β-Halogeno Ether Synthesis of Olefinic Alcohols: Stereochemistry and Conformation of 2-Substituted 3-Halogenotetrahydro-pyran and -furan Precursors

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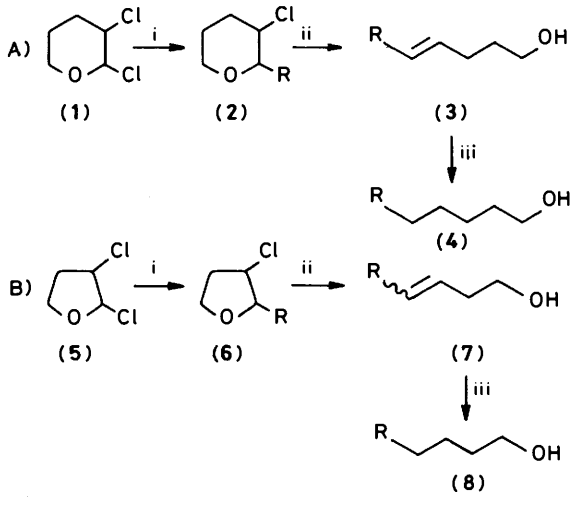
Ring-scission of *cis*- or *trans*-2-alkyl-(or aryl-) 3-chlorotetrahydropyrans proceeds regioselectively and highly stereoselectively to give (*E*)-alk-4-en-1-ols, but in the parallel tetrahydrofuran series (*Z*)-/(*E*)-mixtures, dependent on precursor geometry, are formed. In this paper the stereochemistry and conformation of the tetrahydro-pyran and -furan precursors are considered. The *cis*/*trans*-composition of 2,3-dihalogenotetrahydro-pyrans and -furans made by various routes is reported. Reaction with Grignard reagents gives separable *cis*-/*trans*-mixtures the stereoisomeric composition of which, in the cases examined, does not depend on the stereoisomeric composition of the dihalide, but does vary with the halogen and the composition of the Grignard or dialkylmagnesium; possible reasons are discussed.

The stereochemistry and conformation of the 2-alkyl-(or aryl-)3-chlorotetrahydropyrans is analysed by n.m.r. methods ($J_{2a,3e}$*cis ca.* 1.5 Hz; $J_{2a,3a}$*trans ca.* 9.8 Hz) but assignments for the two tetrahydrofuran series with $J_{2,3}$ 2.6—3.6 and 4.3—5.9 are made uncertain by pseudorotation. The stereochemical identity of the two series is rigorously proved by isolation of *cis*- and *trans*-2-allyl-3-chlorotetrahydrofuran. On the one hand the former is hydrogenated to the *cis*-2-propyl compound, correlated with other members of the alkyl series, but on the other it is oxidised and the acid is converted into the *cis*-*p*-bromophenacyl ester. The stereochemistry and conformation of the latter is rigorously demonstrated by an *X*-ray structure.

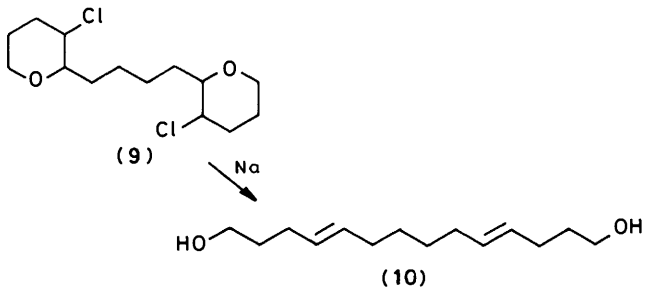
The stereochemistries and conformations of the 2-deuterio- and 2-methoxy-3-chlorotetrahydropyrans are discussed, and consideration is then extended to the 2-alkyl-3-chloro-2-methyltetrahydro-pyran and -furan series.

β-Halogeno ether synthesis using tetrahydro-furans or -pyrans provides an excellent synthetic method for extending an alkyl or aryl residue by four or five carbon atoms in a straight chain containing a double bond (Scheme 1).[1,2] The sequence proceeds



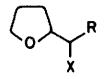
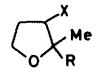
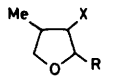
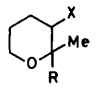
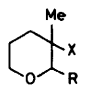
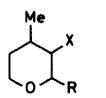
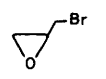
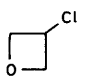
Scheme 1. β-Halogeno ether synthesis using tetrahydropyran and tetrahydrofuran derivatives. *Reagents:* i, RMgX; ii, Na; iii, hydrogenation

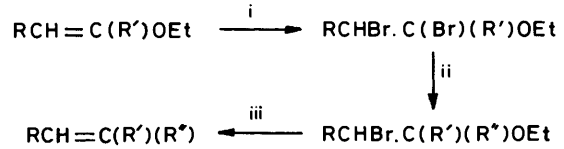
easily and in good yield and, since its introduction, has been used in the synthesis of a variety of natural products such as rethrolones,[3] insecticidal amides,[4] capsaicin,[5] pheromones and insect attractants,[6] urushiol,[7] branched-chain acids,[8] polyisoprene models,[9] octahydrophenanthrenes and octalones,[10] as well as other intermediates.[11] Branching can be introduced in the Grignard reagent, or the dihalogeno-tetrahydrofuran or -tetrahydropyran, and the ring scission with electropositive metals can also involve other ring sizes and substitutions (Table 1). A repeat β-halogeno ether synthesis may be carried out by converting the product alcohol into its corresponding halide and Grignard reagent, and reprocessing the latter through Scheme 1.[12] Double extensions such as (**9**) ⟶ (**10**) have also been effected by use of a bis-Grignard reagent.[13]



The synthesis employs the pioneering work of Paul and his school[26] and this, in turn, has antecedents in the Boord synthesis (Scheme 2).[27] Unfortunately, a disadvantage of the Boord synthesis is its poor stereoselectivity, giving mixtures of *Z*- and *E*-olefins.[28] It has been shown that this also applies to the β-halogeno ether ring scission of both the *cis*- and *trans*-2-alkyl-3-chlorotetrahydrofurans, though the regioselectivity is excellent.[1] On the other hand the ring scission of both the *cis*- and *trans*-2-alkyl-3-chlorotetrahydropyrans is highly stereoselective (and completely regiospecific) for *E*-olefinic alcohols.[1] This gives the tetrahydropyran-based reaction substantial interest as

Table 1. Further cyclic β-halogeno ethers, and alcohols formed on ring scission with electropositive metals

Halogeno ether	Alcohol from ring-scission	Ref.
	$RCH{=}CH[CH_2]_3OH$	1, 14, 15
	$R(Me)C{=}CH[CH_2]_2OH$	8*b*, 16, 17
	$RCH{=}CHCH(Me)CH_2OH$	18
	$R(Me)C{=}CH[CH_2]_3OH$	19, 22
	$RCH{=}C(Me)[CH_2]_3OH$	23
	$RCH{=}CHCH(Me)[CH_2]_2OH$	18
	$CH_2{=}CHCH_2OH$	24
	$CH_2{=}CHCH_2OH$	25

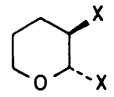
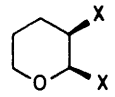


Scheme 2. Boord synthesis. *Reagents:* i, Br_2; ii, R"MgX; iii, Zn

a synthetic procedure, and the purpose of this and the following paper is to explore and understand more fully the stereochemical aspects of Scheme 1 and the reasons for these stereochemical differences.

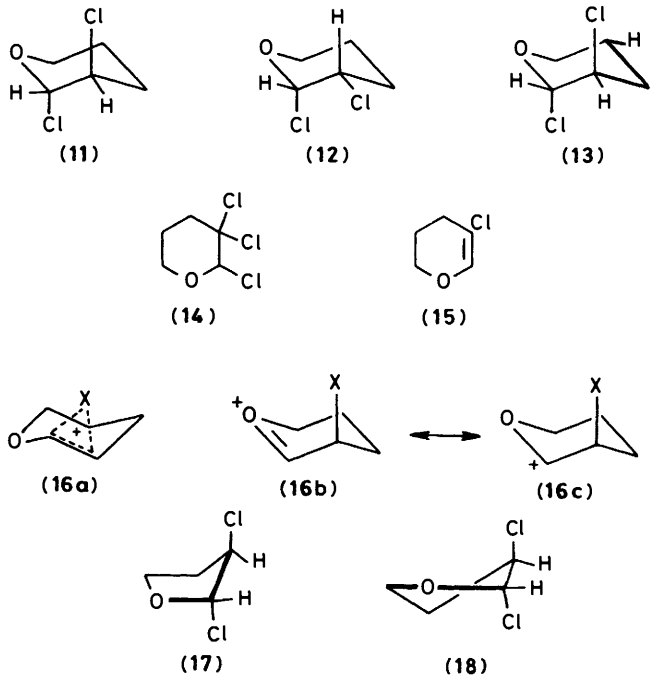
First, the 2,3-dihalogeno precursors (**1**) and (**5**) were considered. In early work, 2,3-dichlorotetrahydropyran made by addition of chlorine to 2,3-dihydropyran was thought to be *trans*-, but Lemieux and Fraser-Reid[29] in an important n.m.r. study showed it to be a *cis–trans*-mixture which could be enriched with the thermodynamically favoured *trans*-isomer by equilibration with tetrabutylammonium chloride. Stone and Daves[30] have also shown that the *cis–trans*-composition of the chlorine addition product is very dependent on solvent polarity. In such 2-chlorotetrahydropyrans the anomeric effect is strongly in evidence, the *trans*-isomer existing as the diaxial form (**11**), and the *cis*-isomer as (**12**). N.m.r. examination of mixtures shows two types of anomeric protons (C_6D_6), one a singlet at δ 5.91, the other a doublet at δ 5.85 ($J_{2,3}$ 3.5 Hz); irradiation through the multiplet at δ 3.83—3.08 located the 3-proton, collapsing the doublet at δ 5.85. These couplings accord with the assigned conformations, *trans*-$J_{2e,3e}$ being

Table 2. Stereoisomeric composition of 2,3-dihalogenotetrahydropyran preparations

Method	%	%	N.m.r. anal.[c]
1. Dihydropyran,[a] Cl_2, ether ≤0 °C	50	50	(A) (B)
2 Tetrahydropyran, Cl_2, CCl_4, 35 °C initiator I_2 or $CBrCl_3$	74	26	(A) (B)
3 Tetrahydropyran, SO_2Cl_2, 65 °C[33]	78	22	(A)
4 Product from (**1**) above, equilibrated with NEt_4Cl in CH_3CN[b]	80	20	(A)
5 Dihydropyran, Br_2, ether 0 °C[34]	88	12	(A) (B)

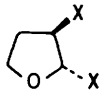
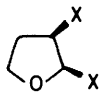
[a] Refers to 4,5-dihydro-6*H*-pyran. [b] Stone and Daves[30] report 35% *cis*- at equilibrium. [c] Integration methods: (A) 100 MHz C_6D_6, (B) 60 MHz, $CDCl_3$, [Eu(fod)$_3$].



smaller than *cis*-$J_{2e,3a}$. The *trans*-isomer had earlier been assigned $J_{2e,3e}$ 1.5 Hz,[29] but the coupling was observed from the 3-proton and possibly represents instead a long-range $J_{3e,5e}$ (W-path) (**13**).

