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ALICYCLIC CARBOXYLIC ACIDS. THE DIALKYLAMINOETHYL ESTERS OF SOME 1-METHYL-3-ALKYLCYCLOHEXANE CARBOXYLIC ACIDS[1]

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Recent studies by Krayer and his collaborators (1) have shown that certain of the alkaloids isolated from the bark of *Erythrophleum guineense* exhibit an effect upon the heart similar to that shown by the cardiac glycosides. The alkaloids of this group appear to be esters of hydrogenated and ring alkylated phenanthrene carboxylic acids with mono- and di-methylaminoethanol (2, 3). It also has been shown that the ester linkage is essential to the cardiac action since the acid formed upon hydrolysis of erythrophleine is ineffective in doses 100 times as large as the effective dose of the ester (1). A survey of the literature failed to disclose any systematic investigation of synthetic aminoethyl esters structurally resembling the erythrophleum alkaloids. In order to define the structural elements that contribute to the effectiveness of these alkaloids, the preparation of some aminoethyl esters of simpler alicyclic carboxylic acids appeared to be of interest. Our attention has been directed first to the synthesis of acids derived from ring alkylated cyclohexanes.

Several methods for the synthesis of cyclohexane carboxylic acids carrying one or more alkyl groups as ring substituents were available. In view of the ease with which a variety of alkyl groups could be introduced into the structure, the procedure developed by Knoevenagel (4) for the synthesis of 3-methyl-5-alkyl-Δ^2-cyclohexenones was selected for initial development. Further steps in the synthesis involved the conversion of the cyclohexenones into the corresponding 3-cyanocyclohexanones by the procedures elaborated by Whitmore and Roberts (6) based on Knoevenagel's earlier observations (5). Preparation of the cyclohexane carboxylic acids was to be completed by hydrolysis of the cyano compounds and reduction of the carbonyl group of the cyanocyclohexanones.

We have been able to confirm the observation of Whitmore and Roberts that 3-cyano-3,5,5-trimethylcyclohexanone is best prepared from isophorone by treatment with sodium cyanide and glacial acetic acid in alcoholic solution whereas the 3-cyano-3-methyl-5-alkylcyclohexanones are best prepared by initial addition of sodium bisulfite to the cyclohexenone followed by treatment of the addition product with sodium cyanide in aqueous solution. It is interesting to note that isophorone dissolves readily on heating with an aqueous sodium

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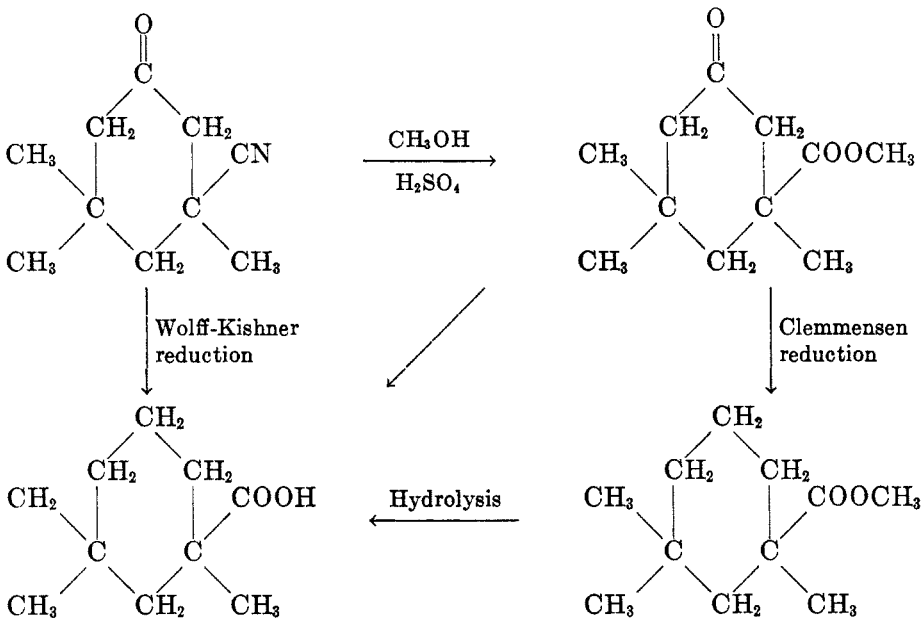
bisulfite solution; however, the addition compound is decomposed almost completely to isophorone upon treatment with sodium cyanide in warm aqueous solution.

