SYNTHESIS OF 4,6-DIMETHYL-6-OCTEN-3-ONE

The monoterpenic acyclic ketone 4,6-dimethyl-6-octen-3-one has recently been isolated by Meinwald and coworkers (119) from the defensive secretion of the 'Daddy longlegs' Leiobunum Vittatum. Structure (XX) has been assigned to this ketone on the basis of its spectral data.

\[
\begin{align*}
\text{H}_3\text{C} & \text{-CH}_2\text{-C} \text{-CH} \text{-CH}_3 \\
\text{CH}_2 & \text{-C} \text{-CH}_3 \\
\text{CH} & \text{-CH}_3
\end{align*}
\]

(XX)

The mass spectrum of (XX) shows a peak at m/e 86 along with other peaks. This is a rearrangement peak and thus \( \gamma \)-hydrogen with respect to carbonyl is expected. However, the absence of a hydrogen atom \( \gamma \) to the carbonyl oxygen atom in 4,6-dimethyl-6-octen-3-one does not vitiate the proposed structure in the light of the facility of hydrogen migrations in mass spectrometry (120).

The structure of the ketone (XX) was established through its preparation (119) by the aluminium isopropoxide catalysed Claisen rearrangement of 2-methyl-1-buten-3-yl 2-methyl-3-oxopentanoate.
The present studies record straightforward synthesis of the ketone (XX) by the application of well-known Wittig reaction on an appropriate ketone secured through the \( \beta \)-ketosulphoxide intermediate. The various steps involved in the synthesis are outlined in the following chart:

\[
\begin{align*}
\text{C}_2\text{H}_5\text{C}-\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 & \xrightarrow{\Delta} \text{C}_2\text{H}_5\text{CCH}_{\text{3}}\text{CO}_2\text{C}_2\text{H}_5 \\
\text{(XXI)} & \text{(XXII)}
\end{align*}
\]

\[
\begin{align*}
\text{C}_2\text{H}_5\text{CCH}_{\text{2}}\text{CO}_2\text{C}_2\text{H}_5 & \xrightarrow{\Delta} \text{C}_2\text{H}_5\text{CCH}_{\text{2}}\text{CO}_2\text{C}_2\text{H}_5 \quad \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \\
\text{(XXIII)} & \text{(XXIV)}
\end{align*}
\]
Ethyl 2-methyl-3-ketopentanoate (XXII) was obtained in 72.7% yield by alkylating ethyl 3-ketopentanoate (121) with methyl iodide in the presence of sodium dust in anhydrous benzene. This was further alkylated with ethyl bromoacetate in the presence of sodium ethoxide to give ethyl 3-carbethoxy-3-methyl-4-ketohexanoate (XXIII) in 54.3% yield. The ketoester (XXIII) was hydrolysed with concentrated hydrochloric acid to furnish the keto acid
(XXIV). I.R. spectrum showed broad bands at 3250-3000 cm\(^{-1}\) and 1700 cm\(^{-1}\) (-COOH group). The keto acid (XXIV) on esterification with ethanol in benzene gave ethyl 3-methyl-4-ketohexanoate (XXV) in 78.5\% yield. Its infrared spectrum showed characteristic peak at 1740 cm\(^{-1}\) (ester carbonyl). The ketoester (XXV) on ketalisation with ethylene glycol in the presence of catalytic amount of p-toluene sulphonic acid (122) produced the ketal ester (XXVI) in 68\% yield after purification by column chromatography and vacuum distillation.

The ketal ester (XXVI) was transformed into its \(\beta\)-ketosulphoxide (XXVII) on reaction with methyl sulphinyl carbamion (prepared from sodium hydride and dimethyl sulphoxide) (106-107, 123). I.R. spectrum showed characteristic absorption peaks at 1725 cm\(^{-1}\) (carbonyl group), 1040-1060 cm\(^{-1}\) (sulphinyl, ketal group).

The \(\beta\)-ketosulphoxide (XXVII) without distillation was submitted to reductive cleavage with aluminium amalgam in aqueous tetrahydrofuran (106-107, 123) to furnish the crude methyl ketone (XXVIII). After chromatography over alumina (elution with petroleum ether) and subsequent fractionation under reduced pressure, (XXVIII) was obtained in pure state in 50\% yield. It was characterised through infrared absorption peaks at 1720 cm\(^{-1}\) (carbonyl), 1060 cm\(^{-1}\) (ketal group).
The ketal ketone (XXVIII) was subjected to Wittig reaction (124) with ethyl triphenylphosphonium iodide in dimethylsulphoxide in the presence of sodium sulphinyl carbamion to yield 3,5-dimethyl-6,6-ethylenedioxy-2-octane (XXIX) in 75.75% yield after usual purification. I.R. spectrum showed no absorption in the carbonyl region but characteristic peaks at 825 cm\(^{-1}\) (trisubstituted double bond) and 1080 cm\(^{-1}\) (ketal).

The ketal ketone (XXIX) was treated with aqueous hydrochloric acid in acetone (125) at room temperature and the product was purified by fractionation under reduced pressure and column chromatography to afford the ketone (XX) in 72.3% yield. It gave a single spot on t.l.c. plate and its identity was established on the basis of its I.R. and NMR spectra.

I.R. spectrum of the synthetic ketone (XX) showed peaks at 1715, 1665, 1460, 1420, 1380, 1355, 1275, 1108, 1030, 978, 830 and 790 cm\(^{-1}\).

NMR spectrum showed signals at \(\delta 5.2\) (1H, q, \(\text{C} = \text{CH} - \text{CH}_3\)), 2.8 - 1.8 (5H, m, \(\text{H}_2\text{C} -\), -CH-, and -\(\text{CH}_2 = \text{C} = \text{C}\)), 1.61 (3H, s, \(\text{C} = \text{C} - \text{CH}_3\)), 1.5 (3H, d, \(\text{C} = \text{CH} - \text{CH}_3\)) and 1.2 - 0.84 (6H, m, \(\text{CH}_3 - \text{CH}_2\) and \(\text{CH}_3 - \text{CH}\)). The NMR data is identical (119) with that reported for the authentic sample (XX).

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