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# Some derivatives of [gamma]-valerolactone

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# NOTE TO USERS

SOME DERIVATIVES OF $\gamma$-VALEROLACTONE

by

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DOCTOR OF PHILOSOPHY

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Head of Major Department

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# INTRODUCTION

Early in the war, when the supply of natural rubber to the United States was cut off, the problem of finding synthetic substitutes became extremely important.  A possibility considered at that time was the use of levulinic acid (I) as the starting point in the preparation of 1,3-pentadiene (IV) by the following series of reactions:

$$CH_3COCH_2CH_2COOH \xrightarrow[\text{(Raney Ni)}]{+H_2} \underset{\substack{| \quad \quad | \\ O\text{------}CO}}{CH_3CHCH_2CH_2}$$

$$\text{I} \qquad\qquad\qquad\qquad\qquad \text{II}$$

$$\xrightarrow[\text{(CuCrO)}]{\bullet\ +H_2} \underset{\substack{| \qquad\quad | \\ OH \qquad\ OH}}{CH_3CHCH_2CH_2CH_2} \xrightarrow[\text{(Al}_2\text{O}_3)]{-H_2O}$$

$$\text{III}$$

$$CH_3CH:CHCH:CH_2 \quad + \quad CH_2:CHCH_2CH:CH_2$$

$$\text{IV}$$
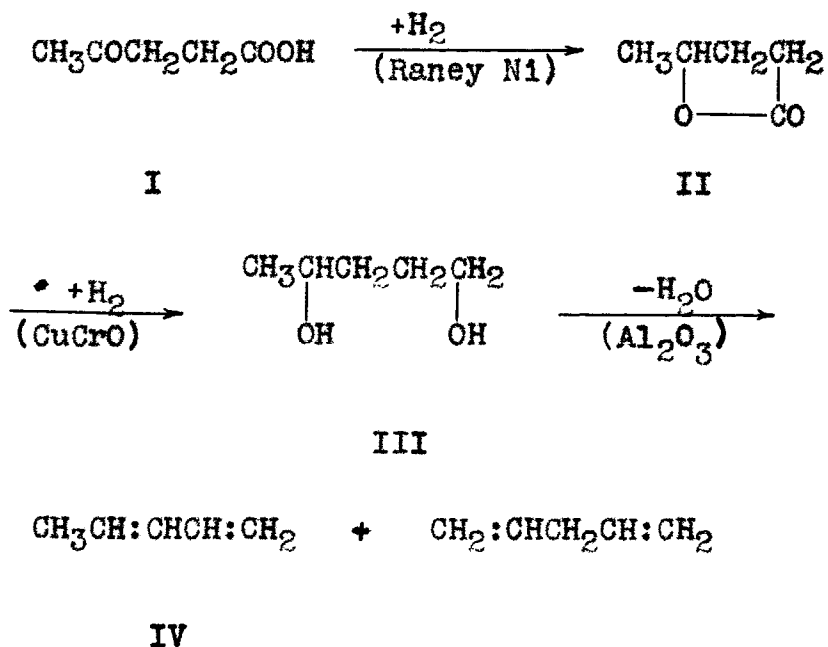
Preliminary studies by Mr. Horace D. Brown showed that the process was possible, although not immediately practical, and he succeeded in obtaining samples of rubberlike material from the copolymerization of 1,3-pentadiene and acrylonitrile. The most significant contribution of Mr. Brown's study was the

successful liquid phase hydrogenation of levulinic acid to
$\gamma$-valerolactone (II) in excellent yield. A similar process
is the subject of a recently issued patent (52) and is reported to be under pilot plant investigation by the Monsanto
Chemical Company.

The present investigation was undertaken for the purpose
of examining some of the reactions of $\gamma$-valerolactone (II)
and 1,4-pentanediol (III) with view to preparing new derivatives
which might prove worthy of further study leading to industrial
applications. The significance of such an investigation becomes apparent when the source of levulinic acid is considered.
Levulinic acid results when any hexose sugar, or carbohydrate
hydrolyzable to a hexose sugar, is heated in aqueous solution
with mineral acid (34, 80, 86). At present, the acid is
manufactured principally from starch. The discovery of new
uses for materials derivable from levulinic acid would provide another approach to the utilization of agricultural by-
products. The successful conclusion of such a research program, which, of course, might require many years, could result in a more intelligent exploitation of our natural resources and would be of great importance in the agricultural
phases of our national economy. The value of any contribution
to a long-term project of this type seems beyond question.

The plastics industry probably offers the most important
potential outlet for large quantities of moderately priced

chemicals. Attention was, therefore, directed to the possibility of using $\gamma$-valerolactone and 1,4-pentanediol as starting points in the synthesis of dibasic acids and amines from which linear polyamides of the "nylon" type could be prepared by the usual condensation methods (16).

Although 1,4-pentanediol has been obtained previously in satisfactory yield by catalytic reduction (31,40), the preparation of this compound was re-examined in the hope of improving the yields and adding refinements to the existing preparative methods.

From the many possible ways in which $\gamma$-valerolactone or 1,4-pentanediol could be utilized in the synthesis of bifunctional acids or amines, two were selected for investigation. The first line of attack proposed to make use of the little known Friedel and Crafts reaction with $\gamma$-valerolactone by means of which Eijkman prepared $\gamma$-phenylvaleric acid (25). It was hoped that it would be possible to cause benzene to condense with two molecular equivalents of the lactone to yield a $\gamma, \gamma$-phenylene-divaleric acid or a derivative of such an acid.

For the second approach, it appeared that application of the recently reported "cyanoethylation" reaction (6,7,8,14,17, 41,45,51,82,85) to 1,4-pentanediol might yield an intermediate dinitrile which could be converted to a dibasic acid by hydrolysis, or to a diamine by hydrogenation. The hydrolysis

of the nitrile proved to be an entirely new approach to the synthesis of $\beta$-alkoxypropionic acids and their derivatives. An extension of the study to a series of structurally related compounds was, therefore, projected and carried out.

MATERIALS, SPECIAL APPARATUS AND GENERAL PROCEDURES

Levulinic acid used in this study was an Eastman Tech-
nical product which was distilled in vacuo before use.
$\gamma$-Valerolactone was prepared from levulinic acid by the
method of Brown (4). This preparation will be described at
the conclusion of this section. Ruzicka's procedure (71) was
followed in the preparation of ethyl levulinate.

Alcohols and glycols used in the preparation of $\beta$-alkoxy-
propionitriles were commercially available chemicals. East-
man White Label chemicals and others of comparable quality
were used without further purification. Practical grades
were distilled before use and fractions boiling over a range
of three degrees or less were employed in the preparations.

The acrylonitrile was an Eastman Practical product. In
preliminary experiments the material was distilled prior to
use but it was found later that the yields of addition pro-
duct did not suffer when it was used without purification.

With one exception, the acids used in the preparation of
the amine salts were commercially available materials. The
reagent quality acids were used directly whereas those of
technical or practical grade were purified by suitable methods.
The glutaric acid was prepared from formaldehyde and diethyl
malonate by a standard procedure (60).

Copper-chromium oxide and Raney nickel catalysts were prepared in the usual way (1, pp. 13, 19). Hydrogenations were carried out in a 500 ml. rocking bomb of standard design (Parr Instrument Co.). A motor-driven booster pump, manufactured by the American Instrument Company, was used to obtain hydrogen at pressures higher than that available from commercial steel cylinders. Standard practices were followed in the reductions. The technique of super-pressure hydrogenation has been adequately treated elsewhere (1, pp. 29-46).

## Preparation of γ-Valerolactone by Brown's Procedure

A copper-lined hydrogenation bomb of 3.85 liters' capacity was used. The charge consisted of 580 g. (5 moles) of distilled levulinic acid and 15 g. of Raney nickel. Hydrogen was introduced to a pressure of 700 p.s.i. The temperature during the reduction was 175-200$^{o}$ and the reaction was complete after three hours. Separation of the catalyst and distillation of the reaction mixture gave 471 g. (94%) of γ-valerolactone of boiling point 87-90$^{o}$ (8-10 mm.).

# $\gamma$-VALEROLACTONE IN THE FRIEDEL AND CRAFTS REACTION

## Review of the Literature

The use of esters as alkylating agents in the Friedel and
Crafts reaction is well known and has been the subject of
several published studies (3, 59, 79). The reaction differs
from the usual Friedel and Crafts alkylation with alkyl
halides in that slightly more than one mole of catalyst must
be used per mole of ester. The reason for this is obvious
when one considers the mechanism of the reaction. The first
step is the cleavage of the ester by the aluminum chloride
to yield an alkyl halide and a salt (59), thus:

$$RCOOR + AlCl_3 \longrightarrow RCOOAlCl_2 + RCl$$
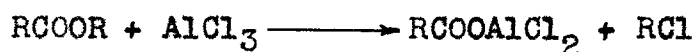
The first molecular equivalent of catalyst used serves only
to bring about this cleavage. After formation of the alkyl
halide has occurred, a slight excess of catalyst is suf-
ficient to cause alkylation of the aromatic component present
(79).

When the ratio of catalyst to ester is doubled and the
reaction time and temperature increased, the salt can react
further (79):

$$RCOOAlCl_2 + AlCl_3 \longrightarrow RCOCl + AlOCl$$
$$\overset{|}{AlCl_3}$$

The active complex thus formed is capable of taking part in an acylation reaction and ketones result. However, a proper choice of conditions makes it possible to confine the reaction to alkylation (59).

Lactones, as cyclic esters, should be expected to undergo a similar reaction. This is indeed the case, although Friedel and Crafts reactions with unhalogenated, aliphatic lactones have been reported by only one investigator. During the course of studies on seven $\gamma$-lactones (25-28), Eijkman reported (25) the preparation of $\gamma$-phenylvaleric acid and $\gamma$-tolylvaleric acid. These acids resulted from the reaction, in the presence of aluminum chloride, of $\gamma$-valerolactone with benzene and toluene, respectively.

Eijkman did not report the yields in his preparations, nor did he determine the position of substitution in the reaction with toluene. In neither case was proof presented to indicate that the $\gamma$-substituted valeric acid was the result. This point assumes significance in view of the fact that isomerization frequently accompanies Friedel and Crafts alkylations (79, pp. 94-97).

## Experimental

### Preparation of γ-phenylvaleric acid by the procedure of Eijkman (25)

To a well-stirred suspension of 50 g. (0.375 mole) of aluminum chloride in 60 g. (0.77 mole) of benzene, there was added dropwise, 30 g. (0.3 mole) of γ-valerolactone. A vigorous reaction with evolution of hydrogen chloride began at once. The mixture was cooled occasionally to keep the reaction under control. After all the lactone had been added, the mixture was heated in a water bath for 25 minutes. It was cooled and poured into a mixture of 100 g. of ice and 100 g. of concentrated hydrochloric acid. The benzene layer was diluted with ether, extracted with dilute hydrochloric acid, washed with water and distilled in vacuo. There was obtained 32.5 g. (61%) of colorless, oily liquid of boiling point 123-126° (0.5 mm.). It was insoluble in water, but dissolved in sodium bicarbonate solution with evolution of carbon dioxide.

Eijkman (25) used the same quantities of reactants in his preparation, but he added the catalyst to a solution of the lactone in benzene.

### Preparation of ethyl γ-phenylvalerate and diethyl γ,γ'-phenylenedivalerate

In experiments in which attempts were made to effect

dialkylation, the crude reaction mixture was esterified to facilitate purification by distillation. The esterification procedure is as follows: The crude acid was mixed with 2.5 to 3 times its volume of absolute ethanol and about one-tenth its volume of concentrated sulfuric acid. After being refluxed for three hours, the mixture was poured into water and the esters were extracted with ether. The ether solution was extracted with saturated sodium bicarbonate solution, washed with water, dried over sodium sulfate and distilled. Yields were then determined upon the basis of the quantities of ethyl esters obtained.

(I) A mixture of 32 g. (0.18 mole) of $\gamma$-phenylvaleric acid, 20 g. (0.2 mole) of $\gamma$-valerolactone and 100 ml. of carbon disulfide was cooled in ice and stirred vigorously while 53.2 g. (0.4 mole) of aluminum chloride was added in small portions during 20 minutes. The ice bath was removed and stirring was continued at room temperature for 24 hours. The mixture was hydrolyzed with ice and hydrochloric acid. After removal of the carbon disulfide layer, the aqueous solution was extracted with ether. The combined ether and carbon disulfide extracts were washed with dilute hydrochloric acid and then with water. Evaporation gave 31 g. of oil which was esterified with ethanol.

The mixture of esters was fractionally distilled to yield 14 g. (38%) of ethyl $\gamma$-phenylvalerate of boiling point

100-103° (1 mm.) and 7 g. (12%) of diethyl $\gamma,\gamma'$-phenylene-divalerate of boiling point 183-190° (1 mm.)

(II) A suspension of 93.1 g. (0.7 mole) of aluminum chloride in 150 ml. of carbon disulfide was vigorously stirred while a solution of 23.4 g. (0.3 mole) of benzene and 60 g. (0.6 mole) of $\gamma$-valerolactone in 50 ml. of carbon disulfide was added dropwise. The mixture became warm and hydrogen chloride was evolved. After being stirred for five hours at room temperature, the reaction mixture was heated to gentle reflux for 30 minutes, and then allowed to stand overnight. The gummy complex was broken up and the mixture was stirred and refluxed for 40 minutes.

Hydrolysis, effected in the usual manner, was followed by ether extraction. Part of the product was lost when the ether solution was spilled. Evaporation of the ether extract gave 21 g. of an acidic gum which was esterified directly.

Upon distillation, the ester mixture gave 4.5 g. (8%) of ethyl $\gamma$-phenylvalerate boiling at 104-110° (1 mm.) and 10.5 g. (11%) of diethyl $\gamma,\gamma'$-phenylene-divalerate of boiling point 185-195° (1 mm.).

There remained 5-6 g. of clear brown residue. This slowly dissolved when refluxed with 50 ml. of 25% sodium hydroxide solution. Acidification of the clear solution caused the precipitation of a gum which was extracted with ether. Evaporation of the ether extract gave 5 g. of an acidic glass

of neutral equivalent 154. Attempts to purify it by recrystal-
lization were fruitless. It is considered likely that this
material was the result of trialkylation. If this be the case,
the yield of trialkylation product (based upon $\gamma$-valerolactone)
was 6%.

(III) A mixture of 40 g. (0.4 mole) of $\gamma$-valerolactone
and 31.2 g. (0.4 mole) of benzene was cooled to $0^\circ$ and stirred
while 66.5 g. (0.5 mole) of aluminum chloride was added in
small portions over a period of 30 minutes. The halide dis-
solved as it was added and the solution became light brown in
color and viscous. No hydrogen chloride was evolved until all
the catalyst had been introduced. Then an explosively violent
evolution of hydrogen chloride began and the reaction went
rapidly out of control. The product was lost.

(IV) A solution of 40 g. (0.4 mole) of $\gamma$-valerolactone
and 31.2 g. (0.4 mole) of benzene in 75 ml. of nitrobenzene
was cooled in a freezing mixture and stirred while 66.5 g.
(0.5 mole) of aluminum chloride was added in small portions
during 20 minutes. The catalyst dissolved and the mixture
took on a yellow color. Inasmuch as no action was observed,
the freezing mixture was removed. After about 10 minutes a
slow evolution of hydrogen chloride began. The mixture was
stirred at room temperature for 18 hours and then heated at
80-90$^\circ$ for 2 hours. The usual hydrolysis was followed by
steam distillation to remove nitrobenzene. The residue was

taken up in saturated sodium bicarbonate solution and
extracted with ether. Acidification and ether extraction
gave 27 g. of thick, brown oil. This was converted to a
mixture of ethyl esters. Distillation gave 13 g. (16%) of
ethyl $\gamma$-phenylvalerate boiling at 104-108$^{\circ}$ (1 mm.) and 11.5
g. (17%) of diethyl $\gamma, \gamma'$-phenylene-divalerate of boiling
point 183-187$^{\circ}$ (1 mm.).

