S Y N T H E T I C S T U D I E S

IN THE

P I P E R I D I N E S E R I E S.

A T H E S I S

for the degree of

Doctor of Philosophy

at the

University of Glasgow

by

T. Walker. B.Sc.

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PART I.

INTRODUCTION.

For many centuries, Opium , an extract of poppy seeds, has been used to relieve severe pain. The active constituent of opium was shown to be the alkaloid Morphine, which is present in amounts of approximately 10%. The unrivalled ability of morphine to alleviate pain through its action on the central nervous system, is unfortunately accompanied by many other actions in the body, many of which are medically undesirable. Among these actions may be mentioned various respiratory, circulatory, gastro-intestinal and emetic manifestations, but by far the most important, and least desirable of these side-effects is the property of causing drug addiction. The administration of morphine to many individuals not only relieves the discomfort of pain, but also causes a pleasant feeling of well-being. Both the relief of discomfort and this feeling of well-being may lead to repeated administration and repeated administration sooner or later leads to addiction.

There are three intimately related, but distinct, phenomena associated with morphine addiction; namely, tolerance, dependence and habituation. This is a largely artificial separation, made for the purpose of description, because the phenomena which make up drug addiction are closely interrelated and interdependent.

The term tolerance is used to indicate the gradual decrease in the effect produced by repeated administration of a fixed amount of the drug, or, conversely, the gradual increase in the dosage of the drug necessary to produce the same effect as the initial dose. It is probably true that tolerance eventually becomes so great that the effect of the initial dose cannot be reproduced by excessive doses.

Dependence is the term used to denote the distortion of normal physiological processes caused by prolonged administration of the addicting drug, and which is shown by the necessity for the presence of an adequate amount of the drug in the body to maintain physical equilibrium. The presence of dependence can be established by the appearance of the characteristic "withdrawal symptoms" when the supply of the drug is cut off. In the case of morphine addicts these symptoms include restlessness, cramps and diarrhoea, and can be relieved instantaneously by a single dose of morphine.

Habituation may be conveniently defined as mental dependence, as opposed to the physical dependence just discussed.

Addiction to opium has of course been prevalent in Oriental countries for many centuries, but during this century it has become a major problem in some other countries, notably the United States of America. Because of this much work has been done on the possibility of finding a drug which exhibits the analgesic potency of/

of morphine without its property of causing drug addiction . Whether this is possible or not remains to be decided, butthere are some points which may be raised in this connection.

Dependence, as distinct from habituation, is a physical phenomenon, and although nothing is known of the mechanism of its development, it seems possible that there is a relationship between it and the chemical structure of the addicting agent. Also, the development of dependence seems to be related to the presence of certain peripheral groups rather than to the structural skeleton of morphine itself, because the numerous derivatives of morphine, prepared by modification of the peripheral groups, whose addiction liability is in some measure known, vary so greatly in the intensity of this factor that it seems improbable that the skeletal structure of morphine plays a decisive part.

There is also direct evidence that the physiological effects of morphine in some measure result from the presence of the various functional groups, since by modification of these groups characteristic morphine actions can be changed, often in a predictable direction. It seems reasonable to expect, therefore, that addiction is also dependent in some way on the presence of these functional groups, and that its intensity may also be modified by chemical change of these groups. Thus it may be possible, by systematic modification of the functional groups, to prepare a derivative of morphine

in/

in which these two properties, analgesia and addiction liability, are dissociated to a suitable extent.

This line of reasoning led to the first of the methods of tackling the problem of morphine addiction. Under the auspices of the U.S. Public Health Service, a very large number of morphine derivatives were prepared by suitable modification of the peripheral groups, and the most promising of these compounds subjected to extensive clinical as well as laboratory tests. The complete results of this investigation are collected in a publication of the U. S. Treasury Department. (I).

These results show :- (a) all the compounds of reasonable analgesic action also possess addiction liability, and (b) changes in the chemical structure of morphine alter the degree of addiction liability and other pharmacological actions including analgesia, but, unfortunately, alter them in the same direction, i.e. no complete dissociation of addition liability and analgesia was obtained.

Consequently, although this investigation yielded a great deal of interesting chemical and pharmacological information about morphine and its derivatives, it did not achieve its primary object, the preparation of a substitute for morphine.

In recent years, a great deal of work has been done along another line of approach to the problem, that of synthesising isolated skeletal fragments of the morphine molecule in the hope that these simpler

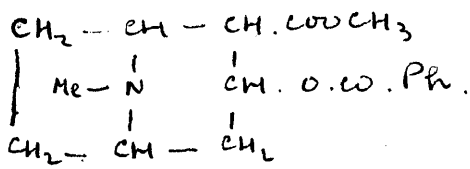
compounds might show the same type of activity as the parent substance. Before this line of approach is discussed more fully, some of the difficulties and uncertainties associated with it as a general method may be considered.

The physical and chemical properties of a compound, melting point, boiling point, solubility, acidity or basicity and so on, are determined in some measure by the molecular weight and by the arrangement of the atoms within the molecule, this arrangement of atoms being represented in a so-called structural formula. These formulae do not indicate on the whole the complete properties of a given compound. In other words, the physico-chemieal properties of a compound cannot be predicted from its structural formula with any degree of certainty, and yet it is just these properties that play a vital part in determining the physiological action of a compound through their effect on the degree of its absorption, its transport and storage in the organism, the place or places of its action and so on. Consequently, the uncertainty concerning the relation between structural formula and physico-chemical properties applies also to the relation between structural formula and physiological action.

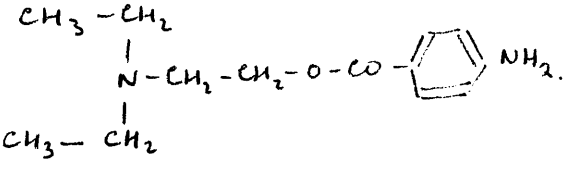
In spite of these difficulties, a large number of synthetic compounds of great medicinal value have been prepared by the organic chemist in a merely empirical way. After a sufficient number of such

compounds had been obtained, it became obvious that within certain relatively limited groups of chemical individuals, some definite rules as to the relation between structural formula and physiological action would be found. One may mention in this connection the antipyretics of the phenyl-pyrazolone type, the great number of hypnotics of the barbituric acid group and the sulphanilamides.

In the past, also, the synthesis of compounds for medicinal use which are related in some way to the natural alkaloidal substance possessing the desired pharmacological properties, has in some cases achieved considerable success. These synthetic substances either reproduced certain parts of the complex natural molecule or simulated them to some degree. Some of these simpler compounds have even largely replaced the parent drug in clinical practice , e.g. one may mention the examples of Cocaine (I) and Procaine (II), Atropine (III) and Syntropan (IV).



I



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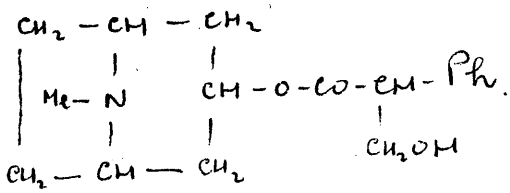

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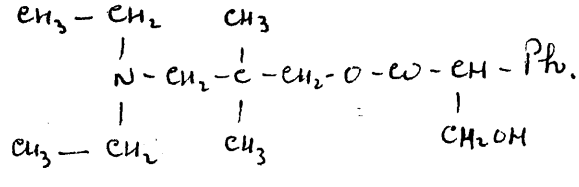
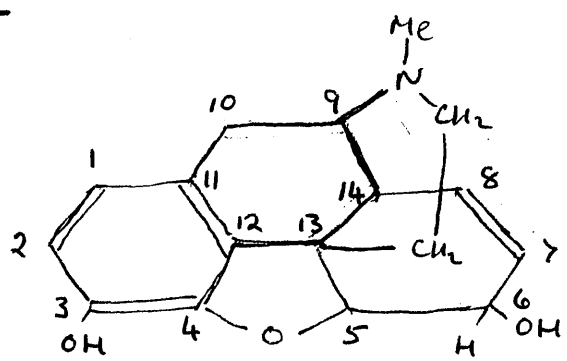


IV

It is interesting to note in connection with the morphine problem, that Procaine and some other effective substitutes for Cocaine do not possess the addiction liability of the latter. Consequently the introduction of these simpler compounds into general use in place of the parent compound went a long way in helping to solve the cocaine addiction problem.

These general observations led to the second method of tackling the morphine problem, and a large number of relatively simple compounds based on the complex morphine molecule have been synthesised. The work done in this field up to 1938 has been reviewed in a publication of the U.S. Treasury Department (2). A brief summary of this work is given below.

First, morphine (V) may be considered as a phenanthrene derivative, and its structure analysed as follows:-



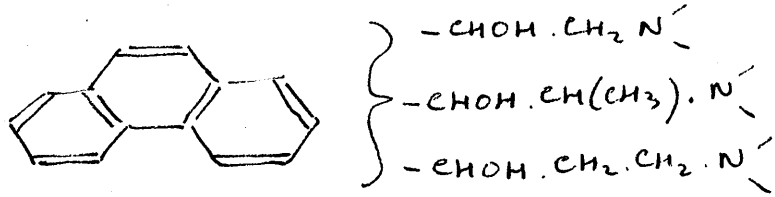
V

- a partially hydrogenated phenanthrene, carrying, besides the phenolic and alcoholic hydroxyl groups and the 4,5 oxygen bridge, an ethyl-methylamino chain

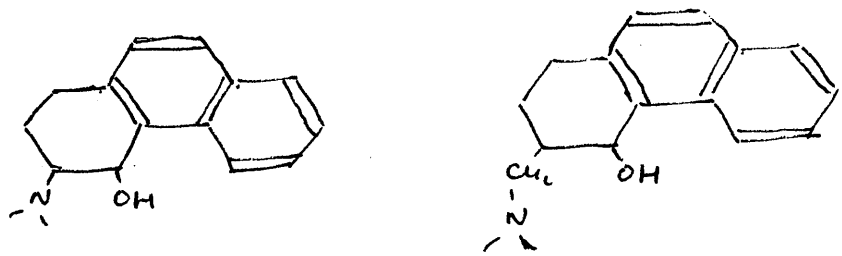
$-CH_2-CH_2-N(CH_3)-$ attached in an unusual way to the 9 and 13 positions of the phenanthrene nucleus.

Therefore it seemed reasonable to make first phenanthrene a starting basis and attach to it and its hydrogenated forms successively the functional groups of morphine.

A series of phenanthrene and hydrophenanthrene derivatives carrying simple hydroxy, amino, carbonyl, and carboxyl groups, or a combination of these groups in the 2, 3 and 9 positions were prepared. These were followed by the synthesis of a large number of phenanthrene and hydrophenanthrene amino-alcohols. These amino-alcohols were divided into two types:-



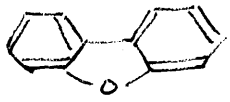
(a)



(b)

- type (a) with the alcohol group and the nitrogen atom in the same side chain attached to various positions in the phenanthrene nucleus, and type (b) where the hydroxyl group and the basic side chain are both

substituents of a reduced ring. These types (a and b) were synthesised because morphine may be considered as an amino-alcohol containing a tertiary nitrogen and a secondary alcoholic group.

The morphine molecule also contains the dibenzofuran ring system  and a series of

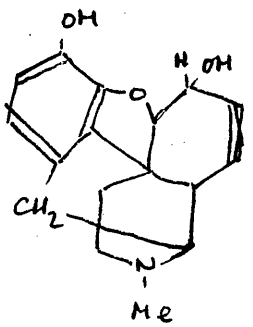
dibenzafuran derivatives analogous to those in the phenanthrene series was prepared.

Of these compounds described, the phenanthrene amino-alcohols of type (b), which bear the closest resemblance to morphine, were the most active, the best derivative having approximately 1/25 of the analgesic action of morphine. The remainder of the compounds showed only feeble or no activity. Thus, while this work did produce some compounds with analgesic activity, it failed to produce a suitable substitute for morphine.

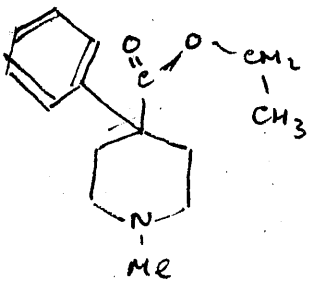
A completely new field was opened up in 1939 by the experiments of Eisleb and Schaumann (3). They made the entirely unexpected discovery that 1-methyl--4-phenyl-4-carbethoxypiperidine (VI), possessed in addition to an antispasmodic action, an analgesic effect approaching that of morphine. The hydrochloride of this compound has passed into general use under the names Dolantin in Germany, Pethidine in Britain and Demerol in the U.S.A.

The structural relationship between morphine and pethidine, pointed out by Schaumann (4) is obvious

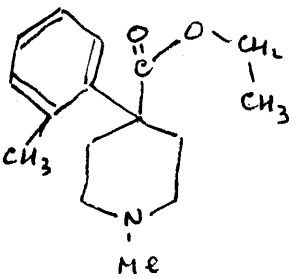
from a consideration of the formulae.



MORPHINE



VI

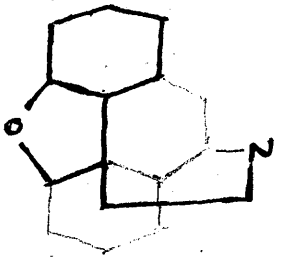
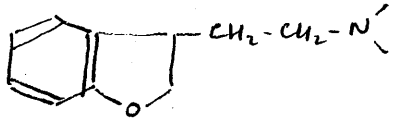


VII

It seems that the $-CO-O-CH_3-CH_3$ group in pethidine simulates the hydroaromatic ring in morphine, and some evidence for this conclusion was obtained when it was discovered that all other compounds of this type with different ester groupings e.g. CO_2Me, CO_2Pr, CO_2Bu, had much lower activity than pethidine itself. This is because only the $-CO_2Et$ group has the correct number of atoms to complete the hydroaromatic ring which is present in morphine. Another interesting feature of pethidine is the quaternary carbon atom; the bulk of the phenyl and carbethoxy groups conferring steric stabilization on the molecule, and giving it a three-dimensional structure similar to the more complex morphine model. The spatial relationship between pethidine and morphine is very readily seen with the aid of models . The introduction of a methyl group

in pethidine (5) as shown (VII) makes it more like morphine and as might be expected, enhances the analgesic activity.

The example of pethidine proved that relatively simple compounds, structurally related to some part of the morphine molecule could have potent analgesic action, and this gave a great impetus to the search for other compounds of this type. A survey of the types of compounds which have been synthesised and pharmacologically tested is given below.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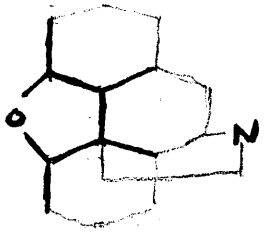
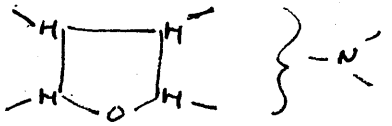
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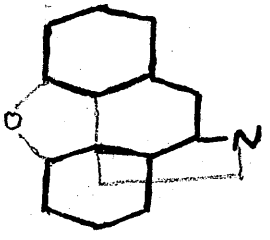
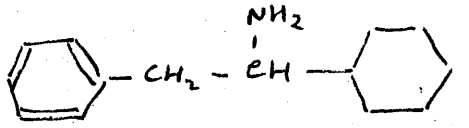
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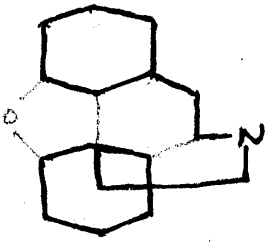
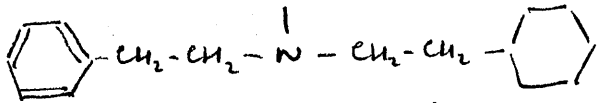
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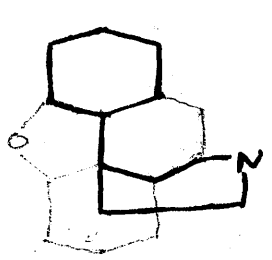

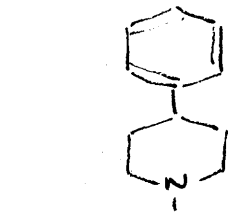

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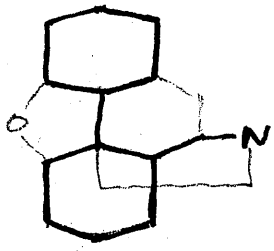

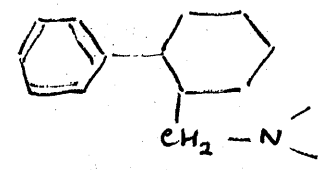

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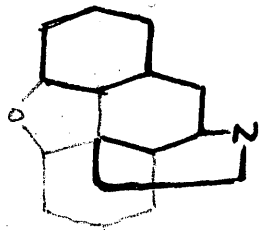
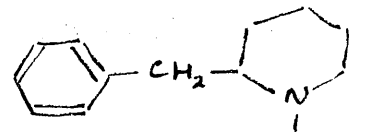
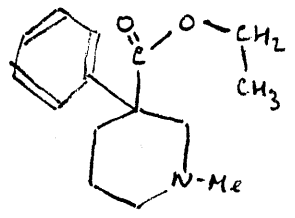




(12.)

A good many of these compounds had some analgesic action but none of them approached pethidine in potency.

Bergel and co-workers (13) prepared 1-methyl--3-phenyl-3-carbethoxypiperidine (VIII), an isomer of pethidine, and gave it the name β-pethidine.

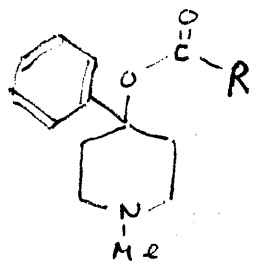


VIII

It was shown to have an analgesic action approaching that of pethidine itself (14). This compound possesses all the structural features present in pethidine, except of course, the piperidine ring carries the phenyl and carbethoxy substituents in the 3-position. As with pethidine, replacement of the carbethoxy group

by any other ester group e.g. CO_2Me, CO_2Pr etc. considerably reduced the activity (14).

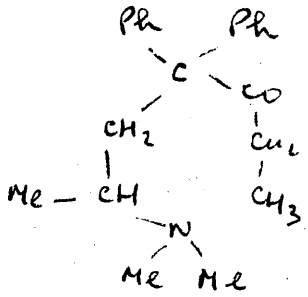
A series of compounds having some relationship to pethidine were synthesised by Jensen and Lundquist (15).



IX

These were 4-acyloxy-4-phenyl--piperidine derivatives, and the most potent of them (IX, R = Et.) had an activity almost equal to morphine itself. The structure of these compounds can be related to that of morphine in the same way as pethidine. As with pethidine, the compound had maximum potency when the acyloxy side chain contained the correct number of atoms to simulate the hydro-aromatic ring of morphine i.e. when the acyl group was propionyl. The conclusions derived from pethidine about the effect of the quaternary carbon atom and the general shape of the molecule can also be applied to this type of compound.

The introduction of Amidone (X) (dl-2-dimethylamino-4:4-diphenylheptan-5-one) added yet another compound with an activity equal to that of morphine (16).

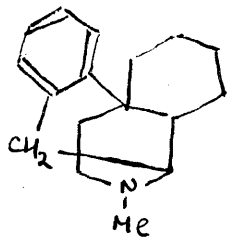


X

This amidone type of compound is slightly more difficult to fit into the picture. It has no exact structural relationship to morphine as have pethidine and the 4-phenyl-4-acyloxy--piperidines. It seems probable

that the second phenyl group serves to effect steric stabilization of the molecule as a whole rather than to simulate the hydroaromatic ring in morphine. The example of amidone seems to indicate that the general spatial configuration of the molecule is more important than any exact relationship between the rings or potential rings of the compound and those of morphine. It also shows that the nitrogen atom need not be included in a ring for the compound to have potent activity; this is in contrast to morphine itself, where opening of the nitrogen ring to give the morphimethines decreases the activity to a very great extent.

In 1946, Grewe (17) claimed the synthesis of the basic carbon nitrogen skeleton ring structure of morphine itself.



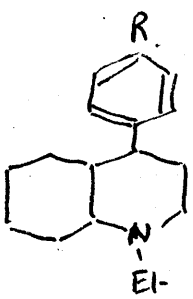
XI

The basic ring structure was given the name "morphinan" and the N-methyl derivative (XI) was shown to have an analgesic action equal to that of morphine.

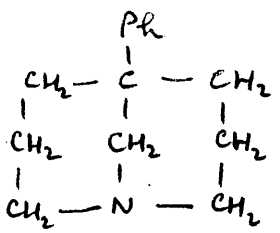
This very potent analgesic action of morphinan, containing only the bare skeleton and none of the peripheral groups of morphine was perhaps rather surprising. Earlier work on morphine derivatives had shown that modification of the functional groups had a profound quantitative effect on the analgesic action of the resulting derivatives, and from this it was concluded that the presence of certain of these

functional groups was probably necessary for the exhibition of strong analgesic action.

