

STEREOCHEMISTRY OF CYCLIC ETHER FORMATION—II¹

INTRAMOLECULAR CYCLISATION OF SECONDARY ALIPHATIC ALCOHOLS TO TETRAHYDROFURAN-TYPE ETHERS

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Abstract—The mechanism and stereochemistry of δ -C atom functionalisation in the reactions of secondary straight-chain aliphatic alcohols with lead tetraacetate, ceric ammonium nitrate, and heavy metal (Pb^{2+} , Hg^{2+} , Ag^+) salts (AcO^- , O^{2-} , CO_3^{2-})-halogen (I_2 , Br_2 , Cl_2) combinations are discussed. By demonstrating the intermediacy of 5-bromo-2-hexanol, it was confirmed that the dark silver oxide-bromine induced cyclisation of 2-hexanol (and alcohols in general) involves (as the other hypohalite reactions) intramolecular 1,5-hydrogen abstraction by alkoxy radicals and formation of δ -bromohydrins. A novel and simple procedure for obtaining tetrahydrofurans from alcohols by way of the hypochlorite reaction, using silver or mercuric salts and chlorine, is described.

In Part I¹ we discussed the steric and mechanistic aspects of eliminative cyclisations of diastereomeric aliphatic disubstituted 1,4-diols and their mono- and disulphonate esters, which were all found to proceed with inversion of configuration at one (1,4-diols) or both (1,4-disulphonates) chiral centres, to give stereoselectively *cis*- or *trans*-2,5-dialkyl-tetrahydrofurans.[†]

We now wish to report some pertinent observations concerning the mechanism and stereochemistry of another approach to 2,5-dialkyl-tetrahydrofuran ring closure, which consists (Scheme 1) of intramolecular cyclisation of aliphatic unbranched secondary monohydric alcohols (1) by way of oxidative functionalisation of a non-activated δ -C atom, whereby 5-membered cyclic

ethers (7) are formed, either directly (pathway 1) (with lead tetraacetate or ceric ammonium nitrate) or via δ -halohydrin intermediates (6, pathway 2) (with heavy metal salts + halogen).

1. Ring closure via δ -carbonium ions (5)

With lead tetraacetate. With this reagent in unpolar solvents (benzene) cyclisations of unbranched 2-, 3- and 4-alkanols (1) (such as 2-hexanol, 2- and 3-heptanol, 2-, 3- and 4-octanol, 3-, 4- and 5-nonanol, 2-decanol, etc) are non-stereoselective,^{3,4} but always, either under thermal (at 80°)^{3,5} or UV-photolytic (at 18°)^{4,6} conditions, the mixture of diastereomeric 2,5-dialkyl-tetrahydrofurans (7) (which is usually obtained in 38–48% yield) contains the *trans*-isomer in excess, the *cis*:*trans* ratio being in the range 40–45:60–55. According to the mechanism proposed for this reaction (Scheme 1, pathway 1),^{3,4,7} the crucial step is the intramolecular 1,5-hydrogen abstraction from the δ -carbon by alkoxy radical (step 3 \rightarrow 4). On the basis of conformational models of the alkoxy radical (3), shown on Scheme 2, in the most favourable conformation (3-A'GA'') \ddagger for this homolytic 1,5-transfer, that δ -H atom is abstracted which has the same prochirality (pro-*R* or pro-*S*) as the configuration (*R* or *S*) of the chiral carbinol (α) C atom, whereas in the other, because of the *gauche* *n*-butane-type R''/C_{β} -H interaction, somewhat less stable conformation (3-A'GG''), \ddagger the δ -hydrogen of opposite prochirality (with respect to the α -carbon configuration) will be transferred. \S Independently of conformational considerations, this has been recently confirmed by kinetic studies, \S which have shown that in the 2-hexyloxy radical (3a) generated from (*R*)-2-hexanol (1a)[†] the pro-(*R*) δ -

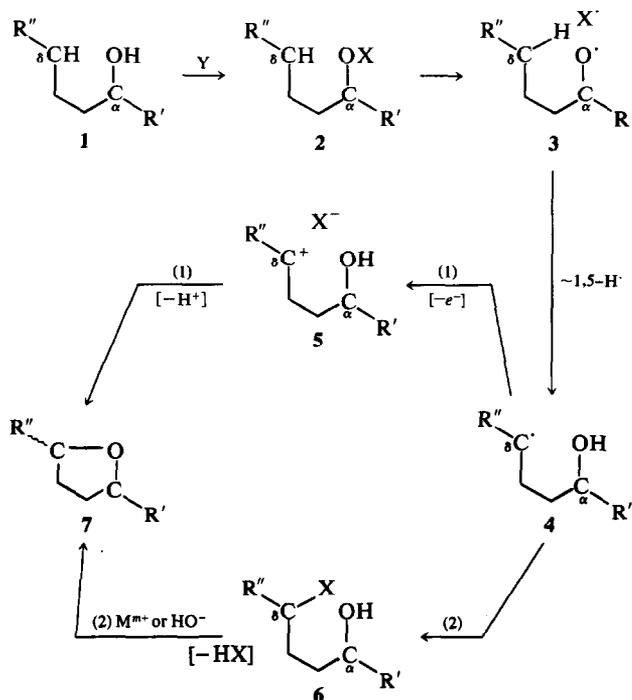
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[†]Mechanism and stereochemistry of various procedures for tetrahydrofuran formation from a primary-tertiary 1,4-diol have also been recently considered.²

\ddagger Abbreviations for conformations discussed in the text and given in Schemes 2 and 4: A' = *anti*-R'/CH₂(γ), G = *gauche*-CH₂(α)/CH₂(δ), A'' = *anti*-CH₂(β)/R'', G'' = *gauche*-CH₂(β)/R''.

\S Two other conformations of the alkoxy radical (3), with a *gauche* R'/CH₂(γ) arrangement (G'), may also be envisaged for the 1,5-abstraction process (3 \rightarrow 4). However, since these conformations are either of similar stability (G'GA'') as, or less stable (G'GG'') than, the conformation of minor importance (3-A'GG'') and cannot alter seriously the steric course of the 1,5-hydrogen migration discussed above, they can be disregarded in the approximate and qualitative considerations of this process.

[†]By means of lead tetraacetate or silver oxide-bromine.