Exploratory studies on the hydrolysis and reduction of the cyanocyclohexanones were carried out with 3-cyano-3,5,5-trimethylcyclohexanone. Alcoholysis of the keto-nitrile with methanol and sulfuric acid (6) led to the corresponding γ-keto-ester. Attempts to reduce the latter by the Clemmensen technique (7) gave the methyl ester of 1,3,3-trimethylcyclohexane carboxylic acid in a maximum yield of 37%; the free acid did not appear among the reduction products. Although the Wolff-Kishner technique had been applied to the reduction of only a few examples of γ-keto-esters (8, 9), it was felt that the Huang-Minlon (10) modification of the procedure might be more effective. Treatment of methyl 3,5,5-trimethylcyclohexanone 3-carboxylate with hydrazine hydrate and potassium hydroxide in diethylene glycol solution led to the formation of the reduced acid in 60% yield. Saponification of the ester accompanied the reduction of the carbonyl group.

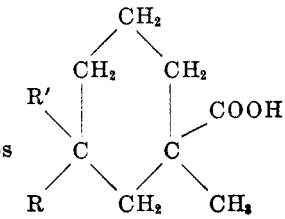


It is likely that saponification of the ester in the modified Wolff-Kishner reaction occurred during the first stage of the process while water was being expelled from the diethylene glycol solution of the reactants. Decomposition of the hydrazone formed during this stage took place at the higher temperature attained after complete removal of the water. This sequence of reactions suggested the possibility of a simultaneous hydrolysis and reduction of the keto-nitriles during the course of the reaction. Newman (11) had attempted to accomplish a one-step hydrolysis and reduction of α-phenyl-β-benzoylpropionitrile using the Clemmensen procedure but the yield of reduced acid was low

and much starting material was recovered. Attempts to reduce keto nitriles in the pyrrole series led to variable results. In the Wolff-Kishner reduction of 2,4-dimethyl-3-cyanopropionyl-5-carbethoxypyrrole only hydrolysis of the cyanide group was observed (12), while a similar reduction of 2,4-dimethyl-3-cyano-5-formylpyrrole led to 2,4,5-trimethylpyrrole and 2,4,5-trimethyl-3-cyanopyrrole (13). The formation of the former presumably involved hydrolysis of the cyanide group and decarboxylation of the resulting acid. To test the procedure α-phenyl-β-benzoylpropionitrile was heated in diethylene glycol with 85% hydrazine hydrate and potassium hydroxide. Reduction and hydrolysis took place simultaneously and α,γ-diphenylbutyric acid was isolated in 63% yield. The product was identical with the material obtained by Newman in

TABLE I

1-METHYL-3-R-3-R′-CYCLOHEXANE CARBOXYLIC ACIDS



R	R′	YIELD, %	B.P., °C.	MM.	M.P., °C.	FORMULA	CALC'D		FOUND	
							C	H	C	H
CH_3	H	72.5	—	—	91–92	$C_9H_{16}O_2$	69.2	10.3	69.2	10.1
C_2H_5	H	75.0	120–129	2	39–40	$C_{10}H_{18}O_2$	70.6	10.6	70.7	10.6
n-C_3H_7	H	91.4	142–144	6	—	$C_{11}H_{20}O_2$	71.7	10.9	71.7	10.9
i-C_3H_7	H	53.4	139–146	3	—	$C_{11}H_{20}O_2$	71.7	10.9	71.5	10.7
C_6H_5	H	75.0	—	—	124–126	$C_{14}H_{18}O_2$	77.1	8.3	77.5	8.3
CH_3	CH_3	69.1	144–147	11	51–52	$C_{10}H_{18}O_2$	70.6	10.6	70.4	10.3

the Clemmensen reduction and showed no depression of the melting point when mixed with a sample that Dr. Newman was kind enough to make available.

