PART I

SYNTHESIS AND REACTIONS OF 2-ARYL-6-OXOCYCLOHEX-1-ENYLACETATES
AND ANALOGUES
SYNTHESIS AND REACTIONS OF SOME 2-ARYL-6-OXOCYCLOHEX-1-ENYLACETATES
AND ANALOGUES

INTRODUCTION.

For the last few decades, steroid chemistry has provided the most exciting and fascinating field of research both to the organic chemists and the biochemists. Apart from the important physiological properties and immense therapeutic applications, the steroids serve as veritable gold mine of interesting problems and are convenient substrates for chemical transformations. There is practically no newly discovered synthetic organic reactions or physico-chemical principles which have not been almost immediately applied in the steroid field. Moreover, during the extensive investigation of the total synthesis of steroids, not only have new chemical reactions been discovered but many earlier ones modified and extremely delicate methods for the selective performance of chemical transformations (polyfunctional steroidal molecules are good substrates for this purpose) developed. The stereochemistry of condensed polycyclic systems have been given a new impetus since the steroid molecules with their intricate molecular geometry serve as an ideal field for investigation of the influence of steric factors on reaction rates and mechanism. In fact, the earlier development of
conformational analysis was entirely based on the reactions of these molecules. Many of the physical methods such as ultraviolet, infrared, and mass spectrometry, optical rotatory dispersion, and molecular rotation which are now the most powerful tools for the determination of structure and stereochemical configuration of organic molecules gained their first cognizance for their application in the steroid field. Biogenetic theories have also been developed based on experiments done in the steroid molecules.

Of the versatile achievements in the steroid chemistry, one that towers above all is perhaps the total synthesis of practically all the principal members of this very big family. Apart from the dazzling ingenuity of the synthetic chemists they display, the methods of total syntheses open up new possibilities for the modification of the steroid molecules. For example, one can change the stereochemistry which enables the precise stereochemical conditions for the hormonal activity of the steroids to be studied. Another major modification is the replacement of carbon atoms of the steroid skeleton by hetero atoms which may cause far-reaching changes in physiological activity and opens up routes for the study of extremely delicate aspects of the mechanism of the action of physiologically active compounds. Lastly, in the future probably the total synthesis may assume considerable industrial value (at present, the industrial total synthesis is restricted solely to the production of estrone) so as to acquire fundamental importance.

It is not the purpose of the thesis to make any attempt to review the many aspects of the steroid reactions and syntheses which are
are aptly covered in various text books\textsuperscript{1-5} and periodicals.\textsuperscript{6-10} The experiments that will be described subsequently in the thesis were designed to explore the possibility of developing new synthetic methods for steroids from starting materials easily available in our laboratory and which for some time past have been used for such purposes but in different ways. Though we failed to achieve the original objective to the desirable extent, we came across some interesting transformations and observations which formed the subject matter of this part of the thesis. Before presenting our results, however, we like to give a short chemical background of the types of compounds we will be dealing with (mostly 2-aryl-6-oxocyclohex-1-enylacetates or propionates), particularly their applications in the steroid field.

One of the earliest and perhaps the most elegant method of synthesising 3,11,17-oxygenated cyclopentenophenanthrene (I) was due to Robinson.¹¹ The synthesis was based on an earlier observation of German workers¹² that hydrolysis of furfurylidene-acetophenone (II) affords 7-phenyl-4,7-di-oxoheptoic acid (III) by means of a boiling mixture of alcohol and concentrated hydrochloric acid, the process involving hydrolytic fission of the furan ring followed by oxidation and reduction. The keto-acid underwent cyclisation smoothly under the influence of alkali to furnish 2-phenyl-5-oxocyclopent-1-enylacetic acid (IV) in good yield. In a similar fashion, furfurylidene-2-acetovanaphthone¹³ was converted into the corresponding tricyclic system (as IV) containing rings A, B and D of the steroids, which with boiling acetic anhydride cyclised to the cyclopentenophenanthrene (V) in excellent yield. A number of derivatives were prepared from it all containing this important ring-system and a very simple reaction

sequence was thus made available which was employed for the synthesis of the corresponding 4-methoxylated compounds (VI and VII), the latter containing oxygen functions at C₃, C₁₁ and C₁₇ which are prerequisites for building up the important steroidal hormones. The method was particularly attractive due to the ready availability of 6-methoxy-2-acetonaphthone¹⁴ and the simplicity of the steps involved. Two formidable obstacles however had to be overcome, namely, reduction of the double bond in the olefinic acid (VI), maintaining the proper stereochemistry and introduction of angular methyl group at C₁₃, to be followed up by cyclisation. Synthesis of the C₁₃-nor- compounds as originally done by Robinson group¹³,¹⁵ and subsequently modified by other workers is summarised in Scheme 1.

The catalytic hydrogenation of the acid (VI) gave a mixture of cis and trans isomers (as VIII) but under alkaline conditions gave the trans acid (VIII) while in acid medium afforded almost exclusively the corresponding cis-isomer. The cyclisation of the acids proved

to be difficult and could only be effected in moderate yield with a mixture of phosphoric anhydride in syrupy phosphoric acid solution* to the same 11,17-diketone (IX) apparently possessing the more stable

* Professor A. J. Birch (ref.45) claims that this was the original discovery of polyphosphoric acid subsequently used as a general and efficient reagent for cyclisation in other cases. 

cis-linkage of rings C and D. The reduction of the diketone (IX) to the monoketone (X) was accomplished by hydrogen in presence of platinum-palladium-charcoal which was earlier known to reduce carbonyl group directly attached to aromatic nucleus. Subsequently, other catalytic methods such as hydrogenation with palladium-charcoal in presence of perchloric acid were used. Attempts to introduce a methyl group by direct methylation of the acid (VIII) led to trimethyl derivative.

Incidentally, more recently the saturated keto-acid (VIII) has been reduced by sodium borohydride to the hydroxy-acid (XI) and the latter converted into diazoketone (XII) and thence into a number of compounds which proved to be antagonists of the mineralocorticosteroids with activities comparable to those of the spiroloctones. The compounds (VI and IX) have also been

22. N. D. Zelinsky, Ber., 1933, 66, 872.
23. K. W. Rosenmund and E. Karg, Ber., 1942, 75, 1850. (Method of K. Kindler)
used for the synthesis of carcinogenic derivatives. 27-29

The first attempt to introduce an angular methyl group in the ketone (X) was made by protecting the active methylene group of cyclopentanone moiety by formation of piperonylidene derivative (XIII). However, the removal of the blocking group proved to be difficult. Johnson's method of removal of benzylidene group 30 from a 9-methyl-l-decalone system by chlorination at the double bond followed by hydrolysis in several stages did not work well because of nuclear chlorination giving 4-chloroketone (XIV). The use of methylanilinomethylene 31 as protecting group proved to be more successful since methylation and subsequent acid and alkali hydrolysis led to the methyl ether of (+)-cis-equilenin (XV) obtained

earlier by Bachmann et al\textsuperscript{32} by a different route. No evidence of the formation of more than one stereoisomer was found in any of these methylations. Two important conclusions, however, were reached: firstly, equilenin and probably other hormones and steroids have the trans configuration at C-D ring junction; secondly, the methylation of \textit{\textalpha} - decalone gave some of the trans-isomer\textsuperscript{33} thus indicating the possibility that the natural trans-series of hormones could be reached through the corresponding hydrochrysene ketones.

An alternative route for the synthesis of the ketones (as VI) is also available. \textit{\textbeta}-Methoxyphenacyl bromide was condensed\textsuperscript{34} with ethyl \textit{\textbeta}-oxo-adipate and the resulting dioxy-diester on alkaline cyclisation formed the keto-acid (XVI) as shown:

\begin{equation}
\begin{array}{c}
\text{MeO} \quad \text{CH}_2\text{CO}_2\text{Et} \\
\text{Br} \quad \text{COCH}_2\text{CH}_2\text{CO}_2\text{Et} \\
\text{Na, Et}_2\text{O} \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\text{KOH, H}_2\text{O} \quad \text{H}_2\text{C} \quad \text{NCO} \\
\text{NCO} \quad \text{MeO} \\
\end{array}
\end{equation}

(XVI)

A number of synthetic studies have been carried out by Maksimov et al\textsuperscript{35} on the keto-acid (XVI).

\begin{itemize}
\item \textsuperscript{34} G. S. Grinenko and V. I. Maksimov, \textit{Zh. Obshch. Khim.}, 1958, \textit{28}, 528.
\end{itemize}
Another interesting variation\(^6\) of Robinson's method consists in the synthesis of the ketone (XVII) with the requisite methyl group and then introduction of a carboxymethyl residue at C\(_{13}\) by the sequence of hydrogenation to a saturated ketone, bromination followed by a malonic ester synthesis, hydrolysis, and decarboxylation to the keto-acid (XVIII) (Scheme 2). Cyclisation of the corresponding acid chloride leads to 11,17-diketone (XIX) of undetermined stereochemistry.

It appears that introduction of the angular methyl group in the perhydrocyclopentenophenanthrene with correct geometry is the major stumbling block in the synthesis. Since our original plan

\[\text{Scheme 2}\]

36. H. A. Weidlich and G. H. Daniels, Ber., 1939, 72, 1590; H. A. Weidlich and M. Meyer-Dellius, Ber., 1939, 72, 1941.
consisted of a novel method for angular methylation in this type of compounds, the different methods available so far for this purpose is briefly summarised here. We have already seen that in the case of 1-decalone system, the arylidene derivatives prepared by condensing with aromatic aldehydes (benzaldehyde, piperonal, furfural etc.,) permit methylation with high yield but they are difficult to eliminate. One very good example of angular methylation-ring contraction sequence may be found in the synthesis of epiandrosterone by Johnson et al.\textsuperscript{37} as shown in Scheme 3.

The second type of protective groupings comprises of substituted hydroxymethylene derivatives which are easily accessible. Treatment with methylaniline affords methylanilinomethylene compounds which are methylated in the usual way. The protective groupings are removed either in two stages: treatment with acid for the removal of the amine, and then with alkali for removal of the hydroxymethylene group, or as more recently pointed out by alkali treatment alone. One interesting variation was introduced by Ireland and Marshall using butylthiomethylene protective grouping as shown in Scheme 4. Unlike the previous method, it does not allow the ring-contraction. In these cases of alkylation,

Scheme 4

the ratio between the products formed depends to a great extent on the stereochemistry (conformation) of the polycyclic compounds used.\[^{40}\]

It has also been shown recently\[^{41}\] that the blocking of the hydroxymethylene group in compound (XX) is unnecessary. Successive treatment with sodium methoxide and potassium amide in liquid ammonia converted this compound into the dianion (XXI) which by direct methylation and subsequent elimination of the hydroxymethylene grouping gives the desired 9-methyl-1-decalone.

