

**THE INFRARED SPECTRA OF MODEL COMPOUNDS  
RELATED TO PODOPHYLLOTOXIN**

by

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**Thesis submitted to the Faculty of the Graduate School  
of the University of Maryland in partial  
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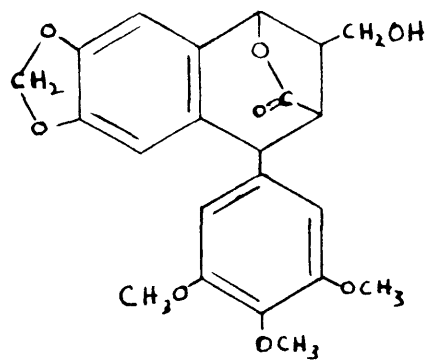
## INTRODUCTION

Podophyllotoxin, a drug obtained from the ground roots of the Podophyllum peltatum (mandrake, may apple) has been shown to have a destructive action on malignant tumors<sup>1,2,3</sup>. As a result, there is a new interest in the structure of the drug and in determining the portion responsible for the anti-carcinogenic activity.

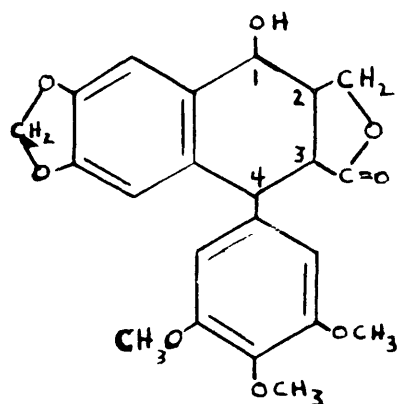
The carbon skeleton of the drug molecule is well established. In 1932, Spath, Wessely, and Nadler<sup>4</sup> and Beresche and Niemann<sup>5,6,7</sup> proposed the following structures for podophyllotoxin (I) and picropodophyllin (II), the compound obtained by the action of basic reagents on podophyllotoxin.

The location of the carboxyl and methylol groups in podophyllic acid (III) was established when podophyllomeronic acid (IV) was obtained from the degradation of podophyllotoxin and picropodophyllin<sup>6,8,9</sup>. In addition, Haworth and Richardson<sup>10</sup> in 1936 synthesized dehydroanhydro-picropodophyllin (V) which proved to be identical to the product obtained by dehydrating and then dehydrogenating picropodophyllin.

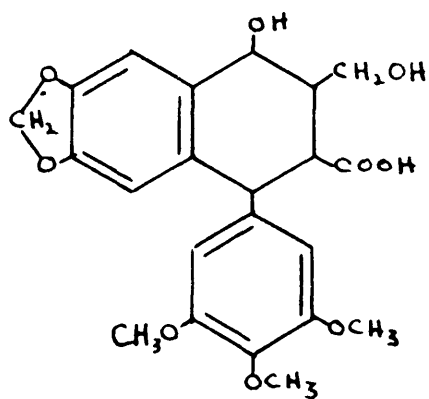
The evidence for the position of the hydroxyl group on carbon-1 was not conclusive. In 1933, Beresche, and Niemann<sup>5,11</sup> oxidized podophyllic acid to obtain the lactone (VI), the structure of which was proven by synthesis. This work eliminated carbon-4 as the site of the free hydroxyl group. However, if the hydroxyl group were placed on carbon-1, it would explain the fact that picropodophyllin could be readily dehydrated, but not podophyllotoxin, and that the same hydroxy acid was obtained by opening the lactone ring of either podophyllotoxin or picropodophyllin. Therefore, it was postulated that picropodophyllin, and podophyllotoxin were structural isomers differing in the hydroxyl group involved in the lactone,



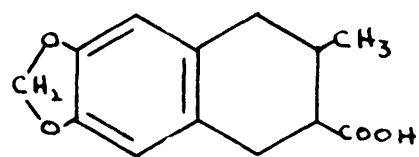
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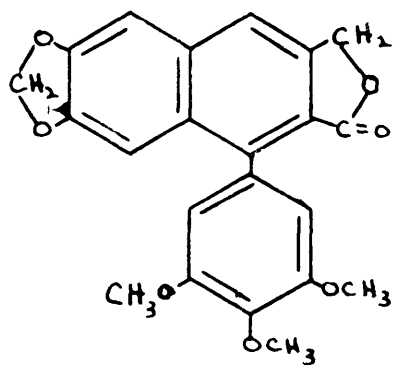
II



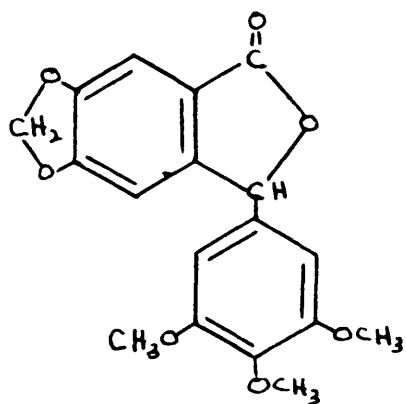
III



IV



V



VI

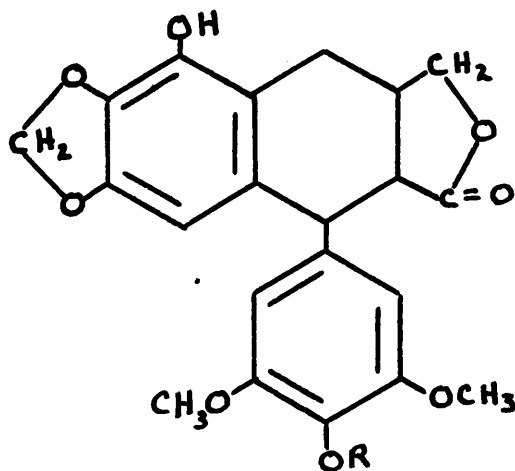
Chart I

and having the same configuration around carbons 1,2, and 3. The quantitative conversion of podophyllotoxin to picropodophyllin by the action of various basic reagents was explained by the difference in strain of the lactone rings.

Thus no positive evidence for the nature of the lactone rings or the position of the hydroxyl group was advanced, and the result of more recent work shows that the Borsche-Spath concepts were incorrect. Drake and Price, at this University, obtained isomeric trihydroxy compounds from the reduction of podophyllotoxin, and picropodophyllin with lithium aluminum hydride.<sup>12,13</sup> If podophyllotoxin and picropodophyllin have the same configuration around carbon-3, and differ only in the hydroxyl group involved in the lactone, identical reduction products should have been obtained.

When acetyl or benzoyl podophyllotoxin is refluxed with sodium acetate in various solvents,<sup>14,15</sup> the corresponding derivatives of picropodophyllin are obtained in good yield. This result, too, is incompatible with the Borsche-Spath formulas. The new evidence led to the conclusion that podophyllotoxin and picropodophyllin differ in configuration around carbon-3, which epimerizes when podophyllotoxin is converted to picropodophyllin.

This concept was further strengthened by the isolation of  $\alpha$  and  $\beta$  - peltatin<sup>16,17</sup> (VII), and the study of the reactions of these analogous compounds.



$\alpha$ -Peltatin - R = H

$\beta$ -Peltatin - R = CH<sub>3</sub>

The peltatins are optically active lactones which are converted to diastereoisomers by the action of basic reagents, as are their acetylated derivatives. These transformations are analogous to those of podophyllotoxin. However, in the peltatins, there is no possibility of an alternate lactone ring. The inversion of the peltatins could be explained only through enolization at carbon-3.

Examination of the models of these types of compounds is fruitless. Both the cis and trans lactones seem to be about equally strained. The examination of the infrared spectra of the peltatins<sup>17</sup> disclosed a small shift in the absorption of the lactone carbonyl group toward higher wave lengths when the peltatins were epimerized, indicating a greater lactone ring stability for the base-stable isomers. Intuitively, the more stable configuration was believed to be cis, and the trans configuration was assigned to the more strained ring. This concept could be extended to podophyllotoxin (trans) and picropodophyllin (cis).

The position of the free hydroxyl group was also investigated. Carbon-4 had been ruled out. Carbon-3 is not a possible site since an enolizable hydrogen must be present at this carbon. Carbon-1 and carbon-2 remain.

A tertiary hydroxyl on carbon-2 would be expected to yield formaldehyde when oxidized with periodic acid, since the periodic oxidation of 1-hydroxymethylcyclohexanol has been shown to be successful. No formaldehyde was detected in the prolonged periodic acid oxidation of picropodophyllin.<sup>15</sup> Meyers at this University failed to obtain any formaldehyde by oxidizing picropodophyllin with lead tetraacetate.<sup>18</sup>

Only carbon-1 remains. Attempts failed to dehydrogenate the secondary alcohol to the ketone with palladium at 230°<sup>9</sup>, or copper chromite in the presence of ethylene at 280° and 150 psi<sup>18</sup>, as did oxidation with potassium

permanganate,<sup>5,9,11</sup> potassium dichromate and chromic oxide, aluminum tertiary butoxide, and ultraviolet irradiation with benzoquinone.<sup>12</sup> In some of the oxidation experiments, large amounts of oxidizing agents were consumed and a good deal of starting material recovered, indicating extensive degradation, possibly the oxidation of the tetralone formed (assuming a secondary alcohol).

Hartwell and Schrecker<sup>15</sup> were able to show that the free hydroxyl group in podophyllotoxin underwent reactions typical of tertiary and secondary benzyl alcohols. They ruled out the tertiary alcohol on the basis of the failure of the periodic acid oxidation. Phosphorus trichloride, thionyl chloride or acetyl chloride react with podophyllotoxin to yield podophyllotoxin chloride, by the replacement of the hydroxyl group. The chloride gives an immediate precipitate with alcoholic silver nitrate, and is readily hydrolyzed in aqueous acetone to a new stereoisomer of podophyllotoxin, epipodophyllotoxin. The reaction with acetyl chloride to give the chloride is analogous to the action of acetyl chloride on phenylmethylcarbinol to give  $\alpha$ -chloroethylbenzene.<sup>19</sup> Still a new stereoisomer was obtained by treating epipodophyllotoxin with piperidine. The new compound, epipicropodophyllin, has the same configuration around carbon-3 as picropodophyllin. The conversion of podophyllotoxin to epipodophyllotoxin, by means of a Walden inversion through the halide, is not compatible with the Borsche-Spath formula. The existence of four diastereoisomers differing only in configuration around carbon-1 and carbon-3, and having a secondary benzyl-type alcoholic group, as well as the other new evidence in recent years, is compatible only with formula II for both podophyllotoxin and picropodophyllin. The compounds are assumed to differ only in the configuration around carbon-3.

## DISCUSSION

The stereochemistry of the lactone ring, and the position of the free hydroxyl group in podophyllotoxin, and picropodophyllin were not known when this work was started. To investigate these aspects of the structure of the drugs, a series of appropriate model compounds were synthesized, and their infrared spectra were empirically compared with the infrared spectra of podophyllotoxin and picropodophyllin.

Part I of the Discussion deals with the synthesis of a series of lactones, and the information obtained from a study of their spectra.

Part II deals with the synthesis of a series of alcohols, and the study of their spectra.

### PART I

#### Lactones Related to Podophyllotoxin

The comparison of the spectra of a large number of compounds has shown that absorption bands occurring at certain frequencies can be correlated with certain bonds or atomic groups within the molecule. Molecules containing a carbonyl group exhibit an absorption band anywhere from  $1810\text{ cm}^{-1}$  to  $1500\text{ cm}^{-1}$ . This band is usually the strongest band in the region. Any strong band between  $1820\text{ cm}^{-1}$  and  $1690\text{ cm}^{-1}$  is almost certainly due to a carbonyl bond.<sup>20</sup> More particularly, the frequency of the band of a carbonyl group usually indicates the type of carbonyl group. Thus bands due to acids are found from  $1700$  to  $1670\text{ cm}^{-1}$ , those due to aldehydes and ketones from  $1725$  to  $1690\text{ cm}^{-1}$ , and those due to ester carbonyls from  $1750$  to  $1725\text{ cm}^{-1}$ .<sup>21</sup>

In their study of a series of carboxylic acid derivatives, Rasmussen and Brettain<sup>22</sup> found that the frequency of the absorption band generally



attributed to the C=O stretching in lactones, varied as the size of the lactone ring.  $\delta$ -Valerolactone has a band at  $1739\text{ cm}^{-1}$  which is of the same frequency as the band found for open chain esters. The corresponding band for  $\gamma$ -butyrolactone was found at  $1770\text{ cm}^{-1}$ , and the band for  $\beta$ -propiolactone at  $1818\text{ cm}^{-1}$ . This shift towards higher frequencies was thought to be associated with ring strain. The strain in the six-membered ring is sufficiently reduced to exert no effect spectroscopically.

Jones, Humphries, and Dobriner<sup>23</sup> in their study of a series of steroids found that  $\delta$ -lactones absorb at  $1742\text{ cm}^{-1}$  and  $\gamma$ -lactones at  $1777\text{--}1780\text{ cm}^{-1}$ . Here again is evidence that the lactone carbonyl associated with a hexacyclic ring absorbs at a lower frequency than the lactone carbonyl associated with a pentacyclic ring.

No appreciable difference in strain can be detected from study of appropriate models of cis and trans lactones related to podophyllotoxin. The conversion of podophyllotoxin to picropodophyllin is quantitative, and if the driving force is the difference in strain between the two lactone rings, then that difference in strain should be considerable, and readily detected by a shift in the frequency of the infrared absorption band.

The infrared spectra of podophyllotoxin and picropodophyllin were obtained with a Perkin-Elmer model 12-C recording spectrometer equipped with a rock salt prism. Podophyllotoxin, m.p.  $157\text{--}158^{\circ}$ , was sufficiently soluble in chloroform and in methylene chloride so that its spectrum could be obtained from a solution of the drug in either of the two solvents in a cell of 0.1 mm. thickness. Picropodophyllin, m.p.  $221\text{--}222^{\circ}$ , was extremely insoluble, and so its spectrum was determined from a concentrated "mull" in mineral oil, pressed between two rock salt plates. The two spectra were rather similar, but seemed to be slightly different in the critical area around  $1775\text{ cm}^{-1}$ . The dispersion

of a rock salt prism at this frequency is poor, and small differences could not be detected with any accuracy. However, a lithium fluoride prism was available, and although the transparency at this region is poor, the dispersion was greatly improved so that the frequency could be determined with an accuracy of  $\pm 1.5 \text{ cm.}^{-1}$ . The calibration could be determined with considerable accuracy since several small, but sharp water bands of known frequency are to be found in this region. To get narrow bands with sharp peaks, dilute concentrations in chloroform were used.

The carbonyl band of podophyllotoxin was found to be  $6 \text{ cm}^{-1}$  higher than that of picropodophyllin. From this information, it may be inferred that the lactone ring of podophyllotoxin is slightly more strained than that of picropodophyllin. No decision could be made as to which was cis and which was trans, although intuitively the cis form might be expected to be the least strained of the two. Also this information does not distinguish between the older Borsche-Spath formulas and the newer concept.

In order to obtain information about the configurations of the lactone rings of podophyllotoxin and picropodophyllin, a series of lactones were prepared and their infrared spectra obtained. The lactones are shown on Chart II. The convention used in this and subsequent charts to denote cis or trans configuration is:



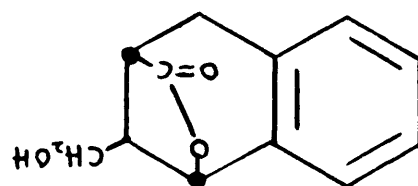
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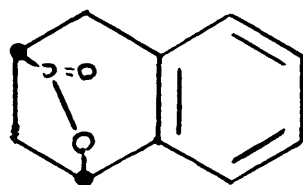
trans

# Chart II

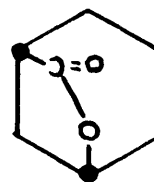
XV



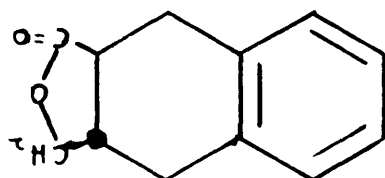
XIV



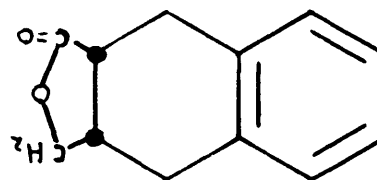
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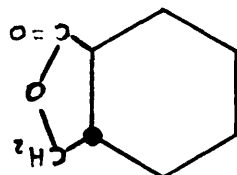
XII



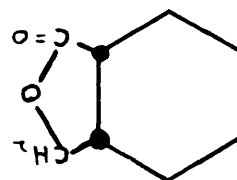
IX



X



XI



Hexahydrophthalide has been obtained by the hydrogenation of phthalide over Raney nickel,<sup>24</sup> and by the hydrogenation of phthalic anhydride in the presence of oxygen-rich platinum black.<sup>25</sup> However, the configuration of the lactone ring of the compound made in either of the two ways is not definitely known.

The stereochemistry of the hexahydrophthalic acids, and their derivatives has been established. When phthalic acid is hydrogenated over platinum black, a hexahydrophthalic acid (XVI), m.p.  $192^{\circ}$ , is obtained.<sup>25</sup> The same acid can also be obtained by condensing maleic anhydride with butadiene, hydrogenating the double bond of the adduct, and opening the anhydride with boiling water.<sup>26,27</sup>

The evidence is that this acid has the cis or meso configuration. Numerous studies have shown that pure cis addition always occurs in the Diels-Alder diene synthesis.<sup>28</sup> The generalization has been made that aromatic compounds hydrogenate predominantly cis under mild catalytic conditions, namely that which occurs over platinum at room temperature, and in the solvent, acetic acid, which gives the most rapid addition.<sup>29</sup> Also, this acid has not been resolved.

If diethyl phthalate is hydrogenated in the presence of Raney nickel, the compound isolated is a diethyl hexahydrophthalate.<sup>30</sup> When this ester is saponified with alcoholic potassium hydroxide, a different hexahydrophthalic acid (XVII), m.p.  $219-220^{\circ}$ , is obtained. The same acid can be prepared by hydrogenating potassium phthalate with nickel oxide at  $300^{\circ}$ .<sup>31</sup> This hexahydrophthalic acid has been resolved using quinine,<sup>32</sup> and therefore, it has the trans configuration. The corresponding diethyl esters have been prepared from the cis and trans hexahydrophthalic acids.<sup>33</sup> The action of alcoholic base on these esters has been studied by Huckel and Groth.<sup>34</sup>

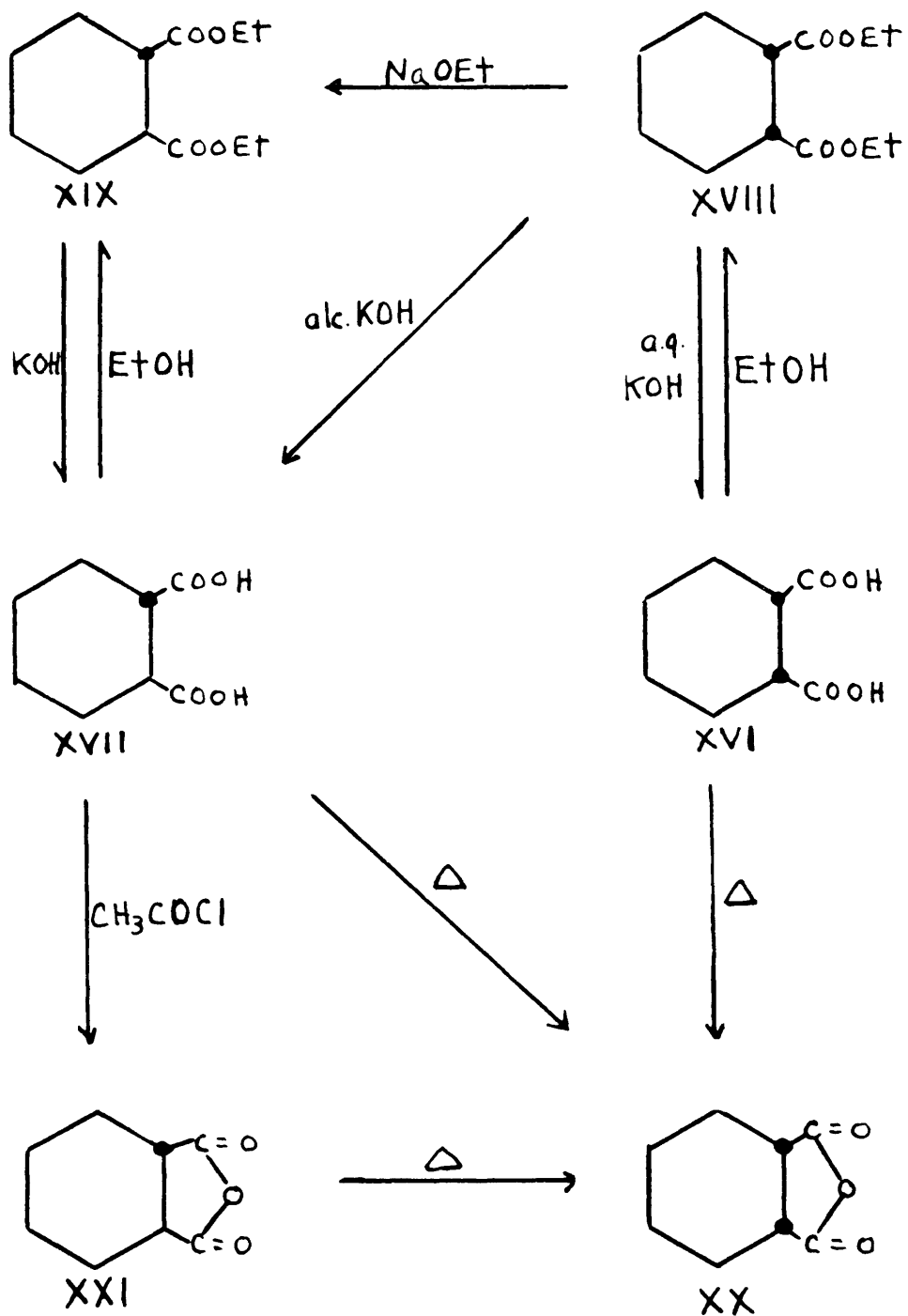


Chart III

If the *cis* diester (XVIII) is heated under reflux with one mole percent of sodium ethoxide in absolute ethanol, it is converted to the *trans* diester (XIX). If it is refluxed with an excess of base in absolute ethanol, the acid isolated is the *trans* acid. The *trans* ester, and the *trans* acid should be more stable than the corresponding *cis* compounds because of steric repulsion. The epimerization is believed to proceed by means of enolization on the carbon alpha to the carbethoxy group. *cis*-2-(3-propionic acid)-Cyclohexanecarboxylic acid does not epimerize. Aqueous base has no effect, and the free carboxylic acids cannot be epimerized this way. The Raney nickel reduction product of diethyl phthalate has been shown to be a mixture of *cis* and *trans* diethyl esters, and the saponification under the Huckle-Croth conditions yielded the *trans* acid exclusively.<sup>30</sup> The *cis* acid (XVI) is converted to its anhydride (XX), m.p. 32°, when it is heated at its melting point.<sup>35</sup> The *trans* acid (XVI) also forms an anhydride (XXI), m.p. 110°, (different from the *cis* anhydride) upon gentle warming with acetyl chloride, but when heated, the less stable *trans* anhydride (XXI) is converted to the *cis* anhydride (XX). Heats of combustion also indicate that the *cis* anhydride is the more stable of the two.<sup>36</sup> If the *trans* anhydride is heated under reflux with a minimum amount of methyl alcohol for a short time, the monomethyl ester of *trans* hexahydrophthalic acid, m.p. 96-97°, is obtained.<sup>32</sup> This ester was saponified with aqueous sodium hydroxide to yield *trans* hexahydrophthalic acid, m.p. 224-224.5°, which is higher than any value recorded in the literature. When methyl hydrogen phthalate is reduced with hydrogen over platinum black, another monomethyl ester of hexahydrophthalic acid, m.p. 68.5-69°, is obtained.<sup>37</sup> Upon saponification with aqueous sodium hydroxide, the *cis*-hexahydrophthalic acid, m.p. 192°, was obtained, and hence this is the *cis* monomethyl ester.

The stereoisomeric lactones of 2-hydroxymethylcyclohexanecarboxylic acid could conceivably be prepared from these monomethyl esters in either of two ways. The ester group could be selectively reduced to the hydroxymethyl group with lithium borohydride, or the unesterified acid group could be converted to the acid chloride, and the acid chloride reduced selectively to the hydroxymethyl group with sodium borohydride.

While aldehydes and ketones are reduced rapidly at room temperature with lithium borohydride, esters are reduced only slowly under forcing conditions. The reaction with acids is complex, and some instances of the reduction, or reactions of an unknown nature, have been reported.<sup>30</sup> Also the free acidic group would react immediately with the lithium borohydride to form an insoluble salt which would make the reduction of the ester group even more difficult.

On the other hand, the reduction of aliphatic acid chlorides with suspensions of sodium borohydride has been reported to proceed smoothly at room temperature.<sup>39</sup> No reaction between sodium borohydride and an ester group has been observed. The yields for polyfunctional acid chlorides are not too good. Chalken and Brown<sup>36</sup> report the reduction of  $\beta$ -carbethoxy propionyl chloride to butyrolactone in only 40% yield. The preparation of carbomethoxy acid chlorides from methyl hydrogen dicarboxylic acids generally gives good yields if the reaction and isolation conditions are mild.<sup>40</sup>

The selective reduction of the proper acid chloride with sodium borohydride was chosen as the better of the two possible courses. Methyl hydrogen phthalate (XXIII), m.p. 82°, was prepared in 83.5% yield by the action of methanol on phthalic anhydride (XXII) according to Ellet and Burgstahler.<sup>41</sup> Vavon and Pleigler<sup>37</sup> have prepared cis methyl hydrogen hexahydrophthalate (XXIV) by hydrogenating 10 gm. of methyl hydrogen phthalate in the presence of 6 g. of platinum black. Using Adams catalyst, as much as 200 g. of

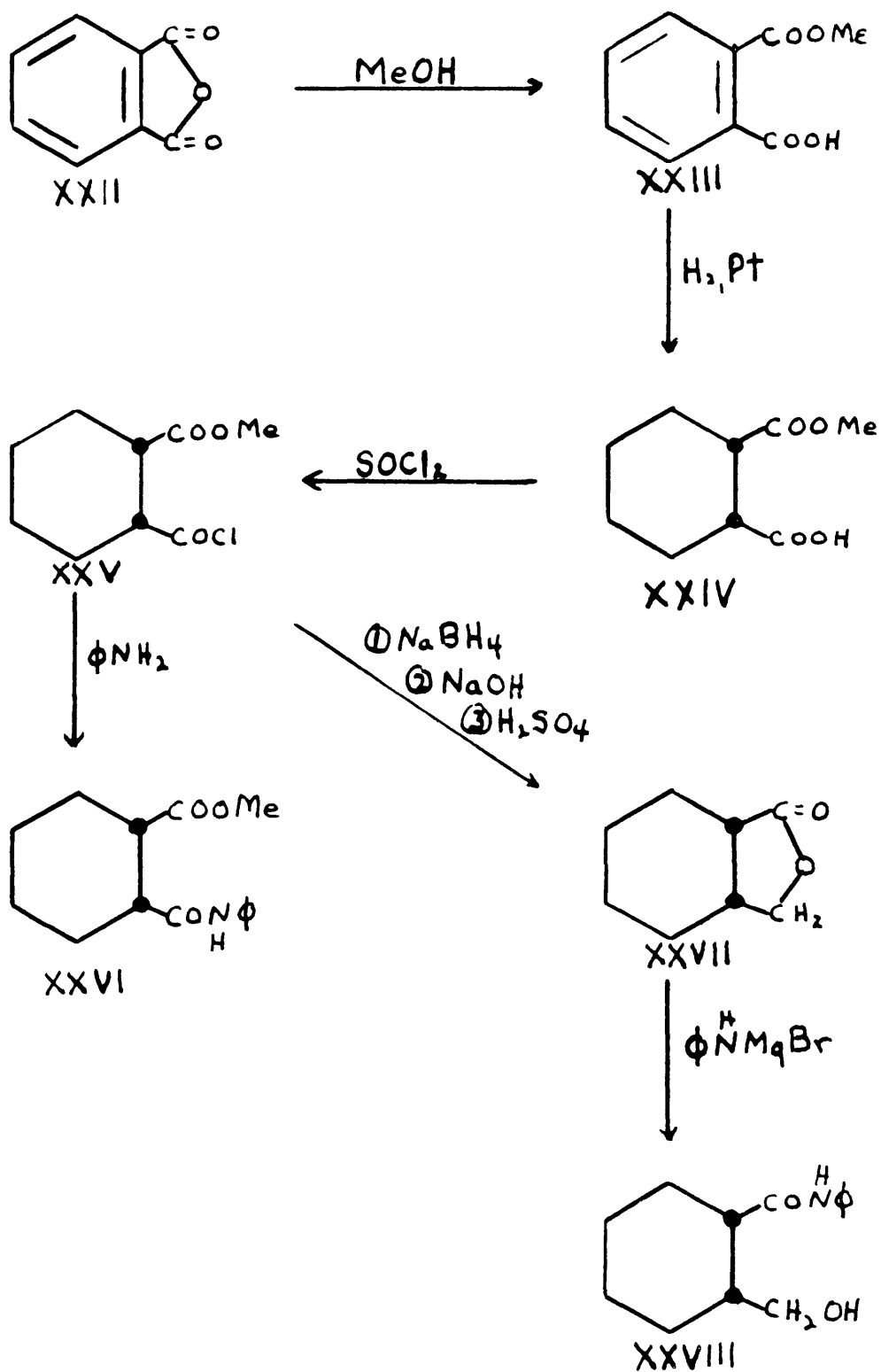


Chart IV



methyl hydrogen phthalate was reduced in 50 g. portions over 1 g. of catalyst. The yield after crystallization from petroleum ether, m.p. 60-80° was 83%.

