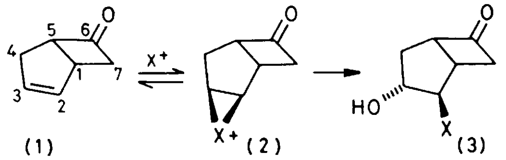
X-Ray Crystallographic Determination of the Conformation of Bicyclo[3.3.0]-octane and Bicyclo[3.2.0]heptane Derivatives and Evidence for an O···C=O Interaction

By ALISTAIR BROWN, ROBERT GLEN, PETER MURRAY-RUST,* and JUDITH MURRAY-RUST
(*Chemistry Department, University of Stirling, Stirling* FK9 4LA, *Scotland*)
and ROGER F. NEWTON
(*Chemical Research Dept., Glaxo Group Research, Ware, Herts.* SG12 0DJ)

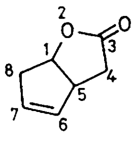
Summary The crystal structures of (**3a**), (**3b**), and (**6**) have been determined and show that in both ring systems the cyclopentane ring takes up an *endo* conformation with the substituents pseudo-axial; this gives rise to trans-annular O··· C=O interactions, which are also seen in related epoxides.

IN two recently reported total syntheses of prostaglandins[1,2] a key step involves the addition of the elements of HOX (X = Cl, Br, I) to bicyclo[3.2.0]hept-2-en-6-one (**1**). The corresponding halohydrin (**3**) is obtained with high regio- and stereo-selectivity, presumably *via* the appropriate *exo* halonium ion (**2**).

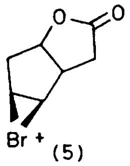


(1) (2) (3)

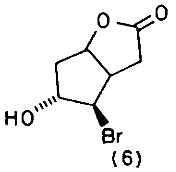
a ; X = Cl
b ; X = Br
c , X = I



(4)



(5)



(6)

In contrast, the oxabicyclo[3.3.0]octenone (**4**) reacts with HOBr *via* the initial formation of both *exo* and *endo* bromonium ions; however the *exo* bromonium ion (**5**) is again attacked regioselectively by the nucleophile to yield only the bromohydrin (**6**).[3] Nucleophilic attack on the bromonium ions (**2**) (at 3α) and (**5**) (at 7α) presumably proceeds through a transition state in which the carbocyclic five-membered ring adopts an *endo* envelope conformation (**7**) with the halogen and hydroxy functions *trans* diaxial.[3] Attack at the alternative site (2α in [3.2.0], 6α in [3.3.0]) would give rise to a transition state with an *exo* conformation for the carbocyclic ring. N.m.r. evidence suggests that in solution the halohydrin (**3b**) exists in a conformation similar to (**7**) with the halogen and hydroxy groups pseudo-axial.[4] We wished to determine whether this tendency of the five-membered ring to adopt an *endo* envelope was due primarily to the conformational preferences of the basic bicyclo[3.2.0]heptane and oxabicyclo[3.3.0]octane ring systems or whether other factors were operating which were peculiar to this substitution pattern. Accordingly we have determined the crystal structures of the halohydrins (**3a**), (**3b**), and (**6**).

Crystal data: reflection data for all three compounds were collected on a 2-circle diffractometer with Mo-K_α radiation. (**3a**). $C_7H_9ClO_2$, M_r = 106·5, monoclinic, space group $P2_1$, Z = 2, a = 9·14(2), b = 6·44(1), c = 6·44(1) Å, β = 104·03(3)°, $F(000)$ = 168, μ(Mo-K_α) = 3·9 cm^{-1}. Crystal size *ca.* 0·3 × 0·2 × 0·2 mm. 551 reflections with $I > 3\sigma(I)$ for $h0$—$6l$ up to 2θ = 55°. The structure failed to refine well because of severe pseudo-symmetry. Bond lengths were constrained and refinement converged at R = 0·11 with hydrogen atoms in calculated positions.† (**3b**)‡ $C_7H_9BrO_2$, M_r = 204·9, trigonal, space group $P3_1$ (from structure determination), Z = 3, a = 10·13(2), c = 6·66(1) Å, $F(000)$ = 306, μ(Mo-K_α) = 50·2 cm^{-1}, $[\alpha]_D^{20.0}$ = −60°.‡ Crystal size *ca.* 0·3 × 0·3 × 0·5 mm. 563 reflections, including 52 Friedel pairs, with $I > 3\sigma(I)$ for $hk0$–6 up to 2θ = 50°. Refinement converged† at R = 0·042 with hydrogen atoms in calculated positions (R for enantiomeric structure 0·054). (**6**) $C_7H_9BrO_3$, M_r = 220·9, triclinic, space group $P1$, Z = 3, D_m = 1·86, D_c = 1·84 g cm^{-3},

