SOME ESTERS AND AMIDES OF HYDROXY ACIDS

By

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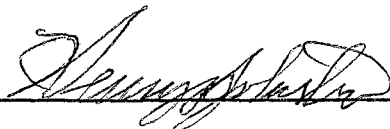for the degree of
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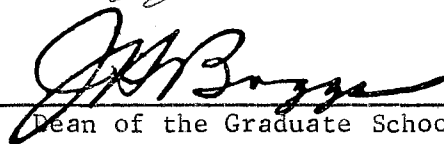SOME ESTERS AND AMIDES OF HYDROXY ACIDS

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CHAPTER I

INTRODUCTION

The general acid-catalyzed reaction of alpha-hydroxy acids with carbonyl compounds can give a class of cyclic compounds midway in structure between acetals and alkylidene esters: the 1,3-dioxolan-4-ones. While not well known, such compounds have been prepared from time to time. They are easily hydrolyzed to regenerate the parent compounds;

$$RCH \begin{matrix} COOH \\ \\ OH \end{matrix} \quad + \quad \begin{matrix} \\ \\ \end{matrix}C=O \quad \xrightarrow{H^+} \quad RCH \begin{matrix} \overset{O}{\overset{\|}{C}}-O \\ \\ O-C- \end{matrix} \quad + \quad H_2O$$
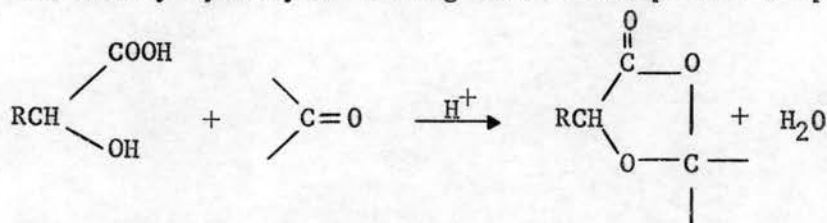
the ease of hydrolysis is in reverse relationship to the reactivity of the carbonyl group. The chloral derivatives prepared by Wallach and Heymer (90) in 1876 and the formaldehyde derivatives prepared by De Bruyn and Van Ekenstein (24) in 1899 constitute fairly stable dioxolanones. The acetone compounds of alpha-hydroxy acids, first prepared by Willstätter and Konigsberger (91), are very easily hydrolyzed in aqueous acid.

In research for this thesis considerable attention was devoted to the acetone compounds of d-tartaric, dl-malic, citric, and mandelic acids, because these promised to give crystalline derivatives, some of them new. A small amount of work was done on the reaction of other carbonyl compounds with these acids. The acetone derivatives herein were prepared generally in the same manner as previously described except that 2,2-dimethoxypropane (ketal) was employed as a scavenger to remove water from the reaction mixture.

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There is some disagreement (9,36,85) as to the exact structure of the bis-acetone compound of tartaric acid. This thesis adds to the general knowledge of the structure.

The only example of solvolysis (other than hydrolysis) of 1,3-dioxolan-4-ones recorded is conversion of the mandelic acid-acetone compound to mandelamide (I) (5,45) and N,N'-dimethylmandelamide (45). Since the acetone derivative of tartaric acid was prepared in fair yield

$$C_6H_5-CH \begin{matrix} O \\ \| \\ C-O \\ | \\ O-C-CH_3 \\ | \\ CH_3 \end{matrix} + NH_3 \longrightarrow C_6H_5-CH \begin{matrix} O \\ \| \\ C \\ O \quad N-H \\ | \quad\quad | \\ H \quad\quad H \end{matrix} + CH_3-\overset{O}{\overset{\|}{C}}-CH_3$$

<div align="center">I</div>
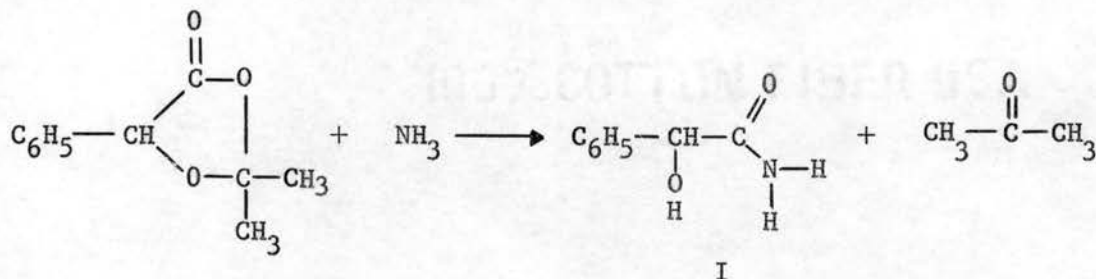
and purification was not difficult, its aminolysis and alcoholysis were studied.

Ketal worked very well as a scavenger to remove water during the formation of acetone derivatives of hydroxy acids; therefore, the scope of the thesis was extended to include methyl esters of the same acids, which also present analogous problems in preparation. The esters available from this reaction were employed to prepare a number of new amides of the acids.

The reactions of I, dl-atrolactamide, 1-hydroxycyclohexane-1-carbox-amide, glycolamide and lactamide to form 2,2-dimethyl-1,3-oxazolidin-4-ones (37,45) yield the only compounds of this type known. The equation for the reaction of mandelamide and acetone is:

$$C_6H_5-CH \begin{matrix} O \\ \| \\ C \\ O \quad N-H \\ | \quad\quad | \\ H \quad\quad H \end{matrix} + CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{H^+} C_6H_5-CH \begin{matrix} O \quad H \\ \| \quad | \\ C-N \\ \quad\quad | \\ O-C-CH_3 \\ | \\ CH_3 \end{matrix} + H_2O$$
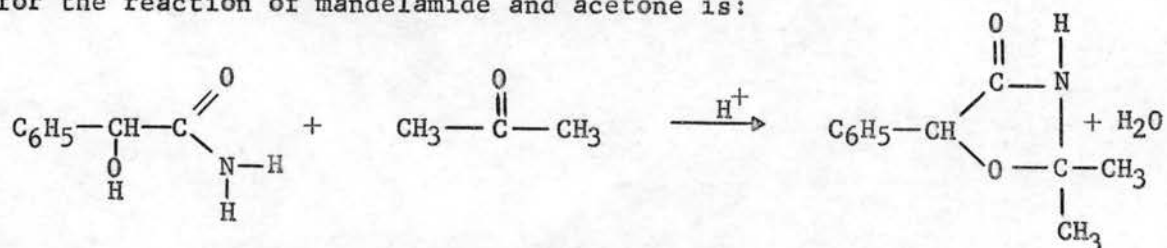
Reactions were attempted to prepare similar new oxazolidinones.

CHAPTER II

HISTORICAL

1,3-Dioxolan-4-ones.

Perhaps fifty compounds of this structure are known, but only those made from the hydroxy acids and carbonyl compounds used in the experimental part are considered here. Since no yield data was reported for a majority of the compounds and the only yield greater than 30 percent is for the acetone derivative of mandelic acid (70 percent), the yields are not tabulated. Table I presents a record of such preparations.

TABLE I

PREPARATION OF 1,3-DIOXOLAN-4-ONES

Hydroxy acid	Carbonyl compound	Reference
Mandelic	Acetone	5,36,78,91
d-Tartaric	Acetone[a]	36,56,85,86
	Formaldehyde	9,24,75,80
	Acetaldehyde	24
	Chloral	15,90
	Benzaldehyde[b]	1,24,33,70
Malic	Formaldehyde	24
	Chloral	90,94
Citric	Formaldehyde	24,47
	Acetaldehyde	24
	Chloral	15,31,70
	Benzaldehyde	1

a. Hertzler (56) prepared the acetone compound of d-tartaric acid in essentially the same way as it was prepared in this research, yield 58.5%, m.p. 95-100°.

b. Erlenmeyer (33) obtained the benzylidenetartaric acid derivative,
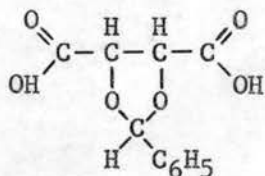
Preparation of Methyl Esters.

Anschutz and Pictet (7) prepared dimethyl d-tartrate using tartaric acid dissolved in excess methanol and saturated with hydrogen chloride gas. The reaction was allowed to proceed for 24 hrs. at room temperature and the solvent was removed. The residue was heated to 100° under reduced pressure for several minutes to remove the water formed in the reaction. The same procedure of adding methanol and hydrogen chloride gas to the residue was repeated twice more. The ester was finally removed from the residue by vacuum distillation (yield 70%).

Several modifications of this process have been developed (38,46,58, 67,77,89,93). Catalysts such as p-toluenesulfonic acid (93) have been used in attempts to increase the yield and convenience. One of the better processes is by Frankland and Aston (38) in which a special apparatus was used with anhydrous sodium sulfate to remove water from the reaction mixture. Very good yields (80-90%) were obtained; however, the apparatus was considered to be limited in its use.

The dimethyl esters of d- and l-malic acids have been prepared in the same manner as the esters of tartaric acid. Here the main consideration is to avoid the use of sulfuric acid as a catalyst. This causes water to be eliminated from dimethyl malate and forms dimethyl fumarate (6,26,35). A large excess of methanol is used and the solution is saturated in the cold with hydrogen chloride gas (6,8,20,26,35,52,88). In most instances the acid catalyst is neutralized with sodium carbonate (6,26,88) or potassium (20,35) carbonate before distillation. The best yield (70.5%) was reported by Clough (20). Kroeger (58) obtained a 22 percent yield using dihydroxyfluoboric acid as a catalyst.

Trimethyl citrate has been prepared on a microscale using diazo-
methane (73) in 54 percent yield. Campbell and Taylor (16) used a
method developed by Clinton and Laskowski (18) to esterify citric acid.
The reaction mixture consisted of methanol, 300 cc. of methylene or
ethylene dichloride, and approximately 3.0 cc. of concentrated sulfuric
acid. The reaction mixture was refluxed until separation of an upper
layer was noticed; this contains the water formed in the reaction. When
the water layer was separated from the reaction mixture and the remaining
methylene or ethylene dichloride solvent was removed by distillation, the
ester remained. After purification, trimethyl citrate was obtained in 56
percent yield.

The trimethyl ester of citric acid has also been obtained by using
citric acid in excess methanol with a continuous flow of hydrogen chloride
gas through the solution (26,34,30). Donaldson et al. (30) obtained a
73 percent yield after one recrystallization from water. The product had
a melting point of 75.0 to 76.5°. In spite of this melting point, there
is some doubt of the purity of this material, since when it was vacuum
distilled the yield dropped to 48 percent. The melting point was then
75.5 to 76.5°.

In a general approach to the preparation of methyl esters, which
however has not been applied to simple hydroxy acids, Lorette and Brown
(59) made use of ketal. The reactions involved in the esterification are:

$$RCOOH + CH_3OH \xrightarrow{H^+} RCOOCH_3 + H_2O$$
$$H_2O + (CH_3)_2C(OCH_3)_2 \xrightarrow{H^+} 2CH_3OH + CH_3COCH_3$$
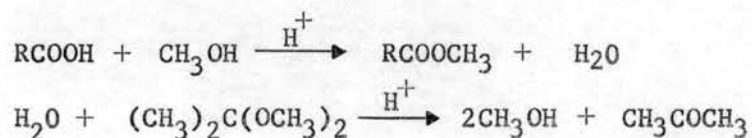
Here the water formed in the esterification reacts to form more methanol.
As a result the process is self-accelerating. In this manner nearly

quantitative yields were obtained. A mixture of dehydrated castor oil acids was esterified with a 99 percent yield. Other esters so formed were dimethyl adipate (94%) and dimethyl oxalate (91%).

Amides.