Using integration of unshifted (C_6D_6) or [Eu(fod)$_3$] shifted ($CDCl_3$) anomeric protons in the n.m.r. spectra, approximate analyses for 2,3-dihalogenopyrans made in various ways are given in Table 2. The more severe conditions of the chlorination of tetrahydropyran, which proceeds *via* 2-chlorotetrahydroyran, elimination of hydrogen chloride, and re-addition of chlorine, seemed responsible for the higher *trans*-content. Analysis for cases 1 and 2 in Table 2 was on distilled specimens, a check being made on undistilled material; in the case of (**3**) however, further reaction occurred during distillation leading to (**14**), presumably formed *via* (**15**). The 2,3-dibromo compound[31] was too unstable to distil satisfactorily and was analysed from the n.m.r. signals of the anomeric protons which were *trans*- (singlet, δ 6.49) and *cis*- (doublet, 6.22, $J_{2e,3a}$ 3 Hz) (C_6D_6). Lemieux and others[29,30] have pointed out that intermediate cations formed from halogen addition to dihydropyran can be viewed as (**16a**)

Table 3. Stereoisomeric composition of 2,3-dihalogenotetrahydrofuran preparations

Method	 % [a]	 % [a]
1 3,4-Dihydrofuran, Cl_2, ether ≤0 °C	62	38
2 Tetrahydrofuran, Cl_2, CCl_4, 35 °C, initiator I_2 or $CBrCl_3$	100	0
3 Tetrahydrofuran, SO_2Cl_2, 65 °C [33]	100	0
4 Product from (1) above, equilibrated with $Et_4N^+Cl^-$ in CH_3CN	100 [b]	0
5 3,4-Dihydrofuran, Br_2, ether, ≤0 °C	100	0

[a] By integration of the 2-anomeric protons (100 MHz, C_6D_6). [b] Further reaction occurs.

and (**16b** ⟷ **16c**). In view of the strong participation of iodine, (**16a**) would be dominant, but in the case of chlorine, (**16b**) would be more important because of the assisted stabilisation by oxygen; the case of bromine would be intermediate. On this basis, formation of *cis–trans*-isomers when chlorine is added to dihydropyran is not unexpected, nor is the formation of a product richer in *trans*- on addition of bromine.

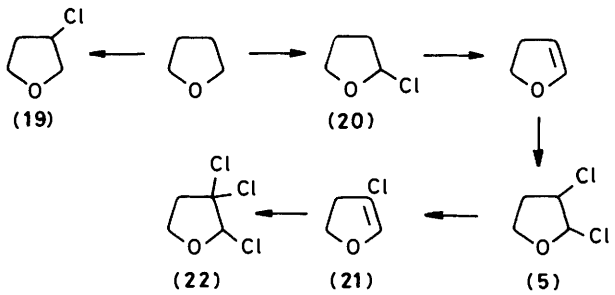
Addition of chlorine to 2,3-dihydrofuran in carbon tetrachloride at 0 °C also gives a mixed 'kinetic product' (Table 3); the two anomeric protons (C_6D_6) are at δ 5.99 (singlet, *trans*-2-He) and 5.82 (doublet, $J_{2e,3a}$ 3.8 Hz, *cis*-2-He).[17] The anomeric effect requires the 2-proton to be equatorial in both *cis* and *trans* forms and the preferred conformation should be the envelope (**17**) or half-chair (**18**) form for the *trans*-compound. Distillation did not alter the composition of the mixture; equilibration with tetramethylammonium chloride in acetonitrile converted it entirely into the *trans*-compound but progressive formation of (**22**) also occurred.* Chlorination of tetrahydrofuran gave a *trans*-product and there is good evidence that the radical chlorination again proceeds *via* 2-chlorotetrahydrofuran (**20**) (which can be isolated at low temperature) followed by elimination of hydrogen chloride and re-addition of chlorine.[32] Some 3-chlorotetrahydrofuran (**19**), which does not readily dehydrochlorinate, was also formed and was present in the crude reaction products (10—15% by g.l.c. on Apeizon) (Scheme 3). Chlorination of tetrahydrofuran at 65 °C with sulphuryl chloride gave only a *trans*-dichloride but it is not effective unless a large excess of tetrahydrofuran is employed. Otherwise, 2,3,3-trichlorotetrahydrofuran (**22**) is produced in considerable amounts, presumably *via* dehydrochlorination of 2,3-dichlorotetrahydrofuran and re-chlorination. Bromination of 2,3-dihydrofuran gave a product which showed a singlet anomeric proton at δ 6.51 (2-H_e, C_6D_6) consistent only with the *trans*-2,3-dibromo structure. Apart from chemical shifts the *trans*-2,3-dichloro- and *trans*-2,3-dibromo-tetrahydrofurans have essentially identical spectra; it is unusual for 5-membered rings not to display involvement in conformational equilibria and this preferred conformation is a consequence of the strong anomeric effect.

* When treated with tetraethylammonium chloride *trans*-2,3-dichlorotetrahydrofuran made by chlorination of tetrahydrofuran in the presence of iodine gave no (**22**). On the other hand (**5**) made by the sulphuryl chloride method readily formed (**22**) (n.m.r. monitoring) and hydrogen chloride. Addition of a little of the product from the iodine-catalysed method however, stopped the reaction and it was inferred that iodine must inhibit the tetraethylammonium chloride catalysed conversion (**5**) ⟶ (**22**). This was confirmed by the chlorination of tetrahydrofuran at 35 °C in sunlight in the presence of bromotrichloromethane as the initiator. The *trans*-dichloro compound (**5**) was then readily converted into trichloro compound (**22**) by tetraethylammonium chloride.

Table 4. 2-Alkyl- and 2-aryl-3-chlorotetrahydropyrans from stereoisomeric mixtures of 2,3-dichlorotetrahydropyrans; comparison of isomer ratios

	2,3-Dichlorotetrahydropyran stereoisomers			
	50% *cis* 50% *trans*		20% *cis* 80% *trans*	
Grignard reagent RMgX in Et_2O (<0.3M)	2-Alkyl-3-chlorotetrahydropyran products [a]			
	% *cis*	% *trans*	% *cis*	% *trans*
R = Me	68	32	—	—
Et	48	52	47	53
Pr	45	55	42	58
Bu	43	57	44	56
Pentyl	53	47	—	—
Pr^i	34	66	35	65
Bu^i	39	61	—	—
Isopentyl	50	50	50	50
Bu^s	22	78	27	73
Ph	0	100	0	100
p-Tolyl	0	100	—	—
Cyclohexyl	33	67	—	—
Phenethyl	37	63	—	—

[a] Analyses by g.l.c. (polyethyleneglycol adipate, PEGA).



Scheme 3. Chlorination of tetrahydrofuran

From the standpoint of β-halogeno ether synthesis 2,3-dihalogenotetrahydropyrans were usually made by treating dihydropyran in diethyl ether with the halogen and then adding this to the appropriate Grignard reagent.[1] The resulting 2-substituted 3-halogenotetrahydropyrans were not necessarily isolated pure but could be subjected to ring scission by sodium directly in diethyl ether.[12] The 2,3-dihalogenotetrahydrofurans were prepared similarly, or, more frequently, by chlorination of tetrahydrofuran.[1] It was known from earlier work that both the 2-alkyl-3-chlorotetrahydro-pyrans and -furans were mixtures of *cis*- and *trans*-isomers separable by fractional distillation; approximate estimates of the isomer ratios were obtained by refractometric analysis.[1,12] On the basis of regularities in b.p., refractive index, g.l.c. retention times *etc.* the two sets of stereoisomers can be readily ordered and *cis*- and *trans*-assignments were made in the earlier work and will be further substantiated later.

Tables 4 and 5 show, over a range of examples, that starting with dichlorotetrahydropyrans or dichlorotetrahydrofurans of different stereoisomeric composition, a particular Grignard reagent gives essentially the same stereoisomeric mixture of 2-alkyl-3-chloro- derivatives, *i.e.* the reaction shows S_N1 characteristics. Use of 2,3-dibromo compounds however, alters

Table 5. 2-Alkyl and 2-aryl-3-chlorotetrahydrofurans from stereoisomeric mixtures of 2,3-dichlorotetrahydrofurans; comparison of isomer ratios

Grignard reagent RMgX in Et_2O (<0.3M)	2,3-Dichlorotetrahydrofuran stereoisomers: 38% *cis* 62% *trans* — 2-Alkyl-3-chlorotetrahydrofuran products[a]		100% *trans* — 2-Alkyl-3-chlorotetrahydrofuran products[a]	
	% *cis*	% *trans*	% *cis*	% *trans*
R = Me	—	—	70	30
Et	66	34	65	35
Pr	—	—	58	42
Bu	54	46	54	46
Pentyl	58	42	58	42
Pr^i	65	35	68	32
Bu^s	53	47	53	47
Ph	—	—	—	100

[a] Analysis by g.l.c. (PEGA).

Table 6. 2-Alkyl-3-bromotetrahydropyrans from 2,3-dibromotetrahydropyran (12% *cis*, 88% *trans*)

Grignard reagent RMgBr in Et_2O (<0.3M)	2-Alkyl-3-bromotetrahydropyran[a]	
	% *cis*	% *trans*
R = Me	18	82
Et	18	82
Pr	9	91
Bu	9	91
Pentyl	8	92

[a] Analysis by g.l.c. (PEGA).

