Crystal and Molecular Structure of 2-(4-Bromophenyl)-*r*-2,4,4,*c*-6-tetramethyl-1,3-dioxan

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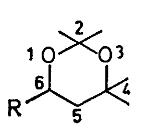
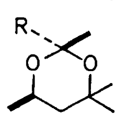
The crystal structure of the title compound (II) has been determined from diffractometer data by the heavy-atom method and refined by full-matrix least-squares techniques to R 0·12 for 635 reflections. The crystals are orthorhombic, space group *Pbca* with $Z = 8$ in a unit cell of dimensions $a = 2765(3)$, $b = 795(1)$, $c = 1316(1)$ pm. The conformation of the 1,3-dioxan ring is a deformed chair with the phenyl substituent axial. This phenyl group has a short non-bonded distance of *ca.* 320 pm with the axial methyl group on C(4) and there is evidence of strain in the 1,3-dioxan ring. The structure is correlated with ^{1}H n.m.r. data for some model 1,3-dioxans.

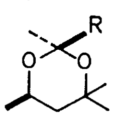
THE stereochemistry of the 1,3-dioxan ring system has been a source of much experimental activity in recent years.[1] One aspect of particular interest to us has been the structures of compounds believed to exist in non-chair or distorted chair forms. On the basis of ^{1}H and ^{13}C n.m.r.[2,3] studies we have concluded that molecules which would possess two methyl groups in *syn*-diaxial positions in chair conformations prefer to exist in certain twist conformations. Although the structure of the chair form of 1,3-dioxan had been established by an *X*-ray diffraction study of 2-(4-chlorophenyl)-1,3-dioxan,[4] no non-chair conformation has been examined by this technique. In view of this situation it seemed appropriate to synthesise model 1,3-dioxans, which might exist in non-chair forms, for study by *X*-ray diffraction.



(I)



(II)



(III)

R = 4-bromophenyl

The first such compound considered was 6-(4-bromophenyl)-2,2,4,4-tetramethyl-1,3-dioxan (I), which would have a severe 2,4-diaxial dimethyl interaction in the chair conformation. However it proved to be extremely labile, decomposing readily in the presence of traces of water or acids; moreover great difficulty was encountered in obtaining crystals suitable for an *X*-ray analysis. Alternative molecules which appeared to merit consideration were the diastereoisomeric 2-(4-bromophenyl)-2,4,4,6-tetramethyl-1,3-dioxans, (II) and (III). For both compounds strong repulsions, either between an axial methyl and an axial phenyl group (II), or two axial methyls (III), occur in chair conformations. An examination of such compounds was also of interest as relatively few studies of the conformational preferences of 2-methyl-2-phenyl-1,3-dioxans had been carried out.[5,6]

Reaction of 2-methylpentane-2,4-diol with the diethyl acetal of 4-bromoacetophenone yielded a crystalline product which g.l.c., ^{1}H, and ^{13}C n.m.r. indicated to be a single isomer. The method of preparation was such as to suggest that it should be the thermodynamically more stable isomer. However the n.m.r. parameters did not allow us to decide unequivocally which diastereoisomer had been formed. We therefore undertook an

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[1] See *e.g.*, E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1.

[2] K. Pihlaja, G. M. Kellie, and F. G. Riddell, *J.C.S. Perkin II*, 1972, 252.

[3] G. M. Kellie and F. G. Riddell, *J. Chem. Soc.* (*B*), 1971, 1030.

[4] A. J. de Kok and C. Romers, *Rec. Trav. chim.*, 1970, **89**, 313.

[5] H. T. Kalff and E. Havinga, *Rec. Trav. chim.*, 1966, **85**, 467.

[6] E. L. Eliel, XXIII Congress Pure Appl. Chem., Butterworths, London, vol. 7, p. 219.

X-ray diffraction study of this compound with the objectives of assigning first, its stereochemistry, and secondly, its conformation.