Since considerable attention in this research, as recorded in the Experimental part, was devoted to the aminolysis of both esters and acetone compounds, a survey of the literature on amides of tartaric, malic and citric acids was made. The results are shown in Table II.

TABLE II

REFERENCES TO AMIDES OF d-TARTARIC, d- OR l-MALIC, AND CITRIC ACIDS

R	N,N'-Di-R-Tartramide	N,N'-Di-R-Malamide	N,N',N"-Tri-Citramide
H	10,19,22,26,40,41,50, 51	2,21,26,42,43,[b]54, 61,[b]63,66,72,88	11,23
Methyl	22,41	39,41	27,55
Ethyl	22,41	39,41	
Propyl	41	39,41	
Isopropyl	41	39,41	
Allyl	41	41	
n-Butyl	41	39,41	
Isobutyl	41	39,41	
Amyl	28		
n-Heptyl	41		
Hydroxymethyl			32
3-Hydroxypropyl			65
2-Chloroethyl	87		
Pentamethylene	40[a]	39[a]	

a. Structure having one pentamethylene radical on each nitrogen.

b. From dl-malic acid.

TABLE II (continued)

R	N,N'-Di-R-Tartramide	N,N'-Di-R-Malamide	N,N',N''-Tri-Citramide
Phenyl	3,14,40,53,71,82	4,13,44,53,88	23,29,68
Benzyl	25,32,40	25,54,62	25
Tolyl	13,40	13,49,53,88	22,48
2,4,5-Trimethylphenyl			68
4-Methoxyphenyl	17,92		
4-Ethoxyphenyl	92		
3-Nitrophenyl	83		76,83,84
Furfuryl	40		
1-Naphthyl	14,40	13	55
2-Naphthyl	14,40	13	65

CHAPTER III

EXPERIMENTAL[1,2,3,4]

Acetone Compound of d-Tartaric Acid (II).

A one-neck, 1000 ml., round-bottom flask was charged with 40.0 g.
(0.266 mole) of finely divided d-tartaric acid (m.p. 168-170°), 200 cc.
(1.6 moles) of ketal (b.p. 77°/742 mm), 400 cc. (5.52 moles) of acetone
(commercial grade), and a magnetic stirring bar. The flask was stoppered
and placed in an ice bath. After the temperature of the flask contents
had come close to 0°, the flask was charged with 40 drops of a 50 percent
BF_3 etherate solution. The mixture was allowed to react for 4 hrs. at 0°.
The solvent was removed by means of a rotary evaporator and an orange-
red syrup-like residue remained. Approximately 200 ml. of ether was used
to dissolve the residue and this solution was washed twice with 100-ml.
portions of cold water. The ether layer was evaporated on the rotary
evaporator. This left an orange-red crystalline residue which was
recrystallized from isopropyl ether. The product was dried over calcium

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[1] All melting points are corrected; all boiling points are uncorrected.

[2] The infrared spectra were determined on a Beckman IR-5A spectro-
photometer with potassium bromide pellets unless otherwise indicated.

[3] The proton magnetic resonance spectra were determined by Mr. A. G.
Horodysky, Oklahoma State University, using a Varian Model A-60 high-
resolution spectrometer fitted with a field-sensing stabilizer
("Super Stabilizer"). Tetramethylsilane was used as an internal
standard.

[4] The nitrogen analyses were performed by the author using a micro-
Kjeldahl procedure (64).

chloride in a vacuum desiccator. This produced 37.1 g (60.7%),
m.p. 99-100°. A recrystallization from absolute ethanol gave m.p.
101° (lit. 102°) (36).

The infrared spectrum (Plate I) shows the carbonyl absorption
maximum at 5.60 μ.

Use of other catalysts in the reaction decreased the yield.
Sulfuric acid gave a 56% yield while Dowex 50 W x 8 (strong cation
exchange resin) and p-toluenesulfuric acid catalysts gave less than 30%
yields.

Acetone Compound of dl-Mandelic Acid (III).

In essentially the same way as for tartaric acid, 10.0 g. (0.066
mole) of dl-mandelic acid, 100 cc. (1.36 moles) of acetone, 50 cc. (0.40
mole) of ketal, and 10 drops of concentrated sulfuric acid were combined
at -7° and allowed to react for 15 minutes. The reaction mixture was
poured into a solution of sodium bicarbonate (10%) at -7°. This was
stirred with a magnetic stirrer for 10 minutes in the ice bath. A white
curdy-looking material developed. The material was suction-filtered and
washed with cold water. After recrystallizing from petroleum ether and
drying over calcium chloride in a vacuum desiccator, the solid weighed
9.34 g. (73%) and had m.p. 45-46° (lit. 47.5°) (36,91).

The infrared spectrum (Plate II) shows the carbonyl absorption
maximum at 5.56 μ.

Attempted Preparation of the Acetone Compound of dl-Malic Acid.

A mixture of 20.0 g. (0.149 mole) of finely divided dl-malic acid,
108 cc. (1.49 mole) of acetone, 28 cc. (0.23 mole) of ketal, and 40 drops
of BF$_3$ etherate solution was made as previously described and allowed to

react in an ice bath for 8 hrs. The solvent was removed on the rotary evaporator and the light-yellow residue was dissolved in ether and washed with water. After the ether was removed on the rotary evaporator, a light yellow syrup remained. The flask was connected to a vacuum pump equipped with a dry-ice acetone bath and the remaining solvent was removed. This produced crystallization. The material reacted with sodium bicarbonate and must have contained free carboxyl groups. However, no suitable solvent could be found from which to recrystallize it and obtain it pure.

Attempted Preparation of the Acetone Compound of Citric Acid.

A mixture of 20.0 g. (0.095 mole) of citric acid monohydrate, 151 cc. (2.1 moles) of acetone, 40 cc. (0.319 mole) of ketal, and 40 drops of BF_3 etherate solution was allowed to react at room temperature for 10 hrs. Removal of the solvent on a rotary evaporator produced a light-orange syrup-like residue. This was dissolved in ether and washed twice with water. The ether layer was evaporated on the rotary evaporator and no residue remained.

Attempted Preparation of the Cyclohexanone Compound of d-Tartaric Acid (IV).

A mixture of 20.0 g. (0.133 mole) of finely divided d-tartaric acid, 200 cc. (1.94 moles) of cyclohexanone, three drops of conc. sulfuric acid, was stirred and heated under reflux for 30 minutes. During this time the d-tartaric acid dissolved. The condenser was then set for distillation and water was azeotropically distilled from the reaction mixture for a period of 10 hrs. The theoretical amount of water to be collected was 5.3 ml., but 10 ml. of an aqueous layer was obtained. As the temperature of the distillation gradually approached 200°, the mixture being distilled became orange-red and was becoming hard to distill. The apparatus was

allowed to cool and 1.0 g. of sodium acetate was added to the reaction

mixture to neutralize the acid catalyst. A short-path vacuum distillation

apparatus was attached. The remainder of the cyclohexanone was removed

over a temperature range of 95-145° at 0.15 mm. The distillate was a

light-yellow oil. Approximately 150 ml. of ether was used to dissolve the

reaction residue, and this was washed twice with 100 ml. portions of

water. When the dark-brown ether layer was freed of ether on the rotary

evaporator, a dark syrup-like residue remained. Several attempts to

obtain a crystalline product from this residue failed. As the residue

was being dissolved with acetone in order to discard it, small needle-

like crystals appeared. The solution was filtered to remove these

crystals and they were recrystallized from acetone and dried as usual:

approximately 1.0 g., m.p. 230°. This melting point matches that of

dodecahydrotriphenylene (69,81), a condensation product of cyclohexanone,

but the nuclear magnetic resonance spectrum of the solid was not that

expected for dodecahydrotriphenylene. The spectrum showed more than

two kinds of hydrogen. The material was not further studied.

Attempted Preparation of IV by Displacement.

II   IV
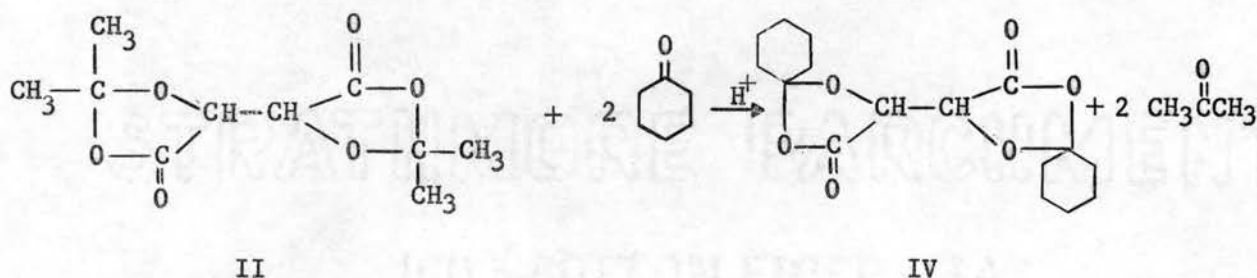
A one-neck, 250-ml., round-bottom flask was charged with 7.68 g.

(0.0333 mole) of II and 6.55 g. (0.0666 mole) of cyclohexanone. This

was heated, to dissolve II, on a steam bath and then the flask was placed in an ice bath. Recrystallization occurred, so the reaction was carried out at room temperature after 3 drops of BF_3 etherate solution was added. An aspirator was attached to the flask intermittently during a week to remove acetone from the reaction mixture. Only a slight discoloration in the reaction flask could be observed. Cyclohexanone was removed from the reaction by heating in vacuo on a steam bath. A yellow-brown crystalline residue remained. A small portion recrystallized from isopropyl ether and dried as usual had m.p. 100°. This is the same melting point as starting material II; no reaction had occurred.

Attempted Preparation of the Propionaldehyde Compound of d-Tartaric Acid.

A mixture of 20.0 g. (0.133 mole) of finely divided d-tartaric acid, 194 cc. (2.67 moles) of propionaldehyde and 10 drops of BF_3 etherate solution was stirred 8.5 hrs. at room temperature. When excess propionaldehyde was removed on the rotary evaporator, a dark syrup-like residue remained. This was dissolved in ether (100 ml.) and washed twice with 50 ml. portions of water. The ether was removed on the rotary evaporator and a dark syrup remained. No crystalline product was obtained.

Preparation of Dimethyl d-Tartrate (V) by Alcoholysis.

II   V
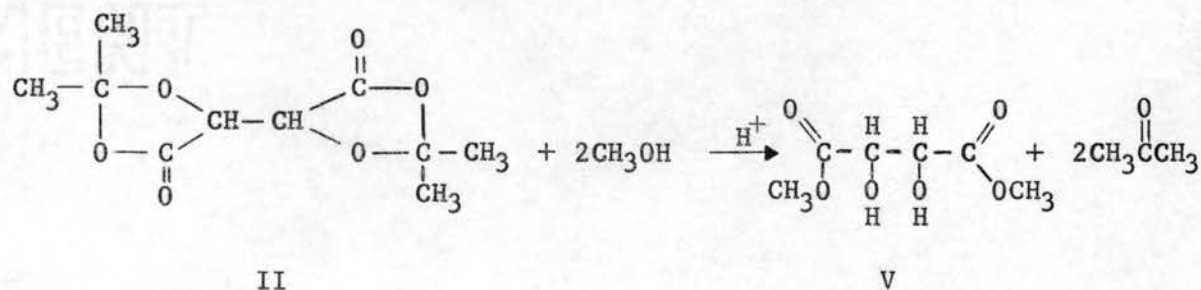
A one-neck, 250 ml., round-bottom flask was charged with 10.0 g. (0.0435 mole) of II, 200 cc. (5.0 mole) of methanol and 2 drops of conc. sulfuric

acid and equipped with a Vigreux distillation head and condenser. As the
esterification proceeded, the acetone-methanol azeotrope was slowly distilled
from the mixture. When no DNP (2,4-dinitrophenylhydrazone) was obtained
upon testing the distillate, the reaction was considered complete. A
solution of 0.3 g. of sodium methoxide in 10.0 ml. of methanol was added
to the reaction mixture to neutralize the acid catalyst. After the
remainder of the solvent was removed, the residue was transferred to
a 25-ml. flask and fractionally distilled. A colorless distillate of
dimethyl d-tartrate, 5.0 g. (65%), b.p. $132^{\circ}/1.95$ mm., lit. $158.5^{\circ}/12$ mm.
(6) and $163^{\circ}/23$ mm. (7) was obtained.