Of the various other methods\[^{42,43}\] for effecting angular methylation, one is particularly relevant to our discussion. The

\[\text{\textbf{Diagram}}\]


method which is based on Stork's reductive alkylation of $\alpha,\beta$-unsaturated ketonic system has been adopted by Birch et al. who used it for methylation of the acid (VI) prior to cyclisation. Treatment of the acid with lithium in liquid ammonia gave the requisite anion (XXII) which on further reaction with methyl iodide gave a mixture of isomeric reduced acids (XXIII and XXIV) in a ratio of 1:3. Although in forming the trans-isomer the methyl group has to approach from the more hindered side of the anion, reaction apparently proceeds with the adjacent large substituents on the anion becoming trans to each other. Though lot of work

has been done on the stereochemistry of metal-ammonia reduction of \( \alpha,\beta \)-unsaturated ketones, no significant investigation has been reported regarding the stereochemistry of this reductive alkylation. The acid (XXIV) (either isomer or mixture) was cyclised with a mixture of polyphosphoric acid and phosphorus oxychloride to the stereoisomeric forms of the diketone in 40% yield from which the trans-isomer (XXV) was separated by chromatography and finally hydrogenated to \((+)-equilenin methyl ether\) (not shown in Scheme 5). The synthesis has also been claimed as a formal total synthesis of equilin since it has now been shown that using improved experimental techniques in metal-ammonia reduction, ring B of the equilenin methyl ether could be reduced. Finally, reduction of the diketone (XXV) with sodium and ethanol in ammonia afforded the dihydro-naphthalene-hydroxy-ketone (XXVI) in 62% yield. Survival of 11-keto group during metal-ammonia reduction has already been established in a related model compound by Mejer.\(^5\) The product (XXVI) has also been converted in good yield into \((+)-estrone.\(^5\)

It will not be out of place to mention that Birch and his associates\textsuperscript{53} also converted Robinson's compound (XXVII), previously mentioned, into a ring-C-aromatic steroidal compound as shown below:

The structures of the compounds (XXVIII and XXIX) have been unambiguously established from spectral data. They could not be, however, isomerised to the corresponding $\alpha,\beta$-unsaturated ketone on treatment with bases or acids.

A similar series of compounds which have been employed by many workers and which led to Johnson's second synthesis of estrone are represented by the structures (XXX, XXXI, and XXXII). They are very much like Robinson's compounds except that cyclopentane is replaced

by cyclohexane ring and additional functional groups are generally present. In Johnson's synthesis (vide infra), the two rings in the molecules form rings A and C of estrone and the synthesis may be called \( AC \rightarrow B \rightarrow D \) type. The synopsis of Johnson's synthesis\(^5^4,5^5\) is outlined in Scheme 6 and 7. Methyl \( \gamma \)-anisylbutyrate (XXXIII)

Scheme 6

\[
\begin{align*}
\text{XXXIII} & \quad \xrightarrow{1. \text{Stobbe cond.}} \quad \text{XXXIV} \\
\text{XXXIV} & \quad \xrightarrow{2. \text{Redn.} \quad 3. \text{Esterfication}} \quad \text{XXXV} \\
\text{XXXV} & \quad \xrightarrow{1. \text{Catalytic Hydrogenation}} \quad \text{XXXVII}
\end{align*}
\]

was readily available\(^5^6\) via the Friedel-Crafts acylation of anisole with glutaric anhydride. This was submitted to Stobbe condensation\(^5^7\) and the resultant unsaturated tricarboxylic acid reduced and the


\(^{57}\) W. S. Johnson and D. H. Daub, Organic Reactions, 1951, 6, 1.
corresponding ester (XXXIV) cyclised and methylated to furnish two epimeric keto-diesters (XXXV and XXXVII). The natural stereoisomer (XXXVII), the geometry of which was subsequently proved by its conversion into estrone, crystallised directly from the mixture in 36% yield. Later, it was found to be more profitable to carry out the combined Stobbe-Dieckmann cyclisation\textsuperscript{58} by using four mole-equivalents of potassium t-butoxide in refluxing t-butanol, the product (XXXVI), m.p. 168° being isolated in 48% yield. Usual reduction, esterification and methylation furnished the saturated keto-ester (XXXVII). This was submitted to Reformatsky reaction (Scheme 7), two products being formed: one a hydroxy-ester and the

\textbf{Scheme 7}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

other a γ-lactone. The facile formation of this γ-lactone was taken as an indication of cis-fused lactone ring. Both these compounds were dehydrated with formic acid to the same unsaturated acid di-ester (XXXVIII). Catalytic hydrogenation of the latter over 30% palladium-on-strontium carbonate proceeded almost stereoselectively giving a dihydro-compound which was shown by subsequent conversion into 14-isoestrone to belong to the unnatural stereochemical series. The mother liquor afforded the epimeric dihydro-compound (XXXIX) only in 5% yield. The acid chloride of this was cyclised by employing inverse Friedel-Crafts technique to a keto diester (XL) which on hydrogenolytic reduction was transformed into a diester (XLI) which proved to be the known isomer of natural configuration. A better route to this estrone precursor was worked out by cyclising the unsaturated acid diester (XXXVIII) to the olefinic compound (XLII) which could undergo hydrogenolytic reduction without affecting the double bond. A second catalytic reduction over 30% palladium-on-strontium carbonate in ethyl acetate solution afforded an 84% yield of the stereoisomer (XLI) of natural configuration. Application of the Arndt-Eistert homologation sequence followed by saponification afforded (+)-homomarriamionic acid methyl ether, m.p. 226° which was converted by known procedure into (+)-estrone methyl ether (XLIII). Similarly, 14-isoestrone was also synthesised from the stereoisomer (XXXIX). Some improvements were later introduced by a Russian group; one of them was to

replace the Arndt-Eistert reaction sequence by Sheehan acyloin condensation of the diester (XLI) with subsequent reduction and dehydration (Scheme 7). In the latter case, the yield of estrone was 4.8% based on glutaric anhydride as compared with 2.3% by Johnson's method.

The intermediate (XXXVII) for the total synthesis of estrone has also been obtained by two other methods. Both of them were developed in India (and yet a third one by Johnson's group). In the first method, ethyl 5-methyl-5-carboethoxy-6-oxocyclohex-1-enylacetate (XLIV) was condensed with anisole in presence of anhydrous aluminium chloride (Scheme 8). The method, though

Scheme 8

For reference, see next page.
ingenious lacked stereospecificity and was improved subsequently by Protiva et al. The second route which is more stereospecific started with the Mannich base of p-methoxyacetophenone which was condensed with ethyl \( \beta \)-oxo-adipate, a reaction which had been much exploited before by Nasipuri et al. (vide infra), to furnish after hydrolysis 2-p-anisyl-6-oxocyclohex-1-enylacetic acid (XLV) in good yield. The double bond was stereospecifically reduced, the acid esterified and the requisite methoxycarbonyl and methyl groups were introduced by Johnson's method via the isoxazole and cyanoester (Scheme 9). The latter was easily converted into keto-diester (XXXVII) by treatment with methanolic hydrochloric acid.

Meanwhile, in our own laboratory, Nasipuri and coworkers (1957-60) were working on a similar line and developed a method for the synthesis of 2-aryl-6-oxocyclohex-1-enylactic (also propionic) acid, which was followed up by Banerjee et al as described above. The objective of the research was to synthesise compounds of the type (XLVI, XLVII and XXXVI) and to employ the first two for the synthesis of D-homostejoids by following AB→D→C pattern. It was hoped that the unfavourable stereochemistry of C–D ring junction
in Robinson synthesis might be altered in case of hydrochrysene ketones. In the first synthesis, \(^{70,71}\) 2-dimethylaminoethyl \(\beta\)-naphthyl ketone (XLVIII)\(^{72}\) was converted into crystalline methiodide and reacted with the potassium derivative of methyl \(\beta\)-oxo-adipate\(^{73}\) (Robinson-Mannich base synthesis\(^{74}\)) (Scheme 10). The product, on hydrolysis and re-esterification afforded methyl

\[
\text{Scheme 10}
\]

\[
\begin{align*}
\text{(XLVIII)} & \xrightarrow{\text{1. MeI}} \text{(XLVI)} & \xrightarrow{\text{1. Pd/H}_2, \text{2. } \text{H}_2\text{O}} \text{(XLIX)} \\
\text{(L)} & \xrightarrow{\text{PPA}} \text{(LI)} & \xrightarrow{\text{Pd/Pt, } \text{H}_2} \text{(LII)}
\end{align*}
\]

\(2\beta\)-naphthyl-6-oxocyclohex-1-enylacetate (XLVI). No attempt was made to characterise the intermediate products. The ester on hydrogenation in presence of colloidal palladium and subsequent

\begin{itemize}
  \item 70. D. Nasipuri, A. C. Chaudhury, and J. Roy, Chem. & Ind., 1957, 422.
  \item 73. J. C. Bardhan, J. Chem. Soc., 1936, 1848.
\end{itemize}
saponification gave the acid (XLIX) which crystallised mainly in one stereoisomeric form, m.p. 170-172° presumably with the two big substituents, phenyl and acetic acid, on opposite side of the cyclohexanone ring. This was cyclised with polyphosphoric acid to 1,2,3,4,4a,11,12,12a-octahydro-1,11-dioxo-chrysene (L) in good yield which was hydrogenated to octahydro-1-oxo-chrysene (LI). The trans geometry was expected from analogy and indicated by the fact that treatment with mineral acid did not change its configuration. The structure was confirmed by its further conversion into chrysene (LII) by reduction with lithium aluminium hydride, followed by aromatisation with 10% palladium-charcoal.75

![Chemical Structures]

(LIII) (LIV) (LV)

In a subsequent paper,76 the corresponding methoxy-compounds (LIII and LIV) were prepared starting from 6-methoxy-2-acetonaphthone. The corresponding furfurylidene derivatives were also prepared77 but no attempt was made to introduce angular methyl group. Incidentally, a useful method of synthesis of phenanthrene was also worked out76

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starting from \( \beta \)-dimethylaminopropiophenone through the compound (LV) using the sequence of reaction described in Scheme 10.

Concurrently with the publication of Banerjee et al., another paper was published from our laboratory (Guha, Rakshit, and Nasipuri, 1960) which described the synthesis of the following compounds almost by identical method:

In view of the work of Banerjee group, further investigations were abandoned in this direction but nevertheless several important conclusions were reached. Firstly, the formation of the unsaturated acid ester (as LIX) was rationalized by postulating that reaction goes through the following sequence (Scheme 11). The initial

**Scheme 11**

![Scheme 11](image-url)
dioxo-diester (LVI) formed by condensation of β-dimethylamino-p-methoxypropiophenone with methyl β-oxo-adipate (or methyl α-methyl-β-oxo-adipate, when R=Me) underwent aldol condensation to give the anion (LVII) which could undergo intramolecular trans-esterification in two ways: either (a) with the acetic acid side chain forming the γ-lactone (LVIII) or (b) with the 5-carbomethoxy group giving rise to the bridged δ-lactone (as LXI). Between these two, the first was preferred resulting to the formation of the acid ester (LIX) after reaction with base. No water was formed in the reaction which explained the high yield (>65%) of the product. The 1,4-lactone-structure (LXI) was, on the other hand, favoured in case of aldol condensation of the higher homologue (LX), obtained by the reaction of β-dimethylaminopropiophenone with ethyl β-oxopimelate79 which underwent base-induced ring opening with simultaneous decarboxylation and afforded the neutral ester (LXII) in good yield. Examples of such extensive decarboxylation through aldolate ion having a carbalkoxy group appropriately situated for trans-esterification are well known.80 The presence of acetate side chain in the case of

anion (LVII) thus had a protecting influence on the ring-carbomethoxy group, providing an alternative and easier way of trans-esterification. The substituted propionic acids of the type (LXII) were later used for the synthesis of tricyclic systems with seven-membered ring (LXIII).81

Secondly, the condensation of the methiodide of 4-diethylamino- butan-2-one with methyl α-methyl-β-oxo-adipate, originally carried out by Robinson and Seijo82 was found, in a similar way, to give the acid-ester (LXIV) instead of the alternative structure (LXIVa), previously proposed. The structure (LXIV) was confirmed by physical data as well as an independent synthesis.83 Obviously, an identical mechanism operated in this case also.

