THE 3-METHYLCYCLOPENTANE-1,2-DICARBOXYLIC ACIDS (NEPETIC ACIDS)

By

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THE 3-METHYLCYCLOPENTANE-1,2-DICARBOXYLIC ACIDS (NEPETIC ACIDS)

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CHAPTER I

INTRODUCTION AND HISTORICAL

The (3S)-methylcyclopentane-1,2-dicarboxylic acids were obtained as degradation products of the methylcyclopentane monoterpenoid nepetalactones (1a) and (1b) as shown in Fig. 1.[1] Nepetalactone is the major component and physiologically active constituent of the catnip plant Nepeta cataria L. Because these acids were first obtained from nepetalactone, they received the trivial name nepetic acids. Although (+)3e has not been obtained from nepetalactone, because it has the S configuration at carbon number three, it is also considered a nepetic acid.

There is also a set of four nepetic acids with the R configuration at carbon number three. These nepetic acids ((-)3a, (+)3c, (-)3e, (-)3g) have been synthesized from (+)-pulegone (2a) and are designated as nepetic acids of the pulegone series to distinguish them from those of the catnip series.[2]

The 3-methylcyclopentane-1,2-dicarboxylic acids will be referred to either as the nepetic acids with the 3S configuration (catnip series) or as the nepetic acids with the 3R configuration (pulegone series). Naming of the individual isomers within a series will be done by giving the

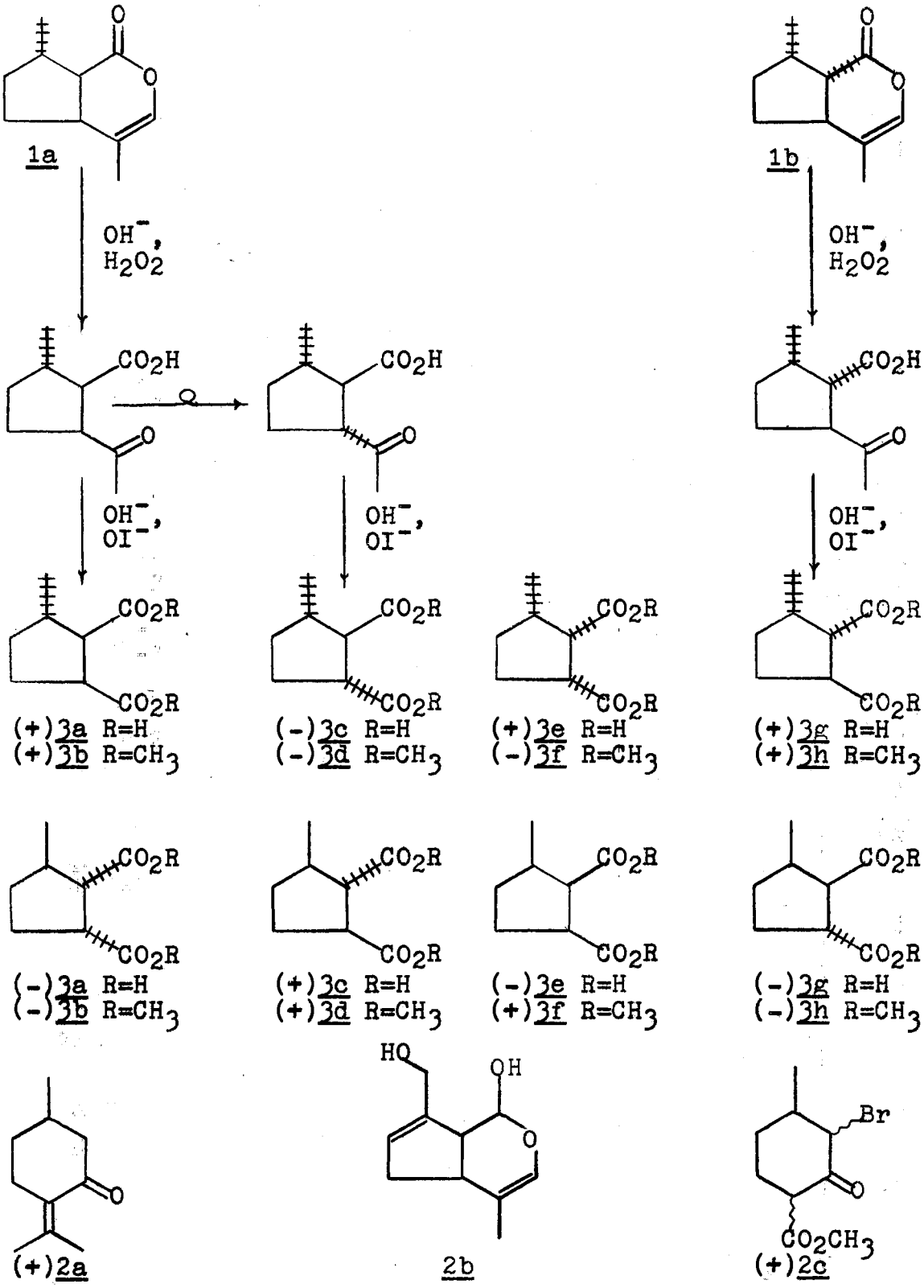


Fig. 1. Synthesis of Nepetic Acids from Various Starting Compounds

relation of the reference ultimate functional group to the second functional group first and the relation of the reference group to the methyl group second.[3] Therefore, nepetic acid (-)3c is designated as the trans, cis-nepetic acid (catnip series) and (-)3g is designated as the trans, trans-nepetic acid (pulegone series).

The nepetic acids are important in the determination of the stereochemistry of methylcyclopentane terpenoids which can be degraded to one of the possible nepetic acids. Some of these methylcyclopentane terpenoids include genipin,[2] pelargone,[4] and monotropein.[5]

The synthesis of the series of (3R)-methylcyclopentane-1,2-dicarboxylic acids shown in Fig. 1 from (+)-pulegone (2a) was completed by P. Hanel to affirm the absolute configuration of genipin (2b) and to compare these optically active 3-methylcyclopentane-1,2-dicarboxylic acids with acids obtained from other natural products.[2,6] The proof of the cis configuration at the ring junction of 2b was accomplished by its conversion to (-)-cis, cis-3-methylcyclopentane-1,2-dicarboxylic acid (3e), and isomerization of (-)3e to (-)3g and comparison with its antipode (+)3g.[7,8] Also obtained from 2b was the nepetic acid (+)3a, the identity of which was established by comparison with (+)3a obtained from nepetalactone.[6,9]

The (3R)-methylcyclopentane-1,2-dicarboxylic acids were obtained by a Favorskii rearrangement of (+)-methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (2c). These

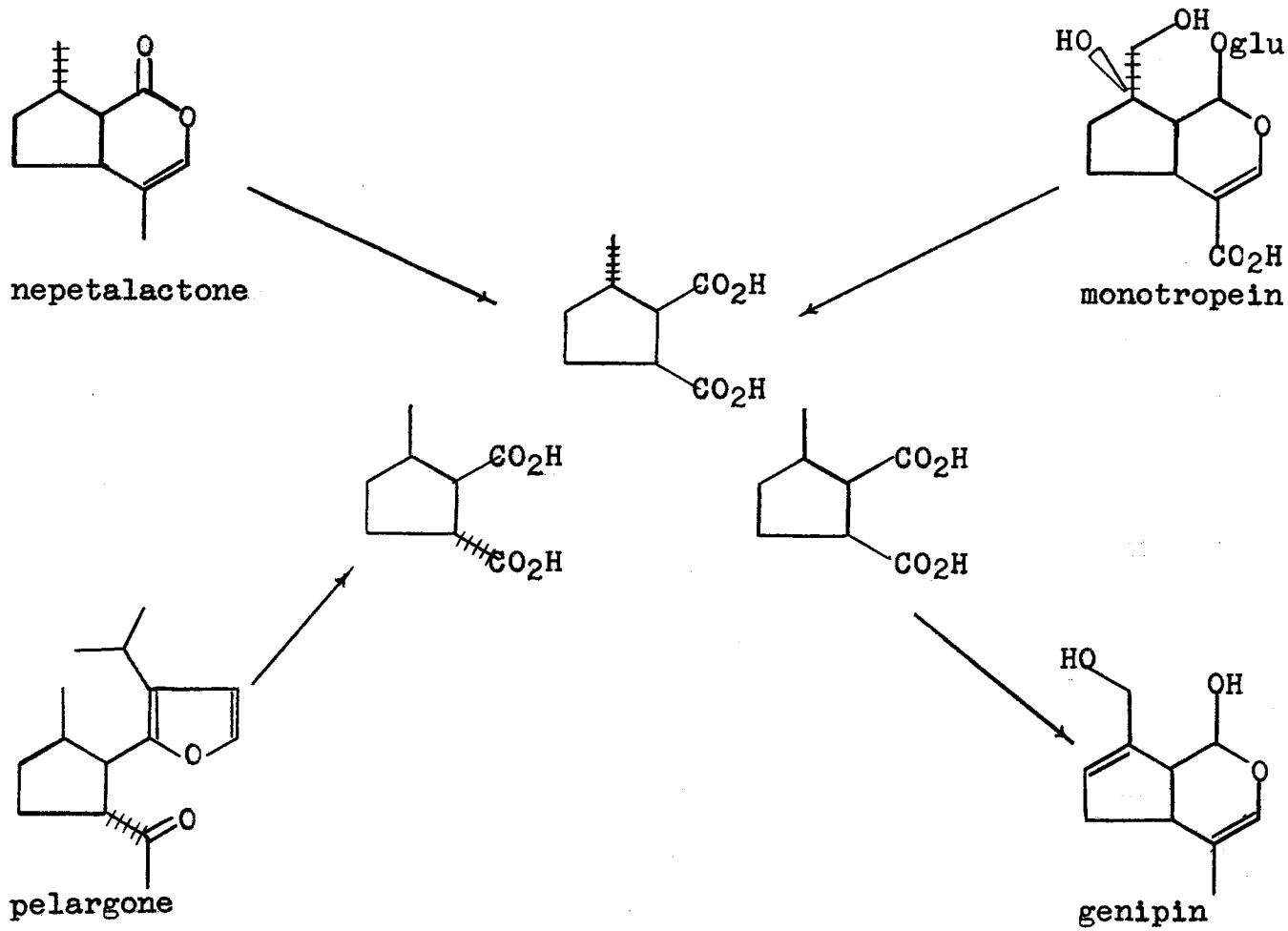


Fig. 2. Synthesis of Nepetic Acids from Methylcyclopentane Monoterpenoids

results prompted the synthesis of the (3S)-methylcyclopentane-1,2-dicarboxylic acids with the hope of varying the products obtained by changing the reaction conditions for the Favorskii reaction. Because the 3-methylcyclopentane-1,2-dicarboxylic acids could be abundantly produced, it became of interest to prepare and study various imide derivatives of these acids.

