

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

By

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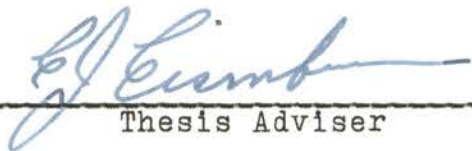
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Thesis Approved:



Thesis Adviser





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610233¹

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CHAPTER I

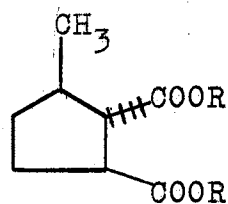
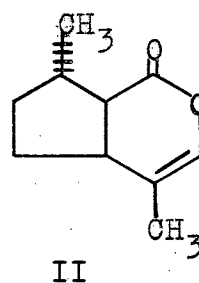
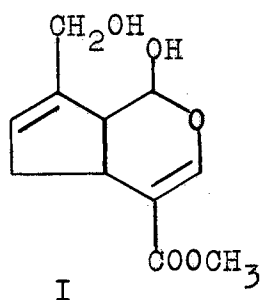
INTRODUCTION

Genipin (I), naturally occurring in Genipa americana L., was shown to have the cis configuration at the ring junction (1). The same absolute configuration occurs at these centers in the methylcyclopentane monoterpenoid nepetalactone (II), found in the common catnip plant, Nepeta cataria L. (2,3). The structure proof of genipin (I) depended on the isomerization of 3-methylcyclopentane-1,2-dicarboxylic acid VI with cis carboxyl groups to the corresponding acid IV with trans arrangement of carboxyl groups (3,4). However, differences in the anticipated optical rotation and melting point of the isomerized trans acid IV and its known enantiomer VIII strongly suggested that IV might actually be contaminated by another isomer III.

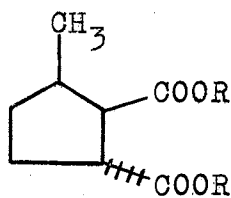
Thus, the exact identity and stereochemistry of each isomer of the 3-methylcyclopentane-1,2-dicarboxylic acids (nepetic acids) becomes important since the configuration and stereochemistry of these acids form the foundation for the assignment of stereochemistry and structure of several of the methylcyclopentane monoterpenoids.

The inconsistencies described above prompted us to attempt synthesis of the remaining unknown isomers of the

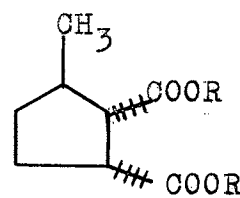
nepetic acids to clarify the stereochemistry and absolute configuration of genipin (I) and other methylcyclopentane monoterpenoids. There are a total of eight optically active diastereoisomeric nepetic acids as illustrated by structures III through X.



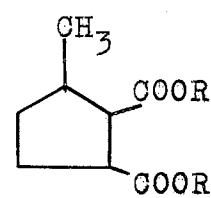
III R = H
 IIIa R = CH₃
 IIIb R = C₂H₅



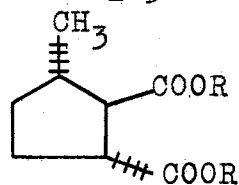
IV R = H
 IVa R = CH₃
 IVb R = C₂H₅



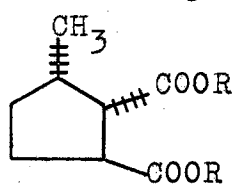
V R = H
 Va R = CH₃
 Vb R = C₂H₅



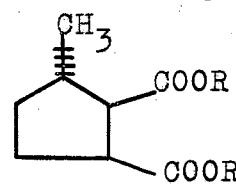
VI R = H
 VIa R = CH₃
 VIb R = C₂H₅



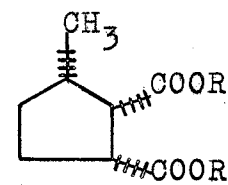
VII R = H
 VIIa R = CH₃



VIII R = H
 VIIIa R = CH₃



IX R = H
 IXa R = CH₃



X R = H
 Xa R = CH₃

The major portion of this thesis is devoted to the synthesis, purification, and establishment of the stereochemistry of the unknown nepetic acids and the description of their physical properties. Correlation of the acid VI obtained by degradation of genipin (I) with VI prepared through an independent synthesis is also described.

The previously mentioned eight optically active nepetic acids may be divided into two series of four structures, of which one series (VII, VIII, IX, and X) have the same absolute configuration as nepetalactone (II) about the common asymmetric center (carbon 3 of VII and carbon 7 of II). Since these nepetic acids are derived from nepetalactone (II), we shall refer to them as nepetic acids of the catnip series. Three of this series of nepetic acids (VII, VIII, and IX) were described by earlier workers (2,5). The fourth nepetic acid (X) remains unknown.

The remaining four nepetic acids (III, IV, V, and VI), are identical to the nepetic acids from the catnip series except that the stereochemistry is reversed for the entire series. That is, III and VII, IV and VIII, V and IX, and VI and X may be matched as antipodes. Otherwise, these pairs have identical physical and chemical properties and members of a pair differ from each other only by producing an equal and opposite rotation of plane-polarized light.

This new series of acids (III, IV, V and VI) was synthesized from (+) pulegone (XVI) and we, therefore, designate them as nepetic acids of the pulegone series to distinguish

them from those of the catnip series (VII, VIII, IX, and X).

It is recognized that the nepetic acids constitute isomers of 3-methylcyclopentane-1,2-dicarboxylic acid. However, for ease of description and to indicate the source of the respective acids we elect to use the names described in the preceding paragraphs. We shall follow the published precedent for naming the individual isomers within a series by giving the relationship of the functional groups first and that of the methyl group and adjacent functional group second (4). For example, structure VII is designated as the trans, trans-nepetic acid (catnip series) and V is designated as the cis, trans-nepetic acid (pulegone series).

CHAPTER II

HISTORICAL

The 3-methylcyclopentane-1,2-dicarboxylic acids (nepetic acids) were first obtained as degradation products of nepetalactone (II) from Nepeta cataria L. (2,6). Nepetalactone (II) is the major component and physiologically active constituent of the catnip plant (6). During the course of proof of structure and absolute configuration of nepetalactone (II), the structure and absolute configuration of the nepetic acid VII at C₃ was established as shown in Fig. 1 by degradation to (+) 2-methylglutaric acid (XIII) and (-)-methylsuccinic acid (XV) (2,5). The absolute configuration of (+)-XIII and (-)-XV had been established by Fredga through quasi-racemate correlation with (-)-lactic acid of known absolute configuration (7).

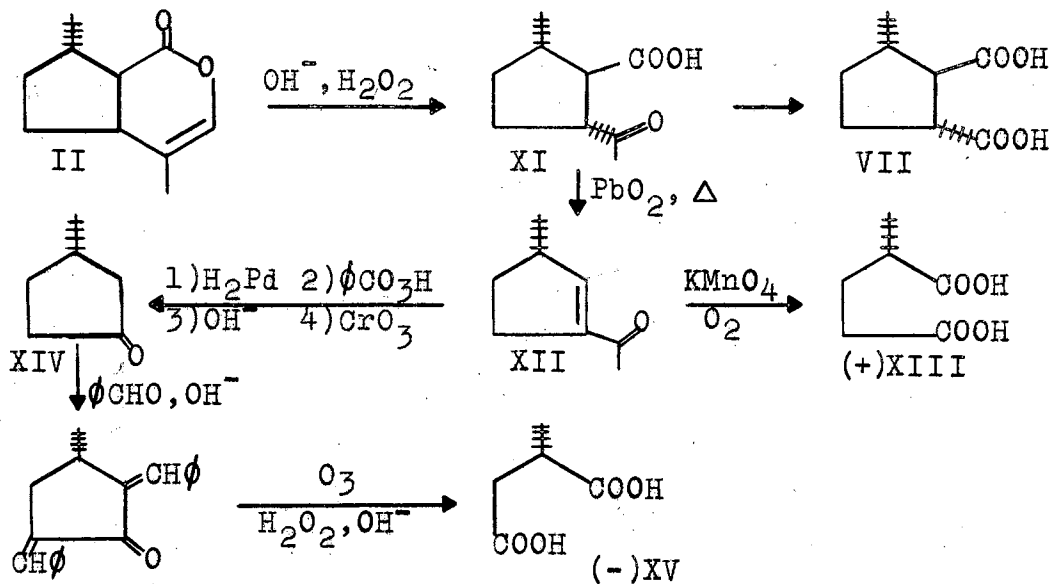


Fig. 1 - Absolute Configuration Proof for the Nepetic Acids

The absolute configuration assignment to nepetalactone (II) at C₇ and consequently nepetic acid (VII) at C₃ was confirmed by correlation with (+)-pulegone (XVI) as shown in Fig. 2 (5). The absolute configuration of the latter had been established as (R), by correlation with shikimic acid and the tartaric acids (8).

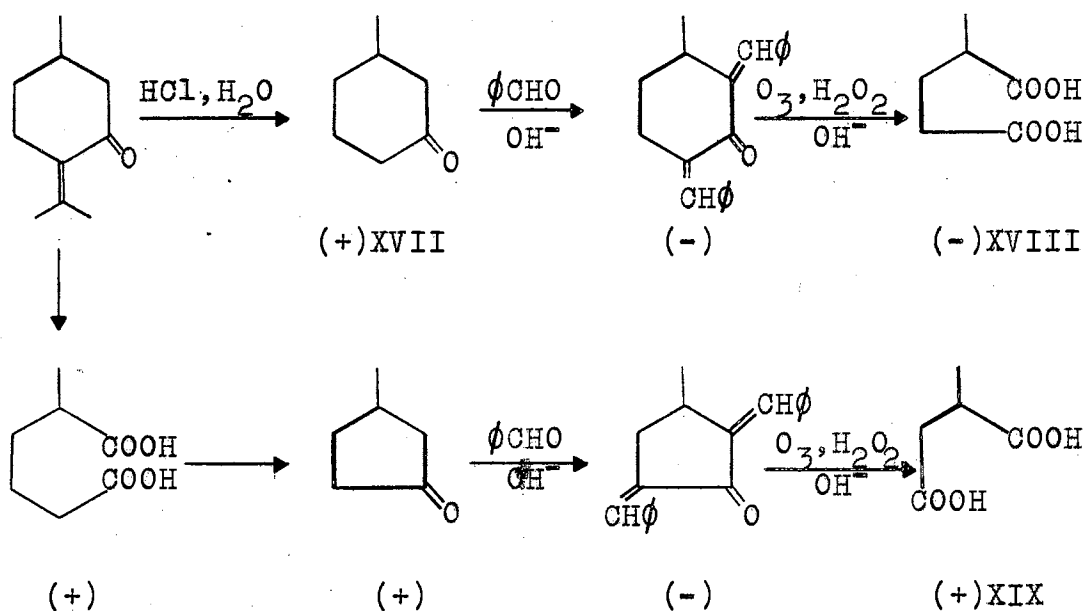


Fig. 2 - Correlation of Absolute Configuration of the Nepetic Acids with (+)-Pulegone (XVI)

Since (-)-methylsuccinic acid (XV) and (+)-2-methylglutaric acid (XIII) obtained as degradation products of nepetalactone had opposite sign of rotation to the corresponding acids (XIX and XVIII respectively) obtained through degradation of (+)-pulegone (XVI), the (S) assignment to C₇ of nepetalactone (II) and C₃ of nepetic acid VII was confirmed.

A second nepetic acid (IX) having the cis,trans configuration was obtained from nepetonic acid (XI) through the reaction sequence of Fig. 3 (2). The cis assignment of carboxyl groups for the nepetic acid IX was based on the insolubility of its barium salt (2). Evidence to suggest the stereochemical assignment of cis,trans configuration to nepetic acid IX was obtained by synthesis of the four possible racemic nepetic acids (racemic pair III and VII through pair VI and X) (4). This synthesis will be described later.