![Diagram](link)

A more detailed study of the direction of aldol cyclisation of the types of compounds obtained by condensation of the methiodide of a number of acyclic Mannich bases with different β-oxo-esters was made subsequently.83

We like to end this discussion by observing that perhaps one of the earliest use of a Mannich base as a possible source of vinyl ketone in Michael condensation (as illustrated in the above reactions) is due to Abdullah who condensed \( \alpha \)-dimethylaminopropiophenone as well as phenyl vinyl ketone with ethyl acetoacetate in presence of sodium ethoxide to furnish 3-phenylcyclohex-2-en-1-one. Subsequently Robinson et al. introduced a major modification in the procedure by using the methiodide of the Mannich base in Michael condensation in place of the free base. The advantage of the methiodide over the Mannich base presumably lies in the liberation of the \( \alpha \beta \)-unsaturated ketone at low concentration at a time, thus avoiding undesired byproducts. Johnson has used dimethyl sulphate in place of methyl iodide, the reaction being conducted in a single operation.

PRESENT WORK.

The present investigation was undertaken with the object of studying a few reactions of the compounds described in the introduction, e.g., 2-aryl-6-oxocyclohex-1-enylacetates and analogues. As already stated, the synthesis of these compounds in high yield and using readily accessible starting materials was first developed in

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our laboratory and we thought it worthwhile to employ some of them for useful synthesis in steroid and other fields, in ways not done by previous workers. One of our original objectives was to introduce an angular methyl group at C-2 in these compounds (XLVI, for example) by direct methylation and to convert the products into D-homosteroids stereoselectively (vide infra). It is well known that in general, increase in D-ring size does not materially affect androgenic activity; by contrast, progestational or estrogenic activity is largely or completely lost. Moreover, some of these synthetic homosteroids may be used for their anabolic activity which is of great therapeutic interest. We were also interested in utilising some of the appropriate derivatives for the synthesis of ring-B aromatic steroids which are comparatively unknown and some of which possesses biological activity. However, our methylation experiments took a turn in a completely different direction and we had to deviate considerably from our original objective in order to deal with this unexpected situation. Nevertheless, we like to present the results of our investigation from the point of view of our original planning. They are summarised below sectionwise, each

A. Attempt to Introduce an Angular Methyl Group in 2-Aryl-6-oxocyclohex-1-enylacetic Esters: A Novel Aromatisation of Cyclohexenone Derivatives.

The synthesis of 2-aryl-6-oxocyclohex-1-enylacetic esters by use of Robinson-Mannich base reaction\(^2\) has already been discussed (Scheme 10). For convenience, a schematic outline is shown below:

\[ \text{Scheme 12} \]

\[
\begin{align*}
1) & \quad \text{ArCOMe} \rightarrow \text{ArCOCH}_2\text{CH}_2\text{NMe}_2 \rightarrow \text{ArCOCH}_2\text{CH}_2\text{NMe}_3 \quad \text{MeI} \\
& \quad \text{ArCOCH}_2\text{CH}_2\text{NMe}_3 \quad \text{COCH}_2\text{CO}_2\text{Et} \quad 1.\text{KOEt} \\
& \quad \text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \quad 2.\text{KOH}, \text{H}_2\text{O} \\
& \quad \text{(LXV)} \quad \text{(LXVI)} \quad \text{(LXVII)}
\end{align*}
\]

\[
\begin{align*}
2) & \quad \text{ArCOCH}_2\text{CH}_2\text{NMe}_3 \quad \text{COCH}_2\text{CO}_2\text{Et} \quad \text{KOEt} \\
& \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \\
& \quad \text{(LXV)} \quad \text{(LXVIII)} \quad \text{(LXIX)}
\end{align*}
\]

Condensation of Mannich base\(^3\) methiodide (LXV) with ethyl \(\beta\)-oxo-adipate (LXVI) furnished 2-aryl-6-oxocyclohex-1-enylacetic acid (LXVII), while condensation of the methiodide with ethyl

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β-oxopimelate (LXVIII) gave the higher homologue (LXIX). In the former case, an intermediate unsaturated acid ester was isolated (see page 25) which on hydrolysis afforded the final product (LXVII). No such acid ester could, however, be detected during the condensation with ethyl β-oxopimelate, the unsaturated ketoester (LXIX) being obtained in a single step and high yield,78 as a result of trans-esterification of the resultant aldolate ion forming an intermediate bridged 6-lactone (vide supra).

Ethyl β-oxo-adipate (LXVI) and ethyl β-oxopimelate (LXVIII) were prepared following the procedure of Guha and Nasipuri in Organic Synthesis79 as shown in Scheme 13. The method is a modification of that reported by Bouveault94 and is essentially the

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94. L. Bouveault, *Compt. rend.*, 1900, 131, 45.
same as that described by Bardhan and Nasipuri. They have also been prepared by condensation of \( \gamma \)-carboethoxybutyryl chloride (in case of ethyl \( \beta \)-oxopimelate) with ethoxymagnesiummalonic ester and cleavage of the resulting acylated malonic ester by \( \beta \)-naphthalene-sulphonic acid or by acetic or propionic acids containing a trace of sulphuric acid (also ref.\(^{98}\)). Recently, Taylor \textit{et al} has criticised the purity of the ethyl \( \beta \)-oxo-adipate prepared by this method and published a modified procedure in which they have condensed \( \beta \)-carboethoxypropionyl chloride with ethoxymagnesium-derivative of ethyl t-butyl malonate.\(^{100}\) The product on being heated in vacuum with \( \beta \)-naphthalene-sulphonic acid followed by distillation afforded pure ethyl \( \beta \)-oxo-adipate. However, this method requires ethyl t-butyl malonate, not available to us and we found the quality of ethyl \( \beta \)-oxo-adipate prepared by our method quite adequate for the present purpose. The same material has been extensively used in our laboratory for other syntheses by Nasipuri and coworkers.\(^{101-105}\)

The following compounds (XLVI, XLVII, LXX and LXXI) were selected for the study of angular methylation. All these compounds were previously synthesised in our laboratory (except LXX) and there is nothing much to report regarding their preparation. Spectroscopic data of these compounds (i.r. and n.m.r.) have now been obtained and they agree well with the structures. The preparation of the unsaturated keto-ester (XLVI) has been studied in detail and it has been possible to improve the yield to a considerable extent (see Experimental). Johnson's modification of Robinson-Mannich base synthesis, namely, use of dimethyl sulphate instead of methyl iodide apparently did not offer any advantage and we followed our old procedure.\textsuperscript{78} The melting point of the keto-ester (XLVI) was found to be 136° which is in slight variance with the reported\textsuperscript{71} m.p. 131°. The n.m.r. of this compound will be discussed later in detail in another connection. The i.r. (in nujol) showed bands at 1730 and 1660 cm\textsuperscript{-1} (ester and

unsaturated ketone respectively) and at 1610 cm\(^{-1}\). All the unsaturated keto-esters of the type (LXX or LXXI) described in this section showed these bands in i.r. spectra and will not be mentioned further.

To our knowledge, no attempt has been made to methylate these compounds (e.g., XLVI) directly. It is now well established that \(\alpha,\beta\) unsaturated ketone loses a gamma proton in presence of a base and is alkylated at the alpha position\(^{106}\) to form \(\beta,\gamma\)-unsaturated ketone. This initial product may be isomerised to an \(\alpha\)-alkyl-\(\alpha,\beta\)-unsaturated ketone but more often undergoes further alkylation as shown in Scheme 1\(^4\). A great number of alkylations of this nature

\[ \text{Scheme 1}^{14} \]

\[ \text{[Diagram]} \]

are known,\textsuperscript{107} where it is often experienced that dialkylation is preferred to monoalkylation. In fact, if one starts with \(\alpha\)-monoalkylated compound, one has to use more drastic condition to obtain the dialkylated product. An explanation has been suggested by Yanagita \textit{et al.}\textsuperscript{108} for this phenomenon which may be summed up as follows:

\begin{align*}
(LXXII) & \rightarrow (LXXIII) \rightarrow (LXXIV) \\
(LXXV) & \rightarrow (LXXVI) \rightarrow (LXXVII)
\end{align*}

They found that the ketone (LXXV) was dimethylated to (LXXVII) much less readily than the ketone (LXXII). Apparently, the mesomeric anion (LXXIV) was formed easily from the intermediate \(\alpha\)-methyl-\(\beta,\gamma\)-unsaturated ketone, while "the electron release properties of the


methyl group at C-4 in compound (LXXV) would suppress the distri-
bution of \( \pi \)-electrons of the \( \Delta^1 \)-double bond to C-3 carbon, preventing
the anion (LXXVI) from assuming the mesomeric form (LXXIV).\(^{108}\)
Nevertheless, many examples are known of dialkylation of the
\( \alpha \)-substituted \( \alpha, \beta \)-unsaturated ketones.\(^{109}\) We were particularly
couraged by the success of methylation of the following two
systems:

\[
\text{(Vida and Gut)}^{110}
\]

\[
\text{(Dasgupta et al)}^{110}
\]

and we hoped to effect methylation of the compounds (XLVI and XLVII)

\[
\text{(LXXVIII)}
\]

\[
\text{(LXXIX)}
\]

109. K. K. Mahalanabis, S. K. Mukhopadhyay and P. C. Dutta,
Chem. Comm., 1968, 1641; H. J. Ringold and S. K. Malhotra,

S. K. Dasgupta, Private Communication; and also L. Velluz, G.
Nomine; and J. Mathieu, Angew. Chem., 1960, 72, 725.
by similar procedure. The product (as LXXVIII) on cyclisation was expected to give the diketone which could be stereospecifically reduced\(^\text{111}\) to trans-stereoisomer (LXXIX). The latter could subsequently be converted into estrone, D-homoestosterone or their 11-keto-derivatives by known procedures.\(^\text{40,45}\)

We like to make a passing remark on this type of methylation which leads to thermodynamically less stable unconjugated \(\alpha\alpha\) -dimethyl-\(\beta,\gamma\)-unsaturated ketone in preference to more stable conjugated \(\gamma,\gamma\)-dimethyl-\(\alpha,\beta\)-unsaturated ketone. As pointed out by House,\(^\text{106}\) the result is reminiscent of the kinetically controlled protonation of mesomeric anions for which a lot of data are available,\(^\text{112}\) and also of the protonation of anions produced during metal-ammonia reduction of aromatic systems.\(^\text{113}\) In all these cases, generally, the less stable (unconjugated) products are obtained. Some examples of protonation as well as alkylation are given in Scheme 15.


Protonation:

i) \( \text{CH} = \text{C} - \text{CO}_2\text{Et} \rightarrow \text{CH} = \text{C} - \text{CH}_2 \text{CH}_2 \text{CO}_2\text{Et} \)

Ref. 112

Scheme 15

Alkylation:

iii) \( \text{Et} \ \text{CN} \rightarrow \text{CN} \rightarrow \text{Et} \)

Ref. 115

In case of protonation, Ingold\textsuperscript{116} has stated that when a proton is supplied by acids to the mesomeric anion of weakly ionising


tautomers of markedly unequal stability, then the tautomer which is
most quickly formed is the thermodynamically least stable; it is also
the tautomer from which the proton is lost quickly to bases. Hine, on
the other hand, has suggested that possibly it might be an outcome
of 'Principle of Least Motion,' which states that those elementary
reactions will be favoured which involve the least change in atomic
position and electronic configuration, and is a direct consequence of
application of transition state theory to the effect of structure on
reactivity. We are not competent enough to pass any judgement upon
it, but we feel that these alkylation reactions seem to belong to
this category and might serve as examples of this principle. Any
way, discussion regarding the Principle of Least Motion is still
inconclusive and its applicability in alkylation reaction is still
more uncertain.

We first attempted methylation of the unsaturated ester (XLVI)
using sodium hydride as base in dimethylformamide. This metal-
solvent system has been widely used for generation of carbamions
from active methylene compounds prior to their alkylation. It has
certain advantages over other metal-solvent combinations. Thus the
use of dimethylformamide (and also dimethylsulphoxide and dimethoxy-
ethane) increases the rates of reaction of enolate (or analogous)

1966, 88, 5525.