Table 7. 2-Alkyl-3-bromotetrahydrofurans from 2,3-dibromotetrahydrofuran (100% *trans*)

Grignard reagent RMgBr in Et_2O (<0.3M)	2-Alkyl-3-bromotetrahydrofuran[a]	
	% *cis*	% *trans*
R = Me	27	73
Et	30	70
Pr	27	73
Bu	28	72
Pentyl	26	74

[a] Analysis by g.l.c. (PEGA).

the situation (Tables 6 and 7), greatly improving the stereoselectivity for *trans*-alkylation. Thus formation of (**28**) involves 70—74% *trans*-alkylation compared with predominating *cis*- when the 2,3-dichloro compounds are used; the same applies in the pyran series. The greater selectivity associated with the bromo series may be associated with the structure of the bromonium intermediates approximating to (**25**) and (**27**) as distinct from (**23**) and (**24**). Stereoelectronic requirements would lead to rear-side attack on the bromonium ions leading mainly to *trans*-alkylation.

The high incidence of *cis*-alkylation in some of the chloro examples of Tables 4 and 5 suggests that a further factor may be stabilisation of transition states involving complexation as in (**29**). As R groups become bulkier, this may become disfavoured and with large groups like phenyl or *p*-tolyl only *trans*-substitution was found. Employment of dialkylmagnesiums in ether–dioxane (Tables 8 and 9) gave predominantly *trans*-alkylation in reactions with either 2,3-dichlorotetrahydropyran or -furan, and one factor leading to this may be

Table 8. 2-Alkyl-3-chlorotetrahydropyrans from 2,3-dichlorotetrahydropyrans (50% *cis*, 50% *trans*) using Grignard variants

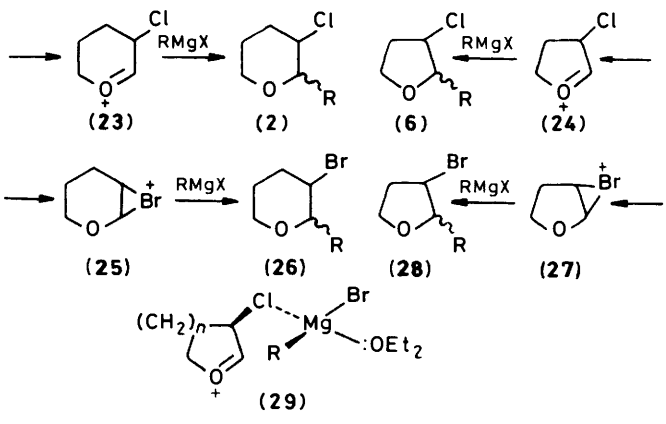
$RMgBr + R_2Mg$ in tetrahydrofuran	2-Alkyl-3-chlorotetrahydropyran[a]	
	% *cis*	% *trans*
R = Me	38	62
Et	28	72
Pr	26	74
Bu	15	85
R_2Mg in Et_2O–dioxane		
R = Me	33	67
Et	9	91
Pr	11	89
Bu	6	94

[a] Analysis by g.l.c. (PEGA)

Table 9. 2-Alkyl-3-chloro- and -3-bromo-tetrahydrofurans from 2,3-dichloro- and 2,3-dibromo-tetrahydrofurans (100% *trans*) using R_2Mg in ether–dioxane

R_2Mg in ether–dioxane	2-Alkyl-3-chlorotetrahydrofuran[a,b]	
	% *cis*	% *trans*
R = Me	38	62
Et	42	58
Pr	25	75
Bu	19	81
	2-Alkyl-3-bromotetrahydrofuran[a,b]	
	% *cis*	% *trans*
R = Me	19	81
Et	11	89
Pr	7	93
Bu	7	93

[a] Analysis by g.l.c. (PEGA). [b] From 2,3-dichlorotetrahydrofuran. [c] From 2,3-dibromotetrahydrofuran.



diminution in the stability of (**29**) when Br is replaced by another R group. The new alkyl will increase the stabilisation of the developing positive charge on magnesium, decreasing the significance of stabilisation by chlorine; only one R group of the dialkylmagnesium is reported to react.[35] Grignard reagents in tetrahydrofuran give results (Table 8) showing preference for *trans*-alkylation and both species RMgBr and R_2Mg may be involved.

Table 10. Coupling constants for stereoisomeric 2-R-3-chlorotetrahydropyrans

Stereoisomers	$J_{2a,3e}$(Hz)	$J_{2a,3a}$(Hz)
High b.p. *cis*-(**30**; R = Me)	1.5	—
Low b.p. *trans*-(**32**; R = Me)	—	9.6
High b.p. *cis*-(**30**; R = Et)	1.5	—
Low b.p. *trans*-(**32**; R = Et)	—	9.6
High b.p. *cis*-(**30**; R = Pr^i)	1.4	—
Low b.p. *trans*-(**32**; R = Pr^i)	—	9.8
High b.p. *cis*-(**30**; R = CH=CH$_2$)	1.5	—
Low b.p. *trans*-(**32**; R = CH=CH$_2$)	—	9.8
Solid *trans*-(**32**; R = Ph)	—	9.8
Solid *trans*-(**32**; R = *p*-MeC$_6$H$_4$)	—	9.8[a]

[a] Lit.[30a] gives 10 Hz.

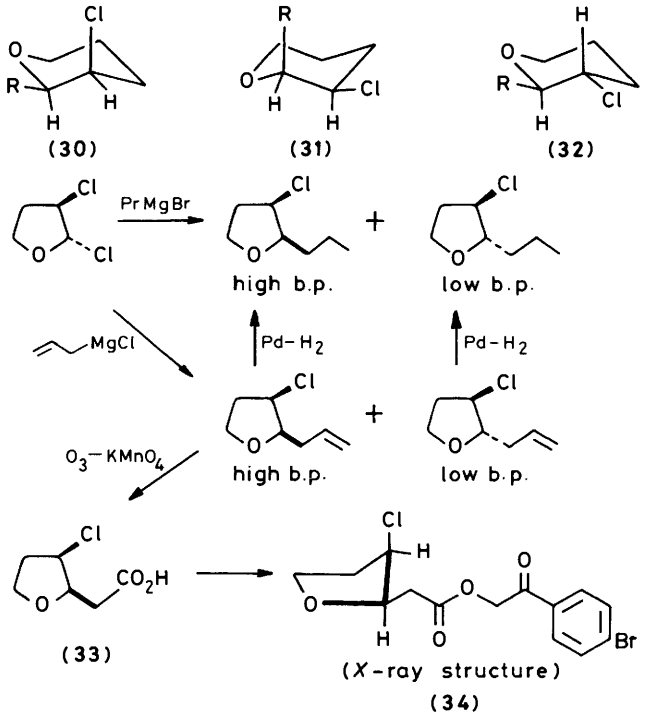
Table 11. Coupling constants for stereoisomeric 2-R-3-Chlorotetrahydrofurans

Stereoisomers	$J_{2,3}$(Hz)	$J_{2,3}$(Hz)
High b.p. *cis*-(**6**; R = Me)	3.5	—
Low b.p. *trans*-(**6**; R = Me)	—	5.6
High b.p. *cis*-(**6**; R = Pr)	3.3	—
Low b.p. *trans*-(**6**; R = Pr)	—	4.6
High b.p. *cis*-(**6**; R = Pr^i)	2.6	—
Low b.p. *trans*-(**6**; R = Pr^i)	—	4.3
High b.p. *cis*-(**6**; R = CH=CH$_2$)	3.3	—
Low b.p. *trans*-(**6**; R = CH=CH$_2$)	—	4.5
High b.p. *cis*-(**6**; R = CH$_2$CH=CH$_2$)	3.6	—
Low b.p. *trans*-(**6**; R = CH$_2$CH=CH$_2$)	—	5.9
Solid *trans*-(**6**; R = Ph)	—	4.5[a]
Solid *trans*-(**6**; R = *p*-MeC$_6$H$_4$)	—	4.5

[a] Stone and Daves[30a] assign the *cis*-stereochemistry.

Assignments of geometry to the separated stereoisomers of both 2-alkyl-3-chloro-tetrahydropyrans[26] and -tetrahydrofurans[12a] have rested on Auwers-Skita generalisations[36] and rates of dehydrochlorination. The former are empirical, and the latter require interpretation with respect to conformation and stereoelectronic control, so that further confirmation has become desirable. The stereochemical problem of the 2-substituted 3-chlorotetrahydropyrans can be settled satisfactorily by n.m.r. methods using spectra in C_6D_6 and $CDCl_3$ with decoupling, INDOR, and discriminatory use of shift reagents where necessary. In a tetrahydropyranoid ring, Karplus calculations indicate a large vicinal coupling (7—10 Hz) for axial–axial (antiperiplanar) protons, whereas axial–equatorial (synclinal) protons have small values (1—4 Hz). With electronegative substituents, vicinal coupling constants are not as large as predicted,[37] and maximal effect is exerted when the substituent is antiperiplanar to one of the two protons involved in vicinal coupling.[38] In this work, *i.e.* 2-alkyl-3-chlorotetrahydropyrans, both chlorine and the ring oxygen constitute electronegative substituents. As a result $J_{2,3}$ values for *cis*-protons may fall into two categories;[39] (a) an axial proton on C-2 and an equatorial on C-3 usually has $J_{2a,3e}$ 1.0—1.5 Hz; (b) an equatorial proton on C-2 and an axial on C-3 usually has $J_{2e,3a}$ 2.5—3.5 Hz. *cis*-2,3-Dichlorotetrahydropyran is an example of the latter, having a strong Edwards-Lemieux anomeric effect, and $J_{2a,3e}$ 3.5 Hz. Rapid chair–chair interconversions can of course result in averaged values.[40]

Table 10 gives $J_{2,3}$ for high- and low-boiling pairs of geometrical isomers. All the high b.p. isomers are confirmed as *cis*- with the important additional information (see following paper) that conformationally their protons are predominantly in the $2_a,3_e$ situation (**30**) rather than (**31**). Values for the low boiling isomers confirm them as *trans*, the 2,3-protons being predominantly *trans*-diaxial (**32**). The two aryl products are also *trans*.



Scheme 4. Configuration assignment for 2-alkyl-3-chlorotetrahydrofurans

2-Alkyl-3-chlorotetrahydrofuran stereoisomers can be similarly classified into two groups on the basis of b.p., refractive index, and relative g.l.c. retention times, and earlier assignments were based on Auwers-Skita and dehydrochlorination information.[12a] Classification into the same two groups is also followed by coupling constant data (Table 11); $J_{2,3}$ is always less for the higher b.p. isomer (assigned *cis*). In tetrahydrofurans showing the anomeric effect (*e.g.* 2-substituent = Cl, OH, OMe *etc.*),[41] J_{cis} vicinal couplings are greater than J_{trans} (*e.g.* $J_{2,3\text{-}trans} = 0$ and $J_{2,3\text{-}cis} = 4$ Hz).[17] The systems of Table 11 do not show the anomeric effect and the rings will be a rapidly interconverting pseudorotational system with n.m.r. data a time-averaged consensus. Consequently the magnitudes of their couplings do not allow unequivocal assignment of geometry, and we have therefore designed a different system for assigning *cis*- or *trans*- geometries to members of the two groups (Scheme (4).

