

454. *Aspects of Stereochemistry. Part VI.* Configuration of the 5-Hydroxy-2-p-nitrophenyl-1,3-dioxans and Further Observations on trans-5-Hydroxy-2-phenyl-1,3-dioxan.*

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trans-5-Hydroxy-2-phenyl-1,3-dioxan (*trans*-1,3-*O*-benzylideneglycerol) is obtained by reduction of 5-oxo-2-phenyl-1,3-dioxan or of its hydrate. The alcohol yields only derivatives of *trans*-configuration on esterification and etherification, and a previous report to the contrary is corrected. Configurations have been assigned to the 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxans (1,3-*O*-*p*-nitrobenzylideneglycerols) and their benzoates and methyl ethers. The alcohols were hitherto unknown.

THE 5-hydroxy-2-phenyl-1,3-dioxan of m. p. 63—64° was first described by Verkade and van Roon¹ and subsequently allocated the *trans*-configuration.² Mixtures of *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxan are easily obtained² by reaction of glycerol with benzaldehyde, and the pure *cis*-isomer is readily isolated by fractional crystallization. The *trans*-isomer cannot be isolated in this way, probably because of the tendency of the molecular complex of *cis*- and *trans*-isomers to crystallise. Melting points are singularly unreliable in assessing the purity of preparations of *trans*-5-hydroxy-2-phenyl-1,3-dioxan since those of the *trans*-isomer and the molecular complex are almost identical and little different from those of *cis*-*trans*-mixtures with 50% or less of *cis*-isomer. Chromatography of a mixture of *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxan on alumina² gave an apparent separation, but reinvestigation has shown that, whereas pure *cis*-isomer is eluted first, *cis*-*trans*-mixtures are subsequently released followed by a negligible amount of pure *trans*-isomer. The compound previously believed² to be *trans*-5-hydroxy-2-phenyl-1,3-dioxan has now been identified as a *cis*-*trans*-mixture. The extent of contamination of *trans*- by *cis*-isomer may be assessed conveniently by infrared spectroscopy on the basis of the strong absorptions at 808 and 832 cm.⁻¹ shown by *cis*- but not by *trans*-5-hydroxy-2-phenyl-1,3-dioxan.

trans-5-Hydroxy-2-phenyl-1,3-dioxan can also be obtained by reduction of 5-oxo-2-phenyl-1,3-dioxan³ with lithium aluminium hydride or of its hydrate³ with sodium borohydride; the *cis*-isomer apparently is not formed in these reactions. Reduction of related cyclohexanone derivatives⁴ yields predominantly, but not exclusively, *trans*-alcohols.

Intermolecular hydrogen bonding does not occur in solutions of the 2-hydroxy-5-phenyl-1,3-dioxans in carbon tetrachloride which are <0.005M, so that the extent of intramolecular hydrogen bonding may be assessed,^{5,6} approximately, from the extinction coefficients for free and bonded hydroxyl groups. *cis*-5-Hydroxy-2-phenyl-1,3-dioxan showed absorption for bonded hydroxyl groups only, at 3590 cm.⁻¹ (ϵ 95), indicating exclusive existence in conformation (I). The stereochemistry of this molecule and the nature of the hydrogen bond have been discussed elsewhere.² The marked tendency of 5-oxo-2-phenyl-1,3-dioxan to form a hydrate (II), which is not shown by 4-phenylcyclohexanone, may be due to stabilization by hydrogen bonding. The hydrate (II) is structurally closely related to *cis*-5-hydroxy-2-phenyl-1,3-dioxan (I) and one of its hydroxyl groups should be hydrogen-bonded. In dilute solution in carbon tetrachloride, 5,5-dihydroxy-2-phenyl-1,3-dioxan showed absorptions of similar intensity at 3540 and 3621 cm.⁻¹ for bonded and free hydroxyl groups respectively. The $\Delta\nu$ value^{5,6} of 81 is

* Part V, *J.*, 1960, 2582.

