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STEREOCHEMISTRY OF REDUCTION OF CYCLIC KETONES BY ALKALI METALS AND BY SODIUM DITHIONITE.

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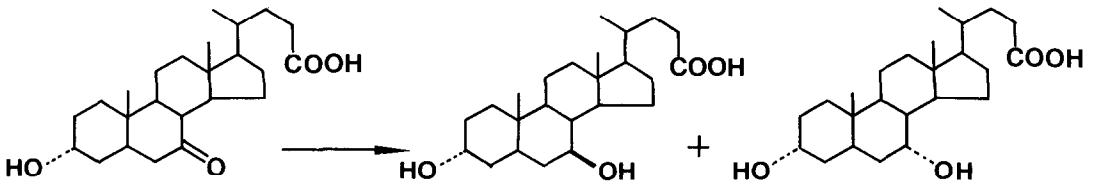
Summary: An opposite stereoselectivity is observed in the reduction of 3α-hydroxy-5β-7-oxo-cholanic acid by alkali metals and by sodium dithionite, contrary to the results reported[1] with other cyclic or bicyclic ketones. An electron-transfer mechanism followed by coupling of the ketyl radical with SO_2^- is suggested for the reduction by sodium dithionite.

The reduction of ketones by sodium dithionite has been recently[1,2,3] a matter of mechanistic controversy. This prompts us to report the results obtained in the reduction of 3α-hydroxy-5β-7-oxo-cholanic acid 1, a key step for the synthesis of the ursodeoxycholic acid 2, an important pharmaceutical drug for dissolution of cholesterol gallstones[4] (eq. 1).

1)



1 2 3

The isomer ratio 2 : 3 is strongly dependent on the nature of the reducing agent (Table 1). Thus ratios of 94 : 6 (entry 8) and 4 : 96 (entry 1) were obtained using alkali metals and sodium dithionite, respectively. This change in stereoselectivity is contrary to the results reported[1,2,3] for the reduction of other cyclic and bicyclic ketones by sodium dithionite and alkali metals.

The stereochemistry will certainly be dependent upon the reduction mechanism, but to draw a conclusive mechanism from the stereochemical reaction course alone is risky, since the factors which govern the stereochemistry of cyclic ketones reduction are not yet fully understood[5]. The controversy concerning the mechanism of the reduction of ketones by sodium dithionite parallels a similar dispute on the sodium dithionite decomposition: formation of the sulfoxylate anion[6] (eq. 2), or homolysis of the S-S bond[7] (eq. 3).

2) $S_2O_4^= + H_2O \rightleftharpoons HSO_2^- + HSO_3^-$

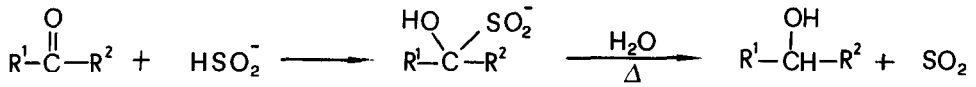
3) $S_2O_4^= \rightleftharpoons 2\,SO_2^-$

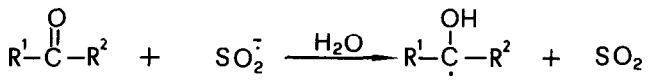
The sulfoxylate anion should lead, by a nucleophilic attack to the carbonyl group, to the α-hydroxysulfinate (eq. 4)[3], whereas the radical anion SO_2^-, observed by e.s.r.[7], should give, via an electron-transfer process, the ketyl radical (eq. 5):

TABLE[a]: Reduction of 3α-hydroxy-5β-7-oxo-cholanic acid 1 (10 mmol)[b].

entry no	solvent (ml)	base (mmol)	reducing agent (mmol)	reaction conditions temp. (°C)	time (h)	conversion[c] (%)	yields[d] (%) 2	3
1[e]	H_2O (70)	$NaHCO_3$ (65)	$Na_2S_2O_4$ (57.5)	100	2	72	4	93
2[e]	H_2O-DMF (1:1 v/v)(70)	$NaHCO_3$ (65)	$Na_2S_2O_4$ (57.5)	100	2	96	7	92
3[e]	H_2O (70)	NaOH (65)	$Na_2S_2O_4$ (57.5)	100	2	98	5	93
4[f]	H_2O (70)	$NaHCO_3$ (65)	$NaBH_4$ (20)	20	0,5	99	2	94
5[f]	H_2O (70)	NaOH (65)	$NaBH_4$ (20)	20	0,5	99	3	93
6	AcOH (70)	-	$Na_2S_2O_4$ (57.5)	100	3	0	-	-
7[g]	nPrOH (80)	-	Na (340)	reflux	3	100	85	15
8[h]	tBuOH (150)	-	K (50)	reflux	0,5	100	94	6

a) All products listed in Table were isolated and identified by comparison with authentic samples. Quantitative analyses were carried out by HPLC and by TLC. HPLC analyses were performed on a Hewlett-Packard 1084/B instrument with a C_8 spheri 5μ Brownlee column. Eluent A : 0,02 M solution of KH_2PO_4 adjusted to pH 3 with H_3PO_4. Eluent B : a solution of 2% (v/v) aqueous H_3PO_4 (6 ml.) in acetonitrile. (M. Paciotti, L. Perinati, F. Gori and P. Rampazzo, J. Chromatogr., submitted for publication). Thin-layer chromatography analyses were performed on pre-coated Silica-gel plates (supplied by Merck). For the analyses of the reaction products, a mixture of chloroform, acetic acid, water (85 : 15 : 0.5) was used as mobile phase. The separated spots were visualized after spraying with a solution of phosphomolibdic acid (5 g) and of sulfuric acid (5 ml) in acetic acid (100 ml) and by heating them at 100-110°C. b) 3α-Hydroxy-5β-7-oxo-cholanic acid 1 was prepared according to a known procedure.[8] c) Conversions are referred to the starting ketone 1. d) Yields, based on the converted ketone 1, were determined on reaction crudes. e) Reaction conditions : sodium dithionite was added, under nitrogen, in four portions during 1 h, and the reaction mixture was heated for additional 2 hrs. A mixture of 1 and 2 and a mixture of 1 and 3, were heated at reflux for 8 h, under the reaction conditions given above, in the absence of sodium dithionite: 1, 2, 3 were found to be unchanged. f) The reaction was carried out at 20°C. Analogous results for the reaction of 1 with sodium borohydride have been reported.[9] g) Data were obtained according to a known procedure.[10] h) Potassium was added in portions, under nitrogen, in 10 min. The solution was refluxed for additional 20 min. Usual work up gave the crude products.

