CHAPTER - III PART-B

SYNTHESIS OF OCIMIN, A NEW NEOLIGNAN FROM OCIMUM AMERICANUM LINN.
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OCIMUM AMERICANUM LINN.*

ABSTRACT

Ocimin, a novel neolignan isolated from Ocimum americanum Linn, has been synthesized for the first time starting from 1,6-di-(p-methoxyphenyl)-1,6-hexanedione (2.2). Sodium borohydride reduction of this dione (2.2) in dioxane-ethanol gave the corresponding diol (2.3) which underwent dehydration using triphenylphosphine-carbon tetrachloride in dioxane to give ocimin (1.1 = 2.4).

INTRODUCTION

Ocimin, a novel neolignan was isolated from Ocimum americanum Linn, by Atal and co-workers. This is the first report of isolation of a neolignan in which the two C₆C₃ units (propenylphenols or allyl phenols) have coupled at the γ-carbon atoms. During the investigation of Ocimum species for useful essential oil constituents, a new strain of Ocimum americanum L. was developed by selection and hybridization. The

essential oil of this new strain obtained by steam distillation of the fresh green plant contains about 70% methyl chavicol. The chavicol and linalool were removed by fractional distillation and the residue remained deposited a solid on chilling. Repeated crystallization of this crude solid from ethylacetate gave Ocimin as white fluorescent flakes (m.p. 168-171°C).

The elemental analysis and mass spectrum (M⁺ 294) of ocimin gave its molecular formula as C₂₀H₂₂O₂. The UV spectrum (MeOH) showed λ_max 265, 273 and 297 nm and the IR(nujol) showed characteristic bands for trans double bond at 1610, 965 and 950 cm⁻¹. The 60MHz PMR (CDCl₃) accounts for only eleven protons indicating that the molecule is a symmetrical dimer. It showed methoxyl protons at 5.8 and allylic methylene protons as broad triplet at 2.4. Two AB doublets at 5.27 and 6.73 (J=8Hz) are due to four aromatic protons. One olefinic proton appeared as a doublet at 6.41 (J=16Hz) indicating the trans nature of the double bond. The other olefinic proton occurred as a complex multiplet between 5.97 to 6.33.

On hydrogenation with Pd/C ocimin absorbed two moles of hydrogen and yielded 1,6-di-(p-methoxyphenyl)-hexane (1.2) m.p. 68°C (Lit² 70-71°C reported as byproduct during the synthesis of podocarpatriene). The elemental analysis and mass spectrum (M⁺ 298) of this hydrocarbon
CHART-1

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\begin{align*}
\text{(1)} & \quad \text{CH} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH} = \text{CH} \\
\text{(2)} & \quad \text{H}_2 \xrightarrow{\text{Pd/C}} \\
\text{(3)} & \quad \text{CO}_2\text{H} + \text{CH}_2 - \text{CO}_2\text{H} \\
\text{(4)} & \quad \text{CH}_2 - \text{CO}_2\text{H} \
\end{align*}
\]
(1.2) gave the molecular formula as C_{20}H_{26}O_{2}. PMR spectrum showed signals at δ 1.4 (4H, s, CH_2-CH_2), 2.5 (2H, t, benzylic CH_2), 3.8 (3H, s, OMe) and 6.7-7.33 (4H, dd, aromatic protons). Thus structure (1.1 ≡ 2.4) was suggested to ocimin on the basis of above data. It was further confirmed by oxidation with potassium permanganate.

Oxidation of ocimin with potassium permanganate furnished two acids, identified as succinic acid (1.4) and p-methoxy benzoic acid (1.3). These acids were characterised by paper chromatography (PC), succinic acid (Rf 0.63), p-methoxy benzoic acid (Rf 0.75); (n-BuOH-5% HOAc, 1:1); by comparison with reference samples. The PMR spectrum of p-methoxy benzoic acid showed signals at δ 3.71 for methoxyl protons and two doublets at 6.60 and 7.63 for aromatic protons.

