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ASSIGNMENT OF *CIS-TRANS* CONFIGURATION TO CONSTITUTIONALLY SYMMETRICAL 2,5-DIALKYL-TETRAHYDROFURANS[1]

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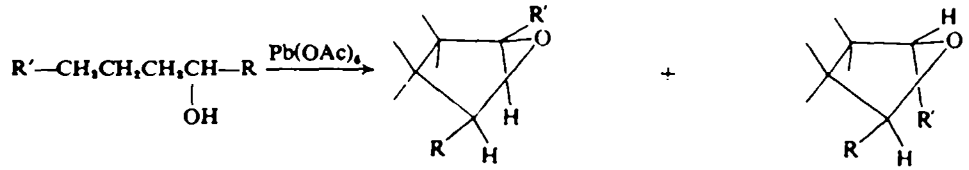
Abstract—The configurations previously assigned to the *cis-trans* stereoisomers of 2,5-dimethyltetrahydrofuran and 2,5-diethyltetrahydrofuran have been established by synthesis, involving the lead tetraacetate oxidation of the corresponding, optically active secondary aliphatic alcohols.

The lead tetraacetate oxidation of unbranched secondary aliphatic alcohols (I), starting from 2-hexanol, affords as major product (33–42%) a mixture of *cis-* (IIA) and *trans*-2,5-dialkyl-tetrahydrofurans (IIB), the ratio *cis*:*trans* (tentative configurations, see below) varying only slightly from 40:60 (for 2-alkanols) to 45:55 (for 4-alkanols).[5,6]



cis *trans*
I IIA IIB

(a) R = R' = Me; (b) R = Me, R' = Et or R = Et, R' = Me; (c) R = Me, R' = n-Pr or R = n-Pr, R' = Me; (d) R = R' = Et; (e) R = Et, R' = n-Pr or R = n-Pr, R' = Et; (f) R = n-Bu, R' = Me; (g) R = Me, R' = n-C_5H_{11}

Scheme 1

Birch and Dean have shown by synthesis[7] and Haresnape by thermodynamic treatment[8] that the isomer of 1,3-dimethylcyclopentane with a lower b.p., lower

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[1a] Part VI, in the series *Lead tetraacetate oxidation of saturated aliphatic alcohols*; paper X in the series *Reactions with lead tetraacetate*; presented at the II *Yugoslav Congress of Pure and Applied Chemistry*. Belgrade, June 16–18 (1966); [b] For paper IX, part V, *Tetrahedron* **22**, 955 (1966).

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[5] V. M. Mićović, R. I. Mamuzić, D. Jeremić and M. Lj. Mihailović, *Tetrahedron Letters* No. 29, 2091 (1963); *Tetrahedron* **20**, 2279 (1964).

[6] M. Lj. Mihailović, Ž. Čeković, Z. Maksimović, D. Jeremić, Lj. Lorenc and R. I. Mamuzić, *Tetrahedron* **21**, 2799 (1965).

[7] S. F. Birch and R. A. Dean, *J. Chem. Soc.* 2477 (1953); *Liebig's Ann.* **585**, 234 (1954).

[8] J. N. Haresnape, *Chem. & Ind.* 1091 (1953).

refractive index and lower density has the *cis*-configuration and the stereoisomer with the higher physical constants has the *trans*-configuration, the *cis*-isomer being thermochemically more stable by 0·53 kcal/mole than the *trans*-isomer.[8–10] This finding is not consistent with a planar conformation of the cyclopentane ring, in which the *cis*-isomer should be not more stable and possibly—because of crowding across the ring—less stable than the *trans*-isomer, but is readily understandable on the basis of the puckered envelope (C_s) form, *cis*-1,3-dimethylcyclopentane existing mainly in the stable quasi-diequatorial conformation and the *trans*-isomer in the somewhat less stable quasi-equatorial-axial conformation.[8,11]

If one assumes that the five-membered ring in 2,5-di-alkyl-tetrahydrofurans (II), obtained by oxidation of secondary aliphatic alcohols (I, Scheme 1), has a similar non-planar envelope form (II),[12] then, by analogy, the *cis*-configuration (IIA) may be assigned[5,6] to the isomeric cyclic ethers (designated in previous papers as stereoisomers "A") of lower b.p., shorter gas-chromatographic retention time (on columns with stationary phases of various polarity, such as 1,2,3-tris(2-cyanoethoxy)propane, polyethylene glycol, apiezon, silicone) and lower refractive index, and the less stable *trans*-configuration (IIB) to the 2,5-dialkyl-tetrahydrofurans (stereoisomers "B") of higher boiling point, longer retention time and higher refractive index (Table 1). Moreover, the Raney nickel hydrogenation of 2,5-dialkyl-furans gave (according to gas chromatography) only one stereoisomeric form of the corresponding tetrahydrofurans (II), which was identical to the isomer "A" (with lower physical constants) of the cyclic ethers (II) obtained from the reaction of lead tetraacetate with secondary aliphatic alcohols (I); this result also suggests the *cis*-configuration (IIA) for the 2,5-dialkyl-tetrahydrofurans ("A") with lower physical constants, since it is improbable that hydrogenation of the unsaturated ring of the 2,5-dialkyl-furans in the presence of Raney nickel would afford only the *trans*-product (IIB).

Our present work shows that the previous assignment[5,6] of the *cis*- and *trans*-configuration to the stereoisomeric 2,5-dialkyl-tetrahydrofurans (II), obtained by oxidation of secondary aliphatic alcohols (I), is correct, and confirms the determination of configuration which was recently reported by Cagnaire and Monzeglio[14] for the geometrical isomers of 2,5-dimethyltetrahydrofuran and which is based on

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[9] M. B. Epstein, G. M. Barrow, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards* **43**, 245 (1949); F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun and G. C. Pimentel, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds.* Carnegie Press, Pittsburgh, Pa. (1953), and subsequent supplements; J. P. McCullough, R. E. Pennington, J. C. Smith, I. A. Hossenlopp and G. Waddington, *J. Amer. Chem. Soc.* **81**, 5880 (1959).