(V)   A solution of 40 g. (0.4 mole) of $\gamma$-valerolactone
and 31.2 g. (0.4 mole) of benzene in 70 ml. of carbon di-
sulfide was cooled in ice and stirred while 66.5 g. (0.5
mole) of aluminum chloride was added in six portions over a
period of 20 minutes. Very little hydrogen chloride was
evolved until all the catalyst had been introduced. Stir-
ring was continued for two hours at 0$^{\circ}$ and then for four
hours at room temperature. After standing overnight, the
mixture was stirred and heated at 90-100$^{\circ}$ for 40 minutes.
Hydrolysis and ether extraction gave 60 g. of brown syrup
which was esterified.

Distillation of the mixture of esters gave 31 g. (38%)
of ethyl $\gamma$-phenylvalerate of boiling point 97-104$^{\circ}$ (1 mm.)
and 32 g. (48%) of diethyl $\gamma, \gamma'$-phenylene-divalerate boil-
ing at 175-183$^{\circ}$ (1 mm.).

The information obtained in the foregoing experiments
is summarized in Table I.

Table I

Alkylations with $\gamma$-valerolactone

| Exp. No. | Reactants Lactone (moles) | Benzene (moles) | Solvent (ml.) | Aluminum chloride (moles) | Products[a] |
|---|---|---|---|---|---|
| I | 0.2 | none[b] | 100 $CS_2$ | 0.4 | 38% A 12% B |
| II | 0.6 | 0.3 | 150 $CS_2$ | 0.7 | 8% A[c] 11% B |
| III | 0.4 | 0.4 | none | 0.5 | ----- [d] |
| IV | 0.4 | 0.4 | 75 $C_6H_5NO_2$ | 0.5 | 16% A 17% B |
| V | 0.4 | 0.4 | 70 $CS_2$ | 0.5 | 38% A 48% B |

[a]The yields were calculated from the amounts of ethyl $\gamma$-phenylvalerate (A) and diethyl $\gamma,\gamma'$-phenylene-divalerate (B) recovered subsequent to esterification of the crude reaction products.

[b] $\gamma$-Phenylvaleric acid (0.18 mole) used instead of benzene.

[c]Six per cent of a substance that may have been trialkylation product was obtained in this experiment.

[d]The reaction went out of control and the products were lost.

Carefully purified ethyl $\gamma$-phenylvalerate had the following physical constants: boiling point 108-109° (1 mm.), $d^{25}_4$ 0.9850, $n^{25}_D$ 1.4898. Levene and Marker (55) report boiling point 112° (1 mm.) and $d^{25}_4$ 0.985 for the levo-form of the ester.

The physical constants for pure diethyl $\gamma,\gamma'$-phenylenedivalerate were as follows: boiling point 165-169° (0.5 mm.), $d^{25}_4$ 1.0212, $n^{25}_D$ 1.4914.

Anal. Calcd. for $C_{20}H_{30}O_4$: $Mr_D$, 94.62; saponification equivalent, 167; C, 71.9; H, 9.04. Found: $Mr_D$, 94.84; saponification equivalent, 169, 171; C, 72.2; H, 9.37.

## Saponification of ethyl $\gamma$-phenylvalerate

A solution of 30.9 g. (0.15 mole) of ethyl $\gamma$-phenylvalerate and 14 g. (0.35 mole) of sodium hydroxide in 60 ml. of 50% ethanol was refluxed for three hours. The mixture was worked up in the usual way to yield 23 g. (86%) of $\gamma$-phenylvaleric acid of boiling point 120-121° (0.5 mm.), $d^{25}_4$ 1.0474, $d^{15}_{15}$ 1.0556, $n^{25}_D$ 1.5113. Eijkman (25) reported $d^{15}_{15}$ 1.0554 for his preparation. For $\gamma$-phenylvaleric acid prepared from 3-phenylbutyl bromide, Levene and Marker (55) reported $d^{25}_4$ 1.040.

p-Bromophenacyl $\gamma$-phenylvalerate. In accordance with the procedure of Shriner and Fuson (76), 1 ml. of $\gamma$-phenylvaleric acid and 1 g. of p-bromophenacyl bromide gave the desired derivative as large, shining, white leaflets. The melting point was 76° after recrystallization from dilute methanol.

Anal. Calcd. for $C_{19}H_{19}O_3Br$: Br, 21.3. Found: Br, 21.1.

Proof that $\gamma$-phenylvaleric acid prepared by the Friedel and Crafts reaction was identical with the compound prepared by other methods (50, 55, 57, 84) was afforded by ring closure to the known 4-methyl-1-tetralone. The previously reported semicarbazone was then prepared from this compound.

4-Methyl-1-tetralone. In accordance with the procedure of Kloetzel (50), 10.5 g. of $\gamma$-phenylvaleric acid was heated with 54 ml. of 80% sulfuric acid for 2.5 hours at 95-100°. The resulting solution was poured into 160 ml. of water and this was extracted with ether. The ether extract was washed with normal sodium hydroxide and then with water. Distillation of the dried ether solution gave 5 g. of 4-methyl-1-tetralone of boiling point 103° (1 mm.) and $n_D^{19}$ 1.5610. Comparable physical constants for this compound are reported to be boiling point 110-111° (1 mm.) (50) and $n_D^{19}$ 1.5620 (84).

4-Methyl-1-tetralone semicarbazone. The semicarbazone was prepared from 1 g. of 4-methyl-1-tetralone using the procedure of Shriner and Fuson (76, p. 145). Recrystallization

from dilute ethanol gave tiny, shining, white leaflets of
melting point 207-209$^o$. The melting point of this compound
has been reported as 210$^o$ (57), 204$^o$ (84) and 209-211$^o$ (50).

Saponification of diethyl $\gamma, \gamma'$-phenylene-divalerate

To a solution of 16 g. (0.4 mole) of sodium hydroxide
in 60 ml. of 50% ethanol there was added 30.1 g. (0.09 mole)
of diethyl $\gamma, \gamma'$-phenylene-divalerate. The mixture was boiled
under reflux for three hours. It was worked up in the
customary fashion to yield 24 g. of a light brown gum of
neutral equivalent 149. The calculated value for the neutral
equivalent of $\gamma, \gamma'$-phenylene-divaleric acid is 139. The
gum formed a sticky, semi-crystalline mush on long standing.
Attempts to obtain the compound in a satisfactorily crystal-
line state failed.

# PREPARATION OF 1,4-PENTANEDIOL

## Review of the Literature

1,4-Pentanediol was first prepared by the reduction of
3-acetopropanol in aqueous solution with sodium amalgam
(18, 32, 56). More recent workers have usually employed
$\gamma$-valerolactone as the starting material. Chemical reducing
agents that have been used are sodium and ethanol (75),
acetic acid and a toluene suspension of sodium (54), and 1%
sodium amalgam in 10% sodium carbonate solution (44). These
methods of preparation have various disadvantages. Working
in aqueous solution complicates the recovery of the glycol
because of its high solubility in water. For example,
$C_0$lman and Perkin (18) reported that 20 to 30 ether extrac-
tions are insufficient to recover all the glycol and that
careful and efficient fractionation is necessary to separate
the product from traces of alcohol and water. Furthermore,
it would appear that strongly basic reducing agents may
have a deleterious effect upon the lactone. Thus, Hückel
and Gelmroth (44) obtained only a 50% yield of 1,4-pentanediol
and 45% of higher boiling material in their preparation.

The advent of copper-chromium oxide as a catalyst for
the hydrogenation of esters to the corresponding alcohols
has made 1,4-pentanediol more easily available. Folkers and

Adkins (31) have prepared the glycol in 78% yield from
$\gamma$-valerolactone. The reaction was carried out without solvent
at 250° and 200 atmospheres' pressure. They also isolated 8%
of n-amyl alcohol. Under the same conditions of temperature
and pressure, ethyl levulinate in dioxane or ethanol solution
gave 60% of 1,4-pentanediol (40).

The catalytic methods have numerous advantages. Clean,
easily purified reaction mixtures are obtained. Working
without solvents simplifies the recovery of the products.
The yields are usually good or can be made so by proper
selection and control of the experimental conditions.

## Reduction of $\gamma$-Valerolactone

### Effect of temperature upon the reaction

(I) The charge consisted of 100 g. (1 mole) of $\gamma$-valero-
lactone and 6 g. of copper-chromium oxide. The initial hydrogen
pressure was 3400 p.s.i. Reduction began at about 225 degrees
with a gauge pressure of 4520 p.s.i., proceeded rapidly at
240-250° and was completed 40 minutes after hydrogenation
commenced. The maximum temperature reached was 254°. Distilla-
tion of the filtered reaction mixture gave 86.5 g. (83%) of
1,4-pentanediol boiling at 125° (16 mm.). The crude reaction
mixture had an odor of 2-methyltetrahydrofuran but none could
be isolated by distillation at atmospheric pressure.

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(II)   A mixture of 100 g. (1 mole) of $\gamma$-valerolactone and 6 g. of copper chromium oxide was hydrogenated with an initial hydrogen pressure of 3120 p.s.i. Absorption of hydrogen began at about 220° and stopped 35 minutes later. The maximum temperature reached was 270°. Upon distillation of the filtered product a fraction was obtained which boiled at 73-88° under atmospheric pressure. This contained water and had a strong odor of 2-methyltetrahydrofuran. The residue was distilled under diminished pressure to yield 10.5 g. boiling from 40° to 124° (16 mm.) and 78 g. (75%) of 1,4-pentanediol of boiling point 124-127° (16 mm.).

(III)   $\gamma$-Valerolactone (100 g., 1 mole) was reduced in the presence of 9 g. of copper-chromium oxide under an initial hydrogen pressure of 3300 p.s.i. The maximum temperature attained was 290°. Distillation of the filtered mixture gave 32 g. of mobile liquid of boiling range, 70-120°. This fraction contained a little water and a strong odor of 2-methyltetrahydrofuran was noted. The remaining material was distilled in vacuo. A fraction boiling from 48° to 124° was discarded. 1,4-Pentanediol was obtained as 33.5 g. (32%) of colorless, viscous liquid of boiling point, 124-127° (16 mm.).

## Isolation and identification of 2-methyltetrahydrofuran

The low boiling fractions (b.p. 70-100° at atmospheric pressure) from several preparations of 1,4-pentanediol were collected and dried with anhydrous potassium carbonate for

several days. The material was refluxed with sodium for three hours and finally distilled from sodium. The material which boiled at 78-80° had the characteristic odor of 2-methyltetrahydrofuran. Other physical constants were found to be $d_4^{20}$ 0.8548 and $n_D^{20}$ 1.406. Zelinskii and Shuikin (93) give the following properties for 2-methyltetrahydrofuran: boiling point 78.5-80° (746 mm.), $d_4^{20}$ 0.8552, and $n_D^{20}$ 1.407.

A solid white cake remained in the distilling flask. This was cautiously treated with small portions of water until it dissolved. A considerable quantity of oily liquid separated from the aqueous solution. It is quite possible that this was a mixture of amyl alcohols which had been converted to the alkoxides by treatment with sodium. It will be recalled that Folkers and Adkins (31) obtained an 8% yield of n-amyl alcohol in addition to 1,4-pentanediol from the copper-chromium oxide catalyzed reduction of $\gamma$-valerolactone.

## Reduction of Ethyl Levulinate

A mixture of 100.8 g. (0.7 mole) of ethyl levulinate and 8 g. copper-chromium oxide was hydrogenated at an initial pressure of 3100 p.s.i. The reduction apparently took place in two stages. An extremely rapid absorption of hydrogen took place at about 160°. Rapid reaction was again observed at 230-240°. Absorption of hydrogen stopped 25 minutes after

the reaction began. The reaction mixture was filtered and distilled in vacuo to yield 52 g. (72%) of 1,4-pentanediol boiling at 123-125°/16 mm.

## Reduction of Levulinic Acid

Brown (4) hydrogenated levulinic acid over copper-chromium oxide at 100 atmospheres and 270° to obtain 62% of $\gamma$-valerolactone and 21% of 1,4-pentanediol. It was felt that an increase in pressure might improve the yield of the glycol at the expense of the lactone.

The charge consisted of 92.8 g. (0.8 mole) of distilled levulinic acid and 8 g. of copper-chromium oxide. The initial hydrogen pressure was 200 atmospheres. Reduction, which began at 190° with a gauge pressure of 267 atmospheres, took place in two steps. About 0.9 mole of hydrogen was taken up at 245° and an equal quantity at 300°. The total time for completion of the reaction (as evidenced by cessation of hydrogen absorption) was one and one-third hours and the maximum temperature reached was 304°.

Fractionation of the filtered product gave 9 g. (11%) of $\gamma$-valerolactone (b.p. 89-92° at 16 mm.) and 36.5 g. (44%) of 1,4-pentanediol (b.p. 122-124° at 15 mm.). A forerun of 18 g. (b.p. 80-103° at atmospheric pressure) contained water and had a strong odor of 2-methyltetrahydrofuran.

## PREPARATION OF 1,4-DI-(2-CYANOETHOXY)-PENTANE AND STRUCTURALLY RELATED COMPOUNDS

### Addition of Acrylonitrile to Alcohols and Glycols

The first observation of the base-catalyzed addition of acrylonitrile to the hydroxyl group of alcohols to form a 2-cyanoethyl ether was probably that of Koelsch (51). Credit for prior publication must, however, go to Bruson and Riener (14).

Koelsch (51), in the course of studies on the Michael condensation of acrylonitrile with various active methylene compounds, observed that when the reaction was carried out in ethanol solution, $\beta$-ethoxypropionitrile was isolated in high yield. Bruson and Riener (14) undertook systematic studies of the reaction and extended it to a number of glycols, isolating, of course, the expected bis-(2-cyanoethyl)-ethers. It has been shown further, that the reaction yields the 2-cyanoethyl ethers of ether alcohols such as 2-methoxyethanol (6, 8, 82), alicyclic alcohols such as cyclohexanol and related compounds (7, 82), and araliphatic and heterocyclic alcohols such as benzyl alcohol (82) and tetrahydrofurfuryl alcohol (6, 8, 82).

The reaction has been carried out with a number of simple aliphatic primary and secondary alcohols (17, 45, 82), in each

case the desired 2-cyanoethyl ether being obtained. Acrylonitrile has been shown to react with water under the conditions of the reaction to yield di-(2-cyanoethyl)-ether (14, 41), presumably by way of ethylene cyanohydrin as the intermediate compound (14). A recent patent (85) reports the reaction of acrylonitrile with aqueous formaldehyde in the presence of sodium hydroxide to yield 2-(hydroxymethoxy)-propionitrile and di-(2-cyanoethoxy)-methane. The formaldehyde apparently reacts as the hydrate.

The addition of acrylonitrile appears to be fairly general with primary and secondary alcohols and high yields of the $\beta$-alkoxypropionitriles are obtained. Tertiary butyl alcohol, however, has been shown (5, 12, 13, 14) to be inert toward acrylonitrile in the presence of bases and can be used as a solvent in the reaction. It has been observed (82) further, that secondary alcohols give lower yields than primary alcohols.

No reaction takes place between alcohols and acrylonitrile in the absence of a catalyst (82). Sodium alkoxides (14, 51), 40% aqueous potassium hydroxide (14), 38-40% trimethylbenzyl-ammonium hydroxide (14, 82), and metallic sodium (17) have been employed to catalyze the reaction.

The reaction undoubtedly reaches an equilibrium condition,

$$ROH + CH_2{:}CHCN \xrightarrow{\text{base}} ROCH_2CH_2CN,$$

inasmuch as unreacted starting materials can be isolated after

neutralization of the catalyst (82). The fact that iso-
propyl alcohol gives a lower yield of addition product than
n-propyl alcohol has suggested that the equilibrium position
is less favorable in the case of a secondary alcohol (82).

