# THE SYNTHESIS OF COMPOUNDS RELATED TO MORPHINE

by

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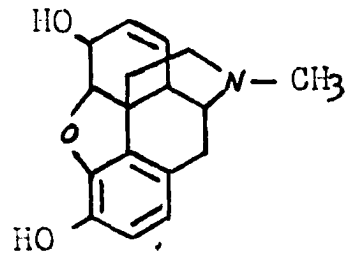
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# INTRODUCTION

Historical. Morphine was the first plant base to be isolated and characterized as such. Though this was accomplished in 1805, more than a century passed before a formula was advanced that would explain the vast amount of experimental evidence accumulated by scores of investigators. The structure of Gulland and Robinson[1],




proposed in 1925, represents morphine as a fused hydrophenanthrene-isoquinoline structure, containing a hydrobenzofuran nucleus as an additional feature. This structure is more or less accepted at the present time; it awaits confirmation through synthesis.

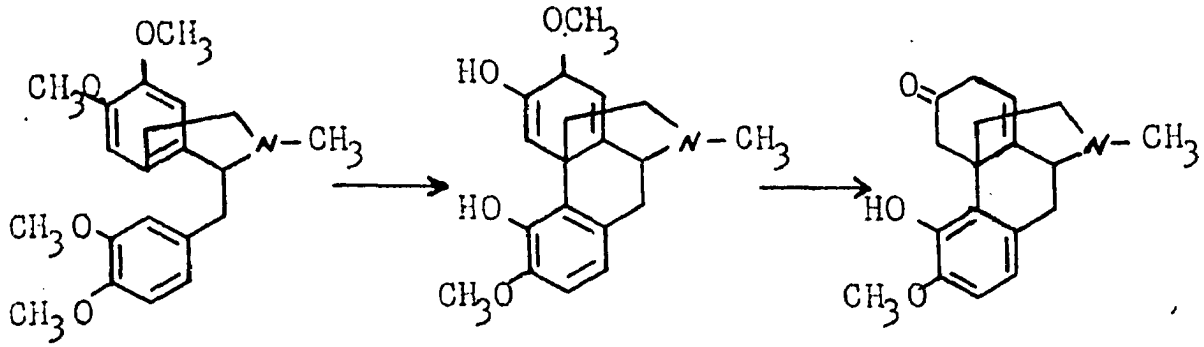
Following preliminary attempts at total synthesis through the apomorphine system[2], the problem soon became one of a study of the preparation of compounds of like structure with the view to possible application of the reactions to the formation of the morphine molecule itself.

The occurrence of laudanosine together with morphine in the opium alkaloids led Robinson to the conclusion that there may be



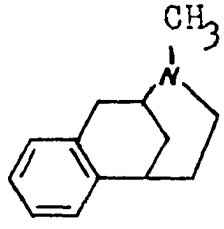
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a biogenetic relationship between the two and he proposed the following scheme for the formation of the requisite ring system[3].

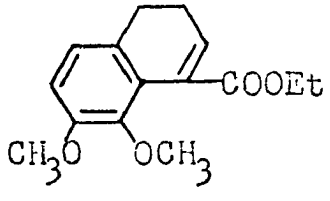


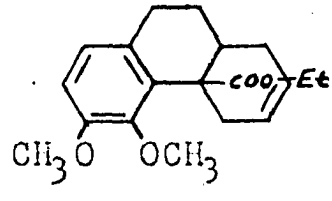
Laudanosine

An unsuccessful attempt by Manske in 1931 to synthesize the grouping[4]:



was followed by the preparation of the hydrogenated phenanthrene nucleus of morphine by Fieser and Holmes[5] by a diene synthesis.



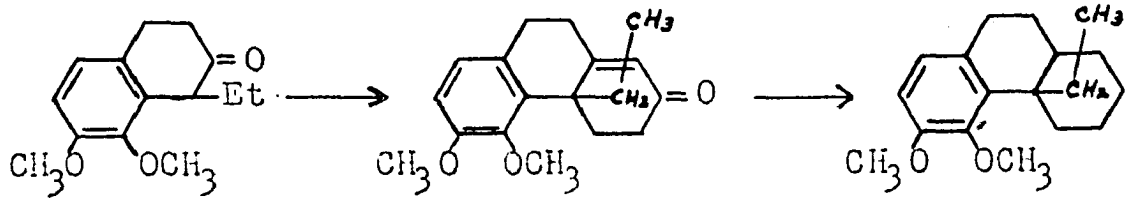


As might be expected, the quaternary group was quite unreactive and the intermediates were difficult to obtain.

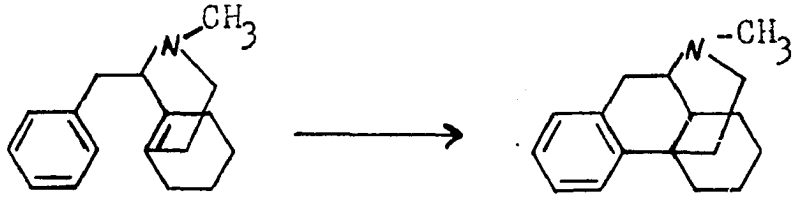
At a later date Ghosh and Robinson[6] prepared the same molecule with an ethyl group at the angular position using a reaction

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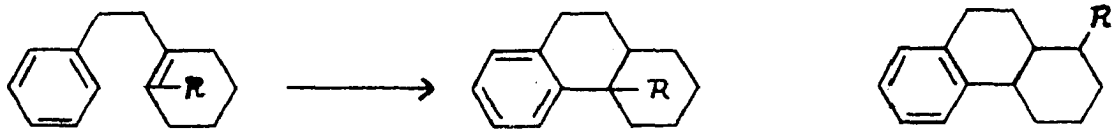
that had been developed earlier in connection with the formation of fused alicyclic rings.



A fulfillment of Robinson's biogenesis was realized by Grewe as a result of an extended series of researches carried out over a period of some seven years[7]. The culminating reaction involving an internal condensation to N-methylmorphinane bears a close resemblance to the internal condensation of laudanosine as envisaged by Robinson in his theory.



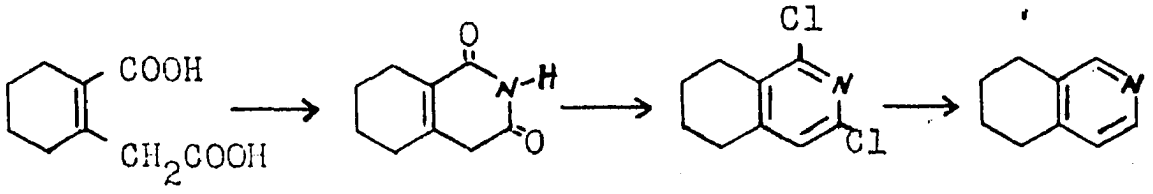
This condensation is based upon earlier work performed by Perlman, Davidson and Bogert[8] and by Cook and Hewett[9] wherein it was found that β-phenylethyl-$\Delta^1$-cyclohexene could be made to undergo an internal condensation to yield as-octahydrophenanthrene. The applicability of this reaction was extended by Grewe to yield phenanthrenes bearing angular groups at the 4a-position.



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Thus, it was found that when R is a hydrocarbon residue, the resultant product has the group in the angular position[10]. However, if R is a polar combination, such as $-CH_2COOH$ or $-CH_2CH_2NMe_2$, the cyclized material is a 1-substituted octahydrophenanthrene[11].

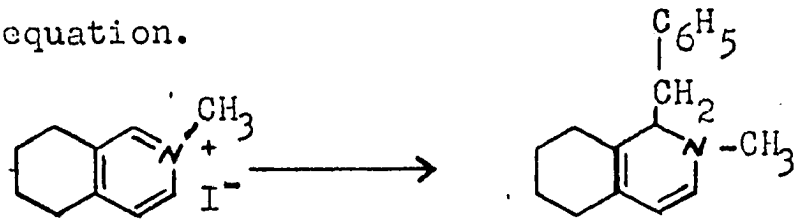
As result of this methodical approach to a very complex problem, it was possible for Grewe to predict that, given the necessary benzyloctahydroisoquinoline, the ring system of morphine would result[7]. The synthesis of this important intermediate was accomplished by a series of interesting reactions[7]. 2-Carbethoxycyclohexanone was condensed with ethyl cyanoacetate under the usual Knoevenagel conditions, and the product was hydrolyzed and decarboxylated to 2-carboxycyclohexeneacetic acid. Treatment with ammonia gave the imide which may be considered as the keto-form of 1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline. Reaction of this with phosphorus oxychloride led to the dichloro compound which upon catalytic hydrogenation yielded 5,6,7,8-tetrahydroisoquinoline.



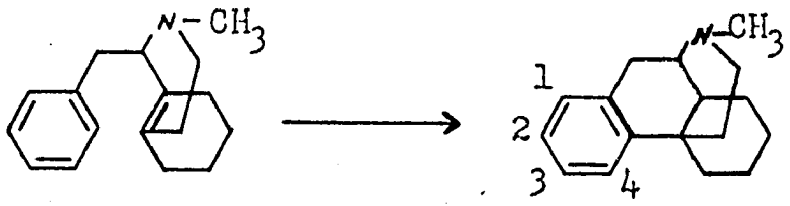

Methyl iodide then gave N-methyl-5,6,7,8-tetrahydroisoquinolinium iodide, which reacted with benzylmagnesium chloride according to

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the following equation.



The conjugated system of this compound made it very susceptible to decomposition but upon catalytic hydrogenation a stable derivative was formed which gave, when warmed with phosphoric acid, the cyclized product, N-methylmorphinane.



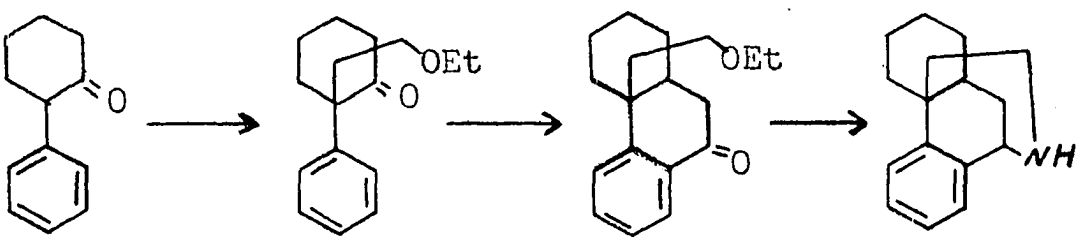
The similarity to the natural product morphine is not limited to the likeness in structure but extends also to the pharmacological activity. The analgesic properties of N-methylmorphinane are reported to be of the same order of magnitude as those of morphine[7].

Following the identical reactions listed above, Schnider and Grussner[12] prepared hydroxy-substituted N-methylmorphinanes. Thus, by using p-methoxybenzylmagnesium chloride in the reaction with the tetrahydroisoquinolinium meth-halide the product was 1-p-methoxybenzyl-N-methyl-1,2,5,6,7,8-hexahydroisoquinoline which was selectively hydrogenated and cyclized as above. If m-methoxybenzylmagnesium chloride was used, the final product was the 2- or 4- substituted morphinane.

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By nitration of N-methylmorphinane itself the 3- and 2- or 4- nitro derivatives were obtained. Reduction of the nitro group and conversion through the diazonium compound gave a mixture of the corresponding hydroxy-N-methylmorphinanes. A pure product was obtained when 1-benzyl-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline was nitrated and carried through reduction to the amine and hydrolysis of the diazonium salt.

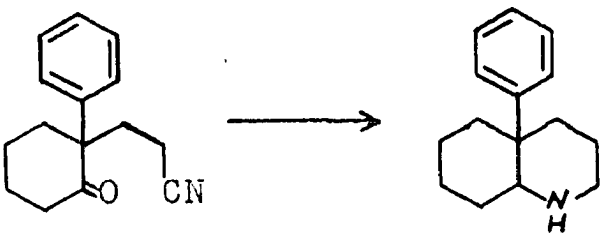
Recent studies using 2-arylcyclohexanones as a starting point have been made by Bachmann and Wick[13], Newman and Magerlein[14], Horning and co-workers[15] and by Boekelheide[16]. Newman and Magerlein accomplished the alkylation of 2-phenylcyclohexanone in the form of its sodio salt with ethoxyethylmethanesulfonate and proceeded through the usual Reformatsky method and ring closure to the phenanthrene nucleus. This phenanthrone was oximated and reduced to yield 9-amino-4a-ethoxyethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene. Cleavage of the ether with hydrobromic acid and treatment of the resulting compound with alkali was reported to give the cyclized product.



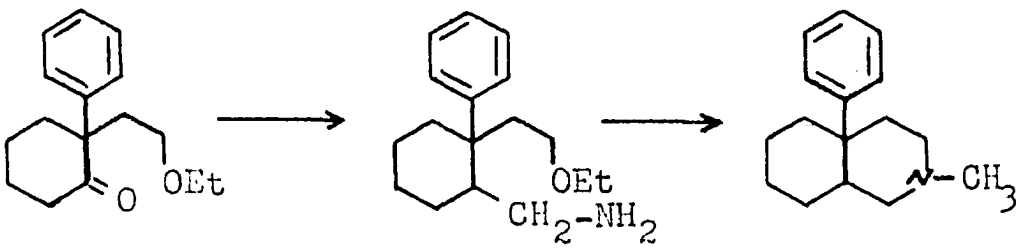

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It will be noted that this latter compound has a seven-membered ring.

The work of Boekelheide[16a] was concerned with the formation of molecules containing the angular phenyl group. 2-Oxo-1-phenylcyclohexanepropionitrile was reduced catalytically in the presence of platinum oxide to give 9-phenyldecahydroquinoline.

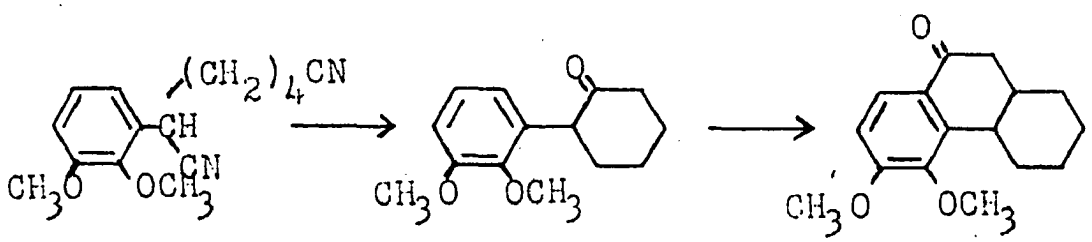



A further extension of this work was reported recently by the same author[16b]. The cyanohydrin of 2-ethoxyethyl-2-phenylcyclohexanone was dehydrated and reduced to give the substituted methyl amine. Cleavage of the ether link and treatment with base caused cyclization to the isoquinoline which was subsequently methylated by formaldehyde and formic acid.

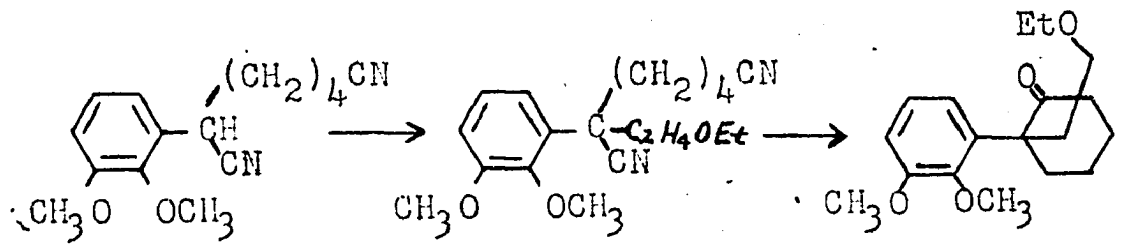



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By means of a Thorpe-Ziegler cyclization Horning has accomplished the synthesis of 2-(2',3'-dimethoxyphenyl)-cyclohexanone[15a]. 2,3-Dimethoxyphenylacetonitrile was alkylated in the presence of sodium amide with δ-chlorovaleronitrile and by means of sodium this compound was cyclized to the cyclohexanoneimine. Hydrolysis and decarboxylation gave the corresponding substituted cyclohexanone which was carried through the Reformatsky reaction, dehydration, reduction and cyclization to the dimethoxyoctahydrophenanthrone.



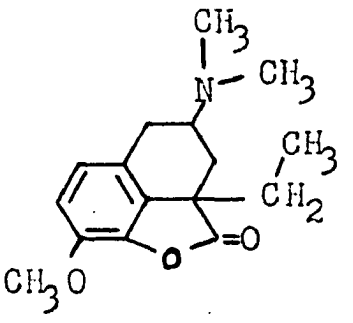
The angular substituent was introduced by alkylation of the pimelonitrile with ethoxyethylbenzenesulfonate prior to the formation of the alicyclic ring[15b].

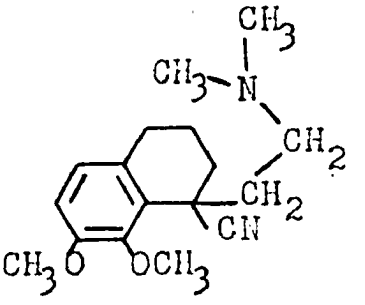


Further work has been reported by Horning and co-workers[15c] involving studies of tetralin analogues of morphine. Compounds

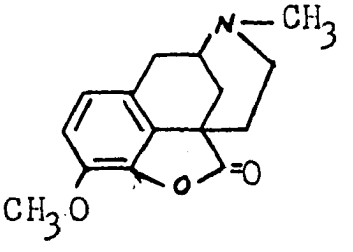
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were synthesized which lack two of the rings of the alkaloid, such as:



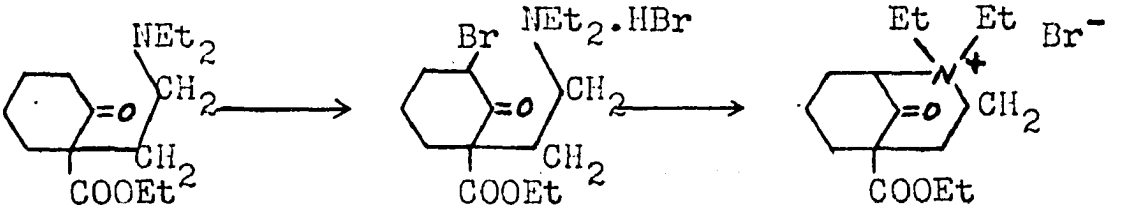


Though the preparation of the logical isoquinoline derivative:



was planned, it has not yet been reported.

