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Note

Sodium-ion-induced ^{1}H-n.m.r. shifts in the assignment of structure to *r*-2-ethyl-5-methyl-*c*- and -*t*-5-(2-methylbenzyloxy)-1,3-dioxane

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Assignment of configuration at a tertiary centre in an organic molecule is often difficult. There are no vicinal proton–proton couplings and often the most useful type of information, particularly in cyclic compounds, is based on ^{13}C chemical shift data[1,2] or $^3J_{C,H}$ coupling[3].

The interaction of sodium ions with certain polyoxygenated compounds may induce[4] changes in the chemical shifts of the resonances of particular protons, and the signals which have the greatest induced shifts may also have a well-defined stereochemical relationship with respect to the constituent oxygen atoms. We now report the use of such sodium-ion-induced shifts in assigning the configuration at the tertiary centre in a pair of compounds which have novel herbicidal activity[5], namely, *r*-2-ethyl-5-methyl-*c*- (**1**) and -*t*-5-(2-methylbenzyloxy)-1,3-dioxane (**2**). The patent[5] described the preparation of a mixture of **1** and **2** in which the *cis* isomer was said to preponderate, but contained no detailed evidence for its configuration although g.l.c. and n.m.r. spectroscopy were used to determine *cis* and *trans* characteristics, and the n.m.r. and i.r. spectra of the mixture showed it to contain ~96% of the *cis* isomer.

An alternative unequivocal synthesis of **1** and **2** was sought which avoided the use of the relatively inaccessible[6–8] starting material, 1,1-di(hydroxymethyl)ethene. An intended route, modelled on that described[9] for the preparation of 5-benzyloxy-5-methyl-2-phenyl-1,3-dioxane† was abandoned when we were unable to obtain crystalline, as did the original workers[9], either the *cis*- (**4**) or *trans*-dioxane (**5**)

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†The configuration of the crystalline material, m.p. 56°, was not specified[9].

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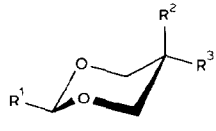
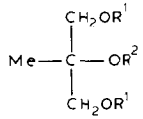
derivatives from the complex mixture of products containing 1,3-dioxane and 1,3-dioxolane stereoisomers. A synthesis based on selective protection of the primary hydroxyl groups in 2-methyl-1,2,3-propanetriol (**3**) was successful.

Reaction of **3** with 2 mol of trityl chloride in pyridine gave the crystalline di-*O*-trityl derivative **6**, which was treated in sequence with sodium hydride and 2-methylbenzyl bromide to yield the crystalline benzyl ether **7** in high overall yield. Cleavage of the trityl groups from **7** by treatment with aqueous trifluoroacetic acid afforded the crystalline diol **8**, acid-catalysed acetalation of which with 1,1-diethoxypropane gave (t.l.c.) two products in roughly equal proportions. Column chromatography gave these products as colourless oils which, on the basis of elemental analyses and ^{1}H-n.m.r. studies, were shown to be *r*-2-ethyl-5-methyl-*c*- (**1**) and -*t*-5-(2-methylbenzyloxy)-1,3-dioxane (**2**).

The isomers had similar ^{13}C-n.m.r. spectra, but a striking difference in the ^{1}H-n.m.r. spectra involved the chemical shifts for the signals of Me-5 (1.02 p.p.m. in the slow-running isomer and 1.57 p.p.m. in the fast-running compound). An indication that the former compound was the *cis* isomer **1** came from a consideration of the reported[10] ^{1}H-n.m.r. spectrum of 2-*tert*-butyl-5,5-dimethyl-1,3-dioxane (**9**), in which equatorial and axial Me-5 resonated at 0.68 and 1.12 p.p.m., respectively. The analogies drawn between the spectra of **1**, **2**, and **9** rest on the reasonable assumption that the preferred conformations of these compounds are as depicted.