When 3-cyano-3,5,5-trimethylcyclohexanone was subjected to the same treatment, 1,3,3-trimethylcyclohexane carboxylic acid could be isolated from the reaction mixture in 69% yield. The general applicability of the procedure became apparent when a group of 3-cyano-3-methyl-5-alkylcyclohexanones was converted into the corresponding cyclohexane carboxylic acids in yields of 53–91% (Table I) upon heating with 85% hydrazine hydrate and potassium hydroxide in diethylene glycol solution.

It should be pointed out that all the acids described in Table I with the exception of 1,3,3-trimethylcyclohexane carboxylic acid may exist as pairs of diastereoisomeric racemates. Although it is rather likely that a single racemate

would predominate, our results do not suffice to establish this fact. One of the products, 1,3-dimethylcyclohexane carboxylic acid has been previously described. Godchot and Cauquil (14) have prepared several isomeric forms of this acid by oxidation of 1-acetyl-1,3-dimethylcyclohexane with sodium hypobromite. The product designated by them as the *cis*, *trans*-1,3-dimethylcyclohexane carboxylic acid appeared to be identical with our acid. Although the melting points of the acid and the amide, 90° and 73°, respectively, were in close agreement with our values, 91–92° and 74°, respectively, we could not duplicate the boiling point of the acid chloride previously reported, 98° at 14 mm. as compared with our value of 87–88° at 16 mm.

All of the acids were converted into acid chlorides by treatment with thionyl chloride and these in turn were converted into simple amides and piperidides (Table IV). All the amides were solid derivatives except 1-methyl-3-ethylcyclohexane carboxamide and in this instance the acid was characterized as the anilide. Only the piperidide of 1-methyl-3-phenylcyclohexane carboxylic acid was a solid; the remaining piperidides were liquids that would not crystallize but could be distilled under diminished pressure.

The dialkylaminoethyl esters were prepared by the interaction of the acid chlorides with an excess of dimethylaminoethanol or diethylaminoethanol. The dialkylaminoethyl esters were liquid products but could be isolated and purified readily as hydrochlorides (Table III). The crude ester hydrochlorides were rather hygroscopic until purified by recrystallization from ethyl acetate when they could be handled without undue difficulty. The hydrochloride of diethylaminoethyl 1-methyl-3-*n*-propylcyclohexane carboxylate remained hygroscopic even after repeated crystallization from ethyl acetate.

The hydrochlorides of the diethylaminoethyl esters of 1,3-dimethyl-, 1-methyl-3-ethyl-, and 1-methyl-3-isopropyl-cyclohexane carboxylic acid were examined pharmacologically by Drs. R. P. Walton and M. DeV. Cotten of the Medical College of the State of South Carolina. We are indebted to them for permission to include the following comments: "The hydrochlorides of these three compounds were tested under the same experimental conditions as had been used in the characterization of a series of common cardiac glycosides (18). In these acute mammalian experiments, each of these compounds produced depression of heart contractile force, excursion amplitude, heart rate, and arterial pressure. Minimal effects were obtained at doses of 1 mg./kg. intravenously and near fatal effects with doses of 20 mg./kg. There were no outstanding quantitative differences in the effects of these three compounds. No evidences of heart stimulant actions were observed in these dose ranges and the apparent absence of any digitalis-like effects was also supported by serial electrocardiograms taken during the experiment. The effects were closely typical of those obtained with procaine under the same conditions, these compounds on a weight basis exhibiting approximately twice the potency as cardiovascular depressants. Experiments of a similar nature were also conducted with the hydrochlorides of the diethylaminoethyl ester of 1,3,3-trimethylcyclohexane carboxylic acid, the dimethylaminoethyl ester of 1-methyl-3-*n*-propylcyclohexane

carboxylic acid, the diethylaminoethyl ester of 1-methyl-3-phenylcyclohexane carboxylic acid and the dimethylaminoethyl ester of 1-methyl-3-isopropylcyclohexane carboxylic acid. Each showed marked cardiovascular depression in doses of 3 mg./kg., the type of effect being similar to that obtained with procaine."

