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Studies on Cyclic Ethers. I. The Structure of Di- and Trialkyl Substituted 1,3-Dioxolanes

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Geometrical isomers of 2,4-dimethyl-, 4,5-dimethyl-, 2,4,5-trimethyl- and 2-ethyl-4-methyl-1,3-dioxolane were prepared and separated by preparative gas liquid chromatography.

These isomers were identified by analysis of the nuclear magnetic resonance spectra of the protons at position 2 in the 1,3-dioxolane ring and their retention volumes on gas chromatography. The deshielding effect of the γ-methyl group on the proton at the position 2 was estimated.

Since the muscarine-like activity of 2-methyl-4-dimethylamino-1,3-dioxolane (I) was reported by Fourneau, *et al.*,[2] 1,3-dioxolane derivatives had attracted much interest pharmaceutically. Harper, *et al.*[3] obtained four optical isomers of I but did not clarify their configurations.

2,4-Dimethyl-1,3-dioxolane (II) which has a similar structure to I, was separated into two isomers by fractional distillation,[4] but it was uncertain which of these was the *cis* and which the *trans* form. Recently, Baker, *et al.*[5] assigned the *cis* form (IIa) to the isomer of II which had the lower boiling point, by comparison of the boiling points, specific densities and strain energies of the two isomers with those of *cis* and *trans*-1,3-dimethylcyclopentane. However, Antheunis and Alderwireldt[6] assigned the *trans* form (IIb) to the same isomer of II, based on the relative yield, refractive index and specific density according to the von Auwers-Skita rule.

In the present investigation, 2,4-dimethyl- (II), 4,5-dimethyl- (III), 2,4,5-trimethyl- (IV) and 2-ethyl-4-methyl-1,3-dioxolane (V) were synthesized as mixtures of the *cis* and *trans* forms, and the isomers were separated by preparative gas chromatography (GLC). The nuclear magnetic resonance (NMR) spectra of these isomers were measured to resolve the above contradiction about the assignment of forms to the isomers of II. Assignment of the *cis* and *trans* forms to the isomers of II, III, IV, and V was based on the values of chemical shifts of a proton at position 2 (C-2) in the 1,3-dioxolane ring.

Result

Baggett, *et al.*[7] measured the NMR spectra of isopropylidene derivatives of certain polyhydric alcohols. They concluded that the signal of a C-2 methyl group in the 1,3-dioxolane ring was shifted to a lower field by the deshielding effect of a substituent at position 4 (C-4) or 5 (C-5), situated on the same side of the plane of the 1,3-dioxolane ring as the C-2 methyl group. Baggett, *et al.*[8] also studied the NMR spectrum of IIa which they synthesized

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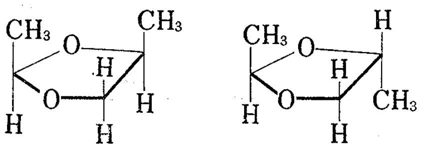
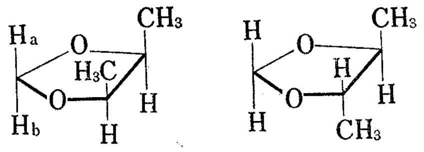


IIa IIb

Fig. 1



IIIa IIIb

Fig. 2

stereospecifically from 1,6-anhydro-β-D-glucopyranose. They observed the signal of the C-2 proton of IIa at τ 5.09 as a quartet, and the signals of the C-2 protons of a mixture of IIa and IIb as quartets at τ 4.97 and τ 5.08, and assigned the signal at τ 4.97 to the C-2 proton of IIb.

In the present study, the isomer of II, which had the lower refractive index and smaller retention volume on GLC using silicon DC 550 as the liquid phase, showed the signal of the C-2 proton at τ 4.98 as a quartet. The other isomer of II, which has a higher refractive index and larger retention volume on GLC, showed the signal of the C-2 proton as a quartet at τ 4.85. The τ values were measured in deuterochloroform containing tetramethylsilane (TMS) as an internal reference. The values of these signals were in a slightly lower field than those of Baggett, *et al.*[8] However, the difference between the τ values of the C-2 protons of these isomers were similar to the difference between the two values obtained by Baggett, *et al.*[8] The GLC was operated with a non-specific liquid phase, (*e.g.* silicon DC 550), so the boiling point of the isomer which has the smaller retention volume should be lower than that of the other isomer. The refractive index of the former was also lower than that of the latter. Therefore, Baker's assignment of the *cis* and *trans* forms of II was concluded to be reasonable.