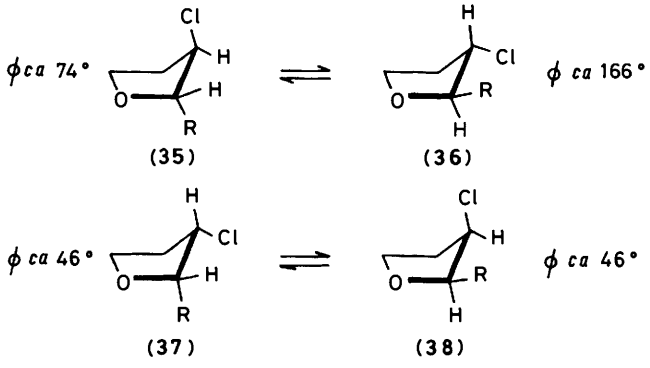
The two stereoisomeric 2-allyl-3-chlorotetrahydrofurans were prepared from 2,3-dichlorotetrahydrofuran and separated by spinning-band distillation. Catalytic hydrogenation of the higher b.p. [longer g.l.c. retention time (PEGA)] isomer gave the higher b.p. isomer of 3-chloro-2-propyltetrahydrofuran and the same was shown for the low b.p. isomers. The high b.p. isomer was then ozonised and oxidised to give 3-chloro-2-tetrahydrofurylacetic acid (**33**). Since this failed to crystallise, it was converted into the *p*-bromophenacyl ester m.p. 105 °C. The structure of this was determined using the heavy atom method by Dr. M. Begley in our laboratory and was shown unequivocally to be the *cis*-compound with the conformation indicated (**34**).* Thus our earlier assignments are, in fact, validated by quite different criteria.

* Puckering of the tetrahydrofuran ring at C-3 and/or C-4 is found in numerous *X*-ray studies of pentofuranose sugars[42] and in n.m.r. investigation of solutions.[43] The *X*-ray structure of (**34**) will be reported in full elsewhere.

Table 12. $J_{2,3\text{-}trans}$ For 2-substituted-3-chlorotetrahydrofurans having 2-substituents of varying electronegativity

	$J_{2,3}$(Hz) ($CDCl_3$)
R = Me	5.6
Ac	2.5
CN	2.1
Bz	2.0
Cl	0

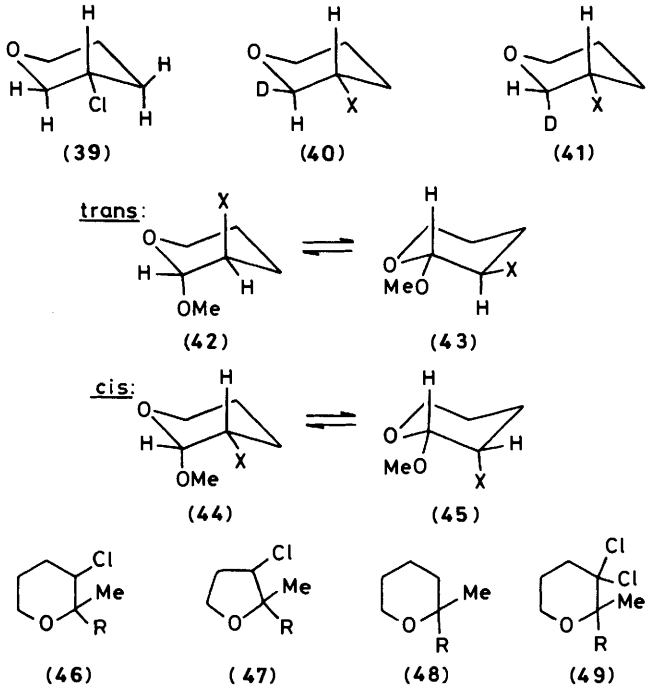
In this series $J_{2,3\text{-}trans}$ coupling constants are thus shown to be larger (4.3—5.9 Hz) than $J_{2,3\text{-}cis}$ (2.6—3.6 Hz). Assignments in the *cis*-series may also be supported by the characteristic 3-H resonance which appears as a quintet or septet because of overlap in the doublet of double doublets at δ 4.4 ($CDCl_3$); in the *trans*-isomer the signal was upfield and usually submerged. By contrast with those 2,3-disubstituted tetrahydrofurans in which the anomeric effect is operative the coupling magnitudes are reversed. This reversal probably arises because of different conformational properties. In systems dominated by the anomeric effect, conformer (**35**) in the *trans*-series and conformer (**37**) in the *cis*-, contribute most strongly to the equilibria, and dihedral angles for these conformations support the observed $J_{2,3\text{-}cis} > J_{2,3\text{-}trans}$. When R is not an electronegative substituent (*e.g.* R = alkyl or Ph), conformational equilibria will probably favour (**36**) in the *trans*-series and (**38**) in the *cis*- (*cf.* the tetrahydropyrans). The effect will be to raise the $J_{2,3\text{-}trans}$ coupling (φ *ca.* 74° ⟶ 166°) and lower $J_{2,3\text{-}cis}$ (3-H nearly coplanar with the ring oxygen). It is not intended to imply that only envelope conformations are involved; arguments applied to half-chair conformations lead to similar, if less marked conclusions.



(35) (36) (37) (38)

The magnitudes of the observed $J_{2,3}$ coupling constants for 2-alkyl-3-chlorotetrahydrofurans would suggest that the *trans*-isomers favour a diequatorially biased equilibrium (**36**) and the *cis*-isomers an equilibrium in which the β-halogen is axial (**38**) [*cf.* the *X*-ray structure (**34**)]. On this basis, replacement of the 2-alkyl group by a series of increasingly electronegative substituents should decrease $J_{2,3\text{-}trans}$ [anomeric effect promoting (**36**) ⟶ (**35**)]. This is shown in Table 12. However, further investigation using variable temperature n.m.r. was not practicable as both *cis*- and *trans*-3-chloro-2-methyltetrahydrofuran showed no change or line broadening down to −108 °C.

Apart from the 2-alkyl- and 2-aryl-3-chlorotetrahydropyrans mentioned, the mechanistic study of the ring scission in the following paper gave rise to a requirement for 2-deuterio- and 3-halogeno-2-methoxytetrahydropyrans. 3-Chlorotetrahydropyran, prepared by reducing *cis*- (50%)/*trans*-(50%)-2,3-dichlorotetrahydropyran with lithium aluminium hydride,[12a] was first examined and had $J_{2a,3a} \sim J_{3a,4a} = 10$ Hz which requires 3-H to be axial and the dominant conformation to be (**39**). However the shift reagent [Eu(fod)$_3$] was used in the n.m.r. work and the analysis assumes that conformational change was not induced. Consequently a low temperature study of the uncomplexed molecule was made as a precaution. There was no line broadening down to −100 °C, also suggesting that conformational equilibrium is not important, one preferred conformation being adopted. 3-Chloro-2-deuteriotetrahydropyran was made similarly using lithium aluminium deuteride. Deuterium incorporation was *ca.* 100%, and based on the n.m.r. integrations of the equatorial and axial 2-protons a 72% 2-De (**40**; X = Cl) and 28% 2a-D (**41**; X = Cl) distribution was attained. A set of measurements using [Eu(fod)$_3$]-shifted spectra gave 65% 2-D$_e$ and 35% 2-D$_a$. The 3-bromo series similarly had 65—70% 2-D$_e$ and 30—35% 2-D$_a$.



(39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49)

A mixture of *cis*- and *trans*-3-chloro-2-methoxytetrahydropyrans was obtained by treating *cis*-(50%)/*trans*-(50%)-2,3-dichlorotetrahydropyran with sodium methoxide in methanol. As the stereoisomers were not readily separable the mixture was analysed by n.m.r. methods ($CDCl_3$). There were two anomeric protons, at δ 4.58 (doublet, $J_{2,3}$ 2.8 Hz) and δ 4.40 (doublet, $J_{2,3}$ 4.1 Hz). In agreement with Lemieux[29] the downfield signal was assigned to the *cis*-isomer and integration showed a 78/22% *cis*/*trans*-mixture. The observed couplings suggest substantial averaging, indicating that conformational equilibria are involved, and the assignments were confirmed by the solvent variation technique (Table 13). Because the anomeric effect is responsive to solvent differences, there is a notable effect on the *trans*-equilibrium as reflected in the averaged $J_{2,3}$ coupling (because $J_{2a,3a} > J_{2e,3e}$); changes in the *cis*-equilibrium do not cause much change in $J_{2,3\text{-}cis}$ (since $J_{2a,3e} \sim J_{2e,3a}$). The mole fraction of (**42**; X = Cl) in the conformational equilibrium (**42**; X = Cl) ⇌ (**43**; X = Cl) for the *trans*-isomer in diethyl ether (the ring scission solvent) was evaluated as $n_a(Et_2O) \sim 0.62$.*

* Calculated from $J_{obs.} = J_A n_a + J_B (1 - n_a)$. Values from the model compounds α- and β-*O*-methyl-2-chloro-mannose and -glucose triacetates, as used by Descotes:[44] $J_{2a,3a}$ 7.5 Hz, $J_{2e,3e}$ 1.1 Hz, $J_{2a,3e}$ 2.0 Hz, $J_{2e,3a}$ 3.8 Hz.

