ALICYCLIC CARBOXYLIC ACIDS:

THE DIALKYLAMINOETHYL ESTERS OF SOME 1-METHYL-3-ALKYL-CYCLOHEXANE CARBOXYLIC ACIDS

By

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A THESIS

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DOCTOR OF PHILOSOPHY

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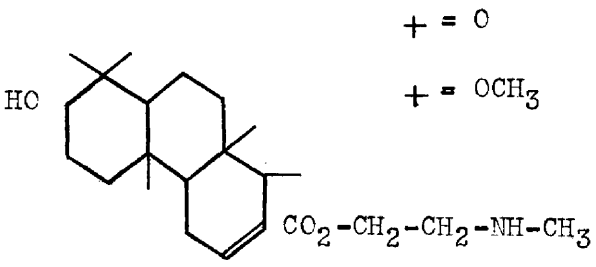
INTRODUCTION

The synthesis of some tertiary aminoesters of the 1-methyl-3-alkyl-cyclohexane carboxylic acids is described in this thesis. These acids are relatively simple compounds which, it is hoped, might simulate the cardiac action of the erythrophloeum alkaloids (1).

The cardiac glycosides, of which digitalis is an example, increase the tone and the work output of the heart, while slowing the heartbeat. Pharmocologists have long believed that the presence of an unsaturated lactone ring in a steroid structure was essential for this type of cardiac action. However, recent studies of the structure of some of the cardiac alkaloids isolated from the bark of erythrophloeum guineense have disproved this hypothesis. These naturally occurring alkaloids have been shown to be monomethylaminoethyl and dimethylaminoethyl esters of monocarboxylic acids of hydrogenated phenanthrene derivatives. Blount and coworkers (2) have suggested a structure for erythrophleine, one of the more abundant of the erythrophloeum cardiac alkaloids:



The positions assigned to the methyl groups in this structure have been questioned by Ruzicka (3, 4, 5), but no new formulation has been proposed.

Many of the erythrophloeum alkaloids have a digitalis-like action, leading to an increase in the work capacity of the heart. Maling and

Krayer (6) have demonstrated that the ester linkage is essential, as the free acid could produce no cardiac action in doses 100 times as large as the effective dosage of erythrophleine. In connection with this discovery, Krayer, Farah, and Uhle (7) have shown that both methylaminoethanol and dimethylaminoethanol improve the work capacity of the failing mammalian heart.

A survey of the chemical literature has failed to disclose any systematic investigation of synthetic aminoesters structurally resembling the erythrophloeum alkaloids. Although the aminoesters of numerous aliphatic, aromatic, and heterocyclic acids have been prepared, these compounds have been investigated primarily for their local anaesthetic properties (8). In order to study the structure essential to the action of the cardiac alkaloids, the preparation of some alkylaminoalkyl esters of simpler alicyclic carboxylic acids is suggested. The present work is one of the first steps in that direction.

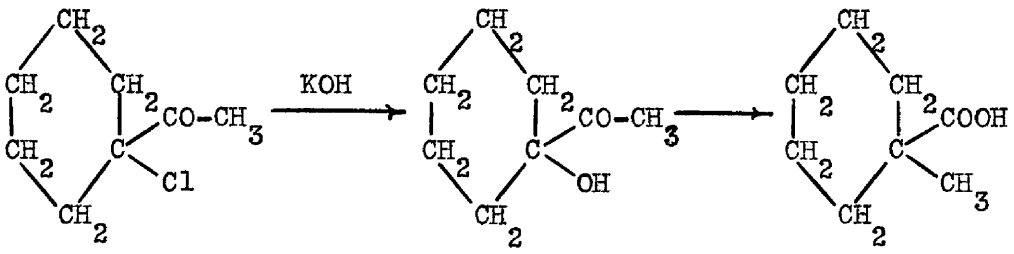
The following syntheses illustrate some of the possible methods for preparing cyclohexane carboxylic acids:

A. Through heating and decarboxylation of the alkylcyclohexane-1,1-dicarboxylic acids, alkylcyclohexane carboxylic acids may be obtained. The intermediates are prepared by the action of sodio-malonic ester on alkyl-1,5-dibromopentanes. Although 2-methylcyclohexane carboxylic acid (9) has been prepared from 1,5-dibromohexane, this method is seriously hampered by the unavailability of the necessary dibromides.

B. Reduction of the alkylbenzoic acids has been accomplished by catalytic and chemical means. Metallic sodium in boiling amyl or capryl

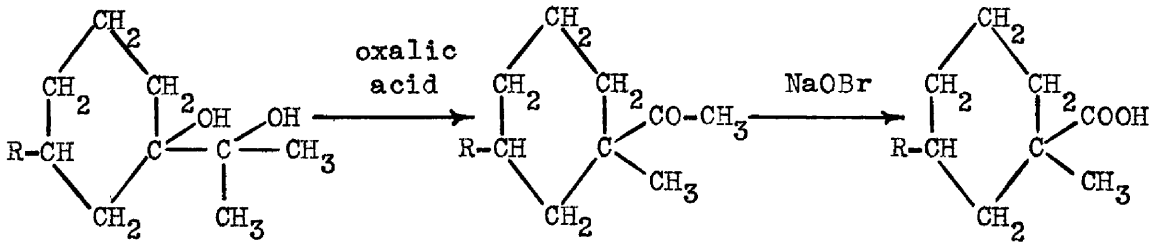
alcohol (10) has been used to reduce the ring in benzoic acid and its homologues. Low pressure hydrogenation using Adams' Platinum Catalyst (37) has also been used. The alkylation of aromatic acids has been described (11), utilizing hydrofluoric acid as the condensation catalyst. Alkylation generally yields the meta isomer. Low yields and the possibility of isomerization are serious limitations of this method.

C. Tchubar and Sackur (12) prepared the 1-methylcyclohexane carboxylic acid by what they termed "a semi-benzilic rearrangement" of 1-chloro-1-acetylcyclohexane.



The usefulness of the reaction as a general preparative method is limited by the unavailability of the starting materials.

D. The 1,3-dimethylcyclohexane carboxylic acid was synthesized by a pinacol rearrangement of 1-methyl-3-cyclohexylisopropyl pinacol and subsequent oxidation (13).



The starting materials for this type of synthesis are not readily available. Furthermore, the reported yield was low.

E. Cyclohexane acids in which the carboxyl group appears on an aliphatic side-chain are prepared by the same methods that are used for the synthesis of the fatty acids. Since the carboxyl group in the acids derived from the cardiac alkaloids is attached directly to an alicyclic ring, the cyclohexane-fatty acids will be disregarded in the present work.

F. The addition of hydrogen cyanide to alkyl-substituted cyclohexanones produces cyanohydrins which may be hydrolyzed and reduced to yield alkylcyclohexane carboxylic acids. The cyclohexanones may be obtained by the catalytic reduction (42) of the 3-methyl-5-alkyl-Δ^2-cyclohexenones which are prepared by a Knoevenagel ring closure (14, 15). The 3-methyl-5-alkylcyclohexane carboxylic acids would result from this synthesis.

G. The synthesis of 1-methyl-3-alkylcyclohexane carboxylic acids is accomplished by the hydrolysis and reduction of 3-cyano-3-methyl-5-alkylcyclohexanones. These ketonitrile intermediates have been prepared from the 3-methyl-5-alkyl-Δ^2-cyclohexenones. It is of interest to note that the 3-methyl-5-isopropylcyclohexenone, itself, has definite properties of cardiac stimulation. Hexetone (26, 27), as this compound is known, has a pharmocological action almost identical with that of camphor.

