Dissolving Metal Reduction of Carboxylic Esters. A Re-evaluation of the Mechanism

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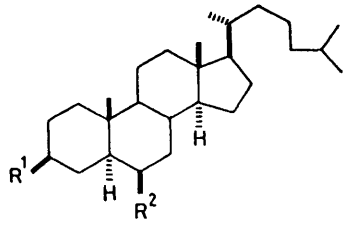
Summary The deoxygenation of carboxylic esters by reduction using potassium solubilised by 18-crown-6 in t-butylamine or lithium in ethylamine is shown to proceed *via* alkyl oxygen cleavage of the derived radial anion; in non-nucleophilic media deoxygenation giving alkane and carboxylate anion is the major pathway.

THE reduction of carboxylic esters by alkali metals is a classic organic transformation. Excess of sodium in ethanol provides two alcohols (Bouveault–Blanc) whereas molten sodium in refluxing toluene gives the acyloin.



(1)

a; $R^1 = R^2 = AcO$
b; $R^1 = R^2 = Bu^tCO_2$
c; $R^1 = OH$, $R^2 = H$
d; $R^1 = R^2 = R^3CO_2$ [see (**2**)]
e; $R^1 = R^2 = H$
f; $R^1 = H$, $R^2 = OH$
g; $R^1 = R^2 = OH$
h; $R^1 = R^3CO_2$, $R^2 = H$

Recently the selective deoxygenation (Li, $EtNH_2$;[1] K, 18-crown-6, Bu^tNH_2;[1] or Na, hexamethylphosphoric triamide, Bu^tOH [2]) of hindered alkyl carboxylates giving alkanes was reported. We suggested that deoxygenation $[(R'CO_2R)^{-\cdot} \rightarrow R'CO_2^- + R\cdot \rightarrow R^- \rightarrow R{-}H]$ was the predominant pathway [hereinafter, pathway (a)]. Otherwise the alcohol was regenerated $[(R'CO_2R)^{-\cdot} \rightarrow R'CO\cdot + RO^-]$ [hereinafter, pathway (b)]. Typically diesters (**1a** and **1b**) gave 5α-cholestan-3β-ol (**1c**) (60 and 79% yield, respectively) where the more hindered axial (6β) ester was selectively deoxygenated.

Our recent results are consistent with the hypothesis that aliphatic or alicyclic esters normally react by path (a) provided that the medium is nucleophile-free.

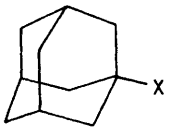
TABLE 1. Reduction of esters and carboxylic acids.[a]

	Substrate	Products (% yield)
1	(**1d**)	(**1e**) (45), (**1c**) (27), (**1g**) (8), (**1f**) (6), (**2b**) (92)
2	(**2b**)	No reaction; 87% (**2b**) recovered
3	(**2b**)	(**2e**) (51) [*via* (**2f**)], (**2b**) (10), (**2c**) (9)
4	(**2g**) + (**1c**)	(**1c**) (69), (**1e**) (15), (**2b**) (85)
5	(**2h**)	$Me[CH_2]_{17}OH$ (53), $Me[CH_2]_{16}Me$ (41), (**2b**) (90)
6	(**3a**)	$n\text{-}C_8H_{17}CH(X)CH_2Y$ X=Y=OAc (67); X=H, Y=OAc+X=OAc, Y=H (5)
7	(**3b**)	$n\text{-}C_8H_{17}CH(X)CH_2Y$ X=Y=OAc (35); X=H, Y=OAc (26); X=OAc, Y=H (8); $n\text{-}C_8H_{17}CH{=}CH_2$ (5)

[a] Reactions 1, 2, and 4—7 were carried out using potassium and 18-crown-6 in t-butylamine at room temperature and reaction (3) with lithium and ethylamine at 17 °C. The crude products from reactions 6 and 7 were acetylated prior to separation.