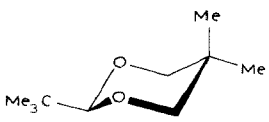


1 R^1 = Et, R^2 = $OCH_2C_6H_4$·o-Me, R^3 = Me
2 R^1 = Et, R^2 = Me, R^3 = $OCH_2C_6H_4$·o-Me
4 R^1 = Ph, R^2 = OH, R^3 = Me
5 R^1 = Ph, R^2 = Me, R^3 = OH

3 R^1 = R^2 = H
6 R^1 = CPh_3, R^2 = H
7 R^1 = CPh_3, R^2 = $CH_2C_6H_4$·o-Me
8 R^1 = H, R^2 = $CH_2C_6H_4$·o-Me

Further evidence for the structures of **1** and **2** was sought from the effect of added sodium ions on their ^{1}H-n.m.r. spectra. Polyoxygenated compounds, with a suitable arrangement of oxygen atoms, can interact[4] with sodium ions in acetone solution and large downfield shifts in the resonances of suitably disposed hydrogen atoms are induced thereby. Particularly relevant is the observation[4] that addition of sodium iodide to solutions of the *cis*- (**10**) and *trans*-5-methoxy-2-phenyl-1,3-dioxane (**11**) produced the greatest effect on H-2 of the *cis* isomer. Dreiding models show that a sodium ion placed at 2.4 Å* from each of the three oxygen atoms in the preferred conformation (**1**) of the *cis* isomer, on the side of the acetal carbon

*This figure lies in the range of many Na–O distances determined by X-ray crystallography[11].



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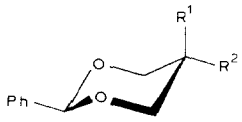

10 $R^1 = OMe, R^2 = H$

11 $R^1 = H, R^2 = OMe$

opposite to the acetal hydrogen, lies close to the axis of the C-2-H bond at the acetal centre and can deshield H-2. In contrast, such complexation with sodium ions cannot occur in the preferred conformation (**2**) of the *trans* isomer. Comparison of the structures of **1** and **2**, with those of **10** and **11**, respectively, indicates similarities and leads to the prediction that the resonance of H-2 in **1** will be shifted more on the addition of sodium ions than that of H-2 in **2**.

The effects of increasing amounts of sodium iodide on the ^{1}H-n.m.r. spectra of solutions of **1** and **2** in acetone-d_6 are shown in Fig. 1. The shift induced in the resonance of H-2 of the slow-running isomer is always greater than that for the fast-running isomer, thus confirming the structures of the two compounds as **1** and **2**, respectively. This assignment is in agreement with the tentative assignment based on a comparison of the chemical shifts of the resonances of Me-5 and indicates the potential of the shift-based method for deducing configuration at a tertiary centre in appropriate polyoxygenated compounds.

EXPERIMENTAL

N.m.r. spectra (internal Me_4Si, unless stated otherwise) were recorded with

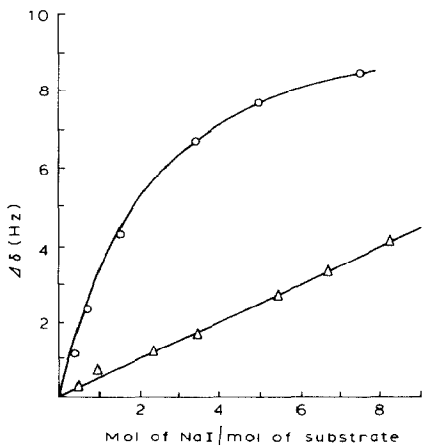

Fig. 1. Induced chemical shifts ($\Delta\delta$) in the resonance of H-2 of the fast-running *trans*-isomer **2** (△) and the slow-running *cis*-isomer **1** (⊙) of 2-ethyl-5-methyl-5-(2-methylbenzyloxy)-1,3-dioxane in acetone-d_6 on addition of sodium iodide.

a JEOL PMX60SI spectrometer. Column chromatography was performed on Kieselgel (Merck, 70–230 mesh).

2-Methyl-1,2,3-propanetriol[6] (**3**). — A mixture of 2-methylprop-2-en-1-ol (25 g, 0.347 mol), aluminium oxide (25 g), tungstic acid (2.5 g, 10 mmol), and water (85 mL) was heated to 60°. Aqueous 30% hydrogen peroxide (39.5 mL, w/v, equivalent to 0.35 mol of peroxide) was added slowly and the temperature of the mixture was maintained at 60° by external cooling. The mixture was then kept for 1 h at 60° and for 2 h at 95°, cooled, filtered, deionised using Amberlite IR-400 (HO^-) and IR-120 (H^+) resins, and concentrated at 80° to give a syrup (30.5 g, 83%). Distillation gave **3**, b.p. 120°/1 mmHg. ^{1}H-N.m.r. data (D_2O, external Me_4Si): ^{1}H, δ 1.10 (s, 3 H, Me), 3.51 (bs, 4 H, H-1,1′,3,3′).

