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MODERN METHODS FOR THE RADICAL DEOXYGENATION OF ALCOHOLS

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CONTENTS

A. INTRODUCTION

Methods for the selective replacement of OH groups by H are becoming more and more important in the synthesis of natural products, particularly of aminoglycosides and complex carbohydrates. For example, deoxy derivatives of aminoglycoside antibiotics exhibit high efficacy against resistant bacterial strains, whereas the corresponding hydroxy precursors are deactivated by enzymatic action (e.g. by phosphorylation). Deoxy-sugars are also essential components of numerous cardenolides and antitumour agents. Deoxygenation methods are, furthermore, of interest in "chiro-economic" syntheses of complex compounds, as carbohydrates can then serve as cheap chiral starting materials.

Numerous methods have been developed for the deoxygenation of alcohols. Conventional syntheses involve the reduction of suitable alcohol derivatives[1-9] such as tosylate, mesylate, sulphate, O-alkylisourea etc, or the nucleophilic replacement of the OH group by halogen or thiolate with subsequent reductive dehalogenation[10-27] or desulphurisation.[28]

Although these reactions, in principle ionic in nature, can be applied successfully to simple, sterically unhindered alcohols, they have limitations and disadvantages as soon as complex, polyfunctional compounds with sterically hindered OH groups are used. The main reasons for this are that reactants and intermediates in ionic reactions are highly solvated and that S_N reactions only take place in low yields, if at all, owing to steric hindrance and dipole repulsion. In addition, rearrangements and eliminations are common side reactions when carbocations appear as intermediates.

Radical reactions offer themselves as an alternative to ionic reactions. Radicals are not solvated and thus less susceptible to steric factors. Moreover, radical reactions take place under neutral conditions, and so are ideally suited for application to sensitive polyfunctional compounds. Radical deoxygenation, i.e. the homolytic cleavage of a C–O bond, can be realised according to Scheme 1 in which a suitable alcohol derivative **1** is converted to an intermediate radical **2**, which fragments by β cleavage into an alkyl radical R· and a carbonyl compound **3**. The alkyl radical R· then reacts with a H donor yielding the corresponding hydrocarbon.

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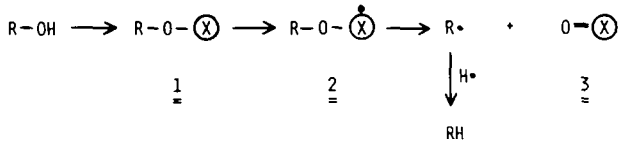


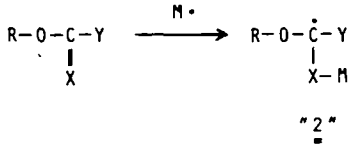
Scheme 1

The intermediate radical **2** can, in principle, be produced in three different ways:

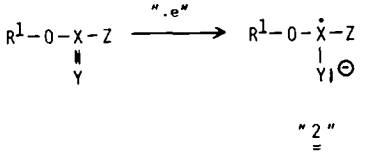
(a) By addition of a radical M˙ onto a CO or heterocarbonyl group (Scheme 2).

(b) By electron transfer to an activated double bond with formation of a radical ion (Scheme 3).

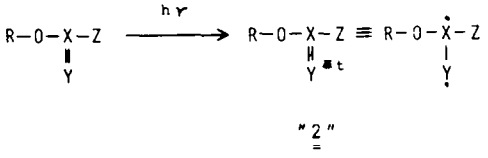
(c) By photolytic excitation of a π system forming the triplet state (Scheme 4).



Scheme 2



Scheme 3



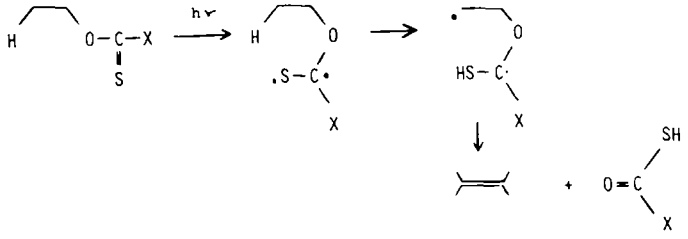
Scheme 4

This report surveys modern methods for the radical-induced replacement of OH groups by H. Deoxygenation processes with other aims in mind, such as the preparation of olefins from 1,2-diols[29–33] or the reductive coupling of alcohols to hydrocarbons,[34,35] are not considered here.

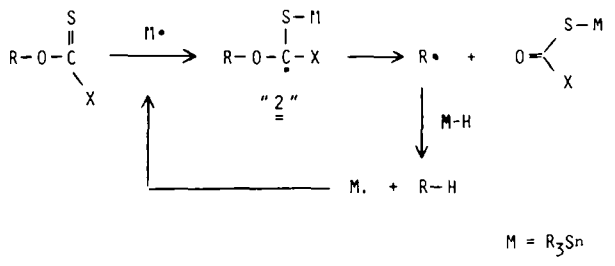
B. FORMATION OF THE INTERMEDIATE RADICAL 2 BY RADICAL ADDITION (ACCORDING TO SCHEME 2)

1. *Deoxygenation via O-alkylthiocarbonyl derivatives (Barton-McCombie Reaction)*

1.1 *Conception and development.* Based on the mechanism[36] of photoelimination in O-alkylthiobenzoates[37] (Scheme 5), Barton and McCombie[38] conceived a novel process for the radical deoxygenation of alcohols. In this process, a radical M˙ capable of forming a stable bond to sulphur should react with an O-alkylthiocarbonyl compound according to Scheme 6 to form an intermediate radical of type **2**, which



Scheme 5

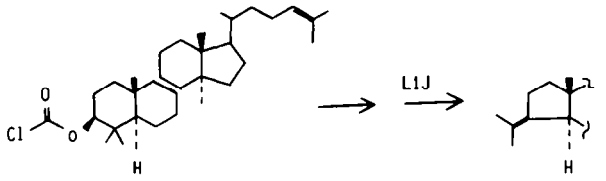


Scheme 6

then fragments into an alkyl radical and carbonyl compound. The driving force of the reaction would be the energy gained by the transition from a C=S to a C=O double bond. On the basis of thermochemical data, trialkyltin radicals—formed from the corresponding tin hydrides (R_3SnH)—seemed to be particularly suitable because the Sn–S bond is very stable and trialkyltin hydrides are also exceptionally good H-donors.

The first experiments on steroid alcohols yielded the desired results. Cholestanol (**4**), for example, could be smoothly converted to cholestane (**7**) via the thiobenzoate **5** (or thioimidazolide **6**) by treatment with tributyltin hydride in boiling benzene. The corresponding deoxygenations of lanosterol (**8**), cholesterol (**9**) and ergosterol (**10**) also occurred in high yields via their S-methyldithiocarbonates **11–13** (Table 1).

That the deoxygenations of **8** and **10** occur without rearrangement is evident proof of the radical character of the reaction. Ionic reactions of these two compounds frequently lead to rearrangements and eliminations. Thus the treatment of lanosteryl chloroformate (**14**) with lithium iodide mainly yields isolanosterol (**15**), the product of a Wagner-Meerwein rearrangement.



14 **15**

In contrast to thiobenzoates, thioimidazolides and dithiocarbonates, the thioformyl and thioacetyl derivatives of aliphatic alcohols furnish the corresponding alcohols as major product upon treatment with tributyltin hydride (Examples **16**, **19**, **20**). This behaviour is explained in Scheme 7—non-stabilised energy-rich radicals **2** (X=H, Me) react with tributyltin hydride by "1.2" addition to give **21** and then the

Table 1. Deoxygenation of alcohols via thiocarbonyl derivatives with Bu_3SnH—a comparison of various derivatives[38]

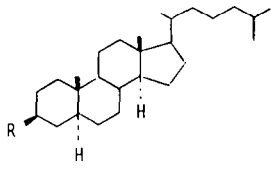
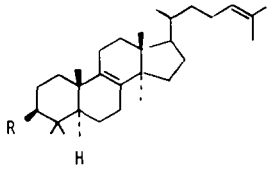
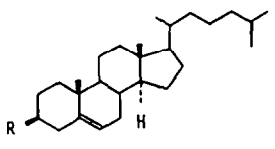
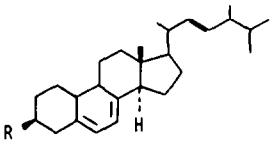
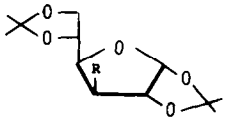
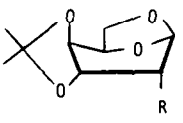
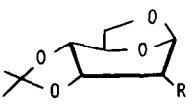
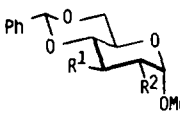
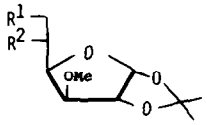
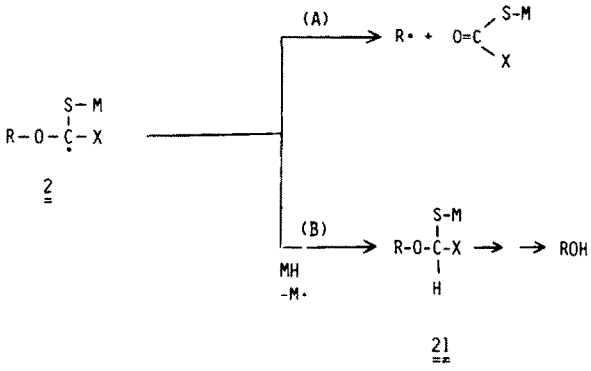
Alcohol	Derivative [Yield (%)]	Deoxy cmpd., R=H Yield (%)
	**5** = R=O-C(=S)-Ph	70-75 (**7**)
	6 : R = O-C(=S)-Im (90)	82
	16 : R = O-C(=S)-H (88)	-
4 : R=OH		
7 : R=H	**17** : R = O-C(=S)-N⟨ ⟩O	-
	**11** : R=O-C(=S)-SCH_3 (85)	83
8 : R=OH		

Table 1 (*Contd*).

Alcohol	Derivative [Yield (%)]	Deoxy cmpd., R=H Yield (%)
 9 : R=OH	12 : R=O-C(=S)-S-CH_3 (92)	78
	18 : R=O-C(=S)-Im (87)	74
	19 : R=O-C(=S)-H (82)	-
	20 : R=O-C(=S)-CH_3 (84)	-
 10 : R=OH	13 : R=O-C(=S)-S-CH_3 (88)	67
 22 : R=OH	23 : R=O-C(=S)-S-CH_3	85
 24 : R=OH	25 : R=O-C(=S)-S-CH_3	94 a)
 26 : R=OH	27 : R=O-C(=S)-S-CH_3	86 a)
 28 : R^1,R^2=OH	29 : R^1=O-C(=S)-Ph, R^2=OH	70
	30 : R^1,R^2 = 	60 (R^1=H, R^2=OH) 30 (R^1=OH, R^2=H)
 31 : R^1=R^2=OH	32 : R^1,R^2 = 	57 (R^1=OH,R^2=H)

a) overall yield

alcohol (Path B). Substituents X (Ph, Im, S–Me) that stabilise radicals extend the lifetime of the intermediate **2** and favour fragmentation (Path A). On the other hand, deoxygenation via a thioformyl derivative can be achieved when the leaving radical R˙ is stabilised by neighbouring groups, for example, by alkyl groups as in the deoxygenation of tertiary alcohols,[39] or by a "β-bond effect"[40] as in the deoxygenation of carbohydrates.