Thionyl chloride was purified in the following manner: The technical product was first refluxed over sulfur, and then rapidly distilled to give a 94% yield of colored product. It was then redistilled through a five-foot column packed with glass helices. A relatively highly colored forerun was removed, after which an 88% yield of very slightly colored product was collected.<sup>42</sup>

A threefold excess of purified thionyl chloride and cis methyl hydrogen hexahydrophthalate were reacted to produce the acid chloride, 2-carbomethoxycyclohexanecarbonyl chloride (XIV), a colorless, viscous oil in 93% yield. A small sample of the acid chloride reacted at room temperature with dry aniline in ether to yield the 2-carbomethoxy cyclohexanecarboxanilide (XXVI), m.p. 97°.

The acid chloride group of the carbomethoxy acid chloride (XIV) was then selectively reduced with sodium borohydride. The initial product isolated had a high saponification equivalent indicating that a good deal of methyl 2-hydroxymethylcyclohexanecarboxylate was present. In subsequent runs, the crude product was saponified with alcoholic sodium hydroxide, and lactonized by heating under reflux with dilute sulfuric acid. The resulting product, 2-hydroxymethylcyclohexanecarboxylic acid lactone (XXVII), a colorless oil, b.p. 146-147°/27 mm. was obtained in 43% yield. It was insoluble in cold sodium bicarbonate and cold sodium hydroxide, but dissolved rapidly in warm sodium hydroxide, and gave the correct saponification equivalent.

The lactone was converted into its anilide, 2-hydroxymethylcyclohexanecarboxanilide (XXVIII), m.p. 155°, by the action of aniline magnesium iodide.

Diethyl phthalate (XXIX) was hydrogenated over Raney nickel to the diethyl hexahydrophthalate (XXX), a colorless liquid, b.p.  $141^{\circ}/11$  mm. The diester, a mixture of cis and trans isomers, was treated with ethanolic potassium hydroxide to epimerize the cis diester, and saponify the ester groups. The trans-hexahydrophthalic acid (XXXI) was obtained in 93% yield after acidification. The white, crystalline compound melted at  $209-215^{\circ}$ . It was converted to the trans anhydride (XXXII) by the action of a six-mole excess of acetyl chloride. After recrystallization from ethyl acetate, the yield was 68%, m.p.  $143-144^{\circ}$ . Baeyer<sup>35</sup> reports a melting point of  $140^{\circ}$  for this compound.

A brief outline for the preparation of methyl hydrogen trans-hexahydrophthalate has been given by both Werner and Conrad<sup>32</sup> and Fichter and Simon.<sup>43</sup> trans-Hexahydrophthalic anhydride (XXXII) was reacted with absolute methanol. The methanol was then evaporated under reduced pressure. No heat was used as this would tend to increase the yield of the dimethyl ester. The residue, a white solid, was extracted continuously in a Soxhlet extractor with petroleum ether, b.p.  $60-80^{\circ}$ . The unreacted anhydride was very insoluble in the solvent. Both the mono and dimethyl esters were soluble, and upon cooling the extract, the monomethyl ester (XXXIII) precipitated in a pure state. The melting point was  $96^{\circ}$  which agreed with the values in the literature. The yield was 92%.

The trans-carbomethoxy cyclohexanecarbonyl chloride (XXXIV) was prepared in exactly the same way as the cis compound. The yield of viscous, colorless oil was 96% after distillation at  $1\text{ mm}$  at room temperature. Treatment with aniline gave the carbomethoxy cyclohexanecarboxanilide (XXXV), m.p.  $127^{\circ}$ . The acid chloride group was selectively reduced with sodium borohydride in refluxing ether in precisely the same way as the cis compound. The lactone (XXXVI), b.p.  $148^{\circ}/44$  mm., was obtained in 46% yield, and had the proper

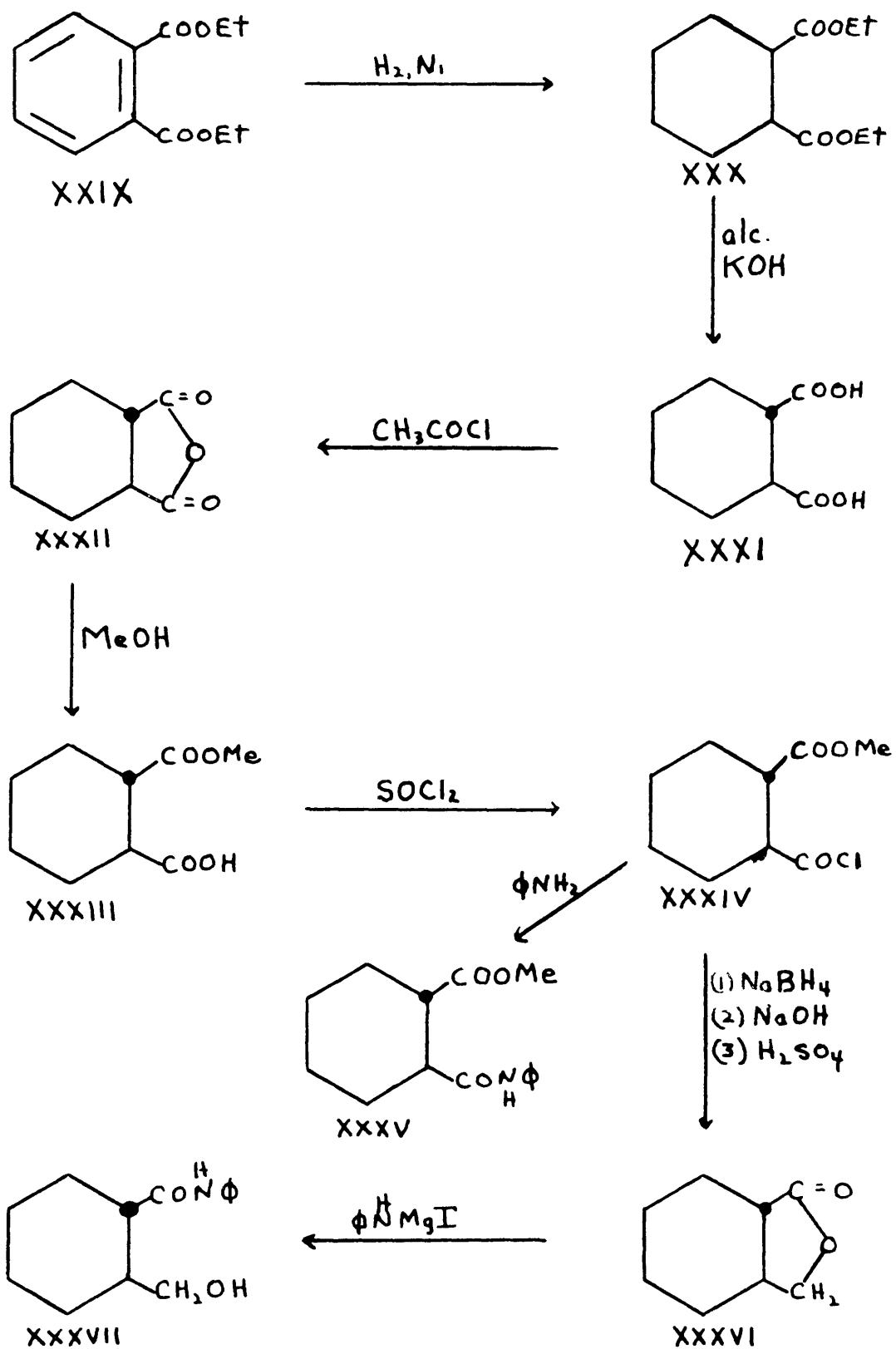


Chart V

saponification equivalent. Treatment with aniline magnesium iodide resulted in the hydroxymethylcyclohexanecarboxyamide (XXVII), m.p. 166°.

	<u>m.p. (cis)</u>	<u>m.p. (trans)</u>
monomethyl ester	55-57°	93-94°
anilide of acid chloride	97°	127°
anilide of lactone	155°	166°

The acid chlorides were prepared under mild conditions, and distilled at room temperature to prevent the loss of methyl chloride and the formation of an anhydride, and also to minimize the possibility of epimerization. Because of steric repulsion, the trans half ester-half acid chloride might be expected to be the more stable compound, and so treatment with thionyl chloride might convert the cis isomer to the trans isomer. Since the isomeric anilides of the acid chlorides having different melting points were obtained, it is assumed that this did not happen. The preparation of isomeric anilides from the lactones indicated that the lactones, too, were isomeric. The melting points of the solid compounds in the cis series are all lower than the melting points of the compounds in the trans series, which indicates that configuration was maintained in each series. This is in agreement with the observation that unsymmetrical cis isomers are nearly always lower melting than the corresponding trans isomers.<sup>44</sup> Other evidence was obtained from the infrared spectra of the lactones, and will be discussed later.

The stereochemistry of the 1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acids, and some derivatives of these acids have been established by the work of Haworth and Slinger.<sup>45</sup> The anhydride of naphthalene-2,3-dicarboxylic acid can be reduced with sodium amalgam to a mixture of cis and trans-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acids. When this mixture is refluxed

with acetyl chloride, an anhydride (XXVIII), m.p.  $254^{\circ}$ , is obtained as a precipitate which can be hydrolyzed to a dicarboxylic acid (XXIX), m.p.  $226-227^{\circ}$ . An isomeric anhydride (XL), m.p.  $183^{\circ}$ , is recovered from the mother liquor of the acetyl chloride reaction, and is hydrolyzed to an isomeric dicarboxylic acid (XLI), m.p.  $195^{\circ}$ . Since the cis form of the acid is meso, and the trans form racemic, and resolvable, the identity of the isomeric acids could be established. The higher melting dicarboxylic acid (XXIX) was resolved by Haworth into its optical isomers with strychnine, establishing it as the trans modification.

Other relationships in this series are analogous to those in the cyclohexane series. The cis dimethyl ester (XLII) is epimerized to the trans dimethyl ester (XLIII) by means of sodium ethoxide in ethanol. Also heating the trans anhydride with acetic anhydride at its boiling point, converts the trans anhydride to the cis anhydride.

Naphthalene-2,3-dicarboxylic acid has been synthesized by Freund<sup>46</sup> and by Waldman<sup>47</sup> by the diazotization of 3-aminonaphthalene-2-carboxylic acid, conversion to the nitrile, and hydrolysis of the nitrile. This procedure could not be duplicated, the difficulty lying in the step involving the Sandmeyer reaction. A small amount of the acid was obtained, reduced with sodium amalgam, and the resulting isomeric acids separated as the anhydrides to confirm the work of Haworth and Slinger.

However, 1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acid had been prepared by Baeyer and Parkin in their classical experiments in the synthesis of alicyclic rings.<sup>48</sup> o-Xylylene dibromide was condensed with ethyl acetylenetetracarboxylate in a sealed tube. The resulting tetracarboxylate was saponified, and then decarboxylated to yield the anhydride of 1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acid, m.p.  $184^{\circ}$ . This is identical with the cis

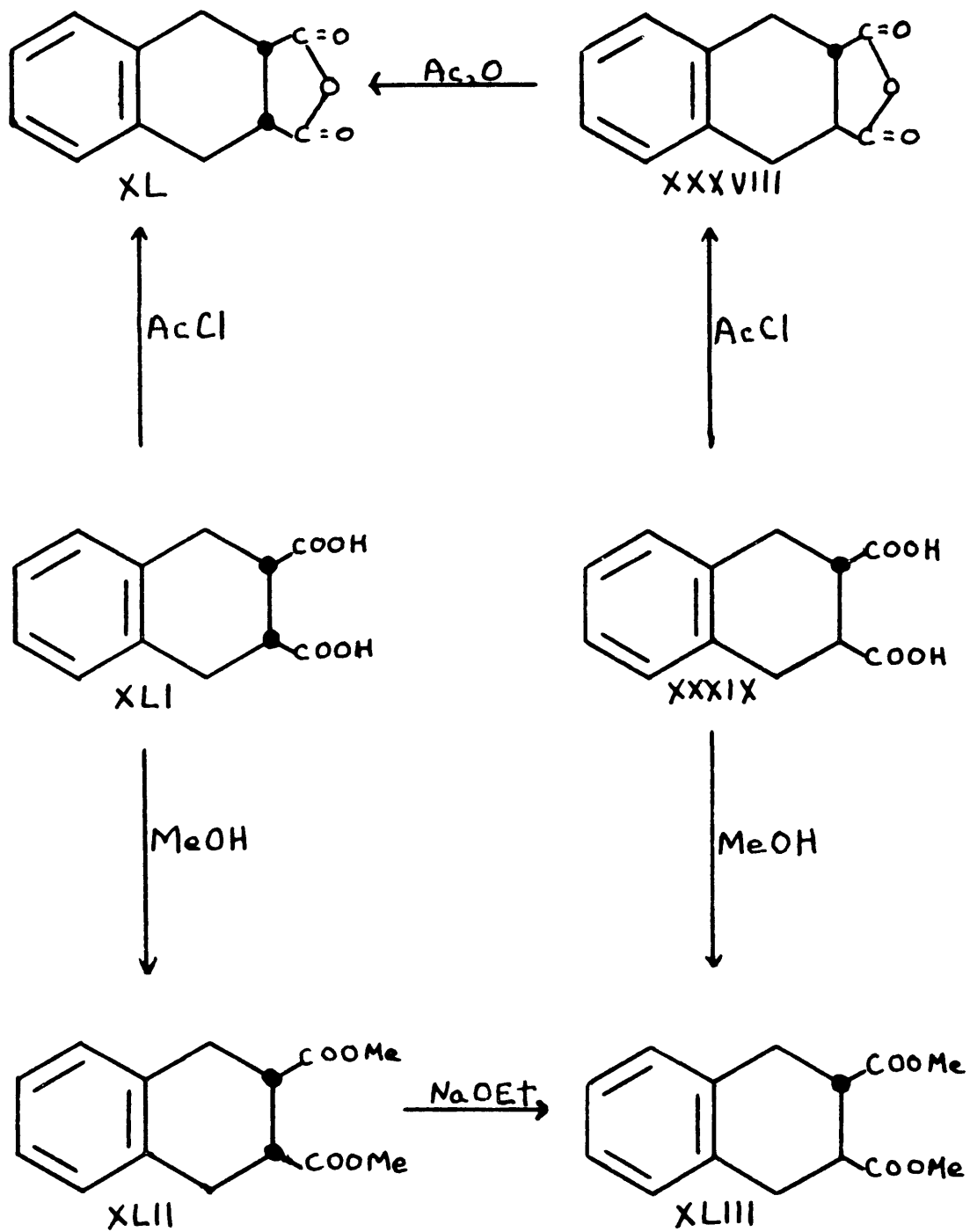


Chart VI

anhydride (XI) prepared by Haworth and Slinger. Another method used was to condense *o*-xylylene dibromide with the sodium salt of ethyl chloromalonate. The halogen was reduced with zinc and acetic acid, and the ring closed by treatment of the sodium salt with iodine. Saponification and decarboxylation led to the same 1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid anhydride.

The procedure used in this work was a modification of the last two procedures. *o*-Xylylene dibromide (XLIV), an extremely lachrymatory white solid, was prepared in 57% yield by the action of bromine on hot (130-135°) *o*-xylene. This compound has been hydrolyzed to phthalyl alcohol establishing the position of the two bromine atoms.<sup>49</sup>

Sodium hydride was added to a large excess of diethyl malonate heated to 90-100°. In this way the excess diethyl malonate served as a solvent for the sodiummalonic ester, which was condensed with the *o*-xylylene dibromide. The resultant tetracarboxylate (XLV), a viscous oil, was isolated by distillation in 79% yield. It was treated successively with sodium ethoxide in absolute ethanol, and bromine to close the ring, and then with ethanolic potassium hydroxide to saponify the ester groups. The tetracarboxylic acid (XLVI) was isolated as a yellow glass. Upon heating to 190°, a vigorous evolution of carbon dioxide occurred. The crude decarboxylated product crystallized on cooling to a brown solid. After recrystallization from petroleum ether-ethyl acetate, and then from acetic acid, a 45% yield of white, crystalline *cis*-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid anhydride (XLI), m.p. 163°, was obtained.

The *cis* anhydride was then converted to the *trans* anhydride. Dimethyl *cis*-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (XLII) was prepared in 86% yield by the action of absolute methanol and hydrochloric acid on the *cis* anhydride. The *cis* diester (XLII) was epimerized, and saponified by first

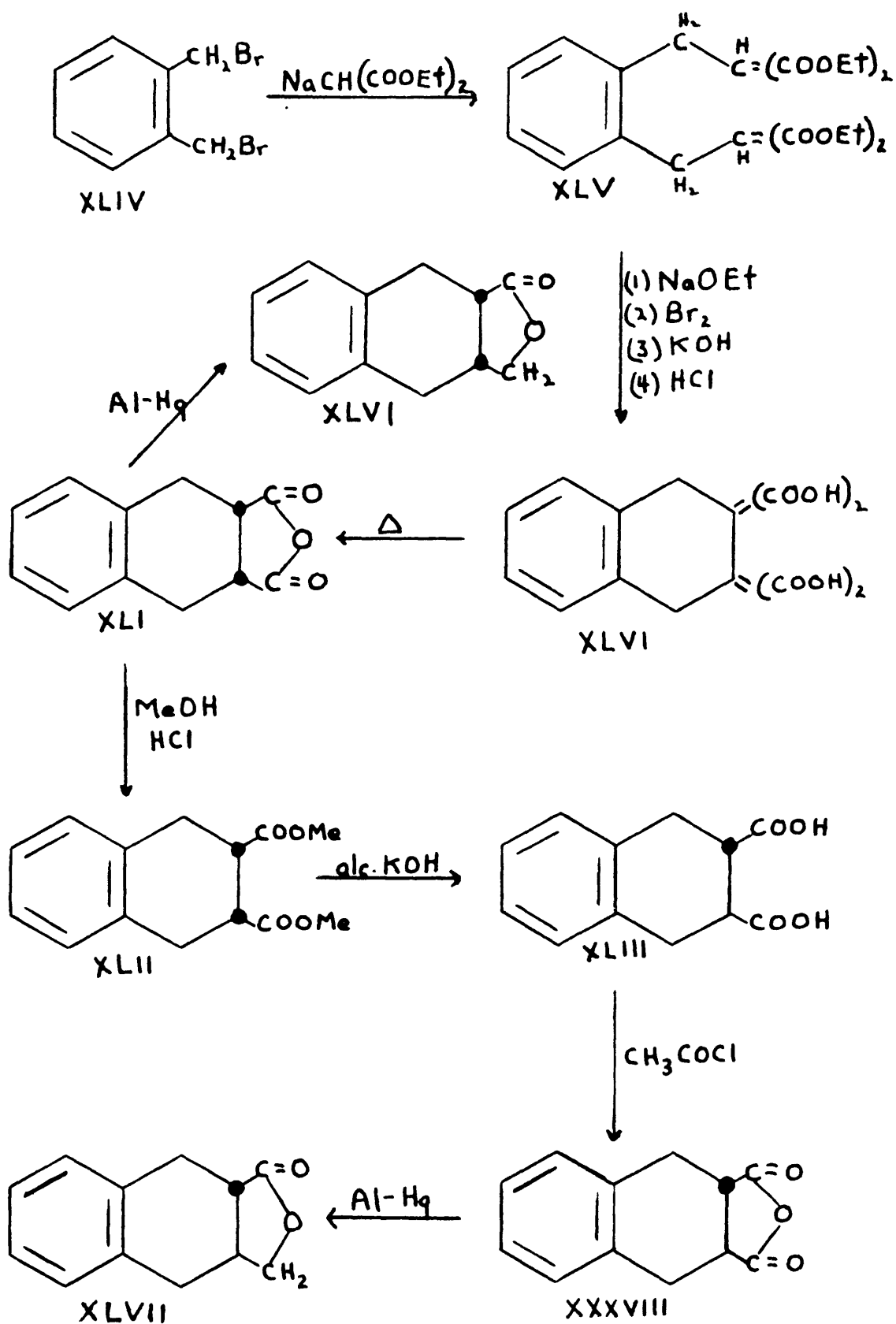


CHART VII



heating under reflux with sodium ethoxide in alcohol, and then replacing the alcohol with water. The yield of trans-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acid (XLIII), m.p.  $221^{\circ}$ , was 92%. The anhydride of the trans acid (XXXVIII), m.p.  $250^{\circ}$ , was obtained in 60% yield by treatment with acetyl chloride.

The anhydride of cis-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic acid (XLI) was treated with a suspension of aluminum amalgam in a mixture of ether, benzene, and dioxane. The resulting alumina sludge was decomposed with sulfuric acid and the cis-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic acid lactone (XLVI) was isolated as a white solid, m.p.  $134^{\circ}$ , in 27% yield after recrystallization from methyl alcohol. Haworth<sup>45</sup> obtained the lactone after an acid decomposition of the alumina sludge, and also by extraction with chloroform with no changes in configuration. He was also able to saponify the lactone with aqueous base, and recover the original lactone after acidification and heating.

The lactone of trans-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic acid (XLVII) was obtained in the same manner using dioxane as the solvent. The yield was 30% and the lactone melted at  $159^{\circ}$ ,  $3^{\circ}$  higher than the value reported by Haworth. This compound, too, could be saponified and relactonized with no configurational changes. Aluminum amalgam is a neutral reagent and it is unlikely that either the anhydride or the lactone ring was opened during the reduction. Also the possibility of enolization is small with this type of reagent. Hence it is likely that there were no changes in configuration during the reduction.

The best evidence available seemed to invalidate the Borsche-Spath formula for podophyllotoxin(I). The C-1, C-3 lactone ring as formulated

would have the *cis* configuration, and be differently strained than the C-2, C-3 *cis-trans* lactones (II), even though it, too, is a pentacyclic lactone. In order to study the C-1, C-3 type of lactone, the lactone of *cis*-3-hydroxycyclohexanecarboxylic acid (XIII), the lactone of *cis*-1,4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid (XIV), and the lactone of 3-hydroxymethyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid were prepared (XV). (See Chart II.)

The lactone of *cis*-3-hydroxycyclohexanecarboxylic acid (XIII) has been prepared by the reduction of *m*-hydroxybenzoic acid with sodium and alcohol,<sup>50</sup> by the hydration of  $\Delta^2$ -cyclohexanecarboxylic acid with sulfuric acid<sup>51</sup> and by the hydrogenation of *m*-hydroxybenzoic acid with Adams catalyst.<sup>52</sup> The first method, that of reduction of *m*-hydroxybenzoic acid with sodium in alcohol was the most convenient, and gave the best yields.

*m*-Hydroxybenzoic acid was prepared in 66.5% yield by the reduction of piperonylic acid with Ramsay nickel alloy in aqueous sodium hydroxide.<sup>53</sup> The *m*-hydroxybenzoic acid in absolute ethanol was treated with a ten-mole excess of sodium. After the sodium dissolved, the mixture was nearly neutralized with concentrated hydrochloric acid and the alcohol was distilled while adding water to replace it. The aqueous solution was then acidified and the fairly soluble hydroxy acids were extracted with ether using a continuous liquid-liquid extractor. The residue after the ether was evaporated crystallized slowly. It was a mixture of *cis* and *trans*-3-hydroxycyclohexane carboxylic acids. The mixture was heated to lactonize the *cis* acid, and then the lactone was distilled leaving the *trans* acid behind. The distillate had a wide boiling range and was partly crystalline and partly liquid. Upon redistillation, most of the compound distilled over a narrow boiling range, and this fraction could be recrystallized from petroleum ether, b.p. 60-80°. It was then

saponified to the cis hydroxy acid which was recrystallized, heated, and distilled. The distillate was recrystallized three times from petroleum ether. Even then it was still an extremely sticky, white solid.

The lactone of cis-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid (XIV) and the hydroxy acid are not reported in the literature. The compound was synthesized in the following manner: The sodium salt of diethyl benzylmalonate (XLVIII) was condensed with ethyl bromoacetate. The resulting tri-carboxylate (XLIX) was saponified, and decarboxylated to benzylsuccinnic acid (L). This in turn was converted to the benzylsuccinnic anhydride (LI) which was cyclized with aluminum chloride to the 4-keto-1,2,3,4-tetrahydro-2-naphthoic acid (LII). This was reduced to 4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid (LIII) with sodium borohydride, and thermally lactonized to the desired lactone (LIV).

Benzylsuccinnic acid is well known, and has been made in a number of ways.<sup>54,55,56</sup> Since a plentiful supply of diethyl benzylmalonate was available, the procedure of Weizmann<sup>56</sup> was adopted. A solution of sodium ethoxide in absolute ethanol was treated in quick succession with diethyl benzylmalonate and ethyl bromoacetate. The reaction mixture was heated under reflux and then the alcohol evaporated. The crude triethyl 1-phenylpropane-2,2,3-tricarboxylate (XLIX) was isolated as an orange oil. It was hydrolyzed with ethanolic potassium hydroxide. After evaporating the alcohol, the potassium tricarboxylate was dissolved in water, the solution acidified, and the crude tricarboxylic acid extracted with copious amounts of ether. A yellow solid was obtained upon removal of the ether. Weizmann obtained an oil at this point, and decarboxylated by heating at 165-170°. Better results were obtained when the 1-phenylpropane-2,2,3-tricarboxylic acid was heated under

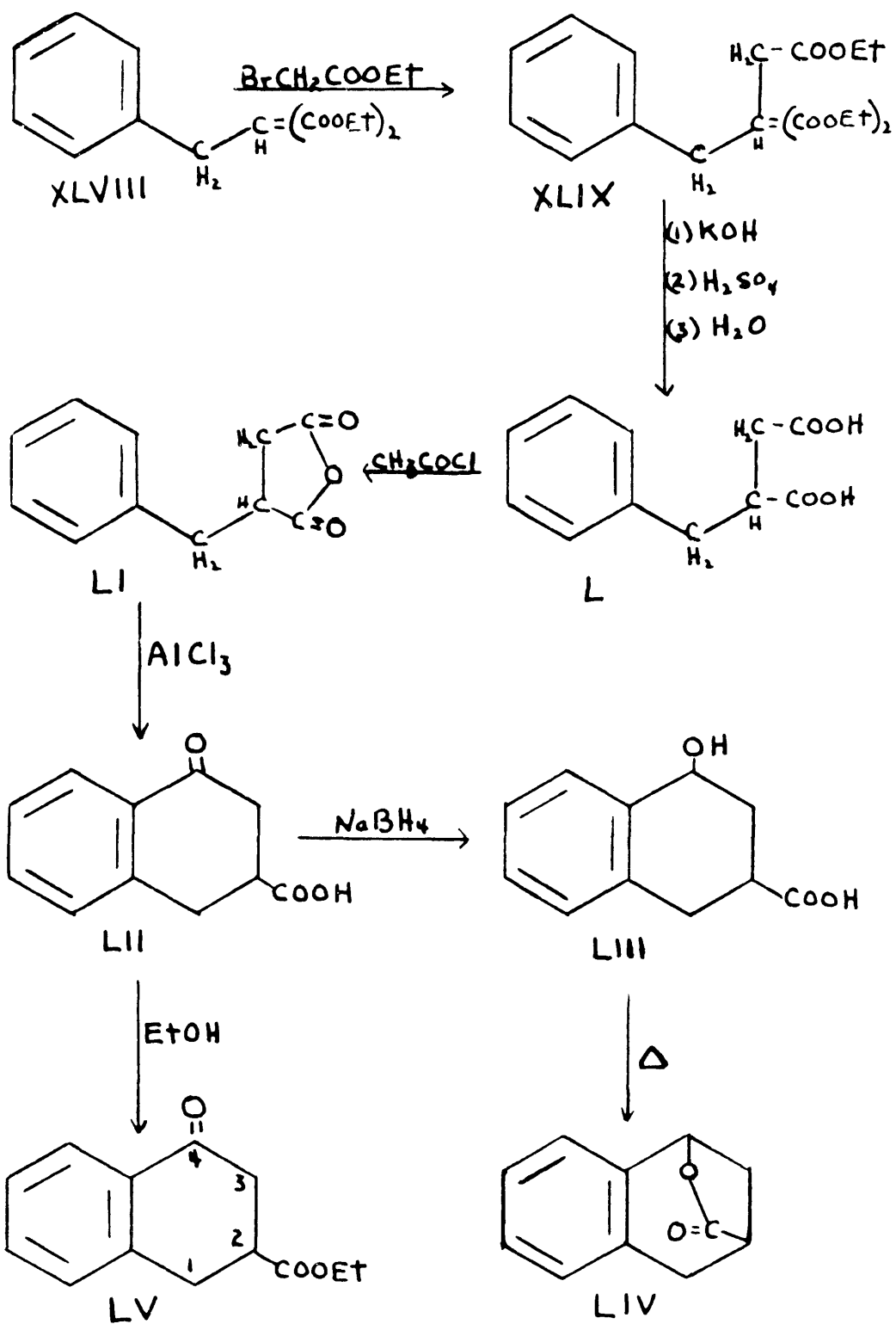


Chart VIII

reflux with water. The compound dissolved readily in the boiling water, was decarboxylated and precipitated upon cooling as slightly tan crystals, m.p. 158-159°. The yield of benzylsuccinic acid from diethyl benzylmalonate was 75%.

