

NEW AND SELECTIVE REACTIONS AND REAGENTS IN CARBOHYDRATE CHEMISTRY

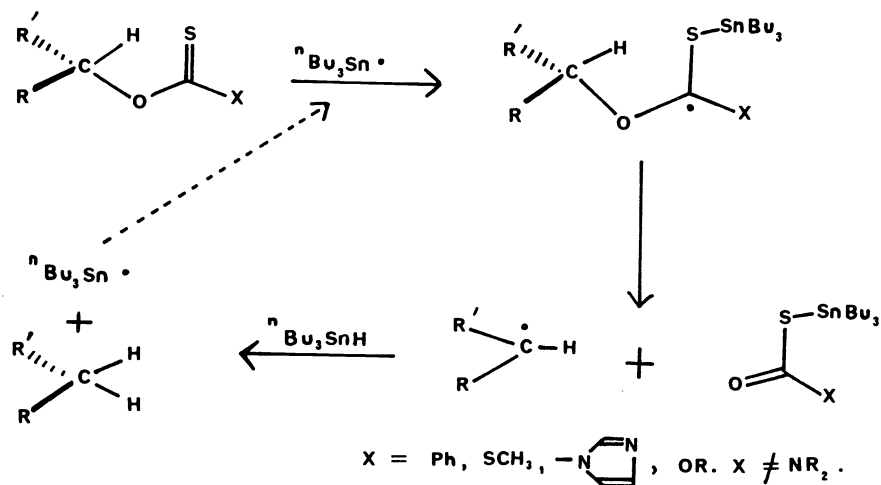
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 91190 Gif-sur-Yvette, France

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-S_N2 mechanism we conceived (3) that a radical chain reaction 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 thiocarbonylimidazolide by tributyl tin hydride or other tin hydride (or germyl hydride) (4) reagent (Fig. 1).



Barton and McCombie, *J.C.S. Perkin 1* 1975, 1574.

FIGURE 1

It is not inappropriate to present some examples of the application of this type of reaction, especially in carbohydrate chemistry.

The first example (Fig. 2) shows the synthesis of 3-deoxyglucose and is taken from our original publication (3).

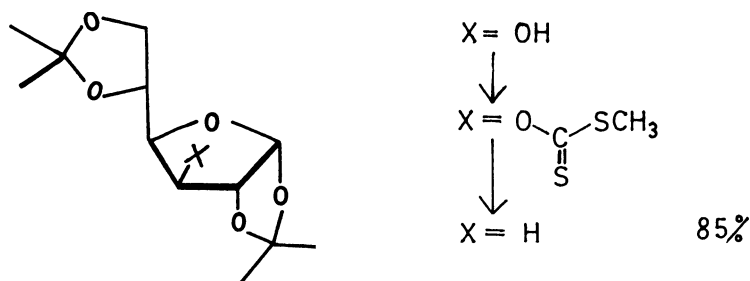
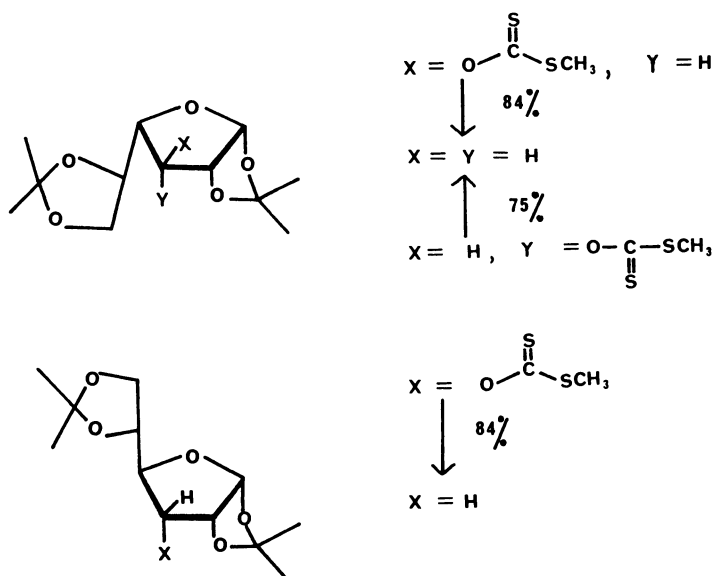


FIGURE 2

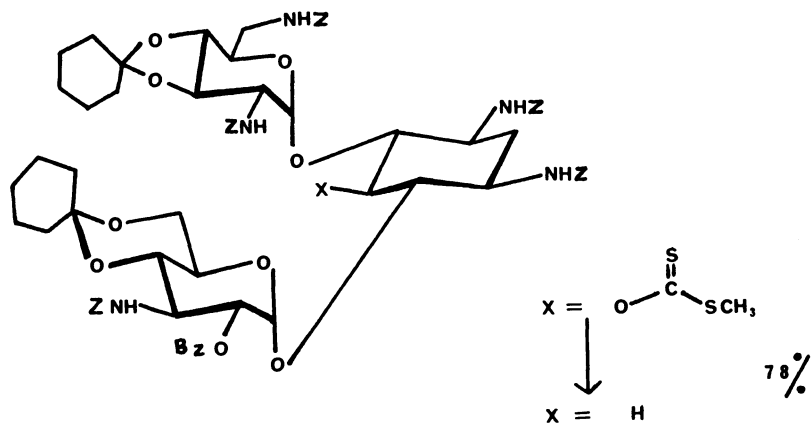
It was Bob Stick (5) who applied (Fig. 3) the reaction systematically for the synthesis of several 3-deoxy-sugars and also for the synthesis (using tributyl tin deuteride) of specifically deuterated deoxy-sugars (6). It should be, of course, a good reaction for the synthesis of tritiated molecules.



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

FIGURE 3

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



Hayashi, Iwaoka, Takeda and Ohki,
Chem. Pharm. Bull., 1978, **28**, 1786.