Scheme 7

Thiocarbamates such as **17** are inert to tributyltin hydrides under normal reaction conditions (toluene, reflux). This is possibly due to formation of a 1,5 H-bond to the sulphur resulting in sterically and electronically disfavoured attack by the tributyltin radical.

Carbohydrates were also among the first successful applications of this deoxygenation method. 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (**22**), 1.6-anhydro-3,4-O-isopropylidene-β-D-galactose (**24**) and the corresponding altrose derivative **26** were converted in high yields into the corresponding 3- or 2-deoxy sugars by tributyltin hydride treatment of the readily available [41] dithiocarbonyl derivatives **23**, **25** and **27** (Table 1). The C(3) deoxygenation of methyl 4,6-O-benzylidene-α-D-glucopyranoside (**28**) via its thiobenzoyl derivative **29** was equally smooth. Prior protection of the C(2)-OH group was unnecessary.

One variation of the technique is the monodeoxygenation of 1,2-glycols via their cyclic thiocarbonates.[42a,b] For example, the glucofuranosyl derivative **31** was regioselectively deoxygenated at C(5) by tributyltin hydride treatment of the thiocarbonate **32**. The C(6)-deoxy derivative is not formed, this being attributed to the greater stability of the secondary C(5) radical compared with the primary C(6) radical.

Regioisomers are formed in the deoxygenation of thiocarbonates derived from two secondary OH groups. Hence, the reaction of the α-D-glucopyranoside-2,3-thiocarbonate **30** with tributyltin hydride leads to both regioisomeric deoxy derivatives in the ratio C(2):C(3) = 1:2 (Table 1).

1.2 *Practical examples.* The deoxygenation process described above has been successfully employed in the meantime by several authors. The range of applications of the method is now illustrated with some selected examples.

(a) *Sterically hindered aliphatic alcohols.* As mentioned in the introduction, radical deoxygenation is particularly suitable in the case of sterically hindered hydroxy groups. This is confirmed, for example, by the smooth deoxygenation[43] of the sterically extremely hindered tricyclic alcohol **33**, a biogenetic precursor of hirsutic acid[44] (Table 2). The technique also provides high yields in the C(3) deoxygenation[45] of 3-epi GA_1 methyl ester **34**, a derivative of the plant growth hormone gibberellin,[46] and in the reduction[47] of the dithiocarbonate of anguidine **35**, an antibiotic from the trichothecene group. Whereas attempts at removing the C(1)-OH group in the azulene ketal **36** by classical methods (e.g. reduction of the mesylate) only led to elimination products, deoxygenation via the corresponding dithiocarbonate nevertheless succeeded in a yield of 38%.[48]

As examples **37** and **38** indicate, the method is equally applicable to the deoxygenation of primary hydroxy groups,[49] although in such cases higher reaction temperatures (130–150°) are necessary, the alcohol otherwise simply being regenerated (*cf* lit. Ref. 38[a]). This is attributed to the lesser stability of primary radicals compared with secondary radicals and is explained by the "1, 2" addition of tributyltin hydride (path B) competing with C–O fragmentation (path A) in Scheme 7.

Table 2. Deoxygenation of sterically hindered aliphatic alcohols via thiocarbonyl derivatives

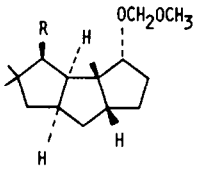
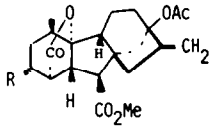
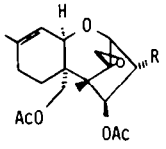
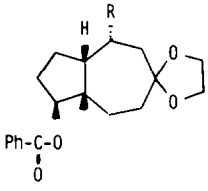
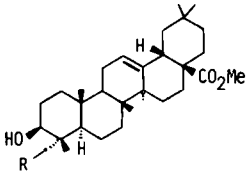
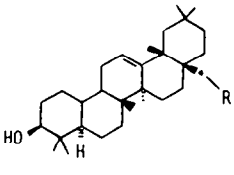
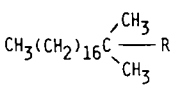
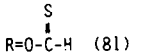
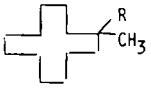
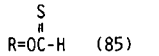
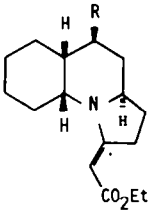
Alcohol	Derivative (Yield %)	Yield of deoxy deriv. (%) (R = H)
 33 : R=OH	R=O-CSSMe	90
 34 : R=OH	R=O-C(=S)-Ph (75)	90 (R=D) 85
 35 : R=OH	R=O-CSSMe	85
 36 : R=OH	R=O-CSSMe (85)	38
 37 : R=OH	R=O-CSSMe (79.)	65
 38 : R=OH	R=O-C(=S)-N(imidazole) (79)	40

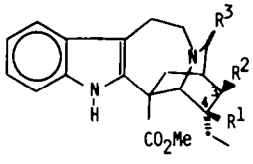
Table 2 (*Contd*).

Alcohol	Derivative (Yield %)	Yield of deoxy deriv. (%) (R = H)
 39 : R=OH	 (81)	83
 40 : R=OH	 (85)	78

Tertiary alcohols can be converted to the corresponding hydrocarbons under mild conditions (80°) and in high yields via thioformyl derivatives[39] (Examples **39** and **40**).

(b) *Alkaloids.* The radical deoxygenation technique has also been successfully applied to alkaloids. As part of his work on the synthesis of gephrotoxin derivatives,[51] Hart[50] achieved the deoxygenation of the quinoline derivative **41**, via the dithiocarbonate **42**, in an overall yield of 90%. In their total synthesis of the antitumour agent vinblastin,[52] Kutney *et al.*[53a,b] selectively removed the C(4)-OH group in the catharanthin derivative **43** via the cyclic thiocarbonate **44**. The reaction of the 3-O-thiobenzoyl derivative **45** with tributyltin hydride gave a 75% yield of the C(3)-deoxy derivative **46**. Classical methods of OH/H exchange via the tosyl and mesyl derivatives failed.





41 : R=OH

↓

42 : R=O-CSSMe

↓

R=H (90% overall)

43 : R^1=R^2=OH, R^3=O

↓

44 : R^1,R^2=  S, R^3=O (98%)

↓

R^1=H, R^2=OH, R^3=O (65%)

- - - - - - - - - - - - - -

R^1=H, R^2=OH, R^3=H_2

↓

45 : R^1=H, R^2=  R^3=H_2 (68%)

↓

46 : R^1=R^2=H, R^3=H_2 (75%)

(c) *Carbohydrates.* Methods of deoxygenation find far more important applications in the carbohydrate field (Introduction). Although primary OH groups can be deoxygenated relatively smoothly by classical (ionic) methods, the S_N exchange of secondary OH groups for H is usually accompanied by

rearrangements and eliminations,[2a-c] poor yields being obtained. In addition to steric hindrance, this is ascribed mainly to electrostatic repulsion between the attacking nucleophile and the C–O dipoles flanking the reaction site.[54,55]

As the examples demonstrate (Table 3), the radical process is not subject to these limitations. The smooth C(4)-deoxygenation[56] of the α-D-mannopyranoside **47** via the thioimidazolide **48** is most impressive, particularly as all attempts to exchange the hydroxy group for hydrogen by an S_N2 process failed and led instead to products of ring contraction.[57]

Pozsgay[58] was able to deoxygenate the α-L-rhamnopyranoside derivatives **49–51** at C(2), C(3) and C(4) in good yields via their corresponding dithiocarbonates. These results are remarkable because conventional deoxygenation methods fail with α-L-rhamnopyranosides (S_N2 exchange at C(2) does not occur; reduction of the C(3) or C(4) tosyl or triflate derivatives leads exclusively to rearranged products[59,60]).

The deoxygenation of the "critical" C(2)-OH group of methyl 3,4-O-isopropylidene-β-L-arabinopyranoside (**52**) has been acheived[61] in 40% yield via the dithiocarbonate **53**, a remarkable yield when one considers that classical methods fail completely[62] and that other techniques, such as photolysis of the thiocarbamate **54**, only give 11% of the C(2)-deoxy derivative.[61]

Furanoses can be selectively deoxygenated in high yields at any chosen position, mainly via the dithiocarbonates. Stick,[63a,b] for example, employed the C(3)-deoxygenation of α-D-galactofuranoside (**55a**), allofuranoside (**56a**) and the extremely hindered gulofuranoside (**57a**) as a key step in the synthesis of abequose and paratose.[64] As part of a total synthesis of (+)-exo-brevicomin,[66] Sherk[65] was able to deoxygenate the α,β-D-xylo-hex-5-enofuranoside **58** at C(2) on a large scale and in good yield.

With the aid of the radical technique Acton[67] succeeded for the first time in deoxygenating the β-D-ribofuranoside derivative **59a** at C(2). This work opened up a new access to analogues of the antitumour agent α-2′-deoxythioguanosine.[68] Surprisingly, the thiobenzoyl derivative **59c** (in contrast to the dithiocarbonate **59b**) reacts with tributyltin hydride to the expected C(2)-deoxy derivative in a mere 11% yield, the main product being the corresponding benzyl ether **59d**. As yet unexplained neighbouring group effects (possibly originating from the C(3)-benzoyloxymethyl group) could be responsible for the unusual course of the reaction.

A variation of the above process, developed by Robins and Wilson,[69] is deoxygenation with tributyltin hydride via phenoxythiocarbonyl derivatives. As was demonstrated on the silyl-protected furanosyl derivatives **60a–c** (Table 3), the reaction occurs in good yield under relatively mild conditions (toluene, AIBN, 75°, 3 hr).

The above monodeoxygenation of 1,2-glycols (see B1.1.) can be successfully applied to 1,3-glycols, as Brown[70] showed with the 2,5-anhydro-α-D-glucitol derivative **61a**. The 6-membered 3,5-thiocarbonate **61b** yields the C(3)-deoxy compound **61c** selectively in 62% yield upon treatment with tributyltin hydride.

The radical deoxygenation method has also found successful application among disaccharides. Defaye[71] was able to deoxygenate the α-D-glucosyl-α-D-glucoside derivative **62a** selectively at C(2′) and simultaneously at C(2) and C(2′) via the corresponding dithiocarbonates **62b** and **62c** in 95% and 92% yields respectively. The exchange of these hydroxy groups for hydrogen, known to be difficult,[2a-c] is most unsatisfactory by traditional methods (for example, nucleophilic substitution of triflate by thiophenoxide and subsequent reduction with Na/NH_3 only gives a 10% yield of the 2,2′-dideoxy derivative[71]).