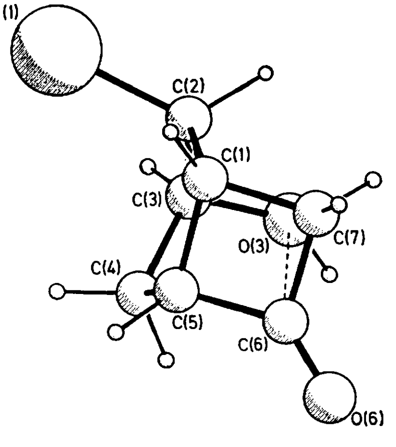


FIGURE 1. The structure of the enantiomer of (**3b**) showing the favourable approach of O(3) to C(6) (short dotted line). The O··· C distance is 3·02(2) Å and the angle O(3)··· C(6)–O(6) is 108°.

---

† 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.

‡ The material used for structure solution was resolved and proved to have the *opposite configuration* to (**3b**) as written.

$a = 6{\cdot}69(2)$, $b = 10{\cdot}60(3)$, $c = 10{\cdot}10(3)$ Å, $\alpha = 61{\cdot}35(3)$, $\beta = 101{\cdot}10(3)$, $\gamma = 107{\cdot}80(3)°$, $U = 597$ Å^3, $F(000) = 330$, $\mu(\text{Mo-}K_\alpha) = 33{\cdot}3$ cm^{-1}. Crystal size *ca.* $0{\cdot}4 \times 0{\cdot}3 \times 0{\cdot}3$ mm. 920 reflections with $I > 3\sigma(I)$ for 0—6*kl* up to $2\theta = 50°$. There are two independent molecules related by a centre of pseudo-symmetry and a third disordered molecule for which only Br was located. Refinement had to be carried out using constrained bond lengths, and converged with $R = 0{\cdot}12$† (with no contribution from the disordered molecule other than Br, and no hydrogen atoms included).

The conformation of all three molecules are very similar and are shown in Figures 1 and 2 [for (**3b**) and (**6**)]. The most striking feature is that the cyclopentane ring has an approximate *endo* conformation so that the halogen and hydroxy groups form pseudo-axial ligands on the cyclopentane ring. The geometries of (**3**) and (**6**) are thus very similar to the proposed transition state (**7**), and the *endo*-conformation of the five membered ring may be partly responsible for the regioselective halohydrin formation.

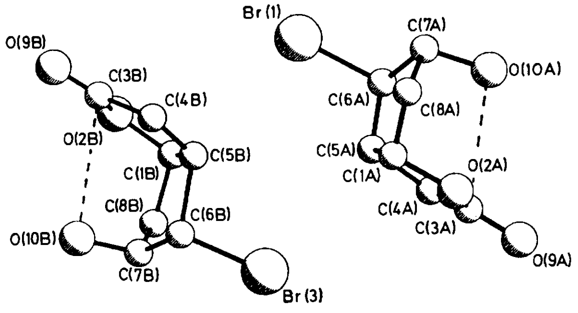
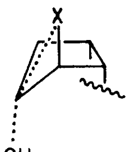
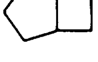


FIGURE 2. The two ordered molecules in the structure of crystals of (**6**), related by a pseudo-centre of symmetry. The O · · · C interaction (av. 3·05(5) Å) is shown by the dotted line and the average O · · · C=O angle is 113°.