2-Methyl-1,3-di-O-trityl-1,2,3-propanetriol (**6**). — To a solution of **3** (3.184 g, 30 mmol) in pyridine (90 mL) was added trityl chloride (17 g, 61 mmol) and 4-dimethylaminopyridine. The mixture was stirred for 72 h at ambient temperature, then poured into ice–water (50 mL), and the aqueous suspension was extracted with dichloromethane (7 × 50 mL). The combined extracts were dried and concentrated to a thick syrup from which pyridine was removed by azeotropic coevaporation with toluene. T.l.c. (light petroleum–ethyl acetate, 5:1) showed the product to be contaminated with triphenylmethanol which was removed by trituration with light petroleum (3 × 50 mL). The residue was crystallised from light petroleum–ethyl acetate to give **6** (15.61 g, 88%), m.p. 185–186°. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.18 (s, 3 H, Me), 2.38 (s, 1 H, OH), 3.24 (bs, 4 H, 2 CH_2O), 7.00–7.60 (m, 30 H, 2 CPh_3).

Anal. Calc. for $C_{42}H_{38}O_3$: C, 85.4; H, 6.5. Found: C, 85.2; H, 6.5.

2-Methyl-2-O-(2-methylbenzyl)-1,3-di-O-trityl-1,2,3-propanetriol (**7**). — Sodium hydride (0.096 g, 4 mmol) was added to a stirred solution of **6** (1.186 g, 2.01 mmol) in 1,2-dimethoxyethane (10 mL), followed by 2-methylbenzylbromide (0.372 g, 2.01 mmol), and the mixture was maintained at 60°. The reaction was monitored by t.l.c. (light petroleum–ethyl acetate, 5:1). On disappearance of **6**, excess of hydride was decomposed by the addition of methanol, and water (2 mL) and a few small pieces of solid carbon dioxide were added. The mixture was concentrated to a thick slurry which was partitioned between water and dichloromethane. The organic layer was separated, the aqueous layer was extracted several times with dichloromethane, and the combined organic solutions were concentrated. Column chromatography (light petroleum–ethyl acetate, 5:1) of the residue gave **7** (1.32 g, 95%), m.p. 158°. N.m.r. data ($CDCl_3$): ^{1}H, δ 1.34 (s, 3 H, Me), 2.16 (s, 3 H, Ar*Me*), 3.26 (d, 2 H, $J_{1,1'} = J_{3,3'} = 10$ Hz, H-1,3), 3.50 (d, 2 H, H-1′,3′), 4.28 (s, 2 H, ArCH_2), 6.92–7.72 (m, 34 H, ArH); ^{13}C, δ 18.7, 19.4 (2 Me), 62.4 (ArCH_2), 65.8 (2 CH_2), 77.5 (C-2), 86.4 (CPh_3), 125.6, 126.7, 127.6*, 128.7*, 129.6, 135.6, 137.4, 143.8 (aromatic C) (*enhanced intensity).

Anal. Calc. for $C_{50}H_{46}O_3$: C, 86.4; H, 6.7. Found: C, 86.1; H, 6.8.

2-Methyl-2-O-(2-methylbenzyl)-1,2,3-propanetriol (**8**). — To a stirred solution of **7** (3.159 g, 4.54 mmol) in the minimum quantity of dichloromethane was

added 9:1 trifluoroacetic acid–water (30 mL) at room temperature, and the mixture, which became bright yellow, was concentrated. T.l.c. (cyclohexane–ethyl acetate, 1:2) showed the solid residue to contain a new slow-running component together with faster running material. Column chromatography (cyclohexane–ethyl acetate, 1:2) gave the slow-running material which crystallised from cyclohexane to afford **8** (0.412 g, 43%), m.p. 89–90°. N.m.r. data ($CDCl_3$): ^1H, δ 1.18 (s, 3 H, Me), 2.34 (s, 3 H, Ar*Me*), 2.68 (s, 2 H, 2 OH), 3.65 (s, 4 H, 2 CH_2O), 4.50 (s, 2 H, ArCH_2), 7.00–7.46 (m, 4 H, ArH); ^{13}C, δ 17.0 (Me), 18.8 (Me), 62.5 (ArCH_2), 66.4 (2 CH_2OH), 77.3 (C-2), 125.9, 127.8, 128.6, 130.2 (aromatic C-3,4,5,6), 136.4 (aromatic C-1,2).