According to Thiem,[72] β-glycosidic disaccharides can also be radically deoxygenated at C(2). This was demonstrated on the β-D-glucopyranosyl-2-deoxy-2-iodo-α-D-manno-pyranoside derivative **63a**. As well as C(2)-methylxanthogenate cleavage, the reaction with tributyltin hydride generated *in situ*[73] also causes a reductive dehalogenation[74] of the C(2′)-halo function with formation of the C(2), C(2′)-dideoxy derivative **63b**.

(d) *Aminoglycosides.* The selective deoxygenation of aminoglycoside antibiotics is an effective modification leading to derivatives active against resistant bacteria.[75a,b] As numerous examples demonstrate, radical-induced deoxygenation is again superior to the ionic process. Deoxygenation via the thiobenzoates and thioimidazolides has proved of particular value because these derivatives can be prepared under neutral conditions[76,77] leaving acid- or base-labile protecting groups on nitrogen intact. Tsuchiya[78] was thus able to prepare 3′-deoxykanamycin A by selective C(3)-deoxygenation of the 3′,2″-bis(imidazolylthiocarbonyl) derivative **64a**. The 2″-thioimidazoyl group was not attacked under the conditions employed.

Table 3. Deoxygenation of carbohydrates via thiocarbonyl derivatives

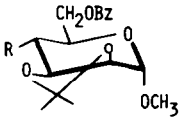
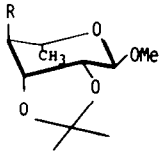
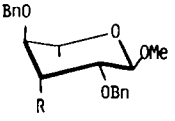
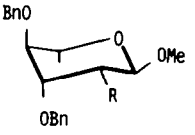
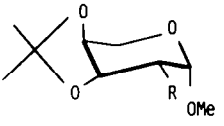
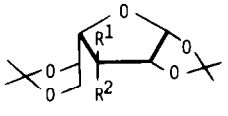
Carbohydrate	Derivative (Yield %)	Yield of deoxy deriv. (R=H) (%)
 47 : R=OH	48 : R=O-C(=S)-N(imidazolyl) (92)	87
 49 : R=OH	R=O-CSSMe (>90)	70
 50 : R=OH	R=O-CSSMe (>90)	51
 51 : R=OH	R=O-CSSMe (>90)	45
 52 : R=OH 54 : R=O-C(=S)-N(Me)$_2$	53 : R=O-CSSMe	40
 55a : R^1=OH, R^2=H 57a : R^1=H, R^2=OH	55b : R^1=O-CSSMe, R^2=H (90) 57b : R^1=H, R^2=OCSSMe (70)	84 (55c : R^1=R^2=H) 75 (57c : R^1=R^2=H)

Table 3 (*Contd*).

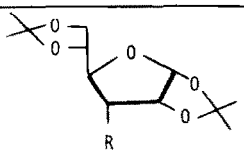
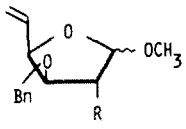
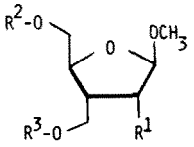
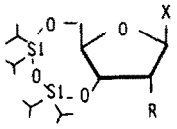
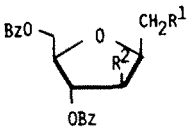
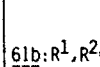
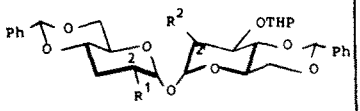
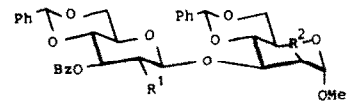
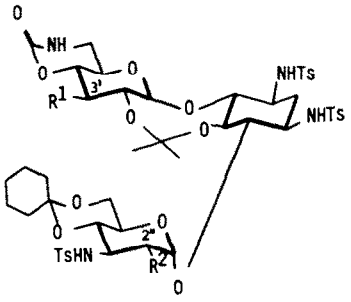
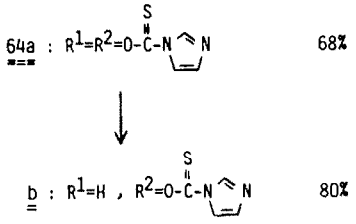
Carbohydrate	Derivative (Yield %)	Yield of deoxy deriv. (R=H) (%)
	56b : R=O-CSSMe (89)	84 (56c: R=H)
56a : R=OH		
	R=OCSSMe (90)	65
58 : R=OH		
	59b : R^1=OCSSMe, R^2=R^3=Bn (82)	67
	59c : R=O-C(=S)-Ph, R^2=R^3=Bz	11 (+59d : R^1=O-CH_2Ph)
59a : R=OH		
		
60a : R=OH, X=OCH_3	R=O-C(=S)-O-Ph	58 a)
b : R=OH, X= 	"	78 a)
c : R=OH, X= 	"	68 a)
	61b: R^1,R^2=  C=S (80)	62 (61c: R^1=OH, R^2=H)
61a : R^1=R^2=OH		

Table 3 (*Contd*).

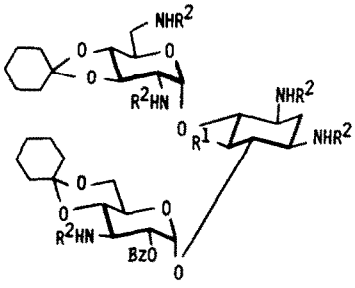
Carbohydrate	Derivative (Yield %)	Yield of deoxy deriv. (R=H) (%)
 62a : $R^1=R^2=OH$	62b : $R^1=R^2=OCSSMe$ (90) c : $R^1=OTHP$, $R^2=OCSSMe$ (92)	95 ($R^1=R^2=H$) 92 ($R^2=H$, $R^1=OTHP$)
 63a : $R^1=OH$, $R^2=I$	$R^1=OCSSMe$ (77)	47 (63b: $R^1=R^2=H$)

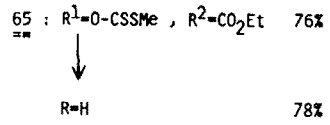
a) Overall yield



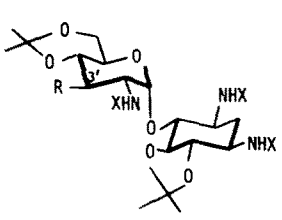


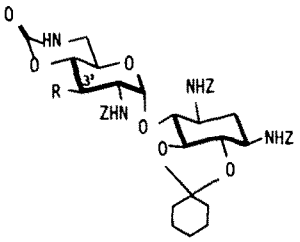
The preparation of 5-deoxykanamycin B[79] by reduction of the dithiocarbonate **65**, and the C(3')-deoxygenation[80] of the paromamine derivative **66a** and the neamine derivative **67a** via the thiobenzoates **66b** and **67b** were just as smooth and in equally high yields.





In the gentamycin class, the smooth C(2'')-deoxygenation[80] of the gentamycin C_2-derivative **68a** (via the thiobenzoate **68b**), and the facile, high yield C(5)-deoxygenation[81] via the gentamycin C_2-5-O-thioformyl derivative **69b** are worthy of special mention here. In addition to these chosen examples numerous other compounds from the gentamycin group have been deoxygenated in the 5-position via thioformyl derivatives[81] and in the 3'-position via thiobenzoates.[80]





66a : R=OH, X=CO_2Et

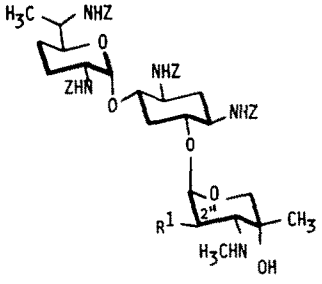
b : R=O-C-Ph (S) 94%

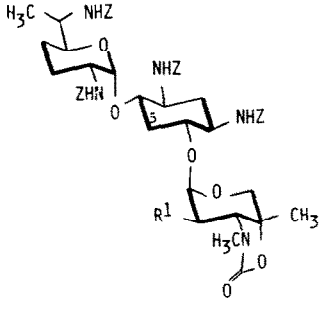
R=H 51%

67a : R=OH

b : R=O-C-Ph (S)

R=H 90%





68a : R^1=OH

b : R^1=O-C-Ph (S) 82%

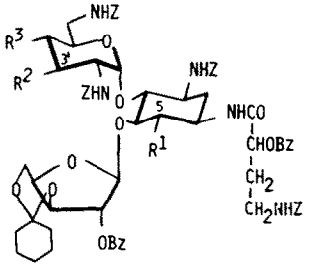
R^1=H 72%

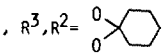
69a : R^1=OH

b : R^1=O-C-H (S) 94%

R^1=H 78%

Radical-induced OH/H-exchange was equally successful in butirosine A.[79] The C(6)-deoxy derivative **70b** was obtained smoothly by tributyltin hydride treatment of the C(6)-methylxanthogenate **70a**. Reduction of the C(3')-phenyldithiocarbonate **71a** gave a high yield of the C(3')-deoxyaminoglycoside **71b**.



70a : R^1=O-CSSMe, R^3,R^2= 

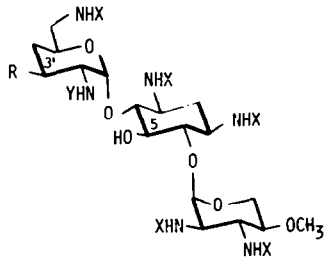
b : R^1=H 80%

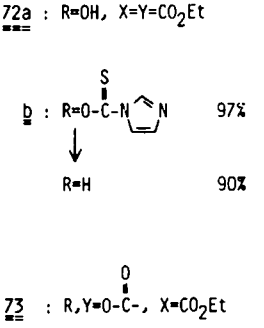
71a : R^1=R^3=OAc, R^2=O-CSSPh

b : R^2=H 82%

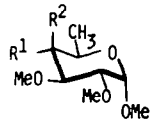
In the C(3')-deoxygenation[82] of the seldomycin factor 5 derivative **72a**, the radical process (via the thioimidazolide **72b**) was found to be the only viable route. Numerous attempts at S_N replacement of the C(3')-tosyl or -mesyl group by iodine failed, leading exclusively to the 2'-N-3'-O-carbonate **73**.

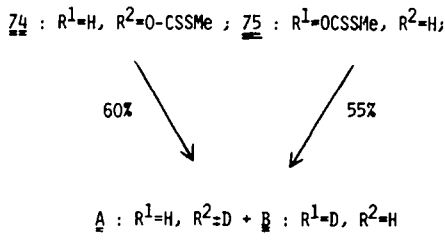
Interestingly, treatment of **72a** with N,N'-thiocarbonyldiimidazole leads to a high yield acylation of the C(3')-OH group alone. Fortunately, the remaining, free C(5)-OH group does not interfere in the subsequent reduction with tributyltin hydride (in dioxan). 3'-Deoxyseldomycin factor 5 has an increased antibacterial activity[82] in comparison to its hydroxy precursor; this is true of most of the deoxyaminoglycosides mentioned above.