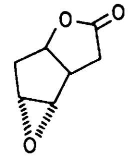
We have confirmed the inherent stability of the *endo* conformation of the bicyclo[3.2.0]heptane system (**8**) by force field calculations; the *exo* conformer appears to be less stable than the *endo* by about 6—10 kJ mol^{-1} (depending on the force field used).



(7)

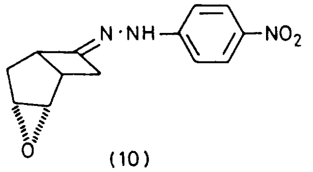


(8)

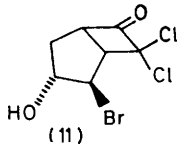


(9)

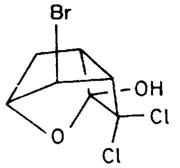
In all three molecules the pseudo-axial OH substituent is forced by the ring conformation towards the carbonyl group and makes O · · · C=O contacts of 3·02(2) Å in (**3b**) and 3·05(2) Å in (**6**).§ The angle between the hydroxylic oxygen atom and the carbonyl group is about 108° in the ketone (**3b**) and 113° in the lactone (**6**).



(10)



(11)



(12)

Dunitz *et al.*[5] have shown that the incipient nucleophilic attack of an oxygen atom on a carbonyl group involves O · · · C=O distances of 2·7 Å (strong) to 3·1 Å (negligible) and that the optimum O · · · C=O angle of attack is about 105°. It seems likely that this effect is present in all three molecules. This interaction should produce small out-of-plane deformations of the carbonyl groups[5] and whilst errors obscure this in (**3a**), (**3b**), and (**6**) we have observed it in the structures of two other related molecules which also show transannular interactions. Structure (**9**) has an O (epoxide) · · · C=O distance[6] of 2·998(2) Å and an out-of-plane carbonyl distortion of 0·010(2) Å, and (**10**) has O · · · C=N = 2·990(3) Å and the out-of-plane distortion is 0·010(3) Å.

It seems certain that this transannular interaction is important in the ground state of several bicyclic ketones and lactones. A striking example is given by (**11**) which can exist largely in the hemiacetal form (**12**).[4] The geometrical requirements for this interaction are fairly stringent[5] and models suggest that the molecules in the present series can only show it if they have a 3α nucleophilic substituent in the bicycloheptane system or a 7α nucelophilic substituent in the bicyclo-octane system. Whether this transannular effect contributes to the regioselectivity of reaction (**2**)→(**3**) is not clear at this stage, but even a weak interaction may be important in stabilising the *trans*-diaxial conformation.

Two of us (A. B. and J. M.-R.) thank Glaxo Group Research (Ware) Ltd. for financial support; R. G. thanks the S.R.C. for a CASE studentship with Glaxo Group Research; and our thanks are due to Dr. S. M. Roberts for helpful discussions.

(*Received*, 20*th July* 1979; *Com.* 784.)

---

§ The constrained refinement in (**3a**) leads to a much closer contact of 2·75 Å, with O . . . C=O = 101° but there could be considerable errors in these values.

[1] M. J. Dimsdale, R. F. Newton, D. K. Rainey, C. F. Webb, T. V. Lee, and S. M. Roberts, *J.C.S. Chem. Comm.*, 1977, 716.
[2] R. F. Newton, C. C. Howard, D. P. Reynolds, A. H. Wadsworth, N. M. Crossland, and S. M. Roberts, *J.C.S. Chem. Comm.*, 1978, 662.
[3] S. M. Ali, N. M. Crossland, T. V. Lee, and S. M. Roberts, *J.C.S. Perkin I*, 1979, 122.
[4] Z. Grudzinski and S. M. Roberts, *J.C.S. Perkin I*, 1975, 1767.
[5] H-B. Bürgi, J. D. Dunitz, and E. Shefter, *Acta Cryst.*, 1974, **B30**, 1517.
[6] P. Murray-Rust, J. Murray-Rust, and R. F. Newton, *Acta Cryst.*, 1979, **B35**, in the press.