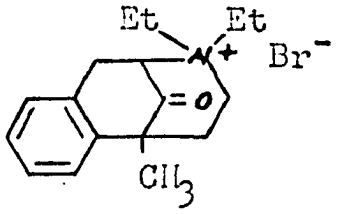
The preparation of the morphane nucleus attempted by Manske was accomplished in 1947 by Barltrop[17]. 2-Carbethoxycyclohexanone was alkylated with 2-chloroethyldiethylamine and the product was brominated. Heating of the free base in toluene solution gave the azabicyclononane system in poor yield.



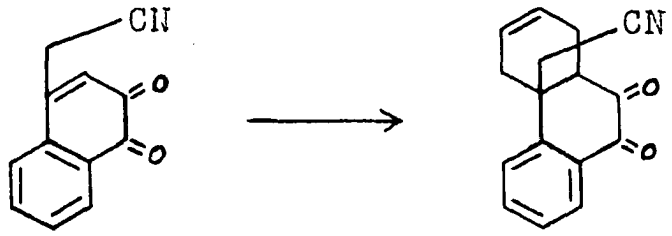
In like manner, 1-methyl-2-tetralone underwent alkylation with

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2-chloroethyldiethylamine, and ring closure gave the expected product.

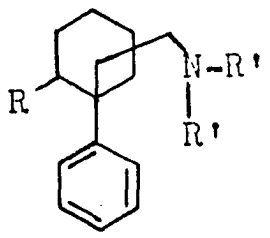



Through the diene synthesis Gates and Newhall[18] have succeeded in preparing an interesting intermediate in a projected synthesis of the morphine-type nucleus. Butadiene in acetic acid solution was condensed with 4-cyanomethyl-1,2-naphthoquinone to give 4a-cyanomethyl-9,10-dioxo-1,4,4a,9,10,10a-hexahydrophenanthrene.




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Purpose of the Investigation. The purpose of this investigation was to study further the reactions of 2-arylcyclohexanones with the view to their possible use in the synthesis of compounds with morphine-like structures. In particular, attention was directed to the synthesis of compounds having the general configuration:




R = H, OH, or O as C = O

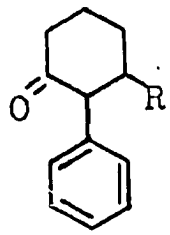
R' = H, alkyl group or acyl

There is a marked correspondence between such structures and an opened morphine molecule. Not a single compound of this type has been prepared. Such compounds would be of interest not only as intermediates in the synthesis of morphine but also for the analgesic activity which they might possess.

Likewise, investigation of the Michael reaction was projected as a possible route to the phenanthrene nucleus in order to obtain compounds with an acid side chain in the 3- position of 2-phenylcyclohexanone. Such an approach places an oxygen atom in the necessary position for the formation of the bridge oxygen

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grouping present in morphine.




R = $-CH(COOEt)_2$ or $-CH_2COOH$

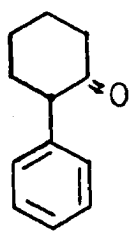
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## RESULTS OF THE INVESTIGATION

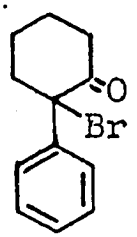
### Michael Reaction on 2-Phenyl-$\Delta^2$-cyclohexenone

Addition of Ethyl Malonate to 2-Phenyl-$\Delta^2$-cyclohexenone. 2-Phenylcyclohexanone was prepared by the method of Newman and Farbman[19] by interaction of 2-chlorocyclohexanone and phenylmagnesium bromide. These authors merely distilled their product under reduced pressure. As will be shown, the material so obtained is not sufficiently pure for our purposes and it was necessary to recrystallize the ketone.

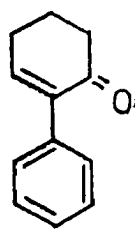
Bachmann and Wick[13] found that when 2-phenylcyclohexanone (I) was treated in carbon tetrachloride solution with a solution of bromine in the same solvent, a copious evolution of hydrogen bromide occurred and the product was the somewhat unstable 2-bromo-2-phenylcyclohexanone (II).




I




II




III

We have found that the yield of bromination product depends to a great extent on the purity of the original ketone. Thus, when material with a melting point of 53-5° was used, the yields were of the order of 10-15% whereas from ketone with a melting point of 59-60°, the yields were 60-70%.



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In one preparation a low-melting modification of the bromo-ketone was isolated in 56% yield after recrystallization from acetone-petroleum ether. The melting point of the new form was 66.5-67°. When the temperature of the bath was held at the melting point, the material almost completely solidified and remelted at 71-72.5°. On standing for three days the melting point changed to 77-80°. When an acetone-petroleum ether solution of this material was seeded with several crystals of an authentic sample of bromo-ketone, m.p. 103-4°, supplied by Dr. Wick, the product melted at 96-96.5°. Similarly, when the low-melting solid was recrystallized from methanol, the melting point was raised to 97-8°. Bromine determination indicated that this new modification had exactly the same composition as the previous one. There is no question that we are dealing with dimorphic forms of the same substance. Final proof was obtained by heating this material under reflux with 2,6-lutidine; an 80% yield of 2-phenyl-$\Delta^2$-cyclohexenone (III) resulted which was identical with the product prepared from the higher-melting form. Attempts to repeat the preparation of the low-melting form gave only the high-melting one.

In view of the fact that the bromo-ketone was prepared only as an intermediate in the synthesis of 2-phenyl-$\Delta^2$-cyclohexenone, it was decided to eliminate the isolation step and to dehydrohalogenate the crude product of bromination directly. By merely refluxing the crude bromo-ketone with 2,6-lutidine and distilling the somewhat colored product in an all-glass apparatus practically



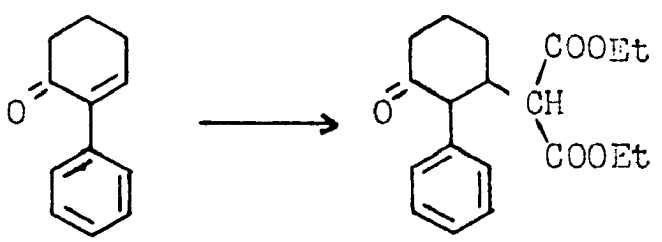
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pure 2-phenyl-$\Delta^2$-cyclohexenone was obtained in a 70% over-all yield.

The Michael reaction involves the addition of active methylene compounds to activated unsaturated systems such as:

$$CH_2{=}CHCOOR + \overset{+}{Na}\ \overset{-}{C}H(COOEt)_2 \longrightarrow \left[\begin{matrix} CH_2\text{-}CHCOOR \\ | \\ CH(COOEt)_2 \end{matrix}\right]^- \quad \overset{+}{Na}$$

A review of the reaction has been given by Connor and McClellan[20] covering the scope and several methods of carrying out the addition. The active methylene compound may take many forms of which ethyl malonate and ethyl cyanoacetate are the most common. In one instance the addition of relatively inactive fluorene to benzalacetophenone has been reported to occur in yields of 2-27% in the presence of a molar equivalent of sodium ethoxide[21]. Usually only catalytic amounts of bases are necessary for the reaction. It was proposed at the outset of the work to attempt the addition of ethyl malonate to the unsaturated system of 2-phenyl-$\Delta^2$-cyclohexenone (III) to give ethyl 3-oxo-2-phenylcyclohexanemalonate (IV).



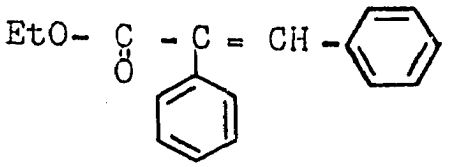

III IV

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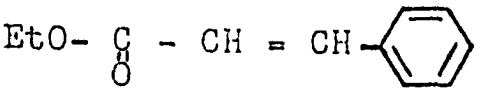
Various methods for carrying out the reaction were tried to no avail. One-sixth equivalent of sodium ethoxide, both in dry ether and in anhydrous ethanol, gave only traces of acidic material upon hydrolysis and decarboxylation of the organic portions of the reaction mixtures, the unsaturated ketone being largely recovered. Likewise, use of piperidine in refluxing ethanol was a failure. It was reasoned that if, as mentioned above, a relatively inactive methylene compound such as fluorene could be made to react by the use of one equivalent of sodium ethoxide, inactivity of the unsaturated molecule might be compensated for in the same way. Accordingly, a solution of 2-phenyl-$\Delta^2$-cyclohexenone, one equivalent of sodium ethoxide and five equivalents of ethyl malonate in absolute ethanol was allowed to stand for forty-eight hours. This procedure proved to be successful and the desired product was obtained in 50-60% yield. The successful addition of malonic ester to the unsaturated ketone is in contrast to the reported failure of ethyl malonate to add to ethyl α-phenylcinnamate (V) which also contains a phenyl group next to the carbonyl group[20]. The addition was attempted by warming for four hours a solution of one mole of the unsaturated ester and one mole of malonic ester with one equivalent of sodium ethoxide in absolute ethanol. No product was obtained whereas under the same conditions ethyl cinnamate (VI) gave an 85% yield of the addition product.



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V



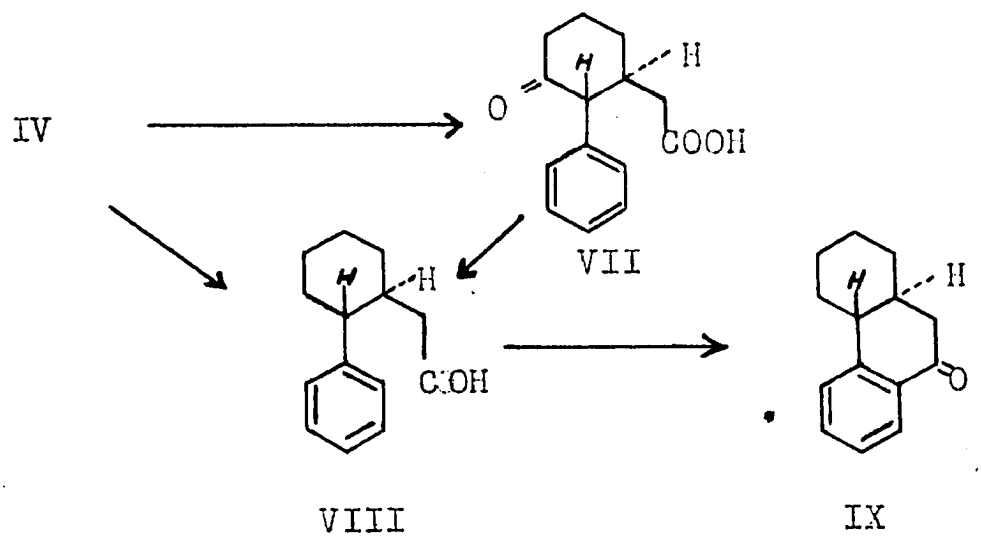
VI

The structure of the material resulting from the addition of malonic ester to 2-phenyl-$\Delta^2$-cyclohexenone was proven by analysis of the crystalline semicarbazone and by degradation to a known product as described in the next section. Several unsuccessful attempts were made to convert the malonic ester derivative (IV) to an α-oximino ester by treatment of the ester with isoamyl nitrite in the presence of sodium ethoxide and also with 85% sulfuric acid according to the methods of Barry and Hartung[22].

Synthesis of cis- and trans- 2-Phenylcyclohexaneacetic Acids and of trans-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene. The substituted malonic ester (IV) which was produced in the Michael reaction was refluxed with a mixture of concentrated hydrochloric acid and acetic acid. Under these conditions the ester was hydrolyzed to the substituted malonic acid which then underwent decarboxylation to yield 3-oxo-2-phenylcyclohexane-acetic acid (VII). This keto-acid was further transformed by Clemmensen reduction into the known 2-phenylcyclohexaneacetic acid (VIII). Similar treatment of the original malonic ester derivative also gave the same product which was entirely of one stereoconfiguration, trans-. This compound was sought by

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Linstead[23] and was previously prepared in pure form by Blumenfeld[24] and by Cook et al. in admixture with its stereoisomer[25]. As further proof of the structure the product obtained by Clemmensen reduction was cyclized to trans-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (IX) in 60% yield by warm sulfuric acid. The product agreed in melting point with that prepared by Blumenfeld[24].

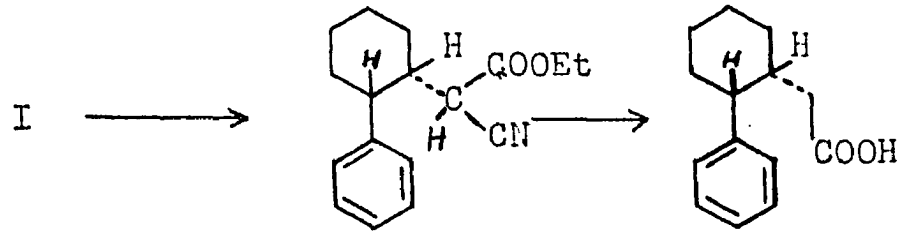



The above series of reactions affords further proof of the structure of the product obtained upon bromination of 2-phenylcyclohexanone[13] (II).

The cis-2-phenylcyclohexaneacetic acid (X) was obtained in a reaction employed in exploratory work. Following the procedure of Cope[26] on other ketones, a mixture of 2-phenylcyclohexanone, cyanoacetic ester, ammonium acetate, acetic acid and palladium-charcoal catalyst was shaken in an atmosphere of hydrogen until no more gas was absorbed. It was found that a slight variation involving doubling the molar proportions of ethyl cyanoacetate

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and the other reagents gave better results than the ratios used by Cope with simpler carbonyl compounds. Hydrogenation was carried out for twenty-four hours and the product was obtained in 64% yield after vacuum distillation. Hydrolysis and decarboxylation gave the known cis-2-phenylcyclohexaneacetic acid (X). Interestingly enough, this was the only product that could be isolated from the hydrolysis mixture and from this it might be assumed that the product of the reductive condensation has the cis- configuration. Thus, methods have been developed for the synthesis of both stereoisomeric forms of 2-phenylcyclohexaneacetic acid.



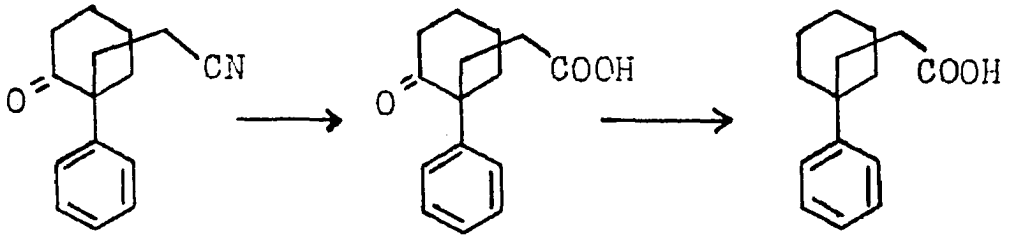

X

It is of interest that in the above described work the phenyl group has exerted directive influence to such a marked extent, in one case yielding a trans- derivative and in the other a cis- form.

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## Synthesis of Phenylcyclohexaneethylamine and Related Amines

Synthesis of 1-Phenylcyclohexaneethylamine. Recently Bachmann and Wick[13] reported the preparation of 2-oxo-1-phenylcyclohexanepropionitrile (XI) by the reaction of 2-phenylcyclohexanone and acrylonitrile in the presence of Triton B (40% aqueous benzyltrimethylammonium hydroxide). The same product was prepared independently by Boekelheide[16a] by interaction of the sodio derivative of the ketone and β-chloropropionitrile.




XI XII XIII

We have carried out the preparation of the cyanoethylated product by both methods and found that the method of Bachmann and Wick gave appreciably better yields and was more convenient. By hydrolysis of the nitrile group the valuable intermediate, 2-oxo-1-phenylcyclohexanepropionic acid (XII), was obtained usually in 80-90% yields. In one preparation the yield was as high as 98%.



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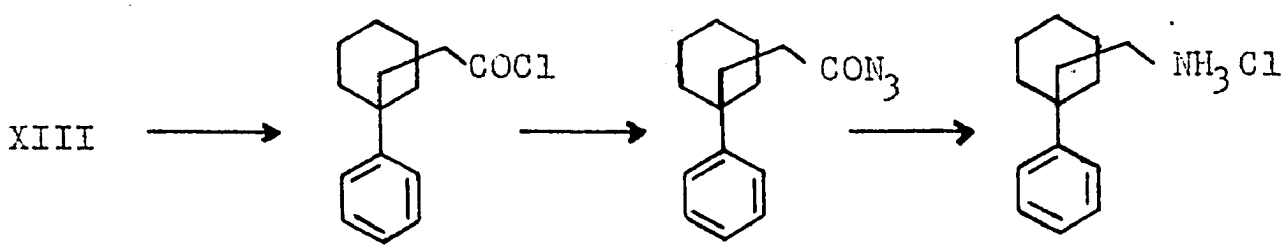
The next step in the synthesis was the conversion of the keto-acid (XII) to 1-phenylcyclohexanepropionic acid (XIII) by reduction of the carbonyl group to a methylene group. One of the usual procedures for accomplishing such a reduction, reaction with zinc and hydrochloric acid (Clemmensen reduction), failed completely; most of the starting keto-acid could be recovered unchanged. This result indicates one of the pronounced effects exerted by the introduction of the extra group in the 2-position.

Heating the semicarbazone of (XII) with a solution of sodium in diethylene glycol led to extensive decomposition and none of the desoxo acid could be isolated. Some reduction was obtained, however, when a solution of sodium in diethylene glycol mixed with hydrazine hydrate was used as the reducing agent, the yield being 38%. Application of the method of Huang-Minlon[27] gave a 90% yield of the product which was obtained in a high state of purity after only one recrystallization. This convenient procedure consists in refluxing a solution of the ketone in diethylene glycol with potassium hydroxide and 85% hydrazine hydrate for one and one-half hours to accomplish formation of the hydrazone. The water and excess hydrazine are then distilled out and the temperature is allowed to rise to 195-200°. Refluxing is continued for several hours and the product is isolated by diluting the reaction mixture and acidifying.