¹ Verkade and van Roon, *Rec. Trav. chim.*, 1942, **61**, 831.

² Baggett, Brimacombe, Foster, Stacey, and Whiffen, *J.*, 1960, 2574.

³ Marei and Raphael, *J.*, 1960, 886.

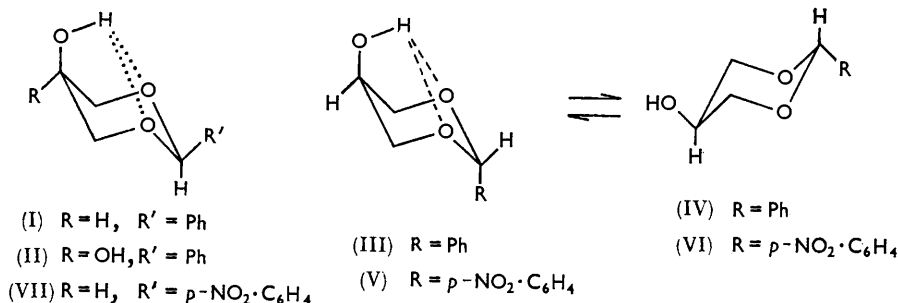
⁴ Eliel and Ro, *J. Amer. Chem. Soc.*, 1957, **79**, 5992.

⁵ Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323.

⁶ Cole and Jefferies, *J.*, 1956, 4391.

much higher than that (41) of, for example, 5-hydroxy-1,3-dioxan⁷ and is indicative⁵ of a strong hydrogen bond.

Pure *trans*-5-hydroxy-2-phenyl-1,3-dioxan showed absorptions at 3633 (ϵ 79) and 3601 cm^{-1} (ϵ 26) for free and bonded hydroxyl groups, indicating an equilibrium mixture of the conformations (III) and (IV) with only a minor proportion of the molecules in conformation (II). The conformation (III) contains a phenyl group in the sterically unfavourable⁸ axial position and the fact that a proportion of the molecules is in this



conformation reflects the strength of the intramolecular hydrogen bond. Comparable effects have been noted in related compounds.² Both *trans*-2- and *trans*-5-deutero-5-hydroxy-2-phenyl-1,3-dioxan show absorptions in the hydroxyl stretching region⁹ closely similar to those of the parent, undeuterated compound.

A comparison may be made between hydrogen-bonding effects in derivatives of cyclohexane-*trans*-1,2-diol and 5-hydroxy-1,3-dioxan. Intramolecular hydrogen bonding in these compounds involves the formation of five-membered rings, and, moreover, the similar $\Delta\nu$ values^{5,7} indicate bonds of similar strength. 1-Isopropylcyclohexane-*trans*-1,2-diol exists exclusively, in dilute carbon tetrachloride solution, in the chair conformation with the isopropyl group equatorial and the hydroxyl groups axial.⁶ The bulk of the isopropyl group is sufficient to anchor the molecule in one conformation and counteract any tendency of intramolecular hydrogen bonding to stabilise the alternative chair conformation with equatorial hydroxyl groups; the ethyl group is not so effective an anchor. The effective bulk of the phenyl group appears from models to be somewhat less than that of the isopropyl group and it is clear that it is not quite adequate to anchor *trans*-5-hydroxy-2-phenyl-1,3-dioxan in conformation (IV). The relative effect of the *t*-butyl group should be evident in *trans*-5-hydroxy-2-*t*-butyl-1,3-dioxan and the synthesis of this compound is being attempted.