1.3 *Stereochemistry of the radical-induced deoxygenation.* To investigate the question whether radical deoxygenation goes via a S_{H^2} process (inversion of configuration), a configurationally stable sp^3 radical (retention) or a planar sp^2 radical intermediate, Stick *et al.*[83] deoxygenated several hexofuranosyl derivatives using tributyltin deuteride. In the reduction of the C(3)-dithiocarbonates **55b** and **57b** (Table 3) with tributyltin deuteride, the (*exo*)-3-deoxy-3-deuterio derivative **55c** ($R^1 = D$ instead of H) was formed exclusively in both cases. This result accords with the assumption of an intermediate radical of sp^2 configuration and the attack of tributyltin deuteride from the less-hindered *exo* side. This mechanistic assumption is given further support from the deoxygenation[84] of the α-D-allofuranoside derivative **56b** (Table 3) and the C(3)-anomer **22** (Table 1), in which tributyltin deuteride treatment furnished the 3-deoxy compounds in both cases in the ratio *exo*[D]: *endo*[D] = 85:15. On the other hand, C(4)-deoxygenation[85] of the *galacto*- and *gluco*-dithiocarbonates **74** and **75** yielded a 1:1 mixture of the two 4-*exo*-[D] and 4-*endo*-[D] isomers A and B. Apparently neither of the two "heterocyclic planes" is favoured in the attack by tributyltin deuteride. The inducing effects of the substituents at C(1), C(2) and C(3), C(5) cancel each other out.

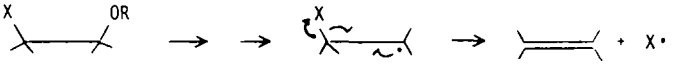




1.4 *Advantages and limitations of the method.* As the above examples have demonstrated, the radical-induced deoxygenation of alcohols via thiocarbonyl derivatives is generally applicable and particularly suitable for sterically hindered polyfunctional compounds. The alcohol derivatives are normally obtainable in high yields under neutral conditions. As has been reported recently, dithiocarbonyl derivatives of alcohols can also be prepared easily and almost quantitatively by the phase-transfer

technique.[41] Functional groups such as ester and ketone, double and triple bonds, epoxide, tosylate and mesylate etc. are unaffected under the reaction conditions. Halogen[74,20] and isocyanide groups,[86] in contrast, are reduced by tributyltin hydride. The deoxygenation process is not applicable to OH groups that have a neighbouring substituent, easily removed under radical conditions, in the β-position. Reaction of the thiocarbonyl derivatives of such alcohols with tributyltin hydride then leads exclusively to olefins, as has been shown for the sulphides **76** and sulphones **77**,[87] and the 1,2-bisdithiocarbonates **78**.[29,79] Mechanistically, this radical olefination[88] (Scheme 8) may be compared with the reduction of vicinal dihalides[89] or β-phenylthio-alkyl bromides[90] with tributyltin hydride, in which the alkyl radical **79** formed in the first step stabilises to the olefin by *anti*-elimination of the substituent X.

Dithiocarbonyl derivatives of β-hydroxyisocyanides also yield olefins with tributyltin hydride, although, in contrast to the above, the alkyl radical is generated by cleavage of the isocyanide group[91] and subsequent loss of the xanthogenate residue.



76 : X=SPh, R=CSSMe

79

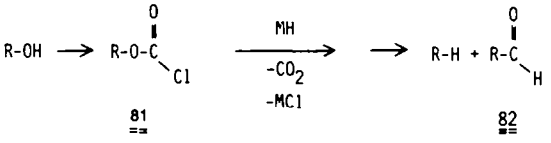
77 : X=SO_2Ph, R=C(=S)-Ph

78 : X=OCSSMe, R=CSSMe

Scheme 8

2. *Deoxygenation via chloroformates*

The reduction of chloroformates **81** to hydrocarbons using organotin hydrides was first described by Kuivila and Walsh[92] for the benzyl ester **81a**. The reaction, which takes place at room temperature, only gives the hydrocarbon in poor yield, the main product being the corresponding formyl derivative **82a**. The same result was obtained by Beak and Mojé,[93] who reduced aliphatic chloroformates with trialkylstannanes and trialkylsilanes.



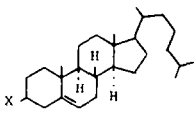
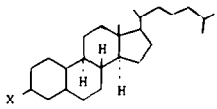
81 **82**

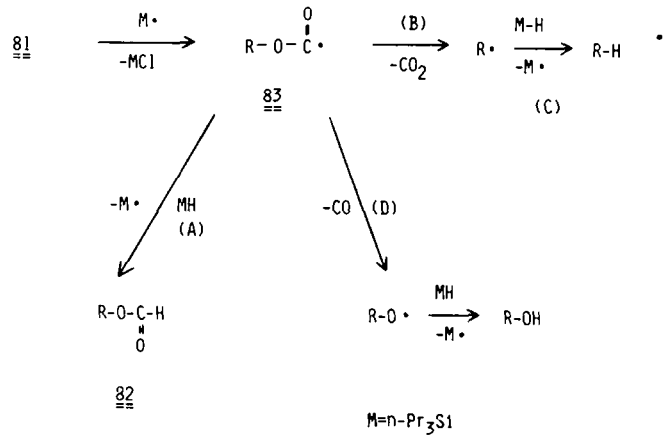
As Jackson *et al.*[94] showed, the reduction of the esters **81** to hydrocarbons can be achieved in excellent yield in some cases if the reaction is carried out at higher temperatures (140–160°) and with tri-n-propylsilane as reducing agent (Table 4).

The dependence of product distribution upon temperature accords with a radical mechanism (Scheme 9) in which, in the first step, the silyl radical generated from tri-n-propylsilane and t-butyl peroxide reacts with the ester **81**, forming the alkoxy-carbonyl radical **83**. **83** stabilises at lower temperatures by H-abstraction, giving the formyl derivative **82** (Path A). Higher temperatures favour fragmentation to the alkyl radical with loss of CO_2 (Path B). The alkyl radical subsequently abstracts H from another Pr_3SiH molecule forming the hydrocarbon and also propagating the radical chain (Path C).

The use of a trialkylsilane instead of a trialkylstannane impedes H-abstraction with formation of the formyl derivative **82** (Path A), owing to the greater stability of the Si–H bond (compared with the Sn–H bond[95]), and thus favours fragmentation (Path B) even more. The H-abstraction in Path C is, however, equally impeded in that less energetic (stabilised) radicals R· only react slowly with Pr_3SiH, as is documented in the low yield of toluene from the reduction of the benzyl ester **81**. Deoxygenation of phenolic OH groups does not succeed because in this case decarbonylation to the phenoxy radical (Path D) is favoured over decarboxylation (Path B).[96] Chloroformates of tertiary alcohols undergo elimination to olefins under the reaction conditions (Example **81g**).[97]

Table 4. Deoxygenation with n-Pr_3Si at 140° via chloroformates **81**

	Reaction time (h)/ Pr_3SiH pro Mol **81** (mol)// $t\text{-}Bu_2O_2$ pro Mol **81** (mol)	Yield of deoxy compound, R=H (%)
a: $PhCH_2X$	8 / 1.4 // 0.9	11
b: $n\text{-}C_8H_{17}X$	4 / 4.6 // 0.5 24 / 1.8 // 0.5	92 85
c: 	4 / 3.2 // 0.9	91
d: $CH_3\text{-}C(=O)(CH_2)_2CH_2X$	17 / 2 // 1	69
e: 	24 / 2.6 // 1	25 (+ )
f: 	24 / 3.4 // 1.1	77
g: Et_3CX	4 / 1.8 // 1.0	18



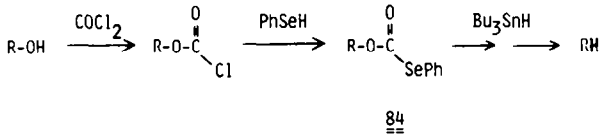
Scheme 9

As a rule the deoxygenation of alcohols via chloroformates is thus limited to simple primary and secondary aliphatic alcohols, not in the least because unusually large quantities (50–110%) of $(BuO)_2$ radical starter are required for high yields to be obtained.

Functional groups such as ketones (Example **81d**) survive the reaction conditions, but side reactions—such as in **81e**—must be expected with more sensitive compounds.

3. *Deoxygenation with tributyltin hydride via phenylselenocarbonates*

Phenyl selenocarbonates **84**, prepared from chloroformates and selenophenol, can be reduced to hydrocarbons, sometimes in very good yields, with tributyltin hydride (Scheme 10).



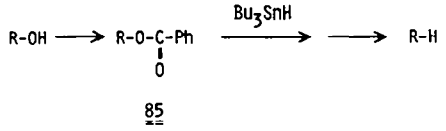
Scheme 10

This process for the deoxygenation of primary and secondary alcohols, developed by Pfenniger *et al.*,[98] has an analogous mechanism to the chloroformate method (see above) but has the advantage of very short reaction times (2–60 min) and only needs catalytic amounts of radical starter (AIBN). This is mainly due to the high affinity of Sn for Se and hence the particularly smooth S_H2 reaction with formation of the alkyloxycarbonyl radical **83** (Scheme 9). High temperatures (144°) are, however, essential for the fragmentation of **83**; otherwise (at 80–100°) mixtures of the formyl derivative **82**, alcohol and alkane are formed (Scheme 9).

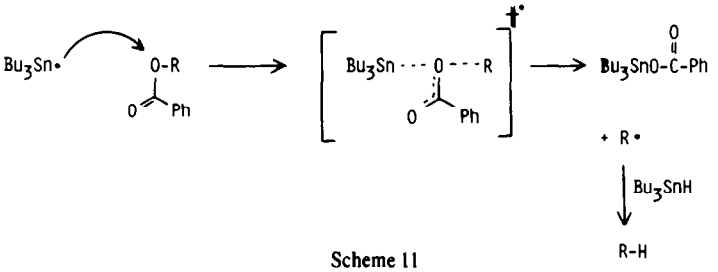
As the examples indicate (Table 5), ester and α,β-unsaturated ketone groups are not affected under the reaction conditions. Rearrangements, as could be expected with β,γ-unsaturated alcohols (Example **84b**), have not been observed (in contrast to **81e**, Table 4). Tertiary alcohols can be smoothly deoxygenated via selenocarbonates (see **84g**) but the preparation of the derivatives **84** can only be achieved in unsatisfactory yield (e.g. **84g** is only obtained in 14% yield, compared with 80–90% in the case of primary or secondary alcohols).

4. *Via benzoates with tributyltin hydride*

Owing to the easy availability of benzoates **85**, the deoxygenation of alcohols with tributyltin hydride via these derivatives seems a very attractive proposition, but only succeeds with alcohols that bear a radical-stabilising substituent in the α-position to the hydroxy group. This method is thus practically limited to benzyl, allyl- and α-keto-alcohols.



This difference in reaction behaviour of benzoates, compared with chloroformates and selenocarbonates, is attributed by Khoo and Lee[99] to a fundamentally different reaction mechanism. Here the tin radical, generated as usual from a tin hydride and initiator or by photolysis, attacks at the ether oxygen in a kind of S_H2 reaction with cleavage to the alkyl radical (Scheme 11). The reaction is thus particularly easy when stabilised alkyl radicals can form. Triphenylmethanol, for example, is deoxygenated via its benzoate **85c** to the extent of 68% within 2 hr, whereas the reaction of the corresponding n-butyl ester **85f** only occurs to 10% even after 50 hr (Table 6).



Scheme 11

The general applicability of the method is further limited because, under the reaction conditions, side reactions occur such as the addition of tributyltin hydride on terminal double bonds (Example **85e**) or isomerisations (Example **85d**).

