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Preparation of the CIS and TRANS Isomers of Methylcyclohexanecarboxylic Acids and Their 2-Diethylaminoethyl Esters

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PREPARATION OF THE CIS AND TRANS ISOMERS OF METHYLCYCLOHEXANECARBOXYLIC ACIDS AND THEIR 2-DIETHYLAMINOETHYL ESTERS

by

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INTRODUCTION

The purpose of this research is to prepare the cis and trans isomers of the 2, 3 and 4-methylcyclohexanecarboxylic acids and their 2-diethylaminoethyl esters.

This series of compounds is of interest because of the anti-tumor activity shown by some ethanolamine derivatives. The compounds to be prepared in this study represent modifications of these structures to determine if further investigation in this area is worthwhile. A pharmacological evaluation of these compounds will be made since many esters of amino alcohols have demonstrated pharmacological activity. The cancer chemotherapeutic and pharmacological test results are not included in this paper, but will be published elsewhere.

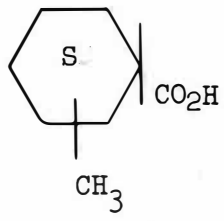
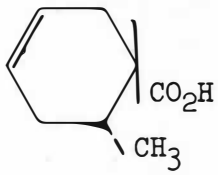
HISTORICAL REVIEW

Methylcyclohexanecarboxylic Acids

A search of the chemical literature reveals various methods by which the cis and trans-methylcyclohexanecarboxylic acids have been made. The structures of interest in this study are listed in Table I.

TABLE I

DESIGNATION OF CARBOXYLIC ACID STRUCTURES

General Structure	Structure number	Methyl group position	Relative configuration of substituents
	I	2	cis
	II	2	trans
	V	3	cis
	VI	3	trans
	VII	4	cis
	VIII	4	trans
	III	2	cis
	IV	2	trans

Some of the previous methods of preparation of the cis and trans-methylcyclohexanecarboxylic acids were reviewed by Macbeth and co-workers (6, 9, 21). When the acids were prepared by the carbonation of a Grignard reagent, they found that the product was a mixture of isomers or was poorly characterized. They also showed that reduction of the toluic acids was more conveniently carried out by catalytic hydrogenation rather

than reduction with sodium and isoamyl alcohol.

The method which Macbeth, Mills and Simmonds (21) used to prepare the cis acid (I) was by the reduction of o-toluic acid with hydrogen in a glacial acetic acid solution at 1 atm. and 100°. Platinum oxide was used as a catalyst. This method was used successfully by others (10, 19). Cope, Fournier and Simmons (7) modified the procedure of Macbeth and co-workers by using more rigorous conditions. A shorter reaction time was effected by using more catalyst, higher pressures and a small amount of concentrated hydrochloric acid. Another approach used was a Diels-Alder condensation of piperylene with acrylic acid. Hydrogenation of the Diels-Alder reaction product (1, 22, 25) gave the cis-2-methyl acid (I).

A variety of methods are recorded for the preparation of trans-2-methylcyclohexanecarboxylic acid (II) in addition to those reviewed by Macbeth, Mills and Simmonds (21). The preparation of the trans acid (II) was effected by the hydrogenation (170 atms., 230-240°) of the sodium salt of o-toluic acid under alkaline conditions using Raney nickel catalyst (21). The condensation of butadiene with crotonic acid (12, 14, 19) affords a means of obtaining trans-2-methyl-4-cyclohexenecarboxylic acid (IV). Subsequent hydrogenation (12, 19) of the acid (IV) gives the acid (II).

Various studies have been made to determine the ways in which either the cis-2-methyl acid (I) or the trans-2-methyl acid (II) may be interconverted. The cis-2-methyl acid (I) has been converted to its trans isomer (II) by heating the acid (I) under reflux with either hydrogen chloride (1, 34) or 4-bromonaphthalene-1-sulfonic acid (7). No epimerization was observed by Alder and Vogt (1) when the methyl ester of the cis-2-methyl acid (I) was treated with sodium methoxide. Heating

the acid (I) with aqueous sodium hydroxide caused little or no change in its configuration (7). Epimerization was shown (21) to occur when the trans acid (II) was esterified with ethanol containing concentrated sulfuric acid. Green and Beroza (14) studied the conditions which were necessary to bring about isomerization of cis-2-methyl-4-cyclohexenecarboxylic acid (III) and its trans isomer (IV). Heating the trans isomer (IV) under reflux with thionyl chloride brought about partial epimerization, however, no epimerization of this isomer (IV) was observed when treated with thionyl chloride at room temperature. Similiar observations with cis-2-methyl-cyclohexanecarboxylic acid (I) were made by Macbeth and co-workers (21). Green and Beroza (14) showed that either potassium hydroxide in diethylene glycol or dilute sulfuric acid failed to isomerize the trans acid (IV) when heated under reflux. They also demonstrated the acid chloride of the cis acid (III) or its trans isomer (IV) was readily epimerized by heating at 150-200°.

Darling, Macbeth and Mills (9) prepared the cis-3-methyl acid (V) by low pressure hydrogenation using platinum oxide catalyst. Other authors (13, 32) have also followed this procedure. Attempts to prepare the trans-3-methyl acid (VI) by the hydrogenation (165°, 125 atm.) of the sodium salt of m-toluic acid using Raney nickel catalyst were unsuccessful (9). Synthesis of the trans-3-methyl acid (VI) was successfully carried out by Hewgill, Jefferies and Macbeth (15) and later by others (13). The synthesis involved a series of stereospecific reactions using isophthalic acid as the starting material. Goering and McCarron (13) studied the carbonation of the Grignard reagents of cis and trans-3-methylcyclohexyl chloride. Contrary to the findings of

earlier investigators, they found that this reaction gave identical mixtures of the cis and trans isomeric acids when starting with either the pure cis or trans chlorides. These mixtures were shown to be identical by their infrared spectra.

When Cooke and Macbeth (6) first began to investigate the epimeric acids and alcohols of the cyclohexane series, they employed the method of Keats (18) to obtain the cis-4-methyl acid (VII) by low pressure hydrogenation. Other authors (11, 14) have also reported the use of this method. Hydrogenation of p-toluamide followed by hydrolysis has been used (34) to prepare the cis acid (VII). Conversion of the cis-4-methyl acid (VII) to its trans isomer (VIII) was effected by heating under reflux with dry hydrogen chloride (11). Cooke and Macbeth (6) prepared the trans-4-methyl acid (VIII) by the pressure hydrogenation (200°, 150-200 atms.) of the sodium salt of p-toluic acid using Raney nickel catalyst.

In the more recent literature, methods of analysis for cis-trans mixtures are given. Quantitative infrared analysis has been applied to mixtures of cis-trans isomers of the methyl esters of the 2-methyl acids [I, II, (19)], the 3-methyl acids [V, VI, (13)] and the sec-butyl esters of the 2-methyl acids [III, IV, (14)]. The isomeric composition of mixtures of the methyl esters of the 2-methyl acids (I, II) has been determined from their refractive indexes (19). Fractionation of mixtures of the isomeric acids (III, IV) has been carried out using silicic acid column chromatography (14). The composition of the mixtures was determined by titration of the various fractions.

