REGIOSELECTIVE SYNTHESES OF OPTICALLY ACTIVE (R)-5-METHYL- AND
(R)-7-METHYL-5,6,7,8-TETRAHYDROQUINOLINES

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Abstract —— Five synthetic routes have been evaluated for the
regioselective preparation of (R)-5-methyl- and (R)-7-methyl-5,6,7,8-
tetrahydroquinolines from (+)-(R)-3-methylcyclohexanone.

In developing synthetic approaches to 5,6,7,8-tetrahydroquinolines containing one
asymmetric carbon in the alicyclic ring1 we have devoted our attention to the synthesis of
(R)-5-methyl- and (R)-7-methyl-5,6,7,8-tetrahydroquinolines (1) and (2). These compounds
are the most convenient starting points for the synthesis of the corresponding optically
active 2,2'-bipyridines and 1,10-phenanthrolines, whose applications receive considerable
attention whether as chiral ligands for asymmetric reactions2 or for the study of the
chiroptical properties of the pyridine chromophore.3

A mixture of racemic (1) and (2) had been prepared by Irie et al. through a straightforward
method of pyridoannelation starting from 3-methylcyclohexanone.4 However no
information about the ratio of the regioisomers was reported. More recently, a mixture of 1
and 2 has been obtained, among other by-products, in the synthesis of (+)-(R)-5-methyl-8-
isopropylidene-5,6-dihydro-7H-quinoline.5

To synthesize 1 and 2, the largely accessible (+)-(R)-3-methylcyclohexanone6 (3) appeared a
very interesting starting material. This paper is concerned with the evaluation of five
synthetic routes to synthesize 1 and 2 from 3.

 Initially, trying Irie's procedure, by heating a benzene solution of (R)-3-
methylcyclohexanone O-allyloxime (4) in a scaled tube, a 30% yield of a 24:76 mixture of 1
and 2 was obtained (Scheme 1). It was impossible to effect any separation of the two isomers
and their ratio was determined on the basis of nmr data.
The most direct synthesis of pyridine derivatives is by condensation of a suitable nitrogen source with appropriate δ-dicarbonyl compounds. These are easily obtained by the reaction of enamines with vinyl aldehydes or ketones.\(^1\)\(^7\)

Morpholine enamine of 3-methylcyclohexanone exists as a 1:1 mixture of two structural isomers.\(^8\) The reaction of this mixture with various electrophiles is known to give adducts whose composition deviates from that of the parent enamines.\(^9\) In some cases only one of the two possible adducts has been obtained.\(^10\) Moreover, to our knowledge no data is reported in the literature about the reaction of enamines of 3-methylcyclohexanone with Michael acceptors.\(^11\)

Thus, a 1:1 mixture of morpholine enamines (5a,b) was allowed to react with acrolein to give cycloaddition adducts (6a,b)\(^12\) (Scheme 2). Treatment of crude (6) with hydroxylamine hydrochloride\(^1\) gave a 25:75 mixture of 1 and 2 in 30% overall yield. It is reasonable to think that the composition of the isomers in 6 is the same found in the final products.

**Scheme 2**

\[
\begin{align*}
3 & \xrightarrow{\text{R}} 5a,b & \xrightarrow{\text{R}} 6a,b & \xrightarrow{\text{R}} 1 + 2
\end{align*}
\]

a: \(R=H, R'=CH_3\)  b: \(R=CH_3, R'=H\)

Reagents: i. morpholine, TsOH, \(C_6H_5\); ii. acrolein, \(C_6H_5\); iii. \(NH_2OH\cdot HCl, 78^\circ C\)
Another route we have followed to obtain 1 and 2 is depicted in Scheme 3. A mixture of 8a and 8b was formed in one step when 3 and acrylonitrile were heated in an autoclave in the presence of 4-methylcyclohexylamine and acetic acid\(^{13}\) (53% yield). Dehydrogenation\(^{14}\) of crude (8a,b) gave a mixture of tetrahydroquinolones (9a) and (9b) in 25:75 ratio (by nmr) which was converted into the corresponding halogen-derivatives (10a) and (10b)\(^{15}\) (70% yield) having the same isomeric ratio. Hydrogenolysis of 10a,b catalyzed by palladium on charcoal\(^{16}\) gave a 25:75 mixture of 1 and 2 in 85% yield. This ratio undoubtedly reflects the composition of the isomer mixture in 8a,b, as confirmed by glc analysis of the mixture obtained in an experiment stopped before completion: beside the final product (8a,b) a 26:74 mixture of isomeric nitriles (7a) and (7b) was detected. A very similar ratio (28:72 by nmr) of nitriles (8a) and (8b) was obtained when the reaction was carried out in atmospheric pressure.

