

Studies on the Reaction between Chloral and Alcohols

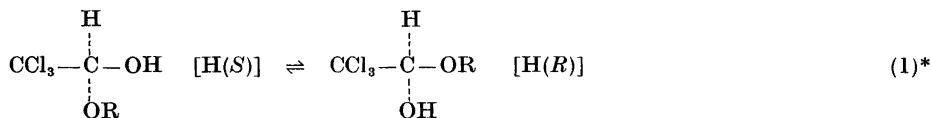
II. Investigation on the Mutarotation of Chloral Hemiacetals Prepared from Chloral and Various Optically Active Alcohols

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The investigations reported in this paper are concerned with the effect of the mutarotation (epimerization) shown by chloral hemiacetals prepared from chloral and optically active alcohols with known absolute configuration. The purpose of these investigations is to see whether or not there is a relationship between the configuration of the optically active alcohol and the direction of the change of rotation appearing during the epimerization as suggested in our previous paper. The experiments carried out demonstrate the existence of such a relationship. Furthermore, the experiments, with alcohols containing non-polar or aromatic groups, seem to indicate that it is possible to predict the direction of the rotational change on epimerization on the basis of a purely steric estimate of the groups surrounding the asymmetric centre in the optically active alcohol.

In a previous paper¹ it was reported that a solution of chloral (*R*)-menthol hemiacetal in hexane showed an effect of mutarotation on addition of catalytic amounts of acetic acid. In the present paper, which concerns further investigations of optically active chloral hemiacetals, it will appear that the mutarotation is a common phenomenon shown by chloral hemiacetals which are prepared from optically active primary, secondary, and, possibly, tertiary monovalent alcohols. The mutarotation is explained by an equilibrium asymmetric transformation (epimerization) of one of the two possible diastereomeric hemiacetals *H*(*R*) and *H*(*S*) to the other.



If the molecular rotation of the hemiacetal mixture and the time are denoted by $[\varphi]$ and t , respectively, then in the case of an effect of mutarotation,

* In the previous paper¹ the letters R and S in eqn. (1) have been interchanged.

the slope $d[\varphi]/dt$ of the curves $[\varphi]$ vs. t , will be different from zero. Cases where $d[\varphi]/dt = 0$, however, do not necessarily mean that no epimerization has occurred but could be explained if the velocity of this process were greater than the velocity of the formation of the hemiacetals.

It was also indicated that there were reasons to expect a relationship between the configuration of the asymmetric centre in the optically active alcohol and the sign of $d[\varphi]/dt$. The present experiments were carried out with the aim of examining this possibility.

First condition for a partial asymmetric synthesis to occur is that the magnitudes of the asymmetric activities, including both steric and polar effects, of the four groups surrounding the asymmetric centre, are different. If the formula of an optically active alcohol is written as $L, M, SC(CH_2)_nOH$ (where L, M, and S stand for large, medium, and small), then the formulation of the above mentioned condition will be that the relative magnitude of the asymmetric activity of the groups L, M, and S are such that $L > M > S$. Usually L, M, and S are used as symbols for the relative bulk of the groups surrounding the asymmetric centre. Here, it is difficult to separate the polar effect from the steric one, thus L, M, and S will, in this and the following papers, be used as symbols of the relative magnitude of the sum of the different asymmetric effects produced by each of the groups considered. Provided the relationship between the configuration of the asymmetric centre in the alcohol used and the sign of $d[\varphi]/dt$ is tenable, the spatial arrangement of the groups $(CH_2)_nOH$, L, M, and S will be the determining factor for the sign of $d[\varphi]/dt$.

A preliminary proof of the validity of this hypothesis, might be found in the fact that $d[\varphi]/dt$ of the epimerization of the chloral hemiacetals produced by (*R*)-2-octanol and (*S*)-2-octanol assumes positive and negative values, respectively, *cf.* Table 1.

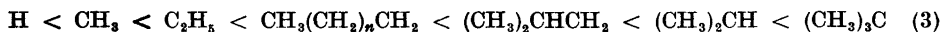
At the present it is not possible to deduce theoretically whether the sign of $d[\varphi]/dt$ will be positive or negative for the epimerization of a chloral hemiacetal prepared from an optically active alcohol with a given configuration. At first it is necessary to get a correlation between the configuration of an optically active alcohol with known configuration and the sign of $d[\varphi]/dt$ produced during the epimerization of its chloral hemiacetal. For other optically active alcohols it may be postulated that those, producing the same sign of $d[\varphi]/dt$ as the above mentioned alcohol, have the same configuration and *vice versa*, but only when the configuration is given in terms of L, M, and S.