Acetylation, benzylation, and *p*-phenylazobenzylation¹⁰ of *trans*-5-hydroxy-2-phenyl-1,3-dioxan yielded chromatographically homogeneous esters of which that from the last reaction was new. All the esters afforded homogeneous *trans*-5-hydroxy-2-phenyl-1,3-dioxan on saponification. The compound, previously used in esterification studies² and believed to be *trans*-5-hydroxy-2-phenyl-1,3-dioxan is now known to have been a *cis-trans*-mixture. On chromatography of a mixture of *cis*- and *trans*-2-phenyl-5-*p*-phenylazobenzyloxy-1,3-dioxan on alumina, the *trans*-ester was eluted first, paralleling the behaviour of the acetates and benzoates.²

Methylation of *trans*-5-hydroxy-2-phenyl-1,3-dioxan gave a homogeneous ether; this also has the *trans*-configuration as its affinity for alumina is less than that of the isomer obtained by methylation of the *cis*-alcohol. A parallel with the behaviour of the benzyl ethers² is provided and the configuration of all these ethers has been confirmed by nuclear magnetic resonance spectroscopy.¹¹

⁷ Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10.

⁸ Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

⁹ Dobinson and Foster, unpublished results.

¹⁰ Baggett, Foster, Haines, and Stacey, *J.*, 1960, 3528.

¹¹ Baggett, Dobinson, Foster, Homer, and Thomas, *Chem. and Ind.*, 1961, 106.

Hibbert and Sturrock¹² considered the cyclic acetal, m. p. 88° rising to 99° on storage, obtained from the reaction of glycerol and *p*-nitrobenzaldehyde to be *cis-trans*-5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan (*cis-trans*-1,3-*O-p*-nitrobenzylidenglycerol). The ring size was shown¹³ by the fact that the two methyl ethers obtained from the *cis-trans*-alcohol mixture could also be obtained by condensation of 2-*O*-methylglycerol with *p*-nitrobenzaldehyde.^{13,14} Although two benzoates were obtained¹³ from the *cis-trans*-alcohol mixture their saponification was not recorded. Repetition of this work gave *cis-trans*-5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan with m. p. 88° which rose rapidly to 95–98° on storage; it seems likely that these two modifications are dimorphs.¹⁵ Benzoylation of the *cis-trans*-alcohol mixture gave¹³ two esters, m. p. 159° and 206° to which the *cis*- and *trans*-configurations, respectively, have been allocated on the following evidence. On chromatography on alumina, the benzoate of m. p. 206° had the weaker affinity for the adsorbent and the *trans*-configuration may be allocated tentatively on analogy with the behaviour of the 5-benzoyloxy-2-phenyl-1,3-dioxans. Saponification of the benzoate (m. p. 206°) gave a 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan, m. p. 134–135°, which can be allocated the *trans*-configuration since, in 0.005M-carbon tetrachloride solution, it has ν_{\max} for free and bonded hydroxyl groups at 3632 (ϵ 110) and 3602 cm.⁻¹ (ϵ 30). This absorption pattern, which is closely similar to that noted above for *trans*-5-hydroxy-2-phenyl-1,3-dioxan, indicates the existence of an equilibrium mixture of the conformations (V) and (VI) in which the latter predominates. Saponification of the benzoate of m. p. 159° gave a 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan, m. p. 108–109°, which had ν_{\max} for bonded hydroxyl at 3593 cm.⁻¹ (ϵ 90) and a very weak absorption at 3633 cm.⁻¹ for free hydroxyl groups indicative of *cis*-configuration and predominant existence in conformation (V). This result closely parallels that noted above for *cis*-5-hydroxy-2-phenyl-1,3-dioxan. *cis-trans*-5-Hydroxy-2-*p*-nitrophenyl-1,3-dioxan had ν_{\max} for free and bonded hydroxyl groups at 3631 (ϵ 65) and 3594 cm.⁻¹ (ϵ 71), showing it to be an approximately equimolar mixture.