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The resulting acid (XIII) was converted into the desired amine by the modified Curtius reaction[28] which involved the preparation of the intermediate azide from the acid chloride and sodium azide. The acid chloride (XIV), prepared by the reaction of the acid with purified thionyl chloride, was dissolved in acetone and the solution was treated with an aqueous solution of sodium azide. The isolated liquid azide (XV) was rearranged by heating in glacial acetic acid. Hydrolysis of the product gave the desired 1-phenylcyclohexaneethylamine hydrochloride (XVI) in the form of colorless water-soluble needles in 67% overall yield.




XIV XV XVI

This is the first example of an amine of this structure to be synthesized.

Synthesis of Cyclic Amines and Derivatives of 2-Oxo-1-Phenylcyclohexaneethylamine. Considerable difficulty was experienced in applying the Curtius reaction to the keto-acid, 2-oxo-1-phenylcyclohexanepropionic acid (XII). When it was treated with thionyl chloride and pyridine in dry ether, the product was

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a liquid which upon reaction with sodium azide gave a crystalline solid melting at 112-3° without decomposition. When this solid was carried through the conditions required for the rearrangement of acid azides, followed by acid hydrolysis of the product, no acid-soluble material resulted. Instead, the starting keto-acid was recovered. In order to make certain that the keto-acid was completely absent in the intermediate steps, the product of treatment with sodium azide was taken up in ether and extracted with aqueous sodium bicarbonate to remove any keto-acid remaining. Nonetheless, the starting acid was recovered in the end. Apparently, then, a neutral compound had been formed in the course of the reactions which was derived from an acid and then reverted to the original acid under hydrolytic conditions.

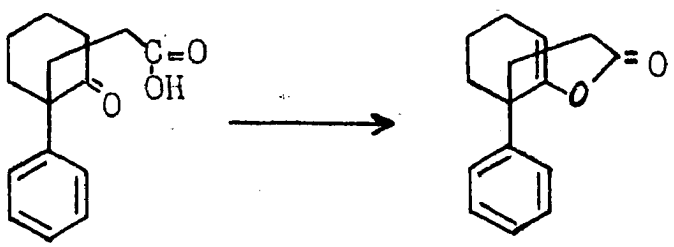
The same neutral product was obtained irregardless of the method of formation of the supposed acid chloride; thionyl chloride, whether in the presence of pyridine or upon refluxing in benzene solution, and also phosphorus pentachloride in the same solvent gave identical products upon treatment with sodium azide in acetone-water. In an attempt to determine whether an acid chloride had actually been formed, aqueous ammonia was substituted for the sodium azide. Again the product was neutral and was shown by mixed melting point to be identical with that obtained with sodium azide. Elementary analysis for nitrogen and sulfur after



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fusion with metallic sodium gave negative results. The possibility that the compound was an acid anhydride was eliminated by the fact that warming with anhydrous methanol had no effect. When the solid was warmed with 0.1 N. sodium hydroxide, it dissolved completely; acidification yielded a crystalline solid which did not depress the melting point of an authentic specimen of 2-oxo-1-phenylcyclohexanepropionic acid. Incidentally, the melting point of this acid and that of the neutral product are nearly the same, the former being 114-5° and the latter 112-3°. However, the mixed melting point was 87-105°.

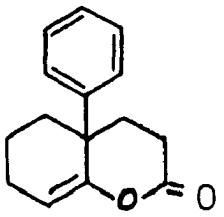
The chemical evidence as well as the analytical results can be interpreted only in terms of an enol-lactone (XVII) formed by esterification of the carboxyl group by the enol form of the ketone, through the acid chloride initially produced.




XVII

Written in a different form, the compound reveals itself to be an α-pyrone with an angular phenyl group.

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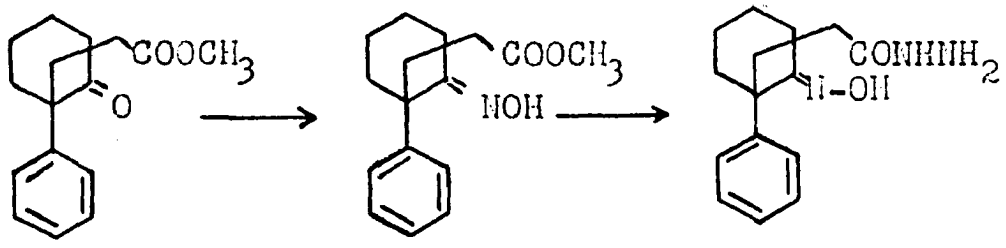


The Curtius reaction has rarely been applied to keto-acids. Fischer and Waibel[29] carried out the reaction on 3-acetyl-5-carbethoxy-2,4-dimethylpyrrole by conversion into the hydrazone-hydrazide which upon treatment with nitrous acid gave the keto-azide. Likewise, Leuchs and Gladkorn[30] prepared the oxime of methyl brucinonate which was converted into the hydrazide and which rearranged in the normal fashion after treatment with nitrous acid.

The latter of these two methods was attempted first. The crystalline methyl ester (XVIII) of the keto-acid was prepared by means of ethereal diazomethane. The excellent method of Cheney and Piening[31] was used to accomplish the oximation in 93% yield. In this procedure one mole of the keto-ester is refluxed with five moles of hydroxylamine hydrochloride and three moles of anhydrous barium carbonate in absolute ethanol. The product was isolated in almost analytical purity. Heating this oximino-ester with 85% hydrazine hydrate in alcohol gave a

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quantitative yield of the oxime-hydrazide (XIX).




XVIII XIX

The possibility of replacement of the oximino group by a hydrazine residue[32] was considered but the analysis of the product indicated an oxime-hydrazide.

Treatment of this hydrazide in dilute hydrochloric acid with an aqueous solution of sodium nitrite gave only a high-melting solid which did not decompose on melting in the usual azide fashion. The compound was soluble in dilute sodium hydroxide upon being warmed and acidification precipitated it unchanged. The analysis indicated a 1:1 ratio of oxygen to nitrogen which bore out the observation that the compound was not an acid azide and the solubility in alkali would appear to indicate that an oximino group was present. Although a fairly plausible structure can be written for the compound, we prefer to await further results. Attempted acid hydrolysis in acetic acid solution led only to extensive decomposition.

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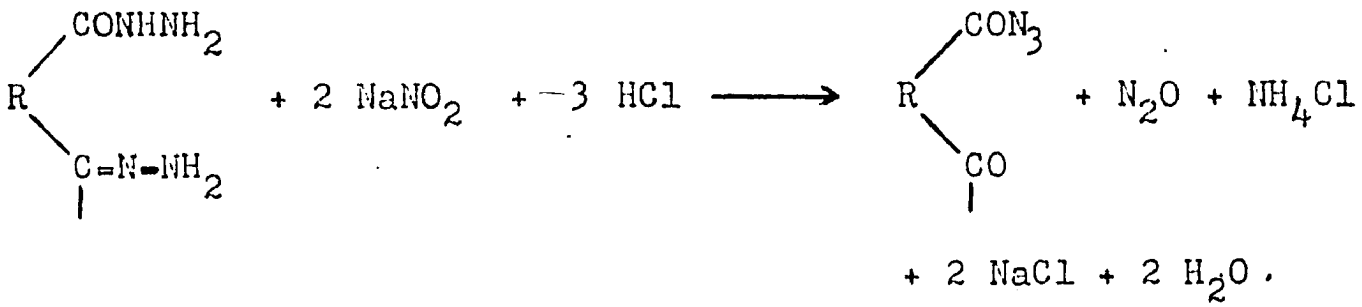
Believing that the hydrogen atom on the =N-OH group was causing difficulty, the free hydrogen of the oximino group was replaced by a methyl group. Treatment of the keto-ester (XVIII) with methoxylamine hydrochloride followed by refluxing with hydrazine hydrate yielded the O-methyl oxime-hydrazide as a crystalline solid. A solution of the methoxime-hydrazide in 3 N. hydrochloric acid was treated with aqueous sodium nitrite solution until a positive starch-iodide test for nitrous acid was obtained. One equivalent of nitrous acid was consumed before the test was positive. The product gave off nitrogen profusely upon being warmed in glacial acetic acid solution. During the hydrolysis of the product of rearrangement, carbon dioxide was copiously evolved. The product was a basic liquid which may be the desired amine, but its characterization was interrupted by the successful preparation of the amine through the hydrazone-hydrazide.

The hydrazone-hydrazide of the keto-acid (XII) was prepared from the methyl ester of the keto-acid and excess hydrazine hydrate in boiling alcohol. A solution of the product in dilute hydrochloric acid solution was treated with aqueous sodium nitrite. After two equivalents of nitrite had been added, the starch-iodide test for nitrous acid was still negative. Addition of a third equivalent did not give a positive test and only after slightly

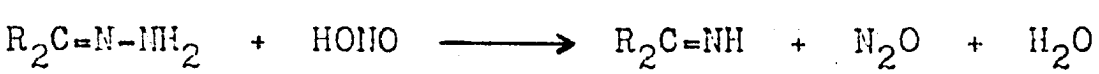


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more than three moles had been added was there an excess of nitrite present. In several attempts 3.4, 3.4, 3.2 and 3.1 equivalents were required. This is of interest since the stoichiometry of the reaction according to published work should require but two moles of nitrous acid:



The reaction of hydrazones with nitrous acid has been studied by Wieland and Horner[33] and according to these authors it proceeds as indicated above, the hydrazone residue being eliminated as nitrous oxide and ammonia.



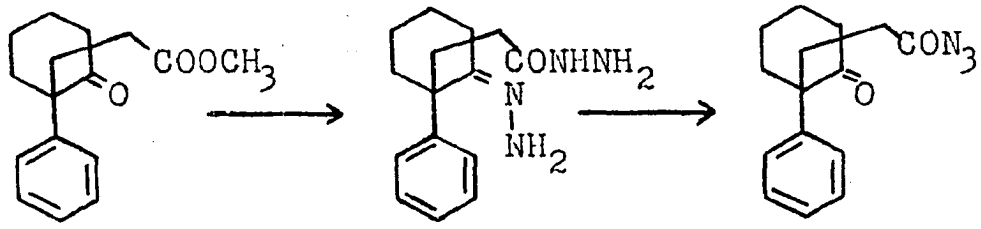


In our reaction the pH was very low and a subsequent reaction might be expected to occur involving the formation of elemental nitrogen from the ammonium ion and nitrite:



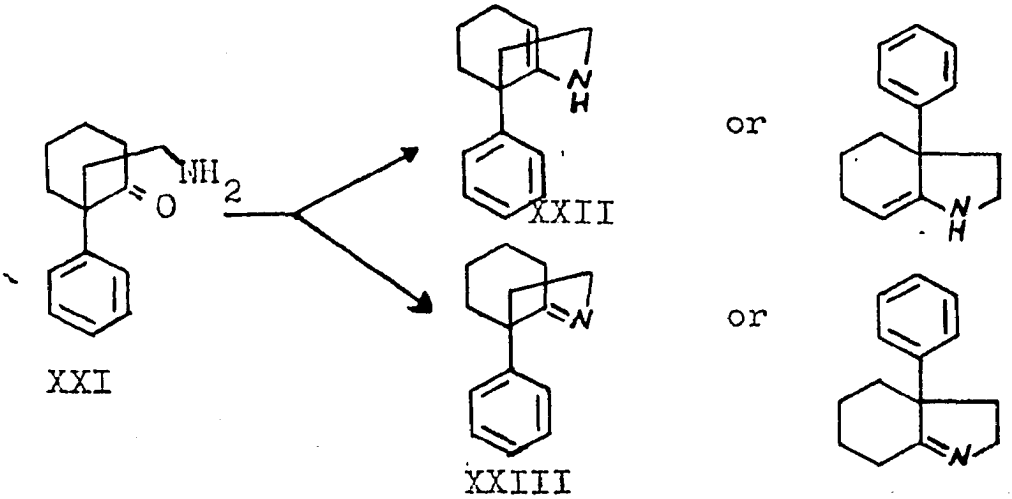
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The liquid azide (XX) decomposed readily with vigorous evolution of gas when warmed in glacial acetic acid solution. The product, presumably the mixed carbamic-acetic anhydride, was hydrolyzed directly by hydrochloric acid to a water-soluble hydrochloride of an amine.




XX

The free amine, which was obtained by addition of alkali to the hydrochloride and purified by evaporative distillation under reduced pressure, was a colorless liquid (68% yield). Analysis showed that the compound contained no oxygen, and the analytical values agreed with those of a compound formed from the keto-amine (XXI) by loss of a molecule of water. The only logical structure for the amine is that of the cyclic product, 9-phenyl-$\Delta^7$-hexahydroindole (XXII), which would result through reaction of the amino group and the carbonyl group.




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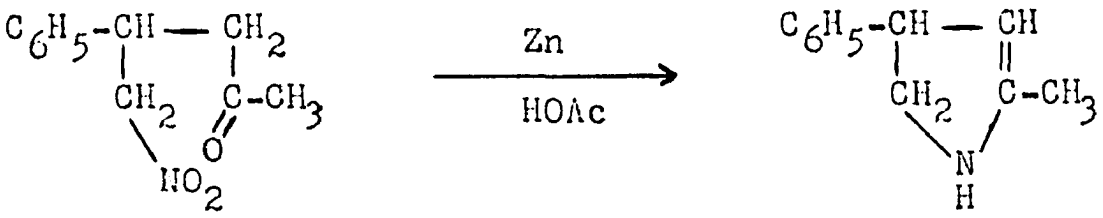
The structure is written as (XXII) rather than (XXIII) because $\Delta^1$-pyrrolines are not known as individuals; (XXIII) is the tautomer of XXII and the compound may react in one form or the other depending on the conditions of the experiment and the reagents involved. On account of its hygroscopic properties the amine hydrochloride was difficult to purify. The picrate proved to be a readily crystallizable derivative which had no tendency to absorb moisture. The analysis of the picrate which was prepared from the free amine agreed with that of the picrate of the cyclic structure and not with that of the keto-amine (XXI). Since the amine from which the picrate had been formed had not been distilled, the result showed that the process of evaporative distillation was not responsible for the cyclization. In order to determine whether the product was already in the cyclic form before the addition of alkali, the amine hydrochloride was converted into the amine picrate without the formation of the free amine by adding one equivalent of sodium hydroxide to a mixture of the amine hydrochloride and picric acid. The product was the picrate of the cyclic amine and the result shows that cyclization had occurred in the acid medium. The amine hydrochloride is undoubtedly the cyclic product; in solution some of the keto-amine structure (XXI) may be present.

The cyclization reaction which takes place is similar to the formation of 2-methyl-4-phenyl-$\Delta^2$-pyrroline by reduction of

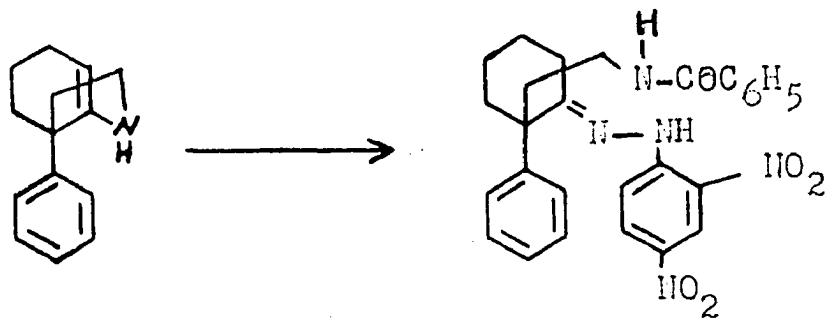


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γ-nitro-β-phenylmethylpropyl ketone by zinc and acetic acid[34].

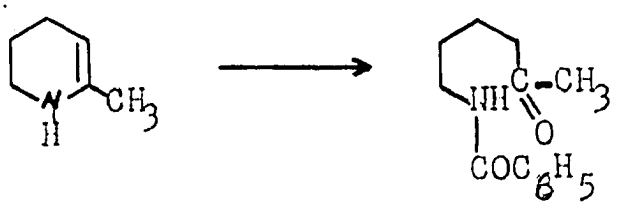



When the cyclic amine (XXII) was treated with benzoyl chloride and aqueous sodium hydroxide in portions (Schotten-Baumann reaction), the product was a viscous liquid which gave an immediate precipitate with 2,4-dinitrophenylhydrazine. Analysis of the crystalline product showed it to be the 2,4-dinitrophenylhydrazone of the open structure, 1-oxo-2-phenylcyclohexaneethyl benzamide (XXIV). The result shows that the following reaction had taken place.



XXIV

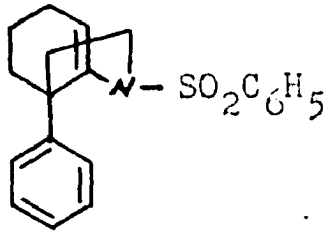
This reaction has a precedent in the formation of a benzoyl-aminoketone in the reaction of 2-methyl-$\Delta^2$-tetrahydropyridine with benzoyl chloride and sodium hydroxide[35].



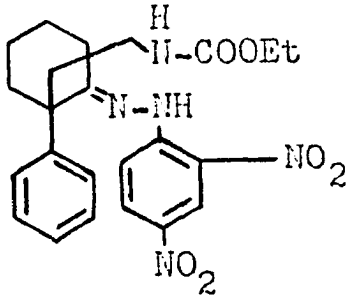
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On this basis the benzoyl derivative, before addition of 2,4-dinitrophenylhydrazine, probably has the benzoylaminoketone structure.

When an aqueous solution of the amine hydrochloride was treated with benzenesulfonyl chloride and sodium hydroxide, a benzenesulfonyl derivative (XXV) of the cyclic amine was produced as was evident from the analysis and the insolubility of the product in alkali.




XXV



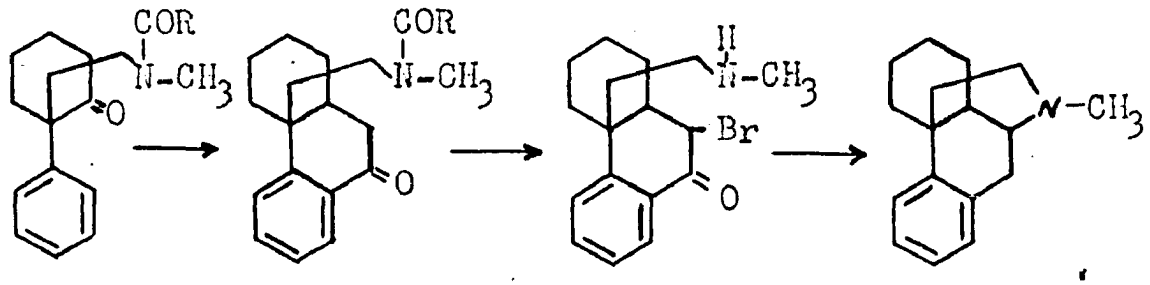

XXVI

By carrying out the rearrangement of the azide (XX) in ethanol the carbethoxy derivative of an amine was obtained. This compound gave an immediate precipitate of the 2,4-dinitrophenylhydrazone (XXVI).