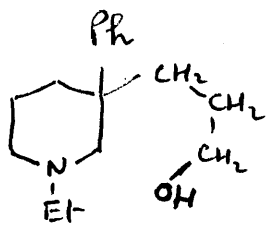
Thus, of the various types of synthetic compounds which show strong analgesic action, all of them except perhaps the β-pethidine and amidone type, have some more or less close structural relationship to morphine.
One feature common to all these analgesics is the presence of a tertiary aliphatic nitrogen atom in the molecule, thus giving these compounds fairly strong basic properties.
However it seemed of interest to prepare some compounds, all tertiary bases , which though not closely related to morphine, possess some interesting structural features.
These compounds are listed below. Their preparation also gave an opportunity for exploring and extending a new method for the synthesis of reduced nitrogen ring systems developed in these laboratories (18).
The synthesis of these compounds is fully discussed in Parts II and III of this thesis.



XII



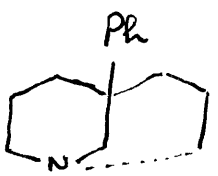
XIII



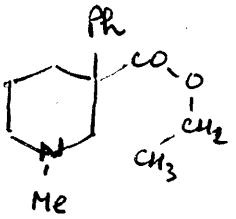
XIV

Group I. 1-Ethyl-4-aryldecahydroquinoline derivatives (XII, R = H,OMe,OH.) It has been shown that 4-aryl--piperidine derivatives show analgesic action (10) and it was desired to ascertain what effect, if any, the addition of the other reduced ring had on the activity. No 4-aryldecahydroquinoline derivatives have previously been tested for analgesic action.

Group II. 5-Phenyl-1-aza-bicyclo-3,3,1-nonane (XIII). Very few compounds containing this bicyclic ring system have been described. The preparation of the 5-phenyl derivative seemed worthwhile, not only as an opportunity for developing a new synthetic method, but also because the molecule has some interesting features.
e.g. some relationship to β-pethidine type, as shown in the following formulae.

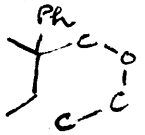
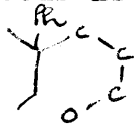
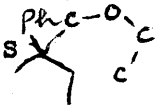
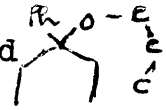


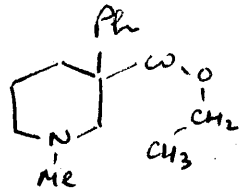
XIII



β-PETHIDINE

Also the general shape of the molecule is interesting. It contains the quaternary carbon atom which seems to be of some importance, and the general three dimensional spatial configuration of the molecule is reminiscent of the type present in pethidine, amidone and morphine itself. No derivatives of this bicyclic ring system have previously been tested for analgesic action.

Group III. This compound, 1-ethyl-3-phenyl-3-γ-hydroxy--propylpiperidine (XIV) has a very close structural relationship to β-pethidine. If the theory that the main function of the carbethoxy group in β-pethidine (and also in pethidine) is to simulate the hydroaromatic ring of morphine is correct, then XIV should have an activity comparable to β-pethidine, since it also has the correct number of atoms to form another ring. The fact that in β-pethidine the order of the atoms is  where as in XIV the order is  perhaps may not be important. With pethidine and the phenacyloxypiperidines the order is  and  respectively and both these types of compounds are potent analgesics; this seems to indicate that the relative positions of the oxygen and carbon atoms are not of primary importance.



β-PETHIDINE.

As yet, the results of pharmacological tests are available only for the decahydroquinoline derivatives (XII, R = H, OMe, OH). Analgesia and toxicity tests are given in the following table (19).

P.TO.

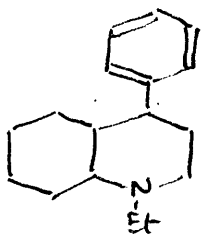
NAME.	RELATIVE ANALGESIC POTENCY.	L.D.50 (mgm./Kgm. (mice.)
4-PHENYL-1-ETHYLDECAHYDROQUINOLINE.HCl.	0.6	81
4-(p-METHOXYPHENYL)-1-ETHYL--DECAHYDROQUINOLINE HCl.	0.7	100
4-(p-HYDROXYPHENYL)-1-ETHYL--DECAHYDROQUINOLINE HBr.	0	120
"PETHIDINE"	1	150

These compounds also show some local anaesthetic action, the most powerful (XII, R = OMe) has a potency of 10% of cocaine hydrochloride. All of these compounds also have some antispasmodic activity, but none of them are highly specific.

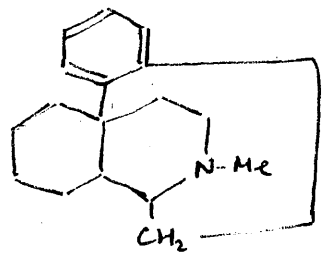
The fairly considerable analgesic activity of these decahydroquinoline derivatives, though not great enough from a clinical point of view, is interesting from a theoretical standpoint. The increase in activity from the phenyl to the *p*-MeO derivative is not unusual, but the complete absence of analgesic activity in the *p*-OH compound is rather surprising when one remembers that methylation of the phenolic -OH group in morphine <u>reduces</u> the analgesic activity to an appreciable extent. Probably this is one of the cases where the physico-chemical properties of the compound play an overwhelming part in deciding pharmacological action.

The demonstration of analgesic action in these decahydroquinoline derivatives also seems to prove once again that close structural relationship to morphine is not necessary for appreciable activity. It is interesting

to note too, that the phenyl derivative (XV) has practically the same molecular weight as Grewe's methyl--morphinan (XVI) although of course the spatial configurations of the molecules are completely different.

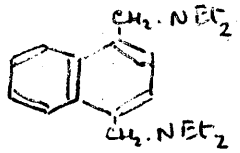


XV



XVI

CONCLUSION.

Whereas substantial practical progress has been made in the synthesis of clinically useful analgesics, the problem of the correlation of chemical structure and analgesic action still remains largely unsolved. Indeed, recent work involving the demonstration of analgesic action in new types of compounds has if anything tended to complicate rather than clarify the situation. The correlation of the chemical structures of pethidine, the phenacyloxypiperidines and morphine shed some new light on the problem, but the examples of some other compounds, including β-pethidine, amidone and the phenyldecahydroquinolines described here, show that strict structural relationship with morphine is not the whole story. This is shown even more clearly by the fact that 1:4-bisdiethylaminomethylnaphthalene (XVII)  prepared in these laboratories by Mr. G. M. S. Donald has an

XVII

analgesic action equal to that of pethidine (19). The demonstration of the appreciable analgesic activity in these oxygen-free compounds methylmorphinan, phenyldecahydroquinolines and this naphthalene derivative, also raises the question of the importance of functional groups in relation to analgesic activity, as these functional groups have been shown to be extremely important in the case of morphine.

The question whether strong analgesic action and addiction liability can be dissociated is also still unanswered. Prolonged clinical tests are required before it can be said that any particular compound does or does not possess addiction liability. Up to the present, only pethidine (20), β-pethidine (21) and amidone (22) have been subjected to these clinical tests. These tests show that all three compounds possess addiction liability, though perhaps not to such a great degree as morphine itself. It may be that strong analgesic action and addiction liability are inseparable, but this can only be proved by extensive tests on a great many more analgesics of various structural types.

Some of the confusion which has arisen as regards the relation between structure and analgesic action is no doubt due to the fact that in this method of tackling the problem, attention is concentrated on the structural formula alone, and the physico-chemical properties of the compound are more or less ignored. As mentioned earlier, these characteristics are of vital importance,

but in the present state of our knowledge we cannot say which particular characteristics are required to confer the desired properties on a given compound. Perhaps some day our knowledge of the mode of action of drugs may be such that the physiological effects of a particular compound may be predicted with certainty from a consideration of its structure and physico--chemical properties, but at present the method of trial and error must suffice. However this method, although undeniably inefficient, combined with the principle of isolating from the complex chemical structure of a natural product those fragments or groups which might be regarded as being responsible for the activity, has often been vindicated in the past by the preparation of relatively simple compounds with useful pharmacological action.

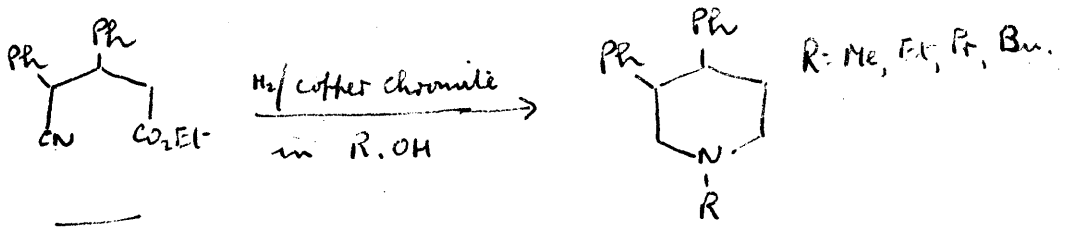
DISCUSSION.

PART II.

Synthesis of 1-ethyl-4-aryldecahydroquinoline derivatives.

In the past, decahydroquinolines have usually been prepared by the complete reduction of the corresponding quinoline derivative by various methods. In the present work, the intention was not only to prepare some 4-aryldecahydroquinoline derivatives, but in doing so, to explore a new method for the synthesis of compounds containing reduced nitrogen ring systems.

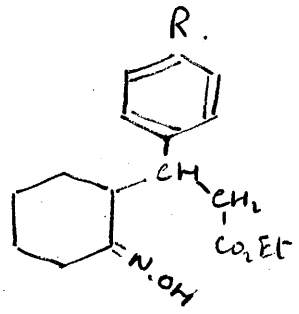
Barr and Cook (23) showed that reduction of γ-cyanoesters with hydrogen and copper chromite catalyst with an alcohol as solvent gave N-alkyl piperidine derivatives, the N-alkyl group being supplied by the alcoholic solvent e.g. reduction of α β -diphenyl-γ--carbethoxybutyronitrile (XVIII) in an alcohol R.OH gave 1-alkyl-3:4-diphenylpiperidine derivatives (XIX).



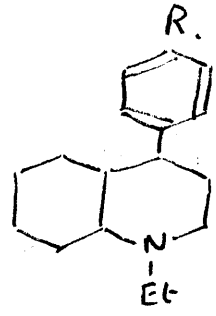
XVIII

XIX

The investigation recorded below was undertaken to find whether this method could be extended to suitable oxime-esters. Accordingly the oximes (XX, R = H, OMe) were prepared.



XX

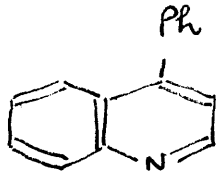


XXI

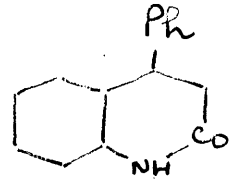
It was found that reduction of these oximes (XX, R = H,OMe) with hydrogen and copper chromite at 200° and 175 atmospheres for 3 hours gave the corresponding 1-ethyl-4-aryldecahydroquinolines (XXI, R = H,OMe) in yields of 80%.

The methoxy derivative (XXI, R = OMe) was demethylated to the corresponding phenyl (XXI, R = OH) with 48% hydrobromic acid in glacial acetic acid. This phenol, obtained in 85% yield, was soluble in dilute sodium hydroxide but gave no colouration with ferric chloride solution. This failure to react with ferric chloride has been reported with other phenolic amines (24).

The constitution of these decahydroquinoline derivatives was proved by the analysis of the free bases and various derivatives. In addition the compound (XXI, R = H) was completely dehydrogenated with palladium



XXII



XXIII

catalyst at 300° to give the known 4-phenylquinoline (XXII) in excellent yield. This 4-phenylquinoline was identified by the analysis of its picrate and by comparison of the melting points of the free base, picrate, sulphate, methiodide and chloroplatinate with those recorded in the literature.

These 4-aryldecahydroquinoline derivatives can exist in eight stereoisomeric forms but in these reductions it seemed that only one of these was formed to the exclusion of all others. The unsubstituted derivative (XXI, R = H) was an oil, but it gave a picrate with sharp melting point, and the methoxy derivative (XXI, R = OMe) was a crystalline sharp melting solid.

In one of the reductions of the oxime (XX, R = H) a fault in the apparatus caused the reduction to be interrupted after one hour, and in this case a very small amount of neutral material different from the oxime was isolated. It was only possible to have a nitrogen analysis done on this compound, but this indicated the possibility that it had the decahydro--quinol-2-one structure (XXIII). Barr and Cook (loc.cit.) showed that 2-piperidones were intermediates in the reduction of γ-cyanoesters to piperidine derivatives.

The mechanism of the reduction of these oximes to 1-ethyldecahydroquinoline derivatives is probably similar to that operating in the production of piperidine derivatives from γ-cyanoesters and may be outlined:-

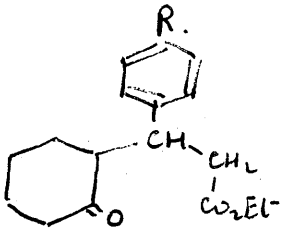
(a) reduction of the oxime group to a primary amine  .

(b) intramolecular reaction between the carbethoxy group and the primary amine with elimination of ethanol and formation of the decahydroquinol-2-one,

(c) reduction of this decahydroquinolone to the decahydroquinoline ,

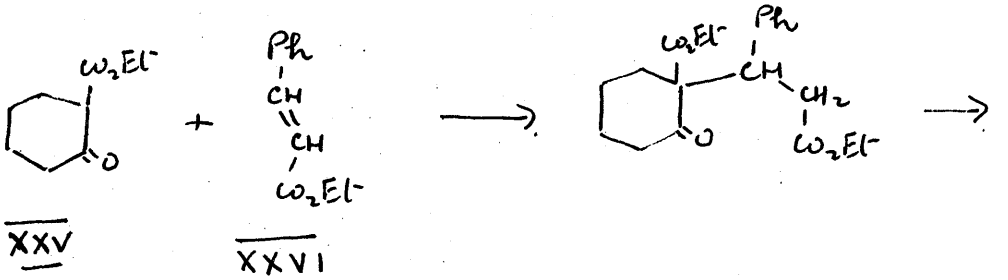
(d) alkylation of the nitrogen atom by the solvent. This type of alkylation by alcohols in the presence of various catalysts at high temperatures has already been recorded (25).

Several methods for the synthesis of the ethyl β-(2-ketocyclohexyl-)-β-arylpropionates (XXIV, R = H, OMe) required in this work were investigated.

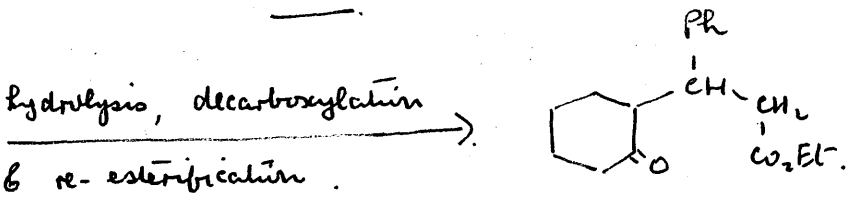


XXIV

The first of these methods is outlined below:-



XXV XXVI

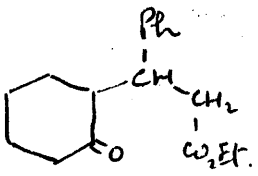


It was found however that the first stage, the Michael addition of ethyl cyclohexanone-2-carboxylate (XXV) to ethyl cinnamate (XXVI) would not take place. The condensation was attempted in ethanol using sodium ethoxide as condensing agent, and also in benzene using a suspension of the sodium salt of the keto-ester. Ethyl cinnamate was also replaced by cinnamonitrile, but in all experiments no trace of a condensation product was found, and the starting materials were mostly recovered unchanged. It has been shown that Michael additions are reversible reactions (26) and that an equilibrium is set up as follows:-

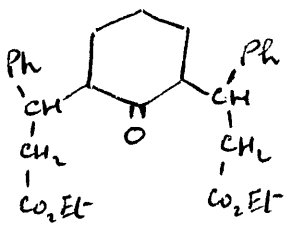
unsat. component + reactive $\text{CH}_2\text{-CH}$ $\rightleftharpoons$ condensation product.

It may be that for some reason in this particular case the equilibrium lies far over to the left.

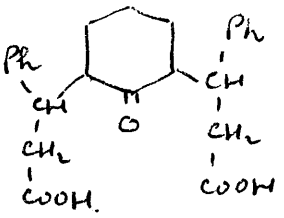
In the next attempt cyclohexanone itself was condensed with ethyl cinnamate in the hope of obtaining



XXVII



XXVIII



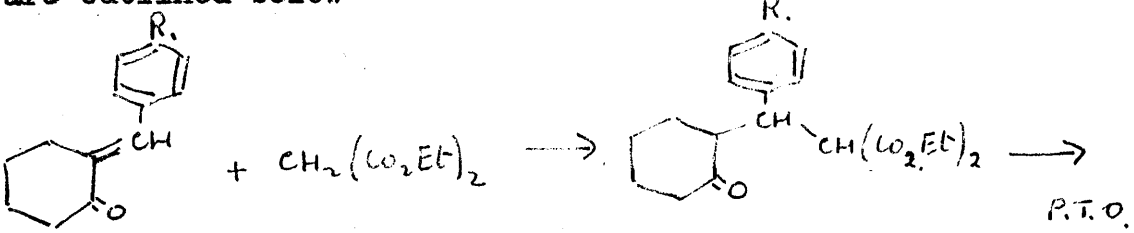
XXIX

the desired keto-ester (XXVII) in one stage. Condensation of one mol. of cyclohexanone and one mol. of ethyl cinnamate with one atom of potassium t-butoxide in

t-butyl alcohol gave a 75-80% yield of a crystalline solid analysing correctly for a compound of the type (XXVIII) i.e. reaction of two mols. of ethyl cinnamate with one mol. cyclohexanone. Some evidence that this condensation product had this type of structure was obtained when it was found that a similar yield could be obtained by the condensation of one half mol. cyclo-hexanone, one mol. ethyl cinnamate and one atom of potassium t-butoxide. On alkaline hydrolysis this compound (XXVIII) gave an acid which should be of the type (XXIX). However this acid was very difficult to purify, and the analysis figures did not entirely agree with the structure. These two compounds (XXVIII and XXIX) gave no ketonic derivatives, and since it was obvious they had not the desired structure, no further investigation of them was made.

The method finally adopted, with some slight experimental modifications, for the preparation of the desired β-(2-ketocyclohexyl)-β-arylpropionic esters

desired β-(2-ketocyclohexyl)-β-arylpropionic and Kunze (26). The various stages of this method, which these authors carried out for the phenyl derivatives (XXX-XXXIV, R = H) are outlined below:-



XXX XXXI

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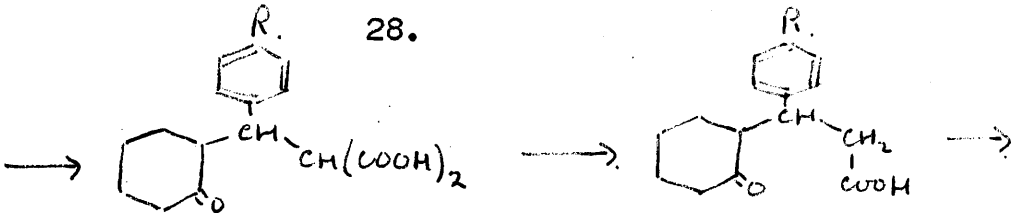
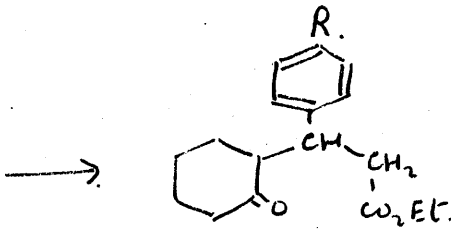


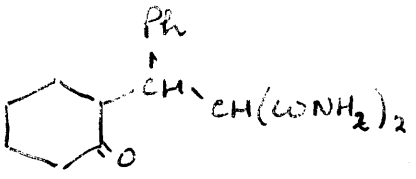
XXXII

XXXIII



XXXIV

Vorlander and Kunze described the product of the reaction between mono-benzylidene cyclohexanone (XXX, R = H) and diethyl malonate as an oil which they could not purify, but which they assumed to be the expected β-(2-ketocyclohexyl)-benzylmalonic ester (XXXI, R = H) as on treatment with a solution of concentrated ammonia in alcohol it gave a compound whose analysis figures agreed with those of the di-amide (XXXV).



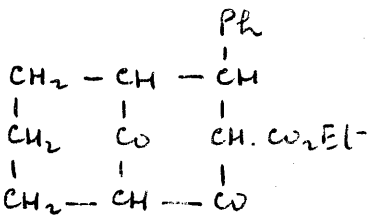
XXXV

Their experimental method consisted of allowing a solution of mono-benzylidene cyclohexanone in benzene to stand in contact with a suspension of the sodium salt of diethyl malonate in benzene for several days. This experiment was repeated using slightly modified conditions. It was found that if the mixture was refluxed for 2 hours,

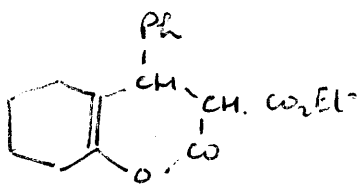
the sodium salt of diethyl malonate gradually went into solution and a homogeneous liquid was obtained. The product was a crystalline solid m.p.69°. This compound gave β-(2-ketocyclohexyl)-benzymalonic acid (XXXII, R = H) in goodyield on hydrolysis with alcoholic potassium hydroxide, and it was thought to be diethyl-β-(2-ketocyclohexyl)-benzylmalonate (XXXI, R = H) of a higher degree of purity than that obtained by Vorlander and Kunze. Analysis showed, however, that this was not the case.

