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# A NOVEL REARRANGEMENT OF THE ADDUCT FROM CS-EPOXIDE AND DIOXAN-2-HYDROPEROXIDE

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Summary: Under mild conditions, nucleophiles add across the cyanide moiety of CS epoxide rather than opening the ring. With hydroxide ion in peroxide-free aqueous dioxan isomeric amides are obtained. Hydrolysis in peroxide containing dioxan affords a novel rearrangement involving carbon-carbon bond fission of the dioxan.

Whilst examining the reactivity of CS epoxide (2)[1,2] towards a variety of nucleophiles with a view to assessing the preferred site of attack (ie ring-opening versus addition to cyanide moiety), it was noted that the course of hydrolyses conducted in aqueous dioxan depended on whether the dioxan contained peroxide (ie 1,4-dioxanyl 2-hydroperoxide).

The epoxide 2 shows high reactivity towards a number of nucleophiles and under mild conditions, addition to the cyano moiety occurs in preference to ring-opening. Generally, these adducts were unstable to chromatography and were characterised by spectroscopic methods (ir, $^{1}$H and $^{13}$C nms and ms) only (see Scheme: compounds 3, 4 and 5). Yields were good and crude products were reasonably pure. Hydroxide ion behaves similarly and in peroxide free aqueous dioxan (1:1), a 5:2 mixture of amides 6a and 6b were isolated in high yield (85-95%). The stereochemistry of the amides was assigned by comparing the chemical shift[5] of the C-H resonance ($\delta$4.81 and $\delta$5.01) with those observed in the dicyano epoxide 2 ($\delta$5.44) and the corresponding diamide[6] ($\delta$4.40). On this basis, the amide with the high field C-H resonance was assigned structure 6a and that to lower field 6b[7]. The ratio of 6a:6b of 5:2 is in accord with expectation where the major product is a result of attack on the least hindered cyanide group, ie trans to the bulky aromatic substituent.

However, when the hydrolysis was performed with "old" undistilled dioxan, then, although 6a and 6b were still isolated as reaction products, the major product was identified as 9. Since the "active" component of "old" dioxan was probably the 2-hydroperoxide, this was synthesised[8] and added to both peroxide-free dioxan and to THF when in both solvents with 2 and base, both 6a, 6b and 9 were isolated in the usual way. The reaction was performed as follows:-

The epoxide 2 (306 mg, 0.0015 mole) and the 2-hydroperoxide (180 mg, 0.0015 mole) were dissolved in freshly distilled dioxan (15 ml). Water (10 ml) was added and the solution cooled to 0-5°. To the rapidly stirred solution, sodium hydroxide (250 mg) in water (5 ml) was added with the temperature maintained below 5°. On completing the addition, the reaction was worked up immediately by addition to water (50 ml), extracted with chloroform (3 x 40 ml) and the chloroform extract dried and concentrated to a pale yellow oil which solidified on storage.

Column chromatography over silica with benzene-acetone (8:2) afforded firstly a mixture of 6a and 6b (as an 8:1 mixture of isomers, 73 mg, 22%) and then 9 (148 mg, 32%) mp 126-8° (ethylacetate-benzene).

In the absence of peroxide, the reaction was performed similarly to yield 6a and 6b only (85-95%) as a 5:2 mixture of isomers. All products were fully characterised spectroscopically.

The structure of 9 was further confirmed by preparation of the acetate (from acetic anhydride-pyridine). In contrast to the amides (6), the nmr spectrum suggested that 9 was a single isomer.

The likely mechanism for the formation of 9 is shown in the Scheme and requires 7 and 8 as intermediates. That nucleophiles add readily across the cyanide moiety of 2 has been demonstrated earlier in the paper. Under basic conditions, dioxan 2-hydroperoxide exists as the anion and will add to 2 to afford 7. Such intermediates were invoked[9] in the hydrolysis of nitriles with basic hydrogen peroxide and in the nitrile catalysed decomposition of t-butyl hydroperoxide[10]. The fate of 7 is two-fold. Part rearranges to 8 which can be isolated from reaction mixtures when using potassium carbonate (1% w/v) or dilute sodium hydroxide (0.2% w/v) as base. Under these conditions, the reaction may be stopped when the tlc shows 6 and 8 only. The addition of more base or longer reaction times results in the disappearance of 8 and the formation of 9. 8 may be purified by a combination of chromatography and recrystallisation although losses are marked due to decomposition. 8 has been fully characterised spectroscopically. In addition to the rearrangement reaction, an alternative mode of decomposition results in the formation of the amide 6a by the mechanism proposed by Berger[10]. Since 9 is formed essentially stereospecifically, it follows that 7 is also a single isomer (reflecting the more selective nature of the bulky peroxide nucleophile as compared to hydroxide ion) and that any amide formed from 7 will also be a single isomer. Since simple basic hydrolysis of 2 will compete with the addition of peroxide and the formation of 7, then the observed 6a:6b ratio of 8:1 reflects the contribution of the formation of 6a from 7 giving amide mixtures richer in 6a than observed in the simple hydrolysis reaction.