FIGURE 4

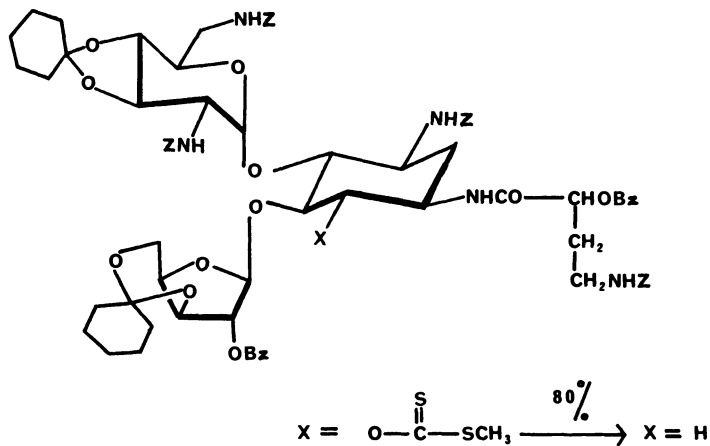


FIGURE 5

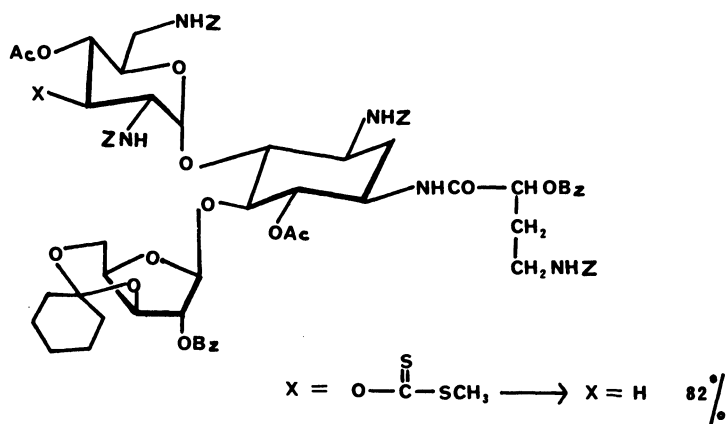
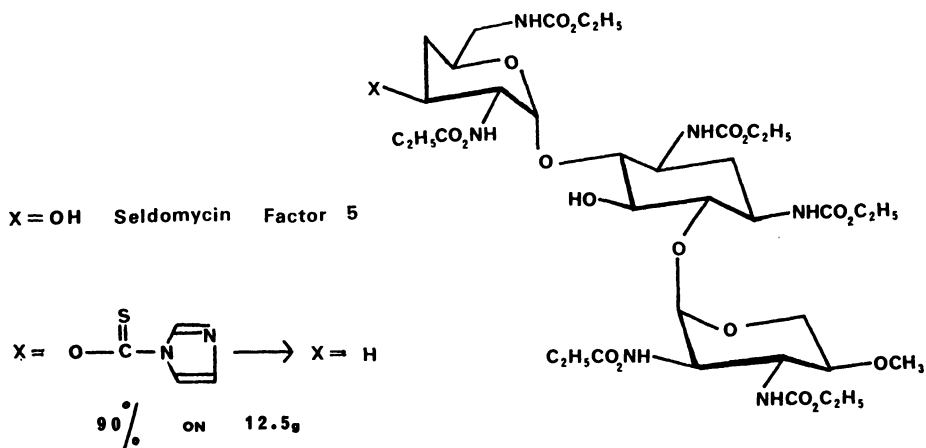


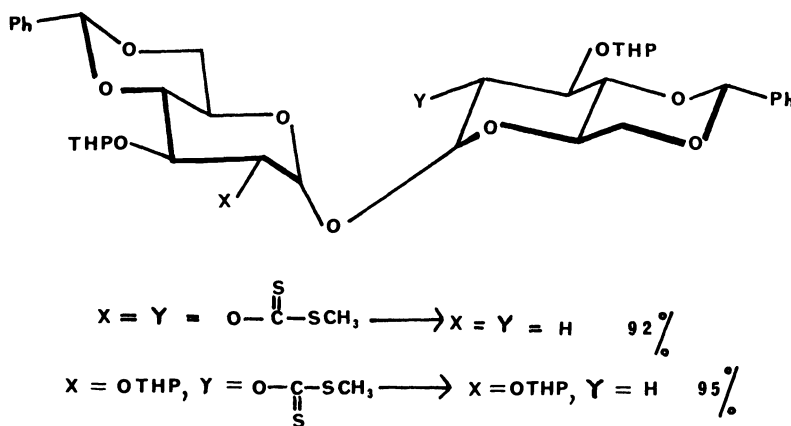
FIGURE 6

The example in Fig. 7 is interesting because the thiocarbonyl radical chain sequence was the only method which permitted the synthesis of the desired deoxy-antibiotic (8). Fig. 8 shows two recent examples that give good yields of 2-deoxygenation of sugars (9).



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

FIGURE 7

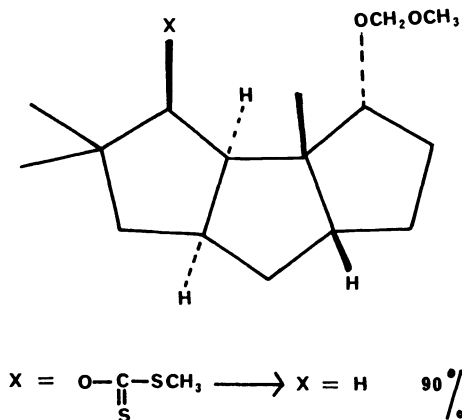


Defaye *et al.*, *Nouveau J. de Chimie*, 1980, **4**, 59.

FIGURE 8

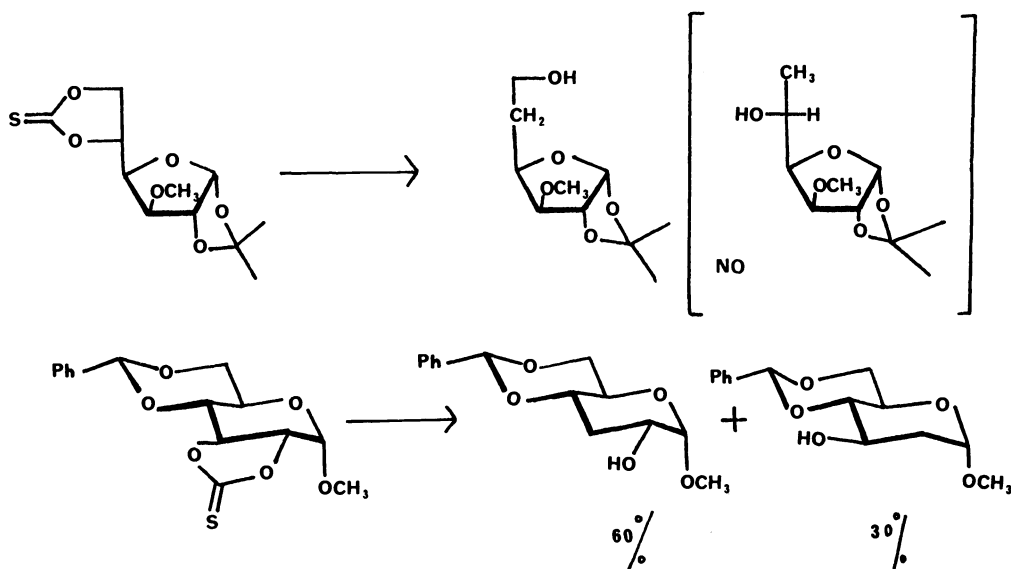
Finally, the reaction is especially good for the deoxygenation of hindered secondary alcohols. Even the most hindered alcohols give xanthate esters without difficulty. A particularly noteworthy example (10) is shown in Fig.9.

