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NEW AND SELECTIVE REACTIONS AND REAGENTS IN NATURAL PRODUCT CHEMISTRY

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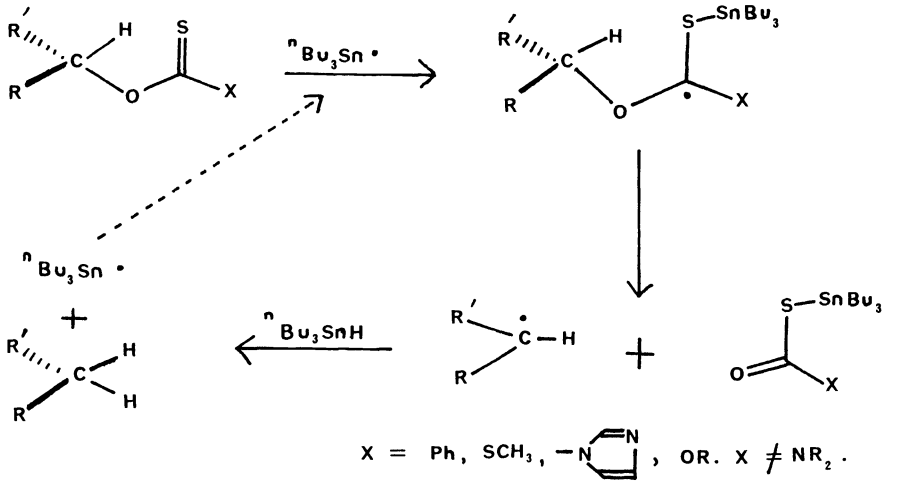
Abstract – Radical reactions are not widely used in the synthetic chemistry of natural products. Nevertheless, they have considerable potential utility, because they are little troubled by steric congestion. Radical deoxygenation of the secondary hydroxyl group is an established process. It has now been supplemented by radical fission, induced by electron transfer, of esters. With hindered esters and with various thiocarbonyl esters, excellent yields of hydrocarbon can now be obtained. Radical deamination of primary, secondary and tertiary primary amines has been developed to give good yields of deaminated products. These radical reactions find application in the chemistry of aminoglycoside antibiotics. Other new radical reactions of synthetic interest will be presented.

As we have argued elsewhere new reactions of importance in chemistry are discovered by conception, by misconception and by accident (1,2). In fact, most of the important reactions of synthetic chemistry have been discovered by accident.

The traditional chemistry of carbohydrate molecules is ionic in mechanism. Faced by the need to deoxygenate secondary hydroxyl groups in aminoglycoside antibiotics by a non-SN_2 mechanism we conceived (3) that a radical chain reac-

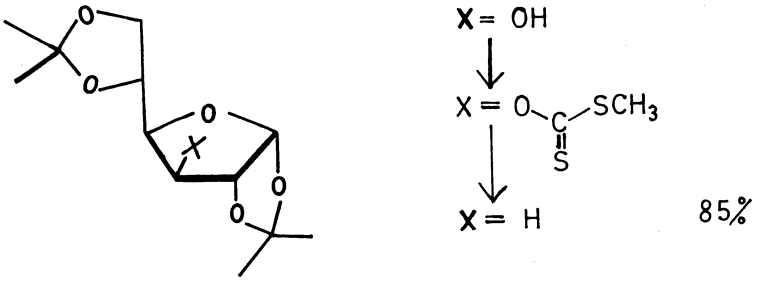


Barton and McCombie, J.C.S. Perk.1 1975, 1574.

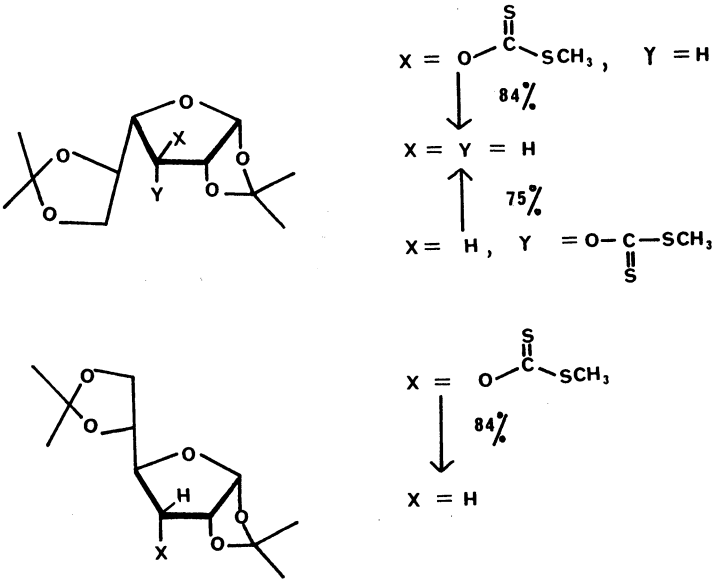
SCHEME 1

tion would be the ideal solution to this problem. Radical chain reactions proceed under neutral conditions and are much less subject to steric hindrance than ordinary ionic reactions. In addition, they are less prone to rearrangement than cationic or anionic reactions. The reaction that we designed (3) was the reduction of a thiocarbonyl ester, xanthate ester or thiocarbonyl-imidazolide by tributyl tin hydride or other tin hydride (or germyl hydride) (4) reagent (see Scheme 1). It is not inappropriate to present some examples of the application of this type of reaction, especially in carbohydrate chemistry.

The first example (Scheme 2) shows the synthesis of 3-deoxyglucose and is taken from our original publication (3). It was Bob Stick (5) who applied (Scheme 3) the reaction systematically for the synthesis of several 3-deoxy-



SCHEME 2

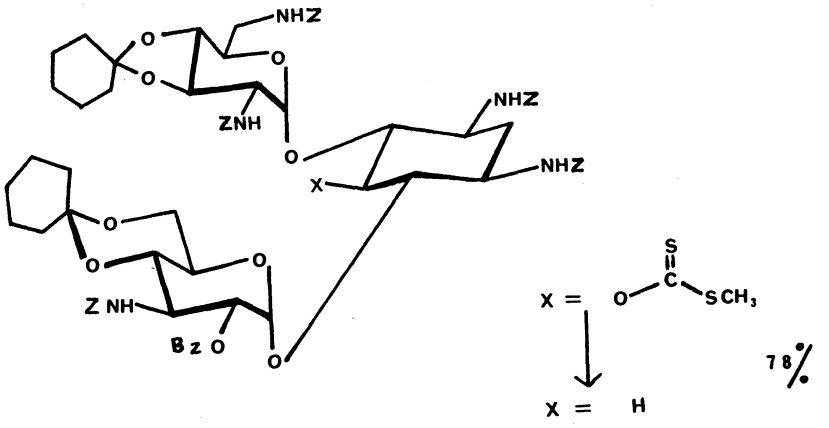


Copeland and Stick, Aust. J. Chem., 1977, 30, 1269.

SCHEME 3

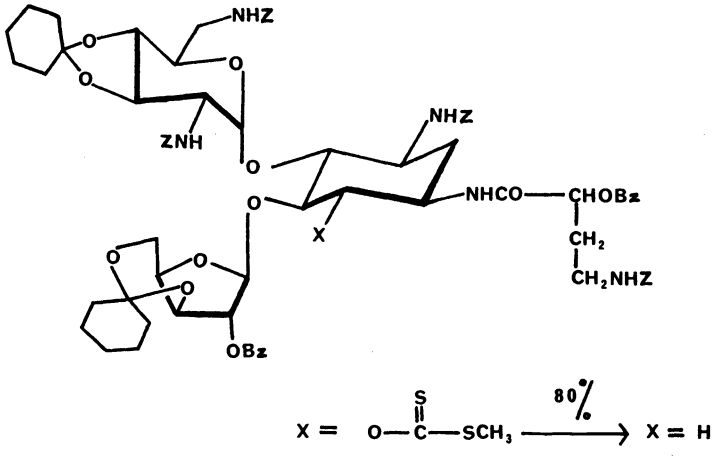
sugars and also for the synthesis (using tributyl tin deuteride) of specifically deuterated deoxy-sugars (6). It should be, of course, a good reaction for the synthesis of tritiated molecules.