As verification of its identity, approximately 1.0 g. of dimethyl
d-tartrate was dissolved in 10 cc. of methanol. Ammonia gas was passed
through the solution and a white crystalline solid appeared. This was
filtered from the solvent and recrystallized from methanol and ester,
m.p. 197° with decomp., lit. 195° (40) and 209° (22) with decomp. for
tartramide.

Preparation of Diethyl d-Tartrate by Alcoholysis.

A mixture of 10.0 g. (0.0435 mole) of II, 100 cc. (1.74 moles) of
absolute ethanol and 2 drops of conc. sulfuric acid was treated like the
one containing methanol just described in the preparation of dimethyl
d-tartrate. Fractionation of the ester gave 6.6 g. (74%) of diethyl d-
tartrate, b.p. $113^{\circ}/0.90$ mm., lit. $280^{\circ}/760$ mm. and $162^{\circ}/19$ mm. (7).

Tartramide was prepared as before except that absolute ethanol was
used as the solvent; m.p. 200° with decomp., lit. 195° (40) and 209° (22)
with decomp.

Preparation of V by Esterification.

A one-neck, 2.0-l. round-bottom flask was charged with 150 g. (1 mole) of d-tartaric acid, 1000 ml. (25 moles) of methanol (commercial grade), 275 ml. (2.2 moles) of ketal, 5 drops of conc. sulfuric acid, and a stirring bar. The flask was attached to an Oldershaw fractionating column with a vapor-dividing head used to separate the methanol-acetone azeotrope from methanol. The timer was originally set for 20 percent take off and the temperature held at $57-59^o$. When the DNP derivative was no longer obtained with the distillate, the temperature rose to 64°. The remainder of the solvent was quickly removed and saved for the next esterification. The total reaction time was 15 hrs. When approximately 225 ml. of ester and solvent remained, the solution was transferred to a 250 ml. flask by rinsing with methanol. This was attached to a short-path vacuum distillation apparatus. The acid catalyst was not neutralized. Distillation produced 147 g. (83%) of dimethyl d-tartrate, b.p. $117^o/0.6$ mm. A very small amount of decomposition occurred towards the end of the distillation.

Preparation of Dimethyl dl-Malate.

Sulfuric Acid Catalyst. A one-neck, 2-l., round-bottom flask was charged with 134 g. (1 mole) of dl-malic acid (m.p. 135°), 275 cc. (2.2 moles) of ketal, 800 cc. (20 moles) of methanol, 5 drops of conc. sulfuric acid and a stirring bar. A procedure analogous to that used in the preparation of dimethyl d-tartrate was followed. The reaction time was 12 hrs. When the concentrate was transferred to a 250 ml. flask, two drops of phenolphthalein indicator was added. The concentrate was titrated with a saturated solution of sodium methoxide in methanol, but no endpoint could be seen. Therefore, a large excess of sodium methoxide was added. By use of a short-path vacuum distillation apparatus, the solution was distilled over a temperature

range of 108-147° at 0.75 mm. No constant temperature could be obtained

in the distillation. Some clear liquid appeared as a distillate but a

solid was collecting in the distillation head. The distillation was dis-

continued and upon cooling the residue in the pot solidifed. The clear

liquid was saved for further fractionation.

A vacuum distillation of the solid residue in the pot was tried again.

With the aid of a heat gun several grams of the solid collecting in the

distillation head was obtained. However, the heat gun would not remove

all of the solid from the distillation head. The distillation was discon-

tinued and the solid remaining in the head was recrystallized from ether,

m.p. 295° with decomp. The solid that distilled over was recrystallized

from ether, m.p. 101-102°. The residue in the pot was recrystallized from

ether, m.p. 143-144°.

A sample of fumaric acid was obtained and the infrared spectrum

matched that of the sample with a melting point of 295°, lit. 293-5° (57).

A mixture of 25 g. (0.215 mole) of fumaric acid, 173 cc. (4.3 moles)

of methanol, 65 cc. (0.52 mole) of ketal, 5 drops of conc. sulfuric acid,

and a stirring bar was refluxed 1 hr. and excess methanol was removed on

the rotary evaporator until approximately 50 ml. of solution remained.

When this was cooled in an ice bath, a crystalline solid appeared; this

was filtered off and washed with cold water. A small portion of this

solid was distilled in a short-path vacuum distillation apparatus. The

distillate was recrystallized from ether and air dried, m.p. 101-102°.

This corresponds to the literature value (57) for dimethyl fumarate.

The remainder of the solid was recrystallized from ether and air-dried,

m.p. 100-102°. This produced 23.5 g. (76%) of dimethyl fumarate.

Equal portions of the substance that melted at 101-102° and dimethyl
fumarate were mixed and then had mixed m.p. 101-102°. The infrared spec-
trum of dimethyl fumarate also matched the spectrum of the substance
melting at 101-102°, and the nuclear magnetic resonance spectrum showed
the two peaks and the 3:1 proton ratio to be expected of dimethyl fumarate.

A small portion of the residue, m.p. 143-144°, from the distillation
pot was placed in water. When sodium bicarbonate was added, most of the
solid dissolved with evolution of carbon dioxide. Since the solid was
evidently a mixture and study of its nature would have deviated consid-
erably from the original problem, time was not devoted to separation and
identification of the components.

The colorless liquid obtained from the original distillation was
placed on a fractionating column with a heated jacket. The liquid was
vacuum distilled. A fraction, b.p. 81°/0.80 mm., was obtained which
showed only one peak on gas-liquid chromatography. An infrared spectrum
was obtained from a film on sodium chloride crystals. Prominent peaks
occurred at 2.88 μ (-OH) and 5.73 μ (ester carbonyl). Both the infrared
spectrum and the nuclear magnetic resonance spectrum indicated the compound
to be dimethyl dl-malate.

Hydrochloric Acid Catalyst. A one-neck, 2-1., round-bottom flask
was charged with 134 g. (1 mole) of dl-malic acid, 800 cc. (20 moles) of
methanol, 275 cc. (2.2 moles) of ketal, 25 drops of conc. hydrochloric
acid, and a stirring bar. The flask was attached to the Oldershaw column
and the solution was allowed to reflux for 4 hrs. An additional 25 drops
of hydrochloric acid was added and the reaction-distillation was carried
on for 6 hrs., until approximately 400 ml. of solution remained. A pH
meter, equipped for non-aqueous titrations, was used in the neutralization

of the acid catalyst. Successive 1 ml. portions of a saturated solution

of sodium methoxide in methanol were added. At the beginning of the

titration, 1 ml. of solution would create a break of 0.1 to 0.2 pH units.

Additions were continued until 1 ml. of the solution created a break of

1.7 pH units. The mixture of ester and methanol was returned to the 2-1.

flask and the remainder of the solvent was removed on the Oldershaw column.

The residual solution (approximately 200 ml.) was transferred to a 250-ml.

flask and distilled using a short-path vacuum distillation apparatus. This

produced 130 g. (80%) of dimethyl dl-malate, b.p. 99°/1.75 mm.; lit. 116°/11 mm.

(54a).

Preparation of Trimethyl Citrate.

Sulfuric Acid Catalyst. A procedure analogous to the preparation of

dimethyl d-tartrate was followed. The flask was charged with 210 g. (1 mole)

of citric acid monohydrate, 552 cc. (4.4 moles) of ketal, 1000 cc. (25 moles)

of methanol and 5 drops of conc. sulfuric acid. The reaction-distillation

was continued for 12 hrs. until approximately 300 ml. of solvent and ester

remained. When the flask was cooled in an ice bath, crystallization

occurred. The crude ester, m.p. $97-104^{\circ}$, was recrystallized from methanol

but then still melted at $97-104^{\circ}$, lit. $75-76.5^{\circ}$ (30) and $78-79^{\circ}$ (57). A

small sample of this material reacted with sodium bicarbonate to evolve

carbon dioxide; evidently the acid was only partly esterified. An additional

125 cc. (1 mole) of ketal, 500 cc. (12.5 moles) of methanol, and 5 drops of

conc. sulfuric acid were added to the partly esterified acid and the reac-

tion was continued for 6 hrs. A small portion of the crude material was

recrystallized from methanol and melted at $90-95^{\circ}$; again a reaction with

sodium bicarbonate was obtained.

This procedure was repeated several times with similar results. No

attempt was made to separate and identify the products.

Hydrochloric Acid Catalyst. A mixture of 210 g. (1 mole) of citric
acid monohydrate, 552 cc. (4.4 moles) of ketal, 1000 cc. (25 mole) of
methanol, and 25 drops of conc. hydrochloric acid was refluxed for 5 hrs.
under the Oldershaw column. An additional 25 drops of conc. hydrochloric
acid was then added along with 63 cc. (0.5 mole) of ketal. The solvent
was removed over a period of 3 hrs. until approximately 500 ml. remained.
This residue was cooled in an ice bath and crystallization occurred. The
crude material, m.p. 70-75°, melted below the literature value 75-76.5^o
(30) and 78-79° (57). The material dissolved in methanol was neutralized
with sodium methoxide as in the preparation of dimethyl dl-malate and
ultimately vacuum distilled. The ester boiled at 143-145°/3.4 mm. It
was recrystallized from methanol to obtain 188 g. (80%) of white crystalline
trimethyl citrate, m.p. 76-77°.

Preparation of Amides By Aminolysis of II. Results are given in
Table III.

TABLE III

PREPARATION[*] OF AMIDES FROM THE ACETONE
COMPOUND OF d-TARTARIC ACID (II).

$RNR'CO(CHOH)_2CONR'R$

R	R'	Moles of II	Moles of Amine	M.p., ^{o}C	Lit. m.p., ^{o}C	References
Methyl	Methyl[d]	0.0130	a	184-186		
H	H	0.0087	b	204.5[c]	208.5-209[c]	22
Methyl	H	0.0130	a	195-196	189	41
Ethyl	H	0.1300	a	213-214	215-215.5	22
n-Butyl	H	0.0130	0.152	197-198	193	41

TABLE III (continued)

* The solvent in all reactions was absolute ethanol.

a. The solutions were saturated with the respective amine, which was generated by warming a 25 percent aqueous solution and dried by passage through two potassium hydroxide drying tubes.

b. The gas was obtained from a cylinder and used as in "a".

c. With decomposition.

d. Also prepared by the aminolysis of 5.0 g. of dimethyl d-tartrate in methanol in the same way. Evaporation of the solvent gave a syrup which when seeded yielded the desired product, m.p. 186-7° (from absolute ethanol). Anal. Calcd. for $C_8H_{16}N_2O_4$: N, 13.72, found: N, 13.44. The infrared spectrum plate III shows the amide-carbonyl absorption maximum at 6.19 μ.

The corresponding reactions of II with diethylamine, di-n-propylamine, di-n-butylamine, ethanolamine, morpholine, and piperidine gave only syrups from which no crystals could be obtained.

By Aminolysis of Esters. The preparation of amides, with corresponding data, from dimethyl d-tartrate, dimethyl dl-malate and trimethyl citrate is given in Table IV.

