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Stereospecific S_N2' Reactions of *exo*-4-Substituted 3-Halogenobicyclo-[3.2.1]oct-2-enes

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Stereochemically pure samples of *exo*-bicyclo[3.2.1]octan-2-ol are obtained from hydrolysis followed by hydrogenation–hydrogenolysis of *exo*-3,4-dihalogenobicyclo[3.2.1]oct-2-enes. Attempted tosylation of the intermediate hydroxy-halides in these reactions by the Tipson procedure gave only *exo*-4-chloro-3-halogenobicyclo-[3.2.1]oct-2-enes. No inversion of configuration was detected in the reactions of *exo*-3,4-dihalogenobicyclo-[3.2.1]oct-2-enes with sodium halides in aprotic dipolar solvents. These results lead to the conclusion that the S_N2' reaction in this system occurs upon covalent substrates with retention of relative configuration but inversion of absolute configuration.

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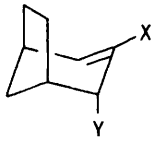
In order to extend our investigations of solvolysis and deamination reactions in the bicyclo[3.2.1]octane system,[1-3] we required stereospecific preparations of further substrates and possible reaction products. Conversions of *exo*-3,4-dibromobicyclo[3.2.1]oct-2-ene (1a) and its dichloro-analogue (2a) into *exo*-bicyclo[3.2.1]-octan-2-ol (3) have already been carried out [4,5] but the extents of the stereospecificity were not reported.

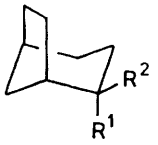


(1)

a; X = Y = Br
b; X = Br, Y = OH
c; X = Br, Y = OTs
d; X = Br, Y = Cl

(2)

a; X = Y = Cl
b; X = Cl, Y = OH
c; X = Cl, Y = OTs



(3) R^1 = OH, R^2 = H
(4) R^1 = H, R^2 = OH

During our reinvestigation of these and the development of other such processes, we found that racemic *exo*-4-substituted 3-halogenobicyclo[3.2.1]oct-2-enes in general undergo substitution reactions at C-4 with *complete* retention of relative configuration. This finding and the realization that the reactions involve inversion of absolute configuration relate to other studies of the mechanism of S_N2' reactions.[6,7]

RESULTS

Hydrolysis of (1a) followed by catalytic hydrogenation–hydrogenolysis under mild conditions as described by Kraus [4] gives *exo*-bicyclo[3.2.1]octan-2-ol (3) in high yield (64—70%) with no detectable contamination (≤2% by conventional g.l.c.) by the diastereoisomeric *endo*-compound (4). Unfortunately, the yield in the preparation of (1a) itself is variable and low (20—50%).[4,8,9] Compound (2a) is more readily made in good yield (*ca.* 75%) by the Makosza method of dichlorocarbene generation.[9,10] Hydrolysis of (2a) followed by the somewhat more forcing hydrogenation–hydrogenolysis conditions described by Bergman [5] gives (3) in good yield (80%) and, as we have now established by capillary g.l.c.s in high stereochemical purity, contamination by (4) being ≤0.4%. [Compounds (3) and (4) are known,[11] their structures are firmly established, and they are readily analysed by g.l.c.[1,12,13]] There appears to be very little scope, and no thermodynamic reason,[14] for inversion of configuration at C-4 during the hydrogenation–hydrogenolysis steps; consequently, (1a) and (2a) must give compounds (1b) and (2b) respectively in the initial hydrolytic step. And under basic conditions, we obtain only the kinetic products (under acidic conditions a small extent of *exo* ⇌ *endo* interconversion would be anticipated [15]). These stereospecifically formed hydroxy-halides were isolated and characterized.

There are two deshielded doublets in the n.m.r. spectra of both compounds, each of which corresponds to a single hydrogen. In compound (1b), the signals are at τ 3.80 (*J* 7.1 Hz) and 6.31 (*J* 2.7 Hz). The spectrum of the dibromide (1a) has corresponding signals at τ 3.75 (*J* 7.1 Hz) and 5.57 (*J* 2.7 Hz). In each case, these signals correspond, respectively, to the vinylic hydrogen at C-2 split by the adjacent bridgehead hydrogen at C-1 and the allylic hydrogen at C-4 [which also bears either the hydroxy-group in (1b) or the second bromine in (1a)] split by the bridgehead hydrogen at C-5.