Benzylsuccinic acid has been cyclized to the 4-keto-1,2,3,4-tetrahydro-2-naphthoic acid (LII) with concentrated sulfuric acid (no yield given),<sup>57</sup> with phosphorus pentachloride, and then aluminum chloride in 45% yield,<sup>58</sup> with acetyl chloride and then aluminum chloride in 61.5% yield,<sup>54</sup> and with acetic anhydride and then aluminum chloride (no yield given).<sup>55</sup>

The cyclization with sulfuric acid was attempted in a variety of conditions. In no case was the yield over 50%. Treatment with anhydrous hydrofluoric acid failed to yield the cyclic ketone. Only starting material was recovered. Benzylsuccinic anhydride (II) was prepared in 86% yield by the action of acetyl chloride on the benzylsuccinic acid. The melting point of 98° was higher than the recorded value of 95-97°.<sup>54</sup>

The Friedel-Craft cyclization with aluminum chloride gave the highest yield when the solvent used was a mixture of nitrobenzene and acetylene tetrachloride. The aluminum chloride was dissolved in a mixture of nitrobenzene and acetylene tetrachloride, and was added to a solution of the benzylsuccinic anhydride in the same solvents. The product was isolated by extraction, rather than by steam distillation. This proved to be no more convenient since a severe emulsion problem was encountered. The yield of 4-keto-1,2,3,4-tetrahydro-2-naphthoic acid was 81.5% from the anhydride, and 70% from the benzylsuccinic acid. The melting point of 149.8° was higher than the recorded values of 145-147°<sup>53</sup> and 149°.<sup>57</sup> The yield too was higher than the reported 71.5% (from the anhydride).<sup>53</sup>

The reduction of the keto acid (LII) to the hydroxy acid (LIII) was most conveniently accomplished by the action of excess sodium borohydride on an aqueous solution of the sodium salt of the keto acid in an open beaker. The melting point of the crude acid was 111-111.5° when heated rapidly. The yield was 80% of theoretical.

The hydroxy acid was heated above its melting point at 125° for one hour. A gas was evolved, and when cool, the resulting compound crystallized readily. The compound could be recrystallized from ethyl alcohol-water, or from petroleum ether, b.p. 60-80°, but had a tendency to "oil out" from these solvents. Therefore, the temperature of the recrystallizing solvents was maintained below 50°. The solution was slowly cooled, and seeded to induce crystalline precipitation. The yield of the lactone of 4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid (LIV), m.p. 63-64°, was 60.5% after three crystallizations. The compound gave a proper saponification equivalent. Since the trans hydroxy acid could not lactonize, the reduction of the keto acid went predominantly *cis*.

Ethyl 4-keto-1,2,3,4-tetrahydro-2-naphthoate (LV) was prepared in 91% yield by the sulfuric acid catalyzed esterification of the keto acid with a tenfold excess of absolute ethanol in the presence of benzene. The water formed was azeotropically distilled with the benzene, and alcohol, to shift the equilibrium of the reaction. The ester was a slightly yellow oil, b.p. 126-130°/0.2 mm. The reported value is 175-177°/15 mm.<sup>57</sup>

If a methylol group could be introduced at carbon-3 in this molecule, it might be possible to prepare the very "stripped" analogue of podophyllotoxin. Two possibilities were considered; the aldol condensation with formaldehyde, and the Claisen condensation with ethyl formate, and the subsequent reduction of the hydroxymethylene group so introduced.

Walker in his review of the reactions of formaldehyde,<sup>59</sup> reports that the reaction of cyclopentanone and cyclohexanone with hydrated lime, and excess formaldehyde led to the production of polyhydroxy compounds analogous to pentaerythritol. However, Mannich and Brosse were able to isolate mono, and tetramethylol ketones from the reaction of cyclohexanone and formaldehyde.<sup>60</sup>

Haworth and Sheldrick<sup>61</sup> reacted 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-4-keto-1,2,3,4-tetrahydro-2-naphthoic acid (LVI) with formalin in aqueous sodium hydroxide. Two methylol groups entered the carbon-2 position, one of them forming a lactone with the carboxyl group. Basic hydrolysis removed one of the methylol groups as formaldehyde, but the other was dehydrated yielding 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-4-keto-3-methylene-1,2,3,4-tetrahydro-2-naphthoic acid (LVIII). Brown at this University attempted to introduce the methylol group into diethyl benzylphenacylmalonate (LIX), but only starting material was recovered.

The Claisen condensation of cyclic ketones with ethyl formate is well known. Von Auers and Krollpfeiffer prepared 2-hydroxymethylene-5-methylcyclohexanone in 53% yield by the condensation of 2-methylcyclohexanone and amyl formate in the presence of sodium.<sup>62</sup> trans-1-Decalone has been formylated in 61% yield with ethyl formate using sodium as the condensing agent.<sup>63</sup>

Haworth and Sheldrick<sup>64</sup> were able to formylate 2-carbethoxy-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-4-keto-1,2,3,4-tetrahydronaphthalene (LX) with ethyl formate and sodium wire in 85% yield. The hydroxymethylene-keto-ester (LXI) was reduced with sodium amalgam to the dihydroxy acid (LXII) in 21% yield. The dihydroxy acid underwent reductive lactonization when heated at its melting point, or when boiled with 10% sulfuric acid to the lactone of 3-hydroxymethyl-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic acid (LXIII).

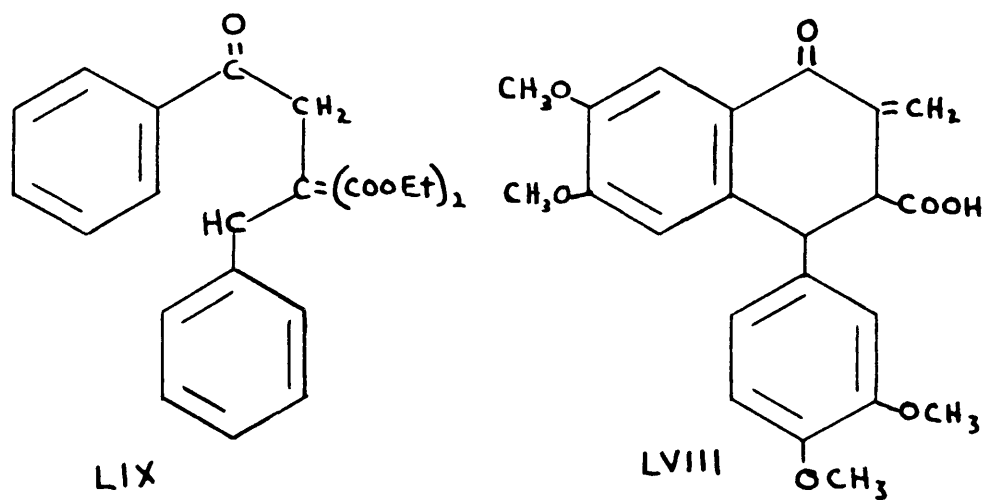
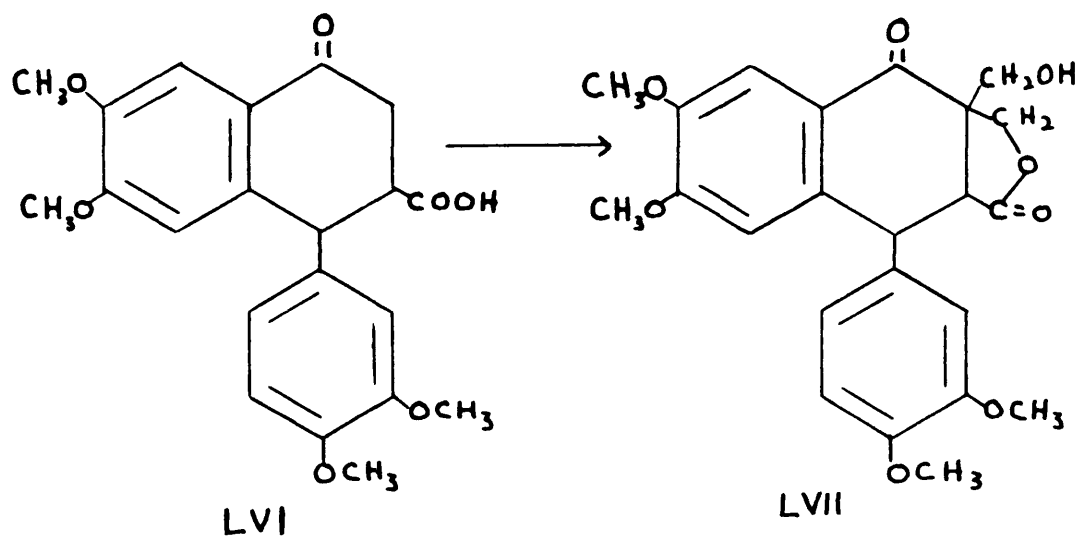


Chart IX



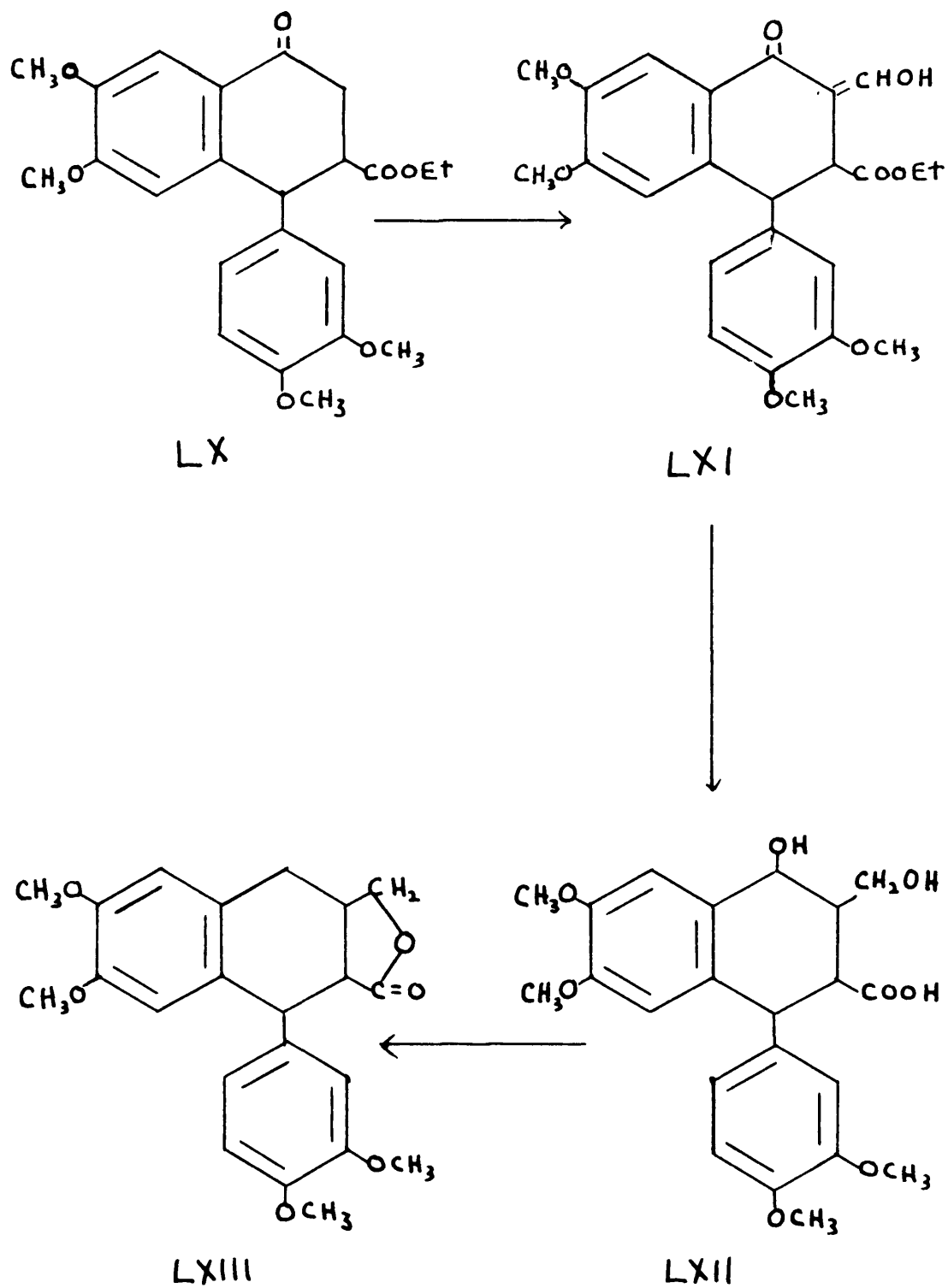


Chart X

More recently, Johnson and his co-workers have formulated 2-methylcyclohexanone in 72% yield, and 5-methoxyhydrindone-1 in 93% yield using alcohol-free sodium methoxide as the condensing agent.<sup>65,66</sup>

Of the two methods, the Claisen condensation with ethyl formate seemed to be the more suitable for introducing a carbon in the carbon-3 position.

Johnson's method using alcohol-free sodium methoxide as the condensing agent, and the older sodium method were both tried.

Using dry sodium methoxide, the yield and the composition of the product varied from run to run. Two moles of sodium methoxide and two moles of ethyl formate were reacted with one mole of the keto-ester (IV) for varying lengths of time, and at varying temperatures. Only once was a crystalline material obtained from the reaction mixture. This was identified as the hydroxymethylene-keto-acid (LXIV), m.p. 152°. On the other runs, a mixture of hydroxymethylene-keto-ester (LXV), and keto-acid (LXIV) were obtained. In one such representative run, the hydroxymethylene-keto-ester was separated from the hydroxymethylene keto-acid by its preferential solubility in benzene. The residue proved to be soluble in sodium bicarbonate, and was quite crystalline, and was recrystallized from chloroform. It gave a deep purple color with ferric chloride, and analyzed correctly for the hydroxymethylene-keto-acid. The hydroxymethylene-keto-ester recovered from the benzene solution was an oil which could not be crystallized. It formed an olive green copper salt which could not be recrystallized. The hydroxymethylene-keto-ester recovered from the acid decomposition of the copper salt was also an oil. It was purified by chromatography. A solution of the oil in benzene was adsorbed on silicic acid. The chromatogram consisted of a narrow, dark brown band, and a diffuse yellow area below it. The chromatogram was eluted with 2% ethanol in benzene, the yellow area separated, and the solvent evaporated.

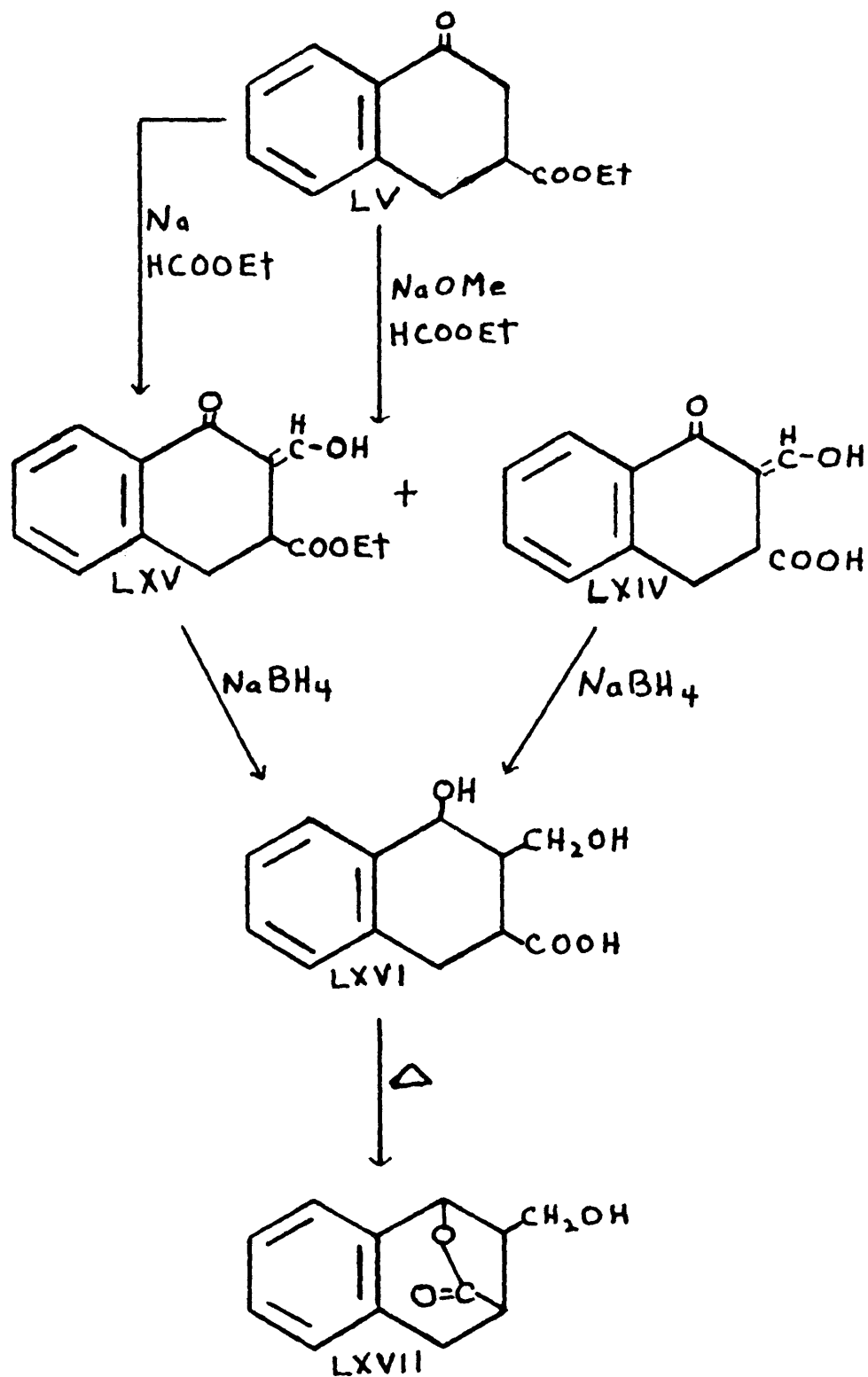


Chart XI

This was repeated once more to give a slightly yellow solid, m.p. 39-40°, after recrystallization from petroleum ether, b.p. 60-80°. The compound dissolved in sodium hydroxide, but not sodium bicarbonate, and gave an intense, purple color with ferric chloride. The yield of hydroxymethylene-keto-acid was 14.7%, and of hydroxymethylene-keto-ester was 32%.

Using sodium sand as the condensing agent, the reaction at room temperature for twelve hours gave a 61% yield of hydroxymethylene-keto-ester after purification by chromatography, and recrystallization from petroleum ether, b.p. 60-80°.

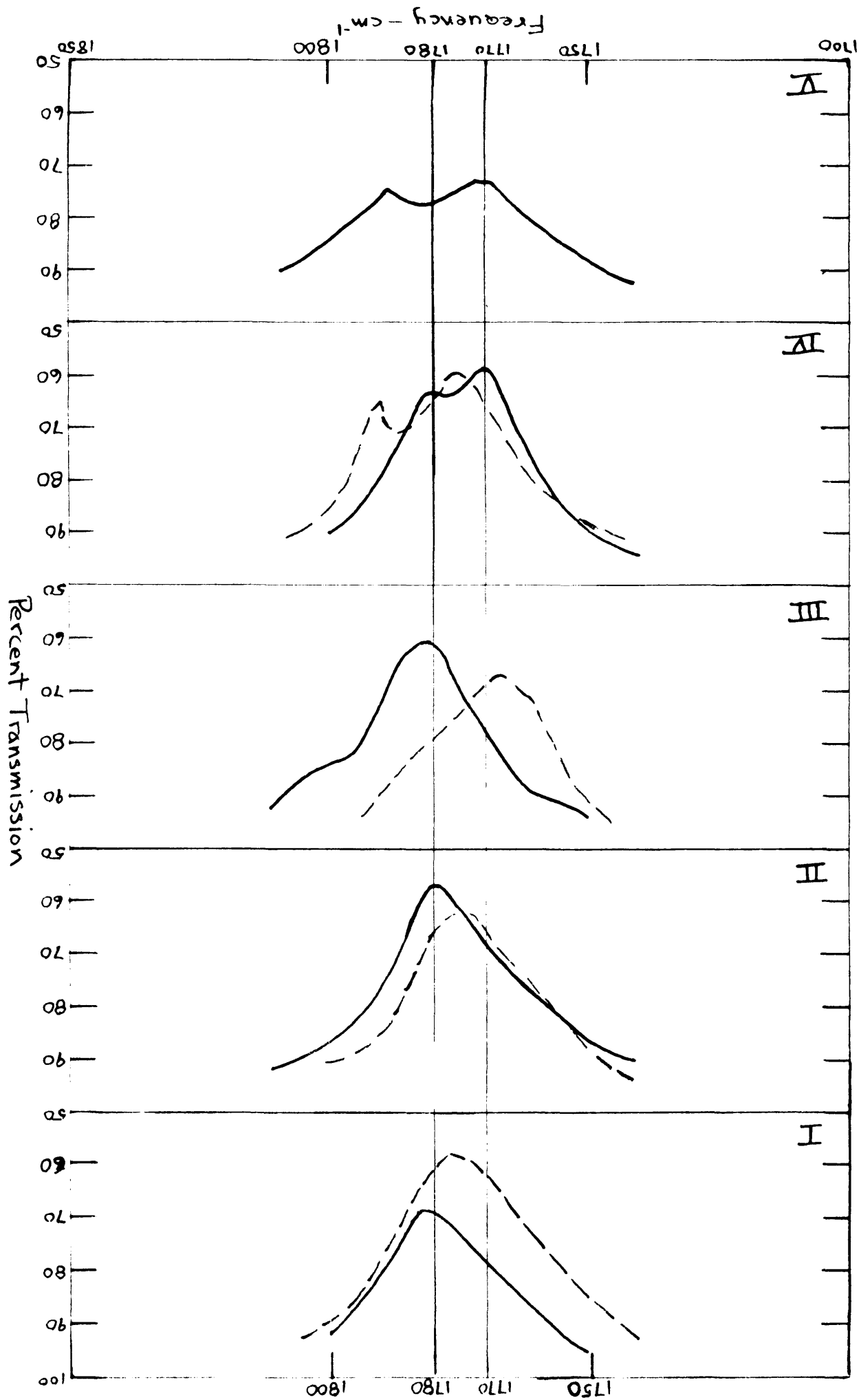
Both the hydroxymethylene-keto-ester, and the hydroxymethylene-keto-acid were reduced with sodium borohydride to 3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic acid (LXVI). The yield was 51% from the acid, and 37% from the ester. The compound decomposed with the evolution of a gas when heated. The solid melted, and then resolidified. The temperature of this phenomenon depended on the rate of heating, and so no melting point was obtained. The carbon and hydrogen analyses for the dihydroxy acid from each source were the same.

The dihydroxy acid from either source was heated under reflux with p-xylene and a gas was evolved. The cooled solution was stored in a refrigerator overnight, and a 95% yield of solid was separated by filtration. It was recrystallized twice from petroleum ether, b.p. 60-80°. The resulting white solid, m.p. 218°, was soluble in hot sodium hydroxide, but not in water or sodium bicarbonate. The infrared spectrum of the compound had a peak of 1780  $\text{cm}^{-1}$  which is the proper frequency for a lactone carbonyl group. The saponification equivalent value, and the carbon and hydrogen analyses were both correct for the lactone of 3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic acid (LXVI).

The spectra of the lactones were recorded between 4000 and 800  $\text{cm}^{-1}$  with a Perkin-Elmer model 12 C recording spectrometer equipped with a rock salt prism. Ten percent solutions of all the compounds except the lactone of 3-hydroxymethyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid (dihydroxy acid) were measured in a 0.1 mm. sodium chloride cell. The solvents used were carbon disulfide, carbon tetrachloride, and chloroform. The spectrum of each compound was obtained from at least two of the solvents. The spectrum of the lactone of the dihydroxy acid was obtained from a concentrated mull in mineral oil pressed between two rock salt windows. The spectra of the *cis* and *trans*-2-hydroxymethylcyclohexanecarboxylic acid lactones (cyclohexane lactones) were quite different, despite their identical carbon and hydrogen analyses and saponification equivalents, indicating that these compounds were different in configuration. Thompson and Torkington<sup>67</sup> report the existence of a C-O band at 1250 to 1050  $\text{cm}^{-1}$  for a series of esters. This band should be found in the spectra of lactones. Unfortunately, not enough lactones were examined to identify these bands with certainty. A strong band at 1780  $\text{cm}^{-1}$  was found for each of the lactones which was identified as the carbonyl stretching band. The dispersion of a rock salt prism at this frequency is poor, and small shifts due to variation in strain could not be detected.

This region was re-examined with a lithium fluoride prism for all the lactones. Ten percent solutions were found to be entirely too concentrated and finally 0.05 M solutions in chloroform, in a 0.1 mm. cell, were used. The lithium fluoride prism was not very transparent in this region, and the spectrum of the dihydroxy acid lactone could, therefore, not be obtained from a mineral oil mull. A 0.05 M solution of the compound in methanol was used.

The carbonyl bands of the *trans*-cyclohexane lactone, and the *trans*-tetralin lactone both appeared at higher frequencies than the bands for the corresponding *cis* compounds. These bands consisted of single peaks.



## LEGEND FOR CARBONYL BAND SPECTRA

- I. \_\_\_\_\_ Podophyllotoxin  
 - - - - - Pieropodophyllin
- II. \_\_\_\_\_ trans-2-Hydroxymethylcyclohexanecarboxylic Acid Lactone  
 - - - - - cis-2-Hydroxymethylcyclohexanecarboxylic Acid Lactone
- III. \_\_\_\_\_ trans-3-Hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic  
 Acid Lactone  
 - - - - - cis-3-Hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic Acid  
 Lactone
- IV. \_\_\_\_\_ 3-Hydroxycyclohexanecarboxylic Acid Lactone  
 - - - - - 4-Hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone
- V. \_\_\_\_\_ 3-Hydroxymethyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic  
 Acid Lactone-2,4

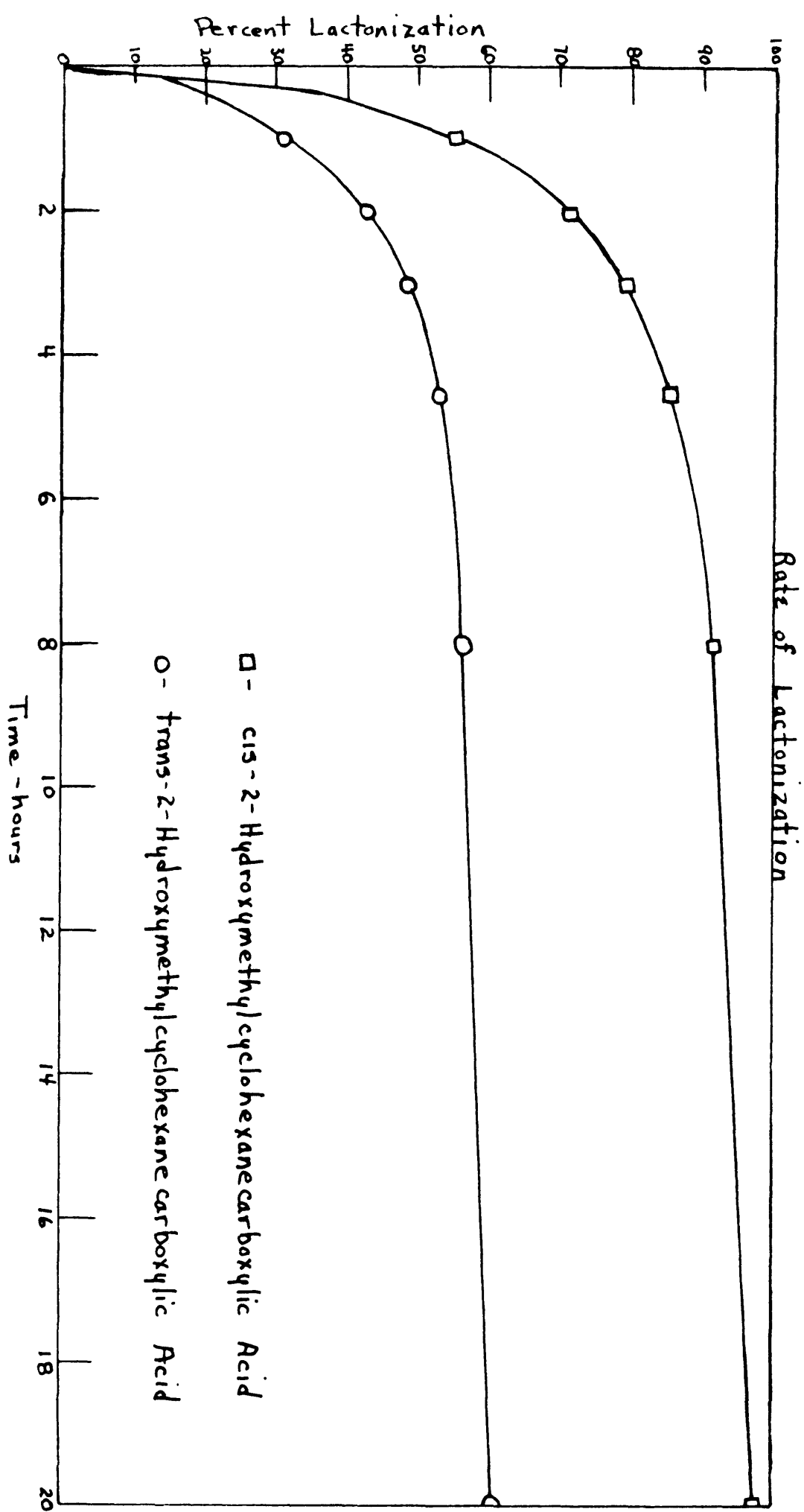
The two lactones, XIII and XIV, (C-1,C-3 lactones) modelled after the Borsche-Spath formula for podophyllotoxin each had a double peak band in this region, the appearance of which was quite different from the bands of podophyllotoxin and picropodophyllin which were single peaks. This physical evidence, as well as the chemical evidence presented in the introduction, rules out the Borsche-Spath formula for podophyllotoxin. The lactone of the dihydroxy acid quite unexpectedly had a double peak band, similar in appearance to the double peaks of the C-1, C-3 lactones. In the absence of any other evidence, this lactone can be considered as a C-1, C-3 type lactone with a free methylol group on carbon-2. .