[10] K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.* **81**, 3213 (1959).

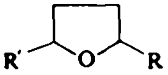
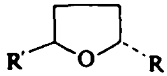
[11] [a] E. L. Eliel, *Stereochemistry of Carbon Compounds* pp. 248–252. McGraw-Hill, New York (1962); [b] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* pp. 200–203. Interscience, New York (1965).

[12] In the other possible non-planar conformation, i.e. the puckered half-chair (C_2) form of the five-membered ring,[11] which is suggested by calculations to be the favoured conformation of tetrahydrofuran itself,[10] it does not appear, according to models, that *cis*-2,5-dialkyl-tetrahydrofurans would be more stable than their *trans*-isomers, since eclipsings and 1,3-interactions of the *cis*-methyl groups (compared to the *trans*-methyl groups) are not minimized as in the case of the envelope form IIA.

[13] D. D. Reynolds and W. O. Kenyon, *J. Amer. Chem. Soc.* **72**, 1593 (1950).

[14] D. Cagnaire and P. Monzeglio, *Bull. Soc. Chim. Fr.* 474 (1965).

TABLE 1. PHYSICAL CONSTANTS OF SOME *cis*- AND *trans*-DIALKYLTETRAHYDROFURANS (II)

R and R′ (Scheme 1)	Run	 *cis*[a] (IIA)			 *trans*[b] (IIB)		
		B.p., °C (760 mm)	n_D(t, °C)	$[\alpha]_D^{21}$	B.p., °C (760 mm)	n_D(t, °C)	$[\alpha]_D^{21}$ (*c*) (EtOH)
R = Me R′ = n-Pr (IIc)	1	141–142[c]	1·4200(20·5)	—	143–144[c]	1·4235(20·5)	—
	2	140–142[d]	1·4198(20·5)	—	—[d]		
R = n-Bu R′ = Me (IIf)	3	166–167[c]	1·4248(20·5)	—	169[c]	1·4281(20·5)	—
	4	164–165[d]	1·4244(20·5)	—	—[d]		
R = R′ = Me (IIa)	5	90–91[e]	1·4029(22)	~0°	92–94[e]	1·4045(22)	−22·95°(2·9)
	6	90–91·5[f]	1·4035(21)	—	93–94[f]	1·4052(21)	—
	7	90–92[g]	1·4031(21)	—	—[g]		
R = R′ = Et (IId)	8	140–142[h]	1·4168(24)	~0°	143–144·5[h]	1·4191(24)	−6·2°(9·2)
	9	140–142[i]	1·4170(24)	~0°	143–144[i]	1·4191(24)	+7·5°(4·9)
	10	140–141[j]	1·4205(19)	—	142–144[j]	1·4222(19)	—
	11	140–142[k]	1·4209(19)	—	—[k]		

[a] Has shorter gas-chromatographic retention times on columns of various polarity (Experimental).

[b] Has longer gas-chromatographic retention times (Experimental).

[c] From $Pb(OAc)_4$ oxidation of the corresponding secondary DL aliphatic alcohol.[5,6]

[d] From Raney Ni hydrogenation of the corresponding (nondissymmetric) 2,5-dialkyl-furan;[5] only the *cis* isomer is obtained.

[e] From $Pb(OAc)_4$ oxidation of (−)-2-hexanol, $[\alpha]_D^{21}$ −10·0° ($c = 4$, EtOH); similar results were obtained with DL-2-hexanol.[6]

[f] From cyclization[18] of inactive (DL and/or *meso*) 2,5-hexanediol (Experimental and also Ref. 14).

[g] From Raney Ni hydrogenation of (nondissymmetric) 2,5-dimethylfuran; only the *cis*-isomer (IIA) is obtained (see also Ref. 14). The same *cis*-2,5-dimethyltetrahydrofuran was prepared by reduction of the ditosylate of *cis*-2,5-dihydroxymethyltetrahydrofuran.[14]

[h] From $Pb(OAc)_4$ oxidation of (−)-3-octanol, $[\alpha]_D^{21}$ −6·1° ($c = 5·2$, EtOH).

[i] From $Pb(OAc)_4$ oxidation of (+)-3-octanol, $[\alpha]_D^{21}$ +7·5 ($c = 4·8$, EtOH). Similar results were obtained with DL-3-octanol.[6]

[j] From cyclization[18] of inactive (DL and/or *meso*) 3,6-octanediol.

[k] From Raney Ni hydrogenation of (nondissymmetric) 2,5-diethylfuran; only the *cis*-isomer (IIA) is obtained.

chemical correlation, i.e. on the LAH reduction of the ditosylate of *cis*-2,5-dihydroxymethyltetrahydrofuran to *cis*-2,5-dimethyltetrahydrofuran.

Since cyclization of alcohols by means of lead tetraacetate does not involve the carbinol carbon-hydroxyl oxygen bond,[6,15] the oxidation of an optically active secondary alcohol of type I (Scheme 1), where R = R′, should afford two constitutionally symmetrical, stereoisomeric 2,5-dialkyl-tetrahydrofurans (II, R = R′), the nondissymmetric (plane of symmetry) *cis*-isomer (IIA, R = R′) being optically inactive and the dissymmetric *trans*-isomer (IIB, R = R′) showing optical activity.

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[15] See K. Heusler and J. Kalvoda, *Angew. Chem.* 76, 518 (1964); *Ibid.* (Intern. English Ed.) 3, 525 (1964), and Refs. therein.