For the synthesis of the N-methylmorphinane structure we wished to have a derivative of the N-methylaminoketone such as (XXVII). From this intermediate it appeared possible to secure the desired structure by means of a Reformatsky reaction, dehydration, reduction and cyclization to the hydrophenanthrene (XXVIII),

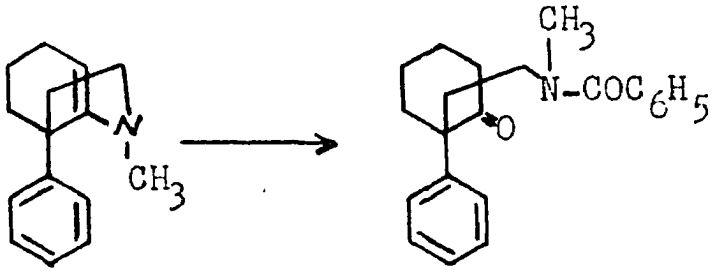
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followed by removal of the acyl group, bromination to XXIX, cyclization and reduction.



XXVII XXVIII XXIX

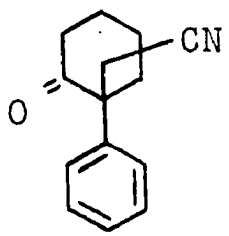
Prior to the elucidation of the structure of the amine, we were trying to find a good method of introducing a single methyl group on the nitrogen atom. The formation of the cyclic amine was fortunate in that it solved this particular problem for us. The cyclic amine has only one hydrogen atom on the nitrogen; this was replaced by reaction with one equivalent of dimethyl sulfate. It is of interest that the N-methylamine (XXX) underwent benzoylation under Schotten-Baumann conditions to (XXXI), which readily formed a crystalline 2,4-dinitrophenylhydrazone. This result shows that the amine need not have a C=N structure in order for hydrolytic cleavage to an aminoketone to occur.



XXX XXXI

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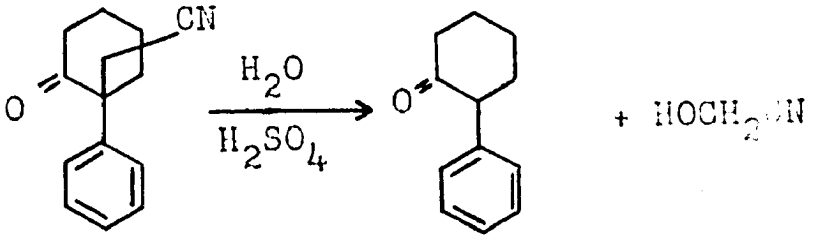
Synthesis of 2-Hydroxy -1-phenylcyclohexaneethylamine. 2-Cyanomethyl-2-phenylcyclohexanone (XXXII) was prepared by treatment of a suspension of the sodio derivative of 2-phenylcyclohexanone in ether-benzene with chloroacetonitrile. The structure is written tentatively as XXXII , but this has not yet been proved unequivocally.



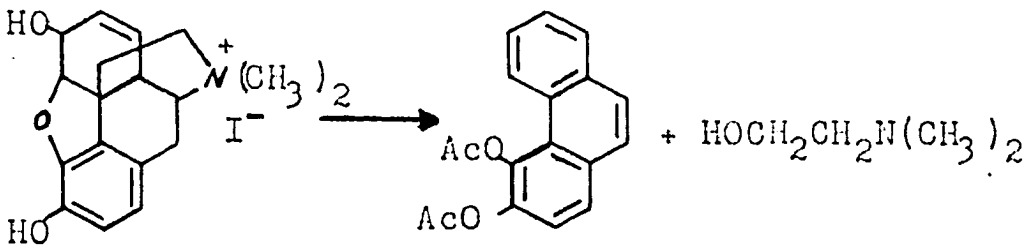

XXXII

The product, obtained in 70-80% yields, showed rather peculiar chemical properties in that it would give no carbonyl derivatives. When warmed with 2,4-dinitrophenylhydrazine reagent, the product was at first an oil which on repeated trituration with methanol crystallized. When recrystallized from methanol, it was found to be the 2,4-dinitrophenylhydrazone of 2-phenylcyclohexanone as shown by its melting point and mixed melting point with an authentic sample. In the reaction the cyanomethyl group was ejected, presumably as hydroxyacetonitrile, through hydrolytic cleavage of the compound.

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The elimination of the cyanomethyl group is paralleled in the reactions of morphine itself[36]. Morphine methiodide (XXXIII), when heated with acetic anhydride yields as the main product the diacetyl derivative of 3,4-dihydroxyphenanthrene or morphol (XXXIV).

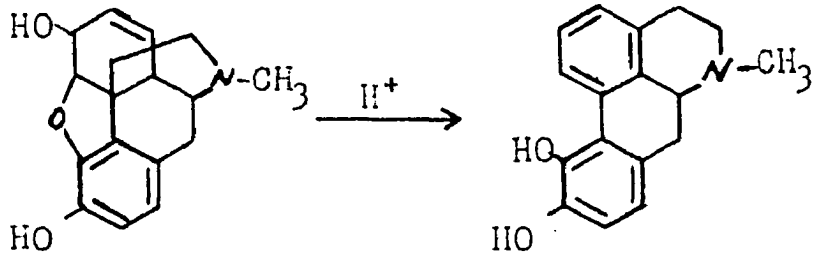



XXXIII XXXIV

Furthermore, treatment of morphine with various acidic reagents gives rise to apomorphine (XXXV) in which the ethaneamine chain has become detached from the quaternary carbon atom and appears

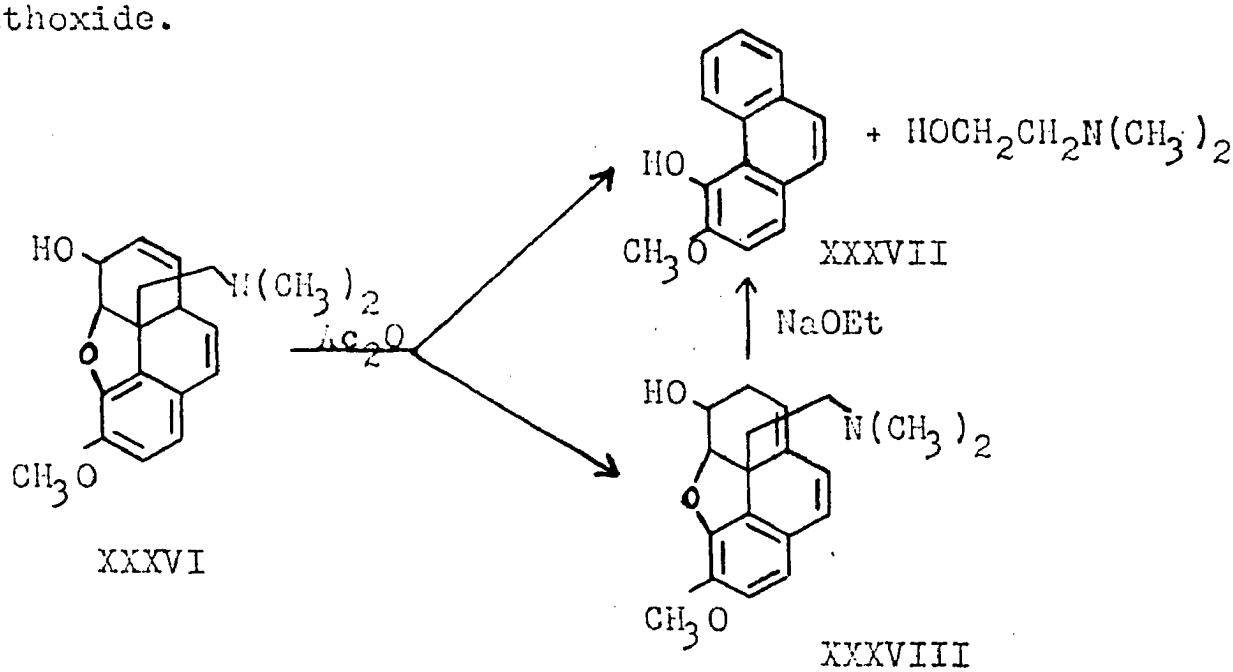
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at the 8-position of the aromatized ring.



XXXV

Similarly, α-methylmorphimethine (XXXVI), formed from codeine methiodide in alkaline solution, yields dimethylaminoethanol and methylmorphol (XXXVII) as well as some β-methylmorphimethine (XXXVIII) in the presence of acetic anhydride; the β-methylmorphimethine can be converted to methylmorphol by treatment with sodium ethoxide.



XXXVI

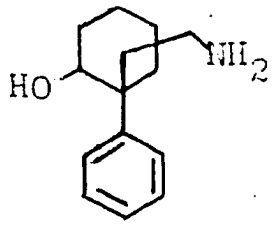
XXXVII

XXXVIII

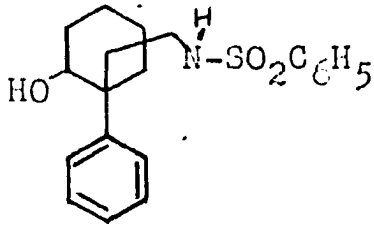
Horning, Horning and Platt[13b] also observed a loss of an ethoxyethyl group from a quaternary carbon atom during acid hydrolysis.

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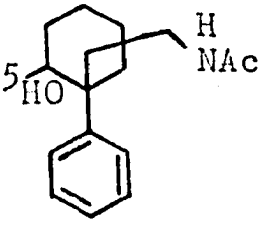
Reduction of our 2-cyanomethyl-2-phenylcyclohexanone (XXXII) proceeded as expected when carried out with an ethereal solution of lithium aluminum hydride. Although the basic portion of the reaction products amounted to 84%, only a low yield of a crystalline substance, presumably 2-hydroxy-1-phenylcyclohexane-ethylamine (XXXIX), could be isolated. That this crystalline product was a primary amine was shown by the solubility, albeit sparing, in aqueous sodium hydroxide of the benzenesulfonyl derivative (XL) prepared by the usual Schotten-Baumann procedure.




XXXIX




XL




XLI

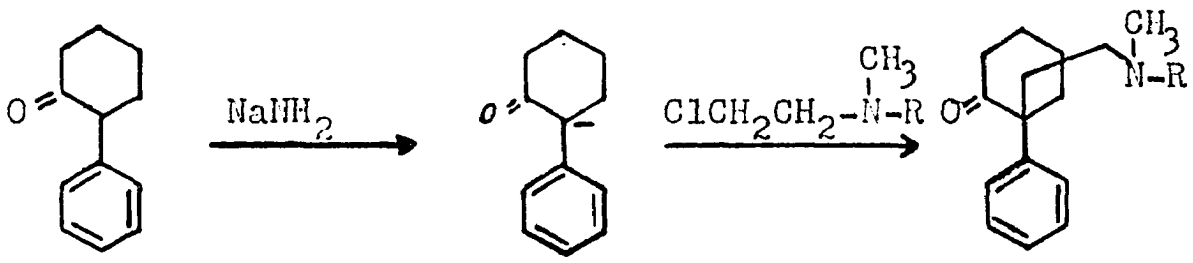
It is not known whether the liquid amine is a stereoisomer of the solid amine or is a cyclic amine.

Catalytic reduction of the nitrile in acetic anhydride solution gave a crystalline acetylamino derivative which is probably (XLI). Neither of these compounds showed the presence of a carbonyl group as might be expected. Oxidation of the hydroxyl to a ketone was attempted according to the method of Oppenauer with aluminum tert-butoxide and acetone and also with chromic anhydride in acetic acid. In both cases the starting material was recovered in good yield.



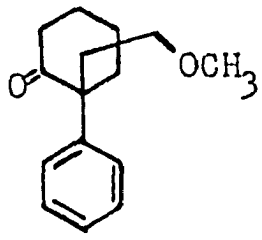
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Other Approaches. Attempts were made to introduce an aminoethyl group directly and indirectly at the 2-position of 2-phenylcyclohexanone by reaction of the sodio derivative of the ketone with a suitably substituted alkyl halide as shown in the following formulation.




Newman and Magerlein[14] were successful in introducing the ethoxyethyl group into 2-phenylcyclohexanone by reaction of the methanesulfonate of ethyl cellosolve, $CH_3SO_2OCH_2CH_2OC_2H_5$, with the sodio derivative of the ketone. According to them the p-toluenesulfonyl ester, $CH_3C_6H_4SO_2OCH_2CH_2OC_2H_5$, was unsuitable on account of the difficulty of separating the reaction product by fractional distillation from the ester which is used in excess. We circumvented this difficulty by hydrolyzing the excess ester (the benzenesulfonyl ester of methyl cellosolve was used) to water-soluble products by short refluxing with a mixture of acetic and hydrochloric acid. After this treatment there was no difficulty in obtaining 2-methoxyethyl-2-phenylcyclohexanone (XLII), a new compound.

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XLII

This compound could probably be converted into an amine by replacing the ether grouping with a halogen by means of hydrobromic acid followed by reaction of the bromide with an amine. We were reluctant to pursue the morphine problem with the ether (XLII) in view of the work by other investigators with similar ethers.

Exploratory work was carried out on methods involving the direct introduction of the aminoethyl group. In the first approach the benzoyl derivative of 2-chloroethylmethylamine was employed. Methylaminoethanol, prepared from ethylene oxide and methylamine[37], was converted into 2-chloroethylmethylamine hydrochloride by treatment with thionyl chloride[38]. This compound had been prepared by Marckwald and Frobenius[39] by cleavage of 2-naphthoxyethylmethyl-p-toluenesulfonamide with hydrochloric acid in a sealed tube. Treatment of an aqueous solution of the amine hydrochloride with benzoyl chloride and two equivalents of alkali gave the benzamide in 85% yield as a colorless liquid. When the sodio derivative of 2-phenylcyclohexanone was treated with an ethereal solution of 2-chloroethylmethylbenzamide, the mixture turned dark red and the only isolable material was the starting ketone.

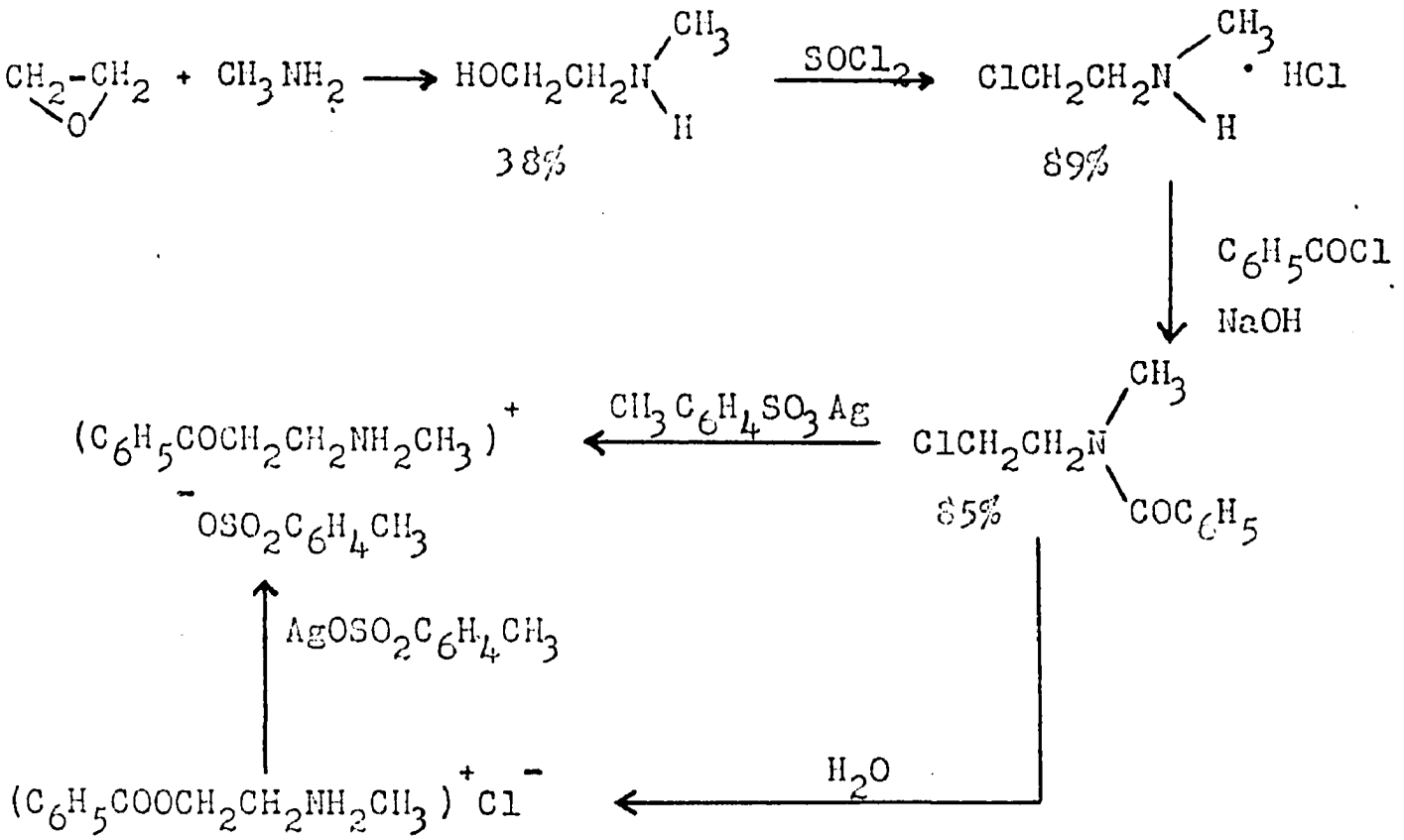
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In order to prepare a more reactive compound, an attempt was made to replace the chlorine atom by the sulfonate group by reaction with silver p-toluenesulfonate. When a solution of the above benzamide in methanol was warmed with silver p-toluenesulfonate, a copious precipitate of silver chloride formed. The product was a colorless oil which crystallized readily. The analysis and solubility characteristics indicated that this was not the ester but a salt. Proof of this was obtained through an independent synthesis which was accomplished by reaction of 2-methylaminoethylbenzoate hydrochloride with silver p-toluenesulfonate.