Pharmacological Activity of Aminoesters

Numerous carboxylic acid esters of tertiary-amino alcohols have been made which possess pharmacological properties. Included in this class of aminoesters are the 2-diethylaminoethyl esters of alkyl-substituted benzoic or cyclohexanecarboxylic acids. The esters of p-alkylbenzoic acid possess anesthetic properties when the alkyl group is either t-butyl (5, 8) or isopropyl (4, 23). Esters of benzoic acid with one or more alkyl subtituents have been prepared and tested. Studies (27) of 2-diethylaminoethyl esters of sterically hindered alkyl-substituted benzoic acids showed that these esters had a considerably longer period of anesthetic action than did procaine. Other similiar aminoesters have been reported in the patent literature (26, 28). Rabjohn (26) has reported the preparation of the 2-diethylaminoethyl-toluates. However, the only property which was reported for these compounds was their half-life of hydrolysis.

There are no references in the literature which report the preparation of the 2-diethylaminoethyl esters of 2, 3 or 4-methylcyclohexanecarboxylic acids. However, some investigation of the 2-diethylaminoethyl esters of alkyl-substituted cyclohexanecarboxylic acids has been made. No attempt has been made to isolate the cis and trans isomers where they occur.

The aminoester hydrochlorides of substituted alicyclic carboxylic acids have been prepared and examined for their spasmolytic activity (31). Test results showed that the most active compounds are the 2-diethylaminoethyl ester hydrochlorides of 1-substituted cycloalkanecarboxylic acids having four to six carbon atoms in the alicyclic ring. In a later paper (29), the conclusion is made that the most potent aminoesters were those

2-diethylaminoethyl ester hydrochlorides of 1-alkylcyclohexanecarboxylic acids where the alkyl group had five carbon atoms. The series of compounds resulting from these two studies were later patented by the authors (30, 35). The local anesthetic action of the 2-diethylaminoethyl ester hydrochlorides of 1-phenyl- and 1-cyclohexylcyclohexanecarboxylic acids was demonstrated to be about equal to that of cocaine (20). No such action was observed when the 1-substituent was a methyl group. Studies of 2-dialkylaminoethyl ester hydrochlorides of various 1-methyl-3-alkylcyclohexanecarboxylic acids resulted in compounds that were effective cardiovascular depressants (36).

Methods of Esterification

The following methods were used in previous studies to prepare the 2-diethylaminoethyl esters of alkyl-substituted benzoic or cyclohexanecarboxylic acids.

The most widely used method of esterification is the Schotten-Baumann reaction. In this method, an acid chloride was treated with a tertiary-amino alcohol in the presence of a strong inorganic base (4, 5), a weak inorganic base (28), pyridine (14), or an excess of the starting amino alcohol (36). Another variation in this technique was to allow the reaction of the aminoester with the hydrogen chloride and thus obtain the product as its hydrochloride derivative (23).

To obtain a desired aminoester hydrochloride, tertiary-alkylamino halides in water or other suitable solvent can be neutralized with a carboxylic acid, evaporated and the residue rearranged by heating, or the neutralized solution can be heated directly to obtain a desired aminoester (16). A modification of this method (26, 27) was carried out

by heating a toluene solution of the acid under reflux with potassium hydrogen carbonate. The reaction mixture was cooled and 2-chlorotriethylamine hydrochloride was added. Upon further heating the desired aminoester was formed and recovered as its hydrochloride. Other investigators achieved esterification by heating a mixture of the acid, 2-chlorotriethylamine hydrochloride, sodium and isopropanol (29, 31).

Aminoesters have been prepared by trans-esterification of the corresponding simple alkyl esters of the selected acid with an amino alcohol in an inert solvent (xylene) using sodium as a catalyst (29, 31).

The preparation of 2-diethylaminoethyl-1-cyclohexylcyclohexanecarboxylate hydrochloride was accomplished by hydrogenation (31). 2-Diethylaminoethyl-1-phenylcyclohexanecarboxylate hydrochloride in a glacial acetic acid solution containing platinum oxide was shaken with hydrogen at 70-80° under a pressure of 50 psi to obtain the saturated product.

EXPERIMENTAL

General

In the following experimental section all melting points and boiling points are expressed in degrees centigrade and are uncorrected.

The materials which were used in this investigation were used as they were obtained unless otherwise noted. Chemicals which were obtained from Eastman Organic Chemicals are: o-toluic acid (#P1646), m-toluic acid (#2288), p-toluic acid (#1459), 2-diethylaminoethanol (#841), 2-chlorotriethylamine hydrochloride (#P6436) and crotonic acid (#P1924). Anhydrous hydrogen chloride and butadiene (instrument grade) were purchased from the Matheson Co., Inc. Platinum oxide catalyst (Lot#9, 82.5% platinum oxide; Lot #25, 86.3% platinum oxide) was acquired from Engelhard Industries, Inc. Reagent grade glacial acetic acid (#2504) and anhydrous potassium hydrogen carbonate (#6736) were obtained from Mallinckrodt Chemical Works.

Fractional distillations under reduced pressure were carried out using one of two available columns. The columns (25 cm. x 8 mm. or 32 cm. x 8 mm.) contained a tantalum wire spiral and were equipped with a heating jacket. Pressure readings, which are given as a whole number, are reliable to the nearest millimeter of mercury, while those which include fractions of a millimeter are reliable to the nearest 0.05 mm. of mercury.

Hydrogenations were carried out on a Parr pressure hydrogenation apparatus (model #3911) equipped with a heater. In general, the following procedure was used for hydrogenations. The starting material was

dissolved in glacial acetic acid which had been distilled from previous hydrogenation reaction mixtures. A quantity of platinum oxide catalyst was added to the solution. The reaction vessel was then clamped on the apparatus. Air was removed from the reaction vessel by flushing five to ten times with hydrogen. After refilling the reservoir and reaction vessel with hydrogen to 60 psi gauge pressure, the reaction mixture was heated with shaking. When the gauge pressure dropped to about 30 psi the reservoir and reaction vessel were refilled with hydrogen to 60 psi. The temperature of the reaction mixture rose to a maximum and was maintained at this temperature until no further hydrogen absorption was observed. The reaction mixture was allowed to cool while remaining on the apparatus, and a final pressure reading was taken. The reaction vessel was then removed from the apparatus and the catalyst was separated from the solution by vacuum filtration using a Buchner funnel and filter paper. About 10 ml. of glacial acetic acid was used to wash the catalyst and the wash was combined with the filtrate. The product was obtained by distillation of the solvent and subsequent fractional distillation of the residue under reduced pressure.