The ready availability of the simple aldehydes was a primary factor in the choice of method G for the synthesis of the alkyl-substituted

cyclohexane carboxylic acids. The historical background of the reactions involved is summarized in the paragraphs which follow.

In 1894 Knoevenagel (14, 15) synthesized a number of 3-methyl-5-alkyl-Δ^2-cyclohexenones by condensation of acetoacetic ester with some simple aliphatic aldehydes in the presence of diethylamine or piperidine. Recent investigators (16, 17, 18, 19) have somewhat simplified the original Knoevenagel technique. By 1904 Knoevenagel (20) and Hann and Lapworth (21) had succeeded in adding hydrogen cyanide to the ethylenic double bond of α,γ-unsaturated aldehydes and ketones. Michael and Weiner (22) suggested that this addition occurred through a 1,4-addition of the alkali cyanide, to which they ascribe the isocyanide structure, followed by a keto shift.

Knoevenagel (20) hydrolyzed 3-cyano-3,5-dimethylcyclohexanone to the 3,5-dimethylcyclohexanone-3-carboxylic acid. No further work was attempted with these compounds until 1948, when Whitmore and Roberts (19) prepared a series of methyl esters of 3-methyl-5-alkylcyclohexanone-3-carboxylic acids by the alcoholysis of the corresponding nitriles.

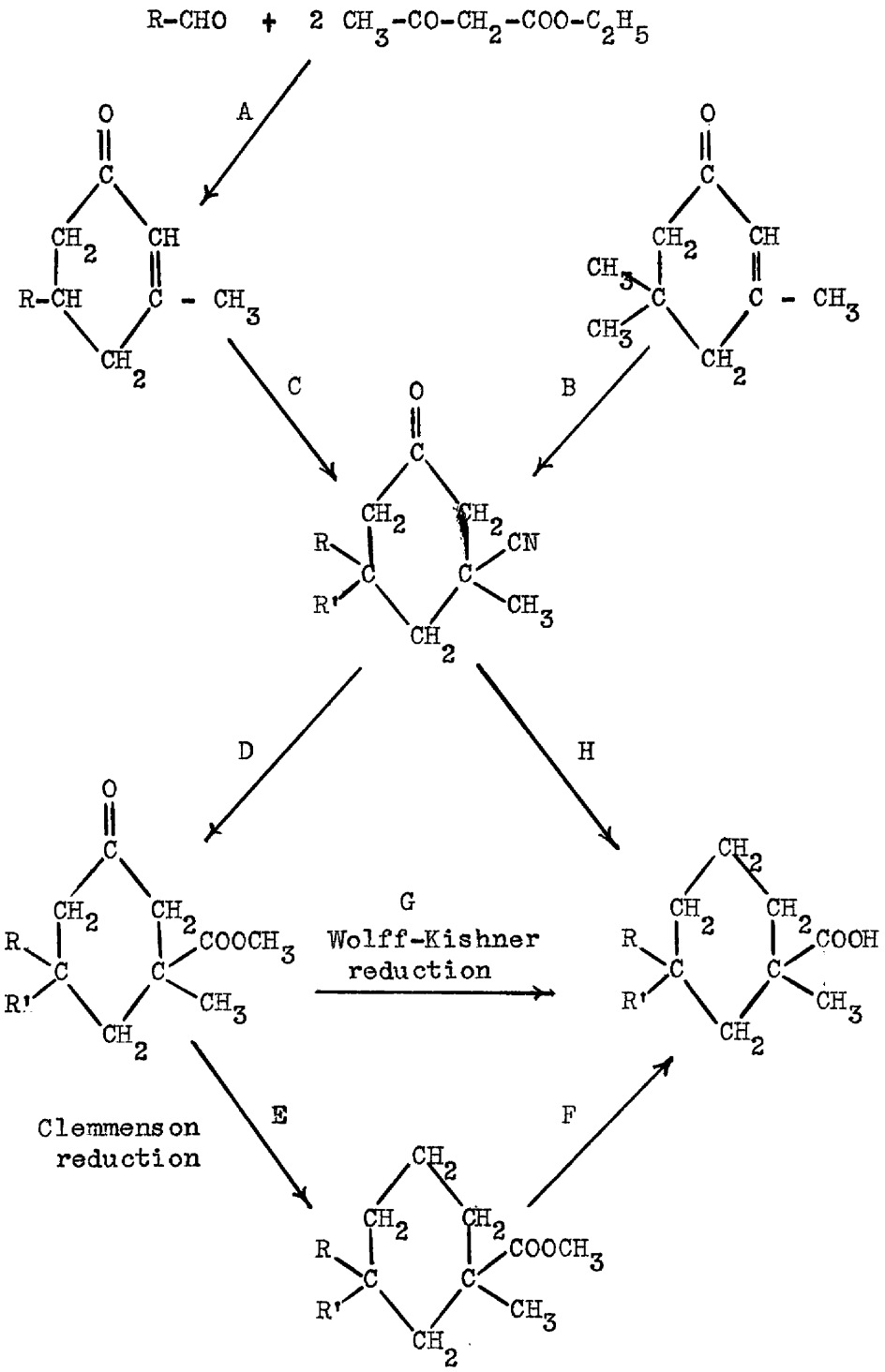
The complete reduction of the keto group of γ-ketoacids has been described by numerous investigators. In 1912 Wolff (23) reduced the hydrazone of levulinic acid with sodium hydroxide. Various modifications of the Wolff-Kishner technique have been employed in the reduction of other ketoacids. Recently, Huang-Minlon (24) prepared γ-(p-phenoxyphenyl)-butyric acid in 95% yield by a modified Wolff-Kishner reduction of the γ-ketoacid. He used potassium hydroxide and the relatively inexpensive 85% hydrazine hydrate in diethylene glycol solution which permitted the attainment of a sufficiently high temperature to drive off the water and

complete the reduction. Newman (25) reduced α-phenyl-β-benzoylpropionic acid by the Clemmensen method, using amalgamated zinc and hydrochloric acid. Newman also attempted a simultaneous hydrolysis and reduction of α-phenyl-β-benzoylpropionitrile and of methyl α-phenyl-β-benzoylpropionate. However, the yield of the hydrocarbon acid was low, considerable quantities of the starting materials being obtained in each case.

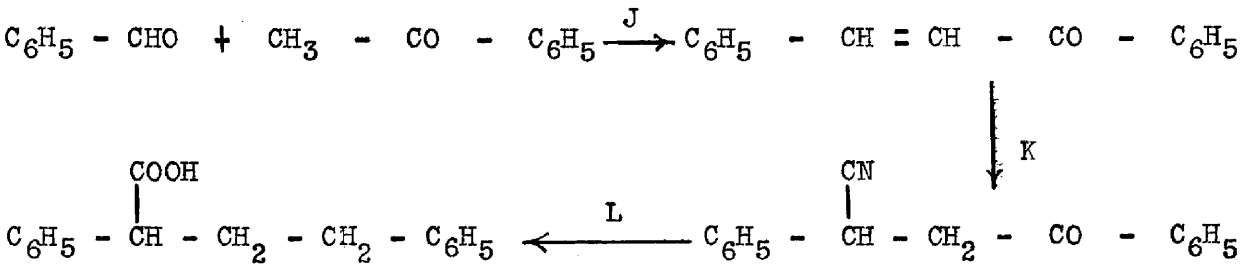
A search of the literature failed to disclose any successful attempt to prepare a hydrocarbon acid by a one-step hydrolysis and reduction using the Wolff-Kishner methods.