(a) $R' = R'' = \text{Me}$; (b) $R' = \text{Me}, R'' = \text{Pr}$; (c) $R' = R'' = \text{Et}$

(A) $X = \text{I}$; (B) $X = \text{Br}$; (C) $X = \text{Cl}$

(1) $Y = \text{Pb}(\text{OAc})_4, X = \text{Pb}(\text{OAc})_3$
 $Y = (\text{NH}_4)_2[\text{Ce}(\text{NO}_3)_6], X = \text{Ce}(\text{NO}_3)_3 (?)$

(2) $Y = \text{M}_2\text{Z}_m + \text{X}_2$

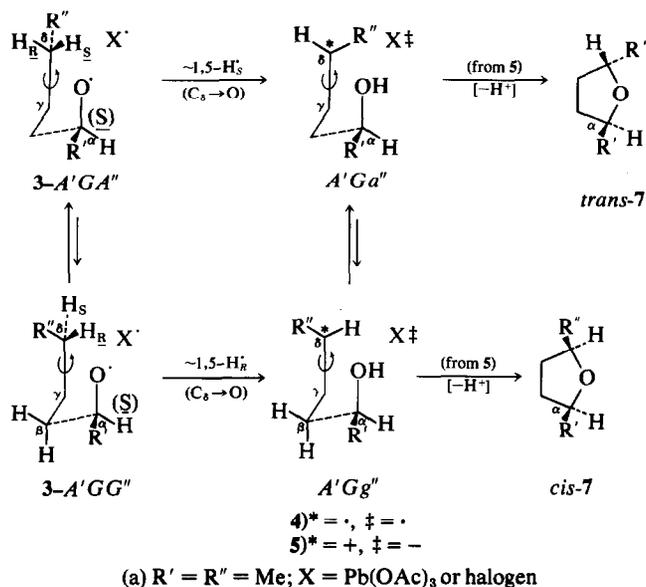
| | | | |
|-----|-------------------------|-------------------------|------------------------|
| M = | Pb^{IV} | Hg^{II} | Ag^{I} |
| Z = | OAc | O, OAc | O, OAc, CO_3 |
| X = | I | I, Br, Cl | I, Br, Cl |

SCHEME 1

hydrogen is abstracted preferentially. Of the two conformations ($A'Ga''$) and ($A'Gg''$) shown on Scheme 2 for the δ -hydroxycarbon radical (4) and the corresponding δ -carbonium ion (5), which are derived from the respective conformations ($A'GA''$) and ($A'GG''$) of the alkoxy radical (3) and which can naturally interconvert by rotation about $C_\gamma-C_\delta$, conformation ($A'Ga''$) is somewhat more stable (because of the quasi-*gauche* *n*-butane-type $R''/C_\beta-H$ interaction in $A'Gg''$), and therefore one would expect the *trans*-ether (t-7) to be formed in a small excess over the *cis*-ether (c-7); that, as mentioned above, is actually the case. A similar *cis* : *trans* ratio (46 : 54) was also observed for the diastereomeric mixture of 2,5-dimethyltetrahydrofuran (7a) obtained (in practically quantitative yield) by heating 5-hexen-2-ol with 20% sulphuric acid, an acid-catalysed intramolecular cycloaddition reaction characteristic for δ,ϵ -unsaturated al-

cohols⁹ which is known to proceed by way of carbon cations (in our case the δ -carbonium ion 5a). These results, once again, strongly support the intermediacy of δ -hydroxy-carbonium ions (5) in the lead tetraacetate reaction of conformationally flexible alcohols.^{3,4,7}

With ceric ammonium nitrate. Little is known about the cyclisation of alcohols with cerium(IV) salts (only 1-pentanol was used as substrate).¹⁰ In our hands, ceric ammonium nitrate reacted with secondary alcohols (1), such as 3-octanol and 2-decanol, in aqueous acetonitrile at 70–85°,¹⁰ to give in rather poor yield (10–15%) the corresponding 2,5-dialkyl-tetrahydrofurans (7). From the reported properties and behaviour of ceric ions in organic oxidation processes¹¹ and the fact that the *cis* : *trans* ratio of the diastereomeric ethers (7) obtained was again in favour of the *trans*-isomer (47–48 : 53–52), it appears that this cyclisation probably resembles



SCHEME 2

the lead tetraacetate reaction (Scheme 1, pathway 1) and also involves intermediate species with δ -carbonium ion character of type 5.

2. Ring closure via δ -halohydrins (6)

The hypiodite reaction. The lead tetraacetate-iodine reagent has found broad applicability for the δ -C atom functionalisation and intramolecular ether formation in polycyclic systems, particularly in steroid alcohols which are conformationally rigid at one or both reacting centres (hydroxyl oxygen and/or δ -C atom).¹²⁻¹⁴ Except in the particular case of 24-cholanol, in which a tertiary δ -C atom as part of the flexible OH containing side-chain is attacked,^{15,*} conformationally mobile acyclic alcohols have not been hitherto used as substrates for this reaction. We have now found that unbranched secondary aliphatic alcohols (1), such as 2- and 3-octanol, could be converted by lead tetraacetate-iodine in cyclohexane[†] to the corresponding 2,5-dialkyl-tetrahydrofurans (7) in satisfactory yields of about 70% (Table 1).

Other metal salts (i.e. of Hg^{II} and Ag^{I}) in combi-

nation with iodine can also* be used for effecting cyclisation of cyclic, polycyclic and open chain alcohols by way of the hypiodite reaction,^{12-14, 16, 17} and Table 1 contains some examples of 2,5-diethyl-tetrahydrofuran (7c) formation from 3-octanol (1c) by means of iodine and mercuric salts (oxide, acetate) or silver salts (oxide, acetate), which were selected from a series of experiments performed in our laboratories.‡ As can be seen, good yields of ether product (7c) (except with silver oxide) were obtained under thermal conditions assisted by irradiation with incandescent light (UV light did not improve cyclisation).