TABLE IV

PREPARATION OF AMIDES FROM METHYL ESTERS

Amine	Moles of Amine	M.p., $^{\circ}$C	μ [b]	Infrared Spectrum plate no.
		d-Tartramides[a]		
2-Hydroxyethyl	0.0562	143-144	6.11	IV
Cyclohexyl	0.0605	218-220	6.13	V

No crystalline products were obtained by use of diethylamine, diisopropylamine, dibutylamine, and morpholine. Ethylenediamine gave a clean solid but it appeared to be polymeric and could not be recrystallized: it decomposed at 200-240°.

dl-Malamides[a]

Ethyl	0.0845	158	6.14	VI
Isopropyl	0.0845	144-145	6.16	VII
Cyclohexyl	0.0822	195-196	6.14	VIII
2-Hydroxyethyl	0.0822	125-126	6.16	IX
Benzyl	0.0822	147-148	6.13	X

No crystalline products were obtained from dimethylamine, diethylamine, dipropylamine, dibutylamine, morpholine, piperidine, and 1-naphthylamine. Ethylenediamine gave a solid, probably polymeric, that decomposed at 215-250° and could not be recrystallized.

Citramides[a]

Methyl	c	179-180[d]	6.10	XI
Ethyl	0.0713	126-127[e]	6.10	XII
n-Butyl	0.0713	96-97[f]	6.11	XIII
Benzyl	0.0727	171-172[g]	6.11	XIV

No crystalline products were obtained from 2-hydroxyethyl-amine, 1-naphthylamine, and piperidine. No reaction occurred between trimethyl citrate and the following amines in two days at room temperature: isopropylamine, dimethylamine, diethylamine,[b] dibutylamine, cyclohexylamine, and morpholine; trimethyl citrate was recovered in each case.

a. 5.0 g. of the dimethyl ester was dissolved in 10 cc. (0.25 mole) of methanol. After the amine was added, the reaction mixture was kept at room temperature for 48 hrs. The amide was recrystallized from absolute ethanol.

b. Amide-carbonyl infrared absorption peak, μ.

c. Same as "a" in Table III.

d. Recrystallized from absolute ethanol; lit. value 124° (55). This value is either that of a different crystalline form or else in error.

e. Recrystallized from carbon tetrachloride.

f. Recrystallized from isopropyl ether.

g. Lit. value 169-170° (25).

h. In an attempt to force reaction, excess diethylamine (containing some diethylammonium chloride catalyst) and trimethyl citrate were heated at reflux for an hour. When excess amine was distilled off in vacuo, the solid residue proved to be only trimethyl citrate, m.p. 76-77° (from absolute ethanol).
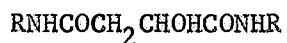
The analytical data for the amides prepared from the methyl esters are given in Table V.

TABLE V

ANALYTICAL DATA ON AMIDES

R	Mol. Formula	N, Calcd.	N, Found
d-Tartramides			
RNHCO(CHOH)$_2$CONHR			
2-Hydroxyethyl	$C_8H_{16}N_2O_6$	11.86	11.32
Cyclohexyl	$C_{16}H_{28}N_2O_4$	8.97	8.57

dl-Malamides

RNHCOCH$_2$CHOHCONHR

Ethyl	C$_8$H$_{16}$N$_2$O$_3$	14.89	14.91
Isopropyl	C$_{10}$H$_{20}$N$_2$O$_3$	12.96	12.53
Cyclohexyl	C$_{16}$H$_{28}$N$_2$O$_3$	9.45	9.00
2-Hydroxyethyl	C$_8$H$_{16}$N$_2$O$_5$	12.72	12.20
Benzyl	C$_{18}$H$_{20}$H$_2$O$_3$	8.97	8.62

Citramides

(RNHCOCH$_2$)$_2$C(OH)CONHR
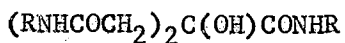
Methyl	C$_9$H$_{17}$N$_3$O$_4$	18.18	17.50
Ethyl	C$_{12}$H$_{23}$N$_3$O$_4$	15.38	14.92
n-Butyl	C$_{18}$H$_{35}$N$_3$O$_4$	11.76	11.20
Benzyl	C$_{27}$H$_{29}$N$_3$O$_4$	9.15	8.90

Attempted Preparation of the Acetone Compound of d-Tartramide.

A one-neck, 100-ml., round-bottom flask was charged with 2.0 g. (0.013 mole) of d-tartramide, 30 cc. (0.41 mole) of acetone, and 15 cc. (0.12 mole) of ketal. The flask was stoppered and placed in an ice bath to which after 20 minutes, 2 drops of conc. sulfuric acid was added and the solution was stirred for 3 hrs. The mixture did not become homogeneous. When excess solvent was evaporated on the rotary evaporator, a syrup-like residue remained. This was dissolved in 100 ml. of ether and washed twice with 50-ml. portions of water. When ether was removed on the rotary evaporator, no residue remained.

Attempted Preparation of the Cyclohexanone Compound of d-Tartramide.

A mixture of 1.0 g. (0.067 mole) of d-tartramide, 100 cc. (0.92 mole) of cyclohexanone and 2 drops of conc. sulfuric acid was stirred at room temperature for 4 hrs. A procedure identical to the one just previously described was followed here; no product was obtained.

This process was repeated except the reaction was heated at reflux for 48 hrs; again no product remained.

Attempted Preparation of the Formaldehyde Compound of d-Tartramide.

A 125-ml. Erlenmeyer flask was charged with 3.0 g. (0.02 mole) of d-tartramide, 50 cc. of a 27 percent aqueous formaldehyde solution, and 2 drops of conc. hydrochloric acid. This was allowed to stand 4 hrs. at room temperature. When the solvent was removed, a white paste remained. This proved insoluble in all solvents tried, so that recrystallization was impossible. The solid was probably a polymer.

Attempted Preparation of the Formaldehyde Compound of N,N'-Diethyl-d-Tartramide.

A procedure like the one just previously described, except that 3.0 g. (0.015 mole) of N,N'-diethyl-d-tartramide, was used. Again a white paste was obtained which had essentially the same properties.

CHAPTER IV

DISCUSSION OF RESULTS

The use of ketal as a water scavenger in the preparation of acetone
derivatives of alpha-hydroxy acids and methyl esters of these acids has
proved satisfactory. Although the only acetone derivatives isolated in
a pure state were those of d-tartaric and dl-mandelic acids, it is believed
that inability to obtain those of malic and citric acids is due to diffi-
culties in their separation and purification rather than failure to form
them. During the water wash to remove the acid catalyst and any unreacted
hydroxy acid, the acetone derivatives of malic and citric acid would pre-
sumably be water soluble if free carboxyl groups remained unesterified in
the reaction. If excess acetone and ketal are used to make the acetone
compound, the acid group remains unesterified; if enough methanol is used
to esterify the acid group, the acetone compound is split by the methanol.
Any unreacted hydroxy acid has to be separated from the "acetone compound-
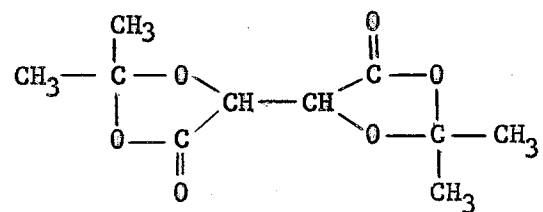acid" and their solubilities are too similar to permit this.

A 50% BF_3 solution in ether proved to be the best catalyst in the
preparation of II. This gave a slightly better yield than the sulfuric
acid catalyst and decreased the formation of tars. When Dowex 50 W x 8
(strong cation exchange resin in the hydrogen form) catalyst became coated
with tars and turned very dark during the reaction, low yields were obtained.
If the Dowex 50 W x 8 resin had worked as a catalyst, its removal from the
reaction mixture by filtration would have been a more convenient way to

24

remove the acid catalyst than the water wash was. Although p-toluene-
sulfonic acid gave less tar formation, it also gave a considerably
decreased yield.

The preparation of methyl esters of hydroxy acids by classical
methods has been difficult because there exists no simple and convenient
way to remove water and shift the equilibrium to better yields. The use
of ketal provides such a way; the acetone byproduct causes no ill effects.
Rather surprisingly, dimethyl dl-malate has never been made from dl-malic
acid. The remarkable difference between sulfuric acid and hydrochloric
acid as a catalyst in the ketal-driven esterification cannot easily be
explained. The present work has verified that sulfuric acid promotes
the elimination of water from dimethyl malate to form dimethyl fumarate;
but the inability of sulfuric acid to cause complete esterification of
citric acid by methanol is unaccountable.

Although the alcoholysis of II was a satisfactory way to prepare
esters in good yield, there is no need for a two-step preparation when
ketal will work successfully as a water scavenger in a one-step esteri-
fication of the acid.

Fisher and Taube (36) have considered the structure of the acetone
compound of tartaric acid to be:

$$CH_3-\underset{\underset{O}{\overset{\overset{CH_3}{|}}{\underset{|}{C}}-O}{\overset{}{\underset{}{}}}\diagdown CH-CH\diagup \underset{\underset{CH_3}{|}}{\overset{\overset{O}{\overset{\|}{C}-O}}{\underset{}{O-C-CH_3}}}$$

but give no actual proof. Tsuzuki (85) has used a different structure

but again no information is given to support this. Both types of structure
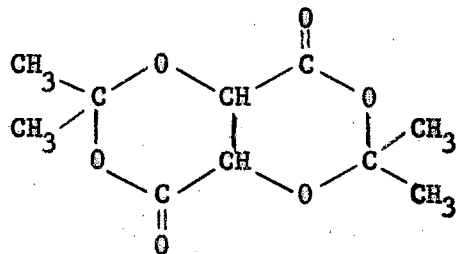
were recognized as possibilities by Austin and Carpenter (9) for the formal-
dehyde derivative, but they gave no evidence to support either form.

The infrared spectrum of II (Plate I) shows a carbonyl peak at 5.60 μ[a].
The infrared spectrum of the acetone derivative of dl-mandelic acid (III)
(Plate II), which can only exist as a five-membered ring, shows a carbonyl
peak at 5.56 μ. The normal location of this peak in 5-membered lactone
rings is 1780-1760 cm^{-1} (12) or 5.62-5.68 μ, whereas for 6-membered lactones
it is 1750-1735 cm^{-1} (12) or 5.71-5.76 μ. This suggests that II contains
5-membered rings, but the carbonyl peak for a 6-membered lactone ring also
containing an ether oxygen should be compared to strengthen the evidence.
No 1,3-dioxan-4-ones are known but an ideal one for the purpose of estab-
lishing location of the carbonyl absorption peak could possibly be prepared
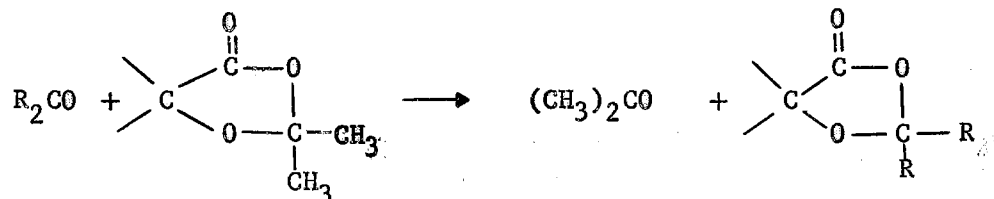from β-propiolactone. However, 1,4-dioxan-2-one is known, and its carbonyl
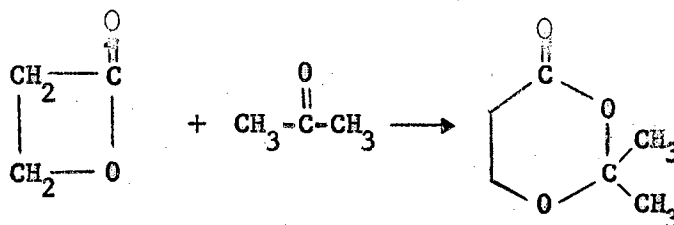
peak is at 5.70 μ (79). It appears that the ether oxygen does not change
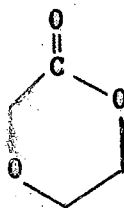
a. Hertzler (56) obtained 1790 cm^{-1} or 5.59 μ.

the carbonyl absorption here, and surely it would not do so in a 1,3-
dioxan-4-one either. Hence no doubt remains that II has the bis-dioxo-
lanone structure proposed by Fischer and Taube.

