# Studies on the Reaction between Chloral and Alcohols

## IV. Investigations on the Mutarotation of Hemiacetals of Chloral and Optically Active Alcohols Containing Additional Asymmetric Centres in Alicyclic Rings
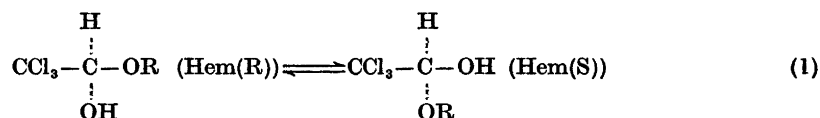
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The mutarotations of chloral hemiacetals of (R)-menthol, (S)-isomenthol, (S)-neomenthol, (R)-neoisomenthol, (R)-borneol, and (S)-isoborneol, all characterized by containing additional asymmetric centres in alicyclic rings, have been studied and compared. It is found that the sign of the rate of change in molecular rotation (at 364 mµ) of the hemiacetal, $d[\varphi]/dt$, depends only on the configuration of the asymmetric carbon atom carrying the hydroxyl group. Consequently, as is the case with alcohols containing only one asymmetric centre, it is possible to predict the sign of $d[\varphi]/dt$ when the configuration of the groups surrounding the hydroxyl-carrying carbon atom is known, and *vice versa*. The possibility of an anomalous course of mutarotation is discussed. This may be expected to occur with one of the four possible diastereomers of a 2,6-dialkyl cyclohexanol if the difference in steric bulk between the two alkyl groups exceeds a certain limit and the molecule is forced into the otherwise unfavorable boat conformation.

Further, on the basis of NMR and kinetic studies conformations are suggested for the hemiacetals and their corresponding intermediates.

In previous papers [1-3] we have reported and discussed the mutarotation shown by hemiacetals made from chloral and optically active alcohols. Hydrocarbons were used as solvents, and the reaction was found to be catalyzed by acetic acid. The mutarotation was explained as an equilibrium asymmetric transformation [4] (epimerization) of one of the two possible diastereomeric hemiacetals, Hem(R) and Hem(S), into the other (1).

$$\underset{\substack{|\\ \mathrm{OH}}}{\overset{\substack{\mathrm{H}\\|}}{CCl_3-C-OR}} \ (\mathrm{Hem(R)}) \ \rightleftharpoons \ \underset{\substack{|\\ \mathrm{OR}}}{\overset{\substack{\mathrm{H}\\|}}{CCl_3-C-OH}} \ (\mathrm{Hem(S)}) \tag{1}$$

The epimerization was observed with primary $(n \geqslant 1)$, secondary $(n = 0)$ and tertiary $(n = 0)$ alcohols (2).

$$L-\overset{\displaystyle M}{\underset{\displaystyle S}{C}}-(CH_2)nOH \qquad (2)$$

(L, M, and S means large, medium and small).

The observed mutarotation disappears when $n > 1$. In secondary alcohols there is no measurable effect when the difference in steric bulk between the three groups L, M, and S is to small.

By investigation of different types of optically active secondary alcohols, it was found that the sign of $d[\varphi]/dt$ was determined by the spatial arrangement of the groups L, M, S, and $(CH_2)_nOH$ surrounding the asymmetric carbon atom in the optically active alcohol. In formula (2) the spatial arrangement is called right-handed and designated by the symbol $L \rightarrow M \rightarrow S$, which means that the sequence of L, M, and S viewed from the asymmetric carbon atom traces a right-handed turn. As already reported, a right-handed spatial arrangement $(L \rightarrow M \rightarrow S)$ of the optically active alcohols makes $d[\varphi]/dt$ negative, whereas a left-handed spatial arrangement makes $d[\varphi]/dt$ positive. This rule was confirmed by investigating 35 different optically active alcohols. Exceptions to this rule were found when the optically active alcohols contained polar or aromatic groups.
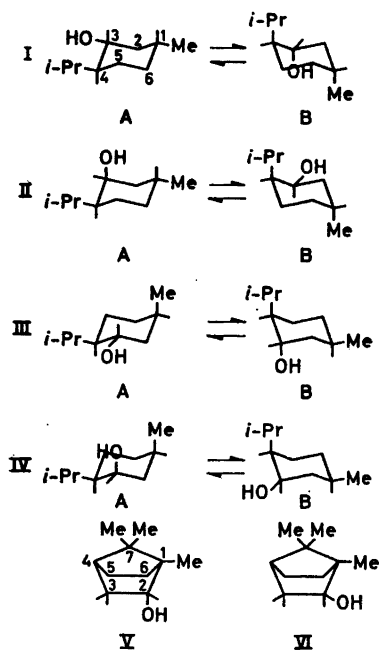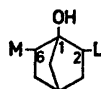
Fig. 1. I A—I B, II A—II B, III A—III B, and IV A—IV B shows the stereoformulas of the conformations of (R)-menthol, (S)-neomenthol, (S)-isomenthol, and (R)-neoisomenthol, respectively, and V and VI the stereoformulas of (R)-borneol and (S)-isoborneol.

