SYNTHETIC ANALGESICS AND ANTISPASMODICS.

A Thesis

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Doctor of Philosophy

at

The University of Glasgow

Presented by

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SYNTHETIC ANALGESICS AND ANTISPASMODICS.

Introduction.

Analgesics are drugs which diminish or abolish the sensation of pain. Antispasmodics are drugs which relax the smooth (involuntary) muscle of the body and thereby relieve spasm, the violent, painful contraction of smooth muscle. Analgesics and antispasmodics are thus allied in man's age-long fight against pain; and while little is known as yet of the manner in which these drugs produce their physiological effects they appear to be related chemically also, for many compounds possess both types of activity.

ANALGESICS.

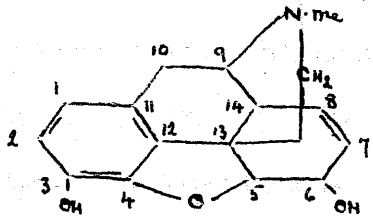
The relief of pain has long been one of the principal objectives of medicine, and of late the realisation of the harmful psychological and physiological effects of pain has added weight to the original, no doubt largely humane, reasons for seeking its alleviation.

Analgesics belong pharmacologically to the class of symptomatic drugs, having mainly a depressant effect on the central nervous system, although it is probable that the autonomic nervous system is also involved[1,2]. They

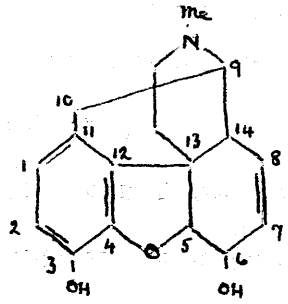
are distinguished from other members of this class in that they produce a specific depression of the sensation of pain without producing unconsciousness or stupefaction: that is, while they do not, in non-toxic doses, affect the senses of sight, hearing, smell or even touch, they do markedly raise the threshold at which a stimulus produces a painful sensation. Other classes of drugs, the anti-pyretics (such as aspirin), and the euphorigenics (the tetrahydrocannabinols), also possess some analgesic activity, but the effect is very much weaker than that of the opiates and they are not classed as true analgesics.

Throughout the entire history of analgesia morphine has played a dominant role, and indeed, until the last decade, it has with a few of its derivatives been the only known drug possessing true analgesic activity. From very early times, at first as the crude extract, opium, and later as the pure alkaloid, morphine has been widely recognised for its analgesic properties; and today, still probably the most common and most effective analgesic, it has become also the model and standard for the synthetic analgesics of the future. Morphine was isolated from opium, the mixture of alkaloids present in the natural extract of poppy seeds, by Sertuerner in 1825, and was recognised as being the main analgesic constituent of the mixture, of which it forms

approximately 10 per cent. The structure now accepted was proposed by Gulland and Robinson[3] in 1925, although owing to the difficulty of synthesising appropriate derivatives conclusive proof of the structure could not then be given. Recent synthetic work of R. Grewe[4] and co-workers, however, has now furnished almost incontrovertible evidence of the correctness of this structure. Various two-dimensional representations of the complex three-dimensional structure are possible: the representation (Ia) given by Gulland and Robinson emphasises the phenanthrene portion of the molecule, while the variation (Ib) later adopted by O. Schaumann[5] and others emphasises the 4-phenylpiperidine portion.



Ia.



Ib.

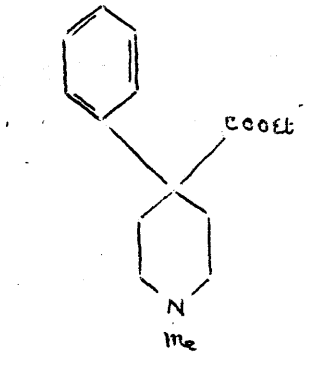
While morphine is even today one of the most indispensable and important drugs used in therapeutics, its beneficial effect in relieving pain is greatly marred by numerous medically-undesirable side reactions. Morphine

depresses the respiratory centre, an effect which is responsible for its toxic properties, produces nausea and has a variety of other effects on the central nervous system. Tolerance probably greater than that which can be acquired for any other drug is very rapidly established. And most serious of all, morphine and its derivatives are the most addictive drugs known, the regular use of morphine for only a few weeks producing addiction which is pathological as well as psychological, and dangerous collapse may result on withdrawal of the drug. On social as well as medical grounds it therefore became desirable to obtain a substitute for morphine, which would be free from the tendency to produce tolerance and addiction, and which would retain the full analgesic effect with a minimum of side-effects. The lack of knowledge of the manner in which drugs exert their pharmacological effects, and the extreme complexity of the system of control of the functions of the body, made it inevitable that the problem be approached in a largely empirical manner.

Intensive work began in 1929, and the first phase involved mainly chemical operation on the morphine molecule, though a number of purely synthetic compounds mostly based on the concept of morphine as a phenanthrene or dibenzfuran

derivative were also prepared. A number of active derivatives of morphine were obtained by relatively minor modification of the various functional groups (the alcoholic and phenolic hydroxyl groups, the ether-oxygen bridge and the tertiary nitrogen atom), and some of these have received considerable recognition as therapeutics, but in no case was the addictive tendency eliminated. The most active of the purely synthetic compounds had a potency approximately $^{1}/_{10}$th that of morphine.

The second phase began in 1938 with the discovery by Eisleb and Schaumann[6] that ethyl-4-phenyl-1-methylpiperidine-4-carboxylate (pethedine, dolantin, demerol; II), originally designed as an antispasmodic, possessed also definite analgesic properties. Closer consideration of this compound revealed that its 4-phenylpiperidine skeleton constituted a portion of the morphine molecule. This chance discovery gave a great impetus to the synthesis of simple compounds based on fragments of the morphine structure and has led to the preparation of a number of compounds of considerable analgesic activity. Most of these compounds have not as yet received sufficient clinical evaluation to permit an estimate to be made of



II.

their addictive tendencies, but it has been shown that in pethidine the danger of addiction, while not eliminated, has been considerably reduced.

This work has been comprehensively reviewed, the first section dealing mainly with morphine and its derivatives by L.F. Small and others[7,8,9,10], and the second, dealing with synthetic compounds, by Bergel and Morrison and other workers[11,12,13]. It is therefore proposed to mention here only the more important information on analgesics gained from this work, and to outline as briefly as possible the extent of the synthetic work. Those portions of the work directly related to the experimental part of this thesis will be treated in more detail in the appropriate sections.

The effects of modification of the functional groups of morphine on the analgesic activity may be summarised as follows:-

Phenolic hydroxyl group. Blocking, by etherification, reduces analgesic activity.

Alcoholic hydroxyl group. Etherification, acetylation or replacement by halogen increases both activity and toxicity. Oxidation to a keto-group or replacement by hydrogen, usually accompanied by saturation of the double bond 7:8, has a

similar effect. All these changes tend to decrease the duration of action.

Ether-oxygen bridge. Rupture of this decreases activity and toxicity.

Tertiary nitrogen atom. This appears to be the most critical point of the molecule. Replacement of the methyl group with other alkyl or alkenyl groups generally decreases the activity. Transformation of the tertiary nitrogen atom to secondary or quaternary almost completely destroys the analgesic activity, as does rupture of the piperidine ring.

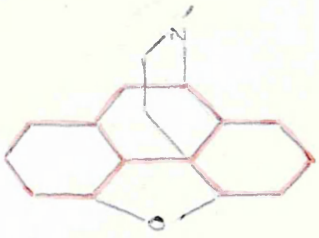
Substitution. In the aromatic ring this decreases activity: in the alicyclic ring the effect varies depending on other features of the molecule.

In the field of synthetic analgesics, the attached table (pp.7a - 7d), which is taken from the review of Bergel and Morrison[11], provides a summary of the main types of compounds which have been prepared, and the fragment of the morphine molecule on which each is modelled. In most cases a number of closely related compounds corresponding to each main type was prepared. It will be noted that not all the compounds depicted possessed marked analgesic activity.

Morphine fragment

Synthetic compounds.

1.

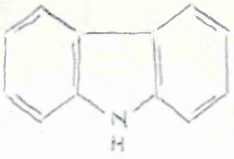


Phenanthrene derivatives

2.

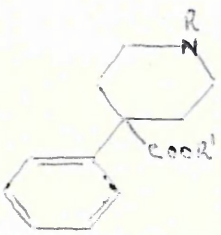
Dibenzfuran derivatives

Carbazole derivatives

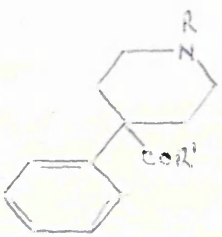


3.

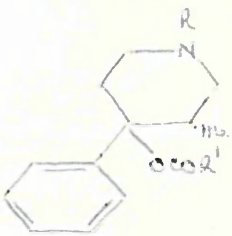
Phenylpiperidine derivatives



Pethidine etc.



Ketobemidone etc.



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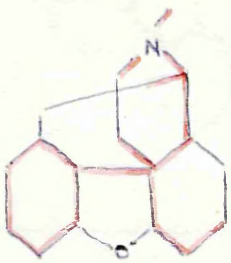
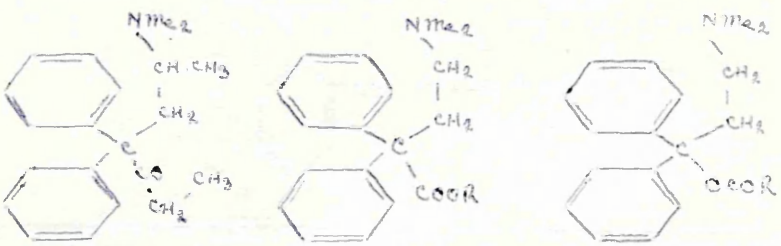
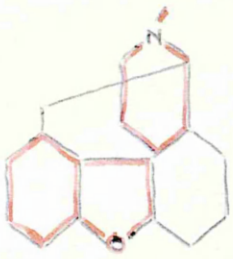
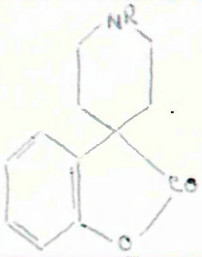
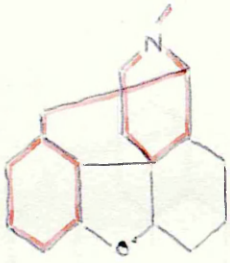
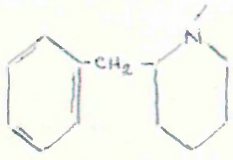
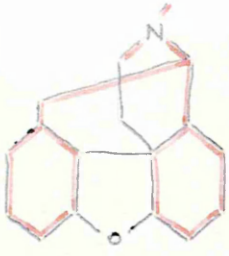
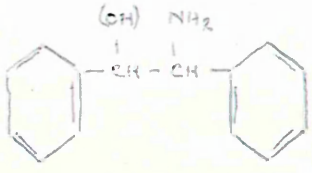
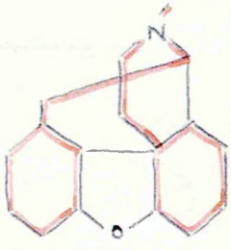
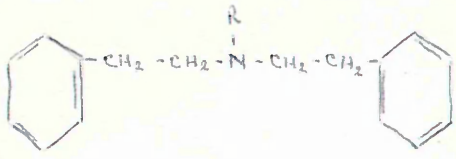
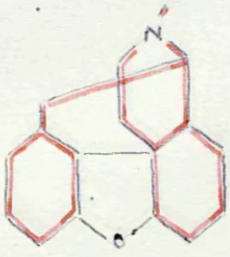
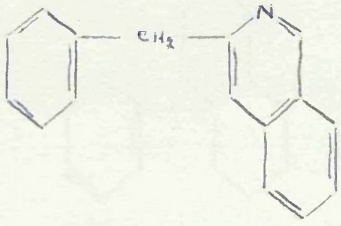
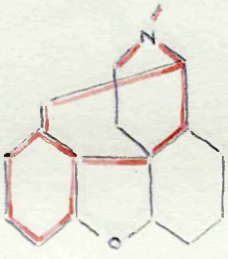
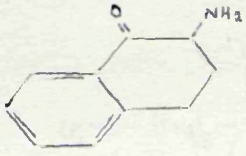
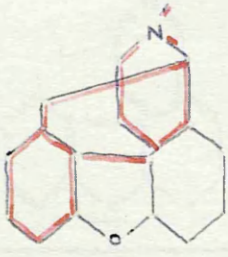
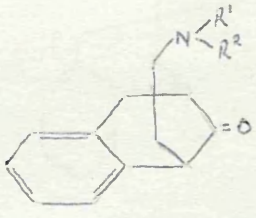
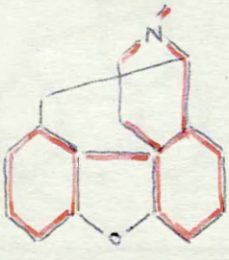
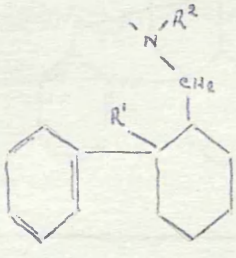


Diphenylpropylamines



Amidone etc.

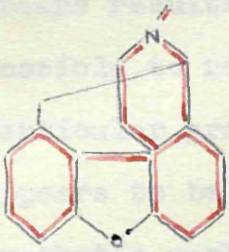
	Morphine fragment	Synthetic compounds
5.		iso Coumaranone 
6.		2-Benzylpiperidines 
7.		Diphenylethylamines 
8.		Bisphenylethylamines 

Morphine fragment	Synthetic compounds
9. 	Benzylisoquinolines 
10. 	2-Amino-1-tetralone 
11. 	1-Dialkylaminoethyl-2-tetralone 
12. 	Phenylaminomethylcyclohexane 

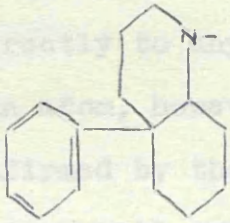
Morphine fragment

Synthetic compounds.

13.

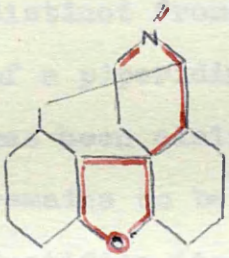


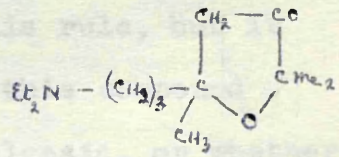
Phenyldecahydroquinoline



Tetrahydrofuran derivatives

14.





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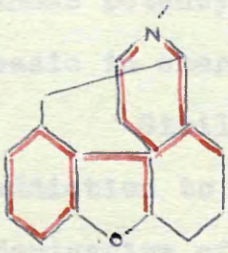
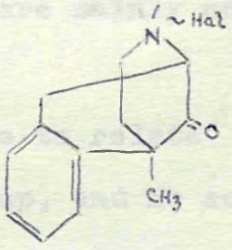
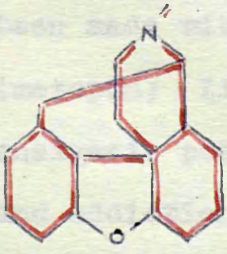


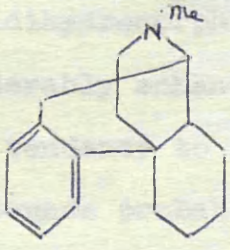


Morphinan

16.



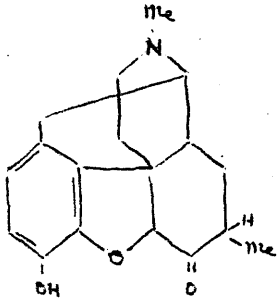
N-Methylmorphinan



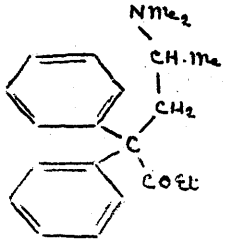
From the work on morphine and related compounds it is seen that while modification of the various functional groups results in modification of the activity, it is not possible to relate analgesic activity directly to any particular group. The tertiary nitrogen atom, however, appears to be essential, and this is confirmed by the later synthetic work, for it is a feature of every well-established potent analgesic. (In synthetic compounds, however, as distinct from morphine derivatives, it need not form part of a piperidine ring.) 3:3-Diphenyl-1-ethyl-2-pyrrolidone[14] has been claimed as a sole exception to this rule, but it remains to be seen whether the potency of this compound justifies its classification as a true analgesic, or whether it should be classed with the antipyretics and euphorigenics whose potency is of a low order and which are mainly non-basic in character.

Similarly, it has not been possible to relate addiction to any particular functional group, and no active derivative of morphine is known which does not produce addiction. However, some advance in this direction has been made with the discovery of methyldihydromorphinone[15] (metopon; III), which combines considerably enhanced analgesic potency with a much reduced tendency to tolerance and addiction. Of the synthetic compounds probably only

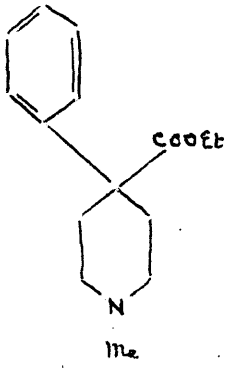
pethidine (II) and amidone (IV) have received sufficient



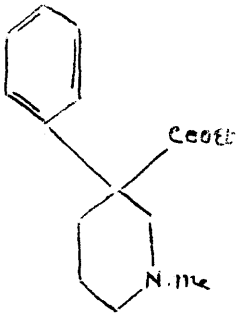
III.



IV.



II.



V.

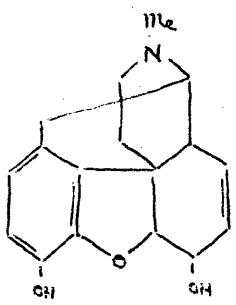
clinical evaluation[16] to permit an assessment to be made, and here again the tendency to addiction is present on a reduced scale. Other new drugs, among them β-pethidine (V), have shown promise in this direction in preliminary trials[16], and give reason to hope that the problem of addiction may soon be overcome.

An encouraging step in the elimination of other undesirable effects has been made by Unna[17] and Hart and McCawley[18] who found that replacement of the N-methyl group of morphine by an N-allyl group eliminated the respiratory depressant effect of the compound, apparently without markedly impairing the analgesic potency. The side-effects of the various synthetic compounds are not yet well established.

Thus by largely empirical methods a fair measure of success has been achieved in the preparation of new compounds in which the analgesic effect is largely dissociated from the undesirable side-effects which accompany it in morphine.

Nevertheless the drugs so far obtained are far from ideal, and a rational basis for future work is greatly to be desired. Progress in this direction has been slow.