The molecular formula for the diester is $C_{20}H_{26}O_5$. Analysis of the crystalline compound gave the empirical formula as $C_9H_{10}O_2$. Using the Rast method, it was found that the molecular weight was approximately 300, thus giving the molecular formula as $C_{18}H_{20}O_4$. Determination of ethoxyl showed that the compound contained only one such group. Thus it seems likely that this compound has been formed by elimination of one molecule of ethyl alcohol from the diester.

There are two ways in which this might be done, bearing in mind that the product must give β-(2-ketocyclohexyl)-benzylmalonic acid on alkaline hydrolysis. The two possible products are shown below (XXXVI and XXXVII).

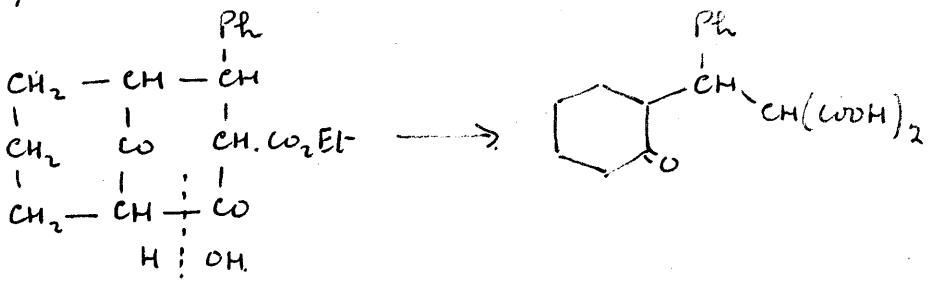


XXXVI

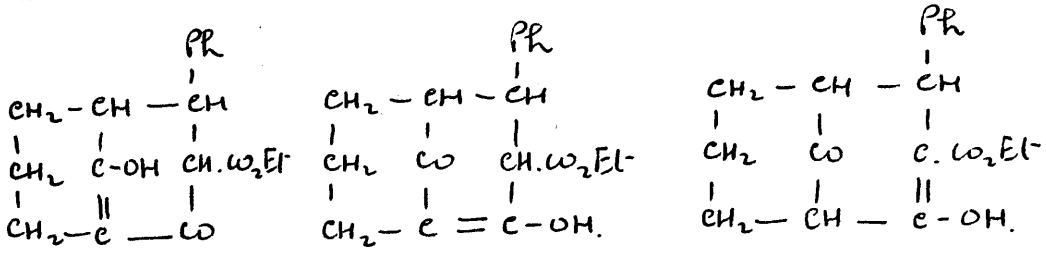


XXXVII

(XXXVI) could possibly be formed by a Claisen condensation between one of the carbethoxy groups and the other reactive methylene group. Hydrolysis with 40% potassium hydroxide might also give the malonic acid, as the compound is a/3-diketone.

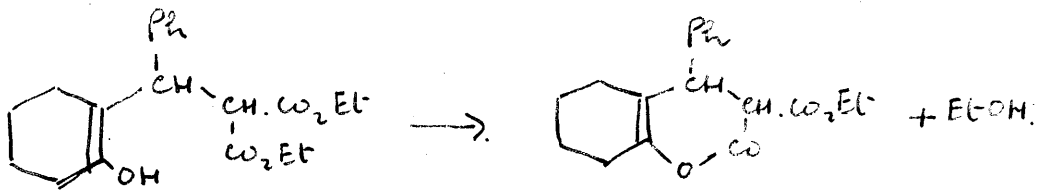


However, this structure is not satisfactory; a compound of this type would almost certainly give a colouration with ferric chloride and be soluble in sodium hydroxide solution. Although it is unlikely that the enolic forms (XXXVIII and XXXIX) would be formed (Bredt's rule), there is no reason why the form (XL) should not be possible.



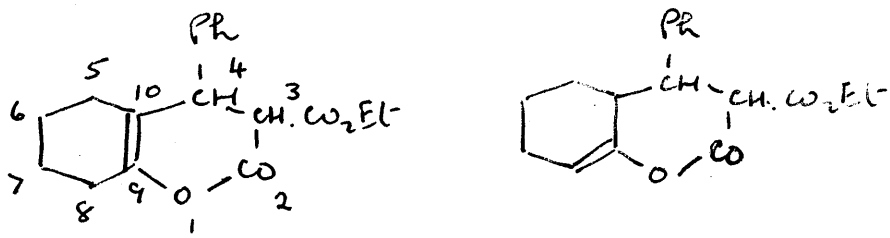
The compound obtained has none of these reactions.

The other possible product (XLII) could be formed by the elimination of ethyl alcohol between the enolic form of the ketone (XLI) and a carbethoxy group.



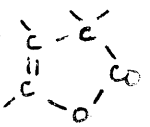
XLI XLII

A compound of this structure would be unlikely to give a colouration with ferric chloride, would be insoluble in cold sodium hydroxide solution, and would certainly give β-(2-ketocyclohexy)-benzylmalonic acid on hydrolysis. Investigation has shown that the compound actually has this lactone structure, i.e. it is 3-carbethoxy-4-phenyl--3:4:5:6:7:8-hexahydrocoumarin. (XLII). (There is no positive proof that the structure is (XLII) and not (XLIII) i.e. the 3:4:5:6:7:10-hexahydro derivative,



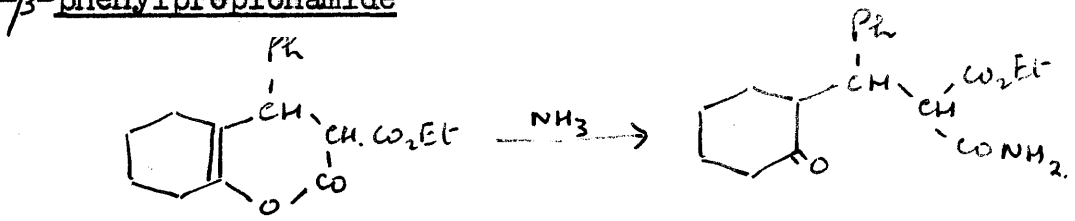
XLII XLIII

but it is considered probable that the double bond is included in the lactone ring.)

As would be expected, the lactone gives no benzylidene derivative, indicating the absence of a reactive methylene group. It also reduces ammoniacal silver nitrate solution, though rather slowly and only on heating. All five-membered unsaturated lactones of the type  reduce silver nitrate solution readily, but the behaviour of six-membered

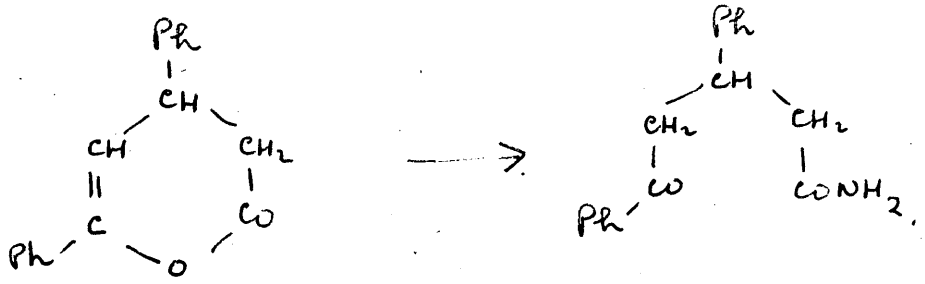
rings is not so definite. There are comparatively few examples of six-membered unsaturated lactones in the literature, and their behaviour with this reagent does not seem to have been investigated.

The lactone takes up bromine immediately: this rapid reaction with bromine is characteristic of all unsaturated lactones of this type. Treatment of an alcoholic solution of the lactone with concentrated ammonia solution gave α-carbethoxy-β-(2-ketocyclohexyl)-β-phenylpropionamide. (XLIV).



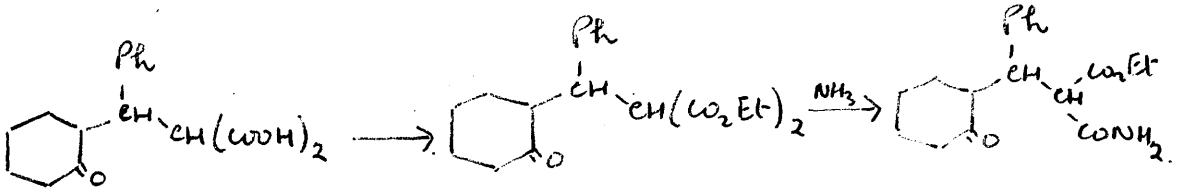
XLIV

This rapture of the lactone ring by ammonia is in accord with the observation of Mannich and Butz (27) who showed that the lactone (XLV) gave the amide (XLVI) on treatment with aqueous alcoholic ammonia.



XLV XLVI

Diethyl-β-(2-ketocyclohexyl)-benzylmalonate (XLVIII) was prepared from the malonic acid (XLVII) by passing a stream of dry hydrogen chloride gas through a solution of the acid in ethanol. The product was a viscous colourless oil, which distilled without decomposition under a high vacuum.

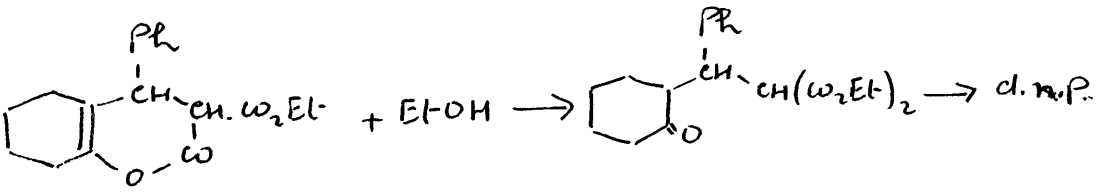


XLVII XLVIII XLIV

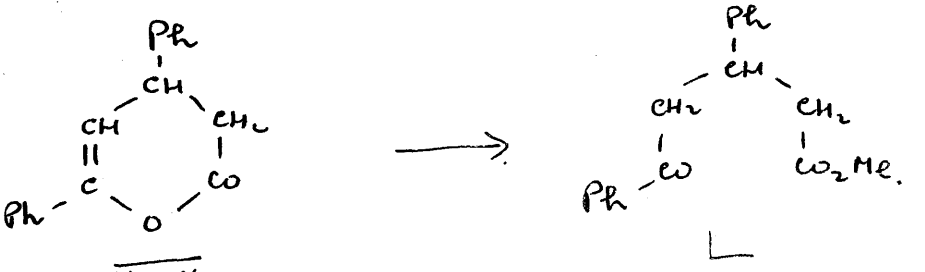
When a solution of the ester (XLVIII) in ethanol was treated with concentrated ammonia and allowed to stand, crystals of the same mono-amide (XLIV) as that obtained from the lactone were deposited. Vorlander and Kunze (loc.cit.) described the di-amide as fairly soluble in cold alcohol; the mono-amide is not very soluble in this solvent and it is probable that in the concentrations used in this experiment, the mono-amide crystallised out as soon as it was formed.

The action of dinitrophenylhydrazine solution on the lactone dissolved in ethanol gave a heavy red oil from which a few orange yellow crystals of the dinitrophenylhydrazone of diethyl-β-(2-ketocyclohexyl)--benzylmalonate (XLVIII) were isolated. The constitution of this compound was proved by a mixed melting point with an authentic specimen prepared from the pure diester. The probable mechanism of this reaction is the addition

of ethyl alcohol to the lactone ring, the reaction perhaps being catalysed by the presence of sulphuric acid.

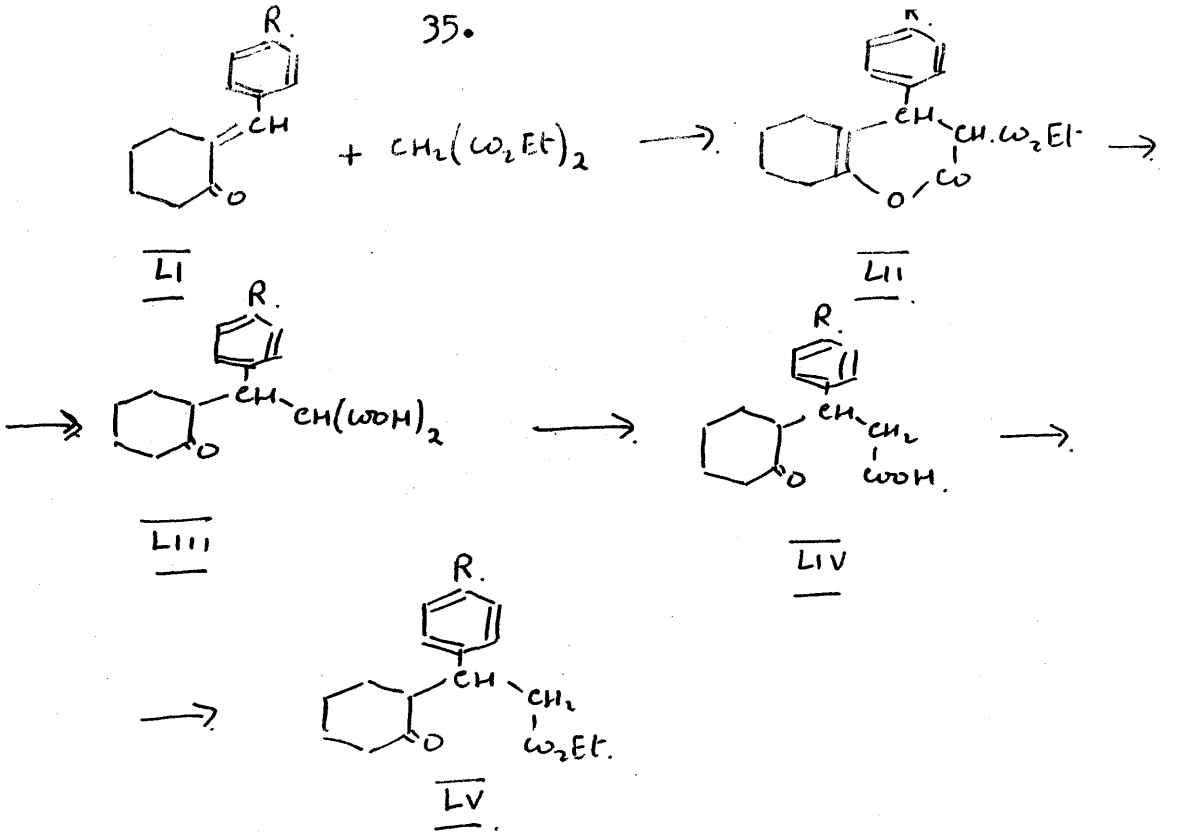


Some support for this mechanism is obtained from the observation by Mannich and Butz (loc.cit.) that if a solution of the lactone (XLIX) in methanol is refluxed, some of the keto-methyl ester (L) is produced.



XLIX

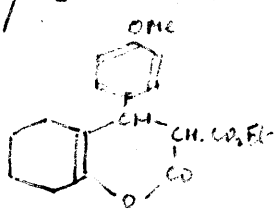
The dinitrophenylhydrazone of the diester was by no means the main product of the action of dinitrophenyl--hydrazine on the lactone, but it was the only crystalline material isolated from the reaction mixture.



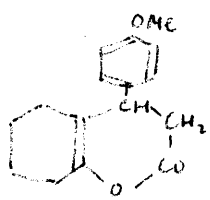
In the p-OMe series, the condensation of mono--anisylidene cyclohexanone (LI R = OMe) with diethyl malonate was carried out under exactly the same conditions as for the benzylidene derivatives. Removal of the benzene gave a viscous oil which would not solidify. This crude oil, on hydrolysis with 40% aqueous alcoholic potassium hydroxide gave β-(2-keto--cyclohexyl)-p-methoxybenzylmalonic acid (LIII, R = OMe) in good yield, and so this oil was used for the next stage of the synthesis without further purification. Since in this condensation the reaction conditions were exactly the same as those used in the unsubstituted phenyl series, this oil was assumed to have the unsaturated lactone structure (LII, R = OMe). This assumption was borne out by experiments which will be described later.

The malonic acids (LIII, R = H,OMe) were decarboxylated to the corresponding β-(2-ketocyclohexyl)-β-arylpropionic acids (LIV, R = H,OMe) by heating at the melting point. These acids, on esterification with concentrated sulphuric acid in ethanol, gave the desired ethyl-β-(2-ketocyclohexyl)-β-arylpropionates (LV, R = H,OMe) in excellent yields.

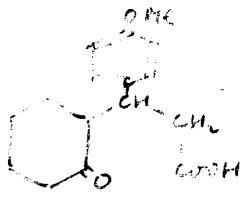
Some unexpected reactions were encountered in the p-MeO series in this synthesis. In an attempt to prove the constitution of the oily condensation product (LII, R = OMe), a small amount was distilled in vacuo. In the first distillation decomposition was extensive, and the gaseous substances produced made it impossible to maintain a high vacuum. The brown oily distillate was redistilled. This time there was little decomposition, and the product was a colourless viscous oil. This oil was dissolved in a small amount of ethanol, and the solution, on standing in the refrigerator for some time, deposited colourless neddles of a compound m.p.113°. Investigation showed it to be 4-p-methoxy-phenyl-3:4:5:6:7:8-hexahydrocoumarin (LVII). Its structure was proved by hydrolysis to β-(2-ketocyclohexyl)-β-p-methoxyphenylpropionic acid (LVIII), and also by



LVI



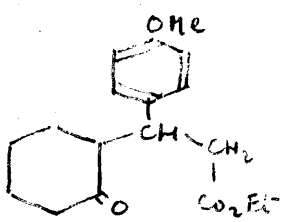
LVII



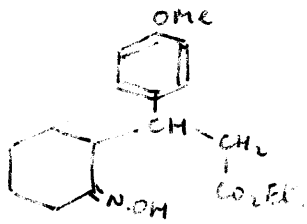
LVIII

a mixed melting point with an authentic specimen of the lactone prepared in a different way. Thus it seems that distillation eliminated a carbethoxy group: from the lactone (LVI). This is in contrast to the other series, where the phenyl derivative distilled unchanged. It may be that the p-methoxy group has some activating effect on the rest of the molecule, and the higher temperature required for the distillation of the methoxy derivative may also be a factor.

The ester (LIX) was obtained as an oil which gave the oxime (LX) in good yield. A small amount of this

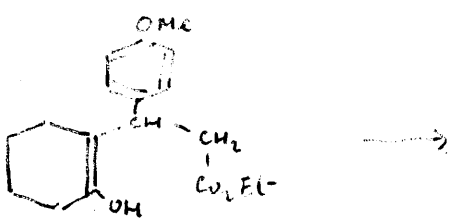


LIX

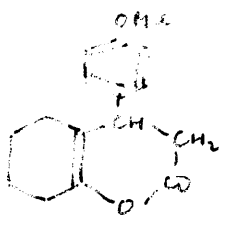


LX

crude oily ester was distilled to obtain an analysis specimen. There was some decomposition, the gaseous products formed making it impossible to maintain a high vacuum. The brown oily distillate was redistilled, giving a colourless oil which on treatment with a little ethanol soon solidified. This compound has m.p.113°, and was shown to be 4-p-methoxyphenyl-3:4:5:6:7:8--hexahydrocoumarin (LXII). A mixed melting point of



LXI

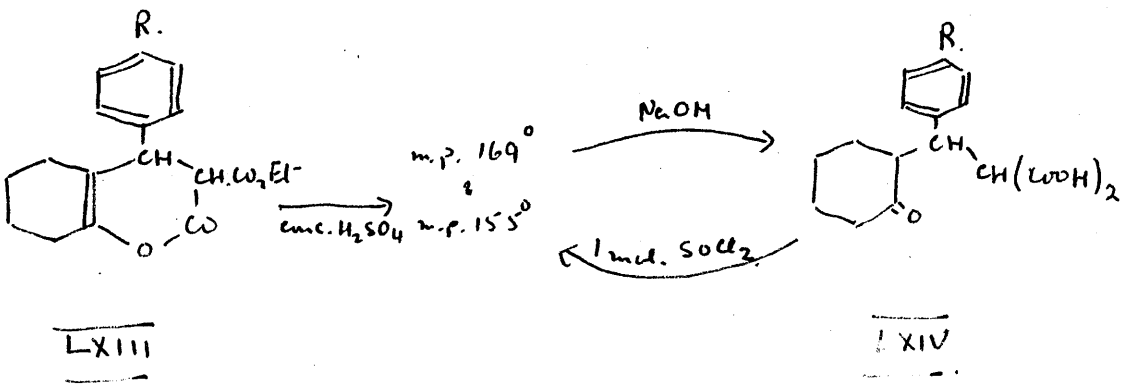


LXII

this compound and an authentic specimen showed no depression. The mechanism of its formation is probably elimination of ethyl alcohol between the carbethoxy group and the enolic form of the ketone (LXI).

The unsaturated lactones, obtained in the Michael reaction between the unsaturated cyclohexanone derivatives and diethyl malonate, have some other interesting reactions. These reactions are described below.