This paper deals with the mutarotation and conformation of chloral hemiacetals made from optically active secondary alcohols containing more than one asymmetric centre. The asymmetric centres are all in alicyclic rings. As objects for the investigation the following members of the menthol series, (R)-menthol, (S)-isomenthol, (S)-neomenthol and (R)-neoisomenthol,[5] were chosen together with (R)-borneol and (S)-isoborneol.[6] Fig. 1 represents the stereoformulas of these alcohols. In the following conformers with an axial hydroxyl group are called *a* conformers and conformers with an equatorial hydroxyl group *e* conformers.

The possibility of using asymmetric synthesis to determine the configurations of optically active alcohols depends mainly on the validity of the following assumption. If $R^1$ and $R^2$ are two groups attached to the asymmetric centre, the question whether $R^1$ or $R^2$ is to be considered the largest one, must be independent of the conformation on the molecule. This condition is fulfilled if the optically active alcohol contains one asymmetric centre; it probably is also, if more asymmetric centres are present in open-chained alcohols. If, however, the alcohol contains several asymmetric centres placed in alicyclic rings, the above-mentioned condition may not be fulfilled, and in connection with this, the conformations of various diastereomers of (3) and (4)
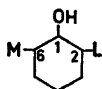


(3): 2-L-6-M-Cyclohexanol                    (4): 2-L-6-M-Bicyclo[2.2.1]heptane-1-ol

have been analyzed. The Newman projections of the eight chair conformations of the four diastereomers (the configuration at carbon atom (1), carrying the hydroxyl group, is (S)) are shown in Fig. 2. In A the hydroxyl groups are equatorial, and in B they are axial. The equatorial hydroxyl groups in A will in all phases be *gauche* to L and H at C(2) as well as to M and H at C(6). The distances from the hydroxyl group to L and M will be the same and L will therefore always be larger than M. Consequently the course of an asymmetric synthesis can be predicted on the basis of a steric estimate. The results of inspection of the conformers under B are listed in Table 1. The steric interac-
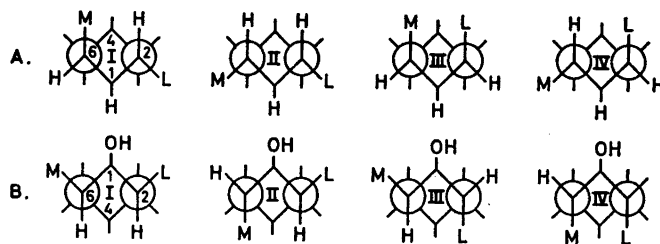


*Fig. 2.* The Newman projection formulas of the eight conformers of 2-L-6-M-(R)-cyclohexanols.

*Table 1.* Interactions in the diastereomers (B in Fig. 2) of 2-L-6-M-1 (*R*)-cyclohexanol with the hydroxyl group fixed in axial position.*

|  |  | B | | | |
|---|---|---|---|---|---|
|  |  | I | II | III | IV |
| C(2) | L | g | g | a | a |
|  | H | a | a | g | g |
| C(6) | M | g | a | g | a |
|  | H | a | g | a | g |

* L = large, M = medium, a = *trans*-diaxial, g = *gauche*.

tion between the hydroxyl group and the L or M group is smaller when they are *trans*-diaxial to each other than when they are *gauche* to each other. When the difference in steric bulk between L and M is small, it may therefore happen that an axial L group acts as a smaller group than an equatorial M group towards an adjacent axial hydroxyl group. Such may be the case with III B in Fig. 2, if the interconversion III B = I A could be prevented. As this is not possible, the course of the asymmetric synthesis studied will normally be determined by the greater stability of I A.
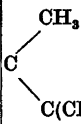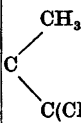
But if a bridge is present, an anomalous asymmetric synthesis may take place. Projection II in Fig. 3 represents such an alcohol with a bridge. According to these arguments — together with the fact that an axial isopropyl group is larger than an equatorial hydrogen atom — none of the four members of the menthol series should give rise to an anomalous asymmetric synthesis; see Table 2.

In the case of (*S*)-isoborneol (Fig. 1, VI) where the hydroxyl group at C(2) is in an equatorial position there is no doubt that C(1) with the methyl group and the isopropylidene bridge represents a larger group than the methylene group vicinal to C(2). This will be the case, even though the equatorial hydrogen atom in this group is eclipsed with the hydroxyl group. Following the above mentioned arguments, one would thus expect (*S*)-isoborneol to give rise to a normal asymmetric synthesis which was found to be the case (Table 2).