The search for a simple pharmacodynamic group responsible for the analgesic effect has not yielded any definite result. The functional groups of morphine, with the exception of the tertiary nitrogen atom, appear not to be of critical importance in themselves as they can be modified considerably without destruction of the activity of the compound, although these modifications do cause changes of potency. A similar state of affairs seems to exist among the synthetic compounds such as pethidine and the 4-phenyl-4-hydroxy-1-alkylpiperidine esters. McDonald and others[16], in considering pethidine, came to the conclusion that the general shape or fit of the whole molecule as compared with morphine is more important than the precise duplication of any one fragment, and the importance of steric arrangement is evident throughout the entire field. The resemblance between pethidine (II) and morphine (I) is marked, and replacement of the carbethoxy group by the isomeric propionoxy group (VI), a change which Lee and co-workers[19] state increases the steric resemblance to morphine, also increases the activity. (The two-dimensional structures shown here do not give an exact steric



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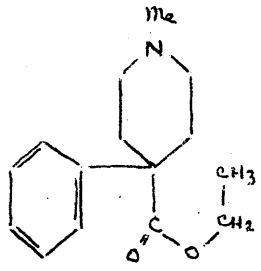

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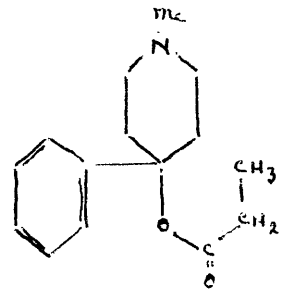
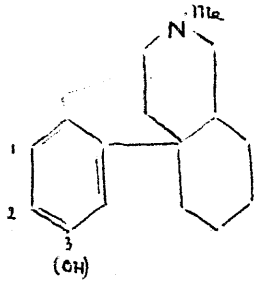
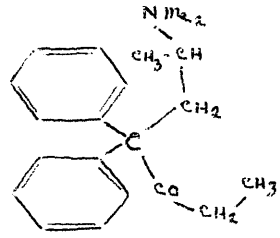


VI

representation of the actual three-dimensional molecules). Lee[20] further speculated that one of the two possible stereoisomers of 1:3-dimethyl-4-phenyl-4-propionoxy-piperidine should bear a particularly close steric resemblance to morphine and should hence be more active than the other; and it was found that the trans isomer was indeed more active than the other. Similarly, it has been shown that N-methylmorphinan[21] and 3-hydroxy-N-methylmorphinan[22] (VII), whose steric resemblance to morphine is extremely close, possess activity of the same order as that of morphine.



VII



IV

And even compounds such as amidone (IV), which at first sight appear to differ considerably from morphine, are believed to have a very close steric similarity.

A correlation of the effect of functional groups and the importance of steric arrangement has been made in the hypothesis of C.C. Pfeiffer[23,24], which relates certain types of pharmacological activity with the nature and spatial arrangement of prosthetic (functional) groups in the drug molecule, and postulates that analgesics exert their pharmacological effect by specifically blocking certain metabolites essential for the central nervous system. Suggesting that greater correlation and understanding of structure-activity relationships might be obtained by depicting structural formulae in three dimensions, with bond distances accurately calculated, a procedure successfully employed by Schueler[25] in relating estrogenic activity to chemical constitution, and assuming a cellular surface action as a possible mode of action of the drugs considered, he has shown the presence of certain prosthetic groups at comparatively critical interatomic distances to be a feature of all drugs possessing marked muscarinic (parasympathomimetic stimulant) action, e.g., acetylcholine, pilocarpine, etc. Similarly, all potent inhibitors of acetylcholine stimulation possess these same groups at the same distance apart, but placed now in the centre of a large umbrella-like molecule. The simplest concept is that these blocking molecules adhere to the receptors on the cell surface by means of the prosthetic groups they contain, and

by their continued adherence and difficult degradation prevent the smaller stimulant molecules reaching the acceptors on the cell. Lack of one or more of the prosthetic groups reduces, but does not entirely destroy, the activity of a compound. Since blocking molecules have a characteristic chemical configuration, Pfeiffer suggests that the hypothesis may be extended to certain other pharmacological series, including the analgesics. He emphasises, however, that while the prosthetic groups and their arrangement may be mainly responsible for the pharmacological action of a drug, this is also strongly influenced by the surrounding molecular structure and the ease of degradation of this in the body: and hence, while it may become possible to predict pharmacological activity from a study of prosthetic groupings, the usefulness of a drug will depend on the associated molecular structure and will still require to be determined by experiment.

This hypothesis has still to be confirmed. Biochemical information in particular is notably lacking, but the collection and correlation of necessary physicochemical data should be facilitated by the availability of the relatively simple synthetic compounds in place of the undoubtedly complex compounds related to morphine.

Thus progress on the theoretical side, while slight as yet, holds promise for the future. On the practical

side considerable success has already been achieved in the production of drugs in which addictive tendency and other side-effects have largely been dissociated from the desired analgesic activity: but here, too, the goal, a potent and completely safe analgesic, still lies ahead.

ANTISPASMODICS.

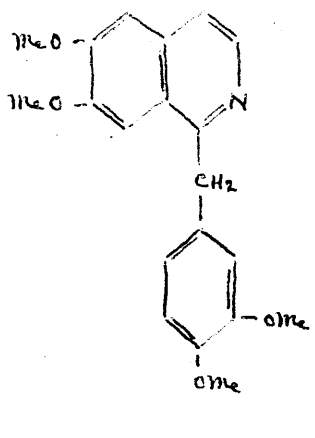
Spasm is the violent, involuntary contraction of smooth (plain, involuntary) muscle, which controls mainly the hollow organs of the body, and is activated by the autonomic nervous system. On account of the disturbing effect of spasm on the proper functioning of the organs controlled by smooth muscle, and hence of the body as a whole (for example in asthma, in which spasm of the bronchial muscles results in arrest of respiration), and because of the pain which usually accompanies it, it is most desirable to have means of relaxing spastic muscle.

The autonomic nervous system consists of two sets of nerves, the sympathetic and the parasympathetic; and most smooth muscles have this double nerve supply, the two sets acting in opposition, as augmentor and inhibitor, to regulate the activity of the muscle. Spasm is commonly related to over-activity of the parasympathetic nervous system; hence stimulation of the complimentary sympathetic nervous system, or, more accurately, simulation of its

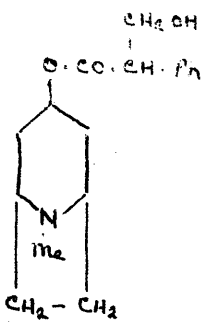
effects, by drugs such as adrenaline will to some extent relieve the condition: these sympathomimetic drugs are not, however, classed as true antispasmodics.

Two types of spasm are to be distinguished. The first, neurotropic (neurogenic) spasm is caused by nervous stimulation of the muscle, and can be simulated by compounds such as acetylcholine, which is believed to be instrumental in conveying the impulse from the nerve to the muscle. The second, musculotropic (myogenic) spasm is caused by direct stimulation of the muscle by compounds such as histamine and barium chloride. In practice it is not always convenient to distinguish which type of spasm is involved, hence it is desirable that an antispasmodic should be active against both types.

Synthetic antispasmodics are based largely on two naturally-occurring drugs, papaverine (VIII) and atropine (IX).



VIII.

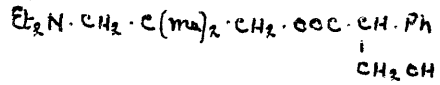


IX.

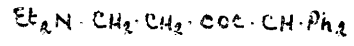
These, however, in addition to the over-abundance of side-effects so common among natural drugs, have the added disadvantage of not being equally effective against both types of spasm. While papaverine is rather more active against musculotropic than neurotropic spasm, and much more active than atropine against musculotropic spasm, atropine is by far the more effective against neurotropic spasm[26]. The aim of synthetic work is a compound combining the papaverine activity against musculotropic spasm with the atropine activity against neurotropic spasm, and free from the side-effects of these drugs.

Atropine (IX) is the tropic acid (phenyl-hydroxy-methylacetic acid) ester of the basic alcohol tropine, and in the search for synthetic antispasmodics it was natural that the effect of substituting other basic alkyl groups in place of the tropine portion of the atropine molecule, or other acids in place of tropic acid, or both, should be extensively investigated. A very large number of esters, based on the concept of atropine as the ester of a basic alcohol and a disubstituted acetic acid, has been prepared, and several useful antispasmodics have thus been obtained. Of these may be mentioned syntropan (the $\beta\beta$ -dimethyl-γ -diethylaminopropyl ester of $\alpha\alpha$ -tropic acid; X), trasentin (β -diethylaminoethyldiphenylacetate; XI) and its hexahydro derivative trasentin-6H (β -diethylaminoethylphenylcyclo-

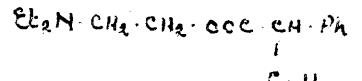
hexylacetate; XII): these are used in the form of salts,



X.



XI.



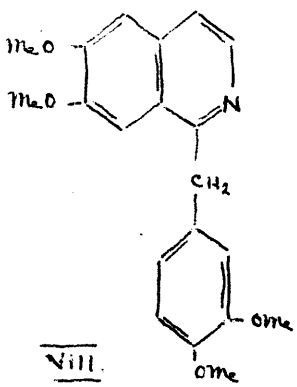
XII.

usually the hydrochloride. The last, trasentin-6H, is reported[27] to have a neurogenic activity comparable to that of atropine, and a musculotropic activity equal to that of papaverine: it is more toxic than atropine, but is relatively free from side effects. Similar esters of xenylacetic acid[28] (in which two phenyl groups are attached to each other as in diphenyl), α-naphthylacetic acid[29] and fluorene-9-carboxylic acid[30] have also been found to possess high activity, the β-diethylaminoethyl ester of the last mentioned being the well-known antispasmodic pavatrine. A number of amides corresponding to these esters has been prepared, but in general these are rather less active.

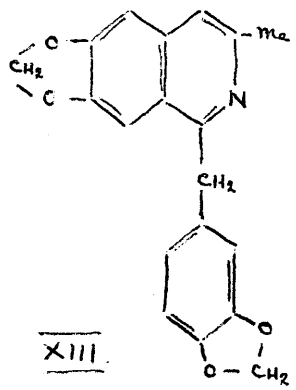
Halpern[31], from his work on esters of phenylalkylacetic acids, has suggested that the basic alcohol portion of the molecule determines the type of activity (neurotropic or musculotropic) of the compound, esters derived from basic

ethanols or propanols being mainly neurotropic, and those from basic pentanols mainly musculotropic antispasmodics; and that the acid portion determines the intensity of the activity. It has not been proved, however, that this relationship holds equally in other sections of the field.

A considerable amount of work has also been done on the papaverine model. Papaverine (VIII) was isolated from opium in 1848, but it was not until 1913 that its antispasmodic properties were discovered. Then the rapidly increasing demand, and the fact that the supply (obtained as a by-product in the extraction of morphine from opium) was limited by international agreement controlling the production of opium, led to a search for synthetic substitutes.



VIII.

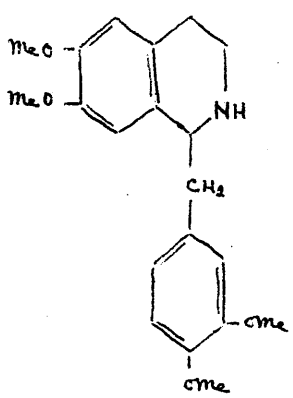


XIII.

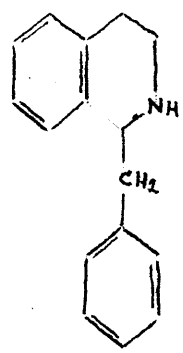
The first aim of this work was the preparation of compounds as close in structure to the natural prototype as possible, and it is probable that these compounds, such as eupaverin (XIII) and perparin (which differs from papaverine only in

that the methoxyl groups have been replaced by ethoxyl), on account of this very close resemblance, retain most of the disadvantages of papaverine, such as the low solubility of its salts and their tendency to hydrolysis.

In an effort to overcome the disadvantages associated with papaverine, Kulz[32] and his associates carried out an extensive examination of less closely related compounds. On the model of 1:2:3:4-tetrahydropapaverine (XIV), which possesses weak antispasmodic properties, they prepared di-β-phenylethylamine (XV), whose structural resemblance is obvious from comparison of the formulae. This compound too exhibited antispasmodic activity, and led to the preparation of an extensive range of similar amines, some of which were more active than papaverine. One of the most successful compounds of this type is ethyldi-γ-phenylpropylamine[33] sestron; XVI), which has a potency more than twice that of papaverine, and more satisfactory physical properties. Simpler, saturated and unsaturated, aliphatic amines, such



XIV.



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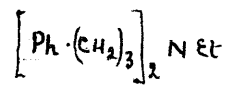


XVI

as ethyldiheptylamine[34] and 2-aminohexene-5[35] have also been shown to possess antispasmodic activity.

Reviews of the work on both atropine-type and papaverine-type compounds have been made by Blicke[34], Raymond[36] and Pfeiffer and Loew[37]. It is seen that, on the theoretical side, little progress has been made in the correlation of chemical constitution and pharmacological activity; for attempts to relate activity to any particular group, or to any one physical property, have been largely unsuccessful, though the hypothesis of Pfeiffer, mentioned previously in the discussion on analgesics, which relates activity to the presence of certain functional groups at specific distances apart, may be a step in this direction. On the practical side, however, musculotropic antispasmodics more active and more clinically useful than papaverine have been prepared; neurotropic antispasmodics equivalent to atropine and relatively free from its side-effects have been obtained; and while none of the synthetic compounds based on papaverine has exhibited marked neurotropic activity, several esters related to atropine have exhibited the desired combination of musculotropic and neurotropic activity in high degree. The search for synthetic antispasmodics, therefore, has achieved considerable success.

Section I.

The Bisdialkylaminoalkylnaphthalenes.

The Bisdialkylaminoalkylnaphthalenes.

The majority of potent synthetic antispasmodics belong to one of two classes, the amines related to papaverine or the basic esters related to atropine. Of the first class, the range of amines which exhibit antispasmodic activity is very wide. Many compounds of the general type $Ar.CH_2.CH(R).NH.CH(R').CH_2.Ar$, where Ar = phenyl or substituted phenyl, and R and R' = hydrogen, alkyl, phenyl or benzyl, show marked activity[32]; and the presence of an N-alkyl group is of practical advantage as the salts of these tertiary amines are more water-soluble and hence more useful clinically. Compounds containing a longer carbon chain, of the type $Ar(CH_2)_3.NR.(CH_2)_3.Ar$, though less closely related structurally to papaverine, are equally active[33], and compounds containing an alicyclic ring in place of the aromatic still retain considerable potency. Even purely aliphatic amines such as 2-aminohexene-5[35] (XVII) and ethyldiheptylamine[34] (XVIII) show some activity. The aminoalkyl grouping is also a feature of the synthetic

$CH_2=CH.CH_2.CH_2.CH(CH_3).NH_2$ (XVII)

$CH_3.(CH_2)_6.N(Et).(CH_2)_6.CH_3$ (XVIII)

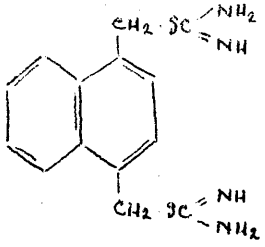
esters related to atropine, occurring for example in trasentin (β-diethylaminoethyl-diphenylacetate), syntropan ($\beta\beta$-dimethyl-γ-diethylaminopropyl ester of dl-tropic

acid) and pavatrine (β-diethylaminoethyl fluorene-9-carboxylate). The same grouping also appears in other miscellaneous active compounds not directly related to either papaverine or atropine, as for example in quinoline derivatives[38] containing aminoalkyl side chains, benzofurenone derivatives[39] such as 3-β-diethylaminoethyl-3-phenyl-2-benzofurenone (amethone), and the α-amino-acetamides[40].

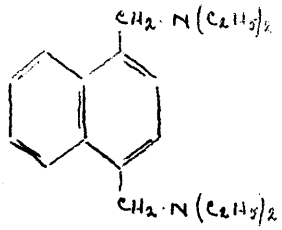
As a basic group of this type is therefore a consistent feature of several classes of compounds possessing antispasmodic activity, it was decided to carry out a preliminary investigation of compounds containing two such basic groups in the molecule in place of the one present in previous compounds, and to this end was planned the synthesis of the following bisdialkylaminomethylnaphthalenes. As these bear also some slight resemblance to analgesics of the diphenylpropylamine and bisphenylethylamine types discussed in the previous section, it was considered possible that they might possess some analgesic as well as antispasmodic activity.

The compounds prepared and submitted for pharmacological testing, in order that a preliminary estimate of the antispasmodic and analgesic properties of this type of structure might be obtained, were 1:4-bis<u>iso</u>thiocarbamidomethyl-

naphthalene (XIX), 1:4-bisdiethylaminomethylnaphthalene (XX), and 1:4-bis-N-piperidylmethylnaphthalene (XXI).



XIX.



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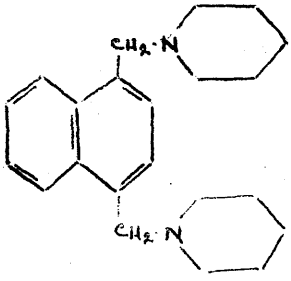
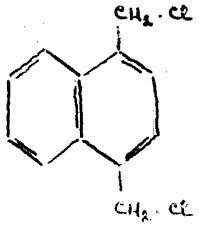


XXI.



XXII.

1:4-Bischloromethylnaphthalene[41] (XXII) was prepared by the chloromethylation of naphthalene with boiling aqueous formaldehyde and hydrochloric acid. The product contains a quantity of the higher-melting 1:5-isomer (m.p. 172°) which is difficult to separate from the 1:4-isomer (m.p. 150°). For the first experiments pure 1:4-bischloromethylnaphthalene, obtained by fractional crystallisation of the crude material from ethanol, was used; but it was found that a cruder material (m.p. ca. 132°),

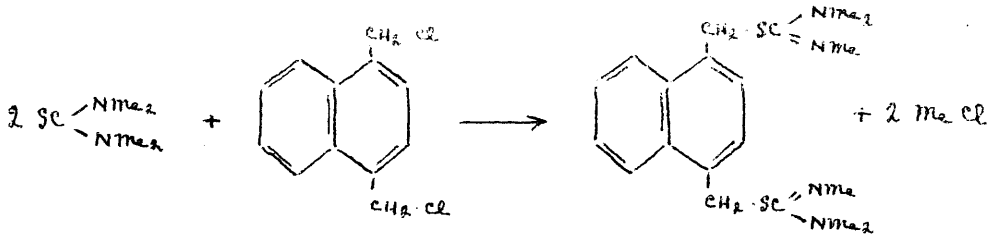
obtained after only one or two crystallisations, was equally satisfactory and this was used in the subsequent condensations.

When 1:4-bischloromethylnaphthalene was refluxed with thiourea in a mixture of benzene and ethanol condensation occurred to give 1:4-bisisothiocarbamidomethylnaphthalene hydrochloride (hydrochloride of XIX) which separated from the reaction mixture, and was also characterised as the picrate.

Condensation occurred similarly between 1:4-bischloromethylnaphthalene and diethylamine on refluxing in benzene solution, to give 1:4-bisdiethylaminomethylnaphthalene (XX), which was characterised as the hydrochloride and the picrate. Diethylamine, however, differs from thiourea in being a sufficiently strong base to compete with the condensation product for the hydrogen chloride liberated in the reaction, and thus tends to be removed from the reaction as insoluble hydrochloride before the condensation can proceed to completion. To obtain complete reaction, therefore, two molecular proportions of diethylamine were used. The mixed bases were then extracted and the excess diethylamine removed by evaporation to leave the desired condensation product. By this general method bisdialkylaminomethylnaphthalenes of this type are most conveniently obtained.

1:4-Bis-N-piperidylmethylnaphthalene (XXI) was similarly prepared by the condensation of 1:4-bischloromethylnaphthalene and piperidine, and was characterised also as the hydrochloride.