118. F. O. Rice and E. Teller, J. Chem. Phys., 1938, 6, 489; 1939,
1, 199; J. Franck and E. Rabinowitsch, Z. Elektrochem.,

anions with alkylating agents substantially in comparison to alcohols or inert solvents. Its advantage over protonic solvents lies in the fact that it does not solvate the enolate anion and consequently does not diminish its reactivity as a nucleophile. On the other hand, it has the ability to solvate the cation separating it from the cation-enolate ion pair and leaving a relatively free anion in the reaction mixture. That the enolate ions do exist in solvents as ion pairs with cations is supported by the observations\textsuperscript{121} that the reactivity of the enolates is often very much influenced by the nature of the cation present, the lithium cation forming more tightly associated ion pairs than sodium and potassium.

The ester (XLVI) was allowed to react with 3 moles of sodium hydride (50% suspension in mineral oil) in dimethylformamide first at room temperature and then at 100$^\circ$ until the evaluation of 1 mole of hydrogen was complete. The resulting red solution was stirred with an excess of methyl iodide. The product on t.l.c. analysis proved to be a complex mixture from which, three compounds (Scheme 16) were isolated by column chromatography as crystalline solids and characterised respectively as 3-β-naphthyl anisole (LXXX; ~70%),

\begin{footnotesize}
\begin{enumerate}
\end{enumerate}
\end{footnotesize}
m.p. 90°, 2-β-naphthyl-5,5-dimethyl-6-oxocyclohex-1-enylacetic acid (LXXXI; 8%), m.p. 212° and the lactone (LXXXII; 5%), m.p. 135-38°. The formation of 3-β-naphthylanisole was absolutely unexpected and its structure was first deduced from n.m.r. spectroscopy, absence of carbonyl peak in i.r. spectrum, and elemental analysis. The n.m.r. spectrum (Fig. 1) showed only aromatic protons (1.85-3.1%) and -OCH₃ (sharp singlet at 6.12%) protons in the ratio of 11:3. Later, its structure was confirmed by synthesis which is outlined in Scheme 17. 3-β-Naphthylcyclohex-2-en-1-one (LXXXIII),¹²² m.p. 99° was prepared by the application of Robinson-Mannich base synthesis using dimethylaminoethyl β-naphthyl ketone and ethyl acetoacetate (modification of

a previous method\textsuperscript{123} followed by hydrolysis. This was smoothly dehydrogenated with 10\% palladium-charcoal in boiling \textit{p}-cymene to furnish the phenol (LXXXIV), m.p. 115\textdegree which was methylated to the ether (LXXX). The identity of the two methyl ethers was established by mixed m.p. which remained undepressed and by superimposable i.r. spectra. Since the phenol (LXXXIV) was subsequently found to be the key compound of this interesting transformation, its structure was further confirmed by n.m.r. spectrum which showed the following peaks: multiplets at 2.0-3.2\texttt{H} (11 H, aromatic protons) and a sharp singlet at 4.98\texttt{T} (1 H, -\texttt{OH}).

It was also characterised by the formation of an acetate, m.p. 73\textdegree. The structure of the dimethylated acid (LXXXI) which was mainly deduced from spectral data and that of the lactone (LXXXII) which was established by spectral data as well as by synthesis will be discussed

later. We like to point out that while the methyl ether (LXXX) always formed as the major product, these two minor components appeared in variable amounts depending on reaction condition and sometimes were missed completely. The yields of these two as shown in Scheme 16 were the maximum obtained at our hand. The t.l.c. analysis showed some other minor components which could not be identified and a gum (10-20%) with very low Rf value.

Incidentally, dehydrogenation of 3-6-naphthylcyclohex-2-en-1-one (LXXXIII) with powdered sulphur (1 atom) at 250° afforded an alkali-soluble product, m.p. 232° in about 40% yield, which contained sulphur and analysed correctly for the compounds (LXXXV or LXXXVI). Apparently, the phenol was first formed which added up sulphur to give the benznaphtho-thiophene — a reaction analogous to the formation of dibenzothiophene from diphenyl.124 This could be a good

![Reaction Diagram]

one-step synthesis of polycyclic thiophene derivatives from easily available arylcyclohexenones. However, we are still not very sure of the structure of the product and work in this direction is in progress.

We next treated the ester (XLVI) with 3 moles of sodium hydride (50% in oil suspension) in dimethylformamide. After the usual 1 mole

Solvent: Chloroform-Benzene (1:9)

SOLVENT FRONT

Mineral oil → A

B → B

C → C

D → UNIDENTIFIED

Fig. 2
of hydrogen was evolved, the solution was heated at 100-110° for 45 min., and the product after decomposition with 2N sulphuric acid analysed on t.l.c. Three spots (in addition to the one due to the mineral oil from sodium hydride) were clearly discernible in the plate (Fig. 2). The upper two were identified (by comparison of \( R_f \) values in three different solvent systems) as the lactone (LXXXVII) and the phenol (LXXXIV). These two were separated on silica gel column, the first to be eluted was the lactone (LXXXVII, 5%) and next came the phenol (LXXXIV, 70%) as a crystalline solid, m.p. 115° (structure confirmed by superimposable i.r. spectra and mixed m.p. determination with a synthetic specimen). In the beginning, we mistook the lactone (LXXXVII) for the acetate of the phenol (LXXXIV) which we expected mechanistically (vide infra), because both of them had the same \( R_f \) values in t.l.c. The i.r. spectrum (Fig. 3) (lactone band at 1815 cm\(^{-1}\)) and elemental analysis, however, conclusively proved its structure as (LXXXVII). The yield of the phenol depended to a large extent on the time of exposure as well as the temperature used. After a number of experiments, it was found that the optimal condition was to treat the ester with 3 moles of sodium hydride in dimethylformamide for 45 min. at 100°. Lower temperature increased
WAVE NUMBER (CM\(^{-1}\))

WAVE LENGTH (MICRONS)

Fig. 3
Fig. 4  I.R. spectra of 3-β-Naphthylphenol (solid line: synthetic; dotted line: rearrangement product)
α-acetylsuccinate\textsuperscript{125} in presence of potassium ethoxide and then hydrolysed and esterified to furnish methyl 4-phenylcyclohex-2-oxo-3-en-1-yl-acetate (XC), m.p. 82° (λ\textsubscript{max.} in ethanol, 220 and 281 nm; log E 3.9 and 4.2 respectively) in good yield.

Both these esters (LXXI and XC) on exposure to sodium hydride and dimethylformamide at 100° afforded the same phenol (LXXXIX), m.p. 80-81° in 50% and 35% yields respectively. The lower yields in case of the phenyl derivatives could not be properly accounted for, and were presumably due to loss during extraction from aqueous dimethylformamide. No other products could be identified from the reaction mixture, although traces of lactones (as LXXXVII) were detected in t.l.c. Similarly methyl 2-α-naphthylcyclohex-6-oxo-1-enylacetate, the preparation and properties of which will be described later, afforded the phenol (XCII) which could not be obtained in crystalline form. Its infra-red spectrum however was found to be superimposable (Fig. 4) with that of a synthetic specimen (also a gum), prepared from 3-α-naphthylcyclohex-2-en-1-one (XCIII).\textsuperscript{122}

The phenol (LXXXIX) was likewise synthesised from 3-phenylcyclohex-

2-en-1-one,\textsuperscript{126} m.p. 64° and compared with that obtained from the esters (LXXI and XC).

We are thus witnessing, for the first time, a novel aromatisation reaction of cyclohexenone derivatives whereby 2-aryl-6-oxo-cyclohex-1-enylacetic esters are found to undergo dehydrogenation to phenols with concomitant loss of acetate side chain on exposure to sodium hydride and dimethylformamide at 100°. Our original objective of introducing a methyl at C-1 using sodium hydride-dimethylformamide as metal-solvent combination is thus completely frustrated. We attribute this failure to the simple fact that unlike ordinary cyclohexenone system (XCIV) where R is an alkyl group, the arylcyclohexenone (XCV) does not form anion at C-3, which is the prerequisite for C-1-alkylation. Instead, sodium hydride abstracts proton from C-5, the resulting enolate ion (XCVI) being stabilised by extended conjugation with the aromatic ring. The reaction sequence in case of both the substrates is shown in Scheme 19. This theory finds support

\textbf{Scheme 19}

\begin{equation}
\begin{array}{c}
\text{(XCVI)} \\
\end{array}
\end{equation}

\textsuperscript{126} F. C. Novello, M. E. Christy, and J. M. Sprague, \textit{J. Amer. Chem. Soc.}, 1953, \textbf{75}, 1330; also ref. 84.
in the isolation and characterisation of the two compounds (LXXXI & LXXXII) from the methylation product. In line with this argument, when the ester (XLVI) was treated with potassium t-amylate in benzene and then methylated, the dimethylated compound (LXXXI) was obtained though in small yield; 60% of the original ester (XLVI) being recovered unchanged. N.m.r. spectrum of the reaction mixture showed no evidence of formation of compound of the type (XCVII) which would show a vinyl proton. As already pointed out, $\alpha$-alkyl-$\alpha$-$\beta$-unsaturated ketones require more drastic treatment for methylation and apparently in case of the $\beta$-aryl-substituent, -CO-CH$_2$- group is exclusively methylated. After our work had been reported, our attention was drawn to a publication where it has been shown that

direct methylation of the ketone (XCVIII) furnished the tetramethylated ketone (XCIX) in low yield along with one aromatised product. It appears therefore that this method of approach is not suitable for methylating cyclohexenone system having a beta-aryl group.

Regarding the mechanism of the above transformation, the following scheme (Scheme 20) is suggested. The enolate anion (C), initially formed by a proton loss to sodium hydride, is converted into the \( \gamma \)-lactone (CI). The latter has two exocyclic double bonds with respect to a five-membered ring and so may be conformationally strained. It would isomerise to the cyclohex-1,4-diene system (CII) even though in so doing it loses some resonance energy.* The latter can easily lose a proton to a base as shown and be converted into

\*It is not necessary that the isomer (CII) should exist in any appreciable amount at any time. In fact, the equilibrium will surely lie very much towards the conjugated lactone (CI).
the anion (CM) which is very likely to be cleaved into a phenolate anion and possibly a ketene. The latter then combines with dimethylamine (originated from dimethylformamide, vide infra) to give N,N-dimethylacetamide which could not be detected by conventional method used in our analysis.

We adduce the following evidences in support of the mechanism:

i) Firstly, it has already been proved by isolation of methylated products (such as LXXXI and LXXXII) that the formation of carbanionic centre in the ester (XLVI) did occur at C-5 instead of C-3.

ii) The intermediate lactone (CII; Ar=β-naphthyl) has actually been isolated by treatment of the ester (XLVI) under milder condition and its structure established (see p. 44). No trace of the acetate corresponding to the structure (CIII; Ar=β-naphthyl) could, however, be isolated. Apparently, this species is a fleeting intermediate losing the acetate moiety perhaps as a ketene. In partial support of this, we have found that when β-naphthyl acetate was treated with sodium hydride in dimethylformamide and the product worked up, β-naphthol was obtained in 100% yield. Formation of ketene is a probable but not a necessary step; because even when β-naphthyl benzoate was submitted to the same reaction condition, β-naphthol was recovered in 100% yield. Here, the cleavage is obviously a result of addition of base to carbonyl followed by C-O bond fission. The exact
fate of benzoyl group could not be determined at present.

\[ \text{Scheme 21} \]

\[ \text{MeOH, HCl} \]

Hydrolysis

(LXX)

*The structure of this ester was corroborated from the following spectral data:

I.r. : \( \nu_{\text{max}} \) (nujol) 1662 and 1730 cm\(^{-1}\) (ester and \( \alpha,\beta \)-unsaturated ketone), and 1610 cm\(^{-1}\).

N.m.r. : (taken in CDCl\(_3\) solution with TMS as internal standard on a 60 MHz machine).