Thus, the oxidation of (−)-2(*R*)-hexanol[15a] (Ia) gave a mixture of both stereoisomeric 2,5-dimethyltetrahydrofurans (IIa) in about 41% yield; upon gas-chromatographic separation on a column of 1,2,3-tris(2-cyanoethoxy)propane (TCEP),[16] the isomer with shorter retention time (and with lower b.p. and lower refractive index; Table 1, run 5) proved to be optically inactive and is therefore *cis*-2,5-dimethyltetrahydrofuran (IIAa), while the isomer with longer retention time (and with higher b.p. and higher refractive index; Table 1, run 5) was optically active (laevorotatory) and has hence the (−)-*trans*-(2*R*, 5*R*)-configuration (IIBa). Cyclization of 2,5-hexanediol[13] afforded again both *cis-trans* 2,5-dimethyltetrahydrofurans (Table 1, run 6) in about the same ratio (*cis*:*trans* = 40:60), whereas the Raney nickel hydrogenation of the corresponding 2,5-dimethylfuran (Table 1, run 7) appears to proceed stereoselectively, with the formation of only the *cis*-isomer. In the same way, i.e. by $P(ObAc)_4$ oxidation of (−)-3(*R*)-octanol and (+)-3(*S*)-octanol (Id),[15a] respectively (Table 1, runs 8 and 9), the *cis*-configuration could be assigned to the inactive 2,5-diethyltetrahydrofuran (IIAd) with lower physical constants, and the *trans*-configuration (IIBd) to the optically active isomer with higher physical constants, the (−)-*trans*-ether obtained from (−)-3(*R*)-octanol having the (2*R*, 5*R*)-configuration and the (+)-*trans*-ether resulting from (+)-3(*S*)-octanol having the (2*S*, 5*S*)-configuration. The ratio of *cis* to *trans* isomer obtained in these oxidations and in the cyclization of 3,6-octanediol (Table 1, run 10), varied from 44:56 to 42:58, while the Raney nickel hydrogenation of 2,5-diethylfuran afforded only the *cis*-isomer of 2,5-diethyltetrahydrofuran (Table 1, run 11).

These results suggest that stability relationships and the conformational rule observed in the cyclohexane[17] and cyclopentane[11] series can be extended to tetrahydrofuran derivatives, at least to 2,5-dialkyl compounds, and that therefore isomers of constitutionally unsymmetrical 2,5-dialkyltetrahydrofurans with lower physical constants should also have the *cis*-configuration[5,6] (Scheme 1 and Table 1, runs 1 and 2 (IIc); runs 3 and 4 (IIf)).

The IR spectra of the *cis*- and *trans*-2,5-dimethyltetrahydrofurans (Fig. 1) and *cis*- and *trans*-2,5-diethyltetrahydrofurans (Fig. 2) show small but characteristic differences (particularly the dimethyl compounds), which can be used for the differentiation between and the identification of the geometrical isomers.

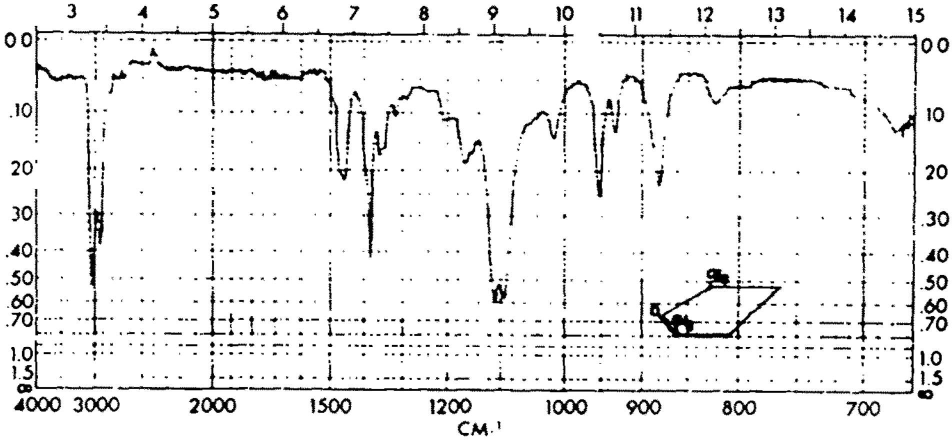
The NMR spectra at 60 Mc/s of the 2,5-dimethyltetrahydrofurans (IIa) and 2,5-diethyltetrahydrofurans (IId) show signals of considerable complexity, which should be resolved in a more powerful magnetic field and subjected to computer calculations in order to obtain information on the conformation of the five-membered ring. The spectrum of 2,5-dimethyltetrahydrofuran (IIa) is of the type $A_3A_3'BB'CC'XX'$, with the following values of chemical shifts; for the *cis*-isomer: δ_A centered at 1·25 (protons of the 2- and 5-methyl group), $\delta_B + \delta_C = 1{\cdot}3\text{–}2{\cdot}2$ (protons at C_3 and C_4), δ_X centered at 3·93 (protons at C_2 and C_6); for the *trans*-isomer: δ_A centered at 1·20 (CH_3-protons), $\delta_B + \delta_C = 1{\cdot}25\text{–}2{\cdot}3$ (protons at C_3 and C_4), δ_X centered at 4·13

[15a] J. A. Mills and W. Klyne in *Progress in Stereochemistry* (Edited by W. Klyne) Vol. 1, pp. 195 and 205. Butterworths, London (1954), and Refs therein. For the configuration of 3-octanols see also P. A. Levene and A. Walti, *J. Biol. Chem.* **94**, 593 (1932).

[16] Both isomers behave similarly on columns of polyethylene glycol (1500), Apiezon L and Silicone GE SF-96.

