GLUTAMIC ACID: CHEMICAL SYNTHESES AND RESOLUTIONS

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I. INTRODUCTION

L-(+)-Glutamic acid is an important key amino acid component of proteins and in metabolic *trans* amination reactions. It has achieved commercial importance in the form of monosodium L-(+)-glutamate monohydrate (MSG) because of its remarkable property of enhancing the flavor of many foods. Production of MSG in 1962 in the United States reached a new high of 29 million pounds.

Syntheses of DL-glutamic acid and its resolution are given in numerous organic and biochemical textbooks. A recent survey given by Greenstein and Winitz (44) cites various procedures used in research but does not cover recent patent literature. This review concerns the recent literature, predominantly patents on the chemical syntheses of DL-glutamic acid. Data from U. S. journals through early 1963 and a fairly good coverage of 1962 foreign journals are included. All

pertinent U. S. patents issued through April, 1963, and almost all 1962 foreign patents are cited. The present survey also includes the special crystallization techniques for resolution of the DL-mixture and racemization of the D-(−)-glutamic acid to DL-glutamic acid. This latter process is important for commercial success. Microbial or enzymatic processes for production or resolution of MSG are not covered by this review, although many new ones have been developed recently. However, it should be mentioned that some glutamic acid is still produced by extraction from sugar beet wastes and by hydrolysis of proteins such as wheat gluten or soybean protein followed by extraction.

II. Syntheses of DL-Glutamic Acid

A. Synthesis of DL-Glutamic Acid from Acrylonitrile and Acrylates

1. Using Oxo Process

The Ajinomoto Company of Japan has selected an oxo reaction starting with acrylonitrile as the best synthetic process for the manufacture of DL-glutamic acid. Initial production at the rate of 300 metric tons per month of L-(+)-monosodium glutamate monohydrate started in January, 1963 (155), at the plant in Yokkaichi City, Mie Pref. A large expansion of this plant is planned, with a total expenditure of $11,000-000. This process is attractive because the acrylonitrile is an inexpensive starting material, to which low-cost carbon monoxide, hydrogen cyanide, ammonia, and water are added, to build the glutamic acid molecule. Most other processes involve appreciable molecular weight losses of the reagents used. Another advantage of the process is the possibility of recovery of the needed hydrogen cyanide as a by-product from the propylene–ammonia route to acrylonitrile. Ajinomoto's best published data show a 66% over-all yield of DL-glutamic acid from acrylonitrile.

The synthesis of glutamic acid from acrylonitrile or acrylates by the oxo process can be broken into three segments:

(1) The oxo process

$$RCH{=}CH_2 + CO + H_2 \xrightarrow[\text{octacarbonyl}]{\text{dicobalt}} RCH_2CH_2CHO \quad \text{I}$$

R = CN or COOY
Y = alkyl

(2) The Strecker synthesis

$$I + NaCN(\text{or } HCN) + NH_3 \rightarrow RCH_2CH_2CHCN \quad \text{II}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NH_2$$

(3) Hydrolysis

The third step is a simple acidic or basic hydrolysis to DL-glutamic acid (III).

$$II + H_2O \xrightarrow[\text{or } H^+]{OH^-} HOOCCH_2CH_2CHCOOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NH_2$$

DL-glutamic acid
III

The oxo reaction was first shown to proceed well (57% yield) with esters of acrylic acid by Gresham and Brooks (45). Many additional publications have appeared (2, 11, 47, 71, 126, 136, 152). The acrylate, dissolved in a nonpolar solvent in the presence of a cobalt catalyst (usually dicobalt octacarbonyl), was heated under pressure with carbon monoxide and hydrogen. The H_2–CO ratios varied from 4:1 to 1:1. The latter ratio was usually quite satisfactory. The temperature was about 120–130° and the pressure 200–500 atm. Yields of substituted propionaldehydes from acrylate esters were about 60–90% depending on conditions.

The first (17) reported oxo reaction of acrylonitrile (in methanol) gave γ,γ-dimethoxybutyronitrile (IV).

$$CH_2{=}CHCN \xrightarrow[CH_3OH]{CO+H_2} (CH_3O)_2CH_2CH_2CH_2CN \quad \text{IV}$$

The reaction conditions for acrylonitrile (73, 74, 28, 84, 92, 107, 208) were generally the same as for the acrylate esters with an 80% maximum yield of β-cyanopropionaldehyde (I).

The use of a polar solvent for this oxo reaction increased the reaction rate as shown in Table I (3, 81).

Table I

Effect of Solvent on the Oxo Reaction Rate

Solvent	Velocity constant k, min.$^{-1}$
Methyl Cellosolve	0.50
1-Propanol	.42
2-Propanol	.40
1-Butanol	.40
Ethanol	.28
Methanol	.24
Acetone	.09
Dioxane	.08
2-Butanol	.07
Benzene	.03
2-Methyl-2-propanol	.016
Nitrobenzene	Decomposition of catalyst, polymerization

Conditions: 160 ml. of solution containing 20 g. of acrylonitrile, and 1 mole % of cobalt carbonyl were charged into an autoclave and pressured to 150 kg./cm.^{2} with CO–H_2 (1:1) and heated at 120°.

The reaction proceeded smoothly and rapidly with the formation of a minimum of side products. The by-products were identified as propionitrile, propionaldehyde, hydroxybutyronitrile, propylamine, and ammonia (86). Acetone or methanol gave the highest

yields, while the other solvents gave good, but slightly lower yields. The effects of solvents on the oxo reaction of acrylonitrile were shown to be different from the effects with ordinary olefins (82). In general, the rate of the reaction was greater in solvents which permit disproportionation of cobalt carbonyl as a Lewis base. Differences in yield of β-cyanopropionaldehyde (I) in different solvents were demonstrated to be due to differences in the extent of the reducing reaction which took place, along with the hydroformylation of acrylonitrile. These facts indicate that the solvents take part in the oxo reaction. It was found that the difference in velocity constants was considerable for acrylonitrile, slightly observable for hexene-1 and cyclohexene, and negligible with hexene-2.