The Favorskii reaction is a base-catalyzed skeletal rearrangement of α-halo ketones, and various mechanisms have been considered to explain the products of this reaction. The most commonly proposed explanations employ the "cyclopropanone intermediate", the "zwitterion intermediate", and the "semibenzilic" mechanisms.

The "cyclopropanone intermediate" mechanism involves the removal of a proton α to the carbonyl group by base, the resulting carbanion being stabilized by pi orbital overlap. Then an S_N2 intramolecular displacement of halogen by the electron-rich carbon atom of the carbanion produces a cyclopropanone intermediate which is subsequently cleaved by base. This cyclopropanone intermediate was proposed by Loftfield after labelling studies indicated that the α and α′ carbon atoms of 2-chlorocyclohexanone became equivalent during the course of the Favorskii rearrangement,[10] as shown in Fig. 3.

In contrast the initially formed carbanion may spontaneously lose halide ion to form the "zwitterion" which in turn collapses to the "cyclopropanone" intermediate or

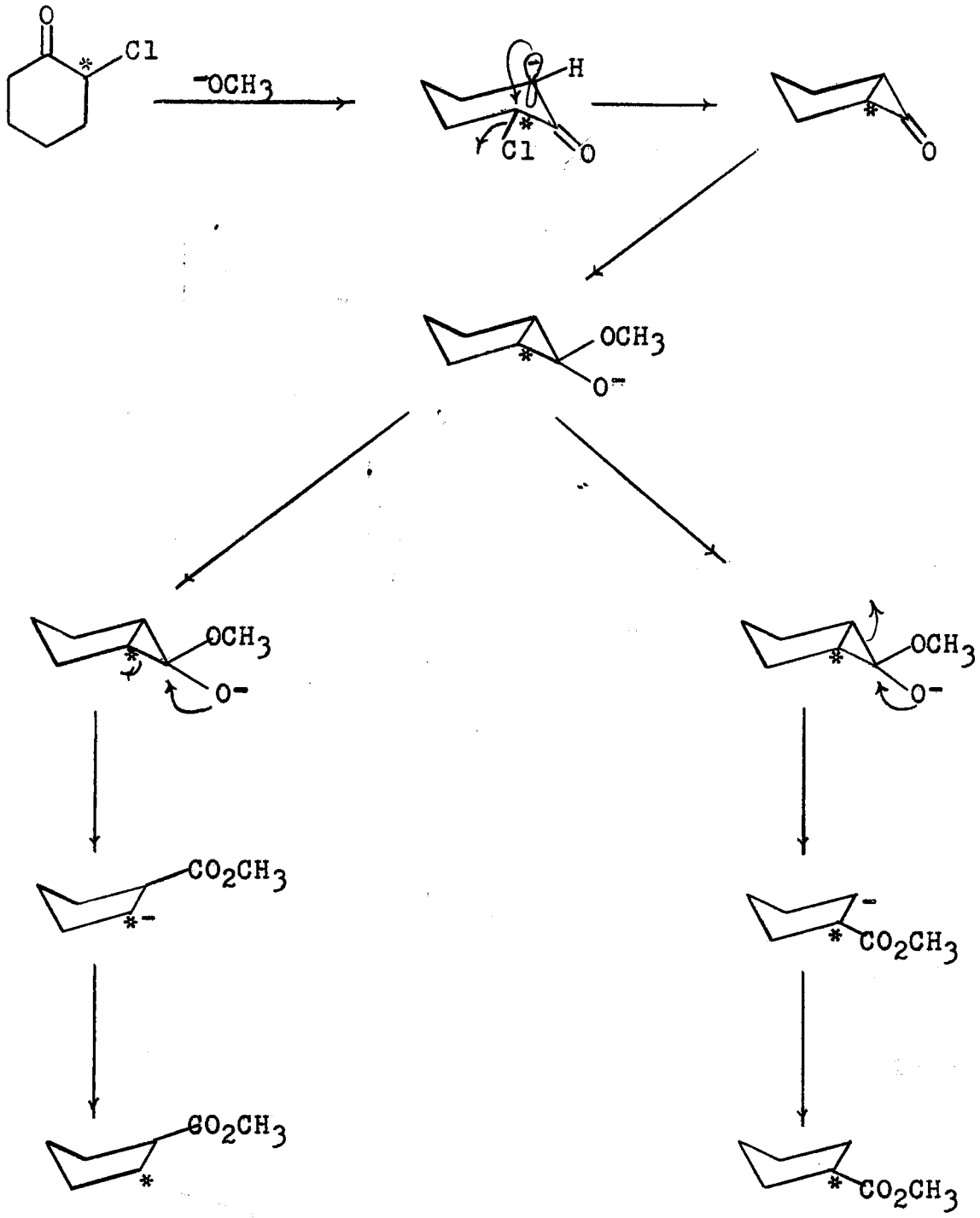


Fig. 3. Favorskii Rearrangement: Cyclopropanone Mechanism

reacts with methoxide to form a methoxy ketone as shown in Fig. 4.[11]

The semibenzilic mechanism appears to operate when the α-halo ketone bears no α′-hydrogen, when the α′-hydrogen is relatively nonacidic, or when steric or strain factors inhibit cyclopropanone formation.[12] In this mechanism, shown in Fig. 5, a base adds to the carbonyl group to give an intermediate species which undergoes rearrangement and loss of halide ion.

The formation of a cyclopropanone intermediate is supported by the synthesis of cyclopropanone derivatives using conditions similar to those for the Favorskii rearrangement. Breslow and co-workers treated α,α′-dibromodibenzyl ketone with triethylamine and obtained good yields of diphenylcyclopropenone. Also, 2,8-dibromocyclooctanone was heated with triethylamine and cycloheptenocyclopropenone was obtained.[13] Pazos and Greene reported the synthesis of 2,3-di-t-butylcyclopropanone from α-bromodineopentyl ketone in the presence of base[14] (Fig. 6).

It has been shown by Turro and Hammond that cyclopropanones in base will form products analogous to those obtained from the Favorskii rearrangement.[15] Treatment of tetramethylcyclopropanone and its methyl hemiketal under appropriate conditions resulted in Favorskii products (Fig. 7).

Because the zwitterion (Fig. 4) is thought to collapse to a cyclopropanone intermediate, the determination of