Scheme 3

![Scheme 3](image)

\[ 3 \xrightarrow{i} 7a,b \xrightarrow{ii} 8a,b \xrightarrow{iii} 10a,b \xrightarrow{iv} 1 + 2 \]

a: R = H, R' = CH\(_3\)  
b: R = CH\(_3\), R' = H

Reagents: i, \(\text{CH}_2=\text{CHCN}\); ii, \(\text{SO}_2\text{Cl}_2\); iii, (PhO)\(_3\)P\(_2\)Cl; iv, Pd/C, H\(_2\)

The alkylation of metallated N,N-dimethylhydrazones (DMH's) is a very efficient method for forming highly regioselective C-C bonds.\(^{17}\) Enders reported that the alkylation of (25)-2-methoxymethyl-1-(3-methylcyclohexyldenamin)pyrrolidine with isopropyl iodide takes place in the 6-position to give, after hydrolysis, a menthone-isomenthone mixture.\(^{18}\)
Moreover, we have recently described a pyridoannelation method based on the regiospecific alkylation of DMH's with 2-(2-bromoethyl)-1,3-dioxolane (BED) followed by acid catalyzed intramolecular cyclization of the iminoacetal intermediates. Following this synthetic strategy, a 8:92 mixture of 1 and 2 was obtained starting from 3 (48% overall yield) (Scheme 4).

**Scheme 4**

\[
\text{3} \quad \text{i} \quad \text{ii} \quad \text{iii} \quad \text{iv} \quad \text{1 + 2}
\]

a: R=H, R' = CH\text{\textsubscript{3}}  b: R = CH\text{\textsubscript{3}}, R' = H

Reagents: i. H\text{\textsubscript{2}}NN (CH\text{\textsubscript{3}})\text{\textsubscript{2}}; ii. LDA; iii. BED; iv. AcOH, 115 °C

All the methods reported above give tetrahydroquinoline (2) as the main product. In order to obtain 1, we attempted to block selectively the 6-position of the ketone (3). Base-catalyzed condensation of 3 with ethyl formate\textsuperscript{20} gave a mixture of 13\textsubscript{a} and 13\textsubscript{b} in a 80:20 ratio by nmr (Scheme 5). Treatment of 13\textsubscript{a,b} with 1,2-ethanedithiol dithiole and potassium acetate in ethanol\textsuperscript{21} produced thiketal ketones (14\textsubscript{a}) and (14\textsubscript{b}) in about 90:10 ratio (62%). Chromatographic purification gave pure 14\textsubscript{a}\textsuperscript{22} but, up to the moment, not in sufficient quantities for our needs. Therefore a mixture of 14\textsubscript{a} and 14\textsubscript{b} (90:10) was converted into the dithiaspirotetrahydroquinolines (17\textsubscript{a}) and (17\textsubscript{b}) according to Scheme 5. Thus 14\textsubscript{a,b} were first transformed into N,N-dimethylhydrazones (15\textsubscript{a,b}) and then alkylated with BED to give 16\textsubscript{a,b} which were used directly in the next step. Heating of crude 16\textsubscript{a,b} in acetic acid produced 17\textsubscript{a,b} (45% overall yield from 15) which, by treatment with Raney-Ni in 7:3 ethanol/water\textsuperscript{23} gave a 90:10 mixture of 1 and 2 (95% yield). The Table summarizes the results obtained in the pyridoannelation of 3 by all the synthetic routes tested.
Scheme 5

![Scheme 5 diagram]

Reagents: i, NaH, HCOOC₂H₅; ii, TsS(CH₂)₂STs; iii, H₂NN(CH₃)₂; iv, LDA; v, BED; vi, AcOH, 115 °C; vii, Raney-Ni, H₂

Table

<table>
<thead>
<tr>
<th>route</th>
<th>yield*</th>
<th>% of 1</th>
<th>% of 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-Allyloxime (4)</td>
<td>30</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>Enamine (5)</td>
<td>26</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Quinolone (8)</td>
<td>36</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Hydrazone (11)</td>
<td>48</td>
<td>8</td>
<td>92</td>
</tr>
<tr>
<td>Hydroxymethylene (13)</td>
<td>22</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

* Overall yield from 3
REFERENCES AND NOTES


11. It has been reported, indeed, that the reaction of the pyrrolidin enamine of $\alpha$-cholestan-3-one with acrolein followed by treatment with hydroxylamine hydrochloride gives only the [3,2-b]pyridine derivative: S. Gladiali, G. Gottarcelli, B. Samari, and P. Palmieri, *J. Chem. Soc., Perkin Trans. II*, 1980, 598.


Selected $^1$H nmr data: (CDCl$_3$) $\delta$ 1.02 (d, J= 6 Hz, 3H); 3.23 (s, 4H). Anal. Calcd for C$_9$H$_{14}$O$_2$S: C, 53.42; H, 6.97; S, 31.69. Found: C, 53.31; H, 7.05; S, 31.75. [$\alpha$]$^2$D +130.3$^\circ$ (c 2.70, cyclohexane).


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