It was found by Marckwald and Frobenius[39] that when 2-chloroethylmethylbenzamide is warmed with water the mixture quickly becomes homogeneous and the material isolated is the salt, 2-methylaminoethylbenzoate hydrochloride, the reaction depending upon both a hydrolysis and a rearrangement. It would appear then that a similar type of reaction had occurred in the treatment of the halide with silver p-toluenesulfonate, the latter probably not being completely anhydrous. The reactions are shown in the following scheme.



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It was thought that the N-carbethoxy compound, $ClCH_2CH_2N(CH_3)COOEt$, might show greater resistance to hydrolysis than the N-benzoyl derivative and could be made to react in the alkylation of the sodio ketone. The substituted urethane (XLIII) was prepared under the usual Schotten-Baumann conditions in 81% yield.

$$(ClCH_2CH_2NH_2CH_3)^+Cl^- + ClCOOEt + 2\ NaOH \longrightarrow \underset{\text{XLIII}}{ClCH_2CH_2NCH_3COOEt} + 2\ NaCl + 2\ H_2O$$

This compound actually did show greater resistance to hydrolysis than the benzoyl derivative since refluxing for twenty-five minutes with water was required to effect complete solution. The

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material isolated in 40% yield was the expected 2-methylamino-ethyl ethylcarbonate hydrochloride (XLIV) as shown by its analysis, ready solubility in water and ionic chlorine.

$$ClCH_2CH_2NCH_3COOEt + H_2O \longrightarrow (EtOOCCH_2CH_2NH_2CH_3)Cl$$

XLIV

The reaction of the halide (XLIII) with the sodio derivative of 2-phenylcyclohexanone has not yet been tried.

In another study it was decided to block the amino group of methylaminoethanol with a p-toluenesulfonyl group and to convert the alcohol to a sulfonyl ester. According to the method of Slotta and Behnisch[37] an aqueous solution of the aminoalcohol and sodium hydroxide was warmed with p-toluenesulfonyl chloride.

$$HOCH_2CH_2\overset{CH_3}{\underset{|}{N}}H + ClSO_2C_6H_4CH_3 \xrightarrow{NaOH} HOCH_2CH_2\overset{CH_3}{\underset{|}{N}}SO_2C_6H_4CH_3$$

$$HOCH_2CH_2\overset{CH_3}{\underset{|}{N}}SO_2C_6H_4CH_3 \xrightarrow[pyridine]{ClSO_2C_6H_4CH_3} CH_3C_6H_4SO_2\text{-}\overset{CH_3}{\underset{|}{N}}\text{-}CH_2CH_2OSO_2C_6H_4CH_3$$

XLV

Conversion of the alcohol to the p-toluenesulfonyl ester (XLV) was accomplished by mixing the reactants in dry pyridine at ice bath temperature. When this compound was recrystallized from

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benzene-petroleum ether, it showed three melting points: 55-56.5°, 72-4°, 82.5-84.5°. These were all obtained on the same sample by holding the bath temperature at the melting point until solidification occurred and then raising it until melting took place again.

When the sodio derivative of 2-phenylcyclohexanone was treated with this ester, a reaction occurred as was evidenced by the formation of a heavy precipitate, presumably sodium p-toluenesulfonate. This reaction is worthy of further study. Unsatisfactory results were obtained with the methanesulfonyl ester of 2-hydroxyethyl-methyl-p-toluenesulfonamide, with 2-chloroethyl-p-toluenesulfonate and 2-chloroethylmethanesulfonate.

The preceding experiments were exploratory in nature; some of the results suggest further reactions which would yield productive results. They were not pursued further at this time because of the success which attended the investigation of the keto-acid (XII).



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## EXPERIMENTAL PART

2-Chlorocyclohexanone. The procedure used to prepare the chloro-ketone was essentially that of Newman and Farbman[19]. A two-liter three-necked flask was fitted with a sealed stirrer, a short condenser to catch any spray and a gas inlet tube leading nearly to the bottom of the flask. To the end of the condenser was attached a bubbler filled with water to indicate the rate of gas flow. The flask was charged with 147 g. (1.5 moles) of cyclohexanone and 450 ml. of water and was weighed. Gaseous chlorine was then passed in to the well-stirred mixture for thirty minutes when the gain in weight amounted to 110 g. (theoretical = 107.5 g.).

The organic layer was separated and the aqueous solution was extracted three times with 150-ml. portions of ether. These extracts were combined with the original organic material and the whole was washed with 150 ml. of water and then with 200 ml. of saturated sodium chloride solution. The residue remaining after drying over sodium sulfate and distilling off the ether was fractionated under reduced pressure and the material boiling at 45-120° under 15 mm. was collected. This fraction, amounting to 165 g., was redistilled through a six-inch Vigreux column whereupon 135 g. of product resulted boiling at 84-6° at 15 mm. pressure (62%). Reported, b.p. 90-1° at 14-5 mm.





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2-Phenylcyclohexanone[19] (I). In a three-liter three-necked flask fitted with an efficient reflux condenser, stirrer and dropping funnel were placed 59.5 g. (2.44 g. atoms) of magnesium and 200 ml. of dry ether. From the dropping funnel was added 50 ml. of a solution of 384 g. (2.44 moles) of bromobenzene in 550 ml. of dry ether. The mixture was then heated gently on the steam bath until reaction occurred and the remainder of the halide was added at such a rate as to cause gentle refluxing. After the addition was completed, the solution was refluxed for one hour.

At the end of this time the Grignard reagent was cooled in an ice bath and with stirring a solution of 255 g. of 2-chlorocyclohexanone in 500 ml. of dry ether was added over a period of two hours. The reflux condenser was then removed from the flask and replaced with a suitable arrangement for distilling off the ether. The solvent was distilled until the glassy residue nearly filled the flask, whereupon the reflux condenser was replaced, 700 ml. of dry benzene was added and the mixture was refluxed on the steam bath over night.

Decomposition of the complex was accomplished by pouring the reaction mixture into a 4-l. beaker containing crushed ice and hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with three 100-ml. portions of benzene, the combined solutions being subsequently dried over calcium chloride.



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Removal of the solvent on a steam bath under reduced pressure gave a dark brown viscous liquid which was subjected to vacuum distillation. By distilling from a 2-l. flask through a twelve-inch Vigreux column the product was obtained as a colorless to light yellow liquid which quickly set to a crystalline solid. The fraction boiling at 108-110° at 0.2 mm. amounted to 190 g. (57%). By recrystallization of the forerun and a small amount of high-boiling material from 60-75° petroleum ether, the yield was raised somewhat.

To be of use in later work the ketone was further purified by repeated recrystallization from petroleum ether; m.p. 58-9°.

2-Phenyl-$\Delta^2$-Cyclohexenone[13] (III). A solution of five grams of 2-phenylcyclohexanone (m.p. 58-9°) in thirty ml. of carbon tetrachloride (Reagent Grade) was placed in a three-hundred ml. three-necked flask equipped with a stirrer, a pressure-equalizing dropping funnel and a drying tube filled with Drierite. In the funnel was placed a solution of 1.54 ml. of bromine (Reagent Grade) in 25 ml. of carbon tetrachloride (Reagent Grade). Dry carbon dioxide was passed through the flask for several minutes by means of a tube attached to the top of the dropping funnel. With continuous flow of gas and vigorous stirring the bromine solution was added drop by drop. The reaction flask was immersed in an ice bath during the entire operation.



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When the addition was completed, the reaction mixture was transferred to a separatory funnel and washed once with cold water and dried over calcium chloride. The solvent was removed under reduced pressure in a water bath the temperature of which did not rise above 30°. The resulting dark oily liquid crystallized readily on standing.

To the residue was added 50 ml. of redistilled 2,6-lutidine and, when solution was complete, the mixture was heated to reflux under a nitrogen atmosphere for twenty minutes. After having cooled, the lutidine hydrobromide was removed by filtration and washed well with ether. The excess lutidine was then distilled off under reduced pressure on a steam bath and the solid remaining was taken up in ether. The resulting solution was washed with dilute hydrochloric acid until the washings were acid and then with sodium bicarbonate solution until neutral. Drying with magnesium sulfate and removal of the ether gave a tan crystalline residue of the unsaturated ketone which was distilled in a one-piece glass apparatus. By conducting the distillation slowly, it was possible to obtain the product as a light yellow oil, quickly setting to a crystalline solid, at a bath temperature of 145-155° (0.1 mm. pressure). Recrystallization of this material from 60-75° petroleum ether gave 3.5 g. (70%) of colorless needles, m.p. 93.94.5° (reported, 95-95.5°).

The yield of unsaturated ketone depends to a large extent on the purity of the 2-phenylcyclohexanone used. Unless it has been



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recrystallized several times from petroleum ether an appreciable amount of tar will result in the bromination step making purification of the final product very difficult. It was found that 2-phenylcyclohexanone with melting point 58-9° will give consistently good yields. Too long heating of the bromoketone with 2,6-lutidine, even in an inert atmosphere, will produce a notable darkening of the reaction mixture with increased difficulty of purification of the final product.

Michael Reaction between 2-Phenyl-$\Delta^2$-Cyclohexenone and Malonic Ester. To a solution of 0.66 g. of sodium (1 equivalent) in 50 ml. of absolute ethanol was added 23.25 g. (5 equivalents) of ethyl malonate and 5 g. of 2-phenyl-$\Delta^2$-cyclohexenone. The flask was stoppered tightly and the mixture swirled until homogeneous.

After having stood at room temperature for forty hours, the mixture was treated with 2 ml. of glacial acetic acid and 25 ml. of water. The aqueous layer was extracted three times with ether and the extracts were added to the organic layer. Drying over sodium sulfate and removal of the ether under reduced pressure gave a solution of the product in ethyl malonate which was distilled at 20 mm. to remove the excess malonic ester. The reddish-yellow oil remaining was then distilled at 0.1 mm., the ethyl 3-oxo-2-phenylcyclohexanemalonate (IV) being collected at 180-5°. Yield: 5.7-6.4 g. (59-67%). Due to the great viscosity



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of the ester, purification by distillation was quite difficult and the semicarbazone was prepared for analysis. It crystallized as small colorless rhombs and after three recrystallizations from methanol melted at 154-5°.

Anal. Calcd. for $C_{20}H_{27}O_5N_3$: C, 61.75; H, 6.94; N, 10.8
Found: C, 61.8 ; H, 6.72; N, 11.18

Hydrolysis of the Michael Product. Two grams of 3-oxo-2-phenylcyclohexanemalonic ester was refluxed under a nitrogen atmosphere for fourteen hours with 15 ml. of glacial acetic acid and 25 ml. of concentrated hydrochloric acid. The solvents were removed on the steam bath under reduced pressure yielding an oil which upon trituration with benzene set to white crystals. More benzene was added, the mixture was warmed to effect complete solution and filtered to remove a small amount of insoluble material. Cooling gave 1 g. (71%) of 3-oxo-2-phenylcyclohexaneacetic acid (VII) as small colorless elongated cubes, m.p. 121-3°. Further recrystallization from benzene raised the melting point to 124-5°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.89
Found: C, 71.58;H, 6.88

Methyl 3-Oxo-2-Phenylcyclohexaneacetate. A solution of 0.49 g. of 3-oxo-2-phenylcyclohexaneacetic acid and 1 ml. of concentrated sulfuric acid in 10 ml. of absolute methanol was heated under reflux for three hours. The cooled reaction mixture was poured



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into water and the oily product was extracted with ether. The combined extracts were washed with water and sodium bicarbonate solution until neutral and dried over sodium sulfate. Removal of the solvent gave a slightly yellow crystalline product which after recrystallization from 60-75° petroleum ether weighed 0.35 g.; m.p. 68-70°. Further recrystallization from the same solvent raised the melting point to 71-73.5°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.2; H, 7.32
Found: C, 73.42; H, 7.43

Dinitrophenylhydrazone. The above ester, when warmed with a methanol-sulfuric acid solution of 2,4-dinitrophenylhydrazine, gave an oil which set to a crystalline solid on standing; m.p. 117-8°. After several recrystallizations from methanol, the dinitrophenylhydrazone formed yellow needles; m.p. 12(-7°.

Anal. Calcd. for $C_{21}H_{22}O_6N_4$: C, 59.2 ; H, 5.17; N, 13.15
Found: C, 59.07; H, 5.24; N, 13.00

trans-2-Phenylcyclohexaneacetic Acid (VIII). Twenty grams of mossy zinc was amalgamated by shaking it with a solution of 2 g. of mercuric chloride in 25 ml. of water containing 2 ml. of concentrated hydrochloric acid for five minutes. The amalgam was washed several times with water by decantation. To the amalgam was added 25 ml. of water and 35 ml. of concentrated hydrochloric acid and then a solution of 1 g. of 3-oxo-2-phenylcyclohexanemalonic ester in 25 ml. of toluene (Reagent Grade)

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was added in such a way as not to touch the zinc. The mixture was then refluxed for thirty hours with frequent additions of fresh acid.

The solvents were decanted from the residual amalgam, the toluene layer was separated, and the aqueous layer was extracted several times with ether. After having been washed with water, the combined organic solutions were exhaustively extracted with 5% sodium bicarbonate solution (until acidification gave no precipitate). Careful acidification with 6 N hydrochloric acid yielded a crystalline solid which was filtered off, washed well with water and dried. The yield of product melting at 109-112° was 0.38 g. (58.6%). One recrystallization from aqueous methanol raised the melting point to 112-112.5°. Blumenfeld[24] reports the melting point of trans-2-phenylcyclohexaneacetic acid to be 112°.

When 3-oxo-2-phenylcyclohexaneacetic acid was subjected to the above treatment, the yield was 61.2%, m.p. 110.5-112°.

trans-1,2,3,4,4a,9,10,10a-Octahydro-9-phenanthrone (IX). A solution of 100 mg. of trans-2-phenylcyclohexaneacetic acid in 3 ml. of concentrated sulfuric acid was warmed on a steam bath for ten minutes. At the end of this time the solution was somewhat colored. When it was poured over chipped ice and stirred, a crystalline solid separated which was taken up in ether, washed with water, dilute sodium bicarbonate solution and again with water. Drying over sodium sulfate and removal of the solvent in

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a current of air gave a white solid which was dissolved in methanol, filtered and diluted to twice its volume with water. A flocculent solid separated which was redissolved by warming. As the solution cooled the product precipitated as fine colorless needles which were filtered off and dried; yield, 60 mg.; m.p. 95.5-96.5° (reported[24], m.p. 96°).

Ethyl cis-2-Phenylcyclohexanecyanoacetate. The following is a modification of the method developed by Alexander and Cope for other ketones[26]. A mixture of 4.35 g. (0.025 mole) of 2-phenylcyclohexanone, 5.66 g. (0.05 mole) of ethyl cyanoacetate, 0.39 g. (0.005 mole) of ammonium acetate, 0.6 g. (0.1 mole) of glacial acetic acid, 0.1 g. of palladium-charcoal catalyst and 10 ml. of commercial absolute ethanol was shaken in an atmosphere of hydrogen for twenty-four hours. At first the uptake of hydrogen was rapid but it soon slowed down. After sixteen hours the rate of absorption was 2 ml. per minute and after twenty-four hours it was 1 ml. per minute.

The catalyst was removed by filtration and 20 ml. of benzene was added to the filtrate. This was washed once with water which in turn was extracted three times with ether. The combined organic solutions were washed three times with 3 N hydrochloric acid and then with sodium bicarbonate until neutral. Drying over sodium sulfate and removal of the solvents under reduced pressure on a steam bath gave 8.5 g. of amber liquid. Distillation of this at

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0.1 mm. yielded 4.3 g. of light-yellow viscous liquid boiling at 149-151° (64%). The forerun amounted to 3.2 g. and deposited crystals on standing. Recrystallization of a sample from petroleum ether gave colorless plates which did not depress the melting point of pure 2-phenylcyclohexanone.

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.25; H, 7.75; N, 5.16

Found: C, 72.48; H, 7.34; N, 5.16

When the hydrogenation was carried out for only sixteen hours, the yield dropped to 47% of the theoretical.

cis-2-Phenylcyclohexaneacetic Acid (X). One gram of cis-2-phenylcyclohexanecyanoacetic ester was refluxed in an inert atmosphere with 20 ml. of glacial acetic acid, 10 ml. of concentrated hydrochloric acid and 5 ml. of water for fifteen hours. Ten ml. more hydrochloric acid was added and the refluxing was continued for three and one-half hours more. A crystalline solid separated from the reaction mixture and the precipitation was completed by dilution with water. The solid was filtered with suction, washed well with water and dried in vacuo. The weight of material, m.p. 165-168.5°, was 0.69 g. (85.2%). One recrystallization from aqueous methanol gave 0.59 g. (73.4%) of cis-2-phenylcyclohexaneacetic acid melting at 168-170°. The same melting point was reported by Cook, Hewett and Lawrence[25].

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2-Oxo-1-phenylcyclohexanepropionitrile (XI). This compound was prepared in two ways: by alkylation of 2-phenylcyclohexanone with β-chloropropionitrile and by cyanoethylation with acrylonitrile in the presence of Triton B.

Alkylation with β-Chloropropionitrile[16a]. In a 300 ml. three-necked flask fitted with a stirrer, reflux condenser and dropping funnel was placed 1.23 g. of finely divided sodamide (10% excess or 80% assay) and 30 ml. of dry benzene. A nitrogen atmosphere was maintained throughout. To the stirred and refluxing suspension of sodamide was added drop by drop a solution of 5 g. of 2-phenylcyclohexanone in 30 ml. of dry benzene. Stirring and refluxing were continued until no more ammonia was evolved (ca. two and one-half hours). The yellow suspension of sodio derivative was then treated at the reflux point slowly with a solution of 3.42 g. of β-chloropropionitrile in 20 ml. of dry ether. The mixture was refluxed for seventeen hours, 30 ml. of water was added and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic solutions were washed several times with water and dried over sodium sulfate. Removal of the solvents gave a light yellow oil which distilled at 146-150° under 0.15-0.2 mm. pressure. Yield: 3.84 g. (58.9%).

