Participation of Sulphonamide Nitrogen in the Rearrangement of the 2-Azabicyclo[2.2.2]octane Skeleton: an Efficient Synthesis of the 6-Azabicyclo[3.2.1]octan-4-one System

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Treatment of the 2-azabicyclo[2.2.2]oct-5-ene imino Diels–Alder adduct (**2**) with *N*-bromosuccinimide in aqueous dimethoxyethane gives the rearranged bromohydrin (**4a**), whose structure is confirmed by *X*-ray crystallographic analysis, and which serves as a precursor to the 6-azabicyclo[3.2.1]octan-4-one (**7**).

In the course of our studies on the synthesis of prosopine,[1] we have sought methods for the regioselective hydration of the double bond of suitably substituted 2-azabicyclo[2.2.2]oct-5-enes such as the 3-*exo*-ester (**2**),† m.p. 140—142 °C, which is readily available in 80% yield from the cycloaddition[2] of the glyoxylate‡ tosyl imine (**1**) to cyclohexadiene, Scheme 1. Regioselective oxymercuration[4] and chlorophenylselenation[5]

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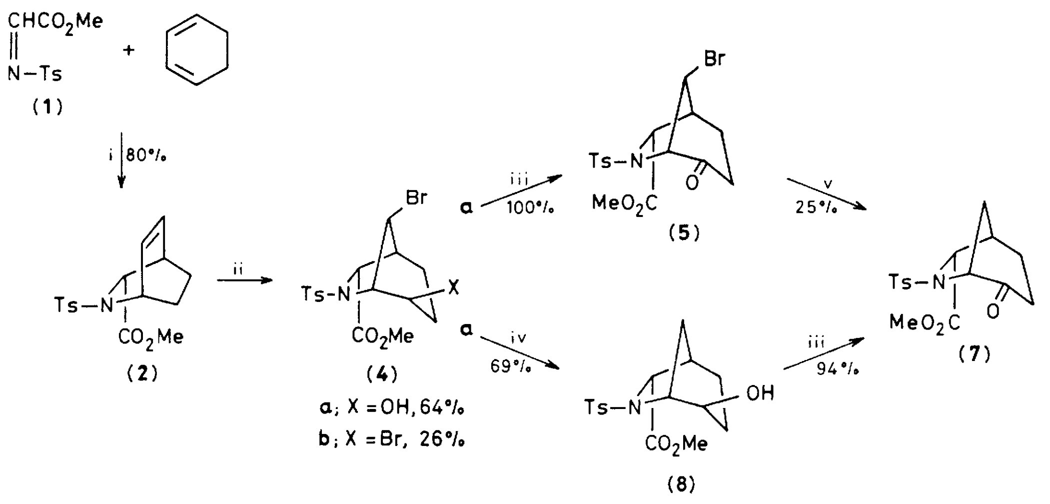
† All new compounds exhibited spectroscopic and analytical data consistent with their structure.

‡ Methyl glyoxylate was most conveniently prepared by equilibrating equimolar amounts of methyl 2,2-dimethoxyacetate and glyoxylic acid monohydrate in the presence of toluene-*p*-sulphonic acid, followed by distillation from P_2O_5, ref. 3. We thank Dr. J. M. Hook for providing us with details of this preparation before publication.



Scheme 1. Ts = p-$MeC_6H_4SO_2$. *Reagents*: i, C_6H_6, heat, 16 h; ii, NBS, $MeOCH_2CH_2OMe$–H_2O; iii, Jones reagent, Me_2CO; iv, Bu_3SnH, C_6H_6, heat; v, Zn, AcOH.

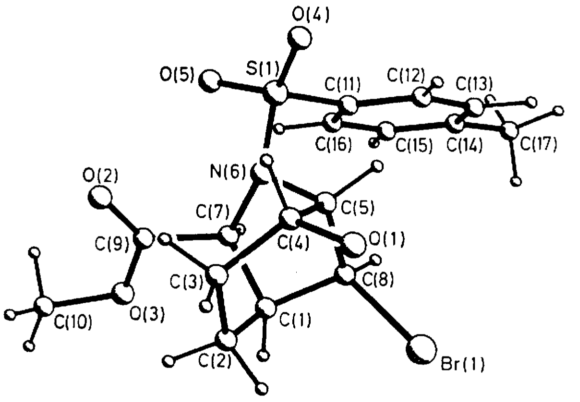
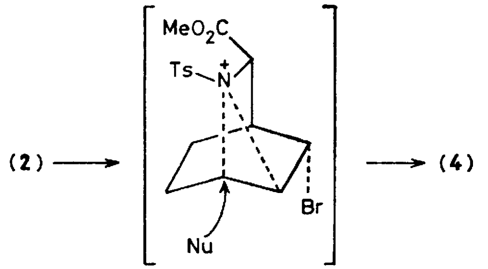