Preparation of Methylcyclohexanecarboxylic Acids

cis-2-METHYLCYCLOHEXANECARBOXYLIC ACID (I) was prepared by modifications of the procedures given by Macbeth, Mills and Simmonds (21) and Cope, Fournier and Simmons (7).

o-Toluic acid (30.0 g., 0.220 moles, recrystallized from benzene) was dissolved in 140 ml. of distilled glacial acetic acid, mixed with 1.20 g. platinum oxide catalyst and hydrogenated between 60-30 and 60-33 psi. The temperature of the reaction mixture was raised from

25 to 98° over a period of 3/4 hrs. and maintained at 93-98° for an additional 1 1/4 hrs. No additional hydrogen absorption was observed after 3/4 hr. from the start of the hydrogenation. The reaction mixture was allowed to cool to 34° for 3/4 hr. Calculations showed that 108% of the theoretical* amount of hydrogen was absorbed.

The solvent was distilled under reduced pressure through a 10 cm. x 2 cm. column containing porcelain saddles. The product (I) was fractionally distilled into four fractions. Fractions 2-4 (25.4 g., 81%) distilled as a colorless oil, b.p. 130-130.5° (10 mm.), n_D^{23} 1.4631. [Lit.: b.p. 119° (11 mm.), n_D^{20} 1.4644 (21)].

trans-2-METHYLCYCLOHEXANECARBOXYLIC ACID (II) was prepared by the method described by Diels and Alder (12).

Crotonic acid [51.6 g., recrystallized from petroleum ether (60-110°)] was placed in a Parr pressure reaction apparatus (model #4501). The bomb cylinder was cooled in a Dry Ice - acetone bath at about -50°. Butadiene (29.7 g., 0.550 mole) was collected in a graduated cylinder partially immersed in a similiar cooling bath. The butadiene was quickly transferred to the bomb cylinder, and the bomb head assembly clamped into place. Heating the bomb to 175° over a period of 2 hrs. caused the pressure to rise to 130 psi. Evidence that the reaction was taking place at the end of 2 hrs. was shown by a steady rise in temperature, with the heater turned off, and a corresponding drop in pressure. After the initial reaction subsided,

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* Various factors which influenced this deviation from a previously determined calibration were not considered. Future theoretical hydrogen absorptions were calculated from this experiment.

the reaction mixture was stirred and kept between 147-174° for 18 hrs. To effect recovery of the products, the bomb cylinder was washed with ether. After removing the ether, the residue was flash distilled between 55-149° and 160-1.40 mm. The resulting product (53.6 g.) was dissolved in 120 ml. glacial acetic acid, mixed with 0.50 g. platinum oxide and hydrogenated between 60-30 and 60-51 3/4 psi at room temperature for 2 hrs. Hydrogen uptake ceased at the end of 1 hr. The catalyst was filtered from the solution, and the acetic acid was distilled from the filtrate at atmospheric pressure. Further distillation into eight fractions gave the impure trans acid (II, 16.6 g., 21% based on butadiene) as summarized below.

Fraction	Appearance	Weight (g.)	b.p. (740.5 mm.)	n_D^{25}	m.p.
6	colorless oil	6.8	236-239°	1.4549	---
7	oily white solid	8.0	239-241	----	40-47°
8	colorless oil	1.8	241-243	1.4562	---

Upon cooling, fractions 6 and 8 solidified. Attempts to recrystallize portions of fraction 6 and 7 from benzene, 95% ethanol or aqueous ethanol were unsuccessful. However, fraction 6-8 were purified by two recrystallizations from petroleum ether (30-60°) which resulted in a white crystalline solid (2.5 g.), m.p. 51-52.5°. [Lit.: b.p. 241-242°, m.p. 52° (34)].

Another preparation of the trans acid (II) had been carried out previously and was done in a manner similiar to the one just described. In the first attempt, using the same amount of reactants, the temperature of the reaction mixture rose to about 280° and a pressure of 155 psi.

After the initial reaction had subsided, the reaction mixture was kept at 120-180° for 4 hrs. Attempts were made to purify the crude trans acid (IV) by distillation under reduced pressure followed by purification via its piperazine salt. These methods were not completely satisfactory because more solidification had occurred in the distillation apparatus than was anticipated, and a pure piperazine salt could not be obtained by recrystallization from dry acetone without a significant loss of product. The crude trans acid (IV) was recovered from its piperazine salt by the method of Macbeth, Mills and Simmonds (21), and the recovered material was hydrogenated. The crude trans acid (II) distilled at atmospheric pressure as a colorless oil (15.2 g., 21% based on butadiene), b.p. 237-245°, n_D^{25} 1.4562. This was crystallized from petroleum ether giving an oily solid (4.8 g.), m.p. 41-48°. Additional solid fractions of impure trans acid (II) were recovered from the petroleum ether solutions (filtrates) resulting from the separate experiments.

cis-3-METHYLCYCLOHEXANECARBOXYLIC ACID (V) was prepared by the procedure used in the preparation of the cis-2-methyl acid (I).

m-Toluic acid (30.0 g., 0.220 moles) was dissolved in 140 ml. of distilled glacial acetic acid, mixed with 1.40 g. platinum oxide and hydrogenated between 60 1/2 - 23 and 60-42 psi. The temperature of the reaction mixture was raised from 25 to 79° over a period of 1 1/4 hrs. and maintained at 76-79° for 1/2 hr. No further hydrogen absorption was observed after 1 1/4 hrs. from the start of the reaction. The reaction mixture was allowed to cool to 29° for 3 hrs. Calculations showed that 97% of the theoretical amount of hydrogen was absorbed.

The acetic acid was distilled at atmospheric pressure through a 47 cm. Vigreux column. The residual material (V) was fractionally distilled into six fractions (27.5 g., 89%). Fractions 2-5 (20.8 g.) distilled as a colorless oil, b.p. 98-99° (1.30-1.80 mm.), n_D^{25} 1.4561-1.4558. [Lit.: b.p. 98-99° (1.2 mm.), n_D^{20} 1.4570 (9)].

cis-4-METHYLCYCLOHEXANECARBOXYLIC ACID (VII) was prepared by the hydrogenation of p-toluic acid similiar to the procedure given for the preparation of the cis acids (I, V).

p-Toluic acid (30.0 g., 0.220 moles) was dissolved in 150 ml. of distilled glacial acetic acid, mixed with 1.20 g. platinum oxide and hydrogenated between 60-28 and 60-43 psi. The temperature of the reaction mixture was raised from 25 to 80° over a period of 1 3/4 hrs. and maintained at 80-82° for an additional 1 1/2 hrs. No further hydrogen absorption was observed after 1 3/4 hrs. The reaction mixture was allowed to cool to 31° for 2 1/2 hrs. Calculations showed that 86% of the theoretical amount of hydrogen had been absorbed. The platinum oxide was then collected on a piece of filter paper and washed with about 10 ml. of glacial acetic acid. The wash was combined with the filtrate.