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) (Fig.10) for the 5 and 6 positions in sugars. This method of synthesis 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 (Fig. 10).



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

FIGURE 9

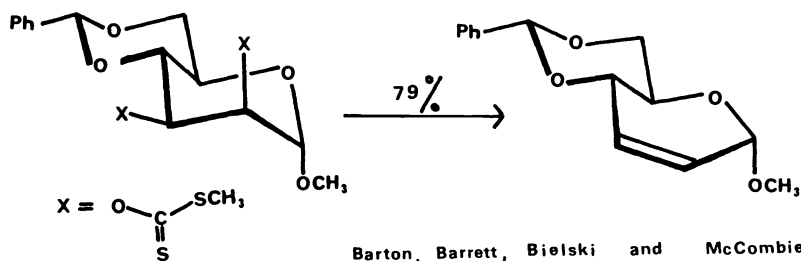
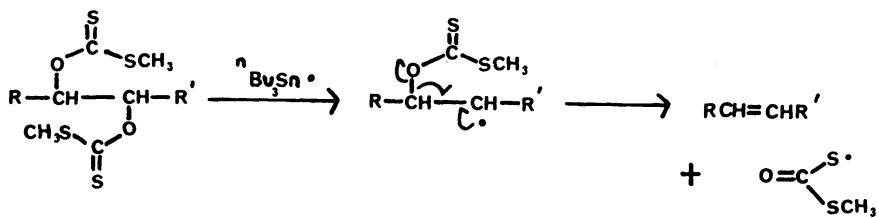


Barton and Subramanian, *J. C. S. Perk.* 1, 1977, 1718.

FIGURE 10

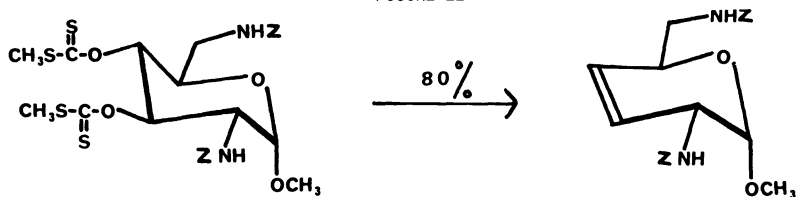
We have, of course, examined the behaviour of α -glycol dithiocarbonyl derivatives. Dithionobenzoates give complex results (3), but 1,2-dixanthate esters fragment (13) smoothly to give olefins (Fig. 11). Being a radical elimination reaction this process gives, when aliphatic α -glycols are used, the more stable *trans*-olefin (see further below). The 1,2-dixanthate elimination was also discovered independently by Hayashi *et al.* (7) (Fig. 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 Fig. 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.



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

FIGURE 11



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

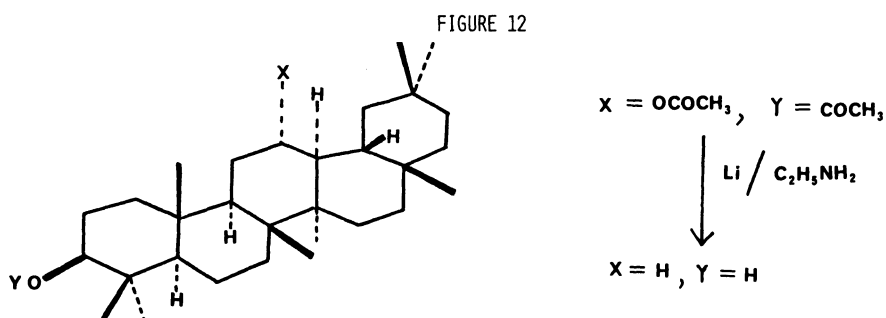


FIGURE 13

Ms Laurette Joukhadar.

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

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

The theory of the electron-transfer reduction of esters can be summarised as in Fig. 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 (Fig. 14).

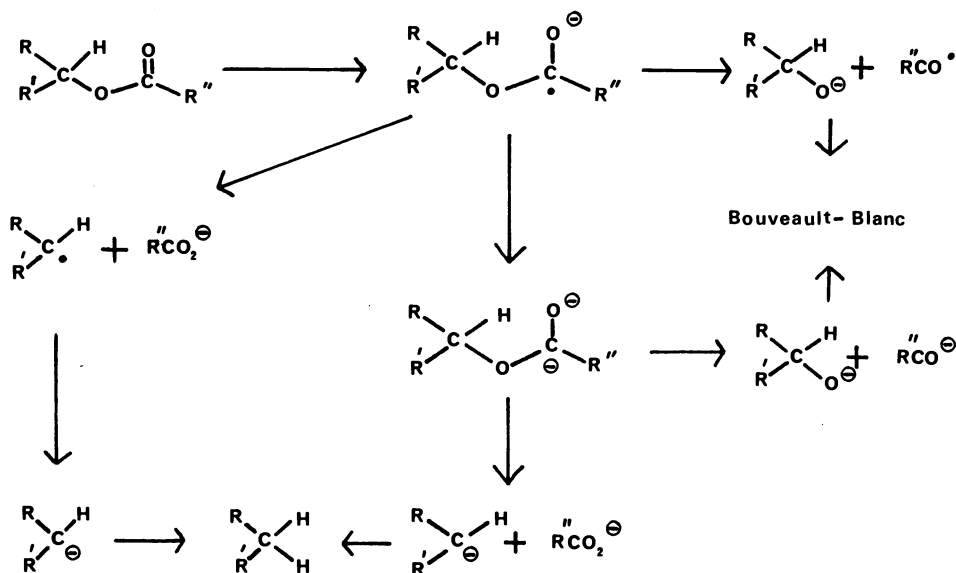


FIGURE 14

The initial example (Fig. 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 (Fig. 15) derivatives of cholestane-3 β ,6 β -diol. The 3 β -OH (equatorial) is, of course, unhindered whilst the 6 β -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 those conditions unless stated to the contrary. Fig. 15 clearly shows that the more hindered is the ester the more completely is it deoxygenated (15).