## Preparation of $\beta$-Alkoxypropionitriles

Early attempts to convert 1,4-di-(2-cyanoethoxy)-pentane
to the corresponding acid indicated the wisdom of a systematic
investigation of the hydrolysis of $\beta$-alkoxypropionitriles.
Accordingly, in addition to the preparation of 1,4-di-(2-
cyanoethoxy)-pentane, the synthesis of a number of structurally
similar compounds is described.

### Procedure

With the exception of $\beta$-ethoxypropionitrile, the mono-
functional $\beta$-alkoxypropionitriles were prepared in accordance
with the procedure of Utermohlen (82). The alcohol (1 to 1.5
moles) was stirred under reflux with 3 ml. of aqueous 40%
potassium hydroxide solution while a molecularly equivalent
quantity of acrylonitrile was added at such a rate that the
temperature did not rise above 35-45°. The reaction vessel
was cooled in water when necessary. The mixture was stirred
for several hours after all the acrylonitrile had been added,
acidified with glacial acetic acid and distilled in vacuo.

The general method of Bruson and Riener (14) was used for the preparation of the cyanoethyl derivatives of the glycols. This was essentially the same as that given above except that the amount of catalyst used was 5-7% of the weight of the glycol and two molecular equivalents of acrylonitrile were added. The mixtures were neutralized with hydrochloric acid. Any variations in the general procedure are given in connection with the individual experiments.

## Monofunctional $\beta$-alkoxypropionitriles of the type $ROCH_2CH_2CN$

$\beta$-Ethoxypropionitrile. In accordance with the procedure of Koelsch (51), a piece of sodium the size of a pea was dissolved in 101 g. (2.2 moles) of absolute ethanol. To the resulting solution, 106 g. (2 moles) of acrylonitrile was added in six portions with frequent shaking. The addition required thirty minutes and the mixture was kept cool by immersion in ice-water. The flask was stoppered and allowed to stand at room temperature for a day. Neutralization with one ml. of glacial acetic acid followed by distillation gave 187 g. (94.5%) of $\beta$-ethoxypropionitrile of boiling point 168-171°. Koelsch (51) reported a yield of 89% and a boiling point of 170-173°.

$\beta$-n-Propoxypropionitrile. A mixture of 90 g. (1.5 mole) of n-propyl alcohol and 3 ml. of 40% potassium hydroxide was

treated with 79.5 g. (1.5 moles) of acrylonitrile. Neutraliza-
tion of the catalyst by means of glacial acetic acid followed
by distillation gave 142 g. (84%) of $\beta$-n-propoxypropionitrile
of boiling point 87-89$^\circ$ (24 mm.) or 84$^\circ$ (19 mm.), $d_4^{20}$ 0.8988,
$d_{20}^{20}$ 0.9006, $n_D^{20}$ 1.4131.

Anal. Calcd. for $C_6H_{11}ON$: N, 12.4. Found: N, 12.2.

$\beta$-iso-Propoxypropionitrile. Acrylonitrile (79.5 g.,
1.5 moles), 90 g. (1.5 moles) of iso-propyl alcohol and 3 ml.
of catalyst gave, subsequent to acidification and distilla-
tion, 125 g. (74%) of $\beta$-iso-propoxypropionitrile boiling at
81-82$^\circ$ (24 mm.). Utermohlen (82) obtained a 69% yield of
product of boiling point 82.5$^\circ$ (25 mm.).

$\beta$-n-Butoxypropionitrile. In like manner, 74 g. (1 mole)
of n-butyl alcohol and 53 g. (1 mole) of acrylonitrile gave
108 g. (85%) of $\beta$-n-butoxypropionitrile boiling at 98% (20
mm.). Utermohlen (82) obtained an 86% yield and found the
boiling point to be 98$^\circ$ (20 mm.).

$\beta$-iso-Butoxypropionitrile. From the reaction of 74 g.
(1 mole) of iso-butyl alcohol with 53 g. (1 mole) of acryloni-
trile in the presence of 3 ml. of 40% potassium hydroxide,
there was obtained, subsequent to acidification and distilla-
tion, 103 g. (81%) of $\beta$-iso-butoxypropionitrile of boiling
point 88-90$^\circ$ (19 mm.) or 91$^\circ$ (20 mm.), $d_4^{20}$ 0.8821, $d_{20}^{20}$
0.8836, $n_D^{20}$ 1.4143.

Anal. Calcd. for $C_7H_{13}ON$; N, 11.0. Found: N, 11.1.

β-sec-Butoxypropionitrile. When 53 g. (1 mole) of acrylonitrile was added to 74 g. (1 mole) of sec-butyl alcohol in the presence of 3 ml. of catalyst, a sluggish reaction took place. Very little heat was evolved so that cooling was not necessary to keep the temperature below $40^\circ$. The reaction mixture was worked up in the usual way to yield 100.5 g. (79%) of β-sec-butoxypropionitrile of boiling point $90^\circ$ (19 mm.), $d^{20}_4$ 0.8880, $d^{20}_{20}$ 0.8896, $n^{20}_D$ 1.4156.

Anal. Calcd. for $C_7H_{13}ON$; N, 11.0. Found: N, 11.3.

β-iso-Amyloxypropionitrile. In the customary manner, 85 g. (0.965 mole) of iso-amyl alcohol and 53 g. (1 mole) of acrylonitrile gave 112 g. (82%) of β-iso-amyloxypropionitrile of boiling point $99^\circ$ (13 mm.), $d^{20}_4$ 0.8818, $d^{20}_{20}$ 0.8834, $n^{20}_D$ 1.4218.

Anal. Calcd. for $C_8H_{15}ON$: N, 9.93. Found: N, 10.1.

β-sec-Amyloxypropionitrile. Acrylonitrile (53 g., 1 mole) was added dropwise to a vigorously stirred mixture of 88 g. (1 mole) of sec-amyl alcohol and 3 ml. of 40% potassium hydroxide. The reaction was slow in starting so 3 ml. more of the 40% potassium hydroxide solution was added after half of the acrylonitrile had been introduced. External cooling was not necessary and the temperature rose to only $42^\circ$. The mixture was stirred for seven hours at room temperature and then allowed to stand overnight. The potassium hydroxide was neutralized by the addition of 6 ml. of glacial acetic acid.

Distillation under diminished pressure gave 99 g. (70%) of colorless liquid, boiling point 98° (16 mm.), $d^{20}_4$ 0.8844, $d^{20}_{20}$ 0.8862, $n^{20}_D$ 1.4205.

Anal. Calcd. for $C_8H_{15}ON$: N, 9.93. Found: N, 9.85.

β-Allyloxypropionitrile. The usual procedure was followed in the reaction of 58 g. (1 mole) of allyl alcohol with 53 g. (1 mole) of acrylonitrile. The yield was 94 g. (85%) of product of boiling point 95° (24 mm.) or 92° (19 mm.), $d^{20}_4$ 0.9380, $d^{20}_{20}$ 0.9396, $n^{20}_D$ 1.4330.

Anal. Calcd. for $C_6H_9ON$: N, 12.6. Found: N, 12.4.

β-(2-Methoxyethoxy)-propionitrile. In accordance with Utermohlen's procedure (82), 95 g. (1.25 moles) of ethylene glycol monomethyl ether was allowed to react with 66.2 g. (1.25 moles) of acrylonitrile to yield 136 g. (85%) of the desired compound boiling at 107-109° (13 mm.). Utermohlen (82) reported a yield of 87% and the boiling point as 98-100° ( 9 mm.) in his preparation.

The β-alkoxypropionitriles are colorless liquids with faint, pleasant odors. The physical constants of some of them are compared in Table II, together with explanatory notes.

Bifunctional β-alkoxypropionitriles of the type $X(CH_2CH_2CN)_2$

Di-(2-cyanoethyl)-ether. The reaction of 71 g. (1 mole) of ethylene cyanohydrin with 56 g. (1.05 moles) of acrylonitrile gave 77 g. (62%) of di-(2-cyanoethyl)-ether boiling at 152-

$156^\circ/3$ mm. The boiling point is reported (14) to be 161-162$^\circ$ (5 mm.).

Table II

Physical constants of some $\beta$-alkoxypropionitriles
$ROCH_2CH_2CN$

| R | Boiling point | | $d^{20}_{20}$ | $n^{20}_D$ |
| | $^\circ$C. | mm. | | |
|---|---|---|---|---|
| Methyl[a,b] | 85.5 | 49 | 0.9420 | 1.4032 |
| Ethyl[a] | 77-78 | 25 | 0.9062 | 1.4068 |
| n-Propyl | 87-89 | 24 | 0.9006 | 1.4131 |
| iso-Propyl[a] | 82.5 | 25 | 0.8969 | 1.4089 |
| n-Butyl | 98 | 20 | 0.8863 | 1.4180 |
| iso-Butyl | 91 | 20 | 0.8836 | 1.4143 |
| sec-Butyl | 90 | 19 | 0.8896 | 1.4156 |
| iso-Amyl | 99 | 13 | 0.8834 | 1.4218 |
| sec-Amyl | 98 | 16 | 0.8862 | 1.4205 |
| Allyl | 95 | 24 | 0.9396 | 1.4330 |
| 2-Methoxyethyl[a] | 98-100 | 9 | -------- | ----- |

[a]Previously prepared. The physical constants are those given by Utermohlen (82).

[b]Not prepared in the present study.

1,2-Di-(2-cyanoethoxy)-ethane. The reaction of 62 g. (1 mole) of ethylene glycol with 117 g. (2.2 moles) of acrylonitrile, carried out in the usual way (14), gave 63 g. (37%) of product of boiling point 158-162$^o$ (1 mm.). Bruson and Riener (14) give 158$^o$ (2 mm.) as the boiling point.

1,3-Di-(2-cyanoethoxy)-propane. Trimethylene glycol (45.6 g., 0.6 mole) reacted with 63.6 g. (1.2 moles) of acrylonitrile to give 98 g. (90%) of the expected dinitrile having the boiling point 165-170$^o$ (1 mm.). The previously reported boiling point is 165$^o$ (1 mm.) (14).

Di-(2-/2 -cyanoethoxy/-ethyl)-ether. In the usual way, 100 g. (0.94 mole) of diethylene glycol was allowed to react with 106 g. (2 moles) of acrylonitrile to yield 129 g. (65%) of the desired compound of boiling point 190-200$^o$ (1-2 mm.). The boiling point given in the literature (14) is 190$^o$ (1 mm.).

1,4-Di-(2-cyanoethoxy)-pentane. (I) A mixture of 62 g. (0.6 mole) of 1,4-pentanediol and 3 ml. of 40% aqueous potassium hydroxide was vigorously stirred and cooled in water while 69 g. (1.3 mole) of acrylonitrile was added dropwise at such a rate that the temperature did not rise above 35$^o$. Stirring was continued at room temperature for five hours. After standing overnight, the mixture was diluted with twice its volume of ether and extracted twice with 60 ml. portions of normal hydrochloric acid and once with water. The washings were extracted once with 50 ml. of ether. The combined ether

extracts were dried with anhydrous sodium sulfate and distilled under diminished pressure. After a forerun of 7 g., 104 g. (83%) of 1,4-di-(2-cyanoethoxy)-pentane was obtained as a colorless liquid of boiling point 157° (1 mm.), $\underline{n}_D^{28}$ 1.4478, $\underline{d}_4^{28}$ 1.005.

_Anal._ Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.3 Found: N, 13.3,13.4.

(II) To a mechanically stirred mixture of 61 g. (0.59 mole) of 1,4-pentanediol and 3 ml. of trimethylbenzylammonium hydroxide (38% aqueous solution), 66.2 g. (1.25 moles) of acrylonitrile was added dropwise. Very little heat was evolved. After five hours' stirring the mixture was clear and colorless, had a strong odor of acrylonitrile, and was completely soluble in water. Upon the addition of 3 ml. of 40% potassium hydroxide the mixture turned light yellow and the temperature rose rapidly to 50-60°. It was cooled in water and stirred overnight. Neutralization of the catalyst, followed by distillation, gave 86 g. (70%) of 1,4-di-(2-cyanoethoxy)-pentane.

(III) To 53 g. (0.51 mole) of 1,4-pentanediol there was added a solution prepared by dissolving a piece of sodium the size of a pea in a little absolute ethanol. It was stirred and cooled in water while 29 g. (0.55 mole) of acrylonitrile was added dropwise. After ten hours' stirring at room temperature 26.5 g. (0.5 mole) more of acrylonitrile was added

and stirring was continued for three hours. The mixture was allowed to stand at room temperature for eight hours. Ether was added and the solution was extracted with dilute hydrochloric acid, then with sodium bicarbonate solution, and finally dried over sodium sulfate. Distillation gave 70 g. (66%) of 1,4-di-(2-cyanoethoxy)-pentane.

1,4-Di-(2-cyanoethoxy)-pentane is an odorless liquid, soluble in organic solvents, but not appreciably soluble in water. Attempts to prepare a solid derivative of the dinitrile by treatment with alkaline hydrogen peroxide (14, 21, 69), condensation with thioglycollic acid and dry hydrogen chloride (19), or conversion to a phlorophenone (42), yielded only oils. A solid iminoester hydrochloride was obtained, however, by the usual methods (66, 67).

Bis-(ethyliminoester hydrochloride) of 1,4-Di-(2-cyano-ethyoxy)-pentane. A mixture of 42 g. (0.2 mole) of 1,4-di-(2-cyanoethoxy)-pentane and 23 g. (0.5 mole) of absolute ethanol (distilled from sodium ethoxide) was treated at $-10^{\circ}C$. with excess, dry hydrogen chloride. The resulting thick syrup set to a mass of white crystals after standing for a week in the refrigerator. After removal of excess ethanol and hydrogen chloride in vacuo the product weighed 75 grams (theoretical yield). A sample taken for analysis was pulverized, washed well with anhydrous ether and dried in

a vacuum desiccator over sulfuric acid.  The result was
a white powder which melted at 103-104$^\circ$ with decomposition
and gas evolution.

Anal. Calcd. for $C_{15}H_{32}O_4N_2Cl_2$:  Cl, 18.89.  Found:
Cl, 18.84, 18.94.

PREPARATION OF 1,4-DI-(3-AMINOPROPOXY)-PENTANE AND DIAMINE SALTS

Review of Pertinent Literature

Nitriles are readily hydrogenated to primary amines over Raney nickel catalyst (1, p. 53). However, an important side reaction is the formation of secondary amines at the expense of primary amines (43, 74, 82, 87, 88, 89). The process can be summarized by the following equations:

$$RC{:}N + H_2 \longrightarrow RCH{:}NH$$

$$RCH{:}NH + H_2 \longrightarrow RCH_2NH_2$$

$$RCH{:}NH + RCH_2NH_2 + H_2$$

$$\longrightarrow (RCH_2)_2NH + NH_3$$
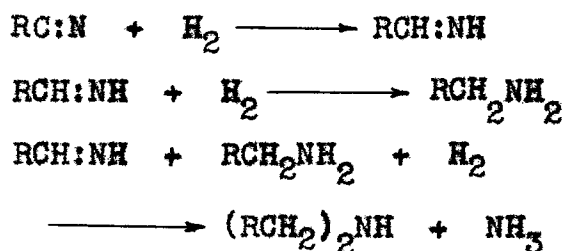
If the reaction is carried out in the presence of ammonia, the last reaction is suppressed and excellent yields of primary amine can usually be obtained (43, 74, 82, 87).