By comparison with the spectra of the cis and trans-cyclohexane lactones, and the cis and trans-tetralin lactones, podophyllotoxin was shown to have a trans lactone ring, and picropodophyllin, a cis lactone ring.

A difference of  $5\text{ cm}^{-1}$  was observed for podophyllotoxin and picropodophyllin,  $8\text{ cm}^{-1}$  for the cyclohexane lactones, and  $14\text{ cm}^{-1}$  for the tetralin lactones. These differences are small when compared with the difference of  $37\text{ cm}^{-1}$  between  $\delta$  and  $\zeta$ -lactones. If these differences in frequency are due to differences in ring strain, then the cis-trans lactones studied do not differ greatly in strain. It is not likely that the quantitative conversion of podophyllotoxin to picropodophyllin can be attributed to this small difference in ring strain.

The rate of lactonisation of the cis and trans-2-hydroxymethylcyclohexane-carboxylic acids was studied. Each lactone was saponified with an excess of standardized, aqueous sodium hydroxide and then enough standardized hydrochloric acid was added to nearly neutralize the basic solution. The aqueous solutions of the hydroxy acids were then heated on a steam bath and, from





time to time, aliquot samples were withdrawn. The samples were titrated with standardized sodium hydroxide to determine the amount of free hydroxy acid present. The cis hydroxy acid was found to lactonize more rapidly and completely than the trans hydroxy acid. At the end of three hours, the cis compound was 79% lactonized, and the trans compound 48%. At the end of twenty hours, when the rate of lactonization of either compound was nearly zero, the cis compound was 97% lactonized, and the trans 61%. The more rapid rate of lactonization and the greater completeness of reaction of the cis compound indicate that it is the more stable of the two. Furthermore, had an enolization occurred during the basic saponification, the two rates would have been the same.

To see if any epimerization took place during saponification of the lactones, the cis and trans-cyclohexane lactones were saponified with aqueous sodium hydroxide, and then lactonized by heating the acidified mixtures under reflux. The lactones, isolated with ether, were distilled and their spectra compared with those of the untreated compounds. The position of the carbonyl peaks indicated that the saponified and relactonized compounds were identical with the starting compounds in each case. Haworth and Slinger<sup>15</sup> were able to saponify and relactonize the cis and trans-tetralin lactones without any changes in configuration. Apparently, these simple lactones are not epimerized by the action of base. If they did enolize, since the rates of lactonization are of the same order, a mixture of cis and trans lactones would be recovered. Therefore, by analogy the small difference in strain in the lactone rings of podophyllotoxin and picropodophyllin could hardly account for the quantitative conversion of podophyllotoxin to picropodophyllin under the influence of basic reagents. It is difficult to formulate a mechanism for the epimerization of podophyllotoxin other than enolization, but why should podophyllotoxin enolize,

and not the model compounds? If indeed the mechanism is one of enolization, then the driving force behind the quantitative epimerization must be the trimethoxyphenyl group on carbon-4 which would then be cis to the carboxyl group in podophyllotoxin and trans to the carboxyl group in picropodophyllin.

## PART II

### Alcohols Related to Podophyllotoxin

The absorption of infrared radiation in the region from  $3700\text{ cm}^{-1}$  to  $2500\text{ cm}^{-1}$  is generally attributed to hydrogen-stretching vibrations.<sup>68</sup> More specifically, the free hydroxyl vibrations, where the hydrogen is not affected by any atom but the oxygen, have a characteristic absorption band between  $3700\text{ cm}^{-1}$  and  $3500\text{ cm}^{-1}$ . If hydrogen bonding occurs, the absorption band is broader, and is shifted to lower frequencies,  $3500\text{-}3100\text{ cm}^{-1}$ . These bands are very useful in identifying the presence of a hydroxyl function in an organic molecule.

In addition, an equally significant but less studied band occurs in the  $1250\text{ cm}^{-1}$  to  $1000\text{ cm}^{-1}$  region. A band in this region may range in intensity from medium to strong, and is generally attributed to the carbon-oxygen stretching vibration.

Early in the history of the application of infrared spectroscopy to organic structure, Weninger<sup>69</sup> noted the existence of a band at  $1040\text{ cm}^{-1}$  in primary alcohols,  $1100\text{ cm}^{-1}$  in secondary alcohols, and  $1160\text{ cm}^{-1}$  in tertiary alcohols. This information could be used to determine the position of the hydroxyl group in a molecule. More recently, Tuot and Lecompte<sup>70</sup> examined the infrared spectra of a series of aliphatic secondary and tertiary alcohols. Their work was in agreement with that of Weninger.

Still more recently, after this work had been almost completed, a study of the carbon-oxygen absorption band of a series of alcohols by Zeiss and

Tsutsui<sup>71</sup> was published. They found that the differentiation between primary, secondary, and tertiary alcohols as proposed by Weninger, and Tuot and Lecompte was not valid. They were able to make certain generalizations about the location of the carbon-oxygen band for varying alcohols which will be discussed later.

If the nature of the hydroxyl group in podophyllotoxin could be established, then its position would be known. A secondary alcohol would be located on carbon-1, a tertiary alcohol on carbon-2, while a primary carbinol would also be located on carbon-2, and would lend support to the Borsche-Spath formula. Therefore, a series of alicyclic and fused aromatic-alicyclic alcohols were synthesized so that their infrared spectra could be studied. It was hoped that information obtained from these model compounds could be applied to podophyllotoxin.

Commercial cyclohexanol was distilled through a three-foot column packed with glass helices. The middle fraction, b.p.  $160^{\circ}$ , was collected, and redistilled through the same column. Again, the middle fraction, b.p.  $160^{\circ}$ ,  $n_D^{20}$  1.4644, was collected.

2-Methylcyclohexanol was prepared by hydrogenating purified o-cresol over Raney nickel according to the directions of Ungnade and Nightingale.<sup>72</sup> The 2-methylcyclohexanol, b.p.  $162-164^{\circ}$ , was isolated in 94% yield by distillation through a one-foot Vigreux column. It was then redistilled through a three-foot column packed with glass helices. The middle fraction, b.p.  $164^{\circ}$ ,  $n_D^{20}$  1.4606, was collected. The phenylurethane of 2-methylcyclohexanol prepared this way has a melting point of  $105-106^{\circ}$  which corresponds to the melting point of the phenylurethane of trans-2-methylcyclohexanol.

3-Methylcyclohexanol, and 4-methylcyclohexanol were prepared in 96% and 92% yield respectively, and purified in the same way. The 4-methylcyclohexanol

is also of the trans configuration, but the 3-methylcyclohexanol is cis.

The configurations of the 2,3 and 4-methylcyclohexanols have been assigned on the basis of viscosity measurements<sup>73</sup> and heat of combustion measurements,<sup>74</sup> assuming that for each pair of isomers, the trans form was the more stable, an assumption which is now believed to be true for the 2- and 4- substituted cyclohexanols, but not for the 3-isomers.<sup>75</sup> Goering and Serres<sup>76</sup> prepared cis and trans-3-methylcyclohexanol from the isomeric 3-hydroxycyclohexanecarboxylic acids by synthetic schemes designed to avoid ambiguities concerning configurations. Comparison of the solid derivatives of these compounds of known configuration showed that the previously accepted assignment of configuration for the 3-methylcyclohexanols was in error.

The physical constants of the three isomeric methylcyclohexanols agreed with the values found in the literature. (Table I.) The physical constants of cis and trans-3-methylcyclohexanol obtained by Mills<sup>78</sup> have been assigned to the configurations obtained by Goering and Serres.

1,2,3,4-Tetrahydro-2-naphthol has been prepared by the hydrogenation of  $\beta$ -naphthol over Raney nickel, and over copper chromite. Musser and Adkins<sup>80</sup> report the preparation of 1,2,3,4-tetrahydro-2-naphthol in 55% yield over Raney nickel. However, Stork<sup>81</sup> obtained a mixture of 57% 5,6,7,8-tetrahydro-2-naphthol, and 27% 1,2,3,4-tetrahydro-2-naphthol. When a little aqueous sodium hydroxide was added to the reaction mixture, the yield of the phenol was 11% and that of the alcohol was 68%. Adkins and Kreek<sup>82</sup> hydrogenated  $\beta$ -naphthol over a variety of nickel catalysts, and in neutral media obtained 80% yields of the phenol, and 6-11% yields of the alcohol. The presence of base changed the yields to 8% phenol and 68% alcohol.

Hydrogenation over copper chromite is superior. Musser and Adkins<sup>80</sup> reported an 87% yield of alcohol only. Dauben, McKusick, and Mueller<sup>83</sup>

TABLE I

Literature Source	Wills <sup>77,78</sup>		Vogel <sup>79</sup>	Ungnade <sup>72</sup>	Found
Compound Physical Constant	cis	trans			
<b>2-Methylcyclohexanol</b>					
$n_D^{20}$	1.4649	1.4615	1.4609	1.4602	1.4606
B.P.			165°	163-164°	164°
M.P. of Phenylurethane	92-93°	105°		105-106°	
<b>3-Methylcyclohexanol</b>					
$n_D^{20}$	1.4573	1.4583	1.4576	1.4545	1.4568
B.P.			172°	168-169°	171°
M.P. of Phenylurethane	92°	103°		91-92°	
<b>4-Methylcyclohexanol</b>					
$n_D^{20}$	1.4614	1.4561	1.4565	1.4551	1.4557
B.P.			172°	170-171°	170°
M.P. of Phenylurethane	103-104°	124-124.5°		124-125°	

obtained a 79% yield of pure alcohol along with an 8.5% yield of phenol. The purity of the alcohol was demonstrated by cryoscopic measurements. The procedure of Dauben, McKusick, and Mueller was followed in this work.  $\beta$ -Naphthol was purified by distillation first from Raney nickel, and then from copper chromite. The molten  $\beta$ -naphthol was then hydrogenated over copper chromite at  $200^{\circ}/3500$  psi. The compound was removed from the bomb with benzene, and the catalyst separated by centrifuging. The solution was then washed with several portions of aqueous sodium hydroxide to convert the 5,6,7,8-tetrahydro-2-naphthol to its sodium salt. Without drying, the low boilers were stripped, and then the residue distilled. An 82% yield of 1,2,3,4-tetrahydro-2-naphthol, b.p.  $119-121^{\circ}/5$  mm. was obtained by distillation through a five-inch Vigreux column. The residue was the sodium salt of the phenol. The alcohol was redistilled through a two-foot column packed with glass helices. The physical constants of the alcohol were b.p.  $120^{\circ}/0.5$  mm.,  $n_D^{25}$  1.5633, and m.p.  $22.6^{\circ}-22.9^{\circ}$ . These values are in agreement with those obtained by Dauben, McKusick, and Mueller.

1, 2,3,4-Tetrahydro-1-naphthol has been prepared in a variety of ways. Strauss and Rohrbacker prepared the compound by the reduction of 1-tetralone with sodium and alcohol in 70% yield.<sup>84</sup> The reduction has also been accomplished with aluminum isopropoxide in 86% yield.<sup>85</sup> Hook and Lang prepared tetraline peroxide and reduced it with sodium sulfite to the alcohol.<sup>86</sup> It has also been prepared by the catalytic hydrogenation of  $\alpha$ -naphthol. Brochet reported the preparation of the 1,2,3,4-tetrahydro-alcohol in 85% yield along with a 15% yield of the 5,6,7,8-tetrahydro-phenol.<sup>87</sup> Musser and Adkins<sup>88</sup> were unable to get any of the alcohol by hydrogenation over Raney nickel. Over copper chromite they succeeded in preparing the alcohol in 35% yield. A 30%

yield of the phenol, and a 10% yield of tetralin were also obtained. This work could not be duplicated. Only 5,6,7,8-tetrahydro-1-naphthol and tetralin were isolated. The alcohol, 1,2,3,4-tetrahydro-1-naphthol, is a substituted benzyl alcohol, and since copper chromite is active as a catalyst for hydrogenolysis,<sup>88</sup> any alcohol formed was probably converted to tetralin.

The other route to 1,2,3,4-tetrahydro-1-naphthol is through the reduction of 1-tetralone which is most conveniently prepared by the air oxidation of tetralin,<sup>89</sup> or by the aluminum chloride cyclization of the acid chloride of  $\gamma$ -phenylbutyric acid.<sup>90</sup>

A large supply of  $\gamma$ -(p-tolyl)-butyric acid was available, and it was decided to cyclize this acid to the 7-methyltetralone-1, and reduce the ketone to 7-methyl-1,2,3,4-tetrahydro-1-naphthol. 7-Methyltetralone-1 has been prepared in 70% yield by treating  $\gamma$ -(p-tolyl)-butyric acid with sulfuric acid,<sup>91,92</sup> and by preparing the acid chloride and cyclizing with aluminum chloride (overall yield-50%)<sup>93</sup>. The former procedure was adopted.  $\gamma$ -(p-tolyl)-Butyric acid was treated with a large excess of concentrated sulfuric acid and heated on a steam bath. The ketone was extracted with ether, and distilled. The yield of 7-methyltetralone-1, b.p. 142°/15 mm., was 65%.

The boiling point of 1-tetralone is 105-105°/2 mm. The boiling point of 1-tetralol is 102-104°/2 mm. It was anticipated that the boiling points of the 7-methyl-analogues would also be close together, and so separation by distillation would not be feasible. Therefore, the alcohol would be best isolated as one of its derivatives, the derivative purified, and the alcohol regenerated from it.

The 7-methyltetralone-1 was reduced smoothly with a slight excess of lithium aluminum hydride in ether. The crude product was freed from any



volatile matter finally with a vacuum pump, and then treated with an excess of phenyl isocyanate. The resulting phenylurethane was readily crystalline. The yield of white crystals, m.p.  $107^{\circ}$ , was 65% after recrystallization from petroleum ether, b.p.  $60-80^{\circ}$ .

Acid hydrolysis of the urethane was rejected since it might dehydrate the alcohol. The urethane was dissolved in a solution of potassium hydroxide in diethylene glycol and saponified at  $150^{\circ}$ . The alcohol was steam distilled from the reaction mixture along with some aniline. It was then isolated from the distillate, by acidifying, and then extracting with ether. The 7-methyl-1,2,3,4-tetrahydro-1-naphthol crystallized on cooling, and a yield of 70.5%, m.p.  $51.5^{\circ}$ , was obtained after recrystallization from petroleum ether, b.p.  $60-80^{\circ}$ .

The 7-methyltetralone-1 was also treated with an equivalent amount of methylmagnesium iodide. The Grignard complex was decomposed with ammonium chloride. The resulting 1,7-dimethyl-1,2,3,4-tetrahydro-1-naphthol was obtained as a yellow oil which was crystallized from petroleum ether by cooling in a dry ice bath, and allowing the mixture to warm to room temperature slowly. After two recrystallizations from petroleum ether, b.p.  $60-80^{\circ}$ , a 67% yield, m.p.  $88.1^{\circ}$ , was obtained.

1-Methylcyclohexanol was prepared by reacting methylmagnesium iodide with cyclohexanone, b.p.  $153-156^{\circ}$ , (purified through the bisulfite addition compound<sup>94</sup>). The yield of 1-methylcyclohexanol was 77.5% after distillation. The compound was distilled twice more through a three-foot Vigreux column. The final fraction had a boiling point of  $70^{\circ}/20$  mm. and melted at  $25.6^{\circ}$ . Values in the literature vary from  $24^{\circ}$  to  $26^{\circ}$ .<sup>71,95,96,97</sup>

The procedure of Gilman, and Catlin<sup>98</sup> was followed to prepare cyclohexylcarbinol. The Grignard reagent from cyclohexyl chloride and magnesium was

treated with dry, depolymerized paraformaldehyde. A yield of 64% of colorless oil, b.p. 91-95°/26 mm. was obtained. The compound was then redistilled through a two-foot column packed with glass helices, and the fraction, b.p. 93°/23 mm.,  $n_D^{20}$  1.4644, was collected. These constants agree very well with those reported in the literature.<sup>99,100</sup>

It was also desirable to prepare 1,2,3,4-tetrahydro-1-naphthylcarbinol, and 1,2,3,4-tetrahydro-2-naphthylcarbinol. The catalytic reduction of methyl 1-naphthoate and ethyl 2-naphthoate over copper chromite results in the formation of small yields of the corresponding naphthyl carbinols, and alkyl naphthalenes.<sup>101</sup> Newman and co-workers have prepared 1,2,3,4-tetrahydro-1-naphthylcarbinol, and 1,2,3,4-tetrahydro-2-naphthylcarbinol by the reduction of the esters of the corresponding tetrahydro acids.<sup>102,103</sup>

Therefore, the means of preparation of 1,2,3,4-tetrahydro-1-naphthoic acid, and 1,2,3,4-tetrahydro-2-naphthoic acid were investigated. The reduction of  $\alpha$  or  $\beta$  -naphthoic acid with Raney nickel alloy yields only the 5,6,7,8-tetrahydro acids.<sup>104</sup> The Raney nickel catalytic hydrogenation of ethyl 2-naphthoate results in the formation of the 5,6,7,8-tetrahydro acid almost exclusively. Reduction of the  $\alpha$ -isomer leads to a 5:3 preponderance of the 5,6,7,8-tetrahydro acid.<sup>101</sup> The Raney nickel catalytic hydrogenation of the free acids gives almost the same results.<sup>105</sup> The mixed tetrahydro acids are then laboriously separated by fractional crystallization, and the pure acids obtained only in small yields. Recently,  $\alpha'$ -phenylglutaric acid was cyclized to the 4-keto-1,2,3,4-tetrahydro-1-naphthoic acid, which was reduced to the 1,2,3,4-tetrahydro-1-naphthoic acid.<sup>106</sup> 1,2,3,4-Tetrahydro-1-naphthoic acid has also been obtained by the reduction of  $\alpha'$ -naphthoic acid with sodium in amyl alcohol,<sup>107</sup> and with sodium in ethyl alcohol.<sup>108</sup> Reduction with sodium amalgam at room temperature leads to the dihydro acid, but when the reduction

is carried out at the boiling point of water, the tetrahydro acid is obtained.<sup>109</sup> Newman and O'Leary<sup>102</sup> hydrogenated methyl 3,4-dihydro-1-naphthoate obtained by the cyclization of ethyl 5-phenyl-2-ketovalerate to obtain ethyl 1,2,3,4-tetrahydro-1-naphthoate.

1,2,3,4-Tetrahydro-2-naphthoic acid has been prepared by the reduction of  $\beta$ -naphthoic acid with sodium in amyl alcohol,<sup>107</sup> and with sodium amalgam in aqueous sodium hydroxide heated under reflux. The reduction with sodium amalgam at room temperature results in the formation of a dihydro acid.<sup>110</sup> The tetrahydro acid was also prepared by the Clemmenson reduction of 4-keto-1,2,3,4-tetrahydro-2-naphthoic acid.<sup>58</sup>

The reduction of  $\alpha$ -naphthoic acid with sodium and alcohol was chosen as the most convenient way to prepare the 1,2,3,4-tetrahydro-1-naphthoic acid.  $\alpha$ -Naphthoic acid prepared by the Grignard method as described by Vogel,<sup>111</sup> was dissolved in absolute ethanol, and a tenfold mole excess of sodium was added rapidly. The resulting alkaline solution was nearly neutralized, the alcohol replaced with water, and the tetrahydro acid precipitated by acidifying the solution. An aqueous solution of the sodium salt was treated with cold, concentrated potassium permanganate to oxidize any dihydro acid. The yield of 1,2,3,4-tetrahydro-1-naphthoic acid, m.p.  $84^{\circ}$ , was 89%. The acid was esterified with ethanol in the presence of benzene, and p-toluene-sulphonic acid, and the water removed by an azeotropic distillation. The ester was reduced with an ethereal solution of lithium aluminum hydride. The resulting crude 1,2,3,4-tetrahydro-1-naphthylcarbinol was heated on a steam bath with phthalic anhydride and dry pyridine to prepare the hydrogen phthalate ester. The yield of the hydrogen phthalate ester of 1,2,3,4-tetrahydro-1-naphthylcarbinol, m.p.  $102^{\circ}$ , after recrystallization from cyclohexane was 75% (from the ester). The ester was saponified with 10% sodium hydroxide to give

an 89.5% yield of 1,2,3,4-tetrahydro-1-naphthylcarbinol. The carbinol was redistilled through a three-foot Vigreux column. Three fractions, all of the same boiling point  $104^{\circ}/0.6$  mm., and the same refractive index,  $n_D^{25}$  1.5596, were obtained. Newman<sup>102</sup> prepared the same compound by the reduction of the ester with sodium in butyl alcohol. His physical constants were: b.p.  $106-109^{\circ}/1$  mm.,  $n_D^{25}$  1.5468. However, the values for the carbon and hydrogen analyses that he reported were not very close to the theoretical values.

$\beta$ -Naphthoic was prepared according to the directions in Organic Syntheses.<sup>112</sup> The acid was dissolved in aqueous sodium hydroxide, the solution heated under reflux, and large amounts of sodium amalgam added over an extended period of time. According to Baeyer,<sup>110</sup> this treatment should have resulted in the tetrahydro acid. A small aliquot of the alkaline solution decolorized several drops of cold potassium permanganate solution indicating the presence of a large amount of dihydro acid. The mixed tetrahydro and dihydro acids were isolated, dissolved in aqueous sodium hydroxide and treated with Raney nickel aluminum alloy according to Papa.<sup>113</sup> The resulting acid did not decolorize potassium permanganate, and was obtained in 76.5% yield. The overall yield from methyl  $\beta$ -naphthyl ketone was 58%. Newman and Mangham report a yield of 53.2% by a somewhat similar method.<sup>103</sup>

The ethyl ester, b.p.  $105^{\circ}/0.7$  mm., was prepared in 85.5% yield, and was reduced with lithium aluminum hydride in ether. Distillation resulted in an 87% yield of 1,2,3,4-tetrahydro-2-naphthylcarbinol, b.p.  $109^{\circ}/0.5$  mm.

The hydrogen phthalate ester, m.p.  $108.5^{\circ}$ , was prepared according to the general directions in Organic Reactions.<sup>114</sup>

The spectra of the alcohols from  $1600$  to  $800\text{ cm}^{-1}$  were measured with a rock salt prism, and from  $4000\text{ cm}^{-1}$  to  $2500\text{ cm}^{-1}$  with a lithium fluoride prism.

Some were measured in the liquid state in a 0.025 mm. cell, and some as ten percent solutions in carbon tetrachloride in a 0.1 mm. cell. The following table shows the position of the C-O band.

<u>Primary Alcohols</u>	<u>C-O Absorption (<math>\text{cm}^{-1}</math>)</u>
Cyclohexyl carbinol	1035 (a)
1,2,3,4-Tetrahydro-1-naphthylcarbinol	1040 (b)
1,2,3,4-Tetrahydro-2-naphthylcarbinol	1036 (b)
 <u>Secondary Alcohols</u>	
Cyclohexanol	1064 (a)
2-Methylcyclohexanol	1052 (a)
3-Methylcyclohexanol	1048 (a)
4-Methylcyclohexanol	1050 (a)
1,2,3,4-Tetrahydro-2-naphthol	1050 (a)
7-Methyl-1,2,3,4-tetrahydro-1-naphthol	1042 (b)
 <u>Tertiary Alcohols</u>	
1-Methylcyclohexanol	1114 (b)
1,7-Dimethyl-1,2,3,4-tetrahydro-1-naphthol	1102 (b)

a - pure liquid

b - 10% solution in carbon tetrachloride

The C-O band for primary alcohols was reported at  $1040 \text{ cm}^{-1}$  by Tuot and LeCompte,<sup>70</sup> and at  $1060 \text{ cm}^{-1}$  by Zeiss and Tsutsui.<sup>71</sup> However, the latter authors recognize that branching on the carbon  $\alpha$  to the hydroxylated carbon results in a shift of  $15 \text{ cm}^{-1}$  to lower frequencies, and that  $\alpha, \beta$  unsaturation promotes even greater shifts in the same direction. The values of the C-O

bands of the primary alcohols fall in the region  $1040-1035\text{ cm}^{-1}$  which agrees with the frequencies predicted by Zeiss and reported by Lecompte.

Secondary alcohols absorb at  $1100\text{ cm}^{-1}$  according to Lecompte. The normal value for a straight chain secondary alcohol is reported as  $1110\text{ cm}^{-1}$  by Zeiss. However, branching at the  $\alpha$ -carbon lowers the frequency by  $15\text{ cm}^{-1}$  and double bond interaction by  $30-50\text{ cm}^{-1}$ . Six-membered cyclic alcohols are shifted to  $1065-1040\text{ cm}^{-1}$ . Cyclohexanol was found to absorb at  $1064\text{ cm}^{-1}$  which agrees with the frequency reported by Zeiss. The values of the other secondary alcohols except for 7-methyl-1,2,3,4-tetrahydro-1-naphthol appear at about  $1050\text{ cm}^{-1}$  which agrees with the value of  $1051\text{ cm}^{-1}$  for  $\alpha$ -decalol as reported by Zeiss. 7-Methyl-1,2,3,4-tetrahydro-1-naphthol is  $\alpha, \beta$  unsaturated, and so its C-O band should appear at a lower frequency. It was found at  $1042\text{ cm}^{-1}$ , a value which almost overlaps the primary cyclic carbinol region.

Tertiary alcohols, according to Lecompte, absorb at  $1160\text{ cm}^{-1}$ . Zeiss reports a normal value of  $1140\text{ cm}^{-1}$  with shifts to lower frequencies accompanying a cyclic structure, branching, or  $\alpha, \beta$  unsaturation. The frequency of 1-methylcyclohexanol was  $1114\text{ cm}^{-1}$  which agreed fairly well with  $1117\text{ cm}^{-1}$  obtained by Zeiss. The 1,7-dimethyl-1,2,3,4-tetrahydro-1-naphthol absorbed at  $1102\text{ cm}^{-1}$ . This shift of  $12\text{ cm}^{-1}$  is due to  $\alpha, \beta$  unsaturation.

The shifts from normal frequencies because of cyclic structure, branching, or double bond interaction cause a good deal of overlapping between the three classes of alcohols, and make the differentiation of primary, secondary, and tertiary alcohols by infrared analysis very difficult. Other bands to be found in this region are those due to the phenyl group, the C-O-C bond in ethers, and the C-O bond in esters, and probably also lactones. Hence, the C-O alcohol band might very well be masked or shifted, by the interaction with the other bands, or not be sufficiently isolated to be assigned with

These difficulties are probably encountered in the spectra of podophyllotoxin, and picropodophyllin, and in the dihydroxy acid lactone, 3-hydroxymethyl-4-hydroxy-2-naphthoic acid lactone. The major bands in the 1120-1020  $\text{cm}^{-1}$  region for the three compounds are tabulated below, and conceivable assignments from the infrared standpoint only are made.

<u>Compound</u>	<u>Frequency (<math>\text{cm}^{-1}</math>)</u>	<u>Conceivable Assignment</u>
Podophyllotoxin	1048	secondary alcohol
	1128	tertiary alcohol
Picropodophyllin	1038	primary or secondary alcohol
	1124	tertiary alcohol
3-Hydroxymethyl-4-hydroxy- 1,2,3,4-tetrahydro-2-naphthoic 1040		primary alcohol
Acid Lactone	1050	secondary alcohol

The position of the hydroxyl group in picropodophyllin, and podophyllotoxin cannot be determined by infrared analysis. Podophyllotoxin has bands in positions characteristic of both secondary, and tertiary alcohols. A primary alcohol can be ruled out. Therefore, on the basis of infrared evidence in this region alone, it is reasonably certain that podophyllotoxin is not a C-1, C-3 lactone as proposed by Borsche-Spath.

The 1038  $\text{cm}^{-1}$  band of picropodophyllin is in the primary alcohol region, but could easily be an overlapping secondary alcohol, and can be attributed to either type of alcohol. From chemical evidence, it is not likely that there is a free primary alcohol in picropodophyllin, and so the band is probably due to a secondary alcohol. The 1124  $\text{cm}^{-1}$  band is found in tertiary

alcohol area. Hence infrared evidence cannot be used to assign the position of the alcohol group in picropodophyllin.