In an attempt to obtain more product (VII) and complete the hydrogenation, an additional 20.0 g. (0.147 moles) of p-toluic acid and 1.10 g. platinum oxide was added to the filtrate and wash. This was then hydrogenated between 60-30 and 60-45 psi. The temperature of the reaction mixture was raised from 25 to 77° over a period of 1 hr. and maintained at 75-77° for 1 3/4 hrs. No further hydrogen absorption was observed after 1 3/4 hrs. The reaction mixture was

allowed to cool to 28° over a period of 1 3/4 hrs. Hydrogen absorption was calculated as 98% of the theoretical amount.

The acetic acid was distilled from the filtrate at atmospheric pressure through a 47 cm. Vigreux column. The product (VII) was fractionally distilled at reduced pressure into six fractions (49.1 g., 94%). The latter five fractions (46.5 g.) distilled as a colorless oil, b.p. 96.5-98° (1.25-1.70 mm.), n_D^{25} 1.4581-1.4580. [Lit.: b.p. 128-130° (13 mm.), n_D^{16} 1.4605 (11)].

trans-4-METHYLCYCLOHEXANECARBOXYLIC ACID (VIII) was prepared by the method of Delephine and Badoche (11).

cis-4-Methylcyclohexanecarboxylic acid [VII, 24.0 g., 0.169 moles, b.p. 98° (1.60-1.70 mm.), n_D^{25} 1.4580] was converted to its trans isomer (VIII) by heating under reflux at about 240° with anhydrous hydrogen chloride bubbling gently through the equilibrium mixture. At the end of 4 hrs. the reaction mixture was cooled and an oily solid resulted. The oily solid was dissolved in petroleum ether (60-110°), and the solution was heated on a steam bath until moist blue litmus paper gave no color change when placed in the effluent vapors. Upon crystallization of the resulting oil (A), two fractions (14.1 g.) were obtained: Fraction 1, m.p. 82-101°, Fraction 2, m.p. 75-98°. Both fractions had a very pungent odor. By placing a piece of moist blue litmus paper in the vapor above the solid, it was shown that not all of the hydrogen chloride had been removed from the product. The fractions were combined, dissolved in 50 ml. ether and washed with 50 ml. distilled water. Evaporation of some of the ether and subsequent crystallization afforded two fractions:

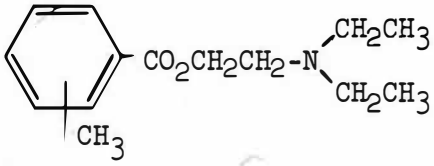
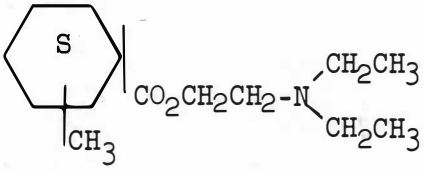
B (8.2 g.), m.p. 102-109°; C (1.8 g.), m.p. 105-110°. [Lit.: m.p. 111° (11)]. Material obtained from further crystallization of oil (A) was combined with the filtrate of C. The ether was removed, and this oil was crystallized from pentane giving a third fraction D (1.4 g.) m.p. 85-100°.

Preparation of 2-Diethylaminoethyl Esters

The structures listed in Table II appear in the experimental discussion which follows.

TABLE II

DESIGNATION OF THE AMINOESTER STRUCTURES

General structure	Structure number(s)	Methyl group position	Relative configuration of substituents
	IXa[1], IXb	2	---
	X	3	---
	XI	4	---
	XIIa, XIIb, XIIc	2	cis
	XIII	2	trans
	XIV	3	cis
	XV	4	cis
	XVI	4	trans

(1) The letter has been introduced to distinguish between different experiments for preparing the same compound.

2-DIETHYLAMINOETHYL-o-TOLUATE (IXa) was prepared by the Schotten-Baumann method (33).

A solution of 30 ml. (0.41 mole) of thionyl chloride (Baker, purified)

in 25 ml. of dry benzene was added to a solution of 40.0 g. (0.294 moles) of o-toluic acid in 50 ml. of dry benzene. One hour was required for the addition while the reaction mixture was being warmed. The reaction mixture was then heated slowly over a period of 1 hr. until it began refluxing. Heating under reflux was continued for 5 hrs. until no hydrogen chloride was being evolved. The reaction mixture was allowed to stand overnight at room temperature. Removal of the benzene and excess thionyl chloride was effected by distillation. The residue was fractionally distilled under reduced pressure into four fractions through a short Vigreux column. Fractions 1 and 4 were pale yellow. Fractions 2-3 (20.4 g., 45%) distilled as a colorless liquid, b.p. 83-85° (7-5 mm.). [Lit.: b.p. 99-100° (14 mm.) (2)] .

Sixteen grams of dark residue remained from the distillation which later solidified. The residue was decolorized with carbon and recrystallized twice from absolute ethanol. This purified residue had a melting point of 38-39° which corresponded to the melting point of the anhydride of o-toluic acid. [Lit.: b.p. 220-221° (11 mm.), m.p. 39° (2)] .

Fifty milliliters (0.38 moles) of freshly distilled 2-diethylaminoethanol was added in small portions with shaking and cooling to 23.8 g. (0.153 moles) of o-toluoyl chloride. A solid mass resulted and it was necessary to add 50 ml. anhydrous ether to facilitate further mixing of the reactants. The reaction mixture was allowed to stand at room temperature for 18 hrs. Saturated sodium carbonate solution (100 ml.), 50 ml. distilled water and 25 ml. ether were added to the reaction mixture. The ether solution of the product and the aqueous layer were separated, and the aqueous layer was extracted with 30 ml. of ether. The ether

extracts were combined and washed with two 50-ml. portions of distilled water. After drying the ether solution with anhydrous sodium sulfate, the ether was removed. The residue was then fractionally distilled under reduced pressure into four fractions. The latter three fractions (IXa, 31.0 g., 75%) distilled as a colorless oil, b.p. 133-135.5° (1.90-2.15 mm.), n_D^{25} 1.5021-1.5020.

2-DIETHYLAMINOETHYL-cis-2-METHYLCYCLOHEXANECARBOXYLATE (XIIa) was prepared by the hydrogenation of the ester (IXb) by the method of Tilford, VanCampen and Sheldon (31). The ester (IXb) was prepared in a manner similiar to that described for the ester (IXa).