For maximum yields, it was necessary to remove the oxo catalyst before the Strecker reaction. This was accomplished by treatment of the oxo mixture with mineral acid followed by an ion-exchange treatment (4, 88, 90, 208), by distillation (6), or by passing air through the reaction mixture, which caused the catalyst to precipitate as cobalt oxide (83, 91).

The Strecker reaction, the next step in the over-all synthesis, was performed by treating the oxo products from methyl acrylate, with hydrogen cyanide to form the cyanohydrin, then with ammonia followed by hydrolysis to give DL-glutamic acid (46, 48). Alternatively, the oxo reaction mixture from acrylonitrile has been heated with hydrogen cyanide and ammonia (74, 85, 136), or with sodium cyanide, ammonium chloride, and ammonia, followed by hydrolysis to give DL-glutamic acid (72, 73, 153).

An elegant modification of the Strecker synthesis involved contacting β-cyanopropionaldehyde with a countercurrent flow of the hydrogen cyanide-containing gas mixture, resulting from the reaction of methane or carbon monoxide with ammonia, in the presence of excess ammonia; then hydrolyzing the products to produce DL-glutamic acid (89). The excess of ammonia is a key factor in this process. It was found (87) that hydrogen cyanide–ammonia mixtures were stable when a fivefold excess of ammonia was present. The largest degree of undesirable polymerization of hydrogen cyanide occurred when the ratio of ammonia to hydrogen cyanide was less than 1:1. The yield of DL-glutamic acid from this modification of the Strecker synthesis was 83% (90). This is the maximum reported to date for this reaction. Since the oxo reaction yield was 80%, the over-all yield from acrylonitrile to DL-glutamic acid was 66%.

$$\underset{\text{I}}{CH_3OOCCH_2CH_2CHO} \xrightarrow[CN^-]{NH_3,\ CO_2} \underset{\text{III}}{CH_3OOCCH_2CH_2CH(CO{-}NH)(NH{-}CO)}$$

(hydrolysis)

Another route, the Bucherer hydantoin synthesis, gave a 50% yield of DL-glutamic acid from the aldehyde produced in the oxo process (11, 185).

2. *Using Cyanoacetic Acid, Nitroacetic Acid, or Glycine (?)*

Cyanoacetic ester was condensed with acrylonitrile in one synthesis of DL-glutamic acid (165).

$$CH_2{=}CHCN + NCCH_2COOR \rightarrow \underset{\text{V}}{NCCH_2CH_2CH(CN)(COOR)}$$

$$\text{V} + HN_3 \rightarrow \underset{\text{VI}}{NCCH_2CH_2CH(CN)(NH_2)} \xrightarrow{\text{hydrolysis}} \underset{\text{III}}{\text{III}}$$

The initial condensation was carried out at 60° in 3 hr., and the reaction with hydrazoic acid was accomplished in sulfuric acid at 40° in 8 hr. Hydrolysis of the dinitrile in sulfuric acid was routine.

Similarly, esters of nitroacetic acid and acrylates were employed to give DL-glutamic acid (202).

$$O_2NCH_2COOR + CH(COOR){=}CH_2 \rightarrow \underset{\text{VII}}{ROOCCH_2CH_2CH(NO_2)COOR}$$

$$\text{VII} \xrightarrow[\text{catalyst}]{H_2} ROOCCH_2CH_2CH(NH_2)COOR \xrightarrow{\text{hydrolysis}} \underset{\text{III}}{\text{III}}$$

An improbable preparation of DL-glutamic acid was reported from glycine and acrylonitrile (39), but this patent application has been abandoned.

$$CH_2{=}CHCN + H_2NCH_2COOH \not\rightarrow NCCH_2CH_2CH(NH_2)COOH \rightarrow \underset{\text{III}}{\text{III}}$$

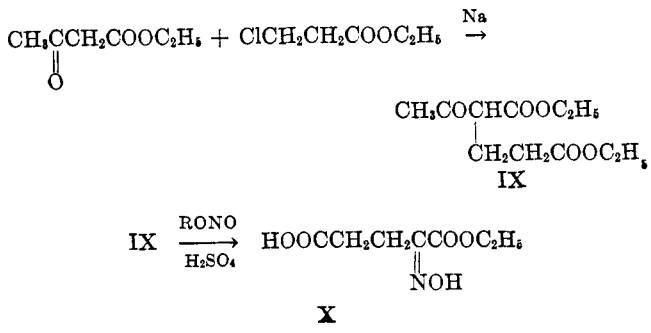
Although specific quantities were cited, we could not repeat this reaction (anhydrous) in our laboratory. Glycine has been cyanoethylated in aqueous base to give the expected bis-N,N-(2-cyanoethyl) glycine (VIII) (120).

$$CH_2{=}CHCN + H_2NCH_2COOH \xrightarrow{\text{aq. } OH^-} \underset{\text{VIII}}{(CNCH_2CH_2)_2NCH_2COOH}$$

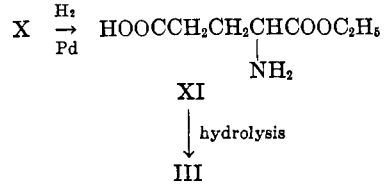
B. SYNTHESIS OF DL-GLUTAMIC ACID FROM ACETOACETIC ESTER

Syntheses of DL-glutamic acid from acetoacetic ester and β-chloropropionate were reported in 1930 (50) and in 1939 (119). In 1942 (54) the conversion