The hypobromite reaction, using as reagent bromine in combination with mercuric (oxide, acetate) or silver (oxide, acetate, carbonate) salts, represents an alternative procedure for producing five-membered cyclic ethers (7) from alcohols (1).^{8,9, 13b, 16, 18-25} § The results obtained by applying this method to straight-chain 2- and 3-alkanols are given in Table 2. The following observations, concerning the formation of 2,5-dialkyl-tetrahydrofurans (7), should be mentioned: (i) The yields of ether products (7) do not depend markedly on the presence (diffuse daylight) or absence of light (dim light or dark),¹⁶ on the solvent used (pentane, cyclohexane or carbon tetrachloride), on the reaction temperature (0°, room temperature or 35°),¹⁶ on the rate of bromine addition; (ii) however, the ether yield is influenced by the quality of the metal oxides (and other salts) particularly silver oxide (freshly prepared, air or vacuum dried compounds kept in the dark are more efficient than commercial products),¹⁶ and, in the case of silver oxide, can be increased by the addition of tetrahydrofuran²² or pyridine; (iii)

*Whereby a mixture of unsubstituted and β -iodo-ethers is formed in 80% yield.

†In benzene as solvent the yield of ether products (7) was considerably lower.^{12, 14}

‡Ring closure of 2-octanol with mercuric oxide-iodine was described previously.¹⁶

§In addition to heavy metal compounds-halogen, other reagents have been also used for the conversion of alcohols (1) via hypohalites (2) to cyclic ether products (7), such as N-iodo- or N-bromosuccinimide and iodine,^{14, 26} *t*-butyl hypochlorite-iodine,^{13b, 27} and potassium *t*-butoxide and iodine or bromine.^{13b, 27}

Table 1. The hypiodite reaction with 3-octanol (1c)

| Run | Reaction conditions ^a (ROH:metal salt:I ₂) ^b | Time ^c (hr.) | Products ^d and yields (%) ^e | | |
|-----|---|--|---|------------|--|
| | | | 2,5-Diethyl- tetrahydrofuran (7c) (<i>cis-trans</i> ratio) | 3-Octanone | Unreacted alcohol (1c) + acetate |
| | | <u>Pb(OAc)₄+I₂^f</u> | | | |
| 1. | Cyclohexane, Δ, <i>i-hν</i> (1:4:1·2)+CaCO ₃ (4) | 2 | 73* (59:41) | — | 21 |
| 2. | Cyclohexane, Δ, <i>i-hν</i> (1:4:1·2)+CaCO ₃ (4) | 2 | 75 ^h (61:39) | — | 17 |
| 3. | Cyclohexane, 20°, <i>i-hν</i> (1:2·8:1·3) | 12 | 50 (61:39) | 4 | 26 |
| 4. | Benzene, Δ, <i>i-hν</i> (1:3:1·2) | 8·5 | 30 (55:45) | 17 | 38 |
| | | <u>HgO^g+I₂ⁱ</u> | | | |
| 5. | CCl ₄ , Δ, <i>i-hν</i> (1:3:4) | 6 | 78 (57:43) | 10 | 5 ^k |
| 6. | CH ₂ Cl ₂ , 20°, UV- <i>hν</i> (1:3:2·7) | 6 | 74 (57:43) | 7 | 7 ^k |
| | | <u>Hg(OAc)₂^j+I₂</u> | | | |
| 7. | Cyclohexane ^m , Δ, <i>i-hν</i> (1:3:2·7) | 5·5 | 73 (53:47) | 6 | 9 |
| | | <u>Ag₂O^g+I</u> | | | |
| 8. | Cyclohexane ^m , Δ, <i>i-hν</i> (1:3:2) | 6·5 | 33 (55:45) | 22 | 30 ^k |
| | | <u>AgOAc^g+I₂</u> | | | |
| 9. | Cyclohexane ^m , Δ, <i>i-hν</i> (1:4:2) | 1 | 74 (53:47) | 10 | 8 |

^aSolvent, temperature (Δ = reflux), irradiation (*i-hν* = incandescent light, i.e. 250–500 w. tungsten lamp; UV-*hν* = UV light, i.e. high pressure mercury lamp). Runs were usually performed with 15 mmoles of alcohol (1) in 150–250 ml of solvent.

^bMolar ratio of reactants.

^cUntil disappearance of iodine colour.

^dMajor products.

^eMean values from at least two identical runs. Yields calculated from analytical gas chromatograms.

^fWith 2-octanol (1b), under conditions of run 1, the yield of 2-methyl-5-propyltetrahydrofuran (7b) was 76% and the *cis:trans* ratio 59:41.

^gUnder conditions of run 1, but with a 1:3:1·3 molar ratio of reactants (ROH:Pb(OAc)₄:I₂) and without added CaCO₃, the reaction time was 5·5 hr. and the yield of ether product (7c) 67% (*cis:trans* ratio = 59:41).

^hUpon treatment of the reaction mixture with 10% methanolic KOH.

ⁱPrepared as described previously.¹⁶

^jThis reaction with 2-octanol (1b) afforded 61% of corresponding tetrahydrofuran (7b)¹⁶ in a *cis-trans* ratio of 58:42.

^kOnly alcohol (1c).

^lDried commercial or freshly prepared product.

^mPentane is unsuitable as solvent for this reaction.

the yields of ether products (7), as noted previously,²³ are particularly high with silver acetate and nearly quantitative with silver carbonate.

The hypochlorite reaction. When alkyl hypochlorites (2C, Scheme 1) derived from secondary (and primary) aliphatic alcohols (1) are decomposed photolytically (or thermally), they rearrange to (in some cases isolable) δ-chlorohydrins (6C),^{28,29} which cyclise in the presence of base to ether products (7).²⁹ However, the applicability of this interesting and efficient reaction leading to tetrahydrofurans is somewhat limited by the rather elaborate technique required for the preparation of sensitive secondary alkyl hypochlorites (2C), which involves treatment

of alcohols (1) with preformed hypochlorous acid in the dark at 0°, etc.²⁸⁻³⁰ We have now found that the hypochlorite reaction, as a method of preparative value for the synthesis of cyclic ethers (7), could be readily and conveniently achieved, without special precautions (Table 2), by simple addition of a solution of chlorine in carbon tetrachloride (in dim light and at room temperature) to a mixture of 2- or 3-alkanol (1) and silver or mercuric salt in the same solvent, followed by treatment (without isolation of the δ-chlorohydrin (6C) produced with base, (or, in the case of silver salts, by prolonged stirring of the original reaction mixture). The yields of tetrahydrofurans (7) obtained by this procedure (Table 2,