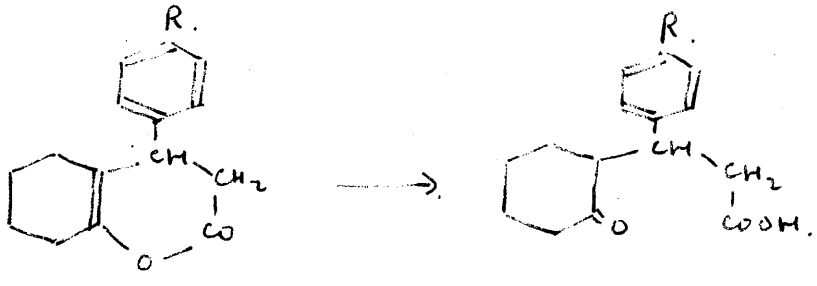
Treatment of the lactones (LXIII, R = H,OMe) with concentrated sulphuric acid gave in both cases crystalline products m.p.169° and 155° respectively in very good yields. These compounds crystallised well from ethanol and analysed for $C_{16}H_{16}O_4$ and $C_{16}H_{15}O_4$ (OMe) respectively. They were insoluble in cold alkali, but on refluxing they went into solution and acidification yielded the corresponding malonic acids (LXIV, R = H,OMe) in theoretical yields.



LXIII LXIV

These compounds (m.p. 169° and 155°) could also be prepared by the action of one molecule of thionyl chloride on the corresponding malonic acid (LXIV, R = H,OMe)

in benzene solution. They melted without decomposition (indeed the unsubstituted compound could be distilled under a high vacuum b.p. 170°/0.4 m.m.) but on heating to over 200°, they decomposed with evolution of carbon dioxide to give the unsaturated lactones (LXV, R = H,OMe) respectively in good yields. These lactones (LXV, R = H,OMe) analysed correctly, decolourised a solution of bromine in carbon tetrachloride , and on hydrolysis with alkali gave theoretical yields of the corresponding mono-carboxylic acids (LXVI, R = H,OMe). The identity of these acids was proved by mixed melting points with authentic specimens prepared by decarboxylation of the corresponding malonic acids (LXIV, R = H, OMe).

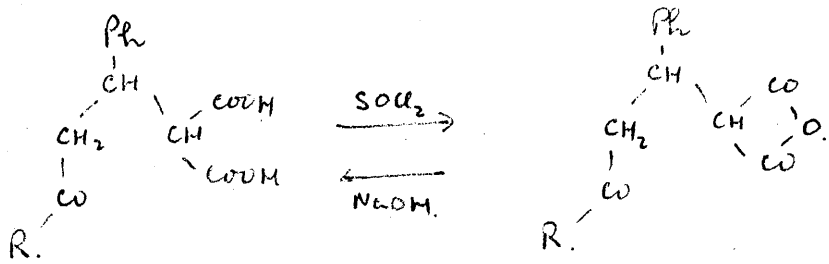


LXV LXVI

Also the p-methoxy lactone (LXV, R= OMe) was identical with specimens of this compound prepared as mentioned before.

A study of the literature seems to indicate two possible structures for these compounds m.p. 169° and 155°. Mannich and Butz (27) reported the preparation of the first crystalline mono-substituted malonic anhydrides (LXVIII, R = CH_3,Ph). They were prepared by refluxing the malonic acids (LXVII, R = CH_3, Ph) with one molecule

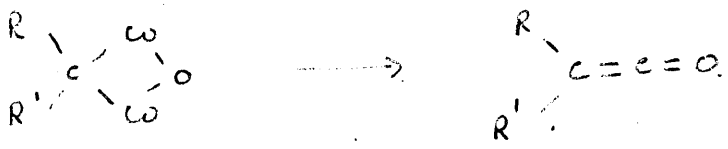
of thionyl chloride in benzene.



LXVII LXVIII

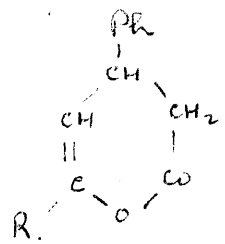
These anhydrides were stable crystalline compounds, unchanged by cold aqueous alkali, but on refluxing an alkaline solution gave the malonic acids (LXVII, R = R = CH_3,Ph) in theoretical yields.

Staudinger (28) prepared a series of di-substituted malonic anhydrides of the type (LXIX, R,R' = alkyl); these anhydrides were hygroscopic, reacting with water to give the corresponding malonic acid. Staudinger also showed that on heating they lost carbon dioxide to give ketenes(LXX, R,R' = alkyl).



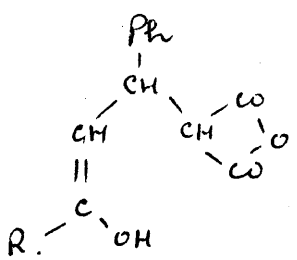
LXIX LXX

The anhydrides prepared by Mannich and Butz however gave on heating at a temperature considerably above the melting point, not the expected ketenes but the unsaturated lactones (LXXI, R = CH_3,Ph).

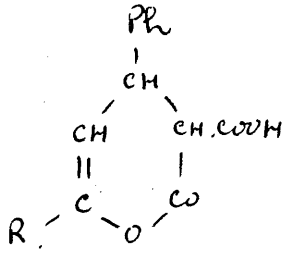


LXXI

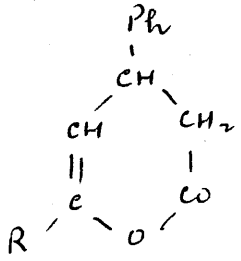
The mechanism postulated by these authors was intramolecular acylation of the enolic form of the ketone (LXXII, R = CH_3, Ph) to give (LXXIII, R = CH_3,Ph), followed by loss of carbon dioxide to give the lactones (LXXIV, R = CH_3,Ph).



LXXII



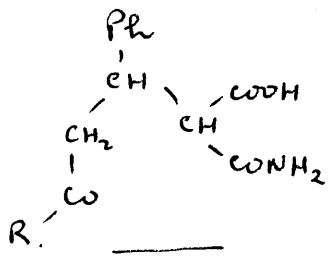
LXXIII



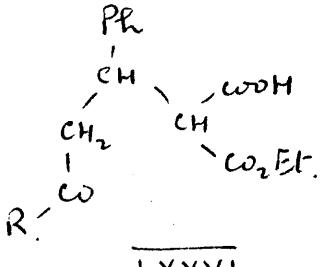
LXXIV

Other evidence advanced by Mannich and Butz for the anhydride structure of their compounds was:-

(a) If a solution of the anhydrides in benzene, saturated with dry ammonia gas, was refluxed, the product was the half-acid amide (LXXV, R = CH_3,Ph).



LXXV



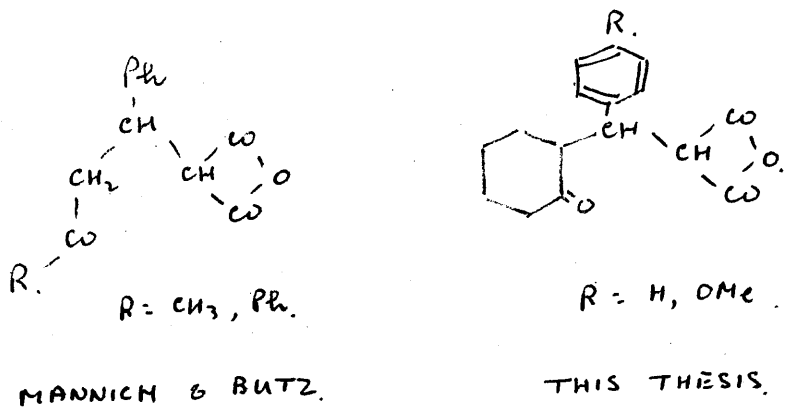
LXXVI

(b) Prolonged refluxing of a solution of the anhydrides in ethanol gave some of the half-acid ester (LXXVI, R = CH_3,Ph).

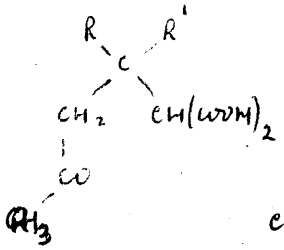
Both these reactions, of course were in complete agreement with the anhydride structure.

From a comparison of the methods of preparation and general properties of the compounds (m.p. 169° and 155°)

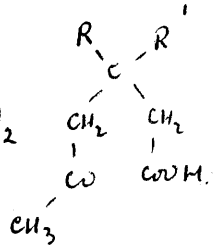
described in this thesis and those compounds prepared by Mannich and Butz, it seems certain that they have the same type of structure. However, the unusual stability of these anhydrides, which is so completely different from that of the compounds described by Staudinger, raised the question whether this structure was indeed the correct one. Suspicion was also aroused by the fact that the only stable crystalline malonic anhydrided so far described all had a very similar structure as shown below:-



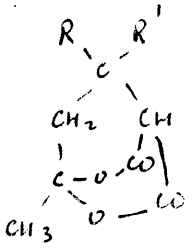
In a series of papers reporting the investigation of several examples of keto-lactol tautomerism, Qudrat-i-Khuda (29) showed that compounds of type (LXXVII, R,R' = alkyl) gave, on heating at the melting point, the expected mono-carboxylic acids (LXXVIII, R,R' -= alkyl) and some of the dilactones (LXXIX, R,R' = alkyl), and he postulated the lactol structure (LXXX, R,R' = alkyl) as an interimediate in the formation of these dilactones.



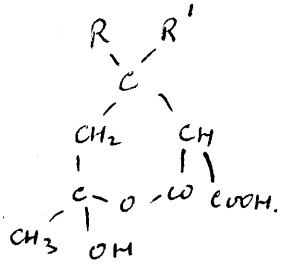
LXXVII



LXXVIII



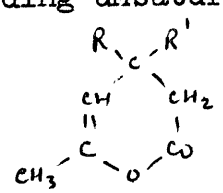
LXXIX



LXXX

He also showed that the percentage of dilactone formed was in order R,R' = cyclohexane ring $\rangle$ cyclopentane ring $\rangle$ $\rangle$ Et_2 $\rangle$ EtMe $\rangle$ Me_2, and attributed this to the effect the various sized groups R and R' had on the general valency angles in the molecule e.g. the bigger the groups R and R', the nearer will the -COOH and C=O groups lie in space to each other, thus making the lactol structure (LXXX) more stable. Since the percentage of dilactone formed is dependent on the amount of lactol structure present, it follows that the larger the groups R and R', the higher the percentage of dilactone which will be formed. In this series, this effect reaches its peak when R,R' is a cyclohexane ring, as is borne out by the experimental evidence.

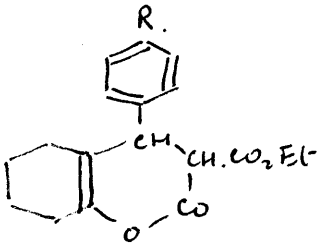
These dilactones described by Qudrat-i-Khuda were stable crystalline compounds, which on hydrolysis with alkali gave theoretical yields of the corresponding keto-malonic acids. On heating at temperatures of about 200° these dilactones lost carbon dioxide to give the corresponding unsaturated lactones of the type (LXXXI).



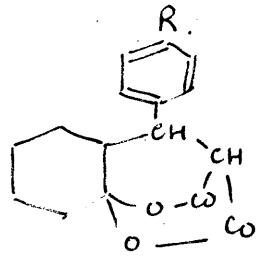
LXXXI

It will be seen that the properties of these dilactones are exactly the same as those of the compounds m.p. 169° and 155° and also the "malonic anhydrides" described by Mannich and Butz. The question arises therefore, whether all these compounds have this dilactone structure.

The two methods of preparation are quite in accordance with this view. The lactonisation of γδ - unsaturated acids and esters under the influence of acidic reagents is well known, and the formation of the dilactones (LXXXIII, R = H,OMe) from the unsaturated lactones (LXXXII, R = H,OMe) with sulphuric acid is analogous.

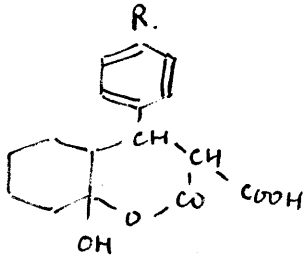


LXXXII

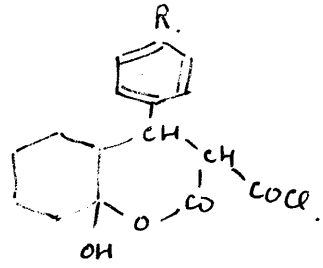


LXXXIII

The other method of preparation, treatment of the corresponding malonic acid with one molecule of thionyl chloride is also readily explained if the presence of some of the malonic acid in the lactol form (LXXXIV) in solution is assumed.



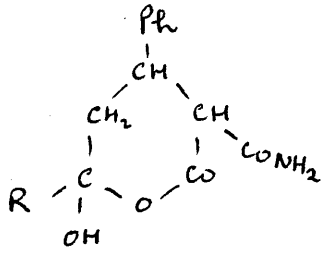
LXXXIV



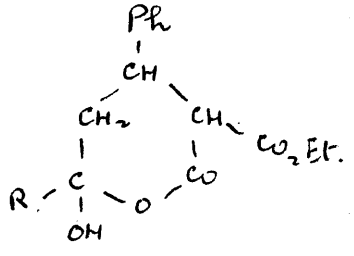
LXXXV

Reaction with one molecule of thionyl chloride would give the acid chloride (LXXXV), which could readily ring close to the dilactone with elimination of hydrochloric acid.

The reactions of the compounds of Mannich and Butz with ammonia and ethyl alcohol are also no proof against the dilactone structure. It is conceivable that these reagents could break the lactone ring to give (LXXXVI) and (LXXXVII) respectively, which are merely the lactol forms of the half-acid amide and ester obtained by Mannich and Butz.



LXXXVI



LXXXVII

From general stability considerations, the dilactone structure is more probable than the anhydride form, but the evidence advanced in the literature does not prove or rule out either structure conclusively. Accordingly some further experimental evidence was sought.

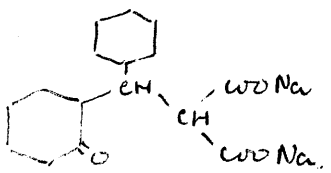
The obvious method for distinguishing between these two structures, i.e. ketonic reagents, gave inconclusive results. Treatment of the unsubstituted phenyl derivative (m.p. 169°) in absolute ethanol with dinitrophenylhydrazine solution gave, after standing some time, a heavy red oil which ultimately yielded some solid material. Repeated recrystallisation eventually

gave a fairly pure compound m.p. 171°. The analysis of this compound however, did not allow any definite structure to be assigned to it. (See Experimental). The fact that some reaction did take place with dinitrophenylhydrazine solution is no proof against the dilactone structure, since it is possible that the lactone ring could be opened by the action of the ethanol or even by the dinitrophenylhydrazine itself, thus leaving the keto group free to react in the normal way.

Some reduction experiments were then carried out. The compound m.p. 169° was untouched by palladium black catalyst and hydrogen in acetone solution, but with Adams PtO_2 catalyst in acetic acid or ethanol took up 2.8 mols. of hydrogen per mol. of compound. This accurate figure for the hydrogen uptake was obtained from a micro-hydrogenation carried out by Mr. J. M. L. Cameron. The product from this micro--hydrogenation was identical with that obtained from reduction on a larger scale. This product was a crystalline solid m.p. 137° which analysed correctly for $C_{16}H_{22}O_4$ thus confirming the absorption of 3 mols. of hydrogen (compound m.p. 169° is $C_{16}H_{16}O_4$). With the particular batch of catalyst used, it is extremely likely that a phenyl group such as is present in this molecule would undergo reduction to the cyclohexane derivative, thus accounting for all 3 mols. of hydrogen taken up. This evidence indicates the dilactone

structure to be correct since the keto group present in the malonic anhydride form would certainly have been reduced under these conditions in addition to the phenyl group, thus requiring 4 mols. of hydrogen.

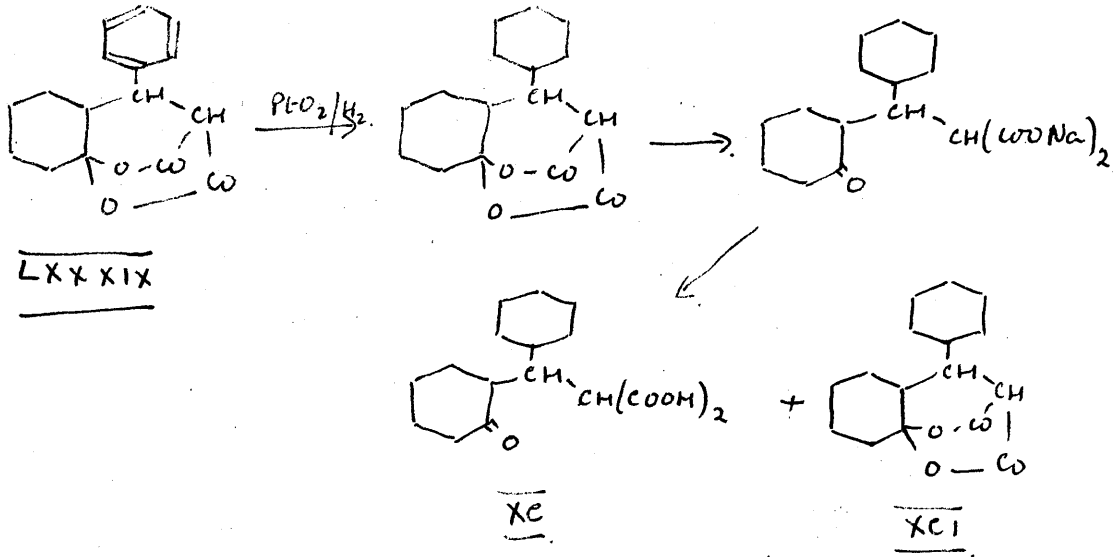
The reduction product m.p. 137° was insoluble in cold sodium hydroxide, but on refluxing went into solution. On cooling, this solution deposited crystals of the sodium salt of an acid. It melted fairly sharply at 280-1° with decomposition, and might be expected to be (LXXXVIII).



LXXXVIII

Analysis figures agreed with such a structure + 6 mols. of water of crystallisation. It is perhaps rather surprising that this compound should retain this water of crystallisation even after drying in vacuum at 100°. The melting point was also unchanged after drying. A Acidification of an aqueous solution of this sodium salt with dilute hydrochloric acid gave a solid which melted over a range between 110 -125° with evolution of a gas. On recrystallisation, however, the melting point rose steadily to 137°, when the compound melted without decomposition and was shown to be identical with the product originally obtained in the reduction. It appears probable that acidification gave a mixture of the dilactone (XCI) and the malonic acid (XC) and that on recrystallisation the less soluble dilactone was

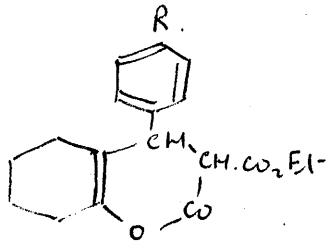
obtained. Thus this series of reactions may be represented:-



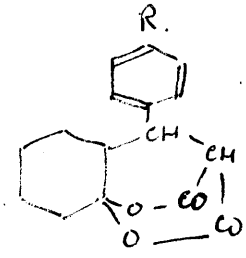
LXXXIX XC XCI

Attempts to isolate the malonic acid (XC) from the mother liquors were unsuccessful, only the dilactone (XCI) being obtained, and it may be that during recrystallisation further lactonisation of this malonic acid took place. This phenomenon of lactonisation was not encountered in the unreduced malonic acid derived from (LXXXIX), but it was reported by Qudrat-i-Khuda (loc.cit.) for some of his compounds.

Attempts to formulate this series of reactions on the assumption that the malonic anhydride structure was correct were unsuccessful. Consequently it appears that the compounds of m.p. 169° and 155° prepared from the unsaturated lactones (XCII, R = H,OMe) with concentrated sulphuric acid have the dilactone structure (XCIII, R = H,OMe). By analogy, the "malonic anhydrides" of Mannich and Butz also have this type of structure.



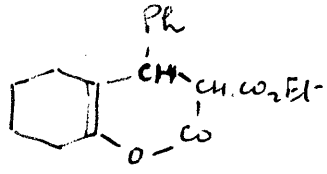
XCII



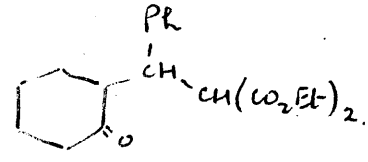
XCIII

Models of (XCIII) show that there is no strain in these molecules, whereas in the malonic anhydride form there is considerable strain in the formation of the 4-membered anhydride ring.

Before it was discovered that the compound obtained from the Michael reaction was the lactone (XCIV) and not the diester (XCV) an attempt was made to prepare the oxime.



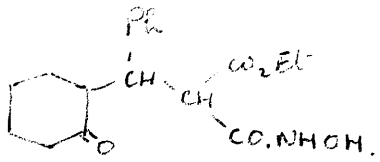
XCIV



XCV

A solution of thelactone in ethanol was treated with hydroxylamine hydrochloride and sodium acetate in water. After standing overnight addition of water gave a solid compound, which was extremely soluble in acetone and alcohol, but gave crystals from benzene/light petroleum (60°-80°) m.p. 138°. It contained nitrogen, was insoluble in dilute sodium carbonate, but soluble in sodium hydfoxide solution, and its solution in alcohol gave a deep red colouration with ferric chloride.