Table 13. Solvent effects on $J_{2,3}$ for *cis*- and *trans*-2-methoxy-3-halogenotetrahydropyrans

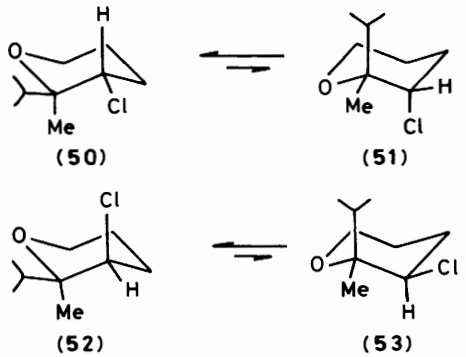
	2-Methoxy-3-halogenotetrahydropyrans			
	(**42**; X = Cl) ⇅ (**43**; X = Cl)	(**44**; X = Cl) ⇅ (**45**; X = Cl)	(**42**; X = Br) ⇅ (**43**; X = Br)	(**44**; X = Br) ⇅ (**45**; X = Br)
Solvent	$J_{2,3\text{-}trans}$	$J_{2,3\text{-}cis}$	$J_{2,3\text{-}trans}$	$J_{2,3\text{-}cis}$
Et_2O	3.5 Hz	2.8 Hz	3.9 Hz	3.0 Hz
MeOH	4.0	2.8	—	—
$CDCl_3$	4.1	2.7	4.5	2.8
CD_3CN	4.6	2.9	5.4	3.0

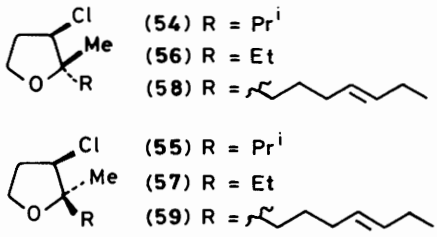
The mole fraction of (**44**; X = Cl) in the equilibrium (**44**; X = Cl) ⇌ (**45**; X = Cl) for the *cis*-isomer was $n_a(Et_2O) \sim 0.44$. The anomeric effect is more dominant in the *trans*-isomers than in the *cis*- and estimation of the mole fractions for [(**42**; X = Cl) + (**44**; X = Cl)] in the mixture (78% *cis*-) gave $n_a(Et_2O) \sim 0.49$.

cis- and *trans*-3-Bromo-2-methoxytetrahydropyran (*ca.* 1:3) were made by bromomethoxylation of dihydropyran at low temperature. The isomers could not be separated and the mixture was analysed by n.m.r. ($CDCl_3$), the two 2-anomeric doublets being at δ 4.62 ($J_{2,3}$ 2.8 Hz) and δ 4.52 ($J_{2,3}$ 4.5 Hz). Again, the downfield signal was assigned to the *cis*-isomer and confirmation made by solvent variation (Table 13). Integration indicated 73% *trans* in the mixture and, using the same models as for the chlorides, gave $n_a(Et_2O) \sim 0.55$ for the *cis*-equilibrium and $n_a(Et_2O) \sim 0.41$ for the *trans*. Thus the anomeric effect in this case is larger for the *cis* and the reversal may be due to the larger bromine causing increased 1,3-diaxial repulsions tending to disfavour conformers (**42**; X = Br) and (**45**; X = Br), enhancing the anomeric effect in the *cis*-relative to the *trans*-equilibrium. Estimation of the mole fraction of [(**42**; X = Br) + (**44**; X = Br)] in the mixture (73%-*trans*) gave $n_a(Et_2O) \sim 0.43$.

In the following paper the ring-scission of 2-alkyl-3-chloro-2-methyltetrahydro-pyrans (**46**)[10a,20] and -furans (**47**) is also considered and their stereochemical and conformational properties are therefore discussed at this point. Yields were relatively low from the intermediate 2,3-dichloro-2-methyltetrahydropyrans (30—40%), due to side-product formation. One of these (**48**) was isolated for R = Bu^n and a second is expected to be (**49**); a scheme for the origins of such by-products is reported.[22] Compounds of type (**46**) were also difficult to separate into stereoisomers but in the case of (**46**; R = Pr^i) the mixture of *cis*- and *trans*-tetrahydropyrans (45:55 by g.l.c.) was partly resolved by fractional distillation, and separation was completed by preparative g.l.c. From its n.m.r. spectrum the major low b.p. product with the smaller g.l.c. retention time (PEGA) is tentatively assigned the *cis*-3-chloro-2-isopropyl-*r*-2-methyltetrahydropyran* (**50**) stereochemistry.

The spectrum ($CDCl_3$) showed the 3-H resonance as a doublet of doublets (*J* 9.2, 5.5 Hz) at δ 4.05 and these couplings, though somewhat averaged, are consistent with a predominantly axial 3-proton because the 9.2 Hz coupling contains a large $J_{3a,4a}$ contribution. The β-halogen is therefore predominantly equatorial. The 2-isopropyl is expected to be equatorial to avoid axial 1,3-repulsions and the isomer is thus tentatively assigned the configuration (**50**) ⇋ (**51**). The other stereoisomer, *trans*-3-chloro-2-isopropyl-*r*-2-methyltetrahydropyran (**52**) showed 3-H as a triplet at δ 4.00, *J* 3 Hz, consistent with an equatorial position and indicating an axial β-halogen. The 2-isopropyl substituent is again expected to have equatorial orientation and the isomer is tentatively considered to be represented as (**52**) ⇋ (**53**).





The two 3-chloro-2-isopropyl-*r*-2-methyltetrahydrofurans (**47**; R = Pr^i) (ratio 40:60 by g.l.c.) could also be separated by preparative g.l.c. Configurations were assigned by reference to the chemical shift of the methyl groups of *cis*- and *trans*-3-chloro-2-methyltetrahydrofuran (*cis*-δ 1.32; *trans*- δ 1.25); the methyl *cis*- to chlorine is more deshielded. On this basis the lesser, lower b.p., shorter g.l.c. retention time (PEGA), component was assigned the *cis*-3-chloro-2-isopropyl-*r*-2-methyltetrahydrofuran geometry (**54**) (δ 1.19); the methyl of the other isomer (**55**) resonated at δ 1.04. Although the stereoisomeric 3-chloro-2-ethyl-*r*-2-methyltetrahydrofurans could not be separated, g.l.c. showed a 64:36 mixture with the lesser component being (**56**) which had δ(Me) at 1.25; (**57**) had the methyl resonance at δ 1.20. Similarly, the (*E*)-3-chloro-2-hept-4-enyl-*r*-2-methyltetrahydrofurans could not be separated but were obtained as a mixture of *cis*-3-chloro-*r*-2-methyl (70%, δ 1.25) (**58**) and *trans*-3-chloro-*r*-2-methyl (30%, δ 1.20) (**59**) isomers.

With this information on the stereochemistry of the precursory 2-substituted 3-halogenotetrahydro-pyrans and -furans available, attention is turned in the following paper to the stereochemistry of the ring scission of such compounds by electropositive metals.

Experimental

See also the following paper for details of certain compounds mentioned in the discussion.

2,3-*Dichlorotetrahydropyran* (**1**).

From 2,3-*Dihydro*-4H-*pyran*.—2,3-Dihydro-4*H*-pyran (84 g) in either dry diethyl ether (referred to as ether) or carbon tetrachloride (100 cm^3) was maintained at 0 to −5 °C (solid CO_2–methanol), and dried (H_2SO_4) chlorine passed into the stirred solution until it acquired a green tinge (*ca.* 1 h). Excess of chlorine was then removed by the addition of small amounts of 2,3-dihydro-4*H*-pyran and the solvent was removed under reduced pressure. Distillation gave the 2,3-dichloride (*cis* + *trans* mixture, *ca.* 50:50 by n.m.r.) (144 g, 92%), b.p. 78—82 °C/12 mmHg, n_D^{24} 1.4940, *m*/*z* 119, 121 (3:1) (corresponding

* In this notation *r*- signifies the reference group (methyl) to which *cis*- or *trans*-prefixes apply.

to $M - Cl$), $\delta(C_6D_6)$ 5.91 (*trans*-2-H $w_{\frac{1}{2}}$ 4 Hz), 5.85, (d, $J_{2,3}$ 3.5 Hz, *cis*-2-H), 3.83—3.08 (3 H, m), and 2.20—0.65 (4 H, m) (lit.,[12] b.p. 88—90 °C/20 mmHg, n_D^{20} 1.4946).

Equilibration. The 2,3-dichloride (5 g) (50% *trans*) was diluted with dry acetonitrile (5 cm^3) and saturated with tetraethylammonium chloride. After 30 min the mixture was diluted with pentane, filtered, and the acetonitrile layer further extracted with pentane. The pentane layers were bulked and the solvent removed under reduced pressure. Distillation gave the 2,3-dichloride (80% *trans* by n.m.r.) (3.5 g), b.p. 78—82 °C/12 mmHg, n_D^{24} 1.4923. An impurity was identified as 3-chloro-5,6-dihydro-4*H*-pyran (**15**). The mass spectrum of the 2,3-dichloride showed impurity ions corresponding to (**15**) at *m/z* 118, 120 (3:1) (M^+) [C_5H_7ClO requires *M*, 118, 120 (3:1)], and an impurity resonance at $\delta(C_6D_6)$ 6.54. The mass spectrum also revealed trace amounts of 2,3,3-trichlorotetrahydropyran (**14**) at *m/z*, 153, 155, 157 (9:6:1) (corresponding to $M - Cl$). Both impurities co-chromatographed (Apiezon) with authentic samples on g.l.c. Reaction times of up to several days enhanced the formation of 3-chloro-5,6-dihydro-4*H*-pyran (≤22% by n.m.r.) but the trichloride was still only observed in trace amounts (<1%).

From Tetrahydropyran.—Method A. Dry chlorine was passed into tetrahydropyran (48.3 g), in carbon tetrachloride (50 cm^3) containing iodine (0.25 g), whilst the temperature was maintained at 30—35 °C (water bath coolant). The 2,3-dichloride[1,12] (74% *trans* by n.m.r.) (69 g, 79%), b.p. 78—90 °C/17 mmHg, n_D^{20} 1.4390—1.4960 (lit.,[12] b.p. 86—90 °C/20 mmHg, n_D^{20} 1.4945) was red (iodine contamination).

Method B. Chlorination of tetrahydropyran (50 g) with sulphuryl chloride (154 g) at 65 °C using Nersasion's procedure[33] for the chlorination of tetrahydrofuran, gave a crude product (46 g) which was identified [g.l.c. (Apiezon), and n.m.r.] as the 2,3-dichloride (78% *trans* by n.m.r.). Distillation, however, gave impure 3-chloro-5,6-dihydro-4*H*-pyran (**15**), b.p. 60—70 °C/17 mmHg (compared with an authentic sample), impure 2,3-dichlorotetrahydropyran, b.p. 70—85 °C/17 mmHg, and impure 2,3,3-trichlorotetrahydropyran (**14**), b.p. 85—93 °C/17 mmHg. Elution of this latter fraction through a small column (SiO_2) [benzene–light petroleum (2:1)] afforded the trichloride of *ca.* 90% purity, $\delta(C_6D_6)$ 5.89 (2-H, s), *m/z*, 153, 155, 157 (9:6:1) (corresponding to $M - Cl$), almost identical with an authentic sample.