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Cyanoethylation[13]. Ten grams of 2-phenylcyclohexanone was dissolved in 80 ml. of pure dioxane and 1 ml. of Triton B solution was added. While vigorously stirred, this mixture was treated slowly with a solution of 3.6 g. of acrylonitrile in 10 ml. of pure dioxane. Stirring was continued for three hours and the reaction mixture was poured into 500 ml. of water. A little sodium chloride was added to break the emulsion and the organic material was extracted out with ether. Washing with water and drying over magnesium sulfate followed by removal of the solvent gave a yellow liquid which distilled at 151-2° at 0.5 mm.; yield, 9.78 g. (75%).

2-Oxo-1-phenylcyclohexanepropionic Acid[13] (XII). Under an atmosphere of nitrogen 14.54 g. of 2-oxo-1-phenylcyclohexanepropionitrile was refluxed for fifteen hours with a mixture of 50 ml. of glacial acetic acid, 20 ml. of concentrated hydrochloric acid and the same volume of water. The cooled reaction mixture was poured into 200 ml. of water and cooled in an ice bath and scratched until crystallization occurred. The solid was filtered with suction and washed well with water. It was then dissolved in dilute sodium hydroxide solution and extracted twice with ether to remove a small amount of insoluble material. Slow acidification of this solution in an ice bath gave a large mass of white crystals which were filtered off and recrystallized from aqueous methanol; yield, 14.84 g. (94.3%); m.p. 113-114°.



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Semicarbazone. One gram of the keto-acid, 1 g. of semicarbazide hydrochloride and 2.45 g. of sodium acetate trihydrate were warmed on a steam bath for fifteen minutes with several ml. of methanol and a few drops of water. The product which separated on cooling was recrystallized from aqueous methanol as small colorless prisms, m.p. 202-3°; yield, 0.98 g. (79.6%). Several recrystallizations from aqueous methanol failed to raise the melting point.

Anal. Calcd. for $C_{10}H_{21}O_3N_3$: C, 53.4; H, 7.93 ; N, 13.88
Found: C, 53.64; H, 7.85 ; N, 13.88

1-Phenylcyclohexanepropionic Acid (XIII). One gram of 2-oxo-1-phenylcyclohexanepropionic acid, 0.77 g. of potassium hydroxide, 2 ml. of 85% hydrzine hydrate and 10 ml. of diethylene glycol were heated under reflux for one and one-half hour. The reflux condenser was then removed and heating was continued until the temperature, as indicated by a thermometer suspended in the boiling mixture, rose to 195-200°. The reflux condenser was reinserted and heating was continued at this temperature for five hours. The cooled reaction mixture was diluted with water and acidified with concentrated hydrochloric acid. The white precipitate thus formed was filtered off and washed well with water. Recrystallization from aqueous methanol gave 0.8 g. of product as colorless glistening plates, m.p. 98.5-100°, in the first crop and 0.05 g., m.p. 96.5-98°, in the second. Total yield: 0.85 g. (90%).



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Four recrystallizations from aqueous methanol raised the melting point to 99-100°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.5; H, 8.62

Found: C, 77.26; H, 8.60

1-Phenylcyclohexaneethylamine Hydrochloride (XVI). A mixture of 0.2 g. of 1-phenylcyclohexanepropionic acid, 2 ml. of purified thionyl chloride and 3 ml. of dry benzene was heated under gentle reflux for one-half hour. The somewhat dark solution was evaporated to dryness under reduced pressure. Three ml. of dry benzene was added and removed in the same fashion. The colored liquid remaining was dissolved in 3 ml. of acetone (Reagent Grade) and cooled in an ice bath during the rapid addition of a solution of 0.28 g. (5 equivalents) of sodium azide dissolved in 2 ml. of water. After having stood for ten minutes in the ice bath, this mixture was diluted with water and the resulting oil was taken up in ether, washed well with water and dilute sodium bicarbonate solution and dried over magnesium sulfate.

The light yellow liquid remaining after removal of the ether under reduced pressure at room temperature was treated with 3 ml. of glacial acetic acid and warmed gently on a steam bath. Nitrogen was evolved readily and heating was continued for several hours. Five ml. of concentrated hydrochloric acid was added and the solution was refluxed for twelve hours. A small amount of insoluble

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oil was removed from the cooled hydrolysis mixture by extraction with ether and the aqueous layer was made alkaline with sodium hydroxide. The liberated amine was taken up in ether, washed several times with water and reconverted to the hydrochloride by extraction of the ethereal solution with four 5 ml. portions of 6 N hydrochloric acid. This solution was evaporated to dryness under reduced pressure on a steam bath leaving a colorless oil which crystallized readily. Recrystallization from acetone-petroleum ether gave 0.14 g. (68%) of white flocculent needles, m.p. 245-7° (dec.). Three recrystallizations from the same solvent mixture raised the melting point to 253-4° (dec.).

Anal. Calcd. for $C_{14}H_{22}NCl$: C, 70.1 ; H, 9.2 ; N, 5.84; Cl, 14.81

Found: C, 69.62; H, 8.84; N, 5.75; Cl, 14.97

Action of Thionyl Chloride and Sodium Azide on 2-Oxo-1-phencyclohexanepropionic Acid. One gram of 2-oxo-1-phenylcyclohexanepropionic acid was heated to gentle reflux with 5 ml. of dry benzene and 5 ml. of purified thionyl chloride for one hour. The volatile materials were removed under reduced pressure and 3 ml. more of dry benzene was added and removed. The light yellow crystalline solid remaining was dissolved in 10 ml. of acetone (Reagent Grade) and cooled in an ice bath during the addition of a solution of 1.3 g. of sodium azide in 3 ml. of water. The mixture was allowed to stand in the cold for ten minutes and then was diluted with a large amount of water. The precipitated oil which solidified quickly upon cooling and scratching was filtered off

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and dried; weight, 0.9 g.; m.p. 111-114°; mixed m.p. with 2-oxo-1-phenylcyclohexanepropionic acid, 87-105°. The enol-lactone (XVII) was recrystallized several times from methanol as dense colorless cubes; m.p. 113.5-114.5°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.94; H, 7.02
Found: C, 78.60; H, 6.97

Methyl 2-Oxo-1-phenylcyclohexanepropionate (XVIII). Five grams of 2-oxo-1-phenylcyclohexanepropionic acid dissolved in 100 ml. of ether was treated with excess ethereal diazomethane until evolution of nitrogen ceased and a permanent yellow color was produced. The mixture was allowed to stand one-half hour and the unreacted methylating agent was removed by concentration of the solution in a stream of air accompanied by gentle heating on a steam bath. The colorless solution of the ester was washed once with dilute sodium bicarbonate solution and once with water and dried over magnesium sulfate. The light yellow oil remaining after removal of the solvent, when distilled under reduced pressure, yielded 4.8 g. (91%) of colorless viscous liquid at 146°/0.05 mm.

After standing seven days, this material solidified and was recrystallized from petroleum ether as small colorless prisms, m.p. 52-3°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.9 ; H, 7.69
Found: C, 73.74; H, 7.82



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Oxime of Methyl 2-Oxo-1-phenylcyclohexanepropionate. In 15 ml. of absolute ethanol was dissolved 1.57 g. of the keto-ester and 2.1 g. of hydroxylamine hydrochloride and 3.58 g. of anhydrous barium carbonate was added. While protected from moisture by a calcium chloride tube, this mixture was refluxed for sixteen hours. The cooled reaction mixture was filtered through FilterCel and the clear filtrate was diluted with water. Cooling and scratching caused the precipitated oil to crystallize as colorless prisms which were filtered off, washed well with water and dried *in vacuo*; yield, 1.54 g. (93%); m.p. 126-126.5°. The analytical sample melted at 126-7° after several recrystallizations from aqueous methanol.

Anal. Calcd. for $C_{16}H_{21}O_3N$: C, 69.85; H, 7.64; N, 5.09
Found: C, 69.77; H, 7.70; N, 5.14

Oxime-Hydrazide of 2-Oxo-1-phenylcyclohexanepropionic Acid (XIX). A mixture of 1.54 g. of the oxime-ester, 5 ml. of 85% hydrazine hydrate and 3 ml. of ethanol was heated under reflux for one hour. Water was added to the cooled reaction mixture and the crystalline solid was filtered off, washed with ether and water and dried in a vacuum desiccator over calcium chloride and sulfuric acid. The dried product weighed 1.54 g. (99.7%); m.p. 192.5-193.5°. Three recrystallizations from methanol gave the analytical sample as colorless cubes, m.p. 194°.



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Anal. Calcd. for $C_{15}H_{21}O_2N_3$: C, 65.5; H, 7.64; N, 15.27
Found: C, 65.5; H, 7.81; N, 15.54

Reaction of the Oxime-Hydrazide of 2-Oxo-1-phenylcyclohexane-propionic Acid with Nitrous Acid. A solution of 100 mg. of the oxime-hydrazide in 10 ml. of 3 N hydrochloric acid was cooled in an ice bath and stirred vigorously during the slow addition of a solution of 0.09 g. of 97% sodium nitrite in 10 ml. of water. A positive starch-iodide test was obtained after 7 ml. of this solution had been added. Thus, 2.4 equivalents of nitrite were consumed. The chalky solid resulting was filtered out and dried in vacuo; weight, 75 mg.; m.p. 204-210° with darkening at ca. 180°. Three recrystallizations from methanol raised the melting point to 217-8°.

Anal. Found: C, 74.77; H, 7.42; N, 8.52

A sample of this material was found to be completely soluble in 0.1 N sodium hydroxide solution upon warming. Acidification gave a white precipitate which after recrystallization from aqueous methanol and drying melted at 213-5°. Attempted acid hydrolysis led only to extensive decomposition.

Methoxylamine Hydrochloride[40]. A cold solution of 69 g. of sodium nitrite in 200 ml. of water containing chipped ice was treated slowly with a solution of 104 g. of sodium bisulfite in



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200 ml. of water. The mixture was then cooled in an ice-salt bath and 20 ml. of glacial acetic acid was added drop by drop with vigorous stirring. One hundred ml. of a saturated solution of potassium acetate in water was then added and the mixture was cooled and scratched until crystallization occurred. The solid was filtered with suction, washed with a little cold water and dried in a vacuum desiccator. Yield: 90.9 g. (35.6%).

The 90.9 g. of potassium hydroxylaminedisulfonate was suspended in a solution of 23.8 g. of sodium hydroxide in 250 ml. of water and stirred vigorously and cooled in ice during the slow addition of 50 g. of dimethyl sulfate. The mixture was then allowed to come to room temperature with stirring over a period of one and one-half hour. Gentle reflux for several minutes served to decompose the unreacted dimethyl sulfate. One hundred ml. of concentrated hydrochloric acid was added and refluxing was continued for eighteen hours.

Sodium hydroxide pellets were added to the reaction mixture until it was strongly basic. This alkaline solution was then subjected to distillation the distillate being collected in 200 ml. of 6 N hydrochloric acid. Distillation occurred between 80° and 96°. Evaporation of this acid solution to dryness under reduced pressure on a steam bath gave a white crystalline residue which was dissolved in absolute ethanol. Addition of dry ether caused precipitation of the hydrochloride as small prisms.

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Successive filtrations and treatments of the mother liquors with ether gave 17.98 g. of methoxylamine hydrochloride, m.p. 140-2° (sealed tube); reported by Jones[41], m.p. 148-9°.

O-Methyloxime of 2-Oxo-1-Phenylcyclohexanepropionhydrazide. A mixture of 1.18 g. of methyl 2-oxo-1-phenylcyclohexanepropionate, 1.81 g. of methoxylamine hydrochloride, 2.69 g. of barium carbonate and 15 ml. of absolute ethanol was refluxed for seventeen hours. The solid was removed by filtration through Filter-Cel and the filtrate was diluted with water. The precipitated oil was taken up in ether, washed well with water and dried over sodium sulfate. The liquid remaining after removal of the solvent was heated under reflux for one hour with 3 ml. of 85% hydrazine hydrate and 4 ml. of ethanol. The reaction mixture was poured into water and the oil thus formed was crystallized by cooling. This solid was filtered off, dried in vacuo and recrystallized from benzene-petroleum ether; yield, 0.76 g.; m.p. 129-130°. Concentration of the mother liquor gave a second crop: 0.12 g., m.p. 126-130°. The analytical sample crystallized as small colorless prisms, m.p. 129-130°.

Anal. Calcd. for $C_{16}H_{23}O_2N_3$: C, 66.45; H, 7.95; N, 14.53
Found: C, 66.62; H, 7.81; N, 14.91

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Reaction of the O-Methyloxime-hydrazide with Nitrous Acid.

A solution of 0.41 g. of the O-methyloxime in 20 ml. of 3 N hydrochloric acid was cooled in an ice bath and stirred vigorously during the addition of a solution of 1.06 g. of 97% sodium nitrite in 40 ml. of water. A positive starch-iodide test was obtained when 4 ml. of this solution had been added (4 ml. contained one equivalent). Stirring in the cold was continued for twenty minutes and the gummy azide was extracted into ether. The ether solution was washed with water and dilute sodium bicarbonate until neutral and dried over magnesium sulfate. Removal of the ether gave 0.35 g. of almost colorless viscous liquid. This was dissolved in 3 ml. of glacial acetic acid and heated on a steam bath. A vigorous evolution of nitrogen occurred and lasted for ten minutes. Heating was continued for twenty minutes after the first reaction had subsided and then 5 ml. of concentrated hydrochloric acid and 3 ml. of water were added. When heated to boiling, this mixture evolved carbon dioxide readily as evidenced by the precipitation of barium carbonate produced by passing the exit gases through saturated barium hydroxide solution. After one hour the hydrolysis appeared to be complete and the cooled reaction mixture was diluted with water and extracted twice with ether to remove a small amount of insoluble oil. Evaporation of the aqueous layer to dryness gave 0.32 g. of gummy oil which crystallized partially upon drying in a vacuum desiccator. This was dissolved



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in water and treated with sodium hydroxide solution until strongly alkaline. A flocculent solid formed which was taken up in ether, washed three times with distilled water and dried over magnesium sulfate. When the solvent was removed, a brown liquid remained. This amine has not yet been characterized.

Curtius Degradation of 2-Oxo-1-phenylcyclohexanepropionic Acid. One gram of methyl 2-oxo-1-phenylcyclohexanepropionate (XVIII) was heated under reflux for one and one-half hour with 4 ml. of 85% hydrazine hydrate and 2.5 ml. of ethanol. The solvents and excess hydrazine were removed under reduced pressure on a steam bath leaving the presumed hydrazone-hydrazide as a colorless glass. This was dissolved in 40 ml. of 3 N hydrochloric acid and extracted once with ether to remove a small amount of insoluble material. While cooled in an ice bath and vigorously stirred, this solution was treated with 0.77 N sodium nitrite solution until a positive starch-iodide was obtained. Sixteen ml. or 3.2 equivalents were required. The mixture was stirred in the ice bath for fifteen minutes and the gummy azide was extracted out with ether, washed with dilute sodium bicarbonate solution until neutral and dried over magnesium sulfate.

Removal of the solvent at room temperature gave 0.87 g. (76.2%) of a slightly yellow viscous liquid. Three ml. of glacial acetic acid was added and the almost colorless solution warmed

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gently on a steam bath. A vigorous evolution of nitrogen occurred and lasted about ten minutes at the full heat of the bath. The mixture was heated one-half hour and a solution of 7 ml. of concentrated hydrochloric acid and 3 ml. of water was added. When heated to reflux, this mixture evolved carbon dioxide readily over a period of about thirty minutes. Refluxing was continued for one-half hour more (one hour total) before the cooled reaction mixture was diluted with water and extracted with ether to remove the slight turbidity that resulted. Solid sodium hydroxide pellets were added to the clear slightly yellow solution until it was definitely alkaline. An oil separated which was extracted into ether and washed five times with distilled water to remove inorganic salts. At this stage the ether layer appeared almost colorless but upon extraction of this with 3 N hydrochloric acid the aqueous layer assumed a yellow color. Five portions of 5 ml. each of acid were used to transfer the amine to the aqueous phase. Evaporation of this to dryness under reduced pressure on a steam bath gave a light yellow glass weighing 0.67 g.

The benzenesulfonamide was prepared by dissolving the above obtained amine hydrochloride in 20 ml. of water and adding 0.35 ml. of benzenesulfonyl chloride. While stirred vigorously, this mixture was treated slowly with a solution of 0.5 g. of sodium hydroxide in 10 ml. of water until a permanent alkaline reaction was obtained toward Alk-Acid paper. Stirring was continued for



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about one hour more after which the mixture was heated to 100° for fifteen minutes. After acidification, the hard solid was broken up with a stirring rod and filtered and washed well with water and dried *in vacuo*. A solution of the compound in 2:1 benzene-petroleum ether was passed through a column of activated alumina 8 mm. in diameter and 60 mm. long. Elution was accomplished with 30 ml. of the same solvent mixture. The colored impurities remained adsorbed in the first 10 mm. and the product obtained upon removal of the solvents in a current of air was colorless. Recrystallization from aqueous methanol gave 0.67 g. of colorless plates in the first crop, m.p. 125-7°. The second crop, obtained by concentration of the solution and further dilution with water, weighed 0.02 g.; m.p. 121-3°. Further recrystallization from aqueous methanol gave the analytical sample as colorless plates; m.p. 127-8°.

Anal. Calcd. for $C_{20}H_{23}O_3NS$ (keto form):
C, 67.2; H, 6.45; N, 3.92; S, 8.96

Found: C, 70.83; H, 6.34; N, 4.13; S, 9.44

Calcd. for $C_{20}H_{21}O_2NS$ (cyclic form):
C, 70.8; H, 6.2 ; N, 4.15; S, 9.44

In a direct preparation of the amine hydrochloride from the isocyanate, 4.74 g. of the methyl ester was heated under reflux with 25 ml. of ethanol and 7 ml. of 85% hydrazine hydrate for two and one-half hours. After removal of the solvents and excess



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hydrazine under reduced pressure, the residue was dissolved in 100 ml. of 3 N hydrochloric acid and treated with a solution of 6.48 g. of 97% sodium nitrite in 50 ml. of water. Thirty-three ml. or 3.3 equivalents of nitrite were required to produce a positive starch-iodide test. The gummy azide was extracted into benzene, washed with sodium bicarbonate solution and dried over magnesium sulfate. The benzene solution was filtered and heated cautiously under reflux until the first vigorous evolution of gas ceased and then more strongly for fifteen minutes more. The cooled reaction mixture was treated with 50 ml. of concentrated hydrochloric acid and again heated carefully while carbon dioxide was liberated freely. Refluxing was continued for nine hours and the benzene layer was separated. After the aqueous phase had been washed several times with ether, it was evaporated to dryness under reduced pressure on a steam bath to yield 3.7 g. of the hydrochloride as a viscous glassy mass.