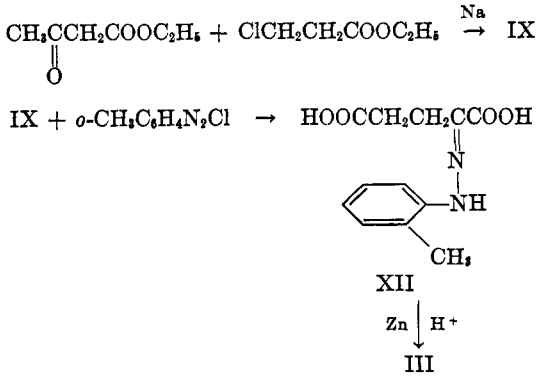
of substituted acetoacetic esters to α-oximino esters (IX), followed by reduction with hydrogen-over-palladium, was shown to give the corresponding amino acids. The yield of DL-glutamic acid was 74%.



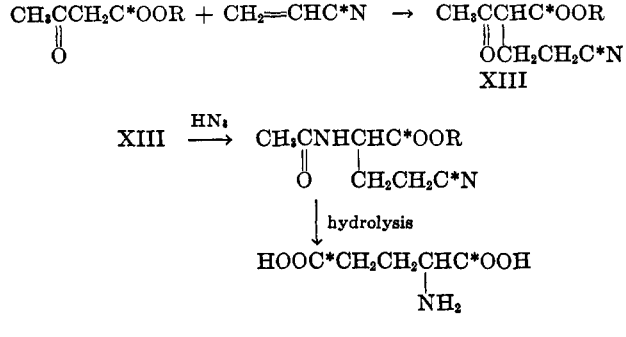
R = alkyl



The reduction of the *o*-tolylhydrazone of α-ketoglutaric acid with zinc dust in acetic acid gave good yields of glutamic acid (81–87%). In this case, the intermediate hydrazone was prepared from acetoacetic ester (30).

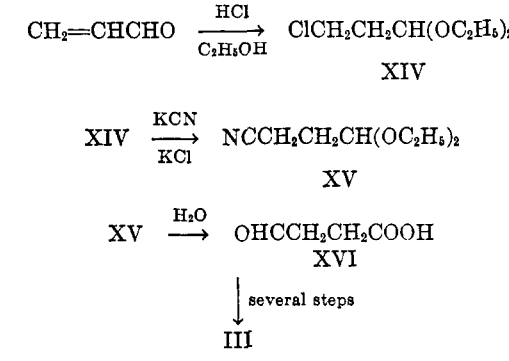


A condensation of labeled acrylonitrile with labeled acetoacetic ester, followed by reaction with hydrazoic acid and hydrolysis, gave a 76% yield of DL-glutamic acid-1,5-C_2^{14} (195).

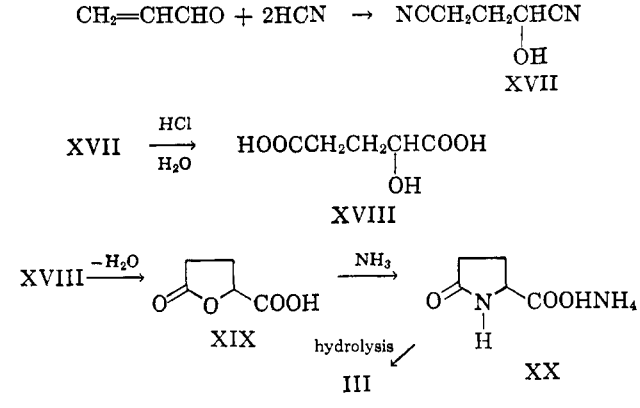


C. SYNTHESIS OF DL-GLUTAMIC ACID FROM ACROLEIN AND ACROLEIN DIMER

An early synthesis of glutamic acid from acrolein through β-formylpropionic acid (XVI) was accomplished by the following route (102)

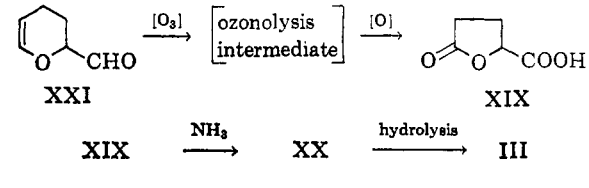


The reaction of two moles of hydrogen cyanide with one mole of acrolein at 50°, followed by hydrolysis with hydrochloric acid, was reported to give α-hydroxyglutaric acid lactone (XIX) (101). It was converted to DL-glutamic acid, in good yields, by heating at 200–250° with anhydrous or aqueous ammonia (96–98, 160).



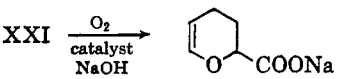
The reported over-all yield of α-hydroxyglutaric acid lactone (XIX) was about 37%. It is interesting to note that reaction of two moles of hydrogen cyanide with one mole of acrolein at 5° with an alkaline catalyst gave β-cyanopropionaldehyde (I), the same intermediate that is obtained in the acrylonitrile–oxo synthesis (200).