In the reaction of other carbonyl compounds with d-tartaric acid,
insolubility of the acid is the major problem. If the reaction mixture
is raised to reflux temperature to increase the solubility, a self-aldol
condensation reaction of the carbonyl compound becomes much worse. The
formation of tars does not allow crystallization of the product after the
general work-up. For the displacement reaction, there was no way to open

$$R_2CO + \underset{}{\overset{}{C}} \underset{O-C-CH_3}{\overset{O}{\underset{CH_3}{\overset{\|}{C-O}}}} \longrightarrow (CH_3)_2CO + \underset{}{\overset{}{C}} \underset{O-C-R}{\overset{O}{\underset{R}{\overset{\|}{C-O}}}}$$

and close the ring and the reaction failed for the same reason that the

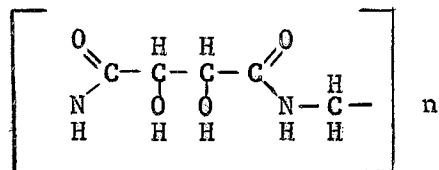$$R_2CO + (CH_3)_2C(OCH_3)_2 \longrightarrow R_2C(OCH_3)_2 + (CH_3)_2CO$$

corresponding reaction of ketal itself was extremely slow (60). Presumably
on this basis the reaction should have been between tartaric acid and
cyclohexanone, with II to take up the water; but then the solubility
problem would have been back.

The aminolysis of II and the methyl esters of the acids produced
several new amides not previously found in the literature. Why the secondary
amines did not react with trimethyl citrate presents an interesting problem,
but no explanation can be given. Although the dioxolanones react like
methyl esters to give amides, it is thought that the Schiff bases produced
by reaction of the acetone byproduct with excess amines will sometimes
not allow the amides to crystallize.

The reaction of d-tartramide and dimethyl-d-tartramide with formaldehyde

formed polymers, presumably of general structure:

$$\left[\begin{array}{c} \overset{O}{\underset{H}{\overset{\diagdown}{N}}}C-\overset{H}{\underset{O}{\overset{|}{C}}}-\overset{H}{\underset{O}{\overset{|}{C}}}-C\overset{\diagup O}{\underset{H}{\diagdown}}N-\overset{H}{\underset{H}{\overset{|}{C}}}- \end{array}\right]_{n}$$

When a less reactive carbonyl compound (acetone) was used, the reaction would not proceed at all to form the oxazolidinone, apparently because of complete insolubility of the d-tartramide.

CHAPTER V

SUMMARY

In the preparation of 1,3-dioxolan-4-ones and methyl esters of

hydroxy acids ketal works very well as a water scavenger. The prepa-

ration of the 1,3-dioxolan-4-ones of dl-malic and citric acids could

probably be accomplished in this manner if the problem of their sepa-

ration and purification could be overcome. Since the methyl esters

can be distilled from the tars, no problems of purification are met

and good yields are obtained. It is very convenient to use ketal in

esterification reactions to remove water because no special apparatus

or anhydrous drying agent is needed. There is no advantage in making

the esters from 1,3-dioxolan-4-ones, but in the preparation of acetone

compounds alcohols must be avoided as solvents to keep from shifting

the equilibrium to produce esters.

The bi-dioxolanone structure given by Fischer and Taube for the

acetone compound of tartaric acid is the correct one.

Although the reaction of other carbonyl compounds with the

hydroxy acids tested did not produce crystalline compounds, maybe a

procedure using ketal can still be made to succeed.

The new amides prepared from methyl esters and the acetone

compound of tartaric acid add to the general abundance of amides of

hydroxy acids already on record, although practically no such amides

are known which are derived from secondary amines.

The oxazolidinones now known were prepared from monoamides. Use

of the monoamides evidently decreases the chances for polymerization,

because d-tartramide and N,N'-diethyl-d-tartramide formed polymers with

formaldehyde. In the attempted reaction of acetone with tartramide,

the tartramide was insoluble and did not react.

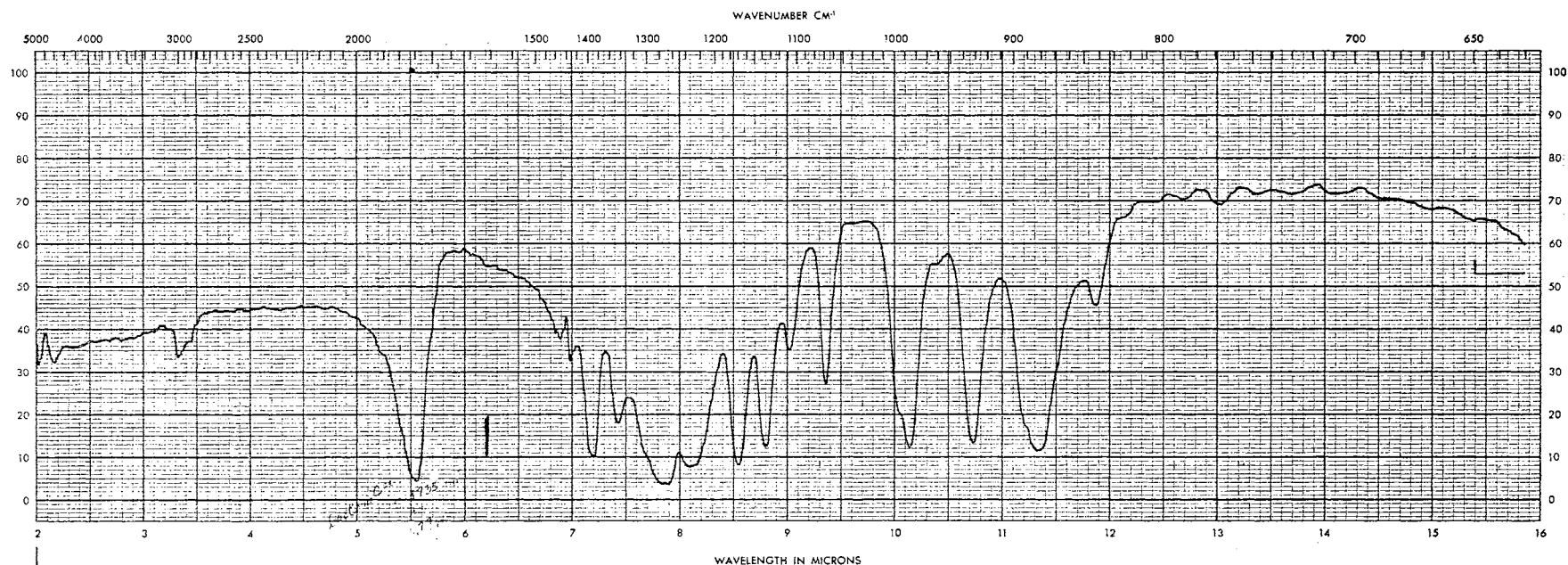# PLATE I

Acetone Compound of d-Tartaric Acid

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS

PLATE II

Acetone Compound of dl-Mandelic Acid

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
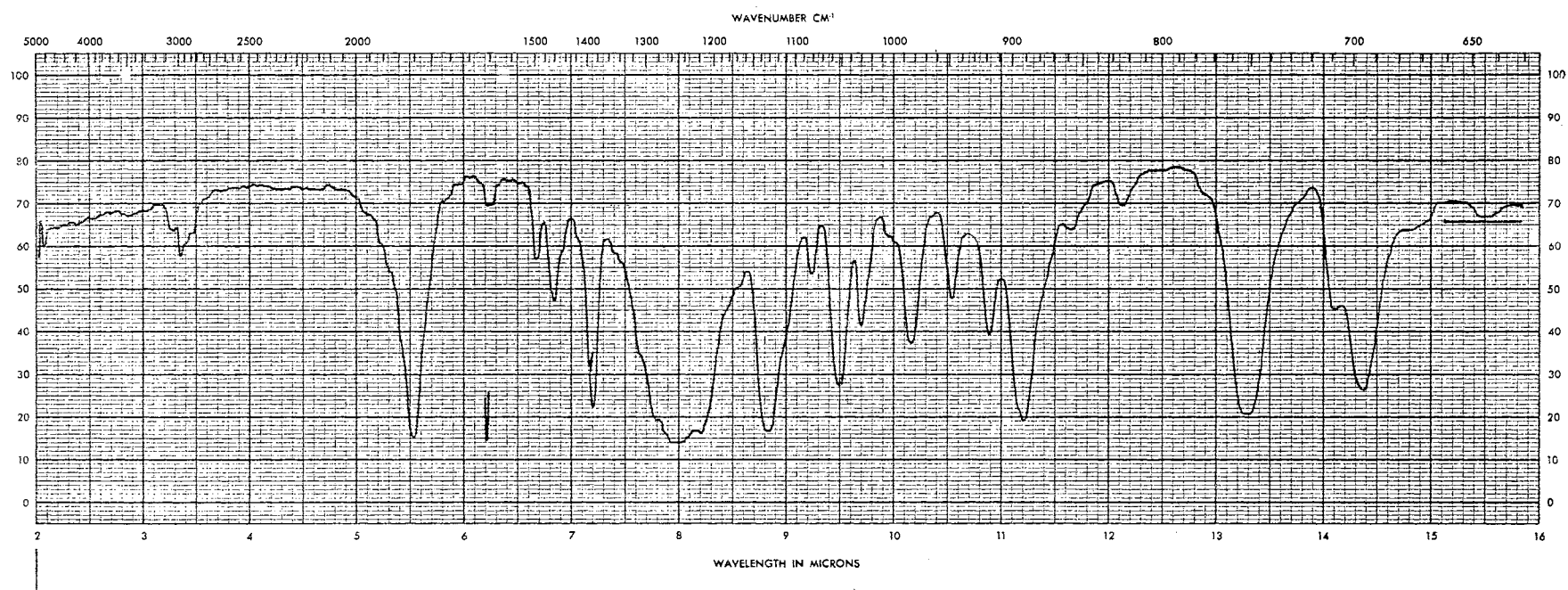
PLATE III