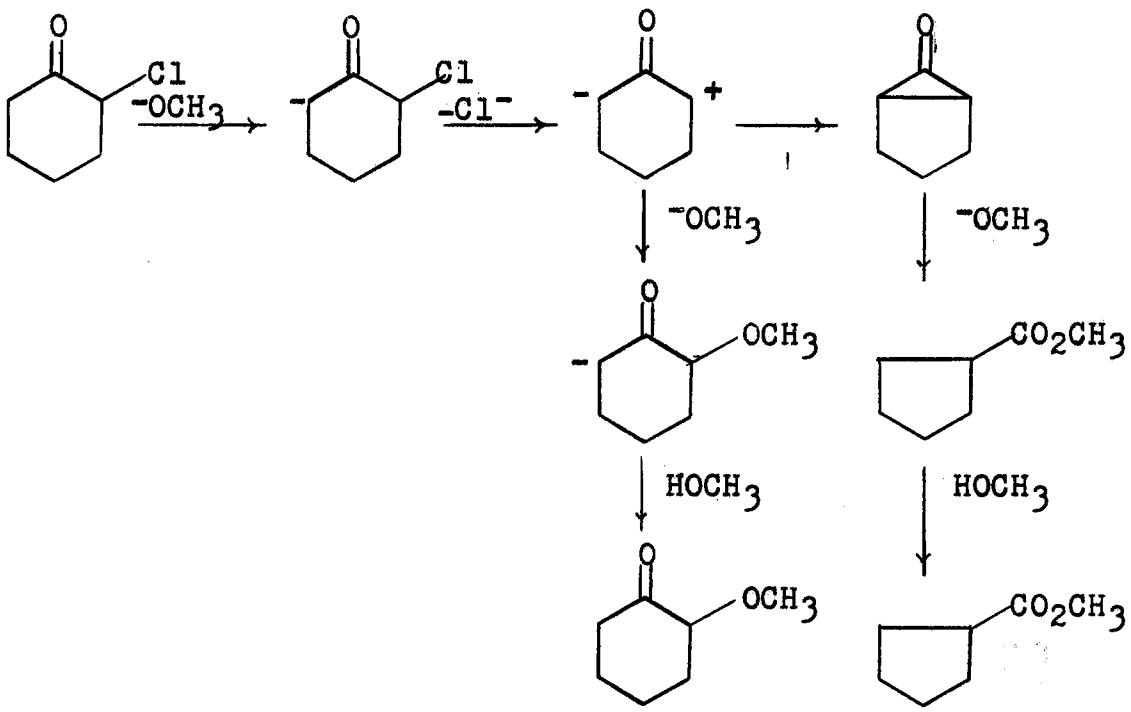


Fig. 4. Favorskii Rearrangement: Zwitterion Mechanism

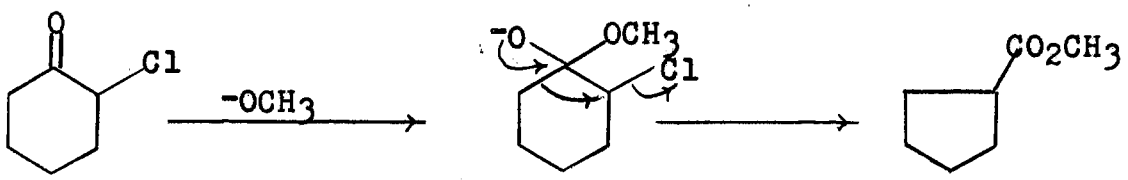


Fig. 5. Favorskii Rearrangement: Semibenzilic Mechanism

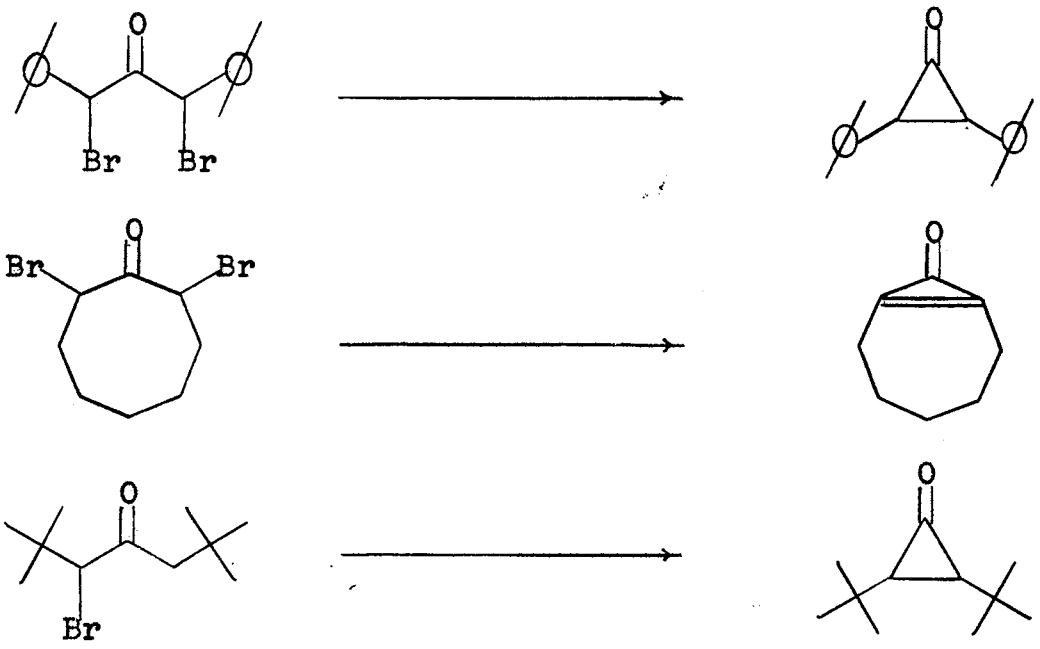


Fig. 6. Cyclopropanone Derivatives from Favorskii-Type Reactions

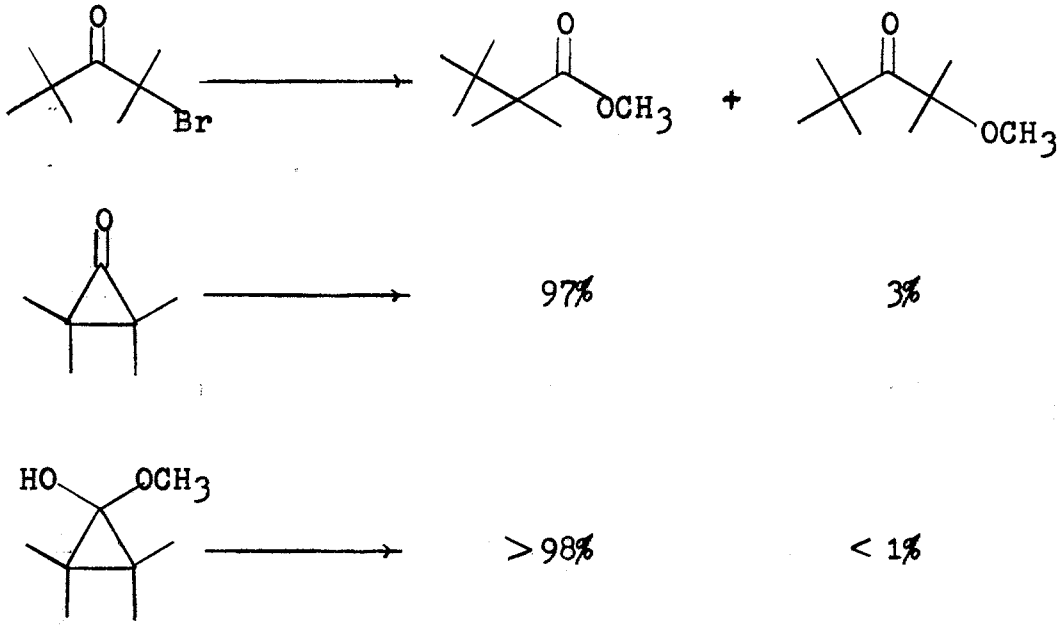


Fig. 7. Favorskii Products from Cyclopropanone Derivatives

whether a concerted cyclopropanone intermediate or the zwitterion intermediate is operating is decided from stereochemical factors. For the concerted cyclopropanone intermediate, inversion of configuration is expected, but for the zwitterion intermediate, racemization is expected.

Stork and Borowitz studied the Favorskii rearrangement of both cis and trans 1-chloro-2-methylcyclohexyl methyl ketone and found in both cases almost complete inversion, which suggests that the concerted process shown in Fig. 8 is the more plausible route.[16] However, it was later shown that the stereospecificity of the reaction depended upon the polarity of the solvent system.[11] To account for these results, it was suggested that polar solvents aid the loss of chloride to form a dipolar intermediate while in nonpolar solvents the cyclopropanone intermediate predominates.

Labelling experiments on the rearrangement of 2-bromocyclobutanone in deuterium oxide have shown that deuterium is not incorporated into the cyclopropanone portion of the product (Fig. 9). The results of these studies indicate that the reaction does not proceed by a cyclopropanone or zwitterion mechanism; however, a semibenzilic mechanism does fit the experimental data.[17]

Warnhoff and co-workers studied the Favorskii rearrangement of cyclic α-bromo ketones of the type shown in Fig. 10 with n equal to six, seven, or eight.[18] Under the conditions (NaOD-D_2O-EtOD), the compounds with n equal to six or seven underwent rearrangement by an unsymmetrical

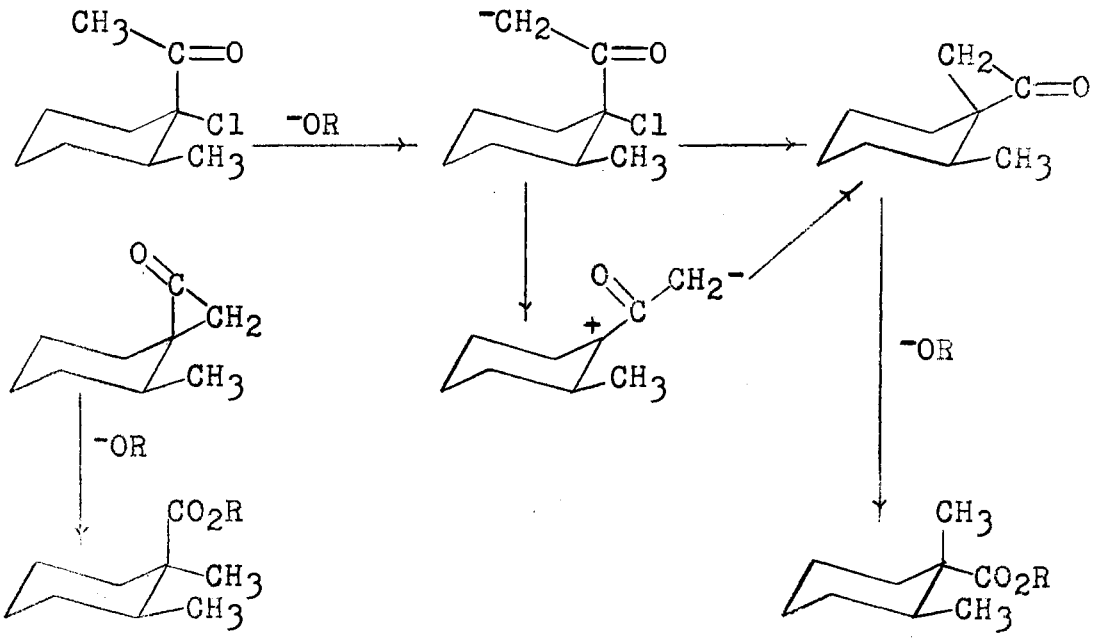


Fig. 8. Favorskii Reaction of 1-Chloro-2-methylcyclohexyl Methyl Ketone

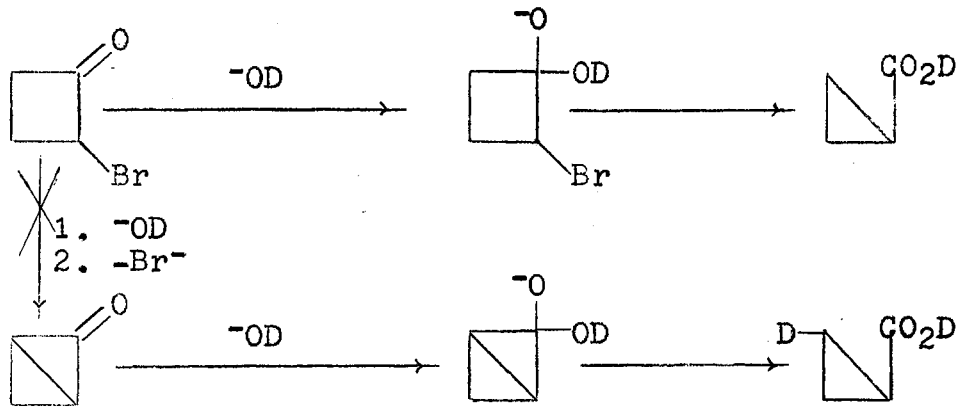


Fig. 9. Favorskii Reaction of 2-Bromocyclobutanone

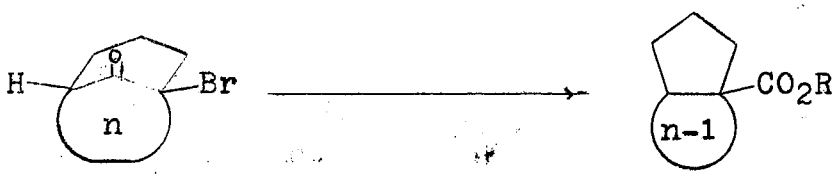


Fig. 10. Favorskii Reaction: Warnhoff's Modification

intermediate, while the compound with n equal to eight rearranged by a symmetrical intermediate. In the presence of the stronger base sodium t-butoxide, the compound with n equal to seven underwent rearrangement to a symmetrical product. These results indicate that the path of the reaction may depend upon the difference in base strengths of the proton acceptors.