In compound (2b), the analogous signals are at τ 3.95 (*J* 7 Hz; vinylic hydrogen at C-2) and 6.35 (*J* 3 Hz; allylic hydrogen at C-4) compared with τ 4.00 (*J* 7.0 Hz) and 5.93 (*J* 2.5 Hz), in (2a). There can be no doubt that the hydrogens at C-4 in all four compounds (1a and b) and (2a and b) are equatorially disposed and, consequently, the hydroxy-groups in (1b) and (2b) are axial. The hydrolyses of the allylic halides, therefore, have occurred with complete retention of relative configuration.

When preparations of the tosylates (1c) and (2c) were attempted,[16] only dihalides (1d) [from (1b)] and (2a) [from (2b)] were obtained. The sample of (2a) obtained from (2b) *via* (2c) was identical with the initial sample of (2a). The n.m.r. spectrum of (1d) showed the familiar pair of deshielded doublets: the vinylic hydrogen at C-2, τ 3.75 (*J ca.* 7 Hz), *cf.* 3.75 (*J* 7.1 Hz) in (1a), and the C-4 allylic hydrogen, τ 5.88 (*J ca.* 3 Hz), *cf.* 5.93 (*J* 2.5 Hz) in (2a). Again, therefore, compounds are obtained stereospecifically with reten-

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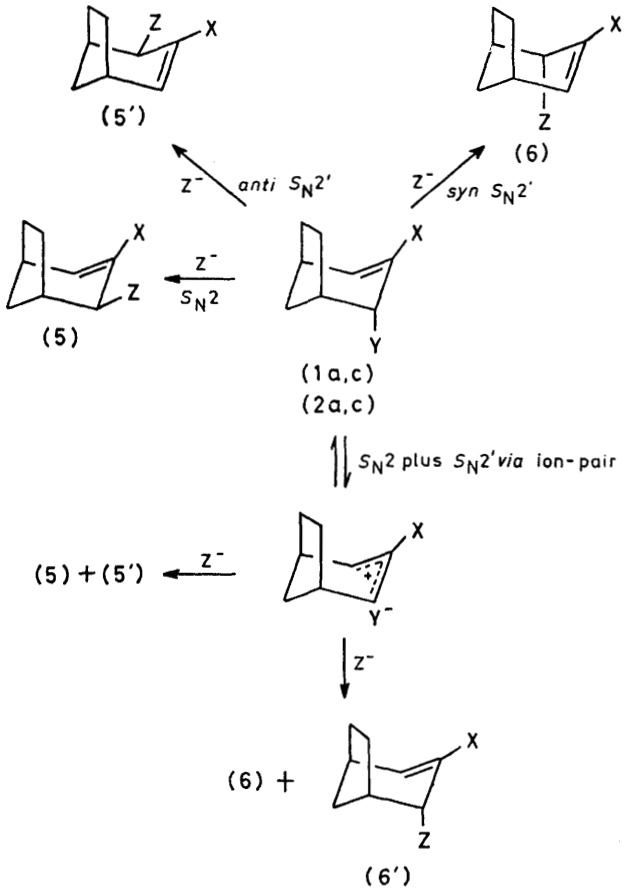
tion of relative configuration, the C-4 substituent remaining axial. The sample of the mixed dihalide (1d) obtained in the attempted tosylation of (1b) was indistinguishable from the single product of the reaction of (1a) with sodium chloride in dimethyl sulphoxide (DMSO). In this experiment, the coupling constants were measured accurately (90 MHz); J 7.1 Hz for the C-2 vinylic hydrogen and 2.7 for the C-4 allylic one. Sodium chloride and (2a) in either DMSO or dimethylformamide gave no new product by g.l.c. and n.m.r. Either no reaction takes place or, more likely, chloride exchange occurs with complete retention of relative configuration which, with racemic (2a), corresponds to a degenerate reaction. An analogous result was obtained with (1a) and sodium bromide in DMSO. [Due to adventitious water in the DMSO, there was some hydrolysis of (1a) in this reaction to give (1b).] There was no halide exchange in the reaction of sodium bromide and the dichloride (2a) in DMSO.