In contrast, the deoxygenation of tertiary α-ketoalcohols takes place much more easily and in higher yields, as Redlich *et al.*[100] demonstrated on several ketosugars (see **85g–i**). The high stereoselectivity

Table 5. Deoxygenation via selenocarbonates **84** with Bu_3SnH

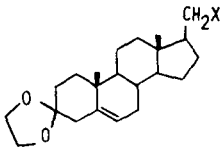
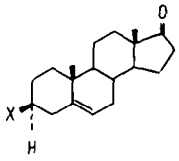
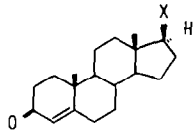
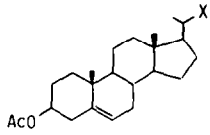
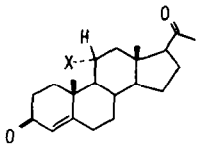
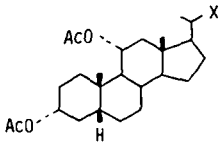
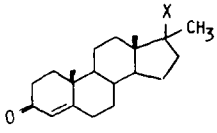
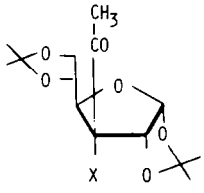
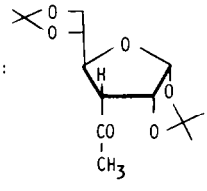
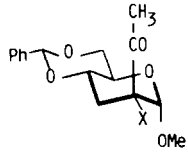
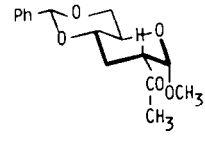
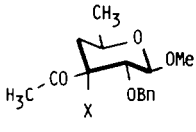
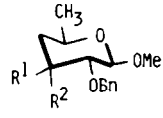
84	R-X (X=O-C(=O)-SePh)	Temp. (°C)	Yield of deoxy compound R-H (%)
a		164	66
b		144	73
c		144	54
d		144	90
e		144	83
f		144	83
g		80	81

Table 6. Deoxygenation via benzoates **85** with Bu_3SnH

85	R-X (X=O-C(=O)-Ph)	Temp. (°C) Reaction time (h)	Yield of deoxy compound (%)
a:	$PhCH_2X$	130 / 3.5 [b]	75
b:	Ph_2CHX	130 / 6 [c]	78
		80 / 24 [d]	62
c:	Ph_3CHX	130 / 2 [b]	68
d:	$PhCH=CHCH_2X$	130 / 2.5 [b]	65 (mixture of $PhCH=CHCH_3$ and $PhCH_2-CH=CH_2$)
e:	$CH_2=CH-CH_2X$	80 / 7 [b]	-- ($Bu_3Sn-CH_2-CH_2-CH_2X$, 41%)
f:	n-BuX	130 / 50 [b]	(10) [a]
g:		110 / 2 [d]	80: 
h:		110 / 2 [d]	80: 
i:		110 / 2 [d]	 64 (R^1=CO-CH_3, R^2=H) 16 (R^1=H, R^2=CO-CH_3)

[a] Calcd. from $Bu_3SnOCOPh$ obtained; [b] UV; [c] n-Bu_2O_2; [d] AIBN

observed is explained with an intermediate, planar sp^2 radical and attack of the tin hydride under "steric approach control", i.e. from the less hindered side of the heterocycle (*cf* B.1.3).

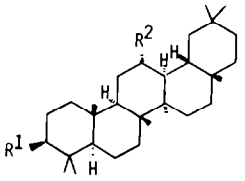
C. GENERATION OF THE INTERMEDIATE RADICAL BY ELECTRON TRANSFER (ACCORDING TO SCHEME 3)

1. *Deoxygenation via carboxylates*

1.1. *With alkali metals as electron source* ("*Dissolving metal reduction*"). As is well-known, carboxylates are reduced by alkali metals to alcohols in the presence of a proton source (e.g. EtOH) (Bouveault–Blanc Reduction[101]); in the absence of proton donors acyloins are formed.[102a-d] In the meantime several reports of deviations from this "classical" manner of reaction have appeared.

Sterically hindered methyl carboxylates mainly yield the free carboxylic acid under Bouveault-Blanc reduction conditions,[103–106] and in the case of benzyl esters the formation of dibenzyl has been observed.[107] The reaction of per-O-acetylgentamycin C_1 with sodium in liquid ammonia also took a "surprising" course, 4″-deoxygentamycin C_1 being isolated in 11% yield.[108]

As Barton *et al.* found recently,[109] sterically hindered OH groups can be smoothly deoxygenated with $Li/EtNH_2$ via the acetyl derivatives. This was first shown with 3β, 12α-diacetoxy-13α-oleanane **86a**. Interestingly, $Li/EtNH_2$ selectively deoxygenates the 12α-OH group; the less sterically hindered 3β-OH group is unaffected and merely regenerated from its acetate.

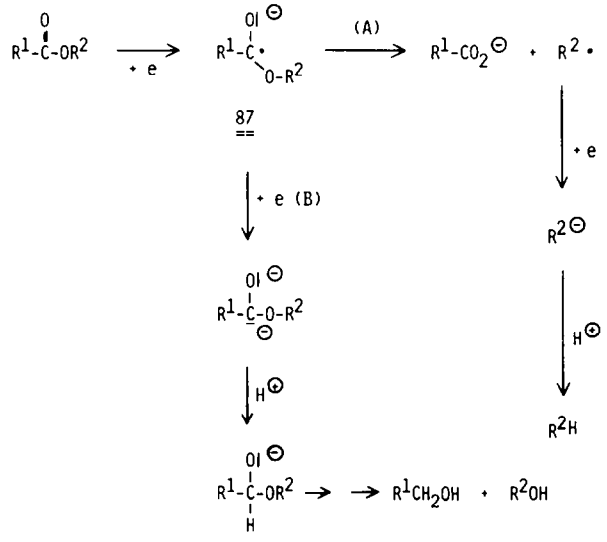


86a : $R^1=R^2=OAc$

↓ Li / $EtNH_2$

b : $R^1=OH$, $R^2=H$ 85%

The unusual course of the reaction, in comparison to Bouveault–Blanc reduction or acyloin condensation, can be explained according to Path A in Scheme 12 in which the radical anion **87**, formed by electron transfer, fragments to an alkyl radical and carboxylate anion. Reduction of the alkyl radical to carbanion and subsequent protonation furnishes the hydrocarbon.



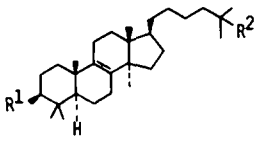
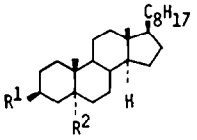
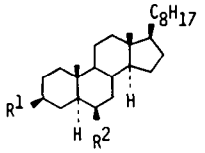
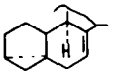
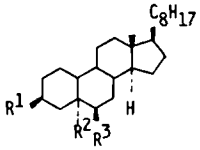
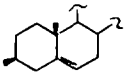
Scheme 12

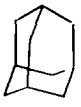
Further investigations[110,111] have shown that deoxygenation with $Li/EtNH_2$ occurs relatively smoothly at room temperature in the case of tertiary and sterically hindered secondary OH groups, but fails for primary and non-hindered secondary OH groups (Table 7, Examples **88a**, **89a**). This difference in reaction behaviour is ascribed to a competing amidolysis of the carboxylate by ethylamine, releasing the alcohol. Replacement of ethylamine by tertiary butylamine and the use of K/18-crown-6[112] instead of Li were found to have a favourable effect. For example, the deoxygenation of 5α-cholestan-3β,6β-diol was achieved under these conditions to give the C(6)-deoxy derivative **90f** in 71% yield via the isobutanoyl derivative **90c**. Only 16% **90f** was obtained with $Li/EtNH_2$.

Furthermore, as was demonstrated with the diol **90a**, bulky acyl residues cause a marked increase in yield of deoxy product. For example, only the sterically hindered 6β-OH group was deoxygenated in 56 and 71% yields respectively upon reduction of the acetoyl derivative **90b** and isobutanoyl derivative **90c**. Deoxygenation of the less hindered 3β-OH group succeeded as well in 40 and 51% yields when the pivaloyl derivative **90d** and adamantoyl derivative **90e** were used.

The relatively low yields of alkane from sterically unhindered alcohols, even when potassium/t-$BuNH_2$/18-crown-6 is used, is ascribed to competing transacylation. It was found that under the reaction conditions the crown ether is reduced to an alkoxide radical, which acts as a powerful nucleophile. This

Table 7. Deoxygenation with alkali metals via carboxylates

Alcohol	Derivative	Reaction conditions	Product yield (%)
 **88a** : R^1=R^2=OH	**88b** : R^1=R^2=OAc	Li/$EtNH_2$	75 (R^1=OH, R^2=H)
 **89a** : R^1=R^2=OH	**89b** : R^1=R^2=OAc	Li/$EtNH_2$	66 (R^1=OH, R^2=H)
 **90a** : R^1=R^2=OH **f** : R^1=OH, R^2=H	**90b** : R^1=R^2=AcO	K/t-$BuNH_2$/ 18-crown-6	56 (**90f**)
	c : R^1=R^2= $(CH_3)_2CHCO_2$	"	71 (**90f**)
		Li/$EtNH_2$	16 (**90f**)
	d : R^1=R^2= t-$C_4H_9CO_2$	K/t-$BuNH_2$/ 18-crown-6	37 (**90f**) 30 (R^1=R^2=H) 10 (R^1=H, R^2=OH)
	e : R^1=R^2= $AdCO_2$ [a]	"	45 (R^1=R^2=H), 27 (**90f**), 6 (R^1=H, R^2=OH)
5α-Cholestan-3β-ol (**4** : R=OH, see Tab. 1)	**91** : R=$AdCO_2$ [a]	K,Na/t-$BuNH_2$/ aza-crown [b]	90 (R=H) 52 [c] (R=H)
n-$C_{17}H_{35}CH_2$R (**92a** : R=OH)	**92b** : R=OAc	"	49 (R=H)
	c : R=$AdCO_2$ [a]	"	74 (R=H)
Ergosterol (**10** : R=OH) (see Tab. 1)	R=$(CH_3)_3CO_2$	K,Na/t-$BuNH_2$/ 18-crown-6	87:  **93**
 **94a** : R^1=R^2=R^3=OH	**94b** : R^1=R^2=R^3= OAc	Li/$EtNH_2$	81:  **95**

a) Ad= 

b) "Aza-crown"= 1,4,7,10,13,16-Hexamethyl-1,4,7,10,13,16-hexa-aza-cyclooctadecane

c) -48°C

undesired competitive reaction can be suppressed by using the more stable aza-crown ether analogue 1,4,7,10,13,16-hexamethyl-1,4,7,10,13,16-hexa-aza-cyclooctadecane instead of 18-crown-6, and/or a eutectic sodium–potassium mixture[113] instead of K alone. Under these conditions 5α-cholestan-3β-ol **4** was deoxygenated in 90% yield via the adamantoyl derivative **91**. Deoxygenation of primary alcohols also occurs in good yields. Octadecan-1-ol (**92a**) was converted to octadecane in 49% yield via the acetate **92b** and in 74% yield via the adamantoyl derivative **92c**.