In connection with this work attempts were made to condense 1:4-bischloromethylnaphthalene with tetramethylthiourea. This might be expected to occur with difficulty,



if at all, involving as it does considerable rearrangement within the thiourea molecule. However, when bischloromethylnaphthalene and tetramethylthiourea were refluxed in xylene solution for approximately twenty hours reaction did occur, and a quantity of insoluble, deliquescent salt separated from the reaction mixture. This decomposed on distillation to give tetramethylthiourea, and was hence presumed to be the methochloride of tetramethylthiourea. It was therefore apparent that some condensation had actually occurred. The reaction, however, was slow and incomplete, and it was not possible to isolate any of the desired condensation product from the non-volatile tetramethylthiourea also present in the mixed basic product of the reaction.

Specimens of 1:4-bis*iso*thiocarbamidomethylnaphthalene hydrochloride, 1:4-bisdiethylaminomethylnaphthalene hydrochloride and 1:4-bis-*N*-piperidylmethylnaphthalene hydrochloride were submitted for pharmacological testing, and the results of the tests on the first two of these have been published[42]. Both of these compounds showed some antispasmodic activity, which was approximately 1/6th that of pavatrine against barium-induced spasm but only very slight against spasm induced by histamine or acetylcholine. As antispasmodics, therefore, these compounds are not particularly successful. Both compounds, however, displayed an unexpected activity as analgesics. Both were approximately equal to pethidine in potency when tested on mice, and while 1:4-bis*iso*thiocarbamidomethylnaphthalene hydrochloride (hydrochloride of XIX) was approximately twice as toxic as pethidine, 1:4-bisdiethylaminomethylnaphthalene hydrochloride (hydrochloride of XX) had less than half the toxicity of pethidine. Unlike pethidine, which produces motor excitement, both these compounds were depressant. Bisdiethylaminomethylnaphthalene hydrochloride, the more promising compound on account of its low toxicity, was then submitted for clinical trial, but the preliminary report of this was less satisfactory and indicates that the compound is in practice a less efficient analgesic than pethidine. Extracts from

this report are given below:-

"The analgesic qualities of this drug have been tried in a number of selected cases of pain due to nervous system disease (syringomyelia, brachial plexus, pressure lesion and tabes dorsalis), and in a few cases of pain due to pleural lesions. Doses of 25 - 100 mg. intravenously proved ineffective as analgesics, and it was found to be effective in doses of .5 g. and upwards. At a dose of .5 g. intravenously it confers relief of pain which corresponds in some cases to that given by 100 mg. of pethidine intravenously; other patients thought it less effective but of longer duration; analgesia wears off in about four hours, though some effect may remain for a longer period. Orally it has not been satisfactory as too large a bulk has been necessary; it has not been tried in tablet form. The flavour is unpleasant; it should be noted that in doses of .5 g. intravenously it is detected by taste after the usual time interval and gives a good indication of circulation time (arm-tongue). No side effects have as yet been apparent. It does not appear to be a euphoriant."

These tests, therefore, while indicating that the compounds already tested are unlikely to be of direct practical value, nevertheless do establish the analgesic

potentialities of this bisdialkylaminomethylnaphthalene type of structure. And this is of interest, not only because this is a new type of compound to exhibit analgesic activity, but also because of the relative simplicity of the structure. As has been mentioned before, considerable efforts are now being made to correlate analgesic activity with chemical constitution; and tentative speculations have already been made, as, for example, Pfeiffer's speculations on the possible significance of the electrostatic effects of functional groups and the interatomic distances between them. While it is probable that much biochemical and physicochemical information will require to be obtained before any such correlation can be achieved, compounds of the bisdialkylaminomethylnaphthalene type, and possibly even simpler related compounds, should be of value in establishing the minimum chemical requirements for an analgesic, and in providing simple models for the study of physicochemical relationships.

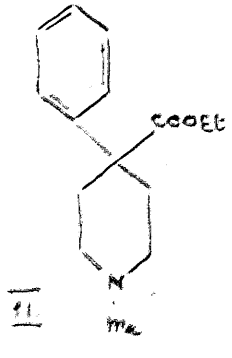
Section 2.

The 4-phenyl-4-hydroxypiperidines.

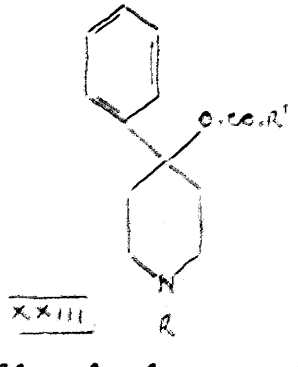
The 4-phenyl-4-hydroxypiperidines.

Pethidine (II), introduced in 1939 by Eisleb and Schaumann[6] was the first totally synthetic analgesic to compete seriously with morphine in clinical practice. In addition to considerable analgesic potency it possessed the advantages of a considerably reduced tendency to cause addiction and a relatively simple structure as compared with the complexity of morphine, and it was natural that this success should inspire further work on similar piperidine derivatives.

One line of approach was the preparation by Jensen and Lundquist[43] of a number of esters of 4-phenyl-4-hydroxy-1-methylpiperidine of the type (XXIII; R = Me), in which



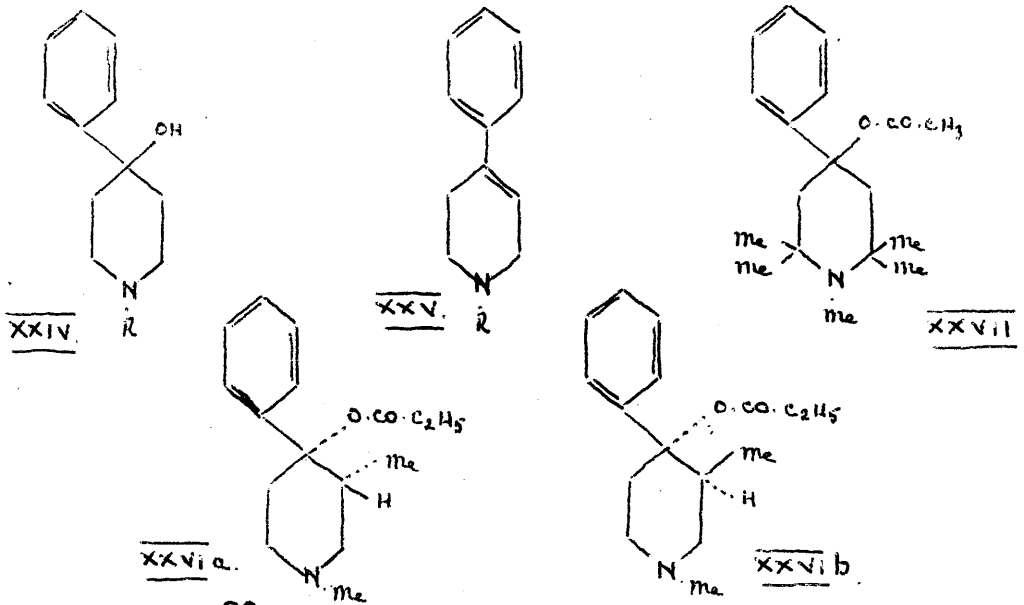
II



XXIII

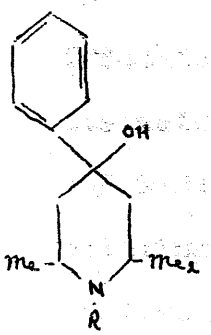
the carbethoxy group of pethidine is 'reversed' in the form of the ester group. Of the series (R' = Me, Et, Pr) prepared by these workers the propionoxy derivative (XXIII; R' = Et) was found to be the most active, having 5 - 10 times the potency of pethidine (i.e., approximately the same

potency as morphine). Lee and his associates[44] later carried out an intensive investigation of this group of compounds, and confirmed that maximum activity is obtained when in (XXIII) R = Me and R' = Et. Increase in the length of R decreases activity, while branching of it leads to increased stability of the ester group to hydrolysis. These workers also found that while the piperidols (XXIV) themselves showed only slight activity, the tetrahydropyridines of type (XXV) obtained from these by dehydration were moderately active, 1-ethyl-4-p-methoxyphenyl-1:2:5:6-tetrahydropyridine possessing approximately 1/3rd the potency of pethidine. The saturated piperidines obtained by hydrogenation of the tetrahydropyridines were of equal activity. Replacement of the phenyl group by an alkyl, cycloalkyl, heterocyclyl or heterocycloalkyl[45] group invariably decreased the activity; the only compound of interest being 4-cyclohexyl-4-propionoxy-1-methylpiperidine, with a potency about 1/3rd that of the phenyl analogue. This is the first potent analgesic not to contain a phenyl ring, and has the added advantage over its phenyl counterpart in that it is reasonably stable in aqueous solution. The most active compound of this piperidine type was 1:3-dimethyl-4-phenyl-4-propionoxypiperidine (XXVI). From the conception of morphine as a derivative of trans-octahydroisoquinoline, an assumption as yet unproved, Lee

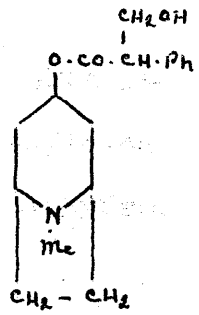


and Ziering[20] calculated that one of the two possible stereoisomers (the trans) should bear a particularly close steric resemblance to morphine, and speculated that it should therefore be more active than the other isomer. This proved to be the case, one isomer being over 5 times as potent as morphine, while the other approximately equalled morphine in potency. A further development in this field was the preparation by Badger and others[46] of 4-phenyl-4-acetoxy-1-methyl-2:2:6:6-tetramethylpiperidine (XXVII), for which analgesic activity is claimed.

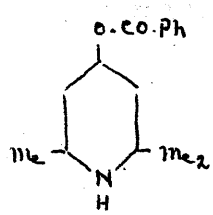
It was therefore decided, in continuation of the above work, to explore further the effect of alkyl substituents in the piperidine ring of these 4-phenyl-4-acyloxy-1-alkylpiperidines, and to this end was planned the synthesis of 4-phenyl-4-hydroxypiperidine (XXVIII; R = H) and the corresponding N-methyl compound, from which it was expected a series of esters of the desired type could be



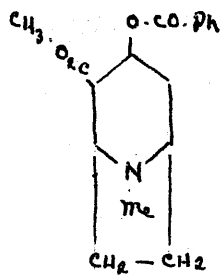
XXVIII.



IX.



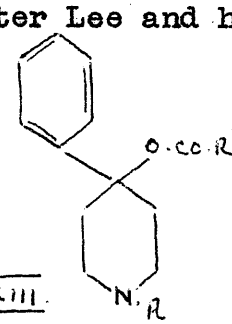
XXIX.



XXX.

obtained. As these compounds are related to the natural antispasmodic atropine (IX) in the same sort of way in which the synthetic local anaesthetics the eucaines (XXIX) are related to the naturally occurring cocaine (XXX), and in view of the proved antispasmodic activity of the related compounds pethidine and the 4-phenyl-4-acetoxy-1-methyl-piperidines, it was expected that they might possess anti-spasmodic as well as analgesic activity.

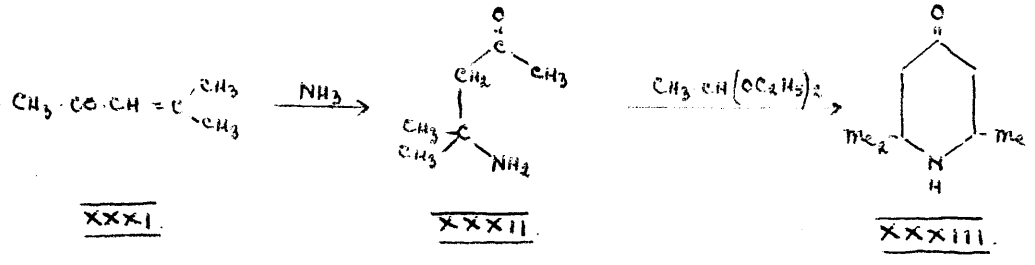
Jensen and Lundquist[43], and later Lee and his associates[44,47], obtained 4-aryl-4-acyloxypiperidines of type (XXIII) by reaction of the



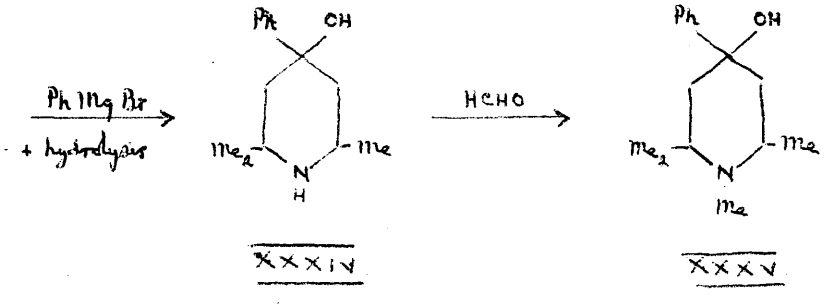
XXIII.

appropriate 4-piperidone with arylmagnesium halide, followed by esterification of the carbinol so obtained with the appropriate acid. This method was followed in the preparation of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidines by the following route:-

Mesityl oxide (XXXI) condensed with aqueous ammonia in the cold to form 4-amino-4-methylpentan-2-one[48] (diacetonamine; XXXII) which was isolated as the hydrogen oxalate. This oxalate condensed with acetal on refluxing



XXXI XXXII XXXIII



XXXIV XXXV

in ethanol solution to give the hydrogen oxalate of 2:2:6-trimethyl-4-piperidone[49] (vinyldiacetonamine; XXXIII), from which the piperidone itself was isolated. 2:2:6-Trimethyl-4-piperidone reacted with phenylmagnesium bromide,

and on decomposition of the Grignard complex with aqueous ammonium chloride[50] gave 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine (XXXIV), isolated as the hydrochloride, from which the free base was obtained and characterised as the hydrochloride, hydrogen oxalate, picrate and acetate.

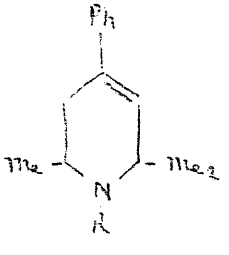
The product isolated directly from the reaction was proved by mixed melting point determination and by extraction of the base to be essentially the hydrochloride of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine. The analysis, however, was neither satisfactory nor consistent, and the melting point (250 - 251°) differed slightly from that (247 - 248°) of an authentic specimen of the hydrochloride prepared from the purified base. This may be a solvated form of the hydrochloride, and probably contains other impurities which are not readily separated by crystallisation. An increase in the time of refluxing of the reaction mixture slightly increased the yield of this material, but the base isolated was less pure.

2:2:6-Trimethyl-4-phenyl-4-hydroxypiperidine is dimorphic. The stable form crystallises in colourless needles (from light petroleum) m.p. 91 - 92°. When this form is distilled, or heated in alcohol solution for several hours, a second form, colourless prisms (from light petroleum) m.p. 96 - 97° is obtained: on repeated crystallisation this

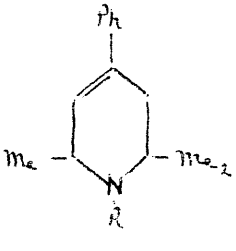
reverts to the original form.

1:2:2:6-Tetramethyl-4-piperidone is not readily available, as piperidones of the type (XXXIII) are resistant to direct N-methylation[51]. The corresponding alcohols, however, are readily methylated, and on warming with aqueous formaldehyde 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine was readily converted to 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine (XXXV), which was characterised as the hydrochloride and picrate.

Both these tertiary alcohols (XXXIV and XXXV) readily undergo dehydration, especially in acid media, though slight dehydration occurs also during distillation in vacuum. On warming with alcoholic hydrogen chloride 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine gave 2:2:6-trimethyl-4-phenyl-1:2:5:6- (or 1:2:3:6)-tetrahydropyridine (XXXVI or XXXVII; R = H), a colourless oil, darkening



XXXVI

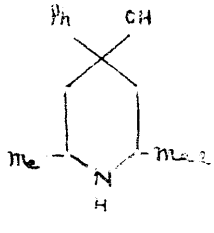


XXXVII

rapidly on exposure to air, which was characterised as the hydrochloride and hydrogen oxalate. Even the mild acid conditions used in the preparation of salts may bring about

partial dehydration, and in the preparation of the hydrochloride of 2:2:6-trimethyl-4-phenyl-hydroxypiperidine by the addition of hydrogen chloride to an ether solution of the basic alcohol, a quantity of the hydrochloride of the dehydrated product was also isolated. 1:2:2:6-Tetramethyl-4-phenyl-4-hydroxypiperidine was similarly dehydrated with equal facility to give 1:2:2:6-tetramethyl-4-phenyl-1:2:5:6-(or 1:2:3:6)-tetrahydropyridine (XXXVI or XXXVII; R = Me), also a colourless oil which darkened rapidly on exposure to air, and which was characterised as the picrate. Attempts to obtain urethane derivatives of these alcohols by reaction with phenylisocyanate also resulted in dehydration of the alcohol, the water eliminated reacting with the phenylisocyanate to form carbanilide.

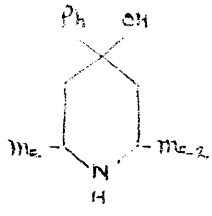
Attempts to obtain ethers of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine of the type (XXXVIII) were unsuccessful. Treatment of the hydroxypiperidine with the appropriate alcohol in the cold in the presence of sulphuric acid catalyst[52] was without effect, and warming merely brought about dehydration. Treatment of the Grignard complex formed from 2:2:6-trimethyl-4-piperidone and phenylmagnesium bromide with dimethyl sulphate was ineffective under mild conditions,

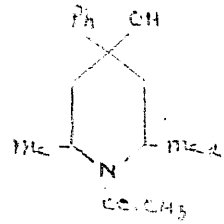


XXXVIII

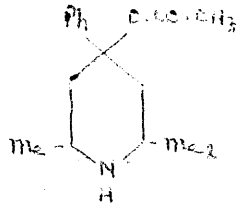
and yielded only the hydroxypiperidine; under more vigorous conditions a basic oil was obtained which, however, decomposed when purification by fractional distillation in vacuum was attempted.

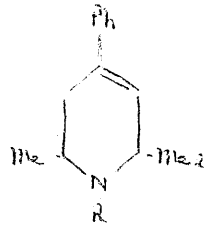
Attempts to esterify 2:2:6-trimethyl- and 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine were largely unsuccessful. When 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine (XXXIV) was treated with acetic anhydride the

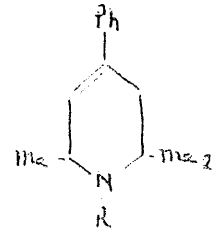




amino group proved much more reactive than the hydroxyl, and the only product isolated was 1-acetyl-2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine (XXXIX). Treatment of the Grignard complex formed from 2:2:6-trimethyl-4-piperidone and phenylmagnesium bromide with acetic anhydride, however, did give a very small quantity of 2:2:6-trimethyl-4-phenyl-4-acetoxypiperidine acetate (acetate of XL), which was also

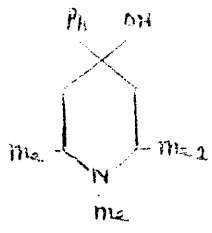




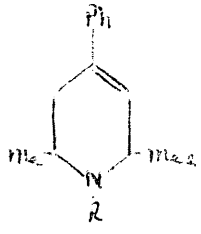


characterised as the hydrochloride: the main bulk of the product was the tetrahydropyridine (XXXVI or XXXVII; R = H). The acetoxypiperidine acetate is evidently formed during the distillation of the mixed product of the reaction by partial decomposition of the acetoxypiperidine with liberation of acetic acid, which then combines with another molecule of the acetoxypiperidine to form the salt. The small quantity of salt isolated compared with the much larger proportion of tetrahydropyridine indicated, however, that the bulk of the tetrahydropyridine must be formed during the reaction or the subsequent decomposition of the Grignard complex, and not by decomposition of the ester during distillation. When the reaction was repeated under milder conditions, however, practically no acetylation occurred and the product was mainly the hydroxypiperidine (XXXIV); though the isolation of a small quantity of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine acetate (acetate of XXXIV) from the product after distillation indicated the formation of a small quantity of the unstable ester in the reaction.