EXPERIMENTAL

6-(4-*Bromophenyl*)-2,2,4,4-*tetramethyl*-1,3-*dioxan* (I).—This compound was prepared by a method similar to that previously described,[3] using 1-(4-bromophenyl)-3-methylbutane-1,3-diol and 2,2-dimethoxypropane (Found: C, 56·25; H, 6·5; Br, 26·4. Calc. for $C_{14}H_{19}BrO_2$: C, 56·2; H, 6·35; Br, 26·8%), m.p. 68—69 °C.

2-(4-*Bromophenyl*)-r-2-4,4-c-6-*tetramethyl*-1,3-*dioxan*.—The diethyl acetal of 4-bromoacetophenone and freshly distilled 2-methylpentane-2,4-diol (1 : 1) were mixed and warmed for 1 min. A crystal of toluene-*p*-sulphonic acid was added and the mixture left in a sealed flask at room temperature for 3 days. The precipitate was dissolved in dry ether and shaken with a small quantity of anhydrous sodium carbonate. After filtration and removal of the solvent the *product* was recrystallised five times from methanol (Found: C, 56·35; H, 6·45. $C_{14}H_{19}BrO_2$ requires C, 56·2; H, 6·35%), m.p. 80 °C.

Crystal Data.—$C_{14}H_{19}BrO_2$, $M = 299$. Orthorhombic, $a = 2765(3)$, $b = 795(1)$, $c = 1316(1)$ pm, $U = 2\cdot893 \times 10^9$ pm^3, $D_m = 1\cdot385$ g cm^{-3} (by flotation in aqueous potassium carbonate), $Z = 8$, $D_c = 1\cdot373$ g cm^{-3}, $F(000)$ 1232. Space group *Pbca* (D_{2h}^{15} No. 61). Mo-K_α radiation, $\lambda = 71\cdot07$ pm; μ(Mo-K_α) = 41·2 cm^{-1}.

Crystallographic Measurements.—Unit cell dimensions and space group were determined from oscillation and Weissenberg photographs taken with Cu-K_α ($\lambda = 154\cdot18$ pm) radiation. Although the crystals were apparently satisfactory when examined optically, they gave extremely poor reflections corresponding to several crystallites with a mosaic spread of *ca.* 2°. Several recrystallisations from methanol were performed in an attempt to remove this defect, but no improvement was obtained. This phenomenon has been observed for other 1,3-dioxans.[7]

In a preliminary examination 11 crystals were photographed and the least unsatisfactory was used for data collection. This crystal (0·3 × 0·3 × 0·4 mm) was exposed to Mo-K_α radiation on a Hilger and Watts linear diffractometer. Levels $hk0$—6 and $h0$—$4l$ were collected with a large ω scan (up to 5°) to overcome the poor crystallinity. Intensities were corrected for the appropriate Lorentz and polarisation factors, but no absorption corrections were applied and reflections with an intensity $< 2\cdot5\sigma(I)$ were rejected. 635 Reflections were obtained.

Structure Determination.—The position of the bromine atom was deduced by inspection of the three-dimensional Patterson function, and the analysis thereafter proceeded directly on the basis of the phase-determining heavy-atom method.[8] The complete structure was revealed after 3 cycles of structure-factor and electron-density calculations.

Structure Refinement.—The structure was refined by a full-matrix least-squares method. Unit weights were employed for all reflections, as no other weighting scheme gave a significant improvement. Introduction of anisotropic temperature factors after cycle 5 (R 0·16) reduced R to 0·12, although it is unlikely that these have much physical significance in view of the poor quality of the intensity measurements. As a result, the σ values of the light atoms were fairly high, owing to the lack of data and its poor quality. Hydrogen atoms were not included at any stage of the analysis.*

All computations were performed on the Stirling University Elliott 4130 computer with programmes described in ref. 9.