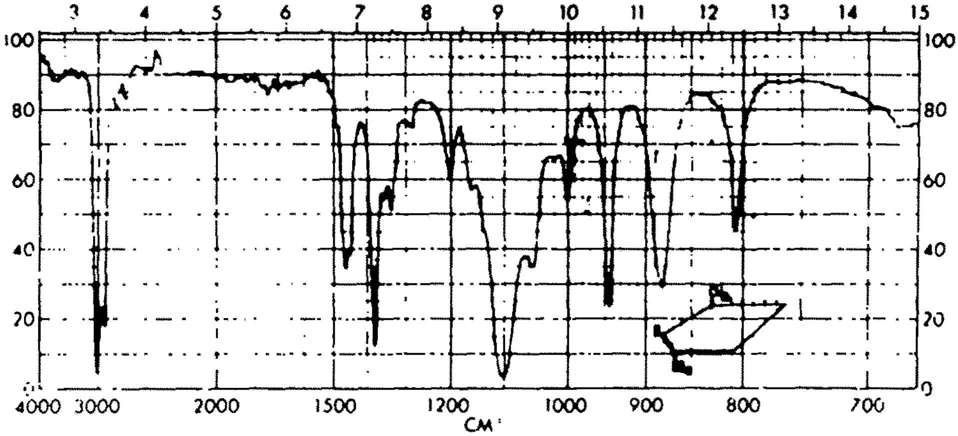
[17] See for example Ref. 11*a* pp. 211–219, and Ref. 11*b* pp. 50–58 and 173–178.

(protons at C_2 and C_5); $\Delta\delta_X = 0{\cdot}20$ or 12 c/s. In the NMR spectra of the 2,5-diethyltetrahydrofurans (IId) the signals of the α-protons (at C_2 and C_5) are centered: for the *cis*-isomer at $\delta_X = 3{\cdot}77$, for the *trans*-isomer at $\delta_X = 3{\cdot}87$; $\Delta\delta_X = 0{\cdot}10$ or 6 c/s. As can be seen, for both compounds (IIa and IId) the signals δ_X of the α-protons are



cis

(a)

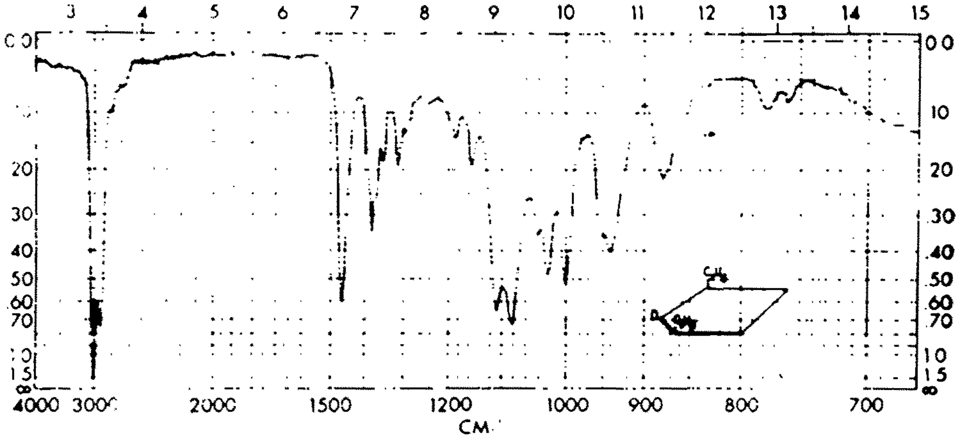


trans

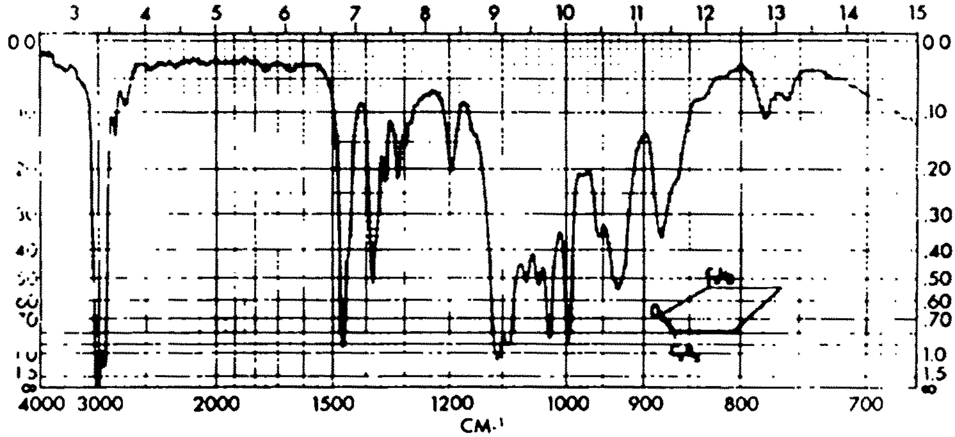
(b)

FIG. 1. IR spectra of the stereoisomeric 2,5-dimethyltetrahydrofurans

displaced downfield in the *trans*-isomer, indicating a deshielding effect of the axial 2 (or 5) methyl group on the axial 5 (or 2) α-proton in the quasi-equatorial-axial conformation of the *trans*-2,5-dialkyltetrahydrofuran IIB (a and d). Such a behaviour can be compared to the similar deshielding effect of an axial 3-methyl group on an axial 1-carbinol proton, resulting in a downfield shift of the carbinol proton signal of about 10 c/s, observed by Eliel *et al.*[18] in the NMR spectra of *cis*-3,3,5-trimethylcyclohexanol, 3,3,5,5-tetramethylcyclohexanol and 3,3-dimethylcyclohexanol (with respect to the signals of the axial 1-carbinol protons of *cis,cis*-3,5-dimethylcyclohexanol, *cis*-3,3,5-trimethylcyclohexanol and *cis*-3-methylcyclohexanol, which do not contain such axial 3-methyl groups).



cis



trans

FIG. 2. IR spectra of the stereoisomeric 2,5-diethyltetrahydrofurans

In most previously reported preparations, which consisted in cyclization reactions[13,19] or hydrogenation of the furan ring,[20] 2,5-dimethyltetrahydrofuran (IIa) was

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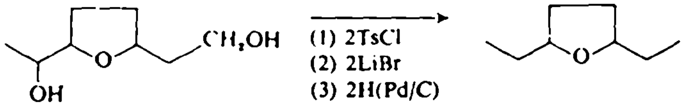
[18] E. L. Eliel, M. H. Gianni and Th. H. Williams, *Tetrahedron Letters* No. 17, 741 (1962).

