CHEMISTRY OF β ARYL GLUTAconIC ACIDS

Part VII. Constitution of the so-called Hydroxy-Anhydrides

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The peculiar and outstanding property of the anhydrides of glutaconic acids containing a mobile hydrogen atom lies in their titratibility with alkalis and colourations with ferric chloride. Till now, the only theory proposed to account for these remarkable properties was the idea of hydroxy-anhydride—anhydride tautomerism, due to Thorpe 1.

\[
\begin{align*}
\text{CH–CO} & \quad \leftrightarrow \quad \text{CH–CO} \\
\text{H} & \quad \text{O} & \quad \text{H} & \quad \text{O}
\end{align*}
\]

But this was unable to explain why it was not possible to prepare, with the exception of αβ dimethyl glutaconic anhydride, neutral acetyl or benzoyl derivatives of these bodies, although the corresponding chloro derivatives could be isolated in some cases.

The systematic investigation of the acetylation and benzoxylation of the β aryl glutaconic anhydrides by the present author, 2, 3, 4 led to the isolation of products which were proved to be C-acetyl or C-benzoyl glutaconic anhydrides (A). The alternative glutaconyl acetic acid constitution 5 (B), which Limaye and Bhave attempted so emphatically to defend 6, seems to

\[
\begin{align*}
\text{CH–CO} & \quad \leftrightarrow \quad \text{CH–CO} \\
\text{CH} & \quad \text{O} & \quad \text{CH} & \quad \text{O}
\end{align*}
\]

1 Thole and Thorpe, J.C.S., 1911, 101, 2211.
3 Gogte, J. Univ. Bombay, 1939, 8, 208.
4 Gogte, ibid., 1940, 9, 127.
5 Limaye and Bhave, ibid., 1933, 2, 82.
6 Bhave, Rasayanam, 1938, 1, 127.
have lost its basis, especially after the publication of the work on the
\(\alpha\)-C-benzoyl-glutaconic anhydrides.

Einhorn’s method, \textit{i.e.}, the action of an acid chloride and pyridine,
appears to be a simpler and more general method for the C-acylations
of \(\beta\) aryl glutaconic acids than the alternative Perkin’s method. As
Einhorn’s method is known to yield generally the O-acyl derivatives, these
\(\alpha\)-C-acylations and especially the further \(\alpha\gamma\)-C di-acylations to produce
\(\alpha\gamma\)-C-diacyl-glutaconic anhydrides of the types\(^3\) (C), gave rise to a doubt as
to the existence of a reactive hydroxy group in the \(\beta\) aryl glutaconic an-
hydrides. This indicated that the reactive hydrogen atom responsible for all
the above reactions, instead of tautomerising to the neighbouring carbonyl
group, wanders somewhere else. The apparent identity of the \(\alpha\)-C-
benzoyl-\(\gamma\)-C-\(p\). bromobenzoyl-\(\beta\) (4 methoxy-phenyl)-glutaconic anhydride (I)
and the \(\alpha\)-C-\(p\). bromo benzoyl-\(\gamma\)-C benzoyl-\(\beta\) (4 methoxy-phenyl) gluta-
conic anhydride\(^4\) (II) indicated a symmetrical tautomeric structure (III) for
the \(\beta\) aryl glutaconic anhydrides, where the dotted lines represent half of
the normal valency. Thus,

\[
\text{(I)} \quad \text{(II)} \quad \text{(III)}
\]

\[
\text{CH}_2\text{O-C}_6\text{H}_4\text{C} \quad \text{CH}_2\text{O-C}_6\text{H}_4\text{C} \quad \text{CH}_2\text{O-C}_6\text{H}_4\text{C}
\]

\[
\text{C-O-C}_6\text{H}_4\text{Br} \quad \text{C-O-C}_6\text{H}_5 \quad \text{C-O-C}_6\text{H}_5
\]

\[
\begin{align*}
\text{R-C-H} & \quad \text{O} & \quad \text{R-C-H} & \quad \text{O} \\
\text{H-C} & \quad \text{O} & \quad \text{H-C} & \quad \text{O}
\end{align*}
\]