2,3-*Dibromotetrahydropyran.*

Bromine (18 g) was added dropwise to a stirred solution of 2,3-dihydro-4*H*-pyran (8.4 g) in dry carbon tetrachloride (20 cm^3) at 0 °C. Removal of the solvent under reduced pressure afforded the crude dibromide (88% *trans* by n.m.r.) in quantitative yield. Distillation resulted in its dehydrobromination (in agreement with Paul[31]).

2,3-*Dichlorotetrahydrofuran* (**5**).

From 2,3-*Dihydrofuran.*—2,3-Dihydrofuran was prepared by a literature method[45] *via* the base catalysed Bu^{t}OK—Bu^{t}OH rearrangement of commercial 2,5-dihydrofuran. The product was isolated by spinning band distillation, b.p. 52—54 °C (lit.,[46] b.p. 54—56 °C), $\nu_{max.}$ 1 619 cm^{-1}. 2,3-Dihydrofuran (10 g) in dry ether or carbon tetrachloride (79 cm^3) was maintained at 0 to −5 °C and treated with dry chlorine. The solvent was evaporated and the residue distilled to give the 2,3-dichloride (62% *trans* by n.m.r.), b.p. 57—60 °C/14 mmHg, n_D^{20} 1.4837; *m/z* 105, 107 (3:1) (corresponding to $M - Cl$) (lit.,[12] b.p. 65—70 °C/22 mmHg, n_D^{20} 1.4840).

From Tetrahydrofuran.—Method A. The 2,3-dichloride was prepared by the method of Crombie and Harper.[1] Dry chlorine was passed into dry tetrahydrofuran (300 g) in carbon tetrachloride (250 cm^3) containing either iodine (1.5 g) or bromotrichloromethane (0.3 g), whilst the temperature was maintained at 30—35 °C. The reaction was followed by n.m.r. and was complete after 30 h. The 2,3-dichloride (100% *trans* by n.m.r.) (73—85%), b.p. 60—63 °C/18 mmHg, n_D^{21} 1.4870 (lit.,[1] 63—66 °C/21 mmHg, n_D^{20} 1.4841) was red when iodine was used as the initiator, but colourless from the bromotrichloromethane reaction. 3-Chlorotetrahydrofuran (**19**) [*m/z*, 106, 108 (3:1) (M^+)] was also produced (10—15%) and was isolated by preparative g.l.c. (Carbowax 20M) from the forerun, b.p. 49—58 °C/18 mmHg. Spectral data for this were identical with those of an authentic sample.

Method B. Tetrahydrofuran (0.5—2 mol) was chlorinated with sulphuryl chloride (1 mol) at 65 °C using the method described by Nersasion.[33] When a fourfold excess (2 mol) of tetrahydrofuran was employed the 2,3-dichloride (100% *trans* by n.m.r.) (57—68%), b.p. 60—64 °C/20 mmHg, n_D 1.4840, was obtained relatively pure (Nersasion reports 79%, b.p. 50—53 °C/13 mmHg, n_D^{20} 1.4839). When equimolar, or a slight excess of, tetrahydrofuran was employed the 2,3-dichloride, b.p. 53—55 °C/13 mmHg, was contaminated with 2,3,3-trichlorotetrahydrofuran (**22**) (≤32% by n.m.r.). This side product was isolated by spinning band distillation, b.p. 69—72 °C/20 mmHg.

Reaction of 2,3-*Dichlorotetrahydrofuran with Tetraethylammonium Chloride.*—The 2,3-dichloride (5 g) was diluted with dry acetonitrile (5 cm^3) and saturated with tetraethylammonium chloride. The mixtures were kept for varying times and worked up. *cis*:*trans*-2,3-Dichlorotetrahydrofuran ratios were obtained through the intensities of the two 2-anomeric proton resonances, and *trans*-2,3-dichloro:2,3,3-trichlorotetrahydrofuran ratios through g.l.c. peak area ratios (Apiezon, 120 °C; the trichloride had the longer retention time).

2,3-*Dibromotetrahydrofuran.*—Bromine (9 g) was added dropwise to a stirred solution of 2,3-dihydrofuran (3.5 g) in dry carbon tetrachloride (10 cm^3) at 0 °C. Removal of the solvent under reduced pressure afforded the dibromide (100% *trans* by n.m.r.) in quantitative yield, *m/z* 149, 151 (1:1) ($M^+ - Br$).

cis- *and* trans-2-*Substituted* 3-*Halogenotetrahydro-pyrans and -furans. Analytical Procedure.*—The 2,3-dihalide (2 mmol) in dry ether or THF (2 cm^3) was added to a shaken solution of the Grignard reagent (6 mmol) (from an excess of magnesium turnings and alkyl bromide) in dry ether or THF (25 cm^3), with cooling (ice–water), under nitrogen. After the reaction had ceased the mixture was further shaken for 10 min and poured into ice–water, acidified, and extracted with ether. The ether solution was washed with aqueous alkali and water, dried, and evaporated. The residue was then analysed by g.l.c. (PEGA, 80—140 °C). Excepting R = Ar, only two major g.l.c. peaks were observed; the *trans*-isomers always possessed the shorter retention time. Isomer product ratios (±1% from an average of 2—3 readings) were obtained by taking ratios of relative peak areas. The validity of the method was confirmed for weighed mixtures.

cis- *and* trans-2-*Substituted* 3-*Halogenotetrahydro-pyrans and -furans. Substitution of the* 2,3-*Dihalides in Ether–Dioxane* ('R_2Mg') *Solvent.*—The Grignard reagent (6 mmol) was similarly prepared in dry ether (25 cm^3) and dry dioxane (large excess) added. The precipitated magnesium bromide–dioxane complex was not removed and the solution containing the dialkylmagnesium reagent was used directly (dialkylmagnesium formation does not appear to be reversible). The 2,3-dihalide

(2 mmol) in dry ether (2 cm^3) was added and the above procedure followed.

2-Alkyl(or Aryl)-3-chlorotetrahydropyrans: Preparative Procedure.—2,3-Dihydro-4*H*-pyran (1 mol) was chlorinated in dry ether (200 cm^3), to yield ethereal 2,3-dichlorotetrahydropyran (50% *trans*). Alkyl- (or aryl-) magnesium bromide (1.5 mol) was prepared in dry ether (300 cm^3) from magnesium (36 g) and the alkyl (or aryl) bromide (1.5 mol). This was cooled (ice), stirred, and the 2,3-dichloride added dropwise using more ether if necessary. After storage overnight, the reaction mixture was poured into ice–water, acidified with concentrated hydrochloric acid, and the aqueous phase extracted with ether. The ethereal solution was washed with aqueous alkali and water, dried, and evaporated. Fractional distillation afforded *cis*- and *trans*-2-alkyl-3-chlorohydropyrans.

2-Alkyl-(or Aryl)-3-chlorotetrahydrofurans.—Similarly, *trans*-2,3-dichlorotetrahydrofuran (1 mol) (prepared from the chlorination of THF in carbon tetrachloride in the presence of iodine) in dry ether (200 cm^3) was added dropwise to a rapidly stirred solution of the Grignard reagent (1.5 mol) in dry ether (300 cm^3).

2-Alkyl-3-bromotetrahydrofurans.—2,3-Dihydrofuran (1 mol) in dry ether (200 cm^3) was treated with bromine (1 mol), and an ethereal solution of the 2,3-dibromide added dropwise to a rapidly stirred solution of the Grignard reagent (1.5 mol) in dry ether (300 cm^3).

cis- *and* trans-3-*Chloro*-2-*methyltetrahydropyrans.*—The *cis*- and *trans*-pyrans [370 g, 74%, from 2,3-dihydro-4*H*-pyran (4 mol)], b.p. 50—75 °C/20 mmHg, were prepared using methylmagnesium bromide. Spinning band distillation afforded the *trans*-pyran, b.p. 153—155 °C (lit.,[47] 154 °C) [Found: M^+, 134, 136 (3:1). $C_6H_{11}ClO$ requires *M*, 134, 136 (3:1)], and the *cis*-pyran, b.p. 170—172 °C (lit.,[47] b.p. 172 °C) [Found: M^+, 134, 136 (3:1). $C_6H_{11}ClO$ requires *M*, 134, 136 (3:1)].

cis- *and* trans-3-*Chloro*-2-*ethyltetrahydropyrans.*—The *cis*- and *trans*-pyrans [208 g, 70%, from 2,3-dihydro-4*H*-pyran (3 mol)] b.p. 52—76°C/14 mmHg, were prepared using ethylmagnesium bromide. Spinning band distillation afforded the *trans*-pyran, b.p. 56—61 °C/14 mmHg, n_D^{24} 1.4550 (lit.,[26b] b.p. 69 °C/22 mmHg, n_D^{20} 1.4559) (Found: C, 56.6; H, 8.5. Calc. for $C_7H_{13}ClO$: C, 56.6; H, 8.6%), and the *cis*-pyran, b.p. 72—76 °C/14 mmHg, n_D^{24} 1.4621 (lit.,[26b] b.p. 84 °C/22 mmHg, n_D^{20} 1.4651) (Found: C, 56.7; H, 8.6%). A low b.p. side product obtained from the forerun by preparative g.l.c. (Carbowax 20M) was identified as 2-ethyltetrahydropyran (Found: M^+, 114.1049. Calc. for $C_7H_{14}O$: *M*, 114.1045); δ(CCl_4) 3.85 (1 H, dm, *J* 12 Hz), 3.4—2.85 (2 H, m), 1.9—1.1 (8 H, m), and 0.88 (3 H, t, *J* 7 Hz).

cis- *and* trans-3-*Chloro*-2-*isopropyltetrahydropyran.*—The *cis*- and *trans*-pyrans [72 g, 60%, from 2,3-dihydro-4*H*-pyran (0.75 mol)], b.p. 50—75 °C/22 mmHg (lit.,[5] b.p. 65—110 °C/12 mmHg) were not completely separated by fractional distillation (helices packed glass column). Further purification by preparative g.l.c. (PEGA) afforded the lower b.p. *trans*-isomer and the higher b.p. *cis*-isomer. A low b.p. side product obtained by preparative g.l.c. (PEGA) was identified as 2-isopropyltetrahydropyran (Found: M^+, 128.1215. Calc. for $C_8H_{16}O$: *M*, 128.1201), *m/z*, 85 (base peak) (corresponding to $M^+ - Pr^i$); δ($CDCl_3$) 3.98 (dm, $J_{6a,6e}$ 12 Hz, 6-He), 3.42 (m, *J* 12 Hz, 9.6 Hz, 6-Ha), 2.92 (ddd, *J* 10, 6.5, 1.6 Hz, 2-H), 1.93—1.05 (7 H, m), 0.93 (3 H, d, *J* 7 Hz), and 0.87 (3 H, d, *J* 7 Hz).