Little work has been done on the reduction of $\beta$-alkoxypropionitriles. Whitmore and co-workers (87) hydrogenated di-(2-cyanoethyl)-ether and obtained a 25% yield of a compound which they assumed to be di-(3-aminopropyl)-ether. It was subsequently shown by Wiedeman and Montgomery (88) that the compound reported by Whitmore, et al., was very likely 3-aminopropanol. By carrying out the reduction of di-(2-cyano-ethyl)-ether in the presence of anhydrous ammonia the latter workers were able to isolate 20% of di-(3-aminopropyl)-ether

and 35-40% of 3-aminopropanol.

Utermohlen (82) prepared nine simple 3-alkoxypropylamines by hydrogenation of the corresponding β-alkoxypropionitriles in the presence of liquid ammonia and Raney nickel. The yields varied from 25% to 78%. The formation of secondary amine was apparently responsible for some of the lower yields (around 50%). β-Benzyloxypropionitrile gave the expected amine, 3-benzyloxypropylamine, in only 25% yield. In this case considerable cleavage was reported to have taken place at the oxygen atom. This is not surprising inasmuch as benzyl ethers in general are readily cleaved by hydrogen over Raney nickel to yield toluene and an alcohol (83). Furthermore, the formation of 3-aminopropanol in the reduction of di-(2-cyanoethyl)-ether, as reported by Wiedemann and Montgomery (88), can only be accounted for by a similar cleavage. It would appear, then, that the hydrogenation of β-alkoxypropionitriles may be complicated by rupture of the ether linkage in addition to the usual side reactions.

Reduction of 1,4-Di-(2-cyanoethoxy)-pentane

In the 500 ml. hydrogenation bomb there was placed 70 g. (0.33 mole) of 1,4-di-(2-cyanoethoxy)-pentane and 4 g. of Raney nickel catalyst. The bomb was cooled to -50° in a bath of dry ice and acetone (in order to prevent excessive

loss of ammonia by evaporation); 30 ml. of liquid ammonia was added and the bomb was sealed. Hydrogen was introduced to an initial pressure of 200 atmospheres. Reduction began at about 80°, proceeded rapidly at 115-120°, and was complete in 50 minutes. The maximum temperature reached was 122°. The bomb was emptied and rinsed with alcohol. Distillation of the combined product and rinsings, after removal of the catalyst, gave 55.5 g. (77%) of 1,4-di-(3-aminopropoxy)-pentane boiling at 132-135° (2 mm.),

$d_4^{24}$ 0.9448, $n_D^{24}$ 1.4596.

__Anal.__ Calcd. for $C_{11}H_{26}O_2N_2$: N.E., 109.2; N, 12.8.
Found: N. E., 110.4, 110.0; N, 12.6.

A forerun of approximately 5 g., boiling over a 20° range, was obtained. The residue decomposed extensively at 200-230° when an attempt was made to distill it under a pressure of 1 mm. Another experiment using hydrogen at an initial pressure of 130 atmospheres gave substantially the same yield of amine (82%).

1,4-Di-(3-aminopropoxy)-pentane is a colorless liquid which exhibits only faintly the odor which is characteristic of amines. It is soluble in organic solvents and miscible with water in all proportions. Its aqueous solution is strongly basic to phenolphthalein (a 5% solution has a pH in excess of 11) and can be titrated to a sharp end point using

methyl red indicator. Upon being exposed to the air, the amine rapidly absorbs carbon dioxide and eventually forms a sticky gum. An attempt to prepare the hydrochloride of this amine by precipitation from anhydrous ether solution with dry hydrogen chloride gave an oil which could not be induced to crystallize. The picrate was likewise obtained as an oil.

In view of the rather interesting properties of 1,4-di-(3-aminopropoxy)-pentane, it was felt that its fatty acid salts might prove to be of some value as surface active agents. Accordingly, the preparation of a series of these salts was undertaken. Dibasic acids were included, because the diamine salts of dibasic acids are important as nylon intermediates (15).

<p align="center">Salts of 1,4-Di-(3-aminopropoxy)-pentane</p>

## Procedure

The salts were prepared in 2-3 gram quantities by the following general methods:

A. Solutions of the calculated quantities of the diamine and acid in appropriate amounts of absolute ethanol were well mixed and evaporated to dryness.

B. The calculated quantity of the solid acid was added to the diamine which had been dissolved in a little ethanol. The solution was evaporated to dryness.

C. The calculated amount of the solid acid was added to a solution of the diamine in water. The resulting mixture was evaporated to dryness.

D. Aqueous solutions of the theoretical quantities of the diamine and acid were well mixed and then evaporated to dryness.

Further details are given in connection with the individual experiments.

## Preparation of the salts

1,4-Di-(3-aminopropoxy)-pentane disulfamate. Using method B, 2.22 g. (0.0102 mole) of 1,4-di-(3-aminopropoxy)-pentane and 1.94 g. (0.02 mole) of sulfamic acid gave a colorless oil which crystallized to an extremely hygroscopic, white, waxy solid upon standing in a vacuum desiccator. The melting point was about $65^{\circ}$. When an attempt was made to recrystallize it from a mixture of absolute ethanol and ether, the substance darkened and melted at a much lower temperature.

1,4-Di-(3-aminopropoxy)-pentane diacetate. Treated by method A, 1.20 g. (0.02 mole) of acetic acid and 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane gave a sticky oil which could not be induced to crystallize even after long standing in a vacuum desiccator.

1,4-Di-(3-aminopropoxy)-pentane dipropionate. When 1.48 g. (0.02 mole) of propionic acid and 2.18 g. (0.01 mole) of

1,4-di-(3-aminopropoxy)-pentane were allowed to react in essential accordance with procedure A, there resulted a sticky oil which could not be brought to crystallization even after long standing in a vacuum desiccator over concentrated sulfuric acid.

1,4-Di-(3-aminopropoxy)-pentane dibutyrate. In accordance with procedure A, 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane was treated with 1.76 g. (0.02 mole) of butyric acid. The result was a sticky oil which was placed in a vacuum desiccator. It resisted all attempts to cause it to solidify.

1,4-Di-(3-aminopropoxy)-pentane dilevulinate. By method A, 2.32 g. (0.02 mole) of distilled levulinic acid and 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane gave a sticky gum which could not be induced to crystallize. It became dark brown in color on standing in a vacuum desiccator. A similar phenomenon has been observed in attempts to prepare ammonium levulinate by evaporating an ammonium hydroxide solution of levulinic acid.

1,4-Di-(3-aminopropoxy)-pentane dibenzoate. Benzoic acid (2.44 g., 0.02 mole) and 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane, when treated by method A, gave a gum. After long standing in a vacuum desiccator, a few crystals formed. In an attempt to cause the entire mass to solidify, the mixture was triturated with a little ether and

absolute ethanol. The crystals dissolved and an uncrystal-
lizable glass resulted.

1,4-Di-(3-aminopropoxy)-pentane oxalate. When treated
by procedure A, 1.26 g. (0.01 mole) of oxalic acid dihydrate
and 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane
gave an immediate white precipitate. This was filtered,
washed with absolute ethanol and dried to yield 3.3 g. of
white powder melting at 197-199°. Recrystallization from
dilute ethanol gave white crystals of melting point 196-198°.
This salt was the only one of the entire series which was
insoluble in absolute ethanol.

Anal. Calcd. for $C_{13}H_{28}O_6N_2$: N, 9.09. Found: N, 9.65.

1,4-Di-(3-aminopropoxy)-pentane malonate. Malonic acid
(1.04 g., 0.01 mole) and 2.18 g. (0.01 mole) of 1,4-di-
(3-aminopropoxy)-pentane gave, by procedure A, a colorless,
sticky gum which could not be caused to crystallize even on
long standing in a vacuum desiccator.

1,4-Di-(3-aminopropoxy)-pentane succinate. In accordance
with procedure A, 1.18 g. (0.01 mole) of succinic acid and
2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane gave
a colorless oil which slowly crystallized to a white solid
melting at 119-122°. Recrystallization from ether-absolute
ethanol gave a white powder of melting point 121-122°.

Anal. Calcd. for $C_{15}H_{32}O_6N_2$: N, 8.33. Found: N, 8.42.

1,4-Di-(3-aminopropoxy)-pentane glutarate. By method
B, 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane
and 1.32 g. (0.01 mole) of glutaric acid gave a gum. This
was allowed to stand in a vacuum desiccator with occasional
stirring. It did not crystallize.

1,4-Di-(3-aminopropoxy)-pentane adipate. When treated
by procedure A, 1.46 g. (0.01 mole) of adipic acid and 2.18
g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane gave a
clear glass. After long standing in a vacuum desiccator the
substance began to crystallize. This was hastened by tri-
turation with an ether-ethanol mixture. The result was
a hard, white solid melting at 136-138$^{\circ}$. It was recrystal-
lized from ether-absolute ethanol to yield a white powder of
unchanged melting point.

Anal. Calcd. for $C_{17}H_{36}O_6N_2$: N, 7.69. Found: N, 7.92.

1,4-Di-(3-aminopropoxy)-pentane sebacate. In accordance
with method A, 2.02 g. (0.01 mole) of sebacic acid and 2.18
g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane gave a
glass which solidified to a light yellow, crystalline mass
on long standing in a vacuum desiccator. It was extremely
hygroscopic and melted indefinitely at about 50$^{\circ}$. Upon re-
crystallization from a mixture of ether and absolute ethanol,
the compound separated as an oil and could not subsequently
be obtained in the solid state.

<u>1,4-Di-(3-aminopropoxy)-pentane maleate</u>. 1,4-Di-(3-aminopropoxy)-pentane (2.18 g., 0.01 mole) and 1.16 g. (0.01 mole) of maleic acid gave, by method B, a gum which rapidly solidified to a white substance of melting point 120-122°. Recrystallization from a mixture of absolute ethanol and ether yielded a white powder melting at 129-131°.

<u>Anal</u>. Calcd. for $C_{15}H_{30}O_6N_2$: N, 8.38. Found: N, 8.62.

<u>1,4-Di-(3-aminopropoxy)-pentane itaconate</u>. Treatment of 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane and 1.30 g. (0.01 mole) of itaconic acid by procedure C, gave a gum which resisted all efforts to cause it to crystallize.

<u>1,4-Di-(3-aminopropoxy)-pentane phthalate</u>. Using method B, 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane was treated with 1.66 g. (0.01 mole) of phthalic acid. There resulted a cream colored solid melting at 120-122°. After recrystallization from an ether-absolute ethanol mixture, a white powder of melting point 125-126° was obtained.

<u>Anal</u>. Calcd. for $C_{19}H_{32}O_6N_2$: N, 7.29. Found: N, 7.38.

<u>1,4-Di-(3-aminopropoxy)-pentane dioxalate</u>. Procedure D was followed in the treatment of 1.09 g. (0.005 mole) of 1,4-di-(3-aminopropoxy)-pentane with 1.39 g. (0.011 mole) of oxalic acid dihydrate. The result was a white solid of melting point 85-95°. Two recrystallizations from mixtures of ether and absolute ethanol gave a white powder melting at

$108\text{-}110^{\circ}$. This compound, in contrast with the normal oxalate, was easily soluble in hot absolute ethanol.

Anal. Calcd. for $C_{15}H_{30}O_{10}N_2$: N, 7.04. Found: N, 7.26.

1,4-Di-(3-aminopropoxy)-pentane dimalonate. Malonic acid (2.08 g., 0.02 mole) and 1,4-di-(3-aminopropoxy)-pentane (2.18 g., 0.01 mole) gave, by method C, a colorless glass which could not be induced to crystallize.

1,4-Di-(3-aminopropoxy)-pentane disuccinate. In accordance with procedure C, 1.09 g. (0.005 mole) of 1,4-di-(3-amino-propoxy)-pentane and 1.18 g. (0.01 mole) of succinic acid gave a colorless oil which slowly changed to a white solid of melting point $86\text{-}89^{\circ}$. Upon recrystallization from ether-absolute ethanol, a white powder melting at $92\text{-}94^{\circ}$ was obtained.

Anal. Calcd. for $C_{19}H_{38}O_{10}N_2$: N, 6.17. Found: N, 6.33.

1,4-Di-(3-aminopropoxy)-pentane diglutarate. When method C was applied to 2.18 g. (0.01 mole) of 1,4-di-(3-aminopropoxy)-pentane and 2.64 g. (0.02 mole) of glutaric acid, there resulted a colorless, sticky gum which could not be brought to crystallization.

1,4-Di-(3-aminopropoxy)-pentane diadipate. In accordance with procedure C, 1.09 g. (0.005 mole) of 1,4-di-(3-amino-propoxy)-pentane and 1.46 g. (0.01 mole) of adipic acid gave an oil. When allowed to stand in a vacuum desiccator this

slowly solidified in rosettes of glistening needles of melting point 97-99$^o$. Recrystallization from a mixture of ether and absolute ethanol gave white crystals melting at 102-103$^o$.

Anal. Calcd. for $C_{23}H_{46}O_{10}N_2$: N, 5.49. Found: N, 5.53.

1,4-Di-(3-aminopropoxy)-pentane dimaleate. Application of method C to 1.09 g. (0.005 mole) of 1,4-di-(3-aminopropoxy)-pentane and 1.16 g. (0.01 mole) of maleic acid gave an oil which, on standing overnight in a vacuum desiccator crystallized to a white solid of melting point 80-85$^o$. When an attempt was made to recrystallize it from ether-absolute ethanol, an oil separated from the cooled solution, and the compound could not be obtained in the solid state, thereafter.

1,4-Di-(3-aminopropoxy)-pentane diphthalate. Phthalic acid (1.66 g., 0.01 mole) and 1.09 g. (0.005 mole) of 1,4-di-(3-aminopropoxy)-pentane gave, by procedure B, a transparent gum which resisted attempts to cause it to crystallize.

All of these salts were deliquescent substances which were very soluble in water. The resulting solutions showed a strong tendency to foam. With the exception of the normal oxalate, they were easily soluble in absolute ethanol. They were, of course, insoluble in such solvents as ether and benzene. Although the majority of the solid compounds appeared to be amorphous, X ray examination* of the oxalate and succinate showed sharply defined powder diagrams,

* Kindly carried out by Mr. Harvey Dube.

Table III

Melting points of some salts of
1,4-di-(3-aminopropoxy)-pentane

| Salt | Melting point, °C. |
|------|--------------------|
| Disulfamate | $\underline{ca}$. 65 |
| Diacetate | oil |
| Dipropionate | oil |
| Dibutyrate | oil |
| Dilevulinate | gum |
| Dibenzoate | gum |
| Oxalate | 196-198 |
| Malonate | gum |
| Succinate | 121-122 |
| Glutarate | gum |
| Adipate | 136-138 |
| Sebacate | $\underline{ca}$. 50 |
| Maleate | 129-131 |
| Itaconate | gum |
| Phthalate | 125-126 |
| Dioxalate | 108-110 |
| Dimalonate | gum |
| Disuccinate | 92-94 |
| Diglutarate | gum |
| Diadipate | 102-103 |
| Dimaleate | 80-85 |
| Diphthalate | gum |

indicating that the derivatives were microcrystalline in nature. The physical properties of the salts are summarized in Table III. It will be noted that well-defined, solid salts were obtained only from dibasic acids having an even number of carbon atoms.

HYDROLYSIS OF 1,4-DI-(2-CYANOETHOXY)-PENTANE AND RELATED
COMPOUNDS

Review of Methods by Which $\beta$-Alkoxypropionic
Acids Have Been Prepared

The majority of the previously reported simple $\beta$-alkoxy-
propionic acids have been prepared by the hydrolysis of their
esters (29, 30, 36, 37, 61, 63, 65). The necessary esters
have usually been obtained by a metathesis between a sodium
alkoxide and a $\beta$-halogenopropionic ester (2, 23, 29, 30,
36, 37, 38, 47, 61, 62, 63, 64, 65).

$$RONa \ + \ XCH_2CH_2COOR \longrightarrow ROCH_2CH_2COOR \ + \ NaX$$

In practice, only alkoxides and esters having the same alkyl
groups have been used, presumably in order to prevent the
formation of mixtures by alcoholysis.