These studies mentioned above and many more indicate that no one proposed mechanism can successfully explain all experimental results. The mechanism depends upon the type of compound reacting and the experimental conditions used, and in some cases more than one mechanism is probably operating. Definite conclusions can only be reached after studying the various products of individual reactions.

CHAPTER II

DISCUSSION

The four (3S)-methylcyclopentane-1,2-dicarboxylic acids (+)-t-3-methyl-r-1, c-2-cyclopentanedicarboxylic acid (3a), (-)-c-3-methyl-r-1, t-2-cyclopentanedicarboxylic acid (3c), (+)-c-3-methyl-r-1, c-2-cyclopentanedicarboxylic acid (3e), and (+)-t-3-methyl-r-1, t-2-cyclopentanedicarboxylic acid (3g) were synthesized and separated.[19] These are nepetic acids of the catnip series and, unless otherwise stated, all references to nepetic acids will be to those of the catnip series.

The procedure finally adopted in the synthesis of the nepetic acids is shown in Fig. 11.[6,20] The first problem involved the resolution of (±)-3-methylcyclohexanone (4). This was accomplished through recrystallization of the amine bisulfite salts obtained from the reaction with sulfur dioxide and (+)-α-methylphenethylamine.[21] The resolved (-)-(3S)-methylcyclohexanone was treated with sodium hydride and dimethyl carbonate to form a mixture of (-)-methyl 2-oxo-4-methylcyclohexanecarboxylate (5a) and methyl 2-oxo-6-methylcyclohexanecarboxylate (5b).[22,23] This mixture was brominated and then treated alternately with alkali and acid in a Favorskii rearrangement to produce the

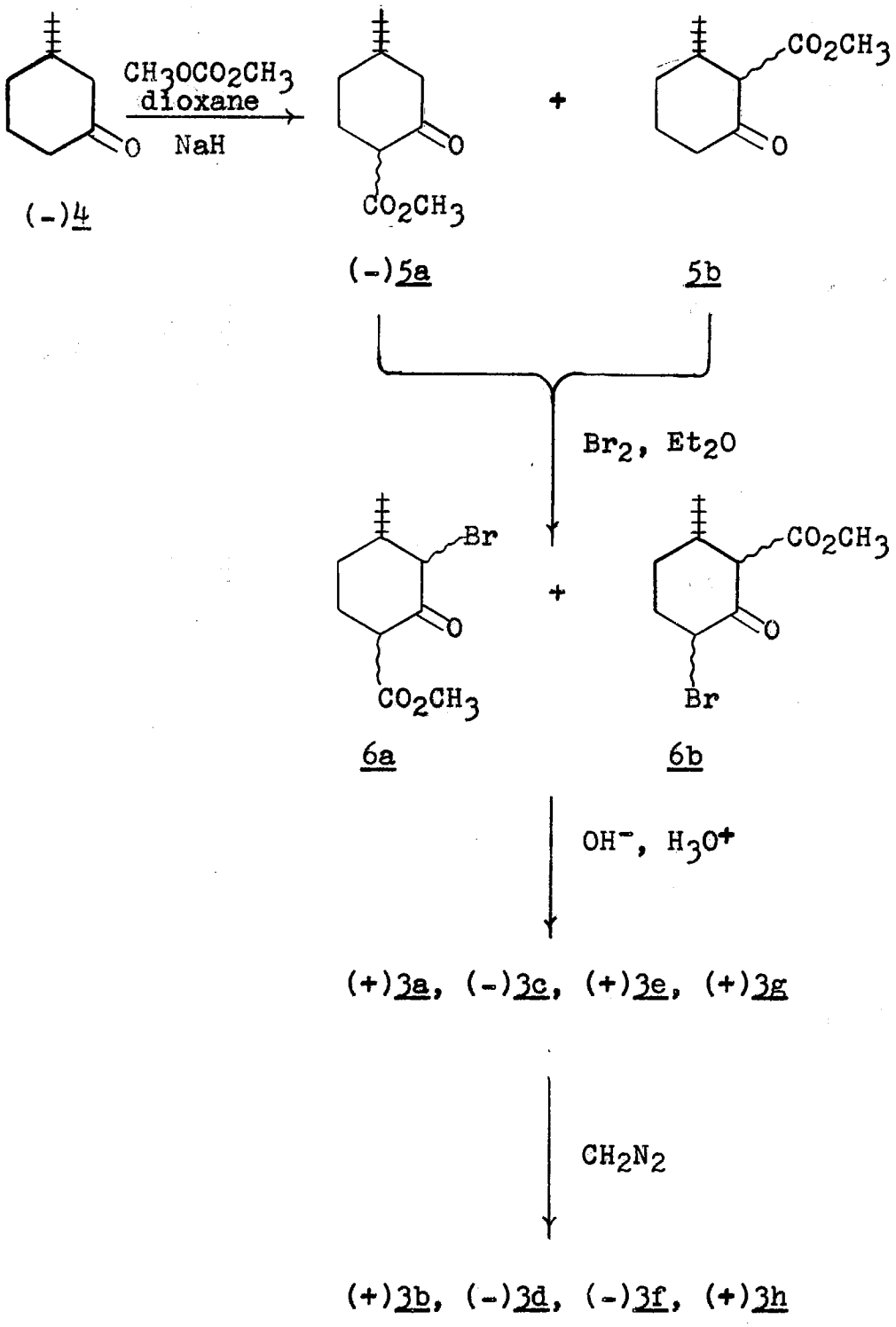


Fig. 11. Nepetic Acid Synthesis

four nepetic acids (3a, 3c, 3e, 3g). A convenient method of extracting the acids as their dimethyl esters from the aqueous reaction medium by reaction with an ether solution of diazomethane was established after studies were made on several model dicarboxylic acids.[24] It was determined that dicarboxylic acids containing at least four carbons and no additional functional groups could be extracted as dimethyl esters into the ether layer on treatment with an ether solution of diazomethane. Otherwise, as in the case of dimethyl oxalate and dimethyl tartrate, the dimethyl esters formed would remain in the water layer.

A typical reaction of crystalline (±)5a to form the nepetic acids as shown in Fig. 11 gave essentially the same ratio of nepetic acids as the reaction of a mixture of (±)5a and (±)5b. This surprising result raised a question as to the purity of (±)5a in a typical reaction mixture and whether we possibly were working in all cases with mixtures of (±)5a and (±)5b. Mixtures of (±)5a and (±)5b could not be analyzed directly by glc because both compounds showed decomposition during analysis. The nmr spectra failed to give adequate resolution and were also unsuitable for distinguishing these isomers. In order to determine the ratio of (±)5a to (±)5b in a typical reaction mixture, the reactions of Fig. 12 were applied to (±)5a and to a mixture of (±)5a and (±)5b.[6,20] The ester (±)5a was cleaved with alkaline hydrogen peroxide, and the solution was acidified and extracted with an ether solution of diazomethane to give

