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RELEVANT DIFFERENCES IN THE STERIC COURSE OF THE CLEAVAGE OF AN AZIRIDINE AND OF THE CORRESPONDING EPOXIDE

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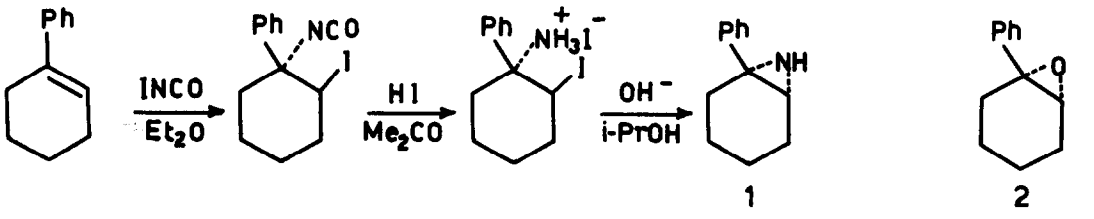
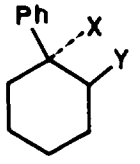
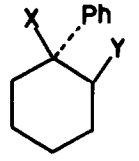
The chemistry of aziridine derivatives has been extensively investigated in recent years,[1] but relatively little is known about the steric course of the opening of their ring, particularly for aryl substituted ones.[2] We have therefore undertaken a study involving the comparison of ring cleavage reactions of representative aziridines with those of their epoxide analogues, which are much better characterized from the stereochemical point of view, in order to establish what analogies, or what differences exist in the stereochemical behaviour of the two ring systems. We report here the first results obtained with the aziridine-epoxide couple 1 and 2, which we chose because the steric course of the reactions of 2 has been extensively investigated and found to be particularly sensitive to the reaction conditions.[3]

The aziridine 1 was obtained through the iodoisocyanate route,[4] and was found to be easily purified by chromatography and quite stable, in contrast with a previous report on the same compound prepared by a different method.[5] It was characterized as the 2,4,6-trinitrobenzenesulphonate salt, m.p.121.5°, and as the phenylcarbamoyl derivative, m.p.193-195°. Compounds 1 and 2 were subjected to several types of ring opening reactions under acidic, neutral and basic conditions, and the results are summarized in Tables I and II.

In all examined cases the opening of the three-membered ring of 1, and probably also of 2, under acidic conditions (Table I) involves exclusively the tertiary benzylic C-O bond, in accordance with an A-1, or borderline A-2 mechanism. The products of reactions 1) - 3) are the two amino alcohols 3 and 8[6] from the aziridine 1, and the two diols 4 and 9 from the epoxide 2.[3a] In







3 : X = OH; Y = NH_2
4 : X = Y = OH
5 : X = $OCOCCl_3$; Y = $NH_3^+CCl_3CO_2^-$
6 : X = OH; Y = $NHCOCCl_3$
7 : X = Cl; Y = $NH_3^+Cl^-$

8 : X = OH; Y = NH_2
9 : X = Y = OH
10 : X = $OCOCCl_3$; Y = $NH_3^+CCl_3CO_2^-$
11 : X = OH; Y = $OCOCCl_3$
12 : X = Cl; Y = OH

reaction 4) the salt 5, m.p.135-135.5°, and a small amount of 10 are formed from 1; 5 gives 6 by acyl migration on treatment with Na_2CO_3. Only 7, m.p. 167-168.5°, is isolated from 1 in reaction 5). Compounds 11 and 12 are obtained from 2 in the latter two reactions.[3a,c]