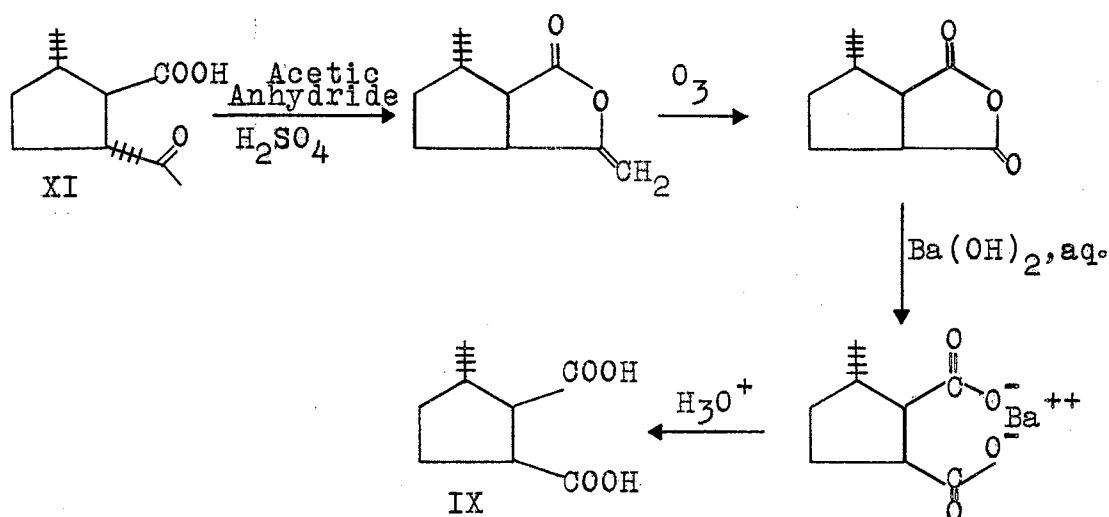


Fig. 3 - The Degradation of Nepetonic Acid (XI) to cis,trans-Nepetic Acid (IX)

A third nepetic acid in the catnip series, the trans, cis isomer VIII, was obtained by degradation of the nepetalactone isomer XX to a new nepetonic acid (XXI), which in turn was converted as shown in Fig. 4 to the trans, cis-nepetic acid (VIII) (3).

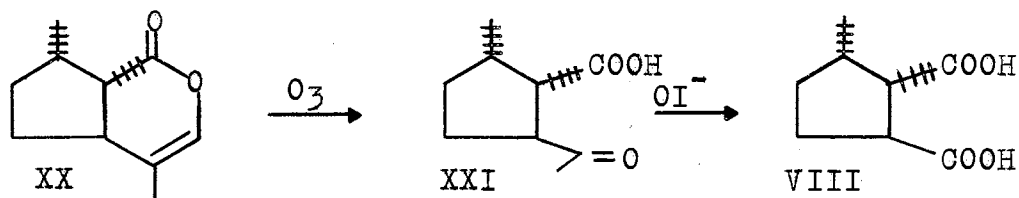


Fig. 4 - Preparation of trans,cis-Nepetic Acid (VIII)

The remaining cis,cis-nepetic acid (X) of the catnip series has not been described, but a method for its preparation from either of the trans nepetic acids (VII and VIII) has been developed and is described in the experimental work of this thesis.

A synthesis of the racemic 3-methylcyclopentane-1,2-dicarboxylic acids was reported by Fargher and Perkins (9) in 1914. This synthesis was repeated and found to give not acids of the nepetic acid series but rather the acid XXII as shown in Fig. 5 (4).

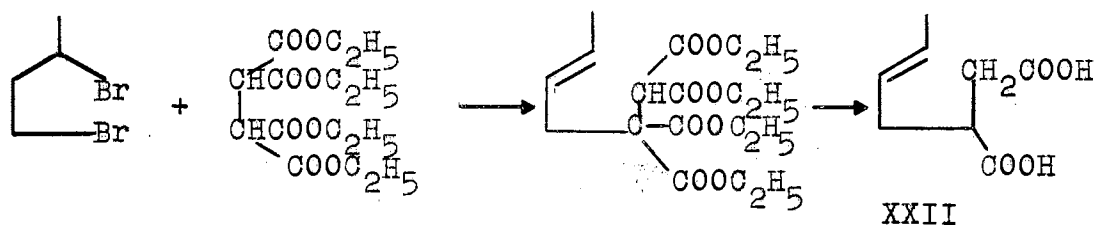


Fig. 5 - The Fargher and Perkins Alleged Synthesis of the Racemic 3-Methylcyclopentane-1,2-dicarboxylic Acids

A synthesis of the racemic nepetic acids (racemic pairs III and VII, IV and VIII, V and IX, and VI and X) was accomplished as shown in Fig. 6 by conversion of the keto ester XXIII to the cyanohydrin followed by dehydration and hydrolysis to the methylcyclopentenedicarboxylic acids XXIV and XXV

(4). Hydrogenation of XXIV gave two crystalline acids, each

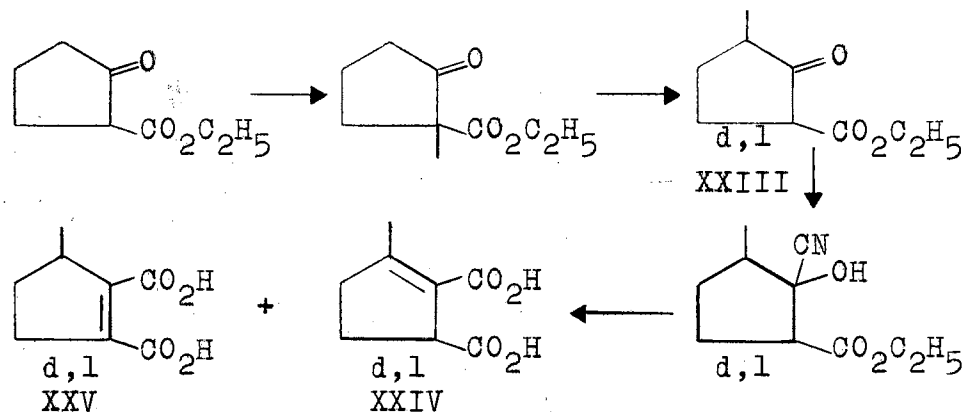


Fig. 6 - Synthesis of the Racemic Nepetic Acids

a racemate. On the assumption that cis addition of hydrogen to the double bond of XXIV took place, these acids were assigned the (\pm) cis,cis and (\pm) trans,cis configurations as illustrated by combining the pairs of enantiomeric nepetic acids VI and X, and IV and VIII respectively. The cis relationship of the carboxyl groups in (\pm) cis,cis-nepetic acid (pair VI and X) was established through formation of an insoluble barium salt and ready formation of an anhydride from which a single racemic nepetic acid (pair VI and X) was obtained upon hydrolysis (2,4).

Hydrogenation of the anhydride of the acid XXV followed by hydrolysis also yielded two separable acids. One was identified as the racemic cis,cis-nepetic acid (pair VI and X) previously obtained, while the new isomer was assigned the cis,trans configuration (racemate pair V and IX). The cis,trans configuration of this latter nepetic acid was confirmed by the formation of an insoluble barium salt and the ease of formation of an anhydride from which only a single racemic nepetic acid (pair V and IX) was obtained upon hydrolysis.

In order to prepare the remaining racemic trans,trans nepetic acid (pair III and VI), each of the enantiomeric dimethyl ester pairs IV_a and VIII_a, V_a and IX_a, and VI_a and X_a were separately heated at reflux temperature in a solution of sodium methoxide in methanol for 24 hours. After hydrolysis the trans,trans-nepetic acid (racemic pair III and VII) was isolated in varying amounts from each of the reaction mixtures. The trans,trans structure of pair III and VII followed from its difference in properties from the other isomers (2,4).

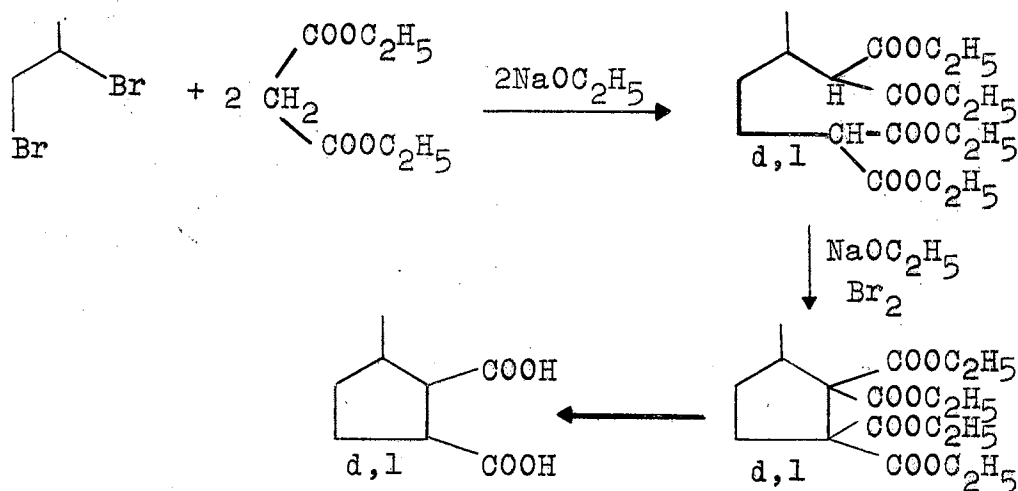


Fig. 7 - Blomquist's Synthesis of the Nepetic Acids

As shown in Fig. 7, Blomquist and co-workers (10) using a variation of the procedure of Fargher and Perkins (9) (see Fig. 5) were able to prepare a crude acid mixture containing what they thought to be a mixture of the four nepetic racemates. However, a sample of this mixture of acids did not give an insoluble barium salt, this indicated the absence of

any of the isomers with cis carboxyl groups (4). From refractive index studies of the methyl esters of the mixture of acids it appeared that nearly equal amounts of the racemic trans,trans- and trans,cis-nepetic acids were present (4).

To date only isomers IV and VI of the nepetic acids (pulegone series) have been described (1,11). The other nepetic acids III and V of this series have not appeared in the literature. The cis,cis-nepetic acid (VI) was reported to be a degradation product of genipin (I) and was obtained as shown in Fig. 8 by hydrogenation of I to XXVI followed by

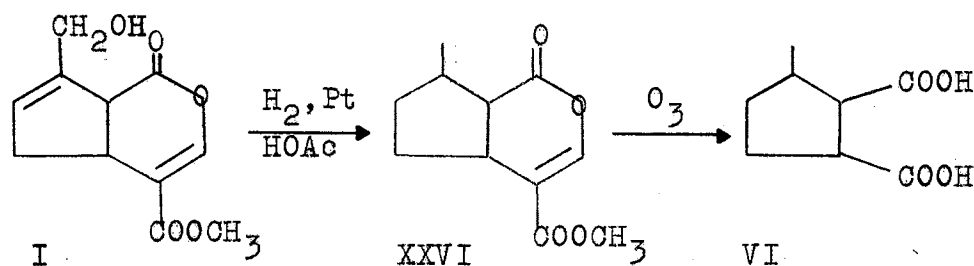


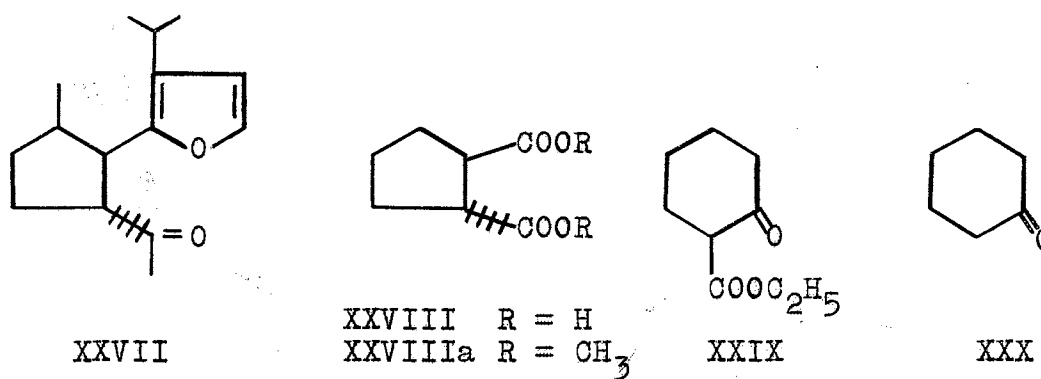
Fig. 8 - The Degradation of Genipin to cis,cis-Nepetic Acid (VI)

oxidation with ozone and alkaline hydrogen peroxide to crude acid VI which was purified through its barium salt (1). An elemental analysis indicated that this acid corresponded to the nepetic acids in composition, and the formation of an insoluble barium salt suggested cis arrangement of the carboxyl groups. However, its physical properties did not correspond to any of the three known nepetic acids (catnip series). This suggested that the remaining cis,cis-nepetic acid X or its enantiomer VI had been obtained. Confirmation of the cis,cis configuration was obtained by comparison of the infra-

red spectra of the new acid and its dimethyl ester with the spectra obtained from the racemic cis,cis-nepetic acid (pair VI and X) and its dimethyl ester (pair VI_a and X_a) (4).

To distinguish between structures VI and X for the unknown acid, the methyl half-ester was prepared, isomerized and hydrolyzed to give a new acid, m.p. 95-100°, $[\alpha]_D -66^\circ$, which did not form an insoluble barium salt and therefore must have been a nepetic acid with trans carboxyl groups. This new acid was considered to be either IV of the pulegone series or VIII of the catnip series. The known nepetic acid VIII melted at 114°-115° C and exhibited a +85° specific rotation which was opposite in sign to the rotation of the new acid. Therefore, although significant melting point and specific rotation differences existed it was concluded that the trans,cis and cis,cis nepetic acids (IV and VI respectively) derived from genipin were of the pulegone series.