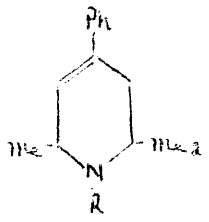
An intensive effort to obtain esters of 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine was still less successful. Treatment of this alcohol (XXXV) with acetic



XXXV



XXXVI

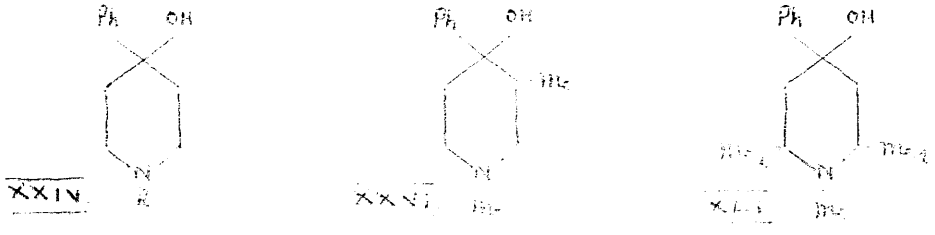


XXXVII

anhydride alone or in the presence of an inert diluent failed to produce any reaction at temperatures up to 100°: the addition of basic or acidic catalysts (pyridine, sodium acetate or sulphuric acid) resulted in formation of the tetrahydropyridine (XXXVI or XXXVII; R = Me) in varying amounts. Acetyl chloride brought about dehydration more rapidly than acetic anhydride under corresponding conditions. Treatment of the Grignard complex formed from 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine and ethylmagnesium bromide with acetic anhydride also gave a mixed product containing varying amounts of the tetrahydropyridine: though the isolation of a small quantity of a deliquescent salt in one case suggested the formation and subsequent spontaneous decomposition of a small quantity of the desired ester.

The difficulty of esterifying 2:2:6-trimethyl- and 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine was unexpected, as the preparation of a number of similar phenyl-

piperidol esters has been reported. Jensen and Lundquist[43] obtained the methyl, ethyl and propyl esters of 1-methyl-4-phenyl-4-hydroxypiperidine (XXIV; R = Me), the two latter



by the use of the appropriate acyl chloride in an inert solvent (ether, acetone). Lee and associates[44], working on the same piperidol, found that the use of acyl chlorides tended to produce dehydration, but considerably extended the range of esters by the reaction of acid anhydrides either on the piperidol or on the Grignard complex formed from the piperidone, and by these methods were able to prepare several esters (e.g., the phenylacetic) which Jensen and Lundquist failed to obtain. These workers[45] also obtained similar esters of 1:3-dimethyl-4-phenyl-4-hydroxypiperidine (XXVI), while G.M. Badger and associates[46] have recently reported the preparation of the propyl ester of the very closely related 1:2:2:6:6-pentamethyl-4-phenyl-4-hydroxypiperidine (XLI). All the techniques employed by these workers were used without success in attempts to obtain esters of 2:2:6-trimethyl- and 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine. There is no doubt that these

last two piperidols are dehydrated with exceptional facility, since, for example, 1:2:2:6:6-pentamethyl-4-phenyl-4-hydroxypiperidine was successfully esterified by the action of acetyl chloride in benzene solution on warming, a procedure which in the case of 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine resulted in very rapid dehydration. Moreover, the esters, when formed, appear to be particularly unstable, the propyl ester of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine decomposing on distillation in vacuum and that of 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine apparently decomposing spontaneously, whereas the more stable esters of the piperidols of type (XXIV) containing a branched 1-alkyl chain (e.g., 1-isobutyl-4-phenyl-4-propionoxypiperidine) can be distilled without change. This instability made the isolation of small quantities of these esters from the accompanying unchanged material and dehydration products impracticable.

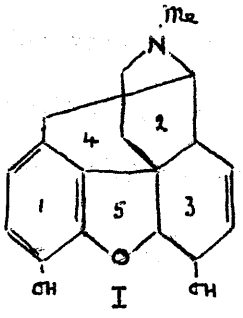
Specimens of 2:2:6-trimethyl- and 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine hydrochlorides have been submitted for pharmacological testing. Although the alcohols are normally much less active than the corresponding esters, nevertheless from a knowledge of their analgesic potency (if any), an estimate may be obtained of the therapeutic or distherapeutic effect of methyl substituents in

the piperidine ring of compounds of this 4-phenyl-4-acyloxypiperidine type.

THE DECAHYDROISOQUINOLINES.

The success of pethidine, and the identification of its 4-phenylpiperidine skeleton as a portion of the morphine molecule, in addition to giving a direct stimulus to work on piperidine derivatives, also led to the dissection of the morphine molecule into other fragments which might form the framework for further series of potentially active compounds. Of these, two related fragments which have received some attention are the decahydroquinoline structure formed by rings 2 and 4 of morphine, and the octahydroisoquinoline structure formed by rings 2 and 3.

On the quinoline model J.W. Cook[42,53] and his associates prepared a number of 4-phenyl-1-ethyldecahydroquinoline derivatives of type (XLII), the most active of which, 4-p-methoxyphenyl-1-ethyldecahydroquinoline, was considerably less potent than pethidine. The corresponding



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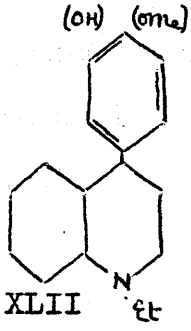
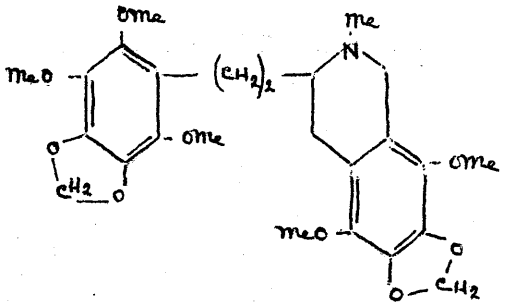


XLII

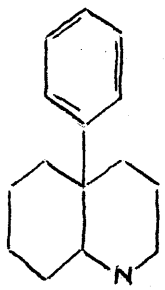
compound without substituent in the phenyl ring had approximately the same activity, while the compound containing

a p-hydroxy substituent on the phenyl group was inactive.

Several workers have copied the isoquinoline model. Kulz and his associates[54] claimed analgesic properties for extensively substituted 1-arylalkyltetrahydroisoquinoline



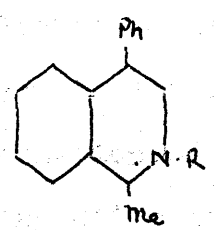
XLIII



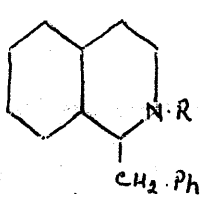
XLIV

derivatives of type (XLIII), whose resemblance to morphine is obvious from the formula given, while Boekelheide[55] prepared 10-phenyldecahydroquinoline (XLIV) as a simplified representation of the isoquinoline structure containing an angular aryl group formed by rings 1, 2, and 3 of morphine (I).

The synthesis of a number of 2-alkyl-4-phenyl-1-methyldecahydroisoquinolines (XLV) was planned as an extension of this work, and also the synthesis of a number of 1-benzyl-2-alkyldecahydroisoquinolines (XLVI). These latter resemble particularly closely, in only slightly simplified form, a



XLV



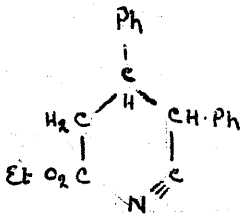
XLVI

SECTION 3.

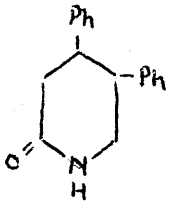
THE DECAHYDROISOQUINOLINES.

major portion of the morphine skeleton (I ; rings 1, 2 and 3).

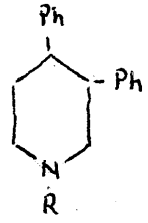
Adkins and Connor[56], and more recently Grundmann[57], have stated that copper chromite catalyst is ineffective in bringing about the reduction of nitriles. Barr and Cook[58], however, found that γ-cyanoesters of type (XLVII) are



XLVII



XLVIII



XLIX

readily reduced by hydrogenation over this catalyst to give N-alkylpiperidines of type (XLIX), in which the N-alkyl group is provided by the alcohol used as solvent. Badger, Cook and Walker[59] confirmed this and extended the scope of the reaction. From the work of Barr and Cook (loc.cit.) and of Koelsch[60] it is clear that the conversion of γ-cyanoesters into N-alkylpiperidines proceeds in four stages:-

1) Reduction of the cyano group.
2) Intramolecular condensation with the elimination of alcohol to give the piperidone (XLVIII) which has been isolated in certain cases.
3) Reduction of the piperidone to the piperidine.
4) Alkylation of the piperidine by the alcohol used as solvent.

Thus it has been shown that not only can certain cyanides be reduced by the use of copper chromite catalyst, but that indeed this reaction provides a new and convenient method for the preparation of N-alkylpiperidines. Appropriate γ-cyanoesters were obtained by the Michael reaction, and thus it was possible to prepare, for example, 3:4-diphenyl-1-alkylpiperidines in two operations from phenylacetonitrile and ethyl cinnamate.

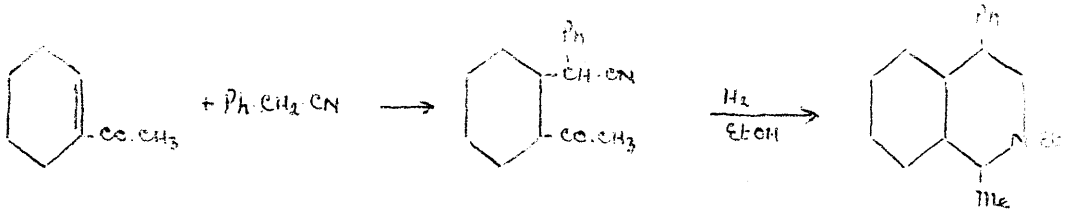
Barr and Cook (loc.cit.) extended this method to the synthesis of a decahydroisoquinoline derivative by reductive-cyclisation of an appropriate cyano-ketone. 1-Acetylcyclohex-1-ene[61,62] and phenylacetonitrile in the presence of sodium ethoxide condensed to give α-2-acetylcyclohexylphenylacetonitrile (L), which on hydrogenation in ethanol over copper chromite catalyst underwent reductive-cyclisation to give a colourless liquid base; the composition of the base (and its picrate derivative) being in agreement with its identification as 4-phenyl-1-methyl-2-ethyldecahydroisoquinoline (LI). It was decided to repeat this work in order to confirm the identity of the product, and this having been satisfactorily achieved, to extend it to the synthesis of other N-alkyl-4-phenyl-1-methyldecahydroisoquinolines by carrying out the hydrogenation in a variety of alcoholic solvents.

4-Phenyl-1-methyl-2-ethyldecahydroisoquinoline.

1-Acetylcyclohex-1-ene[61,62] was prepared from cyclohexene and acetyl chloride by the Friedel-Crafts' reaction in carbon disulphide in the presence of stannic chloride, followed by elimination of hydrogen chloride from the intermediate chloro-ketone by refluxing with diethyl-aniline. The product was characterised by the semicarbazone, m.p. 220° (decomp.) (Darzens[61] records a melting point of 220° for the semicarbazone). The oxime was also prepared, by refluxing 1-acetylcyclohex-1-ene for 4 hours with an aqueous alcoholic solution of hydroxylamine hydrochloride and potassium hydroxide, and crystallised from aqueous methanol in colourless needles m.p. 61-62°. (Darzens[61] and Wallach[63] respectively record the melting point of the oxime as 90° and 99°.) This oxime appears to be the stereoisomer of that previously reported. It was unchanged when irradiated with ultra-violet light for 3 hours. The same product was obtained when acetylcyclohexene was treated with hydroxylamine hydrochloride in pyridine at 100°. It may be noted that Wallach (loc.cit.) prepared the oxime in the cold.

The Michael condensation between acetylcyclohexene and phenylacetonitrile in the cold in presence of sodium ethoxide gave α-2-acetylcyclohexylphenylacetonitrile (L),

m.p. 120°. (Barr and Cook[58] record a melting point of 120°



L LI

for -2-acetylcyclohexylphenylacetonitrile.). This was further characterised by the semicarbazone, m.p. 229-230° (decomp.).

Hydrogenation of α-2-acetylcyclohexylphenylacetonitrile in ethanol over copper chromite catalyst (prepared as in Organic Syntheses[64] except that the decomposition of the complex was carried out by the original Adkins[65] method of heating over a free flame), gave a liquid base distilling at 166°/2.5 mm., which was converted to the picrate. The picrate appeared to be a mixture, and this was confirmed when on fractional crystallisation from ethanol it was separated into two stereoisomeric compounds, "α"-4-phenyl-1-methyl-2-ethyldecahydroisoquinoline picrate, m.p. 178-179°, and "β"-4-phenyl-1-methyl-2-ethyldecahydroisoquinoline picrate, m.p. 209-210° (decomp.). From the picrates were obtained the corresponding bases (LI), 'α'-4-phenyl-1-methyl-2-ethyldecahydroisoquinoline, b.p. 155°/2 mm., and 'β'-4-

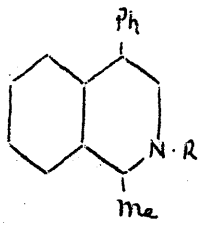
phenyl-1-methyl-2-ethyldecahydroisoquinoline, b.p. 136°/1 mm. The base (b.p. 135°/1 mm.) and picrate (m.p. 187-190°) reported by Barr and Cook (loc.cit.) obviously consisted of a mixture of these 'α' and 'β' isomers.

4-Phenyl-1-methylisoquinoline.

In order to confirm the identity of the bases obtained above a portion of the mixed base was dehydrogenated by heating at 300-320° with palladium black catalyst. The product was identified by analysis and by melting point (78-79°) as 4-phenyl-1-methylisoquinoline (Krabbe[66] records a melting point of 79° for 4-phenyl-1-methylisoquinoline). The picrate was also prepared, and its composition confirmed by analysis, but the melting point, 229-230° (decomp.), is not in accordance with that recorded by Krabbe (loc.cit.), who records a melting point of 206° for 4-phenyl-1-methylisoquinoline picrate.

Despite the divergent melting points of the picrates it was considered that the identity of the bases obtained by reductive-cyclisation of α-2-acetylcyclohexylphenylacetonitrile was substantially established by the above work, and the synthesis was extended to the preparation of other N-alkyl-4-phenyl-1-methyldecahydroisoquinolines. Hydrogenation of acetylcyclohexylphenylacetonitrile in methanol gave

'α'- and 'β'-4-phenyl-1:2-dimethyldecahydroisoquinolines (LII; R = Me) which were characterised as the corresponding picrates, through which salt the separation was achieved by fractional crystallisation. Similarly, hydrogenation of acetylcyclohexylphenylacetonitrile in n-propanol gave 'α'- and 'β'-4-phenyl-1-methyl-2-n-propyldecahydroisoquinolines (LII; R = n-Pr), separated and characterised as before by means of the picrates.



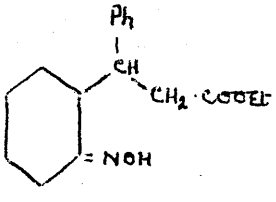
LII

In each case, it will be noted, two stereoisomeric decahydroisoquinolines were obtained. The relative proportions of the two isomers in the mixed basic product of the reduction reaction, as indicated by the amounts of the 'α' and 'β' picrates isolated, were not constant however, but appeared to vary regularly through the series of N-alkyldecahydroisoquinolines prepared. In the case of the N-methyldecahydroisoquinolines the approximate ratio was $\alpha : \beta = 1:1$; for the N-ethyl compounds $\alpha : \beta = 2\text{-}3 : 1$; and for the N-n-propyl compounds $\alpha : \beta = 10 : 1$. These ratios are approximate only, but they give an indication of the rapid decrease in the proportion of the 'β' isomer on ascent of the homologous series. The 'β' isomer corresponds to the picrate of higher melting point, and the

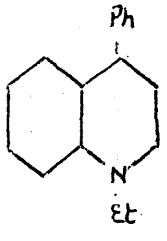
base of (probably) lower boiling point. As eight optically inactive stereoisomeric forms of compounds of this type (LII) may be expected, it is not possible to define the configurations of these 'α' and 'β' isomers.

The synthesis of N-alkyl-4-phenyl-1-methyldecahydroisoquinolines by the reductive-cyclisation of oxime-esters.

Badger, Cook and Walker[53] showed that suitable oxime-esters could be reduced to N-alkylpiperidine derivatives in a very similar manner to the γ-cyanoesters above. For example, these workers obtained 4-phenyl-1-ethyldecahydroquinoline (LIV) in satisfactory yield by the reductive-



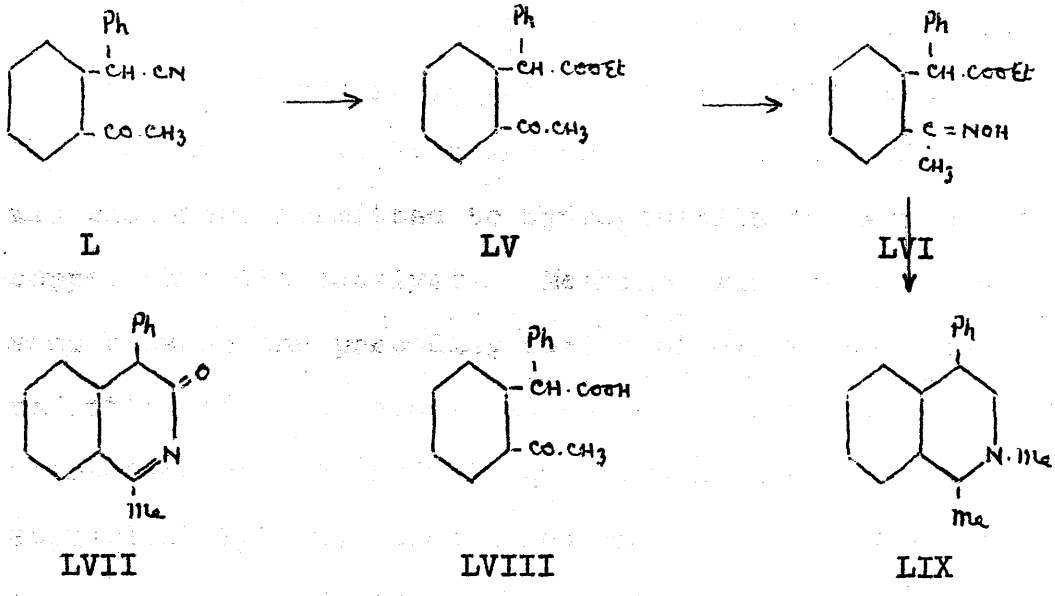
LIII



LIV

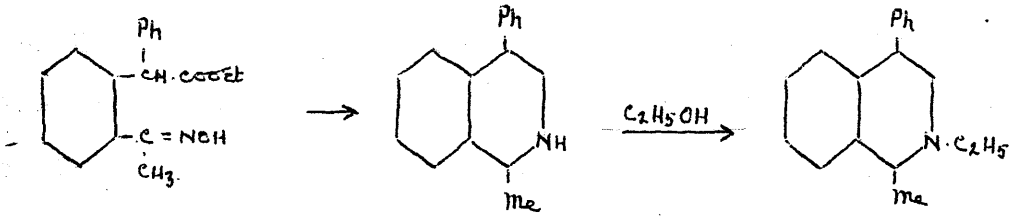
cyclisation of the oxime of ethyl β-2-ketocyclohexyl-β-phenylpropionate (LIII) in ethanol in presence of copper chromite catalyst. The possibility of synthesising N-alkyldecahydroisoquinolines by this method was therefore investigated.