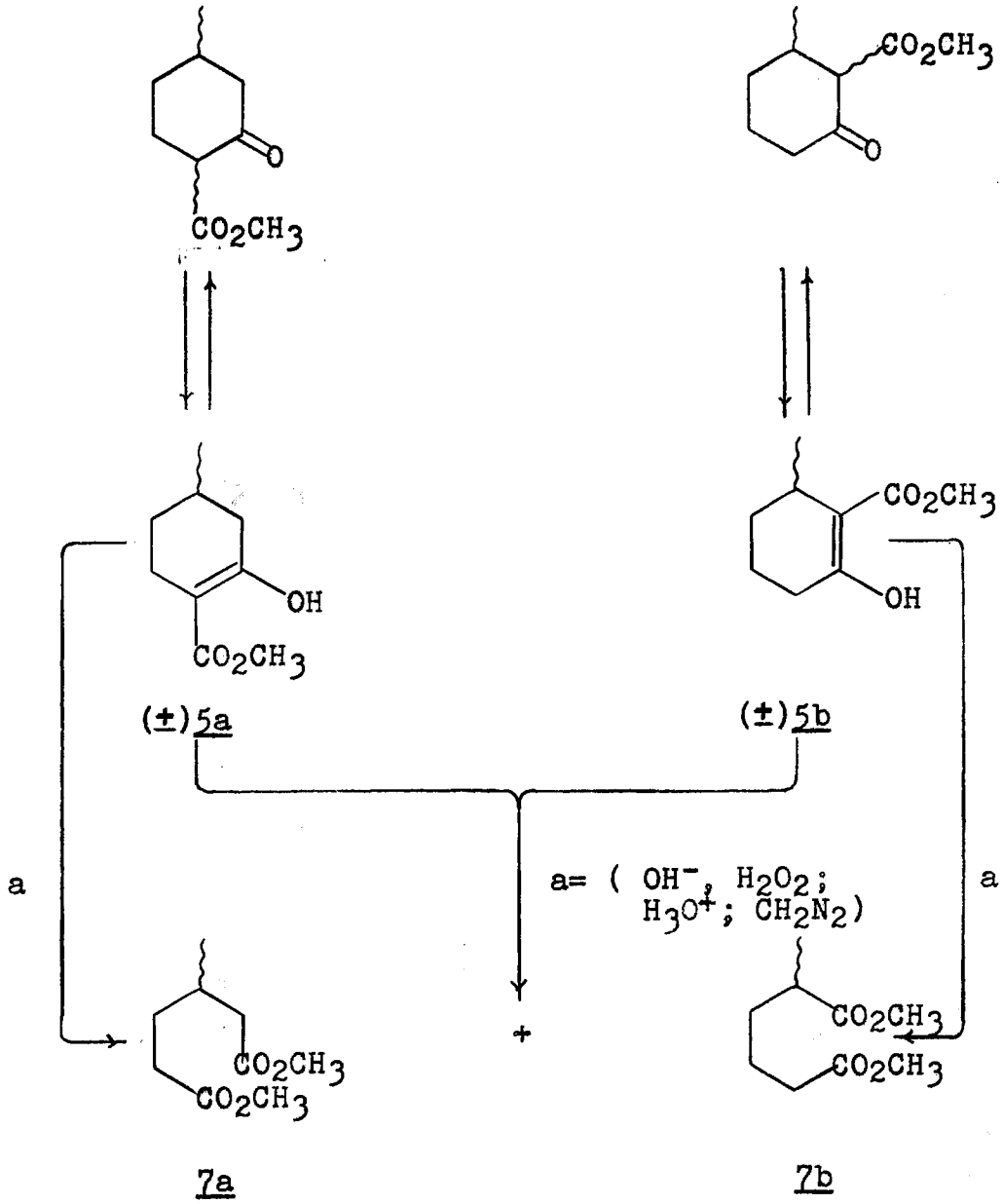


Fig. 12. Oxidation of β-Oxo Esters with Alkaline Hydrogen Peroxide

dimethyl 3-methyladipate (7a). Similarly (±)5b was cleaved and esterified to give dimethyl 2-methyladipate (7b). Both products could be distinguished by glc studies and they were conclusively identified by comparison with known standards. The ratio of (±)5a to (±)5b in a typical reaction mixture from the reaction of(±)4 was determined by using the cleavage technique shown in Fig. 12 and analyzing the ratio of 7a to 7b by glc. The ratio of (±)5a:(±)5b was 85:15. Because enantiomers are known to react identically, the ratio of (-)5a to 5b in the mixture from the reaction of (-)4 is identical to the ratio of (±)5a to (±)5b for the reaction of (±)4, i.e., (-)5a:5b = 85:15.

Although the above procedure was the method finally adopted for synthesizing the (3S) nepetic acids, another method was also tried. This method involved the resolution of a derivative of (±)5a. This resolution was accomplished by preparing a derivative using optically active menthol as shown in Fig. 13.[6,25] This transesterification procedure involves the addition of a large excess of the alcohol to be exchanged to a toluene solution containing the appropriate ester. If possible the boiling point of the solvent should be lower than the boiling point of the exchanging alcohol and higher than that of the alcohol being removed from the starting ester. The reaction of (±)5a with (+)-menthol (8) produced the β-oxo esters (+)9a and (+)9b. Also, the reaction of (±)5a with (-)-menthol (8) produced the β-oxo esters (-)9a and (-)9b. The esters (+)9a and

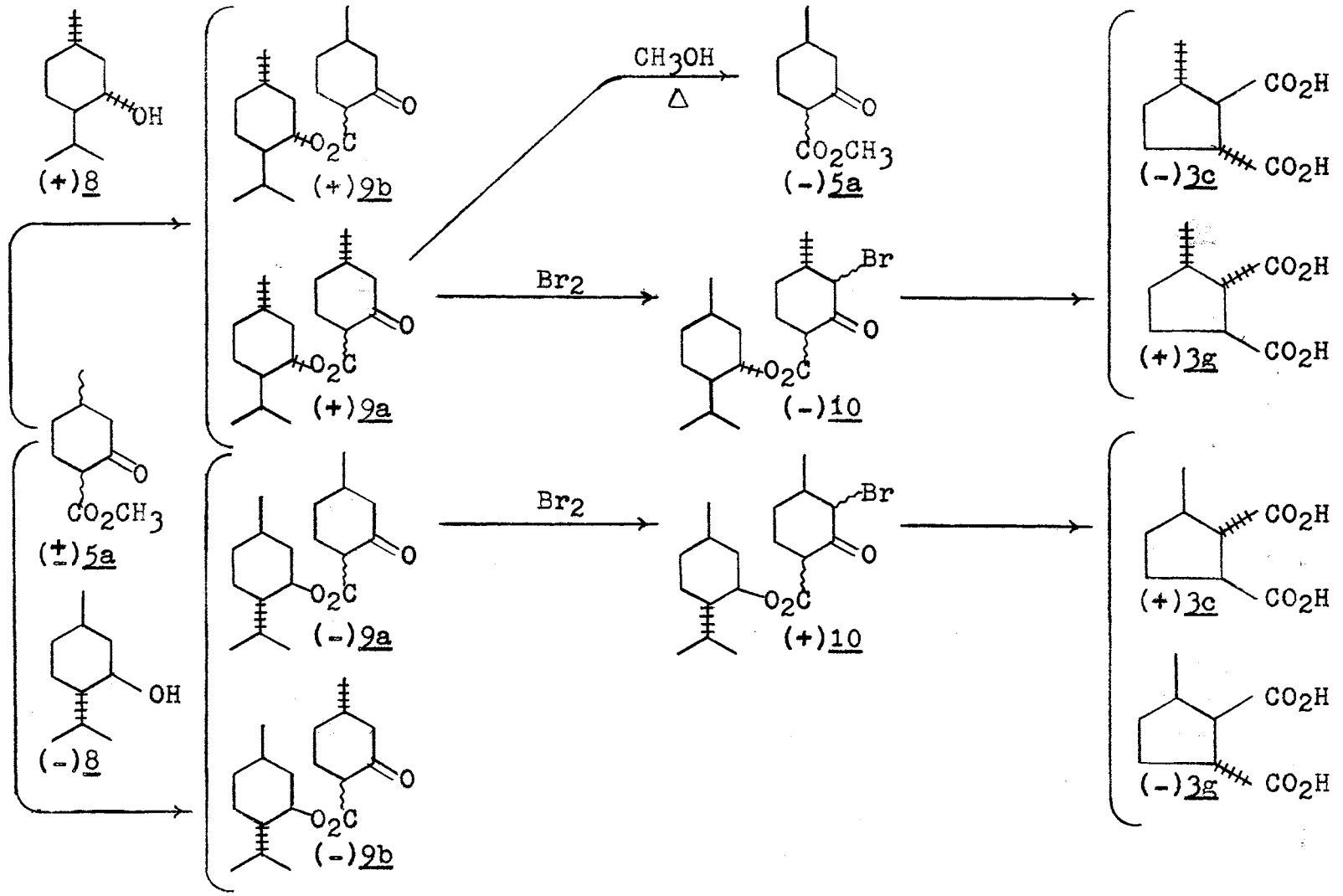


Fig. 13. The Synthesis of Nepetic Acids via Optically Active Menthyl Esters

(-)9a were crystalline and could therefore be separated from the reaction mixture from the appropriate reaction. These crystalline, optically active β-oxo esters were used in subsequent steps to prepare resolved nepetic acids. Bromination of (+)9a gave the menthyl γ-bromo-β-oxo ester, (-)-10, which on successive treatment with alkali and acid yielded the 3S-trans-nepetic acids, (-)3c and (+)3g. Thus this method can be used to prepare some of the nepetic acids of both series. The other menthyl β-oxo esters, (+)9b and (-)9b, were not crystalline and were not studied except to confirm that the isomer (+)9b is not crystalline, since an independent preparation from (+)5a and (+)8 gave an oil. That effective resolution of the C-4 centers of (+)9a and (-)9a had been achieved was established when (+)-9a was obtained from the reaction of (+)5a and (-)8 as well as from (±)5a and (-)8. As further proof, (+)9a, obtained from the reaction of (±)5a and (+)8, was heated in the presence of a large excess of methanol and pure, resolved (-)5a was recovered from the reaction mixture. However, the production of resolved (3S)-nepetic acids by this method became impractical because of the limited amount of (+)-menthol (8) available. Also, because of the need to convert (+)9a to (-)5a before completing the synthesis reactions, if cis nepetic acids as well as trans nepetic acids were desired, the procedure involving resolution of (±)4 to (-)4 was more desirable.

A question brought forth by the experimental results

was why predominately trans nepetic acids were obtained from the Favorskii rearrangement of the menthyl γ-bromo-β-oxo esters whereas substantial cis nepetic acids could be obtained from the Favorskii rearrangement of methyl γ-bromo-β-oxo esters. Assuming that the rearrangement of both compounds proceeds by the same mechanism and the suggested mechanism is one of the possible mechanisms mentioned earlier for the Favorskii rearrangement, the probably results are shown in Figs. 14 and 15. As Fig. 14 indicates, if the cyclopropanone mechanism is correct, then the favored initially formed products have the stereochemistry of trans nepetic acids. If the semibenzilic mechanism is operating, then the initially formed products are of the cis configuration. The initially formed half-ester products may then epimerize before hydrolysis to form the other nepetic acids. To show that epimerization does occur, the (3R)-cis, cis dimethyl ester was hydrolyzed in acid to give the (3R)-cis, cis nepetic acid (-)3e and about 10% of the other 3R nepetic acids. Also, the (3R)-cis, trans ester was hydrolyzed to the cis, trans acid (-)3a and about 2% to the trans, trans acid (+)3a. However, the esters having trans functional groups retained their stereochemistry during hydrolysis to the corresponding trans acid.

