Reduction of Steroidal Ketones with Aminoiminomethanesulphinic Acid

By **Josef E. Herz** and **Lilia Albert de Márquez,*** Department of Chemistry, Centro de Investigación y de Estudios Avanzados del IPN, Apartado Postal 14—740, México 14, D.F. Mexico

Some representative oxo-steroids were treated with aminoiminomethanesulphinic acid and the products were analysed by g.l.c. The 3- and 6-ketones were reduced; 20-ketones did not react. The results indicated that the reducing agent favours back-side attack. The olefinic double bond of cholest-4-en-3-one is reduced before the oxo-group is affected.

ALTHOUGH aminoiminomethanesulphinic acid (formamidinesulphinic acid; thiourea *SS*-dioxide) [1] has been used extensively for bleaching in the textile industry, few applications have been made of this reducing agent in preparative organic chemistry.[2,3] Recently Nakagawa and Minami [4] reported its use for reduction of some aliphatic, alicyclic, and aromatic ketones. We now describe its application to the reduction of some steroidal ketones.

Nakagawa and Minami [4] reported that aminoiminomethanesulphinic acid (AIMS) in the presence of aqueous sodium hydroxide reduced a series of ketones, in yields of 75—100%. We found, when applying these conditions to 5α-cholestan-3-one, cholest-4-en-3-one, and 3β-hydroxy-5α-pregnan-20-one, that reduction proceeded in low yield (about 20% overall) or not at all. However, when a stronger alkaline reagent, sodium n-propoxide in n-propyl alcohol, was used in the presence of an excess of reducing agent, the reaction proceeded satisfactorily in the case of three 3-ketones and one 6-ketone. The reduction of a 20-oxo-group, however, was still not achieved. The fact that the reaction proceeds better in the presence of a stronger base could indicate that the ketone may have to be enolised before it is reduced. The 20-oxo-group, however, was not reduced in the presence of the even stronger base, methyl-lithium, owing to a competing Grignard-type addition.[5]

All the products of these reductions are well known steroidal alcohols. The product mixtures were analysed by g.l.c. and t.l.c. and the products were identified by their retention times relative to cholestane on two different stationary phases and by their R_F values in two different developing systems. The results are summarised in the Table.

In the case of 5α-cholestan-3-one the ratio of isomers is the same in all three types of reductions, the equatorial isomer being overwhelmingly favoured. The results of the reduction of 3β-hydroxy-5α-cholestan-6-one indicate that AIMS favours back-side attack to a larger extent than lithium aluminium hydride. The reduction of cholest-4-en-3-one apparently proceeds through prior saturation of the double bond. When the reduction is incomplete, 5α-cholestan-3-one and 5β-cholestan-3-one can be detected. The 20-oxo-group in 3β-hydroxy-5α-pregnan-20-one is not reduced under these conditions. The difference in reactivity between the 3- and the 20-oxo-groups was used to reduce 5α-pregnan-3,20-dione preferentially to a 4 : 1 mixture of 3β- and 3α-hydroxy-5α-pregnan-20-ones.

Comparison between aminoiminomethanesulphinic acid (AIMS), Bouvault–Blanc, and lithium aluminium hydride reductions

Substrate	Products	Yields (%) AIMS	Na–ROH †	$LiAlH_4$ †
5α-Cholestan-3-one	5α-Cholestan-3α-ol	10		10
	5α-Cholestan-3β-ol	90	100	90
3β-Hydroxy-5α-cholestan-6-one	5α-Cholestan-3β,6α-diol	16	95	33
	5α-Cholestan-3β,6β-diol	84	5	67
Cholest-4-en-3-one	5α-Cholestan-3β-ol	44	Both reductions give cholest-4-en-3-ols	
	5α-Cholestan-3α-ol	23		
	5β-Cholestan-3α-ol	33		
5α-Pregnane-3,20-dione	3β-Hydroxy-5α-pregnan-20-one	80	Both reagents reduce both oxo-groups	
	3α-Hydroxy-5α-pregnan-20-one	20		

† D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 133.

EXPERIMENTAL

5α-Cholestan-3-one and 3β-hydroxy-5α-cholestan-6-one were obtained from Aldrich Chemical Co., and cholest-4-en-3-one and 3β-hydroxy-5α-pregnan-20-one from Fluka AG. Standard steroidal alcohols for comparison were obtained from Fluka AG. *NO*-Bistrimethylsilylacetamide was purchased from Pierce Chemical Co. The stationary phases HI–EFF 8BP and SE-30 and the support Gas-Chrom Q (100—120) were obtained from Applied Science Labs., Inc.

Aminoiminomethanesulphinic acid (AIMS) was prepared [6] by oxidation of thiourea (Merck) with hydrogen peroxide.

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[4] V. Nakagawa and K. Minami, *Tetrahedron Letters*, 1972, 343.
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[6] J. Böeseken, *Proc. Acad. Sci. Amsterdam*, 1936, **39**, 717 (*Chem. Abs.*, 1936, **30**, 6331[6]).

Reduction with AIMS and Sodium Hydroxide in Ethanol.—To a solution of the steroidal ketone (0·5 mmol) and AIMS (3 mmol) in 96% ethanol (20 ml) was added, at room temperature, sodium hydroxide (5 mmol) in water (2 ml). After 24 h under reflux the solution was neutralized with hydrochloric acid and extracted with dichloromethane. The overall yields of reduction products, as determined by t.l.c. and g.l.c., were 10—20% for the steroids tested.

Reduction with AIMS and Sodium Propoxide in n-Propanol.—The steroidal ketone (0·5 mmol) was added to a solution of sodium propoxide [from sodium (20 mmol)] in n-propanol (30 ml). AIMS (6 mmol) was added with stirring at room temperature. The mixture was refluxed for 24 h, neutralized with hydrochloric acid, and extracted with dichloromethane.

Attempted Reduction of 3β-Hydroxy-5α-pregnan-20-one with AIMS and Methyl-lithium.—To a solution of the steroid (1 mmol) in dry benzene (40 ml) was added slowly, under nitrogen, a 2M-solution (6 ml) of methyl-lithium in ether. After 1 h at room temperature AIMS (8 mmol) was added and the mixture was refluxed for 24 h, neutralized with hydrochloric acid, and extracted with dichloromethane. The product was shown by g.l.c. to be 20-methyl-5α-pregnane-3β,20-diol, identical with an authentic sample.[5]

Chromatography.—T.l.c. comparisons were carried out on 0·25 mm silica gel plates in chloroform and in chloroform–methanol (95 : 5). G.l.c. was performed on a Pye 105 gas chromatograph equipped with a flame ionization detector and a disc integrator [5 ft × 1/8 in columns packed with 3% HI-EFF 8BP on GasChrom Q (100—120 mesh) or with 3% SE-30 on GasChrom Q (100—120 mesh)]. The alcohols were analysed as their trimethylsilyl ethers, obtained by reaction with *NO*-bistrimethylsilylacetamide, and identified by comparison of their retention times relative to 5α-cholestane [7] with those of known standards.

[3/169 *Received*, 24*th January*, 1973]

[7] J. E. Herz and E. González, *J. Chromatog.*, 1968, **34**, 251.