trans-3-*Chloro*-2-*Phenyltetrahydropyran.*—The *trans*-pyran [41 g, 65%, from 2,3-dihydro-4*H*-pyran (0.32 mol)], b.p. 82—84 °C/0.2 mmHg, m.p. 36—37 °C (lit.,[26a] m.p. 39.5—40.5 °C), with no *cis* material (by g.l.c. and n.m.r. analyses) was obtained.

trans-3-*Chloro*-2-p-*tolyltetrahydropyran.*—The trans-*pyran* [26 g, 61%, from 2,3-dihydro-4*H*-pyran (0.2 mol)], b.p. 85-87 °C/0.2 mmHg, n_D^{23} 1.5411 [Found: C, 68.5; H, 7.1%; M^+, 210, 212 (3:1). $C_{12}H_{15}ClO$ requires C, 68.5; H, 7.15%; *M*, 210, 212 (3:1)]; δ($CDCl_3$) 7.12 (4 H, m, ArH), 4.02 (d, *J* 9.8 Hz, 2-Ha), 4.05—3.15 (3 H, m), 2.27 (3 H, s, Me), and 2.40—1.46 (4 H, m); no *cis* product was obtained.

cis- *and* trans-3-*Chloro*-2-*vinyltetrahydropyrans.*—The *cis*- and *trans*-pyrans [37 g, 51%, from 2,3-dihydro-4*H*-pyran (0.5 mol)], b.p. 60—84 °C/15 mmHg, were obtained by reaction of the 2,3-dichloride (in diethyl ether) with vinylmagnesium bromide (in THF). Fractional distillation (helices column) did not completely separate the isomers. Further purification by preparative g.l.c. (PEGA) afforded the lower b.p. trans-*isomer*, [Found: C, 57.2; H, 7.5; M^+, 146, 148 (3:1). $C_7H_{11}ClO$ requires C, 57.3; H, 7.5%; *M*, 146, 148 (3:1)]; $\nu_{max.}$ 1 642 cm^{-1}, and the higher b.p. cis-*isomer* [Found: C, 57.15; H, 7.3%; M^+, 146, 148 (3:1). $C_7H_{11}ClO$ requires C, 57.3; H, 7.5%; *M*, 146, 148 (3:1)]; $\nu_{max.}$ 1 642 cm^{-1}.

[2-^{1}H]- *and* [2-^{2}H]-3-*Halogenotetrahydropyrans* (**39**)—(**41**).—3-Chlorotetrahydropyran was prepared by the method of Crombie *et al.*[12a] 2,3-Dichlorotetrahydropyran (16 g) (50% *trans*) in dry ether (35 cm^3) was treated with lithium aluminium hydride (1 g) in dry ether (40 cm^3) to give the monochloride (**39**) (9.3 g, 75%) b.p. 52—55 °C/14 mmHg, n_D^{20} 1.4619 (lit.,[12a] b.p. 52—54 °C/13 mmHg, n_D^{20} 1.4626) [Found: M^+, 120, 122 (3:1). C_5H_9ClO requires *M*, 120, 122 (3:1)].

Using identical conditions, the reaction of the 2,3-dichloride (16 g) (50% *trans*) with lithium aluminium deuteride (1 g) afforded 3-chloro[2-^{2}H]tetrahydropyran (**40**) and (**41**) (65—72% *trans*-2-De by n.m.r.) (10 g, 77%), b.p. 52—55 °C/14 mmHg [Found: M^+, 121, 123 (3:1). C_5H_8DClO requires *M*, 121, 123 (3:1)]. The deuterium orientation was estimated by n.m.r. integration of the multiplets at δ 4.07—3.68 (2-He) and 3.58—3.26 (2-Ha).

Similarly, the reaction of a freshly prepared ethereal solution of 2,3-dibromotetrahydropyran (88% *trans*) [from 2,3-dihydro-4*H*-pyran (0.2 mol) in dry ether (50 cm^3) and bromine (0.2 mol)] with lithium aluminium hydride (2 g) in dry ether (80 cm^3) gave 3-*bromotetrahydropyran* (24 g, 75%), b.p. 56 °C/16 mmHg, n_D^{23} 1.4940 [Found: C, 36.6; H, 5.5%; M^+, 164, 166 (1:1). C_5H_9BrO requires C, 36.4; H, 5.45%; *M*, 164, 166 (1:1)]; δ($CDCl_3$) 4.20—3.72 (3 H, m), 3.62—3.33 (2 H, m), 2.32 (1 H, equatorial, m), and 2.10—1.55 (3 H, m). The reaction with lithium aluminium deuteride yielded the 3-bromo[2-^{2}H]tetrahydropyran (65—70% *trans*-2-De by n.m.r. integration) (73%), b.p. 56 °C/16 mmHg, [Found: M^+, 165, 167 (1:1). C_5H_8BrDO requires *M*, 165, 167 (1:1)]; δ($CDCl_3$) 4.20—3.72 (2.30 H, m) and 3.62—3.33 (1.70 H, m). The [Eu(fod)$_3$]-shifted spectra of the 3-bromotetrahydropyrans were closely similar to those for the chlorides.

cis- *and* trans-3-*Chloro*-2-*methoxytetrahydropyrans* (**42**)—(**43**) *and* (**44**)—(**45**).—2,3-Dichlorotetrahydropyran (50% *trans*) (155 g) in dry ether (250 cm^3) was added dropwise to a stirred solution of sodium methoxide in methanol [from sodium (24.2 g) and methanol (500 cm^3)]. The mixture was refluxed (1.5 h), cooled, filtered, and the solvent evaporated. Distillation of the residue gave the chloro acetal (78% *cis*- by n.m.r.; 85 g, 57%), b.p. 74—75 °C/18 mmHg, n_D^{17} 1.4614 (lit.,[48] b.p. 74—75 °C/18 mmHg, n_D^{12} 1.4680); δ($CDCl_3$) 4.58 (d, *J* 2.8 Hz, *cis*-2-H), 4.40

(d, *J* 4.1 Hz, *trans*-2-H), 4.07—3.36 (6 H, m), 3.42 (s, MeO), and 2.38—1.54 (4 H, m).

cis- *and* trans-3-*Bromo*-2-*methoxytetrahydropyran*.—Low temperature bromomethoxylation of 2,3-dihydro-4*H*-pyran (1 mol) using the procedure of Sweet and Brown,[49] afforded the bromoacetal (22%), b.p. 48—49 °C/0.6 mmHg, $n_D^{17.5}$ 1.4869; δ($CDCl_3$) 4.62 (d, *J* 2.8 Hz, *cis*-2-H), 4.52 (d *J* 4.5 Hz, *trans*-2-H), 4.20—3.40 (6 H, m), 3.44 (s, MeO), and 2.58—1.34 (4 H, m). Integration of the 2-proton doublets showed the *trans*-isomer to be formed as 73% of the mixture (Sweet and Brown[49] report an 83% yield of pure *trans*-product, b.p. 87 °C/12 mmHg, n_D^{25} 1.4843).

cis- *and* trans-3-*Chloro*-2-*methyltetrahydrofurans*.—Reaction of *trans*-2,3-dichlorotetrahydrofuran with methylmagnesium bromide gave *cis*- and *trans*-3-chloro-2-methyltetrahydrofurans (131 g, 59%, from 1.84 mol of 2,3-dichloride), b.p. 32—43 °C/14 mmHg. Spinning band distillation gave the *trans*-isomer, b.p. 45—50 °C/28 mmHg, n_D^{20} 1.4408 (lit.,[1] b.p. 130 °C, n_D^{20} 1.4420) [Found: M^+, 120, 122 (3:1). Calc. for C_5H_9ClO: *M*, 120, 122 (3:1), and the *cis*-isomer, b.p. 62—64 °C/28 mmHg, n_D^{20} 1.4531 (lit.,[1] b.p. 145 °C, n_D^{20} 1.4520) [Found: M^+, 120, 122 (3:1). Calc. for C_5H_9ClO: *M*, 120, 122 (3:1)]. Spinning band distillation was more efficient at atmospheric pressure *cis*- (b.p. 146—147 °C) and *trans*- (b.p. 129—131 °C). Reaction of 2,3-dichlorotetrahydrofuran containing some 2,3,3-trichlorotetrahydrofuran (**22**) ('Nersasion product') with methylmagnesium bromide yielded 3-chloro-4,5-dihydrofuran (**21**) as a side product, isolated by preparative g.l.c. (Apiezon) from the forerun, b.p. 30—32 °C/14 mmHg, n_D^{20} 1.4632 (lit.,[50] b.p. 56 °C/100 mmHg, n_D^{20} 1.4642) [Found: M^+, 104.0025, 106.9992 (3:1). Calc. for C_4H_5ClO: *M*, 104.0028, 106.9997 (3:1)]; $\nu_{max.}$ 1 640 cm^{-1}; δ(CCl_4), 6.29 (1 H, t, *J* 2 Hz, olefinic), 4.38 (2 H, t, *J* 9 Hz, CH_2O), and 2.78 (2 H, td, *J* 9, 2 Hz).

cis- *and* trans-3-*Chloro*-2-*isopropyltetrahydrofurans*.—Reaction of *trans*-2,3-dichlorotetrahydrofuran with isopropylmagnesium bromide yielded *cis*- and *trans*-3-chloro-2-isopropyltetrahydrofurans (56%, from 0.85 mol 2,3-dichloride), b.p. 63—80 °C/25 mmHg. Spinning band distillation gave the *cis*-isomer, b.p. 75—80 °C/25 mmHg, n_D^{20} 1.4599 (lit.,[12a] b.p. 178 °C, n_D^{19} 1.4568), and the *trans*-isomer, b.p. 63—68 °C/25 mmHg, n_D^{20} 1.4471 (lit.,[12a] b.p. 164 °C, n_D^{19} 1.4482).