The dimer of acrolein (2-formyl-3,4-dihydro-2*H*-pyran) (XXI) also proved suitable as a starting material for glutamic acid synthesis. The reactions involved were ozonolysis, oxidation, ammoniation, and hydrolysis as follows (108, 135)



The reaction was carried out by dissolving acrolein dimer in a suitable organic solvent such as acetic acid, methylene chloride, or ethyl acetate; adding an ozone–oxygen mixture at −70 to 15°; and then oxidizing the resulting product with oxygen or hydrogen peroxide. The highest yields were obtained when oxygen was used for the oxidation. Oxidations of the ozonolysis intermediate and the aldehydic moiety were accomplished simultaneously and gave α-hydroxyglutaric acid lactone (XIX). Ammoniation of this product, as described previously, followed by hydrolysis gave DL-glutamic acid. The maximum reported yields were about 40%.

A more efficient synthesis from acrolein dimer (XXI) was obtained by oxidizing the aldehyde before ozonization. This was accomplished with silver oxide under anhydrous conditions (204), by the Tischenko reaction (203), or preferably by oxygen (or air) in aqueous base, in the presence of a catalyst of silver oxide in combination with a base metal oxide (67). Other catalytic oxidations have been reported (125).

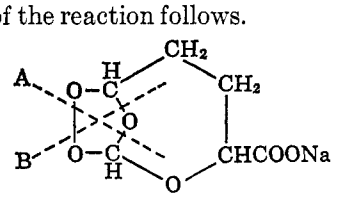


XXII

The resultant product, the sodium salt of 3,4-dihydro-2*H*-pyran-2-carboxylic acid (XXII), was ozonized in aqueous solution, followed by oxidation with hydrogen peroxide or oxygen, ammoniation, and hydrolysis to yield DL-glutamic acid. Similarly, the ethyl ester of 3,4-dihydro-2*H*-pyran-2-carboxylic acid was a suitable substrate in this reaction. Maximum reported over-all yields were 78% (109).

A study of the ozonolysis in methanol of unsymmetrical olefins, specifically dihydropyran (194), indicates that in an aqueous solution, a hydroxy hydroperoxy butyl formate would be the first intermediate, in the ozonization of sodium 3,4-dihydro-2*H*-pyran-2-carboxylate (XXII). If correct for this case, a secondary oxidation would not be required to obtain α-hydroxyglutaric acid lactone (XIX). However, for maximum yields, the second oxidation was necessary. This indicates that the electron-withdrawing influence of the carboxyl group has changed the course of the reaction to favor the elimination of carbon dioxide rather than formate. The evidence shows that both of the possible intermediates were obtained (109).

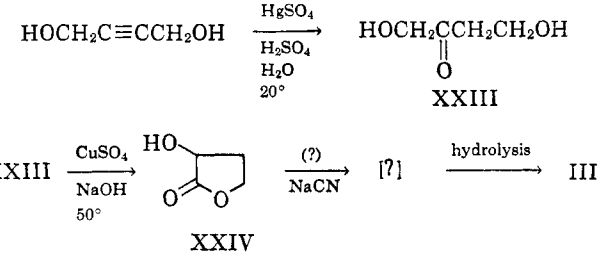
An oversimplified graphical illustration of the possible courses of the reaction follows.



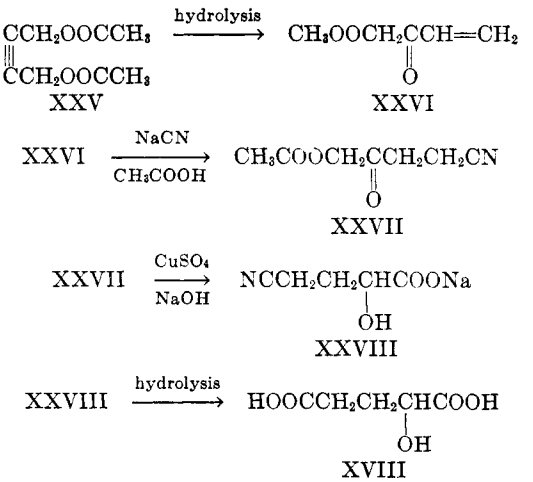
Cleavage of the postulated ozonolysis intermediate by route A in aqueous solution would produce the hydroxyhydroperoxy formate and ultimately α-hydroxyglutaric acid lactone (XIX). Cleavage by route B would give a sodium α-hydroxy-γ-formylbutyrate with elimination of carbonate. This intermediate requires further oxidation to produce the desired lactone XIX.

D. SYNTHESIS OF DL-GLUTAMIC ACID FROM 1,4-BUTYNEDIOL

One unconfirmed synthesis of glutamic acid from 1,4-butynediol has been shown by a combination of two patents. The first (192) described the production of ketobutanediol (XXIII), by reaction of mercuric sulfate in aqueous sulfuric acid with 1,4-butynediol, followed by reaction with copper sulfate and sodium hydroxide, which gave α-hydroxybutyrolactone (XXIV), in 78% yield. The second (191) showed the reaction of α-hydroxybutyrolactone (XXIV) with sodium cyanide at 180–190°, and hydrolysis of the reaction products, which gave DL-glutamic acid in 52% yield. The over-all reaction was



Another recent (190) unconfirmed patent shows 1,4-butynediol diacetate (XXV) as a starting material for the preparation of α-hydroxyglutaric acid (XVIII, 75% yield) which could be converted to DL-glutamic acid as described in a later section.



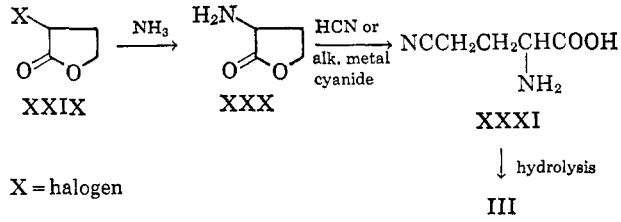
E. SYNTHESIS OF DL-GLUTAMIC ACID FROM BUTYROLACTONE

Substituted butyrolactones prepared from butyrolactone are suitable intermediates for glutamic acid

synthesis. All of the syntheses involve heating the substituted butyrolactone with a cyanide.