Peaks at 2.0-2.9\( \tau \) (multiplets) - 7H - Aromatic protons
6.5\( \tau \) (sharp singlet) - 3H - CO\(_2\)-CH\(_2\)-
7.2-7.6\( \tau \) (irregular multiplets) - 8H - CO-CH\(_2\)-
and C=CH\(_2\)- (four methylene protons)

Multiplet centred at 7.9\( \tau \) (irregular multiplets) - 2H - CH\(_2\)-CH\(_2\)-CH\(_2\)-
submitted to the same reaction conditions, i.e., treated with sodium hydride in dimethylformamide at 100° did not undergo any appreciable extent of aromatisation. A very faint spot was observed in t.l.c. with the same R_f value as that of the phenol (LXXXIV) but it could not be isolated. Apparently, a good leaving group like acetate facilitates the transformation. It might be pointed out, however, that the driving force of the above transformation is certainly not the stability of the departed ion such as CH_2COOR, but the conversion of a cyclohexadiene system into aromatic ring. Thus when the acid (CV), m.p. 161°, was treated similarly with sodium hydride in dimethylformamide, the phenol (LXXXIV) was isolated although in comparatively poor yield (~25%). It is possible that the optimal condition for this transformation has not been found. In this case, the formation of the lactone (as Cl) is extremely remote and the only mechanism we can suggest is given in Scheme 22, where doubly

*charged acetate anion has been shown as a departing group. The
Solvent: Chloroform-Benzene (1:9)

SOLVENT FRONT

Mineral oil → A

B

OH

C

C

D

UNIDENTIFIED

Fig. 5
exclusion of a dianion of the type \( \Theta \text{CH}_2\text{CO}_2 \) particularly in a medium where solvation of anions is minimum is certainly energetically a very unfavourable process. But we can not see how we can avoid it unless we accept the still more improbable theory that an enol-lactone (e.g., CI) is formed somehow in the reaction. We mention this because in t.l.c. of the product (Fig. 5) we found a spot that might be due to the lactone (CI; Ar=\( \beta \)-naphthyl), previously isolated. Its formation, however, could be attributed to the action of mineral acid on the anion (CVI) during work-up* as shown below:

\[
\begin{align*}
\text{(CVI)}
\end{align*}
\]

As regards the species, \( \Theta \text{CH}_2\text{CO}_2 \) as a departing group, the closest analogy that we can find is the hydrolysis of ethyl acetooacetate into two molecules of acetic acid in presence of strong alcoholic alkali:

\[
\begin{align*}
\text{CH}_3\text{COCHCO}_2\text{Et} &\xrightarrow{\text{OH}} \text{CH}_3\text{CO}_2^- + \text{RCH CO}_2^- \\
(R=H \text{ or alkyl})
\end{align*}
\]

In all text-books (see, for example, Roberts and Caserio, "Basic Principles in Organic Chemistry", W. A. Benjamin, Inc. New

*In fact, treatment of the acid (CV) with sodium hydride in boiling benzene and decomposition of the product with mineral acid afforded a semisolid which showed two spots in t.l.c., the upper one (very faint) corresponding to that of the lactone (CI).
York, 1964, p. 543), however, this cleavage has been shown as the reverse of Claisen condensation (which is no doubt true) keeping the ester function up to the final stage of the reaction, thus avoiding the problematic existence of RCHCO₂⁻.

\[
\begin{align*}
\text{CH}_3\text{C}-\text{CHR} & \quad \text{OH} \\
\text{CH}_3\text{C}-\text{CHR} & \quad \text{OH} \\
\text{CH}_3\text{CO}_2^- + \text{RCH}_2\text{CO}_2\text{Et} & \quad \text{OH} \\
\end{align*}
\]

In the present case, the equilibrium between the two anions (CVI and CVII) is very much in favour of the former since the conformational restraint present in the γ-lactone intermediate (CI), formed when the ester is used, is absent. This may be one of the major factor responsible for the lower yield of the phenol (LXXXIV) when the acid (CV) is used in the above transformation.

iv) 3-β-Naphthylcyclohex-2-en-1-one (LXXXIII) did not afford any detectable amount of phenol under identical conditions. This also offers additional support that some sort of leaving group is essential for the aromatisation to occur. The position of the acetate side chain in the cyclohexenone ring may not be very vital. For example, the compound (XC) has also been converted into the phenol (LXXXIX) (vide supra) in slightly lower yield. The probable mechanism is shown in Scheme 23. The extraction of proton from the conjugated diene (XCa) will obviously need a very strong base.

We are currently studying the above transformation with the
esters (CVIII and CIX)\(^*\) in order to complete the different substitution pattern in the 3-phenylcyclohex-2-en-1-one system and make a quantitative study of the conversion into the phenol (LXXXIX).

One final point must be clarified before we close this discussion. Sodium hydride in itself does not bring any change (except forming the anion) in these systems. This has been proved by treating the ester (XLVI) with sodium hydride in benzene when one

\*The two esters (CVIII and CIX) have already been synthesised by A. Mitra and S. R. Roy Choudhury of our laboratory.
mole of hydrogen evolved but the compound was recovered unchanged. Obviously, dimethylformamide undergoes some change when heated with sodium hydride. Decomposition of formates and formamides in presence of sodium hydride is well known and occurs usually with the formation of sodio-N,N-dialkylamine, carbon monoxide and hydrogen, according to the following two general equations:

\[
\text{ROCHO} + \text{NaH} \rightarrow \text{RONa} + \text{CO} + \text{H}_2 \quad \ldots (1)
\]

\[
\text{R}_2\text{NCHO} + \text{NaH} \rightarrow \text{R}_2\text{N}\text{Na} \oplus \text{CO} + \text{H}_2 \quad \ldots (2)
\]

For example, when butyl formate was refluxed with equimolecular quantity of sodium hydride in 1,2-dimethoxyethane (glyme), approximately two moles of gas evolved and 68% butanol was isolated from the product. Similar cleavage\(^{129}\) of HCOOEt, HCONPhMe, HCONPhCH\(_2\)CH\(_2\)NPhHCO and HCONEt\(_2\) gave EtOH, PhNHMe, PhNH(CH\(_2\))\(_3\)NPh and NHEt\(_2\) in 70, 70, 79 and 40% yields respectively. Ether, dimethylsulphoxide and monoglyme have been used as solvents and Ph\(_3\)CNa and Me\(_3\)CONa were found to be equally effective as sodium hydride. The intermediate alkoxides and amine anions were trapped readily in the presence of an alkylating agent. Thus cleavage of HCONPhMe with NaH in the presence of PhCH\(_2\)Br gave 30% of MePhNCH\(_2\)Ph. No products arising from an intermediate carbanion were detected even when the reaction was carried out in carbon monoxide at 100 atmosphere pressure. Cleavage (80%) of butyl formate by potassium t-butylate in deuterated dimethyl sulphoxide gave enriched (1.5%) HCO\(_2\)Bu containing

---


D entirely as DCO\textsubscript{2}Bu showing that some exchange had occurred through an unidentified mechanism.

We observed, however, that when a suspension of sodium hydride in dimethylformamide was heated at 100° for 1 hr., no appreciable gas evolution took place even after addition of water at the end, indicating that sodium hydride has been entirely consumed. Distillation of the acidified mixture revealed the presence of formaldehyde in the distillate which was identified through the formation of dimedone derivative.\textsuperscript{131} It appears, therefore, that under the present condition, the decomposition took place according to the following equation:

\[ \text{Me}_2\text{NCHO} + \text{NaH} \rightarrow \text{MeN-CH}_2\text{O} + \text{Na} \rightarrow \text{Me}_2\text{N Na} + \text{HCHO} \]

Formaldehyde was also chased out from the heated mixture of sodium hydride and dimethylformamide and identified. Thus the effective base is most possibly the sodio-derivative of dimethylamine which is similar to N-lithioethylenediamine, a reagent\textsuperscript{132} well known for aromatisation of hydroaromatic rings.\textsuperscript{133,134} An example is given below. This type of aromatisation apparently occurs as a result of

\begin{itemize}
  \item \textsuperscript{131} E. C. Horning and M. G. Horning, \textit{J. Org. Chem.}, 1946, \textit{71}, 95.
\end{itemize}
Fig. 6 Infrared spectrum of the lactone of 2-9-Naphthyl-t-methyl-6-hydroxyphenylacetic Acid
migration of double bond and has nothing to do with dehydrogenation.
Under the present condition, carvone afforded only 15% of carvacrol, the rest of the product being unidentified gum.

In the conclusion of this section, we want to discuss the structure of the two minor components (LXXXI and LXXXII) isolated from the methylation product of (XLVI) (after hydrolysis). The i.r. and n.m.r. spectra of the two compounds are given below:

\[ \text{I.r.: } \gamma_{\text{max}} \text{(nujol) } 1710, 1670 \text{ and } 1608 \text{ cm}^{-1} \]
\( \text{carboxyl group and } \alpha,\beta\text{-unsaturated ketone); also } 1380 \text{ and } 1352 \text{ cm}^{-1} \)
\( \text{(indication of geminal dimethyl group)} \)

\[ \text{I.r.: } \gamma_{\text{max}} \text{(KBr) } 1785 \text{ (}\gamma\text{-lactone)} \text{ and } 1620 \text{ cm}^{-1} \text{ (Fig.6)} \]

N.m.r. (taken in CDCl\text{\textsubscript{3}} with TMS as the internal standard on a 60 MHz machine) shows the following peaks:
### LXXXI: Multiplets at 2.05-2.75 T 7H Aromatic
- Broad singlet at 6.75 T 2H
- Broad triplet centred at 7.24 T (J=6 Hz) 2H
- Broad triplet centred at 8.00 T (J=6 Hz) 2H
- Sharp singlet at 8.78 T 6H

The structure of the dimethylated keto-acid (LXXXI) could not be unambiguously established. I.r. and n.m.r. spectra are no doubt in accord with the proposed structure but there would be very little difference in n.m.r. spectrum if the geminal dimethyl groups are placed at C-3 (as in CX) instead of C-5 as in structure (LXXXI). The methylene protons signal agrees better with -CO-C=CH₂-grouping (see the spectrum of XLVI, Fig. 10) than -CO-CH₂-CH₂- formulation. The signal for the keto-methylene protons generally appear at slightly higher field (7.5-7.6 T).\(^{135}\) Besides, the results of methylation\(^{128}\)

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135. G. V. D. Tiers, Tables of T-values for a variety of organic compounds, 1958; see, for example, cycloheptanone (-CH₂-CO at 7.58 T)
of the unsaturated ketone (XCVIII), as recorded earlier, are also in conformity with the proposed structure (LXXXI). The confirmation of the structure (LXXXII) (vide supra) is another additional proof.

In addition to the evidence of spectral data, the structure of the lactone (LXXXII) was confirmed by synthesis (Scheme 24). The methiodide of the Mannich base of 2-acetonaphthone was condensed in the usual way with ethyl α-methyl-β-oxo-adipate (CXI), the product...
hydrolysed with alkali and on acidification afforded 2-β-naphthyl-5-methyl-6-oxocyclohex-1-enylacetic acid (CXII), m.p. 153-55°. The latter on dehydrogenation with palladium-charcoal furnished the lactone (LXXXII), m.p. 141°. The identity was established by mixed m.p. determination as well as by comparison of i.r. spectra.

Ethyl α-methyl-β-oxo-adipate (CXI)\textsuperscript{136} required in this connection was prepared by methylation of ethyl β-oxo-adipate. A better method was to start from ethyl α-methy lacetoacetate\textsuperscript{137} which could be obtained in pure form through methylation of the acetoacetate enamine followed by condensation with β-carboethoxypropionyl chloride and ammonolysis of the product.