Thionyl chloride (15 ml., 0.21 moles) was added to a solution of o-toluic acid (13.6 g., 0.100 mole, recrystallized from benzene) in 20 ml. dry benzene. Heat was slowly applied to the reaction mixture for 2 hrs. until refluxing occurred. The solution was heated under reflux for an additional 1 1/2 hrs. until no further hydrogen chloride was being evolved. By setting the condenser down, the benzene and excess thionyl chloride were removed by distillation at atmospheric pressure. The crude o-toluoyl chloride was distilled under reduced pressure into three fractions. The latter two fractions (8.8 g., 57%) distilled as a clear liquid, b.p. 91-96.5° (9 mm.).

o-Toluoyl chloride (8.8 g., 0.057 moles) was dissolved in 20 ml. dry benzene. This solution was added in portions with shaking and cooling to a solution of 15 ml. (0.11 mole) of 2-diethylaminoethanol in 20 ml. dry pyridine. The addition was completed within 1 hr., and the reaction mixture was then allowed to stand at room temperature for 16 hrs. The reaction mixture was extracted with two 40-ml. portions of

water leaving a benzene solution of the crude product. The combined aqueous extracts were made alkaline to litmus with 10% sodium hydroxide, and extracted with 30 ml. benzene. The two benzene solutions were combined and dried over anhydrous sodium sulfate. Benzene and pyridine were distilled from the dried benzene solution at atmospheric pressure. The residue was fractionally distilled under reduced pressure into five fractions. The latter three fractions (IXb, 9.8 g., 74%) distilled as a colorless oil, b.p. 140-142° (2 mm.), n_D^{24} 1.5038.

2-Diethylaminoethyl-o-toluate (IXb, 9.8 g., 0.042 moles) was dissolved in 60 ml. of reagent grade glacial acetic acid, mixed with 0.31 g. platinum oxide and hydrogenated between 60-54 1/4 and 60 1/4 - 52 psi. The temperature of the reaction mixture was raised from 25 to 92° over a period of 1 1/4 hrs. and was maintained at 92° for 1 hr. The reaction mixture was cooled to room temperature during a period of 1 hr. and then reheated to 87° over a period of 3/4 hr. After the temperature had been maintained between 87-89° for 2 hrs., the reaction mixture was allowed to cool and remain on the apparatus overnight (16 1/2 hrs.). Although the reaction mixture had been under the pressure of hydrogen a total of 22 1/2 hrs., only a negligable amount of hydrogen was absorbed during the final 16 hrs. The hydrogen uptake was 100% of the theoretical value.

The platinum oxide was recovered and washed. The acetic acid was distilled from the solution under reduced pressure (100 mm.). The residue was fractionally distilled under reduced pressure into four colorless fractions. Further distillation data is tabulated below.

Fraction number	Weight g.	b.p. (1 mm.)	n_D^{22}
3	1.4	74-116°	1.4570
4	2.4	116-118	1.4609
5	3.0	118	1.4602
6	1.6	118	1.4599

2-DIETHYLAMINOETHYL-cis-2-METHYLCYCLOHEXANECARBOXYLATE (XIIb) was prepared by the method of Schotten-Baumann (33).

Eastman practical grade (#P246) thionyl chloride was freshly distilled (b.p. 76°, $n_D^{22.5}$ 1.5167) for the preparation of the acid chloride of the cis-2-methyl acid (I). Thionyl chloride (19 ml., 0.26 moles) was added in two portions to a solution of cis-2-methylcyclohexanecarboxylic acid (I, 25.0 g., 0.176 moles, $n_D^{22.5}$ 1.4630) in 10 ml. dry benzene. The reaction mixture was warmed slowly to 95° over a period of 2 hrs. and heated under reflux for an additional hour until very little hydrogen chloride was being evolved. Benzene and excess thionyl chloride were distilled from the reaction mixture over a period of 1 hr. with the temperature of the residue being kept between 108-134°. The crude cis-2-methylcyclohexanecarbonyl chloride was then distilled under reduced pressure into three fractions. The latter two fractions (25.8 g., 90%) distilled as a clear liquid, b.p. 77.5-80° (10 mm.). [Lit.: b.p. 80° (16 mm.) (3)].

The cis-2-methylcyclohexanecarbonyl chloride (25.0 g., 0.155 moles) was dissolved in 20 ml. dry benzene. This solution was added in portions with shaking and cooling to a solution of 32 ml. (0.24 moles) of 2-diethylaminoethanol in 40 ml. dry pyridine. The addition was completed within

1 hr., and the reaction mixture was allowed to stand at room temperature for 19 hrs. Fifty-five milliliters of distilled water was added to the reaction mixture. The benzene layer was separated, and the aqueous layer extracted with two portions of ether, 50 ml. and 40 ml. respectively. In order to insure the complete recovery of the product (XIIb), 5% sodium hydroxide was added to the aqueous layer. An oil appeared, which was separated from the aqueous layer. The alkaline aqueous layer was extracted with 50 ml. ether. The four non-aqueous extracts were combined and distilled at atmospheric pressure to remove the ether, benzene and pyridine. The residue was fractionally distilled under reduced pressure into five fractions. A summary of the properties of the distillate are given below.

Fraction number	Weight g.	b.p.	P mm.	$n_D^{25.5}$
4	2.0	49-135	2.35-3.00	1.4402
5	1.9	135-136.5	3.00-3.20	1.4580
6	5.8	136.5-138	3.20-3.45	1.4587
7	14.6	138-139	3.45-3.70	1.4571
8	7.3	139-139.5	3.70-3.80	1.4563

Subsequent esterifications were carried out by the method of Rabjohn (26). This method involves the condensation of the potassium salt of the carboxylic acid and 2-chlorotriethylamine with the elimination of potassium chloride.

In general, the following procedure was used. The starting acid was added to a 500 ml. round-bottom flask equipped with a Dean-Stark water trap and condenser. The acid was dissolved in dry toluene

(250 ml. per 0.1 mole of acid) and mixed with two equivalents of potassium hydrogen carbonate. To prepare the potassium salt of the acid, the reaction mixture was heated under reflux for 1-4 hrs. After cooling, one equivalent of 2-chlorotriethylamine hydrochloride (recrystallized from absolute ethanol-absolute ether) was added to the reaction mixture and heated under reflux for an additional 20-25 hrs. The reaction mixture was allowed to cool, and the gelatinous precipitate of potassium chloride was removed from the toluene solution by filtration. The gelatinous precipitate was washed twice with about 50 ml. portions of dry toluene, and the wash was combined with the filtrate. Recovery of the product from the filtrate was effected by either distillation or preparation of a hydrochloride derivative.

The acids to which the above method was applied are listed in Table III along with the experimental conditions and yields.

2-DIETHYLAMINOETHYL-trans-2-METHYLCYCLOHEXANECARBOXYLATE (XIII) was recovered by distillation. The largest portion of the toluene was removed by distillation at atmospheric pressure through a 47 cm. Vigreux column. After the remainder of the toluene had been removed under reduced pressure, the residue was fractionally distilled by further lowering of the pressure. Six fractions (22.7 g., 85%) were obtained. The latter five fractions distilled as a colorless oil, b.p. 114.5-115.8° (2.35-2.60 mm.), n_D^{25} 1.4542-1.4541.