PRESENT WORK

Ocimin (1.1 ≡ 2.4), a novel neolignan isolated by Atal et al from the essential oil of Ocimum americanum Linn, was assigned the structure on the basis of spectroscopic and degradative evidence. We undertook the synthesis of ocimin since it has not been reported earlier.

Friedel-Crafts acylation of anisole with adipoyl chloride (2.1) using anhydrous aluminium chloride gave
The reduction of the dione (2.2) to diol (2.3) followed by dehydration would give ocimin (2.4). The dione (2.2) was insoluble in ethanol so the reduction was carried out in dioxane-ethanol mixture to give 1,6-di-(p-methoxyphenyl)-1,6-hexanediol (2.3) in excellent yield. m.p. 132-33° IR(nujol, Fig.1) : 3390 (-OH), 1618, 1590 cm⁻¹. PMR(60MHz, Fig.2) taken in CDCl₃+ drop of d₆-DMSO was in complete agreement with the structure assigned: δ 1 to 2 showed a broad multiplet for eight methylene protons, at 2.95 was a broad singlet due to two hydroxyl protons, a singlet for six protons at 3.72 was due to two methoxyl protons, a triplet at 4.3 was due to two benzylic methine protons. The aromatic protons showed the characteristic AA'BB' pattern of a p-disubstituted aromatic ring: a doublet at 6.73 was due to protons ortho to methoxyl group and other doublet at 7.17 was assigned to protons meta to methoxyl group.

The dehydration of the diol (2.3) using pyridine-phosphorous oxychloride, p-toluenesulphonic acid, anhydrous copper sulphate in benzene, neutral alumina, iodine and phthalic anhydride gave undesired product. Dehydration of benzylic alcohols using acid catalysts is known to cause problems. Dehydration of
encecalinol (3.1) using p-toluenesulphonic acid in benzene gave intermolecular dehydration product and polymeric material. In the preparation of 4,7-dimethoxyindene (3.3) from the corresponding indanol (3.2), it was found that commonly used acid catalysts gave low yields and tarry products. The benzylic diol (2.3) is activated by the presence of p-methoxyl group and appears to be sensitive to acidic conditions of dehydration and there is also a possibility of polymerization of the resulting olefin. The other possibility is the formation of a cyclic ether (3.4) as in the case of diol (3.5) which undergoes cyclization to (3.6) with sulphuric acid.

In view of the above problems we went through the literature and found that two groups of workers have used triphenylphosphine and carbon tetrachloride for the dehydration of sensitive alcohols. It is known that the formation of secondary alkyl bromides and chlorides from the corresponding alcohols, a trialkyl or triarylphosphine, and a tetrahalomethane (or hexachloroacetone) proceeds with both high conversions and yields. The halogenation reaction sequence has been elegantly summarized by Appel in a review article. The reaction proceeds in two steps, intermediate formation (3.7) and intermediate decomposition (3.8) as shown with triphenylphosphine and carbon tetrachloride as the chlorinating agent. Intermediate decomposition occurs
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\begin{align*}
\text{CHART-3} \\
(C_6H_5)_3P + CCl_4 & \rightarrow \left[ (C_6H_5)_3P\text{Cl} \right] CCl_3^- \\
\left[ (C_6H_5)_3P - \text{Cl} \right] CCl_3^- & \rightarrow \left[ (C_6H_5)_3P - \text{OR} \right] \text{Cl}^- + \text{CHCl}_3 \\
\left[ (C_6H_5)_3P - \text{OR} \right] \text{Cl}^- & \rightarrow \text{RCl} + (C_6H_5)_3\text{PO}
\end{align*}
\]
with extensive inversion of configuration rendering this synthetic technique as one of the better methods for getting alkyl chlorides with known stereochemical integrity. This reaction is normally free from the interference of rearrangement and elimination, although occasionally an alkene is formed together with the halide. Slight change in the halogenation reaction conditions i.e., use of slightly high temperature leads to the formation of olefin in high yields.