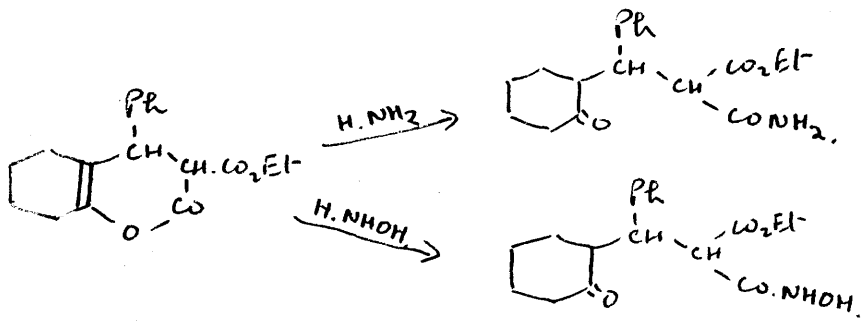
Analysis figures agreed with a molecular formula of $C_{18}H_{23}O_5N$, i.e. addition of one colecule of NH_2OH to to the lactone ($C_{18}H_{20}O_4$). The evidence available on this compound seems to indicate that it has the structure (XCVI)



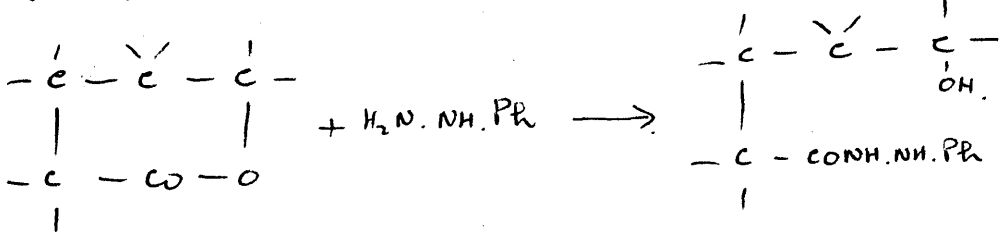
XCVI

i.e. it is a hydroxamic acid derivative.

Thus it seems that the action of hydroxylamine on the lactone is very similar to that of concentrated ammonia:-



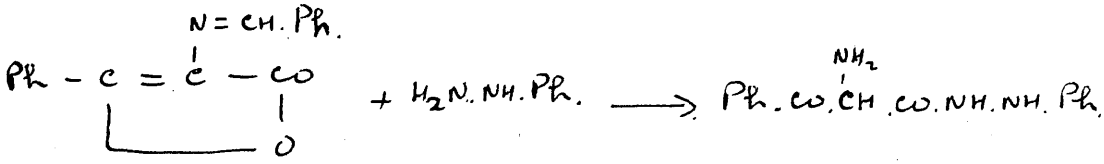
Little work has been done on the action of ketonic reagents on unsaturated lactones, but it is well known that saturated lactone (XCVII) reacts with e.g. phenylhydrazine to give the phenylhydrazide of the hydroxy acid (XCVIII).



XCVII XCVIII

Only one example could be found in the literature which

is of interest in connection with this work. Minunni, Ottaviano and Spina, (30) showed that the action of phenylhydrazine on the lactone (XCIX), in addition to giving the free amine, split the lactone ring to form the phenylhydrazide of the keto-acid (C).



XCIX C.

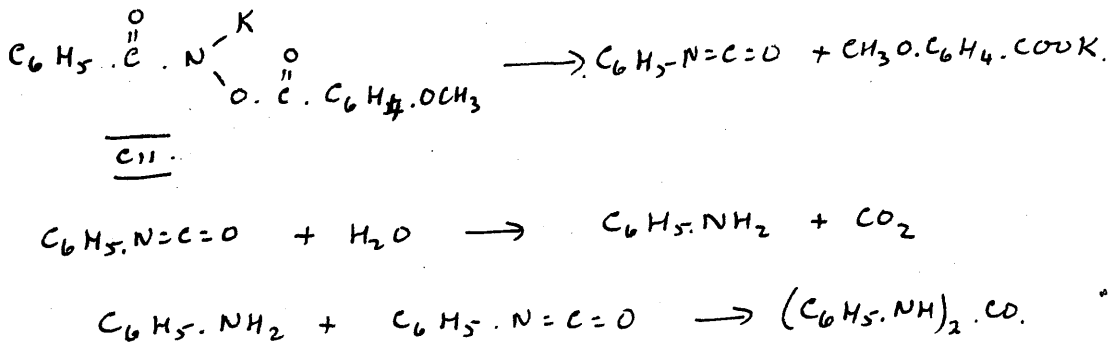
Hydroxamic acids give characteristic red colourations with ferric chloride, and are weakly acidic, which might account for the fact that the product from the hydro-coumarin and hydroxylamine is insoluble in sodium carbonate but soluble in sodium hydroxide. Some hydroxamic acids reduce Fehling's solution, but there are many exceptions to this; the compound obtained from the lactone does not reduce Fehling's solution but reduces hot ammoniacal silver nitrate.

Hydroxamic acids and their derivatives as a general rule undergo the Lossen rearrangement e.g. Lossen (31) heated benzoyl benzohydroxamate (CI) and obtained phenyl isocyanate. $Ph.CO.NH.O.CO.Ph \longrightarrow Ph.N=C=O$

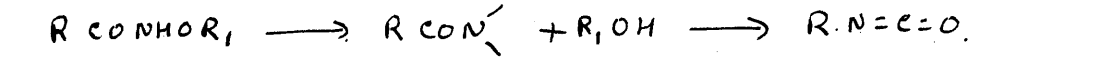
CI

The same author (32) also reported that boiling a solution of the potassium salt of anisoylbenzohydroxamate (CII) in water, gave diphenylurea, potassium anisoate and carbon dioxide. The mechanism of the reaction was

shown to be:-



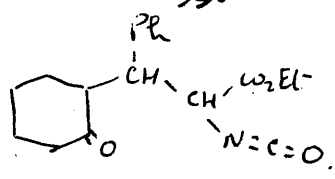
The general reaction may be represented:-



where R = H, or an acyl radical.

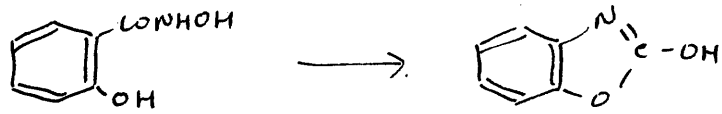
There are many experimental conditions which can be used in this reaction, but the main ones are:- 1) boiling the potassium salt of an acyl derivative in water, 2) treatment of an acyl derivative with thionyl chloride. A few cases have been reported where destructive distillation of the free acid was used. (33).

If the compound obtained from the lactone is a hydroxamic acid, it might be expected to undergo a similar type of reaction. It was found that on heating at the melting point, it decomposed to give a crystalline product m.p. 154°, whose analysis figures gave the molecular formula as $C_{18}H_{21}O_4N$, i.e. one molecule of water has been eliminated. The compound was stable, insoluble in dilute sodium carbonate, but soluble in sodium hydroxide solution, and so was certainly not the expected isocyanate derivative (CIII).



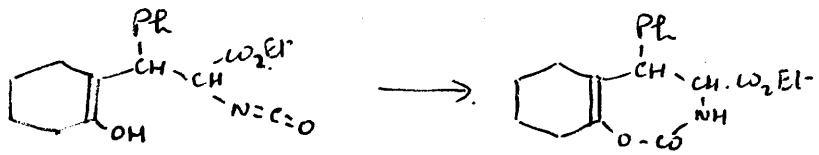
CIII

It also gave a purple colouration with ferric chloride. However, there is another possibility. Marquis (34) showed that salicylhydroxamic acid (CIV) on treatment with thionyl chloride, gave oxycarbanil (CV)

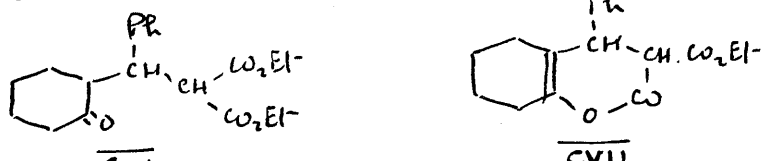


CIV CV

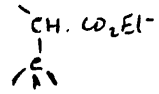
i.e. intramolecular reaction of the isocyanate formed with the -OH group. It is possible therefore that the enolic form of the ketone would react in the same way:-



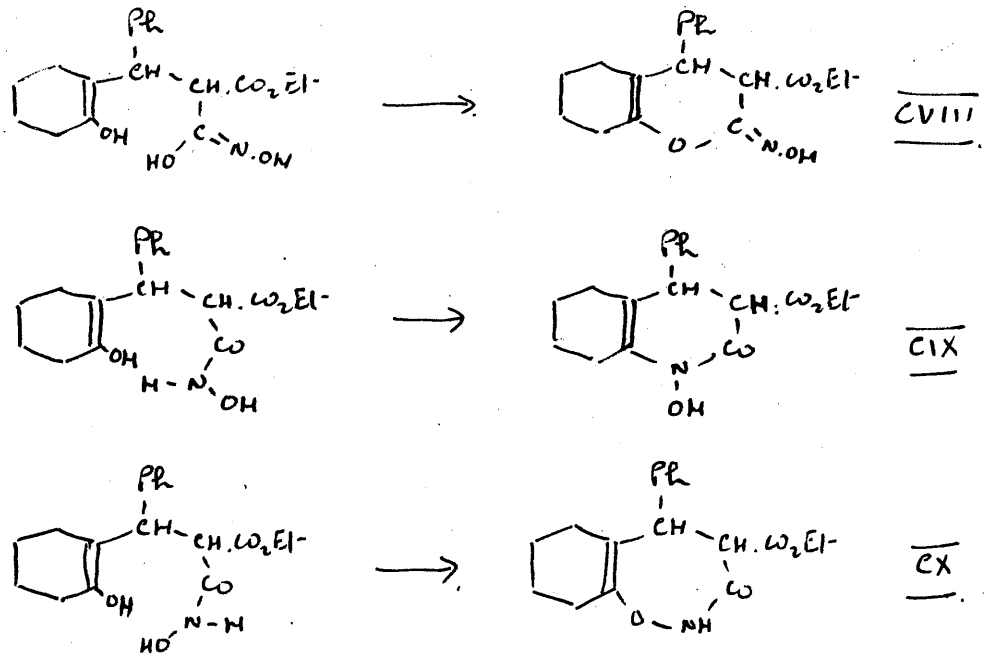
This compound would give the same analysis results; but it was found that treatment of a solution of this product (m.p. 154°) in ethanol with dinitrophenylhydrazine gave, as one of the products, a small amount of the dinitrophenylhydrazone of diethyl-β-(2-ketocyclohexyl)--benzylmalonate. (CVI).



CVI CVII

(c.f. action of dinitrophenylhydrazine on the lactone (CVII) Thus the carbon system  must be present in the molecule and an isocyanate can not be an intermediate in the reaction.

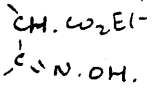
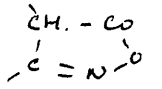
Since the -H and -OH groups in the structure $R.CON\begin{matrix}H\\OH\end{matrix}$ are fairly reactive (c.f. elimination of H_2O to form $R.CON<$), the possibility of intramolecular elimination of water between one or other of these groups and the enolic form of the ketone was considered. (The conditions under which water was eliminated to give this compound viz. heating at the melting point, are fairly mild compared with those usually required to effect a Lossen rearrangement under the influence of heat alone, and the enolic form of the ketone has been postulated as an intermediate in other reactions.)
The possible products are shown below:-



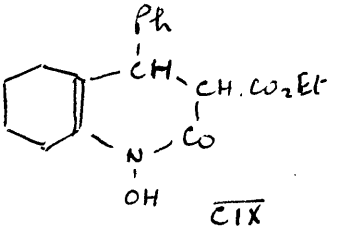
All these compounds (CVIII, CIX and CX) may be considered as hydroxamic acid derivatives:-

CVIII = $R.\underset{\underset{OR'}{|}}{C}=N.OH$ CIX = $R.CON\begin{matrix}R'\\OH\end{matrix}$

CX = $R.CONH.OR'$

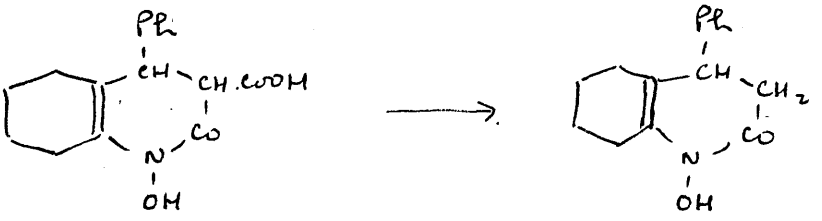
and it would be difficult to distinguish between them since they would all be very similar in reaction. However, Yale (35) states that compounds of type (CX) give no colouration with ferric chloride solution, and so it is unlikely that the compound has this structure. The compound (CVIII) contains the grouping  and it might be expected that elimination of alcohol would take place readily to give  The compound, however, is quite stable and melts without decomposition.

This evidence, of course, is by no means conclusive, but, of the three possible structures, the most likely seems to be (CIX).



CIX

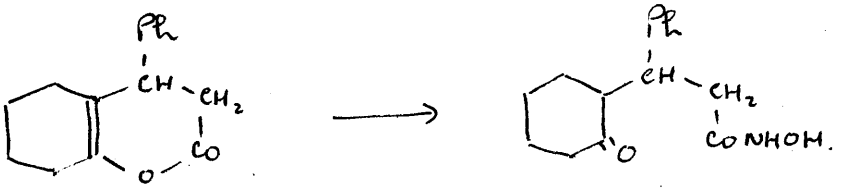
Hydroxamic acid derivatives of this type are fairly stable to alkali, so the compound was hydrolysed with aqueous alcoholic potassium hydroxide in order to prove the presence of the carbethoxy group. The product, crystallised from benzene, had m.p. 146°, was soluble in dilute sodium carbonate, gave a purple colouration with ferric chloride, and analysed correctly for (CXI).



CXI CXII

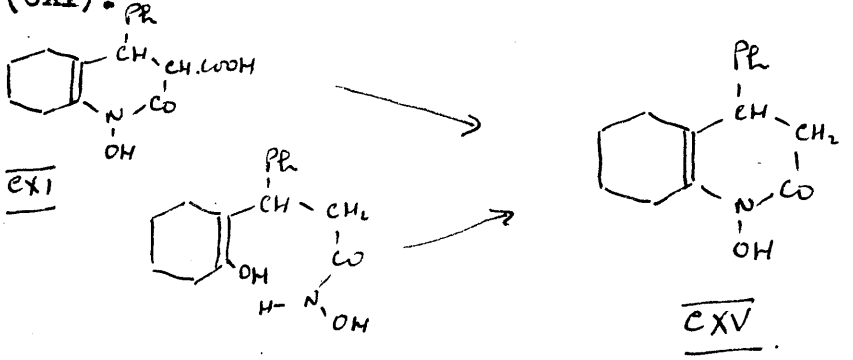
This carboxylic acid lost carbon dioxide at the melting point to give presumably (CXII), but this product was an oil, which was not obtained crystalline. It was insoluble in dilute sodium carbonate, soluble in sodium hydroxide, and gave the characteristic purple colouration with ferric chloride.

In an attempt to link up with this work, the lactone (CXIII) was treated with hydroxylamine.



CXIII CXIV

The product was a solid, but a satisfactory analysis specimen could not be prepared, since it seemed to decompose on recrystallisation. It was insoluble in sodium carbonate, soluble in sodium hydroxide and gave the characteristic deep red colouration with ferric chloride. On analogy with the carbethoxy derivative, the structure was probably (CXIV). At the melting point it decomposed to give an oil (CXV) which should be identical with that obtained from the decarboxylation of (CXI).

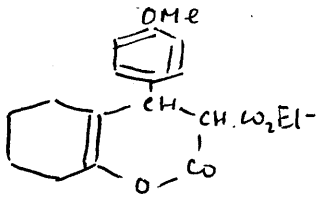


CXI CXV

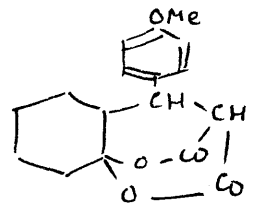
The identity of these two compounds was not proved as neither was obtained crystalline. A comparison of their solubilities in sodium carbonate and sodium hydroxide, and the colourations given with ferric chloride, however, showed that there was at least a possibility that the two compounds were one and the same.

For various reasons, no further work was done in this field, and the formulation given here for this rather unusual series of compounds is, consequently, only tentative.

It is convenient to mention here the evidence which showed that the product of the Michael reaction between mono-anisylidene cyclohexanone and diethyl malonate was the unsaturated lactone (CXVI). (See page 35.).



CXVI



CXVII

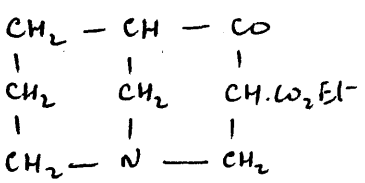
1) The action of concentrated sulphuric acid on the oily product gave the dilactone (CXVII) in a yield comparable to that obtained from the pure unsubstituted phenyl derivative.

2) Treatment of the oil with hydroxylamine hydrochloride and sodium acetate gave an oil which was not obtained crystalline, but which gave the same deep red colouration with ferric chloride as the "hydroxamic acids" just discussed in the phenyl series.

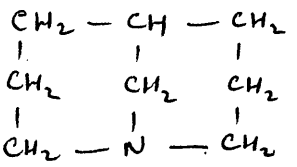
PART III.

Synthesis of 3-γ-hydroxylpropyl-3-phenyl-1-ethylpiperidine and 5-phenyl-1-azabicyclo-3:3:1-nonane.

The first synthesis of a compound containing the 1-azabicyclo-3:3:1-nonane ring system was reported by McKelvain and co-workers (36) who prepared ethyl isogranatanine carboxylate (CXVIII).



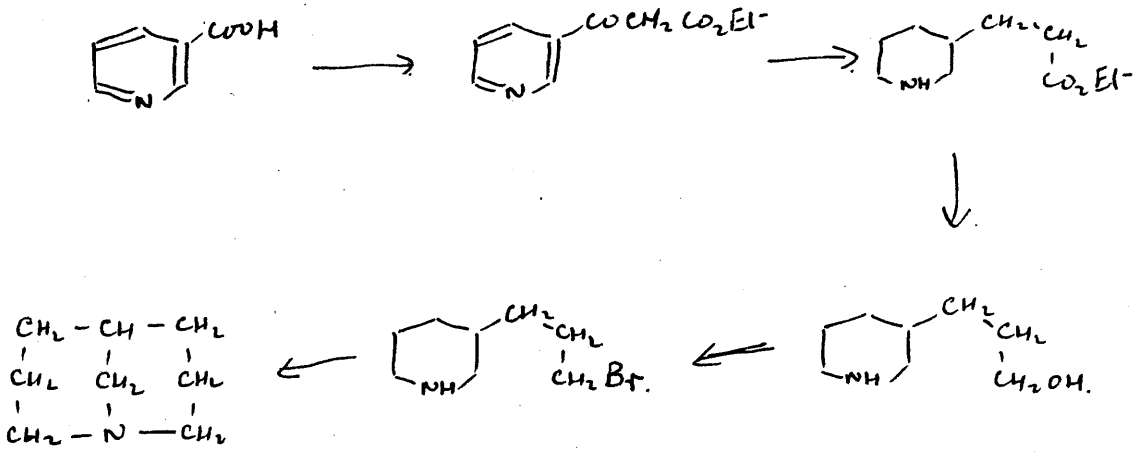
CXVIII



CXIX

Many unsucessful attempts were then made to synthesise the parent compound (CXIX) until finally its preparation was reported by Prelog (37).

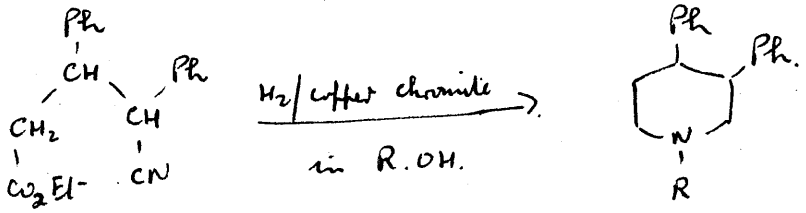
Their synthesis is outlined below:-



However, since this method is lengthy, gives very poor over-all yields, and cannot be adapted to the preparation of the 5-phenyl derivative, it was decided to investigate

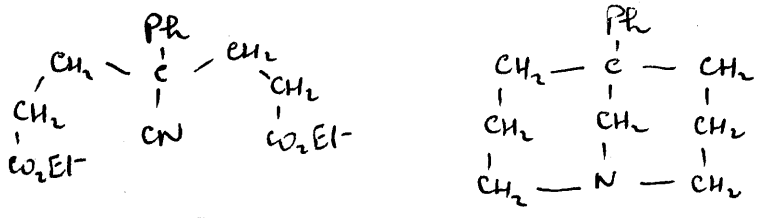
a new synthetic method for this type of compound.

Although Adkins (38) had stated that copper chromite catalyst was ineffective for the reduction of nitrile groups, Barr and Cook (23) found that reduction of γ-cyanoesters with hydrogen and copper chromite, using alcohols as solvents, gave N-alkylpiperidine derivatives in excellent yield, the N-alkyl group being furnished by the alcoholic solvent e.g. reduction of α/β -diphenyl-γ-carbethoxybutyronitrile (CXX) with hydrogen and copper chromite gave 1-alkyl-3:4-diphenyl--piperidines (CXXI).