Striking examples (Schemes 4, 5 and 6) are provided in the biologically important deoxygenation of aminoglycoside antibiotics by Hayashi et al. (7). The

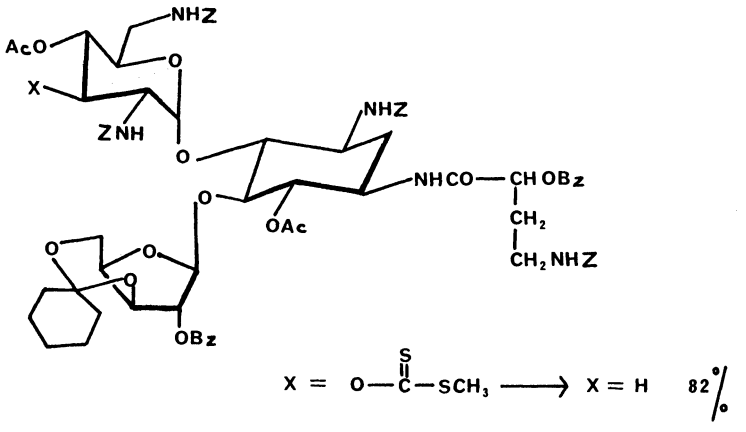


Hayashi, Iwaoka, Takeda and Ohki,
Chem. Pharm. Bull., 1978, 26, 1786.

SCHEME 4

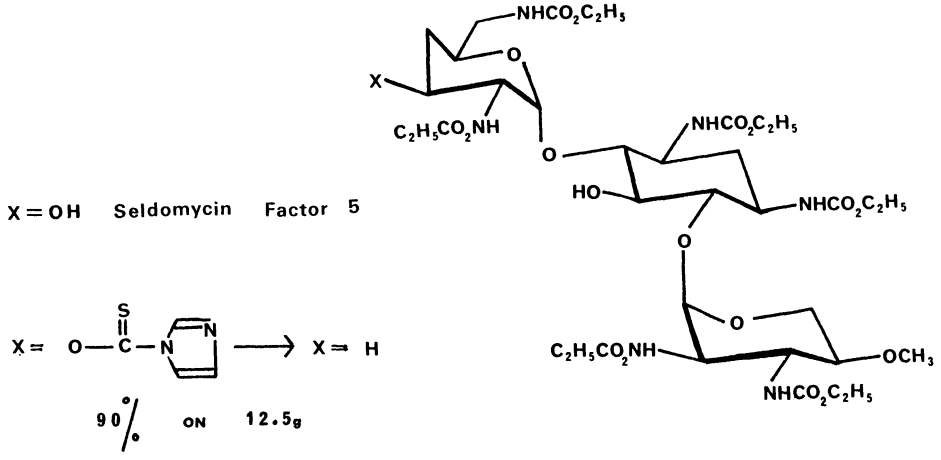


SCHEME 5



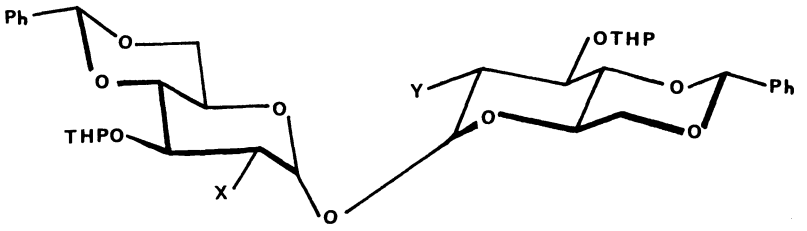
SCHEME 6

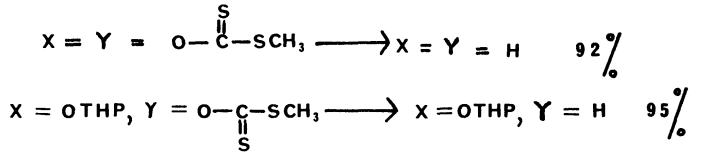
example in Scheme 7 is interesting because the thiocarbonyl radical chain sequence was the only method which permitted the synthesis of the desired deoxy-antibiotic (8). Scheme 8 shows two recent examples that give good yields of 2-deoxygenation of sugars (9). Finally, the reaction is especially good for the deoxygenation of hindered secondary alcohols. Even the most hindered alcohols give xanthate esters without difficulty. A particularly noteworthy example (10) is shown in Scheme 9.



Carney et al., J. of Antibiotics, 1978, 31, 441.

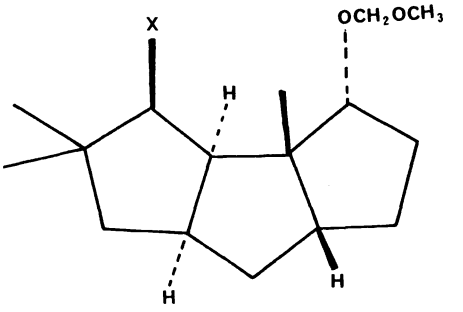
SCHEME 7

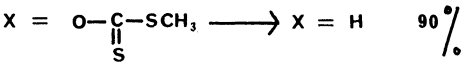




Defaye et al., Nouveau J. de Chimie, 1980, 4, 59.

SCHEME 8

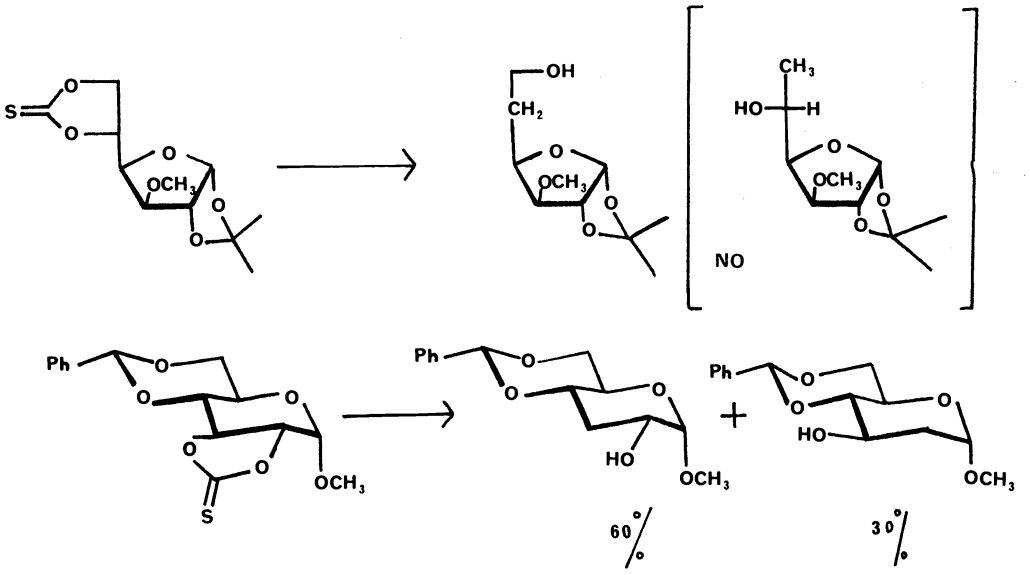




Tatsuta et al., J. Amer. Chem. Soc., 1979, 101, 6116.

SCHEME 9

Primary alcohols are not deoxygenated by thiocarbonyl reduction. Therefore, a thiocarbonate based on a primary alcohol and a secondary alcohol should be reduced only at the secondary position. This has been demonstrated (11) (Scheme 10) for the 5 and 6 positions in sugars. This method of synthesis

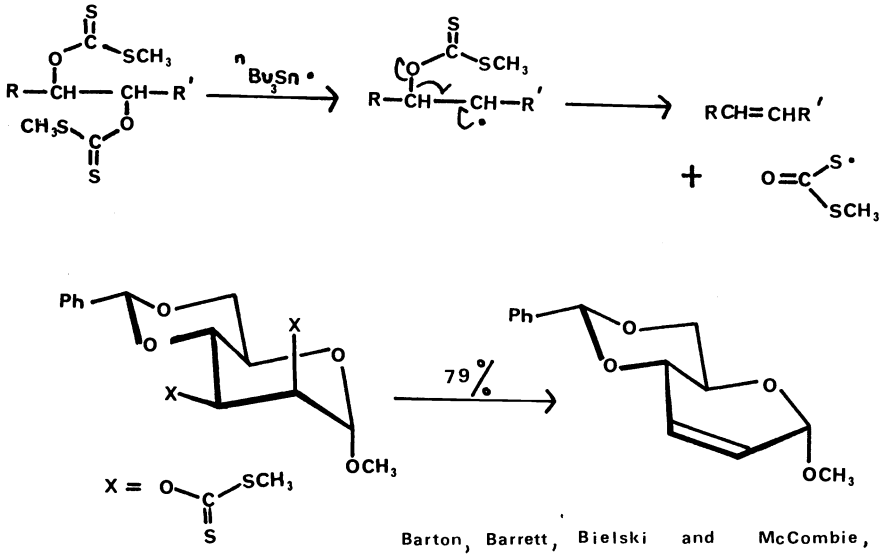


Barton and Subramanian, J. C. S. Perk. 1, 1977, 1718.