α-2-Acetylcyclohexylphenylacetonitrile (L) was hydrolysed with alcohol and sulphuric acid to give



ethyl-α-2-acetylcyclohexylphenylacetate (LV). The identity of this product was confirmed by alkaline hydrolysis to the acid (LVIII) and comparison with an authentic specimen of α-2-acetylcyclohexylphenylacetic acid prepared directly by alkaline hydrolysis of α-2-acetylcyclohexylphenylacetonitrile. In this latter hydrolysis a quantity of non-acidic material was also isolated, which appears to be 4-phenyl-1-methyl-5:6:7:8:9:10-hexahydro-3-isoquinolone (LVII), formed evidently by intramolecular cyclisation of the intermediate amide with elimination of the elements of water. A similar cyclic product was obtained in the condensation of malonamide with 1-phenylacetylcyclohex-1-ene (p.61).

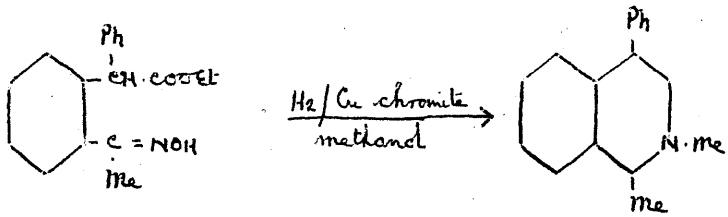
All attempts to obtain a crystalline oxime (LVI) of ethyl α-2-acetylcyclohexylphenylacetate were unsuccessful, the product invariably being an oil. This crude product was therefore submitted to hydrogenation in methanol over copper chromite catalyst. Methanol was preferred as solvent because the preceding series of experiments on the reduction of cyanoesters had shown that the two possible stereoisomeric decahydroisoquinolines were obtained in approximately equal quantities when the reduction was carried out in methanol, whereas when higher alcohols were used the proportion of the 'β' isomer of the decahydroisoquinoline decreased considerably: and it was therefore considered that the probability of isolating both isomers, should these actually be formed in the reduction of the oxime-ester, would be ehhanced by carrying out the reduction in methanol. Barr and Cook[58] have shown that when the reduction of cyanoesters is carried out in an inert solvent such as dioxane the small amount of alcohol formed during the cyclisation is sufficient to cause partial alkylation of the product:



LVI LI

but it was considered that the small amount of ethanol

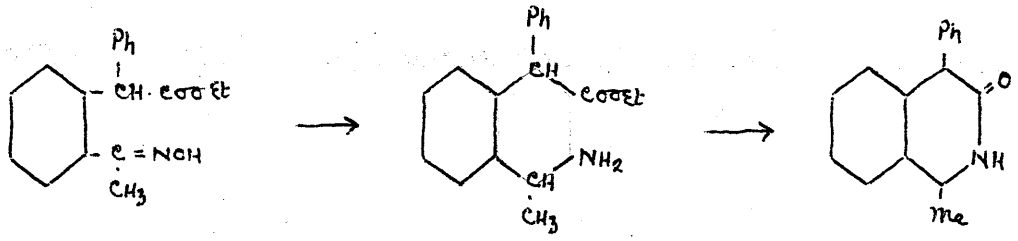
produced in the reductive-cyclisation of this oxime-ester (LVI) would be insignificant compared with the large volume of methanol used, and this proved to be the case. The small yield of basic material from the reduction was fractionally distilled, and the first fraction was identified by means of the picrate as the 'β' isomer of 4-phenyl-1:2-dimethyldecahydroisoquinoline (LIX). Strangely enough,



LVI LIX

this product appeared to be homogeneous, and unaccompanied by the 'α' isomer which would certainly have been detected had it been present in any significant proportion.

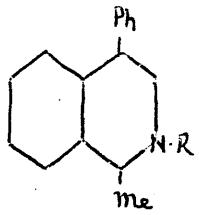
The second fraction of the distillate, which was now insoluble in dilute hydrochloric acid, solidified, and by fractional crystallisation was separated into two isomeric components. In view of the acid-insolubility of these compounds, and the fact that reductive-cyclisations of this type are known to proceed by way of the piperidones (Barr and Cook[58]; Badger, Cook and Walker[53]), these two compounds are regarded as isomeric 4-phenyl-1-methyldecahydro-3-isoquinolones (LXI). These are evidently formed during

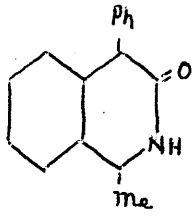


LVI LX LXI

distillation, by intramolecular cyclisation with elimination of the elements of water from the acid-soluble amine-ester (LX). The two isomers are probably of the same type as those of the decahydroisoquinolines previously encountered.

The isolation of two stereoisomeric forms of these N-alkyl-4-phenyl-1-methyldecahydroisoquinolines (LII) from the reductive-cyclisation of the cyano-ketone α-2-acetyl-

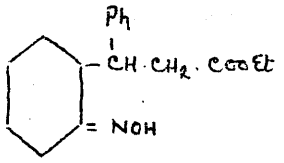




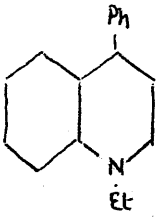
LII LXI

cyclohexylphenylacetonitrile, and of two stereoisomeric forms of the intermediate 4-phenyl-1-methyldecahydro-3-isoquinolone (LXI) from the reductive-cyclisation of the oxime-ester (LVI) is of some interest, as it will be recalled that Badger, Cook and Walker[53] isolated only one isomer of 4-phenyl-1-ethyldecahydroquinoline (LIV)

following similar hydrogenation of the oxime-ester (LIII;

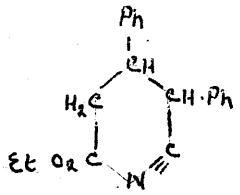


LIII

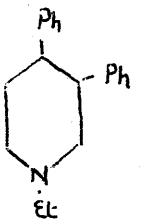


LIV

oxime of ethyl β -2-ketocyclohexyl-β -phenylpropionate). The yield in this case was approximately 60%, but the stereochemical homogeniety of the product was remarked upon. The same authors also obtained 4-p-methoxyphenyl-1-ethyldecahydroquinoline, by a similar method, in 70% yield free or almost free from stereoisomers. On the other hand, Barr and Cook[58] isolated two stereoisomeric 3:4-diphenyl-1-ethylpiperidines (XLIX) from the similar



XLVII



XLIX

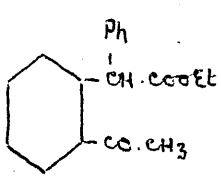
reductive-cyclisation of ethyl- γ -cyano- βγ -diphenylbutyrate (XLVII).

Specimens of 2-methyl-4-phenyl-1-methyldecahydroisoquinoline, 2-ethyl-4-phenyl-1-methyldecahydroisoquinoline and 2-n-propyl-4-phenyl-1-methyldecahydroisoquinoline, in

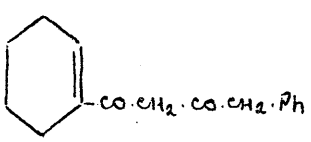
the form of aqueous solutions of the hydrochloride of the mixed isomeric bases, were submitted for pharmacological testing.

The condensation of 1-acetylcyclohex-1-ene with ethyl phenylacetate.

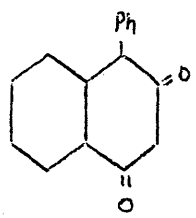
It was thought that ethyl α-2-acetylcyclohexylphenylacetate (LV) might be more readily available by direct Michael condensation of acetylcyclohexene and ethyl phenylacetate. In point of fact, however, a Perkin type condensation appeared to be favoured. None of the desired keto-ester was obtained, but the solid product of the reaction was separated by fractional crystallisation into two isomeric compounds of melting point 198° and 170° respectively, both of which gave dioxime derivatives. Microhydrogenation over Adams' catalyst in acetic acid resulted in an absorption of hydrogen equivalent to 6.05 and 5.9 double



LV



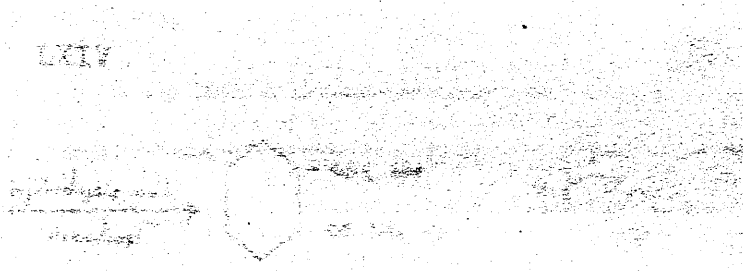
LXII



LXIII

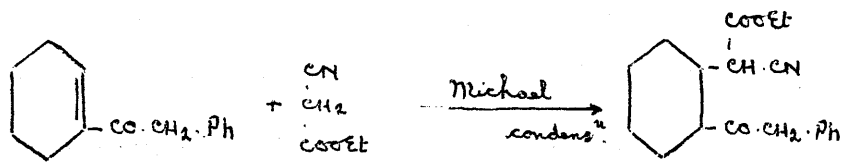
bonds per molecule respectively. As it was not possible to isolate and identify the products of the microhydrogenations, the identity of these condensation products could

not be established, but formulae (LXII) and (LXIII) are suggested as possible structures for these products.

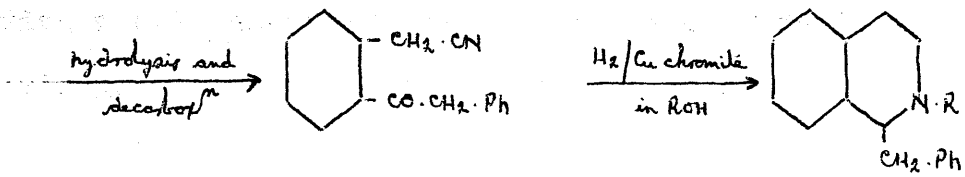


N-Alkyl-1-benzyldecahydroisoquinolines.

It was planned to extend this method of reductive-cyclisation to the synthesis of N-alkyl-1-benzyldecahydro-isoquinolines of type (LXVII) from cyano-ketones of type (LXV), an obvious route to the desired cyano-ketone being



LXIV LXV



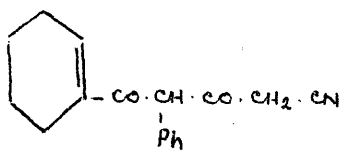
LXVI LXVII

the Michael condensation of 1-phenylacetylcyclohex-1-ene (LXIV) with ethyl cyanoacetate, followed by hydrolysis of the ester group of the product (LXV) and decarboxylation.

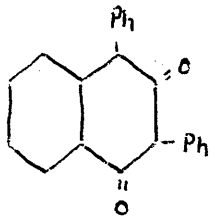
1-Phenylacetylcyclohex-1-ene was prepared by the Friedel-Crafts' reaction between cyclohexene and phenyl-acetyl chloride in carbon disulphide in the presence of stannic chloride, followed by elimination of hydrogen chloride from the intermediate chloro-ketone by refluxing with diethylaniline (Cook[67]). By using an excess of cyclo-hexene in the condensation the yield of phenylacetylcyclo-

hexene with respect to the less readily available starting material, phenylacetyl chloride, was improved considerably.

The condensation between phenylacetylcyclohexene and ethyl cyanoacetate in the presence of sodium ethoxide appeared, however, to take place by the Perkin method rather than the Michael, and none of the desired condensation product (LXV) was isolated. The solid product of the reaction, which appeared to be homogeneous, contained no ethoxyl group. No derivative (oxime, semicarbazone or dinitrophenylhydrazone) of a ketonic function could be obtained, but treatment with acetic anhydride yielded a diacetyl derivative. Microhydrogenation over Adams' catalyst in acetic acid, assuming



LXVIIIa



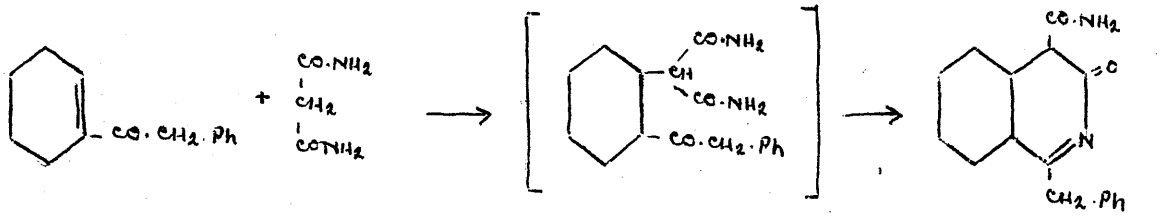
LXVIIIb

a molecular weight of 267, indicated the presence of 3 double bonds per molecule, but it was not possible to isolate and identify the product of the microhydrogenation. The identity of the condensation product therefore could not be established, but it is suggested that the structure may be of the type (LXVIIIa) or (LXVIIIb).

In both cases, therefore, where an ester was

condensed with an acylcyclohexene it was found that a Perkin type condensation appeared to be favoured in preference to the Michael. To avoid this difficulty the practicability of using compounds such as malonamide and cyanoacetamide which do not contain an ester grouping, in place of ethyl cyanoacetate, was investigated.

Malonamide[68], prepared from diethylmalonate and aqueous ammonia, condensed with 1-phenylacetylcyclohex-1-ene on refluxing in ethanol in the presence of sodium ethoxide, to give a colourless crystalline product in 38% yield. This product, however, proved on analysis to be not the

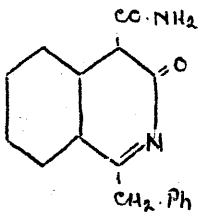


LXIX LXX

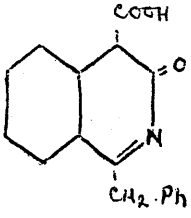
simple Michael addition product (LXIX), but 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxyamide (LXX), evidently formed from the Michael addition product by intramolecular cyclisation with elimination of the elements of water. (A similar cyclisation occurred during the hydrolysis of α-2-acetylcyclohexylphenylacetonitrile, p. 52). The possibility of this cyclisation was foreseen, and the

cyclic product was not considered disadvantageous for the purposes of the synthesis.

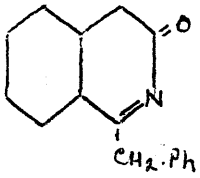
Treatment of this compound (LXX) in cold concentrated sulphuric acid with sodium nitrite solution (Bouveault[69]) was completely ineffective in converting the amide group to carboxyl. When, however, the compound was dissolved in 40% sulphuric acid at 100° and then treated with sodium nitrite solution (Gatterman[70]; Biltz and Kamman[71]) the desired acid, 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid (LXXI) was obtained in excellent yield. This acid then readily underwent de-



LXX



LXXI

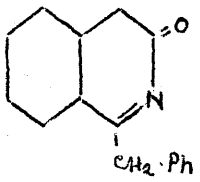


LXXII

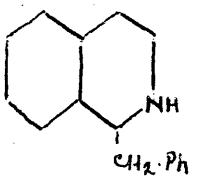
carboxylation when heated a few degrees above the melting point, to give 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone (LXXII).

This isoquinolone, however, proved completely resistant to hydrogenation over copper chromite catalyst, and was recovered unchanged after being submitted to hydrogenation in ethanol for 4 hours at 200° and 180 atm., the most severe conditions obtainable. Koelsch[60], synthesising

substituted piperidines, used sodium in boiling butyl alcohol to reduce pyridine derivatives to the corresponding piperidines, and also to reduce piperidones to piperidines. This method was therefore applied to 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone, and from the reduction product a



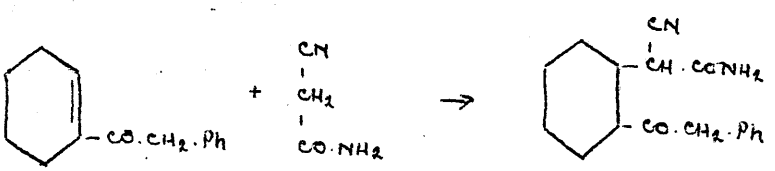
LXXII



LXXIII

small yield of a colourless, liquid base was isolated, which was converted to the hydrogen oxalate and identified as 1-benzyldecahydroisoquinoline hydrogen oxalate (hydrogen oxalate of LXXIII). A small quantity of non-basic oil which was also isolated appeared to be an intermediate product of the reduction.

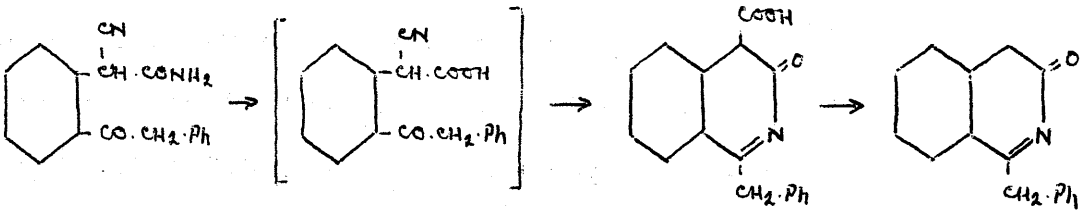
Cyanacetamide[68], prepared from ethyl cyanoacetate and aqueous ammonia, also condensed with 1-phenylacetylcyclohex-1-ene on refluxing in ethanol in the presence of sodium ethoxide. In this case the normal Michael addition product, α-2-phenylacetylcyclohexylcyanoacetamide (LXXIV) was obtained in 21% yield, and no cyclic product corresponding



LXXIV

to that (LXX) obtained from the condensation of phenylacetylcyclohexene and malonamide was observed.

