Epoxy Ring-opening Reactions of *endo*- and *exo*-3,4-Epoxy-6-azabicyclo-[3.2.0]heptan-7-ones

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The epoxide ring in the β-lactams (2) and (3) was opened regioselectively with aqueous hydroiodic acid; attack by iodide occurred at C-3 preferentially. Thiophenolate ions attacked the epoxy-lactam (2) at C(4) with high selectivity while the epoxide (3) was attacked at C(3) exclusively. The differing selectivities of attack by nucleophiles at the epoxide units are explained in terms of an interplay of steric and electronic impositions owing to the neighbouring β-lactam ring.

ACID- and base-catalysed ring-opening reactions of epoxy-cyclopentane derivatives have received only scant attention.[1] In our recent work in this field we demonstrated that acid-catalysed epoxy ring-opening reactions of epoxy-2-oxabicyclo[3.3.0]octan-3-ones and epoxybicyclo[3.2.0]heptan-6-ones are subject to pronounced stereocontrol (Figure 1).[2] We based our rationale for the observed effects on the following assumptions. (a) In the epoxy ring-opening reactions the requisite C–O bond cleavage is well advanced in the transition state; as a consequence, acid-catalysed epoxy-ring opening leads to a build up of a partial positive charge at the inverting centre. (b) Non-bonded interactions present in the products will also be present to a significant extent in the product-like transition states. The approach of the nucleophile to the epoxide unit is assumed to be in the axial mode, although an oblique approach path would explain the product distributions equally well.[3] (c) Polar effects exert little or no influence on the product distributions.

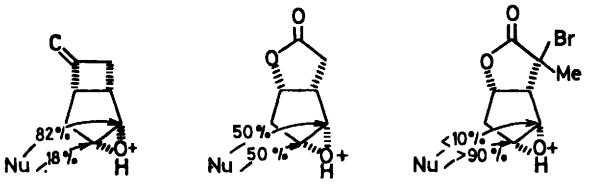
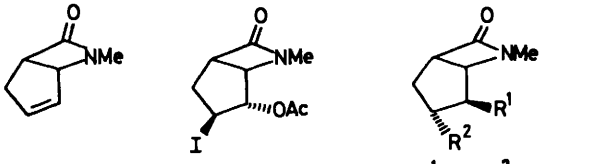


FIGURE 1

It was of interest to study the same reactions of the analogous epoxy-β-lactams to determine whether electronic effects due to the polar nature of the lactam unit would over-ride the stereochemical demands that we had observed earlier. Regioselective opening of these epoxy-lactams would also allow further progress towards the synthesis of naturally occurring β-lactams and analogues.

The synthetic routes from the lactam (1) to the epoxides (2) and (3) are straightforward.[4,5] Treatment of the *endo*-epoxide (2) with aqueous hydroiodic acid gave two iodohydrins (4) and (5). Acetylation of these iodohydrins gave a mixture of the isomeric acetates (6) and (7) in the ratio 3 : 1. The two esters were separated by preparative chromatography. The major product (6) was characterised by n.m.r. spectroscopy which also indicated that the substituents at C(3) and C(4) were *pseudo*-equatorial ($J_{3,4}$ 10 Hz). The minor product (7) was identical to the material formed by addition of HOI to the unsaturated lactam (1), followed by acetylation. The iodo- and acetoxy-moieties in (7) are *pseudo*-axial ($J_{3,4}$ *ca.* 1.0 Hz), the *endo*-envelope conformation being preferred for this molecule.[6] Note that a control experiment showed that the iodohydrin (5) did not isomerise under the conditions employed for the epoxy ring-opening.