The isomer of III with the smaller retention volume on GLC, was obtained by acid catalyzed condensation of formaldehyde and *dl*-2,3-butanediol, which was converted from *meso*-2,3-butanediol by the method of Lucas, *et al.*[9] Shlchita, *et al.*[10] synthesized D(—)-4,5-dimethyl-1,3-dioxolane by acid catalyzed condensation of formaldehyde and D(—)-2,3-butanediol. Neither of the two carbon-oxygen bonds of the diol were cleaved during formation of the 1,3-dioxolane ring in this reaction. Therefore, the isomer obtained from *meso*-2,3-butanediol should be *cis*-4,5-dimethyl-1,3-dioxolane (IIIa), and the other isomer obtained from *dl*-2,3-butanediol should be *trans*-4,5-dimethyl-1,3-dioxolane (IIIb).

The NMR signals of the two C-2 protons of IIIa were obtained at τ 4.89 and 5.21. As shown in Fig. 2, one (Ha) of the two C-2 protons is *cis* to the C-4 and C-5 methyl groups, the other (Hb) is *trans* to those. Due to the deshielding effects of these methyl groups on Ha, the signal of Ha was shifted to a lower field, appearing at τ 4.89. The signal of Hb appeared at τ 5.21 because it was not influenced by the deshielding effects of these methyl groups. On the other hand, the C-2 protons of IIIb gave only one signal at τ 5.02 as a singlet. The two C-2 protons of IIIb are equivalent, as shown in Fig. 2, so it is reasonable that they only gave one signal between the signals of Ha and Hb of IIIa.

Gagnaire and Robert[11] obtained 2-phenyl-4,5-dimethyl-1,3-dioxolane from *meso*-2,3-butanediol, and identified the two geometrical isomers by the chemical shift of the C-2 proton. They considered that the signal of the C-2 proton of 2-phenyl-*trans*-4, *trans*-5-dimethyl-1,3-dioxolane was shifted to a lower field due to the phenyl group which was parallel to the symmetric plane because of hindrance of free rotation of the phenyl group at position 2 of the 1,3-dioxolane ring. However, the chemical shifts of Ha and Hb of IIIa were equal to those of 2-pehnyl-*trans*-4, *trans*-5-dimethyl-1,3-dioxolane (τ 4.90[11]) and 2-phenyl-*cis*-4, *cis*-

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[9] H.J. Lucas, F.W. Mitchell Jr, and H.K. Garner, *J. Am. Chem. Soc.*, 72, 2138 (1950).

[10] L.P. Shlichita, J.K. Inman, and H.J. Lucas, *J. Am. Chem. Soc.*, 77, 3784 (1955).

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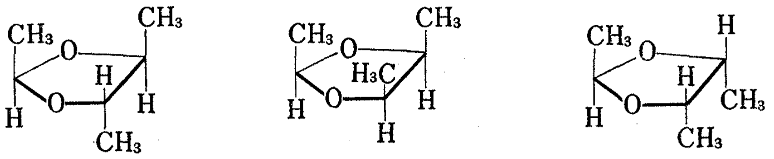
5-dimethyl-1,3-dioxolane (τ 5.25[11]), respectively. IIIa and IIIb, which have no phenyl group at position 2, had similar spectra, so it seems probable that the signal of the C-2 proton of 2-phenyl-*trans*-4, *trans*-5-dimethyl-1,3-dioxolane was shifted 0.35 ppm to a lower field due to the deshielding effect of not only the phenyl group but also the methyl groups at positions 4 and 5.