As was the case with the cyclic malonamide condensation product (LXX), the Bouveault[69] method was ineffective in converting this amide to the corresponding acid. When the Gatterman[70,71] method was used this amide proved very sparingly soluble in dilute sulphuric acid, and it was necessary to carry out the reaction in 50% sulphuric acid at 140° to maintain the amide in solution: under these conditions a vigorous reaction ensued on addition of sodium nitrite solution. From the product of the reaction were isolated a quantity of unchanged α-2-phenylacetylcyclohexylcyanoacetamide (30%) and an acid (50%), which, however, proved to be not the expected α-2-phenylacetylcyclohexyl-

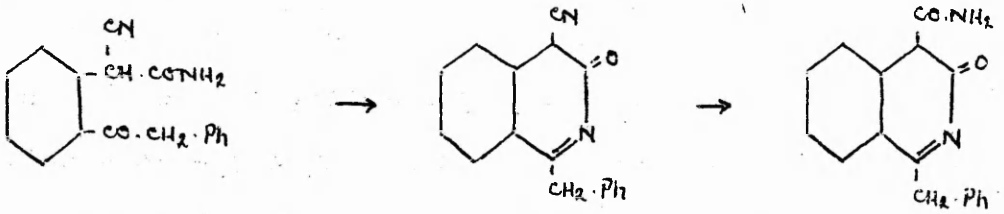


LXXIV LXXV LXXI LXXII

cyanoacetic acid (LXXV), but the cyclic product 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid (LXXI) identical with that previously obtained by the action of sodium nitrite on 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxyamide (LXX), the cyclic product of the

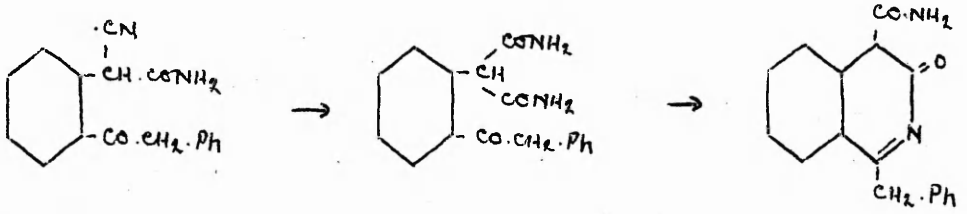
condensation of malonamide and phenylacetylcyclohexene. The identity of the acid was confirmed when on decarboxylation it gave 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone (LXXII) identical with that obtained previously.

Two possible routes may be suggested to account for the formation of this cyclic acid (LXXI). Under the rather severe conditions of the Gatterman reaction α-2-phenylacetylcyclohexylcyanoacetamide may undergo intramolecular



LXXIV LXXVI LXX

cyclisation with elimination of water to form the cyclic nitrile (LXXVI), followed by hydrolysis of the nitrile group to give the cyclic amide (LXX), which, as has already been shown, reacts readily with nitrous acid to give 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid. Alternatively, hydrolysis of the nitrile group of α-2-phenylacetylcyclohexylcyanoacetamide may occur first to give the di-amide (LXIX) which is known from the previous



LXXIV LXIX LXX

experiments to cyclise readily under comparatively mild conditions to give the cyclic amide (LXX), which reacts with nitrous acid to give 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid. The relative resistance of the cyano-amide (LXXIV) to cyclisation, as evidenced by the structures of the products of the Michael reactions of phenylacetylcyclohexene with malonamide and cyanoacetamide respectively, and the fact that the non-acidic portion of the product of the Gatterman reaction consisted entirely of unchanged phenylacetylcyclohexylcyanoacetamide and no evidence of any intermediate such as the cyclic nitrile (LXXVI) was found, strongly support the second hypothesis.

[illegible]

The [illegible]methylnaphthalenes

1:4-Dichloromethylnaphthalene (XVIII): 1:4-Dichloromethyl-naphthalene was prepared by the chloromethylation of [illegible] naphthalene with boiling aqueous formaldehyde and [illegible] chloric acid[44]. The reaction product, [illegible] crystallised from ethanol to a melting point [illegible] by [illegible]°, and this ... material was used in the [illegible] required experiments.

EXPERIMENTAL.

1:4-[illegible]methylnaphthalene ([illegible]). 1:4-Di-chloromethylnaphthalene ([illegible] g.) was dissolved in [illegible] benzene ([illegible] c.c.) and heated to boiling. [illegible] thiourea ([illegible] g.) in ethanol (150 c.c.) was added [illegible] a colourless precipitate formed [illegible] was refluxed for a further 30 minutes, when the reaction appeared complete. The mixture was then cooled and the solid product, 1:4-[illegible]methylnaphthalene [illegible] chloride, filtered off and crystallised from dilute hydro-chloric acid in small colourless needles ([illegible] g.; m.p. [illegible] (decomp.).

Found : C, 44.[illegible]; H, 4.[illegible]; [illegible]

[illegible] requires : C, [illegible]; H, [illegible]; [illegible]

Section 1.

The Bisdialkylaminoalkylnaphthalenes.

1:4-Bischloromethylnaphthalene (XXII): 1:4-Bischloromethylnaphthalene was prepared by the chloromethylation of naphthalene with boiling aqueous formaldehyde and hydrochloric acid[41]. The reaction product, m.p. 120-130°, was crystallised from ethanol to a melting point of approximately 132°, and this semi-pure material was used in the subsequent experiments.

1:4-Bisthiocarbamidomethylnaphthalene (XIX): 1:4-Bischloromethylnaphthalene (2.0 g.) was dissolved in dry benzene (25 c.c.) and heated to boiling; a solution of thiourea (1.5 g.) in ethanol (30 c.c.) was added dropwise. A colourless precipitate formed immediately, and the mixture was refluxed for a further 30 minutes, when the reaction appeared complete. The mixture was then cooled and the solid product, 1:4-bisthiocarbamidomethylnaphthalene hydrochloride, filtered off and crystallised from dilute hydrochloric acid in small colourless needles (0.9 g.), m.p. 270-271° (decomp.).

(Found : C, 44.8; H, 4.6; N, 14.5

$C_{14}H_{18}N_4S_2Cl_2$ requires : C, 44.6; H, 4.8; N, 14.8%).

The picrate was prepared from the hydrochloride in aqueous solution, and crystallised from acetone in yellow needles, m.p. 219-220° (decomp.).

	Found :	C, 41.2; H, 3.0
$C_{32}H_{22}O_{14}N_{10}S_2$	requires :	C, 41.0; H, 2.9%

1:4-Bisdiethylaminomethylnaphthalene (XX): 1:4-Bischloromethylnaphthalene (1.5 g.) was dissolved in dry benzene (25 c.c.) and heated to boiling; diethylamine (2.2 g.) in dry benzene (10 c.c.) was added dropwise and the mixture refluxed for 10 hours. After cooling the mixture was shaken with concentrated sodium hydroxide solution, the benzene layer separated and the aqueous portion extracted with benzene. The combined benzene solution was dried over anhydrous sodium sulphate, and evaporated, and the oil obtained was heated at 100° for 1 hour to remove excess diethylamine. The oil was then dissolved in benzene and extracted with dilute hydrochloric acid, the acid extract basified with sodium hydroxide solution, and extracted with benzene. This benzene extract was dried over anhydrous sodium sulphate and evaporated, and the oil obtained was distilled at 168-170°/1 m.m., giving a slightly cloudy,, colourless oil (0.8 g.), which darkened on standing. 1:4-Bisdiethylaminomethylnaphthalene hydrochloride, prepared from this base in ether solution, crystallised from

ethanol/ether in small colourless needles, m.p. 228-229° (decomp.).

	Found :	C, 63.1;	H, 8.3;	N, 7.0
$C_{20}H_{32}N_2Cl_2$	requires :	C, 63.2;	H, 8.6;	N, 7.3%

The picrate, prepared from the base in ethanol solution, crystallised from acetic acid in yellow needles, m.p. 203-204° (decomp.).

	Found :	C, 50.7;	H, 4.6;	N, 14.9
$C_{32}H_{36}O_{14}N_5$	requires :	C, 50.8;	H, 4.8;	N, 14.8%

1:4-Bis-N-piperidylmethylnaphthalene (XXI): 1:4-Bischloromethylnaphthalene (3.0 g.) was dissolved in dry benzene (25 c.c.) and heated to boiling; to this a solution of piperidine (5.0 g.) in dry benzene (20 c.c.) was added dropwise. A colourless crystalline precipitate began to form immediately, and the mixture was refluxed for a further 40 minutes, when the reaction appeared complete. After cooling the mixture was shaken with sodium hydroxide solution, the benzene layer separated, and the benzene washings of the aqueous layer added to this. The benzene solution was then dried over anhydrous sodium sulphate and evaporated, and the oil obtained was heated at 140°/14 m.m. for 1 hour to remove excess piperidine. The oil was then dissolved in benzene and extracted with dilute hydrochloric acid, the acid extract basified with sodium hydroxide solution and extracted with

benzene. This extract, dried over anhydrous sodium sulphate and evaporated, gave a light brown oil, which decomposed slightly at 200°/14 m.m. without distilling, and was purified by chromatography through alumina; the pale yellow product partly solidified. 1:4-Bis-N-piperidylmethylnaphthalene hydrochloride was prepared from this base in ether, and crystallised from ethanol in colourless plates, m.p. 305-306° (decomp.).

	Found :	C, 66.9;	H, 8.2;	N, 6.9
$C_{22}H_{32}N_2Cl_2$	requires :	C, 66.8;	H, 8.1;	N, 7.1%

From this hydrochloride was obtained the base, 1:4-bis-N-piperidylmethylnaphthalene, which crystallised from ethanol in colourless prisms m.p. 135-136°.

	Found :	C, 82.1;	H, 9.3;	N, 8.7
$C_{22}H_{30}N_2$	requires :	C, 82.0;	H, 9.3;	N, 8.7%

Attempted condensation of 1:4-bischloromethylnaphthalene and tetramethylthiourea.

1:4-Bischloromethylnaphthalene (5.0 g.) was dissolved in dry xylene (25 c.c.) and the solution heated to boiling; the theoretical quantity of tetramethylthiourea (5.25 g.) in dry xylene (25 c.c.) was added dropwise and the solution refluxed for 15 hours. A quantity of colourless solid separated during this time and was filtered from the cold solution; a small additional quantity was obtained after a

further 6 hours' refluxing. This solid was deliquescent, and its aqueous solution was proved to contain chloride ion: it was therefore presumed to be the methochloride of either tetramethylthiourea or the desired condensation product. The compound decomposed on distillation to give tetramethylthiourea, m.p. 79° (after crystallisation from petroleum ether), which was identified by comparison with an authentic specimen, thus confirming its identification as the methochloride of tetramethylthiourea. The xylene solution after the removal of this solid was extracted with dilute hydrochloric acid, the acid extract basified with sodium hydroxide solution, and extracted with benzene. This extract was dried over anhydrous sodium sulphate and evaporated, to give a small yield of an oily solid, presumably a mixture of the desired condensation product and unreacted tetramethylthiourea, which started to decompose on distillation, and could not be separated.

In another experiment the reaction mixture, after being refluxed for 21 hours, cooled and filtered, was allowed to stand at room temperature for 1 month. A further quantity of the methochloride separated, but again no product could be isolated from the residual solution.

Section 2.

The 4-Phenyl-4-hydroxypiperidines.

2:2:6-Trimethyl-4-piperidone (XXXIII): 4-Amino-4-methylpentan-2-one (diacetonamine) was prepared by condensing mesityl oxide with aqueous ammonia in the cold, and isolated as the hydrogen oxalate[48]. This condensed with acetal in ethanol solution[49] to give the hydrogen oxalate of 2:2:6-trimethyl-4-piperidone (vinyldiacetonamine), from which the base 2:2:6-trimethyl-4-piperidone was extracted.

2:2:6-Trimethyl-4-phenyl-4-hydroxypiperidine (XXXIV): To a Grignard solution prepared in the usual way from bromobenzene (66.8 g.), magnesium (10.2 g.) and ether (150 c.c.), a solution of 2:2:6-trimethyl-4-piperidone (20 g.) in ether (25 c.c.) was added dropwise with stirring. When the vigorous reaction had subsided the solution was refluxed for 1 hour, cooled, and the complex decomposed by pouring into a mixture of ice and aqueous ammonium chloride solution (100 c.c.). After standing overnight the solid was filtered, dried, and washed with ether; the product was then extracted from the accompanying magnesium hydroxide with hot ethanol, and crystallised from ethanol/ether in colourless prisms, m.p. 250-251° (decomp.). From this hydrochloride by basification with sodium hydroxide solution and extraction with ether was obtained the base, 2:2:6-trimethyl-4-phenyl-4-

hydroxypiperidine, which crystallised from 80/100° petroleum ether in colourless needles, m.p. 91-92° (13.0 g.)

	Found : C, 76.7; H, 9.9; N, 6.6
$C_{14}H_{21}ON$	requires : C, 76.7; H, 9.6; N, 6.4%

The hydrochloride, prepared from the base in ether solution, crystallised from ethanol/ether in colourless prisms, m.p. 247-248° (decomp.).

	Found : C, 65.8; H, 8.5; N, 5.7
$C_{14}H_{22}ONCl$	requires : C, 65.7; H, 8.6; N, 5.5%

During the preparation of this hydrochloride a small quantity was isolated of another material, which crystallised from ethanol/ether in colourless prisms, m.p. 266-267° (decomp.), and was identified by comparison with an authentic specimen as 2:2:6-trimethyl-4-phenyl-1:2:5:6 (or 1:2:3:6)-tetrahydropyridine hydrochloride (see below). This was evidently derived by dehydration of the 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine.

The picrate, prepared from the base in ether solution, crystallised from water in yellow prisms, m.p. 188-189° (decomp.).

	Found : C, 53.6; H, 5.4; N, 12.8
$C_{20}H_{24}O_8N_4$	requires : C, 53.6; H, 5.4; N, 12.5%

The hydrogen oxalate, prepared from the base in ether solution,

crystallised from ethanol/ether in small colourless needles, m.p. 201-202° (decomp.).

	Found :	C, 62.2;	H, 7.5;	N, 4.8
$C_{16}H_{23}O_5N$ requires :		C, 62.1;	H, 7.4;	N, 4.5%

The acetate crystallised from acetone in colourless prisms, m.p. 223-224° (decomp.).

	Found :	C, 69.2;	H, 8.9;	N, 5.2
$C_{16}H_{25}O_3N$ requires :		C, 68.8;	H, 9.0;	N, 5.0%

The product, m.p. 250-251°, isolated directly from the Grignard reaction, was proved by comparison with an authentic specimen to be essentially the hydrochloride of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine. The analysis, however (Found : C, 57.0; H, 7.2; N, 5.4%), did not correspond, and varied appreciably with different specimens: no reason for this was found. Increasing the time of refluxing increased slightly the yield of this material from the reaction, but also promoted the formation of other products which rendered isolation of the pure base more difficult.

When 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine was distilled (107-110°/1.5 m.m.) some dehydration occurred. The product from distillation, or from refluxing in ethanol solution for 5 hours, crystallised from petroleum ether in colourless prisms, m.p. 96-97°. This appears to be a

crystalline modification of the original base. It did not depress the melting point of the original base, and on repeated crystallisation reverted to the original form, colourless needles, m.p. 91-92°.

2:2:6-Trimethyl-4-phenyl-4-hydroxypiperidine did not give a urethane derivative on treatment with phenylisocyanate. Dehydration of the alcohol occurred and carbanilide, formed by reaction of the phenylisocyanate with water eliminated from the alcohol, was isolated.

2:2:6-Trimethyl-4-phenyl-1:2:5:6 (or 1:2:3:6)-tetrahydropyridine (XXXVI or XXXVII; R = H): 2:2:6-Trimethyl-4-phenyl-4-hydroxypiperidine (1.75 g.) in ethanol (15 c.c.) was saturated with hydrogen chloride and heated at approximately 80° for 6 hours, during which time the solution was periodically resaturated with hydrogen chloride. The solution was then cooled, basified with dilute sodium hydroxide solution, and extracted with ether. The extract was dried over anhydrous sodium sulphate, evaporated, and the oil obtained distilled at 90-95°/0.5 m.m. to give a pale yellow oil (1.5 g.) which darkened rapidly on exposure to air. The hydrochloride was prepared from this base in ether solution, and crystallised from ethanol/ether in colourless prisms, m.p. 266-267° (decomp.).

	Found : C, 70.6; H, 8.3; N, 6.1
$C_{14}H_{20}NCl$	requires : C, 70.8; H, 8.4; N, 5.9%

The hydrogen oxalate was prepared from the base in ether solution, and crystallised from ethanol/ether in colourless prisms, m.p. 207-208° (decom.).

Found :	C, 65.8; H, 6.9; N, 5.1
$C_{16}H_{21}O_4N$ requires :	C, 66.0; H, 7.2; N, 4.8%

The picrate was also prepared, but could not readily be separated from that of the unchanged alcohol with which it was contaminated.

Attempted etherification of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine (XXXIV).

With alcohol and acid catalyst: 2:2:6-Trimethyl-4-phenyl-4-hydroxypiperidine (0.2 g.) was dissolved in methanol (1 c.c.) and concentrated sulphuric acid in methanol solution was added till the mixture was slightly acidic. The mixture was then allowed to stand at room temperature for 2 hours, then basified with sodium hydroxide solution and extracted with ether. From this ether extract only unchanged starting material (0.1 g.) was isolated.

Under the same conditions, when methanol saturated with hydrogen chloride was used in place of the sulphuric acid solution, a mixed product resulted which could not be separated. When the time of reaction was increased to 6 hours the only product isolated was 2:2:6-trimethyl-4-

phenyl-1:2:5:6 (or 1:2:3:6)-tetrahydropyridine, identified by comparison with an authentic specimen..

Identical results were obtained using ethanol in place of methanol.

By dimethyl sulphate on the Grignard complex: 2:2:6-Trimethyl-4-piperidone (5.0 g.) was reacted as before with a Grignard solution (50% excess) prepared from bromobenzene (16.7 g.), magnesium (2.55 g.) and ether (75 c.c.), and the solution refluxed for 8 hours. The solution was then cooled and the theoretical quantity of dimethyl sulphate (13.4 g.) in ether (30 c.c.) added dropwise with stirring. After the addition was complete the solution was refluxed for 1 hour, then cooled and decomposed with ice and aqueous ammonium chloride. The solid product (7.6 g.) was filtered, washed with ether and crystallised from ethanol/ether in colourless prisms, m.p. 250-251° (decomp.). By comparison with an authentic specimen this was identified as the hydrochloride of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine. A further quantity (1.9 g.) of 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine was obtained on basification of the aqueous liquor.

In another experiment the reaction of the piperidone with the Grignard solution was carried out as above. To

this solution in the cold was then added 150% excess of dimethyl sulphate (33.5 g.) in benzene (100 c.c.), the mixture refluxed for 10 hours, then cooled and decomposed with ice and aqueous ammonium chloride as before. No solid separated. Basification of the aqueous portion of the liquor with sodium hydroxide solution and extraction with ether yielded a small quantity of basic oil. Extraction of the organic portion of the liquor with dilute hydrochloric acid, followed by basification of the acid extract with sodium hydroxide solution and extraction with ether gave a brown basic oil (3.25 g.), which did not solidify, and which decomposed on distillation.

2:2:6-Trimethyl-4-phenyl-4-acetoxypiperidine (XL): 2:2:6-Trimethyl-4-piperidone (5.0 g.) was reacted as before with phenylmagnesium bromide solution (50% excess) and the mixture refluxed for 13 hours. Acetic anhydride (11.0 g.; 200% excess) in ether solution was then added in the cold and the solution refluxed for a further 9 hours, then cooled and decomposed with ice and excess 6N hydrochloric acid. The aqueous liquor was separated, basified with sodium hydroxide solution and extracted with chloroform. This extract, dried over anhydrous sodium sulphate and evaporated, gave a basic oil (0.3 g.) distilling at 110-120°/2 m.m., and

a quantity of unreacted piperidone (0.7 g.). From the oil was isolated a very small quantity of colourless crystalline material, insoluble in ether, which crystallised from ethanol/ether in colourless prisms, m.p. 176-177° (decomp.), and whose composition is in agreement with its identification as 2:2:6-trimethyl-4-phenyl-4-acetoxypiperidine acetate.