Table 2. The hypobromite and hypochlorite reaction with 2-alkanols (1)

| Run | Alcohol (1) (Change of conditions) | Products ^a and yields (in %) ^b | | |
|--|---|--|---------------------|--------------------------|
| | | 2,5-Dialkyl- tetrahydrofuran (7) (<i>cis-trans</i> ratio) | Ketone ^c | Unreacted alcohol (1) |
| <u>HgO^d + Br₂^e</u> | | | | |
| 1. | 2-Hexanol (1a) | (7a) 71 (57:43) | 3 | 16 |
| 2. | 2-Octanol (1b) | (7b) 63 (61:39) | 10 | 15 |
| 3. | 2-Octanol (1b) (+ CaCO ₃ , 2 mol. equiv.) | (7b) 66 (60:40) | 5 | 20 |
| 4. | 3-Octanol (1c) | (7c) 75 (61:39) | 6 | 13 |
| 5. | 3-Octanol (1c) (i-hν, 1.5 hr) ^f | (7c) 67 (62:38) | 10 | 17 |
| <u>Ag₂O^d + Br₂^{e,g}</u> | | | | |
| 6. | 2-Hexanol (1a) | (7a) 48 (54:46) | 22 | 20 |
| 7. | 2-Octanol (1b) | (7b) 49 (56:44) | 20 | 24 |
| 8. | 3-Octanol (1c) | (7c) 47 (53:47) | 19 | 29 |
| 9. | 3-Octanol (1c) (+ THF, 2 mol. equiv) | (7c) 62 (53:47) | 8 | 12 |
| 10. | 3-Octanol (1c) (+ pyridine, 2 mol. equiv) | (7c) 60 (55:45) | 12 | 12 |
| <u>AgOAc + Br₂^{e,h}</u> | | | | |
| 11. | 2-Octanol (1b) | (7b) 72 (53:47) | 5 | 15 ⁱ |
| 12. | 3-Octanol (1c) | (7c) 74 (54:46) | 4 | 14 ⁱ |
| <u>Ag₂CO₃ + Br₂^{e,h}</u> | | | | |
| 13. | 2-Hexanol (1a) | (7a) 97 (55:45) | 3 | — |
| 14. | 2-Octanol (1b) | (7b) 96 (53:47) | 3 | — |
| 15. | 3-Octanol (1c) | (7c) 97 (53:47) | 2 | — |
| <u>HgO^d + Cl₂^j</u> | | | | |
| 16. | 2-Hexanol (1a) | (7a) ^k 43 (54:46) | 20 | 28 |
| 17. | 2-Octanol (1b) | (7b) ^k 52 (53:47) | 12 | 26 |
| <u>Ag₂CO₃ + Cl₂^j</u> | | | | |
| 18. | 2-Octanol (1b) | (7b) ^k 44 (52:48) | 23 | 27 |

^aMajor products.

^bMean values from two or more identical runs. Yields calculated from analytical gas chromatograms.

^cCorresponding to starting alcohol.

^dPrepared as described previously.¹⁶

^eReaction conditions: pentane as solvent, temp. 20°, dim light (flask protected by black paper) or diffuse (indirect) light (runs 5, 9, 10, 12), molar ratio ROH: metal salt: Br₂ = 1:2:1:2. The use of CCl₄ or cyclohexane as solvent had no noticeable effect on product distribution.

^fIrradiated with incandescent light after addition of bromine. In this reaction the yield of ether (7) was usually nor markedly affected by heat, light or subsequent treatment with 10% aqueous KOH.

^gThe quality of Ag₂O has a marked influence on product distribution.^{16,22,23} The effect of light, temperature and solvent polarity in this reaction was discussed previously.^{16,22,23,25}

^hReproducibly good results in ether yield were obtained with these combinations, using either commercial or freshly prepared silver compounds.^{23,25}

ⁱAlcohol (1) and its acetate.

^jReaction conditions: CCl₄ as solvent, temp. 20°, dim light (flask protected by black paper) or dark, molar ratio ROH: metal salt: Cl₂ = 1:2:2.5, chlorine was added as a 5% carbon tetrachloride solution.

^kAfter treatment of the reaction mixture (which contains the δ-chlorohydrin 6c) with 2N aqueous sodium hydroxide.

runs 16, 17 and 18) can be probably improved, by looking for and selecting optimal reaction conditions (in the present study no efforts have been made in this direction).

The mechanistic course of the hypohalite reactions leading to cyclic ether products (**7**) has been established to proceed according to Scheme 1, pathway 2, for the case of the hypochlorite reaction ($X = Cl$), by preparing hypochlorites (**2C**) and isolating the δ -chloro alcohols (**6C**), whereby the intramolecular rearrangement **2** \rightarrow **6** is induced by light (visible or UV), heat or is silver-catalysed,^{13, 24, 28-30} and also, very probably, for the case of the *mercuric oxide-bromine* induced hypobromite reaction ($X = Br$), in which tertiary hypobromites (**2B**), generated *in situ* from alcohols, and the corresponding δ -bromohydrins (**6B**), produced from (**2B**) by irradiation (with visible or UV light), thermally or by metallic silver in the dark, were presumably detected by spectral means.^{18b, 24} According to available evidence, the hypiodide reaction has also been formulated by the sequence given in Scheme 1, pathway 2 ($X = I$);^{12-14, *} although δ -iodohydrins (**6A**), produced by photolytically (visible or UV light) or thermally induced rearrangement of the (*in situ* formed) hypiodites (**2A**), are too unstable to be isolated, their presence in this reaction has been confirmed in several instances (in the steroid field) by conversion to γ -iodo- or γ -hydroxy-ketones and other derivatives.^{14, 31}

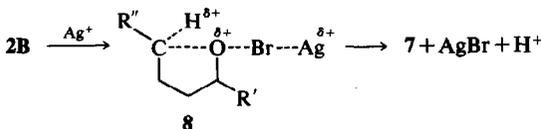
However, for the hypobromite reaction in which tetrahydrofurans (**7**) are formed from alcohols (**1**) by means of the *silver oxide (or other silver salts)-bromine* combination in the dark, controversial mechanistic interpretations have been presented.¹⁸⁻²⁴ From the fact that in this reaction with the tertiary 1,3,3-trimethylcyclohexanol the corresponding δ -bromohydrin (of type **6B**) could not be detected, it was proposed that silver ions act as electrophilic catalyst to promote direct conversion of the hypobromite (of type **2B**) to the ether product (of type **7**) via a transition state (**8**) containing oxygen with cationic character.^{18b} Solvent²² and anion²³ effects have been taken as supporting evi-

dence (or at least as not inconsistent) with such a view.