Adamantane-1-carboxylic esters of sterols were chosen for study since these permit ready identification of the fragments derived from both acyl and alkyl residues on

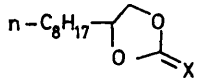
reduction. Adamantanecarboxylate esters† [prepared using KH, 18-crown-6, and (**2a**)] and cyclic carbonates (**3a** and **b**) were reduced by their addition in tetrahydrofuran (THF) to potassium and 18-crown-6 in t-butylamine. The reduction was complete when the blue colour was restored; quenching and chromatography gave the products shown in Tables 1 and 2. In all cases reduction of the ester (**1h**) gave 5α-cholestane (**1e**) and acid (**2b**) with the latter



(2) (≡ R^3X)

a; X = COCl
b; X = CO_2H
c; X = CH_2OH
d; X = CONHEt
e; X = CHO
f; X = CH(–O)O or CH(–O)NEt
g; X = CO_2Et
h; X = $CO_2[CH_2]_{17}Me$

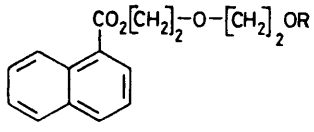
substantially predominating. The possibility that this difference resulted from competitive hydrolysis by adventitious water was unlikely since rigorous drying was used and in entry 5, Table 2, iodomethane was added before the ester to scavenge any water. The ratio of (**1e**) : (**2b**) was not increased. The yields of acid (**2b**) and alkane (**1e**) were decreased at lower temperature. Deoxygenation was a minor pathway (owing to competitive deacylation) on lithium–ethylamine reduction giving (**1c**) and (**2d**). In the presence of excess electrons or at low temperature both transacylation [giving (**2d**)] and radical anion fragmentation [giving (**1e**)] were suppressed and the two-electron Bouveault–Blanc products (**1c**) and (**2c**) formed. Entry 4, Table 1 shows that ester deacylation by an alkoxide competed with reduction. In entry 7, Table 1, predominance of the primary acetate was consistent with deoxygenation *via* the radical anion, not the dianion.



(3)

a; X = O
b; X = S

18-Crown-6 was found to be fragmented on reaction with potassium in t-butylamine. When the blue colour faded acidification followed by acylation with 1-naphthoyl chloride gave a complex mixture. Chromatography gave products including *N*-t-butyl-1-naphthamide and the oily esters (**4a**, **b**, and **c**) characterised by spectral data and high



(4)

a; R = H
b; R = CH_2CH_2OEt
c; R = $(CH_2CH_2O)_2Et$

resolution mass spectroscopy. Clearly, during ester reduction complete deoxygenation was prevented by competitive deacylation by crown fragments. The so-formed acylated fragments were subsequently reduced [pathway (a)] giving the carboxylate anion. Thus, in the absence of nucleophiles [pathway (a)] predominated. The selective deoxygenation of hindered esters followed from suppression of competitive deacylation.[3]

TABLE 2. Reduction of the ester (**1h**)[a]

	Amount/mmol of Ester (**1h**), metal[b], 18-crown-6	% Yield of products (1e)	(1c)	(2b)	(2c)	(2d)
1	1·04, 38, 11	43	57	96	2	—
2	0·84, (31 + 18), (6 + 4)	32	68	81	0	—
3	1·03, 13, 4	43	37	84	0	—
4	1·03, 14, 4·5	45	44	93	7	—
5	1·20, 28, 7	30	57	92	0	—
6	1·09, 36, 6	27	66	77	5	—
7	1·04, 36, 6	15	81	71	0	—
8	1·17, 29,0	1	93	0	69	0
9	1·15, 22, 0	7	85	4	4	92
10	1·17, 272, 0	4	94	4	65	0
11	1·03, 65, 0	5	92	2	29	51
12	0·45, 100, 0	0	58	0	66	0

[a] Reactions were carried out at 46 (1,2), 20 (3—5), 17 (9—11), −45 (6), −53 (7), or −73 °C (8), in t-butylamine and THF (1—3, 6, 7), t-butylamine with potassium added last (4), 1,2-dimethoxyethane and iodomethane (5), ethylamine and THF (8, 9), ethylamine (10), or ethylamine THF, and t-butyl acetate (11). In reaction 2 extra crown and potassium were added after the ester. Reaction 12 was carried out under standard Bouveault–Blanc conditions. [b] Reactions 1—7, metal = K; 8—11, Li, and 12, Na.

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† All new compounds were fully characterised by microanalysis and spectral data.

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[3] *Cf.* H. W. Pinnick and E. Fernandez, *J. Org. Chem.*, 1979, **44**, 2810.