Found :	C, 67.1; H, 8.1; N, 4.6
$C_{18}H_{27}O_4N$ requires :	C, 67.3; H, 8.4; N. 4.4%

This acetate, dissolved in ethanol and treated with hydrogen chloride, gave a product which crystallised from ethanol/ether in colourless prisms, m.p. 238-239° (decomp.), whose composition is in agreement with its identification as 2:2:6-trimethyl-4-phenyl-4-acetoxypiperidine hydrochloride.

Found :	C, 64.3; H, 7.9; N, 4.8
$C_{16}H_{24}O_2N$ Cl requires :	C, 64.5; H, 8.1; N, 4.7%

The remainder of the oil, which did not solidify, was converted to the hydrochloride in ether solution, and the product crystallised from ethanol/ether in colourless prisms, m.p. 264-265° (decomp.). This was identified by comparison with an authentic specimen and by analysis as 2:2:6-trimethyl-4-phenyl-1:2:5:6 (or 1:2:3:6)-tetrahydropyridine hydrochloride:

Found :	C, 70.9; H, 8.3; N, 5.4
$C_{14}H_{20}N$ Cl requires :	C, 70.8; H, 8.4; N, 5.9%

In another experiment, where a smaller excess (10%) of acetic anhydride was used, and the time of refluxing after its addition reduced to 3 hours, the product obtained was an oil (3.5 g.) which distilled at 122-125°/3 m.m. From this was isolated a few milligrams of a material which crystallised from acetone in colourless prisms, m.p. 223-224° (decomp.), whose composition is in agreement with its identification as 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine acetate:

	Found : C, 69.2; H, 8.9; N, 5.2
$C_{16}H_{25}O_3N$	requires : C, 68.8; H, 9.0; N, 5.0%

comparison with a specimen prepared directly from 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine confirmed this. The acetate, dissolved in ethanol and treated with hydrogen chloride, gave a product which crystallised from ethanol/ether in colourless prisms, m.p. 244° (decomp.). This was identified by comparison with an authentic specimen and by analysis as 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine hydrochloride:

	Found : C, 66.0; H, 8.7; N, 5.5
$C_{14}H_{22}O$ N Cl	requires : C, 65.7; H, 8.6; N, 5.5%

The remainder of the oil, by conversion to the hydrochloride and comparison with an authentic specimen, was proved to be mainly 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine.

1-Acetyl-2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine (XXXIX): 2:2:6-Trimethyl-4-phenyl-4-hydroxypiperidine (0.25 g.) was refluxed with excess acetic anhydride (2.5 g.) for 5 minutes; the solution was then cooled, basified with sodium hydroxide solution and extracted with chloroform. The extract was washed with dilute hydrochloric acid to remove basic material, dried over anhydrous sodium sulphate and evaporated, giving an oil (0.25 g.) which solidified on standing. Crystallisation from 80/100° petroleum ether gave a colourless crystalline material which melted sharply at 121-122°: consistent analyses, however, could not be obtained. From this material by fractional crystallisation from 80/100° petroleum ether was isolated 1-acetyl-2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine (0.1 g.), in colourless elongated prisms, m.p. 112-113°:

Found :	C, 73.2; H, 8.8; N, 5.1
$C_{16}H_{23}O_2N$ requires :	C, 73.6; H, 8.8; N, 5.4%

No other product could be isolated from the remaining material.

1:2:2:6-Tetramethyl-4-phenyl-4-hydroxypiperidine (XXXV): 2:2:6-Trimethyl-4-phenyl-4-hydroxypiperidine (2.0 g.) was heated with 40% formaldehyde solution (2.0 g.) at 100°. After 1 hour a vigorous reaction occurred and the whole mass

solidified. The solid was washed free from formaldehyde with water, dried at 100° and crystallised from light petroleum. 1:2:2:6-Tetramethyl-4-phenyl-4-hydroxy-piperidine formed colourless needles, m.p. 133-134°.

	Found : C, 77.4; H, 9.7; N, 6.2
$C_{15}H_{23}ON$	requires : C, 77.3; H, 9.9; N, 6.0%

The hydrochloride, prepared from the base in ether solution, crystallised from ethanol/ether in colourless prisms, m.p. 243-244° (decomp.).

	Found : C, 66.8; H, 8.9; N, 5.4
$C_{15}H_{24}ON\,Cl$	requires : C, 66.8; H, 8.9; N, 5.2%

The picrate, prepared from the base in ether solution, crystallised from acetic acid in yellow prisms, m.p. 230-231° (decomp.).

	Found : C, 54.8; H, 5.9; N, 11.8
$C_{21}H_{26}O_8N_4$	requires : C, 54.6; H, 5.6; N, 12.1%

The hydrogen oxalate was unsatisfactory, apparently on account of dehydration of the alcohol.

1:2:2:6-Tetramethyl-4-phenyl-4-hydroxypiperidine did not give a urethane derivative with phenylisocyanate, but dehydration occurred and the water eliminated reacted to form carbanilide.

1:2:2:6-Tetramethyl-4-phenyl-1:2:5:6 (or 1:2:3:6)-tetrahydropyridine (XXXVI or XXXVII; R = Me): 1:2:2:6-Tetramethyl-4-phenyl-4-hydroxypiperidine (0.5 g.) in ethanol (10 c.c.) was saturated with hydrogen chloride and heated at 80° for 7 hours, during which time the solution was periodically resaturated with hydrogen chloride. The solution was then basified with sodium hydroxide solution and extracted with ether. The extract, dried over anhydrous sodium sulphate and evaporated, gave a brown, basic oil which did not solidify. This base was converted to the picrate in ethanol, and 1:2:2:6-tetramethyl-4-phenyl-1:2:5:6 (or 1:2:3:6)-tetrahydropyridine picrate crystallised from ethanol in yellow needles, m.p. 161-162° (decomp.)

	Found : C, 57.5; H, 5.4; N, 12.6
$C_{21}H_{24}O_7N_4$	requires : C, 57.6; H, 5.4; N, 12.6%

Attempted esterification of 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine (XXXV).

a). With acetic anhydride. The acetylation of 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine with acetic anhydride was investigated over a wide range of conditions. The alcohol was unaffected when treated with acetic anhydride, alone or diluted with benzene, for 1 hour at temperatures up to 100°. Acetic anhydride with pyridine, sodium acetate or a trace of concentrated sulphuric acid as catalyst caused

dehydration of the alcohol to a varying extent, depending on the severity of the conditions: only unchanged alcohol and (sometimes) the dehydration product could be isolated from the mixed product of the reaction.

b). With acetyl chloride. Acetyl chloride in the cold, with or without an inert diluent (ether, benzene) brought about complete dehydration of the alcohol within 48 hours. In the presence of a basic catalyst (pyridine, dimethylaniline) acetyl chloride gave a mixed product similar to that obtained above.

c). By acetic anhydride on the Grignard complex. A solution of ethylmagnesium bromide was prepared in the usual way from magnesium (0.25 g.), ethyl bromide (1.1 g.) and ether (5 c.c.), refluxed for 2½ hours. 1:2:2:6-Tetramethyl-4-phenyl-4-hydroxypiperidine (0.2 g.) in ether solution was added slowly in the cold to 2 c.c. of this solution, and the mixture refluxed for 1½ hours, when a colourless solid separated. The mixture was then cooled in ice while acetic anhydride (2.0 g.) was added dropwise with shaking; further precipitation occurred. The mixture was refluxed gently for 30 minutes, cooled and decomposed by pouring on to ice/acetic acid. No solid separated. The aqueous layer was separated, washed with ether, basified with sodium carbonate and extracted with chloroform: the extract was dried over anhydrous

sodium sulphate and evaporated, giving a brown oil (0.2 g.). From this oil was isolated a few milligrams of an ether-insoluble, deliquescent solid. On account of its deliquescence this product could not be further investigated, but its properties indicated its identification as a salt of one of the basic products appearing in the reaction. The remaining oil was a mixture from which no identifiable material could be isolated.

In another experiment, after the addition of acetic anhydride to the solution containing the Grignard complex of the alcohol, the reaction mixture was allowed to stand at room temperature for 1½ hours, then decomposed as before. In this case the only product isolated was unchanged alcohol (.05 g.), isolated as the picrate and identified by comparison with an authentic specimen. The remainder of the product was a mixed oil from which no identifiable product could be isolated.

Section 3.

The Decahydroisoquinolines.

1-Acetylcyclohex-1-ene (LXIV): 1-Acetylcyclohex-1-ene was prepared from cyclohexene and acetyl chloride by the Friedel-Crafts' reaction in carbon disulphide in the presence of stannic chloride, followed by elimination of hydrogen chloride from the intermediate chloro-ketone by refluxing with diethylaniline[61,62], and was characterised by the semicarbazone, m.p. 220° (decomp.). (Darzens[61] records a melting point of 220° for the semicarbazone.)

1-Acetylcyclohex-1-ene (8.0 g.) was added to a solution of hydroxylamine hydrochloride (5.0 g.) and potassium hydroxide (3.0 g.) in water (13 c.c.): ethanol was added until a clear solution was obtained and the mixture refluxed for 1 hour. Further potassium hydroxide solution was added to neutralise the mixture and refluxing continued for a further 3 hours. The mixture was then poured into water and made slightly acid with dilute hydrochloric acid. The solid (3.0 g.) which separated crystallised from aqueous methanol, giving 1-acetylcyclohex-1-ene oxime (2.1 g.) as colourless needles, m.p. 61-62°.

	Found: C, 69.3; H, 9.3; N, 9.9
$C_8H_{13}ON$	requires: C, 69.1; H, 9.1; N, 10.1%

In another experiment, where acetylcyclohexene was heated at 100° for 4 hours with hydroxylamine hydrochloride in pyridine solution, the same product was obtained. (Darzens[61] and Wallach[63] respectively record the melting point of the oxime as 90° and 99°.) This oxime was irradiated with ultra-violet light for 3 hours without effect.

α-2-Acetylcyclohexylphenylacetonitrile (L): To a mixture of 1-acetylcyclohex-1-ene (20 g.) and phenylacetonitrile (20 g.) was added slowly a solution of sodium ethoxide (from 4.0 g. sodium and 80 c.c. dry ethanol): after standing at room temperature for 4 hours the mixture was poured into 10% hydrochloric acid (250 c.c.), and the resulting α-2-acetylcyclohexylphenylacetonitrile (22.5 g.) separated overnight and crystallised from ethanol in colourless prisms, m.p. 119-120°. (Barr and Cook[58] record a melting point of 120° for α-2-acetylcyclohexylphenylacetonitrile.) Treated with semicarbazide hydrochloride in aqueous pyridine this gave the semicarbazone, which crystallised from ethanol in colourless prisms, m.p. 229-230° (decomp.).

	Found:	C, 68.4;	H, 7.4; N, 18.8
$C_{17}H_{22}ON_4$	requires:	C, 68.5;	H, 7.1; N, 18.8%

After separation of the α-2-acetylcyclohexylphenylaceto-

nitrile from the reaction product a quantity of oil remained. When a portion of this was treated with semicarbazide hydrochloride in aqueous pyridine a small yield of the above acetylcyclohexylphenylacetonitrile semicarbazone was isolated. On dilution of the pyridine solution with water a small yield of another colourless material was obtained, which melted at ca. 175° after crystallisation from aqueous ethanol: this material was difficult to purify and was not identified.

4-Phenyl-1-methyl-2-ethyldecahydroisoquinoline (LI): α-2-Acetylcyclohexylphenylacetonitrile (10.4 g.) in ethanol (500 c.c.) was hydrogenated at 200° and 175 atm. for 2 hours, with copper chromite catalyst[64] (3.0 g.; prepared by ignition over a free flame). The catalyst was filtered off, and the solution evaporated under reduced pressure; the oil obtained was dissolved in ether and extracted with dilute hydrochloric acid, the acid solution basified with sodium hydroxide solution containing some ammonia to prevent precipitation of residual chromium salts, and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and evaporated, giving a colourless oil (9.0 g.) distilling at 166°/2.5 m.m. This base in ether solution was converted to the picrate, which was separated by fractional crystallisation from ethanol into two isomeric

4-phenyl-1-methyl-2-ethyldecahydroisoquinoline picrates:-

A) long yellow needles, m.p. 178-179°

$C_{24}H_{30}O_7N_4$ requires : C, 59.3; H, 6.2; N, 11.5%

and B) small yellow needles, m.p. 209-210° (decomp.)

Found : C, 59.5; H, 6.2; N, 11.7

$C_{24}H_{30}O_7N_4$ requires : C, 59.3; H, 6.2; N, 11.5%

$C_{24}H_{30}O_7N_4$ requires : C, 59.3; H, 6.2; N, 11.5%

From each picrate was obtained the corresponding isomer of the base, 4-phenyl-1-methyl-2-ethyldecahydroisoquinoline:-

A) colourless oil, b.p. 155°/2 m.m.

Found : C, 84.0; H, 10.3; N, 5.4

$C_{18}H_{27}N$ requires : C, 84.0; H, 10.5; N, 5.4

and B) colourless oil, b.p. 136°/1 m.m.

Found : C, 84.2; H, 10.3; N, 5.5

$C_{18}H_{27}N$ requires : C, 84.0; H, 10.5; N, 5.4%

An attempt to prepare the hydrochloride of the mixed base was unsuccessful as the product was deliquescent.

The relative amounts of the isomeric picrates isolated indicated that the isomeric bases were present in the original mixed product in the ratio A : B = 2-3 : 1 approximately.

4-Phenyl-1-methylisoquinoline: The mixed 4-phenyl-1-methyl-2-ethyldecahydroisoquinoline (1.5 g.) was heated with

palladium catalyst (.15 g.) at 300-320° till evolution of gas became negligible and practically the theoretical amount had been collected (8 hours). The product was then extracted with ether, the ether evaporated and the product distilled at 150-154°/1 m.m. to give a light brown oil (1.25 g.). This was converted to the picrate and after crystallisation from ethanol and benzene alternately gave 4-phenyl-1-methylisoquinoline picrate in small yellow needles, m.p. 229-230° (decomp.).

	Found :	C, 59.2;	H, 3.6; N, 12.8
$C_{22}H_{16}O_7N_4$	requires :	C, 58.9;	H, 3.6; N, 12.5%

(Krabbe[66] records a melting point of 206° for the picrate of 4-phenyl-1-methylisoquinoline.)

From the picrate was obtained the base, a pale yellow oil distilling at 140° (bath)/1 m.m., which solidified on standing and on crystallisation from petroleum ether gave 4-phenyl-1-methylisoquinoline in colourless elongated prisms, m.p. 78-79°.

	Found :	C, 88.0;	H, 6.1; N, 6.4
$C_{16}H_{13}N$	requires :	C, 87.7;	H, 6.0; N, 6.4%

(Krabbe, loc.cit., records a melting point of 79° for 4-phenyl-1-methylisoquinoline).

An attempt to prepare the methiodide of this base was unsuccessful as the product was unstable.

4-Phenyl-1:2-dimethyldecahydroisoquinoline (LII; R = Me): α-2-Acetylcyclohexyl-phenylacetonitrile (10.0 g.) in methanol (500 c.c.) was hydrogenated at 200° and 190 atm. for 4 hours with copper chromite catalyst (3.0 g.). The basic product was extracted as before, and distilled at 150-155°/2 m.m., giving a colourless oil (7.0 g.) and leaving a non-volatile residue (2.0 g.) which was not investigated. The picrate of the oil was prepared in ether, and by fractional crystallisation from ethanol was separated into two isomeric 4-phenyl-1:2-dimethyldecahydroisoquinoline picrates:-

A) small yellow needles, m.p. 176-177°

	Found :	C, 58.6;	H, 6.1; N, 12.1
$C_{23}H_{28}O_7N_4$	requires :	C, 58.5;	H, 5.9; N, 11.9%

and B) long yellow needles, m.p. 205-206° (decomp.)

	Found :	C, 58.7;	H, 5.7; N, 12.1
$C_{23}H_{28}O_7N_4$	requires :	C, 58.5;	H, 5.9; N, 11.9%

From each picrate was obtained the corresponding isomer of the base, 4-phenyl-1:2-dimethyldecahydroisoquinoline:-

A) colourless oil, b.p. 152°/1.5 m.m.

	Found :	C, 84.0;	H, 10.3; N, 5.4
$C_{17}H_{25}N$	requires :	C, 84.2;	H, 10.1; N, 5.7%

and B) colourless oil, b.p. 141°/1.5 m.m.

	Found :	C, 84.0;	H, 10.1; N, 5.8
$C_{17}H_{25}N$	requires :	C, 84.2;	H, 10.1; N, 5.7%

The relative amounts of the isomeric picrates isolated indicated that the isomeric bases were present in the original mixed product in the ratio A : B = 1 : 1 approximately.

4-Phenyl-1-methyl-2-n-propyldecahydroisoquinoline (LII; R = n-Pr): α-2-Acetylcyclohexylphenylacetonitrile (15.0 g.) in n-propanol (500 c.c.) was hydrogenated at 200° and 155 atm. for 2 hours with copper chromite catalyst (4.5 g.). The basic product was isolated as before, and distilled at 173-178°/3 m.m. giving a colourless oil (15.4 g.). This base in ether solution was converted to the picrate, which was separated by fractional crystallisation from ethanol into two isomeric 4-phenyl-1-methyl-2-n-propyldecahydroisoquinoline picrates:

A) yellow needles, m.p. 148-149°

Found :	C, 60.0; H, 6.4; N, 11.5
$C_{25}H_{32}O_7N_4$ requires :	C, 60.0; H, 6.4; N, 11.2%

and B) yellow needles, m.p. 184-185° (decomp.)

Found :	C, 60.3; H, 6.2; N, 11.2
$C_{25}H_{32}O_7N_4$ requires :	C, 60.0; H, 6.4; N, 11.2%

From each picrate was obtained the corresponding isomer of the base, 4-phenyl-1-methyl-2-n-propyldecahydroisoquinoline:

A) colourless oil, b.p. 147-149°/0.8 m.m.

Found :	C, 83.9; H, 10.3; N, 4.8
$C_{19}H_{29}N$ requires :	C, 84.1; H, 10.7;, N, 5.2%

and B) colourless oil, b.p. 175° (bath)/0.7 m.m.

	Found : C, 83.9; H, 10.5; N, 5.0
$C_{19}H_{29}N$	requires : C, 84.1; H, 10.7; N, 5.2%

The relative amounts of the isomeric picrates isolated indicated that the isomeric bases were present in the original mixed product in the ratio A : B = 10 : 1 approximately.

α-2-Acetylcyclohexylphenylacetic acid (LVIII): α-2-Acetylcyclohexylphenylacetonitrile (4.0 g.) was refluxed for 3 hours with potassium hydroxide (15.0 g.) in water (30 c.c.) and ethanol (40 c.c.). The solution was then diluted with water (30 c.c.), washed with ether, acidified with dilute hydrochloric acid and again extracted with ether. This extract was dried over anhydrous sodium sulphate and evaporated, giving a yellow oil (1.5 g.) which solidified on standing, and on crystallisation from 80/100° petroleum ether gave α-2-acetylcyclohexylphenylacetic acid in colourless prisms, m.p. 146-147°.