DISCUSSION

The final atomic co-ordinates, isotropic temperature factors, bond lengths and angles, and torsion angles are presented in Tables 1—4. In spite of the poor quality of the data, which introduces large errors into the calculated parameters, the structure of the compound can be clearly seen. The 1,3-dioxan ring exists in a deformed chair conformation with the 2- and 6-methyl groups in *cis*-equatorial positions, and the phenyl group in an axial orientation (Figure 1), *i.e.* the isomer formed is (II). The severity of the 1,3-diaxial repulsion between the phenyl group and the axial 4-methyl group, C(42) (contact distance 320 pm) is not of sufficient magnitude to force the ring into a twist conformation, but it does severely distort the chair. Both the phenyl ring and the axial 4-methyl group are displaced outwards so

TABLE 1

Fractional co-ordinates with estimated standard deviations in parentheses

	x/a	y/b	z/c
Br	0·0020(2)	0·5392(5)	0·2679(3)
C(11)	0·1160(12)	0·2187(36)	0·4482(25)
C(12)	0·1304(9)	0·2891(30)	0·3486(22)
C(13)	0·0943(11)	0·3888(40)	0·2937(24)
C(14)	0·0490(11)	0·4137(37)	0·3425(33)
C(15)	0·0379(10)	0·3387(28)	0·4297(30)
C(16)	0·0713(10)	0·2650(28)	0·4944(25)
C(21)	0·1806(15)	0·2445(66)	0·5838(36)
C(41)	0·1224(12)	−0·2844(48)	0·5915(29)
C(42)	0·0803(13)	−0·1564(40)	0·4570(26)
C(61)	0·2307(11)	−0·1006(48)	0·3014(29)
C(2)	0·1595(15)	0·1288(56)	0·5020(34)
C(4)	0·1287(12)	−0·1600(40)	0·5044(29)
C(5)	0·1704(11)	−0·2117(37)	0·4451(25)
C(6)	0·1832(10)	−0·0726(37)	0·3674(26)
O(1)	0·1953(7)	0·0774(25)	0·4315(18)
O(3)	0·1393(7)	−0·0047(25)	0·5572(17)

TABLE 2

Isotropic temperature factors × 10^{-4} (pm^2), with estimated standard deviations in parentheses

Br	6·0(2)	C(42)	4·0(11)
C(11)	3·7(10)	C(61)	5·0(12)
C(12)	2·3(8)	C(2)	2·9(9)
C(13)	3·6(10)	C(4)	3·3(10)
C(14)	3·8(10)	C(5)	4·2(11)
C(15)	2·8(9)	C(6)	3·2(9)
C(16)	3·1(9)	O(1)	4·0(6)
C(21)	4·6(12)	O(3)	4·5(7)
C(41)	4·6(11)		

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* Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20531 (9 pp.). For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (items less than 10 pp. are sent as full size copies).

[7] G. M. Kellie, J. Murray-Rust, P. Murray-Rust, and F. G. Riddell, unpublished observations.

[8] J. M. Robertson and I. Woodward, *J. Chem. Soc.*, 1937, 219; 1940, 36.

[9] A. Griffiths and M. T. G. Powell, 'Crystal '69,' computer program for the Elliott 4130.

TABLE 3

Interatomic distances and angles *

(*a*) Bonded distances (pm) with estimated standard deviations in parentheses

Br–C(14)	194(3)	C(2)–O(1)	145(4)
C(13)–C(14)	136(5)	C(2)–O(3)	139(4)
C(13)–C(12)	152(5)	C(61)–C(6)	159(5)
C(14)–C(15)	133(5)	C(6)–C(5)	157(5)
C(12)–C(11)	146(5)	C(6)–O(1)	147(4)
C(11)–C(16)	137(5)	C(5)–C(4)	145(5)
C(11)–C(2)	162(5)	C(42)–C(4)	144(5)
C(16)–C(15)	134(5)	C(4)–C(41)	154(5)
C(2)–C(21)	153(5)	C(4)–O(3)	146(4)

(*b*) Interbond angles (°)