Lukas, Ma, McClosky and Wolff (11) also recently reported the isolation of the trans,cis-nepetic acid (IV) through the degradation of furopelargone A (XXVII), a minor constituent in the essential oil of Geranium bourbon. The melting point of acid IV (106-110°) obtained by Wolff was in rough agreement with that of VIII (m.p. 114°). The specific rotation of these acids (-76° and +85° respectively) were of opposite sign and of the same order.



Brenner (12) has reported the synthesis of trans-cyclopentane-1,2-dicarboxylic acid (XXVIII), a compound similar to the nepetic acids because of the ring size and presence of vicinal carboxyl groups. The synthesis of acid XXVIII rested upon the intermediate ethyl 2-oxocyclohexanecarboxylate (XXIX) prepared by combining diethyl oxalate with cyclohexanone (XXX) in the presence of ethanolic sodium ethoxide and decarbonylating the product (13). An improved procedure for preparing β -keto esters was described by Corey and co-workers (14). This one-step addition of a carbomethoxy group of the cyclohexanone XXXI eliminates the decarbonylation step. This reaction sequence is illustrated in Fig. 9.

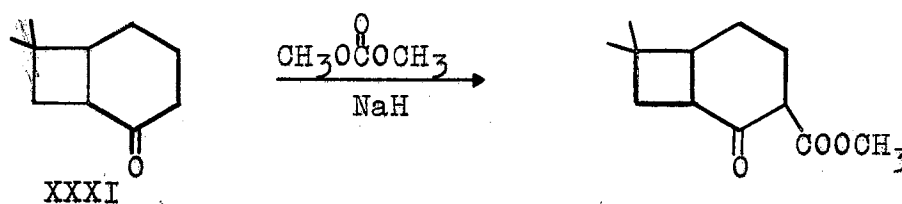
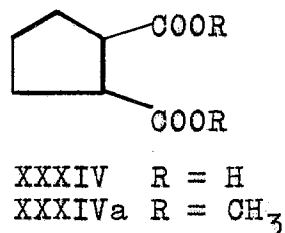
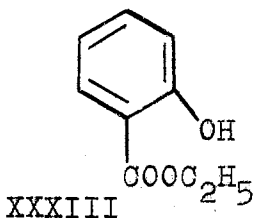
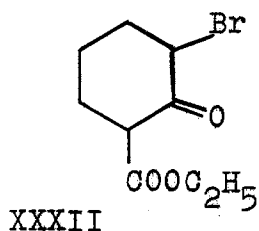


Fig. 9 - Corey's β -Keto Ester Synthesis

Brenner (12) showed that addition of liquid bromine to a cold ethereal solution of ethyl 2-oxocyclohexanecarboxylate (XXIX) gave ethyl 3-bromo-2-oxocyclohexanecarboxylate (XXXII).

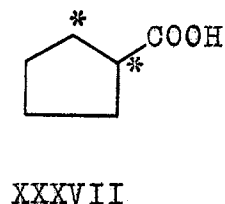
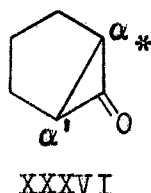
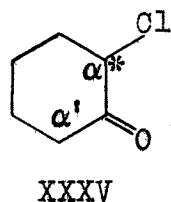
Distillation of bromo keto ester XXXII at atmospheric pressure followed by vacuum distillation gave in low yield a liquid which was identified as ethyl salicylate (XXXIII) (12). Treatment of bromo keto ester XXXII with aqueous ethanolic sodium hydroxide resulted in rearrangement to trans-cyclopentane-1,2-dicarboxylic acid (XXVIII) in 90% yield. The identity of XXVIII was established by comparison with authentic material. This Favorskii-type rearrangement will be discussed later.



An insight to the relative stability of the cis vs trans configurations of vicinal carbomethoxy groups on the cyclopentane ring was obtained by Fonken (15) through equilibration studies. These studies showed that the equilibrium mixture of the dimethyl esters of cis and trans-cyclopentane-1,2-dicarboxylic acids (XXXIVa and XXVIIIa respectively) was 90% trans-dimethyl ester XXVIIIa and 10% cis-dimethyl ester XXXIVa after each had been separately heated at reflux temperature in methanolic sodium methoxide for 2 to 14 hours. These equilibrium data were considered reasonable when the envelope configuration of the cyclopentane ring was taken into consideration (15).

The rearrangement of α -halo ketones (cyclic and aliphatic) in the presence of certain bases to give salts of

carboxylic acids such as described in Brenner's work is known as the Favorskii rearrangement. The reaction course of the Favorskii rearrangement was established by Loftfield (16a,b). By labelling the halogen-bearing carbon (α carbon) of 2-chlorocyclohexanone (XXXV) with ^{14}C and subsequent Favorskii rearrangement with ethoxide ion, Loftfield showed that an intermediate must have been present in which the α and α' carbons were equivalent as shown by XXXVI. These results were explained by the cyclopropanone intermediate XXXVI. It was reasoned that cleavage of XXXVI could occur at either α carbon. This was verified when half the labeled carbon was found at each of these two carbons in the product cyclopentanecarboxylic acid (XXXVII).



Two major stereochemical mechanisms have been proposed as the predominant path of reaction. The first of these is the one arising from the work of Loftfield (16a,b), in which the first step of the reaction is the formation of a mesomeric carbanion by removal of an α' hydrogen followed by an SN_2' type displacement of chlorine at the α carbon to form the cyclopropane intermediate XXXVI.

More important to our studies is the mechanism proposed by Aston and Newkirk (17) in which the α and α' carbon atoms are at some time equivalent. This concept was supported by

the work of Burr and Dewar (18). These authors proposed an intermediate representing various states of a zwitterion shown as follows:

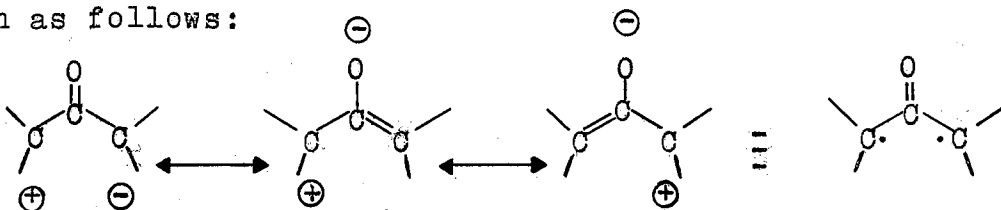


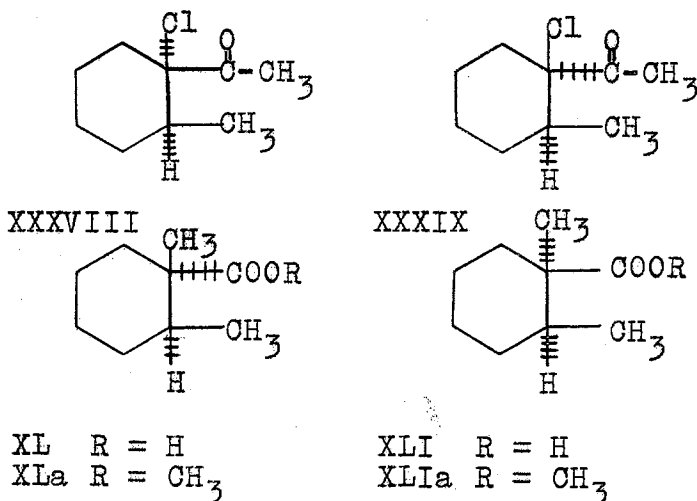
Fig.10-Zwitterion Intermediate in the Favorskii Rearrangement

The intermediate in Fig. 10 was formed by simultaneous loss of an α' hydrogen and the α halogen, and collapse to the cyclopropanone ring intermediate.

Both mechanisms have enolate formation through loss of an α' hydrogen as the first and rate-determining step and both proceed through a cyclopropane intermediate; therefore no conclusions have been reached through kinetic studies to distinguish these mechanisms. However, it was noted that these mechanisms could be distinguished by using compounds such as the isomeric 1-chloro-2-methylcyclohexyl methyl ketones (XXXVIII and XXXIX) since the two mechanisms differ during halogen removal (19). A synchronous SN_2' displacement would involve inversion of configuration at the α carbon, whereas a delocalized zwitterion formation of the type shown in Fig. 10 would alter the stereochemistry and product formation would be determined by steric factors.

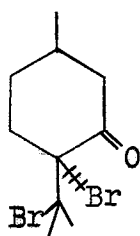
Stork and Borowitz (19) in studying the trans- and cis-isomers of 1-chloro-2-methylcyclohexyl methyl ketone (XXXVIII and XXXIX respectively) concluded that the formation of the cyclopropanone intermediate is concerted (or synchronous)

with inversion of configuration at the halogen-bearing carbon. The Favorskii rearrangement of the ketone XXXVIII was accomplished by adding it to a suspension of dry sodium benzyl-oxide in ether under a nitrogen atmosphere at 15-20°. Hydrolysis gave cis-1,2-dimethylcyclohexanecarboxylic acid XL, thereby showing inversion had taken place at the halogen-bearing carbon atom of XXXVIII. In support of this, the rearrangement of ketone XXXIX under the same conditions yielded the trans-1,2-dimethylcyclohexanecarboxylic acid XLI (19).

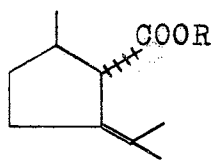


House and Gilmore (20) suggested that either or both mechanistic routes may operate depending upon reaction conditions. A reinvestigation of Sterk and Borowitz's (19) (XXXVIII) system showed that inversion or retention may result depending on polarity of the reaction medium. Reaction of ketone XXXVIII with a solution of sodium methoxide in methanol, which is considered to be strongly polar, yielded a mixture of the methyl esters of XL (40.5% XLa

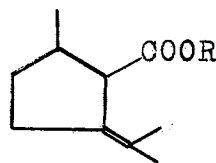
formed with inversion at the α -carbon) and of XLI (51.5% XLIa formed with retention of configuration at the α -carbon). However, reaction of XXXVIII with a suspension of sodium methoxide in 1,2-dimethoxyethane, considered to be a less polar system, produced the methyl ester XLa in 94.6% yield. The foregoing established the dependence of stereochemistry of the Favorskii rearrangement on the polarity of the reaction medium for the 1-chloro-2-methylcyclohexyl methyl ketones (XXXVIII and XXXIX) and possibly other systems.



XLII



XLIII R = H
 XLIIIa R = CH₃



XLIV R = H
 XLIVa R = CH₃

A stereospecific Favorskii rearrangement of pulegone dibromide XLII has been reported (21). Treatment of XLII with an excess of sodium ethoxide in either ethanol or dimethoxyethane gave trans-pulegenic acid (XLIII). Similarly, treatment of XLII with an aqueous potassium hydroxide solution gave a mixture of the trans- and cis-pulegenic acids (XLIII and XLIV respectively). Epimerization studies with the methyl esters XLIIIa and XLIVa showed the equilibrium ratio to be 70:30 trans-isomer to cis-isomer. These studies further showed that product specificity as well as stereospecificity depends largely on reaction conditions used in the Favorskii rearrangement.

CHAPTER III

DISCUSSION

The four 3-methylcyclopentane-1,2-dicarboxylic acids (nepetic acids III through VI) having (R) configuration at the methyl-bearing carbon were synthesized, separated, and purified. Two of these acids, the trans,trans and cis,trans acids III and V, were previously undescribed in the literature. The four isomeric acids III through VI have the same absolute configuration (R configuration) at the methyl-bearing carbon as the starting compound pulegone (XVI). Therefore these acids are named the pulegone series of nepetic acids as contrasted to the series of 3-methylcyclopentane-1,2-dicarboxylic acids having opposite absolute configuration (catnip series acids VII through X). Unless otherwise stated, all references to nepetic acids will be to the pulegone series.

The initial step of the synthetic procedure was the acid hydrolysis of pulegone (XVI) to (+)-3-methylcyclohexanone (XVII). This reaction was studied in detail by varying the concentration of hydrochloric acid used, the speed of stirring and the volume of steam which distilled XVII from the reaction flask. The best acidic condition found was a 1:2 volume ratio of concentrated hydrochloric acid to water. Vigorous agitation of the two-phase reaction mixture and a steady flow of external steam were found to give the best

results. Two different routes used for the synthesis of the nepetic acids are shown in Fig. 11.