trans-3-*Chloro*-2-*aryltetrahydrofurans*.—Reaction of *trans*-2,3-dichlorotetrahydrofuran with phenylmagnesium bromide yielded *trans*-3-chloro-2-phenyltetrahydrofuran (45 g, 65%, from 0.35 mol, 2,3-dichloride), b.p. 130—132 °C/15 mmHg, n_D^{23} 1.5411 (lit.,[51] b.p. 129—130 °C/14 mmHg). Similar reaction with *p*-tolylmagnesium bromide gave trans-3-*chloro*-2-p-*tolyltetrahydrofuran* (54%, from 0.2 mol 2,3-dichloride), b.p. 121—122 °C/3.5 mmHg, n_D^{23} 1.5372 [Found: C, 66.9; H, 6.9%; M^+, 196, 198 (3:1). $C_{11}H_{13}ClO$ requires C, 67.1; H, 6.6%; *M*, 196, 198 (3:1)]; δ($CDCl_3$) 7.20 (4 H, AA'BB' q, ArH), 4.94 (1 H, d, *J* 4.5 Hz, 2-H), 4.16 (3 H, m, 3-H, 5-H, 5'-H), and 2.64—1.98 (5 H, m, with 3 H, s, Me at 2.32).

cis- *and* trans-3-*Chloro*-2-*vinyltetrahydrofurans*.—Reaction of *trans*-2,3-dichlorotetrahydrofuran (in THF) with vinylmagnesium bromide (in THF) yielded cis- and trans-3-*chloro*-2-*vinyltetrahydrofurans* (58%, from 0.5 mol 2,3-dichloride), b.p. 47—62 °C/15 mmHg [Found: C, 54.4; H, 6.5%; M^+, 132, 134 (3:1). C_6H_9ClO requires C, 54.3; H, 6.8%; *M*, 132, 134 (3:1)]. Fractional distillation (helices column) was not efficient and the isomers were further purified by preparative g.l.c. (PEGA) to give the *cis*-furan (b.p. 58—62 °C/15 mmHg), $\nu_{max.}$ 1 643 cm^{-1}, and the *trans*-furan (b.p. 47—52 °C/15 mmHg), $\nu_{max.}$ 1 642 cm^{-1}. The low b.p. *trans*-isomer had the shorter g.l.c. retention time.

cis- *and* trans-2-*Allyl*-3-*chlorotetrahydrofurans*.—Reaction of *trans*-2,3-dichlorotetrahydrofuran with allylmagnesium chloride (from allyl chloride and magnesium powder in ether at ice temperature) gave *cis*- and *trans*-2-allyl-3-chlorotetrahydrofurans (62%, from 0.5 mol of 2,3-dichloride), b.p. 74—80 °C/21 mmHg. G.l.c. analysis (PEGA) showed the *cis*-isomer to constitute 86% of the mixture. Preparative g.l.c. (PEGA) yielded the trans-*furan* [(Found: C, 57.0; H, 7.5. $C_7H_{11}ClO$ requires C, 57.3; H, 7.5%), $\nu_{max.}$ 1 640 cm^{-1}], and the cis-*furan* [(Found: C, 56.9; H, 7.3. $C_7H_{11}ClO$ requires C, 57.3; H, 7.5%), $\nu_{max.}$ 1 640 cm^{-1}]. Fractional distillation gave the *cis*-furan, b.p. 78—80 °C/21 mmHg, and the *trans*-furan, b.p. 70—73 °C/21 mmHg.

cis- *and* trans-3-*Chloro*-2-*propyltetrahydrofurans*.—Reaction of 2,3-dichlorotetrahydrofuran with propylmagnesium bromide yielded cis- and trans-3-*chloro*-2-*propyltetrahydrofurans* (18.6 g, 63%, from 0.2 mol 2,3-dichloride), b.p. 63—75 °C/15 mmHg (Found: C, 56.2; H, 8.7. $C_7H_{13}ClO$ requires C, 56.5; H, 8.75%). Fractional distillation gave the *trans*-furan, b.p. 63—64 °C/15 mmHg, and the *cis*-furan, b.p. 74—75 °C/15 mmHg.

Hydrogenation of cis- *and* trans-2-*Allyl*-3-*chlorotetrahydrofuran*.—The *cis*-allyl compound (5.4 g) was hydrogenated over 10% palladium-on-charcoal in methanol (50 cm^3) until hydrogen uptake was complete. The mixture was filtered and distilled to give *cis*-3-chloro-2-propyltetrahydrofuran (4.4 g, 79%), b.p. 72—76 °C/15 mmHg, identical with that described above (i.r. n.m.r., g.l.c. retention time).

Similar hydrogenation of the *trans*-allyl compound (300 mg) followed by preparative g.l.c. isolation (PEGA) of the product gave *trans*-3-chloro-2-propyltetrahydrofuran (122 mg), identical with that described above (i.r., n.m.r., g.l.c. retention time).

cis-3-*Chloro*-2-*tetrahydrofurylacetic Acid* p-*Bromophenacyl Ester* (**34**).—*cis*-2-Allyl-3-chlorotetrahydrofuran (6 g) in methanol (50 cm^3) was cooled to −60 °C and a mixture of O_2–O_3 (1 dm^3/min) passed into the stirred solution. The reaction was monitored by t.l.c. [SiO_2, benzene–ethyl acetate (9:1)] and when complete, dimethyl sulphide (4.5 cm^3) was added. The mixture was stirred until it attained room temperature and then concentrated under reduced pressure, extracted with light petroleum (b.p. 40—60 °C), and the extract washed with water and dried. Evaporation of the solvent gave a crude mixture of 3-chlorotetrahydro-2-furylacetaldehyde and its corresponding acid. The mixture was refluxed in the presence of potassium permanganate (30 min). Excess of permanganate was destroyed (sodium hydrogen sulphite) and the mixture concentrated under reduced pressure, extracted with light petroleum (b.p. 40—60 °C) and the extract washed with water and dried. Evaporation of the solvent gave *cis*-3-chlorotetrahydro-2-furylacetic acid (**33**), which was purified as its p-*bromophenacyl ester* by p.l.c. [silica gel HF_{254}, benzene–ethyl acetate (9:1)]. Recrystallisation from ethanol afforded the pure ester (**34**) [920 mg] as colourless plates, m.p. 105 °C (EtOH) (Found: C, 46.2; H, 3.9. $C_{14}H_{14}O_4BrCl$ requires C, 46.5; H, 3.9%), *m/z*, 183, 185 (1:1) (base peaks; no parent ion was observed); $\nu_{max.}$(KBr) 1 741, 1 699 cm^{-1}; $\lambda_{max.}$($CHCl_3$) 259 nm (ε 18 200); δ(CD_3COCD_3), 7.87 (4 H, AA'BB' q, ArH), 5.45 (2 H, s, CO_2CH_2CO), 4.77 (ddd, 1 H, *J* 3.3, 2.6, 1.5 Hz, 3-H), 4.33 (1 H, td, $J_{2,2}$ 6.8 Hz, $J_{2,3}$ 3.3 Hz, 2-H), 4.2—3.6 (2 H, 9 lines, 5-H_2, 2.86 (2 H, d, $J_{2',2}$ 6.8 Hz, CH_2CO_2), 2.65 (m, 4-H), and 2.22 (dddd, *J*, 14, 7.5, 4, 1.5 Hz, 4-H).

trans-3-*Chloro*-2-*cyano*-, 2-*Acetyl*-3-*chloro*-, *and* 2-*Benzoyl*-3-*chlorotetrahydrofurans*.—*trans*-2,3-Dichlorotetrahydrofuran

(70 g) and dry cuprous cyanide (60 g) were heated at 100 °C on a steam-bath for 3 h with stirring. On cooling, ether was added and the mixture filtered through Supercel. Evaporation and distillation gave *trans*-3-chloro-2-cyanotetrahydrofuran (39 g, 60%), b.p. 92—93 °C/17 mmHg (lit.,[52] b.p. 87 °C/13 mmHg) [M^+, 131, 133 (3:1). C_5H_6ClNO requires M, 131, 133 (3:1)]; δ($CDCl_3$) 4.80 (1 H, d, $J_{2,3}$ 2.1 Hz, 2-H), 4.72 (1 H, overlapped, dd, J 6, 2.1 Hz, 3-H), 4.22 (2 H, dd, J 8, 6 Hz, 5-H_2), and 2.9—2.1 (2 H, m, 4-H_2).

Reaction of methylmagnesium iodide with *trans*-3-chloro-2-cyanotetrahydrofuran yielded the unstable *trans*-2-acetyl-3-chlorotetrahydrofuran (56%) [Found: M^+, 132, 134 (3:1). C_6H_9ClO requires M, 132, 134 (3:1)]. Rapid short path distillation (air bath, temp. 60 °C/14 mmHg) gave a colourless product, $\nu_{max.}$ 1 721 (CO); δ($CDCl_3$) 4.63 (1 H, quintet, J 5, 3, 2.5 Hz, 3-H), 4.50 (1 H, d, $J_{2,3}$ 2.5 Hz, 2-H), 4.28—4.12 (2 H, m, 5-H_2) and 2.40—2.16 (5 H, m, with 3 H, s, Me at 2.26). The sample decomposed within a few hours.

Similarly, *trans*-2-benzoyl-3-chlorotetrahydrofuran was prepared using phenylmagnesium bromide, m.p. 40 °C (EtOH) (lit.,[52] m.p. 52 °C), $\nu_{max.}$ 1 684 cm^{-1} (CO); δ($CDCl_3$) 8.01 (2 H, m, ArH), 7.48 (3 H, m, ArH), 5.32 (1 H, d, $J_{2,3}$ 2.0 Hz, 2-H), 4.80 (1 H, dd, J 5.5, 2 Hz, 3-H), 4.24—4.08 (2 H, m, 5-H_2), and 2.60—1.05 (2 H, m, 4-H_2).

[2-^{1}H]- *and* [2-^{2}H]-3-*Chlorotetrahydrofurans*.—Treatment of *trans*-2,3-dichlorotetrahydrofuran (16 g) with lithium aluminium hydride (1 g) in ether,[12a] afforded 3-chlorotetrahydrofuran (9 g, 75%), b.p. 54—58 °C/25 mmHg, n_D^{20} 1.4538 (lit.,[12a] b.p. 59—61 °C/30 mmHg, n_D^{20} 1.4532) [Found: M^+, 106, 108 (3:1) C_4H_7ClO requires M, 106, 108 (3:1)]. Similar reaction with lithium deuteride gave 3-chloro[2-^{2}H]tetrahydrofuran (75%), b.p. 54—58 °C/25 mmHg [Found: M^+, 107, 109 (3:1). C_4H_6DClO requires M, 107, 109 (3:1).

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