	Found : C, 73.7; H, 7.8
$C_{16}H_{20}O_3$	requires : C, 73.8; H, 7.7%

A quantity of non-acidic material (0.4 g.) was also isolated, which contained nitrogen and crystallised from 80/100° petroleum ether in colourless plates, m.p. 222-223°.

Analysis supports the identification of this material as 4-phenyl-1-methyl-5:6:7:8:9:10-hexahydro-3-isoquinolone.

Found	: C, 79.7; H, 8.0; N, 5.9
$C_{10}H_{19}ON$ requires	: C, 79.7; H, 7.9; N, 5.8%

Ethyl- α-2-acetylcyclohexylphenylacetate (LV): α-2-Acetylcyclohexylphenylacetonitrile (10.0 g.) was refluxed for 17 hours with a mixture of 95% ethanol (20 g.) and concentrated sulphuric acid (20 g.). The solution was then cooled and diluted with water (50 c.c.), the ester extracted with ether, the extract washed with sodium carbonate solution, dried over anhydrous sodium sulphate and evaporated, giving ethyl α-2-acetylcyclohexylphenylacetate, a colourless oil, b.p. 166-168°/1 m.m. (6.0 g.).

Found	: C, 75.2; H, 8.3
$C_{18}H_{24}O_3$ requires	: C, 75.0; H, 8.3%

A portion of this ester (0.75 g.) was hydrolysed by refluxing for 3 hours with a solution of potassium hydroxide (2.0 g.) in ethanol (4 c.c.) and water (2 c.c.). The solution was then diluted with water (15 c.c.), washed with ether, acidified with dilute hydrochloric acid and again extracted with ether. This extract was dried over anhydrous sodium sulphate and evaporated, giving a pale yellow solid which distilled at 190-200° (bath)/1 m.m., and crystallised from petroleum ether in colourless prisms, m.p. 146-147°

(0.35 g.). By comparison with an authentic specimen this was identified as α-2-acetylcyclohexylphenylacetic acid, thus confirming the identity of the ester from which it was obtained.

Oxime of ethyl α-2-acetylcyclohexylphenylacetate (LVI): Ethyl α-2-acetylcyclohexylphenylacetate (5.0 g.) was refluxed with hydroxylamine hydrochloride (2.5 g.) and sodium acetate (5.0 g.) in aqueous alcoholic solution for 3 hours. The mixture was then poured into water and the product extracted with ether, the extract dried over anhydrous sodium sulphate and evaporated, giving an oil (5.0 g.) which did not solidify. A similar oily product was obtained when the ester was treated with hydroxylamine hydrochloride in pyridine solution at 100°.

Hydrogenation of the oxime of ethyl α-2-acetylcyclohexylphenylacetate (LVI).

The oil obtained above (2.5 g.) in methanol (100 c.c.) was hydrogenated at 200° and 145 atm. for 2 hours using copper chromite catalyst (1.0 g.). The catalyst was then filtered off and the alcoholic solution evaporated giving a yellow oil which partly solidified. This was dissolved in dilute hydrochloric acid, washed with ether, the solution basified with dilute sodium hydroxide solution, and again

extracted with ether. The extract was dried over anhydrous sodium sulphate and evaporated. The basic product on distillation gave two fractions:-

a) a colourless oil (0.1 g.), b.p. 146° (bath)/1 m.m. This oil in ether solution was converted to the picrate (0.15 g.), m.p. 189-193° (crude), which crystallised from ethanol in yellow needles, m.p. 202-203° (decomp.), and was identified by comparison with an authentic specimen as 'β' 4-phenyl-1:2-dimethyldecahydroisoquinoline picrate. No trace of the corresponding 'α' isomer was found,

b) a colourless solid (0.15 g.), which was separated by fractional crystallisation from 80/100° petroleum ether into two isomeric products whose composition supports their identification as isomeric 4-phenyl-1-methyldecahydro-3-isoquinolones:

1) Colourless needles, m.p. 168-169° (.02 g.)

Found :	C, 79.0;	H, 8.6;	N, 5.4
$C_{16}H_{21}ON$ requires :	C, 79.0;	H, 8.6;	N, 5.7%

2) Colourless needles, m.p. 180-181° (.05 g.)

Found :	C, 79.3;	H, 8.5;	N, 5.9
$C_{16}H_{21}ON$ requires :	C, 79.0;	H, 8.6;	N, 5.7%

Condensation of 1-acetylcyclohex-1-ene with ethyl phenylacetate (LXII, LXIII).

A solution of sodium ethoxide (from 6 g. of sodium

and 120 c.c. of ethanol) was added slowly to a mixture of 1-acetylcyclohex-1-ene (30 g.) and ethyl phenylacetate (26 g.): little reaction was apparent in the cold, so the mixture was refluxed for 5 hours. The mixture was then cooled and poured into 10% hydrochloric acid (375 c.c.). The solid product which separated on standing overnight was filtered off and washed with petroleum ether which removed a quantity of oil, leaving a yellow powder (33 g.). By fractional crystallisation from aqueous ethanol this was separated into two main products:

a) small colourless needles, m.p. 197-198° (from aqueous ethanol)

[Found: C, 79.0; H, 7.5
$C_{16}H_{18}O_2$ requires: C, 79.3; H, 7.4%]

and b) colourless prisms, m.p. 169-170° (from 80/100° petroleum ether)

[Found: C, 79.0; H, 7.4
$C_{16}H_{18}O_2$ requires: C, 79.3; H, 7.4%]

These were present in the original mixture in the approximate proportions a : b = 1 : 10. The petroleum ether washings from the reaction product contained an oil from which no identifiable material could be isolated.

Microhydrogenation of these two products over Adams' catalyst in acetic acid, assuming a molecular weight of 242 in each case, resulted in hydrogen absorption equivalent to

6.05 double bonds per molecule in the case of a), and 5.9 in the case of b).

The oxime of product a) was obtained by treating the material (1.0 g.) in pyridine (20 c.c.) with a solution of hydroxylamine hydrochloride (2.0 g.) in the minimum quantity of water, and allowing the mixture to stand at room temperature for 48 hours, then diluting with water. A gum separated, which solidified on prolonged standing (3 weeks). Washing with benzene removed a quantity of red oil from this, leaving a colourless solid (0.4 g.) which crystallised from aqueous ethanol to give the dioxime in colourless needles, m.p. 124-125° (decomp.):

	Found : C, 69.0; H, 7.6; N, 9.9
$C_{16}H_{20}O_2N_2$	requires : C, 70.6; H, 7.4; N, 10.3%

The oxime of product b) was obtained similarly by treating a solution of b) (0.2 g.) in pyridine with a concentrated aqueous solution of hydroxylamine hydrochloride (0.2 g.) and allowing the mixture to stand at room temperature for 48 hours. On dilution of this solution with water a colourless solid (0.2 g.) separated, which crystallised from aqueous ethanol to give the dioxime in small colourless needles, m.p. 218-219° (decomp.):

	Found : C, 70.6; H, 7.4; N, 9.9
$C_{16}H_{20}O_2N_2$	requires : C, 70.6; H, 7.4; N, 10.3%

Hydrogenation of this dioxime - b) at 135-145° and 130 atm. in ethanol over copper chromite catalyst resulted in decomposition of the dioxime without the formation of any basic product.

1-Phenylacetylcyclohex-1-ene (LXIV): A mixture of cyclohexene (210 g.) and phenylacetyl chloride (100 g.; prepared from phenylacetic acid and distilled at 92°/10 m.m.) was added slowly with stirring to a solution of stannic chloride (500 g.) in carbon disulphide (1200 g.), the temperature being maintained below -5°. After the addition was complete the mixture was allowed to stand for 2 hours at -5°, then overnight at room temperature. Decomposition of the intermediate chloroketone and isolation of the product were then carried out in the usual way (Cook[67]) to give 1-phenylacetylcyclohex-1-ene (69 g.), b.p. 150-154°/4 m.m., which was characterised by the semicarbazone, m.p. 169-170° (Cook, loc.cit., records a melting point of 168-169° for the semicarbazone of 1-phenylacetylcyclohex-1-ene).

Condensation of 1-phenylacetylcyclohex-1-ene with ethyl cyanoacetate (LXVIII).

A solution of sodium ethoxide (from 2.5 g. of sodium and 50 c.c. of ethanol) was added slowly with stirring to a

mixture of 1-phenylacetylcyclohex-1-ene (10 g.) and ethyl cyanoacetate (5.5 g.), and the mixture allowed to stand at room temperature for 4½ hours. The mixture was then poured into 10% hydrochloric acid, and a solid product separated on standing overnight. This was washed rapidly with ether, which removed a quantity of oil, and crystallised from benzene in colourless prisms (6.0 g.), m.p. 199-200°:

	Found : C, 76.2; H, 6.3; N, 5.0
$C_{17}H_{17}O_2N$	requires : C, 76.4; H, 6.4; N, 5.2%

This product did not give an oxime, semicarbazone or 2:4-dinitrophenylhydrazone. It gave a yellow colour with ferric chloride solution; was moderately soluble in dilute sodium carbonate solution from which it was precipitated on addition of dilute hydrochloric acid; and was not hydrolysed when heated at 55° for 3 hours with aqueous alcoholic potassium hydroxide solution. An ethoxyl determination gave a negative result.

Treatment with acetic anhydride in pyridine for 3½ hours at room temperature gave a diacetyl derivative, which crystallised from aqueous ethanol in colourless prisms, m.p. 129-130°:

	Found : C, 72.1; H, 6.0; N, 4.1
$C_{21}H_{21}O_4N$	requires : C, 71.8; H, 6.0; N, 4.0%

Condensation of malonamide with 1-phenylacetylcyclohex-1-ene (LXX).

Malonamide was prepared from diethylmalonate and concentrated aqueous ammonia[68], and crystallised from ethanol in colourless prisms, m.p. 170°. This (6.75 g.; 10% excess) was dissolved in dry ethanol (300 c.c.) with heating, 1-phenylacetylcyclohex-1-ene (12 g.) was added to the hot solution, and then a solution of sodium ethoxide (from 1.7 g. of sodium and 30 c.c. of ethanol) was added dropwise with stirring. The colour of the solution darkened immediately and a little solid precipitated. The solution was refluxed for 12 hours, during which time evolution of ammonia occurred. The mixture was then evaporated to approximately 50 c.c., poured into excess 10% hydrochloric acid (200 c.c.) and allowed to stand overnight. The solid which separated was filtered, washed with ether and then with a little warm ethanol which removed a quantity of oil, giving an almost colourless solid (6.8 g.). This crystallised from ethanol to give 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxyamide in colourless prisms, m.p. 257-258° (decomp.).

	Found :	C, 71.6;	H, 7.0;	N, 9.8
$C_{17}H_{20}O_2N_2$ requires :		C, 71.8;	H, 7.0;	N, 9.9%

The washings from the reaction product yielded an oil from which only a little unchanged malonamide could be isolated.

1-Benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid (LXXI): 1-Benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxyamide (2.0 g.) was dissolved in 40% sulphuric acid (130 c.c.) at 100°, and with constant stirring sodium nitrite (1.0 g.) in water (10 c.c.) was introduced very slowly under the surface of the hot solution by means of a capillary. An extremely vigorous reaction occurred with copious evolution of gas. After the addition was complete the solution was heated for a further 5 minutes till evolution of gas ceased, then was cooled and diluted with water (ca. 200 c.c.). The solid which separated was dissolved in dilute sodium carbonate solution, the solution filtered to remove a little dark residue, and then acidified with dilute hydrochloric acid to give a pale yellow solid (1.8 g.). This crystallised from aqueous ethanol to give 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid in colourless plates (or needles), m.p. 204-205° (decomp.)

Found :	C, 71.9; H, 6.2; N, 5.0
$C_{17}H_{19}O_3N$ requires :	C, 71.6; H, 6.7; N, 4.9%

1-Benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone (LXXII): 1-Benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid (1.82 g.) was heated at 210°. The solid melted, a vigorous evolution of gas occurred, and after approximately 15 minutes the mass resolidified. The product crystallised from ethanol to give 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone (1.3 g.) in colourless needles, m.p. 244-245° (decomp.)

Found :	C, 80.6; H, 7.1; N, 6.1
$C_{16}H_{19}ON$ requires :	C, 79.7; H, 7.9; N, 5.8%

1-Benzyldecahydroisoquinoline (LXXIII): 1-Benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone (0.5 g.) was dissolved in dry n-butyl alcohol (10 c.c.) at the boiling point, and to this hot solution was added sodium (0.76 g.) all at once; refluxing was then continued for 30 minutes. The pasty mixture was washed with water (3 c.c.) and then acidified with dilute hydrochloric acid (10 c.c.). The alcohol was then evaporated, water being added as required to maintain the volume of the aqueous solution. The aqueous solution was then extracted with ether, and from this extract was obtained a quantity (0.3 g.) of non-basic oil. The aqueous solution was then basified with sodium hydroxide solution, extracted with ether, the extract dried over anhydrous sodium sulphate and evaporated, giving a basic oil (0.1 g.).

This appeared to decompose slightly on distillation at 130-140° (bath)/0.8 m.m., and was converted to the hydrogen oxalate in ether solution. Crystallisation from ethanol/ether gave 1-benzyldecahydroisoquinoline hydrogen oxalate in colourless needles, m.p. 161-162° (decomp.)

Found :	C, 68.1; H, 7.3; N, 4.6
$C_{18}H_{25}O_4N$ requires :	C, 67.7; H, 7.8; N, 4.4%

Condensation of cyanoacetamide with 1-phenylacetylcyclohex-1-ene (LXXIV).

Cyanoacetamide was prepared from ethyl cyanoacetate and concentrated aqueous ammonia[68], and crystallised from ethanol in colourless prisms, m.p. 119°. This (3.5 g.; 10% excess) was dissolved in dry ethanol (75 c.c.) with heating, 1-phenylacetylcyclohex-1-ene (7.5 g.) was added to the hot solution and then a solution of sodium ethoxide (from 1.1 g. of sodium and 25 c.c. of ethanol) was added dropwise with stirring. The colour of the solution darkened immediately and some solid precipitated. The solution was refluxed for 7 hours, during which time evolution of ammonia occurred. The mixture was then evaporated to approximately 50 c.c., poured into 10% hydrochloric acid and allowed to stand overnight. The solid which separated was filtered, washed with ether and then with a little warm ethanol which

removed a quantity of oil, giving a cream powder (2.2 g.). This crystallised from ethanol to give α-2-phenylacetylcyclohexylcyanoacetamide in colourless needles, m.p. 247-248° (decomp.)

	Found : C, 71.9; H, 7.1; N, 10.1
$C_{17}H_{20}O_2N_2$	requires : C, 71.8; H, 7.0; N, 9.9%

The washings from the reaction product yielded an oil, from which a further quantity (0.7 g.) of the above product was precipitated on addition of ether. The remaining oil was distilled, giving a first fraction distilling at 90-94°/1 m.m., identified as unchanged phenylacetylcyclohexene, and a second fraction distilling at 120-140°/1 m.m. with some decomposition, which appeared to be a mixture. From the non-volatile residue a further small quantity of α-2-phenylacetylcyclohexylcyanoacetamide was isolated.

Reaction of α-2-phenylacetylcyclohexylcyanoacetamide with sodium nitrite and sulphuric acid (LXXI).

α-2-Phenylacetylcyclohexylcyanoacetamide (0.3 g.) was dissolved in 50% sulphuric acid (50 c.c.) at 140°, and sodium nitrite (0.2 g.) in water (2 c.c.) was introduced very slowly, with constant stirring, under the surface of the hot solution by means of a capillary. An extremely vigorous reaction occurred with copious evolution of gas.

After the addition was complete the solution was heated for a further 5 minutes till evolution of gas ceased, then cooled and diluted with water (ca. 150 c.c.). The solid which separated was dissolved in dilute sodium carbonate solution, and a quantity of insoluble material filtered off. This material (0.1 g.) was identified by comparison with an authentic specimen as unchanged α-2-phenylacetylcyclohexylcyanoacetamide. The sodium carbonate solution was acidified with dilute hydrochloric acid, giving a pale yellow solid (0.15 g.) which crystallised from ethanol in colourless plates, m.p. 204-205°, and was identified by comparison with an authentic specimen as 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone-4-carboxylic acid.

A portion of the above acid was heated at 210°, when it melted, evolution of gas occurred, and after approximately 15 minutes the mass resolidified. The product crystallised from ethanol in colourless needles, m.p. 244° (decomp.), and was identified by comparison with an authentic specimen as 1-benzyl-5:6:7:8:9:10-hexahydro-3-isoquinolone, thus confirming the identity of the acid.

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SUMMARY.

S U M M A R Y.

Synthetic Analgesics and Antispasmodics.

Three types of compound were investigated, the 1:4-bisdialkylaminoalkylnaphthalenes, certain 4-phenyl-4-hydroxypiperidines and a number of substituted decahydroisoquinolines.

In order that a preliminary estimate might be made of the antispasmodic and analgesic potentialities of the 1:4-bisdialkylaminoalkylnaphthalene type of structure, three compounds of this type, 1:4-bisdiethylaminomethylnaphthalene, 1:4-bisisothiocarbamidomethylnaphthalene and 1:4-bis-N-piperidylmethylnaphthalene were prepared by condensation of 1:4-bischloromethylnaphthalene with the appropriate base, and were submitted for testing in the form of the hydrochlorides. Reports on the first two of these indicate that, while the antispasmodic activity is slight, they possess an analgesic potency of the same order as that of pethidine. This is a new class of compound to show pronounced analgesic activity.

2:2:6-Trimethyl- and 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine were prepared with a view to investigating the therapeutic effect of nuclear alkyl substituents in the 4-phenyl-4-hydroxypiperidine esters, which are known

to be potent analgesics. Mesityl oxide was condensed with ammonia to form 4-amino-4-methylpentan-2-one (diacetonamine), which then condensed with acetal to give 2:2:6-trimethyl-4-piperidone (vinyldiacetonamine); treatment of this with phenylmagnesium bromide and decomposition of the resultant complex gave 2:2:6-trimethyl-4-phenyl-4-hydroxypiperidine, from which 1:2:2:6-tetramethyl-4-phenyl-4-hydroxypiperidine was obtained by methylation with formaldehyde. The ease with which these piperidols underwent dehydration, however, rendered the preparation of the desired esters impracticable, though some estimate of the effect of the substituents may be obtained from the piperidols themselves, which were submitted for testing in the form of the hydrochlorides. A number of related compounds prepared in the course of this work are also described.

On the model of the octahydroisoquinoline portion of the morphine molecule a series of N-alkyl-4-phenyl-1-methyldecahydroisoquinolines was prepared for testing for analgesic activity. α-2-Acetylcyclohexylphenylacetonitrile, prepared by the Michael condensation of 1-acetylcyclohex-1-ene and phenylacetonitrile, underwent reductive-cyclisation when hydrogenated in alcohol solution

over copper chromite catalyst to yield two stereoisomeric N-alkyl-4-phenyl-1-methyldecahydroisoquinolines, the nature of the N-alkyl group depending on the alcohol used as solvent. The N-methyl, N-ethyl and N-n-propyl compounds were prepared and submitted for testing. The similar reductive-cyclisation of the oxime of ethyl α-2-acetylcyclohexylphenylacetate was also investigated, and the method was extended in a modified form to the synthesis of 1-benzyldecahydroisoquinoline.