It should be noted that bands due to the C-O-C ether linkages, and to the C=O lactone linkage, should also be expected in this general region, and may modify, or mask the position of the alcohol bands, so that a definite assignment is not possible.

The dihydroxy acid lactone has bands which could be attributed to primary or secondary alcohols and so the nature of the lactone ring of this compound cannot be ascertained from absorption bands in this region.



## EXPERIMENTAL

All melting points are corrected.

### Diethyl Hexahydrophthalate.

The procedure of Price and Schwarz<sup>30</sup> was followed in hydrogenating 555 g. (2.5 moles) of diethyl phthalate over Raney nickel to yield 509 g. (89%) of diethyl hexahydrophthalate, b.p. 141°/11 mm.

### trans-Hexahydrophthalic Acid.

To 382 g. (1.67 moles) of diethyl hexahydrophthalate was added a solution of 20 g. (0.36 moles) of potassium hydroxide in 2200 ml. of 95% ethanol. The resulting solution was heated under reflux for two hours. Then 200 g. (3.6 moles) of potassium hydroxide was added, and the reaction mixture was again heated under reflux for two hours. The alcohol was distilled as water was dropped in to replace it. When the vapor temperature reached 100°, the distillation was stopped. The reaction mixture was cooled, and strongly acidified with 325 ml. of concentrated hydrochloric acid. The white precipitate that formed was separated by filtration, washed with water, and dried at 100°. The trans-hexahydrophthalic acid weighed 268 g. (93%) and melted at 209-215°.

### The Anhydride of trans-Hexahydrophthalic Acid.

Two hundred and two grams (1.18 moles) of trans-hexahydrophthalic acid, and 620 g. (7.90 moles) of freshly distilled acetyl chloride were heated under reflux for twelve hours. The excess acetyl chloride was distilled, finally under diminished pressure. The residue, a brown solid, was recrystallized from 400 ml. of ethyl acetate in the presence of decolorizing carbon to yield 97 g. of white solid, m.p. 143-144°. An additional 25.7 g. of white solid, m.p. 143-144° was obtained by concentrating the mother liquor. The

total quantity of trans-hexahydrophthalic acid anhydride, m.p. 143-144°, was 122.7 g. (68%).

Baeyer<sup>35</sup> reports the melting point as 140°.

#### Methyl Hydrogen trans-Hexahydrophthalate.

A mixture of 106 g. (0.69 moles) of trans-hexahydrophthalic acid anhydride and 750 ml. (18.6 moles) of absolute methanol was heated to boiling on a steam bath as rapidly as possible, and then heated under reflux with shaking for eight minutes. The resulting solution was then cooled rapidly in an ice bath, and transferred to a 2-l. filtering flask equipped with a capillary tube which reached to the bottom of the flask. The side arm was connected to a water aspirator, and the solvent was evaporated under diminished pressure for thirty-six hours. The white residue was transferred to the thimble of a Soxhlet extractor, extracted for fifteen hours with petroleum ether, b.p. 60-80°, and the extract cooled in a refrigerator for twelve hours. The resulting precipitate was separated by filtration, and dried in a vacuum oven at 60° to yield 118 g. (92%) of methyl hydrogen trans-hexahydrophthalate, m.p. 96°.

Werner and Conrad<sup>32</sup> report a melting point of 96°, and Fichter and Simon<sup>43</sup> report 96-97°.

#### trans-2-Carbomethoxycyclohexanecarbonyl Chloride.

In a Hickman still were placed 15.7 g. (0.085 moles) of methyl hydrogen trans-hexahydrophthalate, and 20 ml. (0.278 moles) of thionyl chloride. The mixture was stirred with a magnetic stirrer for sixteen hours at room temperature. The excess thionyl chloride was then evaporated under reduced pressure. Dry, thiophene-free benzene, 10 ml., was added, and evaporated under reduced pressure. This procedure was repeated for 10 ml. more benzene.

The residue was then distilled at 14 mm, warming the still with an oil bath heated at 40°. The distillate was a colorless oil which weighed 16.6 g. (96%).

trans-2-Carbomethoxycyclohexanecarboxanilide.

To 1 g. (0.0049 moles) of trans-2-carbomethoxycyclohexanecarbonyl chloride was added 2 ml. (0.025 moles) of dry aniline in 25 ml. of anhydrous ether. A yellow precipitate formed immediately. The mixture was stirred at room temperature for one hour and was then transferred with 25 ml. of water to a separatory funnel. The ether layer was separated, and washed successively with 5% hydrochloric acid, water, 5% sodium bicarbonate, and water. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The slightly yellow solid residue was recrystallized twice from petroleum ether-benzene and a white solid, m.p. 127°, was obtained.

Analysis:

Calculated for  $C_{15}H_{19}O_3N$ : C-68.95; H-7.28; N-5.36.

Found: C-69.21, 69.09; H-7.27, 7.29; N-5.49, 5.36.

The Lactone of trans-2-Hydroxymethylcyclohexanecarboxylic Acid.

In a 200-ml. three-necked flask, fitted with a dropping funnel, a mercury-sealed mechanical stirrer, and a condenser to which was attached a calcium chloride drying tube, were placed 50 ml. of sodium-dried ether, and 9.4 g. (0.235 moles) of sodium borohydride. The mixture was stirred rapidly to obtain a fine suspension, and 25.2 g. (0.12 moles) of trans-2-carbomethoxycyclohexanecarbonyl chloride in 25 ml. of sodium-dried ether was added through the dropping funnel. The suspension was stirred vigorously, and heated under reflux for twenty-four hours. After cooling in an ice bath, water was added cautiously to decompose the reduction complex. Finally a total of 50 ml. of water was added, and the mixture was stirred for four hours. An emulsion

was formed which was broken by centrifuging at 1800 r.p.m. in a 200-ml. centrifuge bottle. The ethereal layer was separated, and the aqueous layer extracted with 50 ml. of ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. A solution of 5.5 g. (0.11 moles) of sodium hydroxide in 35 ml. of 95% ethanol was added, and the resulting solution was heated under reflux for three hours. Then the alcohol was distilled, and water was gradually added so that the alcohol was displaced. The solution was cooled, acidified with dilute sulfuric acid, and the resulting mixture was heated under reflux for fifteen minutes. The mixture was cooled and extracted with three 50-ml. portions of ether. The combined ethereal extracts were washed with water, dried over magnesium sulfate, filtered, and the ether evaporated. The residue, a colorless oil was distilled through a three-foot Vigreux column. Three fractions were collected.

- (1)  $n_D^{20}$  1.4762
- (2)  $n_D^{20}$  1.4761
- (3)  $n_D^{20}$  1.4763

The trans-2-hydroxymethylcyclohexanecarboxylic acid lactone, b.p.  $114.8^\circ/44$  mm. weighed 7.9 g. (46%).

#### Analysis:

Calculated for  $C_8H_{12}O_2$ : C-68.53; H-8.62.

Found: C-68.76, 68.66; H-8.56, 8.55.

#### Saponification Equivalent:

Calculated for  $C_8H_{12}O_2$ : 110.2

Found: 139.5, 110.3

trans-2-Hydroxymethylcyclohexanecarboxanilide.

In a 100-ml. three-necked flask, fitted with a condenser to which a calcium chloride drying tube was attached, a dropping funnel, and a magnetic stirrer, were placed 1 g. (0.041 atoms) of magnesium turnings and 20 ml. of sodium-dried ether. Through the dropping funnel was added 5.8 g. (0.041 moles) of dry methyl iodide in 10 ml. of dry ether to form the Grignard reagent. The solution was cooled in an ice bath, and 4.0 g. (0.043 moles) of dry aniline in 10 ml. of dry ether was added cautiously through the dropping funnel. Methane was vigorously evolved. When the reaction subsided, the reaction mixture was stirred thirty minutes more. Then 2.5 g. (0.018 moles) of the lactone of trans-2-hydroxymethylcyclohexanecarboxylic acid in 10 ml. of dry ether was added, and the reaction mixture was heated under reflux for fifteen minutes. The reaction mixture was cooled in an ice bath, and dilute hydrochloric acid was added to decompose the "Grignard" and to neutralize the aniline. The ether layer was separated, and the aqueous layer extracted with ether. The combined ethereal extracts were washed successively with 5% hydrochloric acid and water, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue, a yellow solid, was recrystallized twice from petroleum ether-benzene to yield a white solid which melted at 166°.

Analysis:

Calculated for  $C_{11}H_{19}O_2N$ : C-72.06; H-8.22; N-6.01

Found: C-72.09, 71.95; H-8.01, 8.25, N-6.08, 6.35.

Methyl Hydrogen Phthalate.

The directions of Eliel<sup>41</sup> were followed to prepare methyl hydrogen phthalate. Phthalic anhydride, 296 g. (2 moles) and 200 ml. (5 moles) of absolute methanol were reacted to produce 265 g. of methyl hydrogen phthalate,

m.p. 82-82.5°. By concentrating the mother liquors, an additional 35 g., m.p. 82°, was obtained, bringing the total to 300 g. (83.5%) of white crystals.

Methyl Hydrogen cis-Hexahydrophthalate. In a typical run, 50 g. (0.277 moles) of methyl hydrogen phthalate was dissolved in 100 ml. of glacial acetic acid and hydrogenated in the presence of 1 g. of Adams catalyst. The absorption of hydrogen stopped when the theoretical amount was taken up. The supernatant liquid was removed by decantation, and the platinum washed with acetic acid. The decanted solution and washings were combined, and the acetic acid evaporated under reduced pressure. The residue was a viscous oil which crystallized slowly. The reduction product from 213 g. of half-ester was recrystallized from 100 ml. of benzene plus 850 ml. of petroleum ether, b.p. 60-80°, to yield 182 g. (83%) of methyl hydrogen cis-hexahydrophthalate, m.p. 66-67°.

Vavon and Pleignier<sup>37</sup> report a melting point of 68.5°.

cis-2-Carbomethoxycyclohexanecarbonyl Chloride.

The reaction of 20 g. (0.10 moles) of methyl hydrogen cis-hexahydrophthalate and 24 ml. (0.33 moles) of thionyl chloride, run in the same way as for the trans compound, resulted in 20.5 g. (93%) of cis-2-carbomethoxycyclohexanecarbonyl chloride.

cis-2-Carbomethoxycyclohexanecarbonyl Chloride.

The reaction between 1.0 g. (0.0049 moles) of cis-2-carbomethoxycyclohexanecarbonyl chloride and 2 ml. (0.025 moles) of dry aniline was conducted in the same way as for the trans compound. The resultant derivative melted at 97°.

## Analysis:

Calculated for  $C_{15}H_{19}O_3N$ : C-68.95; H-7.28; N-5.36.

Found: C-69.21, 69.00; H-7.28, 7.38; N-5.60, 5.62.

The Lactone of cis-2-Hydroxymethylcyclohexanecarboxylic Acid. The cis lactone was prepared in the same way as the trans lactone. The reduction of 20.5 g. (0.10 moles) of cis-2-carbomethoxycyclohexanecarbonyl chloride with 7.65 g. (0.19 moles) of sodium borohydride yielded 6.1 g. (43%) of cis-2-hydroxymethylcyclohexanecarboxylic acid lactone, b.p. 116-117°/17 mm.,  $n_D^{20}$  1.4769.

## Analysis:

Calculated for  $C_8H_{12}O_2$ : C-68.53; H-8.62

Found: C-68.62, 68.35; H-8.45, 8.53

## Saponification Equivalent:

Calculated for  $C_8H_{12}O_2$ : 110.2

Found: 110.0, 110.6

cis-2-Hydroxymethylcyclohexanecarboxanilide.

The anilide was prepared in the same way as the anilide of the trans lactone. The cis-2-hydroxymethylcyclohexanecarboxanilide melted at 151.5°.

## Analysis:

Calculated for  $C_{14}H_{19}O_2N$ : C-72.1; H-8.22; N-6.01

Found: C-72.23, 71.94; H-8.27, 8.14; N-6.22, 6.07

o-Xylylene Dibromide.

The directions of Perkin<sup>49</sup> were followed to make the dibromide. Accordingly, 50 g. (0.47 moles) of o-xylene, b.p. 114°, was reacted with 160 g. (1 mole) of bromine at 130-135°. The crude o-xylylene dibromide obtained was recrystallized from petroleum ether, b.p. 60-80°, to yield 71 g. (57%) of

white, extremely lachrymatory crystals, m.p.  $93^{\circ}$ .

Tetrasth $\alpha$ -o-Xylenedimalonate.

In a 200-ml. three-necked flask equipped with a magnetic stirrer, a calcium chloride drying tube, and a thermometer reaching almost to the bottom, was placed 80 ml. of diethyl malonate. The mixture was stirred, and heated to  $80^{\circ}$  by means of an oil bath. Then 3.20 g. (0.127 moles) of sodium hydride (95%) was added in small portions so that each portion was dissolved before the next was added. The temperature was maintained at  $90-100^{\circ}$  to keep the sodiomalonic ester in solution. A solution of 16.8 g. (0.0635 moles) of o-xylylene dibromide in 60 ml. of diethyl malonate at  $60^{\circ}$  was added slowly to the stirred solution of the sodiomalonic ester, the temperature being maintained at  $100-110^{\circ}$ . After stirring for 12 hours at  $100-110^{\circ}$ , the reaction mixture was cooled, a few drops of acetic acid added, and the sodium bromide removed by centrifuging. The resulting solution was distilled. The solvent, diethyl malonate, was removed at  $65^{\circ}/0.1$  mm. The viscous residue was transferred to a Hickman still, and distilled from an oil bath at  $150^{\circ}$ , the pressure being 1  $\mu$ . A colorless oil, 21.3 g. (79%), was obtained.

The Anhydride of cis-1,2,3,4-Tetrahydro-2,3-naphthalenedicarboxylic Acid.

A solution of 2.3 g. (0.1 moles) of clean sodium in 100 ml. of absolute ethanol (distilled from magnesium ethoxide) was prepared in a 200-ml. three-necked flask equipped with a magnetic stirrer, a dropping funnel, and a condenser to which was attached a calcium chloride drying tube. To this solution was added 21.3 g. (0.05 moles) of xylylene dimalonic ester in 20 ml. of absolute ethanol. The solution was cooled in an ice bath, and 8.0 g. (0.05 moles) of bromine was added dropwise. The bromine was decolorized at once, and



sodium bromide precipitated. The reaction mixture was stirred for one hour at room temperature and the sodium bromide was then separated by centrifuging. The alcoholic solution was transferred to a 250-ml. flask and a solution of 15 g. (0.27 moles) of potassium hydroxide in 50 ml. of water was added. The mixture was heated under reflux for eight hours. Then the alcohol was distilled as water was gradually added to replace it. The resulting solution was cooled, acidified with 6N hydrochloric acid, and extracted with four 150-ml. portions of ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue was a yellow glass which could not be crystallized. It was heated at 190° and a gas was evolved. When the reaction subsided, the residue was cooled. A brown solid resulted which was recrystallized once from petroleum ether-ethyl acetate, and then twice from acetic acid to give 4.9 g. (45%) of a white solid, m.p. 183°.

<sup>45</sup> Haworth and Perkin<sup>46</sup> report a melting point of 183° for cis-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid anhydride.

Dimethyl cis-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylate.

To 2.5 g. (0.0124 moles) of cis-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid anhydride, was added 16 g. (0.5 moles) of absolute methyl alcohol. Dry hydrochloric acid was bubbled in until 0.2 g. was absorbed. The resulting solution was heated under reflux for two hours, and the mixture concentrated under reduced pressure. Again 16 g. of methyl alcohol and 0.2 g. of gaseous hydrochloric acid were added. The resulting solution was stirred at room temperature for twelve hours and then heated under reflux for two hours. Concentration under reduced pressure resulted in a yellow oil which crystallized on standing. The solid was recrystallized twice from petroleum ether, b.p. 60-80°

to yield 2.7 g. (88%) of dimethyl cis-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylate, m.p.  $67^{\circ}$ . The literature value is  $68.5^{\circ}$ .<sup>45</sup>

trans-1,2,3,4-Tetrahydro-2,3-naphthalenedicarboxylic Acid.

To a solution of 0.65 g. (0.028 moles) of sodium in 50 ml. of commercial absolute ethanol was added 2.7 g. (0.013 moles) of dimethyl cis-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylate. The solution was heated under reflux for three hours. Then the alcohol was distilled as water was added gradually to replace it. The resulting solution was cooled, and then acidified with concentrated hydrochloric acid. A white solid precipitated which was separated by filtration, washed with water and dried in a vacuum oven at  $60^{\circ}$ . The weight of trans-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid was 2.2 g. (92%). It melted at  $221^{\circ}$ . The reported value is  $226-227^{\circ}$ .<sup>45</sup>

The Anhydride of trans-1,2,3,4-Tetrahydro-2,3-naphthalenedicarboxylic Acid.

To 2.2 g. (0.010 moles) of trans-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid was added 21 ml. (0.3 moles) of acetyl chloride, and the mixture was heated under reflux for three hours. The mixture was cooled and the resulting precipitate separated by filtration. After drying, 1.7 g. of a white solid, m.p.  $230-239^{\circ}$  was obtained. The solid was then heated under reflux with 20 ml. of acetyl chloride. This time 1.5 g. of a solid, m.p.  $236-245^{\circ}$ , was obtained. It was then recrystallized once from petroleum ether-ethyl acetate, and then from acetic acid to yield 1.2 g. (60%) of trans-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid anhydride, m.p.  $253^{\circ}$ . The reported melting point is  $254^{\circ}$ .<sup>45</sup>

The Lactone of trans-3-Hydroxyethyl-1,2,3,4-tetrahydro-2-naphthoic Acid.

Granular aluminum, 3 g. (0.111 atoms), was etched with warm 10% sodium hydroxide. The aluminum was washed twice with water, and once with 95% ethanol.

It was then covered with 2% mercuric chloride, and shaken for thirty seconds. The mercuric chloride was decanted, and the amalgamated aluminum was washed twice with water, then with alcohol, and finally with ether. A solution of 600 mg. (2.97 moles) of trans-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylic acid anhydride in 50 ml. of dioxane was added. The reaction mixture was stirred with a magnetic stirrer for forty-eight hours, during which time a total of 6 ml. of water was added gradually. After forty-eight hours, the reaction mixture was a gray sludge. It was transferred to a 200-ml. beaker with the aid of 20 ml. of water, and a solution of 12 ml. (0.22 moles) of concentrated sulfuric acid in 50 ml. of water was added. The mixture was stirred for sixteen hours to decompose the alumina sludge. Most of the sludge had decomposed by this time, and 50 ml. of chloroform was added, and the resulting mixture filtered. The residue and the aqueous layer were washed with 50 ml. of chloroform, and the combined chloroform layers were evaporated. The residue was an oil which solidified on scratching. Then 0.2 g. (0.005 moles) of sodium hydroxide in 5 ml. of water was added and the mixture was heated under reflux for fifteen minutes, cooled, acidified with 10% sulfuric acid, and heated under reflux for fifteen minutes. After cooling, the mixture was extracted with chloroform. The chloroform layer was washed with 5% sodium bicarbonate, and then with water. The chloroform was evaporated, and the white crystalline residue was recrystallized twice from methyl alcohol to yield 170 mg. (30%) of trans-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic acid lactone, m.p. 159°. Haworth and Slinger report a melting point of 156°<sup>45</sup>.

#### Analysis:

Calculated for  $C_{12}H_{12}O_2$ : C-76.57; H-6.43

Found: C-76.56, 76.46; H-6.39, 6.48

The Lactone of cis-3-Hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic Acid.

The cis lactone was prepared in essentially the same way as the trans lactone. cis-1,2,3,4-Tetrahydro-2,3-naphthalenedicarboxylic acid anhydride, 0.75 g. (0.0037 moles), dissolved in 20 ml. of dioxane, 11 ml. of benzene, and 14 ml. of ether was reduced with 3.5 g. (0.130 atoms) of aluminum amalgam to yield 205 mg. (29.5%) of cis-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic acid lactone, m.p.  $134^{\circ}$ . The reported melting point is  $133-134^{\circ}$ .<sup>45</sup>

**Analysis:**

Calculated for  $C_{12}H_{12}O_2$ : C-76.57; H-6.43

Found: C-76.37, 76.36; H-6.28, 6.44

m-Hydroxybenzoic Acid.

The procedure of Schwenk and Papa<sup>53</sup> was followed to prepare m-hydroxybenzoic acid. Crude m-hydroxybenzoic acid, 51 g. (83.5%), was obtained from the Raney nickel alloy reduction of 83 g. (0.5 moles) of piperonylic acid. Recrystallization from 200 ml. of water yielded 46.0 g. (75.3%) of white crystals, m.p.  $202^{\circ}\text{C}$ .

The Lactone of cis-3-Hydroxycyclohexanecarboxylic Acid.

The procedure of Perkin and Tattersall<sup>50</sup> was followed in a general way to prepare the lactone.

One and a half liters of absolute alcohol was prepared by distilling commercial absolute ethanol from magnesium ethoxide. It was distilled into a 5-l. three-necked flask equipped with two efficient spiral condensers, and a four-foot, wide bore, Liebig condenser. To the alcohol was added 60 g. (0.43 moles) of m-hydroxybenzoic acid, and the alcohol was brought to a boil. Then 230 g. (10 moles) of clean sodium metal cut in one centimeter cubes was added as rapidly as possible. When the reaction had subsided, the Liebig condenser was replaced with a mercury-sealed mechanical stirrer, and the reaction mixture

was stirred and heated under reflux until all of the sodium dissolved. Then 2 l. of water and 750 ml. (9 moles) of concentrated hydrochloric acid were added. The alcohol in the reaction mixture was rapidly distilled, as water was added through a dropping funnel, until the temperature of the distillate indicated that the ethanol had been displaced. The distillation was then continued without the addition of water until the sodium chloride began to precipitate. The volume was then about 1½ l. The solution was cooled, strongly acidified with concentrated hydrochloric acid, and enough water added to dissolve the precipitated salt. The acidified reaction mixture was then transferred to a liquid-liquid extractor, and extracted continuously with ether at a rapid rate for twenty-four hours. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue was 41 g. (65%) of a light yellow oil which consisted of mixed *cis* and *trans* hexahydroxyacids. It crystallized slowly on standing.

The mixed acids were heated at 180° to lactonize the *cis* acid, and then distilled. The distillate, b.p. 120-140°/20 mm., weighed 21 g. Upon redistillation, 19 g. (30.3%) of *cis*-3-hydroxycyclohexanecarboxylic acid lactone, b.p. 125-127°/20 mm., was obtained. The distillate crystallized slowly, but never became wholly crystalline.

Recrystallization from 85 ml. of petroleum ether, b.p. 60-80°, resulted in 12.6 g. of a white, sticky solid. The mother liquor was concentrated to 40 ml., and an additional 3.2 g. of the solid was obtained.

The lactone, 15.8 g. (0.126 moles), was heated under reflux with a solution of 5.5 g. (0.138 moles) of sodium hydroxide in 75 ml. of water for thirty minutes. The resulting solution was cooled, acidified with 6 N hydrochloric acid, and saturated with salt. The mixture was then extracted ten times with 75-ml. portions of ether. The ethereal solution was dried over anhydrous

magnesium sulfate, filtered, and the ether evaporated. The residue was 17.2 g. of a white solid. It was recrystallized once from 35 ml. of ethyl acetate to yield 14.9 g. of cis-3-hydroxycyclohexanecarboxylic acid, m.p.  $132^{\circ}$ .

The acid was heated at  $180^{\circ}$  for thirty minutes, and distilled, to yield 11.5 g. of cis-3-hydroxycyclohexanecarboxylic acid lactone, b.p.  $128-129^{\circ}/22$  mm., which was then recrystallized three times from petroleum ether, b.p.  $60-80^{\circ}$ .

**Analysis:**

Calculated for  $C_7H_{10}O_2$ : C-66.64; H-7.99

Found: C-66.67; H-8.02

**Saponification Equivalent:**

Calculated: 126.15

Found: 126.0, 126.7

**Benzylsuccinic Acid.**

The procedure of Weizmann<sup>56</sup> was followed. The sodium salt prepared from 160 g. (0.64 moles) of diethyl benzylmalonate, b.p.  $120^{\circ}/0.15$  mm., and 14.7 g. (0.64 moles) of sodium was condensed with 107 g. (0.64 moles) of ethyl bromoacetate, b.p.  $65^{\circ}/12$  mm. The resultant crude triester was saponified with alcoholic potassium hydroxide, and the crude tricarboxylic acid was obtained as an oil. Weizmann decarboxylated by heating the oil at  $160^{\circ}$ . The procedure was changed to decarboxylating the crude tricarboxylic acid by heating under reflux with 300 ml. of water for five hours. The tricarboxylic acid went into solution readily, and upon cooling, the dicarboxylic acid precipitated. It was separated by filtration, washed with cold water, and dried in a vacuum oven to yield 100 g. (75%) of benzylsuccinic acid, m.p.  $158-159^{\circ}$ . Weizmann reports the melting point as  $160-161^{\circ}$ .

### Benzylsuccinic Anhydride.

Freshly distilled acetyl chloride, 225 ml. (3.16 moles), and 153 g. (0.735 moles) of benzylsuccinic acid were heated under reflux. The acid dissolved in about thirty minutes, and the acetyl chloride was refluxed for two hours more. The acetyl chloride was then distilled under reduced pressure leaving a slightly tan solid residue. The residue was decolorized with carbon and recrystallized from 140 ml. of benzene and 240 ml. of petroleum ether, b.p. 60-80°, and the resultant solid was dried in a vacuum oven at 60° for twenty-four hours. The benzylsuccinic anhydride weighed 120 g. (86%), and melted at 98°. Beach and Legg<sup>55</sup> and Haworth<sup>54</sup> report a melting point of 95-97°.

### 4-Keto-1,2,3,4-tetrahydro-2-naphthoic Acid.

In a one-liter three-necked flask equipped with a drying tube, a mercury-sealed mechanical stirrer, and an Erlenmeyer flask attached by means of a section of wide bore rubber tubing, were placed 300 ml. of nitrobenzene, and 200 ml. of acetylene tetrachloride, both dried and distilled. The liquid in the flask was stirred, and 185 g. of anhydrous aluminum chloride was added slowly from the Erlenmeyer addition flask. When the addition was complete, the resulting viscous, green solution was cooled to 5°.

To a 2-l. three-necked flask equipped with a mercury-sealed mechanical stirrer, a thermometer and a Claisen adapter containing a calcium chloride drying tube and a dropping funnel, were added 120 g. (0.63 moles) of benzylsuccinic anhydride, 100 ml. of nitrobenzene, and 100 ml. of acetylene tetrachloride. The mixture was rapidly stirred, and the anhydride dissolved. Upon cooling to 5°, however, some precipitated out, and the resultant was a fine slurry. To the rapidly stirred slurry, cooled continuously by means of an ice-bath, the solution of aluminum chloride previously prepared was slowly

added so that the temperature did not exceed  $5^{\circ}$ . This took about one hour. The result was a greenish, brownish, viscous solution which was stirred in an ice-bath for four hours and then placed in a refrigerator at  $5^{\circ}$  for forty-four hours.

At the end of that time, the contents of the flask was poured over 500 g. of crushed ice, and 350 ml. of concentrated hydrochloric acid. This procedure resulted in an emulsion which was partially broken by centrifuging at 1800 r.p.m. for thirty minutes in 200-ml. centrifuge bottles. The liquid phase was decanted leaving a pink gelatinous residue which was dissolved in 800 ml. of 10% sodium hydroxide. The decanted liquid was transferred to a separatory funnel, the organic layer separated, and the aqueous portion extracted with ether. The organic and ethereal layers were then combined, and extracted with three 300-ml. portions of 5% sodium hydroxide. The combined alkaline extracts were washed with ether and then slowly added with stirring to 500 g. of ice plus 350 ml. of concentrated hydrochloric acid. A pink gelatinous precipitate soon appeared. The reaction mixture was placed in a refrigerator to digest for fifteen hours. The precipitate was then finely crystalline. It was separated by filtration, washed well with water, and dried in a vacuum oven. The resultant pink solid was recrystallized from 1200 ml. of water, using decolorizing carbon, to yield 96 g. of 4-keto-1,2,3,4-tetrahydro-2-naphthoic acid. An additional 2 g. were recovered from the mother liquor resulting in a total of 98 g. (81.5%) of white crystals, m.p.  $149.8^{\circ}$ . Hsworth<sup>54</sup> reports a melting point of  $145-147^{\circ}$ , and Atwood, Stevenson, and Thorpe<sup>57</sup> report a melting point of  $149^{\circ}$ .

4-Hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid.

Ten grams (0.0526 moles) of 4-keto-1,2,3,4-tetrahydro-2-naphthoic acid was dissolved in a solution of 2.3 g. (0.0575 moles) of sodium hydroxide in



50 ml. of water. The solution was stirred and 2.0 g. (0.050 moles) of sodium borohydride dissolved in 25 ml. of water was added. The temperature was maintained below  $30^{\circ}$ , and the solution was stirred for two hours. After cooling to  $5^{\circ}$ , concentrated hydrochloric acid was added with great caution until the excess sodium borohydride was decomposed. The crude hydroxy acid precipitated after cooling in a refrigerator for several hours. The precipitate was separated by filtration, washed with water, and dried in a vacuum desiccator to yield 8.0 g. (79.5%) of 4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid, m.p. 111-111.5 $^{\circ}$  (heated rapidly).

The Lactone of 4-Hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid.