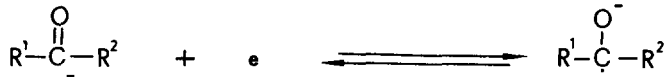
4) 

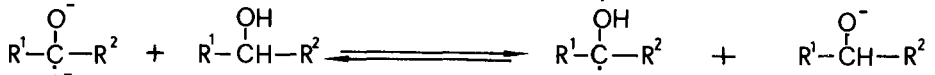
5) 

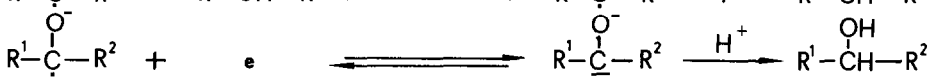
The electron-transfer, when it is iso or exergonic, often occurs at or near diffusion-controlled rate.[11]
The redox potential of $S_2O_4^{=}$ is high enough[12] (eq. 6) to make the transfer of an electron to the carbonyl group possible.

6) $4OH^- + S_2O_4^{=} \rightleftharpoons 2SO_3^{=} + 2H_2O + 2e \qquad E^0 = 1{,}12\ V$

However, the reduction through an overall electron-transfer mechanism involves two steps (eq. 9 or 10) with different energetics.

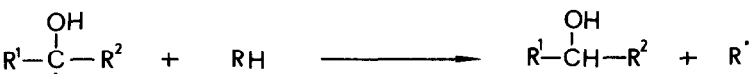
7) 

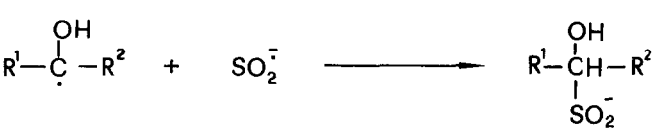
8) 

9) 

10) 

The redox potential of the α-hydroxyalkyl radical Me-$\dot{C}$(OH)-Me ($E°$=-0.8 to -0.9 V) is considerably higher than that of the corresponding radical anion Me-$\dot{C}(O^-)$-Me ($E°$=-1.9 to -2 V). Thus, on the basis of the redox potentials, the reduction should occur on the α-hydroxyalkyl radical R^1-$\dot{C}$(OH)-R^2. It should be noted however that this species is present at lower concentration with respect to the corresponding radical anion because the equilibrium (8) is shifted to the left, the pka values of α-hydroxylalkyl radicals being approximately 5 units lower than those of the parent alcohols.[13]
Even so the second electron-transfer (eqs. 9 or 10) is energetically much less favoured than the first electron-transfer (eq. 7) and it is certainly incompatible with the redox potential of $S_2O_4^{=}$, but not with the redox potential of alkali metals ($E°$ = -2.7 to -3 V).
As a matter of fact, beside the nucleophilic mechanism and the unlikely two-step electron-transfer[1] a third mechanism can be envisaged for the reduction of ketones by sodium dithionite: an initial thermodynamically allowed electron-transfer (eqs. 6-7), followed by a hydrogen atom transfer (eq. 11) or more likely by the scavenging of the ketyl radical by SO_2^- radical anion (eq. 12).

11) 

12) 

α-Hydroxysulfinates, so obtained, should lead by thermal decomposition[3] to the corresponding alcohols (eq. 4), thus the different stereochemistry of reduction between alkali metals and sodium dithionite could be explained.
The behaviour of cyclopropylketones in the reduction with sodium dithionite,[2] leading to the cyclopropyl alcohols, would appear to exclude the formation of a ketyl radical, since it is known[11] that cyclopropylcarbinyl radicals rearrange to ring-opened products very fast (rate constant 10^7 - 10^8 s^{-1}).[14]
The formation of cyclopropylalcohols is certainly incompatible with reaction (11), but not with the reaction (12) for which a diffusion-controlled rate can be foreseen.
In summary, α-hydroxysulfinates can be formed via both nucleophilic attack of HSO_2^- (eq. 4) and via electron-transfer (eqs. 7, 8) followed by the scavenging of the ketyl radical by SO_2^-. (eq. 12)
However, the nucleophilic mechanism is unlikely, since under neutral or mildly acidic conditions, where HSO_2^- is certainly present,[6] no reduction takes place (Table, entry 6).
Thus, in the case in hand, the very similar stereoselectivities found with $NaBH_4$ and $Na_2S_2O_4$ should not be taken as proof in favour of the nucleophilic mechanism.
A unique mechanism cannot be invoked to explain the reduction of all the ketones by sodium dithionite, since the redox potential of carbonyl function can considerably change from one ketone to an other: as a matter of fact, it is likely that the reduction of pyruvic acid by sodium dithionite occurs in two steps, both involving an electron-transfer mechanism, because the redox potential of $MeC^{\cdot}(OH)COOH$ has been estimated to be + 0.25 V.[15]

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