The following notation is used: Provided that the sequence L, M, and S traces a right- or left-handed-turn when viewed from the asymmetric centre, it will be indicated by a right- or leftpointed arrow placed between the symbols L, M, and S. $L \rightarrow M \rightarrow S$ means that the sequence of L, M, and S is right-handed and $L \leftarrow M \leftarrow S$ means that the sequence is left-handed. A right-handed sequence of L, M, and S in an optically active alcohol corresponds to the Fischer projection shown in formula (2).



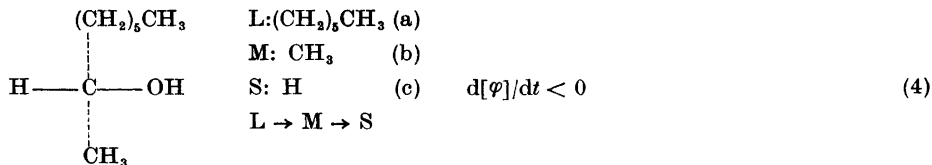
In connection with the postulate that two different optically active alcohols producing the same sign of $d[\varphi]/dt$ must have the same configuration or, in more exact terms, the same sequence of L, M, and S, it must be emphasized that knowledge of the sequence of L, M, and S does not have to be synonymous with the knowledge of the absolute configuration, when this is expressed in terms of the (*R,S*)-nomenclature and *vice versa*. The common idea of absolute configuration refers only to the geometrical arrangement in space of the groups surrounding the asymmetric centre and not to their function as controlling factors of the steric course in an asymmetric synthesis.

Therefore, after determination of the sequence of L, M, and S, the second condition for determining the absolute configuration of an optically active alcohol $a,b,cC(CH_2)_nOH$ by the method of asymmetric synthesis must be the possibility of correlating the groups a, b, and c one by one with L, M, and S. It must also be noted that the asymmetric activity of a group, due to intramolecular interaction with the other parts of the reacting molecule, can be very different in different types of asymmetric synthesis. It is therefore necessary for every new type of asymmetric synthesis used, to determine experimentally the relative magnitude of the asymmetric activities of the various groups which surround the asymmetric centres in the alcohols considered. Fortunately investigations made by McKenzie,² Prelog,³ Ingold,⁴ a.o. on this subject make it probable that the asymmetric activities of alkyl groups are of only steric nature. It is then possible to arrange the alkyl groups in priority series of increasing bulk according to (3).



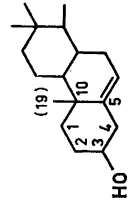
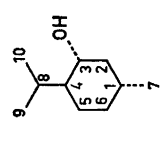
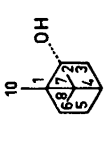
which should then be expected to remain unchanged in various types of asymmetric synthesis.

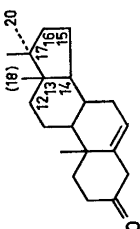
On this basis, that is the means of correlating the actual groups a, b, and c with L, M, and S in optically active alkanols, it is now possible to advance a postulate correlating the sign of $d[\varphi]/dt$ with the configuration of $a,b,cC(CH_2)_nOH$ ($a > b > c$) as well as with the configuration of $L,M,SC(CH_2)_nOH$. (*R*)-2-octanol will be used as a standard (4).



The sequence of the relative bulk of the groups surrounding the asymmetric centre in (*R*)-2-octanol is $CH_3(CH_2)_5 \rightarrow CH_3 \rightarrow H$ which gives rise to a right-handed sequence of L, M, and S.

The combination of this statement with the empirical fact that the sign of $d[\varphi]/dt$ is negative, forms the basis of the following formulation: A negative sign of $d[\varphi]/dt$ for the epimerization of chloral hemiacetals prepared from optically active alcohols corresponds to a right-handed sequence of L, M, and S for all optically active alcohols and in particular in optically active