An alternative and more convenient method for the syn-
thesis of $\beta$-alkoxypropionates would appear to be the addition
of an alcohol to an alkyl acrylate in the presence of the
corresponding alkoxide.

$$ROH \ + \ CH_2{:}CHCOOR' \xrightarrow{\ RONa\ } ROCH_2CH_2COOR'.$$
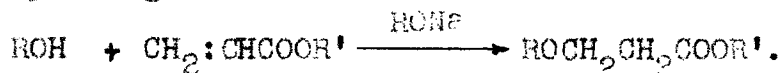
This reaction, which is analogous to the addition of alcohols
to acrylonitrile (6, 7, 8, 17, 45, 51, 82), was first ob-
served by Purdie and Marshall (68) and subsequently reported
by Goss and Ingold (35) and Koelsch (51). It was studied
rather extensively in very recently published work (70). It
seems to be generally applicable to monohydric alcohols although

In some cases the yields leave something to be desired. An advantage of this method of preparation is the fact that the alkyl groups of the alcohol and acrylic ester need not be the same (70). A comparison of the cost of the $\beta$-halogenopropionic acids with that of the commercially available alkyl acrylates further favors this reaction as a preparative method for $\beta$-alkoxypropionic esters.

An interesting and perhaps useful procedure was employed by Jones and Powers (46) in the synthesis of $\beta$-methoxypropionic acid. These workers added one mole of free $\beta$-chloropropionic acid to a solution prepared by dissolving two gram atoms of sodium in excess methanol and refluxed the resulting mixture. $\beta$-Methoxypropionic acid was liberated from the dry sodium salt by treatment with hydrochloric acid.

The literature contains a few other references to methods by which $\beta$-alkoxypropionic acids have been prepared. These, although perhaps not generally applicable, may be of interest. They will be mentioned here inasmuch as some of them will be referred to later.

$\beta$-Ethoxypropionic acid has been prepared by the oxidation of $\beta$-ethoxypropionaldehyde with atmospheric oxygen in the presence of manganous acetate and acetic acid (73) and by the high temperature reaction of diethyl ether with carbon dioxide in the presence of a catalyst (22).

$\beta$-n-propoxypropionic acid and $\beta$-iso-propoxypropionic acid
have been reported (58) as resulting from the following series
of reactions:

$$C_3H_7OCH_2CH_2COCH:C(CH_3)_2 + O_3$$

$$\xrightarrow{H_2O} C_3H_7OCH_2CH_2COCOOH + (CH_3)_2CO$$

$$C_3H_7OCH_2CH_2COCOOH \xrightarrow{O} C_3H_7OCH_2CH_2COOH + CO_2$$
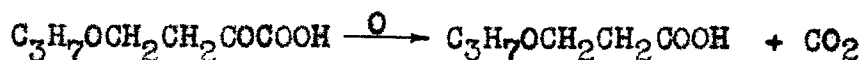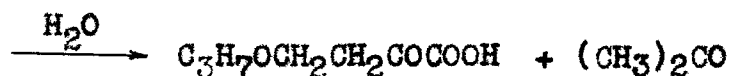
Sokolow (77) and Wislicenus (90, 91) have observed that
when a water solution of $\beta$-iodopropionic acid is heated with
freshly prepared silver oxide, there results a mixture of
$\beta$-hydroxypropionic acid, di-(2-carboxyethyl)-ether, and an
unidentified isomer of the latter acid. From the mixture of the
sodium salts of these acids, Wislicenus (90, 91) extracted
sodium $\beta$-hydroxypropionate with hot 95% ethanol. He then dis-
solved the sodium salt of di-(2-carboxyethyl)-ether in hot 90%
ethanol and reported that this salt crystallized in long, white
needles when the solution was cooled. Neither of these workers
made any attempt to isolate di-(2-carboxyethyl)-ether as the
free acid.

While the present investigation was in progress a patent
(9) was issued which described the preparation of esters of
di-(2-carboxyethyl)-ether. Di-(2-cyanoethyl)-ether was
hydrolyzed by mineral acid and the resulting mixture was
treated with an alcohol in the presence of an acidic catalyst.
Here, too, the free di-(2-carboxyethyl)-ether was not isolated.

It is worthy of note that none of these methods has been

applied to glycols in an attempt to prepare dibasic acids

of the $\beta, \beta'$-alkylenedioxy-dipropionic type. As a matter of

fact, it seems doubtful that any of the classical methods

would be entirely satisfactory for such a preparation. Except

for the single reference (9) contained in the patent litera-

ture describing the preparation of esters of di-(2-carboxy-

ethyl)-ether, the $\beta$-alkoxypropionitriles have apparently

never been considered as starting materials for the synthesis

of even the simplest $\beta$-alkoxypropionic acids. Kilpi (48)

studied the kinetics of the hydrolysis of $\beta$-methoxypropionitrile

and $\beta$-ethoxypropionitrile by hydrochloric acid in 50% ethanol

solution but did not report the products of the reaction.

Basic Hydrolysis of $\beta$-Alkoxypropionitriles

Basic hydrolysis of 1,4-di-(2-cyanoethoxy)-pentane

I. To a solution of 12 g. (0.3 mole) of sodium hydroxide
in 100 ml. of water, there was added 21 g. (0.1 mole) of 1,4-
di-(2-cyanoethoxy)-pentane. The mixture was stirred and
heated to gentle reflux for 12 hours. Acidification and
evaporation to dryness in vacuo were followed by chloroform
extraction. Evaporation of this extract gave 22 g. of light
brown oil having the neutral equivalent 177. The calculated
value for the expected dibasic acid is 124. The material
showed no tendency to crystallize.

Distillation was attempted at a pressure of 1 mm. or
less. Distillate was collected over a boiling range of $97^{\circ}$
to $200^{\circ}$. No definite fractions were observed and profound
decomposition began when the temperature of the heating bath
exceeded $135\text{-}140^{\circ}$.

II. This experiment was carried out in an attempt to
purify the hydrolysis product as its ethyl ester. The
method chosen for the esterification was one which had been
successfully employed by Drushel and Holden (24) in the
preparation of esters of $\beta$-hydroxypropionic acid.

A mixture of 21 g. (0.1 mole) of 1,4-di-(2-cyanoethoxy)-
pentane and 10 g. (0.25 mole) of sodium hydroxide in 100 ml.

53

of water was refluxed gently for eight hours. Forty milliliters
of 5.88 N sulfuric acid was added and the mixture was evaporated.
The dried residue was thoroughly extracted with 150 ml. of
absolute ethanol. To the filtrate there was added 12.8 g.
(0.08 mole) of anhydrous copper sulfate and the mixture was
gently boiled under reflux for 16 hours. After cooling and
filtration, the ethanol was distilled from a water bath to
yield a dark oil. This was mixed with water and extracted
with ether. The ether solution was dried over sodium sulfate
and evaporated. The residue, which amounted to only eight
milliliters, was distilled in vacuo. Four grams of distillate
boiled from $100^{\circ}$ to $165^{\circ}$ (1-2 mm.). An equal quantity was un-
distillable. The distillate gave a strong test for the presence
of esters (20), but its further purification was not attempted.

Basic hydrolysis of di-(2-cyanoethyl)-ether

To a 24% (by weight) sodium hydroxide solution (32 g.,
0.8 mole, of sodium hydroxide in 100 ml. of water) there was
added 43.4 g. (0.35 mole) of di-(2-cyanoethyl)-ether. The
mixture was stirred and refluxed for seven hours and then
evaporated to dryness in vacuo. To the dry residue, 70 ml.
of cold, concentrated hydrochloric acid was added. The re-
sulting mixture was evaporated and extracted with chloroform.
Removal of the chloroform gave 51 g. of a viscous, tan syrup.
The neutral equivalent was found to be 126. The calculated

value for the expected dibasic acid, di-(2-carboxyethyl)-ether, is 81.

One gram of this acidic mixture was treated with thionyl chloride and then poured slowly into cold concentrated ammonium hydroxide. The resulting solution was evaporated to dryness and extracted with chloroform. Evaporation of the chloroform extract gave an uncrystallizable oil. No di-(2-carbamylethyl)-ether, which has been reported (14) to melt at 146°, could be isolated.

The remainder of the material was titrated to the phenol-phthalein end point with 3N sodium hydroxide and the solution was evaporated. The dry salt was extracted with boiling 95% ethanol. The residue was boiled with 400 ml. of 90% ethanol and filtered. There was a large quantity of material which was insoluble in 90% ethanol. None of the salt described by Wislicenus (90, 91) separated from the solution even on long standing in the refrigerator.

## Basic hydrolysis of β-ethoxypropionitrile

A solution of 36 g. (0.9 mole) of sodium hydroxide in 125 ml. water was mixed with 49.5 g. (0.5 mole) of β-ethoxypropio-nitrile and refluxed for four hours. It was acidified by adding 83 ml. of concentrated hydrochloric acid and then evaporated to dryness in vacuo. The residue was extracted with ether and the ether extract was distilled in vacuo.

Four grams boiled below 120° (20 mm.). Twenty grams of material distilled at 120-130° (20 mm.) with decomposition (heating bath at 180-220°). This fraction was not homogeneous and had a strong, vinegary odor. A considerable quantity of light brown residue remained in the distilling flask. The distillate dissolved in dilute sodium bicarbonate with evolution of carbon dioxide and reduced large quantities of 2% potassium permanganate solution with formation of manganese dioxide.

On standing overnight the substance polymerized to a transparent, colorless, elastic solid which was insoluble in alcohol or chloroform but dissolved slowly in sodium bicarbonate solution, with liberation of carbon dioxide, to yield a clear solution of unusually high viscosity.

## Acid Hydrolysis of $\beta$-Alkoxypropionitriles

### Procedure

Hydrolysis studies were carried out by heating a mechanically stirred mixture of a $\beta$-alkoxypropionitrile and one to two times the calculated quantity of concentrated hydrochloric acid. The reaction times and temperatures are given in connection with the individual experiments. After completion of the hydrolysis, the reaction mixtures were worked up in accordance with one of the following procedures:

A. The reaction mixture was evaporated to dryness _in vacuo_ with heating on a water bath. The residue was taken up in acetone or ether and filtered with suction. The ammonium chloride remaining was carefully washed with the solvent. The liquid acids were isolated by vacuum distillation of the combined filtrates. The solid acids crystallized, of course, upon evaporation of the filtrates under diminished pressure.

B. The reaction mixture was diluted with water in sufficient quantity to dissolve the precipitated ammonium chloride. The organic layer was diluted with ether and separated and the aqueous solution was extracted several times with ether. Distillation, _in vacuo_, of the combined ether extracts gave the desired $\beta$-alkoxypropionic acids.

The yields of the monobasic acids were calculated upon the basis of the neutral equivalents of the partially purified (once distilled) compounds. With the exception of $\beta$-ethoxypropionic acid, they were then carefully purified by distillation, using a 20 cm., asbestos-wrapped, Vigreux fractionating column, before the densities and indices of refraction were determined. The yields of the dibasic acids were determined from the neutral equivalents of the crude compounds.

Neutral equivalent data plus agreement of reported and found values for physical constants were considered to afford sufficient identification for the liquid acids that had been

prepared previously. Although the preparation of $\beta$-n-butoxy-
propionic acid and $\beta$-iso-butoxypropionic acid has been re-
ported (65), their physical constants do not seem to be
available. They were, therefore, subjected to carbon and
hydrogen analysis.

The monobasic acids were characterized, when possible,
by preparation of the solid p-bromophenacyl esters in
accordance with a standard procedure (76). Another well known
method (39, 76) served for the conversion of the dibasic acids
to solid amides. Of the four amides obtained, three have
been prepared recently by other means (10, 11, 14).

## Preparation of monobasic $\beta$-alkoxypropionic acids and their derivatives

$\beta$-Ethoxypropionic acid. I. $\beta$-Ethoxypropionitrile
(49.6 g., 0.5 mole) was treated with 60 g. (0.6 mole) of con-
centrated hydrochloric acid for two hours at room temperature
and 45 minutes at 90-100$^o$. The experiment was completed by
method A to yield 16.5 g. of unreacted $\beta$-ethoxypropionitrile
boiling at 167-171$^o$ (atmospheric pressure) and 22 g. of
$\beta$-ethoxypropionic acid of boiling point 117-120$^o$ (17 mm.) and
$d^{20}_4$ 1.0635.

Anal. Calcd. for $C_5H_{10}O_3$: N. E. 118.1. Found: N. E.,
119.7, 120.3.

When corrected for the amount of $\beta$-ethoxypropionitrile

recovered, the yield was found to be 55% of the theoretical quantity. Palomaa (61) gives the constants for $\beta$-ethoxypropionitrile as boiling point 119-120$^\circ$ (19 mm.) and $\underline{d}^{20}_4$ 1.0641.

II. A mixture of 49.5 g. (0.5 mole) of $\beta$-ethoxypropionitrile and 100 g. (1 mole) of concentrated hydrochloric acid was heated for six hours at 70-80$^\circ$ and 30 minutes at 90-100$^\circ$, The reaction mixture was worked up by procedure A. The acetone solution was evaporated and distilled under reduced pressure. There was no fore-run and there was obtained 50.5 g. (86%) of $\beta$-ethoxypropionic acid of boiling point 118-121$^\circ$ (19 mm.).

p-Bromophenacyl $\beta$-ethoxypropionate. The derivative separated as an oil when the reaction mixture was cooled. The entire mixture was evaporated to yield an oil which slowly solidified. The solid was leached with water and dried. The product was recrystallized by dissolving it in a small quantity of 95% ethanol at room temperature and then cooling the solution to -20$^\circ$. Large, shining, white leaflets of melting point 47-48$^\circ$ resulted.

Anal. Calcd. for $C_{13}H_{15}O_4Br$: Br, 25.4. Found: Br, 25.1

As a further check on the identity of $\beta$-ethoxypropionic acid, two of its known derivatives were prepared.

Ethyl β-ethoxypropionate. To a solution of 22 g. (0.186 mole) of β-ethoxypropionic acid in 35 ml. of absolute ethanol there was added 2 ml. of saturated, alcoholic hydrogen chloride. The mixture was gently refluxed for 20 hours. Most of the excess alcohol was removed by distillation from a water bath. The residue was diluted with an equal volume of ether, extracted three times with saturated sodium bicarbonate solution and once with water. After drying over sodium sulfate it was distilled to give 19.5 g. (72%) of colorless liquid of boiling point $65^{\circ}$ (16 mm.), and $d_4^{20}$ 0.9585. There was no forerun and no residue. Palomaa and Kilpi (64) give boiling point $62-63^{\circ}$ (13 mm.) and $d_4^{20}$ 0.9590 for ethyl β-ethoxypropionate.

β-Ethoxypropionyl chloride. β-Ethoxypropionic acid (35.4 g., 0.3 mole) was heated under reflux in a boiling water bath while 42.6 g. (0.36 mole) of distilled thionyl chloride was added dropwise at such a rate that the volume of material in the flask did not increase to any appreciable extent. Heating was continued for 45 minutes after all the thionyl chloride had been added. Distillation under diminished pressure gave 37 g. (90%) of colorless liquid of boiling point $50-52.5^{\circ}$ (15 mm.) or $27-28^{\circ}$ (2 mm.) and $d_4^{20}$ 1.0740. For β-ethoxypropionyl chloride Leimu (53) reports boiling point $28-28.5^{\circ}$ (2 mm.) and $d_4^{20}$ 1.0737.