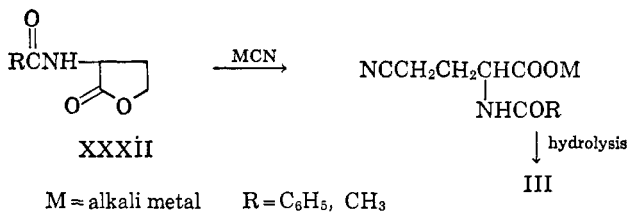
1. From α-Halogenated γ-Butyrolactone (XXIX)

The reported reaction sequence follows (143).



The ammoniation was done in aqueous ammonia. Treatment of the product with barium hydroxide gave α-aminobutyrolactone (XXX). The aminolactone reacts with alkali metal cyanides at 200–250° or with hydrogen cyanide in refluxing alcohol to produce α-amino-γ-cyanobutyric acid (XXXI), which on hydrolysis yielded DL-glutamic acid. It is unexpected that this reaction should proceed as well as described, in view of the instability of the amino compound XXX. If desired, the halogenated butyrolactone XXIX may be treated first with cyanide, then with ammonia to obtain the same results. The over-all yield was 40%.

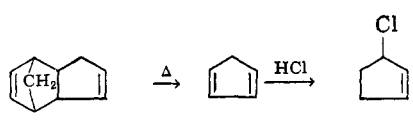
2. From α-Benzoylamino-γ-butyrolactone (XXXII) (154)



The reaction consists of fusing an alkali metal cyanide with benzoyl (or acetyl) aminobutyrolactone and hydrolyzing the resulting product to DL-glutamic acid. The over-all yield was 70%.

F. SYNTHESIS OF GLUTAMIC ACID FROM DICYCLOPENTADIENE

Dicyclopentadiene, a low-cost, readily available chemical, has been the center of much interest as a raw material for glutamic acid synthesis. All of the reported syntheses have the first two steps in common, both of which are well known, *i.e.*, cracking of dicyclopentadiene, followed by hydrochlorination of the resulting cyclopentadiene to form 3-chlorocyclopentene (124).

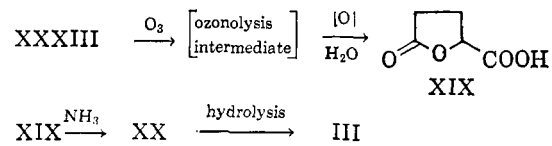


Both cyclopentadiene and XXXIII are unstable at room temperature, but can be stored at low temperatures.

From 3-chlorocyclopentene (XXXIII), several approaches to DL-glutamic acid have been taken.

1. Ozonization and Oxidation

3-Chlorocyclopentene reacts with ozone in suitable organic solvents to give an ozonolysis intermediate, which was oxidized to α-hydroxyglutaric acid lactone (XIX) (95, 100, 159, 172). Conversions of α-hydroxyglutaric acid lactone to DL-glutamic acid have been cited in other sections of this review. The reaction scheme follows.



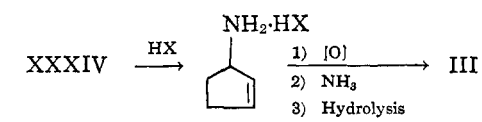
The ozonolysis of 3-chlorocyclopentene was accomplished by the simple addition of a mixture of ozone in oxygen to a solution of XXXIII in an organic solvent, such as methylene chloride, carbon tetrachloride, acetic acid, methyl acetate, and the like. The organic solvents were replaced by water to achieve cleavage and/or hydrolysis of the ozonolysis intermediates. Simultaneously, the products were oxidized with either oxygen, oxygen containing catalytic quantities of ozone, hydrogen peroxide, or nitric acid. The oxidation product XIX was converted readily with ammonia under pressure to ammonium DL-2-pyrrolidonecarboxylic acid (XX), which was hydrolyzed to DL-glutamic acid.

In this synthesis, as with acrolein dimer, the structure of the ozonolysis intermediate was not determined.

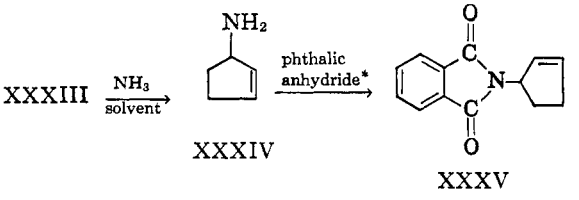
2. Ammoniation and Oxidation

The 3-chlorocyclopentene (XXXIII) molecule may also be employed in a different route: ammoniation, followed by oxidation, and hydrolysis to yield DL-glutamic acid. Cyclopentenylamine (XXXIV) was formed by reaction of 3-chlorocyclopentene with ammonia in a solvent such as toluene, in a suitable autoclave at room temperature (179). Yields were much lower when the reaction was done at atmospheric pressure in methanol or ethanol (99, 184). When this route is used, the amino group must be protected by a suitable blocking agent.

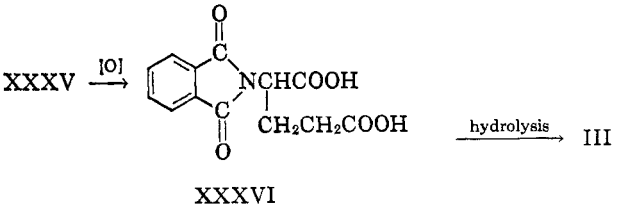
Inorganic acid salts were suitable blocking agents for cyclopentenylamine, if subsequent oxidations were carried out with ozone and hydrogen peroxide (or oxygen). Yields by this technique approached 35% (137, 183, 184).