[19] J. Colonge and A. Lagier, *Bull. Soc. Chim. Fr.* 17 (1949); I. F. Belskil, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.* 142 (1962); B. T. Gillis and P. E. Beck, *J. Org. Chem.* **28**, 1388 (1963).

[20] E. V. Whitehead, R. A. Dean and F. A. Fidler, *J. Amer. Chem. Soc.* 73, 3632 (1951); E. A. Youngman, F. F. Rust, G. M. Coppinger and H. E. De La Mare, *J. Org. Chem.* **28**, 144 (1963).

not separated into its isomers. By fractional distillation and gas-chromatographic separation (on polyethylene glycol) of the products obtained by hydrogenation of 2,5-dimethylfuran at 150–200° over a nickel-on-kieselguhr catalyst, Kyryacos *et al.*[21] isolated the pure isomers of 2,5-dimethyltetrahydrofuran;[22] however, they attributed the *cis*-configuration to the isomer with a higher b.p. (92° ± 0·5°) and longer gas-chromatographic retention time, and the *trans*-configuration to the compound of lower b.p. (90° ± 0·5°) and shorter retention time. According to their IR spectra and to our own spectra (Fig. 1), their assignment of configuration should be reversed. Arnett and Wu[23] prepared 2,5-dimethyltetrahydrofuran (IIa) by cyclization of 2,5-hexanediol and assigned the *cis*-configuration to the compound (without actually isolating the isomers) of longer retention time (on a column of polyethylene glycol on Celite) and superior basicity. According to our finding (see above and Experimental), the *cis*-isomer has a shorter gas-chromatographic retention time on the same column, and therefore the results of these authors on the relative basicities of the *cis*- and *trans*-2,5-dimethyltetrahydrofurans should be reinvestigated and probably inversed. As already mentioned, assignment of configuration to the stereoisomeric 2,5-dimethyltetrahydrofurans was recently achieved by synthesizing the *cis*-isomer from the corresponding *cis*-dihydroxymethyl compound (LAH reduction of the ditosylate).[14]

2,5-Diethyltetrahydrofuran (IId) was previously prepared by cyclization of 3,6-octanediol,[24] and probably consisted of a *cis-trans* mixture. On the other hand, Gerlach and Prelog[25] obtained 2,5-diethyltetrahydrofuran (IId) from the optically active (+)-diol (III), *via* the corresponding ditosylate and dibromide, and since the cyclic ether did not show optical rotation, it was assigned the *cis*-configuration (IIAd). However, no physical constants are given for this compound.



optically active (+)
III

optically inactive (*cis*)
IIAd

Other products isolated upon the $Pb(OAc)_4$ oxidation of 2-hexanol and 3-octanol (ketone corresponding to the starting alcohol, unrearranged and rearranged fragmentation compounds, unreacted alcohol and its acetate, etc.) were described in detail in previous papers[1b,5,6] (see also Experimental). It is of interest to note that in the reaction of (+)-2-hexanol (Ia) and (−)-3-octanol (Id) with lead tetraacetate the corresponding acetates (IVa and IVd) were formed with complete retention of configuration (Scheme 2). This observation indicates that acetylation of hydroxyl groups in the lead tetraacetate reaction does not involve cleavage of the C—O bond in the starting alcohol, in a S_N2 type substitution on the carbinol carbon atom or with the formation of carbon

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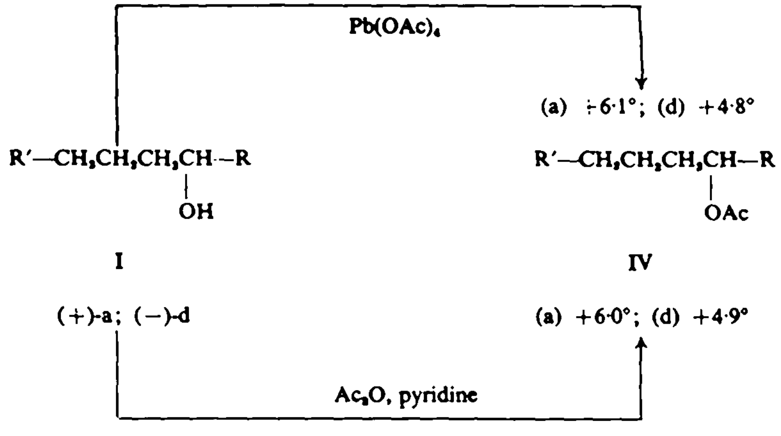
[21] G. Kyryacos, H. R. Menapace and C. E. Boord, *Analyt. Chem.* **31**, 222 (1959).

[22] We are indebted to Dr. Kenneth W. Greenlee, Department of Chemistry, The Ohio State University, Columbus, Ohio, USA, for kindly furnishing us details of these experiments.

[23] E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.* **84**, 1684 (1962).

[24] Yu. K. Yurév, G. Ya. Kondrateva, P. A. Akishin and A. A. Derbeneva, *Zh. Obshch. Khim.* **22**, 339 (1952).

[25] H. Gerlach and V. Prelog, *Liebig's Ann.* **669**, 121 (1963).

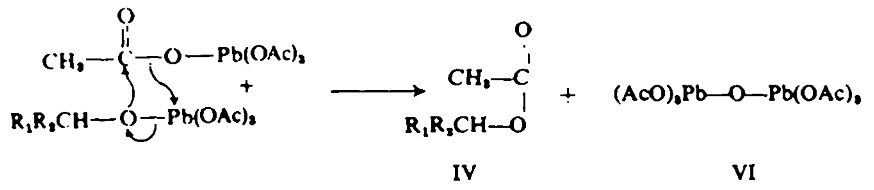


(a) R = R' = Me; (d) R = R' = Et

(The angle values refer to specific rotations in EtOH, at concentrations (g/100 ml) of 4–6)

Scheme 2

radicals or cations,[26] but that it proceeds either by esterification of the starting alcohol or the corresponding alkoxy lead triacetate, $R_1R_2CH—O—Pb(OAc)_3$ (which is formed as the primary intermediate), with acetic acid or acetic anhydride generated in the course of the reaction,[27,28] and/or, in a similar way, by nucleophilic attack of the hydroxyl oxygen atom of the alcohol on one of the carboxylate carbon atoms of lead