DISCUSSION

Preparation of the 1-methyl-3-R-3-R'-cyclohexane carboxylic acids involved the series of reactions diagrammed below:



The following reactions were also carried out:



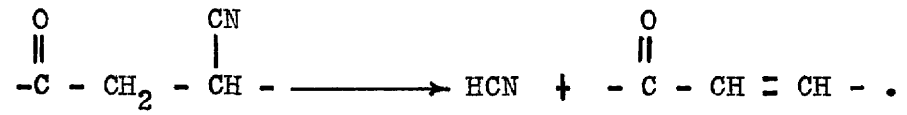
The practicality of each of the above steps is evaluated in this section. The exact procedures are described in the section titled "Experimental".

The Δ^2-cyclohexenones (reaction A) prepared in this report have all been previously described (14, 15, 16, 17, 18, 19). The original procedure of Knoevenagel (14) was closely followed except for one major variation. Whereas the bis ester was originally saponified and decarboxylated before steam distillation by boiling under reflux with concentrated aqueous alkali for four hours, it was found that the yield was not diminished by boiling for only fifteen minutes prior to steam distillation. The reflux period could not be eliminated entirely because the initial saponification was a highly exothermic reaction which proceeded with considerable rapidity when sufficient heat had been applied. Although most of the yields were unchanged by the shortened reflux time, a 10% increase was noted in the yield of 3,5-dimethylcyclohexenone.

3-Cyano-3,5,5-trimethylcyclohexanone (reaction B) was synthesized by direct addition of hydrogen cyanide to isophorone (19, 20). Two attempts to prepare the same compound from the sodium bisulfite addition product were unsuccessful. Almost quantitative recovery of the starting material was obtained.

Whitmore and Roberts (19) reported poor results on the direct addition of hydrogen cyanide to 3,5-dimethylcyclohexenone. However, they prepared the 3-cyano-3-methyl-5-alkylcyclohexanones (reaction C) successfully from the bisulfite addition intermediates, although in all cases, 20-30% of the starting material was recovered. After distillation of the products, considerable tarry residue remained.

The high recovery of starting material suggested that the ketonitrile decomposed (20) according to the equation



The replacement of the sulfonic acid radical by the cyanide group was ordinarily carried out on a boiling water bath. If the above decomposition actually occurs, it might be retarded by using a lower temperature. One experiment was performed in which the 1,3-dimethylcyclohexenone-bisulfite addition product was heated only to 65° C. in the presence of aqueous sodium cyanide. But four hours of heating were required for a sizable organic layer to form. Distillation of this organic material yielded mostly 1,3-dimethylcyclohexenone. In another experiment with the same bisulfite addition product, 50 ml. of benzene was added to the flask just after the addition of the aqueous sodium cyanide. The purpose of the benzene layer was to dissolve the ketonitrile as it separated from the aqueous solution of the bisulfite addition product. The reaction was carried out on a boiling water bath with the temperature of the internal aqueous phase at 90° C. The yield of 3-cyano-3,5-dimethylcyclohexanone was 60.4%, an increase of more than 12% over the method not making use of the benzene layer. Appreciable improvements in the yields of the ethyl and the isopropyl homologues also were achieved by use of the benzene layer. However, the n-propyl compound showed no improved yield and there was actually a decreased yield in the case of 3-cyano-3-methyl-5-phenylcyclohexanone.

The improved yields may be the result of (1) lower reaction temperature, (2) dilution of the product, or (3) both. That the dilution effect does play some part in the greater yields is demonstrated by the absence of tarry residue after the distillation of the ketonitriles prepared by use of the benzene layer.

The 3-cyano-3-methyl-5-cyclohexanones prepared in the present work have all been previously described (19, 20).

Of the alicyclic acids prepared in this thesis, the 1,3,3-trimethylcyclohexane carboxylic acid was the first prepared because of the easy synthesis of the 3-cyano-3,5,5-trimethylcyclohexanone from isophorone.

Methyl 3,5,5-trimethylcyclohexanone-3-carboxylate was prepared by the alcoholysis (reaction D) of the ketonitrile by refluxing a methanol-sulfuric acid solution of the cyanide for several hours. A yield of 65% of the ketoester was obtained. The carbonyl group of the ketoester was then reduced (reaction E), using zinc amalgam and hydrochloric acid according to the method of Clemmenson. The average yield for this reduction was about 37%. The acid prepared by hydrolysis (reaction F) of the reduced ester melted at 51-52° C. when recrystallized from 50% isopropyl alcohol. Because of the low overall yield, a more satisfactory method of producing the acid was sought.

A study of the literature pertaining to the Wolff-Kishner reduction (33) revealed several instances in which γ-ketoacids had been reduced. The Huang-Minlon modification (24) was tried because it eliminated the handling of metallic sodium; made use of the relatively inexpensive 85% hydrazine hydrate; was applicable to larger quantities; and achieved

high temperatures without the use of pressure. Using this method for the reduction of methyl 3,5,5-trimethylcyclohexanone-3-carboxylate (reaction G) produced a yield of 60.3% of the 3,5,5-trimethylcyclohexane carboxylic acid, melting at 50-51° C. when recrystallized from 50% isopropyl alcohol. The mixed melting points of the acids prepared by the Clemmenson and the Wolff-Kishner reductions showed no depression.

Although the Wolff-Kishner reduction of methyl 3,5,5-trimethylcyclohexanone-3-carboxylate gave a far better yield of the alicyclic acid than the procedure using the Clemmenson reduction, the feasibility of a simultaneous hydrolysis-reduction of the ketonitrile was investigated. Using the Clemmenson method of reduction, Newman (25) had failed to obtain the hydrocarbon acid in one step from α-phenyl-β-benzoylpropionitrile. The Wolff-Kishner reduction of various ketonitriles (reaction H) was carried out by H. Fischer and coworkers (35, 36) using metallic sodium and hydrazine hydrate in alcohol under pressure at 165-180° C., but the simple reduced acids were not among the products reported. However, the Wolff-Kishner reduction was viewed with interest because the alkaline-aqueous conditions of the aforementioned Huang-Minlon modification should hydrolyze the nitrile prior to reduction of the carbonyl group.

To test the procedure, α-phenyl-β-benzoylpropionitrile was prepared (reactions J and K) and converted to α, γ-diphenylbutyric acid in 63% yield by this one step method (reaction L). The 3-cyano-3,5,5-trimethylcyclohexanone was subjected to the same conditions, which produced a 69% yield of 1,3,3-trimethylcyclohexane carboxylic acid. The

distilled product solidified and was recrystallized from 50% isopropyl alcohol, melting at 50-52° C. The mixed melting point with the acid prepared by the Clemmenson reduction showed no depression.

In addition to the hydrocarbon acid, a small amount of a high melting by-product was obtained in the Wolff-Kishner reduction of α-phenyl-β-benzoylpropionitrile. Azines have frequently been observed as by-products of the Wolff-Kishner reduction (33), consequently, it was thought that the high melting by-product obtained might be the azine of α-phenyl-β-benzoylpropionic acid. However, the nitrogen analysis of the product indicated the presence of almost twice the amount of nitrogen calculated for the azine. Although the compound does not dissolve in 0.1N sodium hydroxide, its solubility in 10% aqueous alkali and subsequent recovery by acidification strongly suggests the presence of a ring unstable to strong alkali. A compound purporting to be the pyridazone was described by Almström (34) who described it as a substance melting at 154-165° C. and characterized it only by a carbon and hydrogen analysis. In attempting to prepare the pyridazone, we obtained a product melting at 167-169° C.* and which did not appear to be identical with the by-product of the Wolff-Kishner reduction. Unfortunately, the identity of the by-product remains undetermined.