In (*R*)-borneol (V, Fig. 1), as in (*S*)-isoborneol, the hydroxyl group is eclipsed with one of the hydrogen atoms in the methylene group vicinal to the hydroxyl group. But the axial hydroxyl group in (*R*)-borneol is farther from the isopropylidene bridge than the equatorial hydroxyl group in (*S*)-isoborneol. It might thus be assumed that the largest group in (*R*)-borneol is the methylene group and an anomalous asymmetric synthesis would occur. But as shown in Table 2, this is not the case.

In connection with these investigations the following questions arise: What is the conformation of the alicyclic ring in 1) the starting alcohol 2)

Table 2. Predicted and observed sign of d[φ]/dt of chloral hemiacetals.

| Name of alcohol | Relative bulk [c] | | | Sequence | Sign of d[φ]/dt | | Configuration Ref. |
|---|---|---|---|---|---|---|---|
| | L | M | S | | Predicted | Observed | |
| (R)-Menthol [a] | CH(CH₃)₂ | CH₃ | H | L→M→S | negative | negative | 5 |
| (S)-Neomenthol | CH(CH₃)₂ | CH₃ | H | L←M←S | positive | positive | 5 |
| (S)-Isomenthol | CH(CH₃)₂ | CH₃ | H | L←M←S | positive | positive | 5 |
| (R)-Neoisomenthol [b] | CH(CH₃)₂ | CH₃ | H | L→M→S | negative | negative | 5 |
| (R)-Borneol [a] | $\begin{array}{c} CH_3 \\ / \\ C \\ \backslash \\ C(CH_3)_2- \end{array}$ | CH₂— | H | L→M→S | negative | negative | 6 |
| (S)-Isoborneol [b] | $\begin{array}{c} CH_3 \\ / \\ C \\ \backslash \\ C(CH_3)_2- \end{array}$ | CH₂— | H | L←M←S | positive | positive | 6 |

[a] Investigations of these alcohols have been reported in previous papers.[2]
[b] The mutarotation in these cases is very small.
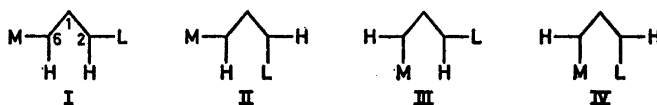[c] L = large, M = medium, S = small.



Fig. 3. Modified Newman projection formulas of the four diastereomers of 2-L-6-M-bicyclo[2.2.1]-heptan-1(R)-ol. The hydroxyl group at C(1) is in the equatorial position.

the hemiacetal 3) the reaction intermediate? The first problem has been attacked from several points of view.[5] These investigations show that the position of the hydroxyl group in menthol is purely equatorial and in neo-menthol purely axial (Fig. 1, I A and II A, respectively), whereas isomenthol neoisomenthol are equilibrium mixtures of the two chair conformers of each alcohol. In isomenthol, contrary to neoisomenthol, the amount of e conformer is larger than the amount of a conformer. Studies on a great number of sub-stituted cyclohexanes [6] and cyclohexanols [7-9] with known conformations have shown that the NMR signal from an axial proton at a carbon atom carrying a hydroxyl group (protons which are fixed to the hydroxyl carbon atom are in the following called X protons) is found at a higher field than the signal

from a corresponding equatorial proton; see Table 3. Because the NMR spectra of the X proton often appears as a very complicated pattern, it can be difficult to give the exact value of the true chemical shift. We have taken the mid-point value. This choice may explain the small discrepancies between our value and the value determined by others. The formation of chloral hemiacetals is accompanied by a paramagnetic shift of the X-proton (Table 3). This shift amounts to 0.27 ppm for axial protons and 0.08—0.10 ppm for equatorial protons. The approximate amount of the *e* conformer in isomenthol and the *a* conformer in neoisomenthol seems to be rather unaffected by the hemiacetal formation. When both of the chair conformers are present, a time-average signal appears and it is difficult to evaluate the amount of each conformer. To solve this problem the method of band width has been used.[9,10] The band width of the X proton is the distance between the farthest separated lines that can be attributed to this proton in the resolved spectrum. The mole fraction equilibrium constant can be expressed as (4):

$$K = \frac{W_a - W}{W - W_e} \tag{4}$$

Table 3. τ values [a] of the X proton in the following secondary alcohols and their chloral hemiacetals.