Br–C(14)–C(13)	115	C(2)–O(3)–C(4)	115
Br–C(14)–C(15)	119	C(21)–C(2)–O(3)	105
C(13)–C(12)–C(11)	115	C(21)–C(2)–O(1)	112
C(13)–C(14)–C(15)	126	C(61)–C(6)–O(1)	103
C(14)–C(15)–C(16)	122	C(61)–C(6)–C(5)	116
C(14)–C(13)–C(12)	114	C(6)–C(5)–C(4)	104
C(12)–C(11)–C(16)	122	C(5)–C(6)–O(1)	108
C(12)–C(11)–C(2)	109	C(5)–C(4)–C(42)	121
C(11)–C(16)–C(15)	118	C(5)–C(4)–C(41)	108
C(11)–C(2)–C(21)	108	C(5)–C(4)–O(3)	112
C(11)–C(2)–O(1)	110	C(42)–C(4)–C(41)	99
C(11)–C(2)–O(3)	107	C(42)–C(4)–O(3)	115
C(16)–C(11)–C(2)	127	C(41)–C(4)–O(3)	98
C(2)–O(1)–C(6)	114	O(1)–C(2)–O(3)	115

(*c*) Intermolecular distances (pm)

C(13) · · · O(3^{I})	344(10)

O(3^{I}) is at $-1 + x, \frac{1}{2} - y, -\frac{1}{2} + z$.

* Estimated standard deviations of all angles 2°.

TABLE 4

Torsion angles (°).* A torsion angle A–B–C–D is positive if, when viewed in projection along bond B→C, the sense of rotation from BA to CD is clockwise

C(6)–O(1)–C(2)–O(3)	+45
C(1)–C(2)–O(3)–C(4)	−41
C(2)–O(3)–C(4)–C(5)	+49
O(3)–C(4)–C(5)–C(6)	−56
C(4)–C(5)–C(6)–O(1)	+58
C(5)–C(6)–O(1)–C(2)	−57

* Estimated standard deviations are 2°.

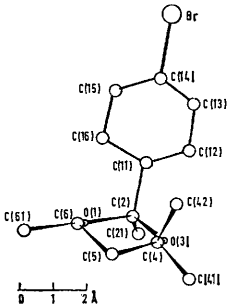


FIGURE 1 A view of the molecule, projected on the benzene ring, showing the atomic numbering scheme

that the axial bonds (parallel in a perfect chair) intersect at an angle of 30°. In addition the C(2) end of the molecule is considerably flattened compared with the undistorted chair form of 2-(4-chlorophenyl)-1,3-dioxan.[4] The C(2)–O(3)–C(4)–C(5) side of the ring, along which the principal non-bonded interactions take place, is flatter than the C(2)–O(1)–C(6)–C(5) side.

As a result of a study of some 1,3-dioxans with axial 2-aryl substituents, Eliel suggested that these axial groups might be able to bend outward from the ring,[10] and hence reduce their non-bonded interactions with the *syn*-axial protons at C(4) and C(6). For axial alkyl groups he considered that such deformations would be less likely. Eliel's conclusions appear to be partially supported by the structure of (II), in which much of the non-bonded strain in the molecule is relieved by the phenyl group leaning out from the ring. In contrast 2,2,4,4,6-pentamethyl-1,3-dioxan appears to favour a twist conformation.[2,3]

As a further means of relieving the 1,3-diaxial strain, the phenyl group in (II) rotates slightly so that it presents a broadside appearance to the axial methyl group (Figure 2). Although this involves an increase in the repulsions between the *ortho*- and 6-axial protons, these considerations are outweighed by the consequent reduction in the repulsions between the phenyl group and the axial methyl group. Such rotamers are often adopted by phenyl groups in the solid state,[11] and have been considered[12] to be due to packing forces in the crystal. However, for this molecule it is more likely that the preferred orientation of the phenyl ring is controlled by intramolecular forces.