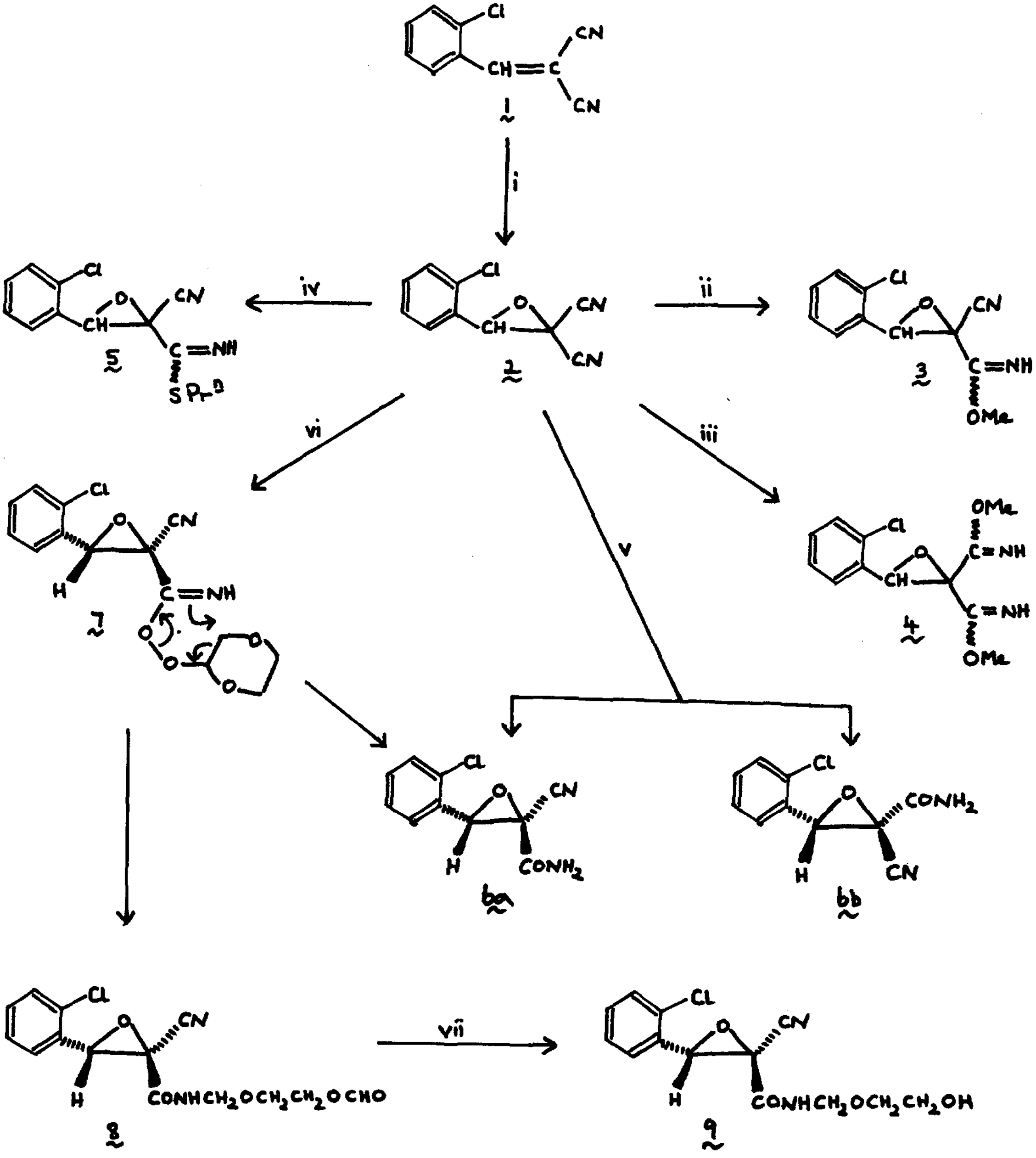
## References

1. CS is a potent sensory irritant. For background and some pertinent references see G.R.N. Jones and M.S. Israel. *Nature*, 228, 1315 (1970).

2. The epoxide 2 was conveniently synthesised by agitating a solution of CS in ethyl acetate with an excess of aqueous sodium hypochlorite until tlc (petrol-EtOAc, 9:1) showed an absence of CS. The organic phase was separated, washed, dried, evaporated and the residue recrystallised from petrol (bp 30-40) containing a few percent of ether. The yield is in excess of 90% and improves on previous procedures[3,4].

3. D.H. Rosenblatt and G.H. Broome. *J. Org. Chem.*, 28, 1290 (1963).

4. A. Robert, J.J. Pommeret, E. Marchand and A. Foucand. *Tetrahedron*, 29, 463 (1973).



REAGENTS:- i NaClO/H$_2$O/EtOAc ii MeOH/NEt$_3$ iii NaOMe/MeOH
iv $^{n}$PrSH/NEt$_3$ v NaOH/H$_2$O/DIOXAN vi NaOH/H$_2$O/DIOXAN/PEROXIDE vii NaOH

SCHEME

5. Chemical shifts were measured in $(CD_3)_2CO$.

6. The diamide was prepared from **6**. See A. Robert and A. Foucand. Bull. Soc. Chim. Fr., 2537 (1969).

7. Deshielding by cyanide relative to amide in gem. disubstituted epoxides has been observed in analogues of **6**. See ref 6.

8. J. Gierer and I. Pettersson. Acta Chem. Scand., 22, 3183 (1968). Using this method, it was observed that the use of shorter reaction times (3 x 8 h, ie 24 h in total) gave a superior product which afforded spectroscopically pure dioxan 2-hydroperoxide after only one recrystallisation. Conversions were in the order of 0.5%.

9. J. Wiberg. J. Amer. Chem. Soc., 75, 3961 (1953).

10. H. Berger. Trans. Faraday Soc., 58, 1137 (1962).

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