EXPERIMENTAL

Cyclohexenones. The 3-methyl-5-alkyl-Δ^2-cyclohexenones were prepared by the Knoevenagel condensation (4) of ethyl acetoacetate with a number of aldehydes as modified by Horning, *et al.* (15). The 5-methyl, 5-ethyl, 5-*n*- and iso-propyl, and 5-phenyl derivatives were prepared by the condensation of ethyl acetoacetate with acetaldehyde, propionaldehyde, *n*- and iso-butyraldehyde, and benzaldehyde, respectively.

3-Cyano-3-methyl-5-alkylcyclohexanones. The 3-cyano-3-methyl-5-alkylcyclohexanones were prepared by the interaction of aqueous sodium cyanide and the sodium bisulfite addition products of the 3,5-dialkyl-Δ^2-cyclohexenones as described by Whitmore and Roberts (6). The 3-cyanocyclohexanones with methyl, ethyl, *n*- and iso-propyl, and phenyl as substituents in the 5 position were prepared by this procedure.

3-Cyano-3,5,5-trimethylcyclohexanone. Whitmore and Roberts (6) have described the preparation of this product by a method analogous to that employed for the synthesis of α-phenyl-β-benzoylpropionitrile from benzalacetophenone (16). The same preparation has been employed successfully in this laboratory. Attempts to prepare the cyano compound from the sodium bisulfite addition product of isophorone were unsuccessful. In a typical experiment 34 g. of isophorone was heated under reflux with 34 g. of sodium bisulfite in 75 ml. of water. The isophorone dissolved completely within 30 minutes. On treatment of the solution with 15 g. of sodium cyanide dissolved in 35 ml. of water and warming the mixture on a water-bath at 90° for an hour, an immiscible liquid separated. After extraction of the reaction mixture with benzene and fractionation of the benzene solution, isophorone was recovered (85–90% in different experiments) together with a small amount of higher-boiling material that appeared to be impure cyano compound. When the reaction with sodium cyanide was carried out at lower temperature (65° and 80°), the isophorone separated more slowly but the amount recovered was about the same.

1,3,3-Trimethylcyclohexane carboxylic acid. A. Clemmensen reduction. A solution of 12.5 g. (0.063 mole) of methyl 3,5,5-trimethylcyclohexanone 3-carboxylate, prepared according to Whitmore and Roberts (6), in 75 ml. of 95% methanol was added in portions over a period of three hours to a boiling mixture of 30 ml. of water, 10 ml. of methanol, 50 ml. of concentrated hydrochloric acid, and the amalgamated zinc from 50 g. of granulated zinc and 3 g. of mercuric chloride. After complete addition of the keto ester, the mixture was boiled under reflux for eight hours during which a further 40 ml. of concentrated hydrochloric acid was added in portions. Methyl 1,3,3-trimethylcyclohexane carboxylate was isolated from the reaction mixture in yields of 4–6 g. (25–37%) in several experiments as a colorless liquid of camphor-like odor distilling at 103–108° at 24 mm. Saponification was accomplished by boiling 10 g. of the ester with a solution of 20 g. of potassium hydroxide in 25 ml. of water for two hours. After acidification with hydrochloric acid and extraction with benzene, the acid was distilled under reduced pressure, b.p. 144–147° at 11 mm. The product solidified on cooling. Recrystallization from 50% isopropyl alcohol gave 8 g. (86%) of 1,3,3-trimethylcyclohexane carboxylic acid as colorless plates, m.p. 51–52°.

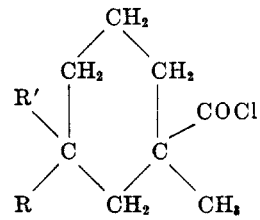
B. Wolff-Kishner reduction of the keto ester. The Huang-Minlon modification of the Wolff-Kishner reduction was employed (10). A mixture of 16 g. of methyl 3,5,5-trimethylcyclohexanone 3-carboxylate, 15 g. of sodium hydroxide, and 15 ml. of 85% hydrazine hydrate in 150 ml. of diethylene glycol was boiled under reflux for an hour after which the condenser was removed and heating continued until the temperature of the reaction mixture had risen to 195°. The condenser was then replaced and heating was continued for three hours under reflux. The product was isolated by acidification of the reaction mixture with hydrochloric acid, extraction with benzene, and distillation under reduced pressure,