The 1-methyl-3-alkylcyclohexane carboxylic acids were prepared in satisfactory yields (53-91%) by the modified Wolff-Kishner reduction of the ketonitriles. The corresponding acid chlorides were prepared, from

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* uncorrected.

which, the dimethylaminoethyl and diethylaminoethyl esters were made. In addition, the simple amides and piperidyl amides were prepared.

Of the alicyclic acids described in Table III, only the 1,3-dimethylcyclohexane carboxylic acid had previously appeared in the literature (13). In 1938 Godchot and Cauquil reported the preparation of this acid and its amide, listing the melting points as 90° C. and 73° C., respectively. In the present work the melting points of the corresponding compounds were found to be 91-92° C. and 73° C.,* respectively. Although the melting points of the acid and its amide agreed with those previously reported (13), the acid chloride was found to distill at 85-86° C.* at 16 mm. as compared with the previously reported boiling point of 98° C. at 14 mm. Although the possible existence of geometric and optical isomers in this group of compounds is recognized, this does not appear to explain the discrepancy in the observed boiling point of the acid chloride, since the acid and the amide appeared to be identical with the products obtained by Godchot and Cauquil.

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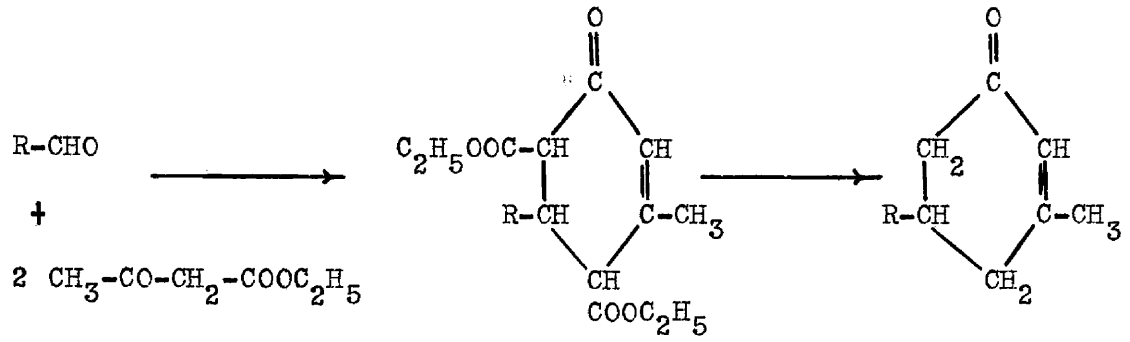
* uncorrected.

EXPERIMENTAL

1. PREPARATION OF INTERMEDIATES

3-Methyl-5-alkyl- Δ^2-cyclohexenones



These cyclic α, β-unsaturated ketones were synthesized by the Knoevenagel reaction (14, 15). The preparation of 3,5-dimethylcyclohexenone illustrates the general procedure. In a 3 liter round-bottom flask, equipped with dropping funnel, stirrer, and thermometer, was placed 132 g. (3 moles) of acetaldehyde, freshly prepared by depolymerization of paraldehyde, and 780 g. (6 moles) of reagent grade ethyl acetoacetate. The flask was cooled to -5° C. by means of a salt-ice bath. During the next five hours, 15 ml. of diethylamine was added in small portions. The mixture was then refrigerated for 24 hours and allowed to stand at room temperature for another 24 hours. By this time, the crude bis ester had formed large yellow crystals on the bottom of the flask.

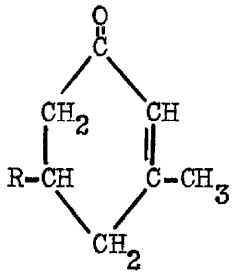
The reaction mixture containing the crude bis ester was heated with 600 g. of sodium hydroxide dissolved in 4 liters of water. Saponification and decarboxylation was accomplished by boiling the mixture under reflux for fifteen minutes and then subjecting it to steam distillation until seven liters of distillate was collected. The distillate was saturated

with sodium chloride, the organic layer was separated, and the aqueous layer was extracted with two 500 ml. portions of benzene. The combined organic layer and benzene extracts were dried over anhydrous sodium sulfate and distilled under diminished pressure.

Because of its low vapor pressure, the steam distillation of 3-methyl-5-phenylcyclohexenone was not practical. The crude bis ester of this compound was refluxed with the aqueous alkali for four hours. The reaction mixture was cooled and extracted with two 500 ml. portions of benzene. After removal of the benzene by distillation, the ketone was distilled under diminished pressure. The cyclohexenones are described in Table I. Unless otherwise noted, all melting points and boiling points represent corrected values.

TABLE I

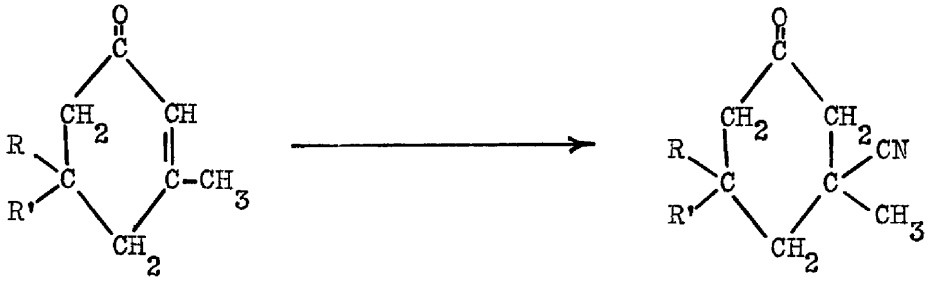
3-Methyl-5-R- Δ^2-cyclohexenones



R	Yield	Boiling point*	Mm. pressure
Methyl	50.8%	212-217° C.	849
Ethyl	40.0	122-125° C.	19
n-Propyl	31.0	117-121° C.	11
Isopropyl	43.7	111-113° C.	9
Phenyl	45.6	159-168° C.	2

* All tabulated melting points and boiling points are corrected, unless otherwise noted.

3-Cyano-3-methyl-5-alkylcyclohexanones



With the exception of the nitrile from isophorone, the cyclic ketonitriles were synthesized by the addition of sodium bisulfite to the unsaturated ketone (19, 20), followed by replacement of the sulfonate group by a cyanide group. The unsaturated ketone (0.25 mole) was refluxed with a solution of 31.5 g. (0.166 mole) of sodium metasulfite in 75 ml. of water. The organic layer dissolved within 20 to 30 minutes. A warm solution of 15.2 g. (0.31 mole) of sodium cyanide in 35 ml. of water was then added and the mixture was heated on a boiling water bath for one hour. The ketonitrile formed an oily layer on top of the aqueous phase. This layer was separated and the aqueous layer was extracted with two 50 ml. portions of benzene. The organic material and the benzene extracts were combined and dried over anhydrous sodium sulfate. After removal of the benzene by distillation, the residue was distilled under diminished pressure.

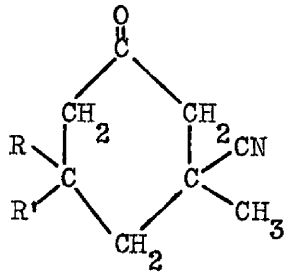
In separate attempts to increase yields, a 50 ml. benzene layer was employed to take up the ketonitrile as it separated from the aqueous layer. Some yields were appreciably improved by this slight departure. The ketonitriles are described in Table II.