CXX CXXI

As an extension of this reaction it was decided to investigate the reduction of a compound containing one nitrile group and two suitably placed ester groupings in the hope that a bicyclic type of compound would be obtained in one operation. The compound investigated was diethyl-γ-phenyl-γ-cyanopimelate (CXXII) which might possibly give the desired 5-phenyl-1-azabicyclo--3:3:1-nonane (CXXIII).



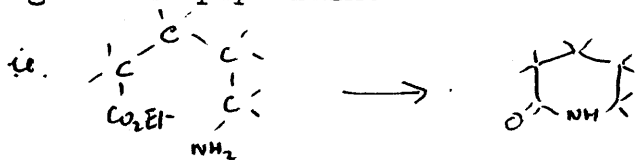
CXXII CXXIII

This would afford a very convenient synthesis, since this diester can be obtained in high yield in two operations from phenylacetonitrile and acrylonitrile.

Barr and Cook (loc.cit.) showed that the various stages in the reduction of γ-cyanoesters to piperidine derivatives were as follows:-

a) reduction of $-CN \rightarrow CH_2NH_2$.

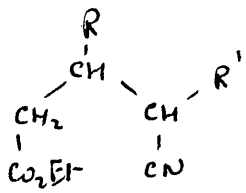
b) intramolecular condensation of the $-CO_2Et$ group with the $-NH_2$ group with elimination of ethyl alcohol to give the piperidone



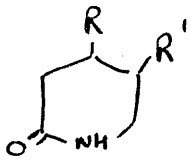
c) reduction of the piperidone to the piperidine derivative.

d) alkylation of the nitrogen atom by the solvent.

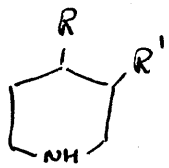
Koelsch and co-workers (39) also carried out some experiments on the reduction of γ-cyanoesters to piperidine derivatives, but their method involved two operations.



CXXIV



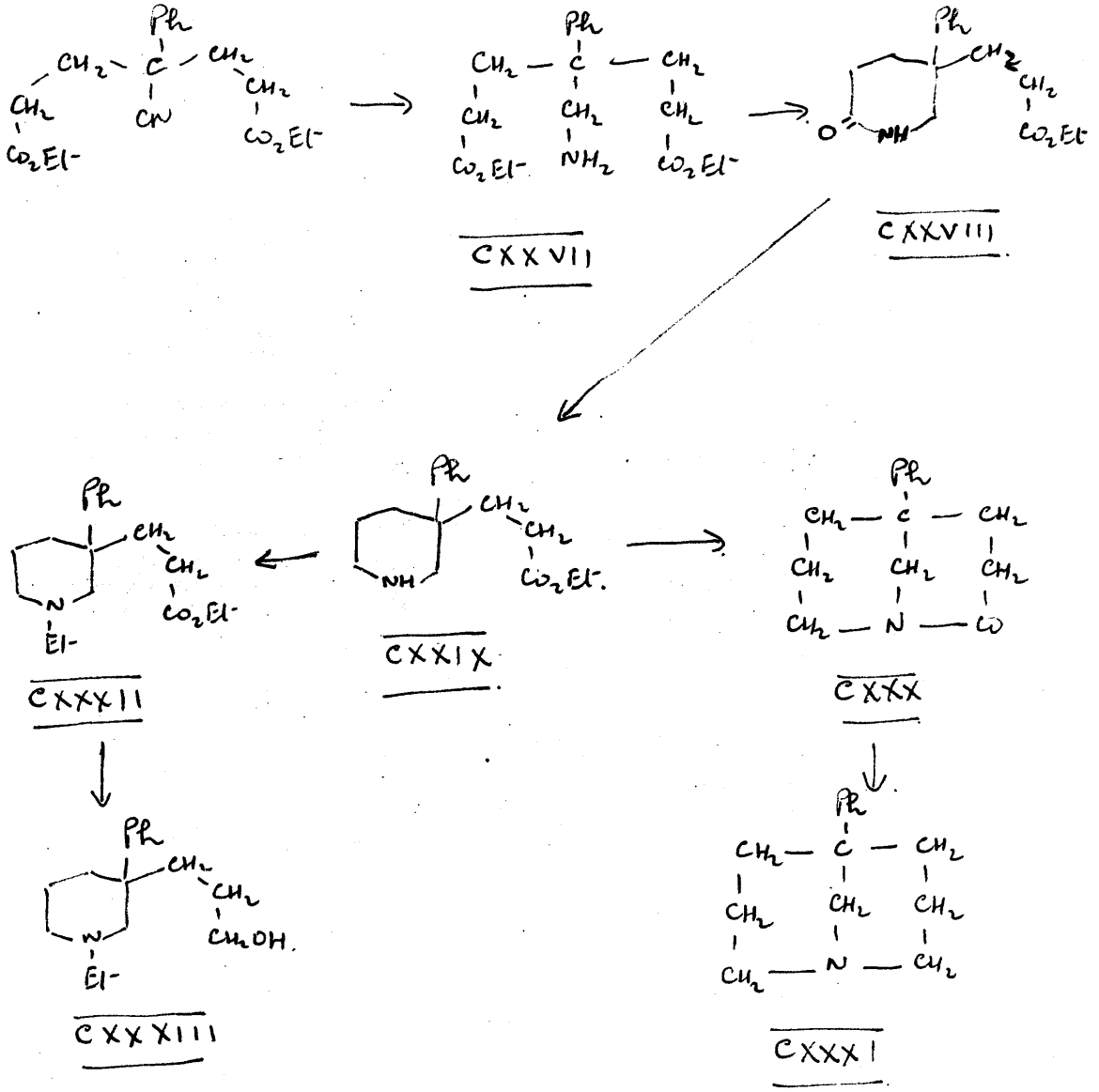
CXXV



CXXVI

Reduction of esters of type (CXXIV) with Raney Nickel catalyst gave the piperidones (CXXV) which were then reduced with sodium in n-butyl alcohol to the piperidine derivatives (CXXVI).

In the case of diethyl-γ-phenyl-γ-cyanopimelate (C ...) therefore, the course of the reduction may be represented as follows:-



CXXVII CXXVIII CXXIX CXXX CXXXI CXXXII CXXXIII

First, reduction would give the amine (CXXVII), followed by elimination of ethyl alcohol to the piperidone (CXXVIII), which would then be further reduced to the piperidine derivative (CXXIX). At this stage there are two possibilities:-

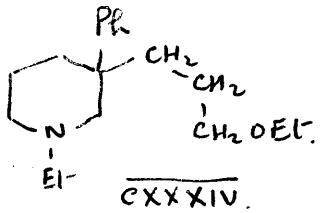
a) a further condensation of the remaining carbethoxy group with the secondary amine group might

take place to give (CXXX) which on further reduction would give 5-phenyl-1-azabicyclo-3:3:1-nonane (CXXXI).

or

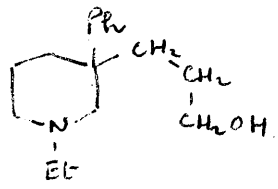
b) if the reduction were carried out in ethanol alkylation of the >NH group by the solvent might occur to give (CXXXII), thus rendering further ring-closure impossible. Further reduction of the carbethoxy group in this compound would then possibly give the alcohol (CXXXIII).

Barr and Cook (23) reported that reduction of the diester (CXXVII) with copper chromite in ethanol gave as the main product a basic oil analysing correctly for 3-γ-ethoxypropyl-3-phenyl-1-ethylpiperidine (CXXXIV).



CXXXIV

However this oil gave no solid derivatives, and it seemed desirable to investigate this reduction more closely. Accordingly a series of reductions of the diester with hydrogen and copper chromite in ethanol was carried out. The product, finally obtained in practically theoretical yield, was a basic oil which distilled at a constant temperature. It gave a crystalline oxalate and picrolonate, analyses of which indicated the base to be 3-γ-hydroxypropyl-3-phenyl--1-ethylpiperidine (CXXXIII).



CXXXIII

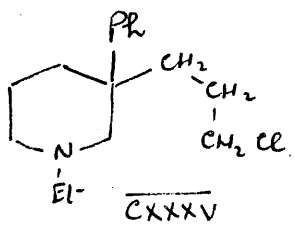
However, attempts to obtain further evidence for the structure of this compound did not meet with any great success. A sample of the base recovered from the pure crystalline oxalate was used in the following experiments.

The base gave both a picrate and a methiodide, but neither was obtained solid. Treatment of a solution of the base in ether with dry hydrochloric acid gas, gave the hydrochloride as an oil which solidified on standing. Analysis figures of this hydrochloride however were not in very good agreement with those of the alcohol. (See Experimental.)

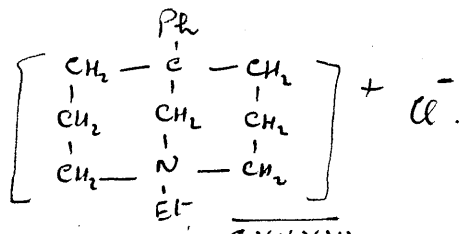
Some attempts were also made to prove the presence of the hydroxyl group. The base reacted with metallic sodium with evolution of hydrogen. When a mixture of 3:5-dinitrobenzoyl chloride and the base in benzene was refluxed, some of the hydrochloride of the base + a compound m.p. 221° were precipitated. The production of the hydrochloride showed that some reaction had taken place with evolution of hydrochloric acid, but a search of the mother liquors did not yield any solid material. The analysis figures of the compound m.p. 221° (Found: C, 41.94; H, 1.80; N, 14.38%) showed that it could not possibly be a product of reaction between the

base and 3:5-dinitrobenzoyl chloride, and no structure could be assigned to it.

A solution of the base in benzene was treated with thionyl chloride in an attempt to prepare the chloro derivative (CXXXV). It was hoped to rearrange this compound to the etho-chloride of 5-phenyl-1-aza--bicyclo-3:3:1-nonane (CXXXVI) which could then be compared with an authentic sample prepared from the bicyclic compound and ethyl chloride.



CXXXV



CXXXVI

The base reacted vigorously with thionyl chloride, giving a very dark coloured solution. However, the only products isolated were a very little unchanged base and an intractable black tar.

Thus, although the positive evidence available on this reduction compound indicated the alcohol structure (CXXXIII) as the most probable, this structure was not conclusively proved.

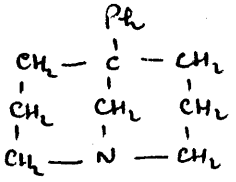
In one reduction, a very small amount of 5-phenyl-1-azabicyclo-3:3:1-nonane was isolated along with the alcohol, but in all other experiments only the alcohol was obtained in very good yield.

Thus it seems that on reduction in ethanol, alkylation of the intermediate piperidine derivative by the solvent takes place to the almost complete exclusion

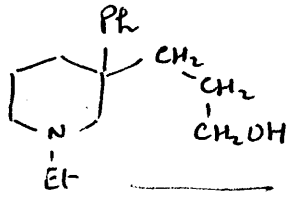
of the other possible reaction i.e. further ring-closure by the carbethoxy group.

A series of reductions of the diester in a non-alcoholic solvent, dioxan, were then carried out in the hope that alkylation of the intermediate piperidine derivative might be reduced, thus allowing the formation of the bicyclic compound. The possibility of alkylation of the intermediate cannot be entirely eliminated by reduction in dioxan, because some ethyl alcohol is produced in the first ring-closure to form the piperidone (CXXVIII). Indeed Barr and Cook (loc.cit.) showed in one case that an N-ethyl piperidine derivative could still be obtained, though in reduced yield, by the reduction of a γ-cyano ethyl ester in dioxan.

Two products were isolated from the reduction of the diester in dioxan, 5-phenyl-1-azabicyclo-3:3:1-monane (CXXXI) and the same alcohol (CXXXIII) obtained from the reduction in ethanol.



CXXXI



CXXXIII

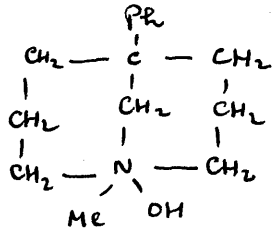
The relative amounts of these products appeared to vary with the concentration of the diester and also with the relative proportions of catalyst used in the reduction. Reduction of 10g. diester in 400c.c. dioxan with 5g. copper chromite gave (CXXXI) in 30-40% yield, and a very small amount of the alcohol (CXXXIII). In addition there was some very high boiling basic

material which decomposed on distillation and was not further investigated. When the concentration of the diester was 20g. or more in 400c.c. dioxan with 5g. catalyst, the yield of bicyclic compound was considerably less, and the relative proportion of alcohol was higher. In this case also there was an appreciable quantity of very high boiling basic material.
(Full details of these reductions are given in Experimental)
Thus it appeared that the ethanol produced during this reduction had in this case an appreciable effect on the subsequent course of the reaction.

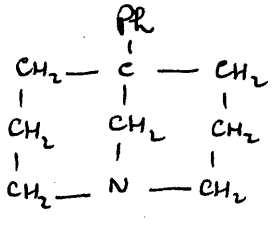
The identity of the basic alcohol obtained in dioxan and that from reduction in ethanol was proved by mixed melting points of their oxalates and picrolonates.

5-Phenyl-1-azabicyclo-3:3:1-nonane (CXXXI) was a crystalline solid m.p. 64°. It gave a crystalline picrate and methiodide, and all three compounds analysed correctly.

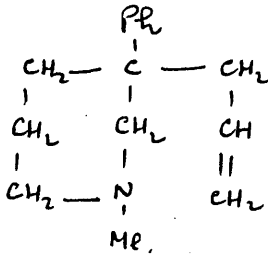
An attempt was made to prove conclusively the structure of this compound by the Hoffmann degradation method.



CXXXVI



CXXXI

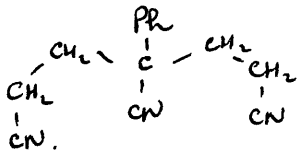


CXXXVII.

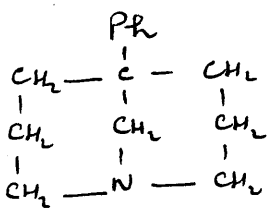
The quaternary hydroxide (CXXXVI) was prepared by shaking a solution of the methiodide in water with

silver oxide. On heating, however, this hydroxide split off methyl alcohol to give the original bicyclic compound (CXXXI) instead of undergoing the expected degradation to give (CXXXVII). This abnormal reaction is by no means unknown; many examples for various types of compounds have been reported in the literature (40), but no attempted degradations of the 1-azabicyclo--3:3:1-nonane ring system have been reported.

A series of reductions of γ-phenyl-γ-cyanopimelo--nitrile (CXXXVIII) with hydrogen and copper chromite in dioxan was also carried out.

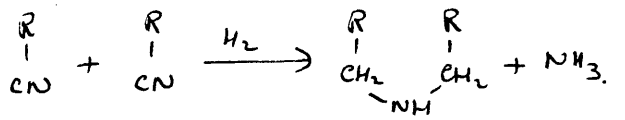


CXXXVIII



CXXXIX

It is well known that catalytic reduction of a nitrile usually gives rise to quite a high proportion of secondary amine e.g.



It seemed of interest to find whether this reaction could be applied to a compound containing two suitably placed nitrile groups in the molecule, with the production of a nitrogen ring system, and also whether it could be extended to a compound containing three suitable placed nitrile groups with the production of a tertiary amine. If this happened with the trinitrile (CXXXVIII) the product would of course be 5-phenyl-1-azabicyclo-3:3:1--nonane (CXXXIX).

No examples of this rather speculative type of reduction have been previously reported in the literature.

Dioxan was the obvious choice for solvent in this investigation. If an alcoholic solvent were used, the resulting alkylation of the intermediate primary and secondary amines formed would introduce a great many complications, and would not allow the reaction to go to completion in the desired way.

The results obtained in this investigation were so variable that it is difficult to give a coherent account of them. Reductions carried out under apparently identical conditions did not always give consistent results, but one fact that emerged was that the method of preparation of the copper chromite was important. The catalyst was prepared in two ways, and these two batches gave slightly different products.

In both cases the preparation of the crude mixed copper and barium ammonium chromates was as described in Organic Syntheses (41), but the chromate was decomposed in two ways.

Catalyst A. was prepared by heating the crude chromate in an electric furnace at 470°-500° for one hour.

Catalyst B was prepared by heating the chromate over a free bunsen flame until decomposition set in. The flame was then withdrawn and the heat evolved in the reaction was sufficient to cause complete decomposition. This was the original method used by Adkins (38).

[illegible].

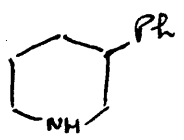
Reduction with catalyst A.

The concentration of the trinitrile in the dioxan seemed to have some effect here. Reduction of 10g. trinitrile in 400c.c. dioxan gave, in addition to a great deal of ammonia:-

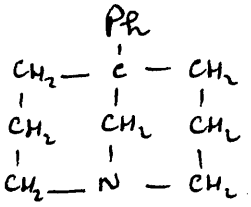
a) a small amount of 3-phenylpiperidine (CXL)

b) a 20% yield of 5-phenyl-1-azabicyclo-3:3:1-nonane (CXXXIX).

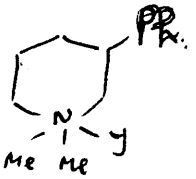
c) high boiling basic material which decomposed on distillation and was not further investigated.



CXL



CXXXIX



CXLI

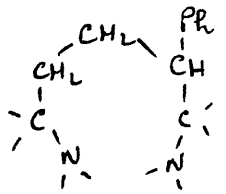
The constitution of the 3-phenylpiperidine formed in this reduction was proved by the analysis of its picrate, and comparison of the melting point of its benzoyl derivative with that reported in the literature. In addition, when methyl iodide was added to the base, a considerable amount of heat was evolved, and 1-methyl-3-phenylpiperidine methiodide (CXLI) was isolated. This compound has not been described in the literature, but analysis figures agreed with this view of its constitution . This is the normal behaviour of piperidine derivatives e.g. piperidine itself reacts violently with methyl iodide to give the methiodide of 1-methylpiperidine.

3-Phenylpiperidine was an oil with a strong basic

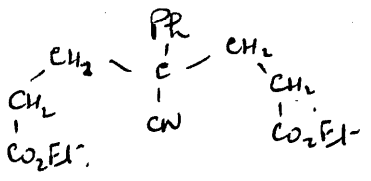
smell. When a thin film of the base was allowed to stand in contact with the atmosphere, the oil was gradually converted into a mass of crystals. This compound had m.p. 81° but it decomposed on recrystallisation and an analysis specimen was not obtained. However, this solid gave the picrate of 3-phenylpiperidine on treatment with picric acid in ethanol, and it also dissolved in dilute hydrochloric acid with effervescence. Thus it was very probably the carbonate of 3-phenylpiperidine, formed by absorption of water and carbon dioxide from the atmosphere.

3-Phenylpiperidine was obtained in varying yields in all the reductions of the trinitrile with both types of catalyst, and two possibilities for the mechanism of its formation suggest themselves.

1) Splitting off of one $-CH_2CH_2CN$ side chain by hydrogenolysis at some stage, giving a compound of type (CXLII) which on further reduction would give 3-phenylpiperidine and ammonia.



CXLII

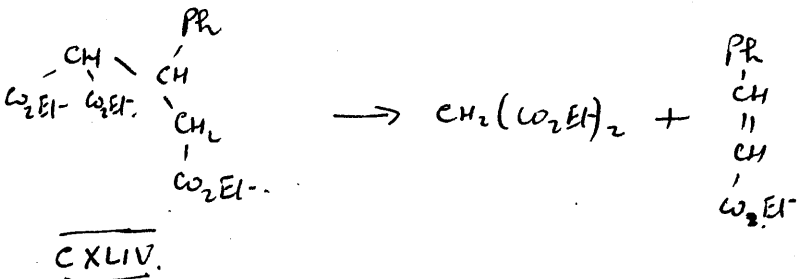


CXLIII

This mechanism seems unlikely, as the same type of reaction might be expected in the reduction of the very similar diester (CXLIII) and no evidence that this happens was obtained.

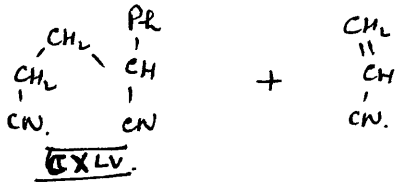
2) It has been shown that Michael additions are

reversible reactions e.g. Ingold (42) showed that boiling a solution of (CXLIV) in ethanol containing sodium ethoxide split the molecule to give diethyl malonate and ethyl cinnamate.



(CXLIV)

Since the trinitrile is formed by the Michael addition of phenylacetonitrile and acrylonitrile, it may be that something similar happens in the reduction to give (CXLV) and acrylonitrile.



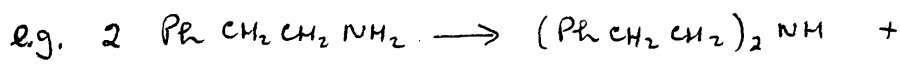
(CXLV)

(CXLV) could then be reduced to 3-phenylpiperidine. If this mechanism is correct, the presence of ammonia in the reaction mixture must play an important part. In the reduction of the diester, where again a similar effect might be expected, there is no ammonia present, and no decomposition seems to occur.