2-DIETHYLAMINOETHYL-cis-3-METHYLCYCLOHEXANECARBOXYLATE (XIV) was recovered in the same manner as the ester (XIII). Five fractions (19.5 g., 81%) were obtained. The latter four fractions distilled as a colorless oil, b.p. 114-114.3° (1.50-1.70 mm.), n_D^{25} 1.4542-1.4539.

TABLE III

ESTERIFICATION DATA FOR ESTERS PREPARED BY THE METHOD OF RABJOHN

Acid			I[1] hr.	II[2] hr.	Product yield			
Number	Weight g.	Moles			Number	Ester weight g.	Hydrochloride weight g.	Percent
m-toluic	13.6	0.100	3	23 1/4	X	---	22.6	79
p-toluic	13.6	0.100	1 1/2	26 1/2	XI	---	24.8	89
I	4.3	0.030	3	20	XIIc	---	6.6[3]	80
II	15.7	0.111	4	24 1/2	XIII	22.7	---	85
V	14.2	0.100	2	21	XIV	19.5	---	81
VII	14.2	0.100	2	21 1/4	XV	11.2	---	46
VIII	10.3	0.0725	1 1/4	24 1/2	XVI	12.8	---	73

(1) Reflux time used to prepare potassium salt.

(2) Reflux time used to prepare ester.

(3) m.p. 100-106°.

2-DIETHYLAMINOETHYL-cis-4-METHYLCYCLOHEXANECARBOXYLATE (XV) was recovered from its impure hydrochloride. Two samples of the hydrochloride had been obtained by Method B (p. 29) and recrystallized from absolute ethanol - absolute ether, but the bulk of the material had a melting point of 110-158°.

To recover the ester (XV), the impure solid hydrochlorides and their filtrates of recrystallization were recombined, and the solvents were removed. The residue was treated with 100 ml. of 10% sodium hydroxide and 100 ml. of ether. The ether extract was washed with two 50-ml. portions of distilled water and dried with anhydrous magnesium sulfate. After the drying agent was removed, the ether was evaporated. The residue was then fractionally distilled under reduced pressure into six fractions. Fraction 1 [b.p. 26° (2.80-2.00 mm.), n_D^{25} 1.4343] was distilled and removed from the distillation apparatus. Fractions 2-6 [XV, 11.2 g., 46% based on the acid (VII)] were obtained by further fractional distillation of the residue. The latter five fractions distilled as a colorless oil, b.p. 115-116.5° (1.82-1.92 mm.), n_D^{25} 1.4551-1.4550.

Two drops of fraction 1 were tested with about 5 ml. of 2% alcoholic silver nitrate. Silver chloride was precipitated indicating fraction 1 contains the chlorine atom. An infrared spectrum of fraction 1 was obtained. The spectrum showed the absence of an alcohol absorption at about 3300 cm^{-1} and an ester or carboxylic acid absorption at about 1725 cm^{-1}. Medium intensity absorptions at 775 and 715 cm^{-1} indicate the presence of a carbon-chlorine bond. The conclusion was made that fraction 1 was mainly 2-chlorotriethylamine and that the esterification reaction was incomplete.

2-DIETHYLAMINOETHYL-trans-4-METHYLCYCLOHEXANECARBOXYLATE (XVI) was also recovered in the same manner as the ester (XIII). Six fractions (12.8 g., 73%) were obtained. They distilled as a very pale yellow oil, b.p. 118-119° (2.15-2.40 mm.), n_D^{25} 1.4533-1.4530.

Preparation of Hydrochlorides

Three methods were used to prepare the hydrochloride derivatives of aminoesters. METHOD A was the procedure of Ziegler and Herbst (36) in which ethereal hydrogen chloride was added dropwise with shaking to a dried ether solution of the aminoester. Ethereal hydrogen chloride was added until the supernatant liquid was distinctly acidic when tested with Congo red paper. The aminoester hydrochloride was recovered by vacuum filtration and washed with a small portion of anhydrous ether.

METHOD B was used by Rabjohn (26) to recover aminoester hydrochlorides containing an benzene ring. In this method anhydrous hydrogen chloride was bubbled slowly through a dry toluene solution of the aminoester while the reaction mixture was being shaken. Addition was continued until the supernatant liquid was distinctly acidic to Congo red paper. The hydrochloride derivative was recovered by vacuum filtration and washed with a small portion of dry toluene. This method was satisfactory for the preparation of the toluate ester hydrochlorides, but the ester hydrochlorides derived from saturated acids precipitated as a difficult-to-filter gel. When this type of gel was obtained, addition of anhydrous ether to the toluene-aminoester hydrochloride mixture improved the filterability of the aminoester hydrochloride.

METHOD C is similiar to method B except anhydrous ether was used as a solvent in place of toluene.

After the crude hydrochloride was obtained, it was dried under water pump vacuum for 1-2 hrs. A water bath (ca. 70°) was used to warm the hydrochloride and was allowed to cool during the time of drying. The recrystallizations gave a material whose melting points agreed within 0.5°. Recrystallizations were carried out by dissolving the hydrochloride on a steam bath in a volume (ml.) of absolute ethanol of about three times the weight (g.) of the hydrochloride. Anhydrous ether was added slowly to the solution until a precipitate appeared. The precipitate was then redissolved with absolute ethanol. A stopper was placed on the flask, and the solution was allowed to cool to room temperature before placing it in the refrigerator. The hydrochlorides were recovered by vacuum filtration and were washed with anhydrous ether. Drying of the recrystallized hydrochlorides was accomplished in the same manner as the crude hydrochlorides.

Analytical samples of the hydrochlorides were prepared by recrystallization from absolute ethanol - absolute ether. They were dried under water pump vacuum for about 20 min. and placed in a desiccator containing phosphorus pentoxide for 1-2 days. The carbon-hydrogen analyses were carried out by the Galbraith Laboratories, Inc., Knoxville, Tennessee.

Table IV contains data pertinent to the preparation, purification and analysis of the various hydrochlorides.

TABLE IV

PREPARATION, PURIFICATION AND ANALYSIS OF HYDROCHLORIDES

Amino-ester structure number	Crude hydrochloride			Purified hydrochloride m.p.	Analysis, %[1]			
	Method prepared	m.p.	Number of recrystal-izations		Calculated[2]		Found	
					C	H	C	H
IXa	A	112-123°	3	134.5-135.5°	61.86	8.16	62.01	8.24
X	B	155-156	1	155.5-156.5	61.86	8.16	62.01	8.15
XI	B	149-150	1	149-150	61.86	8.16	62.02	8.08
XIIa	A	105-109	4	120-120.5	---	---	---	---
XIIc	A[3]	100-106	4	119-120.5[4]	60.52	10.16	60.62	10.03
XIII	C	110-117	2	117-117.5	60.52	10.16	60.30	9.96
XIV	C	90-96	3	100-101	60.52	10.16	60.59	10.21
XV	C	106-113	5	123.5-124.5	60.52	10.16	60.61	10.26
XVI	C	154-155	1	154-155	60.52	10.16	60.76	10.16

(1) The melting points of the analytical samples were the same as the purified hydrochloride except for XIIc (m.p. 118.5-119°) and XVI (m.p. 154.5-155.5°).