According to the cyclopropanone mechanism of Fig. 14, the thermodynamically less stable cis nepetic acids are formed by epimerizations of the initially formed trans nepetic acids. Because cis products are not produced from

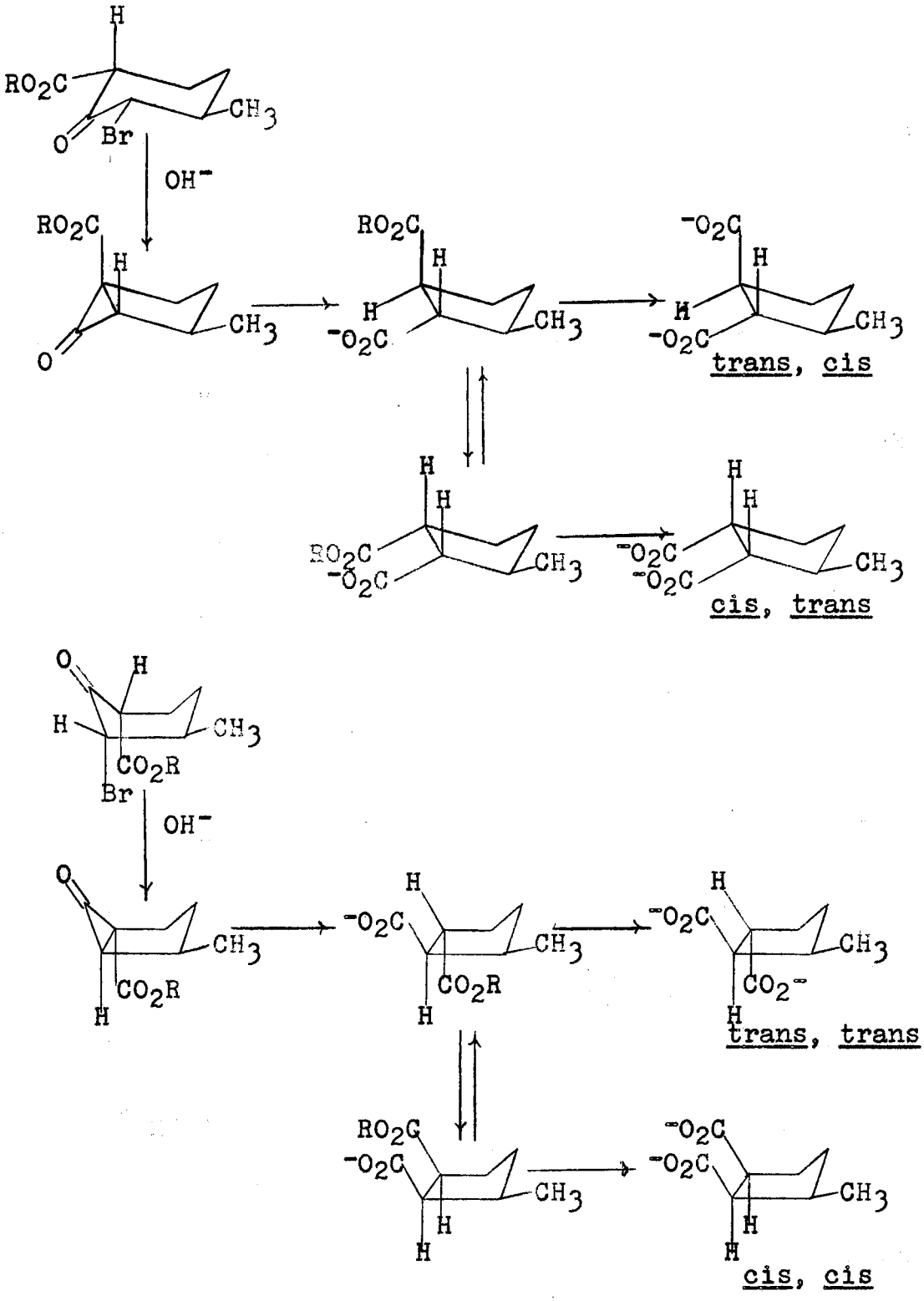


Fig. 14. Cyclopropanone Mechanism in the Formation of Nepetic Acids

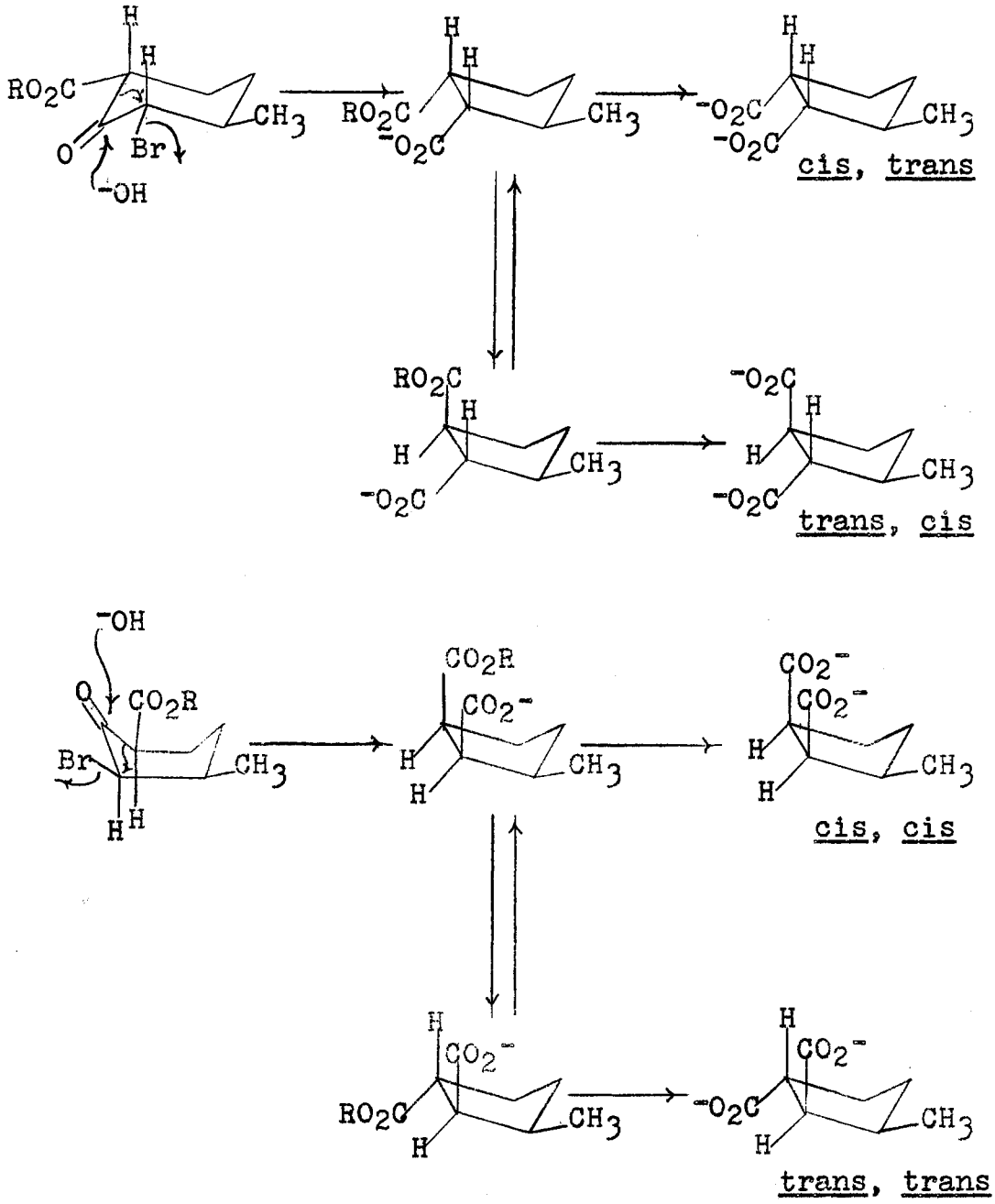


Fig. 15. Semibenzilic Mechanism in the Formation of Nepetic Acids

the reactions of the menthyl γ-bromo-β-oxo esters under the usual conditions, the cyclopropanone mechanism seems more reasonable. However, the experimental results from the reaction of the methyl γ-bromo-β-oxo esters show a higher concentration of cis products than might be expected. For the semibenzilic mechanism of Fig. 15 to be operating, epimerization would have been from the thermodynamically less stable cis products to the thermodynamically more stable trans products with either much more rapid epimerization occurring for the menthyl ester owing to lower activation energy or more time for epimerization because of slower hydrolysis of the menthyl half ester owing to steric hindrance. To determine which mechanism was the more likely, the brominated β-oxo esters were given minimal exposure to dilute aqueous alkali and the solutions then were acidified and extracted to minimize epimerization. In the experiment with (+)5a, the methyl half-esters produced were converted to the dimethyl esters in the usual manner and their ratios were determined by glc studies. A large amiunt of cis products were formed. The menthyl half-ester products from (-)9a were converted to the diols 11, 12, 13, and 14 with lithium aluminum hydride, as shown in Fig. 16, and the resulting mixture was analyzed by glc through comparison with diol standards prepared from pure (3R)-nepetic acids. In both cases the cis products were favored when the Favorskii reaction was terminated promptly. Similar experiments with bases of varying strength indicated that cis products

