Tetrahedron Letters No. 27, pp 2369 - 2372, 1977. Pergamon Press. Printed in Great Britain.

SELECTIVE REDUCTION OF STEROIDAL DIKETONES WITH POLY(N-ALKYLIMINOALANES)

Mario Paglialunga Paradisi, Giampiero Pagani Zecchini and Aurelio Romeo*
Centro di Studio per la Chimica del Farmaco del C.N.R., Istituto di Chimica
Farmaceutica dell'Università, 00185 Rome, Italy

(Received in UK 3 May 1977; accepted for publication 23 May 1977)

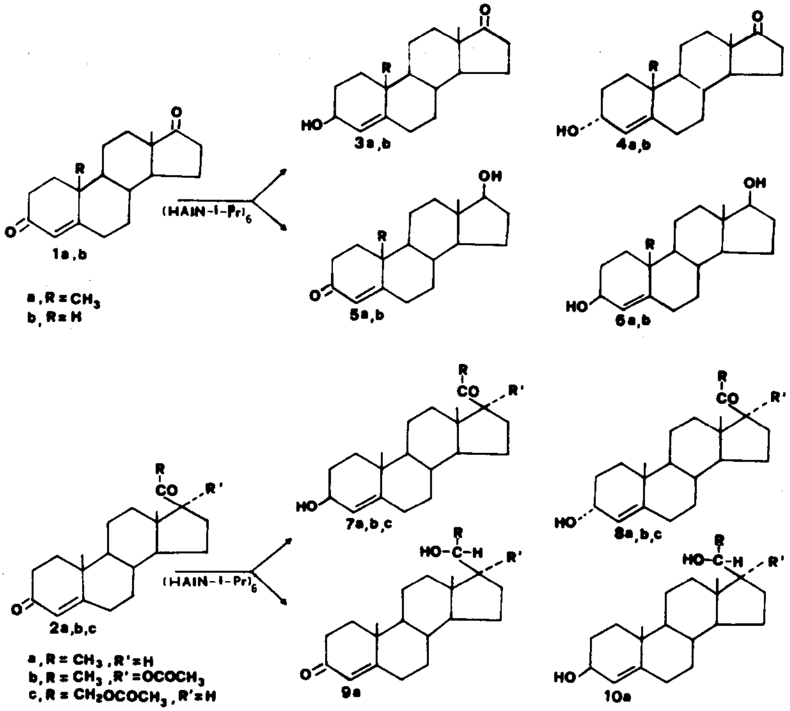
Although reductions of diketones by metal hydrides have been extensively studied, prediction of the regioselectivity and the stereochemical outcome of these reactions has been uncertain and has generated considerable discussion.[1]

Recently, much work has been carried out on the synthesis and characterization of poly(N-alkyliminoalanes) (PIA), and many simple routes to these hydrides have been described in view of their interest as active polymerization cocatalysts.[2] Nevertheless, little is known of the behaviour of PIA as reducing agents of organic functional groups, in spite of their remarkable solubility in different aprotic solvents.[3] As part of a programme concerned with a systematic investigation on the ability of these hydrides to react with polyfunctional compounds, in this communication we report the reduction of some steroidal diketones with poly(N-isopropyliminoalane) $(HAlN\text{-}i\text{-}Pr)_6$. All the reactions were carried out in dry benzene at room temperature using a 3:1 molar ratio of diketone/poly(N-isopropyliminoalane).[4]

Reduction of androst-4-ene-3,17-dione (1a) afforded, together with starting material, 3 β-hydroxyandrost-4-en-17-one (3a) as the main product, the epimeric 3 α-hydroxyandrost-4-en-17-one (4a), testosterone (5a) and androst-4-ene-3 β,17 β-diol (6a). The reduction of estr-4-ene-3,17-dione (1b) gave a mixture which was found similar to that obtained from 1a (see table 1).

The regioselectivity of these reactions is quite different from that observed by Norymberski and Woods[1a] who reported that 17-ketones of the androstane series were preferentially reduced with sodium borohydride in the presence of the 4-en-3-one group. Furthermore, the selective reduction of the 3-keto group of 1a with sodium borohydride in 2-propanol (as suggested by Mateos)[1b] under the conditions described by Kupfer[1c] has been shown to be unsuccessful[1d,e]. The remarkable regio- and stereo-selectivity exibited by poly(N-isopropyliminoalane), prompted us to extend these reductions to some diketones of the pregnane series.

SCHEME



On reducing progesterone (2a) we obtained a product distribution consistent with the above results (see table 1). Nevertheless, we have been able to isolate only the epimeric allylic alcohols 7b,8b from 3,20-dioxo-pregn-4-en-17α -yl acetate (2b) and 7c,8c from 3,20-dioxo-pregn-4-en-21-yl acetate (2c).

Table 1

Product composition (%) *

Starting material	3β-OH,17-CO	3α-OH,17-CO	3-CO,17β-OH	3β-OH,17β-OH	diketone recovered
1a	46	8	7	7	25
1b	45	12	4	4	14
	3β-OH,20-CO	3α-OH,20-CO	3-CO,20(R)-OH	3β-OH,20(R)-OH	
2a	43	7	6	10	18
2b	59	10	-	-	23
2c	49	12	-	-	15

* The yields were calculated by NMR analysis of chromatographic fractions.