Picrate. The picrate of the amine was prepared in two ways. In one procedure the amine was set free with aqueous alkali and extracted into ether. The ether solution was washed with water and treated with a saturated ethereal solution of picric acid whereupon the picrate separated as a yellow liquid which crystallized readily upon being cooled and scratched. Further



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recrystallization from methanol gave an analytical sample as small bright yellow prismatic plates; m.p. 147.5-148.5°.

Anal. Calcd. for $C_{20}H_{22}O_8N_4$ (cyclic amine): C, 56.1; H, 4.67; N, 13.09

Calcd. for $C_{20}H_{24}O_9N_4$ (keto-amine) : C, 53.8; H, 4.94; N, 12.56

Found: C, 56.66; H, 4.7; N, 12.91

In the second method of forming the picrate a standard solution of alcoholic sodium hydroxide containing exactly one equivalent of base was added slowly to a well-stirred alcoholic solution of the amine hydrochloride and one equivalent of picric acid. The product precipitated readily and, after being heated to boiling, was filtered. Recrystallization from methanol yielded yellow plates, m.p. 147-8° alone and 146.5-148° when mixed with the picrate prepared above.

N-Carbethoxy-2-oxo-1-phenylcyclohexaneethylamine. Five grams of methyl 2-oxo-1-phenylcyclohexanepropionate, 7.5 ml. of 85% hydrazine hydrate and 25 ml. of ethanol were refluxed for three hours. The solvents and excess hydrazine were removed under reduced pressure on a steam bath and the glassy residue was dissolved in 100 ml. of 3 N hydrochloric acid. Extraction of this solution with ether served to remove a small amount of insoluble material.



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While cooled in an ice bath and stirred vigorously, the hydrazide solution was treated slowly with a solution of 13.65 g. of 97% sodium nitrite in 60 ml. of solution. Twenty ml. of nitrite solution (3.33 equivalents) were required before the starch-iodide test was positive. A vigorous evolution of gas was noted during the addition. Stirring was continued for ten minutes and the azide was extracted into ether, being subsequently washed with sodium bicarbonate until neutral and dried over magnesium sulfate.

The ether was removed under reduced pressure at room temperature and the yellow residual liquid was dissolved in 10 ml. of absolute ethanol. Cautious heating on a steam bath under a reflux condenser gave a vigorous evolution of gas which lasted about ten minutes. After the initial reaction was completed, the mixture was refluxed for one-half hour and the alcohol was distilled off under reduced pressure. Distillation of the residue under high vacuum gave a colorless very viscous liquid boiling at 148-150° at 0.03 mm. Under the conditions of distillation some decomposition occurred and the originally colorless compound assumed a slight color toward the end of the operation. The yield was 3 g. (55%).

Due to the nature of the urethane, it was deemed best not to attempt further purification by distillation but rather to prepare a derivative for analysis. Treatment of the above obtained material in methanol solution with 2,4-dinitrophenylhydrazine



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reagent gave an immediate yellow-orange solid which after four recrystallizations from methanol formed orange-yellow micro prisms; m.p. 138-138.5°.

Anal. Calcd. for $C_{23}H_{27}O_6N_5$: C, 58.9; H, 5.76; N, 14.92
Found: C, 59.28; H, 5.67; N, 14.91

In another preparation, the urethane obtained from 1 g. of the keto-ester was evaporatively distilled to give 0.94 g. (84.5%) of slightly yellow liquid at 150-5° under 0.1 mm. pressure.

9-Phenyl-$\Delta^7$-hexahydroindole (XXII). Five grams of methyl 2-oxo-1-phenylcyclohexanepropionate was converted to the hydrazone-hydrazide by refluxing with 7.5 ml. of 85% hydrazine hydrate and 25 ml. of ethanol for three hours. The solvents and excess hydrazine were removed under reduced pressure on a steam bath and the glassy residue was dissolved in 100 ml. of 3 N hydrochloric acid. After extraction with ether, the clear aqueous solution was treated with a solution of 6.85 g. of 97% sodium nitrite in 50 ml. of solution. Thirty ml. of this solution or 3 equivalents were required to give a positive starch-iodide test. The azide was extracted into ether, washed with sodium bicarbonate solution until neutral and dried over magnesium sulfate. The ether was removed under reduced pressure at room temperature and the residual liquid was dissolved in 10 ml. of glacial acetic acid. Cautious heating of this solution gave a vigorous evolution of nitrogen which lasted about ten minutes. Heating was continued for one hour when a



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solution of 10 ml. of concentrated hydrochloric acid and 5 ml. of water was added. This mixture was refluxed for one and one-half hour and the solvents were removed under reduced pressure on a steam bath leaving a brown viscous mass. Water was added to dissolve the hydrochloride and a small amount of insoluble oil was removed by extraction with ether. When the aqueous solution was made strongly alkaline, the amine separated as an oil which was taken up in ether, washed with water and dried over sodium sulfate. Removal of the solvent gave a reddish brown liquid which was distilled under reduced pressure to yield 2.6 g. (68%) of colorless, rather mobile liquid boiling at 98-100° at 0.1 mm.

The analytical sample was obtained by evaporative distillation twice at 90-100° at 0.1 mm.

Anal. Calcd. for $C_{14}H_{17}N$ (cyclic amine):
C, 84.45; H, 8.54; N, 7.03

Calcd. for $C_{14}H_{19}ON$ (keto-amine):
C, 77.45; H, 8.75; N, 6.45

Found: C, 83.70; H, 8.56; N, 6.91

2,4-Dinitrophenylhydrazone of 2-Oxo-1-phenylcyclohexane-ethylbenzamide (XXIV). A small sample of the above prepared base was treated with benzoyl chloride and then with aqueous alkali in portions, each addition being accompanied by vigorous shaking. A white gum precipitated which could not be made to crystallize.



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When this material was dissolved in methanol and treated with a solution of 2,4-dinitrophenylhydrazine sulfate, there was an immediate formation of a yellow crystalline solid which after repeated recrystallization from acetic acid-methanol formed yellow elongated prisms; m.p. 218.5-219°.

Anal. Calcd. for $C_{27}H_{27}O_5N_5$: C, 64.60; H, 5.39: N, 13.98
Found: C, 64.63; H, 5.45; N, 13.66

1-Methyl-9-phenyl-$\Delta^7$-hexahydroindole (XXX). A solution of 1.42 g. of 9-phenyl-$\Delta^7$-hexahydroindole in 3 ml. of methylethyl ketone was treated with 0.9 g. (1 equivalent) of dimethyl sulfate and cooled in an ice bath until the flask no longer became warm upon removal from the bath. After having stood at room temperature for sixteen hours, the wine-colored solution was heated under reflux for one hour. Five ml. of water was added and refluxing was ontinued for three hours. At the end of this time the solution was somewhat lighter in color and was diluted with 20 ml. of water and made strongly alkaline with sodium hydroxide. An oil separated which was taken up in ether, washed several times with water and dried over sodium sulfate. Removal of the ether gave a red liquid which was subjected to evaporative distillation. A colorless liquid which weighed 1.35 g. (88.7%) distilled at 75-80° under 0.05-0.1 mm. pressure. Upon standing for one-half hour in a closed flask this material began to turn red. In view of this fact the picrate was prepared for analysis.

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Picrate. A solution of the amine in ether was treated with a saturated solution of picric acid in ether. An oil formed which crystallized readily upon being cooled and scratched. After four recrystallizations from methanol, the picrate was obtained as yellow prismatic plates, m.p. 142-3°; mixed with the picrate of the starting amine; m.p. 117-128°.

Anal. Calcd. for $C_{21}H_{22}O_7N_4$ (cyclic amine):

C, 57.0; H, 4.97; N, 12.66

Calcd. for $C_{21}H_{24}O_8N_4$ (keto-amine):

C, 54.8; H, 5.22; N, 12.18

Found: C, 57.28; H, 5.19; N, 12.40

2,4-Dinitrophenylhydrazone of 2-Oxo-1-phenylcyclohexaneethyl-methylbenzamide. A small amount of the above amine was treated with excess benzoyl chloride and aqueous sodium hydroxide was added in portions with vigorous shaking. The gummy product which refused to crystallize was dissolved in methanol and a solution of 2,4-dinitrophenylhydrazine in methanolic sulfuric acid was added. The mixture was warmed for several minutes on a steam bath and cooled. The precipitated oil crystallized after standing in the cold for thirty hours. The solid was collected and recrystallized from a mixture of methanol and acetic acid and then three times from benzene-petroleum ether. The product formed rosettes of very fine yellow-orange needles; m.p. 172-4°.

Anal. Calcd. for $C_{28}H_{29}O_5N_5$: C, 65.26; H, 5.63; N, 13.6

Found: C, 65.65; H, 5.72; N, 13.5



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2-Cyanomethyl-2-phenylcyclohexanone (XXXII). In a 300 ml. three-necked flask provided with a stirrer, reflux condenser and dropping funnel was placed a suspension of 1.23 g. of finely divided sodamide (10% excess of 80% assay) in 25 ml. of dry benzene. A nitrogen atmosphere was provided and a solution of 5 g. of 2-phenylcyclohexanone in 20 ml. of dry benzene was added slowly to the refluxing suspension of sodamide. When ammonia was no longer evolved (ca. two and one-half hours), the flask was cooled in an ice bath and 50 ml. of dry ether was added. The stirred and cooled mixture was then treated slowly with a solution of 2.6 g. (20% excess) of redistilled chloroacetonitrile (Eastman, White Label) in 10 ml. of dry ether. The mixture was then heated under reflux for three hours. During this time the flocculent solid changed to a granular crystalline one and the mixture darkened considerably. The cooled reaction mass was then treated with 100 ml. of water and the ether-benzene solution was separated. The dark aqueous layer was extracted several times with ether and the combined organic solutions were washed with water, 4 N hydrochloric acid and then with sodium bicarbonate solution until neutral and dried over sodium sulfate. After the solvent had been removed under reduced pressure, the residue was distilled *in vacuo*. The fraction boiling at 126-130° (mostly 126-8°) at 0.2 mm. amounted to 4.45 g. (72.7%).

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.9 ; H, 7.04; N, 6.57

Found: C, 77.75; H, 6.98; N, 6.00

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Reduction of 2-Cyanomethyl-2-phenylcyclohexanone with Lithium Aluminum Hydride. In a 300 ml. three-necked flask fitted with a stirrer, reflux condenser and dropping funnel was placed 30 ml. of 1.3 molar ethereal lithium aluminum hydride solution. A nitrogen atmosphere was provided and a solution of 2 g. of 2-cyanomethyl-2-phenylcyclohexanone in 20 ml. of dry ether was added slowly to the well-stirred hydride solution. A heavy white precipitate formed at once. Stirring was continued for forty-five minutes and the mixture was allowed to stand for fourteen hours at room temperature. The excess hydride was decomposed by cautious addition of 25 ml. of water. Ten grams of sodium potassium tartrate was added to the mixture and the ether layer was separated, the aqueous suspension being extracted four times with the same solvent. The extracts were washed several times with water and then six times with 15 ml. portions of 6 N hydrochloric acid. Fifty percent sodium hydroxide solution was added to the acid extract until it showed a basic reaction. The somewhat oily crystalline precipitate, after filtration and drying, weighed 1.68 g. Further addition of base to the filtrate yielded 0.05 g. more. Total weight: 1.73 g. (84%). Upon recrystallization from a mixture of benzene and petroleum ether, 0.64 g. of material, presumably 2-hydroxy-1-phenylcyclohexaneethylamine (XXXIX), could be obtained that was free from oil; m.p. 132.5-133.5°. The analytical sample,

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m.p. 133.5-134.5°, was obtained by further recrystallization from the same solvent mixture as long colorless needles.

Anal. Calcd. for $C_{14}H_{21}ON$: C, 76.75; H, 9.59; N, 6.39
Found: C, 77.85; H, 8.98; N, 6.02

Benzenesulfonamide (XL). To a solution of 0.2 g. of 2-hydroxy-1-phenylcyclohexaneethylamine in 10 ml. of 0.1 N hydrochloric acid was added 0.17 g. of benzenesulfonyl chloride. With vigorous shaking, a solution of 1 g. of sodium hydroxide in 5 ml. of water was added in 1 ml. portions. The mixture was warmed on a steam bath for fifteen minutes and after acidification the hard precipitate which had formed was filtered off and recrystallized from aqueous methanol. The first crop, weighing 0.24 g., melted at 130.5-131.5°. A second crop weighed 0.02 g. and melted at 128-130°. Total yield: 0.26 g. (79.2%). Further recrystallization from aqueous methanol yielded colorless glistening plates, m.p. 130.5-131.5°. Mixed melting point with the free amine: 106-125°.

Anal. Calcd. for $C_{20}H_{25}O_3NS$: C, 66.9 ; H, 6.96; N, 3.9; S, 8.92
Found : C, 67.54; H, 6.66; N, 3.8; S, 9.33

Catalytic Reduction of 2-Cyanomethyl-2-phenylcyclohexanone. Three grams of the cyanomethyl ketone (XXXII) was dissolved in 15 ml. of acetic anhydride and 0.2 g. of Adams' catalyst was added. When this mixture was shaken in an atmosphere of hydrogen,

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two equivalents of gas were absorbed after one and one-half hour. After two hours 850 ml. had been taken up and the rate of absorption decreased markedly. The shaking was stopped after 890 ml. had been fixed and the mixture was filtered. The acetic anhydride was decomposed by addition of methanol to the warm solution and the acid and excess methanol were removed under reduced pressure. An oil remained which readily deposited crystals from benzene-petroleum ether. Recrystallization from the same solvent mixture gave 1.06 g. of material; m.p. 138-141°. Further recrystallization from benzene-petroleum ether gave pure 2-hydroxy-1-phenylcyclohexaneethylacetamide (XLI); m.p. 142-3°.

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.5 ; H, 8.81; N, 5.36
Found: C, 73.21; N, 8.50; N, 5.16

Methoxyethylbenzenesulfonate. Twenty grams of methyl cellosolve and 50 ml. of pyridine (dried over sodium hydroxide pellets) were dissolved in 50 ml. of dry benzene and cooled in an ice bath. With swirling, 55.7 g. of benzenesulfonyl chloride was added and the mixture was allowed to stand in the cold for one and one-half hour. At the end of this time it was poured slowly into 100 ml. of ice cold 6 N hydrochloric acid. The benzene layer was separated and the aqueous was extracted three times with ether. The combined organic solutions were washed several times with water and dried over sodium sulfate. Removal of the solvents and distillation under reduced pressure gave 35 g. (61.6%) of colorless liquid boiling at 136-141° at 0.2 mm. pressure.



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2-Methoxyethyl-2-phenylcyclohexanone (XLII). A 1-liter three-necked flask was fitted with a stirrer, reflux condenser and a dropping funnel. A nitrogen atmosphere was provided and a suspension of 7.25 g. (10% excess of 80% assay) of finely divided sodamide in 100 ml. of dry benzene was added. This was heated to reflux and stirred during the slow addition of 29.5 g. of 2-phenylcyclohexanone dissolved in 110 ml. of dry benzene. After two and one-half hours of refluxing, 100 ml. of dry ether was added and then 43.93 g. (20% excess) of methoxyethylbenzenesulfonate in 75 ml. of dry ether was added. After having refluxed for eleven hours, the solution, containing a heavy white precipitate, was treated with 200 ml. of water and the organic layer was separated. The aqueous layer was extracted several times with ether and the solvents were removed without drying. The liquid remaining was then heated under reflux with 100 ml. of glacial acetic acid, 20 ml. of concentrated hydrochloric acid and 20 ml. of water for one-half hour. Most of the acetic acid was distilled off under reduced pressure and the residue was poured into water. The resulting emulsion was extracted several times with ether and the organic solution was washed with water and then with sodium bicarbonate until neutral. Drying over sodium sulfate and evaporation of the solvent gave a yellow liquid which was distilled under 0.5 mm. pressure to give 25.5 g. (64.9%) of colorless viscous liquid boiling at 138-140°. In three other preparations on a smaller scale following this same procedure the yields were 55%, 56% and 53%.

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Semicarbazone. The derivative, prepared in the usual manner, crystallized from aqueous methanol as small colorless prisms; m.p. 185.5-186°.

Anal. Calcd. for $C_{16}H_{23}O_2N_3$: C, 66.4 ; H, 7.95; N, 14.53
Found: C, 66.58; H, 7.90; N, 14.13

2,4-Dinitrophenylhydrazone. Prepared in methanolic sulfuric acid, the compound formed yellow needles after several recrystallizations from methanol; m.p. 133-4°.

Anal. Calcd. for $C_{21}H_{24}O_5N_4$: C, 61.2 ; H, 5.82; N, 13.6
Found: C, 61.83; H, 5.39; N, 14.54

Methylethanolamine[37]. In a three liter three-necked flask was placed 600 ml. of 40% aqueous methylamine solution and 360 ml. of water. A Dry Ice cooled reflux condenser, a stirrer and a gas inlet tube were attached and 140 ml. of ethylene oxide was allowed to vaporize into the flask through the inlet tube leading almost to the bottom of the flask. The mixture was cooled in an ice-salt bath and was stirred vigorously throughout the addition which required about three hours. Stirring in the cold was continued for about two hours more and then the reaction mixture was distilled at atmospheric pressure through a twelve inch Vigreaux column. The fraction boiling at 140-164° was collected and redistilled through the same apparatus. The yield of material obtained in the fraction 156-9° was 65.7 g. (38.8% based on ethylene oxide).