Attempts to resolve *cis-trans*-5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan completely by chromatography on alumina were unsuccessful. A small proportion of the *trans*-alcohol was eluted first followed by *cis-trans*-mixture; the *trans*-alcohol, surprisingly, has the weaker affinity for alumina. The chromatographic properties of the 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxans may be affected, if not dominated, by the nitro-group since a significantly more polar solvent mixture was required to elute the 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxans than the 5-hydroxy-2-phenyl-1,3-dioxans from alumina.

cis-trans-5-Hydroxy-2-*p*-nitrophenyl-1,3-dioxan was readily converted into a mixture of methyl ethers¹³ which could be separated by chromatography on alumina to yield pure isomers with m. p. 139° and 106°. By analogy with the behaviour of the benzyl and methyl ethers of 5-hydroxy-2-phenyl-1,3-dioxan the isomer of m. p. 139°, which had the greater affinity for alumina, may be tentatively assigned the *cis*-configuration. Equilibration of each of the methyl ethers at room temperature in benzene containing hydrogen chloride gave a mixture containing *ca.* 70% of the isomer, m. p. 106°, to which the *trans*-configuration may therefore be allocated on the basis of arguments detailed in a previous paper.² The assigned configurations have been confirmed by nuclear magnetic resonance spectroscopy.¹¹

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 60–80°.

trans-5-Hydroxy-2-phenyl-1,3-dioxan.—(a) A solution of 2-phenyl-1,3-dioxan-5-one³ (1 g.) in ether (*ca.* 20 ml.) was added to a slurry of lithium aluminium hydride (0.5 g.) in ether (50 ml.),

¹² Hibbert and Sturrock, *J. Amer. Chem. Soc.*, 1928, **50**, 3374.

¹³ Hibbert and Carter, *J. Amer. Chem. Soc.*, 1928, **50**, 3376.

¹⁴ Hibbert, Whelen, and Carter, *J. Amer. Chem. Soc.*, 1929, **51**, 302.

¹⁵ Dobinson, Foster, and Stacey, *Tetrahedron Letters*, 1959, No. 1, p. 1.

and the mixture was boiled under reflux for 2 hr. Excess of reducing agent in the cooled mixture was decomposed with ethyl acetate. After addition of water the mixture was filtered and the residue was washed with ether. Evaporation of the combined and dried (Na_2CO_3) ethereal solutions gave a solid residue which recrystallised from benzene-light petroleum, yielding *trans*-5-hydroxy-2-phenyl-1,3-dioxan (0.55 g., 54%), m. p. 63–64°.

(b) A solution of 5,5-dihydroxy-2-phenyl-1,3-dioxan³ (0.1 g.) and sodium borohydride (0.2 g.) in ethanol (30 ml.) was stored at room temperature for 1 day. The pH of the mixture was adjusted to 7 with acetic acid and the solution was then evaporated to dryness in the presence of sodium carbonate. The residue was extracted with benzene, the extract was concentrated, and the residue recrystallised from benzene-light petroleum to yield *trans*-5-hydroxy-2-phenyl-1,3-dioxan (35 mg., 38%), m. p. 63–64°.

In neither product was the *cis*-isomer detected.

Infrared Spectra of the 5-Hydroxy-2-phenyl-1,3-dioxans.—The extent of contamination of samples of *trans*-5-hydroxy-2-phenyl-1,3-dioxan with the *cis*-isomer can be assessed from the infrared spectra (Nujol mull or KCl disc) since the *cis*-compound has absorptions (cm^{-1}) at 808s, 832s, 931s, 1083w, 1290b, and 1342b which are not present in the spectrum of the *trans*-isomer. However, only the absorptions at 808 and 832 cm^{-1} may be used reliably to detect the *cis*-isomer. The spectrum of an equimolar *cis-trans*-mixture showed a broad absorption at 1087 cm^{-1} but not the absorptions at 931, 1083, 1290, and 1342 cm^{-1} . Mixtures containing more than 50% of the *trans*-compound absorbed at 931 cm^{-1} .