2-Phenylethanol gave 90% of styrene by distillation of the reaction mixture at atmospheric pressure and under reduced pressure, 2-phenyl ethyl chloride was formed which indicates temperature as the major factor turning this reaction into elimination. The reaction conditions for elimination vary from alcohol to alcohol. The overall reaction can be written as follows:

\[
RCH_2CHR'OH + Ph_3P + CCl_4 \rightarrow RCH=CHR' + Ph_3PO + CHCl_3 + HCl
\]

The diol we intended to dehydrate, is a solid insoluble in carbon tetrachloride. To overcome this difficulty we used a mixture of dioxane and carbon tetrachloride which yielded a homogeneous solution. Use of dioxane should also increase the reaction temperature which will favour elimination of the chloride formed. The diol (2.3) on treatment with triphenylphosphine-carbon tetrachloride in dioxane gave ocimin (2.4), purified by column chromatography to
yield fluorescent flakes, m.p. 170-71\(^\circ\). IR(nujol, Fig. 3) showed peaks characteristic of a trans double bond at 1610, 965 and 950 cm\(^{-1}\). The 100MHz PMR(CDCl\(_3\), Fig. 4) was in complete agreement with structure and accounts for only 11 protons indicating that the molecule is a symmetrical dimer. The allylic methylene appeared at \(\delta 2.35\) as a broad triplet with J=3Hz and the methoxy proton as a singlet at 3.8. One olefinic proton which is also benzylic appeared as a doublet at 6.4 with J=16Hz indicating clearly the trans nature of the double bond. The other olefinic proton appeared at 5.9-6.3 as a complex multiplet due to coupling to other olefinic proton and methylene protons and a large coupling of 16Hz could be easily deduced from this multiplet also. The aromatic protons appeared as an AA'BB' quartet characteristic of a p-disubstituted benzene ring: a doublet at 6.82 is due to protons ortho to methoxyl with J=8Hz and other doublet at 7.27 is due to protons meta to methoxyl and J=8Hz. The spectral data is in complete agreement with the reported one for this compound. This represents the first synthesis of ocimin (2.4).

* In spite of repeated requests we were unable to obtain the spectra of the natural product from the authors.
In view of the difficulties encountered in the dehydration of 1,6-di-(p-methoxyphenyl)-1,6-hexanediol (2.3) we resorted to alternate approach for the synthesis of ocimin starting from 1,6-di-(p-methoxyphenyl)-1,6-hexanedione (2.2). This ketone (2.2) was reduced by Huang-Minlon modification of Wolff-Kischner method\textsuperscript{15} to 1,6-di-(p-methoxyphenyl)-hexane (2.5). The reduced product which could be called as tetrahydroocim in (1.2) has been obtained by catalytic hydrogenation of ocim in (1.1) by Atal \textit{et al}\textsuperscript{1} during the structural investigation. The spectral and other physical data for (2.5) was in complete agreement with the reported one. m.p.71-72\degree C

IR(nujol, Fig.5) : 1612, 1587, 820 cm\textsuperscript{-1} PMR(90MHz, Fig.6): showed a broad peak at $\delta$ 1.45 due to eight methylene protons which are not benzylic, the benzylic methylenes appeared as a triplet at 2.54 with J=7.5Hz, the methoxyl groups appeared at 3.75 as a singlet. The aromatic protons appeared as AA'BB' quartet with J=8.5Hz characteristic of a p-disubstituted benzene ring: The doublet at 6.74 is assigned to protons \textit{ortho} to methoxyl group and the other doublet at 7.00 is assigned to protons \textit{meta} to methoxyl group. Bromination of (2.5) with N-bromosuccinimide (NBS) followed by dehydrobromination with alkali or LiBr/LiCO\textsubscript{3}/DMF method\textsuperscript{16} would give ocim in. Reaction of (2.5) with NBS in carbon tetrachloride using benzoyl peroxide as the initiator gave tarry material. Evolution of a fuming gas, probably
HBr, was observed during the reaction. The probable explanation is that the bromide formed is activated by the p-methoxyl group and undergoes elimination rapidly under the reaction conditions. The HBr formed might be inducing the polymerization of the diene formed.
Fig. 2