The data in Table I reveal a profound difference in the steric course of the reactions of 1 and 2, the aziridine showing a much stronger tendency than the epoxide to anti opening, particularly for the reactions run in low polarity aprotic media -reactions 4) and 5) - where one goes from an almost quantitative anti to a quantitative syn cleavage. The steric course and the regiospecificity of the opening of protonated three-membered heterocycles can usually be interpreted on the basis of a borderline mechanism with a transition state being somewhere between purely bimolecular A-2 and purely monomolecular A-1 extremes.[7] The regiospecificity observed for the reactions in Table I rule out an A-2 transition state (which should involve attack at the less hindered carbon), even for those cases that give high percentages of trans adducts. It rather appears that the borderline transition states (or intermediates) in the reactions of 1 involve less bond breaking than those for the reactions of 2, which should be much nearer to the A-1 type.[3] Therefore the attack by the nucleophile from the syn side is hindered much more in the aziridinium than in the oxyranium ion, the trans adduct being the main or only product. This difference in behaviour probably depends on the higher base strength of the aziridine, which stabilizes its protonated form with respect to the aminocarbonium ion,

TABLE I - Ring Opening under Acidic Conditions

Reagent System	Reaction conditions	Aziridine adducts % trans	Aziridine adducts % cis	Epoxide adducts % trans	Epoxide adducts % cis
1) 0.2N $HClO_4$ in H_2O	24 hr at 20°	80	20	36	64
2) 0.2N H_2SO_4 in 80% DMSO-H_2O	5 hr at 5°	95	5	64	36
3) 10% HCl in H_2O	24 hr at 20°	30	70	5	95
4) CCl_3COOH in C_6H_6	48 hr at 20°	95	5	0	100[a]
5) Anh.HCl in Et_2O (satd.)	15 min at 20°	main prod.	--[b]	0	100[c]

[a] Ref. 3a. [b] No evidence was found for its formation. [c] In $CHCl_3$ (Ref. 3c).

TABLE II - Hydrolysis under Basic and Neutral Conditions

Reagent System	Reaction conditions	Aziridine (X=NH) %A	%B	%C	Epoxide[a] (X=O) %A	%B	%C
6) 0.3N KOH in 85% DMSO-H_2O	70 hr at 100°	no reaction			6	94	0[b]
7) 2N KOH in H_2O	5 hr at 100°	74	0	26[c]	43	57	0[d]
8) H_2O	2 hr at 100°	60	0	40	33	8	59[e]

[a] Position of attack was established by using optically active 2, by the method described in ref. 3d. [b] Ref. 3d. [c] Much unreacted aziridine. [d] Some unreacted epoxide. [e] Much unreacted epoxide.

much more than the protonated oxirane is stabilized with respect to the hydroxy carbonium ion.

The apparently anomalous results of the hydrolysis with aqueous HCl -reaction 3) - must be due to the fact that in these cases Cl^- competes with H_2O as the nucleophile, so that the amino alcohols 3 and 8 and the diols 4 and 9 are formed at least in part in a secondary non-stereospecific hydrolytic step from the intermediate chloro amines and chlorohydrins. It is actually found that when 7 is subjected to the reaction conditions it gives 3 and 8 in a 25 to 75 ratio; similarly, 12 and the corresponding trans-chlorohydrin yield 4 and 9 in a 7 to 93 ratio.

Under basic conditions 1 reacts much more slowly than 2 (Table II), and is recovered unchanged from the most strongly nucleophilic and basic medium (KOH in DMSO, reaction 6), whereas 2 is slowly opened, at least 94% by anti attack on the β-carbon.[3d] Under less basic conditions, -reaction 7)- the epoxide still gives 100% anti opening, but only 57% β-attack. The aziridine reacts more slowly, less stereoselectively and with exclusive α-attack. In pure water 1 reacts faster than in base, and also faster than 2, the reaction being even less stereoselective; β-attack is almost suppressed also for the epoxide derivative. It can be concluded that, whereas the unprotonated epoxide can react, even if very slowly, through an S_N2-type mechanism at the less hindered β-carbon, the aziridine ring cannot undergo such a reaction. Only when the conditions are less basic, opening of the aziridine ring takes place at the tertiary carbon, and it probably goes through a borderline A-2 mechanism involving nucleophilic attack on the very small amount of protonated form, which is present at equilibrium.

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