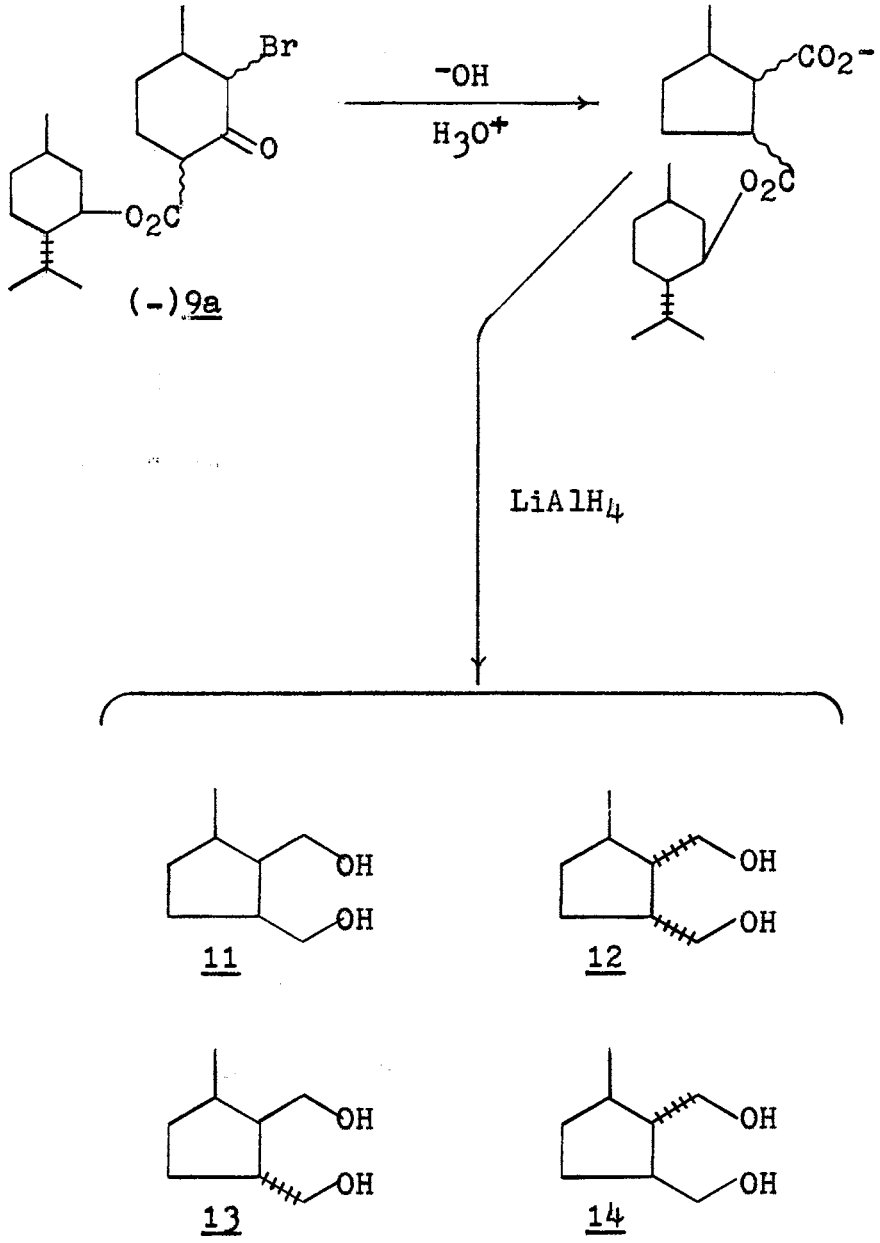


Fig. 16. Preparation of Diols from Menthyl Half Esters

were favored when weaker bases with less epimerizing power were used.

These results indicate that of the common mechanisms proposed for the Favorskii rearrangement, the semibenzilic mechanism seems more reasonable for the system of the alkyl 4-methyl-2-oxo-3-bromocyclohexanecarboxylates.

In order to study the reactions further, the synthesis of other alkyl 4-methyl-2-oxocyclohexanecarboxylates was attempted. The reaction mixture containing (±)5a and (±)5b was prepared from (±)4 as shown in Fig. 11 and crude (±)5a was crystallized from the reaction mixture and purified by recrystallization from petroleum ether. The transesterification procedure was used to synthesize the esters shown in Fig. 17 from (±)5a. Because the esters formed turned out to be oils, they were not used for the synthesis of nepetic acids.

Also, because the crystallization of (±)5a from the mixture increased the percentage of (±)5b present in the mixture, its purification from the reaction medium became of interest. Through successive cropping of (±)5a from the reaction mixture the ratio of (±)5a to (±)5b was decreased to about 40:60. The mixture was then vacuum distilled with about seven cuts taken. The last cut contained only (±)5b, measured as shown in Fig. 12.

Because of their potential physiological interest, the synthesis of nepetic acid imides was attempted. The nepetic acid (-)-t-(3R)-methyl-r-1, c-2-cyclopentanedicarboxylic

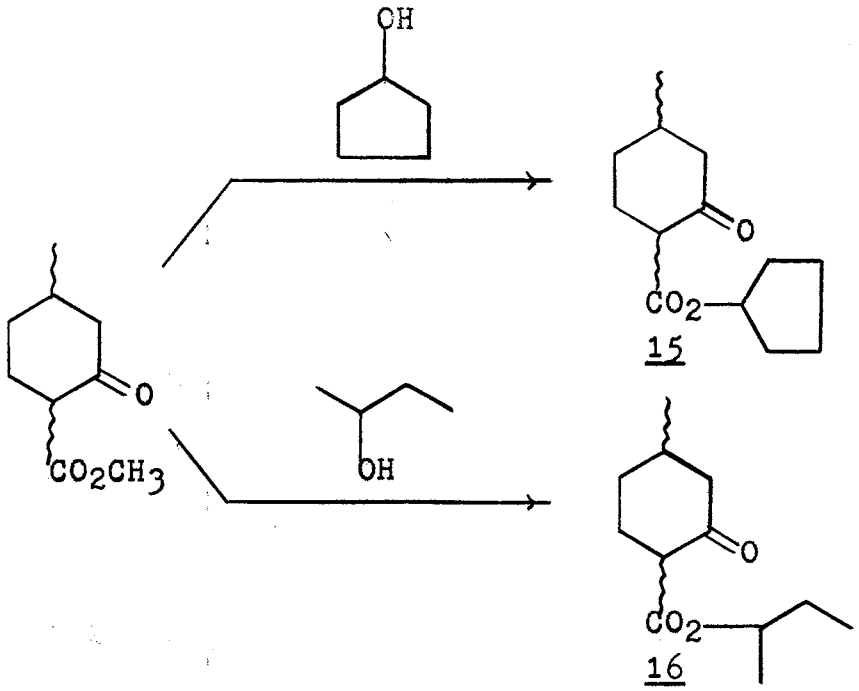
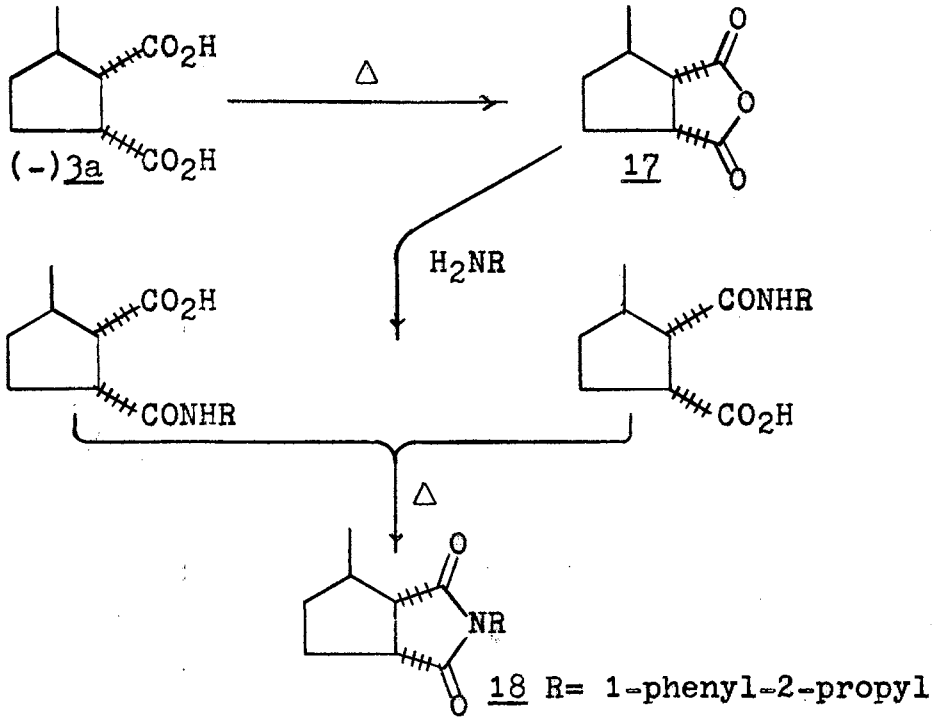


Fig. 17. Preparation of β-Oxo Esters



18 R= 1-phenyl-2-propyl

19 R= 2-hydroxyethyl

Fig. 18. Conversion of the Nepetic Acid (-)3a to N-Alkylimides

acid (3a) was used in this synthesis because of its abundance and the need to use a nepetic acid with cis carboxyl groups.[26] Nepetic acids with trans carboxyl groups probably would not cyclize to form the five-membered imide ring. The general procedure followed is shown in Fig. 18. The anhydride 18 was formed by heating (-)3a and driving off the water as it was formed. The amines used were ethanolamine and 1-phenyl-2-propanamine (l-amphetamine). These were added to the nepetic anhydride dissolved in toluene and they reacted immediately to form the half amides. Under reflux conditions, the amides underwent ring closure to the imides. In the case of l-amphetamine, because of extreme differences in solubility, the amides could easily be separated from the imide. The amides melted over a narrow range indicating that one form, possibly the one whose formation is least subject to stearic hindrance, was the predominate one.

CHAPTER III

EXPERIMENTAL

Infrared spectra were obtained with a Bechman IR-5A spectrometer; the nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal standard (δ=0) and carbon tetrachloride as the solvent where possible. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Preparation of Diazomethane from N,N'-Dinitro-N,N'-dimethylterephthalamide (EXR-101).

In a 500-ml reaction flask, a solution of 2.4 g of sodium hydroxide in 20 ml of water, 50 ml of Carbitol (diethylene glycol monoethyl ether), and 150 ml of ether were cooled to 0°C, and then 7.1 g of EXR-101 was added at one time. Magnetic stirring was started and the reaction mixture was warmed slowly. The evolution of diazomethane became apparent at 15° to 20°. In the 30° to 40° range, the diazomethane and ether distilled and condensed to a bright yellow solution. The mixture was collected until the yellow color of the EXR-101 in the reaction flask and the color of diazomethane in the distilling ether

disappeared. During the reaction, the receiving flask was cooled with Dry Ice. A white precipitate of polymethylene formed in the bottom of the reaction flask as the reaction neared completion.

Test of the Ability of an Ether Solution of Diazomethane to Extract Water-soluble Diacids and an Anhydride as their Dimethyl Esters from an Aqueous Solution.[24]

The acids and anhydride were each placed in approximately 10 ml of water and a diazomethane solution in ether was added until the slight yellow color of diazomethane remained after its addition. Because of the volumes that became involved, this was sometimes hard to distinguish. After completion of the reaction, the water and ether layers were separated and the solvents were removed under vacuum.

Tartaric Acid

The diazomethane was added to an aqueous solution containing 0.1547 g (0.001 mol) of tartaric acid and it reacted rapidly with the acid. After the reaction was completed, the product fractions in the ether and in the water were separated. The fraction in the ether weighed 0.0321 g; the fraction in the water weighed 0.1600 g. These results indicate that although the dimethyl ester is formed, most of it remains in the water solution.

Succinic Acid

The diazomethane reacted rapidly with 0.1216 g (0.001

mol) of acid in an aqueous solution to give a quantitative yield of dimethyl succinate, which went completely into the ether layer.