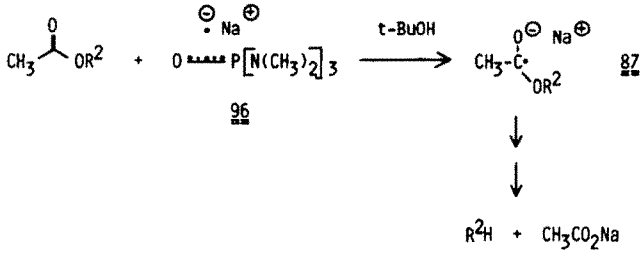
Temperature has a critical influence on the course of the reaction, as shown with the example **91**. At room temperature deoxygenation occurred in high yield, whereas, at lower temperatures (e.g. −48°), Bouveault-Blanc reduction takes over with release of the alcohol and reduction of the acyl component. Apparently the lifetime of the radical anion is longer under these conditions thus favouring further reduction to the dianion and subsequent Bouveault–Blanc reaction (Scheme 12, Path B).

It should be mentioned at this point that radical anions of the type **87** generally fragment to carboxylate and alkyl radical at room temperature—as has been confirmed by experiments (*cf* also C1.2.). The Bouveault–Blanc reduction and acyloin condensation are thus *exceptions* to this rule and due to specific reaction conditions.

The process described above permits, as a matter of choice, not only the selective OH→H exchange of tertiary or sterically hindered secondary OH groups, but also the deoxygenation of primary and sterically unhindered secondary alcohols. The applicability of the method is limited in so far as rearrangements and eliminations can occur in special cases. For example, deoxygenation of ergosterol (**10**) gave the cyclopropyl derivative **93** in high yield; the 1.2 diol **94a** was converted in 81% yield to the olefin **95** via the diacetyl derivative **94b**. Deoxygenation of carbohydrates by this method has not yet been realised.

For the sake of completeness, the long-known and smooth deoxygenation of allylalcohols[114] and α-ketoalcohols[115] via the acetyl derivatives by treatment with $Li/EtNH_2$ and Ca/NH_3 should be mentioned here. The driving force in these reactions is the formation of the stable allyl radical (or anion) and the enolate respectively (*cf* here the deoxygenation of α-ketoalcohols with Zn/acetic acid[116]).

1.2. *Electron transfer by radical anions.* The deoxygenation method discovered by Pete and Deshayes[117] is a variant of the above process. Here, alcohols are converted in good yields, via their acetates, into hydrocarbons with Na/HMPTA/t-BuOH (Scheme 13).

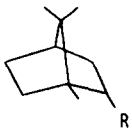
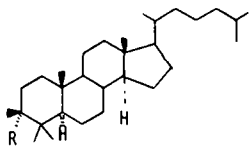
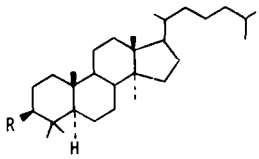


Scheme 13

As a difference to the previously described method, the radical anion **96**,[118] generated from sodium and hexamethyl-phosphoric triamide (HMPTA), functions as electron donor. Although the radical anion **87** (see Scheme 12) is assumed to be an intermediate, as in the alkali metal/amine reduction, the reaction has different characteristics. Tertiary alcohols are also deoxygenated in excellent yields (Example **100**, Table 8) but the deoxygenation of sterically hindered secondary OH groups gives lower yields than that of primary (Example **97** and **98**, **101**). The best results are, moreover, obtained with *acetyl* derivatives; the extent of deoxygenation declines with esters of higher carboxylic acids. Tertiary butanol has a decisive influence on the course of the reaction. As has been shown with 5α-cholestan-3β-ol (**4**), a 38% yield of 5α-cholestane was obtained in the absence of t-butanol but a 69% yield when t-butanol was added.

The details of the reaction mechanism, and particularly the role of t-butanol, are still unexplained. Pete's suggested protonation of the radical anion **87** by t-butanol and subsequent fragmentation to carboxylic acid and alkyl radical is, however, improbable from a consideration of pKa values.[119] The results for sterically hindered secondary OH groups, contrasting as they do with those of the alkali metal/amine reduction, are possibly due to impeded electron transfer by the bulky HMPTA radical and competing transacylation by dimethylamine (from $HMPTA^{\cdot\ominus}/Na^{\oplus}$[118]). Olefinic double bonds

Table 8. Deoxygenation with Na/HMPTA/t-BuOH via carboxylates

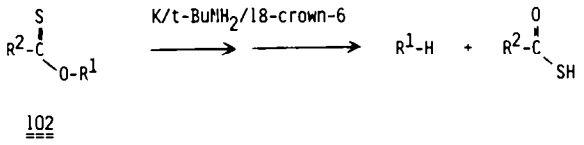
Alcohol	Carboxylate: R^1-CO_2R, R=	Deoxy cmpd. yield (%)
$CH_3(CH_2)_7CH_2R$ (97: R=OH)	CH_3	56
 98	CH_3	32
Cyclohexanol (99)	CH_3	40
5α-Cholestan-3β-ol (4 : R^2=OH)	CH_3	69 (38) [a]
	H	30
	$(CH_2)_5CH_3$	52
	Ph	45
Cholest-5-en-3β-ol (9 : R=OH)	CH_3	65 (Cholestane)
 100 : (R=OH)	CH_3	95
 101 : (R=OH)	CH_3	50

[a] Without t-BuOH

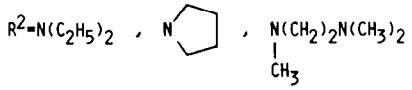
are reduced under the reaction conditions. Cholest-5-en-3β-ol (**9**), for example, gives a 65% yield of 5α-cholestane via its acetyl derivative.

2. *Deoxygenation via thiocarbamates* **102**

As has been discussed in Section C1.1, the deoxygenation of primary and non-hindered secondary alcohols, via their carboxylic esters, sometimes leads to unsatisfactory results owing to competing transacylation. Thiocarbamates of the type **102** ($R^2 = NR_2$, Scheme 14) should be inert towards nucleophilic attack under the reaction conditions (K, t-$BuNH_2$, 18-crown-6, RT) and hence furnish higher yields of deoxy product.



102



Scheme 14

As the examples show (Table 9), this assumption is confirmed by experiment.[120a,b] 5α-Cholestan-3β-ol (**4**) and octadecan-1-ol (**92a**), for example, were converted to the corresponding hydrocarbons in high yield via their N,N-diethylthiocarbamates.

A whole series of other derivatives such as thioacetates, S-methyl xanthogenates and even N-monosubstituted thiocarbamates regularly gave poorer results. As N,N-dialkylthiocarbamates are readily available in high yield from the corresponding S-methyl xanthogenates, this method is a useful complement to the process described in Section C1.1. The mechanism of the reaction is assumed to involve the fragmentation of a radical intermediate, a thio analogue of **87** (see Scheme 12), as in the case of carboxylates. The driving force is the transition from a C=S to the more stable C=O double bond.

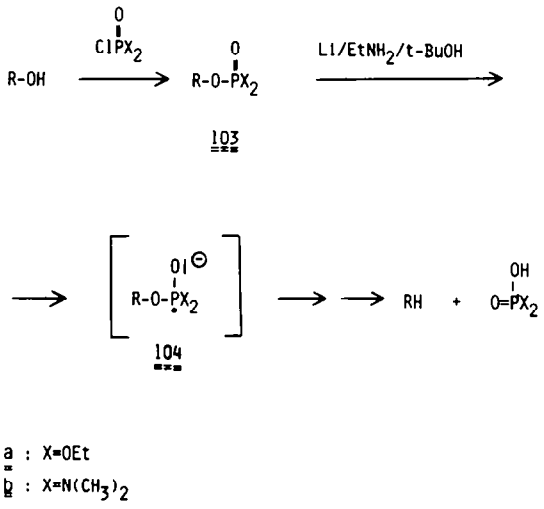
3. *Deoxygenation with* $Li/EtNH_2$ *via phosphates and phosphoramidates*

3.1 *Aliphatic alcohols.* Ireland *et al.*[121] have developed a very effective method for deoxygenation of alcohols by reduction of the phosphates **103a** or phosphoramidates **103b** with $Li/EtNH_2$ (Scheme 15).

As the examples demonstrate (Table 10), the deoxygenation occurs in excellent yield with primary, secondary and tertiary alcohols. Furthermore, the phosphate derivatives **103a,b** are readily available in practically quantitative yield by treatment of the alcohol with diethyl phosphochloridate or N,N,N',N'-tetramethyl phosphochlorodiamidate. (A very efficient method using N,N-dimethyl phosphodich-

Table 9. Deoxygenation with $K/t\text{-}BuNH_2$/18-crown-6-via thiocarbamates **102**

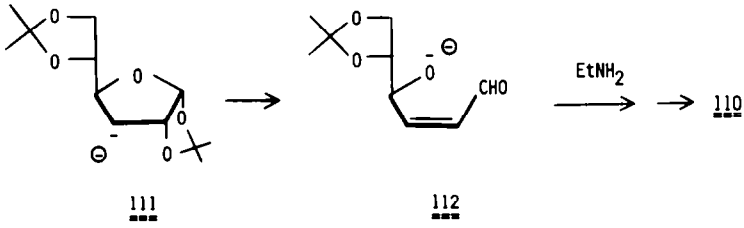
Alcohol	Derivative 102, R^2=	Deoxy cmpd. yield (%)
5α-Cholestan-3β-ol (4 : R=OH)	Et_2N	86
		74
5α-Cholestan-3β,6β-diol (90a)		62 (5α-Cholestane) 15 (90f) 12 (5α-Cholestan-3β-ol)
n-Octadecanol (92a)	Et_2N	87
22 (s. Tab. 2)	Et_2N	14



Scheme 15

loroamidate has recently been developed[122] for the preparation of phosphoramidates **103b** of extremely sterically hindered alcohols.) Olefinic double bonds remain intact (even in β,γ-unsaturated alcohols) during the reaction with $Li/EtNH_2$ (Examples **106** and **9**). This method may also be applied to the deoxygenation of carbohydrates. Oida *et al.*[123] reported the successful C(3)-deoxygenation of the 2-deoxy-2-amino-α-D-glucopyranoside derivative **109** in 72% yield via the phosphorodiamidate, although the urethane protecting group was cleaved to a certain extent. In contrast to this, the expected C-(3)-deoxy-sugar was not obtained from the α-D-glucofuranose derivative **22** under the same conditions, but rather a high yield of N-ethyl-dideoxyhexofuranosylamine (**110**).

The formation of **110** can be explained by the formation of an intermediate C(3)-anion **111**, which reacts further to the α-β-unsaturated aldehyde **112** with elimination of the 1,2-isopropylidene group. Reduction of the double bond and aminolysis then leads to the furanosylamine **110**.



Attempts at deoxygenating the primary C(6)-OH group in the galactopyranoside **113** via its phosphorodiamidate failed. Reaction with $Li/EtNH_2$ led here to exclusive formation of the original alcohol **113**. This behaviour is in conflict with Ireland's observations that primary aliphatic alcohols such as **107** can be almost quantitatively deoxygenated via phosphorodiamidates.