A more satisfactory blocking was obtained by reaction of cyclopentenylamine with an anhydride such as phthalic anhydride. The reactions were

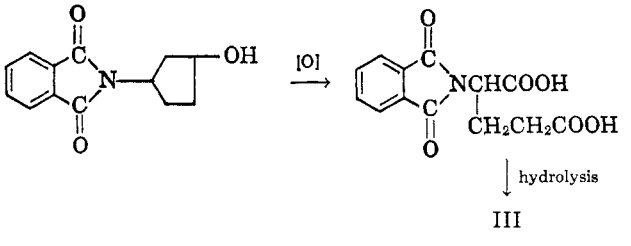


* Varied acid anhydrides were used.



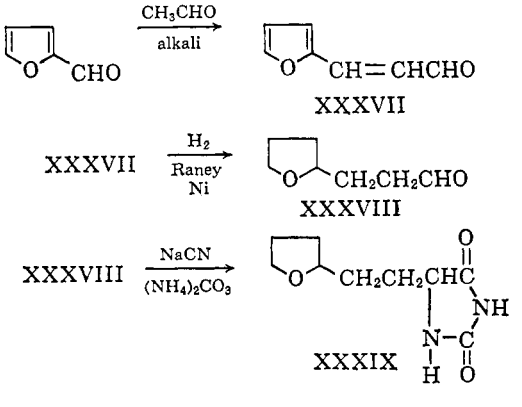
The oxidation of XXXV was accomplished with nitric acid, chromium trioxide, potassium permanganate (179), or ozone (183).

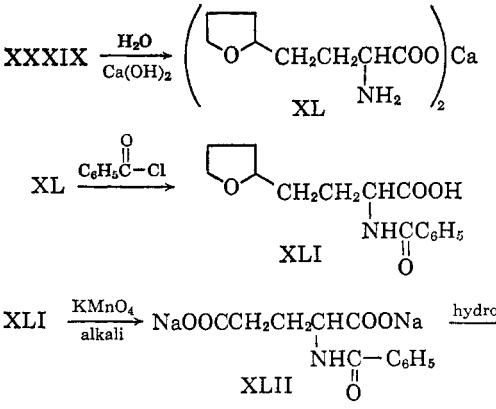
A modification of the above blocking technique involved hydration of the double bond of N-substituted cyclopentenylamine in sulfuric acid to form N-substituted 3-aminocyclopentanol. Oxidation of this intermediate results in the production of fewer side products, such as aspartic acid (180). Over-all yields were 35 to 40%.



G. SYNTHESIS OF DL-GLUTAMIC ACID FROM FURFURAL

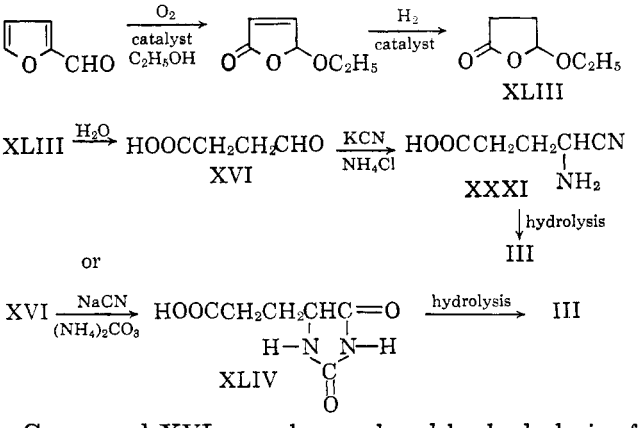
The synthesis of glutamic acid from furfural has not proved to be attractive (139). Yields for the most part were poor, and the reaction sequences were somewhat involved. For example, DL-glutamic acid has been synthesized as follows (62).



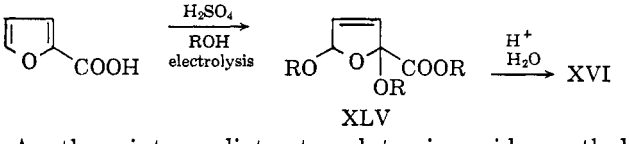


The yields on the individual steps are fair, but the over-all yield was <5%, based on furfural.

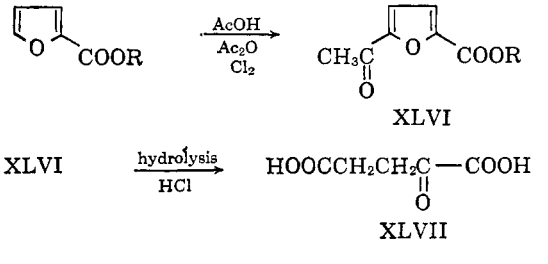
Syntheses employing photochemical oxidation of furfural using eosin or chlorophyll as catalysts have been published which cite yields as high as 39% (177, 207). The reactions were stated to be



Compound XVI was also produced by hydrolysis of 2,5-dialkoxy-2,5-dihydrofurancarboxylic acid (XLV) (128, 130), which had been obtained by electrolytic oxidation of furancarboxylic acid in alcoholic solution (52).



Another intermediate to glutamic acid, methyl 5-acetoxyfuroate (XLVI), was obtained by introducing chlorine into a solution of methyl furoate in acetic acid and acetic anhydride (132). Hydrolysis of the product gave α-ketoglutaric acid (XLVII), which can be converted to DL-glutamic acid by methods described later.