On the other hand, the following findings suggest that the silver salt-bromine induced cyclisation of alcohols (in the dark) also proceeds homolytically according to Scheme 1, pathway 2 ($X = Br$): (i) Comparable product distribution in the silver acetate-bromine reaction of alcohols (in the dark) and in other processes which are known to involve alkoxy radicals (of type **3**) as intermediates;⁹ (ii) loss of optical activity on the asymmetric δ -carbon atom in the dark silver oxide-bromine cyclisation of (+)-(*S*)-2,5-dimethyl-2-heptanol;²⁰ (iii) the (probably) detected intermediacy of the tertiary δ -bromohydrin (of type **6B**) in the reaction of 2-methyl-2-pentanol with mercuric oxide-bromine in the dark and in the presence of some silver oxide;²⁴ (iv) deuterium isotope effect measurements (using δ -deuterio alcohols as substrates) which, when combined with calculations, have shown that the relative rates of, and activation free energy differences for, intramolecular 1,5-abstraction of the diastereotopic hydrogens from the δ -carbon atom (Scheme 2, step 3 \rightarrow 4) are comparable in both the dark silver oxide-bromine reaction and the lead tetracetate oxidation of alcohols.⁸

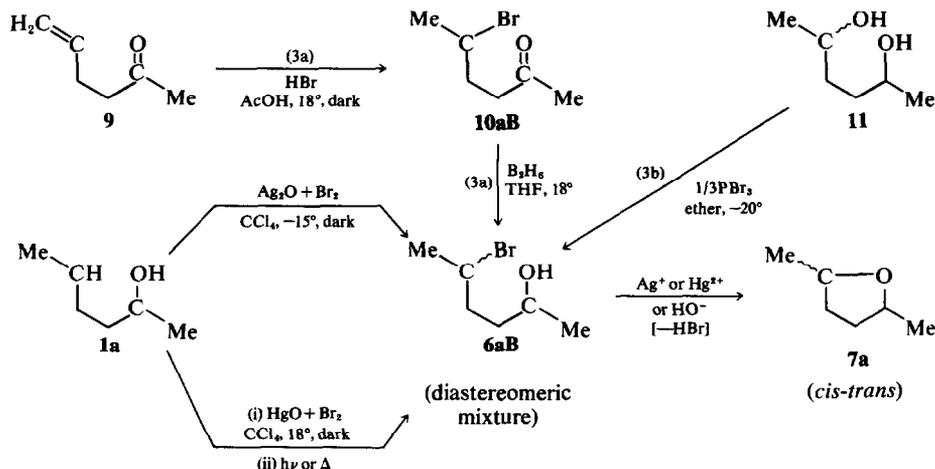
We have now demonstrated the correctness of this free radical mechanistic course (Scheme 1, pathway 2, $X = Br$) for the silver salt-bromine reaction, by slowly treating 2-hexanol (**1a**) and silver oxide (in carbon tetrachloride) with bromine (molar ratio of reactants 1:1:1) in the dark at -15° ; spectroscopic measurements (IR, NMR) of the filtered solution showed the presence of 5-bromo-2-hexanol (**6aB**), which increased only slightly upon irradiation of the solution with visible light (tungsten 500 w. lamp) or heating at $45-60^\circ$ in the dark. A similar experiment with 2-hexanol (**1a**), mercuric oxide and bromine (molar ratio 1:0.75:0.75) in the dark at 20° showed that the amount of δ -bromohydrin (**6aB**) was very small in the original (filtered) solution, but that it increased considerably upon irradiation or heating (in the dark) at 60° . The δ -bromohydrin (**6aB**) from both reactions was compared and found to be identical with a synthetic product obtained via 5-hexen-2-one (**10aB**) according to Scheme 3a. (Treatment of 2,5-hexanediol (**11**) with the calculated amount of phosphorus tribromide at low temperature (Scheme 3b) afforded 5-bromo-2-hexanol (**6aB**) in poor yield.)

These results, together with the facts (i) that 5-bromo-2-hexanol (**6aB**) in carbon tetrachloride is not converted to ether (**7a**) when heated at $35-45^\circ$ for 24 hr (in the dark or in daylight),[†] or upon irradiation with visible or UV light (at room temp) for 8 and 4 hr, respectively, and (ii) that it cyclises quantitatively to 2,5-dimethyltetrahydrofuran (**7a**, Scheme 3) when treated (in carbon tetrachloride or pentane solution at room temperature in the dark or in daylight) with silver oxide, silver acetate, silver



*The same mechanistic course (Scheme 1, pathway 2, $X = NO$), up to product (**6**), also applies to the photolysis of nitrite esters (Barton reaction).¹²⁻¹⁴

[†]However, in refluxing carbon tetrachloride (in the dark) it cyclises slowly to 2,5-dimethyltetrahydrofuran (**7a**) (after 4 hr about 10%, after 24 hr 70-75%). When subjected to gas chromatography (steel column, TCEP adsorbed on Chromosorb) at 50° it undergoes quantitative ring closure to ether product (**7a**).



SCHEME 3

carbonate or mercuric oxide, whereby this ring closure is much faster with silver salts,* indicate

*Thus, by using 2 mmoles of δ -bromohydrin (6aB) and 4 mmoles of M^{m+} , cyclisation to ether (7a) (in carbon tetrachloride at room temperature in the dark) was complete (according to NMR) after 5–10 min with Ag^+ salts, whereas with HgO it required about 45–50 min.

†Which is usually present in silver salts.

‡It is not known whether metallic mercury can initiate homolytic decomposition of hypobromites (2B). If it could, then the decrease (or absence) of catalytic effect on step (2B \rightarrow 3) in the mercuric oxide-bromine reaction might be due to the fact that metallic mercury is ordinarily not present in mercuric salts.

§The slow decomposition (2B \rightarrow 3) at room temperature in this case being mainly a thermal process.

¶These differences in behaviour of silver salts and mercuric salts would explain why δ -bromohydrins (6B) could not be previously obtained in the "pure" silver salt-bromine reaction of alcohols (1).