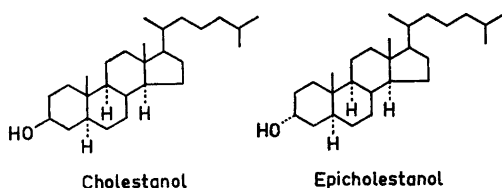
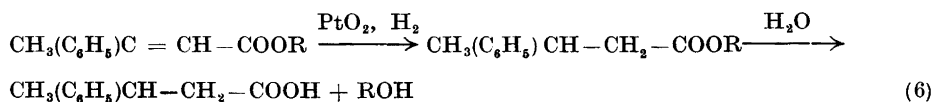
Formula and Name of alcohol	Relative bulk			Sequence.	Sign of $d[\varphi]/dt$		Configuration, Lit.
	L	M	S		Predicted	Observed	
	$(\text{CH}_2)_5\text{CH}_3$ $\text{H}-\text{C}-\text{OH}$ $\quad \quad \quad \text{CH}_3$ (R)-2-Octanol	$\text{CH}_3(\text{CH}_2)_5$	CH_3		H	L → M → S	
$(\text{CH}_2)_5\text{CH}_3$ $\text{HO}-\text{C}-\text{H}$ $\quad \quad \quad \text{CH}_3$ (S)-2-Octanol	$\text{CH}_3(\text{CH}_2)_5$	CH_3	H	L ← M ← S	positive	positive	Klyne ⁶
CH_3CH_3 $\text{HOCH}_2-\text{C}-\text{H}$ $\quad \quad \quad \text{CH}_3$ (S)-2-Methyl-1-butanol	CH_3CH_3	CH_3	H	L ← M ← S	positive	positive	Freudenberg and Homann ⁷
 (-)-Cholesterol	$\text{C}(4)\text{H}_5\text{C}(5)$	$\text{C}(2)\text{H}_2\text{C}(1)\text{H}_2$	H	L ← M ← S	positive	undeterminable	Fieser ¹⁰
 (R)-Menthol	$\text{C}(4)\text{HC}(8)\text{H}(\text{CH}_2)_2$	$\text{C}(2)\text{H}_3$	H	L → M → S	negative	negative	Prelog ³
 (R)-Borneol	$\text{C}(1)\text{H}(\text{C}(10)\text{H}_3)\text{C}(7)\text{H}(\text{CH}_3)_2$	$\text{C}(3)\text{H}_2$	H	L → M → S	negative	negative	Prelog ³

 <p>17-α-Methyltestosteron</p>	C(13)CH ₃	C(16)H ₂ C(15)H ₂	C(20)H ₃	L \leftarrow M \leftarrow S	positive	positive	Fieser ¹⁰
	COOC ₂ H ₅	C ₆ H ₅	H	L \rightarrow M \rightarrow S	negative	negative	Eliel ⁹
	COOC ₂ H ₅	CH ₃	H	L \leftarrow M \leftarrow S	positive	negative	Eliel ⁹
	COOC ₂ H ₅	CH ₂ COOC ₂ H ₅	H	L \leftarrow M \leftarrow S	positive	negative	Eliel ⁹
	C ₆ H ₅	CH ₃	H	L \leftarrow M \leftarrow S	positive	negative	Eliel ⁹
	C ₆ H ₅	CH ₃	H	L \rightarrow M \rightarrow S	negative	positive	Eliel ⁹
	CH ₃ CH ₂ CH=C(CH ₃) ₂	CH=CH ₂	CH ₃	L \leftarrow M \leftarrow S	positive	positive	Cornforth, <i>et al.</i> ¹¹
	CH ₃						
	CH ₃						
	CH ₃						

formula $a,b,cC(CH_2)_nOH$, how large can n be in order to retain an observable asymmetric effect? (b) What difference in appearance must two groups "a" and "b" have in order to produce an asymmetric effect; *i.e.*, is, for example, the difference between 4-methylpentyl and 3-methylpentyl great enough to produce an observable asymmetric effect? In cholesterol the difference between "a" and "b" appears first at the third carbon atom counted from the carbon atom carrying the oxygen atom, (see Table 1). The effect of epimerization is, however, as expected in this case, so small that no definite conclusions can be drawn.

2. This section is concerned with optically active alcohols containing more than one asymmetric centre or having the asymmetric centres placed in an alicyclic ring. The results obtained with these types of alcohols are listed in Table 1.

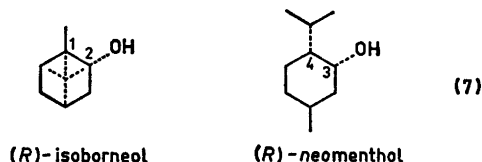
As seen from Table 1, the observed results can, as previously, be predicted on the basis of a purely steric estimate. The asymmetric carbon atom which forms the basis for the $d[\varphi]/dt$ determining sequence of L, M, and S seems to be the asymmetric carbon atom carrying the hydroxyl group. But the possibility that the asymmetric carbon atoms placed farther away can be the factor determining $d[\varphi]/dt$ can not be rejected. The predictions in all cases investigated so far were correct. This may, of course, be due to the contributions from the nearer and the farther asymmetric centres operating in the same direction. An example of an asymmetric synthesis with the asymmetry-determining factor placed farther away from the asymmetric carbon atom carrying the hydroxyl group, is the heterogeneous Pt-catalysed hydrogenation of, α -cholestanol and epicholestanol esters of β -methyl cinnamic acid, respectively, carried out by Vavon and Jacobowicz⁸ (6).



The final product was in both cases the same enantiomer of β -phenylbutyric acid. The fact that the only difference between α - and epicholestanol is that the two alcohols have opposite configurations at the OH-carrying carbon atoms, showed that the asymmetric course was solely determined by the configurations of the asymmetric carbon atoms placed farther away.