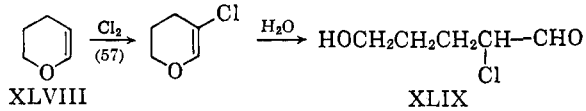
H. SYNTHESIS OF DL-GLUTAMIC ACID FROM GLUTARIC ACID

Glutaric acid is available in relatively large quantities from the oxidation of numerous organic compounds. For example, it is a by-product of oxidations which produce adipic acid. The first step in the synthesis of DL-glutamic acid is the preparation of an α-halo derivative of glutaric acid. These derivatives have been prepared by several routes.

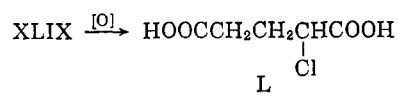
1. *Preparation of α-Chloroglutaric Acid and Derivatives*

a. From Dihydropyran

Chlorination of dihydropyran (XLVIII) followed by hydrolysis and oxidation yielded α-chloroglutaric acid (L).

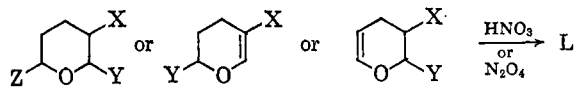


XLVIII XLIX



L

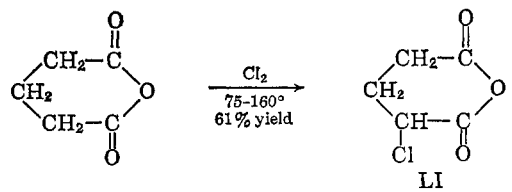
The oxidation was done in aqueous nitric acid; thus the hydrolysis and oxidation took place simultaneously (138). Polysubstituted pyrans were oxidized in a similar manner with nitric acid or nitrogen oxides and gave α-chloroglutaric acid (L) (181, 182).



X = halogen
Y and Z = halogen, oxygen, or hydroxy, alkoxy, or pyranyl ether group.

b. From Glutaric Anhydride

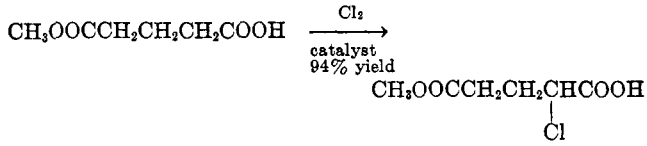
Glutaric anhydride was chlorinated readily to the α-chloro anhydride (LI) (104), which was converted to DL-glutamic acid as shown later.



LI

c. From Glutaric Esters

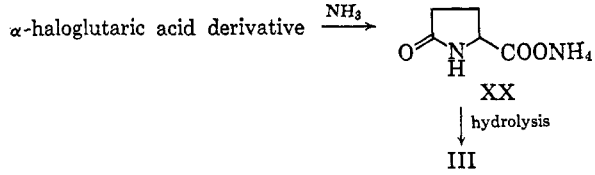
Chlorination of glutaric acid esters with chlorine, thionyl chloride, or sulfuryl chloride was done preferably in the presence of a catalyst such as phosphorus or phosphorus trichloride (103, 168, 188).



2. *Conversion of α-Chloroglutaric Acid and Derivatives to DL-Glutamic Acid*

The conversion of α-haloglutaric acid derivatives to DL-glutamic acid has been accomplished by two methods:

a. By reaction with aqueous or anhydrous ammonia, followed by hydrolysis of the lactam intermediate (160, 168, 187, 201).

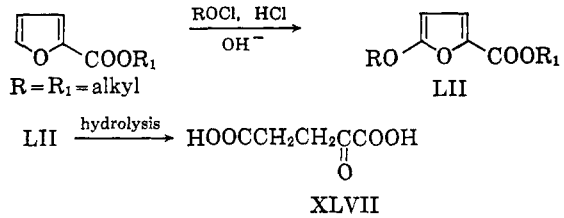


Reaction temperatures over 200° gave a maximum yield of 91%.

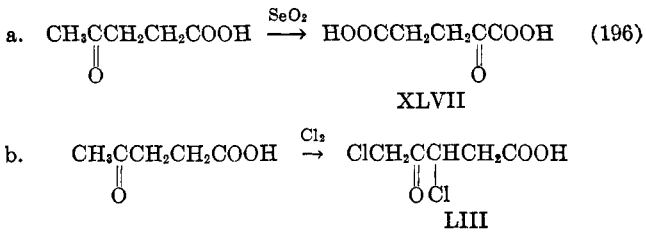
b. By reaction with potassium phthalimide followed by hydrolysis to give DL-glutamic acid. The reaction in refluxing dimethylformamide gave a 76% yield of DL-glutamic acid (157). If N^{15}-phthalimide was used, N^{15}-glutamic acid was obtained (118).

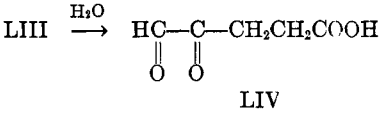
3. *Synthesis of DL-Glutamic Acid from α-Ketoglutaric Acid*

α-Ketoglutaric acid (XLVII) has been produced by several methods, in addition to the well known microbiological syntheses. Furancarboxylic esters, for example, have been oxidized in high yields to α-ketoglutaric acid esters (53, 129, 131, 171).

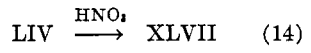


Levulinic acid or its dichloro derivative was oxidized to α-ketoglutaric acid (XLVII).