The spectra in the hydroxyl stretching region were obtained from CCl_4 solutions of the alcohols in 2 or 3 cm. layers (fused quartz cells), by means of a Unicam S.P. 100 spectrometer equipped with a grating (3000 lines per in.). Frequencies were checked against water vapour and ammonia bands. The concentration of the alcohols was always $<0.005\text{M}$ in order to eliminate intermolecular hydrogen bonding; the extinction coefficients, ϵ , are maximum values and are equal to $(1/cl) \log_{10} (I_0/I)$ with l in cm. and c in moles/l. *cis*-1,3-*O*-Benzylidene-glycerol had ν_{max} at 3590 cm^{-1} (ϵ 95) for bonded hydroxyl groups and the *trans*-isomer at 3633 (ϵ 79) and 3601 cm^{-1} (ϵ 26) for free and bonded hydroxyl groups respectively.

Chromatographic Behaviour of the 5-Hydroxy-2-phenyl-1,3-dioxans.—A solution of the 5-hydroxy-2-phenyl-1,3-dioxan(s) (ca. 90 mg.) in benzene (3 ml.) was introduced on to alumina² (10 g.; activity Brockmann III), and the column was eluted with benzene. Fractions (20 ml.) were collected and their contents (mg.) are shown in the Table. The fractions obtained from the *cis-trans*-mixture were analysed qualitatively by infrared spectroscopy; fractions 5 and 6 contained *cis*-isomer, fractions 7–15 *cis-trans*-mixtures with progressively less *cis*-isomer, and fraction 16 *trans*-isomer.

Behaviour of the 5-hydroxy-2-phenyl-1,3-dioxans on alumina.

Fraction	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Recovery (%)
<i>cis</i> -Isomer ...	8.0	16.8	11.0	9.7	7.6	5.7	5.2	4.6	4.0	2.5	2.0	7.9 ^a					96.0
<i>trans</i> -Isomer				7.1	11.4	8.9	8.0	7.4	6.7	6.0	5.6	4.8	4.0	3.5	2.3	9.2 ^a	94.5
1:1 <i>cis-trans</i> -Mixture				6.2	17.8	11.5	9.3	15.0	12.0	7.6	5.2	4.4	3.8	2.3	8.5 ^a		97.6

^a Residual material on the column eluted with ether.

Derivatives of trans-5-Hydroxy-2-phenyl-1,3-dioxan.—Treatment of *trans*-5-hydroxy-2-phenyl-1,3-dioxan (40 mg.) with *p*-phenylazobenzoyl chloride (82 mg., 1.5 mol.) in dry pyridine (3 ml.) by the method previously described¹⁰ gave a chromatographically homogeneous *p*-phenylazobenzoate (78 mg., 89%), m. p. 190–191° (from benzene-light petroleum) (Found: C, 70.9; H, 5.4; N, 7.4. $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4$ requires C, 71.1; H, 5.2; N, 7.2%). Saponification of the *p*-phenylazobenzoate regenerated chromatographically homogeneous *trans*-5-hydroxy-2-phenyl-1,3-dioxan.

Methylation of *trans*-5-hydroxy-2-phenyl-1,3-dioxan (0.25 g.) with ether (2.5 ml.), methyl iodide (25 ml.), and silver oxide (0.25 g.) in the usual manner gave the *methyl ether* (110 mg., 44%), b. p. 121–123°/0.1 mm., m. p. 40–42° (without recrystallization) (Found: C, 67.7; H, 7.1. $\text{C}_{11}\text{H}_{14}\text{O}_3$ requires C, 68.0; H, 7.2%).

5-Hydroxy-2-p-nitrophenyl-1,3-dioxans.—(a) *cis-trans-Mixture*. *cis-trans-5-Hydroxy-2-p-nitrophenyl-1,3-dioxan* (37%) was prepared by essentially the method of Hibbert and Carter¹³ and had m. p. 88—90° which rose rapidly to 96—98° on storage. Hibbert and Carter¹³ record a similar behaviour. Melting and resolidification of the compound m. p. 88—90° gave the compound m. p. 96—98°. It is likely that these compounds are dimorphs.