SCHEME 10

of 5-deoxy-sugars nicely complements the ionic reactions of 5,6-thiocarbonates which lead (12) to 6-deoxy-sugars. Naturally, when the thiocarbonate is based on two secondary alcohols a mixture of two regioisomeric deoxy-sugars results (see Scheme 10).

We have, of course, examined the behaviour of α-glycol dithiocarbonyl derivatives. Dithionobenzoates give complex results (3), but 1,2-dixanthate esters fragment (13) smoothly to give olefins (see Scheme 11). Being a radical

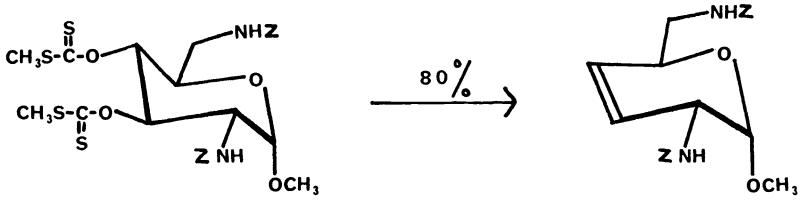


Barton, Barrett, Bielski and McCombie, J.C. S. Chem. Comm., 1977, 866; J.C. S. Perk. 1, 1979, 2378.

SCHEME 11

elimination reaction this process gives, when aliphatic α-glycols are used, the more stable trans-olefin (see further below). The 1,2-dixanthate elimination was also discovered independently by Hayashi et al. (7) (see Scheme 12).

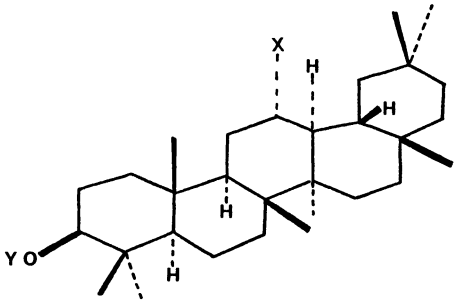
We now discuss what we consider to be a second, non-chain, radical reaction for the deoxygenation of alcohols. It was discovered by accident. In a routine reduction by lithium and ethylamine of the diacetate shown in Scheme 13 we confidently expected to obtain the corresponding diol without inversion of configuration at the (13) α-carbon (14). In fact, Ms Joukhadar, who did the experiment, obtained a high yield of mono-deoxy-compound (15). After so many years of routine Bouveault-Blanc reductions to give alcohols this was a surprising accident.

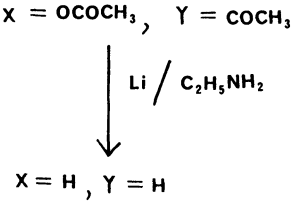


Hayashi, Iwaoka, Takeda and Ohki, Chem. Pharm. Bull., 1978, 26, 1786.

SCHEME 12

ACCIDENT





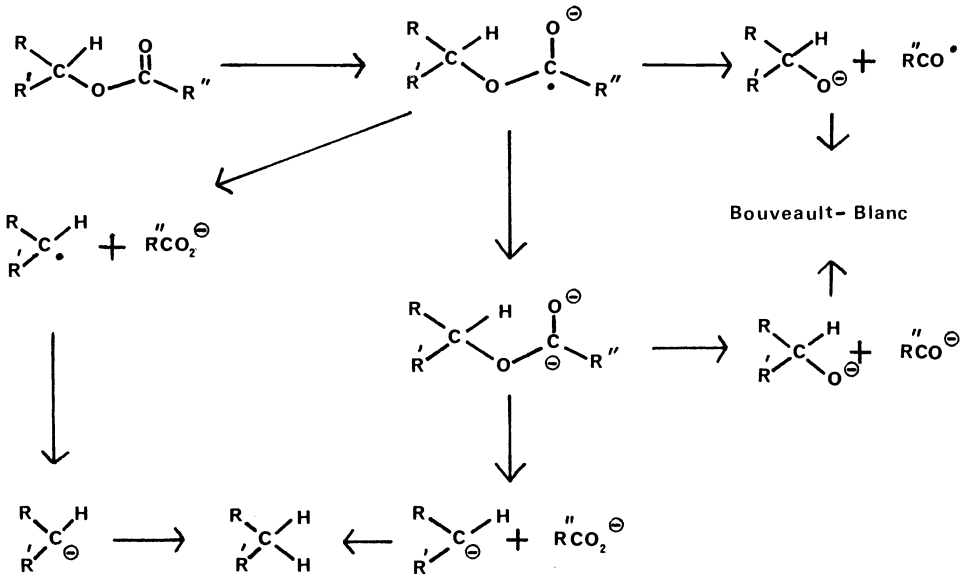
Ms Laurette Joukhadar.

Boar, McGhie, Misra, Barrett, Barton and Prokopiou,

J.C.S. Chem. Comm., 1978, 68.

SCHEME 13

The theory of the electron-transfer reduction of esters can be summarised as in Scheme 14. The traditional Bouveault-Blanc reaction involves the cleavage of the carbonyl oxygen bond of the ester and can involve the transfer of 1 or 2 electrons before the cleavage occurs. The alkyl oxygen - carbon cleavage which we accidentally discovered also involves in principle the same transfer of one or two electrons (see Scheme 14).

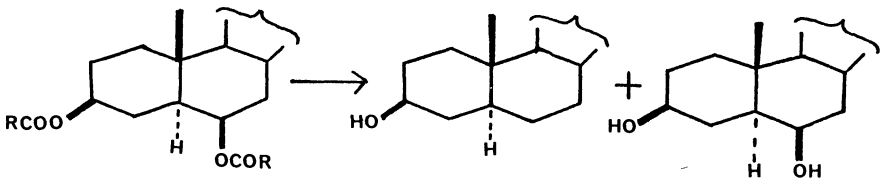


SCHEME 14

The initial example (Scheme 13) of alkyl oxygen-carbon cleavage suggested that a hindered ester was deoxygenated whilst a relatively unhindered ester was not. We investigated systematically this possibility using (Scheme 15) derivatives of cholestane-3β,6β-diol. The 3β-OH (equatorial) is, of course, unhindered whilst the 6β-OH (axial) is moderately hindered. Our respected colleague Dr. A.G.M. Barrett suggested that potassium should be soluble in hindered primary amines like t-butylamine if 18-crown-6 was added. This proved to be a valuable suggestion since one could work conveniently at room temperature, as well, of course, at other temperatures at will. The data reported in this article were obtained under these conditions unless stated to the contrary. Scheme 15 clearly shows that the more hindered is the ester the more completely is it deoxygenated (15).

This work, and further more extensive investigations (16), has convinced us that the transfer of an electron under non-protonating conditions to an aliphatic or alicyclic ester is normally followed by radical fission to give RR'CH• and $R''CO_2^{\ominus}$ (see Scheme 14). However, this reaction is often not observed because of competitive nucleophilic attack by nucleophiles frequently present in amine or ammonia solutions (see further below).