2,4,5-Trimethyl-1,3-dioxolane (IV)·was separated into three isomers (IVa, IVb, and IVc), as shown in Fig. 3, and the forms of these were assigned by Salomaa and Kankaanperä[12] on the basis of several physical constants other than the NMR spectra. The signals of the C-2 protons of IVa, IVb, and IVc were obtained at τ 4.84, 4.99, and 4.67, respectively. The chemical shifts of the C-2 protons of IVa (τ 4.84) and IVb (τ 4.99) were equal to those of IIb (τ 4.85) and IIa (τ 4.98): the steric situations of the C-2 protons relative to the C-4 and C-5 methyl groups of IVa and IVb were equal to those of IIb and IIa, respectively, and the methyl group which was *trans* to the C-2 proton, had no effect to the chemical shift of the latter. The signal of the C-2 proton of IVc was shifted to a lower field by the deshielding effect of the two methyl groups at position 4 and 5. The difference between the chemical shifts of the C-2 protons of IVb and IVc was 0.32 ppm, which was equal to the difference between the chemical shifts of the two C-2 protons (Ha and Hb) of IIIa.



IVa IVb IVc

Fig. 3

2-Ethyl-4-methyl-1,3-dioxolane (V) was also separated into two isomers by the method used to separate those of II. These were assigned the *cis* and *trans* forms based on their refractive indices and retention volumes on GLC by analogy of the isomers of II. The signals of the C-2 proton of the *cis* form (Va) and *trans* form (Vb) appeared as triplets at τ 5.04 and 5.16, respectively. These signals were 0.18 ppm towards a higher field than the signals of IIa and IIb. However, the difference between the chemical shifts of the C-2 protons of Va and Vb was equal to that between those of IIa and IIb.

Table I. Chemical Shifts of Ring Protons of 1,3-Dioxolane Derivatives

Position of ring proton	C-2	C-4	C-5
cis-2,4-Dimethyl-1,3-dioxolane (IIa)	4.98	5.84	6.09 6.57
	(4.99[a] 5.08[b])	(5.99)[a]	(6.03[a] 6.77[a])
trans-2,4-Dimethyl-1,3-dioxolane (IIb)	4.85	5.77	5.89 6.63
	(5.11[a] 4.97[b])	(6.14)[a]	(6.23[a] 6.69[a])
cis-4,5-Dimethyl-1,3-dioxolane (IIIa)	4.89 5.21	5.90	5.90
trans-4,5-Dimethyl-1,3-dioxolane (IIIb)	5.02	6.44	6.44
2,*cis*-4,*trans*-5-Trimethyl-1,3-dioxolane (IVa)	4.84	6.36	6.36
2,*cis*-4,*cis*-5-Trimethyl-1,3-dioxolane (IVb)	4.99	5.88	5.88
2,*trans*-4,*trans*-5-Trimethyl-1,3-dioxolane (IVc)	4.67	5.78	5.78
cis-2-Ethyl-4-Methyl-1,3-dioxolane (Va)	5.16	5.85	6.10 6.61
trans-2-Ethyl-4-Methyl-1,3-dioxolane (Vb)	5.04	5.78	5.93 6.63

a) Antheunis and Alderweireldt[6] *b*) Baggett, *et al.*[8]

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[12] P. Salomaa and A. Kankaanperä, *Acta. Chem. Scand.*, **16**, 1532 (1962).

Table II. Relative Retention Volumes of 1,3-Dioxlolane Derivatives

Liquid phase	Silicon DC 550[a]	Triethanolamines[b]
1,3-Dioxolane	1.0	1.0
cis-2,4-Dimethyl-1,3-dioxolane (IIa)	0.9	1.4
trans-2,4-Dimethyl-1,3-dioxolane (IIb)	1.0	1.5
cis-4,5-Dimethyl1,3-dioxolane (IIIa)	1.4	2.1
trans-4,5-Dimethyl-1,3-dioxolane (IIIb)	1.1	1.6
2,*cis*-4,*transe*5-Trimethyl-1,3-dioxolane (IBa)	1.4	2.7
2,*cis*-4,*cis*-5-Trimethyl-1,3-dioxolane (IVb)	1.1	2.3
2,*trans*-4,*trans*-5-Trimethyl-1,3-dioxolane (IVc)	0.9	1.8
cis-2-Ethyl-4-methyl-1,3-dioxolane (Va)	1.3	3.0
trans-2-Ethyl-4-methyl-1,3-dioxolane (Vb)	1.4	3.3

a) 25% by weight on Shimalite *b*) 15% by weight on C-22
column temp., 72°;column length, 1.5m; detector temp., 122°; carrier gas, N_2; flow rate, 60 ml/min

The chemical shifts of the ring protons of II, III, IV, and V are summarized in Table I. The relative retention volumes of these compounds on GLC are given in Table II.

