CHAPTER V

SYNTHESIS OF AN INTERMEDIATE METHYL
3 - METHYL - 3 - ( 2' - METHOXY - 5' - METHYLPHENYL )
BUTANOATE FOR HIMASECOLONE SYNTHESIS
CHAPTER-V
SYNTHESIS OF AN INTERMEDIATE METHYL 3-METHYL-3-(2'-
METHOXY-5'-METHYLPHENYL) BUTANOATE FOR HIMASECOLONE

ABSTRACT

Alkylation of e-cresol with \( \beta,\beta \)-dimethyl acrylic acid using concentrated sulphuric acid yielded 4,4,6-trimethyl dihydrocoumarin (2.2). Treatment of (2.2) with sodium hydroxide and dimethyl sulphate gave methyl 3-methyl-3-(2'-methoxy-5'-methylphenyl) butanoate (2.3). The ester (2.3) has been converted by Rao and John to himasecolone (2.8), a phenolic sesquiterpene from Cedrus deodara.

INTRODUCTION

Polyphenolic constituents belonging to lignans and dihydroflavonol groups were reported from butanol soluble fraction of the extract of Cedrus deodara wood. The chloroform soluble fraction of the extract was found to be a very complex mixture of closely running compounds on TLC which could not be resolved. However, the separation of this fraction into acidic and neutral portions led to a reasonable separation which resulted in the isolation of isopimaric acid (1.1) and a new novel seco-sesquiterpene.
himasecolone\(^3\) (1.2) in addition to himachalol (1.3)\(^4\) and centdarol (1.4).\(^5\) The latter two compounds (1.3; 1.4) have been reported earlier from the hexane fraction.

Himasecolone was obtained as a colourless oil, homogenous by TLC and HPLC, optically inactive, with the molecular formula \(\text{C}_{15}\text{H}_{22}\text{O}_2\) \((\text{M}^+ m/z \ 234.162)\). Its IR spectrum showed a peak at 1700 cm\(^{-1}\) corresponding to carbonyl group, and at 3380, 1608 and 1500 cm\(^{-1}\) assigned to phenolic -OH and aromatic C=C. It was further supported with UV maxima at 280nm which showed a bathochromic shift on addition of alkali. The PMR spectrum (270MHz) showed three singlets: at \(\delta \ 1.16\) corresponding to gem-dimethyl, at 2.02 due to acetyl-methyl and at 2.23 for aryl-methyl. A sharp doublet at 6.46, a double doublet at 6.97 and a broad singlet at 6.84 revealed the presence of 1,2,4-aromatic substitution pattern. The above data indicate the presence of an aromatic ring with side chain \((\text{C}_{8}\text{H}_{15}O)\) containing gem-dimethyl and keto groups in the molecule.

The PMR spectrum of himasecolone recorded after addition of trichloroacetyl isocyanate (TAI) showed the signal at \(\delta \ 9.17\) corresponding to the carbamate proton. The two non-equivalent gem-dimethyl were shown at 1.16 and 1.20 and one aryl methine signal was shifted downfield suggesting the propable ortho
disposition of the phenolic -OH to the six carbon side chain.

The mass spectrum of himasecolone exhibited an intense ion at m/z 149, indicating benzylic cleavage fragment ion. A strong ion at m/z 43 suggests the presence of a terminal -COMe group in the side chain. This was confirmed by its lithium aluminium hydride (LiAlH₄) reduction to a secondary carbinol (1.5). The PMR spectrum of this carbinol showed a doublet at 1.06 corresponding to a secondary methyl and a quartet (should be a sextet) at 3.64 due to a secondary carbinolic proton (-CH₂-OH) which was established by decoupling experiments. The acetylation of (1.5) resulted in diacetyl derivative (1.6) whose IR spectrum demonstrated bands at 1758 and 1725 cm⁻¹ and PMR spectrum showed signals for an aliphatic and aromatic acetoxy methyl at 1.78 and 2.14 respectively and a secondary methine H at 4.65. In the aromatic region, only one aryl methine showed an acetylation induced paramagnetic shift of 0.1 ppm indicating that the other ortho- and para-positions with respect to the phenolic -OH were occupied by the methyl groups and the C₆ side chain. The negative Gibb's test supports the absence of free para position. Hence, the side chain should be ortho- to the phenolic hydroxyl. The mass spectral fragmentation pattern and the decoupling experiments
when the irradiation at $\delta 2.30$ in the 270MHz spectrum showed a marked change in one of the methylene proton multiplets at $\delta 1.28$, confirming the structure of the side chain as $\text{-C(\text{Me})_2CH_2CH_2CH_2COMe}$. The above data and biogenetic considerations suggest structure (1.2) for himasecolone. This was supported by the mass spectral fragmentation of its diacetyl derivative (1.6), which showed intense ions at m/z 191 and 149 due to benzylic cleavage with and without loss of carbene respectively from the phenoxyacetetyl function which could easily stabilize as a tropylium or quinonoid ion by the loss of H. Additional confirmation was obtained by the $\text{^{13}C}$ NMR chemical shifts of the aromatic carbons and the $\text{^{13}C-^1H}$ coupling pattern observed in the NOE enhanced single frequency spectrum which were consistent with the calculated values for structure (1.2). The chemical shifts of the side chain carbons were comparable with reported values in taylorione (1.7) which has a similar side chain.