The lack of 20-hydroxy-steroids may be attributed to the increase in steric hindrance at the 20-carbonyl group. The steric hindrance at saturated carbonyl is presumably the main factor which, in the absence of electrophilic catalysis, permits the observed preferential reductions. In agreement with this, the reduction of 5α-androstane-3,17-dione yielded a mixture of starting material (19%), 3β-hydroxy-5α-androstan-17-one (35%), 3α-hydroxy-5α-androstan-17-one (10%), 17β-hydroxy-5α-androstan-3-one (7%) and a crude product(~10%) consisting probably of 5α-androstan-3β,17β-diol which was not further characterized.

Table 2

Physical constants[5] and NMR data (δ values) [6] of epimeric allylic alcohols obtained from Δ^4-3,17 and Δ^4-3,20 steroidal diketones.

Compound	Mp °C	$[\alpha]_D$	δ (ppm)					
			3-H	4-H	18-H	19-H	21-H	$-OCOCH_3$
3a	135-6	+132°	4.14	5.32	0.87	1.05		
4a	196-9	+209°	4.07	5.50	0.88	1.00		
3b	135-6	+123°	4.15	5.43	0.89			
4b	195-6	+206°	4.14	5.58	0.90			
7a	160-1	+140°	4.16	5.31	0.63	1.04	2.10	
8a	126-8	+254°	4.08	5.48	0.63	0.97	2.10	
7b	198-200	+37°	4.15	5.31	0.63	1.04	2.07	2.01
8b	168-9	+85°	4.08	5.48	0.63	0.97	2.07	2.01
7c	155-7	+143°	4.13	5.30	0.67	1.03	4.60	2.13
8c	168-70	+209°	4.08	5.48	0.67	0.96	4.60	2.13

So far as we are aware, poly(N-isopropyliminoalane) is the only reagent suitable for selective reduction of the 4-en-3-one group in the presence of a 17-keto group (in the androstane series).

REFERENCES AND NOTES

1) a) J.K.Norymberski and G.F.Woods, J.Chem.Soc.,3426(1955); b) J.L.Mateos, J.Org.Chem.,24,2034(1959) ; c) D.Kupfer, Tetrahedron, 15,193(1961) ; d) M.G.Ward, J.C.Orr and L.L.Engel, J.Org.Chem.,30(5),1421(1965) ; e) P.D. Klimstra and F.B. Colton, Steroids,10(4),411(1967) ; f) P.T.Lansbury and J.O.Peterson, J.Am.Chem.Soc.,85,2236(1963) ; g) M.Stefanovic and S.Lajsic, Tetrahedron Letters,19,1777 (1967).

2) S.Cucinella,G.Dozzi,C.Busetto and A.Mazzei, J.Organometal.Chem.,113,233(1976), and references cited therein.

3) a)G.M.Giongo,F.Di Gregorio,N.Palladino and W.Marconi,Tetrahedron Letters,34,

3195(1973) ;b) E.Cernia,G.M.Giongo,F.Marcati,W.Marconi and N.Palladino, Inorg. Chim.Acta,11,195(1974).

4) Reductions were usually performed by addition of a known amount of $(HAlN\text{-}i\text{-}Pr)_6$ to a stirred benzene solution of steroidal diketone (0.5 g in 10 ml) in a nitrogen atmosphere. After 3 hours, the mixture was carefully hydrolysed (cooling) with a small amount of water, the solution was separated by filtration and the solid residue washed with benzene. The combined benzene solution was washed with water, dried and evaporated under vacuum. Column chromatographies were carried out on Woelm basic alumina (Brockmann grade III), and preparative layer chromatographies on Merck HF_{254} silica gel (layers 0.5 mm thick).

5) M.p.s were measured on a Kofler hot-stage apparatus. Optical rotations were taken at 20°C with a Schmidt-Haensch polarimeter for solutions in chloroform in a 1 dm cell.

6) NMR spectra were measured for solutions in deuteriochloroform (tetramethylsilane as internal standard) with a Varian EM-390 spectrometer. The signal for the 4-H appears for 3α-hydroxy-ketones as an apparent doublet (J = 4.5 Hz) and is 0.15-0.18 ppm downfield than the corresponding signal of the 3β-analogues, which is a broad singlet, while the 3-H resonance of the 3β-derivatives occurs at slightly lower field (0.08-0.01 ppm) than that of the corresponding 3α-derivatives (broad multiplet for both series). The signal for 21-CH_2 appears as an AB quartet (J = 16.5 Hz).

7) IR and NMR data are fully compatible with the structures shown ; the physical properties of known compounds agree with literature data ; all new products gave satisfactory elemental analyses.

Acknowledgment

We thank Dr. Salvatore Cucinella (SNAM Progetti S.p.A.) for providing the poly(N-isopropyliminoalane).