Scheme 3

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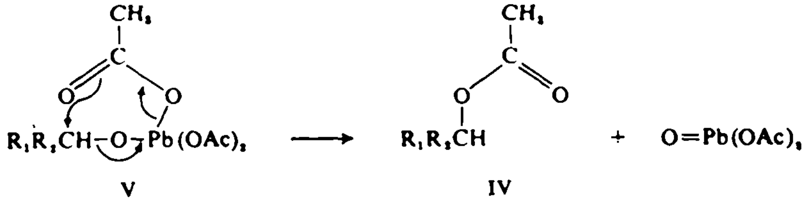
[26] Although a S_Ni type substitution (with retention of configuration) in the intermediate alkoxy lead acetate, through a cyclic six-membered transition state V, though improbable (because of C—O bond breaking), cannot be *a priori* disregarded.



[27] M. Lj. Mihailović, Z. Maksimović, D. Jeremić, Ž. Čeković, A. Milovanović and Lj. Lorenc, *Tetrahedron* 21, 1395 (1965).

[28] W. A. Mosher, C. L. Kehr and L. W. Wright, *J. Org. Chem.* 26, 1044 (1961).

tetraacetate, as proposed by Moon and Lodge[29] and, in a modified version involving alkoxy lead triacetate instead of the free alcohol, by Heusler[30] (Scheme 3).

EXPERIMENTAL[35]

B.ps and m.ps are uncorrected. Gas chromatography: Perkin–Elmer instrument, Model 116-E, equipped with thermistor detectors. For preparative separations up to 150° columns consisting of 1,2,3-tris(2-cyanoethoxy)propane (TCEP) adsorbed on Chromosorb P 60/80 (40%) or of polyethylene glycol 1500 (PEG) adsorbed on Celite (25–30%) were used, while for higher temps the columns were filled with Apiezon L on Celite (30–40%) or with Silicone GE SE-96 on Chromosorb P (30%); the temp of the columns, the sensitivity of the detector and the press and flow rate of the carrier gas (dry H) were adjusted according to the fractions which were analysed (see below). IR spectra: Perkin–Elmer Infracord, Model 137, and NMR spectra: Varian A-60 spectrometer.

The preparation of lead tetraacetate, drying of the reagents and the oxidations in benzene were carried out as described previously.[8] The products, upon separation by gas chromatography, were identified and characterized on the basis of their physical properties (b.ps,[36] refractive indices, retention times, IR and NMR spectra, m.ps of solid derivs), which were usually compared with those of authentic compounds, synthesized by independent routes.

cis- *and* trans-2,5-*Dimethyltetrahydrofuran*

Lead tetraacetate oxidation of 2-hexanol (Ia). Commerical DL-2-hexanol (Fluka) was resolved into its enantiomers by conversion to the acid phthalate[37] followed by fractional crystallization of the corresponding brucine salt.[38] Hydrolysis of the separated diastereoisomeric brucine salts and saponification of the resulting enantiomeric acid phthalates[37] afforded (+)-2-hexanol, b.p. 137–138°, n_D^{23}

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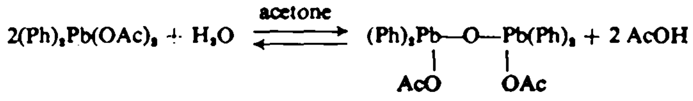
[29] S. Moon and J. M. Lodge, *J. Org. Chem.* **29**, 3453 (1964).

[30] K. Heusler, Personal communication. In view of the ionic character of lead tetraacetate,[31] Heusler considers that the two molecular species containing tetravalent lead and involved in the acetylation process (Scheme 3), are associated between themselves through acetate anions, similarly to bridging of lead atoms by acylate groups in trimethyl lead acetate,[32] which has also an ionic acetate group;[33] moreover, a close analogy to the lead oxane structure VI (not isolated) is found in the formation of the organo dilead oxane compound VIII (isolated and characterized) from diphenyl lead diacetate (VII) and small amounts of water (this equilibrium reaction being shifted to the right by addition of diazomethane, which captures the formed acetic acid):[34]



$$2(Ph)_2Pb(OAc)_2 + H_2O \underset{}{\overset{\text{acetone}}{\rightleftarrows}} (Ph)_2\underset{\displaystyle AcO}{\underset{|}{Pb}}-O-\underset{\displaystyle OAc}{\underset{|}{Pb}}(Ph)_2 + 2\,AcOH$$

VII VIII

[31] K. Heusler, H. Labhart and H. Loeliger, *Tetrahedron Letters* No. 32, 2847 (1965).

[32] M. J. Janssen, J. G. A. Luijten and G. J. M. van der Kerk, *Rec. Trav. Chim.* **82**, 90 (1963).

[33] R. Okawara and H. Sato, *J. Inorg. Nucl. Chem.* **16**, 204 (1961).

[34] E. M. Panov, N. N. Zemlyanskii and K. A. Kocheshkov, *Dokl. Akad. Nauk SSSR* **143**, 603 (1962).

[35] We thank Mrs. R. Tasovac and Miss R. Dimitrijević, from the Microanalytical Laboratory of our Department, for the elemental microanalyses they carried out. All substances described in this paper gave correct values for C% and H%.

[36] B.p. micro-determinations were performed according to the modified (capillary) Emich method. See N. D. Cheronis, *Micro-and Semimicro Methods, Technique of Organic Chemistry* (A. Weissberger Editor-in-chief) Vol. VI, pp. 190–192. Interscience, New York (1954).

[37] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **99**, 45 (1911).

[38] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **105**, 830 (1914).