So far the phenolic sesquiterpenoids in angiosperms have been represented by elvirol (1.8) and sesquichamaenol (1.9), which were believed to originate from their biogenetic precursors, sesquicarene (1.10) and $\text{\text{-}-cadinene}$, by oxidative ring scission followed by aromatization. It may, however, be mentioned that a number of phenolic sesquiterpenes have also been
reported from marine source. The newly isolated himasecolone in Cedrus deodara is significant since it is the first report of the occurrence of a phenolic sesquiterpenoid in a gymnosperm. Obviously himasecolone has formed by an analogous sequence of reactions from $\beta$-himachalene (1.11), i.e. oxidative cleavage of C-10, C-11 olefinic bond followed by aromatization.

**PRESENT WORK**

Agarwal and Rastogi have reported in 1981 the isolation of himasecolone (2.8) as a new phenolic sesquiterpene and the structure assigned is based on physico-chemical evidence. In order to provide synthetic evidence for the structure we undertook the synthesis of himasecolone (2.8). The plan was to synthesize methyl 3-methyl-3-($'$$'_{2}'$-methoxy-5'-methylphenyl)butanoate (2.3) and then elaborate the side chain to the required structure. The natural choice to get (2.3) would be the alkylation of a suitable aromatic substrate with $\beta,\beta$-dimethylacrylic acid. Alkylation of $p$-cresol with $\beta,\beta$-dimethylacrylic acid (2.1) in the presence of concentrated sulphuric acid at 160-80°C gave 4,4,6-trimethyl dihydروcoumarin (2.2), m.p.63°C. IR(nujol, Fig.1) showed a strong band at 1775 cm$^{-1}$ due to lactone carbonyl. The PMR spectrum (50MHz, Fig.2) was in
agreement with the structure. A strong singlet peak for six protons at $\delta$ 1.33 is assigned to the gem-dimethyl group, a singlet at 2.30 is assigned to the aromatic methyl and a singlet for two protons at 2.50 is due to the methylene protons. The three aromatic protons appeared as a multiplet between $\delta$ 6.65 and 7.20.

The next step was to convert this lactone (2.2) to the ester (2.3). We decided to methylate the disodium salt of (2.2) with dimethylsulphate which would give the required ester (2.3). The lactone was dissolved in sodium hydroxide and treated with dimethyl sulphate to yield methyl 3-methyl-3-(2'-methoxy-5'-methylphenyl) butanoate (2.3), thus methylation and esterification being achieved in one step. IR spectrum (Neat, Fig.3) showed a strong band at 1745 cm$^{-1}$ due to the ester function. The PMR spectrum (60MHz, Fig.4) was in complete agreement with the structure. A strong peak at 1.40 for six protons, is due to the gem-dimethyl, a singlet for three protons at 2.20 is assigned to the aromatic methyl, a singlet at 2.70 for two protons is due to the methylene group and singlets at 3.33 and 3.72 are due to the methoxyl of the ester and the aromatic ether respectively. The three aromatic protons appeared as a multiplet between $\delta$ 6.60 and 7.00. A trace amount of acid (2.9) was also obtained in the above reaction.
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\text{CHART-2}
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When the work was at this stage we visited the Indian Institute of Science, Bangalore and realized that Prof. Krishna Rao and John have already synthesized himasecolone in 1979 under the name himaphenolone. They predicted it to occur in nature as a bio-congener of \( \beta \) -himachalene (1.11). Unfortunately, Agarwal and Rastogi have not mentioned anything about Prof. Rao's paper which led us to believe that himasecolone is a entirely new product.