Anal. Calc. for $C_{12}H_{18}O_3$: C, 68.5; H, 8.6. Found: C, 68.2; H, 8.5.

r-*2-Ethyl-5-methyl*-c- (**1**) *and* -t-*5-(2-methylbenzyloxy)-1,3-dioxane* (**2**). — A mixture of **8** (0.205 g, 0.97 mmol), 1,1-diethoxypropane (0.41 g, 3.1 mmol), *p*-toluenesulphonic acid monohydrate (10 mg), and light petroleum–toluene (3:1, 40 mL) was heated under reflux conditions in a flask fitted with a Soxhlet extractor containing dry molecular sieves type 4A). After 24 h, anhydrous sodium acetate (0.1 g) was added to the cooled solution, and the suspension was stirred vigorously for 2 h, filtered, and concentrated. T.l.c. (cyclohexane–ethyl acetate, 4:1) of the resulting oil revealed components with R_F 0.4 and 0.5. Column chromatography (cyclohexane–ethyl acetate, 9:1) then gave, first, **2**, isolated as a syrup (81 mg, 33%). N.m.r. data ($CDCl_3$) data: ^1H, δ 0.94 (t, 3 H, *J* 7 Hz, *Me*CH_2), 1.20–2.00 (m, 2 H, MeCH_2CH), 1.57 (s, 3 H, MeC), 2.32 (s, 3 H, Ar*Me*), 3.54 (d, 2 H, $J_{4,4'} = J_{6,6'} = 10$ Hz, H-4,6), 3.92 (d, 2 H, H-4',6'), 4.36 (t, 1 H, *J* 5 Hz, MeCH$_2$C*H*), 4.44 (s, 2 H, ArCH_2), 7.00–7.48 (m, 4 H, Ar*H*); ^{13}C, δ 8.3 (CH_3CH_2), 18.8 (Me), 19.4 (Me), 27.6 (MeCH_2), 62.3 (ArCH_2O), 68.5 (C-5), 74.7 (C-4,6), 103.4 (C-2), 125.9, 127.8, 128.4, 130.2 (aromatic C-3,4,5,6), 136.4, 136.5 (aromatic C-1,2).

Anal. Calc. for $C_{15}H_{22}O_3$: C, 72.0; H, 8.9. Found: C, 72.2; H, 9.2.

Eluted second was **1**, isolated as a syrup (119.6 mg, 49%). N.m.r. data ($CDCl_3$): ^1H, δ 0.96 (t, 3 H, *J* 7 Hz, *Me*CH_2), 1.02 (s, 3 H, MeC), 1.20–2.08 (m, 2 H, MeCH_2CH), 2.38 (s, 3 H, Ar*Me*), 3.54 (d, 2 H, $J_{4,4'} = J_{6,6'} = 12$ Hz, H-4,6), 4.18 (d, 2 H, H-4',6'), 4.45 (t, 1 H, *J* 5 Hz, MeCH$_2$C*H*), 4.61 (s, 2 H, ArCH_2), 7.00–7.60 (m, 4 H, ArH); ^{13}C, δ 8.3 (CH_3CH_2), 18.2 (Me), 18.9 (Me), 27.9 (MeCH_2), 63.6 (ArCH_2O), 69.7 (C-5), 72.9 (C-4,6), 102.8 (C-2), 125.8, 127.4, 128.6, 130.0 (aromatic C-3,4,5,6), 136.6, 136.9 (aromatic C-1,2).

Anal. Calc. for $C_{15}H_{22}O_3$: C, 72.0; H, 8.9. Found: C, 72.1; H, 8.9.

Measurement of induced shifts. — The procedure used was that described[4], in which sodium iodide was added in aliquots to a solution of the substrate in acetone-d_6, and the spectrum was determined after each addition.

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