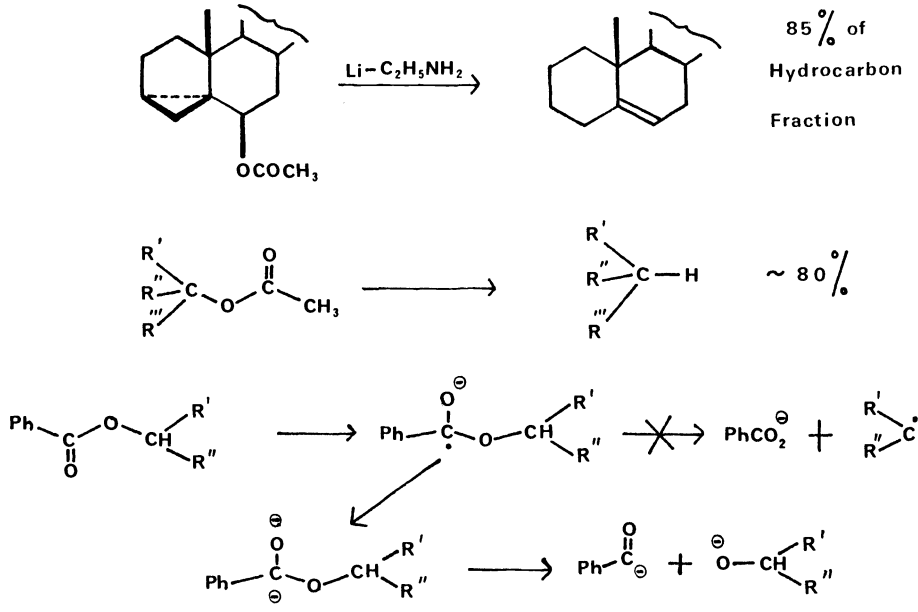
Thus (Scheme 16), reduction of 3α,5-cyclo-5α-cholestan-6β-yl acetate gave a hydrocarbon fraction (45%) which comprised cholest-5-ene (85%) and 3α,5-cyclo-5α-cholestane (15%). The formation of the former hydrocarbon is indicative (17) of radical opening of the cyclopropane ring. Reduction of tertiary esters always gave excellent yields of hydrocarbon whereas reduction of aroma-



R =			
H	⟶	0%	+ 86%
Me		56	27
iso Pr		71	19
^{t}Bu		79	9

K / 18 – crown-6 / $^{t}BuNH_2$ / R.T.

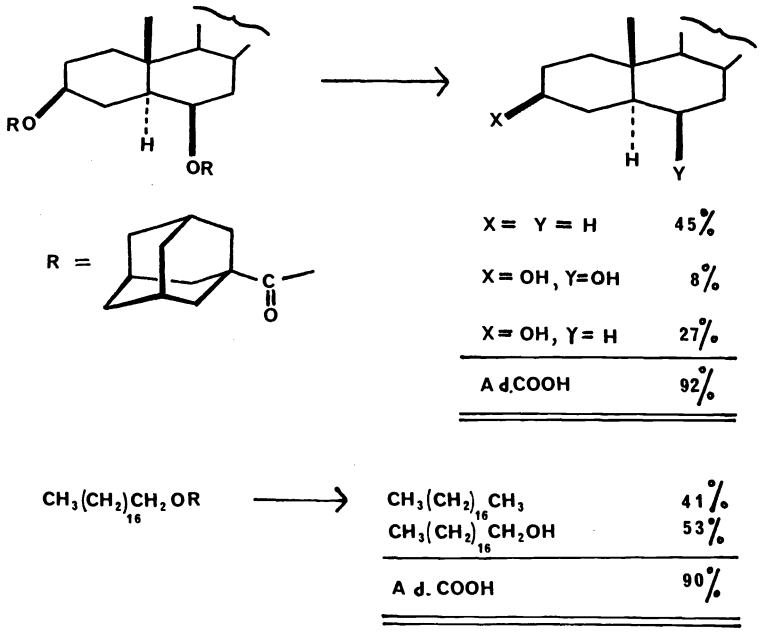
SCHEME 15



SCHEME 16

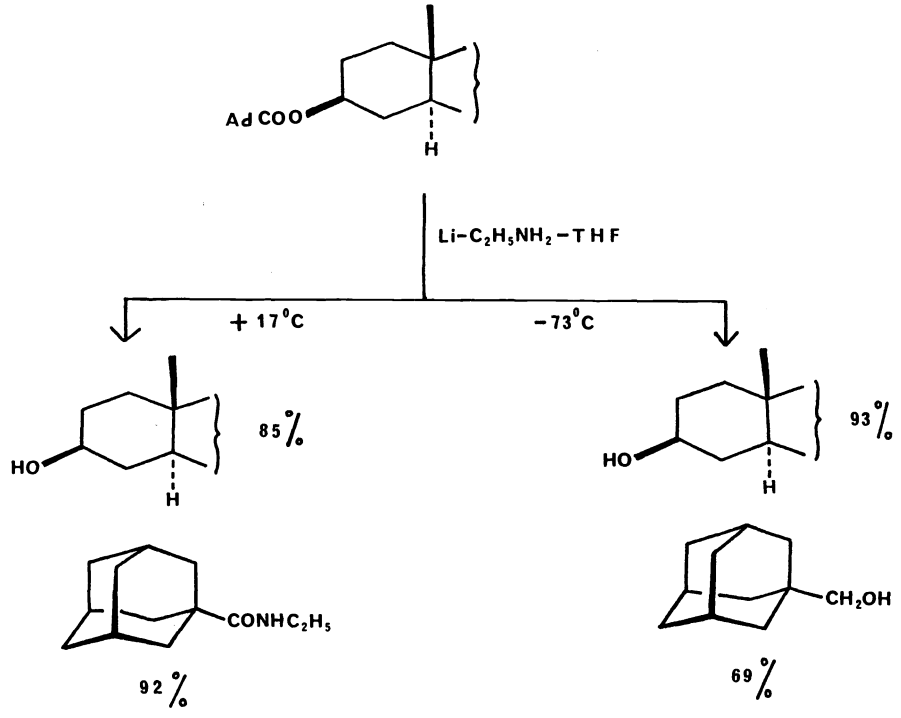
tic esters gave no hydrocarbon (Scheme 16). Tertiary radicals are more stable than secondary so the improved yield is to be expected. The non-formation of hydrocarbon on benzoate reduction is explained by the enhanced stability of the initially formed radical-anion because of the aryl ring.

An investigation of the fate of the acid fragment of the ester proved revealing. Thus (Scheme 17) reduction of cholestane-3β,6β-diyl diadamantanoate gave extensive deoxygenation, but exclusive recovery of adamantoic acid (92%). The blank experiment showed that the potassium salt of adamantoic acid was stable indefinitely under these reduction conditions. Similarly reduction of the adamantanoate ester of cetyl alcohol gave significant reduction (41%), but exclusive recovery (90%) of the acid fragment.



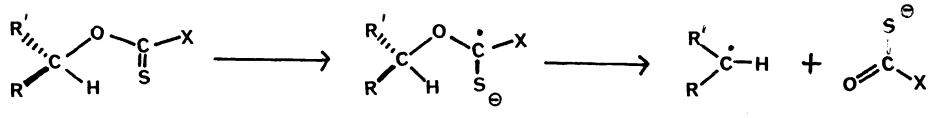
SCHEME 17

Some experiments in ethylamine using lithium as reductant proved interesting (Scheme 18). Attempted reduction of cholestan-3β-yl adamantanoate at 17° gave exclusively unchanged cholestanol (85%) and the ethylamide of adamantanoic acid (92%). Thus the lithium ethylamide, formed from traces of water or

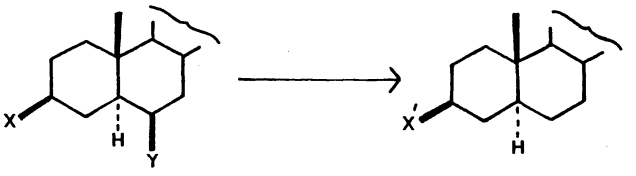


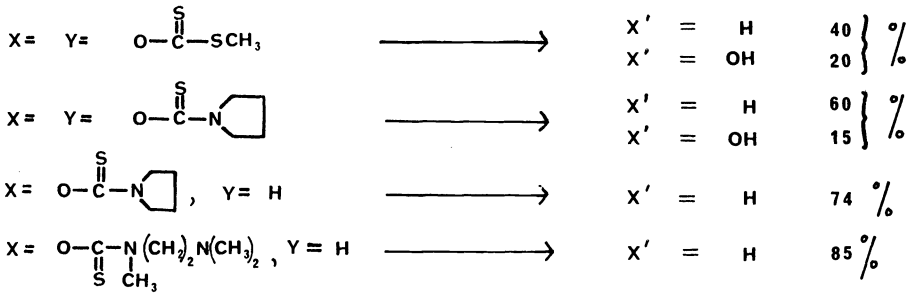
SCHEME 18

catalytically from traces of metal salts, provoked a nucleophilic attack which was faster than the reduction process the speed of which is limited by the dissolution of the metal. In contrast, a reduction at -73° produced normal Bouveault-Blanc products. We consider that the Bouveault-Blanc reaction takes place when protonation at the ethereal oxygen of the radical-anion is possible (Scheme 14), or when the initial radical-anion does not fragment because of the low temperature and thus is reduced further to the dianion which fragments to $RR'CHO^{\ominus}$ and $R''CO^{\ominus}$. The latter explanation may be responsible for the results obtained at -73° Incidentally, the protonation of the initial radical anion on carbonyl oxygen by an alcohol, or by water, is surely excluded by pKa considerations (18).