(CDCl₃ + D₂O - DMSO)
Fig. 3
EXPERIMENTAL

General

Adipic acid (Riedel), triphenylphosphine (Riedel), NBS(S.R.L.) and sodium borohydride (BDH) were used. Dry dioxane was prepared by refluxing the dioxane (BDH) with sodium pieces and distillation followed by pressing sodium wire.

The IR spectra were recorded on Perkin-Elmer Infracord or Beckman instruments; the PMR on T-60, Varian XL-100 or Perkin-Elmer 90MHz spectrometers.

Adipoyl Chloride

Redistilled thionyl chloride (73 ml) was added slowly to a well dried adipic acid (50g) during 50 minutes. It was heated on water-bath at 50-60° and when the evolution of hydrogen chloride gas had ceased (about 4 hr), the excess of thionyl chloride was removed in vacuo, followed by adipoyl chloride (46 ml), b.p. 150-52°/20mm (Lit. 17 125°/11mm).

1,6-Di-(p-methoxyphenyl)-1,6-hexanedione (2,2)

Adipoyl chloride (30 ml) was added dropwise to an ice-cool mixture of anhydrous aluminium chloride (60g) and anisole (40 ml) taken in dry carbon disulphide (120 ml) during 40 minutes with constant stirring. It was stirred for one more hour under same conditions after the addition was over. It was then
stirred at room temperature for 2 hr and poured into a mixture of con. hydrochloric acid (150 ml) and crushed ice (500g). The crude solid was filtered and washed with saturated sodium carbonate (3x100 ml). It was recrystallized from dioxane-ethanol mixture (45g), m.p.143-44° (Lit. 3 145-46°).

1,6-Di-(p-methoxyphenyl)-1,6-hexanediol (2.3)

1,6-Di-(p-methoxyphenyl)-1,6-hexanediol (2.2, 2g) was dissolved in dioxane (30 ml) and ethanol (10 ml) mixture and to the stirred solution, sodium borohydride (0.49) was added in small portions. The reaction mixture was stirred at room temperature for 4 hr, heated on water-bath at 60° for 6 hr and poured into a saturated solution of ammonium chloride (150 ml). The white precipitate of (2.3) obtained was filtered and recrystallized from aqueous ethanol (1.8g), m.p.132-33°. IR(nujol, Fig.1) : 3390 cm⁻¹ (-OH), 1618 and 1590 (aromatic C=C); PMR(60MHz, CDCl₃+ drop of d₆-DMSO, Fig.2) : \[ J \text{ to } 2 \{ 8H, b, (CH₂)₄ \}, 2.95(2H, bs, 20H), 3.72(6H, s, 2×OMe), 4.3(2H, t, J=6Hz, 2×Ar-CH₂OH), 6.73(4H, d, J=8.5Hz, Ar-H ortho to OMe) and 7.17(4H, d, J=8.5Hz, Ar-H meta to OMe). \]
Analysis

\[ \text{Found: C, 72.58; H, 8.06.} \]
\[ \text{requires: C, 72.72; H, 7.9%}. \]
Ocimin (2.4)