(2) Analyses of IXa-XI were calculated for $C_{14}H_{22}ClNO_2$. Analyses of XIIa-XVI were calculated for $C_{14}H_{28}ClNO_2$.

(3) An attempt to prepare the hydrochloride of XIIb by Method B was unsuccessful.

(4) A melting point of 111-116° was determined for a mixture of equal amounts of the purified hydrochlorides XIIc and XIII.

Instrumental Analysis

INFRARED SPECTRA were obtained for the acids and for the aminoesters. The spectra were obtained with a Perkin-Elmer Model 21 spectrophotometer and assignment of bands was made according to Jones and Sandorfy (17).

Spectra of the acids were obtained with 5% carbon tetrachloride solutions with the solution placed in a 0.1 mm. sodium chloride cavity cell. The characteristic absorbances which were common to the five acids are listed in Table V.

Of particular interest in this study is the comparison of the spectra of the cis and trans isomers. The notable differences are listed below.

trans-2-METHYL ACID (II) vs. cis-2-METHYL ACID (I)

1) A peak at 1209 cm^{-1} (m, s)* in II appeared as three peaks (m, p) in I at 1230, 1215 and 1197 cm^{-1}.
2) A peak at 1145 cm^{-1} (m, s) in II was resolved into two peaks (w, s) in I at 1158 and 1132 cm^{-1}.
3) A peak at 854 cm^{-1} (w, s) in II was absent in I.

cis-4-METHYL ACID (VII) vs. trans-4-METHYL ACID (VIII)

1) A peak at 1341 cm^{-1} (w, s) in VII was not resolved from a peak at 1310 cm^{-1} (m, s) in VIII.
2) A peak at 1240 cm^{-1} (s, b) in VII appeared as three peaks at 1295 (m, p), 1263 (m, s) and 1215 cm^{-1} (m, s) in VIII.
3) A peak at 1145 cm^{-1} (m, s) in VII was resolved into two peaks (w, s) at 1166 and 1039 cm^{-1} in VIII.

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* Peak characteristics are given as (A, S), where A is the relative intensity of absorbance defined as strong (s), medium (m) or weak (w), and S is the peak shape defined as broad (b), poor resolution (p) or sharp (s).

TABLE V

CHARACTERISTIC INFRARED ABSORPTIONS OF THE CIS AND TRANS METHYLCYCLOHEXANECARBOXYLIC ACIDS AND THEIR 2-DIETHYLAMINOETHYL ESTERS

cis and trans Methylcyclohexanecarboxylic Acids		
Wave number cm^{-1}	Peak characteristics	Group
3040	s, b	-OH of $-CO_2H$
2900	s, b	$\rightarrow CH$, $\rangle CH_2$, $-CH_3$
2660-2640	s, b	-OH of $-CO_2H$
1700	s, b	$\rangle C{=}O$ of $-CO_2H$
1460-1453	m, s	$\rangle CH_2$
1425-1420	m, s	-OH of $-CO_2H$ dimer
1388-1382	w, s	$-CH_3$
940-935	s, b	-OH of $-CO_2H$ dimer
cis and trans 2-Diethylaminoethyl-Methylcyclohexanecarboxylates		
2920	s, s	$\rightarrow CH$, $\rangle CH_2$, $-CH_3$
1732-1727	s, s	$\rangle C{=}O$ of $-CO_2-$
1458-1453	s, s	$\rangle CH_2$
1390-1384	s, s	$-CH_3$
1260-1245	m or w, p	$-CH_3$
1175	s, b	$\rightarrow CN\langle$
1143-1135	s, p	$-CH_3$
1090-1083	s, p	$\rightarrow CN\langle$
1075-1068	s, p	$\rightarrow CN\langle$
1047-1037	m or w, p	$\rightarrow CN\langle$
1012-997	m or w, p	Sub. ?

No comparison of the cis-3-methyl acid (V) was made, since the trans-3-methyl acid (VI) was not available. However, the spectrum of the cis-3-methyl acid (V) showed marked similarity to the spectrum of the trans-2-methyl acid (II).

A similar comparison of the esters (XIIa*, XIII, XIV, XV, XVI) was made. Their spectra were obtained with the liquid aminoester placed in a sodium chloride cell of 0.02 mm. thickness. The characteristic absorbances which were common to the five esters are listed in Table V.

A comparison of the aminoester spectra of the cis and trans isomers was made.

trans-2-METHYL ESTER (XIII) vs. cis-2-METHYL ESTER (XIIa)

1) A peak at 1233 cm^{-1} (w, s) in XIII was absent in (XIIa).
2) A marked increase in intensity at 731 cm^{-1} (w, b) in XIII was observed.
3) Slight increases in intensity of peaks were observed in XIII at 1384, 1329, 1256 and 1135 cm^{-1} as opposed to similiar peaks in XIIa.

trans-4-METHYL ESTER (XVI) vs. cis-4-METHYL ESTER (XV)

1) A peak at 1325 cm^{-1} (w, b) in XVI appeared as two peaks (w, s) at 1348 and 1302 cm^{-1} in XV.
2) An absorption at 1010 cm^{-1} (w, p) in XVI appeared where no absorption had occured in XV.
3) A peak at 973 cm^{-1} (w, s) in XVI was absent in XV.
4) Slight increases in intensity of absorption were observed in XVI at 1384 and 1252 cm^{-1} as opposed to similiar peaks in XV.

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* Fraction 5 of the cis-2-methyl ester (XIIa) was used.

A comparison of the spectra of the cis-2-methyl esters (XIIa, XIIb) and the trans-2-methyl ester (XIII) was made. Comparison showed that three fractions of the ester (XIIb) contained the trans-2-methyl ester (XIII) and that the concentration of the trans ester (XIII) increased with increasing boiling point.

Although the spectra of the cis-trans isomers showed some differences, no logical pattern of differentiating their spectra could be established. Some differences in the spectra of the acids were observed, and these differences were generally associated with the reported methyl-rocking frequencies (1250, 1210-1200, 1170, 1155-1135, 1141-1132 cm^{-1}). However, the introduction of additional methyl groups interfered with the observation of these differences in the spectra of the aminoesters.

NUCLEAR MAGNETIC RESONANCE spectra were obtained for the hydrochlorides of the purified aminoesters (XIIb-XVI). Dr. George Slomp of the Upjohn Co., Kalamazoo, Michigan, obtained the spectra with a Varian A-60 Spectrometer and also made the assignment of peaks. The spectra were compared qualitatively to the spectra of the dimethylcyclohexanes obtained by Musher (24).