X = ? SCH_3, NR_2, etc.



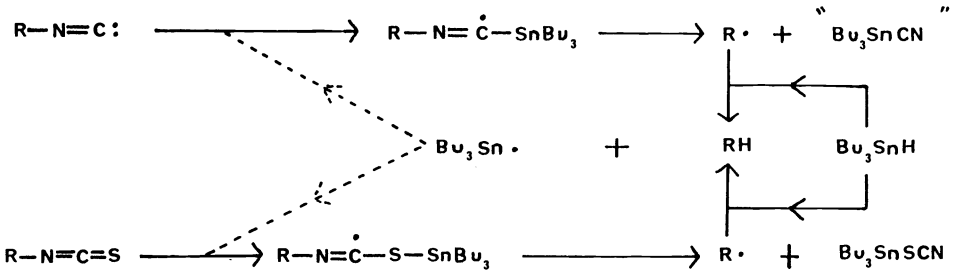


SCHEME 19

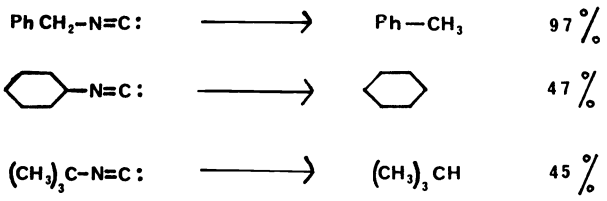
Based on those results we were able to conceive of a new family of deoxygenation systems (19). Clearly, if the failure of deoxygenation with primary and unhindered secondary esters is due to amidolysis, the best way to avoid this is to take esters which are reformed by the amidolysis reaction. Scheme 19 shows xanthate and, especially, thiocarbonylamide esters which satisfy this proposition and which give good yields of deoxygenated product. In addition, they are easy to synthesise by amine displacement on xanthate esters. The diethylaminothiocarbonyl ester of cetyl alcohol gave 87% of hydrocarbon.

In support of our mechanistic proposals we would cite the smooth deoxygenation of esters when photolysed at 250 mμ in hexamethylphosphoramide (20). This must be a fragmentation of the radical-anion and it works even for unhindered esters. Similarly the reduction of esters by sodium in hexamethylphosphoramide affords deoxygenation with varying efficiency (21). Electron transfer reduction of other sulphur or phosphorus esters has been the subject of recent publications (22).

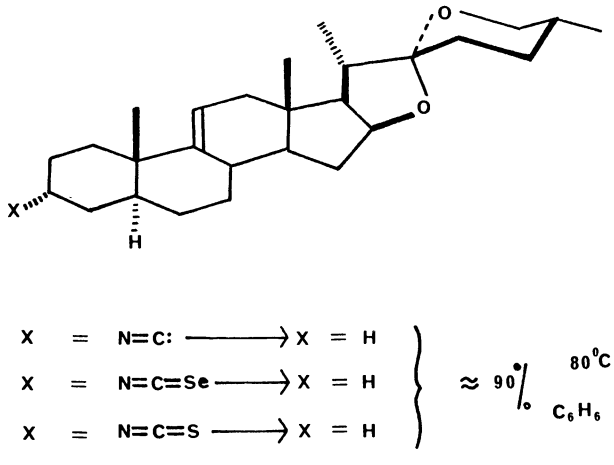
We now turn to another radical-chain reaction. It would also be interesting to remove selectively, and by radical processes, the amino-functions present in aminoglycoside antibiotics. We conceived (Scheme 20) that this should be possible using isonitriles, isothiocyanates or isoselenocyanates as substrates and a tin hydride as a reducing agent. In fact, we soon discovered that the reduction of isonitriles by tributyl tin hydride was already known, but was reported to give poor yields for secondary and tertiary isonitriles (23). We decided therefore to start with isothiocyanates and isoselenocyanates. In a suitable model compound (Scheme 21) both gave excellent yields (90%) of



Cf. Saegusa et al., J. Amer. Chem. Soc., 1968, 90, 4182.



SCHEME 20

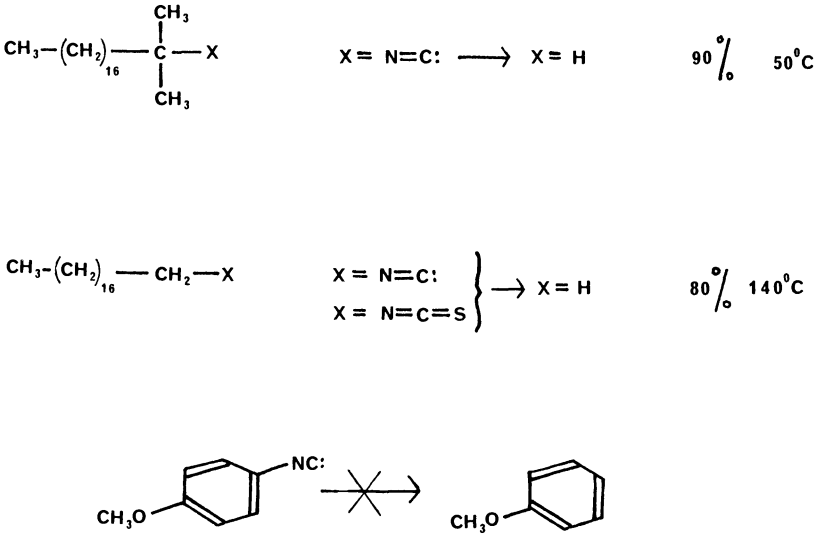


SCHEME 21

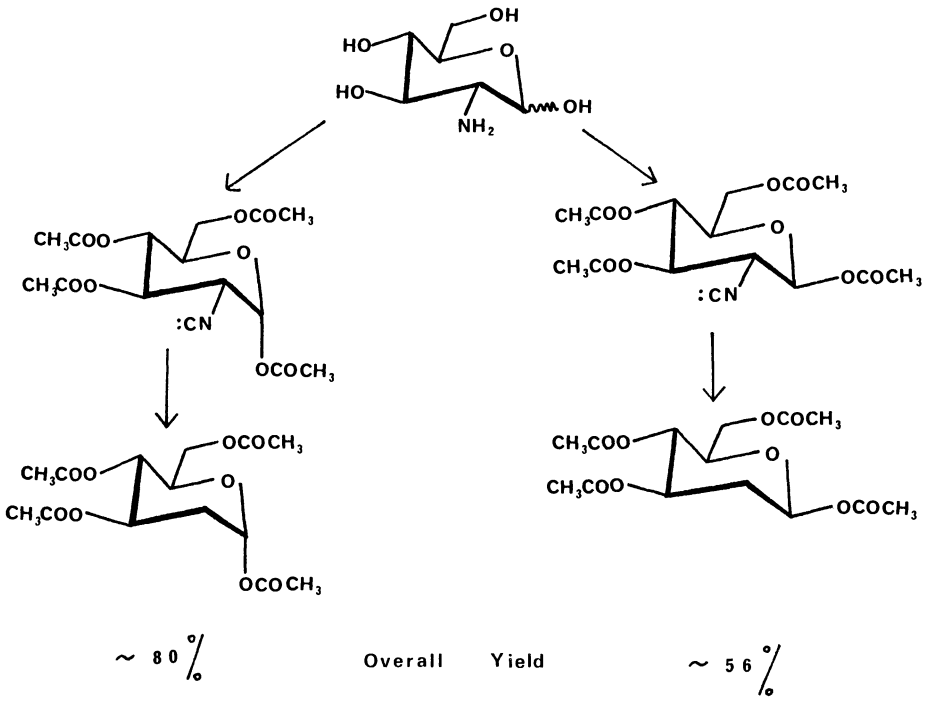
deaminated product. However, the corresponding isonitrile also afforded the same yield. Indeed, a careful study of the course of the reaction showed that the isothiocyanate and the isoselenocyanate were first reduced to the isonitrile before deamination (24).

The excellent yields for the reduction of secondary isonitriles in benzene or in toluene under reflux could be duplicated (Scheme 22) for tertiary isonitriles (in benzene) and for primary isonitriles (in xylene). The marked difference in ease of reduction of tertiary, secondary and primary isonitriles makes selective reduction possible. Aromatic isonitriles are not reduced under any of the conditions we have examined.