(1) (6)

(7) R^1 = I; R^2 = OAc
(9) R^1 = SPh; R^2 = OAc
(10) R^1 = OH; R^2 = I
(11) R^1 = OH; R^2 = SPh

The regioselectivity of the nucleophilic attack on the protonated epoxide (2) is essentially the same as that observed in related reactions involving 3-methoxycyclopentene epoxide.[7] This shows that the electron-withdrawing NMe group mitigates against a build up of positive charge at C(4), forcing the reaction to proceed mainly through the sterically less favoured transition state which involves severe eclipsing of the C(4)–O and C(5)–N bonds [Scheme, path (a)]. The iodohydrin (5) is

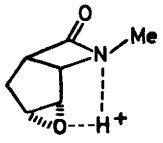


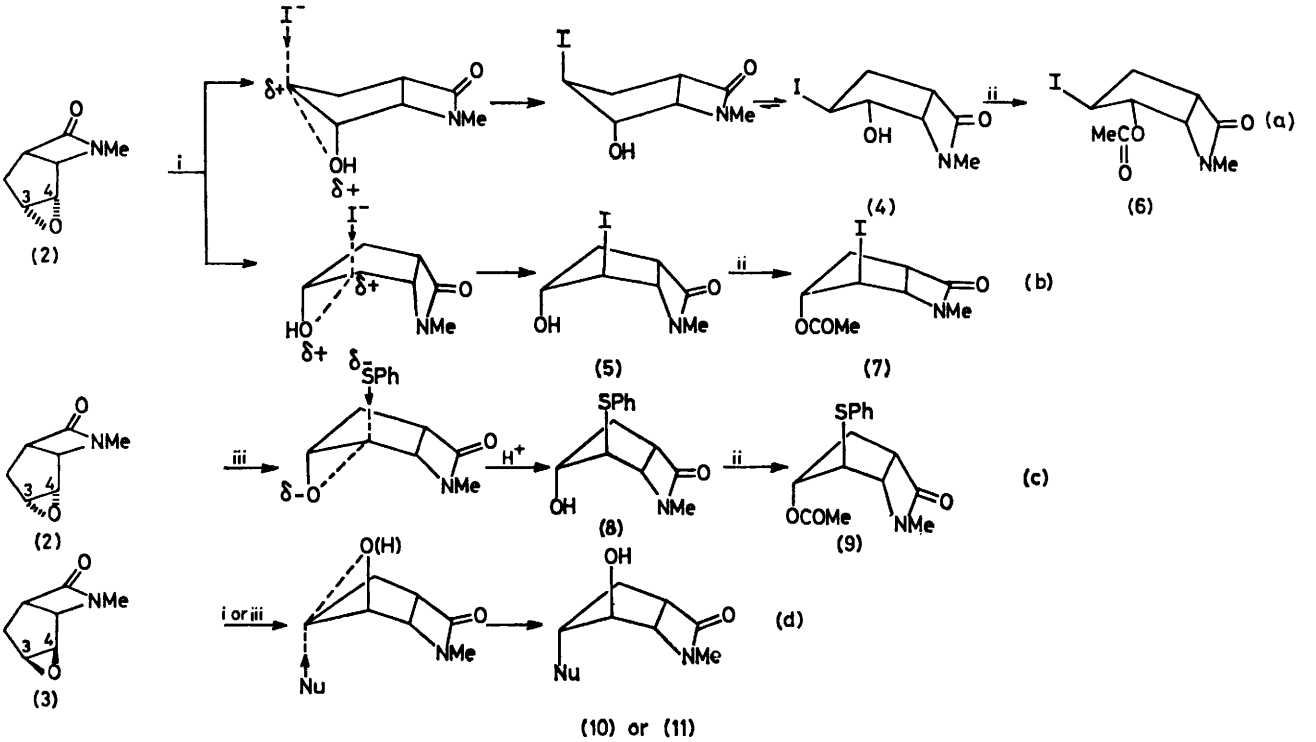
FIGURE 2

formed through the alternative sterically favoured, electronically disfavoured transition state [Scheme, path (b)]. A complementary reason for preferential fracture of the C(3)–O bond could be that the intramolecular hydrogen bond formed within the protonated epoxide is preserved in this way (Figure 2).[8]

As expected, thiolate anions attack the epoxide unit in the lactam (2) at C(4) with very high selectivity (>95%) to give the lactam (8) since a build up of positive charge at C(4) is not required in the transition state of this reaction [Scheme, path (c)].[9] The phenylthio-

alcohol (8) was identified through formation of the acetate (9) and n.m.r. spectroscopy [the *endo*-envelope conformation is preferred for the lactam (9), $J_{3,4}$ *ca.* 1.0 Hz].