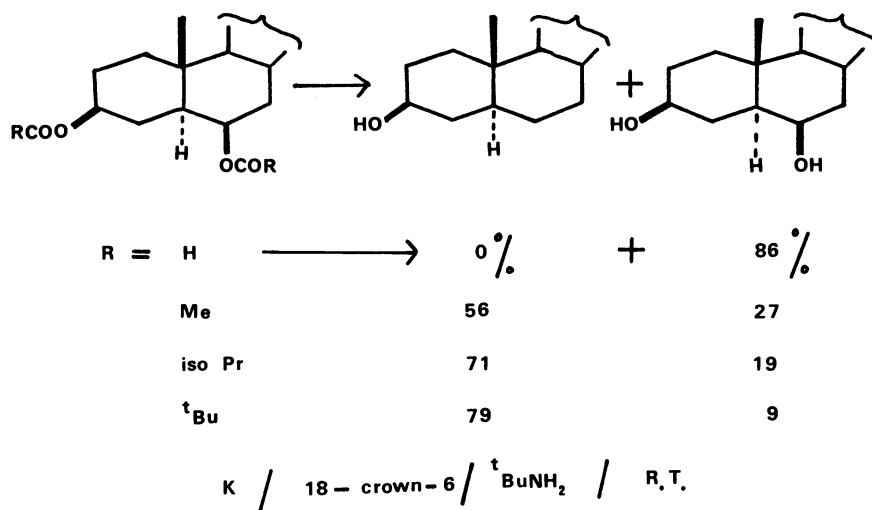


FIGURE 15

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 $RR'CH\cdot$ and $R''CO_2\cdot$ (Fig. 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 (Fig. 16), reduction of $3\alpha,5\text{-cyclo-}5\alpha\text{-cholestan-}6\beta\text{-yl acetate}$ gave a hydrocarbon fraction (45%) which comprised $\text{cholest-}5\text{-ene}$ (85%) and $3\alpha,5\text{-cyclo-}5\alpha\text{-cholestane}$ (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 aromatic esters gave no hydrocarbon (Fig. 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.

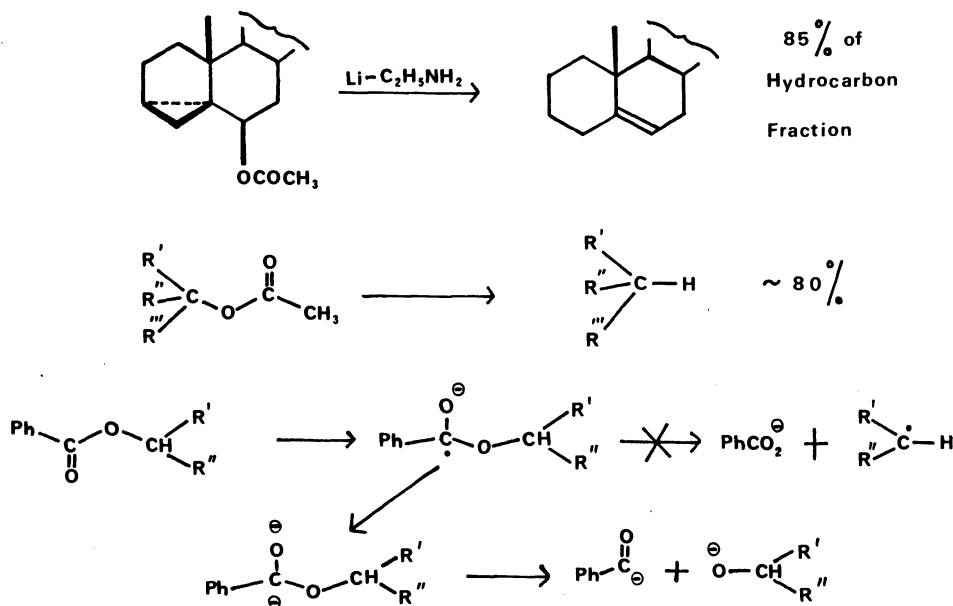


FIGURE 16

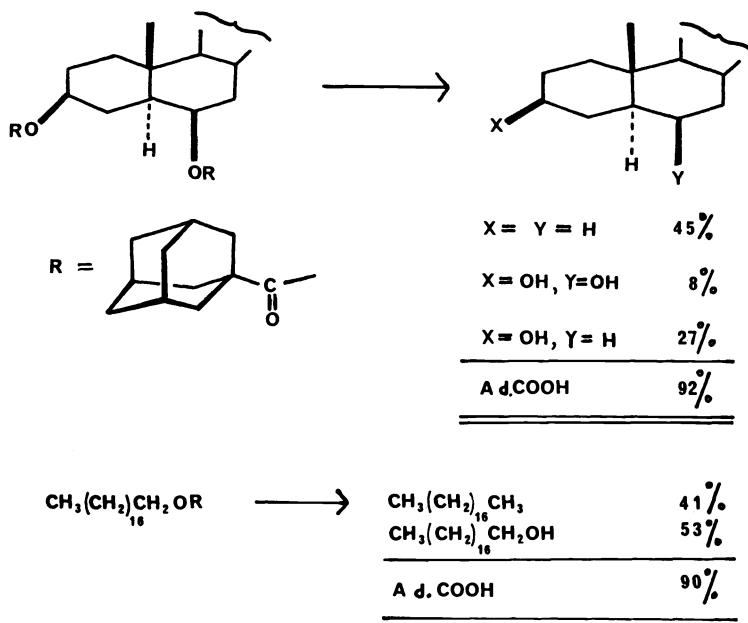


FIGURE 17

An investigation of the fate of the acid fragment of the ester proved revealing. Thus (Fig. 17) reduction of cholestane-3 β ,6 β -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.