A simple example of the application of the reaction is given in Scheme 23, which shows two different routes from the readily available glucosamine to 2-deoxyglucose (24).

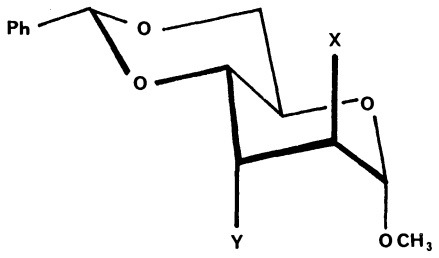


SCHEME 22



SCHEME 23

It was naturally of interest to examine the possibilities of 1,2-elimination reactions of a radical character based on isonitrile reduction. We used, as model compounds, the readily available derivatives of glucose shown in Scheme 24. Neighbouring OH, OAc (see Scheme 23) and even O-mesylate were not



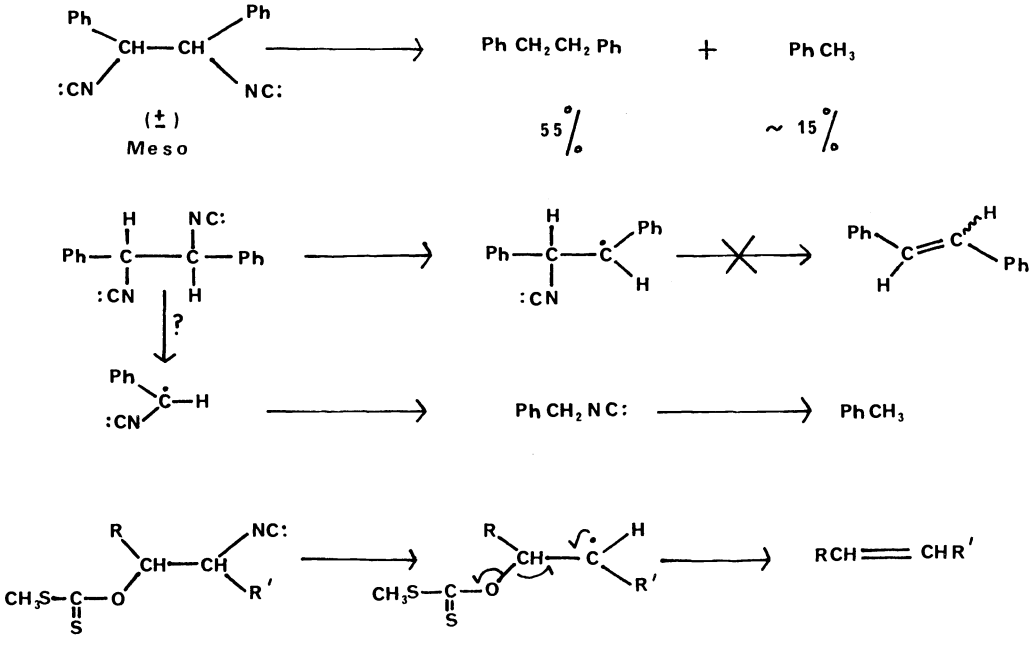
X = N≡C:, Y = OH ⟶ X = H, Y = OH 92%

X = N≡C:, Y = OMs ⟶ X = H, Y = OMs 77%

X = N≡C:, Y = O–C(=S)–SCH3 ⟶ X, Y = ~CH=CH~ 90%

SCHEME 24

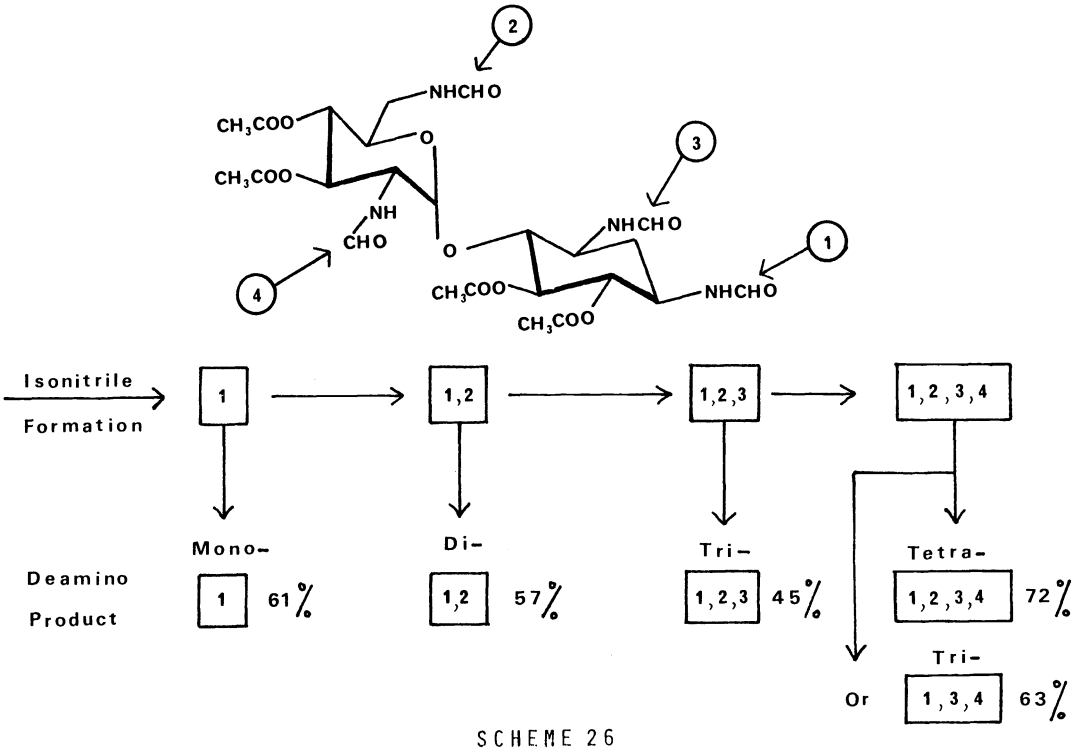
affected by the radical reduction of an isonitrile group. In contrast, the presence of an α-xanthate function afforded an excellent yield of olefin. We were interested to find out if it was the isonitrile or the xanthate function which was the trigger group for the elimination. Scheme 25 shows that both (±)- and meso- 1,2-diisonitrilo-bibenzyl gave the saturated bibenzyl on reduction with minor amounts of toluene. The toluene may come from radical fragmentation of the starting material. Since the intermediate radical in this Scheme 25 should lose isonitrile (cyanide) radical even more easily than



SCHEME 25

in the sugar example in Scheme 24, it is clear that it is the isonitrile function which triggers the elimination of the xanthate residue and not vice-versa. Olefin forming radical reactions should find a place in Organic Synthesis (25).

We have also made a study of the selective deamination of neamine (Scheme 26) (26). In brief, neamine can be formylated and then acetylated in quantitative yield. This compound can then be dehydrated to isonitrile derivatives in the order indicated ①, ②, ③, ④. The mono-, di-, tri- and tetra-isonitriles thus obtained could all be smoothly deaminated to the corresponding desamino-