The mechanism of the reaction, and in particular the different ways of reacting among carbohydrates, has not, as yet, been elucidated in detail but fragmentation of the radical anion **104** to an alkyl radical and phosphate is assumed to be the key step (*cf* Scheme 15 and, in analogy, Scheme 12).

3.2 *Phenols.* Deoxygenation of phenolic OH groups by reduction of the corresponding aryl diethyl phosphates **114** with Na/NH_3 was first described by Kenner and Williams.[124] In careful experiments, Pelletier and Locke[125] were unable to reproduce the excellent reported yields in the case of polycyclic aromatics. Rossi and Bunnett[126] subjected the reaction to close examination and, after a slight modification to the method, obtained very high yields of aromatic hydrocarbons in some cases (Table 11). To prevent the competing Birch reduction of the aromatic ring, the Kenner–Williams method was modified by addition of sodium benzoate as an electron scavenger before acidification of the reaction mixture. In this way aryl radical anions are (re)-oxidised to aromatics. Olefinic double bonds (Example **121**) and CO groups (Example **120**) are inert under these reaction conditions, but NO_2 groups are reduced (Example **122**).

Table 10. Deoxygenation with Li/$EtNH_2$ via phosphates **103a** and phosphorodiamidates **103b**

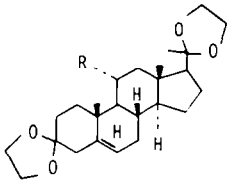
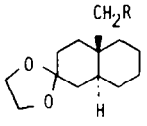
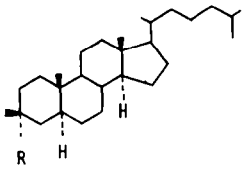
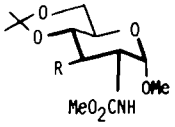
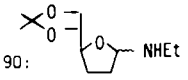
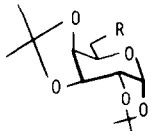
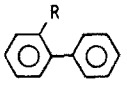
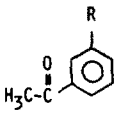
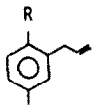
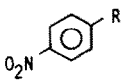
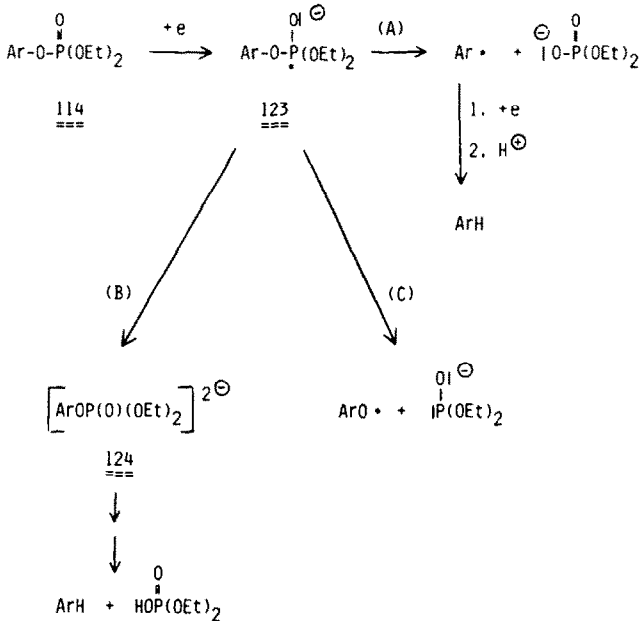
Alcohol	Derivative (yield, %)	Deoxy cmpd. yield (%)
 105 : R=OH	$R{=}OP[N(CH_3)_2]_2$ (90)	92
 106 : R=OH	$R{=}OP[N(CH_3)_2]_2$ (93)	92
 107 : R=OH	$R{=}OP[N(CH_3)_2]_2$ (92)	97
 108 : R=OH	$R{=}OP[N(CH_3)_2]_2$ (82)	91
Cholest-5-en-3β-ol (9)	$R{=}OP[N(CH_3)_2]_2$	96
5α-Cholestan-3β-ol (4)	" (91)	99
 109 : R=OH	$R{=}OP[N(CH_3)_2]_2$ (75)	72
22 (s. Tab. 2)	" (85)	90:  110
 113 : R=OH	"	—

Table 11. Deoxygenation of phenols via aryl diethyl phosphates **114** with alkali metals in liq. NH_3

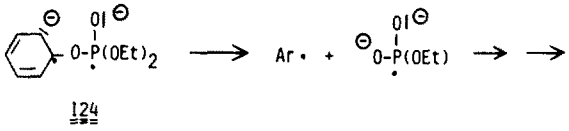
Phenol	Metal	Deoxy cmpd. (R=H), yield (%)
 **115** : R=OH	K	77
 **116** : R=OH	K	92
 **117** : R=OH	K	77
 **118** : R=OH	K	96
 **119** : R=OH	K	28
 **120** : R=OH	Na	71
 **121** : R=OH	Li	81
 **122** : R=OH	Li	13

Bunnett and Rossi proposed the fragmentation of the radical anion **123** to aryl radical and phosphate[127] (Path A, Scheme 16) as reaction mechanism because they were able to detect aryl radicals by trapping reactions.[128] On the other hand, Closson *et al.*[129] favoured the fragmentation of the dianion **124** (Path B), formed by transfer of a second electron. As was demonstrated, the reaction of aryl phosphates with reducing agents weaker than Na/NH_3 (e.g. $Na^{\oplus}$/anthracene$^{\cdot\ominus}$) and with a lower concentration of electron donor led mainly to regeneration of the phenol. Under these conditions, this behaviour is explained by the more rapid fragmentation of the radical anion **123** to a phenoxy radical (Path C) compared with further reduction to the dianion **124** (Path B).



Scheme 16

At this point attention should be drawn to the generally different reaction mechanism for the deoxygenation of aliphatic alcohols compared to that of phenols. Whereas alkyl phosphates, after transfer of *one* electron, fragment to the alkyl radical via the radical anion **104**, the transfer of *two* electrons is necessary in the case of aryl phosphates to provoke the desired cleavage. Otherwise fragmentation to the stable phenoxy radical occurs (*cf* here the fragmentation of phenoxycarbonyl radicals in B2). According to Closson the dianion **124** is to be regarded as a diradical anion whereupon the fragmentation can occur easily in the sense of an anionic 1,2-elimination (Scheme 17).



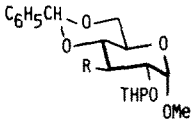
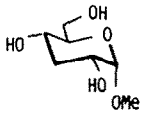
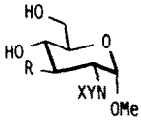
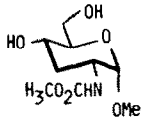
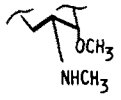
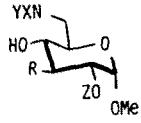
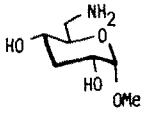
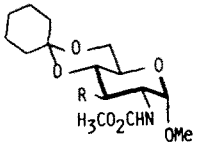
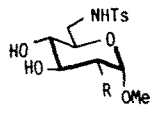
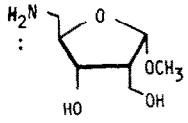
Scheme 17

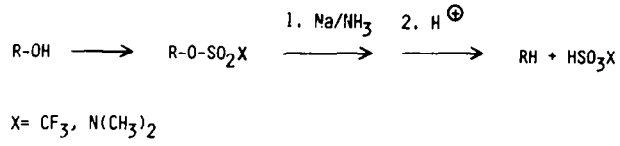
4. *Deoxygenation via sulphonates*

4.1. *Aliphatic alcohols.* Toluenesulphonates of aliphatic alcohols are cleaved almost quantitatively to alcohol and sulphinate upon treatment with Na/NH_3[130] or $Na^{\oplus}$/naphth$^{\cdot\ominus}$.[131] In contrast, reaction of alkanesulphonates (e.g. mesylates) with $Na^{\oplus}$/naphth$^{\cdot\ominus}$[132] or potassium[133] leads to a 20–30% yield of the corresponding hydrocarbon.

As Tsuchiya *et al.* discovered, alcohols can be deoxygenated via trifluoromethanesulphonyl[134] or N,N-dimethylsulphamoyl[135] derivatives in high yields using Na/NH_3 (Scheme 18). This was demonstrated on several carbohydrates (Table 12). The sulphamoyl derivatives generally gave higher yields of deoxy compound than the triflates, but the latter are more readily available under milder conditions from the alcohol and trifluoromethylsulphonic anhydride.

Table 12. Deoxygenation with Na/NH_3 via trifluormethanesulphonyl and N,N-dimethylsulphamoyl derivatives

Alcohol	Derivative	Yield (%), product
	$R=OSO_2N(CH_3)_2$	80 
125 : R=OH		
	$R=OSO_2N(CH_3)_2$, X=H , $Y=CO_2CH_3$	91 
126 : R=OH		
	$R=OSO_2N(CH_3)_2$, $X=CH_3$, $Y=T_{OS}$	90 
	$R=OSO_2N(CH_3)_2$, X=H , $Y=T_{OS}$, Z=H	79 
127 : R=OH	$R=OSO_2N(CH_3)_2$, X,Y=N_2 , Z=H	81 "
	$R=OSO_2CF_3$, X=H , $Y=T_{OS}$, Z=Ac	48 "
	$R=OSO_2CF_3$	80 (R=H)
128 : R=OH		
	129b : $R=OSO_2CF_3$	45 : 
129a : R=OH		130
22	$R=OSO_2CF_3$	



Scheme 18

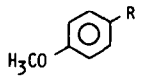
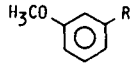
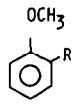
As the examples show, the method is not generally applicable. Although the C(3)-deoxygenation of α-D-glucopyranosides is relatively smooth, the reaction of 2-O-trifluoromethylsulphonyl-α-D-glucopyranoside **129b** with Na/NH_3, for example, leads to the rearranged furanoside **130**. The C(3)-deoxygenation of methyl 1,2:5,6-di-O-isopropylidene-α-D-glucopyranoside (**22**) via its triflate was unsuccessful. Protecting groups such as benzylidene, O-acetyl, N-benzyloxycarbonyl, N-tosyl and azide are either removed or reduced (azide) under the reaction conditions. As in the reduction of alkyl phosphates,[132] the reaction mechanism is assumed to involve the fragmentation of a radical anion intermediate to an alkyl radical.

4.2. *Phenols.* According to Kenner and Williams[124] phenols can be relatively easily deoxygenated by reduction of their methanesulphonates with sodium in liquid ammonia. This was confirmed later by Closson *et al.*[136] on a series of examples (Table 13). Here—and in the case of the aryl phosphates (see C3.2)—there was observed a marked dependency of product composition upon the strength and/or concentration of the reducing agent. With $Na^{\oplus}$/naphthalene$^{\cdot\ominus}$ the major product was phenol, whereas with Na/NH_3 (and higher concentrations of electron donor) the aromatic hydrocarbons were obtained in good to excellent yields. Mechanistically, this behaviour is explained analogously to Scheme 16 by the different fragmentations of radical anions (type **123**) and of dianions (type **124**).