¶¶However, when subjected to gas chromatography at 50–60° (steel column, TCEP on Chromosorb), it behaves as the corresponding δ -bromohydrin (6aB), i.e. it undergoes ring closure to the tetrahydrofuran (7a).

**After 24 hr (in carbon tetrachloride at room temp in diffuse light) conversion of 5-chloro-2-hexanol (6aC) 3 mmoles) to 2,5-dimethyltetrahydrofuran (7a), using 6 mmoles of M^{m+} , was: over 90% with Ag_2O , about 70–75% with Ag_2CO_3 or AgOAc , and about 50% with HgO .

††Subjecting commercial 2,5-dimethyltetrahydrofuran (7a) to conditions used in the hypohalite reactions described above (or to aqueous 2N NaOH, HBr or HCl (in pentane)) did not change noticeably the original *cis:trans* ratio (56:44) of the recovered ether (the final ratio being in the range 56–60:44–40). Also, control cyclisation reactions (in pentane) with different proportions and concentrations of 2-hexanol (1a), mercuric or silver oxide and bromine, showed that the amount of halogen (using metal oxide:bromine molar ratios of 1:0.5, 1:1 and 1:1.3) in these hypobromite reactions did not affect the *cis:trans* ratio of ether (7a) product, which was always in the range 55–60:45–40.

that in the silver salt-bromine reaction (Scheme 1, pathway 2, X = Br) of (aliphatic) alcohols (1) silver (as metal²³† or ion) catalyses in the dark homolysis of the hypobromite (2B) to the alkoxy radical (3) and, as cation, is very efficient (as electrophilic catalyst) in promoting ring closure of the intermediate δ -bromohydrin (6B) to the tetrahydrofuran product (7), whereas in the mercuric salt-bromine reaction the catalytic effect in the dark on hypobromite decomposition (2B \rightarrow 3) is much weaker (or non-existent)‡§ and mercuric ions are slower in effecting eliminative cyclisation of the δ -bromo alcohol (6B \rightarrow 7).¶

5-Chloro-2-hexanol (6aC, Scheme 1) formed in the hypochlorite reaction of 2-hexanol (1a) with mercuric oxide and chlorine in carbon tetrachloride (Table 2, run 16) was found to be identical (IR, NMR) with an authentic product obtained by diborane reduction of 5-chloro-2-hexanone. As expected, 5-chloro-2-hexanol (6aC) is less reactive than the corresponding δ -bromohydrin (6aB); it remains largely unchanged upon refluxing in carbon tetrachloride (in the dark or in daylight) for 12 hr,¶ and cyclises only slowly to ether (7a) when treated with silver salts or mercuric oxide in carbon tetrachloride or pentane (at room temp in diffuse light).**

The stereochemistry of the ether products (7) formed in the hypohalite reactions of unbranched secondary aliphatic alcohols (1) is also indicative of a common mechanistic course (Scheme 1, pathway 2). Namely, as can be seen from Tables 1 and 2, in all these reactions with heavy metal salts (Pb^{4+} , Hg^{2+} , Ag^+) and halogen (I_2 , Br_2 , Cl_2), which are non-stereoselective, the diastereomeric composition of the 2,5-dialkyl-tetrahydrofuran products (7) is always similar and opposite to that obtained in the lead tetraacetate oxidations (*vide supra*), i.e. the *cis*-isomer (*cis*-7) predominates slightly, whereby the *cis:trans* ratio is in the range 60–55:40–45.††

Since it has been established that cyclisation of 4-chloro-1-butanol (and *trans*-4-chlorocyclohexanol) to tetrahydrofuran in aqueous-alkaline solution (and in pure water for δ -chlorobutanol) takes place by an S_N2 process,³² it was reasonable to assume that in the case of 5-bromo-2-hexanol (**6aB**) and 5-chloro-2-hexanol (**6aC**) aqueous-alkaline (or aqueous) hydrolytic ring closure to ether (**7a**) would also follow a bimolecular displacement mechanism with inversion of configuration at C-5. We have found that the diastereomeric (*erythro-threo*) mixture of 5-bromo-2-hexanol (**6aB**), obtained by diborane reduction of the corresponding bromoketone (according to Scheme 3a), afforded the same *cis-trans* ratio (55-53:45-47) of 2,5-dimethyltetrahydrofuran (**7a**) when treated at 60° with H₂O (15 hr) or aqueous 2N NaOH (6 hr), or at 18-25° (for 10 hr) with aqueous 2N NaOH, AgNO₃ or Hg(NO₃)₂, or at 18-22° in pentane (or carbon tetrachloride) solution (for 2-3 hr) with Ag₂O, AgOAc, Ag₂CO₃ or HgO.* Similarly, the *erythro-threo* mixture of 5-chloro-2-hexanol (**6aC**), prepared by diborane reduction of the corresponding chloroketone, always cyclised, under these various conditions, to the ether (**7a**) in a *cis:trans* ratio of

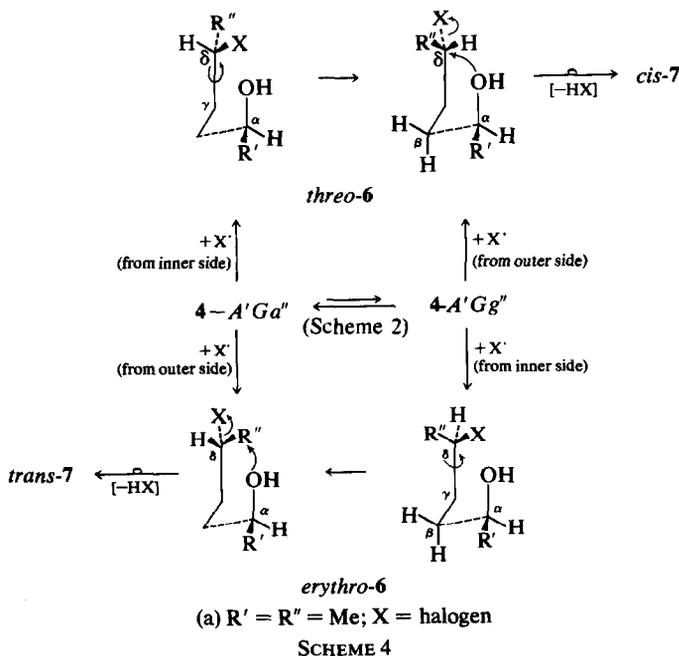
56-54:44-46, whereby with silver and mercuric salts reaction times were 32 and 45 hr, respectively.