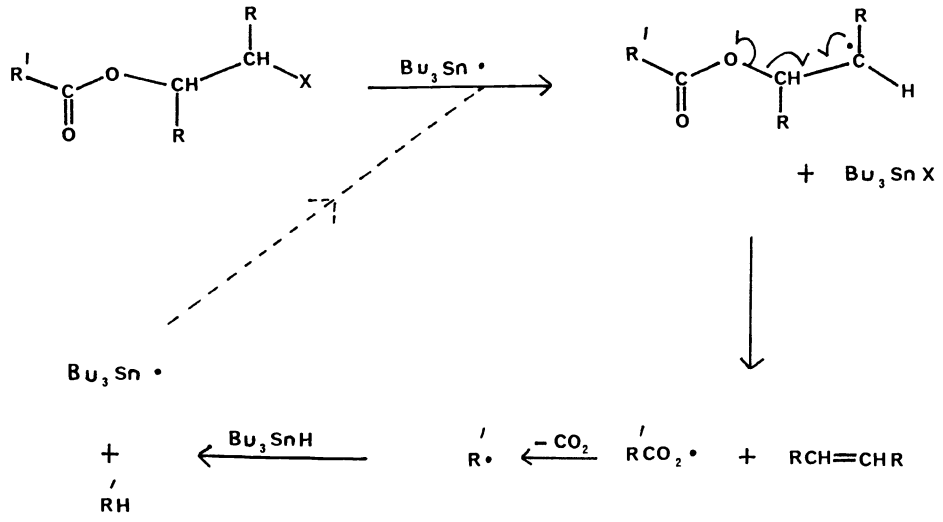


SCHEME 26

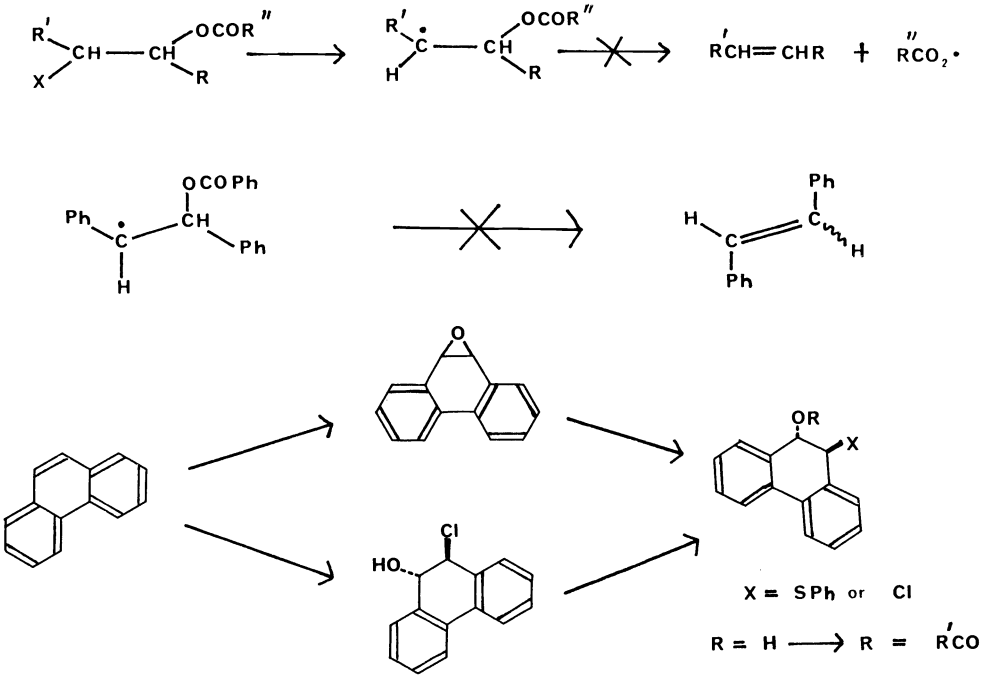
compounds. The primary isonitrile function, as expected, was less reactive than the other secondary isonitriles. It is clear that selective deamination of aminoglycoside antibiotics will now be possible.

Radical deaminations of the same kind have recently been used in an elegant manner in the manipulation of β-lactam antibiotics (27).

Finally, we present a new method for the conversion of a carboxylic acid into the corresponding (nor-) hydrocarbon. At present this operation can be effected by pyrolysis of per-esters in a suitable hydrogen atom donor solvent. However, the temperatures used are relatively high and the yields not satisfactory (28). We conceived (Scheme 27) that an olefin forming β-elimination of the type that we have already discussed several times above would be a novel way of producing cleanly an acyloxy-radical. However, ordinary vicinal halohydrin esters can be reduced smoothly by tributyl tin hydride without any sign of elimination (for example, see Scheme 28). We supposed that a more substantial driving force was needed and therefore concentrated on 9(10)-dihydrophenanthrene derivatives. Our first studies were made using the alcohol obtained by opening phenanthrene-9(10)-epoxide (29) with thiophenoxide anion. Later, we found that the corresponding chlorohydrin (30) esters were even better giving an easier work-up procedure (Scheme 28). In any case tributyl tin hydride reduction of such esters gave radicals which fragmented (Scheme 29) to give acyloxy-radicals and phenanthrene. A temperature of 80° (boiling benzene) was sufficient for the smooth fragmentation of acyloxy radicals based on primary, secondary and tertiary acids in the aliphatic and alicyclic series (31). Higher temperatures would be needed to obtain good

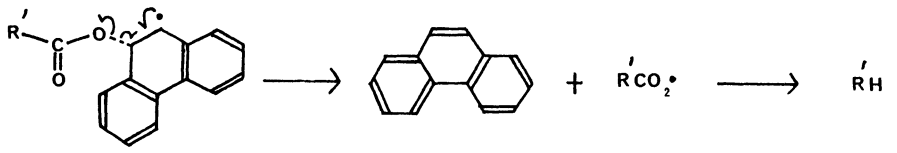


SCHEME 27

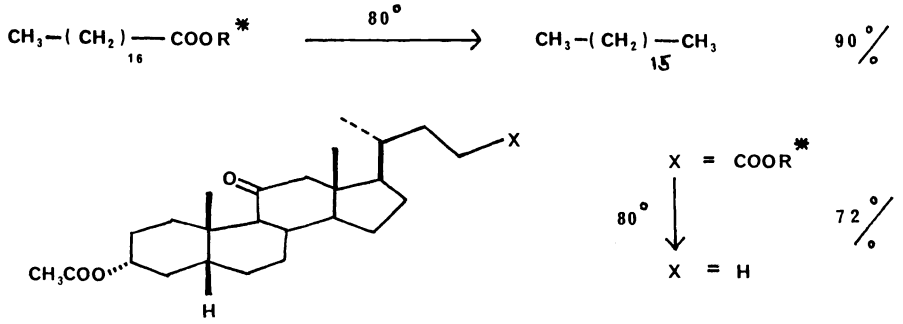


SCHEME 28

yields in the decarboxylation of certain aromatic acids. Typical examples are shown in Schemes 29, 30 and 31. In Scheme 32 we give two examples of the decarboxylation of sugar acids. No doubt, this reaction can be applied generally to the problem of the reductive decarboxylation of uronic acids.



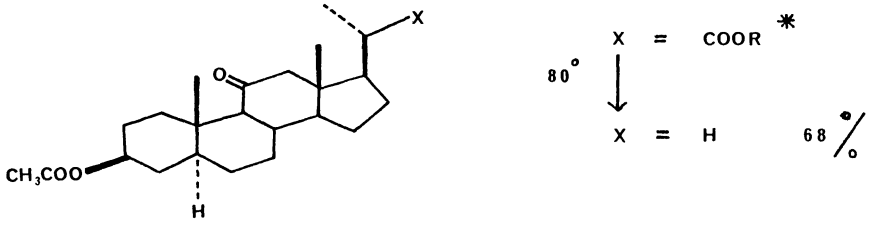
PRIMARY



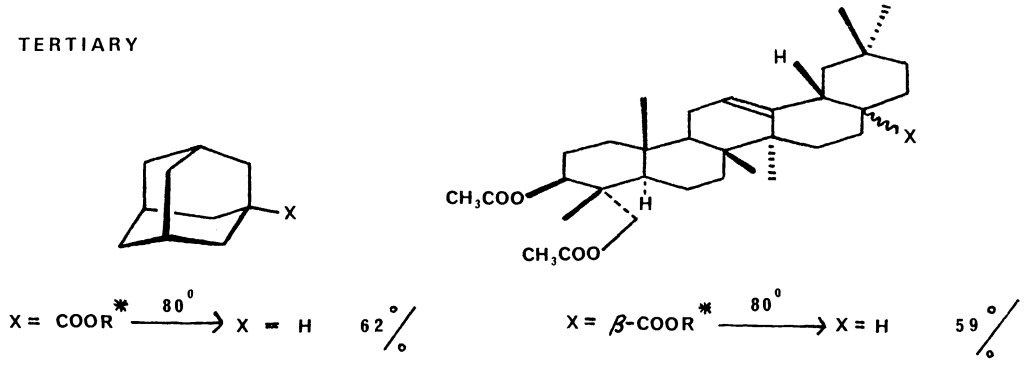
SCHEME 29

The above examples will have shown how radical chain reactions can provide useful synthetic procedures especially in carbohydrate chemistry. In addition it is possible in certain cases to discover these reactions by conception.