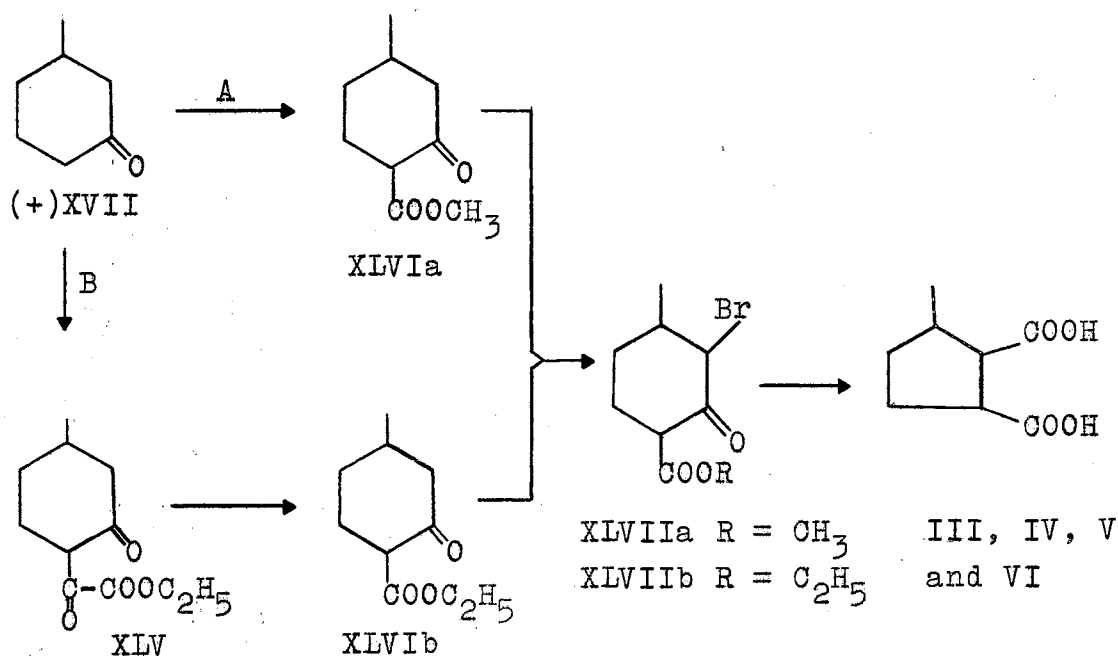


Fig. 11 - Synthesis of the Nepetic Acids (Pulegone Series)

The major difference in routes A and B in Fig. 11 is that the former route requires one less step for the synthesis. Synthesis route B was studied first because a literature precedent existed for synthesis of the similar compound trans-cyclopentane-1,2-dicarboxylic acid (XXVIII) (12). The major disadvantage of route B lies in the preparation and purification of ethyl (4-methyl-2-oxocyclohexyl) glyoxylate (XLV) in that the reagents must be completely anhydrous to obtain reasonable yields. Also, considerable difficulty was encountered during distillation of XLV and frequently the yields were low due to tar formation. This capricious step and the subsequent decarbonylation to give ethyl 4-methyl-2-oxocyclohexanecarboxylate (XLVIb) can be

avoided by substituting route A which is the more efficient and provides a 56% overall yield of nepetic acids as compared to the yields of 10-12% through route B.

The synthesis of the methyl 4-methyl-2-oxocyclohexanecarboxylate (XLVIa) through route A rather than the β -keto ester XLVIb via route B was made possible by Corey's work on the direct condensation of XXXI and dimethyl carbonate to give a β -keto ester (14). Prior to this the condensation of dialkyl carbonates with cyclohexanones was believed to give primarily condensation at oxygen rather than carbon (22). Corey's method entails use of a powerful base such as sodium hydride in dioxane solvent (14). Corey's conditions were adopted for the synthesis of the β -keto ester XLVIa.

While the Corey approach to the synthesis of XLVIa is considered to be superior, certain precautions are necessary. It was observed that during the condensation of dimethyl carbonate and (+)-3-methylcyclohexanone (XVII) large volumes of hydrogen were evolved and the reaction became so vigorous that it was difficult to control if addition of XVII was too rapid. Temperature control is essential to moderate the reaction. Caution should also be exercised during decomposition of the reaction mixture since excess sodium hydride is present.

There was no improvement in yield of XLVIa when the mineral oil diluent was washed from the sodium hydride.

An attempt was made to prepare the β -keto ester XLVIb by substituting diethyl carbonate for dimethyl carbonate in the condensation with (+)-3-methylcyclohexanone (XVII). How-

ever, gas chromatography of the main fraction from distillation of the reaction product showed it to be a complex mixture. An infrared spectrum of this fraction showed a striking similarity to that of the β -keto esters XLVIa and XLVIb. Gas chromatography comparison of the distillation fraction with XLVIb prepared via route B (Fig. 11) indicated that XLVIb was one of the components of the complex mixture. It may be possible to improve the selectivity of the condensation by eliminating any excess sodium hydride and carefully controlling the temperature during the reaction and while decomposing the reaction mixture.

The key step of the synthesis was the Favorskii rearrangement of the bromo keto esters XLVIIa or XLVIIb to the nepetic acids (acids III through VI). This was accomplished by adding bromine to an ether solution of the β -keto ester XLVIa or XLVIb and subjecting the resulting bromo keto ester XLVIIa or XLVIIb to a Favorskii rearrangement in a boiling solution of ethanolic sodium hydroxide (12). The reaction product was an oily mixture of the nepetic acids III, IV, V, and VI accompanied by phenolic material and other minor by-products. Some of the by-products are believed to consist of methylcyclopentane monocarboxylic acids. The phenolic material, as yet unidentified, can be destroyed with potassium permanganate without noticeable attack of the nepetic acids. In work-up it was found that any aqueous solution containing the nepetic acids must be strongly acidic in order to release the acids and get good yields upon extraction with ether.

Once the nepetic acids were synthesized, their separation into pure isomers and stereochemical assignment became paramount. Preliminary analytical studies with gas chromatography using phenyldiethanolamine succinate (PDEAS) and Apiezon L columns indicated that the dimethyl esters of the nepetic acids could be separated. Four major peaks representing the four dimethyl nepetates were observed. The individual gas chromatography peaks were identified by successively adding small amounts of dimethyl nepetates of known absolute configuration and stereochemistry and observing an increase in peak height and area.

The pair of cis-esters Va and VIa, shown to be cis through formation of water-insoluble barium salts of the parent acids, were observed to have the longer retention times and therefore were represented by the last two peaks of the gas chromatography trace. The dimethyl nepetate VIa was known to have the cis,cis configuration because it was derived from hydrogenation of genipin (I) and was used to establish the identity of the fourth peak in the gas chromatogram. Therefore, the cis,trans-ester Va corresponded to the third peak.

The known trans,trans-dimethyl nepetate (VIIa) from the catnip series was also available and was used to identify the first peak of the gas chromatogram (2,4). Therefore, the remaining and second peak was assigned to the trans,cis-dimethyl nepetate (IVa). In summary the peaks due to the dimethyl nepetates appeared on the gas chromatogram in the

following order: trans,trans; trans,cis; cis,trans and cis,cis.

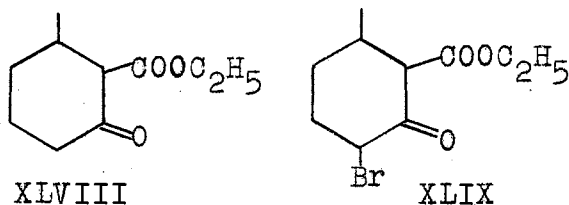
An inconsistent ratio of nepetic acids formed in the Favorskii rearrangement was observed. Particularly noticeable was the decreased percentage of cis isomers V and VI in later runs.

The Favorskii rearrangement was studied in detail to determine why these cis isomers should be formed in relatively lower yields during some reactions. Since the concentration of base was nearly the same in every reaction, this factor was probably not responsible for the relative decrease in yield of the cis isomers. The Favorskii rearrangement of bromo keto ester XLVIIb was carried out at room temperature and also at the reflux temperature. In both reactions the concentration of the base was held constant. Gas chromatography analysis of the esterified reaction products revealed that the nepetic acids formed in the reaction carried out at room temperature were significantly richer in the cis,trans and cis,cis acids V and VI as compared to the nepetic acids from the reaction carried out at the reflux temperature. The cis acids were essentially absent in the reaction product isolated from the latter reaction.

These studies indicate that the sterically least favored isomers will form at the lower reaction temperature. These observations are in keeping with what is known about the strongly polar solution of sodium hydroxide, water, and

ethanol used for the Favorskii rearrangement (20,21). Under such conditions the cyclopropanone intermediate is probably formed from the Zwitterion intermediate (see Fig. 10), and thus product formation would be determined by steric considerations (17,18).

A study of the mechanism of the Favorskii rearrangement must be deferred until a precise knowledge of the composition of mixtures of the keto esters XLVib and XLVIII as well as the bromo keto esters XLVIIb and XLIX is known. At present it is not known whether ethyl 6-methyl-2-oxocyclohexanecarboxylate (XLVIII) is a contaminant of ethyl 4-methyl-2-oxocyclohexanecarboxylate (XLVib). Application of physical methods of analysis such as n.m.r., infrared spectroscopy and gas chromatography failed to solve the problem.

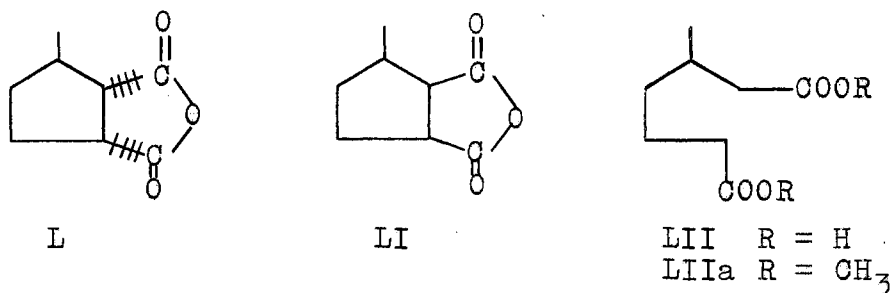


If XLVIII is present, it is a contaminant which does not alter the carbon skeleton of the final products (nepetic acids) but may have a pronounced effect on the ratio of nepetic acid isomers in the product mixture through formation of ethyl 3-bromo-6-methyl-2-oxocyclohexanecarboxylate (XLIX) which may provide an entirely different stereochemical reaction course.

Initially we intended to isolate the individual nepetic acids by preparative gas chromatography of their corresponding dimethyl esters. However, the relative small difference in

retention times between the trans,cis- and the cis,trans-dimethyl nepetates (IVa and Va) indicated that initial separation of the trans acids III and IV from the cis acids V and VI would be helpful.

The mixture of trans nepetic acids III and IV was obtained almost free of the cis acids V and VI by crystallization of the oily mixture of all four isomers, or using the reaction products from the higher temperature Favorskii rearrangement reactions which contain essentially no cis acids.



The mixture of cis nepetic acids V and VI was isolated either as a water-insoluble barium salt mixture or from a mixture of their respective anhydrides L and LI. However, the separation of the cis acid isomers via their barium salts from a mixture of all four nepetic isomers was not complete. Analysis of the water-soluble material after work-up showed that some of the cis acids remained. In addition, small amounts of the trans acids were detected upon work-up of the water-insoluble material. Good yields of a mixture of the two cis acids V and VI relatively free from the trans acids III and IV were obtained upon hydrolysis of the mixture of cis anhydrides L and LI formed by treatment of the oily

mixture of all four nepetic acids with acetic anhydride. This method also provided a separation from any β -methylpimelic acid (LII) which might have formed. The dimethyl ester (LIIa) has nearly the same retention time as cis,cis-dimethyl nepetate (VIa).

Since the esterification of large amounts of nepetic acids using diazomethane was impractical, the method of Clinton and Laskowski (23) was used to prepare the dimethyl esters, which were formed in good yield. The diethyl esters of the nepetic acids were also prepared but showed no advantage over the dimethyl esters in ease of preparation or in the resolution of their gas chromatography peaks.

Apiezon L was found to be the better of the columns available for gas chromatographic separation of the dimethyl nepetates when the factors of peak resolution, column substrate bleeding and sample capacity were taken into account. Initial separations of the individual trans dimethyl nepetates (IIIa and IVa) using a half-inch diameter column was not complete and required a second separation. This two-step separation procedure with the limitation of 0.5-ml. sample injection proved to be inefficient as only 15-20% recovery was obtained.

The trans,trans-dimethyl ester IIIa and trans,cis-dimethyl ester IVa were separated and obtained as pure samples with relative efficient recovery through preparative gas chromatography using a large-diameter column. The time

involved in this separation was comparatively short and only one pass through the column was necessary. The esters IIIa and IVa were saponified to the trans,trans- and trans,cis- nepetic acids (III and IV respectively) and each was characterized by comparison of melting points with the corresponding isomers VII and VIII of the catnip series (2). The dimethyl esters IIIa and IVa were characterized by comparison of their infrared spectra with those of the corresponding racemic dimethyl esters (4).