$\beta$-n-Propoxypropionic acid. A mixture of 79.1 g. (0.7 mole) of $\beta$-n-propoxypropionitrile and 140 g. (1.4 moles) of concentrated hydrochloric acid was heated for three hours at 70-80° and then for thirty minutes at 100°. Using acetone as the solvent, procedure A was followed to obtain 74 g. of colorless liquid boiling at 117-123° (13 mm.) and having the neutral equivalent 130. This represents a yield of 80%. Pure $\beta$-n-propoxypropionic acid has the following physical constants: boiling point 87° (1 mm.), $d_4^{20}$ 1.0237 and $n_D^{20}$ 1.4233.

Anal. Calcd. for $C_6H_{12}O_3$: N. E., 132.1. Found: N. E., 132.0.

Physical constants reported (58) for $\beta$-n-propoxypropionic acid are as follows: boiling point 110-112° (9 mm.) and $n_D^{19}$ 1.4230.

p-Bromophenacyl $\beta$-n-propoxypropionate. This derivative crystallized from the reaction mixture on cooling and had the melting point 57-59°. It was recrystallized from a mixture of ethanol and water to yield glistening, white leaflets melting at 57-58°.

Anal. Calcd. for $C_{14}H_{17}O_4$ Br: Br, 24.3. Found: Br, 24.2.

$\beta$-iso-Propoxypropionic acid. Treatment of 79.1 g. (0.7 mole) of $\beta$-iso-propoxypropionitrile and 140 g. (1.4 moles) of concentrated hydrochloric acid, in the manner described for the preparation of $\beta$-n-propoxypropionic acid, gave 55.5 g. of

colorless liquid of boiling point 115-121$^o$ (13 mm.) and neutral equivalent 129. The yield was, therefore, 60%. There was a considerable quantity of brown residue. The physical constants for pure $\beta$-iso-propoxypropionic acid were found to be boiling point 85.5-86$^o$ (1 mm.), $d^{20}_4$ 1.0192, and $n^{20}_D$ 1.4202.

Anal. Calcd. for $C_6H_{12}O_3$: N. E., 132.1. Found: N. E., 131.3.

Previously reported (58) physical constants for $\beta$-iso-propoxypropionic acid are boiling point 125-126$^o$ (22 mm.) and $n^{20}_D$ 1.4202.

p-Bromophenacyl $\beta$-iso-propoxypropionate. The compound separated as an oil from the reaction mixture. Evaporation of the entire mixture gave an oil which solidified on standing. The solid was leached with water and recrystallized by solution at room temperature in a small quantity of 95% ethanol and cooling to -20$^o$. The result was tiny, white plates of melting point 44-44.5$^o$.

Anal. Calcd. for $C_{14}H_{17}O_4Br$: Br, 24.3. Found: Br, 23.9.

$\beta$-n-Butoxypropionic acid. A mixture of $\beta$-n-butoxypropionitrile (76.2 g., 0.6 mole) and 90 g. (0.9 mole) of concentrated hydrochloric acid was heated for three hours at 70-80$^o$ and for 15 minutes at 100$^o$. Completion of the experiment in accordance with procedure A gave 68.5 g. of crude acid boiling at 120-140$^o$ (13 mm.). The neutral equivalent of the material, 165, indicated a yield of 69%. Pure $\beta$-n-butoxypropionic acid had the

following physical constants: boiling point 96-97.5$^{\circ}$ (1 mm.), $d_4^{20}$ 0.9929, and $n_D^{20}$ 1.4268.

Anal. Calcd. for $C_7H_{14}O_3$: N. E., 146.1; C, 57.5; H, 9.67. Found: N. E., 147.3; C, 57.1; H, 10.0.

p-Bromophenacyl $\beta$-n-butoxypropionate. This derivative crystallized from the reaction mixture on standing at room temperature. Cooling and filtration gave product of m. p. 54-55$^{\circ}$. This was recrystallized by dissolving it in a little 95% ethanol at room temperature and cooling the solution to -20$^{\circ}$. The compound consisted of shining, white leaflets melting at 55$^{\circ}$.

Anal. Calcd. for $C_{15}H_{19}O_4Br$: Br, 23.3. Found: Br, 23.0.

$\beta$-iso-Butoxypropionic acid. $\beta$-iso-Butoxypropionitrile (76.2 g., 0.6 mole) was treated with 120 g. (1.2 moles) of concentrated hydrochloric acid for 3.75 hours at 75-80$^{\circ}$. The reaction mixture was worked up by method B to give 63 g. of material boiling at 105-110$^{\circ}$ ( 5 mm.) and having the neutral equivalent 157. Hence, the yield was 67%. The physical constants for pure $\beta$-iso-butoxypropionic acid were found to be boiling point 89-90$^{\circ}$ (1 mm.), $d_4^{20}$ 0.9843, $n_D^{20}$ 1.4227.

Anal. Calcd. for $C_7H_{14}O_3$: N. E., 146.1; C, 57.5; H, 9.67. Found: N. E. 146.0; C, 57.0; H, 9.74.

p-Bromophenacyl β-iso-butoxypropionate. The derivative
crystallized from the reaction mixture on standing at room
temperature as soft, white, fibrous needles melting at 57-59$^o$.
Solution in a little dilute ethanol at room temperature
followed by cooling to -20$^o$ yielded white needles of melting
point 57.5-58.5$^o$.

Anal. Calcd. for $C_{15}H_{19}O_4Br$: Br, 23.3. Found: Br, 23.2.

β-sec-Butoxypropionic acid. A mixture of 76.2 g. (0.6
mole) of β-sec-butoxypropionitrile and 60 g. (0.6 mole) of
concentrated hydrochloric acid was heated for four hours at
75-80$^o$. Completion of the preparation by procedure B gave
54 g. of crude acid having the boiling range 85-120$^o$ (5 mm.).
The neutral equivalent, 161, indicated a yield of 56%. Pure
β-sec-butoxypropionic acid had the following physical constants:
boiling point 90-91.4$^o$ (1 mm.), $d^{20}_4$ 0.9946, and $n^{20}_D$ 1.4252.

Anal. Calcd. for $C_7H_{14}O_3$: N. E., 146.1; C, 57.5; H,
9.67. Found: N. E., 146.4; C, 57.3; H, 9.76.

p-Bromophenacyl β-sec-Butoxypropionate: An oil separated
from the reaction mixture on standing at room temperature. The
entire mixture was evaporated to dryness. The resulting oil
could not be induced to crystallize under any conditions.

β-iso-Amyloxypropionic acid. β-iso-Amyloxypropionitrile
(84.6 g., 0.6 mole) was treated with 120 g. (1.2 moles) of
concentrated hydrochloric acid for 3.25 hours at 70-80$^o$. Sub-
sequent to completion of the experiment in accordance with

procedure A, there was obtained 76.5 g. of liquid of boiling point 138-150$^{\circ}$ (14 mm.) and neutral equivalent 188. The yield was 69%. Twice fractionated $\beta$-iso-amyloxypropionic acid had the following physical constants: boiling point 100$^{\circ}$ (1 mm.) or 137$^{\circ}$ (12 mm.), $\underline{d}^{20}_{4}$ 0.9697, $\underline{d}^{18}_{18}$ 0.9725, and $\underline{n}^{20}_{D}$ 1.4285.

Anal. Calcd. for $C_8H_{16}O_3$: N. E., 160.2. Found: N. E., 162.7.

Comparable physical constants given in the literature for $\beta$-iso-amyloxypropionic acid are boiling point 135$^{\circ}$ (12 mm.) (29, 30) and $\underline{d}^{18}$ 0.974 (36, 37).

p-Bromophenacyl $\beta$-iso-amyloxypropionate. This derivative crystallized from the reaction mixture on cooling to 0$^{\circ}$. Filtration gave fine, white needles melting at 53-54$^{\circ}$. The compound was recrystallized by dissolving it in dilute ethanol and cooling the solution to -20$^{\circ}$. There resulted glistening needles of melting point 56$^{\circ}$.

Anal. Calcd. for $C_{16}H_{21}O_4Br$: Br, 22.4. Found: Br, 22.2.

$\beta$-sec-Amyloxypropionic acid. A mixture of 70.4 g. (0.5 mole) of $\beta$-sec-amyloxypropionitrile and 100 g. (1 mole) of concentrated hydrochloric acid, heated for 3.5 hours at 75-85$^{\circ}$ and worked up by method A, gave 44 g. of crude product of boiling range 126-150$^{\circ}$ (16 mm.) and neutral equivalent 179. This corresponds to a yield of 49.2%. The low yield was due

in part to accidental spillage of some of the ether solution before distillation. The physical constants of the pure compound were boiling point 100-101.4$^{\circ}$ (1 mm.), $\underline{d}_4^{20}$ 0.9833, and $\underline{n}_D^{20}$ 1.4289.

Anal. Calcd. for $C_8H_{16}O_3$: N. E., 160.2; C, 60.0; H, 10.1. Found: N. E., 159.4; C, 59.7; H, 10.3.

p-Bromophenacyl β-sec-amyloxypropionate. This compound failed to crystallize from the reaction mixture. Evaporation gave an oil which could not be caused to solidify under any conditions.

β-Allyloxypropionic acid. A mixture of 66.6 g. (0.6 mole) of β-allyloxypropionitrile and 90 g. (0.9 mole) of concentrated hydrochloric acid was heated at 70$^{\circ}$ for four hours. The experiment was completed by procedure B to yield 21 g. of unreacted β-allyloxypropionitrile and 22 g. of crude β-allyloxypropionic acid of boiling range 93-120$^{\circ}$ (6 mm.). The neutral equivalent, 156, indicated a yield of 24%. These two quantities of material were fractionally distilled to yield 18.5 g. of β-allyloxypropionitrile (boiling point 71-75$^{\circ}$ at 6 mm.) and pure β-allyloxypropionic acid of boiling point 111-112$^{\circ}$ (6 mm.) or 84$^{\circ}$ (1 mm.), $\underline{d}_4^{20}$ 1.0604 and $\underline{n}_D^{20}$ 1.4423. Correction of the yield for the amount of nitrile recovered gave a value of 33%.

Anal. Calcd. for $C_6H_{10}O_3$: N. E., 130.1; C, 55.4; H, 7.75. Found: N. E., 130.8; C, 55.3; H, 8.17.

p-Bromophenacyl β-Allyloxypropionate. The desired compound crystallized from the reaction mixture upon cooling it to $-15^{\circ}$. Filtration gave a white powder melting at $35-38^{\circ}$. It was recrystallized by dissolving it at room temperature in a small quantity of 95% ethanol. The resulting solution was chilled to $-20^{\circ}$ and filtered to yield tiny, white plates of melting point $38-39^{\circ}$.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: Br, 24.4. Found: Br, 24.3.

β-(2-Methoxyethoxy)-propionic acid. A solution of 77.4 g. (0.6 mole) of β-(2-methoxyethoxy)-propionitrile in 120 g. (1.2 moles) of concentrated hydrochloric acid was heated at $70-80^{\circ}$ for three hours. Using acetone as the solvent, method A was followed in working up the reaction mixture. There was obtained 67 g. of product boiling at about $125^{\circ}$ (2 mm.). The neutral equivalent, 150, indicated a yield of 75%. Pure β-(2-methoxyethoxy)-propionic acid had the following physical constants: boiling point 109.5-110.5 (0.5 mm.), $d_4^{20}$ 1.1146 and $n_D^{20}$ 1.4356.

Anal. Calcd. for $C_6H_{12}O_4$: N. E., 148.2; C, 48.6; H, 8.16. Found: N. E., 150.8; C, 48.3; H, 8.35.

p-Bromophenacyl β-(2-methoxyethoxy)-propionate. This compound separated from the reaction mixture as nacreous, white leaflets on cooling to $0^{\circ}$. It melted to an oil on warming to room temperature and could not be satisfactorily purified. The approximate melting point was $15^{\circ}$.

The $\beta$-alkoxypropionic acids are colorless liquids having little or no odor. They are all soluble in the common organic solvents. In water, the ethoxy-, iso-propoxy-, allyloxy-, and 2-methoxyethoxy- derivatives are easily soluble whereas $\beta$-n-propoxypropionic acid is only slightly so. None of the higher members of the series is appreciably soluble in water. The physical constants and yields of the compounds are given in Table IV. Table V gives the crystalline form and melting points of the p-bromophenacyl $\beta$-alkoxypropionates.

## Preparation of dibasic $\beta$-alkoxypropionic acids and their derivatives

Di-(2-carboxyethyl)-ether. A mixture of 62 g. (0.5 mole) of di-(2-cyanoethyl)-ether and 200 g. (2 moles) of concentrated hydrochloric acid was stirred vigorously and heated for six hours at 70-80$^o$ and then for 30 minutes at 100$^o$. The reaction product was isolated by method A, using acetone as the solvent. Evaporation of the extract gave 81 g. (100%) of a tan syrup which, upon standing overnight, solidified to a nearly white, crystalline mass. The neutral equivalent of this material was 83.6 indicating a purity of 97%. It melted at 35-40$^o$ and was rather hygroscopic. It was very soluble in ether, alcohol or water, but insoluble in petroleum ether.

Some difficulty was experienced in recrystallizing this compound because of its solubility characteristics and low melting point. It had a strong tendency to separate as an oil

## Table IV

Physical constants and yields of $\beta$-alkoxypropionic acids

$ROCH_2CH_2COOH$
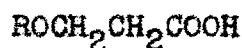
| R | Boiling point, °C. | mm. | $n_D^{20}$ | $d_4^{20}$ | Yield, % |
|---|---|---|---|---|---|
| Ethyl[a] | 117-120 | 17 | ---- | 1.0635 | 86 |
| n-Propyl[b] | 87<br>120 | 1<br>13 | 1.4233 | 1.0237 | 80 |
| iso-Propyl[c] | 85.5-86<br>118 | 1<br>13 | 1.4202 | 1.0192 | 60 |
| n-Butyl[d] | 96-97.5 | 1 | 1.4268 | 0.9929 | 69 |
| iso-Butyl[d] | 89-90 | 1 | 1.4227 | 0.9843 | 67 |
| sec-Butyl | 90-91.4 | 1 | 1.4252 | 0.9946 | 56 |
| iso-Amyl[e] | 100<br>137 | 1<br>12 | 1.4285 | 0.9697 | 69 |
| sec-Amyl | 100-101.4 | 1 | 1.4289 | 0.9833 | 49 |
| 2-Methoxyethyl | 109.5-110.5 | 0.5 | 1.4356 | 1.1146 | 75 |
| Allyl | 84<br>111-112 | 1<br>6 | 1.4423 | 1.0604 | 33 |

[a] Previously prepared. Palomaa (61) gives boiling point 119-120° (19 mm.) and $d_4^{20}$ 1.0641.

[b] Previously prepared. Literature (58) gives boiling point 110-112° (9 mm.) and $n_D^{19}$ 1.4230.

[c] Previously prepared. Literature (58) gives boiling point 125-126° (22 mm.) and $n_D^{20}$ 1.4202.

[d] Previously prepared (65) but physical constants not reported.

[e] Previously prepared. Literature gives boiling point 135° (12 mm.) (29, 30) and $d^{18}$ 0.974 (36, 37).

## Table V

Properties of p-bromophenacyl $\beta$-alkoxypropionates

$ROCH_2CH_2COOCH_2COC_6H_4Br-p$

| R | Crystalline form* | Melting point °C. |
|---|---|---|
| Ethyl | Large leaflets | 47–48 |
| n-Propyl | Shiny leaflets | 57–58 |
| iso-Propyl | Tiny plates | 44–44.5 |
| n-Butyl | Shiny leaflets | 55 |
| iso-Butyl | Fibrous needles | 57.5–58.5 |
| sec-Butyl | Oil | ---- |
| iso-Amyl | Glistening needles | 56 |
| sec-Amyl | Oil | ---- |
| Allyl | Tiny plates | 38–39 |
| 2-Methoxyethyl | Oil | Ca. 15 |

* All of the solid derivatives were white substances.

at temperatures far below its melting point. The acid was
purified by dissolving it in hot ether. To the boiling
solution, petroleum ether (b. p. 60-70$^o$) was added until
cloudiness just appeared. The solution was clarified by
adding a few drops of ether. It was then cooled to room
temperature, seeded, cooled slowly to a final temperature of
around -40$^o$ and quickly filtered. This was repeated until
material of constant melting point was obtained. Pure di-
(2-carboxyethyl)-ether consists of hard, white crystals melt-
ing at 60-61$^o$. The compound boils at 189-192$^o$ (1 mm. or less)
with slight decomposition.