Four grams of the hydroxy acid was heated at  $125^{\circ}$  for one hour. Upon cooling, a yellow oil was obtained which crystallized on cooling and scratching. The solid was recrystallized twice from a mixture of alcohol and water and once from petroleum ether, b.p.  $60-80^{\circ}$ . The compound exhibited a strong tendency to oil out of solution. The temperatures of the recrystallizing solvents were, therefore, kept below  $50^{\circ}$ . They were cooled slowly and seeded to induce crystalline precipitation rather than "oiling out." After three recrystallizations, 2.2 g. (60.5%) of 4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid lactone, m.p.  $63-64^{\circ}$ , was obtained.

Analysis:

Calculated for  $C_{11}H_{10}O_2$ : C-75.83; H-5.78

Found: C-75.70; H-5.94

Saponification Equivalent:

Calculated for  $C_{11}H_{10}O_2$  - 174.2

Found: 174.0, 174.7

Ethyl 1-keto-1,2,3,4-tetrahydro-2-methylthiote.

A solution of 60 g. (0.316 moles) of the keto acid in 200 ml. (3.43 moles) of absolute ethanol, 75 ml. of dry benzene, and 1 ml. of concentrated sulfuric acid was heated under reflux for five hours. The solvent was then slowly distilled at a 10:1 reflux ratio, until no more ternary azeotrope distilled. The level of liquid in the still was maintained by the addition of a mixture of anhydrous benzene and alcohol in the ratio of 32 ml:17 ml.

The contents of the flask was heated under reflux for four hours more, and then the solvent was rapidly distilled until the volume was about one-fourth of the original volume. Finally, the solution was concentrated under reduced pressure at 50°. The residue was dissolved in ether and washed with 5% sodium bicarbonate and then water. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. Upon distillation, 63 g. (91%) of slightly yellow oil, b.p. 128-130°/0.2 mm., was obtained.

Ethyl 1-hydroxyethyl-methyl-keto-1,2,3,4-tetrahydro-2-methylthiote.

Sodium sand was prepared by heating a mixture of 20 ml. of sodium-dried xylene, and 0.57 g. (0.025 atoms) of sodium under reflux. By stirring rapidly as the mixture was slowly cooled, the sodium was dispersed and solidified into many small granules. The mixture was thoroughly cooled, washed by decantation with ether, and the sodium dispersed in sodium-dried ether. Then 2.1 g. (0.026 moles) of freshly distilled ethyl formate was added, and the mixture was stirred in an ice bath as 2.18 g. (0.071 moles) of keto-ester was added. The reaction mixture was stirred thirty minutes in an ice-bath. After a while, a white precipitate distinguishable from the sodium metal was obtained. After about an hour, the mixture became gray, brown, and finally orange-yellow. The mixture was placed in a refrigerator for twelve hours, resulting in an orange solid and a brown supernatant solution.

Ice water, 25 ml., was added and the solid dissolved in water. The organic layer was washed with ice water. The aqueous layers were combined and acidified with cold, dilute hydrochloric acid. A brown oil was obtained. It was extracted with ether, and the ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue (2.2 g.), a brown oil, was dissolved in dry benzene and chromatographed on silicic acid. Development resulted in a sharp brown band on top, and a diffuse yellow area below it. The chromatogram was eluted with 2% ethanol in benzene to separate the yellow area from the brown band. The solvent was evaporated to yield a yellow oil. Crystals were obtained from petroleum ether, b.p. 60-80°, and the solid was recrystallized from petroleum ether. A light yellow solid, 1.27 g., m.p. 39°, was obtained. Extreme chilling of the mother liquor in a dry ice bath resulted in the isolation of an additional 0.23 g. of yellow solid. The total weight of ethyl 3-hydroxymethylene-4-keto-1,2,3,4-tetrahydro-2-naphthoate was 1.50 g. (61%).

Analysis:

Calculated for  $C_{14}H_{14}O_4$ : C-68.28; H-5.73

Found: C-67.71; H-5.63

The oils and the solids isolated gave a strong enol test with ferric chloride.

Ethyl-3 Hydroxymethylene-4-keto-1,2,3,4-tetrahydro-2-naphthoate, and 3-Hydroxymethylene-4-keto-1,2,3,4-tetrahydro-2-naphthoic Acid.

To anhydrous methanol, 100 ml., prepared by distilling commercial absolute methyl alcohol from magnesium methoxide, 4.6 g. (0.2 moles) of clean sodium was added. The mixture was heated under reflux, and stirred until the sodium dissolved completely. The methyl alcohol was distilled first at atmospheric pressure, then under diminished pressure, and finally at 200°/0.1 mm.

for two hours. Precautions were taken to keep the sodium methoxide dry. The vacuum was broken with dry nitrogen. Thiophene-free, sodium-dried benzene was added to the cooled sodium methoxide and vigorously shaken to produce a fine suspension. Then 14.8 g. (0.2 moles) of ethyl formate, and 21.8 g. (0.1 moles) of keto-ester were added, the system evacuated, and filled with dry nitrogen. A red precipitate was obtained almost immediately. The reaction mixture was kept at room temperature for twelve hours. Then 75 ml. of water and 10 ml. of ether were added, and the mixture shaken until all of the solid had dissolved. The dark brown aqueous layer was separated and the organic layer was washed with 75 ml. of 5% sodium hydroxide. The aqueous layers were combined, and acidified with dilute hydrochloric acid. The acidified mixture was extracted with ether, the ethereal solution dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue was 23.7 g. of a dark brown oil. A few seed crystals were obtained from a small sample treated with petroleum ether, and the main portion of the oil was seeded to get a dark brown crystalline mass.

The brown crystals were only partially soluble in 150 ml. of benzene. A finely crystalline, slightly yellow residue was left after dissolving the main bulk of the solid in benzene. The residue was recrystallized from petroleum ether -benzene, b.p. 60-80°, and then twice from chloroform to yield 3.2 g. (14.7%) of slightly yellow crystals, m.p. 153°, soluble in sodium bicarbonate, and giving an intense red color with ferric chloride. The carbon and hydrogen analyses of the compound were correct for 3-hydroxy-methylene-4-keto-1,2,3,4-tetrahydro-2-naphthoic acid.

Analysis:

Calculated for  $C_{12}H_{10}O_4$ : C-66.74; H-4.62

Found: C-65.86, 65.97; H-4.62, 4.67.

The benzene solution of the brown crystals was chromatographed on silicic acid. The chromatogram consisted of a sharp brown band, and a diffuse yellow layer. The chromatograph was eluted with 2% alcohol in benzene and the yellow layer was separated from the brown band. The solvent was evaporated under diminished pressure leaving a brown oil which slowly crystallized, but could not be satisfactorily recrystallized. This solid was again subjected to partition chromatography over silicic acid. This time evaporation of the elution solvent resulted in a crystalline yellow residue, 7.8 g., which melted at  $41^{\circ}$  after recrystallization from petroleum ether, b.p.  $60-80^{\circ}$ . It gave an intense ferric chloride test, was soluble in 5% sodium hydroxide, but not 5% sodium bicarbonate, and a mixed melting point with the already analyzed "enol-ester" showed that it was the same substance. It was obtained this time in 32% yield.

The combined yield of "enol-ester", and "enol-acid" was 56.5%.

3-Hydroxyethyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid.

(a) To a solution of 425 mg. (10.6 mmoles) of sodium hydroxide in 20 ml. of water was added 1.0 g. (4.58 mmoles) of enol-acid, resulting in a yellow-red solution. Then 350 mg. (8.75 mmoles) of sodium borohydride dissolved in 5 ml. of water was added dropwise with stirring. The reaction mixture was acidified with concentrated hydrochloric acid. There was no immediate precipitate, but after five hours in the refrigerator, a fluffy white precipitate appeared. It was separated by filtration, washed with water, and dried in a vacuum desiccator. The solid weighed 0.6 g., and 0.52 g. (51%) of 3-hydroxy-ethyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid was recovered after recrystallization from ethyl acetate. The compound did not give a ferric chloride test, and was soluble in sodium bicarbonate. Its melting point could not be determined since it gassed and resolidified when heated. The temperature of

this phenomenon depended on the rate of heating.

**Analysis:**

Calculated for  $C_{12}H_{14}O_4$ : C=64.85; H=6.35

Found: C=64.99; H=6.20

(b) To a solution of 200 mg. (6.5 mmoles) of sodium hydroxide in 25 ml. of water, 1.5 g. (6.10 mmoles) of "enol-ester" was added, and dissolved with stirring. Then 500 mg. (12.5 mmoles) of sodium borohydride in 10 ml. of water was added dropwise. The resulting solution was stirred at room temperature for forty-eight hours, the excess sodium borohydride decomposed by the cautious addition of concentrated hydrochloric acid, and the acidified reaction mixture stored in an ice chest for sixteen hours. The resulting white precipitate was separated by filtration, washed with water, dried in a vacuum desiccator, and recrystallized from ethyl acetate, to yield 0.50 g. (37%) of 3-hydroxymethyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid.

**Analysis:**

Calculated for  $C_{12}H_{14}O_4$ : C=64.85; H=6.35

Found: C=64.70; H=6.25

The Lactone of 3-Hydroxymethyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid.

In a 10-ml. flask was placed 0.5 g. of dihydroxy acid, and 5 ml. of p-xylene. The contents of the flask was heated under reflux for three hours, cooled, and stored for sixteen hours in a refrigerator. The resultant precipitate which weighed 0.44 g. (95%) was filtered, washed with cold petroleum ether, b.p. 60-80°, and recrystallized twice from petroleum ether. The resulting solid weighed 0.28 g. and melted at 218°.

## Analysis:

Calculated for  $C_{12}H_{12}O_3$ : C-70.57; H-5.92

Found: C-70.62, 70.74; H-5.84, 5.94.

Cyclohexanol.

Commercial cyclohexanol (Eastman), 500 ml., was distilled through a three-foot column packed with glass helices. The fraction boiling at  $160^{\circ}$  and weighing 285 g. was collected and redistilled. The middle fraction of the distillate, 140 g., a colorless liquid, b.p.  $160^{\circ}$ ,  $n_D^{25}$  1.4644, was set aside for infrared analysis.

Physical constants reported in the literature:

B.P.  $159^{\circ}$ ,  $n_D^{20}$  1.4600<sup>79</sup>

B.P.  $161.10^{115}$

B.P.  $159^{\circ}$ ,  $n_D^{25}$  1.4644<sup>71</sup>

2-Methylcyclohexanol.

Four hundred grams (3.70 moles) of o-cresol was dissolved in a solution of 165 g. (4.1 moles) of sodium hydroxide in 675 ml. of water. The solution was then steam distilled to remove any non-acidic impurities. The residue was cooled in an ice bath, and 50% sulfuric acid was added until it was strongly acid. The resulting organic layer was separated, washed repeatedly with water, dried over calcium chloride for forty-eight hours, filtered, and distilled from Raney nickel through a two-foot Vigreux column. The fraction boiling at  $90-91^{\circ}/20$  mm. was collected.

The o-cresol was reduced to 2-methylcyclohexanol according to the procedure of Ungnade, and Nightingale<sup>72</sup> using Raney nickel in the presence of a small amount of sodium. The reaction for 324 g. (0.430 moles) of o-cresol took five hours, and 320 g. (94%) of 2-methylcyclohexanol, b.p.  $162-164^{\circ}$ ,

was obtained after distillation through a one-foot Vigreux column. The compound was then redistilled through a three-foot column packed with glass helices at a 5:1 reflux ratio. The middle 100 ml. of distillate, b.p.  $164^{\circ}$ ,  $n_D^{20}$  1.4606, was collected as product.

Physical constants recorded in the literature:

B.P. $163-164^{\circ}$	$n_D^{20}$ 1.4602 <sup>72</sup>
B.P. $165^{\circ}$	$n_D^{20}$ 1.4609 <sup>79</sup>
B	$n_D^{20}$ 1.4616 <sup>77</sup>

### 3-Methylcyclohexanol.

3-Methylcyclohexanol was prepared in the same way as 2-methylcyclohexanol. Three hundred and eight grams (2.85 moles) of m-cresol, b.p.  $104^{\circ}/25$  mm., was reduced to 324 g. (96%) of 3-methylcyclohexanol, b.p.  $169-171^{\circ}$ . The compound was redistilled through a three-foot column packed with glass helices. The fraction boiling at  $171^{\circ}$ ,  $n_D^{20}$  1.4568, and weighing 215 g., was collected as product.

Physical constants from the literature:

B.P. $168-169^{\circ}$	$n_D^{20}$ 1.4545 <sup>72</sup>
B.P. $172$	$n_D^{20}$ 1.4575 <sup>79</sup>
	$n_D^{20}$ 1.4573 <sup>78</sup>

### 4-Methylcyclohexanol.

4-Methylcyclohexanol was prepared in the same way as 2-methylcyclohexanol. p-Cresol, 338 g. (0.31 moles), b.p.  $105^{\circ}/25$  mm., was reduced to 328 g. (92%) of 4-methylcyclohexanol, b.p.  $171-172^{\circ}$ . Upon redistillation through a three-foot glass helix-packed column, the fraction which boiled at  $170^{\circ}$ ,  $n_D^{20}$  1.4557, was collected as product. The weight of pure 4-methylcyclohexanol was 202 g.



Physical constants from the literature:

B.P. 170-171°  $n_D^{20}$  1.4521<sup>72</sup>

B.P. 172°  $n_D^{20}$  1.45617<sup>79</sup>

$n_D^{20}$  1.4561<sup>77</sup>

1,2,3,4-tetrahydro-2-naphthol.

Commercial  $\beta$ -naphthol was distilled in a Von Braun flask, first from Raney nickel, and then from copper chromite. It was then reduced according to Dauben, McNusick, and Mueller<sup>83</sup> over copper chromite at 4000 p.s.i. and 200°.

The weight of 1,2,3,4-tetrahydro-2-naphthol obtained from 426 g. (0.29 moles) of  $\beta$ -naphthol was 360 g. (82%), b.p. 119-121°/5 mm. The 1,2,3,4-tetrahydro-2-naphthol was then redistilled through a two-foot column packed with glass helices. The fraction, b.p. 120°/5 mm.,  $n_D^{25}$  1.5632, n.p. 22.6-22.9°, was collected as product.

Dauben, McNusick, and Mueller in their careful work report the boiling point as 121.5°/5 mm., the refractive index as  $n_D^{25}$  1.5630, and the melting point as 22.9°.

7-Methyltetralone-1.

The procedure for the preparation was essentially that of Kroll, Pfeiffer and Schafer.<sup>91</sup> Student-prepared  $\chi$ -(p-tolyl)-butyric acid was recrystallized to a very slightly tan solid, n.p. 56°, from petroleum ether, b.p. 60-80°.

Fifteen grams (0.081 moles) of the  $\chi$ -(p-tolyl)-butyric acid was added to 75 g. (0.75 moles) of concentrated sulfuric acid which was stirred with a magnetic stirrer. The compound dissolved in a few minutes, and was then heated on a steam bath and stirred for two hours. By this time, the contents of the flask was almost black. It was poured over 200 g. of ice, transferred

to a separatory funnel and extracted three times with 100-ml. portions of ether. The combined ethereal extracts were then washed successively with water, 10% sodium carbonate, and water. The ethereal solution was then dried over anhydrous magnesium sulfate, filtered, and the ether was evaporated. The residue was cooled in an ice bath, and 8.8 g. of brown crystals were obtained.

The procedure was repeated for 100 g. of the terylbutyric acid in 25-g. portions. A total weight of 69 g. of crude ketone was obtained.

The crude ketone was distilled, and 67 g. (65%) of colorless oil, b.p.  $142^{\circ}/15$  mm., was obtained.

Phenylurethane of 7-Methyl-1,2,3,4-tetrahydro-1-naphthol.

In a 100-ml. three-necked flask which had been thoroughly dried and swept with dry nitrogen, and fitted with a magnetic stirrer, a dropping funnel, and an efficient condenser to which a calcium chloride tube was attached, was placed 0.8 g. (.02 moles) of lithium aluminum hydride, and 30 ml. of sodium-dried ether. The mixture was stirred, and the ether gently refluxed until most of the lithium aluminum hydride had gone into solution. Then 8.0 g. (0.05 moles) of 7-methyltetralone-1 dissolved in 15 ml. of sodium-dried ether was added dropwise to the stirred lithium aluminum hydride solution so that the ether refluxed gently. After the addition was complete, the reaction mixture was heated under reflux for one hour, and then cooled in an ice bath. Water was then added with great caution until no further reaction could be detected, and the contents of the flask was poured into 60 ml. of cold 10% sulfuric acid. The mixture was stirred to dissolve the aluminum salts, and transferred to a separatory funnel. The ethereal layer was separated, and the aqueous layer extracted with two

25-ml. portions of ether. The ethereal extracts were combined, dried over magnesium sulfate, filtered, and the ether evaporated on the steam bath, then using aspirator vacuum, and finally for two hours with a vacuum pump. The residue, a yellow oil, weighed 7.7 g.

To 7.0 g. of the yellow oil, 6.5 g. (0.055 moles) of phenyl isocyanate was added, and the resulting solution was warmed on a steam bath for five minutes taking care to exclude moisture. Then the solution was allowed to stand for thirty minutes. Upon cooling, and scratching, a dense white precipitate was obtained which was washed with cold petroleum ether, b.p. 60-80°. Upon recrystallization from 300 cc. of petroleum ether, 8.0 g. (65%) of white solid, m.p. 107°, was obtained.

#### Analysis:

Calculated for  $C_{18}H_{19}O_2N$ : C=76.85; H=6.81; N=4.98

Found: C=77.21, 77.06; H=6.86, 6.81; N=5.68, 5.72.

#### 7-Methyl-1,2,3,4-tetrahydro-1-naphthol.

Three grams (.054 moles) of potassium hydride were dissolved in 40 ml. of diethylene glycol at 120°. Seven grams (.025 moles) of the phenylurethane of the methyltetrahydronaphthol was added, and the resulting solution heated at 150° for one hour and then steam distilled. Nine hundred milliliters of distillate was collected, saturated with sodium chloride, and cooled. Concentrated hydrochloric acid was then added cautiously to neutralize the aniline formed by the hydrolysis of the urethane, and the mixture was extracted four times with 200-ml. portions of ether. The combined ethereal extracts were then washed successively with 5% hydrochloric acid, water, 5% sodium carbonate, and water, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue was a yellow oil

which crystallized when thoroughly chilled and scratched. One recrystallization from 20 ml. of petroleum ether, b.p. 60-80°, resulted in a white solid, 3.0 g. (70.5%), m.p. 51.5°. The compound was recrystallized once again from petroleum ether and the resulting solid melted at 51.5°.

**Analysis:**

Calculated for  $C_{11}H_{14}O$ : C-81.44; H-8.70

Found: C-81.38, 81.78; H-8.60, 8.83

**Cyclohexylcarbinol.**

The procedure of Gilman, and Catlin<sup>98</sup> was used in the preparation of cyclohexylcarbinol. One hundred and eight grams (0.915 moles) of cyclohexyl chloride, b.p. 141-142°, was treated with 22.5 g. (0.92 atoms) of magnesium turnings to form the Grignard reagent, which in turn was treated with 50 g. (1.7 moles) of depolymerized paraformaldehyde. A colorless oil, 66 g. (54%), b.p. 91-95°/26 mm., was obtained. The carbinol was redistilled through a two-foot helix-packed column, and 30 g. of cyclohexylcarbinol, b.p. 93°/23 mm.,  $n_D^{20}$  1.4644, was collected as product.

Physical constants from the literature:

B.P. 88-93°/18 mm.<sup>98</sup>

B.P. 91-92°/23 mm.  $n_D^{20}$  1.4654<sup>99</sup>

B.P. 87°/13 mm.  $n_D^{20}$  1.4639<sup>100</sup>

**α-Naphthoic Acid.**

α-Naphthylmagnesium bromide was prepared from 10.2 g. (0.41 atoms) of magnesium turnings and 86.0 g. (0.41 moles) of α-bromonaphthalene according to Vogel.<sup>116</sup> The Grignard reagent was then added slowly, with stirring to 150 g. of dry ice contained in a 2-l. beaker. The carbon dioxide was allowed to evaporate and a solution of 75 g. of concentrated sulfuric acid

in 250 ml. water was added to decompose the Grignard complex. Then 100 ml. of ether was added, and the aqueous layer separated in a separatory funnel, and extracted with five 75-ml. portions of ether. The ethereal extracts were combined and extracted with five 50-ml. portions of 25% sodium hydroxide, which were combined, cooled, and acidified with concentrated sulfuric acid. The  $\alpha$ -naphthoic acid which precipitated at this point, was separated, washed with cold water, and dried overnight at 103°. Upon recrystallization from toluene, 44 g. (61.5%) of  $\alpha$ -naphthoic acid, m.p. 160°, was obtained. Vogel reports a yield of 68-70% of  $\alpha$ -naphthoic acid melting at 160°.

#### 1,2,3,4-Tetrahydro-1-naphthoic acid.

The directions of Kay and Morton<sup>108</sup> were followed in the preparation of 1,2,3,4-tetrahydro-1-naphthoic acid. Seventeen grams of  $\alpha$ -naphthoic acid was reduced with sodium in alcohol to 15.5 g. (89%) of 1,2,3,4-tetrahydro-1-naphthoic acid, m.p. 84°.

#### Ethyl 1,2,3,4-Tetrahydro-1-naphthoate.

Twenty-nine grams (0.165 moles) of 1,2,3,4-tetrahydro-1-naphthoic acid and 0.6 g. of p-toluenesulphonic acid were dissolved in 95 ml. (1.6 moles) of absolute ethanol and 33 ml. of dry benzene. The solution was heated under reflux for five hours, and then 50 cc. of solvent was distilled through a two-foot helix-packed column over a period of one hour, while adding a mixture of 33 ml. of dry benzene and 17 ml. of absolute ethanol. The solution was heated under reflux for fifteen hours, and then 150 ml. of solvent was distilled over a period of three hours while dropping in 100 ml. of dry benzene and 50 ml. of absolute ethanol. Finally the solvent was evaporated at 60° under reduced pressure. Ether, 150 ml., was added, and

the solution was washed with water, 5% sodium carbonate, and water, dried over magnesium sulfate, and filtered. The ether was evaporated and the crude ester distilled to yield 29.2 g. (86.5%) of colorless oil, b.p.  $110^{\circ}/0.3$  mm.

The Hydrogen Phthalate Ester of 1,2,3,4-tetrahydro-1-naphthylcarbinol.

In a 1-l. three-necked flask equipped with a dropping funnel, an efficient condenser to which a calcium chloride drying tube was attached, and a mercury-sealed mechanical stirrer, and which had been dried and swept with dry nitrogen, 3.5 g. (0.09 moles) of lithium aluminum hydride was dissolved in 150 ml. of sodium-dried ether. Then 29.2 g. (0.143 moles) of ethyl 1,2,3,4-tetrahydro-1-naphthoic acid in 150 ml. of sodium-dried ether was added at such a rate that a gentle reflux of the ether was maintained. The resulting solution was stirred and heated under reflux for an additional hour, and then cooled in an ice bath. Water was then added with great caution until the further addition did not cause a vigorous reaction. There was a great deal of foaming. Finally 150 ml. of 10% sulfuric acid was added to dissolve the aluminum salts. The ether layer was separated, and the aqueous layer extracted with 150 ml. of ether. The combined ethereal layers were dried over anhydrous magnesium sulfate, filtered, and the ether evaporated, finally at reduced pressure. The residue, a yellow oil, weighed 20.7 g.

The oil was dissolved in 25 ml. (0.32 moles) of dry pyridine, 18.9 g. (0.128 moles) of phthalic anhydride was added, and the viscous mixture was stirred on a steam bath for one and one-half hours. After cooling the reaction mixture, 200 g. of ice, 100 ml. of ether, and 45 ml. of cold concentrated hydrochloric acid were added in rapid succession. The ether layer was separated, and the aqueous layer extracted with 100 ml. of ether. The

ether layers were combined, washed with water, and then extracted with two 150-ml. portions of 5% sodium carbonate. The combined sodium carbonate extract was acidified with 600 ml. of hydrochloric acid, and extracted with three 300-ml. portions of ether which were combined, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue was a yellow oil which crystallized upon cooling and scratching. Recrystallization from 300 ml. of cyclohexane afforded 33.5 g. (75.5%) of a white solid, m.p.  $102^{\circ}$ .

Analysis:

Calculated for  $C_{19}H_{15}O_4$ : C-73.54; H-5.85

Found: C-73.62, 73.63; H-5.94, 5.83

1,2,3,4-Tetrahydro-1-naphthylcarbinol.

A solution of 11.5 g. (0.288 moles) of sodium hydroxide in 50 ml. of water was added to 33.4 g. (0.108 moles) of the hydrogen phthalate ester, and the mixture was heated under reflux for two hours. After cooling and saturating with salt, the mixture was extracted with three 150-ml. portions of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated, leaving a residue which weighed 16.8 g. The crude carbinol was distilled yielding 15.7 g. (89.5%) of 1,2,3,4-tetrahydro-1-naphthylcarbinol, b.p.  $102^{\circ}/0.5$  mm.

The carbinol was then redistilled through a three-foot Vigreux column. Three fractions were collected, all boiling at  $104^{\circ}/0.6$  mm., and all of the same refractive index,  $n_D^{25}$  1.5596. Newman reports the refractive index as  $n_D^{25}$  1.5408.

Analysis:

Calculated for  $C_{11}H_{11}O$ : C-81.44; H-8.70

Found: C-81.20, 81.28; H-8.59, 8.72

$\beta$ -Naphthoic Acid.

The directions in Organic Syntheses<sup>117</sup> were followed to prepare  $\beta$ -naphthoic acid. The oxidizing solution was prepared from 163 g. (4.10 moles) of sodium hydroxide in 225 ml. of water, 940 g. of ice, and 120 g. (1.69 moles) of gaseous chlorine. From 64 g. (0.376 moles) of methyl  $\beta$ -naphthyl ketone, 49 g. (75.5%) of  $\beta$ -naphthoic acid, m.p. 184-185° was obtained.

1,2,3,4-Tetrahydro-2-naphthoic Acid.

The first step required a large amount of 3% sodium amalgam. In a 2-l. three-necked flask which was fitted with a dropping funnel, and an inlet tube through which a slow stream of dry nitrogen was introduced, 120 g. of clean, pea sized sodium was placed. A few milliliters of clean mercury was added through the dropping funnel. The flask was heated gently with a flame until the reaction started, and then the rest of the 3800 g. of mercury was dropped in slowly. When about half the mercury had been added, the flask was warmed gently with a free flame, and shaken occasionally to keep the contents fluid and uniform. When all the mercury had been added, the contents of the flask was transferred rapidly to several flat-bottomed enamel pans, so that the thickness of the sodium amalgam layer was about 3/16 in. The pans were placed in vacuum desiccators to cool. When cool, the sodium amalgam was quite hard, and was chopped up into pea-sized pieces.

In a 2-l. filtering flask fitted with a condenser, 22 g. (0.128 moles) of  $\beta$ -naphthoic acid was dissolved in a solution of 8 g. (0.143 moles) of potassium hydroxide in 265 ml. of water. Two hundred grams of 3% sodium amalgam was added and the contents of the flask was heated under reflux for twenty-two hours. The remainder of the sodium amalgam was added in 250 g.



portions over a period of ten hours. By this time, according to Baeyer, the  $\beta$ -naphthoic acid should have been reduced to the tetrahydro acid. A small sample acidified with dilute sulfuric acid, made basic with dilute sodium carbonate and then chilled, decolorized several drops of cold, saturated potassium permanganate, indicating the presence of a large amount of dihydro acid. The supernatant solution was decanted from the mercury, filtered, cooled, and acidified with 200 ml. of concentrated hydrochloric acid. A white precipitate formed which was separated, washed with cold water, and dissolved in 300 ml. of 10% sodium hydroxide. The solution was heated to  $90^{\circ}$  in a 2-l. Erlenmeyer flask, and 40 g. of Raney nickel alloy was added over a forty-minute period in small portions, maintaining the temperature of the mechanically stirred reaction mixture at  $90^{\circ} \pm 2^{\circ}$ . When the addition of alloy was complete, the mixture was stirred at  $90^{\circ} \pm 2^{\circ}$  for one hour more. It was then filtered hot, and the residual nickel was washed with hot water. The filtrate and washings were combined, cooled, and added dropwise to a mixture of 300 ml. of concentrated hydrochloric acid and 200 g. of ice. The resulting white precipitate was separated, and dissolved in 300 ml. of 10% potassium hydroxide. The resulting solution was cooled to  $5^{\circ}$ , 20 g. of ice was added, and then cold saturated potassium permanganate was added to oxidize any remaining dihydro compound. A persistent pink color appeared after three drops. Solid sodium bisulfite was then added to destroy the potassium permanganate. The solution was strongly acidified with concentrated hydrochloric acid. The resulting precipitate was separated by filtration, washed with cold water, and dried at  $60^{\circ}$  in a vacuum oven. The weight of 1,2,3,4-tetrahydro-2-naphthoic acid, m.p.  $96^{\circ}$  was 17.2 g. (76.5%).

Ethyl 1,2,3,4-tetrahydro-2-naphthoate.