Succinic Anhydride

In 10 ml of water was placed 0.1049 g (0.001 mol) of succinic anhydride, which did not all dissolve. When the diazomethane solution was added, evolution of gas could be seen on the surface of the anhydride. However, because only small quantities of the compound reacted before the diazomethane disappeared from the solution, this method of extracting succinic anhydride as a solid is impractical. By heating the solution, the anhydride hydrolyzed to succinic acid, which could then be extracted after the solution cooled.

Oxalic Acid

Diazomethane was added to an aqueous solution containing 0.1299 g (0.0014 mol) of oxalic acid. Upon separation after the reaction was believed complete, only a slight residue remained in the ether layer while the material in the water was identified as oxalic acid.

Preparation of (±)5a and (±)5b from (±)4.

To a four-necked flask fitted with a Teflon paddle stirrer was attached an addition funnel, a condenser, a thermocouple, and a connection to nitrogen gas. Into the flask was added 224 g (2.5 mol) of dimethyl carbonate, 20 g (0.84 mol) of sodium hydride, and 400 ml of dioxane. The

nitrogen gas flush and the stirrer were started. (±)-3-Methylcyclohexanone (4) was added over a two-hour period. The temperature rose from 25° to 75° and was kept at or below 75°. After all (±)4 was added, the reaction mixture was stirred an additional 10 minutes. Acetic acid was then added to the reaction mixture to insure that all of the sodium hydride was used up. A white paste of sodium acetate formed. Sodium bicarbonate in water was added until the mixture was basic. The mixture was extracted twice with ether and the ether solution was washed twice with water. The mixture was placed under vacuum to remove solvents and then distilled at 22° to 100° and 1 mm. The first cut was solvent and lower-boiling organic compounds. The fractions from 35° to 100° were essentially (±)5a and (±)5b.

Preparation of Pure (±)5a from the Mixture of (±)5a and (±)-5b.

The mixture of (±)5a and (±)5b was placed in a refrigerator and allowed to cool until crystals formed. The mixture was filtered rapidly while cold. The filtrate was recooled until more crystals formed and they were filtered out. This process was followed a total of four times. The crude crystals of (±)5a were recrystallized twice from petroleum ether: mp 40-41°; ir (mineral oil) 3.42, 6.02, 6.16, 6.91, 7.33, 7.50, 7.80, 8.19, 8.61, 9.05, 9.17, 9.54, 9.78, 10.50, 11.15, 11.42, and 12.17 μ.

Separation of (±)5b from the Mixture of (±)5a and (±)5b.

The mixture with enriched (±)5b obtained from the above separation was distilled under vacuo with a total of seven cuts taken. The temperature range was 45° to 56° (0.5 mm).

Oxidation of (±)5a and Mixtures of (±)5a and (±)5b.

A sample of (±)5a (0.05 g) and approximately 0.05-ml samples of the cuts taken from the distillation of the mixture (±)5a and (±)5b were each placed in individual vials. A solution of 2 g NaOH in 16 ml of water was cooled to 0° and 8 ml of 30% H_2O_2 were added. The solution was placed into the vials containing (±)5a and (±)5b, equal amounts in all vials. A reaction was evident. The vials were then heated for about one hour on a hot plate. The reaction mixtures were cooled, acidified, and extracted with an ether solution of diazomethane. The ether extract was washed with acidified ferrous sulfate and water, and then dried ($MgSO_4$). The ether solution was concentrated and glc analysis by comparison with independently prepared dimethyl 3-methyladipate and dimethyl 2-methyladipate was undertaken. Of the samples analyzed, the last distillation cut contained pure (±)5b: bp 53-56° (0.5 mm); ir (neat) 3.41, 5.72, 5.82, 6.02, 6.16, 6.91, 7.35, 7.53, 7.80, 8.18, 8.61, 9.20, 9.53, 10.54, and 12.05 μ.

Preparation of Cyclopentyl 2-Oxocyclohexanecarboxylate from Methyl and Ethyl 2-Oxocyclohexanecarboxylate.

To a 500-ml reaction flask was added 50 ml of a mixture of methyl and ethyl 2-oxocyclohexanecarboxylates, 0.68 mol (65 ml) of cyclopentanol, and 155 ml of toluene. The flask was fitted with a distillation column and a condenser. The mixture was reflux distilled and the reaction was monitored by observing the presence of methanol and ethanol in the distillate. After 4.5 hr, an additional 10 ml of cyclopentanol were added to the reaction flask and three additional 25-ml portions of toluene were added every 2 hours. After 9 hr, the toluene and cyclopentanol were removed under vacuum and the product was distilled: bp 120° (5 mm); ir (neat) 3.41, 3.49, 4.30, 5.82, 6.05, 6.17, 7.00, 7.15, 7.36, 7.68, 7.91, 8.19, 8.53, 9.20, 9.43, 10.32, and 11.97 μ.

Preparation of Cyclopentyl 2-Oxo-4-methylcyclohexanecarboxylate (15) from Methyl 2-Oxo-4-methylcyclohexanecarboxylate.

The apparatus and procedure were the same as those used in the preparation of cyclopentyl 2-oxocyclohexanecarboxylate. The materials were 2.22 g (0.013 mol) of (±)5a, 20 ml (0.21 mol) of cyclopentanol, and 50 ml of toluene. After 18 hr an additional 10 ml of cyclopentanol were added. The total refluxing time was two days. The excess toluene and cyclopentanol were removed under reduced pressure to give 2.14 g of 15: bp 95° (0.3 mm); ir (neat) 3.38, 5.80,

6.04, 6.24, 6.90, 7.25, 7.34, 7.49, 7.78, 8.18, 8.59, 9.04, 9.16, 9.61, 10.37, 10.61, 11.38, and 12.04 μ; nmr (CCl_4) δ 1.02 (3Hd), 1.50-2.71 (16Hm), 5.26 (1 H broad s).

Preparation of 2-Butyl 2-Oxo-4-methylcyclohexanecarboxylate (16).

The procedure used in the preparation of cyclopentyl 2-oxocyclohexanecarboxylate was followed and 4.57 g (0.027 mol) of (±)5a, 25 ml of 2-butanol, and 50 ml of toluene were used. The total reaction time was 11 hr. The excess toluene and 2-butanol were removed under aspirator vacuum to give 4.3 g of 16: bp 62° (0.2 mm); ir (neat) 3.39, 5.80, 6.02, 6.15, 6.91, 7.34, 7.50, 7.79, 8.18, 8.58, 9.05, 9.17, 9.56, 9.79, 10.54, 11.14, 11.45, and 12.10 μ; nmr (CCl_4) δ 0.97 (6Hm), 1.47 2.67 (10Hm), 3.60-3.98 (4Hm).

Preparation of Nepetic Anhydride (17) from (-)-t-(3R)-methyl-r-1, c-2-cyclopentanedicarboxylic acid (3a).

Into a microdistillation flask was added 4.85 g of (-)3a. The compound was heated to 150° during which time water formed in the neck of the distillation flask. This water was driven off with a heat gun. Distillation gave 17: bp 96° (0.25 mm); ir (neat) 3.38, 3.47, 5.39, 5.61, 6.48, 6.83, 7.22, 7.52, 7.72, 8.16, 9.00, 9.21, 9.34, 9.64, 10.17, 10.40, 10.92, 12.05, 12.70, 13.70, and 14.99 μ.

Preparation of N-(2-Phenyl-1-methylethyl)nepetimide (18) from Nepetic Anhydride (17) and 1-Phenyl-2-propanamine (l-amphetamine).

Into a 50-ml flask was added 1.64 g (0.0106 mol) of nepetic anhydride (18) in 25 ml of toluene. To the solution was added 1.45 g (0.0108 mol) of l-amphetamine and a white precipitate formed immediately. A condenser with a $CaCl_2$ dryer was attached to the reaction flask and the solution was heated at reflux for five hr. The resulting mixture after reflux was connected to an aspirator and heated to remove the toluene until a gummy matrix remained. Petroleum ether was added and the remaining toluene went into the petroleum ether layer. The product was only slightly soluble in the petroleum ether and easily crystallized out when the petroleum ether was cooled to give a colorless product: mp 156-158° with evolution of gas; ir (KBr) 2.97, 3.38, 3.46, 3.81, 4.25, 5.86, 6.15, 6.44, 6.86, 7.20, 7.74, 8.18, 8.74, 9.06, 9.41, 11.03, 11.56, 12.03, 12.71, 13.37, 14.25, and 15.21 μ.

This ir shows the presence of a carboxyl group, indicating that the product is an amide and not an imide. This amido acid was heated to melting in a microdistillation flask and the water produced was driven off with a heat gun. The resulting imide 18 was dissolved in petroleum ether and recrystallized and then sublimed: mp 59-61°; ir (KBr) 3.38, 3.48, 5.64, 5.89, 6.47, 6.66, 6.85, 7.15, 7.28, 7.52, 7.72, 7.99, 8.47, 8.76, 8.97, 9.15, 9.67, 10.10,

10.90, 11.15, 11.71, 12.56, 13.43, and 14.26 μ; nmr (CCl_4)δ 0.97 (d), 1.36 (d), 1.48-3.50 (m), 4.10-4.70 (m), 7.13 (s); $[\alpha]^{25}$ D -82.2 (c 13.7 $CHCl_3$)

Preparation of N-(2-Hydroxyethyl)nepetimide (19) from Nepetic Anhydride (17) and Ethanolamine.

The procedure used in the preparation of 18 was followed. The quantities used were 2.63 g (0.017 mol) of 18 and 1.044 g (0.017 mol) of ethanolamine in 25 ml of toluene. A white precipitate formed immediately upon addition of the amine to the anhydride in toluene. The total refluxing time was 5 hr, after which the toluene was distilled. Upon addition of petroleum ether, a white precipitate formed. The product, weighing 3.06 g, was sublimed once to give white crystals of 19: mp 69-71° ; ir (mineral oil) 2.94, 3.41, 5.68, 5.96, 6.87, 7.25, 7.52, 7.96, 8.29, 8.43, 8.59, 9.06, 9.25, 9.57, 9.83, 10.29, 10.66, 10.97, 11.19, 11.60, 12.04, 12.55, 12.89, 13.80, and 14.95μ; nmr ($CHCl_3$)δ 1.12 (d), 1.28-3.45 (m), 3.71 (s); $[\alpha]^{25}$ D -18.1 (c 6.0 $CHCl_3$).

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VITA

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