However, the peak resolution between the cis,trans- and the cis,cis-dimethyl nepetates (Va and VIa) was not as good as that obtained for the two trans esters IIIa and IVa. Also large-scale gas chromatography did not lend itself well to the separation of the cis dimethyl nepetates. The separation of the cis,trans- and cis,cis-nepetic acids (V and VI respectively) was made possible through the difference in rates of crystallization of the cis,trans and the cis,cis barium salts. A sample of the cis nepetic anhydrides I and LI was hydrolyzed, treated with barium hydroxide and the resulting mixture was filtered. Work-up of the aqueous filtrate yielded a mixture of acids containing a larger percentage of the cis,cis acid VI than cis,trans acid V when compared to the acid mixture obtained from work-up of the barium salt precipitate. This latter acid mixture was crystallized, and pure cis,trans-nepetic acid (V) was obtained after recrystallization from ether and petroleum ether.

The mixture of acids recovered from the above aqueous

filtrate was treated again with barium hydroxide and filtered. Additional barium salt precipitated after 12 to 15 hours. Since it was known that some separation was accomplished through an initial barium hydroxide treatment and that the cis,cis acid VI also formed an insoluble barium salt, this latter material was assumed to be the barium salt of the cis,cis acid VI. Work-up of the barium salt which precipitated from the filtrate yielded an oil which would recrystallize only after being seeded with a small crystal of the cis,cis acid obtained from the degradation of genipin. Recrystallization of this latter solid afforded pure cis,cis-nepetic acid VI and an admixture of this acid with that obtained from the degradation of genipin showed no depression in melting point.

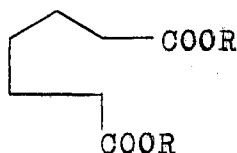
The preparation of cis,cis-acid VI via the formation of cis anhydride mixture L and LI suggests that the remaining unknown cis,cis-acid X of the catnip series could be prepared through this same procedure.

A sample of cis,cis-dimethyl nepetate (VIa) was saponified to determine whether isomerization took place. The saponification mixture was acidified, and extracted with ether. Esterification with diazomethane, followed by gas chromatography showed that isomerization occurred since a mixture of all four nepetic acids III through VI was obtained with the trans,trans acid III as the major component. For this reason, and because of the small difference in retention times between cis,trans- and cis,cis-dimethyl nepetates

(Va and VIa), no attempt was made to separate the mixture of these two esters on large diameter preparative scale gas chromatography column. The n.m.r. spectra of the nepetic acids (III, IV, V and VI) and the respective dimethyl esters (IIIa, IVa, Va, and VIa) provided a useful means of further distinguishing between the individual isomers. The ring methyl protons are apparently influenced enough by the stereochemical environment that the chemical shifts of the protons of the methyl group in the individual acids and esters are different and thus provide a means of identifying a particular isomer. Another distinguishing chemical shift is found for the hydroxyl groups in the isomeric acids and the methoxyl groups in the dimethyl esters.

Brenner (12) reported isolating only the trans-cyclopentane-1,2-dicarboxylic acid (XXVIII) from the Favorskii reaction of ethyl 2-oxo-3-bromocyclohexanecarboxylate (XXXII). Since the preparation of the nepetic acids afforded some of the cis isomers, the reaction with XXXII was repeated to determine if any cis-cyclopentane-1,2-dicarboxylic acid (XXXIV) forms. A sample of ethyl 2-oxocyclohexanecarboxylate (XXIX) was treated with bromine and the resulting bromo keto ester (XXXII) was subjected to the Favorskii reaction under the same conditions used for preparing the nepetic acids (III through VI). The reaction yielded the trans acid XXVIII as the major product, but approximately 5% of the cis acid XXXIV was also found to be present. These results were verified by gas chromatography of the dimethyl esters of the reaction product, and by comparison of

retention times with authentic samples of trans- and cis-esters XXVIIIa and XXXIVa respectively. A third minor unidentified component which was not dimethyl pimelate (LIIIa) was also observed.



LIII R = H
LIIIa R = CH₃

The degradation of genipin (I) was repeated and a sample of cis,cis-nepetic acid (VI) isolated. In the previous work this acid had to be isomerized, which resulted in a mixture of acids with a broad melting point. The major component of the mixture was assigned the trans,cis configuration and on the basis of optical rotation assumed to be the enantiomer of the trans,cis-nepetic acid VIII of the catnip series. Repetition of this work in our laboratory yielded a mixture of acids melting at 90-97° containing trans,cis- and trans,trans-nepetic acids IV and III respectively in a 5.3:1 ratio. The melting point of an admixture of the cis,cis-acid obtained from the degradation of genipin and the cis,cis-acid obtained in our laboratory from pulegone showed no depression, whereas the racemic cis,cis-nepetic acid (pair VI and X) melts at 130-132° (4). Thus the configuration of the cis,cis-nepetic acid (VI) obtained from the degradation of genipin is unambiguously shown to be in the opposite steric series to that of the nepetic acids obtained from nepetalactone (II).

CHAPTER IV

EXPERIMENTAL^{1,2,3,4}

Unless otherwise stated all esterifications were accomplished by adding to a cold ethereal solution of the acid a cold ethereal solution of diazomethane prepared in one of the two following ways:

Preparation of Diazomethane from N-Methyl-N-nitroso-p-toluenesulfonamide (Diazald). A mixture of 35 ml. of Carbitol (diethylene glycol monoethyl ether) and 10 ml. of ether was added to a solution of 6 g. of potassium hydroxide in 10 ml. of water all in a 200-ml. Claisen flask. The flask was fitted with a dropping funnel, condenser, and a water bath

¹ All melting points are corrected, and all boiling points are uncorrected.

² Unless otherwise stated the infrared spectra were determined on Beckman IR-5 and IR-5A spectrometers as films on sodium chloride cells.

³ Grateful acknowledgment is made to Dr. William C. Hamilton and his associates of the Continental Oil Company, Ponca City, Oklahoma for supplying the nuclear magnetic resonance spectra and for use of their preparative gas chromatography equipment.

⁴ The columns used for analytical gas chromatography were 1/8" or 1/2" x 10' columns packed with either PDEAS, Apiezon L or LAC 886 on acid-washed Chromosorb W (60-80 mesh).

held at 70°. To this was added a solution of 21.5 g. of Diazald in 150 ml. of ether over a period of thirty minutes via the dropping funnel. The ethereal solution of diazomethane was collected in a flask set in a dry-ice acetone bath kept at 0° (4).

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°, 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 reaction was assumed complete when the yellow color of the EXR-101 in the reaction flask and of the distilling ether disappeared. During this reaction, the receiver was cooled with dry ice (without acetone) and ether was added from the dropping funnel whenever the amount of ether in the reaction flask became small. By this method, an ether solution containing approximately 2 g. of diazomethane was obtained from 7.1 g. of EXR-101.

During the latter part of the reaction, the lower layer became white and viscous and stirring became difficult.

Preparation of (+)-3-Methylcyclohexanone (XVII) from (+)-Pulegone (XVI). To a 5-l., two-necked flask was added 1,800 ml. of a 33.3% (by volume) solution of concentrated

hydrochloric acid (sp. gr. 1.188) in water. To this was added 1650 ml. (1540 g., 10 mole) of oil of pennyroyal (Fritzche Brothers) containing about 85% pulegone by weight.

The flask was fitted with a steam inlet tube extending into the mixture and a 4-foot Vigreux column to which in turn was attached a flood head. The mixture was heated and agitated vigorously with a magnetic stirrer.

The material which distilled slowly as it formed between 56-80° (approximately 7 hours) consisted mainly of acetone. Steam was then passed into the reacting mixture until organic material ceased to appear in the condensate (approximately 8 hours). The steam distillate was saturated with sodium chloride and the organic layer separated to give crude (+)-3-methylcyclohexanone (XVII) as a light yellow liquid. The crude product was dried over anhydrous magnesium sulfate, filtered, and distilled to give 722 ml. (661 g.) of colorless (+)-3-methylcyclohexanone (XVII), boiling at 168° (58-60°/12.5 mm.). The semicarbazone was prepared and found to melt at 180.5°. Gas chromatography shows that oil of pennyroyal contains several impurities. However, if it is considered to be 85% pulegone, the reaction yield is 69%.

Ethyl 4-Methyl-2-oxocyclohexanecarboxylate (XLVIb) from (+)-3-Methylcyclohexanone (XVII). Four moles (92 g.) of clean sodium were added to 120 ml. of dry ethanol (dried over 3A Linde molecular sieve) in a 5-l., three-necked flask equipped with a dropping funnel, cone stirrer with glass shaft, and a reflux condenser with drying tube. When the

temperature of the sodium ethoxide solution was reduced to less than 10° , a dry, ice cold mixture of 448 g. (4 moles) of (+)-3-methylcyclohexanone (XVII) and 584 g. (4 moles) of diethyl oxalate was added via the dropping funnel over a period of 45 minutes. Vigorous stirring was maintained throughout the addition, after which it was stirred an additional 2 hours at ice bath temperature. A thick slurry formed and the reaction mixture was allowed to stand overnight. The reaction mixture was acidified at temperatures below 14° by dropwise addition of a cold sulfuric acid solution prepared from 112 ml. of concentrated sulfuric acid and 870 g. of crushed ice. The mixture was diluted to 10 liters in a 12-liter separatory funnel and the organic layer separated. The aqueous layer was extracted with benzene and the combined extracts and organic layer washed with water. The benzene was removed by distilling on a steam bath yielding a crude concentrate of ethyl (4-methyl-2-oxocyclohexyl)-glyoxalate (XLV). However, in an attempt to distill XLV, decomposition took place and the distillation was stopped. An attempt to pyrolyze the mixture of crude XLV with powdered soft glass and a trace of iron gave only a low yield of ethyl 4-methyl-2-oxocyclohexanecarboxylate (XLVib). Compound XLV was finally flash-distilled by heating with a heating mantle under reduced pressure to give 266 g. of colorless ethyl (4-methyl-2-oxocyclohexyl)-glyoxalate (XLV), b.p. 110° - 130° / 7 mm. or 117° / 4 mm. The yields ranged from 32% to 37%. Some XLVib may have resulted from

pyrolysis during the distillation of XLV.

Powdered soft glass (2.5 g.) and a trace of iron were added to 411 g. of XLV in a 1-liter distillation flask heated by an oil bath, and stirred with a magnetic stirrer. The oil bath was heated to and held at 165° to 170° and at this temperature 341 g. ethyl 4-methyl-2-oxocyclohexanecarboxylate (XLVIb) was distilled under reduced pressure. The product distilled at 110-130° at varying unknown pressures, and was redistilled at 59 to 60°/2 mm. in 96% yield.

Attempted Preparation of Ethyl 4-Methyl-2-oxocyclohexanecarboxylate (XLVIb) Using Diethyl Carbonate. To a 1-liter, three-necked, round-bottomed flask fitted with a nitrogen inlet, addition funnel, stirring shaft, and condenser was added 85 g. (1.94 mole) of a 56.3% oil dispersion of sodium hydride in 250 ml. of p-dioxane. To this mixture was added 240 ml. (2.0 mole) of diethyl carbonate. The flask was surrounded by a hot water bath (80-85°) and then 60-70 ml. of (+)-3-methylcyclohexanone (XVII) (approximately 0.50 mole 56 g.) in 250 ml. of p-dioxane was added dropwise over a period of 75 minutes. At first, evolution of hydrogen was slow, but after 30 minutes evolution was rapid and the hot water bath was removed. Addition of XVII was discontinued temporarily until the evolution of hydrogen subsided at which time the hot water bath was replaced and addition continued. Heating and stirring was continued for 40 minutes after the addition was completed.

After cooling, the reaction mixture separated into two

layers. Due to the large excess of sodium hydride present, foaming took place and the reaction became hot upon addition of a few ml. of water. After cooling, the reaction mixture was poured into a larger Erlenmeyer flask and decomposed slowly with dilute acetic acid.

The organic layer was separated in a separatory funnel and the aqueous layer extracted three times with ether. The organic layer was combined with the ether extracts and the resulting mixture was washed successively twice with water, twice with sodium bicarbonate solution and twice with water, and finally with saturated aqueous sodium chloride.

The mixture was then dried with anhydrous magnesium sulfate, filtered, and the ether distilled. Distillation yielded several fractions. The major fraction (72-74^o/1.4 mm.) gave an infrared spectrum corresponding closely to that of ethyl 4-methyl-2-oxocyclohexanecarboxylate (XLVIb). However, gas chromatography showed it to be a complex mixture of several compounds.