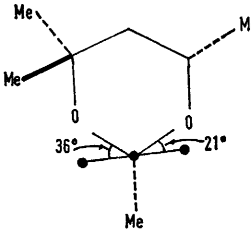
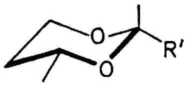
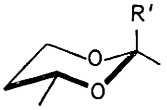


FIGURE 2 The conformation of the phenyl ring

The formation of only one isomer in the reaction warrants some discussion. It would be expected that the synthetic method employed would yield the thermodyamically more stable product. That the compound obtained was indeed the more stable isomer was confirmed by treatment of (II) with acid under conditions known to epimerise 1,3-dioxans. No peaks were observed in the g.l.c. or the n.m.r. spectra which could be assigned to the other stereoisomer. Eliel[6] has shown that for the diastereoisomeric 2,4-dimethyl-2-phenyl-1,3-dioxans (IV) and (V) the isomer (V), which has an



(IV)



(V)

R′ = phenyl

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[10] E. L. Eliel and F. W. Nader, *J. Amer. Chem. Soc.*, 1970, **92**, 3050.

[11] For examples see ref. 4, and H. T. Kalff and C. Romers, *Acta Cryst.*, 1966, **20**, 490.

[12] O. Ermer and J. D. Dunitz, *Helv. Chim. Acta*, 1969, **52**, 1861.

axial phenyl group, is more stable than (IV) by 10 kJ mol^{-1}. The g.l.c. analysis of our equilibration appears to suggest that isomer (II) is at least 13 kJ mol^{-1} more stable than (III). These values are supported by some semiempirical calculations [13] of the energies of similarly substituted cyclohexanes, which indicate that the more stable conformation of 1-methyl-1-phenylcyclohexane is that with an axial phenyl group (ΔG 3·8 kJ mol^{-1}). Further, for 1,1,3-trimethyl-3-phenylcyclohexane, which is analogous to (II), a larger energy difference favouring the axial phenyl is found (ΔG 15·3 kJ mol^{-1}).

The strain which is evident in the structure of (II) and the large energy difference between (II) and (III) is another indication of the extremely high strain involved in a 2,4-diaxial interaction between two methyl groups in a 1,3-dioxan ring.[3]

A detailed analysis of the ^{1}H n.m.r. data for (II) and some model compounds (Table 5) suggests that the distorted chair is the preferred conformation in solution as well as in the solid state. The 4-axial methyl group absorbs *ca.* 0·4 p.p.m. to higher field of similar groups in 2,2,4,4,6-pentamethyl-1,3-dioxan (twist model) and *cis*-2,4,4,6-tetramethyl-1,3-dioxan (chair model). An estimation of the shielding which would result from the deformed chair conformation can be made by determining the methyl proton–phenyl ring distance from the crystal structure. By use of Bovey's tables [14] a shielding of *ca.* 0·5 p.p.m., in good agreement with the observed value, can be calculated for this intramolecular distance.

TABLE 5

^{1}H N.m.r. parameters for some 1,3-dioxans

(*a*) Chemical shifts (τ) [a]

Compound	2-Me	4-Me	6-Me
cis-2,4,4,6-Me$_4$	8·72	8·83 8·85	8·88
2,2,4,4,6-Me$_5$	8·51 8·51	8·83 8·89	8·83
r-2,4,4,*c*-6-Me$_4$-2-(4-BrC$_6$H$_4$)	8·49	8·76 9·29	8·85

(*b*) Coupling constants (Hz)

Compound	$^3J_{5,6(1)}$	$^3J_{5,6(2)}$	$^2J_{5,5}$	$^3J_{6,\mathrm{Me}}$
cis-2,4 4,6-Me$_4$	11·0	2·5		6·2 [a,c]
2,2,4,4,6-Me$_5$	10·9	2·5	−12·9	6·0 [b,d]
r-2,4,4,*c*-6-Me$_4$-2-(4-BrC$_6$H$_4$)	11·6	2·2	−13·0	6·6 [a,d]

[a] In benzene soln. [b] In CCl$_4$ soln. [c] First-order splittings. (±0·3 Hz). [d] LAOCN3 calc. values (±0·2 Hz).

The coupling constants also tend to support the conclusion that the structure found in the crystal predominates in solution as well.

We thank the S.R.C. for a maintenance grant (G. M. K.).

[2/1355 *Received, 13th June*, 1972]

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[13] N. L. Allinger and M. T. Tribble, *Tetrahedron Letters*, 1971, 3259.

[14] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.