b.p. 144–146° at 12 mm. The product solidified on standing at room temperature. Recrystallization from 50% isopropyl alcohol gave 8.5 g. (60%) of 1,3,3-trimethylcyclohexane carboxylic acid as colorless platelets, m.p. 50–51°. The product was readily soluble in dilute aqueous sodium hydroxide and was reprecipitated by addition of dilute hydrochloric acid. There was no depression of the melting point when the product was mixed with the acid obtained by procedure A.

C. Wolff-Kishner reduction of the γ-keto nitrile. 3-Cyano-3,5,5-trimethylcyclohexanone (33 g.) was added to 40 g. of potassium hydroxide and 30 ml. of 85% hydrazine hydrate in 300 ml. of diethylene glycol. After boiling the solution under reflux for an hour the condenser was removed until the internal temperature reached 195°; heating under reflux was continued for four hours. The cooled solution was poured into 400 g. of ice and 100 ml. of concentrated hydrochloric acid. The product was extracted with benzene and purified as in procedure B. After recrystallization from 50% isopropyl alcohol, 25.5 g. (70%)

TABLE II

ACID CHLORIDES OF THE 1-METHYL-3-R-3-R′-CYCLOHEXANE CARBOXYLIC ACIDS



R	R′	B.P., °C.	MM.	FORMULA	CHLORINE	
					Calc'd	Found
CH_3	H	87–88	16	$C_9H_{15}ClO$	20.3	19.9, 20.1
C_2H_5	H	100–103	14	$C_{10}H_{17}ClO$	18.8	18.9, 18.5
n-C_3H_7	H	111–113	15	$C_{11}H_{19}ClO$	17.5	17.2, 17.3
i-C_3H_7	H	110–111	13	$C_{11}H_{19}ClO$	17.5	17.1, 17.3
C_6H_5	H	155–156	5	$C_{14}H_{17}ClO$	15.0	14.8, 15.0
CH_3	CH_3	94–97	15	$C_{10}H_{17}ClO$	18.8	18.6, 18.5

of 1,3,3-trimethylcyclohexane carboxylic acid, m.p. 51–52°, was obtained. The product was identical with the material obtained in procedures A and B by mixture melting point. Analytical data are recorded in Table I.

1-Methyl-3-alkylcyclohexane carboxylic acids. These acids were all prepared from the corresponding 3-cyano-3-methyl-5-alkylcyclohexanones by the Huang-Minlon modification of the Wolff-Kishner reduction. In general, 0.2 mole of the γ-keto nitrile was added to 40 g. of potassium hydroxide and 30 ml. of 85% hydrazine hydrate in 300 ml. of diethylene glycol. The reaction was carried out as described in procedure C. On acidification of the reaction mixture, solid products were separated and recrystallized from aqueous acetone or 50% isopropyl alcohol. Liquid products were extracted with ether or benzene and isolated as in procedure C. Physical constants and analytical data for the acids are given in Table I.

Acid chlorides. To 0.05 mole of the cyclohexane carboxylic acid in a 50-ml. Claisen flask, 18 g. (0.15 mole) of thionyl chloride was added dropwise during 15 minutes. The reaction was moderated by cooling in a cold-water bath. After complete addition of the thionyl chloride the bath was heated to boiling and maintained at this point for two hours. After removal of the excess thionyl chloride, the acid chloride was distilled under diminished pressure. Physical constants and analytical data are included in Table II.