Ethyl 3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (XLVIIb) from Ethyl 4-Methyl-2-oxocyclohexanecarboxylate (XLVIb). One mole (184 g.) of XLVIb was combined with 15 ml. of dry ether in a 5-l., three-necked, round-bottomed flask. To this solution was added dropwise 168 g. (1.05 mole) of bromine over a period of an hour. The reaction mixture was agitated at ice-salt bath temperature throughout the reaction and then diluted with ether and poured over 160 g. of sodium bicarbonate on ice. The ether layer was

separated and the aqueous layer extracted three times with ether. The combined ether extracts were dried with magnesium sulfate, filtered and the ether drawn off under vacuum to yield a crude mixture of ethyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (XLVIIb). A portion of the bromo keto ester XLVIIb was distilled at 130°/0.4 mm. and a center cut was analyzed.

Anal. Calcd. for $C_{10}H_{12}O_3Br$: C, 45.62; H, 5.75; Br, 30.36. Found: C, 45.47; H, 5.49; Br, 30.64.

3-Methylcyclopentane-1,2-dicarboxylic Acids (III-VI)
(Nepetic Acids, Pulegone Series) from Ethyl 3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (XLVIIb). Half the bromo keto ester XLVIIb from the preceding step was added over a period of 10 minutes to a solution of 260 g. of sodium hydroxide in 1-l. of water and 3-l. of 95% ethanol. Nitrogen was passed over the reaction mixture as it was heated with agitation. After 75 minutes, the mixture began to reflux and the remainder of the bromo keto ester XLVIIb was added via a dropping funnel over a period of 20 minutes. The reaction was heated at the reflux temperature for an additional hour. Ethanol was then removed by stripping with a water aspirator and heating on the steam bath. The reaction mixture was cooled and then acidified with concentrated hydrochloric acid and extracted three times with ether. The aqueous layer was extracted continuously for 8 hours. The combined ether extracts were extracted with a solution of sodium bicarbonate. Extraction was continued

until the last two extracts were basic to pH paper.

The sodium bicarbonate-insoluble, ether-soluble layer yielded 10 g. of a dark brown liquid with a phenolic odor. The combined sodium bicarbonate extracts were acidified with 6N hydrochloric acid and extracted with ether. The aqueous solution was continuously extracted with ether for 8 hours. The ether extracts were combined, dried with magnesium sulfate, and filtered and the ether was distilled to give 113 g. of a crude oily mixture of 3-methylcyclopentane-1,2-dicarboxylic acids (III-VI) (nepetic acids of the pulegone series).

To remove the phenolic material, 12 g. of the crude reaction product was treated with a dilute potassium permanganate solution until no more manganese dioxide formed. The mixture was made basic with a 10% sodium hydroxide solution, and then filtered. The filtrate was acidified with 6N hydrochloric acid and extracted with ether. The combined ether extracts were dried and the ether removed on a rotary evaporator at water aspirator pressure yielding 10.2 g. of a mixture of the four nepetic acids trans-trans (III), trans-cis (IV), cis-trans (V), and cis-cis (VI), plus some β -methylpimelic acid (LII) and other minor impurities. The yield of crude acid mixture based on keto ester XLVIb was 55.8%.

The oily mixture crystallized to a slurry. Filtration gave solid material consisting mainly of the trans acids III and IV, while the filtrate (and the major portion) remained a mixture.

When the bromo keto ester (XLVIIb) was agitated at room temperature during the Favorskii rearrangement, other reaction conditions remaining the same, a higher ratio of cis isomers was obtained.

Preparation of Methyl 4-Methyl-2-oxocyclohexanecarboxylate (XLVIa) from (+)-3-Methylcyclohexanone (XVII). To a 5-liter, four-necked flask, fitted with an addition funnel, stirring shaft, nitrogen inlet and a condenser was added 200 ml. of dry benzene. To this was added 100 g. of a 56.3% sodium hydride mineral oil dispersion (2.3 mole NaH), 1000 ml. of dry dioxane, and 560 ml. of dimethyl carbonate (approximately 9 moles) in that order (14). Washing the sodium hydride suspension with benzene did not improve the yield of the final product XLVIa.

To the stirred solution under a nitrogen atmosphere, and at a constant bath temperature of 80-85°, was added dropwise a solution of 153 ml. (140 g., 1.25 mole) of (+)-3-methylcyclohexanone (XVII) in 100 ml. of dry dioxane. After about one hour, the reaction became vigorous, heat was evolved, the solvent began boiling and large amounts of hydrogen gas evolved from the reaction. The hot-water bath was removed until the vigorous reaction abated. The addition of XVII was continued for an additional 1.5 hours.

The hot-water bath was replaced and the reaction mixture was heated at 80° with stirring for an additional 30 minutes. The evolution of hydrogen gas subsided and the reaction mixture became viscous. Stirring was discontinued

and the reaction mixture allowed to cool, and cautiously acidified with aqueous acetic acid. An ice bath was kept available for cooling and to suppress foaming which was experienced at times.

The stirrer was removed and on settling, the reaction mixture separated into two phases. The organic layer was separated and added to the ether extracts of the water layer. This mixture was washed successively with water, twice with sodium bicarbonate, and finally with a saturated sodium chloride solution. A dark-colored emulsion invariably formed which complicated the separation. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated. Distillation at $74^{\circ}/2$ mm. yielded 181 g. (85% yield) of methyl 4-methyl-2-oxocyclohexanecarboxylate (XLVIa), m.p. 22° .

Small scale runs were carried out under a nitrogen atmosphere. This was omitted for those runs larger than 1 mole.

Preparation and Attempted Isolation of Methyl-3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (XLVIIa). A 170-g. (1 mole) sample of methyl 4-methyl-2-oxocyclohexanecarboxylate (XLVIa) was added to 90 ml. of dry ether in a 5-l., three-necked, round-bottomed flask cooled by an ice bath. Bromine (168 g., 1.05 moles) was added dropwise with stirring and cooling over a period of 75 minutes. Upon completion of addition, the reaction mixture was stirred for an additional 15 minutes. Evolution of hydrogen bromide gas was apparent.

The reaction mixture was then diluted with ether and poured over 160 g. of sodium bicarbonate in ice water. This mixture was allowed to stand for 30 minutes, with occasional stirring. The organic layer was separated and the aqueous layer extracted three times with ether. The combined ether extracts were dried with anhydrous magnesium sulfate, filtered, and the ether distilled, giving a crude mixture of methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (XLVIIa).

An attempt was made to distill the bromo keto ester XLVIIa. However, decomposition took place and no further attempts were made to purify or isolate XLVIIa.

Preparation of the Four Nepetic Acids (III through VI) from Methyl 3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (XLVIIa). The reaction product mixture containing the bromo keto ester XLVIIa (from 1.8 moles XLVIa) as previously described was divided and each portion added to a 5-liter flask containing 4000 ml. of 95% ethanol. To each flask was added a solution of 230 g. sodium hydroxide in 770 ml. of water. The reaction mixtures were heated at reflux temperature for three hours under a nitrogen atmosphere. After cooling, the sodium bromide was filtered out and washed well with ether. The filtrate and ether washings were combined and then distilled to remove ethanol and ether. The remaining aqueous solution was strongly acidified with concentrated hydrochloric acid. Continuous extraction with ether for 24 hours and work-up yielded 208 g. (66% of theoretical yield) of crude nepetic acids III through VI. It was important that

the aqueous layer remain strongly acidic during the continuous extraction to insure complete removal of the nepetic acids.

Preparation of a Mixture of the Diethyl Nepetates (IIIb through VIb). A 10 g. sample of a mixture of the four nepetic acids III through VI in a solution of 50 ml. of benzene, 30 ml. of ethanol, and 0.5 ml. concentrated sulfuric acid was heated at reflux temperatures for 6 hours in a 250-ml. flask fitted with a head for azeotropic distillation of water. However, no water layer was observed. The benzene-alcohol mixture was distilled at which time the solution became extremely dark. Vacuum distillation yielded a mixture of IIIb, IVb, Vb, and VIb, the diethyl nepetates, b.p. 105-106°/1.5 mm.

Preparation of a Mixture of the Dimethyl Nepetates (IIIa through VIa). A 22 g. sample of the nepetic acid mixture III through VI was added to 34 ml. methanol, 80 ml. methylene chloride, and 6 ml. of concentrated sulfuric acid and the mixture heated at the reflux temperature for 15 hours. The cooled reaction mixture was washed successively with water, twice with a saturated sodium bicarbonate solution, and again with water (23). The methylene chloride was removed through a rotary evaporator at water aspirator pressure. Distillation yielded 22.1 g. (86.6% yield) of a mixture of the dimethyl nepetates IIIa through VIa, b.p. 62.5°-66.5°/48 mm.

cis Nepetic Anhydrides L and LI from a Crude trans Nepetic Acid Mixture (III and IV). A 275 g. sample of a crude mixture (before potassium permanganate treatment) of trans nepetic acids III and IV was added to a 3-l. flask fitted with a short Vigreux column and distillation head. To this flask was added 1500 ml. of acetic anhydride and the entire mixture was heated at reflux temperature for 14 hours. The acetic acid formed by the reaction was distilled periodically.

After the heating period, the acetic anhydride was distilled at 139° , and the remaining mixture distilled under a vacuum at $83^{\circ}/0.25$ mm. yielding 164.9 g. of a crude mixture of cis,trans- and cis,cis-nepetic anhydrides (L and LI respectively) in 67% yield.

Isolation, Separation and Purification of the cis,trans- and cis,cis-Nepetic Acids (V and VI) from the Mixture of cis-Nepetic Anhydrides L and LI (see Fig. 12). A 160-g. (1.04 moles) mixture of cis,trans- and cis,cis-nepetic anhydrides (L and LI) was heated four hours in the presence of several moles of water. The resulting aqueous solution of nepetic acids was cooled and extracted three times with ether. The aqueous layer was labeled A and retained. The ether extracts were combined, evaporated and the residue was treated with a saturated solution of aqueous barium hydroxide until additional precipitate or cloudiness failed to appear on further addition. The barium salts were filtered out and washed with water. The filtrate and water washings were bottled and