DISCUSSION

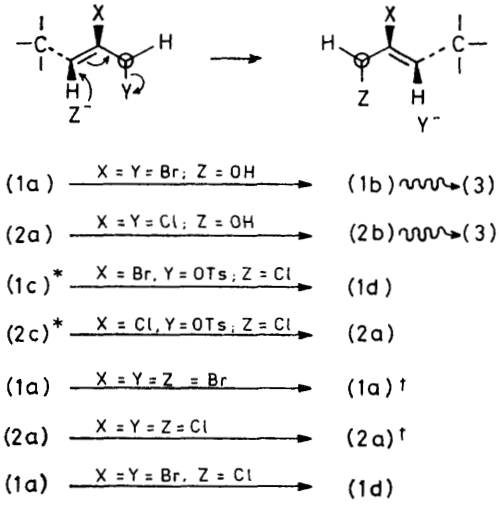
Even though the reactants in this investigation were racemic, the exceptional stereospecificity of the reactions allows us to assess the *absolute* stereochemical course of the substitution steps and to ascribe the mechanisms uniquely.

Scheme 1 includes the reasonable generalized mechanistic possibilities.



SCHEME 1 Bimolecular substitution mechanisms of *exo*-4-substituted 3-halogenobicyclo[3.2.1]oct-2-enes

It is evident that three of the mechanisms shown (S_N2 on covalent allylic substrate, S_N2 plus S_N2' *via* an ion-pair, and *anti*-S_N2' upon covalent substrate *i.e.* with inversion of relative configuration) would give significant yields of a common product from racemic starting material, racemic *endo*-4-substituted material (5) + (5′).[6,17] At least some of this would also be reasonably expected if the hydrolytic substitutions were unimolecular.[15,17] Detection of appreciable quantities of (4) derived from such a product in the hydrolysis and hydrogenation–hydrogenolysis of (1a) and (2a) would, therefore, have been mechanistically ambiguous. However, exclusive detection of racemic (3) in our reaction sequence derived from *exo*-4-substituted material (6) plus (6′) with retention of relative configuration leads inevitably to a



* (1c) and (2c) were not isolated from the reaction of (1b) and (2b) respectively with TsCl.

† Corresponds to a degenerate reaction using racemic starting materials.

SCHEME 2 Products of S_N2' reactions with inversion of absolute configuration and retention of relative configuration upon *exo*-4-substituted 3-halogenobicyclo[3.2.1]oct-2-enes

single reasonable mechanism, *syn*-S_N2' upon covalent starting material,[7] with inversion of absolute configuration. The only other mechanism, which we regard as unreasonable [18] although it would account for the results, is S_N2 with retention of both relative and absolute configuration.

Scheme 2 encapsulates the results required by the relative retention–absolute inversion substitution mechanisms. They are exactly as found in all cases.

Axial hydroxy-groups in saturated analogues of (1b) and (2b), *e.g.* (3), give tosylates by the normal Tipson procedure.[16,19] But the allylic tosylate products from (1b) and (2b) are evidently very susceptible to attack by the powerfully nucleophilic, virtually unsolvated chloride anion which is concomitantly generated from tosyl chloride in pyridine (a very poor solvating medium for anions). Consequently (1c) and (2c) are not isolable but react immediately as shown in Scheme 2 to give (1d) and (2a), respectively.

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In the absence of experiments using either chiral or isotopically labelled substrates, the proposed reactions of (1a) with bromide and (1b) with chloride are (strictly) unproven. But there is no evidence of the formation of any stereoisomers and, in the light of our other results and the work of others,[20] there should be no insurmountable barrier to halide exchange with retention of relative and inversion of absolute configuration leading to a degenerate reaction of racemic starting materials.

EXPERIMENTAL

All g.l.c. was carried out using a Perkin-Elmer model F30 gas chromatograph using nitrogen as carrier gas. The n.m.r. spectra were recorded on Perkin-Elmer R24 (60 MHz) and R32 (90 MHz) instruments. M.p.s are uncorrected.

exo-3,4-*Dibromobicyclo*[3.2.1]*oct-2-ene* (1a).[8]—This compound was prepared by the Makosza [9,10] method in *ca.* 30% yield from norbornene, bromoform, aqueous sodium hydroxide, and a catalytic amount of benzyltriethylammonium chloride. A small sample was recrystallized at low temperature from light petroleum (b.p. 40—60 °C), m.p. −10 to −6 °C; a distilled sample had τ (CCl_4) 3.75 (1 H, d, J 7.1 ∓ 0.2 Hz), 5.57 (1 H, d, J 2.7 ∓ 0.2 Hz), and 7.0—8.8 (8 H, m).