The identity of the 5-phenyl-1-azabicyclo-3:3:1--nonane formed in this reduction was proved by mixed melting points of the free base and picrate.

The mechanism of the formation of this compound is by no means clear. Wimans and Adkins (43) showed that certain primary amines, in the presence of the

usual reduction catalysts and at temperatures above 160°, gave off ammonia smoothly with the production of the corresponding secondary amine in good yield.



e.g. $2\ PhCH_2CH_2NH_2 \longrightarrow (PhCH_2CH_2)_2NH + NH_3$.

It may be that this type of reaction plays an important part in the formation of the bicyclic compound from the trinitrile. This mechanism is specially applicable in this case because of the high temperature used in the reduction, and the proximity of the reacting groups.

When the concentration of trinitrile was increased to 20g. or more in 400c.c. dioxan, reduction with catalyst A gave only 3-phenylpiperidine and high boiling basic oils which gave no solid derivatives and were not further investigated. It may be that this increase in concentration caused the formation of greater amounts of bi-molecular products.

Reduction with catalyst B.

Reduction of the trinitrile in dioxan with catalyst B gave the following products:-

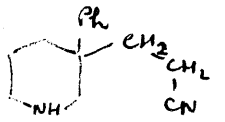
a) 3-phenylpiperidine.

b) a crystalline base m.p. 155°.

c) a high boiling basic oil from which a small amount of a crystalline solid m.p. 247° was obtained.

It has not been possible to assign a definite constitution to either b) or c).

Analyses of b) m.p. 155° and its crystalline picrate, taken in conjunction with a Rast determination of molecular weight, indicated the base to be $C_{14}H_{17-19}N_2$ A possible product is (CXLVI) but the compound was



$C_{14}H_{18}N_2$.

CXLVI

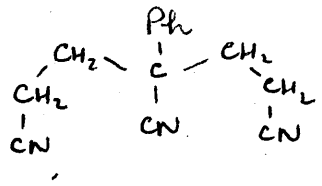
unchanged by boiling 70% sulphuric acid, so it is unlikely that a nitrile group was present. Lack of time prevented further investigation of this product.

Analysis of c) mp. 247° indicated the presence of oxygen in the molecule. This oxygen could only have come in some way from the dioxan solvent. However, this compound was only obtained in very small yield, and no further work was done on it.

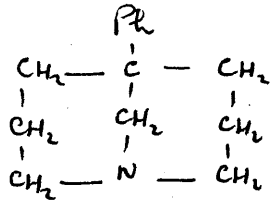
The trinitrile was also reduced with catalyst B in cyclohexane. The products in this case were 3-phenylpiperidine, and high boiling oils which were not identified.

It must be emphasised that the results recorded here represent more or less an average of the results actually obtained in sixteen reductions of the trinitrile. As mentioned before, reductions under apparently identical conditions with the same batch of catalyst did not always give consistent results, but, on the whole, the products obtained followed the general pattern recorded above.

Thus, although it has been shown that reduction of a compound of type (CXXXVIII) does give some bicyclic derivative (CXXXIX), this can not be recommended as a general method for the preparation of this type of compound.



CXXXVIII



CXXXIX

PART IV.

EXPERIMENTAL.

Preparation of ethyl cyclohexanone-2-carboxylate.

The method of Kotz, (44) with modification of King, (45) was used.

Attempted condensation of ethyl cyclohexanone-2-carboxylate. with ethyl cinnamate.

(1) Sodium ethoxide (from Na(2.3g.) and ethanol (25cc.) was added to a solution of the keto-ester (17g.) and ethyl cinnamate (17.5g.) in ethanol. No heat was evolved, so the mixture was refluxed for several hours, cooled in ice, acidified with ice-cold dilute sulphuric acid, and extracted with ether. Fractional distillation yielded only unchanged starting materials along with a small amount of cinnamic acid.

(2) Ethyl cinnamate (17.6g.) in benzene was added to a suspension of the sodium salt of the keto-ester (prepared from Na(2.3g.) and keto-ester (17g.) in benzene (150cc.) and the mixture refluxed for 3 hours. After cooling in ice, the mixture was shaken twice with ice-cold dilute sulphuric acid, twice with water, and the benzene layer separated and dried over anhydrous sodium sulphate. Again only unchanged starting materials were obtained on distillation.

In another experiment, with sodium ethoxide as condensing agent, cinnamoritrile (from dehydration of the

amide with phosphoric oxide) was used in place of ethyl cinnamate. Conditions were as under (1), but again only the starting materials were recovered.

Condensation of cyclohexanone with ethyl cinnamate

(1) A mixture of cyclohexanone (9.8g. 1 mol.) and ethyl cinnamate (17.6g. 1 mol.) was added all at once to a solution of potassium (4g. 1 atom.) in t-butyl alcohol (80cc.). Ether (100cc.) was then added and the mixture refluxed for 2½ hours. The resulting pale yellow solution was cooled, ether (100cc.) added, and shaken up three times with ice-water. The ether layer was separated off, dried over anhydrous sodium sulphate and on evaporation yielded a viscous oil, where solution in hot aqueous alcohol (50%) deposited silky colourless needles (18g.) on cooling.
The product, after several recrystallisations from aqueous alcohol (50%) had m.p. 215° C.

(2) In this experiment cyclohexanone (5g. 1 mol.), ethyl cinnamate (17.6g. 2 mols.) and potassium (4g. 2 atoms.) were used, the conditions being the same as before. The ether solution on evaporation gave 20g. of the same product m.p. 215° C.
(Found: C, 74.78; H, 7.97.
$C_{28}H_{34}O_5$ requires C, 74.66; H, 7.55%)

Attempts to prepare an oxime, semicarbazone, and dinitrophenylhydrazone yielded only unchanged starting

materials.

Hydrolysis of the condensation product.

The compound (m.p. 215°)(1g.) was refluxed with 40% aqueous alcoholic potassium hydroxide for 6 hours. Evaporation of the alcohol and acidification of the alkaline solution yielded a white solid, acidic in nature, which gave very fine white needles from aqueous alcohol (50%). m.p. 257°C.

(Found: C, 72.2; H, 7.38.

$C_{24}H_{26}O_5$ requires C, 73.1; H, 6.6%)

It did not form an oxime, semicarbazone, or dinitrophenylhydrazone.

The method finally adopted for the preparation of mono-benzylidene cyclohexanone was that of R. Poggi and V. Guastalla (46). The observation by these authors that the method of Vorlander and Kunze (47) gave very unsatisfactory results was also confirmed.

3-Carbethoxy-4-phenyl-3:4:5:6:7:8-hexahydrocoumarin.

Mono-benzylidene cyclohexanone (35.7g.) in benzene (100cc.) was added all at once to a suspension of the sodium salt of diethyl malonate in benzene (150cc.) (prepared from sodium (4.33g.) and diethyl malonate (30.1g.), and the mixture refluxed for two hours. The sodium salt of the ester gradually went into solution, and a homogeneous liquid was obtained. The cooled solution was shaken up with ice-cold dilute sulphuric acid, washed with water, dilute sodium carbonate

solution, and water again, and the benzene layer dried over anhydrous sodium sulphate. The benzene and a few drops of unchanged diethyl malonate were distilled off in vacuo, and a little ethanol added to the resulting oil. On cooling, 3-carbethoxy-4-phenyl-3:4:5:6:7:8-hexahydrocoumarin separated out in colourless needles (42g.). A further quantity (8g.) was obtained by distilling the alcohol residue, the product having b.p. 185°/1 m.m. The lactone gave colourless needles from cyclohexane m.p. 69°.

(Found: C, 72.09; H, 6.61; -OEt, 15.4.
$C_{18}H_{20}O_4$ requires C, 72.00; H, 6.66; -OEt, 15.0%)

/3-(2-ketocyclohexyl)-benzylmalonic acid.

The lactone (22g.) was refluxed with excess 40% aqueous alcoholic potassium hydroxide for 1½ hours. On acidification with concentrated hydrochloric acid, the malonic acid separated as an oil which solidified on standing in the refrigerator for several hours. The di-carboxylic acid gave colourless needles from aqueous ethanol (50%) and had m.p. 135°.

(Vorlander and Kunze, (loc.cit.) reported m.p. as 135 -136°.).

/3-(2-ketocyclohexyl)-/3-phenylpropionic acid and ethyl--/3-(2-ketocyclohexyl)-/3-phenylpropionate were prepared according to the method of Vorlander and Kunze, loc.cit.

Oxime of ethyl-β-(2-ketocyclohexyl)-β-phenylpropionate.
A solution of hydroxylamine hydrochloride (3.4g.) and anhydrous sodium acetate (7g.) in the minimum amount of water, was added to a solution of the keto-ester (7g.) in ethanol, and the mixture refluxed for 5 minutes. After standing for several hours, the solution deposited crystals of the oxime of ethyl-β-(2-ketocyclohexyl)-β-phenylpropionate (7g.). It formed colourless needles from ethanol, m.p. 126°.
(Found: C, 70.73; H, 7.92; N, 4.93.
$C_{17}H_{23}O_3N$ requires C, 70.59; H, 7.95; N, 4.84%.)

1-Ethyl-4-phenyldecahydroquinoline.

The oxime of ethyl-β-(2-ketocyclohexyl)-β-phenyl-propionate (13g.) in ethanol (300c.c.) was reduced with hydrogen and copper chromite (48) (6g.) at 200° and 165 atmospheres for 3 hours. The catalyst was filtered off, the alcohol removed in the water bath and the residual oil dissolved in ether. The ether solution was extracted three times with dilute hydrochloric acid, and washed with water. The hydrochloric acid extracts and washings were neutralised with dilute sodium hydroxide solution and the resulting oil extracted with ether; the ether extracts dried over anhydrous sodium sulphate, and the ether distilled off on the water bath. The resulting oil was distilled, giving 1-ethyl-4-phenyldecahydroquinoline (8g.) a colourless oil b.p. 134°/m.m.

(Found: C, 83.97; H, 10.45; N, 5.76.

$C_{17}H_{25}N$ requires C, 84.00; H, 10.3; N, 5.75%.)

In one experiment when the reduction was interrupted after 1 hour, the ether solution of the reduction product, after being extracted with dilute hydrochloric acid, was dried over anhydrous sodium sulphate, and the ether distilled off. The resulting oil deposited a few colourless silky needles of a compound mp. 162°, from a solution in aqueous ethanol.

(Found: N, 5.95.

$C_{15}H_{19}ON$ requires N, 6.14%.)

The picrate of 1-ethyl-4-phenyldecahydroquinoline was prepared in ethanol, and gave yellow needles from glacial acetic acid m.p. 204 -207°.

(Found: C, 58.58; H, 5.97.

$C_{23}H_{28}O_7N_4$ requires C, 58.4; H, 5.93%.)

The hydrochloride of the base was prepared by passing dry hydrochloric acid gas through a solution of the base in ether. The product was an oil which solidified after washing with dry ether and cooling in ice. It was too hygroscopic for melting point determination and analysis.

4-Phenylquinoline.

1-Ethyl-4-phenyldecahydroquinoline (0.55g.) was dehydrogenated by heating with palladium black (48) (0.08g.) at 300° for 6 hours in a stream of dry carbon dioxide. The resulting oil was distilled b.p. 140-5°/2m.m.

and distillate dissolved in ethanol and treated with a solution of picric acid in ethanol. The resulting solid (0.65g.) gave the picrate of 4-phenylquinoline as small yellow needles m.p. 226° on recrystallination from ethanol.

(Found: C, 58.32; H, 2.9; N, 12.63.
$C_{15}H_{11}N.C_6H_3O_7N_3$ requires C, 58.1; H, 3.2; N, 12.9%).
(Koenigs et alia (49) reported m.p. as 225°.)
The free base, recovered from the purified picrate with dilute sodium hydroxide solution, was an oil, which eventually solidified after standing for several weeks. It gave colourless needles from light petroleum m.p. 61°.
(Koenigs (loc.cit.) reported m.p. as 61°.)

The sulphate, prepared in ether with concentrated sulphuric acid, crystallised from water in small colourless prisms m.p. 194°.
(Koenigs (loc.cit.) reported m.p. as 195°.)

The methiodide was prepared by heating a mixture of methyl iodide and the base on the water bath. It gave long yellow needles from ethanol m.p. 222°.
(Koenigs (loc.cit.) reported m.p. as 222°.)

The chloroplatinate was prepared by addition of a few drops of H_2PtCl_6 solution to the base in dilute hydrochloric acid. It was a pale yellow solid, too insoluble for recrystallisation m.p. 244°.
(Koenigs (loc.cit.) reported m.p. 245°.)

Diethyl-β-(2-ketocyclohexyl)-benzylmalonate.

β-(2-ketocyclohexyl)-benzylmalonic acid (3g.) was

dissolved in absolute ethanol, and a stream of dry gaseous hydrogen chloride was passed in until the solution was saturated. After most of the alcohol had been distilled off on the water bath, dilute sodium carbonate solution was added, and the whole extracted with ether. The ether extract was shaken up with dilute sodium carbonate solution and washed with water. After drying over anhydrous potassium carbonate, the ether was removed on the water bath. The resulting oil on distillation gave diethyl-β-(2-ketocyclohexyl)--benzylmalonate (3g.) a colourless viscous oil b.p. 172°/1m.m. (air bath.)

(Found: C, 70.08; H, 7.42.

$C_{20}H_{26}O_5$ requires C, 70.00; H, 7.5%.)

(This compound was described by Vorlander and Kunze, loc.cit., as a crude oil which was not analysed.)

The dinitrophenylhydrazone, prepared in ethanol, gave orange yellow needles from that solvent m.p. 135°-136°.

(Found: C, 59.24; H, 5.68; N, 10.67.

$C_{26}H_{30}O_8N_4$ requires C, 59.3; H, 5.7; N, 10.6%.)

α-Carbethoxy-β-(2-ketocyclohexyl)-β-phenylpropionamide.

(a) Concentrated ammonia solution was added to a hot solution of 3-carbethoxy-4-phenyl-3:4:5:6:7:8-hexahydrocoumarin in ethanol until a faint turbidity appeared. Sufficient hot ethanol was then added to give a clear solution, and the mixture placed in the refrigerator. After standing 2 days, the solution deposited crystals

of α-carbethoxy-β-(2-ketocyclohexyl)-β-phenylpropionamide, wh -carbethoxy-β-(less needles from ethanol, m.p. 183° (decomp.), after several recrystallisations.

(Found: C, 68.09; H, 7.24; N, 4.44.

$C_{18}H_{23}O_4N$ requires C, 68.1; H, 7.25; N, 4.4%.)

(b) A solution of diethyl-β-(2-ketocyclohexyl)-benzyl-malonate in ethanol, treated with concentrated ammonia solution under the same conditions as the lactone above, gave on standing the same mono-amide m.p. 183° (decomp.). A mixed melting point with a specimen of the mono-amide prepared from the lactone gave no depression.

Action of dinitrophenylhydrazine solution on 3-carbethoxy--4-phenyl-3:4:5:6:7:8-hexahydrocoumarin.

A solution of the lactone in ethanol was treated with excess dinitrophenylhydrazine solution, and allowed to stand for several hours. The supernatant liquid was decanted from the heavy red oil formed, and this oil was dissolved in ethyl alcohol. This solution, on cooling in ice, deposited a few orange yellow crystals of the dinitrophenylhydrazone of diethyl-β-(2-keto-cyclohexyl)-benzylmalonate. After several recrystallisations, the mp. was 135°, undepressed by admixture with an authentic specimen.

3-Carbethoxy-4-p-methoxyphenyl-3:4:5:6:7:8-hexahydro-coumarin.

Mono-anisylidene cyclohexanone (46) (21.6g.) in benzene (100c.c.) was added all at once to a suspension

of the sodium salt of diethyl malonate in benzene (100c.c.)(prepared from sodium (2.3g.) and diethyl malonate (16g.) and the mixture refluxed for 2 hours. As in the condensation using mono-benzylidene cyclohexanone, the sodium salt of the ester gradually went into solution, and a homogeneous liquid was obtained. The cooled solution was shaken up with ice-cold dilute sulphuric acid, washed with water, dilute sodium carbonate, and water again, and the benzene layer dried over anhydrous sodium sulphate. Removal of the benzene in vacuo gave 3-carbethoxy-4-p-methoxyphenyl-3:4:5:6:7:8--hexahydrocoumarin (34g.) as a heavy viscous oil. This oil was used in the next stage of the anythesis.

This oil (2g.) was distilled in vacuo, with a considerable amount of decomposition. The viscous brown distillate (b.p. 235°/7m.m.) was redistilled, giving a colourless oil (b.p. 190°/1m.m.). A solution of this oil in ethanol deposited crystals of 4-p-methoxyphenyl-3:4:5:6:7:8-hexanhydrocoumarin (0.4g.) on cooling in ice. This compound gave long colourless needles from ethanol m.p. 113°. A mixed m.p. with a specimen of this lactone prepared in a different manner showed no depression.

3-(2-Ketocyclohexyl)-p-methoxybenzylmalonic acid.

3-Carbethoxy-4-p-methoxyphenyl-3:4:5:6:7:8-hexahydrocoumarin (24g.) was refluxed with excess 40% aqueous alcoholic potassium hydroxide for 1½ hours. After

most of the alcohol had been removed on the water bath, the alkaline solution was acidified with dilute hydrochloric acid. The oily acid obtained soon solidified on standing and was recrystallised from glacial acetic acid, giving β-(2-ketocyclohexyl)-p-methoxybenzylmalonic acid (15g.). The acid crystallised from glacial acetic acid in fine colourless needles with one molecule of acetic acid of crystallisation m.p. 130°.

(Found: C, 60.00; H, 6.68.

$C_{17}H_{20}O_6+C_2H_4O_2$ requires C, 60.00; H, 6.32%.).

β-(2-Ketocyclohexyl)-β-p-methoxyphenylpropionic acid. β-(2-Ketocyclohexyl)-p-methoxybenzylmalonic acid (35g.) was heated on an oil bath at 150° till all evolution of carbon dioxide had ceased. The viscous oil obtained was dissolved in ethyl acetate, and the solution on cooling in ice deposited crystals of β-(2-ketocyclohexyl)-β-p-methoxyphenylpropionic acid (25g.). A further 3g. of the acid was obtained by concentrating the mother liquors. The acid crystallised from ethyl acetate in small colourless needles m.p. 125°-6°.

(Found: C, 69.73; H, 7.18.

$C_{16}H_{20}O_4$ requires C, 69.56; H, 7.24%.).

Ethyl-β-(2-ketocyclohexyl)-β-p-methoxyphenylpropionate. Concentrated sulphuric acid (12g.) was added to a solution of β-(2-ketocyclohexyl)-β-p-methoxyphenylpropionic acid (30g.) in absolute ethanol (150c.c.) and the mixture

refluxed for 2½ hours. After most of the ethanol had been removed, dilute sodium carbonate solution was added, and the whole extracted with ether. The ether extract was washed with dilute sodium carbonate and with water, and finally dried over anhydrous sodium sulphate. Removal of the ether gave ethyl-β-(2-keto-cyclohexyl)-β-p-methoxyphenylpropionate (27g.) as a viscous oil. This oil was used in the next stage of the synthesis without further purification.

The keto-ester (0.5g.) was distilled under high vacuum. The product, a colourless oil (0.25g.) b.p. 195°/1 m.m. solidified on treatment with ethyl alcohol. It gave colourless needles from ethanol m.p. 113°, and was shown to be 4-p-methoxyphenyl-3:4:5:6:7:8-hexahydrocoumarin. A mixed m.p. with an authentic specimen gave no depression.

Oxime of ethyl-β-(2-ketocyclohexyl)-β-p-methoxyphenyl-propionate.

Hydroxylamine hydrochloride (9g.) and anhydrous sodium acetate (18g.) dissolved in the minimum volume of water, was added to a solution of the keto-ester (23g.) in ethanol, and the mixture refluxed for 5 minutes. After standing for several hours, the solution deposited crystals of the oxime (22g). It was recrystallised from ethanol giving colourless needles m.p. 146°.

(Found: C, 67.70; H, 7.78; N, 4.54.

$C_{18}H_{25}O_4N$ requires C, 67.71; H, 7.83; N, 4.4%.)

1-Ethyl-4-p-methoxyphenyldecahydroquinoline.

The oxime (10g.) in ethanol (300c.c.) was reduced with hydrogen and copper chromite (5g.) at 200° and 165 atmospheres for 3 hours. The catalyst was filtered off, the ethanol removed on the water bath and the resulting oil treated with dilute hydrochloric acid, in which it all dissolved. The acid solution was neutralised with dilute sodium hydroxide, and the oil formed extracted with ether. The oil obtained by removal of the ether was distilled, giving 1-ethyl-4-p-methoxyphenyldecahydroquinoline (7g.) a viscous oil b.p. 175°/0.3m.m. This oil solidified on standing, and the base crystallised from ethyl acetate in small colourless needles m.p. 89°.

(Found: C, 79.04; H, 9.84; N, 5.16.

$C_{18}H_{27}ON$ requires C, 79.1; H, 9.9; N, 5.1%.)

The picrate was prepared in ethanol and crystallised from glacial acetic acid in stout yellow needles m.p. 182°-184°.

(Found: C, 57.36; H, 6.01.

$C_{18}H_{27}ON.C_6H_3O_7N_3$ requires C, 57.3; H, 6.00%.)