Conclusion

2,4-Dimethyl-, 4,5-dimethyl-, 2,4,5-trimethyl-, and 2-ethyl-4-methyl-1,3-dioxolane were synthesized and their isomers were separated by preparative GLC.

The NMR signal of a C-2 proton which was *cis* to the two methyl groups at positions 4 and 5 was shifted 0.32 ppm to a lower field due to the deshielding effects of the two methyl groups. When a C-4 methyl group was *trans* to a C-5 methyl group, or when only one methyl group was attached at position 4 or 5, the signal of the C-2 proton of 2-methyl-1,3-dioxolane derivatives was shifted 0.12—0.13 ppm to a lower field due to the deshielding effect of the methyl group.

The assignments of the *cis* and *trans* forms to 2,4-dimethyl-1,3-dioxolane coincided with the assignments of Baker, *et al.*5) and were opposite to those of Antheunis and Alderweireldt.6)

Experimental

NMR spectra were obtained with a Hitachi H-60 (60 MHz) instrument in deuterochloroform, containing TMS as an internal reference.

The isomers were separated and collected with a Shimazu gas chromatograph, Model GC-1B, using a 7.5 m stainless steel column (inner diameter, 1 cm) packed with silicon DC 550 or triethanolamine (15% by weight on C-22 fire brick). The isomers obtained were checked to see that they gave a gas chromatogram with only one peak, using an analytical column packed with silicon DC 550 (25% by weight on Shimalite).

The *cis* and *trans* forms of 2,4-dimethyl-1,3-dioxolane (II) were prepared from 1,2-propanediol and paraldehyde with 40% sulfuric acid as a catalyst by the method of Delepine.13) The isomer with smaller retention volume on GLC was assigned the *cis* form, n_D^{30} 1.4007 (n_D^{25} 1.3922,4) $n_D^{19.8}$ 1.39505)). The isomer with the larger retention volume on GLC was assigned the *trans* form, n_D^{30} 1.4014 (n_D^{25} 1.39384), $n_D^{19.8}$ 1.39635)).

The *cis* and *trans* forms of 4,5-dimethyl-1,3-dioxolane (III) were prepared form paraformaldehyde and 2,3-butanediol by the same method as those of II. The *trans* form (IIIb) was collected by GLC from the reaction products of paraformaldehyde and commercial 2,3-butanediol (98% *meso* form). The *cis* form (IIIa) was also collected by GLC from the reaction products of paraformaldehyde and *dl*-2,3-butanediol (98% *dl* form) which was converted from the *meso* form by the method of Lucas, *et al.*9) The refractive indices of IIIa and IIIb were n_D^{20} 1.4141 and 1.4144 (n_D^{25} 1.395910)), respectively.

2,4,5-Trimethyl-1,3-dioxolane (IV) was prepared from paraldehyde and 2,3-butanediol by the same method used to prepare II. 2, *cis*-4, *trans*-5-Trimethyl-1,3-dioxolane (IVa) was collected by GLC from the reaction products of paraldehyde and *dl*-2,3-butanediol. 2, *cis*-4, *cis*-5-Trimethyl-1,3-dioxolane (IVb)

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13) M. Delepine, *Compt. Rend.*, 131, 745 (1900).

and 2, *trans*-4, *trans*-5-trimethyl-1,3-dioxolane (IVc) were separated by GLC from the reaction products of paraldehyde and *meso*-2,3-butanediol. The retention volume of IVb was smaller than that of IVc. The refractive indices of IVa, IVb and IVc were n_D^{20} 1.3951 (n_D^{25} 1.3922[12]), 1.4019 (n_D^{25} 1.4007[12]) and 1.4038 (n_D^{25} 1.4037[12]), respectively.

2-Ethyl-4-methyl-1,3-dioxolane (V) was prepared from propionaldehyde and 1,2-propanediol by the same method used to prepare II. The *cis* form (Va) was eluted first and the *trans* form (Vb) later on GLC. The refractive indices of Va and Vb were n_D^{24} 1.4029 and 1.4044, respectively.

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