3-Cyano-3,5,5-trimethylcyclohexanone was prepared by the following procedure (17, 18):

138 g. (1.0 mole) of freshly distilled isophorone was dissolved in 3 liters of methanol. Then, 50 ml. of water and 60 g. of glacial acetic acid were added. A solution of 98 g. (2.0 moles) of sodium cyanide in 375 ml. of water was added during fifteen minutes while the mixture was stirred vigorously. The temperature rose to 35° C. Stirring was continued for six hours. The mixture was then allowed to stand unstirred for 48 hours. Using diminished pressure, most of the methanol was removed on a water bath at 65° C. The residue was diluted with 500 ml. of benzene, filtered, and separated. The benzene extract was dried over anhydrous sodium sulfate. The ketonitrile was obtained by distillation as previously described.

TABLE II

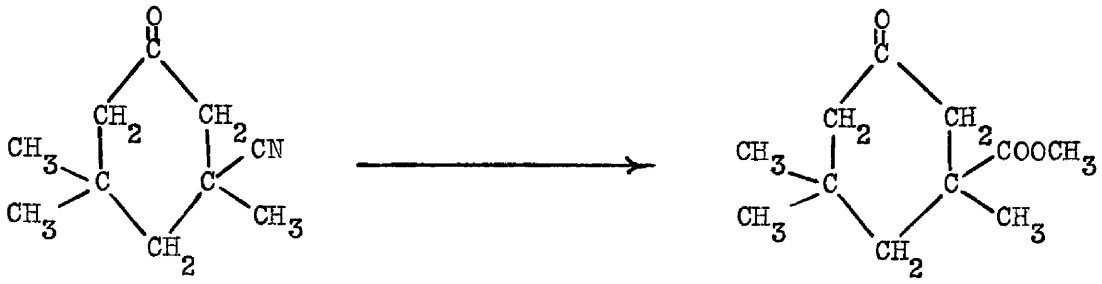
3-Cyano-3-methyl-5-R-cyclohexanones



R	R'	Yield*	Boiling point	Mm. pressure
Methyl	Methyl	45.2%	156-159° C.	19
Methyl	H	48.0 (60.4)	156-159° C.	14
Ethyl	H	43.9 (54.4)	166-169° C.	18
n-Propyl	H	50.3 (48.5)	138-144° C.	3
Isopropyl	H	32.0 (64.5)	144-145° C.	3
Phenyl	H	49.4 (30.0)	185-186° C.	1-2

* Values in parentheses represent yields obtained through the use of a 50 ml. layer of benzene to dissolve the ketonitrile separating from the aqueous bisulfite complex.

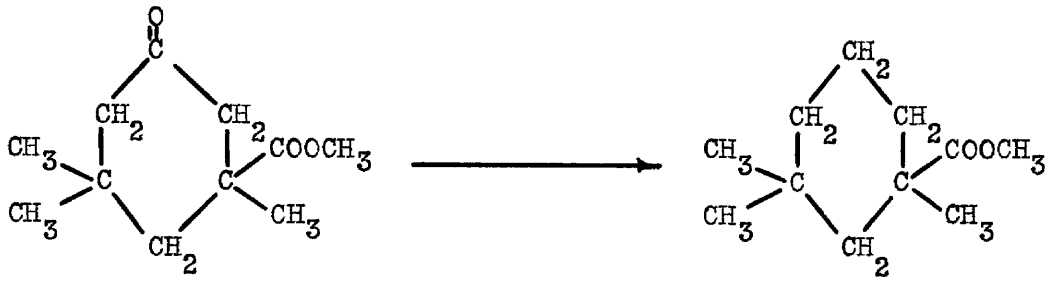
Methyl 3,5,5-trimethylcyclohexanone-3-carboxylate



The alcoholysis (19) of the 3-cyano-3,5,5-trimethylcyclohexanone was accomplished by dissolving 16.5 g. (0.1 mole) of the ketonitrile in 25 ml. of 95% methanol, and adding the solution during 30 minutes to 20 g. of ice-cold 95% sulfuric acid. The mixture was boiled under reflux for seven hours. The flask contents were then poured into a beaker containing 100 g. of an ice-water mixture. The organic layer was taken up in 50 ml. of benzene and the aqueous layer was extracted with two 50 ml. portions of benzene. The combined benzene extracts were washed with 10% potassium carbonate solution and dried over anhydrous sodium sulfate. The benzene was removed by distillation and the product was distilled under diminished pressure. Fourteen grams (70.5% yield) of a clear yellowish oil was obtained, boiling at 134-137°C. at 12 mm.

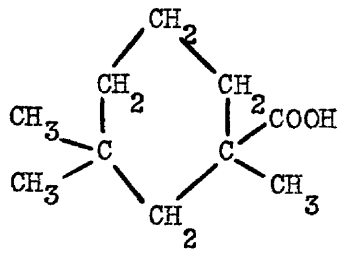
2. PREPARATION OF NEW COMPOUNDS

Methyl 1,3,3-trimethylcyclohexane carboxylate



The reduction of the methyl 3,5,5-trimethylcyclohexanone carboxylate to the ester of the hydrocarbon acid was accomplished by the Clemmenson method (28, 29). A solution of 12.5 g. (0.063 mole) of the ketoester in 75 ml. of 95% methanol was added in portions over a period of three hours to a refluxing mixture of 30 ml. of water, 10 ml. of methanol, 50 ml. of concentrated hydrochloric acid, and the amalgamated zinc made from 50 g. of granulated zinc and 3 g. of mercuric chloride. After the addition was completed, the mixture was refluxed an additional eight hours, during which time another 40 ml. of concentrated hydrochloric acid was added in portions. After cooling, the liquid was decanted from the zinc, diluted with an equal volume of water, and extracted with two 50 ml. portions of ether. The zinc residue was pulverized and extracted with 50 ml. ether. The combined ether extracts were washed with potassium carbonate solution and dried over anhydrous sodium sulfate. The ether was removed by evaporation on a steam bath. The residue was distilled under diminished pressure and the fraction boiling at 103-108° C. at 24 mm. was collected. Four grams (25% yield) of a colorless liquid with a camphor-like odor was obtained.

1,3,3-trimethylcyclohexane carboxylic acid



This acid was prepared by the following three procedures:

A. Saponification of methyl 1,3,3-trimethylcyclohexane carboxylate:- Ten grams of the ester was boiled under reflux with a solution of 20 g. of potassium hydroxide in 25 ml. of water. After two hours, the mixture was cooled and then acidified by the addition of 50 ml. of concentrated hydrochloric acid. The oil which separated was taken up in 50 ml. benzene and dried over anhydrous sodium sulfate. The benzene was distilled off and the residue was distilled under diminished pressure. The fraction boiling at 144-147° C. at 11 mm. was collected. This fraction soon solidified, melting at 50° C. Recrystallization from isopropyl alcohol-water mixture gave 8 g. (86.4%) of white platelets, melting 51-52° C.*

B. Wolff-Kishner reduction of the γ -ketoester:- Sixteen grams of methyl 1,3,3-trimethylcyclohexane carboxylate, 15 g. of sodium hydroxide, and 15 ml. of practical grade 85% hydrazine hydrate were placed in a one liter round-bottom flask containing 150 ml. of diethylene glycol. The flask was equipped with an efficient reflux condenser. The mixture was boiled under reflux for one hour, using a sand bath. The condenser was then removed. After two hours, the temperature rose to 195° C., at