| Name of alcohol | Eliel et al.[8] | Musher[13] | Feltkamp and Franklin[9] | Own results |
|---|---|---|---|---|
| (R)-Menthol | 6.63 | 6.67 | 6.62 | 6.74 |
| Corresponding hemiacetal | | | | 6.47 |
| (S)-Neomenthol | 5.97 | 5.97 | 6.25 | 6.00 |
| Corresponding hemiacetal | | | | 5.90 |
| (S)-Isomenthol | | 6.24 | 5.95 | 6.28 |
| Corresponding hemiacetal | | | | 6.01 |
| (R)-Neoisomenthol | | 5.94 | 6.05 | 6.04 |
| Corresponding hemiacetal | | | | 5.97 |
| (R)-Borneol | | | | 6.07 |
| Corresponding hemiacetal | | | | 5.93 |
| (S)-Isoborneol | | | | 6.44 |
| Corresponding hemiacetal | | | | 6.31 |

[a] Values reported in other units have been converted into τ values.

W is the band width of the X proton and $W_a$ and $W_e$ are the band widths of X protons wholly in axial and equatorial positions, respectively (e and a refer to the position of the hydroxyl group). The values of $W_e$ and $W_a$ are chosen from alcohols with known conformations. These alcohols have to be of nearly the same structures as the ones under investigation. In the study of menthols, Feltkamp and Franklin [9] have thus used analogues in which the isopropyl group of menthol is replaced by a t-butyl group, since the t-butyl group will place itself in an equatorial position. We have instead used menthol and neomenthol and have obtained nearly the same results as Feltkamp and Franklin;[9] see Table 4. The equilibrium concentration of the e conformer is

Table 4. The band width of the X proton and the equilibrium percentage of the e conformer in isomenthol and neoisomenthol.

| Name of alcohol | W in cps | $W_a$ in cps | $W_e$ in cps | Equilibrium % of the e conformer |
|---|---|---|---|---|
| (R)-Menthol | 23 | | 23 | |
| (S)-Neomenthol | 8.5 | 8.5 | | |
| (S)-Isomenthol | 18.5 | | | 69 |
| (R)-Neoisomenthol | 14 | | | 38 |

69 % for isomenthol and 38 % for neoisomenthol. The latter percentage shows that the favored position of the isopropyl group is equatorial even if the hydroxyl group and the methyl group are forced into axial positions. The same procedure could not be applied to the chloral hemiacetals, owing to difficulties with band width measurements.

The last question concerning the conformation of the alicyclic ring in the reaction intermediate. In connection with other reactions, this question has previously been discussed by Hanack.[5] Read and Grubb [11] obtained the following values for the relative rates of esterification with p-nitrobenzoyl chloride in pyridine: menthol 16.5, isomenthol 12.3, neomenthol 3.1, and neomenthol 1.0. In neoisomenthol the methyl group and the hydroxyl group are mainly axial, whereas in neomenthol only the hydroxyl group is axial. From steric considerations one might therefore expect neomenthol to be more rapidly esterified than neoisomenthol, contrary to the experimental evidence.

This incongruity has been explained by Eliel,[12] who assumes that for the esterification to occur the hydroxyl group in both the alcohol and the reaction intermediate has to be equatorially oriented and notes that neoisomenthol contains more of the e conformer than neomenthol. We have found that the relative rates of formation of chloral hemiacetals of neoisomenthol and neomenthol are 2.8 and 1.0. These results are in agreement with the results of Read and Grubb [11] and the explanation given by Eliel.[12]

## EXPERIMENTAL

The conditions under which the various epimerizations were carried out are listed in Table 5. Details about experimental conditions and treatment of the results are given in previous papers.[1,2] All alcohols used except isoborneol were commercial products. Optically active isoborneol was prepared by resolution of the cinchonine salt of isobornyl hydrogen phthalate.[14]

*Acknowledgement.* The author takes pleasure in thanking professor K. A. Jensen for kind and stimulating interest in this work.

*Table 5.* The experimental conditions of the mutarotation of the chloral hemiacetals.

| Name of alcohol | Concentrations (M) | | | $[\varphi]_{364}$ of the alcohol [a] |
|---|---|---|---|---|
| | Chloral | ROH | $CH_3CO_2H$ | |
| (R)-Menthol | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | $2 \times 10^{-3}$ | $-210$ |
| (S)-Neomenthol | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | $2 \times 10^{-3}$ | 97 |
| (S)-Isomenthol | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | 127 |
| (R)-Neoisomenthol | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | 1.7 |
| (R)-Borneol | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | $-132$ |
| (S)-Isoborneol | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | $2 \times 10^{-2}$ | 1.3 |

[a] $[\varphi]_{364}$, the molecular rotation at 364 m$\mu$, was calculated from the reaction of a $10^{-2}$ M solution of the alcohol in heptane. The measurements were carried out in a 1 dm tube.

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