(b) *cis- and trans-Isomers*. *cis-trans-5-Benzoyloxy-2-p-nitrophenyl-1,3-dioxan* (62 mg.), prepared by essentially the method of Hibbert and Carter,¹³ was fractionated on alumina (5 g.) by elution with benzene—light petroleum (2 : 3), yielding, first, the *trans*-isomer (27 mg.), m. p. 206° (from benzene—light petroleum), and then the *cis*-isomer (30.5 mg.), m. p. 159° (from benzene—light petroleum). The *cis-trans*-mixture (3 g.) was dissolved in the minimum volume of ethyl acetate at 70° and the solution cooled slowly. The separated product after recrystallization was *trans-5-benzoyloxy-2-p-nitrophenyl-1,3-dioxan* (0.6 g.), m. p. 206°. The mother liquors at 0° yielded more of the *trans*-compound. The remaining solution was concentrated to one-third volume and cooled to —15°. The separated product was combined with that obtained by repetition of the process and recrystallized from benzene—light petroleum (b. p. 60—80°), yielding *cis-5-benzoyloxy-2-p-nitrophenyl-1,3-dioxan* (0.7 g.), m. p. 159°.

The benzoates were saponified as follows. A solution of the benzoate (124 mg.) in chloroform (3 ml.) was treated with sodium methoxide obtained from sodium (1.1 mol.) and methanol (5 ml.). The mixture was heated to the b. p., then cooled, the excess of alkali was neutralised with carbon dioxide, and the solution evaporated. The residue was extracted with benzene, washed with water, dried (MgSO₄), and recovered. The products appeared to be homogeneous by chromatography on alumina. Thus, *cis-5-hydroxy-2-p-nitrophenyl-1,3-dioxan*, m. p. 108—109° (from benzene—light petroleum), was obtained from the benzoate of m. p. 159° (Found: C, 53.3; H, 5.2; N, 6.0. C₁₀H₁₁NO₅ requires C, 53.3; H, 4.9; N, 6.2%), and likewise the benzoate, m. p. 209°, gave *trans-5-hydroxy-2-p-nitrophenyl-1,3-dioxan*, m. p. 134—135° (from benzene—light petroleum) (Found: C, 53.3; H, 4.9; N, 6.3%).

Solutions (0.005M) of the alcohols in CCl₄ showed the following ν_{\max} for free and bonded hydroxyl groups: *trans*-isomer 3632 (ϵ 110) and 3602 cm.⁻¹ (ϵ 30); *cis*-isomer 3633 (very weak) and 3593 cm.⁻¹ (ϵ 90).

5-Methoxy-2-p-nitrophenyl-1,3-dioxans.—The mixture (125 mg.) of methyl ethers obtained by methylation¹³ of *cis-trans-5-hydroxy-2-p-nitrophenyl-1,3-dioxan* (m. p. 98—100°) was readily fractionated on alumina (10 g.) by elution with benzene—light petroleum (1 : 3) followed by ether—benzene—light petroleum (1 : 5 : 14), to yield *trans-5-methoxy-2-p-nitrophenyl-1,3-dioxan* (44 mg.), m. p. 106—107° (from benzene—light petroleum), and *cis*-isomer (41 mg.), m. p. 138—139° (from benzene—light petroleum). The mixture was also separated by fractional crystallization as described by Hibbert and Carter.¹³

Separate solutions of the *cis*- and *trans*-methyl ethers (100.8 mg.) in benzene (5 ml.) and in benzene (4 ml.) which had been saturated with dry hydrogen chloride were stored at room temperature for 4 weeks. The solutions were then neutralised with sodium carbonate and evaporated and the residues fractionated by chromatography on alumina. The *cis*-methyl ether yielded a mixture containing 69% of *trans*- and 31% of *cis*-isomer, and the *trans*-methyl ether gave a mixture containing 68% of *trans*- and 32% of *cis*-isomer.

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