N,N,N',N' -Tetramethyl-d-tartramide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
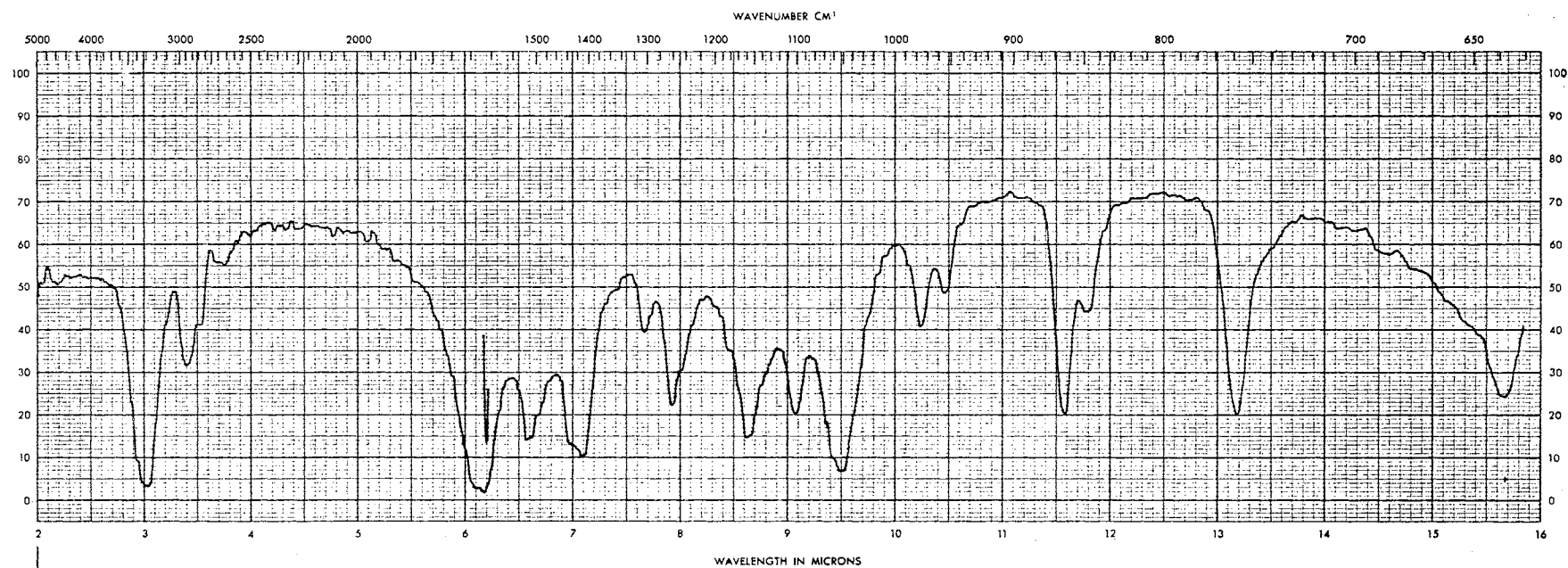
PLATE IV

N,N'-Bis-(2-hydroxyethyl)-d-tartramide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
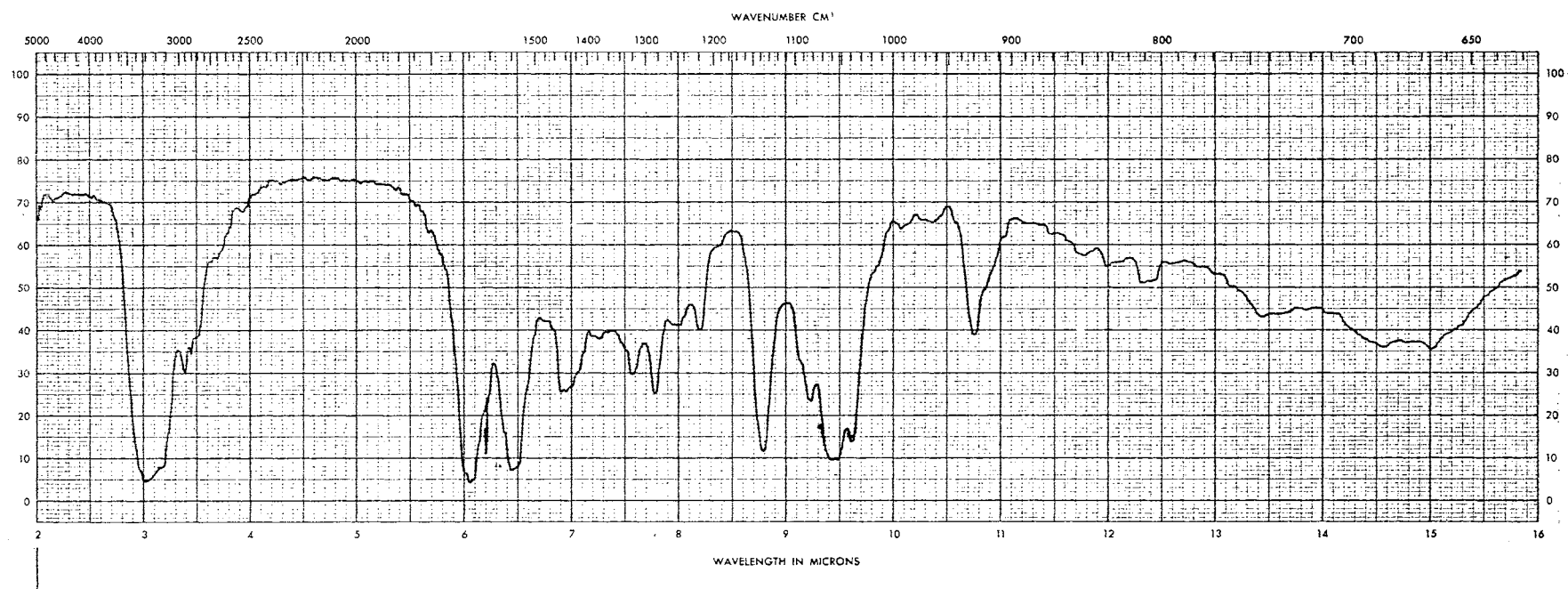
PLATE V

N,N¹-Dicyclohexyl-d-tartramide
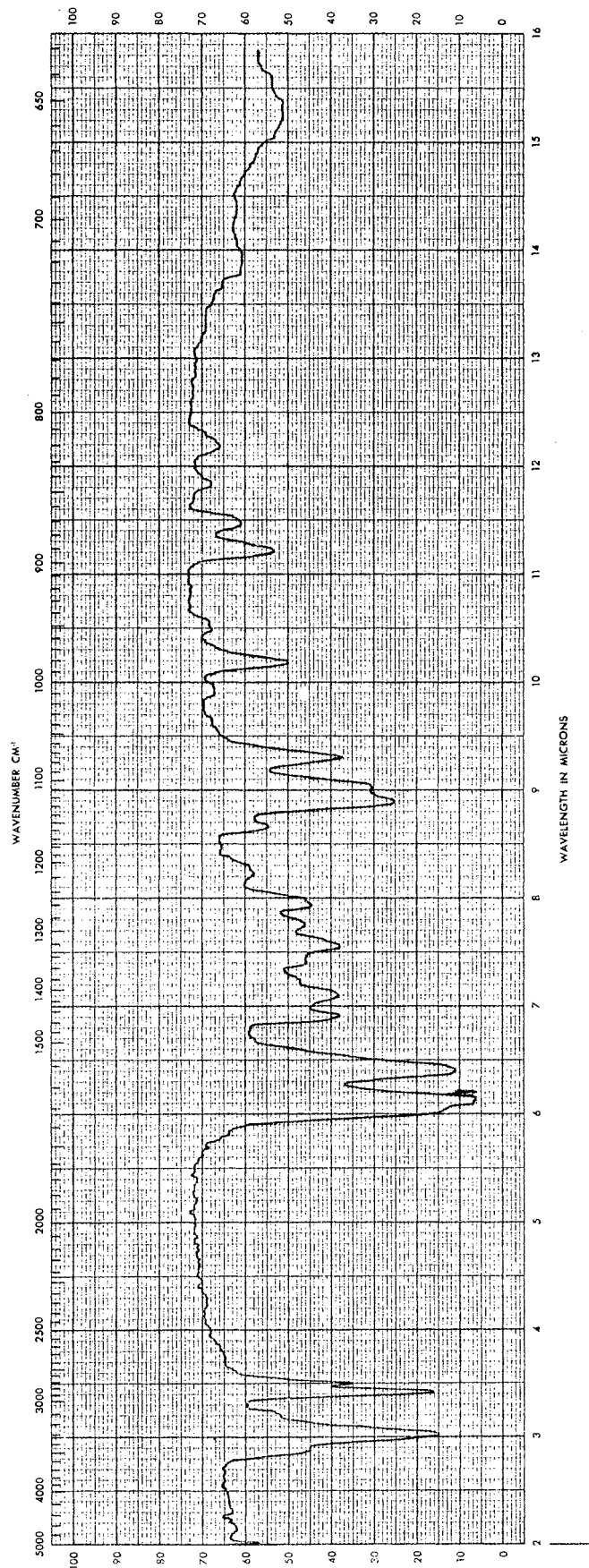
PLATE VI

N,N'-Diethyl-dl-malamide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
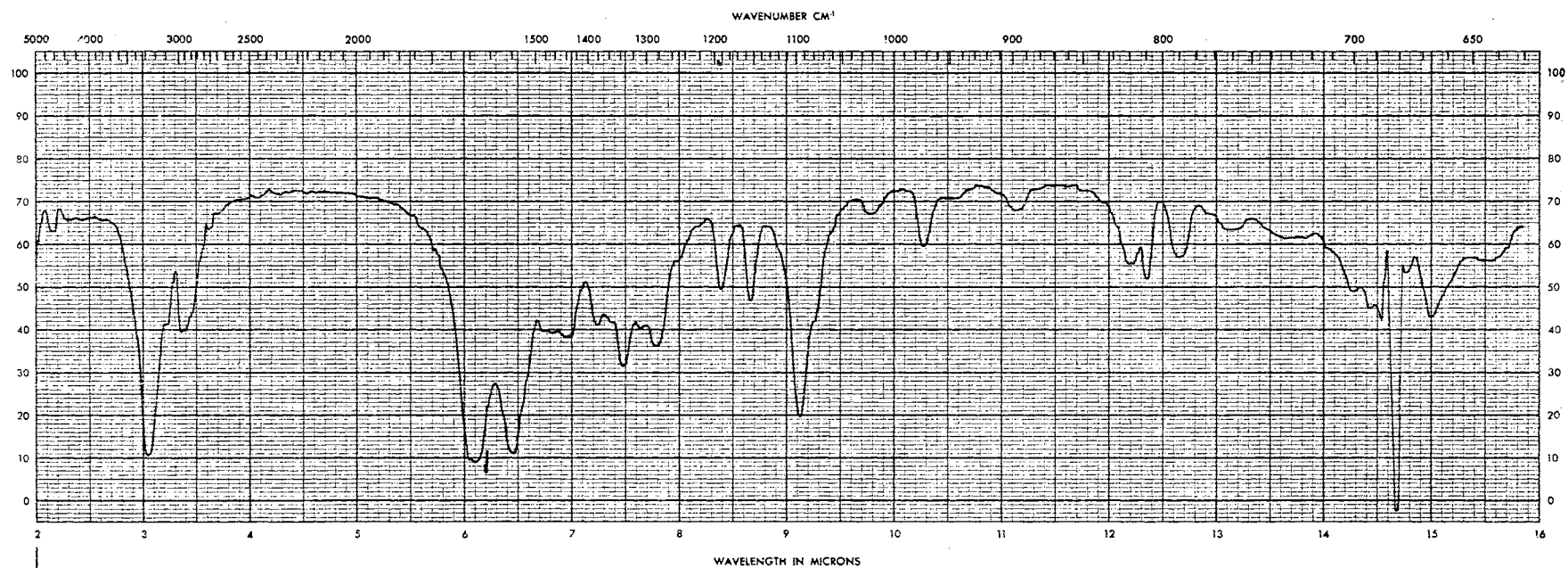
PLATE VII