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2-Chloroethylmethylamine Hydrochloride[38,39]. In a 300 ml. three-necked flask provided with a stirrer, reflux condenser and dropping funnel were placed 11 g. of methylethanol amine and 100 ml. of dry chloroform (Reagent Grade). The flask was cooled in an ice bath and, with stirring, 34.5 g. of thionyl chloride (Eastman Kodak, White Label) was added drop by drop. When the addition had been completed, the mixture was stirred and refluxed for twenty minutes during which time the precipitated hydrochloride dissolved and a clear slightly yellow solution resulted. The solvent and excess thionyl chloride were removed on a steam bath under reduced pressure and the brown crystalline residue was recrystallized from acetone. Two crops of slightly yellow plates resulted, the first melting at 116-7° and the second at 115-6° after drying in vacuo; the combined weights were 16.9 g. (89%). Reported by Marckwald and Frobenius[39], m.p. 112°.

2-Chloroethylmethylbenzamide[39]. Five grams of 2-chloroethylmethylamine hydrochloride was dissolved in 50 ml. of water and cooled in an ice bath. After 5.4 g. of benzoyl chloride had been added, a solution of 3.08 g. of sodium hydroxide in 30 ml. of water was added drop by drop to the well-stirred mixture. Stirring was continued for fifteen minutes after the addition had been completed. The reaction mixture was extracted three times with ether, the ether solution was washed twice with water and dried



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over sodium sulfate. After removal of the solvent under reduced pressure, the residual oil was vacuum distilled to give 6.5 g. (85.4%) of colorless liquid boiling at 126° under 0.2 mm. pressure. There was almost no forerun. The yield of crude amide before distillation was 95-9% of slightly colored rather mobile liquid.

Reaction of 2-Chloroethylmethylbenzamide with Silver p-Toluenesulfonate. To a solution of 1.44 g. of crude 2-chloroethylmethylbenzamide in 50 ml. of anhydrous methanol was added 2.03 g. of silver p-toluenesulfonate and the mixture was refluxed for fifteen minutes on a steam bath. At the end of this time the precipitated silver chloride was filtered off on a sintered glass funnel and the filtrate was evaporated to dryness under reduced pressure. A light yellow viscous liquid remained which crystallized readily on trituration with methanol mixed with 30-60° petroleum ether. The solid was completely dissolved in methanol and the solution was filtered through Filter-Cel to remove a small amount of insoluble material. Cooling of the filtrate gave 1.01 g. of small prisms, m.p. 129.5-131.5°. A second crop was obtained by concentration and cooling of the mother liquor, weighing 0.51 g., m.p. 129-131°. Total yield: 1.62 g. Further recrystallization from methanol gave colorless prisms; m.p. 130.5-131.5°.



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Anal. Calcd. for $C_{17}H_{19}O_4NS$ (ester): C, 61.26; H, 5.7 ; N, 4.2; S, 9.6

Found : C, 59.91; H, 6.08; N, 3.65; S, 9.0

Disagreement of the analytical results with the calculated for the tosyl ester and the ready solubility of the material in water suggested that the reaction product was actually an amine salt.

This was shown as follows. 2-Methylaminoethylbenzoate hydrochloride was prepared from 1 g. of 2-chloroethylmethylamine hydrochloride, 1.08 g. of benzoyl chloride and 0.61 g. of sodium hydroxide. After extraction of the amide with ether and washing with water, the ether solution was dried over magnesium sulfate and the solvent was removed under reduced pressure on a steam bath. The crude benzamide remaining was treated with several ml. of water and heated on a steam bath until complete solution had occurred. The water was distilled off under reduced pressure and the crystalline residue was recrystallized from acetone. Methylaminoethylbenzoate hydrochloride was obtained as long silky needles; weight, 0.88 g. (53.2%); m.p. 142.5-143.5°. (Reported[39], m.p. 143°).

One-half gram of this material was dissolved in 10 ml. of water and treated at about 40° with a solution of 0.64 g. of silver p-toluenesulfonate in 10 ml. of water. The mixture was warmed for ten minutes on a steam bath to coagulate the silver chloride and was then filtered through sintered glass. The filtrate was



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freed of water under reduced pressure and the white solid remaining was recrystallized from methanol. The product after drying in vacuo melted at 130.5-132°. The mixed melting point with the material obtained above was 129-131°.

Anal. Calcd. for $C_{17}H_{21}O_5NS$ (salt):

C, 58.1 ; H, 5.98; N, 3.98; S, 9.1

Found: C, 59.91; H, 6.08; N, 3.65; S, 9.0

Ethyl 2-Chloroethylmethylcarbamate (XLIII). In 10 ml. of water was dissolved 3.1[illegible] g. of 2-chloroethylmethylamine hydrochloride. To this solution, cooled in an ice bath, was added 2.04 g. of ethyl chlorocarbonate and then, with stirring, a solution of 1.95 g. of sodium hydroxide in 20 ml. of water was added drop by drop. Stirring was continued for fifteen minutes more and the reaction mixture was extracted three times with ether; the organic solution was washed several times with water and dried over magnesium sulfate. Removal of the solvent left 3.85 g. of yellow liquid which upon distillation at 9-10 mm. gave 3.27 g. (81.2%) of colorless liquid boiling at 83-4°.

To establish the structure of the urethane and to compare its rate of rearrangement with the benzoyl derivative, 2 g. of 2-chloroethylmethylamine hydrochloride was converted to the urethane and after extraction with ether and washing with water was refluxed with 15 ml. of water for twenty-five minutes before solution was complete. The water was removed under reduced pressure on a steam



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bath and the white crystalline residue was recrystallized from acetone. The ethyl 2-methylaminoethylcarbonate hydrochloride (XLIV) crystallized as small prisms, m.p. 117-8°; yield, 1.15 g. (40.7%). Further recrystallization from acetone raised the melting point to 117.5-118°.

Anal. Calcd. for $C_6H_{14}O_3NCl$: C, 39.2 ; H, 7.63; N, 7.63; Cl, 19.3

Found: C, 39.38; H, 7.75; N, 7.04; Cl, 19.3

2-Hydroxyethylmethyl-p-toluenesulfonamide[37]. In a 500 ml. two-necked flask were placed 15.2 g. of methylethanolamine, 100 ml. of water and 8 g. of sodium hydroxide. A stirrer and reflux condenser were arranged and 38 g. of p-toluenesulfonyl chloride was added. The mixture was then stirred vigorously and heated on a steam bath for three hours. The cooled reaction mixture was then extracted with ether, the extracts being combined and washed with water and dried over sodium sulfate. The yellow oil remaining after removal of the solvent was distilled yielding 35.6 g. (76.9%) of viscous translucent liquid at 175-9° under 0.05 mm. pressure. Slotta and Behnisch prepared this compound as described above but gave no boiling point under reduced pressure.



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p-Toluenesulfonyl Ester of 2-Hydroxyethylmethyl-p-toluenesulfonamide (XLV). In a 500 ml. Erlenmeyer flask was placed 6.65 g. of 2-hydroxyethylmethyl-p-toluenesulfonamide and 25 ml. of pyridine (dried over sodium hydroxide pellets). While being swirled in an ice bath this solution was treated with 11.06 g. of p-toluenesulfonyl chloride dissolved in 50 ml. of dry pyridine in such a way that the temperature of the mixture did not rise above 10°. The mixture was allowed to stand ten hours and was then poured into an ice cold solution of 78 ml. of concentrated hydrochloric acid diluted to 250 ml. with water. The oil that precipitated crystallized upon scratching and was taken up in a mixture of one-third ether and two-thirds benzene. The aqueous layer was extracted several times with ether and the combined solutions were washed twice with dilute hydrochloric acid, once with water and dried over magnesium sulfate. After the solvents had been removed, the residue was recrystallized from aqueous methanol giving 7.33 g. (66%) of colorless granular cubes; m.p. 81-2°. A sample after several recrystallizations melted at 84-5°.

Anal. Calcd. for $C_{17}H_{21}O_5NS_2$: C, 53.2 ; H, 5.48; N, 3.65; S, 16.7

Found: C, 53.13; H, 5.4 ; N, 3.5 ; S, 16.76

Methanesulfonyl Chloride[42]. In a 500 ml. four-necked flask provided with a stirrer, reflux condenser, dropping funnel and



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thermometer was placed 152 g. (105 ml. of material obtained from Standard Oil Co. of Indiana) of methanesulfonic acid. With stirring and the temperature held at 85-90°, 238 g. of thionyl chloride was added over a period of four hours. Heating at 90° and stirring were continued for three hours after the addition was completed. Distillation of the dark reaction mixture at 18 mm. gave 56.7 g. of clear colorless liquid at 67-9° (33%).

The yields reported by Noller and Hearst could not be obtained in two attempts.

Methanesulfonyl Ester of 2-Hydroxyethylmethyl-p-Toluenesulfonamide. A mixture of 50 ml. of dry pyridine, 12.27 g. of 2-hydroxyethylmethyl-p-toluenesulfonamide and 20 ml. of dry benzene was treated in small portions with a solution of 8.65 g. of methanesulfonyl chloride in 10 ml. of dry benzene. The mixture was swirled in an ice bath during the addition of the acid chloride and allowed to stand sixteen hours at room temperature. The reaction mass was poured into ice cold solution of 50 ml. of concentrated hydrochloric acid diluted to 100 ml. with water. A crystalline solid formed and was extracted into a mixture of ether and benzene (about 2 l. were required). This was washed twice with 3 N hydrochloric acid and then with sodium bicarbonate until neutral. After removal of the solvents, the residue was recrystallized from benzene-petroleum ether and gave 14.95 g. of



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product, m.p. 75-80°, in the first crop and 0.[illegible] g., m.p. 72-5°, in the second. As in the case of the tosyl ester, several melting points were observed with this compound: 74-6° and 78-9°. When methanol was substituted as the solvent, the melting point was 78-9°.

Anal. Calcd. for $C_{11}H_{17}O_5NS_2$: C, 43.0; H, 5.54; N, 4.56; S, 20.8

Found: C, 47.26; H, 6.00; N, 4.22; S, 19.31
47.45 6.27
47.57 6.13

Since this compound showed no promise in the alkylation of 2-phenylcyclohexanone, no attempt was made to find an explanation for the analytical results quoted above.

2-Chloroethyl-p-toluenesulfonate[43]. Thirty grams of p-toluenesulfonyl chloride and 25.34 g. of ethylene chlorohydrin were dissolved in 50 ml. of dry benzene and treated while being swirled in an ice bath with 50 ml. of dry pyridine. After having stood at room temperature for three hours, the mixture was treated slowly with 50 ml. of concentrated hydrochloric acid. Separation of the benzene layer and extraction of the aqueous phase gave, after washing with water and drying over sodium sulfate, 32.43 g. (73%) of product as a colorless liquid boiling at 191-2°/14-5 mm.

2-Chloroethylmethanesulfonate. Twenty grams of methanesulfonyl chloride and 20.3 g. of ethylene chlorohydrin were dissolved in 50 ml. of dry benzene and swirled in an ice bath

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during the slow addition of 50 ml. of dry pyridine. The reaction mixture was allowed to stand one and one-half hour before being treated with 100 ml. of 6 N hydrochloric acid. The benzene layer was separated and the aqueous was extracted three times with ether. The combined organic solutions were washed with water and then with sodium bicarbonate solution until neutral and dried over sodium sulfate. The solvents were removed and the residue was fractionated under reduced pressure. A clear colorless oil resulted at 118-9° under 8-9 mm. pressure and weighed 21.8 g. (79.2%).

Another preparation that stood for thirty hours gave only 43% yield.

Anal. Calcd. for $C_3H_7O_3ClS$: C, 22.7; H, 4.42; Cl, 22.35; S, 20.2

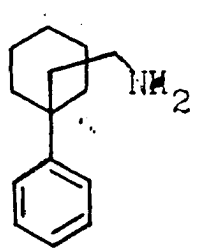
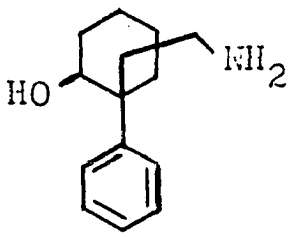
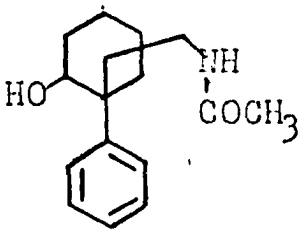
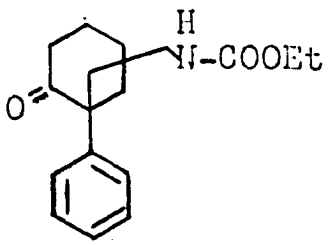
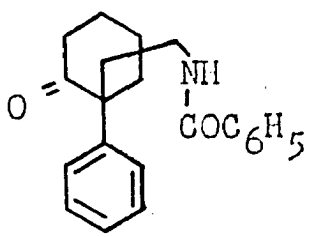
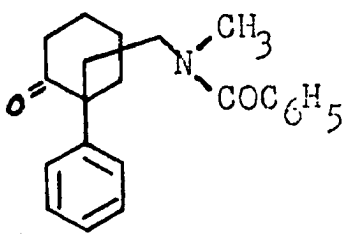
Found: C, 22.9; H, 4.51; Cl, 23.12; S, 19.87

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## SUMMARY

The synthesis of 3-oxo-2-phenylcyclohexaneacetic acid by the Michael addition of malonic ester to 2-phenyl-$\Delta^2$-cyclohexenone was accomplished. New methods for the synthesis of cis- and trans- 2-phenylcyclohexaneacetic acid were developed. From the trans- acid, trans-octahydrophenanthrone was prepared.

The following six amines or derivatives of amines were synthesized.

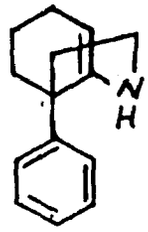
This is the first time compounds of this type have ever been prepared. They should prove to be valuable key intermediates for the synthesis of morphinane and other morphine-like compounds.

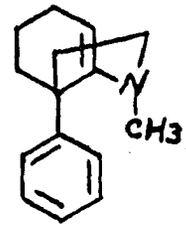


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Because of their similarity to an opened morphine molecule, some of them will be submitted for testing for analgesic activity.

The following two cyclic amines were prepared and their reactions studied. These compounds are hydroindoles with an angular phenyl group. The benzenesulfonyl derivative of one of these was prepared.




Other results of this investigation were:

(1) the preparation of a hydrobenzo-α-pyrone with an angular phenyl group,

(2) the first Curtius reaction involving a δ-keto acid,

(3) the rearrangement of ethyl β-chloroethylmethylcarbamate to ethyl β-methylaminoethylcarbonate hydrochloride by reaction with water.

(4) the preparation of 2-methoxyethyl-2-phenylcyclohexanone from the sodio derivative of 2-phenylcyclohexanone and the benzenesulfonate of methyl cellosolve.

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## REFERENCES


(1) Gulland and Robinson, Mem. Proc. Manchester Lit. Phil. Soc. 69, 79 (1925)

(2) Robinson and Shinoda, J. Chem. Soc. 1926, 1987

(3) Robinson and Sugasawa, ibid. 1931, 3163

(4) Manske, J. Am. Chem. Soc. 53, 1104 (1931)

(5) Fieser and Holmes, ibid. 58, 2319 (1936); 60, 2548 (1938)

(6) Ghosh and Robinson, J. Chem. Soc. 1944, 506

(7) Grewe, Naturwiss. 33, 333 (1946); Chem. Ber. 81, 279 (1948)

(8) Perlman, Davidson and Bogert, J. Org. Chem. 1, 288 (1936)

(9) Cook and Hewett, J. Chem. Soc. 1933, 1098

(10) Grewe, Ber. 76, 1076 (1943); 72, 785 (1939)

(11) Grewe, ibid. 76, 1072 (1943); 72, 1314 (1939)

(12) Schnider and Grussner, Helv. Chim. Acta 32, 821 (1949)

(13) Bachmann and Wick, J. Am. Chem. Soc., (now in press)

(14) Newman and Magerlein, ibid. 69, 942 (1947)

(15) Horning and co-workers, (a) ibid. 69, 2629 (1947); (b) ibid. 70, 2072 (1948); (c) ibid. 70, 2941 (1948)

(16) Boekelheide, (a) ibid. 69, 790 (1947); (b) Abs. Am. Chem. Soc. Meeting, Sept., 1949

(17) Barltrop, J. Chem. Soc. 1947, 399

(18) Gates and Newhall, J. Am. Chem. Soc. 70, 2261 (1948)

(19) Newman and Farbman, ibid. 66, 1551 (1944)

(20) Connor and McClellan, J. Org. Chem. 3, 576 (1939)

(21) Taylor and Connor, ibid. 6, 696 (1941)

(22) Barry and Hartung, ibid. 12, 464 (1947)




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(23) Linstead, Whetstone and Levine, J. Am. Chem. Soc. 64, 2015 (1942)

(24) Blumenfeld, Ber. 74, 524 (1941)

(25) Cook, Hewett and Lawrence, J. Chem. Soc. 1936, 76

(26) Alexander and Cope, J. Am. Chem. Soc. 66, 886 (1944)

(27) Huang-Minlon, ibid. 68, 2487 (1946)

(28) P. A. S. Smith, Organic Reactions III, 373 (1946)

(29) Fischer and Waibel, Ann. 512, 203 (1934)

(30) Leuchs and Gladkorn, Ber. 56, 1780 (1923)

(31) Cheney and Piening, J. Am. Chem. Soc. 67, 734 (1945)

(32) Rothenburg, Ber. 26, 2056 (1893)

(33) Wieland and Horner, Ann. 528, 95 (1937)

(34) Treibs and Dinelli, Ann. 517, 170 (1935)
Sonn, Ber. 68, 148 (1935)

(35) Clipp, Ann. 289, 173 (1896)

(36) Pschorr and co-workers, Ber. 40, 1998 (1907); 62, 321 (1929)
Spath and Hromatka, ibid. 62, 325 (1929)

(37) Slotta and Behnisch, J. Prakt. Chem. 135, 232 (1932)

(38) Ross, J. Am. Chem. Soc. 69, 2983 (1947)

(39) Marckwald and Frobenius, Ber. 34, 3544 (1901)

(40) Traube, ibid. 53, 1477 (1920

(41) Jones, Am. Chem. J. 20, 39 (1898)

(42) Noller and Hearst, J. Am. Chem. Soc. 70, 3955 (1948)

(43) Clemo and Perkin, J. Chem. Soc. 1922, 642

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