Hydrochlorides of the dialkylaminoethyl 1-methyl-3-alkylcyclohexane carboxylates. The following general procedure was used for the preparation of the dimethyl- and the diethylaminoethyl esters of the cyclohexane carboxylic acids. To 0.2 mole of dimethyl- or diethylaminoethanol in a 50-ml. glass-stoppered Erlenmeyer flask, 0.05 mole of the cyclic acid chloride was added dropwise. The mixture was shaken vigorously for five minutes and then allowed to stand at room temperature for two hours with intermittent shaking before it was poured into a separatory-funnel containing 25 ml. of saturated sodium carbonate solution. The free amino ester that separated was taken up in 25 ml. of ether, washed free of the water-soluble amino alcohol by shaking with several portions of water, and then dried over sodium sulfate. The ethereal solution of the ester was decanted from the drying agent and treated with an ethereal solution of hydrogen chloride added dropwise with cooling until the supernatant liquid was distinctly acidic to Congo Red. A large excess of hydrogen chloride was avoided. The white hygroscopic precipitate of hydrochloride was filtered and transferred quickly to a vacuum-desiccator. The ester-hydrochlorides were recrystallized from anhydrous ethyl acetate. All of the hydrochlorides could be purified easily in this manner and were obtained, with one exception, as crystalline products that could be handled in the room atmosphere without apparent absorption of moisture. The hydrochloride of diethylaminoethyl 1-methyl-3-*n*-propylcyclohexane carboxylate remained hygroscopic even after four recrystallizations from ethyl acetate that greatly reduced the yield of product. Other solvents such as absolute ethanol-ether, acetone, and acetone-ether mixtures gave an even less tractable product. Physical constants and analytical data for the amino ester hydrochlorides are given in Table III.

Amides of the cyclohexane carboxylic acids. The acid chloride (1 g.) was added to 20 ml. of concentrated aqueous ammonia in a 50-ml. glass-stoppered Erlenmeyer flask. The mixture was shaken vigorously for five minutes before it was allowed to stand at room temperature for two days with intermittent shaking. With the exception of 1-methyl-3-ethylcyclohexane carboxamide the amides were colorless, crystalline solids. Since the ethyl homolog could not be crystallized, the acid was characterized as the anilide, prepared by interaction of the acid chloride and aniline. Analyses and physical constants of the amides and the anilide are given in Table IV.

The piperidides of the cyclohexane carboxylic acids were prepared by interaction of equimolar amounts of the acid chlorides and piperidine in the presence of a small excess of 10% aqueous potassium hydroxide. Interaction was complete after about two hours of intermittent shaking, when the product was taken up in a small volume of benzene, dried, and fractionated under diminished pressure. Only 1-methyl-3-phenylcyclohexane carboxylic acid gave a solid piperidide; the others were high-boiling, yellowish liquids. After recrystallization of the piperidide of the phenyl analog from isopropyl alcohol, it was obtained as tan crystals, m.p. 55–56°. Analyses and physical constants for the piperidides are included in Table IV.

α,γ-Diphenylbutyric acid. After treatment of α-phenyl-β-benzoylpropionitrile, prepared from benzalacetophenone by interaction with sodium cyanide and acetic acid (16), with potassium hydroxide and hydrazine in diethylene glycol as described in procedure C, α-γ-diphenylbutyric acid was isolated in 63% yield. The acid was purified by distillation, b.p. 196–203° at 1 mm., m.p. 73°. When mixed with a sample prepared and very kindly made available to us by Dr. Melvin S. Newman, no depression of the melting point was observed.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.3; H, 6.6.
Found: C, 80.6; H, 6.6.

The *acid chloride*, prepared in 81% yield by interaction of the acid with thionyl chloride, was obtained as a clear, yellowish liquid, b.p. 154–155° at 1 mm.

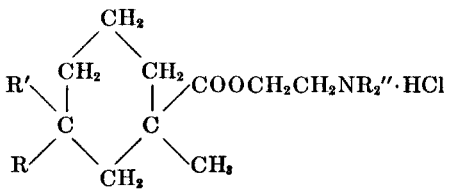
Anal. Calc'd for $C_{16}H_{15}ClO$: Cl, 13.7. Found: Cl, 13.4, 13.5.

The *amide*, prepared from the acid chloride and ammonia, was obtained as colorless needles, m.p. 96°, upon crystallization from methanol.

Anal. Calc'd for $C_{16}H_{17}NO$: N, 5.9. Found: N, 5.8, 5.8.