Since direct methylation of 2-aryl-6-oxocyclohex-1-enylacetate by any metal-solvent combination leads to undesirable side-products, we are currently preparing the non-aromatic analogue (A) which is expected to form anion at C-3 and undergo methylation at C-1 to give β,γ-unsaturated ketoester (B). The latter could be oxidised to the diketonic ester (C) and subsequently converted into tetracyclic steroidal systems.

B. Synthesis and Reactions of 2-α-Naphthyl-6-oxocyclohex-1-enylacetate.

In Section A, we casually mentioned that methyl 2-α-naphthyl-6-oxocyclohex-1-enylacetate (CXIII), like all similar compounds, underwent the aromatisation reaction on exposure to sodium hydride and dimethylformamide at 100° to furnish 3-α-naphthylphenol. We were interested in this compound for several reasons: i) Firstly, we wanted to see how the Robinson-Mannich base synthesis previously applied to 2-acetonaphthone works in case of 1-acetonaphthone. It has been reported that purification of the 3-α-naphthylcyclohex-2-en-1-one (XCIII) offers much difficulty.\(^\text{122}\) ii) Secondly, these compounds (CXIII or substituted) are interesting substrates for studying hindered rotation around 1-naphthyl bond. For example, \(\beta\)-chloro-(2-methyl-1-naphthyl) acrylic acid (CXIV) shows optical stability along with many other 1-naphthalene derivatives due to restricted rotation. iii) Finally, these compounds can be utilised for the synthesis of 3,4-benzophenanthrene (CXV) and its derivatives through a relatively simple series of reactions. Methods for the synthesis

of this hydrocarbon are not many. As will be seen in the sequel, these studies have resulted in some interesting observations regarding the behaviour of the compound (CXIII).

Methyl α-naphthyl ketone (1-acetonaphthone) required for the synthesis was prepared by the application of Friedel-Crafts reaction according to a known procedure. However, our results are found to differ considerably from the literature data. Baddeley et al reported a 98:2 ratio of 1-acetonaphthone to 2-acetonaphthone when naphthalene was allowed to react with acetyl chloride in 1,2-dichloroethane in presence anhydrous aluminum chloride. But the product obtained in our laboratory under identical condition was found to consist of 80 and 20% of α and β-isomer respectively as determined by gas chromatography. They were separated through formation of picrates which differed considerably in solubility. Pure 1-acetonaphthone (solid at low temperature) was isolated from the mixture in 60% yield after regeneration from the picture, m.p. 120.°

The synthesis of 2-α-naphthyl-6-oxocyclohex-1-enylacetic acid (CXVI) was achieved following essentially the procedure described before and is given in Scheme 25.

Scheme 25

In the first method, the methiodide of the Mannich base (CXVII) was condensed with ethyl β-oxoadipate (LXVI) in presence of 1.5 moles
Fig. 7  I. R. spectrum of 2- Naphthyl-6-oxocyclohex-1-enylacetic Acid (hydrated variety)
Fig. 8 I. R. spectrum of 2-o-Naphthyl-6-oxocyclohex-1-enylacetic Acid (Anhydrous variety)
Fig. 8A  I.R. spectrum of 2-α-Naphthyl-6-oxocyclohex-1-enylacetic Acid (Anhydrous variety) in triethylamine
of potassium ethoxide to afford a gummy acid-ester which was directly hydrolysed without any further purification to the acid (CXVI). In the second method, the hydrochloride of the Mannich base and dimethyl sulphate were used instead, the rest of the procedure being almost the same. Purification of the acid offered some difficulty as anticipated. After a few trials, the acid (CXVI) in both the preparations was isolated in crystalline form, through its potassium salt which was sparingly soluble in water and could be recrystallised from hot water. The yields in both the methods were almost identical (55 and 60% respectively). The acid (CXVI) when crystallised from aqueous ethanol afforded white needles m.p. 102°C which analysed for a monohydrate, but when crystallised from ether-petroleum furnished the anhydrous variety, m.p. 127-128°C. The infra red spectrum of the hydrated acid (Fig. 7) showed bands at 1700 and 1650 cm⁻¹ but the anhydrous acid showed two bands at 1732 and 1627 cm⁻¹ (Fig. 8). The substantial shifts from the normal values for \( \alpha, \beta \)-unsaturated ketone and carboxylic acid are perhaps attributable to hydrogen bonded structure shown in Fig. 8. The i.r. spectrum of the corresponding \( \beta \)-naphthyl derivative (Fig. 8B) on the other hand, showed the normal carbonyl bands (1700 and 1665 cm⁻¹). The anhydrous acid in triethylamine showed the expected conjugated ketonic bands at 1665 cm⁻¹ (Fig. 8A), thus confirming the structure.

They afforded the same methyl ester (CXIII), m.p. 77°C; \( \lambda_{\text{max.}} \) (mujol), 1730, 1665, and 1615 cm⁻¹. The ultraviolet spectra of the hydrated acid \( \lambda_{\text{max.}} \) in ethanol, 222, 245, (hump), 270, 282, and 288 nm.; log \( E \), 4.62, 4.08, 3.85, 3.91, and 3.89 respectively and methyl ester (CXIII) \( \lambda_{\text{max.}} \) in ethanol, 222, 243 (hump), 282, and 290 nm.; log \( E \), 4.78, 4.2, 3.96, and 3.86 respectively were almost identical (Fig. 9).
Fig. 9 U. V. spectra of 2-α-Naphthyl-6-oxocyclohex-1-enylacetic Acid (hydrated variety, solid line) and its methyl ester (dotted line)
An alternative synthesis of the unsaturated keto-acid (CXVI) was also achieved to confirm the structure, by application of the method of Johnson et al, as outlined in Scheme 26.

Scheme 26

Methyl γ-1-naphthoylbutyrate (CXVIII) was prepared from the Mannich base (CXVII) methiodide by malonic ester synthesis and then submitted to combined Stobbe-Dieckmann condensation followed by decarboxethoxylation to furnish the acid (CXVI) in poor yield. Its identity with the previously prepared acid was established by superimposable infra-red spectra.

The n.m.r. spectra of the methyl ester (CXIII) and the acid (CXVI) were studied in detail and compared with that of methyl 2-β-naphthyl-6-oxocyclohex-1-enylacetate (XLVI). Since these spectra offer some interesting features, they are reproduced in Fig.s 10, 11, and 12, and the details discussed below.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Position of Peaks (T)</th>
<th>Nature</th>
<th>Proton Count</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(XLVI)</td>
<td>7.24</td>
<td>Triplet (J=6-7Hz)</td>
<td>2H</td>
<td>$\text{O=C-C=C}=-\text{CH}_2$</td>
</tr>
<tr>
<td>(Fig. 10)</td>
<td>7.42</td>
<td>Triplet (J=6-7Hz)</td>
<td>2H</td>
<td>$\text{O=C-CH}_2\text{-CH}_2^-$</td>
</tr>
<tr>
<td>(CXIII)</td>
<td>6.52</td>
<td>Sharp singlet</td>
<td>2H</td>
<td>$\text{-CH}_2\text{-CH}_2^-$</td>
</tr>
</tbody>
</table>

$6.79$, $6.94$ centred at 6.9; $7.75$, $7.20$ (J=15 Hz) 2H $=\text{C-CH}_2^-$ and $\text{C-CH}_2^-$

$7.3$  Multiplet (J=6 Hz) 4H $=\text{C-CH}_2^-$ and

$7.75$  Multiplet (J=6 Hz) 2H $\text{-CH}_2\text{-CH}_2^-$

These two n.m.r. spectra were taken\textsuperscript{144} in CDCl$_3$ solution at

\textsuperscript{144}. We are thankful to Dr. R. W. Richard of Research School of Chemistry, Australian National University, Canberra 2600. A. C. T., Australia, for these n.m.r. spectra.
100 MHz machine. There are several interesting features regarding the spectrum of the α-naphthyl-derivative (CXIII) which are revealed when compared to that of the β-naphthyl-analogue (XLVI). The aromatic protons in both the spectra showed fine splitting which are expected. The most interesting feature of the spectrum of compound (CXIII) was however the signal for the side chain methylene protons (H_A and H_B) which appeared as an AB quartet, centred at 7.03 T, with peaks at 6.79, 6.94, 7.75, and 7.20 T (relative intensities, 1:3:3:1, J = 15 Hz). This could be easily explained if we assume that the rotation around C-1 naphthalene bond is sufficiently restricted, so that the two protons, H_A and H_B are diastereotopic\(^1\) and the preferred conformation (only one enantiomer is shown) is the three dimensional structure (CXIX), where the aromatic plane and the plane of the cyclohexenone ring make an angle of approximately 90° to each other. This will explain not only the above quartet but also the relatively insignificant phenomenon that the carbomethoxy protons in compound (CXIII) appeared at slightly higher field than those in compound (XLVI) (6.52 and 6.38 T respectively; \(\Delta\delta = 14\) Hz).

---

The usual position of CO$_2$Me signal is at 6.30-6.40 T. This is probably due to the fact that in the conformation (CXIX), the carbomethoxy group may come within the shielding cone of aromatic ring. It is to be noted that rotation at other bonds in the acetate side chain is probably free, though in the case of the corresponding acid (CXXI), there is the possibility of hydrogen bonding as shown.

The average position of $\text{-CH}_2\text{-CO}_2\text{Me}$ protons signal (7.03 T) in compound (CXIX) appears at appreciably higher field (6.78 T) than that in compound (XLVI). This is also comprehensible on the basis of the conformation (CXIX). A somewhat similar n.m.r. spectrum (Fig. 13) was obtained for the compound (CXX) (vide Section C) where the methylene protons of the acetate side-chain appeared as an ill-defined quartet centred at 6.88 T. The rest of the spectrum is quite in conformity with the structure (CXX). This could also be attributable to hindered rotation of a lesser degree due to ortho methoxyl substituent.

The n.m.r. spectrum of the acid (CXVI ≡ CXXI) was taken on a 60 MHz machine (Fig. 12) and its details are given below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Position of Peaks (T)</th>
<th>Nature Proton Count</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.24</td>
<td>Broad peak 1H</td>
<td>-CO$_2$H</td>
</tr>
<tr>
<td></td>
<td>2.50</td>
<td>Multiplets 7H</td>
<td>Aromatic</td>
</tr>
<tr>
<td></td>
<td>6.68, 6.96, 7.08 &amp; 7.34</td>
<td>An AB-quartet</td>
<td>H$_{1A}$</td>
</tr>
<tr>
<td>(CXVI)</td>
<td>7.4</td>
<td>Multiplet 4H</td>
<td>=C-CH$_2$- and</td>
</tr>
<tr>
<td></td>
<td>7.76</td>
<td>Multiplet 2H</td>
<td>-CH$_2$-CH$_2$-</td>
</tr>
</tbody>
</table>

(Fig. 12)
<table>
<thead>
<tr>
<th>Compound</th>
<th>Position of Peaks (T)</th>
<th>Nature</th>
<th>Proton Count</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO₂C</td>
<td>3.2</td>
<td>Sharp singlet</td>
<td>1H</td>
<td>Aromatic</td>
</tr>
<tr>
<td></td>
<td>3.39</td>
<td>Sharp singlet</td>
<td>1H</td>
<td>Aromatic</td>
</tr>
<tr>
<td>(CXX)</td>
<td>6.26</td>
<td>Sharp singlet</td>
<td>3H</td>
<td>-OCH₃</td>
</tr>
<tr>
<td>(Fig. 13)</td>
<td>6.40</td>
<td>Sharp singlet</td>
<td>3H</td>
<td>-CO₂CH₃</td>
</tr>
<tr>
<td></td>
<td>6.88</td>
<td>Two doublets</td>
<td>2H</td>
<td>-CH₂-CO₂Me</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>Multiplet</td>
<td>4H</td>
<td>=C-CH₂- and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0=C-CH₂-</td>
</tr>
<tr>
<td></td>
<td>8.3</td>
<td>Multiplet</td>
<td>2H</td>
<td>-CH₂-CH₂-CH₂-</td>
</tr>
</tbody>
</table>

As could be seen, the n.m.r. spectrum of the acid (CXVI) is very similar to that of the ester (CXIII), the same AB quartet due to side chain methylene protons being present. This type of quartet evidently arises from magnetic non-equivalence of the two protons which may be due to either the dissymmetry of the molecule as a result of hindered rotation\(^{143-145}\) (as shown in CXIX and CXXI) or the conformational


Dr. 0. P. Kaltenberg of Institute of Organic Chemistry, Polish Academy of Science, Warsaw, has kindly taken the temperature variant n.m.r. spectra on our behalf.