* uncorrected.

which time the condenser was replaced. Refluxing was continued for three hours. The mixture was then cooled, acidified by the addition of 100 ml. of 6N hydrochloric acid, and extracted with two 50 ml. portions of benzene. The benzene extracts were dried over anhydrous sodium sulfate. After distillation of the benzene, the residue was distilled under diminished pressure. A fraction boiling 144-146° C. at 12 mm. was collected. The entire fraction solidified on standing, forming colorless needles melting at 38-40° C.* The product was soluble in dilute sodium hydroxide and was reprecipitated by dilute hydrochloric acid. Recrystallization from an isopropyl alcohol-water mixture gave 8.5 g. (60.3%) of white platelets melting 50-51° C.*

C. Wolff-Kishner reduction of the γ -ketonitrile:- This method was similar to method B and is described in greater detail on the following page. Several runs were made, a representative yield being about 70%. The product was a white solid. When recrystallized from an isopropyl alcohol-water mixture, white platelets were obtained, melting 50-52° C.*

Mixed melting points were determined on the products of methods A, B, and C. In no case was there a depression of the melting point.

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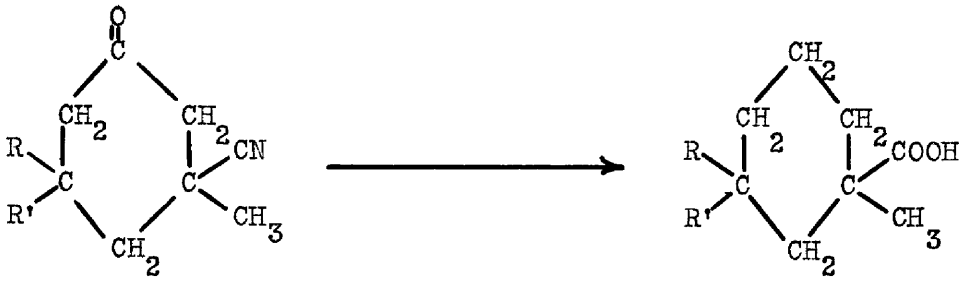
* uncorrected.

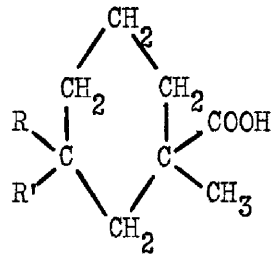
1-Methyl-3-alkylcyclohexane carboxylic acids



To a solution of 40 g. of potassium hydroxide and 30 ml. of 85% hydrazine hydrate (practical) in 300 ml. of diethylene glycol was added 0.2 mole of the γ-ketonitrile. The mixture was boiled under reflux for one hour, using an efficient bulb condenser. The condenser was then removed and the water in the mixture was distilled off under the hood until the internal temperature reached 195° C. The bulb condenser was then replaced, after which refluxing was continued for four hours. The cooled solution was poured slowly onto a mixture of 400 g. of ice and 100 ml. of concentrated hydrochloric acid. If the acid was a solid, it was filtered and recrystallized from an acetone-water mixture or an isopropyl alcohol-water mixture. Liquid products were extracted with ether, dried over anhydrous sodium sulfate, and distilled under diminished pressure. Some of the liquid acids eventually crystallized after prolonged refrigeration. The acids are described in Table III.

TABLE III

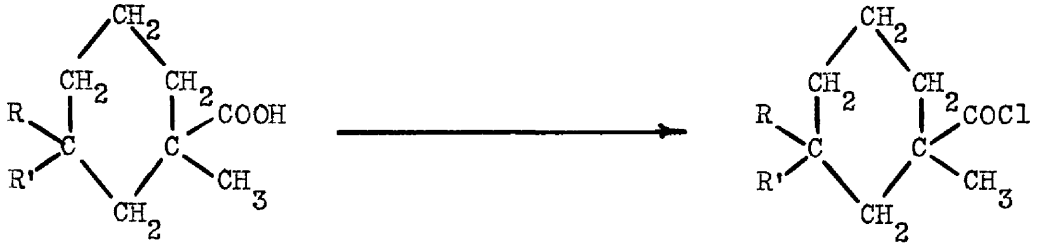
1-Methyl-3-R-3-R'-cyclohexane carboxylic acids



R	R'	Yield %	Boiling pt. °C.	Mm.	Melting pt. °C.*	Carbon, %** Calcd.	Found	Hydrogen,%** Calcd.	Found
Methyl	Methyl	69.1	144-147	11	51-52	70.6	70.4	10.6	10.3
Methyl	H	72.5			91-92	69.2	69.2	10.3	10.1
Ethyl	H	75.0	120-129	2	39-40	70.6	70.7	10.6	10.6
n-Propyl	H	91.4	142-144	6		71.7	71.7	10.9	10.9
Isopropyl	H	53.4	139-146	3		71.7	71.5	10.9	10.7
Phenyl	H	75.0			124-126	77.1	77.5	8.3	8.3

* Uncorrected.
** Carbon and hydrogen were determined by micro-combustion method (38).

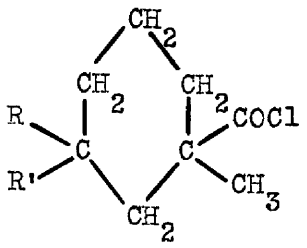
Acid chlorides of 1-methyl-3-alkylcyclohexane carboxylic acids



In a 50 ml. Claisen flask, which served as the reaction vessel, was placed 0.05 mole of the cyclic acid. By means of a dropping funnel, 18.0 g. (0.15 mole) of thionyl chloride was added during fifteen minutes. During the addition, the reaction flask was kept at room temperature by immersion in a cool water bath. The water bath was then brought to boiling, the reaction being thus heated for two hours. After removal of excess thionyl chloride the acid chloride was distilled directly from the reaction flask, using diminished pressure and a free flame. Table IV contains the descriptions of the acid chlorides.

TABLE IV

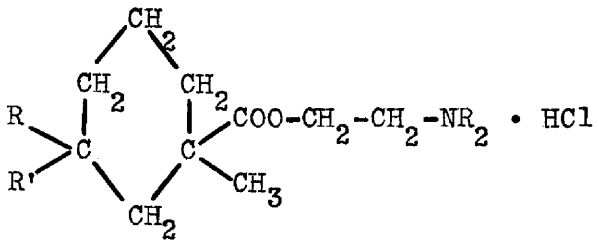
Acid chlorides of 1-methyl-3-R-3-R'-cyclohexane carboxylic acids



R	R'	Yield %	Boiling pt. °C.	Mm.	Chlorine * % Calcd.	% Found
Methyl	Methyl	90.5	94-97	15	18.8	18.6, 18.5
Methyl	H	86.6	87-88	16	20.3	19.9, 20.1
Ethyl	H	88.9	100-103	14	18.8	18.9, 18.5
n-Propyl	H	92.9	111-113	15	17.5	17.2, 17.3
Isopropyl	H	90.4	110-111	13	17.5	17.1, 17.3
Phenyl	H	91.6	155-156	5	15.0	14.8, 15.0

* Chlorine was determined by the Volhard method (39).