For the epoxide (3) electronic and steric factors operate in concert for the acidic (aqueous HI) ring opening reaction so that nucleophilic attack occurs exclusively at C(3) to give the 4 *exo*-hydroxy-lactam (10): attack by sodium thiophenoxide on (3) takes place at C(4) owing to steric control and the lactam (11) was the sole isolated product.



(10) or (11)

SCHEME Reagents: i, HI–H_2O; ii, $(MeCO)_2O$–pyridine; iii, KSPh

EXPERIMENTAL

M.p.s were determined by the capillary tube method. I.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer for neat films unless otherwise stated. N.m.r. spectra were recorded on a Varian EM-360 or Perkin-Elmer R-32 spectrometer (CCl_4 or $CDCl_3$ solvent). T.l.c. was performed using Camlab silica plates. Thick layer chromatography was performed on Anachem Uniplates. Column chromatography was conducted using silica gel MFC (BDH). Anhydrous magnesium sulphate was used for drying solutions in organic solvents.

3-endo-*Hydroxy*-4-exo-*iodo*-N-*methyl*-6-*azabicyclo*[3.2.0]-*heptan*-7-one (5).—*N*-Methyl-6-azabicyclo[3.2.0]hept-3-en-7-one (1) [4] was stirred with *N*-iodosuccinimide [10] in aqueous acetone for 42 h at room temperature. The solution was neutralised with a 5% aqueous solution of sodium hydrogencarbonate and the aqueous solution was extracted with methylene chloride. The combined organic extracts were dried and evaporated and the residue was recrystallized from ethyl acetate to yield the *iodohydrin* (5), m.p. 105—106°, $\nu_{max.}$ 3 350 and 1 750 cm^{-1}, δ 4.7 (1 H, m, H-3), 4.35 (1 H, s, H-4), 4.35 (1 H, m, H-5), 3.8—3.4 (2 H, m, H-1, OH), 2.8 (3 H, s, Me), and 2.4—2.2 (2 H, m, 2 × H-2) (Found: C, 31.6; H, 3.5; N, 5.3. $C_7H_{10}INO_2$ requires C, 31.4; H, 3.5; N, 5.1%).

3-endo-*Acetoxy*-4-exo-*iodo*-N-*methyl*-6-*azabicyclo*[3.2.0]-*heptan*-7-*one* (7).—The iodohydrin (5) was treated with acetic anhydride (1.0 equiv.) in excess of pyridine. After 72 h excess of methylene chloride was added and the organic phase was washed with 2M-hydrochloric acid. The organic solution was dried and evaporated to yield a brown oil which was chromatographed over silica using hexane–ethyl acetate to give the iodoacetate (7) (70%), m.p. 106—108° (ethyl acetate–hexane), $\nu_{max.}$ 1 745 and 1 220 cm^{-1}, δ 5.5 (1 H, d, *J* 4 Hz, H-3), 4.45 (1 H, s, H-4), 4.45 (1 H, m, H-5), 3.9 (1 H, m, H-1), 2.8 (3 H, s, N-Me), 2.6—2.3 (2 H, m, 2 × H-2), and 2.0 (3 H, s, OCOMe) (Found: C, 35.1; H, 3.65; N, 4.4. $C_9H_{12}INO_3$ requires C, 35.0; H, 3.9; N, 4.5%).