In the latter case, the necessary asymmetry is provided by unequal population of the conformational isomers (rotamers) and is illustrated by diethyl acetal of acetaldehyde (CXXII) which shows an AB quartet for the methylene protons.

\[
\begin{align*}
\text{CH}_3\text{CH} & \quad \text{O-CH}_2\text{CH}_3 \\
\text{CH}_3\text{CH} & \quad \text{O-CH}_2\text{CH}_3
\end{align*}
\]

(CXXII)

This kind of asymmetry, however, cannot lead to isolable optical isomers.

To decide which of these two types of asymmetry is operating in the present case, we took the n.m.r. spectra of this methylene group at different temperatures ranging from 28°C to 155°C. The results are shown in Fig. 14 and also tabulated below:


148. Dr. 0. P. Kaltenberg of Institute of Organic Chemistry, Polish Academy of Science, Warsaw, has kindly taken the temperature variant n.m.r. spectra on our behalf.
Fig. 14A
Solvent: Bromoform
Table I (Fig. 14-A)
(Taken in CHBr₃ on a 60 MHz machine with Sweep Width 250 Hz)

<table>
<thead>
<tr>
<th>Temperature</th>
<th>( \gamma_{p_1} - \gamma_{p_2} )</th>
<th>( \gamma_{p_2} - \gamma_{p_3} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>28°</td>
<td>32</td>
<td>16.5</td>
</tr>
<tr>
<td>60°</td>
<td>32</td>
<td>15.5</td>
</tr>
<tr>
<td>90°</td>
<td>31.5</td>
<td>15.0</td>
</tr>
<tr>
<td>110°</td>
<td>31.5</td>
<td>14.5</td>
</tr>
<tr>
<td>130°</td>
<td>31.0</td>
<td>14.0</td>
</tr>
</tbody>
</table>

*\( p_1, p_2, p_3 \) represent the position of the 1st, 2nd and 3rd peaks of the quartet, respectively, the 4th peak being buried into other methylene peaks; J-value is \( \frac{1}{2} (\gamma_{p_1} - \gamma_{p_2}) \) Hz.

Table 2 (Fig. 14-B)
(Taken in CHCl₂-CCL₃ on 60 MHz machine with Sweep Width 250 Hz)

<table>
<thead>
<tr>
<th>Temperature</th>
<th>( \gamma_{p_1} - \gamma_{p_2} )</th>
<th>( \gamma_{p_2} - \gamma_{p_3} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>28°</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>90°</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>130°</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>155°</td>
<td>-</td>
<td>10.5</td>
</tr>
</tbody>
</table>

The main conclusion that we can draw from the data is that there is no sign of any coalescence of the AB quartet with rise in...
temperature. Slightly different pictures of the spectra are probably due to the different viscosities of the solvent at different temperatures. It thus looks like that we are dealing with a case of inherent asymmetry due to conformational preference of certain rotamers and not with dissymmetry arising out of restricted rotation. However, the latter assumption may not necessarily be true and we can not really be sure that the acid (CXVI) could not be resolved into optical antipodes. The equation (eqn. 1)\(^{149}\) that has been widely used to obtain the rate at the coalescence temperature (the temperature at which the minimum between two peaks just disappears) is not strictly valid,\(^{150}\) if the population of the two exchanging sites are not equal

\[
k_c = \frac{\kappa 4^\gamma}{2}
\]

or if the lines are broadened by spin-lattice relaxation or magnet inhomogeneity.

We have two other minor evidences to demonstrate that the two ring systems in (CXVI) are probably nonplanar. The ultraviolet spectra of the acid (CXVI) and the ester (CXIII) (Fig. 9) had a shoulder at 245 nm. (log \(\varepsilon\), ca 4.1) which might be due to an


\(^{150}\) M. Raban and E. Carlson, J. Amer. Chem. Soc., 1971, 93 (3); 685; also see G. Binsch, in 'Topics in Stereochemistry', Vol. 3, edtd. by E. L. Eliel and N. L. Allinger, Interscience Publishers, 1968, p. 97,
isolated cyclohexenone system. This peak is noticeably absent in the spectrum of 3-α-naphthylcyclohex-2-en-1-one (XClII) which has λ_max. 220 (log ε 5.0) and 285 nm. (log ε 4.16).

The second indication of the nonplanarity is that these two compounds could not be fully hydrogenated in presence of palladium or platinum catalyst even at 200° (vide infra). We are currently trying to resolve the acid (CXVI) by classical methods.

Next, we tried to convert the ester (CXIII) into 3,4-benzphenanthrene (CXV) through the following sequence of reaction (Scheme 27):

![Scheme 27](image)

The sequence of reactions has already been tried and found very useful for synthesis of hydrochrysene and chrysene derivations.
However, in this case, we experienced an unexpected difficulty. The ester (CXIII) in contrast to its β-naphthyl analogue could not be fully hydrogenated either with palladium-charcoal or Adam's catalyst even using a high temperature (ca 200°). Use of high pressure reduced the carbonyl group. The best that we could do was to shake a mixture of the ester (CXIII) and 10% palladium-charcoal in ethanol at 80° in an atmosphere of hydrogen under 50 psi for a long period (15-20 hr.). The crude product containing the reduced ester (CXXII) was hydrolysed to the acid (CXXIII) which was cyclised without further purification with polyphosphoric acid (70-80° for 3 hr.). The cyclised product was thoroughly washed with alkali to remove the phenolic material and the neutral part on chromatography afforded the diketone (CXXIV), m.p. 190° \( \nu_{\text{max}} \) (nujol) 1710 and 1678 cm\(^{-1} \) in about 25% yield. A part of the crude acid (CXXIII) was chromatographed on silica gel and obtained in crystalline form, m.p. 175°. The diketone (CXXIV) was reduced with lithium aluminium hydride and then dehydrated and dehydrogenated by heating with 10% palladium-charcoal. The resultant 3,4-benzophenanthrene (CXV), m.p. 69° was characterised by its u.v. spectrum (\( \lambda_{\text{max}} \) in ethanol 227, 270, 280, and 314 nm.; \( \log \varepsilon \) 4.3, 4.65, 4.82, and 4.01 respectively; reported\(^{139} \lambda_{\text{max}} \) in ethanol 216.5, 228, 271, 281, 295, 302, 314, and 326 nm.; \( \log \varepsilon \) 4.65, 4.40, 4.72, 4.87, 4.09, 4.05, 4.0, and 3.67 respectively, and also by the formation of a picrate, m.p. 127°. We also prepared the trinitrofluorenone complex\(^{151} \) which was readily formed and

crystallised from benzene in orange needles, m.p. 174°C.

But for the low yield in the reduction step, the present method for the synthesis of this hydrocarbon would have been one of the most convenient and flexible route. One of the most interesting and recent syntheses\textsuperscript{152} of this hydrocarbon is photocyclisation of \( \beta \)-styrlylnaphthalenes which cyclise solely at the \( \alpha \)-position as shown below. The photocyclisation is normally carried out under condition which permit oxidation of the dihydrocompound.

A second recent synthesis\textsuperscript{139} is shown in Scheme 28, which is self explanatory.

\textbf{Scheme 28}

We next attempted to reduce the unsaturated keto-acid (CXVI) by lithium in liquid ammonia. The reaction of $\alpha,\beta$-unsaturated ketone by dissolving metals (e.g., lithium) is very well-known. The first example of this reaction was recorded in 1952 by Sondheimer et al. who used it in the steroid field. Later on, the mechanism of this reduction, particularly the stereochemistry involved in it, has been discussed by different group of workers, which have already been referred to in Section A. The gross mechanism may be depicted as follows:

1. $\overset{2\text{e}}{-\text{C}=\text{C}=\text{C}=\text{O}} \rightarrow \overset{2\text{e}}{-\text{C}=\text{C}=\text{C}=\text{O}} \rightarrow \overset{\text{H}}{-\text{CH}=\text{C}=\text{C}=\text{O}}$ (A) (B)

2. $\overset{\text{NH}_3}{-\text{C}=\text{C}=\text{C}=\text{O}} \rightarrow \overset{\text{H}_2\text{O}}{-\text{CH}=\text{C}=\text{C}=\text{O}}$ (C)

The reduction may be initiated by the addition of two electrons to the $\alpha,\beta$-unsaturated carbonyl system to give the dianion (A) (mechanism 1) which is protonated at the more basic $\beta$-position to


give the anion (B); or the same anion (B) may be formed in two steps (mechanism 2): first, the generation of an anion radical (C) which is a sufficiently strong base to abstract a proton from ammonia and second, addition of one more electron to form the enolate anion (B). The latter is not sufficiently basic to abstract proton from ammonia and bearing a full negative charge, resists further addition of electron and thus escapes reduction to alcohols. When a more acidic proton donor such as ammonium chloride is added during the isolation process, the enolate is protonated to the ketonic product (D). As already stated, the stereochemistry of the protonation of β-carbon atom has been the subject of numerous discussions; but in general the more stable product is formed and we expected that a similar reduction would convert the acid (CXVI) to the saturated trans-acid (CXXIII). We carried out the reduction accordingly under a variety of conditions using tetrahydrofuran as co-solvent and 4-8 moles of lithium per mole of the acid. (see Experimental). The liquid ammonia was distilled over sodium before use. Under optimal condition, a reduced keto-acid, m.p. 166° was obtained in 80% yield, but this was quite different from the acid (CXXIII) m.p. 175°, previously
isolated from hydrogenation product. The spectral analysis suggested the structure (CXXVI) for the compound. Mass spectrum showed a molecular ion peak at 284; other spectral data are tabulated below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>u.v.</th>
<th>i.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>λ_max. in ethanol log ε</td>
<td>γ_max. (KBr) 1710-1715 cm⁻¹</td>
</tr>
<tr>
<td></td>
<td>223 nm. 4.2</td>
<td>(broad with sign of splitting)</td>
</tr>
<tr>
<td></td>
<td>230 nm. 3.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>273 nm. 3.15</td>
<td></td>
</tr>
</tbody>
</table>

N.m.r. spectra, taken in CDCl₃ on both 60 MHz (Fig. 15A) and 100 MHz machines (Fig. 15B) showed the following peaks:

<table>
<thead>
<tr>
<th>Position of Peaks (tt)</th>
<th>Nature</th>
<th>Proton Count</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.38</td>
<td>Broad</td>
<td>1H</td>
<td>Acidic proton</td>
</tr>
<tr>
<td>2.85</td>
<td>Multiplet</td>
<td>4H</td>
<td>Aromatic proton</td>
</tr>
<tr>
<td>4.16</td>
<td>Singlet with sign of splitting</td>
<td>1H</td>
<td>Vinyl proton</td>
</tr>
<tr>
<td>6.70</td>
<td>Multiplets</td>
<td>14H</td>
<td>Methylene and Methine protons</td>
</tr>
<tr>
<td>7.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The proton magnetic resonance data were in agreement with the structure (CXXVI); the only unusual feature of the spectrum was the signal of the vinyl proton (H*) at 4.16 with a very small J-value of the order of 1-2 Hz. In the spectrum taken on 100 MHz machine
(Fig. 15B), this signal almost appeared as a sharp singlet (the half-width of this peak could not be compared with that of the TMS peak). The reason for this small coupling or almost the lack of it is not clear to us.