The synthesis of Rao and John starts from the \( \alpha \)-cresol methyl ether which they alkylate with \( \beta \)-dimethylacrylic acid to give 3-methyl-3-(2'-methoxy-5'-methylphenyl) butanoic acid (2.9). The methyl ester of (2.9) was then elaborated to himasecolone (himaphenolone) as shown in the chart (2.3 \( \rightarrow \) \( \rightarrow \) 2.8).

We have also obtained the methyl ester (2.3) by a different route (2.1 \( \rightarrow \) 2.3) \( \rightarrow \) since this has been converted into himasecolone by Rao and John\( ^{12} \) we stopped our work at this stage.
EXPERIMENTAL

General

p-Cresol (KL), $\beta,\beta'$-dimethylacrylic acid (SRL) and dimethyl sulphate (Riedel) were used. The IR spectra were recorded on perkin-Elmer Infracord and the PMR on T-60 spectrometer.

4,4,6-Trimethyl dihydrocoumarin (2,2)

A solution of p-Cresol (5.5g) and $\beta,\beta'$-dimethyl acrylic acid (5g) in sulphuric acid (72%, 10 ml) was heated in an oil-bath at 160-80°C for 2.5 hr. The contents were cooled and poured into cold water (50 ml). The dark organic layer was extracted with ether and the ether extract was successively washed with sodium hydroxide (5%, 3x25 ml) and with water (2x40 ml) and dried over anhydrous sodium sulphate. Removal of solvent furnished dark red product (4.1g). A solution of the above dark product (4.1g), sodium hydroxide (10%, 50 ml) and ethenol (50 ml), was refluxed on water-bath (10 hr). The ethanol was removed in vacuo and the residue remained was diluted with water (50 ml). It was extracted with ether (3x40 ml) and the combined ether extract washed with water (3x50 ml) and dried over anhydrous sodium sulphate. Removal of solvent gave gummy material (1.4g) which was not investigated.
The alkaline layer, was acidified with hydrochloric acid (50%). The oily layer formed was extracted with ether and the ether extract washed with water (2x50 ml) and dried over anhydrous sodium sulphate. The removal of ether afforded dark crude product (2.560g). This crude product was filtered through a column of silica gel (60-120 mesh, 30g) to give transparent white crystals of dihydrocoumarin (2.2), 2.135, m.p.63° IR(nujol, Fig.1): 1775 cm⁻¹. PMR (60MHz, Fig.2): δ 1.33 (6H, s, gem-dimethyl), 2.30 (3H, s, Ar-CH₃), 2.50 (2H, s, -CH₂-), 6.65-7.20 (3H, m, Ar-H).

Analysis

Found : C, 75.6; H, 7.5.
requires : C, 75.8; H, 7.4%.

Methyl 3-methyl-3-(2'-methoxy-5'-methylphenyl) butanoate (2.3) from 4,4,6-trimethyl dihydrocoumarin (2.2)

The dihydrocoumarin (2.2, 2.0g) was dissolved in sodium hydroxide (10%, 15 ml) and cooled in an ice-bath. To this dimethyl sulphate (5 ml) was added with stirring during 30 min and the solution refluxed in an oil-bath (2 hr). The contents were cooled and diluted with water (25 ml) and extracted with ether (3x30 ml). The combined ether extract was successively washed with sodium hydroxide (5%, 3x20 ml), water and then dried over anhydrous sodium sulphate. Removal of solvent
furnished the ester (2.3, 1.82g). It was purified by chromatography over silica gel (60-120 mesh, 25g). It was eluted with pet.ether-chloroform (9:1). IR(Neart, Fig.3) : 1745 cm⁻¹ PMR (60MHz, Fig.4) 1.40 (6H, s, gem-dimethyl), 2.20 (3H, s, Ar-CH₃), 2.70 (2H, s, -CH₂-), 3.33 (3H, s, COOCH₃), 3.72 (3H, s, Ar-OCH₃), 6.60-7.0 (3H, m, Ar-H).

Analysis

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<td>C, 71.3; H, 8.3</td>
<td>C, 71.2; H, 8.5%</td>
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REFERENCES