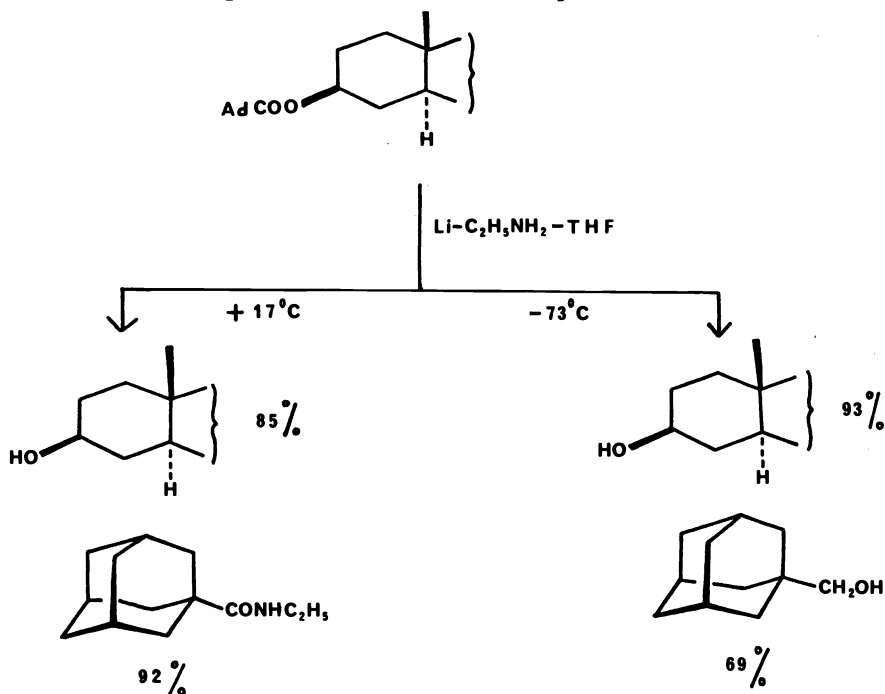


FIGURE 18

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

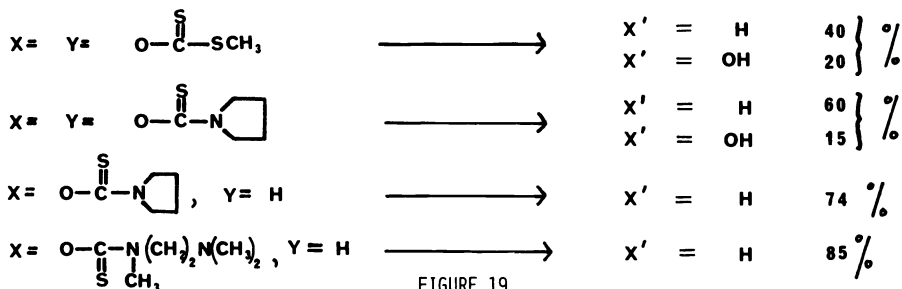
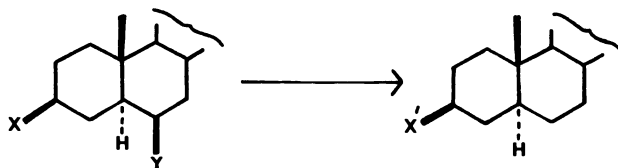
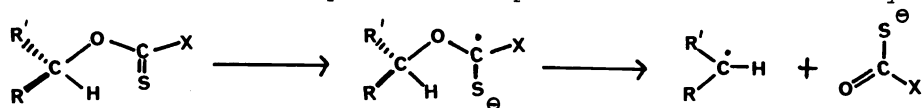
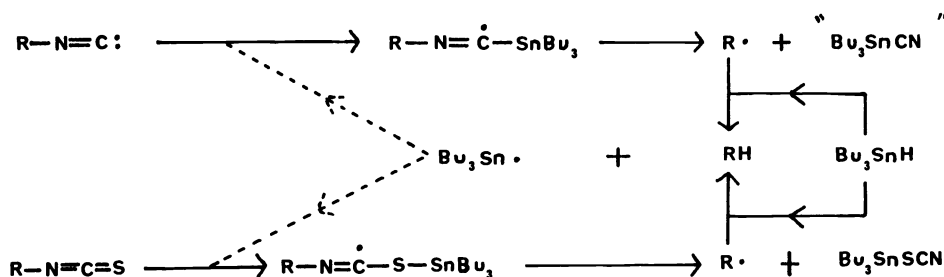


FIGURE 19

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 (Fig. 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).

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. Fig. 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.

CONCEPTION (MISCONCEPTION)



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

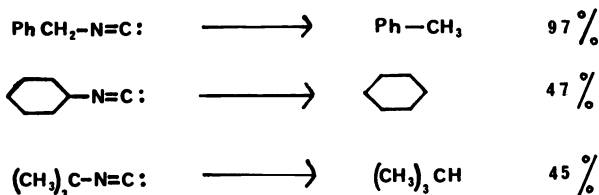


FIGURE 20

In support of our mechanistic proposals we would cite the smooth deoxygenation of esters when photolysed at 250 m μ 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 (Fig. 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 (Fig. 21) both gave excellent yields (90%) of 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).

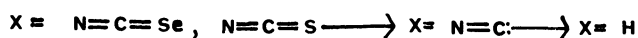
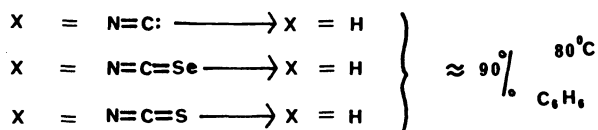
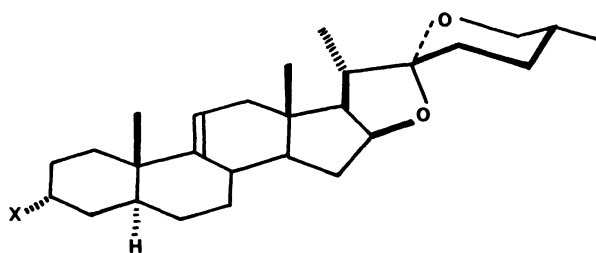