TABLE III

DIALKYLAMINOETHYL 1-METHYL-3-R-3-R′-CYCLOHEXANE CARBOXYLATE HYDROCHLORIDES



R	R′	R″ = CH_3				R″ = C_2H_5			
		M.P., °C.	FORMULA	N		M.P., °C.	FORMULA	N	
				Calc'd	Found			Calc'd	Found
CH_3	H	150–151	$C_{13}H_{26}ClNO_2$	5.3	5.4, 5.4	128–130	$C_{15}H_{30}ClNO_2$	4.8	5.0, 4.6
C_2H_5	H	109–111	$C_{14}H_{28}ClNO_2$	5.1	5.0, 5.0	114–117	$C_{16}H_{32}ClNO_2$	4.6	4.7, 4.7
n-C_3H_7	H	109–110	$C_{15}H_{30}ClNO_2$	4.8	4.9, 4.8	112–116[a]	$C_{17}H_{34}ClNO_2$	4.4	4.7, 4.7
i-C_3H_7	H	147	$C_{15}H_{30}ClNO_2$	4.8	4.8, 4.8	130–133	$C_{17}H_{34}ClNO_2$	4.4	4.6, 4.2
C_6H_5	H	136	$C_{18}H_{28}ClNO_2$	4.3	4.3, 4.3	116–119	$C_{20}H_{32}ClNO_2$	4.0	4.2, 4.0
CH_3	CH_3	159	$C_{14}H_{28}ClNO_2$	5.1	5.0, 5.0	120–121	$C_{16}H_{32}ClNO_2$	4.6	4.7, 4.6

[a] Determined on hygroscopic material

TABLE IV

AMIDES AND PIPERIDIDES OF THE 1-METHYL-3-R-3-R′-CYCLOHEXANE CARBOXYLIC ACIDS

R	R′	AMIDES				PIPERIDIDES				
		M.P., °C.	FORMULA	N		B.P., °C.	MM.	FORMULA	N[a]	
				Calc'd	Found				Calc'd	Found
CH_3	H	74–75	$C_9H_{17}NO$	9.0	8.8, 9.0	128–131	2	$C_{14}H_{25}NO$	6.0	6.2, 6.3
C_2H_5	H	(80–81)[b]	$(C_{16}H_{23}NO)$[b]	5.7[b]	5.7, 5.7	135–138	2	$C_{15}H_{27}NO$	5.7	5.9, 5.8
n-C_3H_7	H	136–137	$C_{11}H_{21}NO$	7.7	7.7, 7.5	141–145	2	$C_{16}H_{29}NO$	5.4	5.4, 5.5
i-C_3H_7	H	82.5–83.5	$C_{11}H_{21}NO$	7.7	7.7, 7.7	143–147	2	$C_{16}H_{29}NO$	5.4	5.6, 5.5
C_6H_5	H	131–133	$C_{14}H_{19}NO$	6.5	6.5, 6.4	—[c]		$C_{19}H_{27}NO$	5.0	4.5, 4.6
CH_3	CH_3	91.5–92.5	$C_{10}H_{19}NO$	8.3	8.2, 8.2	128–131	2	$C_{15}H_{27}NO$	5.7	5.7, 5.6

[a] Nitrogen determined by macro-Kjeldahl analysis using metallic mercury catalyst (17). [b] Anilide. [c] M.p. 55–56°.

SUMMARY

1. Five 1-methyl-3-alkylcyclohexane carboxylic acids and 1,3,3-trimethylcyclohexane carboxylic acid have been prepared. With the exception of the 1,3-dimethyl derivative these acids have not been previously described.

2. The acids were converted into acid chlorides and characterized as amides and piperidides.

3. Dimethyl- and diethyl-aminoethyl esters of the cyclohexane carboxylic acids were prepared by interaction of the chlorides with the appropriate amino alcohols. The amino esters were isolated and characterized as hydrochlorides. A brief statement of their pharmacologic action is given.

4. A new adaptation of the Wolff-Kishner reduction is described in which γ-keto nitriles undergo successive hydrolysis of the cyanide group and reduction of the carbonyl group in a single step. The procedure is applicable to both cyclic and open chain γ-keto nitriles.

EAST LANSING, MICHIGAN

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