Anal. Calcd. for $C_6H_{10}O_5$: N. E., 81.07; C, 44.5; H,
6.18. Found: N. E. 81.77; C, 44.8; H, 6.56.

Di-(2-carbamylethyl)-ether. A mixture of 1 g. (0.0062
mole) of di-(2-carboxyethyl)-ether and 2 ml. of thionyl
chloride was refluxed gently for 30 minutes. The excess
thionyl chloride was removed by warming in vacuo. The residue
was added dropwise, with constant stirring, to 20 ml. of con-
centrated ammonium hydroxide which was cooled to -10$^o$ in a
freezing mixture. The resulting solution was evaporated to
dryness under reduced pressure and extracted with hot absolute
ethanol. Evaporation of the extract gave a light brown solid
melting at about 130$^o$. Five recrystallizations from benzene-
absolute ethanol mixtures gave small, glistening, white rhombs
of constant melting point 143.5-144$^o$. The compound was easily

soluble in water or ethanol, but insoluble in benzene.

_Anal_. Calcd. for $C_6H_{12}O_3N_2$: N, 17.5. Found: N, 17.4.

Bruson and Riener (14) have reported the preparation of di-(2-carbamylethyl)-ether by partial hydrolysis of the corresponding nitrile with alkaline hydrogen peroxide. They give the melting point as $146^o$.

1,2-Di-(2-carboxyethoxy)-ethane. A solution of 63 g. (0.375 mole) of 1,2-di-(2-cyanoethoxy)-ethane in 75 g. (0.75 mole) of concentrated hydrochloric acid was stirred vigorously and heated at $70-80^o$ for three hours. Then 75 g. (0.75 mole) more hydrochloric acid was added and stirring and heating continued for 1.5 hours at $70-80^o$ and 30 minutes at $100^o$. The experiment was completed by method A. The acetone extract was evaporated to yield 77 g. of nearly colorless syrup. Upon standing overnight, this solidified to a white solid of melting point $45-53^o$ and neutral equivalent 110. The yield, therefore, was 94%.

This substance was soluble in acetone or water, slightly soluble in benzene, and insoluble in ether or petroleum ether. It had a pronounced tendency to separate as an oil when recrystallized. It was successfully purified by recrystallization from benzene containing a little acetone. It was necessary to seed the slightly cooled solution and shake it occasionally to prevent the separation of an oil. Five recrystallizations gave 1,2-di-(2-carboxyethoxy)-ethane as sparkling, white

crystals of constant melting point 66$^o$.

Anal. Calcd. for $C_8H_{14}O_6$: N. E., 103.1; C, 46.6; H, 6.86. Found: N. E., 103.5; C, 47.0; H, 7.24.

1,2-Di-(2-carbamylethoxy)-ethane. A mixture of 10.3 g. (0.05 mole) of 1,2-di(2-carboxyethoxy)-ethane and 23.8 g. (0.2 mole) of thionyl chloride was gently heated on a water bath for 1.5 hours. The excess thionyl chloride was removed by warming in vacuo. The residual oil was added dropwise, with constant stirring, to 150 ml. of concentrated ammonium hydroxide maintained at -10$^o$. Evaporation of this solution in vacuo gave a solid residue from which the amide was recovered by extraction with hot ethanol and subsequent evaporation. The crude compound was recrystallized twice from acetone and then four times from benzene-ethanol to give fine, white crystals of constant melting point 123$^o$. The pure substance underwent a sudden change in appearance at 107$^o$ on the micro melting point block. Under rapid heating (10-15$^o$ per minute) it melted rather sharply at 104$^o$ without resolidification. 1,2-Di-(2-carbamylethoxy)-ethane is very soluble in water or ethanol, slightly soluble in acetone, but insoluble in benzene or ether.

Anal. Calcd. for $C_8H_{16}O_4N_2$: N, 13.7. Found: N, 13.6.

The preparation of 1,2-di-(2-carbamylethoxy)-ethane by partial hydrolysis of the corresponding nitrile with 80% sulfuric acid at 55-60$^o$ has been reported (10). The melting

point was given as 123-124$^o$.

<u>1,3-Di-(2-carboxyethoxy)-propane</u>. A mixture of 98 g. (0.54 mole) of 1,3-di-(2-cyanoethoxy)-propane and 216 g. (2.16 moles) of concentrated hydrochloric acid was heated at 70-80$^o$ for four hours and at 95-100$^o$ for thirty minutes. Procedure A was followed in completing the experiment. Evaporation of the acetone solution under reduced pressure gave 118.5 g. of tan syrup which crystallized to a white solid (melting point 65-77$^o$) on standing overnight. The neutral equivalent was 123, indicating a yield of 90%.

The product was purified by recrystallization from benzene containing a little petroleum ether (boiling point 60-70$^o$) to reduce the solubility. Seeding was necessary to prevent the separation of an oil when the solution was cooled. Five recrystallizations gave pure 1,3-di-(2-carboxyethoxy)-propane whose melting point, 86-87$^o$, was unchanged on further recrystallization. The compound, consisting of soft,white crystals, was easily soluble in water, alcohol and acetone, fairly soluble in benzene, and insoluble in ether or petroleum ether. A dilute solution of the sodium salt gave no precipitate with solutions of the chlorides of magnesium, barium or calcium.

<u>Anal</u>. Calcd. for $C_9H_{16}O_6$: N. E., 110.1; C, 49.1; H, 7.32. Found: N. E., 111.1; C, 49.3; H, 7.62.

1,3-Di-(2-carbamylethoxy)-propane. The procedure followed
was the same as that used in the preparation of 1,2-di-(2-carb-
amylethoxy)-ethane. From 11.0 g. (0.05 mole) of crude 1,3-di-
(2-carboxyethoxy)-propane and 23.8 g. (0.2 mole) of thionyl
chloride there was obtained 13.5 g. of the crude amide. This
was recrystallized five times from benzene-ethanol to give
fine, white crystals of constant melting point $124^\circ$. The
melting point of a mixture of this compound with 1,2-di-(2-
carbamylethoxy)-ethane was $95-110^\circ$. 1,3-Di-(2-carbamylethoxy)-
propane is very soluble in water or ethanol, slightly soluble
in acetone, and insoluble in benzene or ether.

Anal. Calcd. for $C_9H_{18}O_4N_2$: N, 12.8. Found: N, 12.5.

Di-(2-/2-carboxyethoxy7-ethyl)-ether. A solution of
106 g. (0.5 mole) of di(2-/2-cyanoethoxy7-ethyl)-ether in 200
g. (2 moles) of concentrated hydrochloric acid was heated at
$70-80^\circ$ for four hours after which the temperature was raised
to $95-100^\circ$ for 40 minutes. The reaction mixture was worked
up in accordance with method A. Evaporation of the acetone
solution under diminished pressure gave 127 g. of tan syrup
having the neutral equivalent 137. The yield, therefore,
was 91%.

This oil could not be induced to crystallize under any
conditions. An attempt to distill the acid at 0.5 mm. or
less failed when it began to decompose at about $225^\circ$. The
derivitization of the compound as the known, solid amide leaves
no doubt as to its structure.

Di-(2-/2-carbamylethoxy/-ethyl)-ether. The amide was
prepared in the usual way using 16 g. (0.064 mole) of crude
di-(2-/2-carboxyethoxy/-ethyl)-ether and 30.4 g. (0.256 mole)
of thionyl chloride. Three recrystallizations (two from
acetone and one from ethanol-benzene) gave tiny, sparkling,
white crystals of melting point 103-103.5$^o$. Di-(2-/2-carb-
amylethoxy/-ethyl)-ether is very soluble in water or ethanol,
fairly soluble in acetone, and insoluble in benzene or ether.

Anal. Calcd. for $C_{10}H_{20}O_5N_2$: N, 11.3. Found: N, 11.2.

This compound has been prepared previously by partial
hydrolysis of the corresponding nitrile with 80% sulfuric
acid at 55-60$^o$ (10), and by heating diethylene glycol with
acrylamide in the presence of trimethylbenzylammonium hydroxide
(11). The melting point reported in each case has been 103-
104$^o$.

The solubility characteristics of the dibasic acids of
the $\beta$-alkoxypropionic type have been given in connection with
the individual experiments. The melting points of the com-
pounds are summarized in Table VI. The melting points of the
amides, which served as derivatives for the acids, are given
in Table VII with appropriate references.

Table VI

Melting points of $\beta$-alkoxypropionic acids of the type

$$HOCOCH_2CH_2-Y-CH_2CH_2COOH$$

| Y | Melting point, °C. |
|---|---|
| -O- | 60-61 |
| -OCH$_2$CH$_2$O- | 66 |
| -OCH$_2$CH$_2$CH$_2$O- | 86-87 |
| -OCH$_2$CH$_2$OCH$_2$CH$_2$O- | Oil |

Table VII

Melting points of $\beta$-alkoxypropionamides of the type

$$H_2NCOCH_2CH_2 - Y - CH_2CH_2CONH_2$$
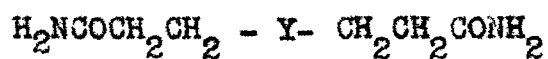
| Y | Melting point, °C. Found | Reported |
|---|---|---|
| -O- | 144 | 146 (14) |
| -OCH$_2$CH$_2$O- | 123* | 123-124 (10) |
| -OCH$_2$CH$_2$CH$_2$O- | 124* | ---- |
| -OCH$_2$CH$_2$OCH$_2$CH$_2$O- | 103-103.5 | 103-104 (10,11) |

* The mixed melting point of these two substances was 95-110°.

## Attempts to prepare 1,4-di-(2-carboxyethoxy)-pentane

Acid hydrolysis of 1,4-di-(2-cyanoethoxy)-pentane. A mixture of 40 g. (0.19 mole) of 1,4-di-(2-cyanoethoxy)-pentane and 76 g. (0.76 mole) of concentrated hydrochloric acid was stirred and heated under reflux for five hours at 80-90$^{\circ}$ and for 15 minutes at 100$^{\circ}$. A white solid began to precipitate after 20 minutes' heating. When water was added to dissolve the ammonium chloride an insoluble liquid layer appeared. This was extracted with chloroform. The chloroform extract was evaporated and dried in vacuo over sulfuric acid to yield 40.5 g. of a light brown syrup which formed a glass at -75$^{\circ}$ and could not be induced to crystallize under any conditions. The neutral equivalent was found to be 199 (Calcd. for $C_{11}H_{20}O_6$: N. E., 124).

A solution of 38 g. of the material in 58 ml. of absolute ethanol to which had been added 3 ml. of saturated, absolute alcoholic hydrogen chloride was gently refluxed for 24 hours. The excess alcohol was distilled from a water bath. The residue was diluted with an equal volume of ether, extracted twice with saturated sodium bicarbonate solution and once with water. The ether solution was dried with sodium sulfate and distilled in vacuo.

Three fractions were obtained. The first boiled at 85-96$^{\circ}$ (1 mm.) and consisted of 17 g. of a colorless liquid which contained chlorine, but no nitrogen and gave a positive

test for the presence of esters (20). The intermediate fraction of 7 g., boiling range 96-146$^o$ (1 mm.), was discarded. The third fraction weighed 9 g., boiled at 146-175$^o$ (1 mm.), contained chlorine and nitrogen and gave a positive ester test.

If, during the hydrolysis of 1,4-di(2-cyanoethoxy)-pentane, one of the ether linkages were ruptured by the action of the concentrated hydrochloric acid, a $\beta$-(chloroamyloxy)-propionic acid might be one of the resulting fragments. This compound would appear as the ethyl ester under the conditions of the foregoing experiment. The principal fraction obtained above was purified and analyzed in view of the possibility that it might be an ethyl $\beta$-(chloroamyloxy)-propionate. Subsequent to redistillation, there was obtained 13 g. of material of boiling point 109-112$^o$ (2.5 mm.), $d_4^{25}$ 1.0325, and $n_D^{25}$ 1.4386.

Anal. Calcd. for $C_{10}H_{19}O_3Cl$: Mr$_D$, 56.63; C, 53.9; H, 8.60; Cl, 15.9. Found: Mr$_D$, 56.75; C, 53.6; H, 8.82; Cl, 15.2.

Alcoholysis of 1,4-di-(2-cyanoethoxy)-pentane. I. The method of Spiegel (78) was used. A mixture of 22 g. (0.105 mole) of 1,4-di-(2-cyanoethoxy)-pentane, 4.14 g. (0.9 mole) of absolute ethanol and 19.6 g. of concentrated sulfuric acid was heated under reflux in an oil bath for six hours. Upon cooling the mixture and pouring it into water, an oil

separated. This was extracted with ether, dried over sodium sulfate and distilled at a pressure of 2 mm. The material boiled over the entire temperature range of 65-200°. Distillation was stopped when decomposition began. No clear-cut fractions were observed and there was considerable undistillable residue.

II. The procedure successfully used by Sabetay (72) in the alcoholysis of alkoxyacetonitriles was followed. A solution of 27 g. (0.74 mole) of dry hydrogen chloride in 46 g. of absolute ethanol was prepared. To it there was added 21 g. (0.1 mole) of 1,4-di-( 2-cyanoethoxy)-pentane. The reaction mixture was protected from the action of atmospheric moisture by means of a calcium chloride tube. The solution became warm at once and after standing for two hours a white precipitate had formed. The mixture was then refluxed for three hours. The precipitated ammonium chloride was filtered and washed with absolute alcohol. When dry it weighed 10 g. (theoretical quantity 10.7 g.). The ethanol solution was diluted with ether, extracted with sodium bicarbonate solution and washed with water. It was dried with sodium sulfate and distilled. Four grams boiled at 65° (15 mm.). The remainder boiled from 35° to 200° (2 mm.) and no clear-cut fractions were observed. There was approximately 0.5 g. of dark residue.

Preparation of 1,4-di-(2-carbethoxyethoxy)-pentane.  I.
The procedure used was patterned after that of Kimball,
Jefferson and Pike for the preparation of ethyl α-phenyl-
acetoacetate (49).  A mixture of 75 ml. of absolute ethanol
(distilled from sodium and diethyl phthalate) and 21 g.
(0.1 mole) of 1,4-di-(2-cyanoethoxy)-pentane was saturated
with anhydrous hydrogen chloride during five hours.  The
mixture was maintained at a temperature of $-10^{o}$, stirred
mechanically, and protected from atmospheric moisture by
means of a calcium chloride tube during this treatment.  It
was then allowed to stand at room temperature for 24 hours.
After removal of excess hydrogen chloride by gentle heating
in vacuo, the solution was poured, with vigorous shaking,
into a mixture of 20 g. of sodium carbonate, 120 ml. of water,
and 200 ml. of ice.  This was extracted at once with three 50
ml. portions of ether.  The ether extract was washed with
four 50 ml. portions of ice-cold 5% sodium chloride solution.
A solution of 20 g. of concentrated sulfuric acid and 140 ml.
of water was shaken with 300 ml. of ice until frost formed on
the outside of the flask.  One-half of this mixture was poured
into the ice-cold ether solution.  After 12 seconds shaking
the acid layer was separated.  The remaining acid was added
in two portions.  After each addition, the mixture was shaken
for 15 seconds and separated as before.  The ether solution
was saved.  The clear, colorless acid solution was heated on

a water bath for 30 minutes at 50°. It soon became cloudy

and an immiscible layer appeared. This was separated, after

cooling, and the aqueous solution was extracted with 25 ml.

of ether. The ether extract was washed with 10 ml. of water

which was added to the acid solution. The acid solution was

heated at 80-90° for 45 minutes, cooled, and extracted as

before. The combined ether extracts were washed with 25 ml.

of 5% sodium bicarbonate solution and 25 ml. of water, and

finally dried over anhydrous sodium sulfate.