exo-3-*Bromo*-4-*hydroxybicyclo*[3.2.1]*oct-2-ene* (1b).[4]—This compound was prepared (87%) from the dibromide (1a) by the method described below for the analogous chlorohydroxy-compound (2b); m.p. [from light petroleum (b.p. 60—80 °C)] 73—74 °C (lit.,[4] 76—77 °C); τ (CCl_4) 3.80 (1 H, d, J 7.1 ∓ 0.2 Hz), 6.31 (1 H, d, J 2.7 ∓ 0.2 Hz), 7.3—7.7 (2 H, m), 7.65 (1 H, s, OH), and 7.9—8.9 (6 H, m).

exo-3,4-*Dichlorobicyclo*[3.2.1]*oct-2-ene* (2a).[5]—This compound was also made by the Makosza [9,10] method in 75% yield; b.p. 40—45 °C at 0.2 mmHg; τ(CCl_4) 4.00 (1 H, d, J 7.0 ∓ 0.2 Hz), 5.93 (1 H, d, J 2.5 ∓ 0.2 Hz), 7.35 (2 H, m), and 7.7—9.0 (6 H, m).

exo-3-*Chloro*-4-*hydroxybicyclo*[3.2.1]*oct-2-ene* (2b).[5]—A mixture of *exo*-3,4-dichlorobicyclo[3.2.1]oct-2-ene (39 g, 0.22 mol), calcium carbonate (32 g, 0.32 mol), acetone (75 cm^3), and water (250 cm^3) was heated under reflux for 3 days. The cooled mixture was filtered and the acetone was distilled under reduced pressure. The residue was extracted three times with ether and the combined ether fraction was washed with dilute hydrochloric acid then with brine and dried (Na_2SO_4). Filtration followed by distillation of the solvent left a pale yellow oil which was distilled, b.p. 74—78 °C at 0.3 mmHg (27.9 g, 80%); τ ($CDCl_3$) 3.95 (1 H, d, J 7 Hz), 6.15 (1 H, s, OH), 6.35 (1 H, d, J 3 Hz), 7.3—7.7 (2 H, m), and 8.0—9.0 (6 H, m).

exo-*Bicyclo*[3.2.1]*octan-2-ol* (3).[11]—(1) From *exo*-3-bromo-4-hydroxybicyclo[3.2.1]oct-2-ene (1b).[4] Compound (1b) (1.71 g, 8.42 mmol) in tetrahydrofuran (50 cm^3) and 1M aqueous sodium hydroxide solution (10 cm^3) was hydrogenated at room temperature under hydrogen at 3 atm pressure in the presence of 10% Pd on charcoal (200 mg) for *ca.* 15 h. The crude mixture was steam-distilled and the distillate was saturated with sodium chloride, then extracted three times with ether. The combined ether phase was dried (Na_2SO_4), filtered, and evaporated to leave the crude crystalline product (0.86 g, 6.81 mmol, 81%). When repeated on a larger scale using unpurified hydroxybromide the apparent yield was 74%. G.l.c. analysis of the crude reaction product, using authentic samples of *exo*- and *endo*-bicyclo[3.2.1]octan-2-ols for comparison, showed no trace of the *endo*-compound (⩽2%) in the alcoholic product (retention times *exo* and *endo*, 10.5, and 11.3 min, respectively, on 2 m 10% FFAP at 150 °C).

(2) From *exo*-3-chloro-4-hydroxybicyclo[3.2.1]oct-2-ene (2b).[5] A redistilled sample of (2b) (1.50 g, 9.46 mmol) in tetrahydrofuran (150 cm^3) and 1M aqueous sodium hydroxide (20 cm^3) was hydrogenated over 10% Pd on charcoal (0.3 g) under hydrogen at 4 atm for 3 days. The crude mixture was steam-distilled and the distillate was extracted three times with ether. The combined ether phase was dried (Na_2SO_4), filtered, and evaporated down to give waxy crystals (0.95 g, 7.53 mmol, 80%). G.l.c. analysis (SCOTDEGS; 110 °C) of the crude product showed the *exo*-alcohol (3) to be essentially pure [contaminated with ⩽0.4% (4) (retention times *exo* and *endo*, 15.0 and 16.6 min, respectively)].