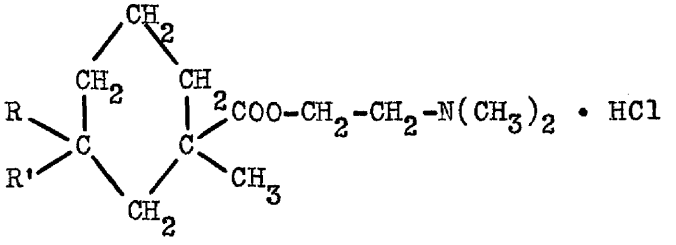
Dialkylaminoethyl 1-methyl-3-alkylcyclohexane carboxylate . hydrochlorides



To 0.20 mole of the dialkylaminoethanol in a 50 ml. glass-stoppered Erlenmeyer flask, 0.05 mole of the cyclic acid chloride was added dropwise. The stopper was wired on and the mixture was shaken vigorously for five minutes. With intermittent shaking, the flask was then allowed to stand for two hours. The contents of the flask were poured into a separatory funnel containing 25 ml. of saturated sodium carbonate solution. The free aminoester which separated was diluted with 25 ml. of ether and then washed free of the water-soluble aminoalcohol with three 25 ml. portions of water. The ether solution of the aminoester was dried over a small amount of anhydrous sodium sulfate for twelve hours. The dry aminoester solution was then decanted into a twelve inch test tube. An ethereal solution of hydrogen chloride was added dropwise, with cooling, until the supernatant fluid in the test tube was distinctly acid to Congo red paper. A large excess of hydrogen chloride was avoided. The white precipitate was filtered quickly through a Buchner funnel, washed with dry ether, and dried in a vacuum desiccator. The filtrate was tested for complete precipitation by adding a few drops of ethereal hydrogen chloride. The ester-hydrochlorides were recrystallized from anhydrous ethyl acetate. Physical constants and analytical data for the dimethylaminoethyl esters are given in Table V. Table VI records similar descriptions of the diethylaminoethyl esters.

TABLE V

Dimethylaminoethyl 1-methyl-3-R-3-R'-cyclohexane carboxylate • hydrochlorides

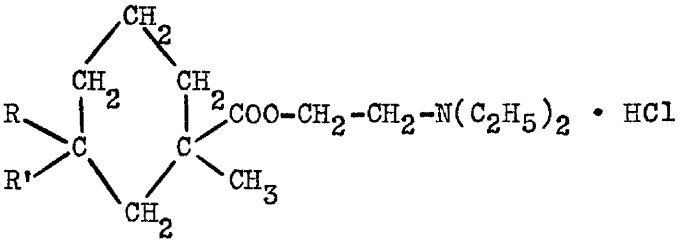


R	R'	Melting point °C.	Nitrogen * % Calcd.	% Found
Methyl	Methyl	159	5.1	5.0, 5.0
Methyl	H	150-151	5.3	5.4, 5.4
Ethyl	H	109-111	5.1	5.0, 5.0
n-Propyl	H	109-110	4.8	4.9, 4.8
Isopropyl	H	147	4.8	4.8, 4.8
Phenyl	H	136	4.3	4.3, 4.3

* Nitrogen was determined by macro-Kjeldahl analysis (40).

TABLE VI

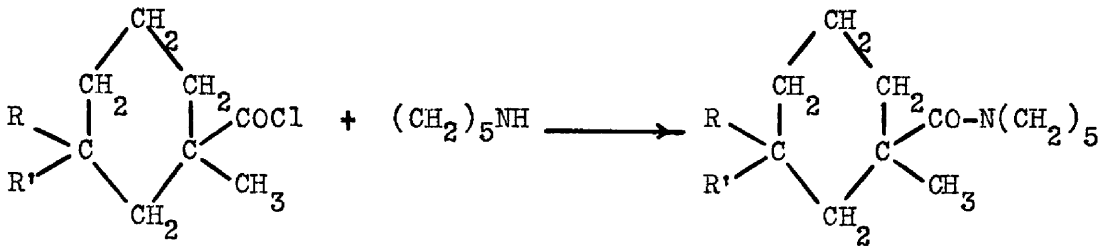
Diethylaminoethyl 1-methyl-3-R-3-R'-cyclohexane carboxylate • hydrochlorides



R	R'	Melting point °C.	Nitrogen ** % Calcd.	% Found
Methyl	Methyl	120-121	4.6	4.7, 4.6
Methyl	H	128-130	4.8	5.0, 4.6
Ethyl	H	114-117	4.6	4.7, 4.7
n-Propyl*	H	112-116	4.4	4.7, 4.7
Isopropyl	H	130-133	4.4	4.6, 4.2
Phenyl	H	116-119	4.0	4.2, 4.0

* Melting point was determined on crude product which was very hygroscopic.
** Nitrogen was determined by macro-Kjeldahl analysis (40).

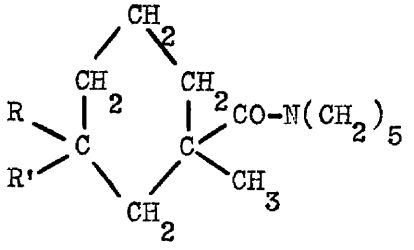
Piperidyl amides of 1-methyl-3-R-3-R'-cyclohexane carboxylic acids



These substituted amides were prepared by the Schotten-Baumann technique (30). Equimolar amounts of the acid chlorides and piperidine were shaken together vigorously for ten minutes in the presence of a slight excess of 10% potassium hydroxide. A glass-stoppered Erlenmeyer flask was convenient for this preparation. Within two hours an oily layer had formed. This was diluted with an equal volume of benzene, separated, dried, and distilled under diminished pressure. Only the phenyl homologue was a solid, the remainder being yellowish, viscous liquids. Recrystallization of the phenyl compound from isopropyl alcohol yielded tan crystals melting at 55-56° C. The piperidyl amides are described in Table VII.

TABLE VII

Piperidyl amides of 1-methyl-3-R-3-R'-cyclohexane carboxylic acids

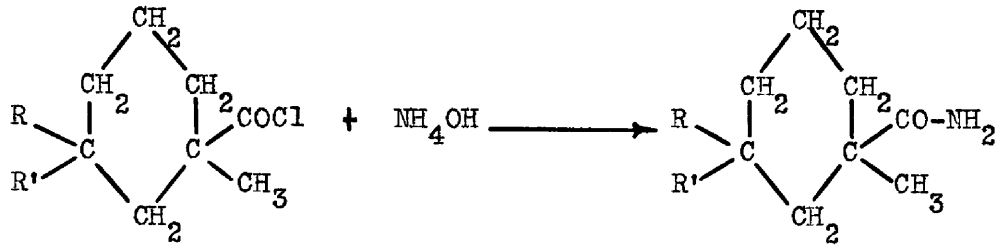


R	R'	Boiling point °C.	Mm.	Nitrogen ** % Calcd.	% Found
Methyl	Methyl	128-131	2	5.7	5.7, 5.6
Methyl	H	128-131	2	6.0	6.2, 6.3
Ethyl	H	135-138	2	5.7	5.9, 5.8
n-Propyl	H	141-145	2	5.4	5.4, 5.5
Isopropyl	H	143-147	2	5.4	5.6, 5.5
Phenyl	H	------*		5.0	4.5, 4.6

* M.p. 55-56° C.