Contrary to this, Prelog *et al.*⁵ have shown that the dominating asymmetric carbon atom, controlling the steric course in the asymmetric synthesis of atrolactic acid for all the optically active alcohols investigated, was the hydroxyl-carrying carbon atom. The possibility of applying these rules to the epimerization of the chloral hemiacetals produced from the optically active

alcohols considered here, cannot be judged at the present time. It will be necessary first to compare the sign of $d[\varphi]/dt$ for such diastereomeric pairs of alcohols where the configurations at the OH-carrying carbon atoms are the same, but different at the neighbour carbon atoms, e.g. (*R*)-borneol with (*R*)-isoborneol and (*R*)-menthol with (*R*)-neomenthol (7).



If the sign of $d[\varphi]/dt$ for these pairs of alcohols is the same, there is justification for applying the rules which are valid for the asymmetric synthesis of atrolactic acid to the epimerization of the chloral hemiacetals prepared from optically active alkanols containing no other polar groups than the OH-group.

Table 2. The experimental conditions of the mutarotation of the chloral hemiacetals.

Name of alcohol	Concentrations (M) of			Solvent		[φ] of the alcohol used ^a
	ROH	Chloral	HAc	Heptane	CH ₂ Cl ₂	
(<i>R</i>)-2-Octanol	0.05	0.05	0.005	+		— 53.2
(<i>S</i>)-2-Octanol	0.05	0.05	0.005	+		+ 35.8
(<i>S</i>)-2-Methyl-1-butanol	0.5	0.5	0.05	+		— 186
(<i>R</i>)-Menthol	0.5	0.5	0.05		+	— 204
(<i>R</i>)-Borneol	0.5	0.5	0.05	+		— 308
17- α -Methyltestosteron	0.5	0.5	0.05		+	+ 468 ^b
(<i>R</i>)-Diethyl mandelate	0.5	0.5	0.05		+	— 907
(<i>S</i>)-Ethyl lactate	0.5	0.5	0.05		+	+ 0.19
(<i>S</i>)-Ethyl malate	0.5	0.5	0.05		+	— 14.1
(<i>R</i>)-1-Phenyl-1-ethanol	0.5	0.5	0.05	+		+ 80.0
(<i>S</i>)-1-Phenyl-1-ethanol	0.5	0.5	0.05	+		— 158
(<i>R</i>)-Linalool	0.5	0.5	0.05	+		— 52.7
(—)-Cholesterol	0.1	0.1	0.01		+	— 479

^a) at 364 $m\mu$ (cf. Ref.¹).

^b) at 436 $m\mu$

The last type of optically active alcohols investigated are those alcohols which contain groups of such a nature that the possibility of intramolecular attraction between the different parts in the molecule exists. The course of the epimerization for such alcohols may therefore be opposite to that predicted on the basis of a purely steric estimate of the groups surrounding the asymmetric centre. So far, only the groups C_6H_5- , $C_2H_5OOCCH_2-$, and C_2H_5OOC- have been observed to have such properties. The results are presented in Table 1.

EXPERIMENTAL

The experimental conditions for the various epimerizations carried out are listed in Table 2.

The reasons for running the experiments under different conditions are as follows: (a) Methylene chloride is used instead of hexane or heptane, when the solubility of the alcohol used is too low in the hydrocarbons; (b) The rotation is measured at $436 m\mu$ instead of $364 m\mu$, when the absorption of the alcohol at $364 m\mu$ is too large to permit determination of the rotation; (c) The alcohol and the chloral concentrations are varied in order to get a reasonable velocity of mutarotation and a suitable accuracy of measurement. More detailed experimental conditions are given in the first paper on this subject.¹

The way of treating the experimental data and of calculating the values of $[\varphi]$ is given in the first paper and will not be repeated here. The results of the epimerizations are presented by the sign of $d[\varphi]/dt$ (cf. Table 1).

The enantiomers of 2-octanol and 1-phenylethanol were prepared by optical resolution of the brucine salts of their hydrogen phthalates.¹² The ethyl esters of (-)-mandelic acid, (-)-malic acid, and (+)-lactic acid were prepared in the usual way by Fischer-Speier esterification. The other optically active alcohols used were commercial products. Gaschromatographic analyses of these alcohols showed that the purity was adequate for the experiments of epimerization with the exception of (-)-borneol which contained 30 % of camphor. As camphor does not react with chloral, the $[\varphi]$ curves of the epimerization with (-)-borneol are included in this paper for the purpose of getting information about the sign of $d[\varphi]/dt$. In this connection it must be emphasized that the optical purity is of minor importance if the purpose of the investigation of the epimerization is the determination only of the sign of $d[\varphi]/dt$.

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