A chemical proof was also given for the structure of the acid (CXXVI). The derived methyl ester, m.p. 124°, was dehydrogenated with one atom of sulphur and the product on hydrolysis afforded the acid (CXXIII) (M=282) which was found to be identical with the previous sample, m.p. 175°. It was also converted into 3,4-benzo-phenanthrene through the diketone (CXXIV) by the sequence of reaction described before.

An attempt to reduce the ester (CXXIII) by Huang-Minlon's modified procedure\(^{156}\) of Clemmensen reduction failed to give the expected product (CXXVII). Instead, a nitrogenous compound was obtained which analysed correctly for the structures (CXXVIIIa and CXXVIIIb). We are not aware of any report of such a transformation during Huang-Minlon reduction though the migration of double bond

\[\text{(CXXVII)} \quad \text{(CXIII)} \quad \text{(CXXVIIIa)} \quad \text{(CXXVIIIb)}\]

during reduction of \(\alpha,\beta\)-unsaturated ketones is quite common.\(^{157}\)

Coming back to the lithium-ammonia reduction product (CXXVI), the formation of this dihydronaphthalene derivative under the present reaction condition is rather unusual, though there are plenty of examples of reduction of naphthalene to 1,4- and 1,2-dihydronaphthalenes (and also to tetralin) using sodium in liquid ammonia. The mechanism for reduction of aromatic system is the same as discussed before and shown here in case of benzene.* But generally it is possible to effect the selective reduction of an \(\alpha,\beta\)-unsaturated carbonyl system in the presence of benzene and naphthalene ring if no alcohol is added.\(^{158}\) An example along our own line can be found in the work of Bürch and Subba Rao\(^{45}\) who methylated the compound (VI) by treating it first with lithium (8 atom) in liquid ammonia and then adding methyl iodide.

\*It may be noted here that the kinetically controlled protonation of the anion (C) to form the nonconjugated diene (D) is representative of a general phenomenon observed in the protonation of mesomeric anion, and may be explained by the Principle of Least Motion previously referred in Section A.


Apparently, no reduction of the naphthalene ring took place. We also reduced the unsaturated keto-acid (CV) under identical conditions and obtained the trans-acid (XLIX p. 23), m.p. 170°. Reduction of 3-α-naphthylcyclohex-2-en-1-one (XCIII) in the same way afforded the substituted cyclohexanone (CXXIX) along with some unreduced starting material. The reduction of the acid (CXVI) to dihydronaphthalene derivative must therefore be attributed to some special structural feature of the acid. We venture to suggest the following mechanism which is based on the fact that due to nonplanarity of the molecule, the carboxyl group is placed very near to C-4 (marked with an asterisk) of the naphthalene moiety and can thus participate in the reduction in some fashion. Dreiding model shows that in the conformation (CXXX), the minimum distance between carboxyl hydrogen and C-4 would be 2A°.

We have already pointed out that the preferred conformation of the undissociated acid (CXVI) may be represented by the structure (CXXI), rather than the one (CXXX). There is really no valid reason for this assumption excepting the rather ambiguous evidence that the carboxylic proton appeared at -0.24T (see Fig. 12), which is rather low if we consider the position (0.38T)
of the same proton in the analogous acid (CXXVI). One would expect an upfield shift of this proton signal in the conformation (CXXX) due to aromatic ring current. When the acid is added to liquid ammonia, however, the carboxylate anion will be formed immediately and the most likely conformation would be the one (CXXXI) where the \(-\text{CO}_2\) will lie above the aromatic plane, away from the carbonyl group. In the structure (CXXXI), there are now two sites for reduction: naphthalene moiety and the double bond of cyclohexenone system. Generally, the sequence of reduction with metal-ammonia is: \(\alpha,\beta\)-unsaturated ketone \(\rightarrow\) styrene or stilbene double bonds \(\rightarrow\) aromatic rings. In this particular case, the sequence may be reversed; firstly, due to the nonplanarity of the two ring systems, the \(\beta\)-carbon will be extremely hindered; secondly, the styryl character of the double bond is destroyed decreasing its reducibility still further. On the other hand, the anion-radical (CXXXII) formed by the addition of one electron to naphthalene molecule may have a good chance for abstracting a proton from the \(\text{NH}_4^+\) ion associated with the nearby carboxylate anion as an ion-pair, and thereby gets reduced. The reduction of the cyclohexenone double bond will next follow independently so that the initial product is the non-conjugated tetrahydro-structure (CXXXIII) which during work-up
with mineral acid is converted into the styryl compound (CXXVI).

Ordinarily, the anion radical formed from naphthalene is reversibly decomposed to the starting material in absence of a good proton donor like alcohol. Here, in effect, the carboxylic proton is helping the reduction of the naphthalene ring by neutralising the anion radical (CXXXII), and thus shifting the equilibrium away from naphthalene. This type of participation of a carboxylic group is not known to our knowledge.

We can not offer any concrete proof for this mechanism. We have found, however, that when the reduction was carried out in liquid ammonia not distilled over sodium, a product, m.p. 155-156° was obtained in good yield which showed three molecular ion peaks having mass no.s 282, 284 and 286 corresponding to dihydro (CXXIII), tetrahydro-(CXXVI), and hexahydro-(CXXXIV) compounds respectively. Evidently, the unconjugated tetrahydrocompound (CXXXIII) isomerised to a certain extent to the styryl system (CXXVI) in situ and then got further reduced to tetralin derivative (CXXXIV). In one case, we isolated this compound (identified by the absence of vinyl proton in n.m.r), m.p. 153-154° (λ_max. in ethanol 225 and 268 nm.; log ε 3.0 and 2.9 respectively; λ_max. in nujol 1710 cm⁻¹) and cyclised it
to the diketone (CXXXV), m.p. 156-157° C (\(\lambda_{\text{max.}}\) 218 and 226 nm.; \(\log \varepsilon\) 4.3 and 4.16 respectively; \(\gamma_{\text{max.}}\) 1705 and 1665 cm.\(^{-1}\)), which on reduction with lithium aluminium hydride gave a diol, m.p. 167-170°.

\[
\begin{align*}
\text{(CXXXV)} & \xrightarrow{\text{LiAlH}_4} \quad \text{(CXXXVI)} \\
\end{align*}
\]

The last-named compound could not be dehydrogenated to 3,4-benzo-phenanthrene which further supported the structure.

As a part of our study of reactions in liquid ammonia, we tried to methylate the acid (CXXXVII) with Li-NH\(_3\)-MeI according to the procedure of Birch and Subba Rao\(^{45}\). The product was

\[
\begin{align*}
\text{(CXXXVII)} & \xrightarrow{\text{Li-NH}_3, \text{MeI}} \quad \text{(CXXXVIII)} \\
\end{align*}
\]

analysed by n.m.r. spectrum which showed angular methyl group at 8.82 ppm, but we could not effect any clean separation of the cis and trans isomers. Work in this direction was discontinued.

C. Experiments on the Synthesis of Ring-B Aromatic Steroids

We have already stated that barring a few isolated cases, not much work has been done towards the synthesis of ring-B aromatic steroids. We record here our attempt to synthesise a compound.
(CXXXIX), which is isomeric with estrone methyl ether and could be transformed into a variety of interesting steroidal analogues by suitable modifications, such as oxidation of ring-A and metal-amine reduction of ring B. The key intermediates for this synthesis were

\[
\text{Scheme 28}
\]

the easily available unsaturated keto-esters (CXX) and (XCL). We prepared the former starting from the methoxytetralin ketone (XCLIV)
by the application of the sequence of reactions already well-established (Scheme 28). \( \beta \)-Naphthol on catalytic reduction with Raney nickel\(^{159} \) afforded an alkali soluble part from which the phenol (XCL\( \text{I} \))\(^{160} \) was isolated in good yield. The corresponding acetate (XCL\( \text{II} \)) on Fries rearrangement\(^{161} \) gave the hydroxyketone (XCL\( \text{III} \)) which was methylated\(^{162} \) and the methyl ether (XCL\( \text{IV} \)) converted into the Mannich base (XCLV). The methiodide of the base was condensed with ethyl \( \beta \)-oxo-adipate (LXVI) in the usual manner to give an acid-ester which on alkali hydrolysis and subsequent esterification afforded methyl 2-(1,2,3,4-tetrahydro-6-methoxy-7-naphthyl)-6-oxocyclohex-1-enylacetate (CXX) in an overall yield of 50% based on the Mannich base. The ester was a crystalline solid, m.p. 100\(^\circ\), formed a red dinitrophenylhydrazone,

![Chemical Structures](image-url)

Fig. 16
m.p. 282°, and showed correct spectral data ($\lambda_{\text{max}}$ in ethanol 225, 245 (hump), 275, and 290 cm$^{-1}$, log $\varepsilon$ 3.90, 3.85, 3.60, and 3.55 respectively; $\gamma_{\text{max}}$ in nujol 1730 and 1665 cm$^{-1}$; for n.m.r. see Fig.13). The corresponding acid (XCLVI) had m.p. 161° which was exposed to sodium hydride in dimethylformamide at 100° as described in Section A. But in this case the t.l.c. of the product showed so many closely situated spots that no attempt was made to isolate the expected phenol.

The ester (CXX) underwent hydrogenation smoothly in presence of 10% palladium-charcoal (quite unlike the $\alpha$-naphthyl-derivative in Section B) to furnish the dihydroester which crystallised from methanol to an isomer, m.p. 100° in 50% yield presumably having the trans-configuration (XCLVII) ($\gamma_{\text{max}}$ in nujol 1735 and 1710 cm$^{-1}$). It afforded a yellow dinitrophenylhydrazone, m.p. 222°, and an acid (XCLVIII), m.p. 175°. The n.m.r. spectrum (Fig.16) of the acid was taken with the hope of gaining some information regarding the stereochemistry of the compounds, but was found unsatisfactory for the purpose.

From the report of Birch et al.\textsuperscript{155} and also from a recent work of House\textsuperscript{163}, we anticipated some difficulty in cyclising the acid (XCLVIII) to the diketone (XCLIX). We therefore synthesised the model compounds (CL), m.p. 80-81° and (CLI), m.p. 168-170° following essentially a similar procedure as described before,\textsuperscript{163}

starting with \( \text{o-methoxyacetophenone} \). The acid \((\text{CLI})\) was treated with a mixture of phosphorus oxychloride and polyphosphoric acid,\(^{164}\) a reagent used successfully by Birch\(^{45}\); but no detectable amount of diketone was obtained. The acid \((\text{XCLVIII})\) likewise did not cyclise under this condition. A trace of a solid was isolated from the neutral part of the cyclised product which showed two carbonyl bands \((1710 \text{ and } 1675 \text{ cm}^{-1})\) in i.r. but in view of the extremely low yield, the method was almost useless.

House has recommended\(^{163}\) a procedure which worked well in case of cyclisation of the acid chloride \((\text{CLII})\). The method consists of treating the acid chloride with anhydrous aluminium chloride using methylene chloride in large volume to avoid intermolecular condensation. Accordingly, we treated the acid \((\text{XCLVIII})\) with oxalyl chloride\(^{165}\) and the resultant acid chloride \((\text{CLIII})\) submitted to the above treatment. A neutral product was obtained in about 40% yield, which in i.r. spectrum (nujol) showed in addition to 1705 cm\(^{-1}\) band due to saturated ketone, a lactonic band at 1795 cm\(^{-1}\) and most

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probably consisted of a substantial amount of the lactone (CLIV). The work in this direction, therefore, had to be abandoned for the present.

We are also preparing the nonmethoxylated analogue of the keto-ester (XCLVIII) which is expected to undergo cyclisation smoothly.