Fifteen grams (0.085 moles) of 1,2,3,4-tetrahydro-2-naphthoic acid was dissolved in a mixture of 90 ml. (1.5 moles) of absolute ethanol and 35 ml. of dry benzene to which 0.3 g. of p-toluenesulphonic acid had been added. The solution was heated under reflux for twelve hours and then distilled through a two-foot helix-packed column so that 50 ml. of solvent was removed in thirty minutes. An additional 33 ml. of dry benzene and 17 ml. of absolute ethanol were added, and the solution heated under reflux for two hours. Fifty milliliters of solvent was distilled in thirty minutes, and the reflux and distillation repeated. The solution was then concentrated under reduced pressure at 60°, cooled, and 50 ml. of ether added. The ethereal solution was washed with water, 10% sodium carbonate, and water, dried with anhydrous magnesium sulfate, and the ether evaporated. Upon distillation, 14.9 g. (85.5%) of a colorless oil, b.p. 105°/0.7 mm., was obtained.

1,2,3,4-Tetrahydro-2-naphthylcarbinol.

A solution of 1.8 g. (0.045 moles) of lithium aluminum hydride in 150 ml. of sodium-dried ether was prepared in a 500-ml. three-necked flask fitted with a magnetic stirrer, a dropping funnel, and a spiral condenser connected to a calcium chloride drying tube. To this solution was added 14.9 g. (0.0730 moles) of ethyl 1,2,3,4-tetrahydro-2-naphthoate in 100 ml. of ether at such a rate that the ether refluxed gently. When the addition was complete, the solution was heated under reflux for an additional thirty minutes. The reaction mixture was then cooled in an ice bath, 30 ml. of water was added cautiously, and the contents of the flask was poured quickly over 100 ml. of cold 15% sulfuric acid. The ether layer was separated, and the

aqueous layer extracted with 50 ml. of ether. The ethereal extracts were combined, washed with dilute sodium carbonate, and water, dried with anhydrous magnesium sulfate, filtered, and the ether evaporated. Upon distillation, 10.8 g. (87%) of a viscous, colorless oil, b.p.  $109^{\circ}/0.5$  mm., was obtained. It was redistilled through a three-foot Vigreux column, and three fractions were obtained, all boiling at  $110^{\circ}/0.8$  mm.

Fraction (1)  $n_D^{25}$  1.5538

Fraction (2)  $n_D^{25}$  1.5549,  $n_D^{20}$  1.5560

Fraction (3)  $n_D^{25}$  1.5549,  $n_D^{20}$  1.5560

Newman and Mangham<sup>103</sup> report  $n_D^{20}$  1.5559 for the carbinol.

#### Analysis:

Calculated for  $C_{11}H_{14}O$ : C=81.44; H=8.70

Found: C=81.28, 81.27; H=8.66, 8.70

#### Hydrogen Phthalate Ester of 1,2,3,4-Tetrahydro-2-naphthylcarbinol.

A mixture of 1.5 g. (9.25 mmoles) of 1,2,3,4-tetrahydro-2-naphthylcarbinol, 1.37 g. (9.25 mmoles) of phthalic anhydride and 2.0 ml. (25 mmoles) of dry pyridine were heated on a steam bath with occasional shaking, taking care to exclude moisture. The viscous mixture was then cooled, and 15 ml. of ether, 10 g. of ice and 3.0 ml. of concentrated hydrochloric acid were added. The ether layer was separated, washed with 5% hydrochloric acid, and water, and then extracted twice with 10-ml. portions of 10% sodium carbonate. The aqueous extracts were combined, washed once with ether, acidified with 6 N hydrochloric acid, cooled, and extracted twice with 10-ml. portions of ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue was a slightly yellow oil which crystallized on cooling and

scratching. Recrystallization from cyclohexane, and then from petroleum ether, b.p. 60-80°, afforded white crystals, m.p. 108.5°.

Analysis:

Calculated for  $C_{19}H_{18}O_4$ : C-73.54; H-5.85

Found: C-73.68, 73.34; H-6.00, 6.08

1-Methylcyclohexanol.

The Grignard reagent formed from 122 g. (0.867 moles) of methyl iodide (dried over calcium chloride and distilled from phosphorus pentoxide), b.p. 41-42°, and 21.3 g. (0.871 atoms) of magnesium turnings was treated with 85 g. (0.867 moles) of cyclohexanone (purified through the bisulfite addition compound), b.p. 155-156°. The complex was decomposed with ammonium chloride, and the ethereal solution dried over anhydrous potassium carbonate. The ether was evaporated, and distillation of the residue gave 76.5 g. (77.5%) of 1-methylcyclohexanol, b.p. 67.5-70°/20 mm. There was almost no forerun, but towards the end of the distillation, the temperature suddenly dropped and a two-phase distillate appeared which probably was composed of the dehydrated alcohol plus water. The distillate was redistilled through a three-foot Vigreux column at a 4:1 reflux ratio. There was a forerun of about 5 ml. of methylhexene and water. The remainder was collected in three fractions:

- (1) up to 69°/26 mm. - 12.5 g.
  - (2) 69-70°/26 mm. - 14.7 g., m.p. 19°
  - (3) 70°/26 mm. - 45.1 g., m.p. 24°
- residue - 4.2 g.

The third fraction was redistilled through a three-foot Vigreux column at a 4:1 reflux ratio and the distillate collected in three fractions:

transferred to a 500-ml. Erlenmeyer flask, and heated on a steam bath with stirring. From time to time, the reaction mixture was cooled quickly to room temperature. A 20.0-ml. aliquot was then removed and titrated with 0.0537 N sodium hydroxide.

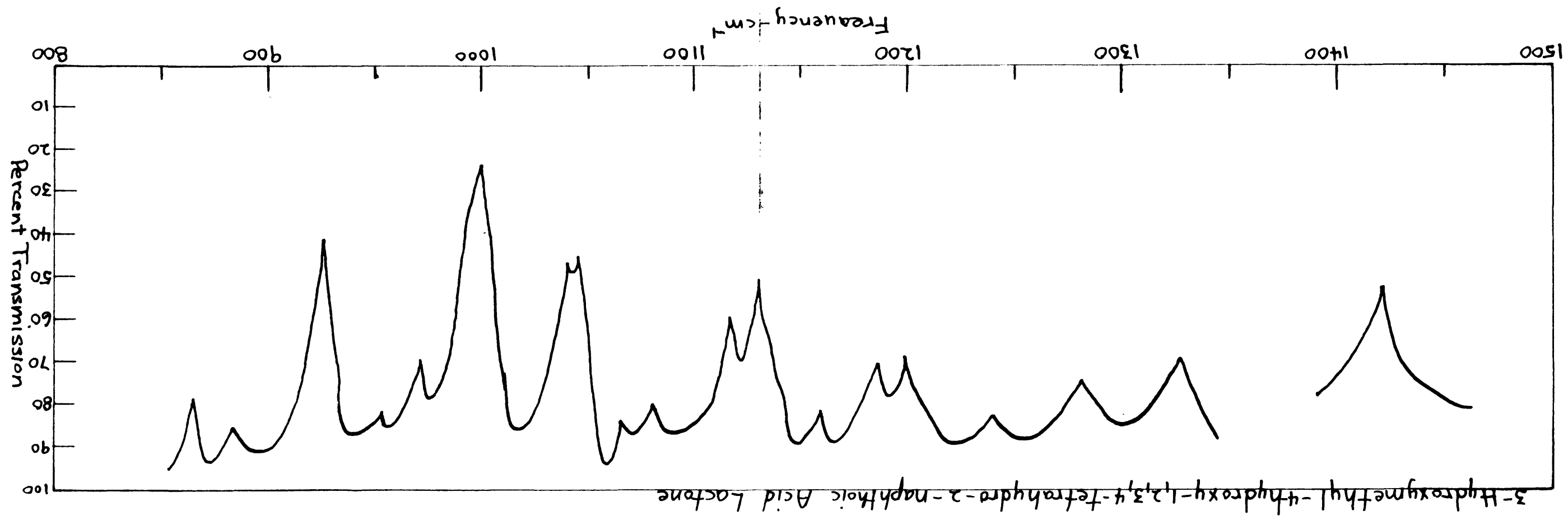
The same procedure was followed for the cis lactone, 0.3048 g. It was saponified with 50.0 ml. of 0.0537 N sodium hydroxide, and nearly neutralized with 48.20 ml. of 0.0554 N hydrochloric acid. The following data were obtained:

Time (hours)	<u>trans lactone</u>		<u>cis lactone</u>	
	ml. base	% lactonized	ml. base	% lactonized
0	2.73	0	3.15	0
1	1.87	32	1.42	55
2	1.57	43	0.92	71
3	1.44	48	0.67	79
4½	1.29	53	0.48	85
6½	1.20	56	0.27	91.4
20	1.07	61	0.10	96.8

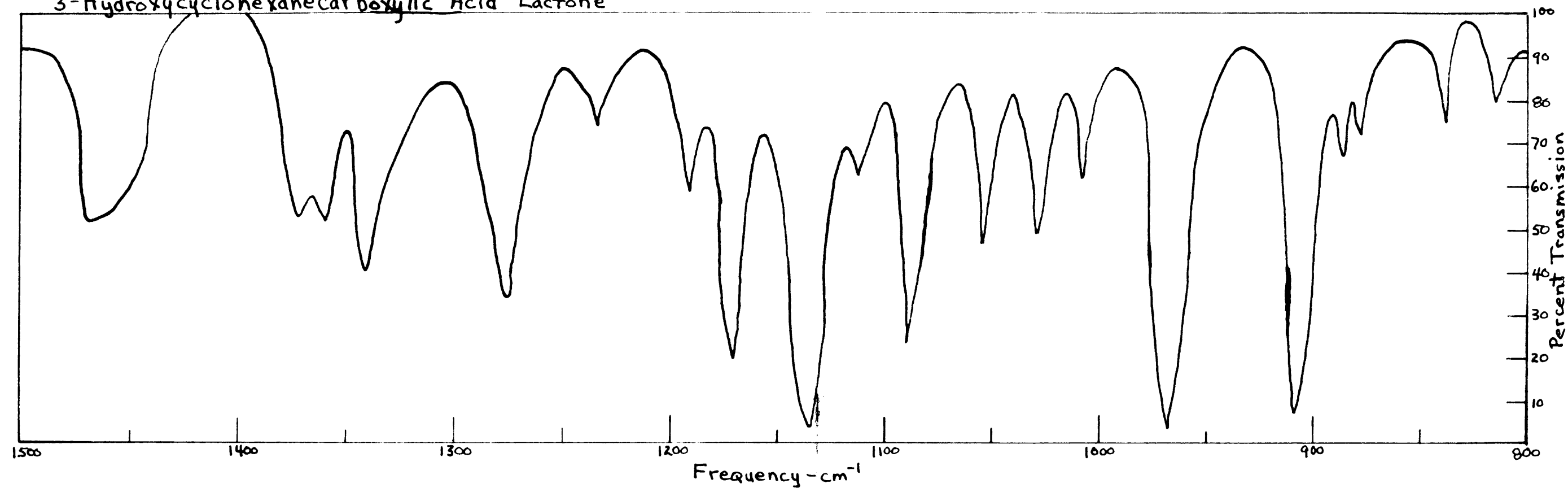
transferred to a 500-ml. Erlenmeyer flask, and heated on a steam bath with stirring. From time to time, the reaction mixture was cooled quickly to room temperature. A 20.0-ml. aliquot was then removed and titrated with 0.0537 N sodium hydroxide.

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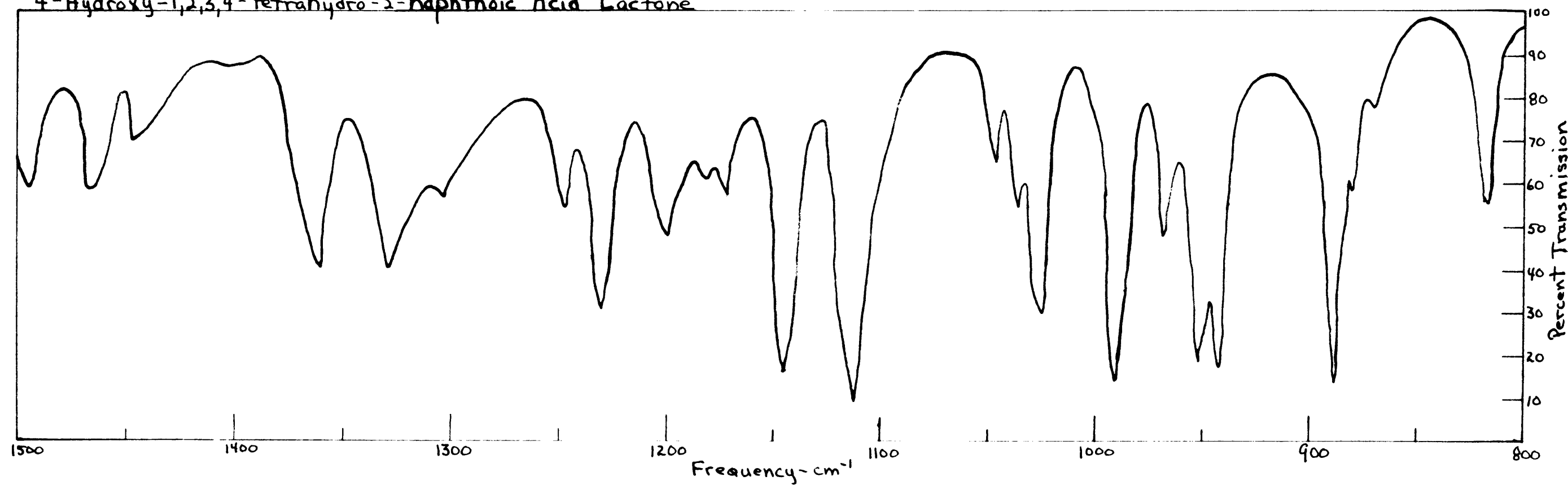
Time (hours)	<u>trans lactone</u>		<u>cis lactone</u>	
	ml. base	% lactonized	ml. base	% lactonized
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1	1.87	32	1.42	55
2	1.57	43	0.92	71
3	1.44	48	0.67	79
4½	1.29	53	0.48	85
8½	1.20	56	0.27	91.4
20	1.07	61	0.10	96.8



3-Hydroxycyclohexanecarboxylic Acid Lactone

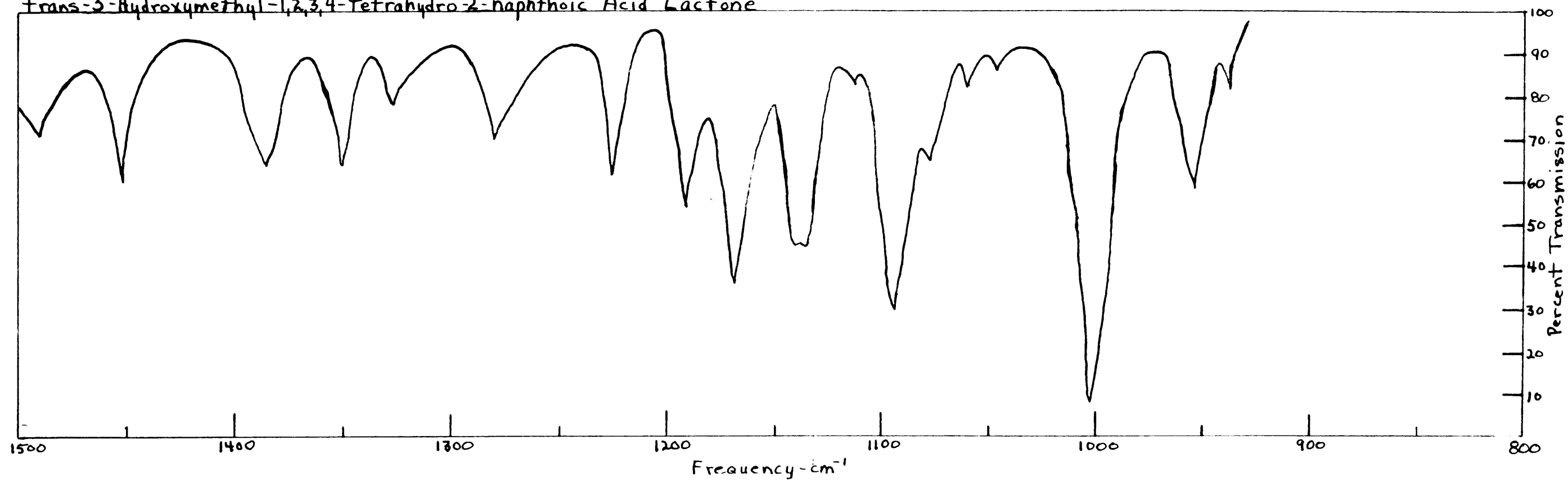


4-Hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone

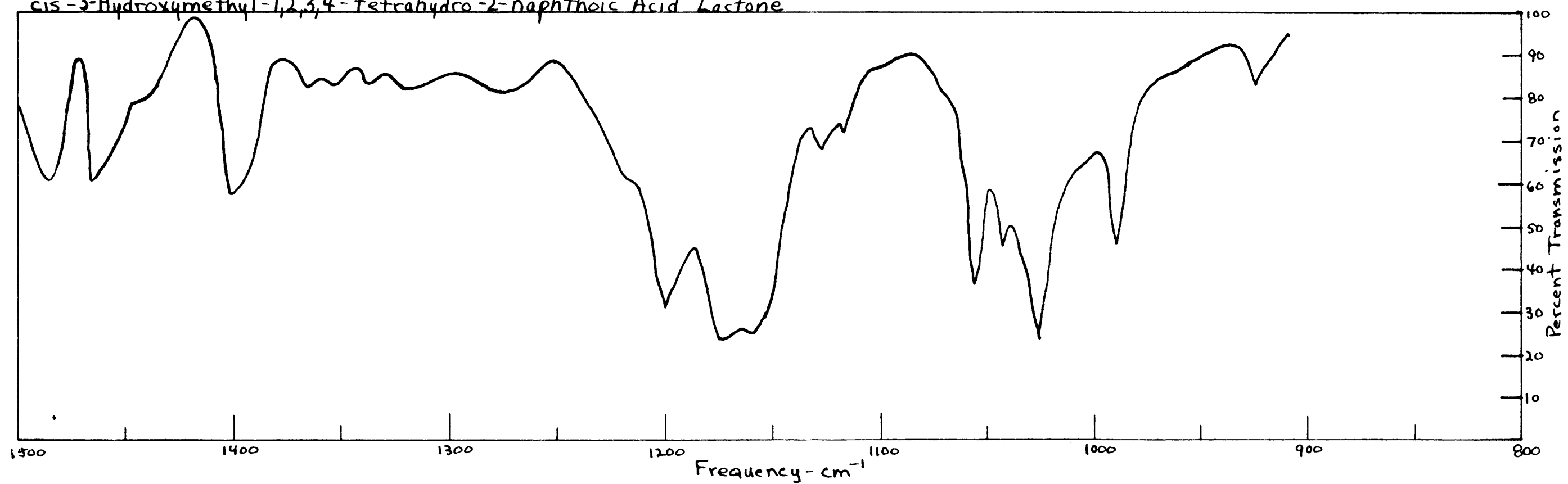




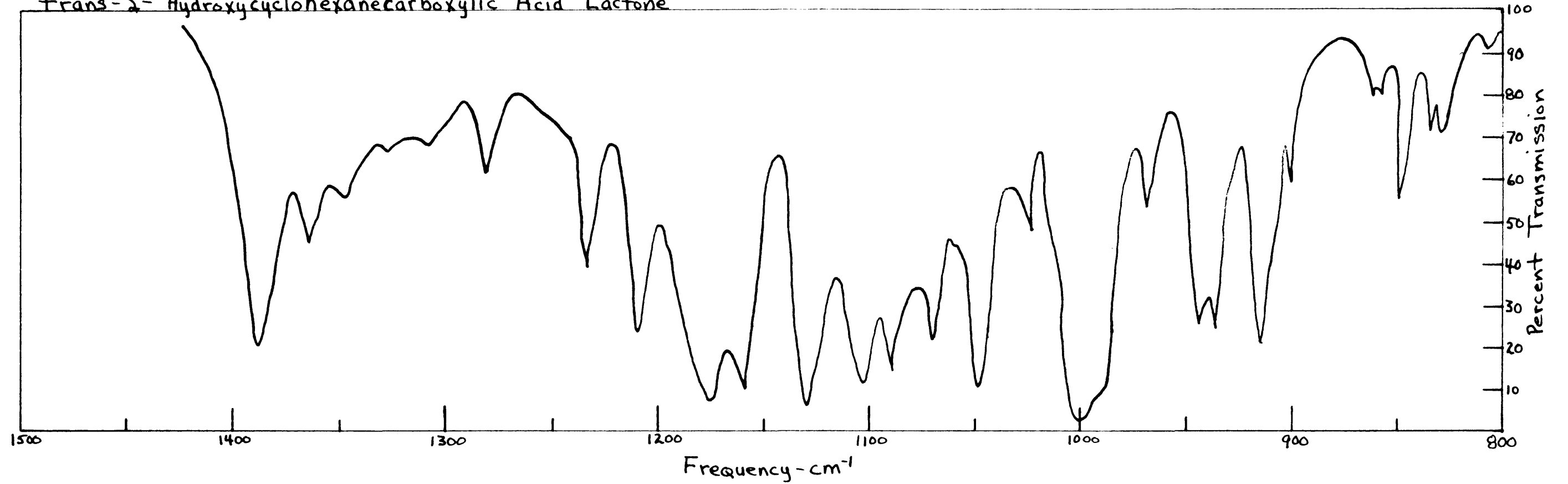
*trans*-3-Hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone



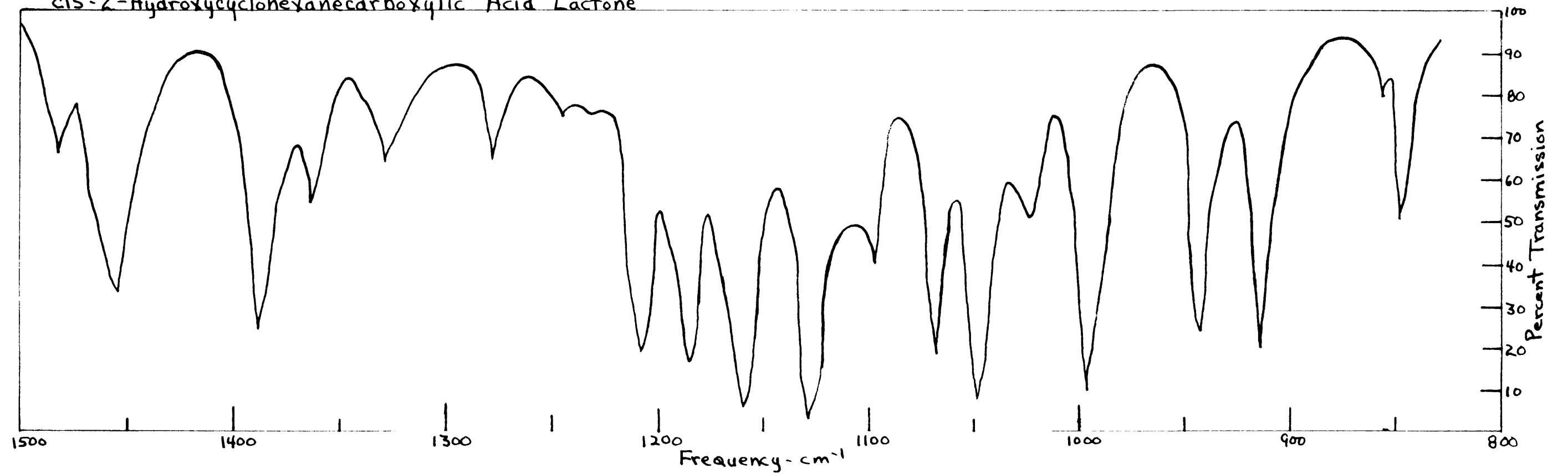
*cis*-3-Hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone

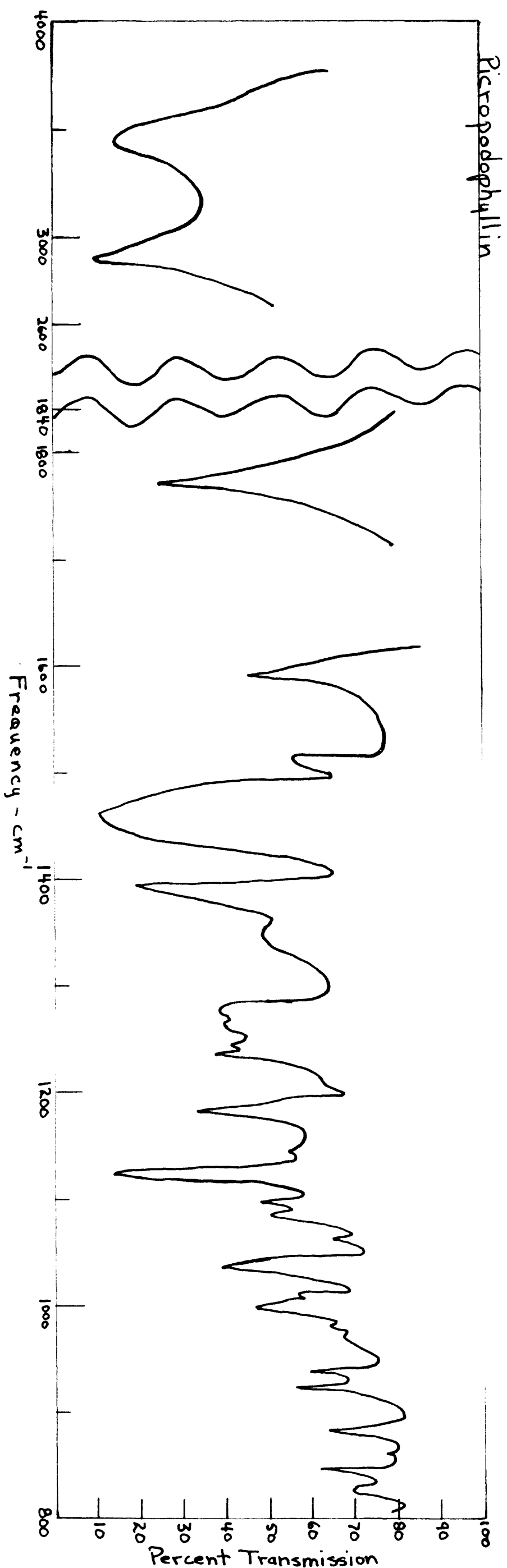
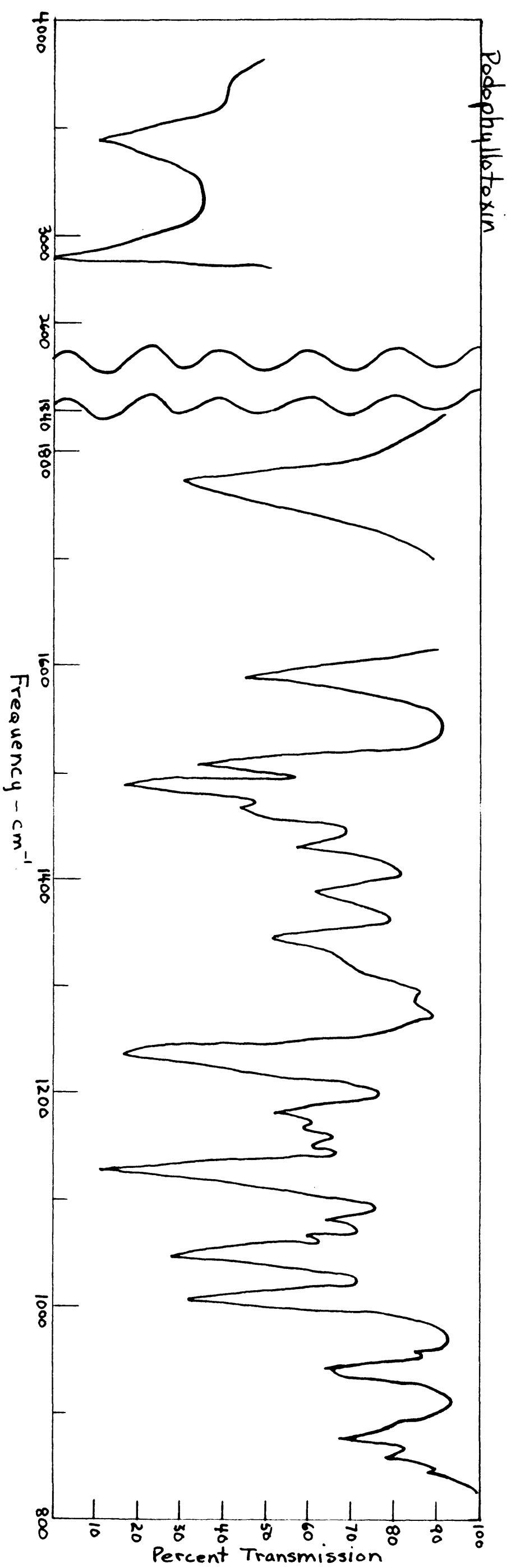