N,N'-Diisopropyl-dl-malamide
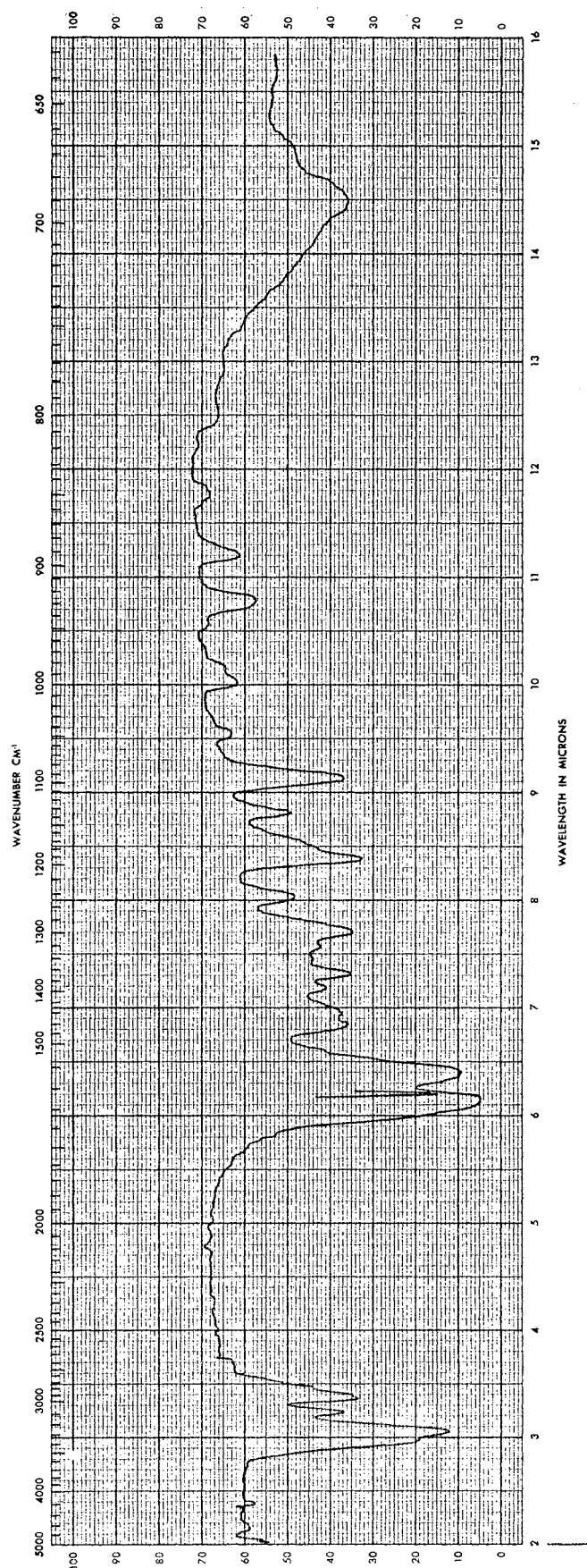
PLATE VIII

N,N'-Dicyclohexyl-dl-malamide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
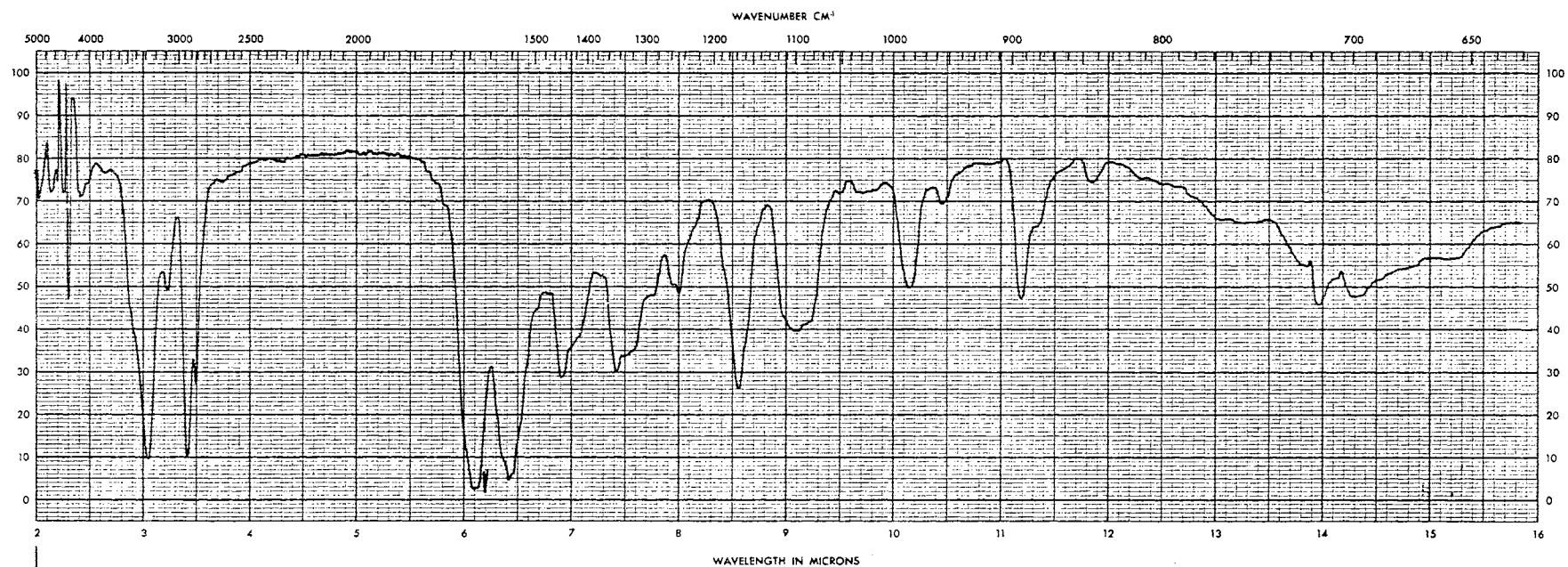
PLATE IX

N,N'-Bis-(2-hydroxyethyl)-dl-malamide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS

PLATE X

N,N'-Dibenzyl-dl-malamide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
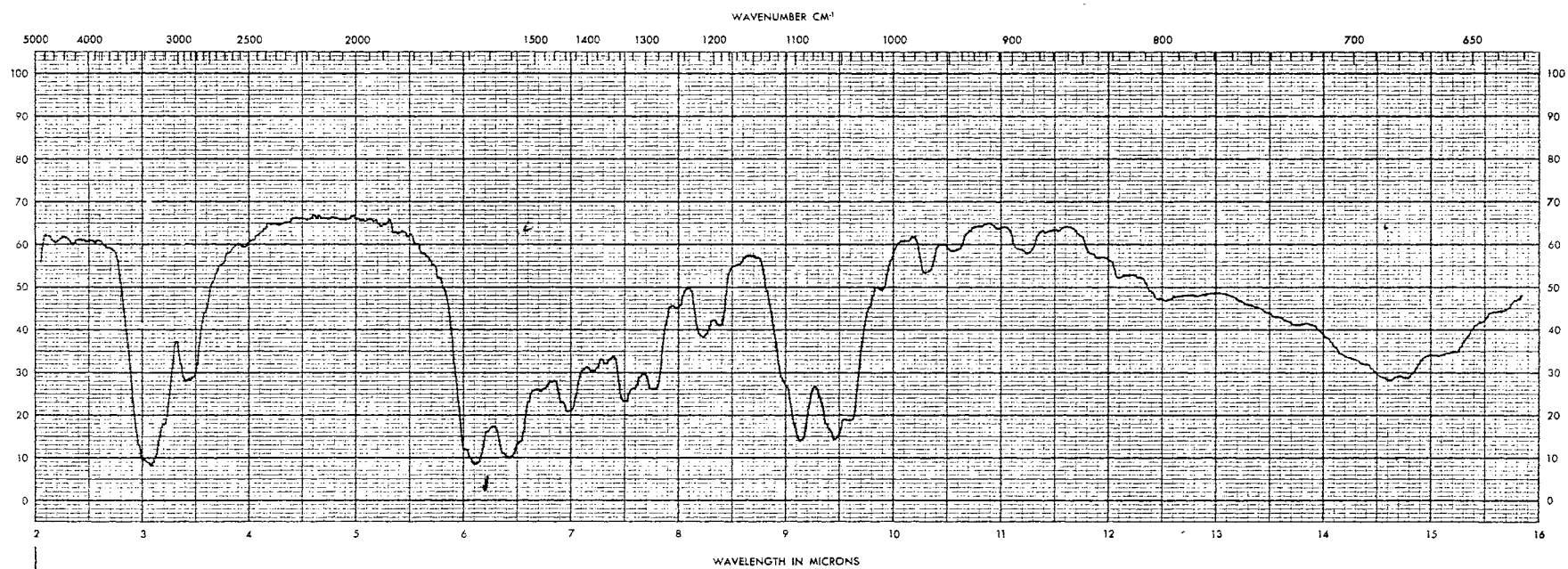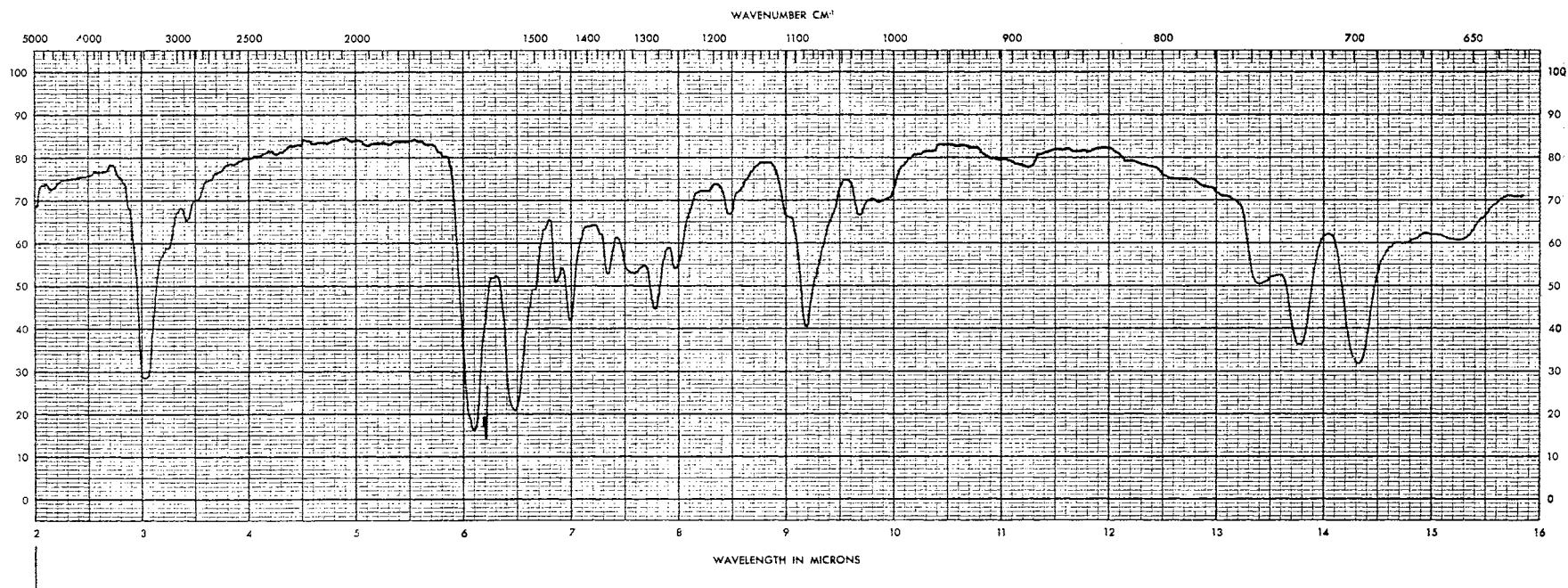
PLATE XI

