USE OF X-RAY DIFFRACTION DATA IN
STEREOCHEMICAL STUDIES OF (-)-MENTHONE
REACTIONS WITH AROMATIC ALDEHYDES

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X-ray diffraction analysis proved that the stereochemical configuration of interaction products of
(-)-menthone with aromatic aldehydes (α,β-unsaturated ketones or β-hydroxyketones) depends on the
generation conditions of intermediate enolate carbanions. In irreversible deprotonation of (-)-menthone
with strong sterically hindered organometallic bases, products of interaction with aldehydes preserve the
1R,4S-configuration; in equilibrium conditions, 1R,4R-diastereomers of the corresponding
α,β-unsaturated ketones are formed with high stereoselectivity.

The reactions of (-)-menthone enolate carbanions with electrophilic carbonyl reagents, including aromatic
aldehydes, are an important method for the molecular design of effective chiral additives to liquid crystal materials
[1]. Elucidating the relation between the molecular structure of chiral compounds and their efficiency in inducing spiral
ordering in mesomorphic systems requires reliable information on the spatial structure of molecules. For chiral additives
obtained on the basis of (-)-menthone, it is important to study stereochemical aspects of the corresponding reactions.
The aim of this investigation is to study the stereochemistry of (-)-menthone interactions with aromatic aldehydes using
X-ray diffraction (XRD) data for products obtained under different conditions.

The reaction of (-)-menthone Ia with aldehydes proceeds via the intermediate formation of enolate
carbanions II and may generally result in ketols (β-hydroxyketones) III, IV and their dehydration
products (α,β-unsaturated ketones V, VI) (Scheme 1):

Scheme 1

\[ \text{Ia, IIa, III, and V are 1R,4S-trans-diastereomers} \]
\[ \text{Ib, IIb, IV, and VI are 1R,4R-cis-diastereomers} \]

An important feature of (-)-menthone Ia is its ability to form isomeric 2- and 4-enolate carbanions IIa and
IIc (Scheme 2). This is an essential prerequisite to the formation of two diastereomeric products — with preservation
of the initial configuration (III and V) and with the inversion of the C(4) chiral center in the α-position relative to the
carbonyl group (IV, VI) (Schemes 1 and 2) — in reactions involving enolate carbanions IIa-c generated under the
equilibrium conditions.

Under normal conditions of base catalysis, (-)-menthone does not react with aromatic aldehydes [2]. Some
progress was made when this reaction was conducted in so-called superbasic media (e.g., dimethylsulfoxide–potassium

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hydroxide) [2, 3]. In this case, one of the two possible diastereomers (V, VI) is formed with high stereoselectivity. The products are identical to those formed in low yields in traditional aqueous-alcohol alkaline media.

Scheme 2

To examine stereochemical selectivity of the reaction under these conditions, we carried out XRD analysis of two products: with \( \text{Ar}=\text{CH}_3\) and \( \text{Cl} \) [2, 4]. In the crystalline state, these compounds have a chair conformation of the cyclohexanone ring with cis-orientation of alkyl groups (methyl is axial and isopropyl is equatorial). Since the C(1) chiral center [R-configuration in the initial \((-\)-menthone [5]) remains intact in this reaction, XRD data on molecular conformation and cis-orientation of 1,4-alkyl groups unambiguously indicate the 1R,4R-configuration of the products.

Thus, both in superbasic and aqueous-alcohol alkaline media, the configuration of the reaction products is that of \((+)-\)isomenthone Ib but not of initial \((-\)-menthone Ia. The inverted configuration of C(4) is determined by the equilibrium character of all reaction stages (see Schemes 1, 2) under the given conditions. Molecular-mechanical calculations showed that cis-2-arylidenem-menthan-3-ones VI are energetically preferable to their trans-diastereomers V, which is one of the factors responsible for the high stereoselectivity of formation of products with the inverted configuration of C(4) [2, 4].

It seems possible to obtain 1R,4S-trans-p-menthan-3-one derivatives (without inversion of the C(4) configuration) under conditions of irreversible generation of intermediate enolate carbanions II (see Scheme 1). This may be realized if pK of the bases exceed those for II by several orders of magnitude. To prevent formation of 4-enolate carbanions IIc, not leading to the target products, the bases must be sterically hindered. For such irreversible deprotonation of asymmetric ketones in the least substituted \( \alpha \)-position, branched lithium dialkylamides [6] are most frequently used; in some cases, including the condensation with aldehydes [7, 8], magnesium or zinc derivatives are preferable.

This approach was used by us to prepare 1R,4S-2-oxymethylene-p-menthan-3-one [9, 10]* using bromo-magnesyldiisopropylamide as a base. We first synthesized \( \beta \)-hydroxyketone IIIa \((\text{Ar}=4,4'-\text{C}_6\text{H}_4\text{C}_6\text{H}_4)\) by deprotonation of \((-\)-menthone with this base followed by the interaction with 4-phenylbenzaldehyde (see experimental section).

The configuration and the spatial structure of ketol IIIa obtained under the specified conditions were determined using XRD data. In this structure, the cyclohexanone ring has a virtually undistorted chair conformation. This is indicated by the alternation of the signs of the torsion angles \( \varphi_1-\varphi_6 \) in the cycle (Table 1), while the absolute values of the angles slightly differ from the value \((60^\circ)\) typical for a regular chair conformation. The alkyl substituents in the 1,4-positions have a trans-equatorial orientation (Fig. 1). Together with the unchanged R-configuration of C(1), this indicates the 1R,4S-configuration of ketol IIIa. Thus, under the given conditions, \( \beta \)-hydroxyketone is formed, in which the initial 1R,4S-configuration of \((-\)-menthone is retained.

In molecules IIIa, the 2-arylhydroxymethyl substituent is trans-equatorial relative to the methyl group at C(1) (see the torsion angles \( \varphi_{11}-\varphi_{13} \) in Table 1) and cis relative to 4-isopropyl. Such a molecular conformation with the 1R,4S-configuration of the alkyl substituent unambiguously indicates the R-configuration of the C(2) chiral center arising in the formation of ketol IIIa.

XRD data show that the crystalline phase of \( \beta \)-hydroxyketone IIIa has a conformation involving an intramolecular

* Under the equilibrium conditions of enolate carbanion formation, a mixture with predominant cis-isomer is obtained [2, 11].