** Nitrogen was determined by macro-Kjeldahl analysis using metallic mercury catalyst (41).

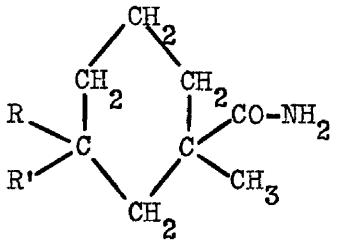
Amides of 1-methyl-3-R-3-R'-cyclohexane carboxylic acid



One gram of the acid chloride was added to 20 ml. of concentrated ammonium hydroxide contained in a 50 ml. glass-stoppered Erlenmeyer flask. The stopper was wired on and the flask was shaken vigorously for five minutes. The mixture was allowed to stand for 48 hours with occasional shaking. With the exception of the ethyl homologue, the simple amides were white crystalline solids. Since the simple amide of the ethyl compound was an oil, the anilide was prepared by substituting 10 ml. of freshly distilled aniline for the ammonium hydroxide in the above procedure. The 1-methyl-3-ethylcyclohexane carboxyl anilide melted at 80-81° C. The amides are described in Table VIII.

TABLE VIII

Amides of 1-methyl-3-R-3-R'-cyclohexane carboxylic acids



R	R'	Melting point °C.	Nitrogen ** % Calcd.	% Found
Methyl	Methyl	91.5-92.5	8.3	8.2, 8.2
Methyl	H	74-75	9.0	8.8, 9.0
Ethyl*	H	80-81	5.7	5.7, 5.7
n-Propyl	H	136-137	7.7	7.7, 7.5
Isopropyl	H	82.5-83.5	7.7	7.7, 7.7
Phenyl	H	131-133	6.5	6.5, 6.4

* Anilide.
** Nitrogen was determined by macro-Kjeldahl analysis (40).

3. MISCELLANEOUS SYNTHESES

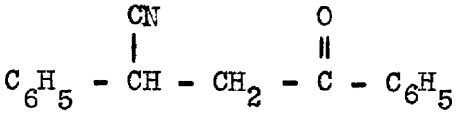
Benzalacetophenone

$$C_6H_5 - CH = CH - \overset{\overset{O}{\|}}{C} - C_6H_5$$

A solution of 109 g. (2.75 moles) of sodium hydroxide in 980 ml. of water and 630 ml. of 95% ethanol (31) was introduced into a 5 liter round-bottom flask fitted with a mechanical stirrer. The flask was cooled externally by ice. With stirring, 260 g. (2.15 moles) of pure acetophenone was poured into the flask. Then, 230 g. (2.15 moles) of USP benzaldehyde was added at once. The temperature was kept near 15° C. for two hours. The milky liquid was refrigerated for twelve hours, by which time, large yellow crystals had formed. The precipitate was filtered through a large Buchner funnel and washed with three 100 ml. portions of water and once with 100 ml. of 50% ethanol. After air-drying, the yield of light-yellow benzalacetophenone was 403 g. (92% yield). M.P. 51-54° C.*

* uncorrected.

α-Phenyl-β-benzoylpropionitrile



This ketonitrile (20, 21, 32) was prepared according to the same procedure that was used for the synthesis of 3-cyano-3,5,5-trimethylcyclohexanone. (See page 19.) The following quantities were used:

208 g. (1.0 mole) benzalacetophenone (crude),

3.5 l. 95% ethanol,

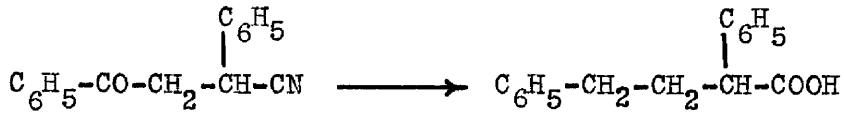
60 g. (1.0 mole) glacial acetic acid, and

98 g. (2.0 moles) sodium cyanide.

187 g. (79.6% yield) of a white crystalline product was obtained, the unrecrystallized product melting at 124-125° C.*

* uncorrected.

α, γ -Diphenylbutyric acid



This acid was prepared by a modified Wolff-Kishner reduction of the ketonitrile. Into a 1 liter flask were introduced 31 g. (0.13 mole) of α-phenyl-β-benzoylpropionitrile, 22 ml. of 85% hydrazine hydrate, 26 g. of potassium hydroxide, and 200 ml. of diethylene glycol. After boiling under reflux for one hour, the condenser was removed and not replaced until the reaction temperature had reached 195° C. The reaction mixture was refluxed for four hours at this temperature.

After cooling to room temperature the flask contents were poured onto a mixture of 75 ml. of concentrated hydrochloric acid and 150 g. of ice. The soft amorphous precipitate was dissolved in ether and dried over anhydrous sodium sulfate. The ether solution was decanted from the drying agent and the ether was removed by evaporation on a steam bath. The remaining liquid was distilled under diminished pressure, giving 20 g. (63%) of α, γ -diphenylbutyric acid boiling 196-203° C. at 1 mm. Upon cooling, a white solid was obtained, melting at 73° C.* A mixed melting point was determined with a sample of the acid obtained from Newman (25).**

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* Uncorrected.

** We are indebted to Dr. Melvin S. Newman for a sample of α, γ -diphenylbutyric acid.

There was no depression of the melting point.

Calcd. for $C_{16}H_{16}O_2$: C, 80.3; H, 6.6.

Found: C, 80.6; H, 6.6.

The acid chloride was prepared by the method previously described. From 20 g. of the acid and 20 ml. of thionyl chloride, 17.4 g. (81.3%) of a clear yellow liquid was obtained, boiling at 154-155° C. at 1 mm.

Calcd. for $C_{16}H_{15}ClO$: Cl, 13.7.

Found: Cl, 13.4, 13.5.

The amide was prepared from the acid chloride. White needles were obtained upon recrystallization from methanol, melting sharply at 96° C.

Calcd. for $C_{16}H_{17}NO$: N, 5.9.

Found: N, 5.8, 5.8.

During one synthesis of α,γ-diphenylbutyric acid, approximately two grams of a crystalline by-product deposited upon the drying agent during drying of the ether extract of the reduction mixture. This substance was recrystallized from acetone, giving 1.5 g. of voluminous white crystals melting at 185-187° C.* The material was insoluble in 0.1N alkali but was dissolved by 10% potassium hydroxide, being reprecipitated by the addition of hydrochloric acid.

Found: C, 76.0; H, 5.5; N, 11.5.

The synthesis of 4,6-diphenyl-4,5-dihydropyridazone was attempted by heating 2 g. of α-phenyl-β-benzoylpropionitrile under reflux for

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* uncorrected.

two hours with 20 ml. of 25% potassium hydroxide and 2 ml. of 85% hydrazine hydrate. After recrystallization from 50% isopropyl alcohol, the product melted at 167-169° C.* and was found to be identical with the compound reported by Almström (34).

Calcd. for $C_{16}H_{14}N_2O$: N, 11.2.

Found: N, 11.0, 11.1.

However, a determination of the melting point of a mixture of the pyridazone and the compound in question showed a considerable depression, indicating that the two compounds are not the same.

The by-product remains unidentified.

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* uncorrected.

SUMMARY

1. Six 1-methyl-3-R-3-R'-cyclohexane carboxylic acids were prepared and described. With the exception of the 1,3-dimethylcyclohexane carboxylic acid, these acids are new compounds.

2. The acid chlorides of the above acids were prepared, from which were made the dimethylaminoethyl and diethylaminoethyl esters of the above cyclohexane carboxylic acids. The esters were characterized in the form of their hydrochloride salts. Simple amides and piperidyl amides of the six acids were also prepared.

3. Some improvements in the procedures for the preparation of 3-methyl-5-alkyl-$\triangle^2$-cyclohexenones and 3-cyano-3-methyl-5-alkylcyclohexanones are reported.

4. A new adaptation of the Wolff-Kishner reduction is described, whereby γ-ketonitriles may be simultaneously hydrolyzed and reduced to the hydrocarbon acid in high yield.

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