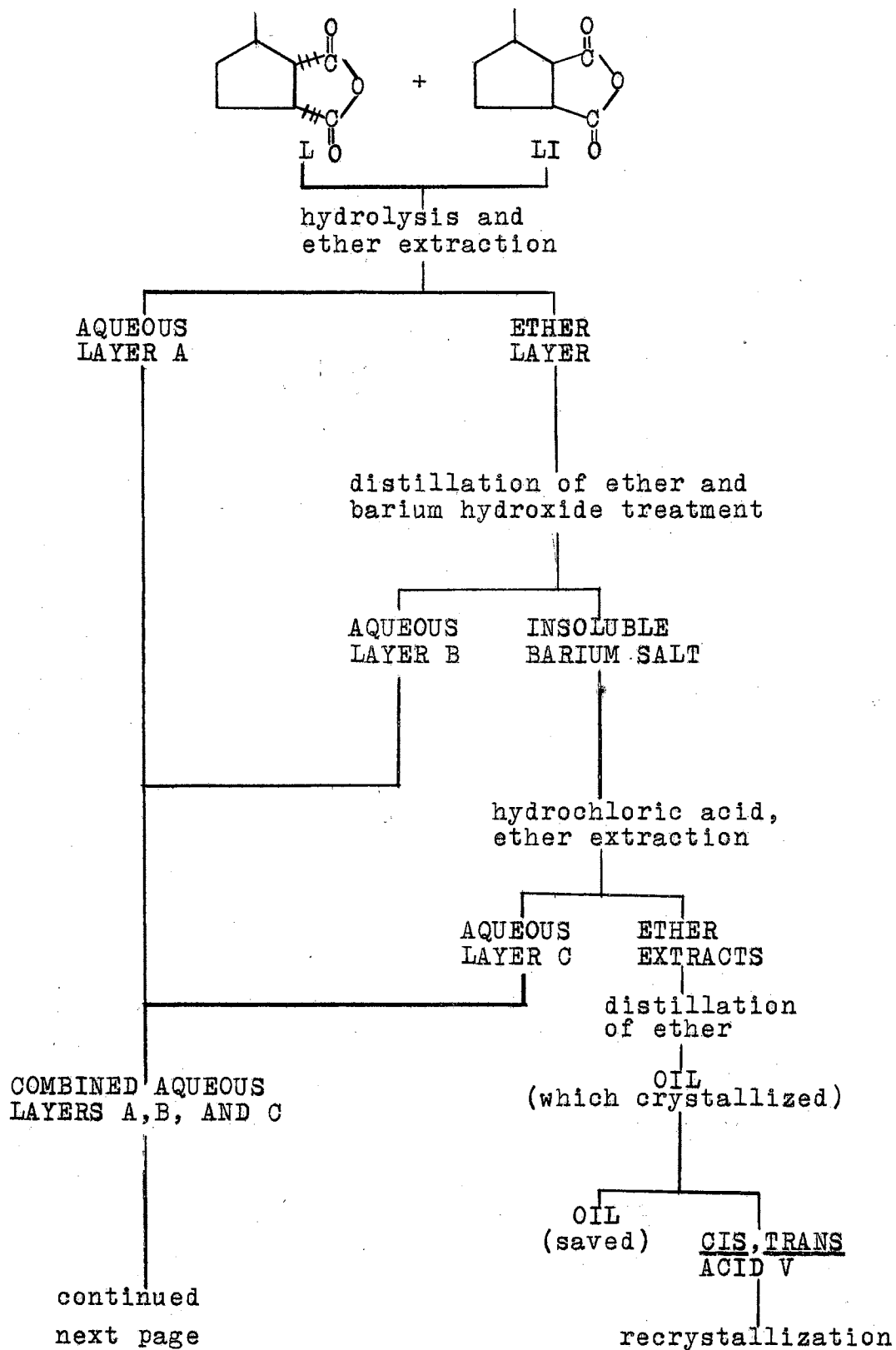


Fig. 12 - Isolation and Separation of cis,trans- and cis,cis-Nepetic Acids

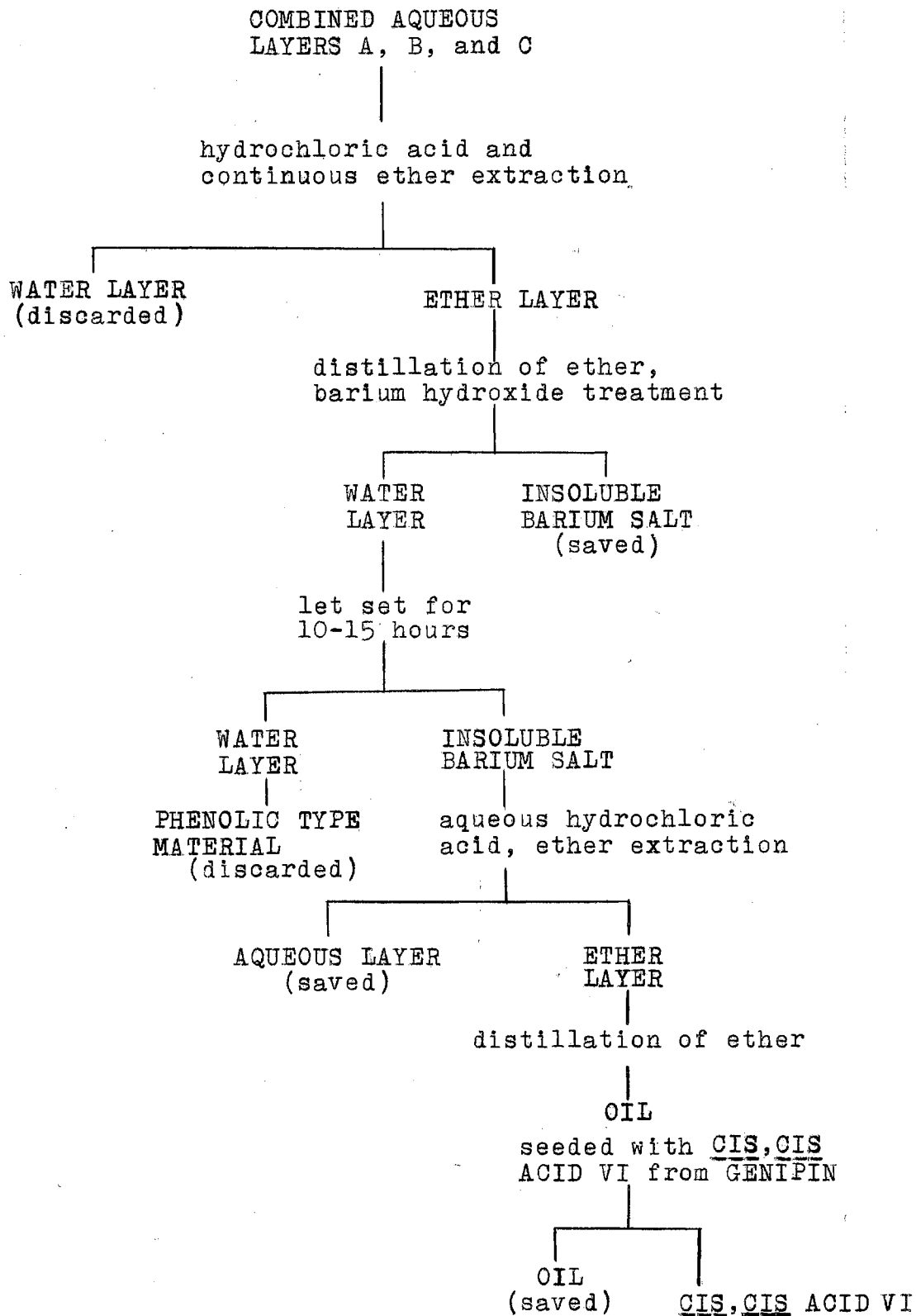


Fig. 12 - (continued) Isolation and Separation of cis,trans- and cis,cis-Nepetic Acids

TABLE I
 N.M.R. SPECTRAL CHARACTERISTICS OF THE NEPETIC ACIDS
 AND THEIR DIMETHYL ESTERS

| Compound | Chemical Shifts (δ) ¹ | | | Stereochemical Assignment |
|----------|---|--------------------------------|------------------|---------------------------|
| | ring CH ₃ ² | -OCH ₃ ² | -OH ³ | |
| III | 1.109 | | 11.9 | <u>trans,trans</u> -acid |
| IV | 0.990 | | 11.2 | <u>trans,cis</u> -acid |
| V | 1.134 | | 12.4 | <u>cis,trans</u> -acid |
| VI | 1.107 | | 10.7 | <u>cis,cis</u> -acid |
| IIIa | 1.109 | 3.68 | | <u>trans,trans</u> -ester |
| IVa | 0.901 | 3.68 | | <u>trans,cis</u> -ester |
| Va | 1.095 | 3.64 | | <u>cis,trans</u> -ester |
| VIa | 1.014 | 3.66 | | <u>cis,cis</u> -ester |

¹ The chemical shifts are given in p.p.m. (δ) downfield from the internal standard of tetramethylsilane (T.M.S.).

² Doublets

³ Singlets

labeled B. The filtered barium salt mixture was acidified with concentrated hydrochloric acid to release the cis-nepetic acids. This solution was extracted five times with ether. The aqueous layer was saved and labeled C. The combined ether layers were dried and evaporated to give 112 g. (64% yield) of a crude mixture of V and VI. This mixture was allowed to crystallize for 3 days. The crystals were removed by filtration and washed with petroleum ether (66-68° fraction) followed by a small volume of cold ether to give 29 g. of crude cis,trans-nepetic acid (V), m.p. 124-126°. Gas chromatography of the dimethyl ester of this crude acid showed it contained 95% of Va. Two additional recrystallizations from ether-petroleum ether gave cis,trans-nepetic acid (V), m.p. 131-132°. Gas chromatography showed it to be free of other isomers. The cis,trans catnip acid IX has m.p. 132° (2). Table I gives the principal chemical shifts from n.m.r. analysis.

The retained aqueous solutions (A, B, and C) containing a mixture of cis-nepetic acids V and VI were combined, strongly acidified and extracted continuously with ether for 12 hours. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated to give 56 g. of a crude mixture of the cis-nepetic acids V and VI in 32% yield. The overall yield of recovered cis-nepetic acids was 96%.

This latter crude mixture of cis-nepetic acids V and VI was treated a second time with saturated aqueous barium

hydroxide solution. The resulting barium salt precipitate was filtered out immediately, and the filtrate allowed to stand at room temperature for 15 hours at which time an additional crop of barium salts was obtained on filtration. This crop of barium salts was treated with hydrochloric acid, extracted with ether, the ether extract dried and evaporated to give 7.6 g. of crude cis-nepetic acids enriched with cis, cis-nepetic acid (VI) as shown by gas chromatography of the dimethyl esters. The 7.6-g. sample of crude cis-nepetic acids was seeded with a small crystal of cis,cis-nepetic acid (VI) obtained from degradation of genipin (I). On standing for four days, needle-shaped crystals developed. Filtration yielded 1.55 g. of crude cis,cis-nepetic acid (VI), m.p. 132-134°. The crude acid was further purified by dissolving in a small volume of ether, adding an equal volume of petroleum ether (b.p. 66-68°), warming the mixture on the steam bath and allowing to cool. Crystallization was initiated by scratching the interior of the flask with a glass rod. The resulting crystals were filtered out and washed with petroleum ether to yield 0.9 g. of pure cis,cis-nepetic acid (VI), m.p. 140-140.5°. An admixture of VI with the cis,cis-nepetic acid from genipin (I) showed no depression in melting point. Table I gives the principal chemical shifts from n.m.r. analysis.

Preparation of a Mixture of the cis-Dimethyl Nepetates Va and VIa from cis-Anhydrides L and LI. To a 5.9-g. sample of nepetic anhydride mixture L and LI was added 10 ml. of

methanol, 20 ml. of methylene chloride, and 1.5 ml. of concentrated sulfuric acid. The resulting mixture was heated at reflux temperature for 14 hours. Water was added to the cooled reaction mixture until two layers were obtained. The mixture was shaken in a separatory funnel and the layers separated. The top aqueous layer was discarded and the methylene chloride layer was washed with a sodium bicarbonate solution at which time the red color, which had persisted throughout the reaction period, disappeared. After washing again with water, the solution was dried with anhydrous magnesium sulfate, filtered, and the methylene chloride distilled, giving 4.7 g. (72.5% yield) of material containing a mixture of cis,trans- and cis,cis- dimethyl nepetates (Va and VIa) as well as some minor impurities which were shown to be present by gas chromatography.

Preparation of cis,trans-Dimethyl Nepetate (Va). A 1.00 g.-sample of cis,trans-nepetic acid (V), m.p. 131-132^o, was esterified with diazomethane. Microdistillation at 1 mm. (oil bath temperature was 115^o) gave approximately 1 ml. of cis,trans-dimethyl nepetate (Va). Table I gives the principal chemical shifts from n.m.r. analysis. The infrared spectrum of Va was almost identical to that of the racemic cis,trans dimethyl ester (4).

Preparation of cis,cis-Dimethyl Nepetate (VIa). An 0.1042 g. sample of cis,cis-nepetic acid (VI), m.p. 141^o, was esterified with diazomethane. Microdistillation at 1 mm. (oil bath temperature was 115^o) gave approximately 0.1 ml. of

cis,cis-dimethyl nepetate (VIa). Table I gives the principal chemical shifts from n.m.r. analysis. The infrared spectrum of VIa was almost identical to that of the racemic cis,cis-dimethyl ester (4).

Isomerization of cis,cis-Dimethyl Nepetate (VIa) During Saponification. A 0.1-g. sample of VIa was added to a solution of 5% sodium hydroxide containing a small amount of methanol, and the resulting mixture was heated at reflux temperature for three hours. The methanol was stripped and the remaining aqueous solution acidified with dilute hydrochloric acid, saturated with sodium chloride, and extracted continuously with ether for 24 hours. The ether extract was dried with magnesium sulfate, filtered, and the ether evaporated, giving a light brown solid. Esterification via diazomethane followed by gas chromatography analysis showed the brown solid to be a mixture of all four isomers with the trans,trans isomer IIIa as the major component.

Preliminary Gas Chromatographic Separation of trans-Dimethyl Nepetates IIIa and IVa. Preparative gas chromatography conditions using the F and M model 770 gas chromatograph were as follows:

(1) 15% Phenyl-diethanolamine succinate (PDEAS) by weight on acid-washed firebrick packed in 6 feet of 3/4" column, preparative flow 4.5, reference flow (analytical) 4.0, detector temperature 250°, injection port temperature 210°, bridge current at 150 ma., back pressure at zero and column temperature of 180°.

(2) 15% PDEAS on Chromosorb W packed in 16 feet of 3/4" column, injection port at 260°, detector at 250°, and column temperature of 200°.

(3) A 20% Apiezon L column (8' x 1/2") under the same set of conditions described in 1.

Collection traps containing steel helices and partially filled with ether were used. These were cooled in a dry ice-acetone bath.

Condition 2 gave the best resolution of peaks. However, the efficiency of sample collection was low and the sample was accompanied by considerable PDEAS column substrate bleed. The substrate contaminant was difficult to remove from the sample. The maximum size sample injected was 0.5 ml.

The column bleed was considerably reduced when condition 3 was used. A preparative scale separation was carried out using 0.5 ml. injections. Trap A was found to contain a 5:1 ratio of trans,trans-ester IIIa to trans,cis-ester IVa. Trap B contained trans,cis-ester IVa and trans,trans-ester IIIa in a 4.3:1 ratio.

Isolation of trans,trans-Dimethyl Nepetate (IIIa). Isolation of the pure trans,trans-dimethyl nepetate (IIIa) was accomplished by reinjecting the sample containing IIIa and IVa in a 5:1 ratio (Trap A). Condition 3 was used and this gave an 0.80 ml. sample of trans,trans-dimethyl nepetate (IIIa) shown by gas chromatography analysis to be free of impurities. The infrared spectrum of IIIa was almost identical to that of the racemic trans,trans dimethyl ester (4).