Musher demonstrated that the ring hydrogens of 1,2-trans-, 1,3-cis- and 1,4-trans-dimethylcyclohexane show a broad peak, while the ring hydrogens of the 1,2-cis-, 1,3-trans- and 1,4-cis-dimethylcyclohexanes show a relatively sharp peak. Similiar observations concerning peak shape were observed with the spectra of the aminoester hydrochlorides. If the comparison between the spectra of the dimethylcyclohexanes and the aminoester hydrochlorides (XIIb-XVI) was valid, then the cis and trans assignments were correct.

EVALUATION OF RESULTS

The methods of preparation and an evaluation of the purity of the various compounds are discussed in this section.

The three cis-methylcyclohexanecarboxylic acids were prepared by low pressure hydrogenation by using a procedure which has some advantages over previously reported procedures. A summary of the conditions which were used is given below as compared to previously reported methods.

References	Weight of acid g.	Weight of catalyst g.	Temperature	Pressure psi	Time required hr.
	30	1.2	60-90°	75-45	1-2
6, 9, 18, 21	10-15	0.5	100	15	5-6
7	15	3.3	room temp.	38-30	2 1/2

It can be seen that a shorter reaction time was effected for larger quantities of starting material by increasing the pressure and the amount of platinum oxide, without using an excessive amount of catalyst. In the hydrogenations carried out in this study, the observation was made that the rate of hydrogen absorption was quite rapid in the temperature range of 60-90° while the reaction mixture was being heated. When the maximum temperature was reached, the rate of absorption would drop rapidly, even if the theoretical amount of hydrogen had not been absorbed. This behavior was noted especially during several attempts to find the optimum conditions for the hydrogenation of o-toluic acid. The reason for this behavior was not apparent, but it seemed to be related to the purity of the acetic acid and the amount of catalyst

added initially.

An evaluation of the purity of the cis acids was made on the basis of refractive indexes. The refractive index of the cis-2-methyl acid (I) was lower (0.0003)* than the reported value, and the refractive index of the cis-3-methyl acid (V) was higher (0.0005) than the reported value. The reported values were based on the work of Macbeth and co-workers who purified the acids via their piperazine salts. Cooke and Macbeth (6) also showed that the cis-4-methyl acid (VII) contained traces of its trans epimer when the acid (VII) was prepared by hydrogenation using platinum oxide catalyst. The refractive index of the trans-2-methyl acid (II) was lower (0.0055) than its cis isomer (II), and the refractive index of the trans-3-methyl acid [VI, Lit.: n_D^{20} 1.4618, (15)] was higher (0.0048) than its cis isomer (V). On this basis the conclusion was made that the cis acids were probably contaminated with trace amounts of their trans isomers.

Attempts were made to prepare the trans acid (II) by the method of Cope, Fournier and Simmonds (7) and by refluxing the cis acid (I) with concentrated hydrochloric acid. No solid trans acid (II) could be isolated in these attempts. Attempted purification via its piperazine salt of the equilibrium mixture, which was obtained from refluxing the acid (I) with concentrated hydrochloric acid, was unsuccessful. Recrystallizations of the trans-2-methyl acid (II) and the trans-4-methyl acid (XIII) were slow and resulted in low yields of pure product. Therefore, it was felt that these acids, which were not absolutely pure, could be

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* A correction factor of -0.00034 per degree centigrade increase in temperature was determined for the acids.

used to prepare the aminoesters and the impurities could then be removed.

Attempts were made to obtain the trans-3-methyl acid (VI) from a mixture of the cis and trans isomers. The mixture was obtained from another source and was derived from the carbonation of the Grignard reagent of 3-methylcyclohexyl bromide. Several fractional distillations of the mixture were attempted using a column packed with Heli-Pack, but no pure trans-3-methyl acid (VI) could be obtained.

Several attempts were made to esterify the cis-2-methyl acid (I) by the Schotten-Baumann technique. Preparation of the ester of the cis-2-methyl acid (I) by using conditions which avoided isomerization (14, 21) was not satisfactory because of the low overall yield and contamination of the ester by what was assumed to be the anhydride of the cis acid (I). When more rigorous conditions were used the product was shown to be a mixture of isomers as demonstrated by the preparation of the ester (XIIb). Hydrogenation of the o-toluate ester (IXb) was used to prepare the cis ester (XIIa). Although this is a useful method for the preparation of the cis esters, no further study of this reaction was carried out.

A convenient way of preparing the aminoesters was by the use of the method reported by Rabjohn. In this method higher overall yields from the acids were obtained, and there was no evidence of extensive isomerization. The only evidence that any isomerization had occurred was implied by the number of recrystallizations which were necessary to purify some of the aminoester hydrochlorides. However, it is possible that this may be due to impure starting material, or some other impurity introduced during the esterification and hydrochloride preparation,

If the assumption that a narrow range (0.0003) of refractive indexes of the various fractions of a distilled aminoester is a sufficient criterion of purity, then the aminoesters which were recovered from esterifications by the method of Rabjohn are relatively pure. Distillation of a mixture of the isomeric 2-methyl esters (XIIb) was shown to give a relatively wide range of refractive indexes (0.0014). This fact supports the above assumption. On this basis, one would conclude that the cis-2-methyl ester (XIIa) prepared by hydrogenation of the o-toluate ester contained traces of the trans ester (XIII).

Purification of the aminoester hydrochlorides was effected by recrystallizations of the crude material until a constant melting point was obtained.

The acids and aminoesters were characterized by their common infrared absorptions. Differences in the infrared spectra due to the cis and trans isomers were noted. Analysis of the nuclear magnetic resonance spectra of aminoester hydrochlorides has provided evidence that the cis and trans assignments are correct. The purpose of examining these compounds by instrumental methods was to verify their absolute purity. This conclusion could not be reached on the basis of the infrared measurements because of the complexity of the spectra. There was no significant shift of the methyl group resonance frequency in the nuclear magnetic resonance spectra, so the absolute purity of the cis and trans ester hydrochlorides could not be proved.

SUMMARY

A review has been made of the methods of preparation of the cis and trans-methylcyclohexanecarboxylic acids. The pharmacological properties and methods of esterification of the 2-diethylaminoethyl ester of alkyl-substituted benzoic and cyclohexanecarboxylic acids have also been reviewed.

Five members of the cis and trans-methylcyclohexanecarboxylic acid series and their 2-diethylaminoethyl esters have been made. The esters have been characterized and further purified as their hydrochlorides. The 2-diethylaminoethyl-toluate hydrochlorides have also been prepared.

A procedure has been used in the hydrogenation of the toluic acids using platinum oxide catalyst which has some advantages over previously reported procedures. In the esterification of the cis and trans acids, it was shown that epimerization could not be avoided when the esters were prepared via the acid chlorides. A better method of esterification on the basis of overall yields and purity of the product was attained by the reaction of the potassium salt of the acid with 2-chlorotriethylamine.

The cis and trans esters have been characterized by their infrared absorptions, and their hydrochlorides have been examined by nuclear magnetic resonance.

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