SECONDARY

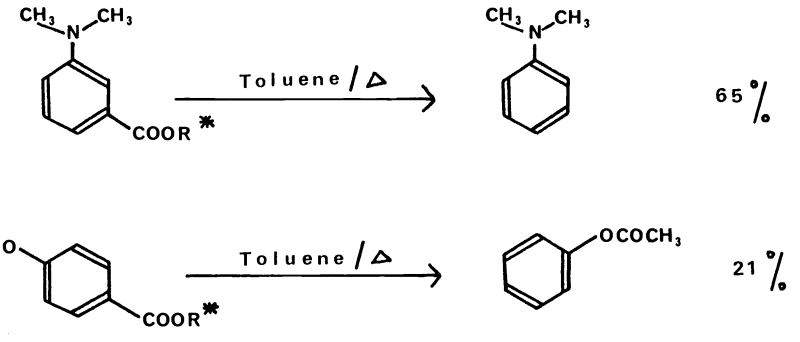


TERTIARY

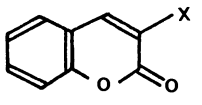


SCHEME 30

AROMATIC

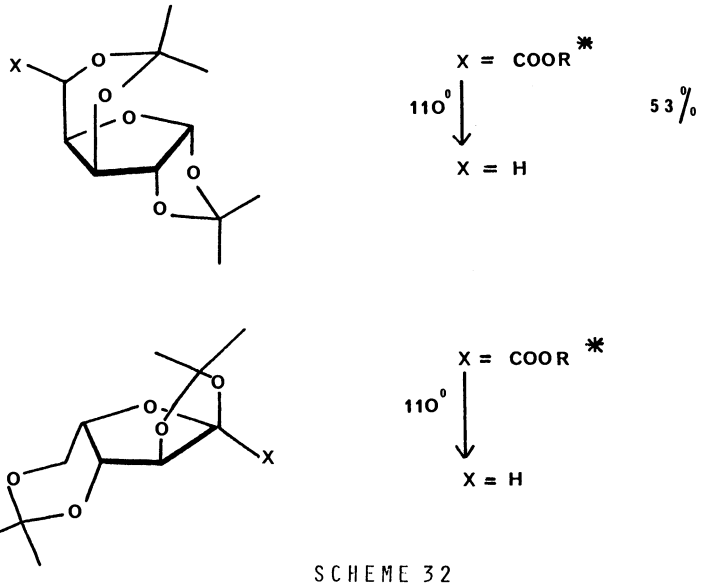


VINYL



X = COOR * ⟶	X = H
Benzene	0 %
Toluene	16 %
Xylene	53 %

SCHEME 31



SCHEME 32

Acknowledgements – We thank all our collaborators whose names have been cited in the References.

REFERENCES

1. D.H.R. Barton, Pure and Appl. Chem., 49, 1241-1249 (1977).
2. D.H.R. Barton in "Frontiers in Bioorganic Chemistry and Molecular Biology" Ed. Y.U. Ovchinnikov and M.N. Kolosov, Elsevier, Amsterdam, 21-37 (1979).
3. D.H.R. Barton and S.W. McCombie, J. Chem. Soc. Perk. I, 1574 (1975).
4. D.H.R. Barton, R.S. Hay-Motherwell and W.B. Motherwell, unpublished observations.

5. C. Copeland and R.V. Stick, Aust. J. Chem., 30, 1269 (1977) ; J.J. Patroni and R.V. Stick, ibid., 31, 445 (1978).
6. J.J. Patroni and R.V. Stick, J. Chem. Soc. Chem. Comm., 449 (1978) ; Aust. J. Chem., 32, 411 (1979).
7. T. Hayashi, T. Iwaoka, N. Takeda and E. Ohki, Chem. Pharm. Bull., 26, 1786 (1978); see also P.J.L. Daniels and S.W. McCombie, U.S.P.4,053,591 (11/10/1977).
8. R.E. Carney, J.B. McAlpine, M. Jackson, R.S. Stanaszek, W.H. Washburn, M. Cirovic and S.L. Mueller, J. Antibiotics, 31, 441 (1978).
9. J. Defaye, H. Driguez, B. Henrissat and E. Bar-Guilloux, Nouveau J. Chim., 4, 59 (1980).
10. K. Tatsuta, K. Akimoto and M. Kinoshita, J. Amer. Chem. Soc., 101, 6116 (1979).
11. D.H.R. Barton and R. Subramanian, J. Chem. Soc. Chem. Comm., 867 (1976) ; J. Chem. Soc. Perk. I, 1718 (1977).
12. D.H.R. Barton and R.V. Stick, J. Chem. Soc. Perk. I, 1773 (1975).
13. A.G.M. Barrett, D.H.R. Barton, R. Bielski and S.W. McCombie, J. Chem. Soc. Chem. Comm., 866 (1977) ; A.G.M. Barrett, D.H.R. Barton and R. Bielski, J. Chem. Soc. Perk. I, 2378 (1979).
14. R.B. Boar, L. Joukhadar, M. de Luque, J.F. McGhie, D.H.R. Barton, D. Arigoni, H.G. Brunner and R. Giger, J. Chem. Soc. Perk. I, 2104 (1977).
15. R.B. Boar, L. Joukhadar, J.F. McGhie, S.C. Misra, A.G.M. Barrett, D.H.R. Barton and P.A. Prokopiou, J. Chem. Soc. Chem. Comm., 68 (1978) ; see also A.K. Mallams, H.F. Vernay, D.F. Crowe, G. Detre, M. Tanabe and D.M. Yasuda, J. of Antibiotics, 26, 782 (1973).
16. A.G.M. Barrett, P.A. Prokopiou, D.H.R. Barton, R.B. Boar and J.F. McGhie, J. Chem. Soc. Chem. Comm., 1173 (1979).
17. A.L.J. Beckwith and G. Phillipou, J. Chem. Soc. Chem. Comm., 658 (1971) ; and references there cited.
18. V. Rautenstrauch, personal communication ; V. Rautenstrauch and M. Geoffrey, J. Amer. Chem. Soc., 98, 5035 (1976) ; E. Hayon and M. Simic, Acc. Chem. Res., 7, 114 (1974).
19. A.G.M. Barrett, P.A. Prokopiou and D.H.R. Barton, J. Chem. Soc. Chem. Comm., 1175 (1979).
20. H. Deshayes, J.P. Pete and C. Portella, Tet. Lett., 2019 (1976) ; J.P. Pete, C. Portella, C. Monneret, J.C. Florent and Q. Khuong-Huu, Synthesis, 774 (1977) ; R. Beugelmans, M.-T. Le Goff, H. Compaignon de Marcheville, Comp. Rend., 269, 1309 (1969).
21. H. Deshayes and J.P. Pete, J. Chem. Soc. Chem. Comm., 567 (1978).
22. O. Oida, H. Sacki, Y. Ohashi and E. Ohki, Chem. Pharm. Bull., 23, 1547 (1975) ; J.A. Marshall and M.E. Lewellyn, J. Org. Chem., 42, 1311 (1977); T. Hayashi, N. Takeda, H. Sacki and E. Ohki, Chem. Pharm. Bull., 25, 2134, (1977) ; T. Tsuchiya, F. Nakamura and S. Umezawa, Tet. Lett., 2805 (1979).
23. T. Saeguasa, S. Kobayashi, Y. Ito and N. Yasuda, J. Amer. Chem. Soc., 90, 4182 (1968).
24. D.H.R. Barton, G. Bringmann, G. Lamotte, R.S. Hay-Motherwell and W.B. Motherwell, Tet. Lett., 2291 (1979) ; D.H.R. Barton, G. Bringmann, G. Lamotte, R.S. Hay-Motherwell, W.B. Motherwell and A.E.A. Porter, J. Chem. Soc. Perk. I, in press.
25. See also B. Lythgoe and I. Waterhouse, Tet. Lett., 4223 (1977).
26. D.H.R. Barton, G. Bringmann and W.B. Motherwell, J. Chem. Soc. Perk. I, in press.
27. D.I. John, E.J. Thomas and N.D. Tyrrell, J. Chem. Soc. Chem. Comm., 345 (1979).
28. Inter alia : K.B. Wiberg, B.R. Lowry and T.H. Colby, J. Amer. Chem. Soc., 83, 3998 (1961) ; P.E. Eaton and T.W. Cole, ibid., 86, 3157 (1964) ; H. Langhals and C. Ruchardt, Chem. Ber., 108, 2156 (1975).
29. S. Krishnan, D.G. Kuhn and G.A. Hamilton, J. Amer. Chem. Soc., 99, 8121 (1977).
30. M.-C. Lasne, S. Masson and A. Thuillier, Bull. Soc. Chim. Fr., 1751 (1973).
31. D.H.R. Barton, H.A. Dowlatshahi, W.B. Motherwell and D. Villemin, J. Chem. Soc. Chem. Comm., in press.