Isolation of trans,cis-Dimethyl Nepetate (IVa). trans,cis-Dimethyl nepetate (IVa) was isolated by reinjecting the sample containing IVa and IIIa in a 4.3:1 ratio (Trap B). This separation and purification was carried out on a 3/8" x 8' column of 60-80 mesh, acid-washed Chromosorb W coated with 15% Apiezon L. The operating conditions of the Aerograph Autoprep model A-700 used for this separation were: column temperature 165°, collector temperature 220° and helium flow 120 ml./min. The collection traps were glass U-tubes containing a nichrome spiral. These traps were cooled in a dry ice-acetone bath. A 0.5-ml. sample injected in 0.05 ml. portions yielded 0.25 ml. of trans,cis-dimethyl nepetate (IVa). The infrared spectrum IVa was almost identical to that of the racemic trans,cis-dimethyl ester (4).

Separation of trans,trans-Dimethyl Nepetate (IIIa) and trans,cis-Dimethyl Nepetate (IVa) Using Preparative Gas Chromatography Employing Large Diameter Columns. Conditions for preparative gas chromatography using the large scale unit employing 4" diameter columns developed by Continental Oil Company were as follows: 20% Apiezon L on 60-80 mesh, acid-washed Chromosorb W, carrier flow 9 l./min. at 10 p.s.i., injection port temperature 250°, column temperature 200°, and thermal detector temperature 250°. A total of 65.4 g. of mixtures containing approximately 65% trans,trans- and 35% trans,cis-dimethyl nepetates (IIIa and IVa) were injected. The sample volumes injected ranged from 7 to 20 ml. The collection traps were cooled by an ice bath. The materials

collected were as follows: one gram of a leading unidentified peak, 25.6 g. of 99% pure trans,trans-dimethyl nepetate (IIIa), 13.2 g. of 99% pure trans,cis-dimethyl nepetate (IVa) and 4.2 grams of a mixture of IIIa and IVa from the by-pass trap. The total recovery was 67%. The sample containing IIIa was distilled at 69°/1.0 mm. and collected. Sample IVa was distilled at 72°/1.1 mm. Table I gives the principal chemical shifts of IIIa and IVa from n.m.r. analysis.

Preparation of trans,trans-Nepetic Acid (III). To 10.0 g. of trans,trans-dimethyl nepetate (IIIa), purified through preparation gas chromatography, was added 250 ml. of a 5% sodium hydroxide solution and 175 ml. methanol. The solution was heated at reflux temperature for 3 hours and the methanol was distilled under reduced pressure. The remaining solution was acidified with hydrochloric acid and extracted with ether three times and then continuously extracted for 28 hours. The combined ether extracts were dried with magnesium sulfate and filtered, and the ether was evaporated, giving 10.3 g. of a light yellow oil which was crystallized upon scratching. Recrystallization from a mixture of ether and Skellysolve F gave 3.5 g. of trans,trans-nepetic acid (III), m.p. 119-120°. Evaporation of the solvents from the mother liquor and recrystallization from a mixture of ether and Skellysolve F yielded an additional 3.6 g. of acid III. The catnip trans,trans-nepetic acid (VII) has m.p. 118° (2). The total yield of trans,trans-nepetic acid (III) was 83%. Table I gives the principal chemical shifts from n.m.r. analysis.

Preparation of trans,cis Nepetic Acid (IV). To 8.0 g. of trans,cis-dimethyl nepetate (IVa) was added 200 ml. of a 5% sodium hydroxide solution and 75 ml. of methanol and the resulting solution was heated at reflux temperature for three hours. Work-up as described for trans,trans-nepetic acid (III) yielded 7.8 g. of a light yellow solid. A single recrystallization of this yellow solid from ether and Skellysolve B yielded 2.0 g. of trans,cis-nepetic acid (IV), m.p. 113-115°, $[\alpha]_{25}^D -88^\circ$ (c 2.1, CHCl₃). The catnip trans,cis-nepetic acid (VIII) has m.p. 114-115° (2). An admixture of IV with the nepetic acid obtained as a degradation product of furopelargone A (XXVII) showed no depression in melting point (11). Table I gives the principal chemical shifts from n.m.r. analysis.

Preparation of a Mixture of trans- and cis-Cyclopentane-1,2-dicarboxylic Acids (XXVIII and XXXIV) (12). To a solution of 14.1 g. of ethyl 2-oxocyclohexanecarboxylate (XXIX) and 5 ml. of dry ether contained in a 100 ml., three-necked, round-bottomed flask placed in a salt ice-water bath was added dropwise 15 g. of bromine with stirring. The reaction mixture was diluted with ether and poured onto a mixture of 20 g. sodium bicarbonate and ice. Extraction with ether and evaporation of the combined ether extracts gave the bromination product XXXII.

The bromination product XXXII was heated at reflux temperature for one hour with a solution of 21 g. of sodium

hydroxide in 70 ml. water, and 1000 ml. of 95% ethanol. Nitrogen was passed over the mixture during the heating period. Most of the alcohol was then evaporated and the solution was acidified with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with ether.

The combined ether extracts were washed with a saturated solution of sodium bicarbonate. The combined sodium bicarbonate washings were acidified with 6N hydrochloric acid, saturated with sodium chloride, and extracted with ether. Drying and evaporating the ether gave 8.6 g. (66% yield) of a crude mixture of cyclopentane-1,2-dicarboxylic acids XXVIII and XXXIV.

Part of the crude reaction product was treated with diazomethane and analysis by gas chromatography showed it to contain trans-ester XXVIIIa, a small amount of cis-ester XXXIVa and a third unidentified peak which was not dimethyl pimelate (LIa). Crystallization of the crude mixture from ether gave pure trans-acid XXVIII, m.p. 159-160°. Ether-petroleum ether recrystallization gave more acid with a lower melting point.

Preparation of Pimelic Acid (LIII) from Ethyl 2-Oxocyclohexanecarboxylate (XXIX) (13). In a three-necked round-bottomed 250-ml. flask fitted with a reflux condenser and a dropping funnel was placed 10 g. (0.25 mole) of sodium hydroxide and 30 ml. of anhydrous methanol (dried over Linde Molecular Sieve 3A). The mixture was stirred by a magnetic stirrer and heated for one-half hour. Stirring and heating

was continued and 10 g. of ethyl 2-oxocyclohexanecarboxylate (XXIX) was added over a period of one hour at which time the reaction mixture became thick and could no longer be stirred with the magnetic stirrer. The mixture was then heated an additional 15 minutes without stirring, and allowed to stand overnight. The reaction mixture was diluted with 60 ml. of water and methyl alcohol was removed by distilling until the temperature of the distillate reached 98° . The reaction mixture was then acidified with 21 ml. of concentrated hydrochloric acid added dropwise with stirring. To the hot solution was added 0.37 g. of Darco and the suspension filtered through a heated Buchner funnel. The filtrate was cooled in the freezer and a white precipitate formed. The precipitate was removed by filtration and dried in the air yielding 6.3 g. (67%) of crude pimelic acid (LIII), m.p. $97-100^{\circ}$.

Preparation of β -Methylpimelic Acid (LII). Ethyl 4-methyl-2-oxocyclohexanecarboxylate (XLVIb) (3.8 g.) was mixed with a solution of 5 g. sodium hydroxide in 20 ml. of water and 200 ml. of ethanol and heated at reflux temperature for one hour. The ethanol was evaporated through a rotary evaporator at water aspirator pressure. The remaining mixture was acidified with 6N hydrochloric acid, then extracted several times with ether. These ether extracts were combined and washed well with a sodium bicarbonate solution, and the combined washings acidified with 6N hydrochloric acid and extracted with ether. The ether extracts were combined and dried with magnesium sulfate, filtered and the ether evapo-

rated to give a mixture containing β -methylpimelic acid (LII). Esterification of the reaction mixture with diazomethane and subsequent gas chromatography showed four peaks, the largest being due to dimethyl β -methylpimelate (LIIa).

Hydrogenation of Genipin (I). A solution of 15 g. of genipin (I) (0.067 mole) in 125 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of three grams of prerduced platinum oxide catalyst. During 19 hours, the solution absorbed approximately 0.084 moles of hydrogen, or 63% of the expected two equivalents. The catalyst was removed by filtration and the solution was treated twice with Norite. The solution was then hydrogenated a second time in the presence of prerduced platinum oxide and found to absorb 0.027 moles of hydrogen during 7 hours. The total uptake of hydrogen was 0.111 moles or 83% of the expected. After removing the catalyst, the acetic acid was distilled under vacuum and the residue was taken up in ether and washed with sodium bicarbonate solution until the washings were basic. The ether solution was dried over anhydrous magnesium sulfate and evaporated to yield 10.6 g. of orange oil.

A small sample of the oil was subjected to thin layer chromatography. The mixture was spotted on a silica gel plate and eluted with a 4:2:1 mixture of petroleum ether (40-50°), benzene, and 95% ethanol. Development with iodine vapor showed six spots, two of which were much larger than the rest. Comparison of the R_f values of the two main com-

ponents with those of samples of 9-deoxy-6,7-dihydrogenipin (XXVI) and 1,9-anhydro-6,7-dihydrogenipin determined under the same conditions indicated that these substances were the chief products. The sample apparently contained only a small amount of genipin despite the incomplete reduction. Its insolubility in ether probably caused it to be removed during the washings. All of the components gave brown spots with iodine except genipin which gave a light purple spot.

Ozonolysis of a Crude Mixture of 9-Deoxy-6,7-dihydrogenipin (XXVI) to *cis,cis*-Nepetic Acid (VI). A solution of 10.6 g. of the total reduction product of genipin (I) in 50 ml. of methylene chloride was cooled to -70° and ozone was run in until the solution turned blue. This required approximately one hour. The solution was then added dropwise to a mixture of 50 ml. of 10% sodium hydroxide and 42 ml. of 30% hydrogen peroxide. The mixture was stirred for 30 minutes and then methylene chloride evaporated in vacuo. An additional 70 ml. of 30% hydrogen peroxide were added and the solution stirred overnight. It was acidified with concentrated hydrochloric acid and sodium sulfite was added. Solid sodium chloride was then added until the solution appeared saturated and it was then extracted five times with ether and the ethereal solution dried over anhydrous magnesium sulfate. Evaporation yielded a colorless oil which was made basic with saturated barium hydroxide solution. The precipitate which formed was filtered and then acidified with 6N hydrochloric acid. After the addition of solid sodium

chloride the solution was extracted three times with ether and the ethereal solution dried over magnesium sulfate and evaporated. A solid was obtained upon trituration of the resulting oil with petroleum ether. This was recrystallized from ether-petroleum ether to give 0.75 g. of solid, m.p. 131-135°. A second recrystallization yielded 0.5 g. of cis, cis-nepetic acid (VI), m.p. 136-138°. A sample melting at 140-141° was obtained through additional recrystallizations. The filtrates from this and similar ozonolysis experiments were combined and evaporated. The barium hydroxide precipitation and work-up were repeated and a sample of the semi-solid which was obtained as the product was treated with diazomethane. Gas chromatography of the resulting esters indicated the presence of the dimethyl esters of cis, cis-nepetic acid and cis, trans-nepetic acid in a ratio of 2.5:1. These are VIa and Va respectively.

Epimerization of cis,cis-Nepetic Acid (VI). A solution of 0.7 g. of cis, cis-nepetic acid (VI) in 4 ml. of reagent grade acetic anhydride was refluxed for six hours. The excess acetic anhydride and acetic acid were removed under vacuum and 4.2 ml. of absolute methanol was added and the solution heated at reflux temperature for two hours after which part of the methanol was distilled to remove any methyl acetate which might have formed. This solution was then poured into a solution of 0.4 g. of sodium in 10 ml. of absolute methanol and heated at reflux temperature for 30 minutes. After the addition of 4 ml. of water, the solution was heated

for one hour longer. The methanol was removed under vacuum and water was added. This was partially removed under vacuum and water and benzene were added and the mixture again evaporated. Sufficient water was then added to dissolve the salts which had precipitated. The solution was acidified and extracted four times with ether and the ether extract was dried and evaporated. The residual oil solidified when treated with petroleum ether to yield 0.6 g. of white solid melting broadly below 100° . This was recrystallized from ether-petroleum ether to give 0.35 g. of white solid, m.p. $90-97^{\circ}$. The filtrate and solid were combined and evaporated. The 0.57 g. of solid which remained was dissolved in ether and treated with diazomethane. After removal of the solvent, the resulting mixture of esters was analyzed by gas chromatography and found, by comparison and mixing with the corresponding previously prepared acid esters, to contain the trans,cis-ester IVa and the trans,trans-ester IIIa in a ratio of 5.25:1.

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