvents. As the steric bulk of the reductant is increased, the steric interactions with axial hydrogens which hinder formation of 5α-product are enhanced, whereas the torsional strain which destabilizes the transition states leading to 5β-product remains relatively constant. This is the tentative explanation of the results of our studies which allowed to find the optimal conditions for reduction. The best appeared to be the reactions performed in cyclic ethers, e.g. $NaBH_4$ reduction in THF in the presence of *p*-toluenesulfonic acid or $NaBH_3CN$ reduction in dioxane in the presence of trifluoroacetic acid. Large excess of borohydride and acid was necessary to ensure completeness of the reduction. However the excess can be reduced by portionwise addition of the reagents. The borohydride reduction permit to avoid using of the expensive platinum catalyst and give a higher stereoselectivity than the catalytic hydrogenation.

EXPERIMENTAL SECTION

Melting points were determined on Kofler apparatus of Boetius type and were uncorrected. Nmr spectra were recorded with Bruker AC 200F Spectrometer using $CDCl_3$ solutions with TMS as an internal standard. Infrared spectra were recorded on a Specord 75 IR as $CHCl_3$ solutions. Mass spectra were obtained at 70 eV with AMD-604 spectrometer. The chromatographic separations were performed on

basic aluminium oxide 150 (type T; 230-400 mesh ASTM) from Merck. All solvents were dried and freshly distilled prior to use.

Analytical procedure:

To a stirred solution of compound (1) and acid catalyst in appropriate solvent sodium (cyano)borohydride was added. The reduction was performed under the required conditions and quenched by pouring into water. The reaction mixture was extracted with chloroform, the organic layer was washed with water, 5% sodium bicarbonate solution, dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. The products were analyzed by ^{1}H-nmr spectra. The percentage of conversion was calculated by disappearance of an olefinic proton signal at δ 4.88. The steroisomeric ratio (2a : 2b) was established on the basis of the 5α-H and 5β-H signals (at δ 3.07 and 3.30, respectively) integration. The results of these studies are presented in Tables 1 and 2.

Preparative procedures:

a) *N-t*-Butyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (2a) and its 5β-epimer (2b) by sodium borohydride reduction in the presence of sulfuric acid.

To a stirred solution of compound (1) (1.0 g; 2 7 mmol) in 100 ml of THF concentrated sulfuric acid (0.4 ml) was added at room temperature. Sodium borohydride (2.5 g; 66 mmol) was then added portionwise during 6 hours. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water, 5% sodium bicarbonate solution, dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Crystallization from dioxane afforded 610 mg (61%) of compound (2a), mp 283-285°C; ir 3412, 3390, 1661, 1508, 1454 cm^{-1}; H-nmr δ 5.86 (br s, 1H, A-ring NH), 5.08 (br s, 1H, side chain NH), 3.05 (dd, J_1 = 11.2 Hz, J_2 = 4.7 Hz, 1H, 5α-H), 2.41 (m, 2H), 1.35 (s, 9H, *N-t*-Bu), 0.90 (s, 3H, 19-H), 0.68 (s, 3H, 18-H), ^{13}C-nmr δ 172.2 (C), 171.6 (C), 60 6 (CH), 57.5 (CH), 55 6 (CH), 51.2 (CH), 51.0 (C), 43.8 (C), 38.5 (CH_2), 35 7 (C), 35.0 (CH), 33.3 (CH_2), 29 5 (CH_2), 29.0 (3 x CH_3), 28.5 (CH_2), 27.2 (CH_2), 24.2 (CH_2), 23.1 (CH_2), 21.1 (CH_2), 13.1 (CH_3), 11.3 (CH_3), mass spectrum 374 (M^+, 100), 359 (17), 319 (12), 274 (25). Anal Calcd for $C_{23}H_{38}N_2O_2$. C, 73 75; H, 10.23; N, 7.48. Found: C, 73.88; H, 10.31; N, 7.43.

The mother liquor was evaporated and the residue was subjected to careful column chromatography on alumina. Elution with benzene-methylene chloride (1:1) afforded compound (2b) (0.06 g) followed by mixture of epimers and pure compound (2a) (0.11 g).

Compound (2b), mp 214-218°C (from methylene chloride - hexane); ir 3418, 3385, 1659, 1511, 1453 cm^{-1}; ^{1}H-nmr δ 5.41 (br s, 1H, A-ring NH), 5.07 (br s, 1H, side chain NH), 3.29 (m, 1H, 5β-H), 2.30 (m, 2H), 1.35 (s, 9H, *N-t*-Bu), 1.01 (s, 3H, 19-H), 0.68 (s, 3H, 18-H); ^{13}C-nmr δ 172.7 (C), 171.7 (C), 59 0 (CH), 57.6 (CH), 55.5 (CH), 51.1 (C), 43.8 (C), 39.7 (CH), 38.7 (CH_2), 35.0 (CH), 34.0 (C), 32.1 (CH_2), 29.0 (3 x CH_3), 27.74 (CH_2), 27.70 (CH_2), 25.2 (CH_2), 24.4 (CH_2), 23.3 (CH_2), 20.8 (CH_2 and CH_3), 13.1 (CH_3); mass spectrum 374 (M^+, 61), 359 (5), 274 (8), 260 (18), 246 (100). Anal. Calcd for $C_{23}H_{38}N_2O_2$: C, 73.75; H, 10.23; N, 7.48. Found: C, 73 98; H, 10.26; N, 7.46.

b) *N-t*-Butyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (2a) by sodium cyanoborohydride reduction in the presence of trifluoroacetic acid.

To a stirred solution of compound (1) (100 mg; 0.27 mmol) in 10 ml of dioxane trifluoroacetic acid (42 μl) was added at room temperature. Sodium cyanoborohydride (0 67 g; 10.8 mmol) was then added and the reaction was continued for 6 h. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water, 5% sodium bicarbonate solution, dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. Crystallization from dioxane afforded 63 mg (63%) of compound (2a), mp 283-285°C.

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