The hydrochloride was prepared by passing dry hydrogen chloride gas through a solution of the base in ether. It gave colourless needles from ethanol/ether m.p. 248°-250°

(Found: C, 69.90; H, 8.82.

$C_{18}H_{28}ONCl$ requires C, 70.00; H, 9.0%.)

1-Ethyl-4-p-hydroxyphenyldecahydroquinoline hydrobromide.

A solution of 48% hydrobromic acid (3c.c.) was added to

a solution of the methoxy base (1.3g.) in glacial acetic acid (1.75 c.c.) and the mixture refluxed for 9 hours. On cooling in ice the solution deposited crystals of 1-ethyl-4-p-hydroxyphenyldecahydroquinoline hydrobromide (1.27g.). The hydrobromide recrystallised from glacial acetic acid in small colourless needles m.p. 227°-228°.

(Found: C, 59.95; H, 7.48.

$C_{17}H_{26}ONBr$ requires C, 60.00; H, 7.64%.)

Dilactone derived from β-(2-ketocyclohexyl)-benzylmalonic acid.

(In this preparation it was found that the best yields were obtained when small quantities were used, the reaction being more easily controlled.)

Concentrated sulphuric acid (3c.c.) was added to solid 3-carbethoxy-4-phenyl-3:4:5:6:7:8-hexahydrocoumarin (2g.) contained in a test-tube. The solid dissolved, with the production of a depp red solution and evolution of a considerable amount of heat. The mixture was stirred with a glass rod and heated on a steam bath for 1 minute, then immediately cooled in ice. The cooled solution was poured into ice-water and the viscous yellow oil produced washed several times with cold water. This oil, on rubbing with a little ethanol soon solidified to give the dilactone (1.6g. 90%).

The dilactone crystallised readily from ethanol, giving colourless needles m.p. 169°.

(Found: C, 70.62; H, 5.98.

$C_{16}H_{16}O_4$ requires C, 70.58; H, 5.88%.).

The dilactone (0.2g.) was refluxed with excess 10% aqueous sodium hydroxide until it all went into solution. Acidification of the cooled alkaline solution with dilute hydrochloric acid gave β-(2-ketocyclohexyl)--benzylmalonic acid (0.2g.) m.p. 135°, undepressed by admixture with an authentic specimen.

4-Phenyl-3:4:5:6:7:8-hexahydrocoumarin.

The dilactone (2g.) was placed in a small Claisen distilling flask and heated gently over a free flame until all evolution of gas had ceased. The viscous oil obtained was distilled directly from the flask and gave 4-phenyl-3:4:5:6:7:8-hexahydrocoumarin (1.5g. 90%) a colourless viscous oil b.p. 170°/1m.m. (air bath.).

(Found: C, 78.56; H, 7.07.

$C_{15}H_{16}O_2$ requires C, 78.8; H, 7.00%.).

The lactone (0.1g.) was refluxed with excess 10% aqueous sodium hydroxide until it had all gone into solution. Acidification of the alkaline solution with dilute hydrochloric acid gave β-(2-ketocyclohexyl)-β-phenylpropionic acid (0.1g.) m.p. and mixed m.p. 125°.

Action of dinitrophenylhydrazine on the dilactone.

A solution of dinitrophenylhydrazine (prepared with concentrated sulphuric acid and ethanol) was added to a solution of the dilactone in hot ethanol. After

standing some time, the solution deposited a heavy red oil. This oil eventually yielded on recrystallisation from ethanol a few orange-yellow needles of a compound m.p. 169°-171°.
(Found: C, 56.19; H, 5.14; N, 10.57%.).

Reduction of the dilactone.

The dilactone (0.4g.) in ethanol was shaken with Adam's PtO_2 catalyst (0.1g.) in an atmosphere of hydrogen, until no more hydrogen was absorbed. The catalyst was filtered off, and the alcohol solution on evaporation gave the hexahydro derivative (0.4g.). This product crystallised from ethanol in colourless branching needles m.p. 137°.
(Found: C, 68.92; H, 7.75.
$C_{16}H_{22}O_4$ requires C, 69.05; H, 7.9%.).

This reduction product was refluxed with a little dilute sodium hydroxide solution until it had all gone into solution. On cooling, this solution deposited crystals of the hexahydrate of the di-sodium salt of β-(2-ketocyclohexyl)-hexahydrobenzyl malonic acid. This product gave small colourless needles from distilled water m.p. 280°-281°.
(Found: C, 42.82; H, 7.77.
$C_{16}H_{22}O_5Na_2.6H_2O$ requires C, 42.9; H, 7.6%.).

A solution of this sodium salt in water was acidified with dilute hydrochloric acid. The oil

originally formed soon solidified on standing. This solid had m.p. 110-125° with evolution of a gas. On recrystallisation from ethanol the m.p. rose to 137°. A mixed m.p. with the original reduction product showed no depression.

Dilactone derived from β-(2-ketocyclohexyl)-p-methoxybenzylmalonic acid.

(As in the case of the phenyl compound, it was found advisable to use small quantities in this preparation.) Concentrated sulphuric acid (3c.c.) was added to the oily 3-carbethoxy-4-p-methoxyphenyl-3:4:5:6:7:8-hexahydrocoumarin (2g.). The oil dissolved, with the evolution of some heat, giving a deep red solution. The mixture was heated on the steam bath for 1 minute, then cooled in ice. The solution was poured into ice-water, and the viscous reddish-yellow oil obtained washed several times with water. This oil was dissolved in ethanol, and after boiling with 2 lots of animal charcoal to remove the red colour, deposited colourless crystals of the dilactone (1.1g.) on cooling in ice. A further quantity of the dilactone (0.2g.) was obtained by concentrating the mother liquors. The dilactone gave colourless needles from ethanol m.p. 154°-155°.

(Found: C, 67.83; H, 6.01.

$C_{17}H_{18}O_5$ required C, 67.55; H, 5.95%.).

The dilactone (0.2g.) was refluxed with excess 10% aqueous sodium hydroxide till it was all in solution.

Addition of dilute hydrochloric acid gave β-(2-keto-cyclohexyl)-p-methoxybenzylmalonic acid. It gave colourless needles from glacial acetic acid m.p. and mixed m.p. 130°.

4-p-Methoxyphenyl-3:4:5:6:7:8-hexahydrocoumarin.

The dilactone (0.5g.) was heated at 200° on an oil bath until all evolution of gas had ceased. The oil obtained was dissolved in a little ethanol, and this solution, on cooling in ice, deposited crystals of 4-p-methoxyphenyl-3:4:5:6:7:8-hexahydrocoumarin (0.30g.). The lactone crystallised in long colourless needles from ethanol, m.p. 113°.

(Found: C, 74.14; H, 6.89.

$C_{16}H_{18}O_3$ requires C, 74.4; H, 6.97%.).

The lactone (0.2g.) was refluxed with excess 10% aqueous sodium hydroxide till it had all dissolved. Acidification of the alkaline solution gave β-(2-keto-cyclohexyl)-β-p-methoxyphenylpropionic acid m.p. and mixed m.p. 126°.

Action of hydroxylamine on 3-carbethoxy-4-phenyl--3:4:5:6:7:8-hexahydrocoumarin.

The lactone (3.3g.) in ethanol (15c.c.) was treated with a solution of hydroxylamine hydrochloride (1g.) and anhydrous sodium acetate (2g.) in the minimum volume of water, and the mixture allowed to stand overnight. 15c.c. of water were then added and the solution placed in the refrigerator for several hours. The oil which

first separated soon solidified, and the amorphous solid (3g.) was filtered off. It was dried by pressing on porous plate and in a vacuum desiccator over potassium hydroxide. Recrystallisation from benzene /light petroleum (60^{o}-80^{o}) gave small colourless needles m.p. 138^{o}. (The benzene and light petroleum were dried over sodium.)
(Found: C, 65.08; H, 6.73.
$C_{18}H_{23}O_5N$ requires C, 64.86; H, 6.9%.).

This product (1g.) was heated on an oil bath at 145^{o} for 5 minutes. The viscous oil obtained was dissolved in a little ethanol, and this solution on cooling in ice deposited crystals of a compound (0.75g.). This product crystallised from ethanol in colourless needles m.p. 154^{o}.
(Found: C, 68.67; H, 6.32; N, 4.4.
$C_{18}H_{21}O_4N$ requires C, 68.57; H, 6.65; N, 4.4%.).

A solution of this product in ethanol was treated with excess dinitrophenylhydrazine solution. After standing for a week, a few orange yellow crystals were deposited. These were filtered off, and after several recrystallisations from ethanol, had m.p. 135^{o}, undepressed by admixture with an authentic specimen of the dinitrophenylhydrazone of diethyl-/3-(2-ketocyclo-hexyl)-benzylmalonate.

The compound (m.p. 154^{o}. 1.5g.) was dissolved in excess 40% aqueous potassium hydroxide, and the solution

heated at 80° for ½ hour. The cooled solution was diluted with a little water, acidified with dilute hydrochloric acid, and extracted with ether. The extracts were dried over anhydrous sodium sulphate, and the ether distilled off. A solution of the resulting oil in dry benzene deposited crystals of a compound (0.9g.) on cooling and scratching. The product crystallised from benzene in very small needles m.p. 146°-147°.

(Found: C, 66.76; H, 5.81; N, 4.77.

$C_{16}H_{17}O_4N$ requires C, 66.89; H, 5.9; N, 4.87%.).

This product lost carbon dioxide at the melting point to give a viscous oil which did not crystallise from any of the common solvents.

Action of hydroxylamine on 4-phenyl-3:4:5:6:7:8--hexahydrocoumarin.

The lactone (0.57g.) in ethanol was treated with a solution of hydroxylamine hydrochloride (0.25g.) and sodium acetate (0.4-0.5g.) in water, and allowed to stand overnight. Water was added, and after the oil obtained had settled, the supernatant liquid was decanted. The oil was washed with water, dried in vacuo over potassium hydroxide, and on treatment with a little dry benzene gave a solid m.p. 140°-158°.(0.3g.). This solid seemed to decompose on attempted crystallisation from benzene.

Reduction of diethyl-γ-phenyl-γ-cyanopimelate.

(a) In Ethanol.

A solution of the ester (23) (20g.) in absolute ethanol (400c.c.) was agitated with hydrogen and copper chromite (41) (10g.) for 3 hours at 210° and 175 atmospheres. The catalyst was filtered off, the alcohol removed on the water bath, and the remaining oil treated with dilute hydrochloric acid, in which it all dissolved. This acid solution was extracted once with ether, then neutralised with dilute sodium hydroxide. The resulting oil was extracted with ether, the ether extracts dried over anhydrous sodium sulphate, and the ether distilled off on the water bath. Distillation of the resulting oil gave 3-γ-hydroxypropyl-3-phenyl-1-ethylpiperidine (15.5g.) as a colourless viscous oil b.p. 140°/0.5m.m.

The oxalate was prepared by the addition of a solution of anhydrous oxalic acid in ether to the base in ether. The solid oxalate formed was filtered off, and crystallised from ethanol in small colourless needles m.p. 198°.

(Found: C, 64.0; H, 7.87; N, 4.49.
$C_{16}H_{25}ON.(COOH)_2$ requires C, 64.1; H, 8.0; N, 4.15%.).

The picrolonate was prepared in alcohol, and gave small yellow needles from the same solvent m.p. 146°-148°.

(Found: C, 61.04; H, 6.0; N, 13.7.
$C_{16}H_{25}ON.C_{10}H_8O_5N_4$ requires C, 61.05; H, 6.4; N, 13.7%.).

The hydrochloride was prepared by passing a stream of dry hydrochloric acid gas through a solution of the base in ether. The oil obtained was washed several times with ether and solidified after standing for some time in the refrigerator. Crystallisation from ethyl acetate gave colourless needle clusters m.p. 166-169°. (Found: C, 66.9; H, 8.5; N, 4.62. $C_{16}H_{26}ONCl$ requires C, 67.7; H, 9.1; N, 4.9%.).

A mixture of 3:5-dinitrobenzoyl chloride and the base in benzene was refluxed for 5 minutes. The solid which was precipitated was filtered off. Evaporation of the benzene filtrate did not yield any solid material. The solid melted over a range 130-160°. It was separated into two fractions by shaking with water:-

a) Water insoluble. This compound was very insoluble in ethanol, very soluble in acetone, and crystallised from benzene in off-white needles m.p. 221°. (Found: C, 41.94; H, 1.8; N, 14.38%.).

b) Water soluble. This solution on treatment with dilute sodium hydroxide gave a basic oil which gave an oxalate m.p. 198°. A mixed melting point with the oxalate of the basic alcohol gave no depression. Thus in this reaction, it seemed that the hydrochloride of the alcohol was one of the products.

Excess thionyl chloride was added to the base in benzene and the solution refluxed for one hour. The

colour of the solution darkened considerably, and there was an appreciable evolution of sulphur dioxide. The benzene and excess thionyl chloride were evaporated off under vacuum, leaving a dark brown gum. This gum was shaken up with water; a very little dissolved but the majority was left as a brown gum from which no pure compound would be isolated. The aqueous extract was treated with dilute sodium carbonate solution, and the resulting basic oil extracted with ether. The ether extract, after drying and evaporation of the ether, yielded a very small amount of oil, which gave a crystalline oxalate, m.p. and mixed m.p. 198°.

Reduction of diethyl-γ-phenyl-γ-cyanopimelate.

(b) In Dioxan.

A series of experiments under various conditions was carried out, but experimental details are only given for two representative reductions. The dioxan was purified by refluxing with sodium for 10 hours followed by distillation from sodium.

(1) The diester (10g.) in dioxan (400c.c.) was reduced with hydrogen and copper chromite (5g.) for 3 hours at 210° and 175 atmospheres. The product, which was all basic, was extracted as in the reduction in ethanol. On fractional distillation it gave:-

a) 5-phenyl-1-azabicyclo-3:3:1-nonane (2.5g.) as a colourless oil b.p. 130-135°/0.4m.m. which solidified on standing. The base gave colourless needles from

light petroleum m.p. 64°.

(Found: C, 83.4; H, 9.4; N, 7.0.

$C_{14}H_{19}N$ requires C, 83.58; H, 9.45; N, 6.96%.).

The picrate prepared in ethanol, gave yellow needles from this solvent m.p. 178°.

(Found: C, 56.09; H, 4.7; N, 13.03.

$C_{14}H_{19}N.C_6H_3O_7N_3$ requires C, 55.81; H, 5.1; N, 13.0%.).

The methiodide was prepared by the addition of methyl iodide to the base; some heat was evolved, and the reaction was completed by heating on the water bath for 5 minutes. The resulting oil set to a glass-like solid on cooling. This product gave colourless needles from ethanol m.p. 236°.

(Found: C, 52.8; H, 6.27; N, 4.07.

$C_{15}H_{22}NI$ requires C, 52.5; H, 6.41; N, 4.08%.).

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b) A few drops of a colourless oil b.p. 145°/0.4m.m. This oil gave an oxalate m.p. 198°. A mixed m.p. with the oxalate of the product of reduction in ethanol showed no depression.

c) A dark brown residue which distilled with decomposition at 240-280°/0.4m.m. This material was not further investigated.

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(2) The diester (20g.) in dioxan (400c.c.) was reduced with hydrogen and copper chromite (5g.) for 4 hours at 215° and 175 atmospheres. The product, all basic, was extracted as before, and gave on

fractional distillation:-

(a) 5-phenyl-1-azabicyclo-3:3:1-nonane (2g.) b.p. 135°/0.5m.m. identified by mixed m.p. of picrate and methiodide.

(b) colourless oil (7g.) b.p. 145°/0.5m.m. It gave an oxalate m.p. 198° and picrolonate m.p. 146°-148°. Mixed m.p.s with these derivatives of the reduction product in ethanol showed no depression.

(c) an appreciable residue which decomposed on distillation as before.

Attempted Hoffmann degradation of 5-phenyl-1-azabicyclo--3:3:1-nonane.

A solution of the methiodide (0.4g.) in water was shaken with freshly precipitated silver oxide (2g.) for 4 hours in a tightly stoppered flask. The solid was filtered off, and a sample of the clear filtrate, which was strongly alkaline, was tested with silver nitrate for the presence of iodide ions. This test was negative, and consequently the reaction had gone to completion. The aqueous solution was evaporated by heating under vacuum, and the resulting oil heated on an oil bath at 200° until all signs of decomposition had ceased. The product, which was completely soluble in ether, gave 5-phenyl-1-azabicyclo-3:3:1-nonane (0.2g). on distillation. This product was identified by mixed melting points of its picrate and methiodide with

authentic specimens. No trace of any other product was found in this reaction.

Reduction of γ-phenyl-γ-cyanopimelonitrile.

As mentioned in PART III, some very variable results were obtained in this investigation, and it is only proposed to give experimental details for some typical reductions.

1) The trinitrile (50) (10g.) in dioxan (400c.c.) was agitated with hydrogen and copper chromite catalyst A (5g.) at 220°-230° and 175 atmospheres until no further hydrogen was taken up (about 3 hours.). The resulting solution had a very strong smell of ammonia. The catalyst was filtered off, and distillation of the dioxan gave a brown oil, which was entirely basic. Fractional distillation of this oil gave:-

a) 3-phenylpiperidine (1g.) as a colourless mobile oil b.p. 85°-90°/0.2m.m.

b) 5-phenyl-1-azabicyclo-3:3:1-nonane (1.5g.) identified by m.p. and mixed m.p. of the free base and picrate.

c) a considerable amount of dark brown residue which did not distil below 250°/0.2m.m. and was not further investigated.

The picrate of 3-phenylpiperidine prepared in ethanol gave stout yellow needles from glacial acetic acid m.p. 209°-210°.

(Found: C, 52.13; H, 4.57; N, 14.2.

$C_{11}H_{15}N.C_6H_3O_7N_3$ requires C, 52.3; H, 4.6; N, 14.3%.).
The benzoyl derivative was prepared by shaking a mixture of the base and excess benzoyl chloride with aqueous sodium, hydroxide until the smell of benzoyl chloride had disappeared. The resulting oil was dissolved in ether, and the ether solution extracted with dilute hydrochloric acid, washed with water, and dried over anhydrous sodium sulphate. The ether solution was evaporated, and the resulting oil gave small colourless prisms of 1-benzoyl-3-phenylpiperidine from ether/ligroin or ethyl acetate m.p. 88°.
(Koelsch (51) reported m.p. as 89°).

The addition of excess methyl iodide to the oily 3-phenylpiperidine resulted in the evolution of a considerable amount of heat. After standing some time, the excess methyl iodide was distilled off from the mixture, and the viscous oil obtained dissolved in ethanol. This solution, on cooling and scratching deposited crystals of 1-methyl-3-phenylpiperidine methiodide. This compound gave colourless needles from ethanol m.p. 231°.
(Found: C, 49.5; H, 6.38; N, 4.32.
$C_{13}H_{20}NI$ requires C, 49.2: H, 6.3; N, 4.4%.).

When a thin film of the base was allowed to stand in contact with the atmosphere, crystals of the carbonate m.p. 80°-81°. were obtained. This compound decomposed on crystallisation from ethyl acetate. It dissolved in dilute hydrochloric acid with effervescence.

2) The trinitrile (20g.) in dioxan (400c.c.) was reduced with hydrogen and copper chromite catalyst A (9g.) at 230° and 175 atmospheres for 5 hours. The product, extracted as before, gave on distillation:-

a) 3-phenylpiperidine (3g.), identified by m.p. and mixed m.p. of its picrate.

b) faint yellow viscous oil (3g.) which distilled over a range 150°-200°/0.5m.m. This product gave no solid derivatives and was obviously a mixture. No pure compound was isolated from it.

c) a considerable dark residue which did not distil.

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3) The trinitrile (10g.) in dioxan (400c.c.) was reduced with copper chromite catalyst B (5g.) at 230° and 175 atmospheres for 4 hours. The product gave on distillation:-

1) 3-phenylpiperidine (1g.) identified by mixed m.p. of picrate.

2) a colourless viscous oil (2g.) b.p. 160°/0.5m.m. which solidified on standing.

The free base gave colourless needles from ethyl acetate m.p. 155°.
(Found: C, 78.26; H, 8.22; N, 12.86%.).

The picrate was prepared in ethanol, and gave long yellow needles from glacial acetic acid m.p. 191°.
(Found: C, 54.49; H, 4.48; N, 15.82%.).
A Rast determination gave the molecular weight of the free base as 223. This compound was unchanged by boiling 70% sulphuric acid.

3) a small amount of a brwon viscous oil b.p. 240°-260°/0.5m.m. A solution of this oil in ethanol deposited colourless needles of a compound m.p. 247° on cooling in ice.
(Found: C, 74.02; H, 6.70; N, 12.53%.).
This compound gave a picrate which crystallised from glacial acetic acid in lemon yellow needles m.p. 222°.
(Found: C, 53.4; H, 4.14; N, 15.83%.).

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4) Reduction of a suspension of the trinitrile (10g.) in cyclohexane (400c.c.) with copper chromite catalyst B (5g.) at 230° and 180 atmospheres for 3 hours, gave:-

1) 3-phenylpiperidine (2g.) identified by mixed m.p. of picrate.

2) colourless viscous oil (2g.) which distilled over a range 160°-190°/1m.m. This fraction gave no solid derivatives.

3) brown residue which did not distil below 260°.

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