FIGURE 21

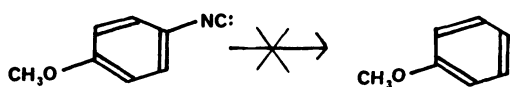
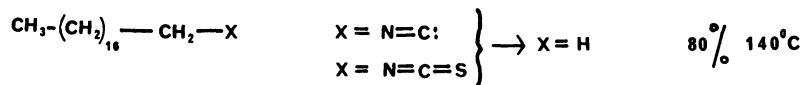
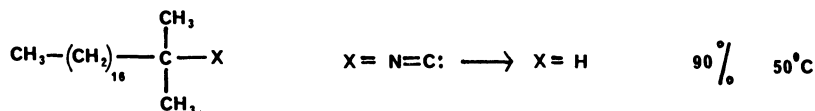


FIGURE 22

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

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

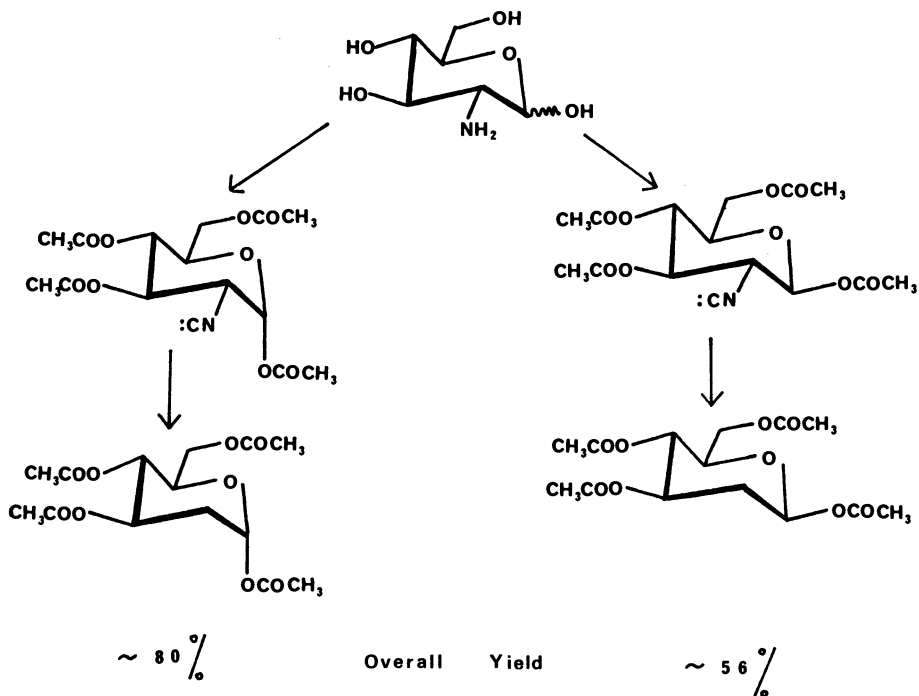


FIGURE 23

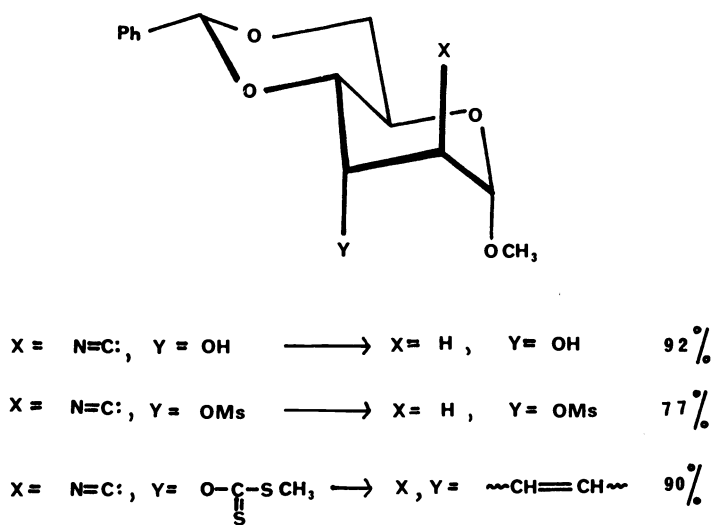


FIGURE 24

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 Fig. 24. Neighbouring OH, OAc (Fig. 23) and even O-mesylate were not effected 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. Fig. 25 shows that both (\pm)- 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 Fig. 25 should lose isonitrile (cyanide) radical even more easily than in the sugar example in Fig. 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).

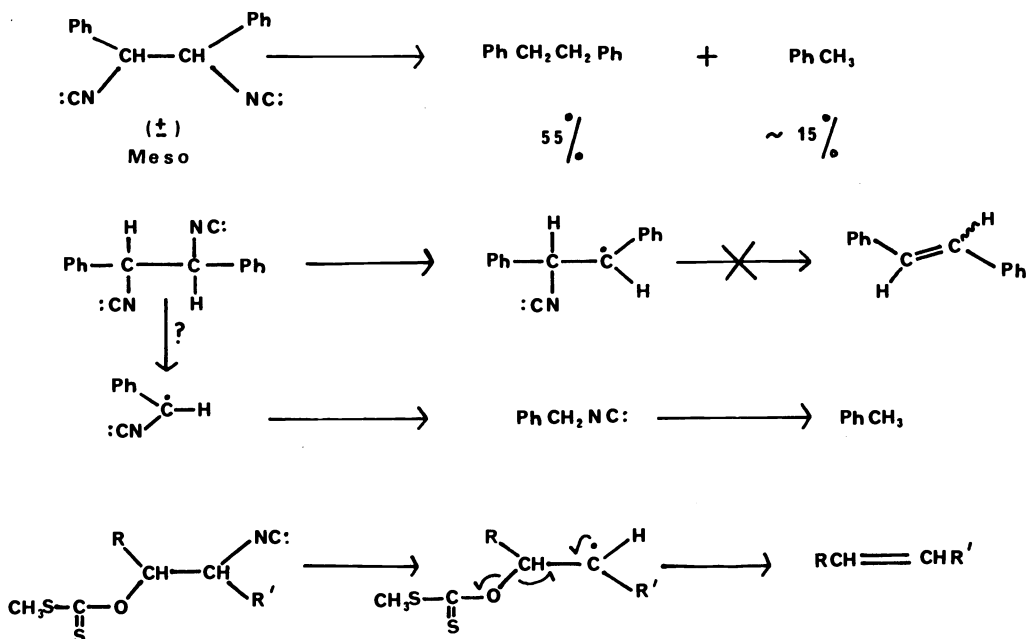


FIGURE 25

we have also made a study of the selective deamination of neamine (Fig. 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 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).