Upon distillation under diminished pressure, there was

obtained 2.6 g. of material boiling at 108-151° (1 mm.) and

10.4 g. (33%) of 1,4-di-(2-carbethoxyethoxy)-pentane of boil-

ing point 151-153° (1 mm.). The first fraction contained a

trace of halogen; the second contained none. Both fractions

gave strongly positive tests for the presence of esters (20).

Neither fraction contained nitrogen.

II. Sixty grams (0.16 mole) of coarsely pulverized

bis-(ethyliminoester hydrochloride) of 1,4-di-(2-cyanoethoxy)-

pentane was added in small portions to 200 ml. of distilled

water at room temperature. The addition was carried out over

a period of twenty minutes and the mixture was stirred con-

tinuously. The solid dissolved readily and no temperature

change was observed, but an oil began to separate at once.

After stirring for fifteen minutes at room temperature the

mixture was heated at 45° for thirty minutes. It was then

cooled and extracted twice with 50 ml. portions of ether.
The other extract was washed with 25 ml. of water which was
returned to the reaction mixture. With continued stirring
the mixture was heated at 90-95$^o$ for 45 minutes. It was
cooled and extracted with two 50 ml. portions of ether.
The combined ether extracts were washed with 50 ml. of 5%
sodium bicarbonate and with 50 ml. of water. After drying
over sodium sulfate the product was distilled in vacuo.

There was obtained 7.5 g. of material of boiling range
60-142$^o$ (0.5 mm.) which contained chlorine but no nitrogen.
The desired product was collected at 142-145$^o$ (0.5 mm.). It
weighed 28 g. (58% yield).

1,4-Di-(2-carbethoxyethoxy)-pentane is a colorless
liquid of $\underline{d}\,^{25}_4$ 1.0174 and $\underline{n}\,^{25}_D$ 1.4363.

Anal. Calcd. for $C_{15}H_{28}O_6$: Saponification Equivalent,
152.2; C, 59.2; H, 9.27. Found: Saponification Equivalent,
151.4, 152.4; C, 59.5; H, 9.54.

Attempted saponification of 1,4-di-(2-carbethoxyethoxy)-
pentane. The conversion of 1,4-di-(2-carbethoxyethoxy)-
pentane to the disodium salt of 1,4-di-(2-carboxyethoxy)-
pentane, by quantitative saponification, was attempted. A
sample of 1,4-di-(2-carbethoxyethoxy)-pentane weighing 1.028
g. was placed in a 25 ml. flask and 5 ml. of 95% ethanol and
two drops of phenolphthalein were added. From a buret, 1.29 N
alcoholic sodium hydroxide was added until the solution was

basic. The mixture was allowed to stand at room temperature until it became colorless. It was again made basic by the addition of a little of the standard base. These operations were continued. After about three hours, when approximately 50% of the calculated amount of base had been added, the mixture began to exhibit a strong odor of ethyl acrylate. This suggested that the ester might have been decomposing into 1,4-pentanediol and ethyl acrylate. The experiment was abandoned.

DISCUSSION

The mechanism by which $\gamma$-valerolactone undergoes the Friedel and Crafts reaction appears to be the same as that for the simple esters. Evidence in support of this is the observation that little or no hydrogen chloride is evolved from the reaction mixture until the catalyst-lactone ratio slightly exceeds unity. The first mole of catalyst probably brings about the formation of an aluminum salt of $\gamma$-chlorovaleric acid which subsequently takes part in the alkylation reaction.

Of incidental importance is the fact that the reaction of $\gamma$-valerolactone with aluminum chloride or related compounds might afford a means for the synthesis of $\gamma$-chlorovaleric acid which would be more convenient than the sealed tube procedure of Wohlgemuth (92).

$\gamma$-Phenylvaleric acid itself has been prepared during the course of a number of studies (50, 55, 57, 84). However, except for the work of Eijkman (25), it has invariably been made by laborious five or six step reactions. This has no doubt been due to the difficulty of obtaining $\gamma$-valerolactone, because the advantages of the single operation of the Friedel and Crafts method of synthesis are obvious. An extension of the reaction to aromatic compounds other than benzene and toluene should make readily available a number of $\gamma$-arylvaleric

acids. Any further study of the use of $\gamma$-valerolactone in the Friedel and Crafts reaction should include an investigation of catalysts other than aluminum chloride.

The polyalkylation of benzene by means of $\gamma$-valerolactone can be effected in good yield. However, the confinement of the reaction to dialkylation does not appear to be immediately possible since, in all the experiments, there were obtained mixtures of mono-, di-, and possibly tri-alkylation products. On the other hand, a crude mixture of this sort, containing mono-, di-, and tri-basic acids (or their esters) might be worthy of investigation as an intermediate in the preparation of a "viscosity-stable" (34, p. 725) polyester or polyamide. On a production basis, the orientation of the substituents in the benzene ring would not be important.

The formation of 2-methyltetrahydrofuran in the hydrogenation of $\gamma$-valerolactone over copper-chromium oxide has not been observed heretofore. It has been reported, however, that reduction of the lactone in the presence of Raney nickel gives some 2-methyltetrahydrofuran (1, p. 78). In this case it was assumed that the compound resulted from direct hydrogenolysis of the carbonyl oxygen without rupture of the lactone ring. The ease with which 1,4-pentanediol can be dehydrated to form the cyclic ether (32, 33, 56) suggests that in the copper-chromium oxide reduction the diol is the precursor of 2-methyltetrahydrofuran. In support of this

mechanism is the fact that higher reduction temperatures result in lower yields of 1,4-pentanediol and increased amounts of 2-methyltetrahydrofuran.

The two-stage reduction of ethyl levulinate can be explained on the basis of the report that the carbonyl group is hydrogenated over copper-chromium oxide at a temperature of $125-150^{\circ}$ (1, p. 51), whereas the hydrogenolysis of the ester linkage takes place at $200-250^{\circ}$ with the same catalyst (1, p. 97). It appears likely that the first step of the reaction involves the reduction of the ketonic ester to form ethyl $\gamma$-hydroxyvalerate. Hydrogenolysis of the latter compound could then take place at a higher temperature with the formation of 1,4-pentanediol and ethanol.

Consideration of the fact that the esters of $\gamma$-hydroxyvaleric acid are reported to undergo decomposition into $\gamma$-valerolactone and an alcohol at moderately high temperatures (81) suggests another possibility for the second step of the reaction. Ethyl $\gamma$-hydroxyvalerate could decompose into $\gamma$-valerolactone and ethanol. Hydrogenolysis of the lactone would then occur in the usual way. The end products would be the same in either case.

The reduction of levulinic acid over copper-chromium oxide at a temperature and pressure higher than those employed by Brown (4) gave a somewhat higher yield of 1,4-pentanediol and a greatly decreased amount of $\gamma$-valerolactone.

The total recovery of products was not as good as that reported by Brown (4), however, and the relatively large quantity of low boiling material obtained suggests the formation of 2-methyltetrahydrofuran and mixtures of amyl alcohols. The use of mixtures of Raney nickel and copper-chromium oxide catalysts in attempts to effect the direct reduction of levulinic acid to 1,4-pentanediol might prove to be an interesting and fruitful study.

The fact that slightly lower yields of $\beta$-alkoxypropionitriles were obtained from secondary alcohols is in accordance with the observations and suggestions of Utermohlen (82). Information gained during the preparation of $\beta$-sec-butoxy- and $\beta$-sec-amyloxypropionitriles suggests further that the heats and rates of reaction may be lower in the addition of secondary alcohols to acrylonitrile.

It seems noteworthy that in the hydrogenation of 1,4-di-(2-cyanoethoxy)-pentane at 120-125° little or no evidence for cleavage at the ether linkages was obtained. It will be recalled that Utermohlen (82) reduced $\beta$-alkoxypropionitriles at 90-100° and reported lowered yields at 125° as a result of cleavage. The very high yields of hydrogenolysis products reported (88) to occur in the reduction of a related compound, di-(2-cyanoethyl)-ether, may indicate that two 2-cyanoethyl groups attached to a single oxygen atom make the system particularly susceptible to rupture.
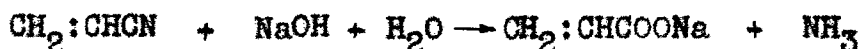
The excellent yield in which 1,4-di-(3-aminopropoxy)-pentane can be prepared, the complete water-solubility of the compound, and its high basic strength make it extremely interesting as a material for further general investigation.

The interesting fact that solid salts of 1,4-di-(3-aminopropoxy)-pentane were obtained only when the acids were dibasic and contained an even number of carbon atoms has been pointed out. Determination of the crystal structures of the solid salts by means of X ray studies might suggest an explanation for this phenomenon.

The complete failure of the attempts to saponify $\beta$-alkoxypropionitriles by treatment with 9-22% sodium hydroxide solution was unexpected. Under the same conditions Bruson and Riener (12, 13) obtained excellent yields of acids from the 2-cyanoethyl derivatives of active methylene compounds. In these cases, however, the 2-cyanoethyl groups were attached to carbon atoms.

The properties of the material isolated from the basic hydrolysis of $\beta$-ethoxypropionitrile suggested that it might have been acrylic acid. A consideration of the facts that the addition of alcohols to acrylonitrile is catalyzed by bases and that an equilibrium is reached between a $\beta$-alkoxypropionitrile on the one hand, and acrylonitrile and an alcohol on the other, may throw some light on the problem. The addition of a base to a pure $\beta$-alkoxypropionitrile might

be expected to cause the formation of some acrylonitrile and an alcohol. Under the conditions of basic hydrolysis it would seem that the following reactions could take place:

$$ROCH_2CH_2CN \xrightarrow{NaOH} ROH + CH_2:CHCN$$

$$ROCH_2CH_2CN + NaOH + H_2O \rightarrow ROCH_2CH_2COONa + NH_3$$

$$CH_2:CHCN + NaOH + H_2O \rightarrow CH_2:CHCOONa + NH_3$$
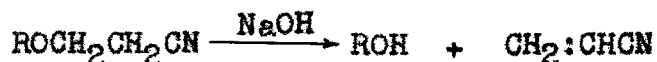
If it is assumed that the conjugated system of double bonds which takes part in the Michael condensation is modified in sodium acrylate, then this compound would not be expected to add an alcohol. The relative amounts of the various substances ultimately resulting would depend upon the rates of the competing reactions involved. It seems possible that this mechanism could account for the formation of the complex mixtures obtained in the basic hydrolysis of $\beta$-alkoxypropionitriles.

The acid hydrolysis of $\beta$-alkoxypropionitriles seems to be a fairly general method for the preparation of $\beta$-alkoxypropionic acids. Slightly lower yields were obtained in the saponification of the $\beta$-sec-alkoxypropionitriles and there was a general decrease in yield as the size of the alkyl group increased. Excellent yields were obtained with the four bifunctional $\beta$-alkoxypropionitriles containing only primary ether linkages.

Inasmuch as little attempt was made to determine

optimum conditions for the hydrolysis of $\beta$-alkoxypropioni-
triles, it is quite possible that the procedure may be sus-
ceptible to improvement. The use of dilute acid and longer
reaction times might improve some of the yields. Neverthe-
less, it is felt that the successful hydrolysis of $\beta$-alkoxy-
propionitriles affords a new and convenient method for the
synthesis of many $\beta$-alkoxypropionic acids. It should be
particularly valuable in the preparation of the $\beta,\beta'$-alkylene-
dioxydipropionic acids for which it is doubtful that any of
the previous methods would be satisfactory. It seems
possible that certain compounds of these types might find
application as wetting or flotation agents.

It is difficult to understand the decomposition of 1,4-
di-(2-cyanoethoxy)-pentane upon hydrolysis with hydrochloric
acid. The fact that lower yields were obtained in the saponi-
fication of $\beta$-sec-alkoxypropionitriles suggests that the com-
pounds containing secondary ether linkages may be more
sensitive to concentrated hydrochloric acid. Should this be
the case, then 1,4-di-(2-cyanoethoxy)-pentane, upon hydrolysis
with concentrated hydrochloric acid, may undergo a cleavage
of some sort at the secondary ether linkage with subsequent
formation of a mixture of hydrolysis products. The isolation
of a chlorine-containing compound from the reaction mixture
indicates a rupture of the molecule with addition of the
elements of hydrogen chloride. The tentative identification,

based upon analytical data, of this compound as the ethyl ester of a $\beta$-(chloroamyloxy)-propionic acid is certainly in support of this suggestion.

The successful conversion, at low temperatures, of 1,4-di-(2-cyanoethoxy)-pentane to the ethyl ester of the corresponding acid, indicates that the compounds are stable under sufficiently mild conditions. However, the low yields obtained, and the length and complexity of the preparation, make questionable the value of further investigation of this problem as an approach to the utilization of $\gamma$-valerolactone and 1,4-pentanediol.

SUMMARY

1.  The preparation of $\gamma$-phenylvaleric acid from benzene and $\gamma$-valerolactone by means of the Friedel and Crafts reaction was re-examined. The $\gamma$-phenylvaleric acid thus obtained was shown to be identical with that prepared by other methods. From $\gamma$-phenylvaleric acid, the solid p-bromophenacyl ester was prepared to furnish a derivative for future reference.

2.  It was found possible to cause benzene to condense with more than one molecular equivalent of -valerolactone to yield a mixture from which $\gamma, \gamma'$-phenylene-divaleric acid was isolated as the diethyl ester. The position of substitution in the benzene ring of this compound was not determined.

3.  Some previously described methods for the preparation of 1,4-pentanediol were reinvestigated. In each case improved yields of 1,4-pentanediol were obtained.

4.  2-Methyltetrahydrofuran was isolated and identified as a by-product in the hydrogenation of $\gamma$-valerolactone to 1,4-pentanediol.

5.  The addition of acrylonitrile to 1,4-pentanediol gave 1,4-di-(2-cyanoethoxy)-pentane which was characterized by conversion to the solid bis-(ethyliminoester hydrochloride).

6.  A series of new $\beta$-alkoxypropionitriles was prepared.

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7.  1,4-Di-(2-cyanoethoxy)-pentane was hydrogenated to yield 1,4-di-(3-aminopropoxy)-pentane. From this diamine a series of salts was prepared using monobasic and dibasic organic acids. Solid salts were obtained only from dibasic acids containing an even number of carbon atoms.

8.  Basic hydrolysis was found to be unsatisfactory for the conversion of $\beta$-ethoxypropionitrile, di-(2-cyanoethyl)-ether, and 1,4-di-(2-cyanoethoxy)-pentane to the corresponding acids.

9.  By means of acid hydrolysis, a series of new monobasic and dibasic acids of the $\beta$-alkoxypropionic type was prepared. These were characterized when possible by suitable solid derivatives such as p-bromophenacyl esters or simple amides.

10.  1,4-Di-(2-cyanoethoxy)-pentane, when subjected to acid hydrolysis, underwent an obscure decomposition. From the resulting mixture, a chlorine-containing acid was isolated as the ethyl ester. The analysis of this ester was in close agreement with that calculated for an ethyl $\beta$-(chloroamyloxy)-propionate.

11.  Two methods were found for the conversion of 1,4-di-(2-cyanoethoxy)-pentane to 1,4-di(2-carbethoxyethoxy)-pentane, the ethyl ester of the corresponding acid. Both of these methods involved the formation, at low temperatures, and the hydrolysis, at ordinary temperatures, of a mineral acid salt of the bis-ethyliminoester.

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