These results seem to indicate that even with Ag⁺- or Hg²⁺-salts, as electrophilic catalysts, which usually cause alkyl halide substitution to proceed by an S_N1 -like mechanism,³³ intramolecular nucleophilic displacement of the 5-halogen by the 2-hydroxyl oxygen in 5-halo-2-hexanols (**6a**) takes place stereoselectively with inversion of configuration at the chiral (C-5) C atom (from which halogen is being eliminated).

On the basis of these considerations and since both the lead tetraacetate oxidation and the hypohalite reactions involve in their first stages (Schemes 1 and 2) the 1,5-radical rearrangement process (3→4) with the same stereochemistry of δ -hydrogen abstraction (*vide supra*),⁸ one would have to assume, in order to account for the steric course, that in the heavy metal salt-halogen reactions, which are not long chain radical processes and may be of the radical pair (cage) type^{13b,14b,18b,24} the halogen† will add to the δ -carbon radical (**4**) preferentially from the same side from which hydrogen was abstracted (i.e. from the side of the hydroxyl group in conformations A'Ga'' and A'Gg''). Because conformation A'Ga'' of the carbon radical (**4**) is somewhat more favourable (*vide supra*), such an inside attack of halogen, shown on Scheme 4, would produce the *threo*- δ -halohydrin (*threo*-**6**) in slight excess over the *erythro*-diastereomer (*erythro*-**6**), and therefore, upon internal cyclisation involving inversion of configuration at the δ -carbon atom, the *cis*-isomer (*cis*-**7**) should predominate in

*Cyclisation of both synthetic δ -bromo- and δ -chlorohydrins (**6aB** and **6aC**) by gas chromatography (steel column, TCEP on Chromosorb) at 40-60°, resulted in a 54:46 ratio of *cis:trans* ether (**7a**).

†Possibly associated in some form (directly or via the metal) to the hydroxylic oxygen.



the resulting *cis-trans* mixture of the ether product (7).*

On the other hand, in the photolytically induced decomposition of 2-hexyl hypochlorite (2aC) prepared from preformed hypochlorous acid and 2-hexanol (1a) according to Walling's procedure,^{29b} i.e. in the absence of heavy metal salts, the *cis:trans* ratio of ether (7a) was very slightly in favour of the *trans*-isomer (*trans*-7a) (49:51). In this reaction, which has been postulated to involve long radical chains,^{13,14b,29,30} it is probable that addition of chlorine atoms to the δ -carbon radicals (Scheme 1, pathway 2, 4 \rightarrow 6C) occurs, in major part, as the chain propagation step by intermolecular transfer from hypochlorite molecules (2C);^{13b,29a} such a transfer process, involving relatively bulky species, would preferentially take place (Scheme 4) from the opposite side of the hydroxyl oxygen (i.e. from the outer side) in conformations *A'Ga''* and *A'Gg''*, so that (since the former conformation is somewhat more stable than the latter) one could expect *erythro*-5-chloro-2-hexanol (*erythro*-6aC) and therefore *trans*-2,5-dimethyltetrahydrofuran (*trans*-7a) to be formed in small excess over (or at least in equal amount as) the corresponding *threo*- δ -chlorohydrin (*threo*-6aC) and the resulting *cis*-ether (*cis*-7a), respectively.

EXPERIMENTAL

Gas chromatography: analytical Varian Aerograph instrument, Series 1400 (flame ionisation detector), and preparative Varian Aerograph instrument, Model 90-P (thermistor detector); the columns (2 m \times 2 mm, 2 m \times 4 mm, 6 m \times 8 mm) consisted of 1,2,3-tris(2-cyanoethoxy)propane (TCEP) or Carbowax 20M adsorbed on Chromosorb P (3.5–10%); carrier gas—H₂ or Ar; temp. programmed from 40°. IR spectra: Perkin-Elmer Grating Spectrophotometer, Model 337 (as film or in CCl₄). NMR spectra: Varian Spectrometer A.60A (60 MHz); CCl₄ solutions and TMS as internal standard (chemical shifts in δ units, coupling constants *J* in Hz). Fractional distillations: well isolated, modified semi-micro Vigreux columns.

For analytical and preparative purposes the separation of, and assignment of the *cis-trans* stereochemistry to, diastereomers of 7 was readily achievable on the basis of differences in gas-chromatographic retention times (the *cis*-isomers having always a shorter retention time^{3-5,34}) and differences in the signal (δ) positions of the α -protons in NMR spectra (the chemical shift of these protons in the *trans*-isomer being displaced downfield with respect to the *cis*-isomer^{4,5,34,35}). Other reaction products were also identified by means of gas-chromatographic retention times and spectral data.

Lead tetraacetate oxidations of alcohols (and the dis-

tribution of ether and other products) were described previously.^{3-6,36}

*Ceric ammonium nitrate oxidations.*¹⁰ A stirred soln of 7.5 mmoles 3-octanol or 2-decanol and 30 mmoles ceric ammonium nitrate in 30 ml H₂O and 30 ml acetonitrile was progressively heated until disappearance of the red colouration (70–75°), followed by 30 min of heating at 80–85°. The cooled mixture was diluted with water, thoroughly extracted with ether, the combined organic layers washed with water, saturated NaHCO₃aq and water, dried (CaSO₄) and the solvents removed by fractional distillation. The products in the residue were separated by gas chromatography and identified by spectral means (yields: 10–15% of tetrahydrofurans (7), 45–55% of unreacted alcohol (1), 15–20% of corresponding ketone).

Hypiodite reactions.^{14,16,17} Under conditions given in Table 1, these reactions were usually carried out with 15 mmoles of alcohol (1) in 150–250 ml of solvent. The metal salt and iodine (eventually +anh. CaCO₃) in solvent were first stirred for 5 min at 20°, followed by the addition of alcohol (1) in solvent. The resulting mixture was then stirred and irradiated under reflux (the 250–500 watt tungsten lamp serving as light and heat source) until disappearance of the iodine colour (and disappearance of Pb^{IV} when Pb(OAc)₂ was used as oxidant). The resulting mixture was filtered, the precipitate washed with ether, the combined filtrates extracted with 10% Na₂S₂O₃aq, NaHCO₃aq and water, the organic soln dried (CaSO₄) and the solvents removed by careful fractional distillation. The products in the residue were separated and analysed by gas chromatography and spectral means (Table 1).