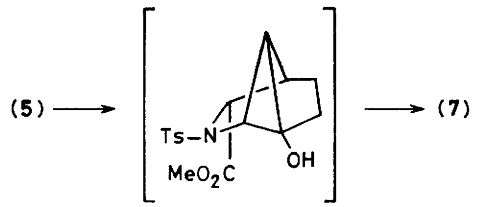
Figure 1. The molecular structure of (**4a**) including the atom numbering scheme adopted. Bond lengths: C(1)–C(2) 1.538(5), C(1)–C(7) 1.547(4), C(2)–C(3) 1.536(6), C(3)–C(4) 1.517(5), C(4)–C(5) 1.539(4), C(5)–N(6) 1.484(4), N(6)–C(7) 1.482(4), C(5)–C(8) 1.517(4), C(1)–C(8) 1.515(5), C(8)–Br(1) 1.958(3), C(7)–C(9) 1.513(4), C(9)–O(2) 1.184(4), C(9)–O(3) 1.330(4), O(3)–C(10) 1.446(5) Å. Bond angles: C(7)–C(1)–C(2) 102.9(2), C(1)–C(2)–C(3) 113.0(3), C(2)–C(3)–C(4) 114.7(3), C(3)–C(4)–C(5) 111.2(3), C(4)–C(5)–N(6) 107.4(2), C(8)–C(5)–N(6) 93.9(2), C(8)–C(5)–C(4) 115.0(3), C(7)–N(6)–C(5) 110.4(2), S(1)–N(6)–C(5) 117.9(2), S(1)–N(6)–C(7) 118.0(2), C(1)–C(7)–N(6) 102.6(2), C(9)–C(7)–C(1) 113.0(3), C(9)–C(7)–N(6) 113.6(2), C(5)–C(8)–Br(1) 117.0(2), C(1)–C(8)–Br(1) 114.4(2), C(1)–C(8)–C(5) 101.5(2)°.

reactions of *N*-alkoxycarbonyl analogues of (**2**) have been reported. However we have been unable to oxymercurate compound (**2**), which supports the hypothesis[4] that the urethane grouping plays an important role in this reaction.

Addition of HOBr to the alkene (**2**) was expected to result in delivery of the hydroxy-group to C-5 as a consequence of the inductive effect exerted by the allylic *N*-tosyl substituent. In the event, the alkene (**2**) reacted with *N*-bromosuccinimide (NBS) in dimethoxyethane–water (3:2) to give the bromohydrin (**4a**),† m.p. 194—195 °C (64%), and the dibromide (**4b**),† m.p. 163—165 °C (26%). The bromohydrin (**4a**) was subjected to *X*-ray structure determination, the results of which are shown in Figure 1. The bromonium ion-induced rearrangement of (**2**) to (**4**) results from attack of Br^+ at the less hindered face of the double bond with participation of the electron-deficient sulphonamide nitrogen to form a species such as (**3**), which collapses to (**4**) under nucleophilic attack. Migration of such an electron-deficient nitrogen atom is an extremely unusual process. Although nitrogen participation in such rearrangements is not totally unprecedented, it has usually been confined to relatively electron-rich nitrogen groups such as *N*-alkyl[6,7] or *N*-alkoxycarbonyl[8] groups. There is only one report[9] of the migration of *N*-tosyl and this occurs in the rearrangement of the relatively strained 7-azabicyclo[4.2.0]oct-3-ene to a 6-azabicyclo[3.2.1]oct-2-ene.



(**3**)



(**6**)

Jones oxidation[10] of the bromohydrin (**4a**) gave the bromoketone (**5**),† m.p. 187—188 °C which upon zinc–acetic acid reduction[11] yielded the debrominated ketone (**7**),† m.p. 150—151 °C in modest yield. The reaction may be a conventional reductive dehalogenation,[12] or it could involve the homo-enol (**6**) as a possible intermediate.[13] The ketone (**7**) was more efficiently prepared by reduction of the bromohydrin (**4a**) with tri-n-butyltin hydride[14] to the alcohol (**8**),† m.p. 170—171 °C, (69%) followed by Jones oxidation to (**7**) in 94% yield.

The bromohydrin (**4a**) crystallised from chloroform–hexane as transparent rectangular blocks, and a suitable single crystal was used in the *X*-ray analysis.

Crystal data: $C_{16}H_{20}BrNO_5S$, $M = 418.29$, orthorhombic, space group *Pbca*, $a = 16.627(3)$, $b = 14.113(2)$, $c = 15.051(3)$ Å, $U = 3531.8$ Å^3, $D_c = 1.569$ g cm^{-3}, $Z = 8$, $F(000) = 1704$, $\lambda(\text{Cu-}K_\alpha) = 1.5418$ Å, $\mu(\text{Cu-}K_\alpha) = 42.53$ cm^{-1}.

3295 Intensity data ($2\theta_{\max} = 125°$) were recorded on a Syntex $P2_1$ diffractometer, and corrected for Lorentz polarisation factors and for absorption. 2547 Unique observed reflections [$F > 4\sigma(F)$] were used to solve the structure by Patterson and Fourier difference techniques, and refine it to $R = 0.050$ ($R' = 0.057$) by full matrix least squares (all non-hydrogen atoms anisotropic). Hydrogen atoms were placed in idealised positions and constrained to ride on the relevant C atom; the methyl groups were refined as rigid bodies. Methylene, methyl, and aromatic H atoms were each assigned common isotropic temperature factors.§

In summary an unusual bromonium ion-induced rearrangement of an *N*-tosyl group in the 2-azabicyclo[2.2.2]oct-5-ene (**2**) has resulted in the stereospecific syntheses of various 6-azabicyclo[3.2.1]octane derivatives in high yield. Few syntheses of this ring system have been reported,[8,15] and the method should be useful for the preparation of a variety of naturally occurring compounds bearing this skeleton.

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§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.