A solution of 1,6-Di-(p-methoxyphenyl)-1,6-hexanediol (2.3, 0.33g) and triphenylphosphine (0.524g) in dry dioxane (10 ml) and carbon tetrachloride (10 ml) was refluxed on water-bath for 10 hr. The solvent was removed in vacuo and the solid residue obtained was chromatographed on silica gel column (60-120 mesh; 10g). Elution with pet. ether-chloroform (3:1) gave (2.4) as fluorescent flakes (0.2g) which was recrystallized from ethyl acetate, m.p.170-71°. IR(nujol, Fig.3) : 1605 (Strong), 965 and 950 cm⁻¹ (trans double bond); PMR(100MHz, CDCl₃, Fig.4) : 2.35(4H, broad triplet, J=3Hz), 3.8 (6H, s, 2xOMe), 5.9-6.3(2H, complex multiplet, 2 x olefinic- H β to phenyl ring), 6.4(2H, d, J=16Hz, 2 x olefinic- H α to phenyl ring and trans with respect to other olefinic-H), 6.82(4H, d, J=8Hz, Ar-H ortho to OMe), 7.27(4H, d, J=8Hz, Ar-H meta to OMe).

Analysis Found : C, 81.5; H, 7.6.
C₂₀H₂₂O₂ requires : C, 81.6; H, 7.5%.

1,6-Di-(p-methoxyphenyl)-hexane (2.5)

A mixture of diketone (2.2, 18.0g) hydrazine hydrate (99%, 30 ml), potassium hydroxide pellets (40g) and ethyleneglycol (300 ml) was warmed on boiling water-bath until most of the potassium hydroxide dissolved. It was refluxed on wire gauze with free flame for 1 hr and then distilled slowly till the thermometer (bulb
dipped into the reaction mixture) showed a temperature of 175\degree. After attaining this temperature, the distillation was stopped and the contents remained in the distillation flask were refluxed for 3 hr. Then it was cooled and upper hydrocarbon layer was separated. The aqueous layer was extracted with ether (3x70 ml). The combined upper layer and ether extracts were washed with water (2x100 ml) and dried over anhydrous sodium sulphate. Removal of solvent furnished an impure solid. It was recrystallized from chloroform-pet. ether (11g, m.p. 71-72\degree; Lit\textsuperscript{2} 68\degree), IR(nujol, Fig. 5): 1612, 1587, 820 cm\textsuperscript{-1}, PMR(90MHz, CDCl\textsubscript{3}, Fig. 6): \(\delta\) 1.45 (8H, multiplet, nonbenzylic methylene protons), 2.54 (4H, t, J=7.5Hz, 2 x Ph-CH\textsubscript{2}-), 3.75 (6H, s, 2 x OMe), 6.74 (4H, d, J=8.5Hz, Ar-H ortho to OMe), 7.00 (4H, d, J=8.5Hz, Ar-H meta to OMe).

Analysis

<table>
<thead>
<tr>
<th></th>
<th>Found</th>
<th>Requires</th>
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<tbody>
<tr>
<td>C(<em>{20})H(</em>{26})O(_2)</td>
<td>C, 80.4; H, 8.9</td>
<td>C, 80.5; H, 8.7%</td>
</tr>
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1,6-Di(p-methoxyphenyl)-1,6-dibromohexane (2.6) and its dehydrobromination

The hydrocarbon (2.5, 10g) was dissolved in dry carbon tetrachloride (50 ml) and to it N-bromosuccinimide (3.5g) and benzoyl peroxide (0.1g) was added. It was heated under reflux till all the solid in the reaction flask floated on carbon tetrachloride (NBS is converted into succinimide;
1.5 hr). Then the contents were cooled in ice and filtered to remove succinimide formed. Removal of solvent on water bath gave a dark, thick residue (10.8g). It was dissolved in ethanol (50 ml) and refluxed (2 hr) on water-bath after adding potassium hydroxide (2.5g) to it. The volume of the solution was reduced to half by removing the ethanol on water-bath. It was cooled and extracted with ether (3x40 ml). Ether layer was washed with water (3x60 ml) and dried over anhydrous sodium sulphate. Evaporation of solvent gave dark, tarry material (9.8g). TLC of this product did not show any trace of ocimin.
REFERENCES


4. a) A. Butenandt and J. Schmidt-Thome, Chem. Ber., 71, 1487 (1938); 72, 182 (1939).