Attempted Tosylation of exo-3-*Chloro*-4-*hydroxybicyclo*[3.2.1]*oct-2-ene*.—A solution of tosyl chloride (2.10 g, 11.0 mmol) in pyridine (4 cm^3) was added dropwise to a solution of (2b) (0.866 g, 5.46 mmol) in pyridine (1 cm^3). The solution was kept at 0 °C for 4 days. The mixture was then diluted with water and extracted three times with ether. The combined ether phase was washed with aqueous copper(II) sulphate, water, then dried (Na_2SO_4), filtered, and evaporated. It was not possible to crystallize the resultant oil. G.l.c. analysis of the crude product (SCOTDEGS; 170 °C) showed a single peak at the same retention time as authentic *exo*-3,4-dichlorobicyclo[3.2.1]oct-2-ene (4.0 min). The n.m.r. spectrum of the distilled product was identical with that of the authentic dichloride (2a). In a repeat of this experiment, the yield of the reaction was 47%.

Preparation of exo-3-*Bromo*-4-*chlorobicyclo*[3.2.1]*oct-2-ene* (1d).—(1) By attempted tosylation of *exo*-3-bromo-4-hydroxybicyclo[3.2.1]oct-2-ene. Crude dry compound (2b) (0.67 g, 3.30 mmol) was treated with tosyl chloride (1.26 g, 6.61 mmol) in pyridine (3 cm^3) at 0 °C for 4 days. An oil was obtained after the usual work-up (0.22 g, 0.99 mmol, 30%). The n.m.r. spectrum of the crude product showed no signals due to the *p*-tolyl group and the i.r. spectrum confirmed the absence of starting material. The quality of the n.m.r. spectrum was improved but not otherwise changed by distillation of the product, τ (CCl_4) 3.75 (1 H, d, J *ca.* 7 Hz), 5.88 (1 H, d, J *ca.* 3 Hz), and 7.2—8.9 (8 H, m).

(2) From *exo*-3,4-dibromobicyclo[3.2.1]oct-2-ene. Compound (1a) (0.339 g, 1.27 mmol) and sodium chloride (0.678 g, 11.6 mmol) in DMSO were heated to 50—55 °C under argon for 24 h. G.l.c. analysis showed the formation of two compounds. The retention time of the lesser one corresponded exactly with that of compound (1b) which is the expected product from reaction of (1a) with adventitious water. The major product (1d), an oil (0.205 g, 0.93 mmol 73%), was isolated by dilution of the mixture with water, ether extraction, evaporation of solvent, and chromatography on alumina (5% deactivated, elution with light petroleum, automatic collection of fractions monitored by g.l.c.). The n.m.r. spectrum was the same as that of the sample prepared by attempted tosylation of (1b) (coupling constant for the C-2 vinylic hydrogen, J 7.1 ∓ 0.2 Hz and for the C-4 allylic hydrogen, 2.7 ∓ 0.2 Hz).

Attempted Isomerization of exo-3,4-*Dichlorobicyclo*[3.2.1]*oct-2-ene*.—(1) A solution of (2a) (redistilled, 2.0 g, 11.3 mmol) and sodium chloride (0.825 g, 14.1 mmol) in freshly distilled DMSO (*ca.* 15 cm^3) was stirred at room temperature for 4 days. Analysis of a portion showed only a single peak

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with the same retention time as starting material. Work-up in the usual way gave an oil (2.0 g, 100%) whose n.m.r. spectrum was identical with that of the starting material.

(2) In an analogous reaction using dimethylformamide as solvent and a reaction time of 7 days at room temperature, starting material was the only compound detected by g.l.c.

Attempted Isomerization of exo-3,4-*Dibromobicyclo*[3.2.1]-*oct*-2-*ene*.—A solution of (1a) (0.50 g, 1.88 mmol) and sodium bromide (0.24 g, 2.33 mmol) in DMSO (5 cm^3) was stirred at 60 °C for 15 h. Analysis by g.l.c. showed only a very slow reaction to give a new peak which was identical in retention time with that of *exo*-3-bromo-4-hydroxybicyclo[3.2.1]oct-2-ene. After an extended reaction time, this product was isolated and shown by n.m.r., i.r., and m.p. to be (1b), formed by reaction of (1a) with adventitious water.

Attempted Preparation of 3-*Chloro*-4-*bromobicyclo*[3.2.1]-*oct*-2-*ene*.—A solution of (2a) (2.0 g, 11.3 mmol) and sodium bromide (1.45 g, 14.1 mmol) in DMSO (20 cm^3) was stirred at room temperature and monitored by g.l.c. (SCOTDEGS; 170 °C). There was no sign of any reaction at all after 3 h.

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