N,N',N''-Trimethylcitramide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
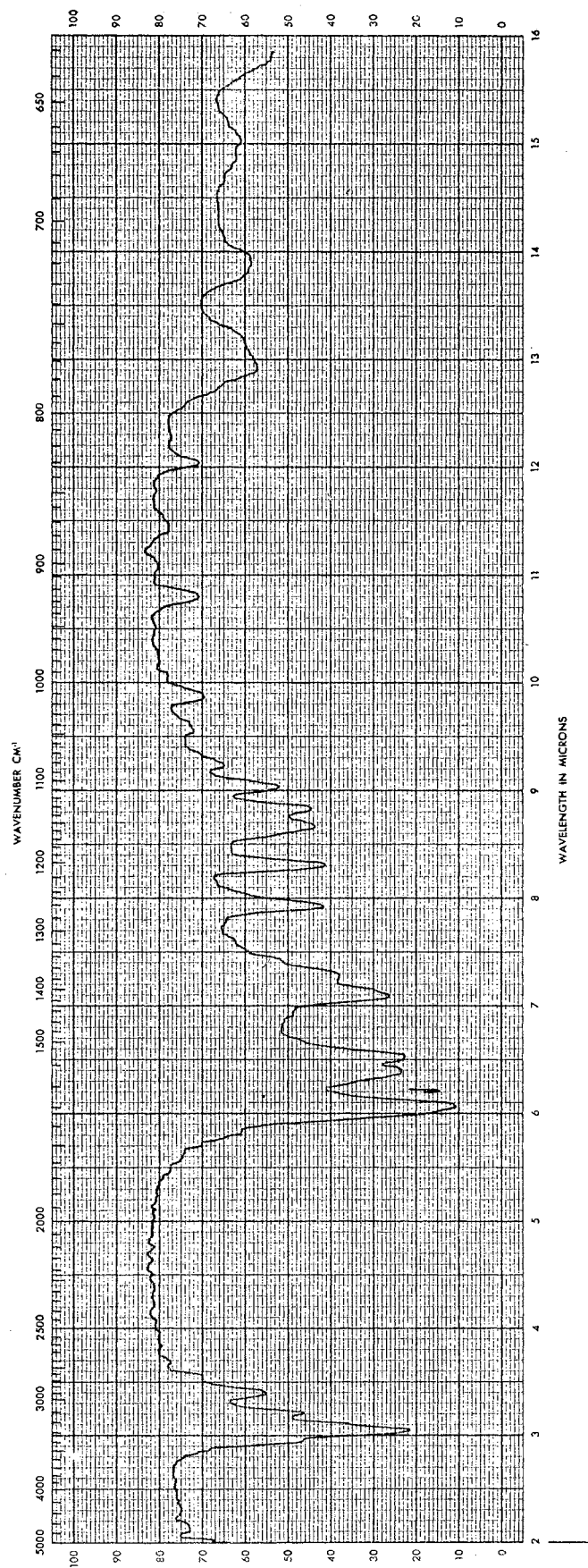
PLATE XII

N,N',N"-Triethylcitramide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS
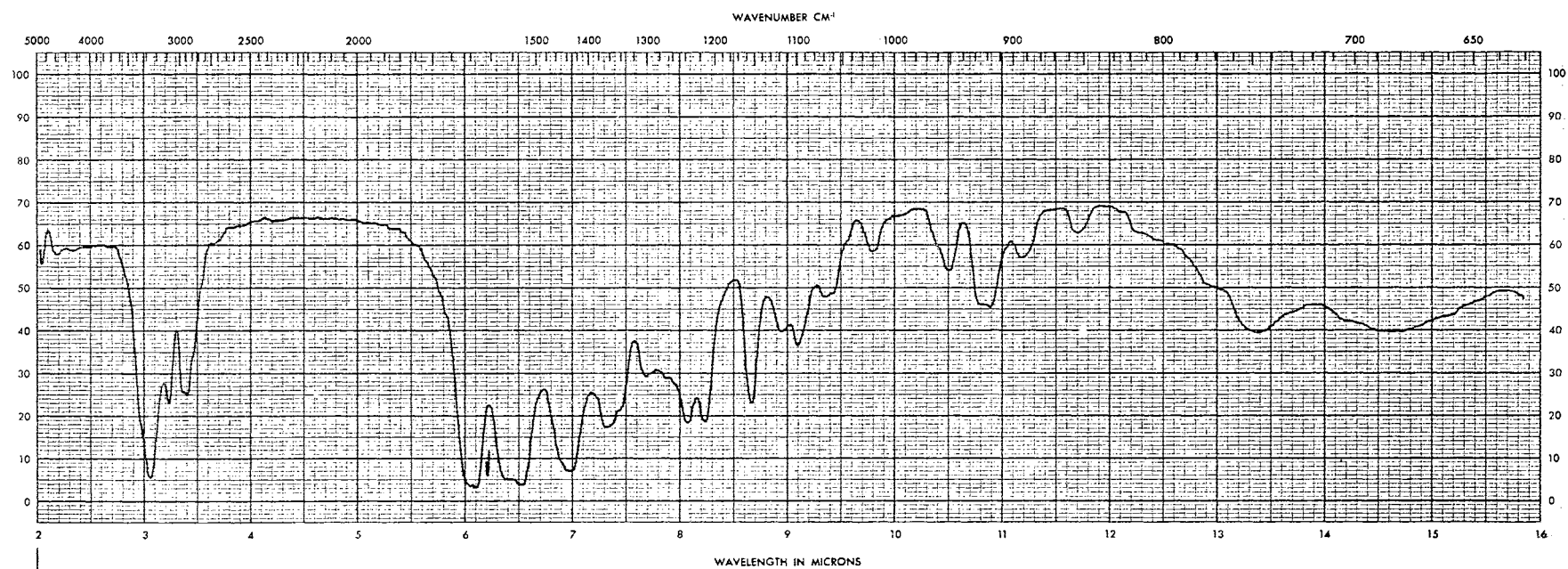
PLATE XIII

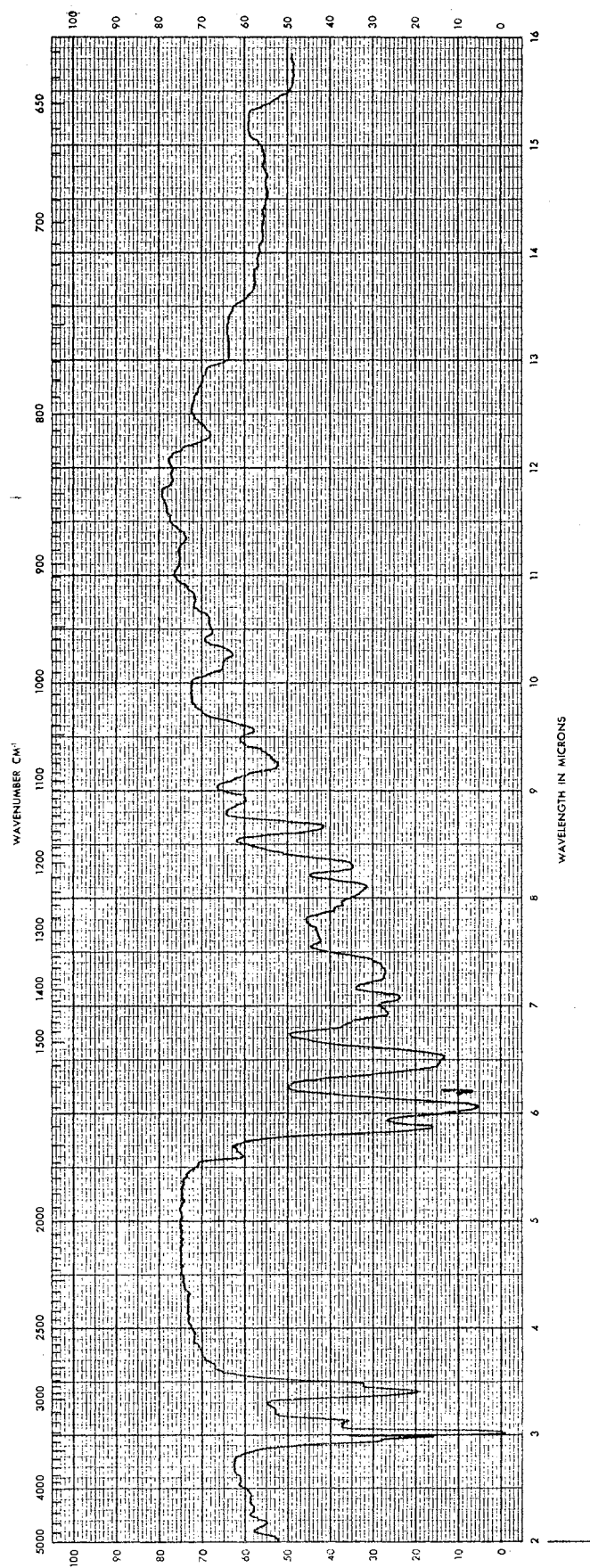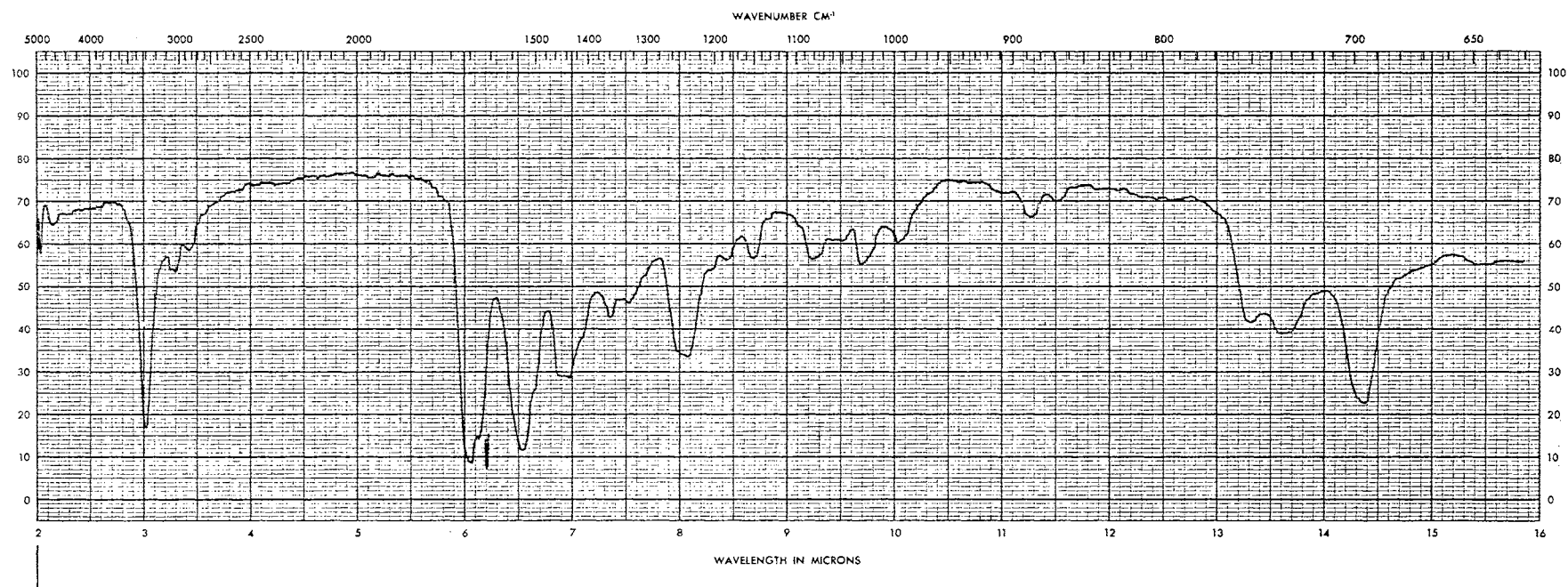N,N',N''-Tri-n-butylcitramide

PLATE XIV

N,N',N"-Tribenzylcitramide

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS

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