5. *Electrochemical deoxygenation via methanesulphonates*

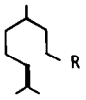
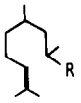
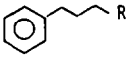
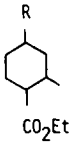
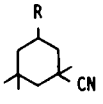
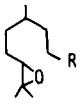
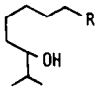
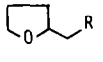
As Shono *et al.*[137] discovered, mesylates can be reduced cathodically at $U_K = -2.5 - 2.7$ V to hydrocarbons, very high yields being obtained in some cases. This method is superior to the reduction of mesylates or triflates with Na/NH_3 in that functional groups such as carboxylate, nitrile, epoxide and olefinic double bonds are unaffected under the reaction conditions used (Table 14). Olefins are formed when a nucleofugic leaving group is in a β-position to the mesylate group (Example **131**). This is consistent with a reaction mechanism analogous to Scheme 19, in which the alkyl radical primarily formed is further reduced to the carbanion and then stabilises by 1,2-elimination, forming the olefin **132.**

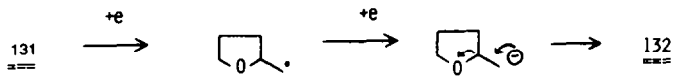
Table 13. Deoxygenation of phenols via methanesulphonates with Na in liq. NH_3

Phenol, R=OH	Deoxy cmpd. R=H, yield (%)
	95
	100 (16) [a]
	65

[a] with $Na^{\oplus}$ Napht$^{\cdot\ominus}$

Table 14. Electrochemical deoxygenation via methanesulphonates ($R–O–SO_2CH_3$)

Alcohol, R=OH	Deoxy cmpd. (R=H), yield (%)
$CH_3(CH_2)_{10}CH_2R$	81
	85
	63
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2R$	70
	83
	57
	71
	87
	72
 131	64 :  132



Scheme 19

D. PHOTOLYTIC DEOXYGENATION (ACCORDING TO SCHEME 4)

In principle two routes are possible for the photolytic deoxygenation of alcohols:

(a) The direct excitation of the alcohol derivative **1** with generation of triplet states and subsequent fragmentation (Scheme 4).

(b) Light absorption by suitable sensitisers that convert the alcohol derivative into the intermediate radical **2** (a radical ion) by electron transfer.

Both possibilities have been verified experimentally.

1. *Carboxylates*

Beugelmans *et al.*[138] were able to detect small amounts of cholestane in the reaction mixture following protracted irradiation of cholestanyl-3β-acetate in HMPTA solution with light of 254 nm wavelength. The experiment was repeated by Pete *et al.*[139] but with the addition of 5% water, whereupon the hydrocarbon was obtained in 80–84% after a short reaction time. Pete also demonstrated that primary, secondary and tertiary alcohols can be equally well deoxygenated under these conditions in good to excellent yields (Table 15). Olefinic double bonds, alcohol, ether, carboxylic acid and acetyl functions are unaffected by the reaction but ketones and halides are reduced.

Table 15. Photolytic deoxygenation in HMPTA/H_2O solution via carboxylates

Alcohol, R=OH	Derivative R=	Deoxy cmpd. yield (%)	Lit.
5α-Cholestan-3β-ol (4)		79	139
		80	"
		52	"
 133	OAc	70	"
Cholest-5-en-3β-ol (9)	OAc	70	"
3β-Methyl-5α-Cholestan-3α-ol (108) (S. Tab. 10)	OAc	67	"
108 : 3-epimer	OAc	70	"

Table 15 (*Contd*).

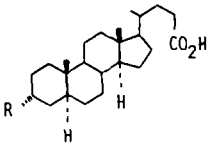
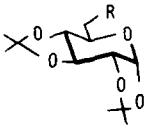
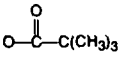
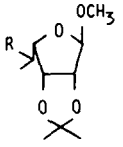
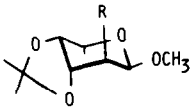
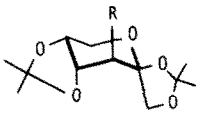
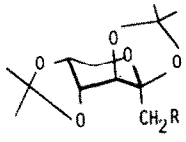
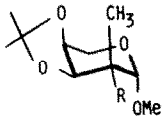
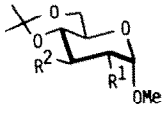
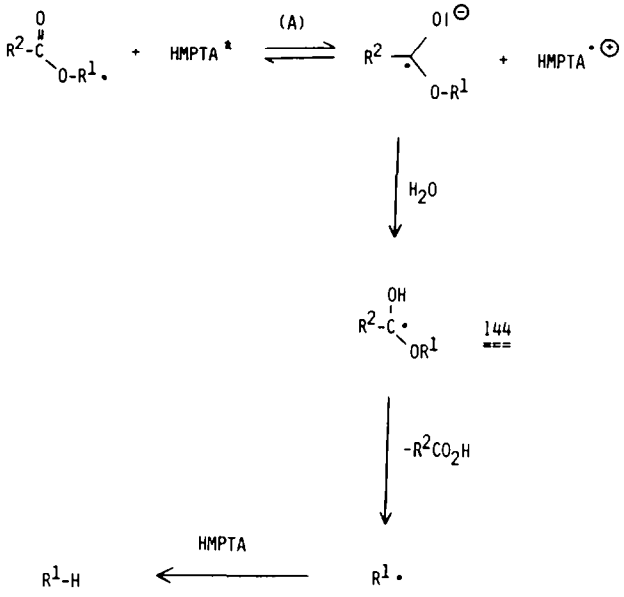
Alcohol, R=OH	Derivative R=	Deoxy cmpd. yield (%)	Lit.
4,4-Dimethyl-5α-cholestan-3β-ol (100, cf. Tab. 8)	OAc	68	139
 134a : R=OH	OAc	87	"
n-$CH_3(CH_2)_7CH_2R$ 135a : R=OH	OAc	70	"
 136	OAc	85	141
		65	140
22	OAc	65	140, 141
		75	140
	$O-SO_2CF_3$	64	142
49 (cf. Tab. 3)	OAc	81	141
49 : C(4)-epimer	OAc	70	140
 137	OAc	78	141
 138	OAc	60	141

Table 15 (*Contd*).

Alcohol, R=OH	Derivative R=	Deoxy cmpd. yield (%)	Lit.
 139	OAc	55	140
 140	OAc	70	140
 141	OAc	60 (ribo:arabino 85 : 15)	140
 142a : R^1=R^2=OH	b : R^1=R^2=OAc	50 (143 : R^1=R^2=H)	140
109 (R=OH) (cf. Tab. 10)	a : R=OAc	88	142
	b : R=OCN$(CH_3)_2$ (S)	72	"
	c : R=OCSCH_3 (S)	57	"
	d : R=OSO_2CF_3	78	"

As shown in Table 15, the method was also successfully applied to carbohydrates and aminoglycosides. Of particular interest is the easy exchange of sterically hindered OH groups such as that in the fructopyranose derivative **139**,[140] as well as the C(2)-deoxygenation of the α-L-fucopyranoside **138**,[141] which is very difficult to achieve by classical methods. Furthermore this method also permits the one-step conversion of 1,2-glycols into saturated hydrocarbons. This was demonstrated by the deoxygenation of the 2,3-diacetylglucoside **142a** to the 2,3-dideoxyhexopyranoside **143**.[140] As Collins[140] found, pivaloyl derivatives deoxygenate in higher yields than the corresponding acetyl compounds. Methyl-1,2:5,6-di-O-isopropylideneglucofuranoside (**22**), for example, was deoxygenated in the C(3)-position in 65% via the acetyl derivative, but in 75% via the pivaloyl derivative. In contrast, benzoyl, formyl and

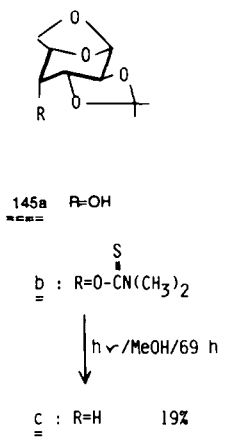
even thiocarbonyl derivatives[142] give lower yields of hydrocarbon (Examples **4** and **109**, Table 15). If HMPTA is replaced by other solvents such as hydrocarbons, alcohols, ether, DMF or DMSO, the reaction fails. As Pete showed, practically all the light is absorbed by HMPTA when a solution of an acetate in HMPTA is irradiated (254 nm). In view of this fact, and with knowledge of the low ionisation potential of HMPTA, Pete *et al.*[143] proposed the transfer of an electron from an excited HMPTA molecule to the carbonyl compound as reaction mechanism (Scheme 20). The radical anion thus formed should then fragment to an alkyl radical (e.g. analogously to Scheme 12). The deoxygenation of 6-β-acetoxy-3:5-α-cyclocholestane provided one indication of the radical character of the reaction, cholest-5-ene being obtained in 60% yield.[143] This accords with the known rearrangement of cyclopropylcarbinyl radicals to homoallyl radicals.[144]



Scheme 20

The manner in which the addition of water accelerates the reaction is still unknown. Pete postulated the protonation of the radical anion to give the OH radical **144** and thus shifting the equilibrium (A) to the right. On the other hand a shift in equilibrium due to hydrolysis of the HMPTA radical cation also seems plausible. The HMPTA decomposition products have not yet been identified.

Photolytic deoxygenation via carboxylates is a particularly useful process when only small quantities of substance are involved. When larger amounts (> 1g) are to be deoxygenated, both longer reaction times (> 60h) and lower yields are to be expected. Complications occur when compounds are used that have other chromophores in addition to the ester group.



2. *Photolysis of trifluoromethanesulphonyl derivatives in* HMPTA/H_2O

Alcohols can also be smoothly deoxygenated to hydrocarbons via their trifluoromethanesulphonates (triflates) under the same conditions described previously for alkanoyl derivatives (254 nm, HMPTA/H_2O). This was demonstrated by Tsuchiya *et al.*[142] for the aminosugar **109** and the furanoside **22** (see Table 15). Interestingly, photolysis of mesylates or tosylates under the same conditions regenerates the alcohol.[139, 142].

3. *Photolysis of thiocarbamates*

In contrast to the methods described in D1 and D2, the photolytic deoxygenation via N,N-dimethylthiocarbamates according to Horton[61] does not require the addition of a sensitiser (such as HMPTA). The reaction is carried out in methanolic solution with unfiltered UV light, but, owing to the long reaction times and low yields of deoxygenated product, is of little preparative value. The α-D-galactopyranoside **113** (Table 10), for example, was deoxygenated at C(6) in only 15% yield after 113 hr irradiation of the corresponding thiocarbamate. The C(4)-deoxygenation of the 1,6-anhydro-β-D-mannopyranose derivative **145a** in 19% yield was equally unsatisfactory.

As Tsuchiya showed,[142] the photolytic deoxygenation via N,N-dimethylthiocarbamates succeeds in high yield when the reaction is carried out in HMPTA (see D1), analogously to the Pete method (Table 15). In this way the 2-aminoglucoside **109** was deoxygenated at C(3) in 72% yield via the thiocarbamate **109b**.

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