1·4124, $[\alpha]_D^{21}$ +11·76° (*c* = 3·39, EtOH),[39,40] and (−)-2-hexanol, b.p. 136–138°, n_D^{21} 1·4120, $[\alpha]_D^{21}$ −10·00° (*c* = 3·96, EtOH).[39,40]

(−)-2-Hexanol (15·3 g, 0·15 mole) in 160 ml dry benzene was oxidized with 73·2 g (0·15 mole + 10% excess) $Pb(OAc)_4$, in the presence of 16·5 g (0·15 mole + 10% excess) anhydrous $CaCO_3$. The reaction was complete after refluxing for 7·5 hr.

The neutral benzene–ether extract was separated by fractional distillation into 4 fractions: 78–79°, 80–81° and 82–100° at 760 mm, and 50–70° at 50 mm. The components of the first three fractions, containing *cis*- and *trans*-2,5-dimethyltetrahydrofuran, were separated by preparative gas chromatography on a TCEP column (8 m × 8 mm) at 50° (H flow rate 100 ml/min), and those of the last fraction on an Apiezon L column (4 m × 6 mm) at 125° (and flow rate 100 ml/min). The following products were obtained:[6] *cis*-2,5-dimethyltetrahydrofuran (17·1%), *trans*-2,5-dimethyltetrahydrofuran (24·1%) (*cis*/*trans* = 41:59), 2-butyl acetate (0·87%), n-butyl acetate (0·73%), 2-hexanone (5·7%), unreacted 2-hexanol (8·6%), 2-hexyl formate (0·80%), 2-hexyl acetate (14·6%). Similar results and the same order of elution of the isomeric ethers (*cis* before *trans*) were also observed on columns with other stationary phases, such as PEG, Apiezon and Silicone.

cis-2,5-Dimethyltetrahydrofuran (IIAa), b.p. 90–91°,[14] n_D^{20} 1·4029, optically inactive; *trans*-2,5-dimethyltetrahydrofuran (IIBa), b.p. 92–94°,[14] n_D^{20} 1·4045, $[\alpha]_D^{21}$ −22·95° (*c* = 2·90, EtOH).[41,42]

The acetate of (+)-2-hexanol (IVa), isolated upon the $Pb(OA_2)_4$ oxidation, b.p. 150–151°, n_D^{21} 1·4025, $[\alpha]_D^{21}$ +6·12° (*c* = 5·10, EtOH), was identical with an authentic acetate, b.p. 152–153°, n_D^{21} 1·4022, $[\alpha]_D^{21}$ +5·98° (*c* = 4·95, EtOH),[39] prepared from (+)-2-hexanol, Ac_2O and pyridine (refluxing for 5 hr), in 76% yield, and purified by gas chromatography on an Apiezon L column (4 m × 6 mm) at 125° (H flow rate 100ml/min).

Cyclization of 2,5-*hexanediol*. Cyclization of 2,5-hexanediol[18], afforded 72% of a mixture of *cis*- and (racemic) *trans*-2,5-dimethyltetrahydrofuran (b.p. 90–93°), which was separated by gas chromatography on a column (6 m × 8 mm) of PEG (t = 58°, H flow rate 87 ml/min). *cis*-Isomer (IIAa), b.p. 90–91·5°, n_D^{21} 1·4035; *trans*-isomer (IIBa), b.p. 93–94°, n_D^{21} 4052; *cis*/*trans* ratio = 40:60.

Raney nickel hydrogenation of 2,5-*dimethylfuran*. Commercial 2,5-dimethylfuran (Fluka) (24·0 g, 0·25 mole) in 25 ml dry ether was hydrogenated in the presence of about 5 g Raney Ni (W-2) (initial press 90–95 atm, temp 105–115°) for 8 hr.[6,43] Fractional distillation of the filtered soln afforded 16·5 g (66%) of IIa, b.p. 90–92°, n_D^{21} 1·4031, which, according to gas chromatography (see above), consists of only the *cis*-stereoisomer.[14]

cis- *and* trans-2,5-*Diethyltetrahydrofuran*

Lead tetraacetate oxidation of 3-*octanol* (Id). The enantiomers of 3-octanol were obtained in the following way. Amylvinylcarbinol, b.p. 73–75° at 15 mm, prepared in 60% yield from n-amyl bromide and acrolein,[44] was resolved *via* the strychnine salt of its acid phthalate.[44,45] Hydrogenation of (−)-n-amylvinylcarbinol, $[\alpha]_D^{21}$ −16·6° (*c* = 7·61, EtOH),[44] [46] with PtO_2 in EtOH, afforded in 85%

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[39] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **103**, 1923 (1913). Since these authors report for (+)-2-hexanol $[\alpha]_D^{20}$ +12·70° (*c* ~ 5, EtOH), the optical purity of our enantiomers would be: 92·6% for (+)-2-hexanol and 78·7% for (−)-2-hexanol.

[40] See also P. A. Levene and A. Walti, *J. Biol. Chem.* **90**, 85 (1931); P. A. Levene, A. Rothen and M. Kuna, *Ibid.* **120**, 759 (1938); T. D. Stewart and D. Lipkin, *J. Amer. Chem. Soc.* **61**, 3299 (1939); F. Barrow and R. G. Atkinson, *J. Chem. Soc.* 638 (1939).

[41] According to the optical purity of starting (−)-2-hexanol,[39] the optical purity of this *trans* cyclic ether (IIBa) would correspond approximately to 78–79%.

[42] When the $Pb(OAc)_4$ oxidation was performed on (−)-2-hexanol of lower optical purity ($[\alpha]_D^{21}$ −6·08° (*c* = 3·75, EtOH)), the *cis*-ether (IIAa) was again optically inactive, while *trans*-2,5-dimethyltetrahydrofuran (IIBa) had $[\alpha]_D^{24}$ −12·92° (*c* = 1·64, EtOH). This specific rotation agrees with that observed for the above described *trans*-ether of higher optical purity.

[43] R. Paul, *Bull. Soc. Chim. Fr.* [5] **2**, 2227 (1935); [5] **5**, 1053 (1938).

[44] S. Murahashi, *Sci. Pap. Inst. Phys. Chem. Res.* **34**, 155 (1937/1938).