C-aryloyl-\(\beta\) aryl- glutaconic anhydrides were observed to hold their
aryloyl groups tenaciously and hence it was not possible to prove the structure
of the compounds (I) and (II) by transforming them into any derivatives of
the \(\alpha\)-C arroyl-glutaconic anhydrides. If one of the substituting groups at
either the \(\alpha\) or \(\gamma\) positions be an acetyl, it would easily be eliminated by acids\(^3\)
and the constitutions of \(\alpha\gamma\)-C acetyl-bezoyl-glutaconic anhydrides could
thus be established. The further acetylations of \(\alpha\)-C benzoyl -\(\beta\) (4 methoxy-
phenyl) glutaconic anhydride\(^1\) or the benzyolation of \(\alpha\)-C acetyl-\(\beta\)-(4
methoxy-phenyl) glutaconic anhydride\(^2\), however, produced liquid reaction
products which could not be purified by distillation, as they lost carbon-
dioxide on heating. Solid \(\alpha\gamma\)-alkoyl-aryloyl-\(\beta\) aryl- glutaconic anhydrides may,
however, be obtained in case different acid chlorides are tried with
various glutaconic anhydrides but the work could not be proceeded with
due to lack of materials.
A more simple and direct method for proving the identity of the α and γ positions in the β aryl-glutaconic anhydrides would be the study of the benzoylation of α-methyl-β aryl-glutaconic anhydrides (IV). In case the α-position is attacked, the resulting α-C benzoyl derivative (V) would be neutral because of the absence of a mobile hydrogen atom. This derivative would, however, give a lactone (VII) by thermal decarboxylation or through the intermediate ketonic acid² (VI). If, however, the γ-position is attacked, the γ-C benzoyl derivative (VIII) would be acidic and give colouration with ferric chloride because of the presence of a mobile hydrogen atom. This γ-derivative would, however, give no lactone by either of the methods¹. In case, however, the C-benzoyl- derivative of the α-methyl-β aryl-glutaconic anhydride titrates as an acid, gives a colouration with ferric chloride and at the same time yields a lactone by the usual methods, we are forced to the conclusion that the C-benzoyl-β aryl-glutaconic anhydride behaves at the same time as an α-benzoyl and γ-benzoyl compound, in other words the α- and γ- positions of α-methyl-β aryl-glutaconic anhydride are identical, and that the reactive hydrogen atom wanders between them.

\[
\begin{align*}
\text{(IV)} & \quad \text{R-C}(-\text{CH-CO})_2 \text{CO} \to \text{R-C}(-\text{CH-CO})_2 \text{CO} \to \text{R-C}(-\text{CH-CO})_2 \text{CO} \\
\text{(V)} & \quad \text{CH}_3 \text{CO-C}_6\text{H}_5 \\
\text{(VI)} & \quad \text{CH}_2 \text{CO-C}_4\text{H}_4
\end{align*}
\]

For the preparation of α-alkyl-β aryl-glutaconic acids, Thorpe and Wood's method⁷ of alkylating the sodium derivative of diethyl-glutaconate by alkyl-halides was employed by Limaye and Bhave⁸ in the case of diethyl-β (4methoxy-phenyl)-glutaconate. On repeating the work of Limaye and Bhave, the present author was unable to isolate any α-methyl

¹ Thorpe and Wood, J.C.S., 1913, 103, 1569.
² Limaye and Bhave, Rasayanam, 1939.
derivative. The reduction of the acid-ester\(^2\) (X) to the \(\alpha\)-ethyl-\(\beta\) (4 methoxy-phenyl) glutaric acid (XIII) could not be effected as each time the lactonic ester (XI) resulted. To prevent this, the further esterification of this acid ester was attempted; the resulting di-ester (XII) could easily be reduced by Wolff's method\(^9\) selectively to give the \(\alpha\)-ethyl-glutaric acid (XIII). All attempts at this esterification, even by the specific silver salt-ethyl iodide method, yielded the lactonic ester (XI) instead.

\[
\begin{align*}
\text{R-} & -\text{CH-CO} \quad & \text{R-} & -\text{CH-CO} \quad & \text{R-} & -\text{CH-CO} \quad & \text{R-} & -\text{CH-CO} \\
\text{CO-CH}_3 & \quad & \text{CO-CH}_3 & \quad & \text{CO-CH}_3 & \quad & \text{CO-CH}_3 & \quad & \text{C}_3H_5 \\
\text{XI} & \quad & \text{XII} & \quad & \text{XII} & \quad & \text{XIII} \\
\end{align*}
\]

A third way for preparing the \(\alpha\)-alkyl \(\beta\) aryl-glutaric anhydrides was the condensation of \(\alpha\)-methyl-acetone-dicarboxylate with phenolic ethers, and identifying the resulting \(\alpha\beta\) and \(\beta\gamma\) isomers of the resulting \(\beta\) aryl-glutaric acids by ozonisation. (Compare Kon et al.) It was, however, found that at lower temperatures, the \(\alpha\) methyl-acetone-dicarboxylate does not condense with phenolic ethers in the presence of sulphuric acid, whereas at higher temperatures it itself gets decomposed. The only way now open thus is to try the benzoylation of any known di-substituted glutaric anhydride, but the work was held up due to lack of materials and is a problem for future research.

Thus, although, the constitution of glutaric anhydrides cannot be said as definitely established, methods have been discovered which will settle the question one way or other, and several new facts have been noticed during the investigation.

Thus,

1. The \(\text{C-acylation of anhydrides of dibasic acids is shown to take place for the first time.}\)
2. The \(\alpha\gamma\)-\(\text{C diacylation of } \beta\text{ aryl glutaric anhydrides is peculiar, and this leads to a general method for synthesising several diphenyl derivatives.}\)
3. The isomeric transformation of the \(\alpha\)-\(\text{C-acetyl-} \beta\text{-aryl glutaric anhydrides into the lactonic esters, by dilute sulphuric acid is remarkable.}\)
4. The thermal decarboxylation of \(\alpha\)-\(\text{C-acyl-} \beta\text{ aryl glutaric anhydrides to produce the corresponding lactones is strange and more work is necessary to elucidate the exact nature of the reaction, although a probable explanation has been suggested.}^4\)

\(^9\) L. Wolff, Ber., 1911, 44, 2769; Annalen, 1912, 394, 86.