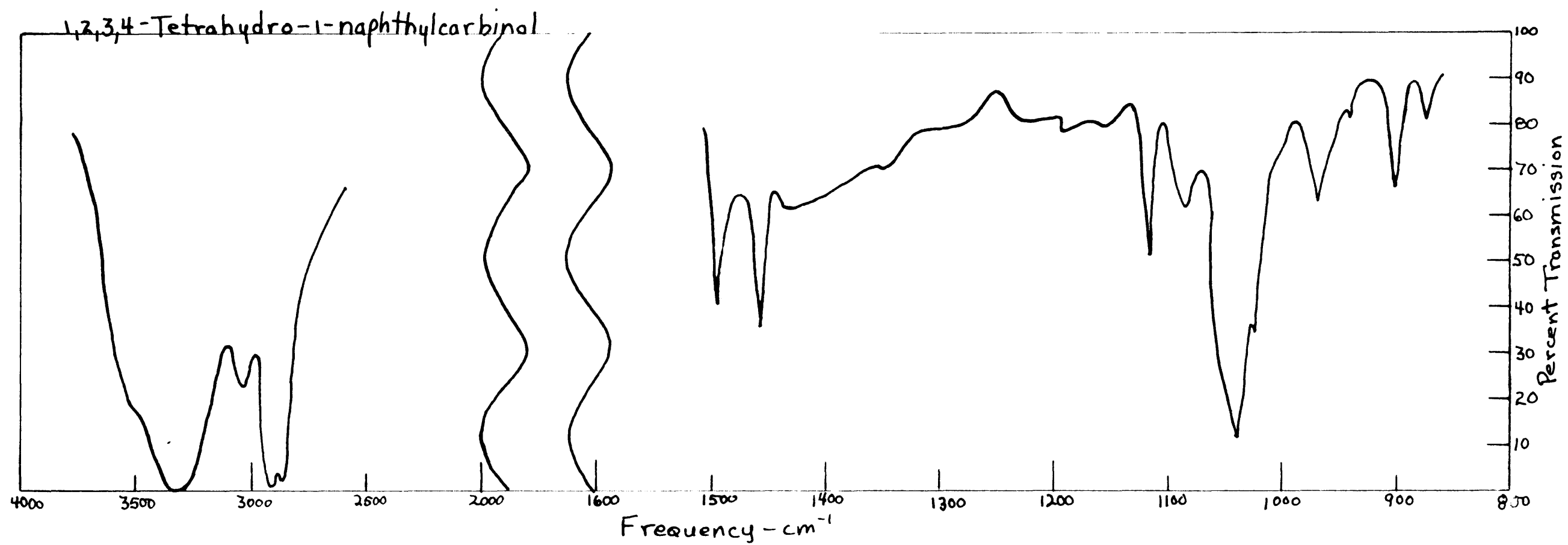
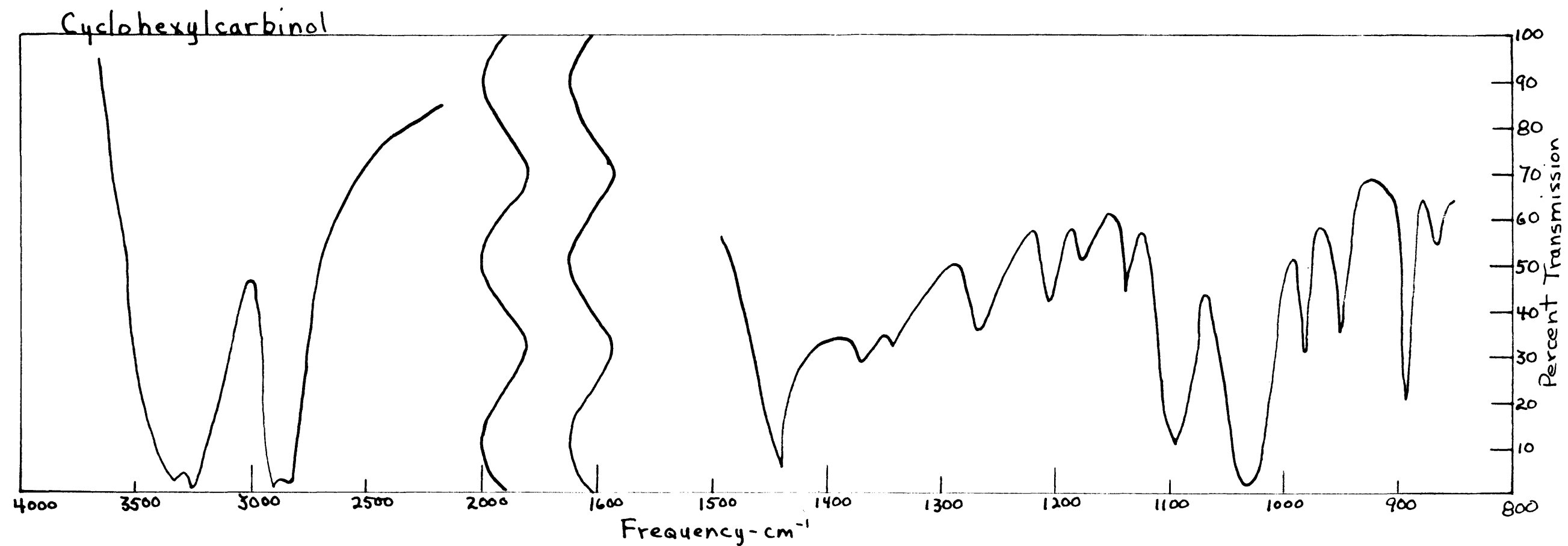
trans-2-Hydroxycyclohexanecarboxylic Acid Lactone

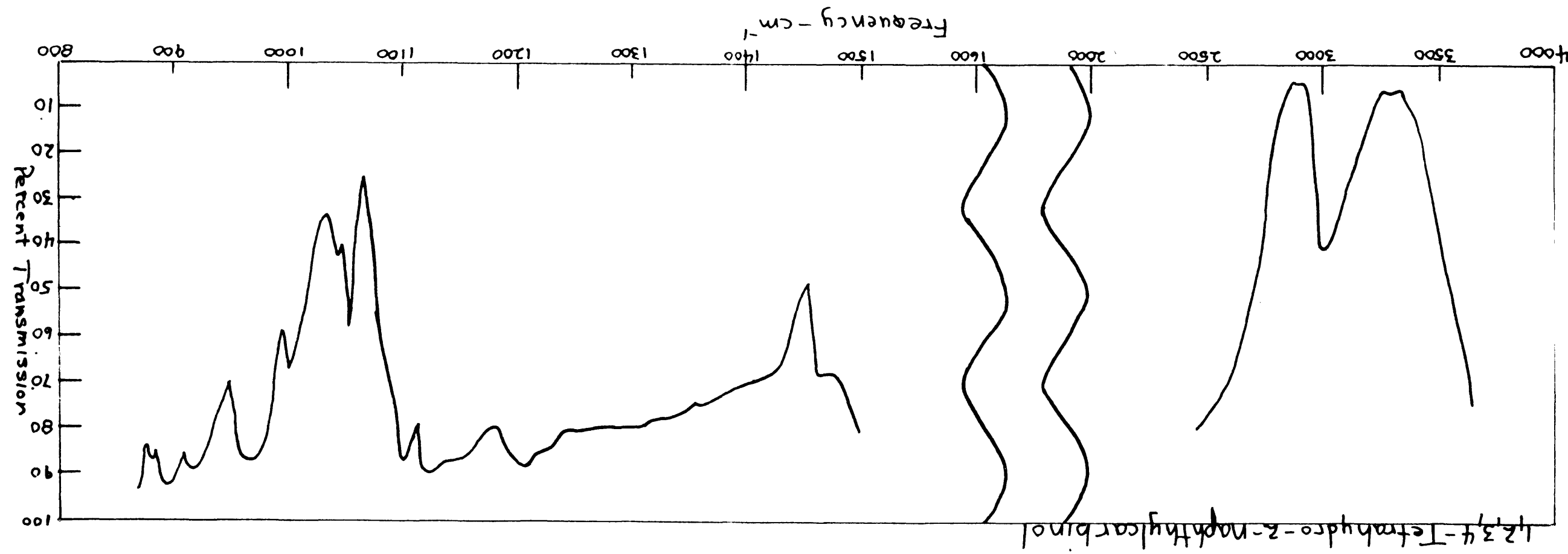
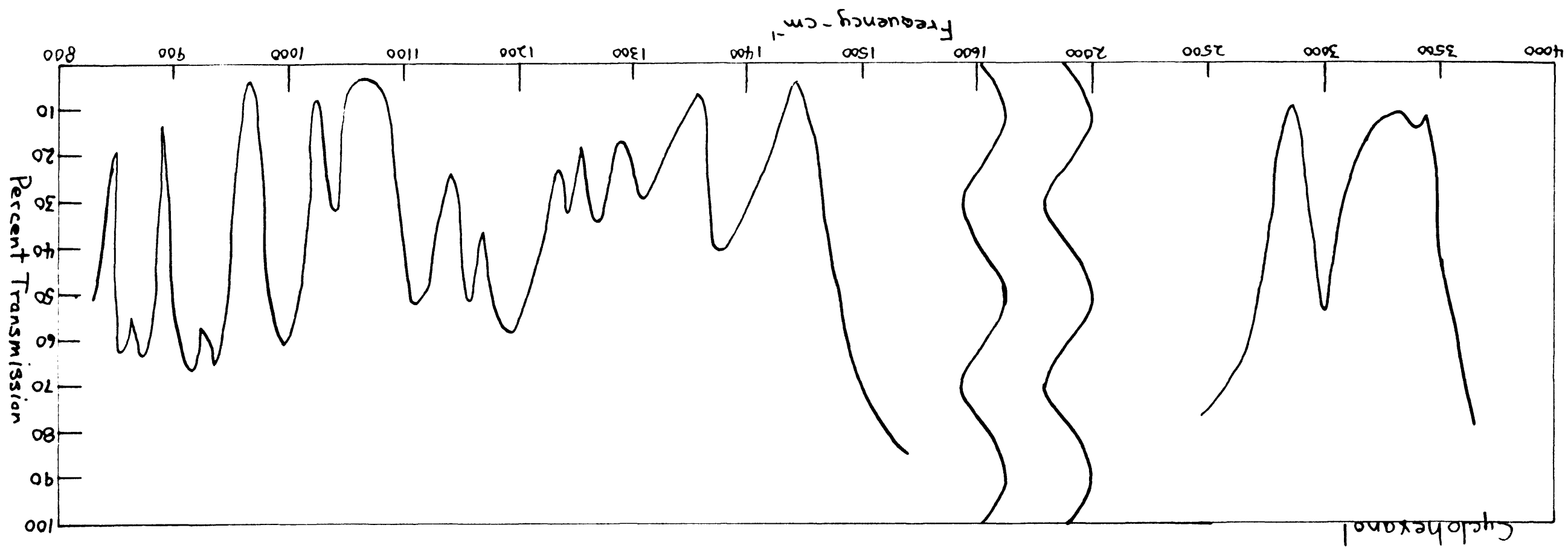


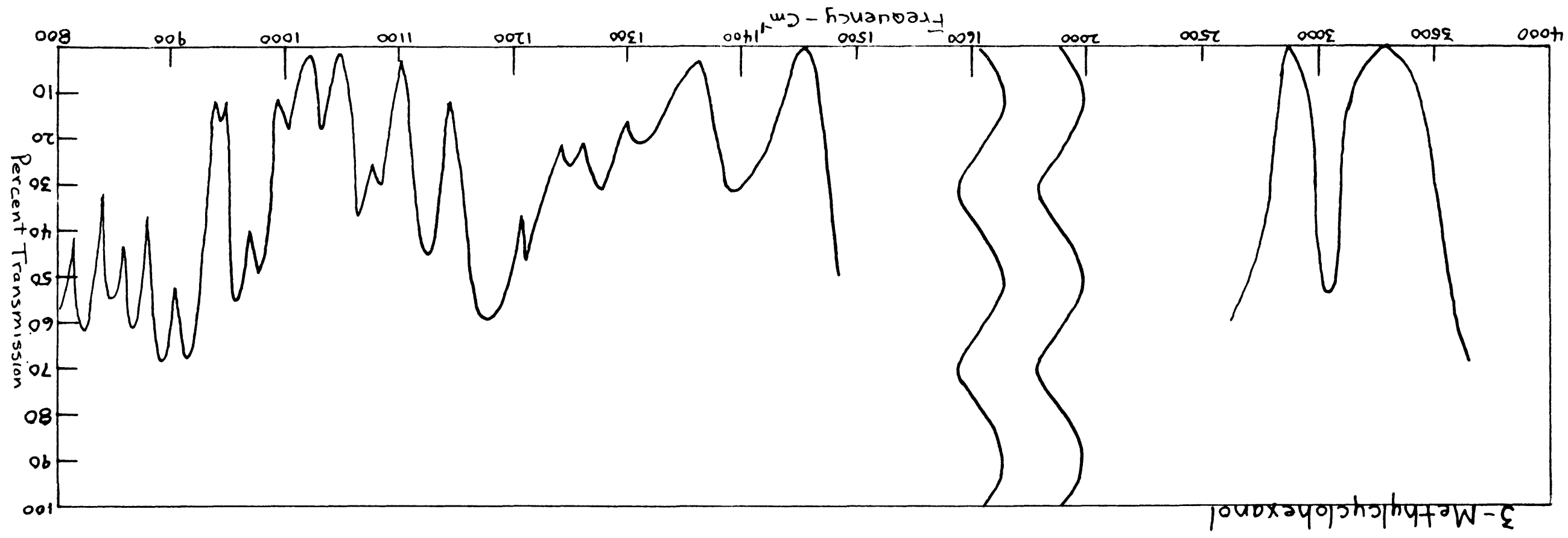
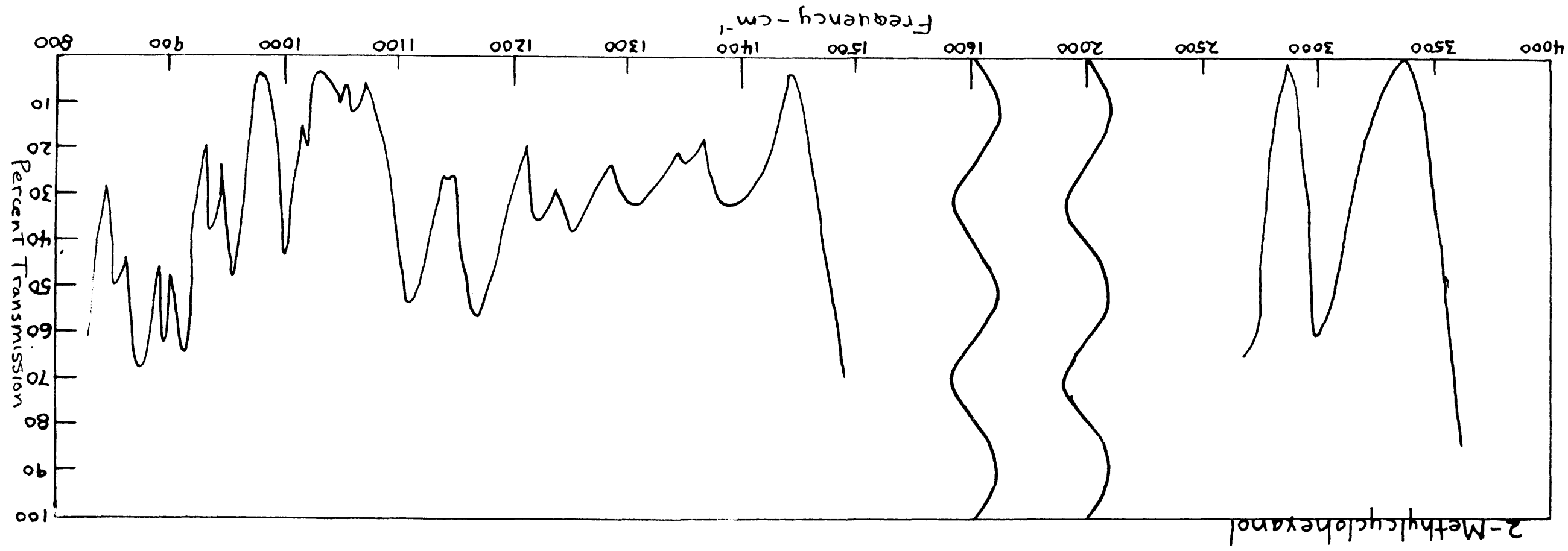
cis-2-Hydroxycyclohexanecarboxylic Acid Lactone

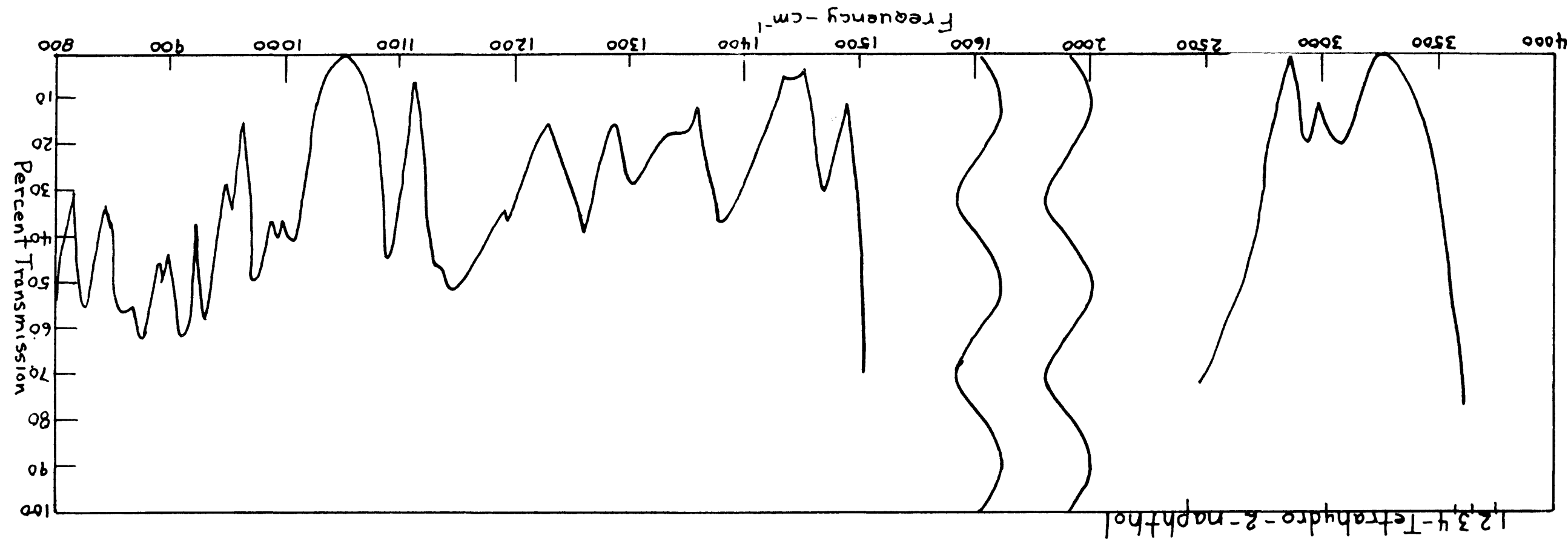
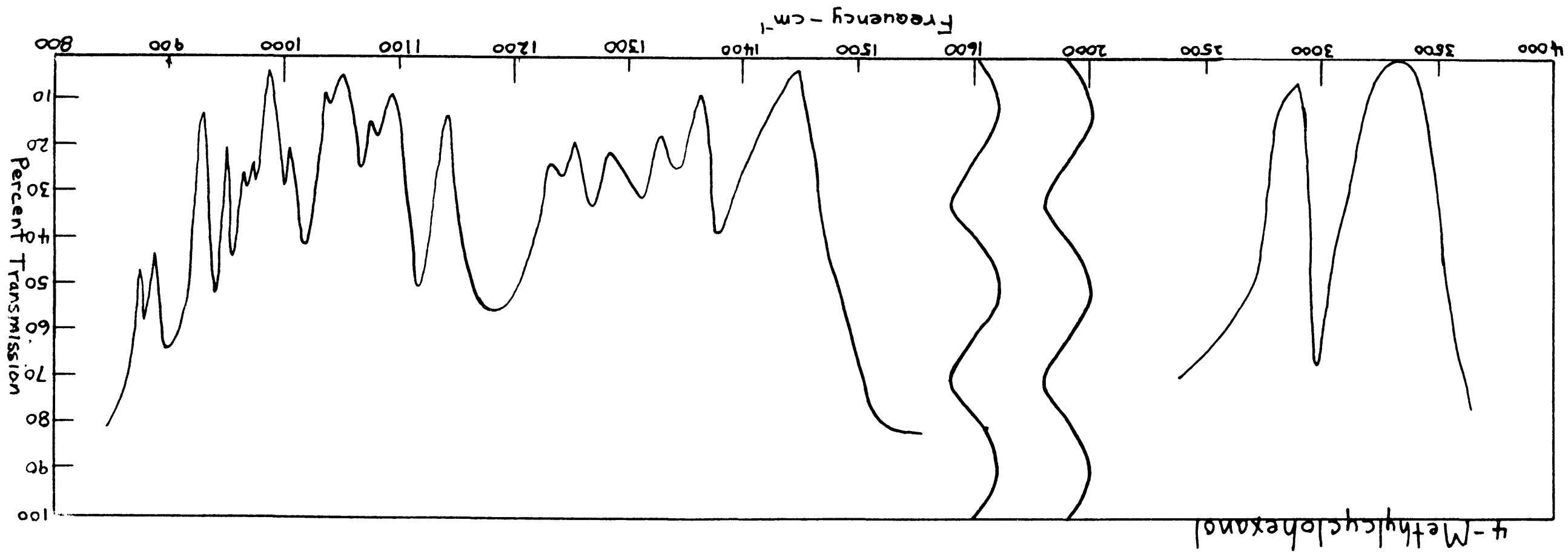


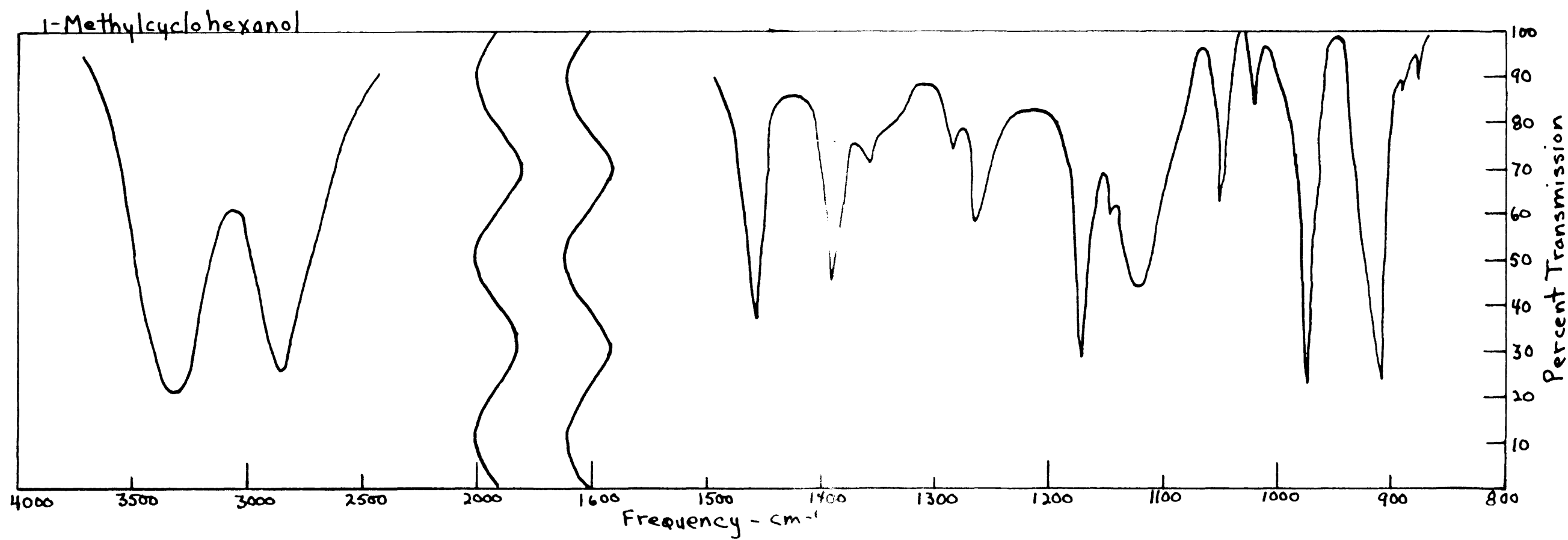
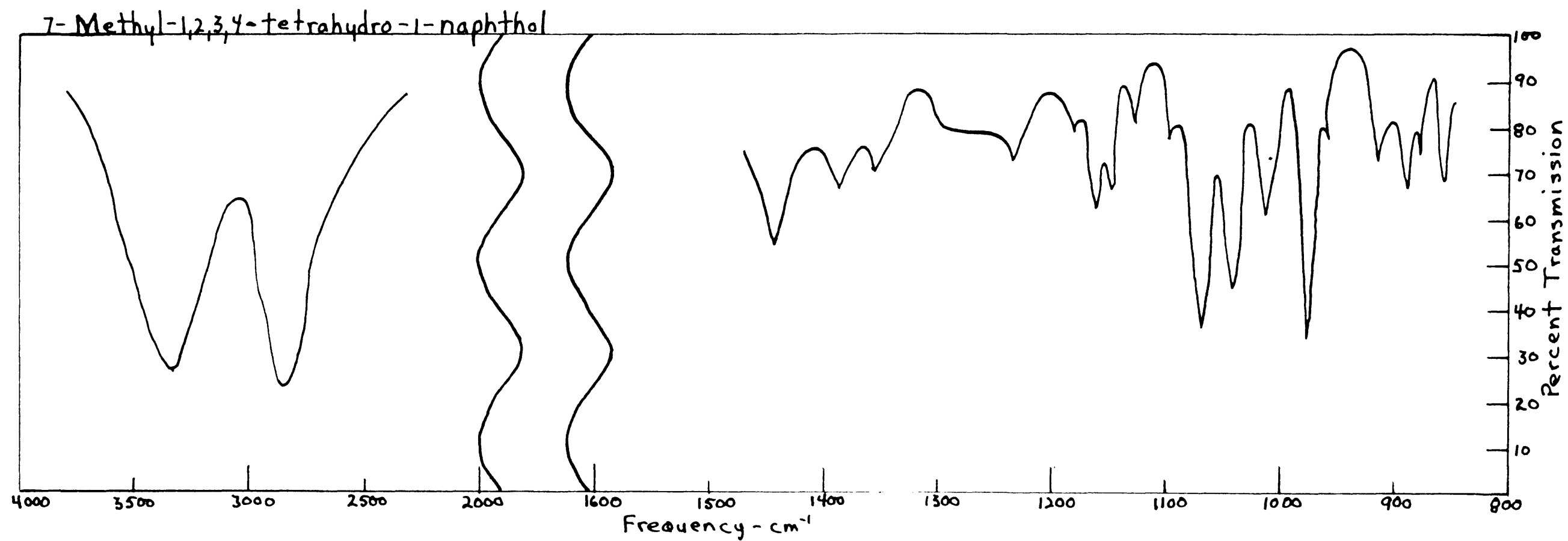




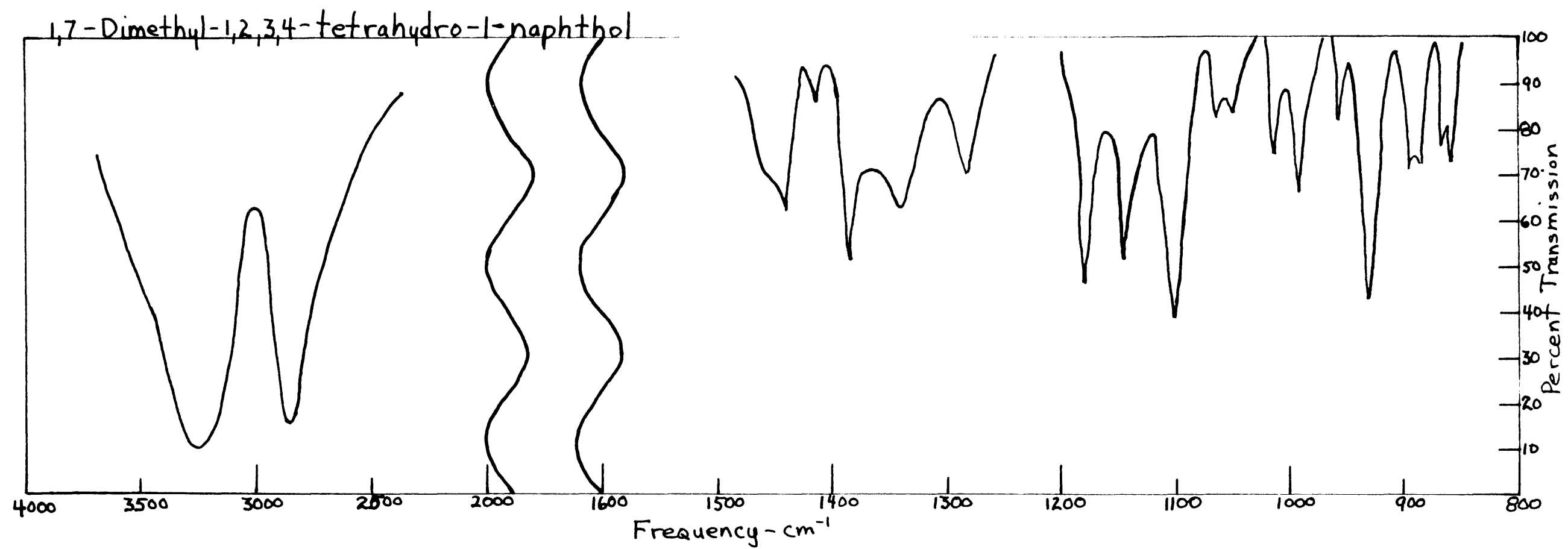












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