Reaction of the Epoxy-lactams (2) *and* (3) *with Hydroiodic Acid.*—The epoxy-lactam was dissolved in acetone, and aqueous hydroiodic acid (1.0 equiv. of a 66% solution of hydrogen iodide in water) was added dropwise with stirring. After 15 h at room temperature, methylene chloride was added and the organic phase was washed with 5% aqueous sodium hydrogencarbonate and with 10% aqueous sodium hydrogensulphite. The aqueous extracts were back-extracted with methylene chloride: the combined organic extracts were dried and evaporated.

From the epoxy-lactam (2) was obtained an inseparable mixture of the iodohydrins (4) and (5) (56%). Acetylation gave a mixture of the iodoacetates (6) and (7) (70%) in the ratio 3 : 1 (by n.m.r. spectroscopy) which was separated by chromatography over silica to give the *iodoacetate* (6), $\nu_{max.}$ 1 760 cm^{-1}, δ 5.1 (1 H, dd, *J* 10, 5 Hz, H-4), 4.25 (1 H, m,

H-3), 4.0 (1 H, dd, *J* 5, 4 Hz, H-5), 3.4 (1 H, dd, *J* 9, 4 Hz, H-1), 2.8 (3 H, s, NMe), 2.6 (1 H, dd, *J* 10, 5 Hz H-2-*endo*), 2.0 (1 H, dd, *J* 10, 4 Hz, H-2-*exo*), and 2.0 (3 H, s, OCOMe) (Found: M^+, 308.986 4. $C_9H_{12}INO_3$ requires *M*, 308.986 3) and the iodoacetate (7). From the epoxy-lactam (3) was obtained the *iodohydrin* (10) (73%) as crystals, m.p. 108°, $\nu_{max.}$ 3 240 and 1 730 cm^{-1}, δ 4.5 (1 H, s, H-4), 4.2 (1 H, m, H-3), 3.9 (1 H, m, H-5), 3.8 (1 H, m, H-1), 3.5 (1 H, m, OH), 2.7 (3 H, s, NMe), and 2.5—2.3 (2 H, m, 2 × H-2) (Found: C, 31.6; H, 3.5; N, 5.8. $C_7H_{10}INO_2$ requires C, 31.6; H, 3.4; N, 5.3%).

Reaction of the Epoxy-lactams (2) *and* (3) *with Sodium Thiophenoxide.*—The epoxy-lactam was dissolved in methanol and freshly prepared sodium thiophenoxide (1.0 equiv.) was added portionwise. The mixture was stirred for 5 h at room temperature. Methylene chloride was added and the organic phase was washed with water, dried, and evaporated.

The epoxy-lactam (2) gave a phenylthio-alcohol (8) (72%) which was acetylated in the usual manner to give the *ester* (9) (95%), $\nu_{max.}$ 1 740 cm^{-1}, δ 7.5—7.2 (5 H, m, C_6H_5), 5.3 (1 H, m, H-3), 4.0 (1 H, d, *J* 4 Hz, H-5), 3.8 (1 H, s, H-4), 3.7 (1 H, d, *J* 4 Hz, H-1), 2.7 (3 H, s, NMe), 2.4—2.2 (2 H, m, 2 × H-2), and 2.0 (3 H, s, OCOMe) (Found: M^+, 249.082 2. $C_{13}H_{15}NO_2S$ requires *M*, 249.082 3). From the epoxy-lactam (3) the *alcohol* (11) (60%) was obtained as a yellow oil after chromatography over silica, $\nu_{max.}$ 3 460 and 1 730 cm^{-1}, δ 7.5—7.1 (5 H, m, C_6H_5), 4.3 (1 H, s, H-4), 3.9 (1 H, m, H-5), 3.7 (1 H, m, H-3), 3.5 (1 H, m, H-1), 2.8 (3 H, s, NMe), and 2.6—2.3 (2 H, m, 2 × H-2) (Found: M^+, 249.082 2. $C_{13}H_{15}NO_2S$ requires *M*, 249.082 3).

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