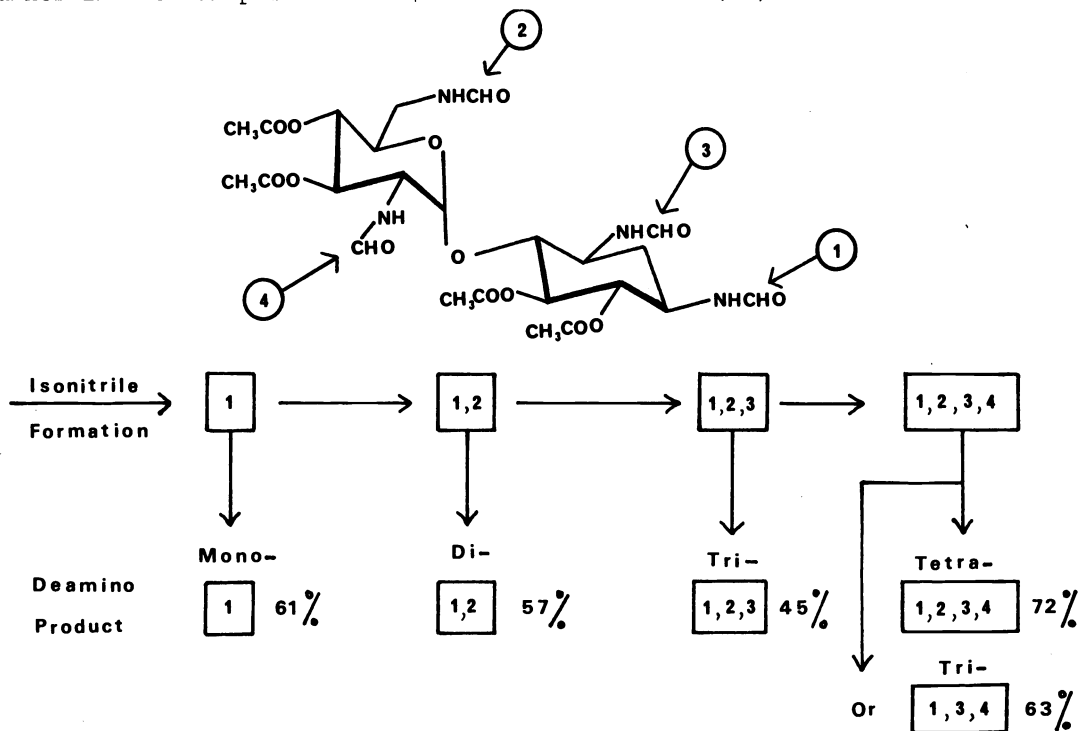


FIGURE 26

CONCEPTION

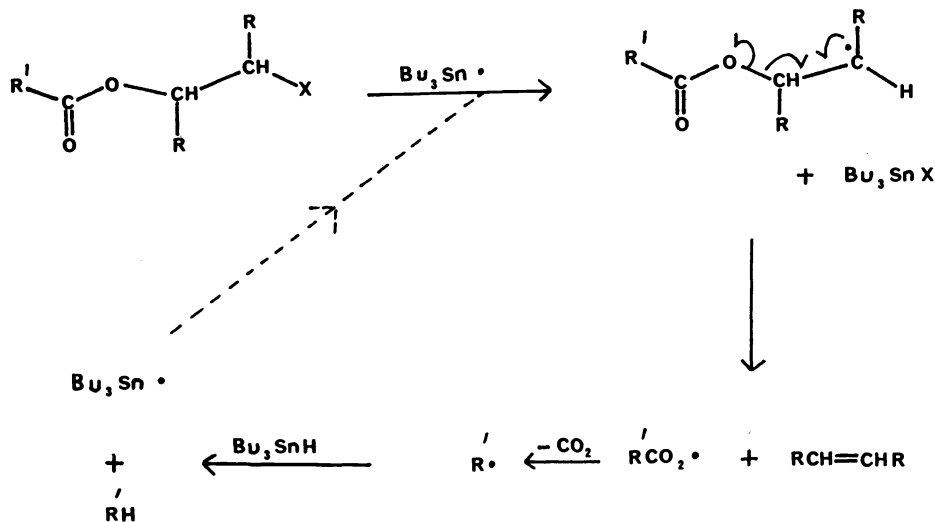


FIGURE 27

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 (Fig. 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 Fig. 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 (Fig. 28).

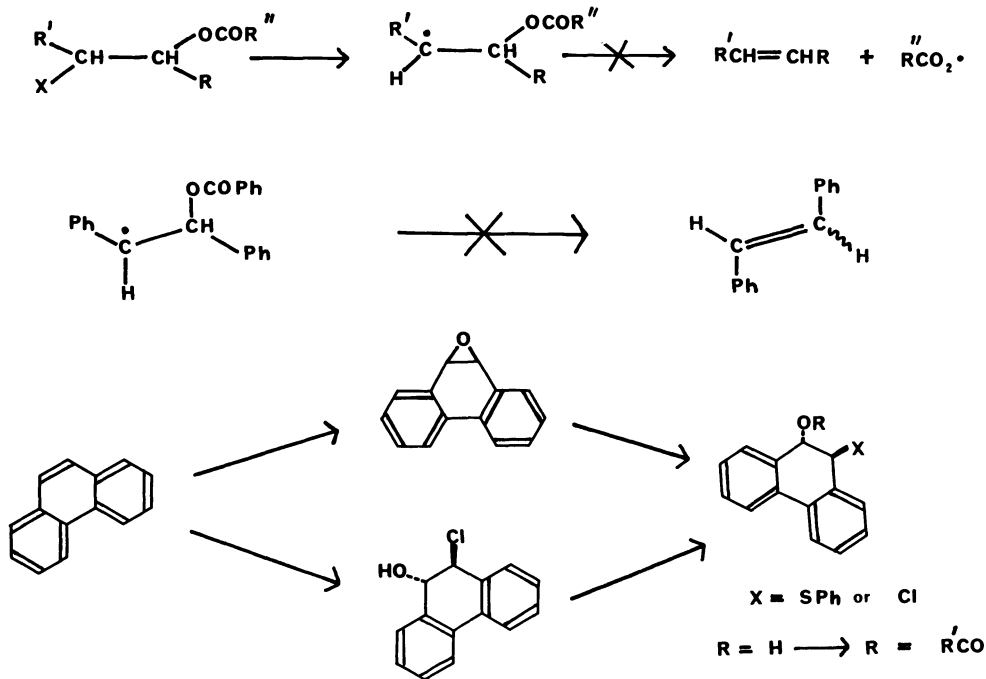
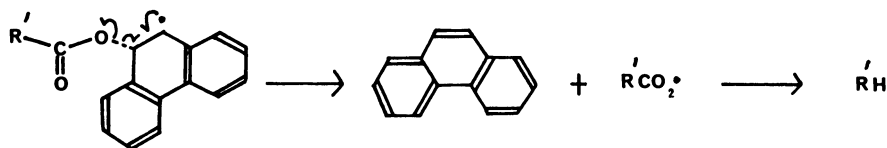