In control experiments, the combined filtrates (after irradiation and heating) were first refluxed for 6 hr with 10% methanolic KOH (4 g KOH in 40 ml), MeOH and part of the solvent mixture were removed by distillation, the residue was treated with water, the layers were separated and the aqueous part was extracted with ether. Drying of the combined organic layers and fractional evaporation of solvents, followed by gas chromatography of the residue, afforded the reaction products.

Hypobromite reactions^{16,18-25} were usually performed, under conditions given in Table 2, with 5–10 mmoles of alcohol (1) and 10–20 mmoles of metal salt in 30–40 ml of solvent (pentane), in dim light at 20°. Bromine (10–20 mmoles) was added in the course of 30 min to the stirred suspension, followed by stirring for another 60 min. The colourless solution was filtered and subjected (directly, after fractional evaporation of solvent, or upon working up as described previously¹⁶) to gas chromatography (Table 2).

Hypochlorite reactions. To a stirred suspension of 10 mmoles alcohol (1) and 20 mmoles of HgO or Ag₂CO₃ in 10–20 ml of carbon tetrachloride, in dim light and under conditions described in Table 2, 25 mmoles chlorine (as a 5% soln in CCl₄, 18 ml) was added at 20° in the course of 60 min. After stirring for another 60 min and filtering, the solvent was carefully removed and the residue (consisting mainly of 6C, unchanged alcohol (1) and corresponding ketone) treated with stirring for 6 hr at 60° with 20 ml of 2N NaOHaq. The resulting mixture was saturated with NaCl, extracted with several portions of ether, the combined organic layers dried (CaSO₄), the solvents carefully removed, and the residue subjected to gas chromatography (Table 2).

Acid-catalysed cyclisation of 5-hexen-2-ol. This alcohol (10 mmoles) in 10 ml 25% H₂SO₄ was heated (with stirring) at 80–90° for 5 hr. Extraction of the Na₂SO₄-

*It is of interest to note that in the diborane reduction (in THF) of both 5-bromo- and 5-chloro-2-hexanone the *threo*-diastereomer of the corresponding δ -halohydrin (6) is also formed in excess, the *threo:erythro* ratio being in both cases again about 55:45, according to the relative amounts of *cis-trans* ethers (7a) obtained upon cyclisation. (The diastereomers of (6a) could not be separated or identified by spectral methods.)

saturated mixture with several portions of ether, drying (K_2CO_3) of the combined organic layers and careful removal of solvent, afforded in over 80–85% yield **7a**, in a *cis*:*trans* ratio of 46:54.

Synthesis of 5-bromo-2-hexanol (6aB), Scheme 3a). Dry HBr (from 40 ml Br_2 and 110 ml tetraline) was slowly introduced at 20° into a light protected soln of 30 g (0.3 moles) 5-hexen-2-one in 120 ml glacial AcOH. The resulting mixture was then left several hr in a HBr atmosphere, after which it was poured onto ice and extracted with several ether portions. The combined ethereal layers were washed with water, $NaHCO_3$ aq and water. After drying ($CaCl_2$) and removal of solvent, the product was fractionated to give 22 g (41%) of **10aB**, b.p. 56° at 1 mm (lit.³⁷ b.p. 135–140 at 100 mm); IR: $\nu_{C=O} = 1715\text{ cm}^{-1}$; NMR: $\delta = 1.73$ (3H at C-6, *d*, $J = 6.5$ Hz), 1.98 (2H at C-4, *m*), 2.12 (3H at C-1, *s*), 2.62 (2H at C-3, *t*, $J = 7$ Hz), 4.10 (1H at C-5, *m*).

Diborane (generated separately from 7 g of $NaBH_4$ and 50 ml BF_3 -etherate in 150 ml diglyme) was introduced at 20° into a stirred (and from light protected) soln of 13.5 g (75 mmoles) 5-bromo-2-hexanone in 100 ml dry THF. The solvent was then removed *in vacuo*, the residue treated carefully with ice-cold 10% H_2SO_4 (until acid), and the aqueous soln extracted with 2–3 portions ether. The combined organic layers were washed with water, $NaHCO_3$ aq and water, and dried ($CaSO_4$). Evaporation of the solvent afforded about 13 g (over 95%) of 5-bromo-2-hexanol (**6aB**); IR: $\nu_{OH} = 3300\text{ cm}^{-1}$; NMR: $\delta = 1.25$ (3H at C-1, *d*, $J = 6$ Hz), 1.73 (3H at C-6, *d*, $J = 7$ Hz), 1.80 (4H at C-3 and C-4, complex *m*), 4.02 (2H, one at C-2 and one at C-5, broad *m*).

Synthesis of 5-chloro-2-hexanol (6aC). Distillation of α -acetyl- γ -valerolactone (b.p. 129–131° at 15 mm)³⁸ with conc HCl and water (according to the procedure for preparing 5-chloro-2-pentanone³⁹) afforded 5-chloro-2-hexanone, b.p. 79–81° at 17 mm (lit. b.p. 73–74° at 14 mm,⁴⁰ 65–68° at 13 mm⁴¹); IR: $\nu_{C=O} = 1715\text{ cm}^{-1}$; NMR: $\delta = 1.52$ (3H at C-6, *d*, $J = 7$ Hz), 2.02 (2H at C-4, *m*), 2.12 (3H at C-1, *s*), 2.63 (2H at C-3, *t*, $J = 7$ Hz), 4.07 (1H at C-5, *m*).⁴²

Diborane (generated separately from 2 g $NaBH_4$ and 10 ml BF_3 -etherate in 100 ml diglyme) was introduced at 20° into a stirred (and from light protected) soln of 6.5 g (50 mmoles) of 5-chloro-2-hexanone in 100 ml THF. Working up as above (for 5-bromo-2-hexanone) afforded in over 90% yield 5-chloro-2-hexanol (**6aC**); IR: $\nu_{OH} = 3350\text{ cm}^{-1}$; NMR: $\delta = 1.18$ (3H at C-1, *d*, $J = 6$ Hz), 1.52 (3H at C-6, *d*, $J = 6.5$ Hz), 1.68 (4H at C-3 and C-4, complex *m*), 3.83 (2H, one at C-2 and one at C-5, broad *m*).

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