[45] P. A. Levene and A. Walti, *J. Biol. Chem.* **94**, 593 (1932).

[46] Y. R. Naves, *Helv. Chim. Acta* **26**, 1992 (1943).

yield (+)-3-octanol, b.p. 75–76·5° at 14 mm, $[\alpha]_D^{21}$ +7·54° (c = 4·77, EtOH);[44,47,48] by the same procedure (+)-n-amylvinylcarbinol, $[\alpha]_D^{21}$ +13·7° (c = 7·03, EtOH),[44,48] gave in 83% yield (−)-3-octanol, b.p. 73–75° at 13 mm, $[\alpha]_D^{21}$ −6·14° (c = 5·2, EtOH).[44,47,48]

The enantiomeric 3-octanols (Id; 13·0 g, 0·1 mole) in 150 ml dry beznene were oxidized with 46·5 g (0·1 mole + 5% excess) $Pb(OAc)_4$, in the presence of 11·0 g (0·1 mole + 10% excess) anhydrous $CaCO_3$. The reaction was complete after refluxing for 8–10 hr.

After removal of the solvents from the neutral benzene-ether extract, the products were distilled and separated into two fractions, b.p. 120–146° at 760 mm and b.p. 63–98° at 40 mm, respectively, leaving a residue (1·2–2·2 g). The components of the first fraction (5·7–6 g), containing *cis*- and *trans*-IId, were separated by preparative gas chromatography on a TCEP column (6 m × 8 mm) at 75°, and those of the second fraction (5·8–6·4 g) on an Apiezon L column (4 m × 6 mm) at 125° (in both cases H flow rate 100 ml/min). The following products were obtained:[a]

Product	Yield (%)	
	From (−)-3-octanol	From (+)-3-octanol
cis-2,5-Diethyltetrahydrofuran	18·2	16·9
trans-2,5-Diethyltetrahydrofuran	24·0	21·4
2-Pentyl acetate	0·56	0·70
1-Pentyl acetate	0·42	0·61
3-Octanone	7·5	9·0
Unreacted 3-octanol	18·0	16·2
3-Octyl formate	1·3	1·2
3-Octyl acetate	14·5	12·7

Similar results and the same order of elution of the isomeric ethers (*cis* shorter retention time) were also obtained with other columns (PEG, Apiezon L, Silicone GE SF-96).

From (−)-3-octanol. *cis*-IIAd, b.p. 140–142°, n_D^{24} 1·4168, no optical activity; *trans*-IIBd, b.p. 143–144·5°, n_D^{24} 1·4191, $[\alpha]_D^{21}$ −6·20° (c = 9·22, EtOH);[49] ratio *cis*/*trans* = 43:57. *From (+)-3-octanol.* *cis*-IIAd, b.p. 140–142°, n_D^{24} 1·4170, no optical activity; *trans*-IIBd, b.p. 143–144°, n_D^{24} 1·4191, $[\alpha]_D^{21}$ +7·47° (c = 4·85, EtOH);[49] ratio *cis*/*trans* = 44:56.

The acetate of (−)-3-octanol (IVd), isolated after the oxidation, b.p. 189–190°, n_D^{20} 1·4150, $[\alpha]_D^{21}$ +4·78° (c = 5·76, EtOH), was identical with an authentic IVd, b.p. 187–189°, n_D^{20} 1·4152, $[\alpha]_D^{21}$ +4·93° (c = 5·82, EtOH),[44,48,50] prepared in 70·5% yield, from (−)-3-octanol, Ac_2O and pyridine (refluxing for 6 hr), and purified by gas chromatography on an Apiezon L column (4 m × 6 mm) at 130° (flow rate 100 ml/min).

Cyclization of 3,6-*octanediol*. Cyclization of 3,6-octanediol[14] (16 g) by means of benzenesulphonyl chloride (19·3 g) in pyridine (34 g),[13] afforded in 70% yield (9·8 g) a mixture of *cis*- and *trans*-2,5-diethyltetrahydrofuran (b.p. 140–143°), which was separated by gas chromatography on a PEG column (6 m × 8 mm) at 62° (H flow rate 87 ml/min). *cis*-IIAd, b.p. 140–141°, n_D^{19} 1·4205; *trans*-IIBd, b.p. 142–144°, n_D^{19} 1·4222; *cis*/*trans* ratio = 42:58.

Raney nickel hydrogenation of 2,5-*diethylfuran*. 2,5-Diethylfuran, b.p. 138–140°, n_D^{21} 1·4510, was prepared by the hydrazine hydrate reduction of 2-acetyl-5-ethylfuran,[51] which was itself obtained according to the sequence: furan → 2-acetylfuran[52] → 2-ethylfuran[51] → 2-acetyl-5-ethylfuran.[51]

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[47] R. H. Pickard and J. Keynon[50] give for (+)-3-octanol $[\alpha]_D^{20}$ +11·13° (c ~ 5, EtOH). According to this value, the optical purity of our enantiomers would be: 67·7% for (+)-3-octanol and 55·2 % for (−)-3-octanol.

[48] Y. R. Naves, *Helv. Chim. Acta* **26**, 1034 (1943).

[49] For the optical purity of these (−)- and (+)-*trans*-ethers see Ref. 47.

[50] J. Kenyon, *J. Chem. Soc.* **105**, 2226 (1914).

[51] M. Féizon and P. Baranger, *Bull. Soc. Chim. Fr.* 1311 (1957).

Freshly distilled 2,5-diethylfuran (31 g, 0·25 mole) in 25 ml diethyl ether was hydrogenated as described for 2,5-dimethylfuran (see above) and afforded 25·6 g (80%) of 2,5-diethyltetrahydrofuran, b.p. 140–142°, n_D^{19} 1·4209, which, according to gas chromatography, represents only the *cis*-ether (IIAd).

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[13] H. D. Hartough and A. I. Kosak, *J. Amer. Chem. Soc.* **68**, 2639 (1946).