FIGURE 28



PRIMARY

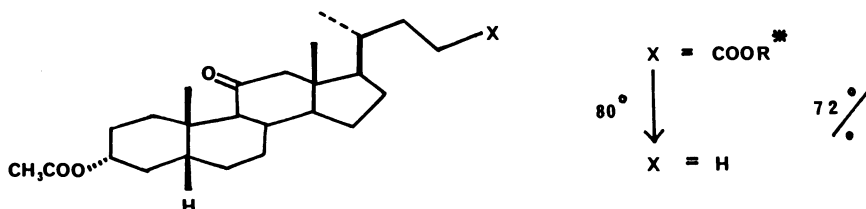
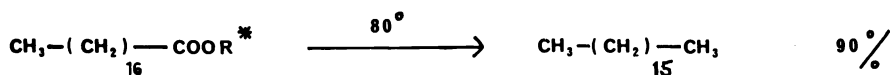
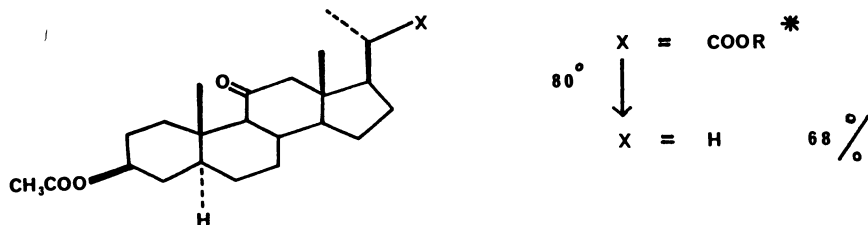


FIGURE 29

In any case tributyl tin hydride reduction of such esters gave radicals which fragmented (Fig. 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 yields in the decarboxylation of certain aromatic acids. Typical examples are shown in Figs. 29, 30 and 31.

SECONDARY



TERTIARY

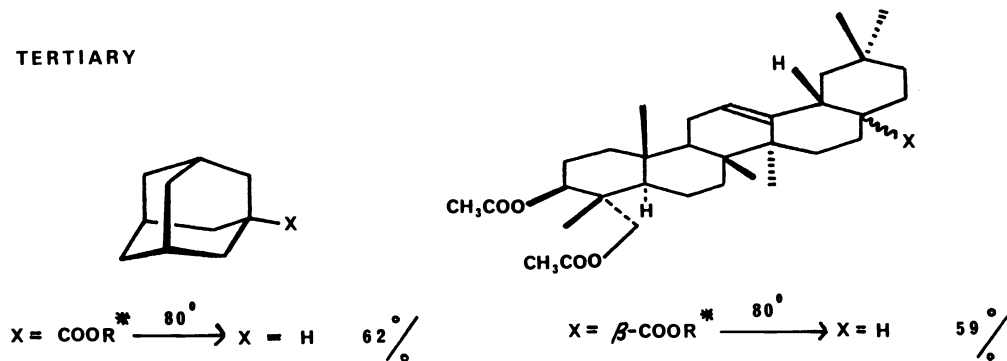
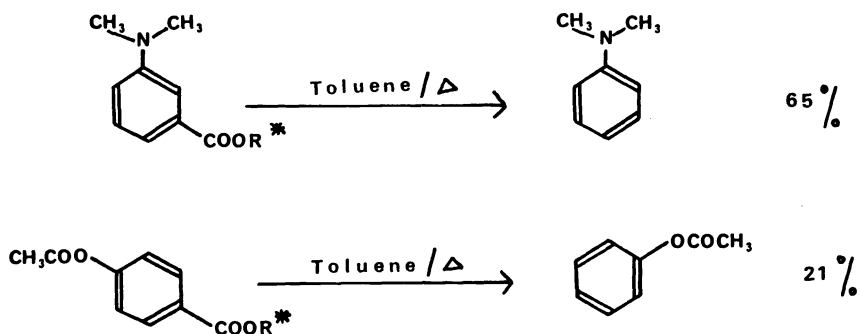
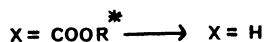
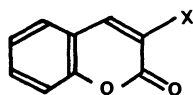


FIGURE 30

AROMATIC



VINYL



Benzene	0 %
Toluene	16 %
Xylene	53 %

FIGURE 31

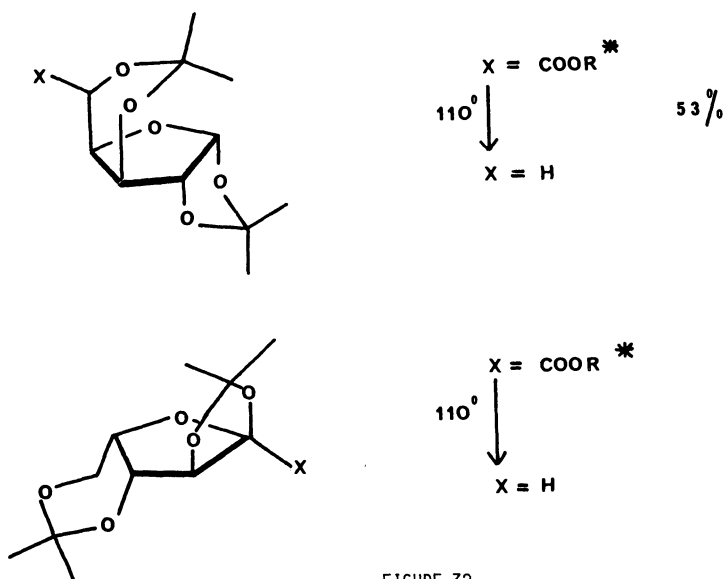


FIGURE 32

In Fig. 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.

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.

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

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