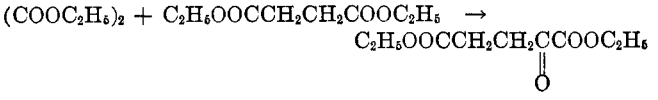


LIV

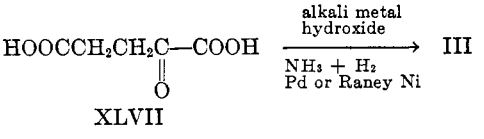


See section J for additional glutamic acid syntheses using levulinic acid.

The reaction of ethyl oxalate with ethyl succinate produced diethyl α-ketoglutaric acid (38).



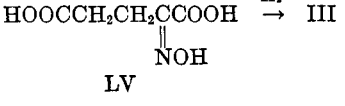
Usually the conversion of α-ketoglutaric acid to DL-glutamic acid was accomplished by reduction in the presence of ammonia or by reduction of its oxime. Early work on reduction of the keto acid was carried out by Knoop and Oesterlin in 1925 (106) and more recently by others (37, 79, 80, 112, 140). The reaction was performed by dissolving α-ketoglutaric acid in water, neutralizing with an alkali metal hydroxide, adding ammonia, and reducing under pressure with hydrogen and a hydrogenation catalyst.



XLVII

Yields as high as 94% have been reported; however, the average yield was 80–85%.

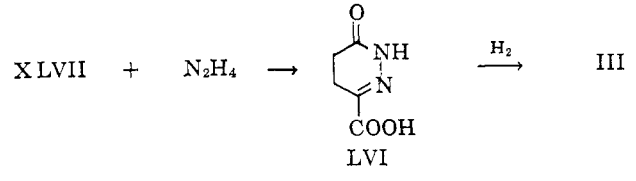
The reduction has been carried out electrolytically after conversion of calcium α-ketoglutarate to oximinoglutaric acid (LV) with hydroxylamine sulfate. The oxime was reduced electrolytically in sulfuric acid with a lead electrode at 0–30° and current density of 3–4 amp./dm.^{2}. The yield was 93% with a current efficiency of 60% (186).



LV

The oxime was reduced as a cobalt complex with hydrogen, under 90 atm. pressure at 100°, in the presence of potassium cyanide to yield DL-glutamic acid (133, 134).

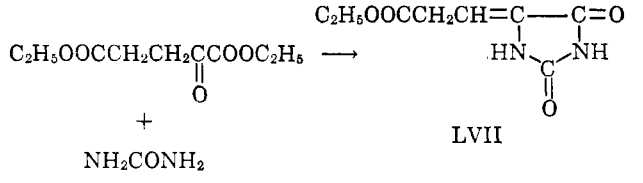
An intermediate formation of a pyridazone (LVI) (105) from α-ketoglutaric acid (XLVII) is another route to DL-glutamic acid (164).



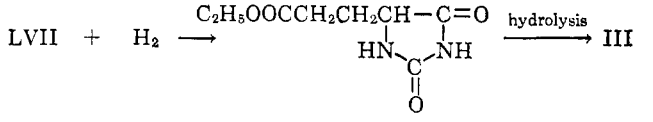
LVI

The reduction step was accomplished in a 90% yield by tin and hydrogen chloride or by electrolysis. Other reducing systems included iron and hydrogen chloride, zinc and sulfuric acid, and sodium amalgam. If palladium-on-charcoal and hydrogen was employed for the reduction, the product (61% yield) was DL-glutamine (105).

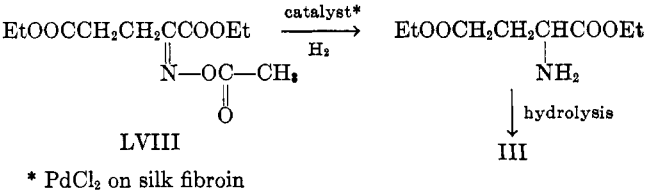
An alternate approach from ethyl α-ketoglutarate was by reaction with urea, reduction to form ethyl Δ^5,β-hydantoinpropionate (LVII), and hydrolysis to DL-glutamic acid (121).



LVII



A partial asymmetric synthesis of glutamic acid was reported by hydrogenation of diethyl α-acetoximinoglutarate (LVIII) in the presence of an asymmetric catalyst. The catalyst was obtained by absorption of palladium chloride on silk fibroin, followed by reduction. The glutamic acid (39% yield) had $[\alpha]^{15}_D$ +2.25° (*c* 7%, in 2 *N* hydrochloric acid) (7). Optically pure L-(+)-glutamic acid has $[\alpha]^{22.4}_D$ +31.4° (*c* 1.00, in 6 *N* hydrochloric acid).

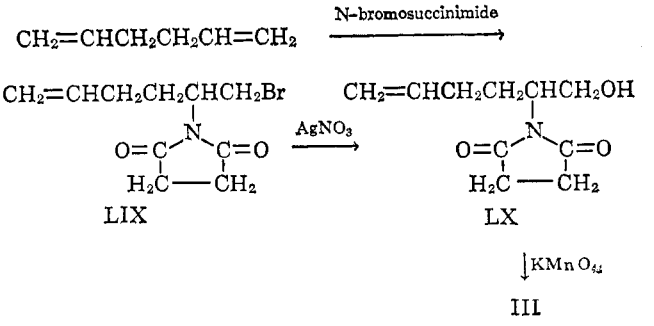


LVIII

* $PdCl_2$ on silk fibroin

I. SYNTHESIS OF DL-GLUTAMIC ACID FROM 1,5-HEXADIENE

The action of N-bromosuccinimide on 1,5-hexadiene gave succinimido-2-bromo-1-hexene-5 (LIX). Treatment of this intermediate with silver nitrate yielded succinimido-2-hexene-5-ol-1 (LX), which was oxidized with potassium permanganate in acetone to DL-glutamic acid (49). No yields were given.

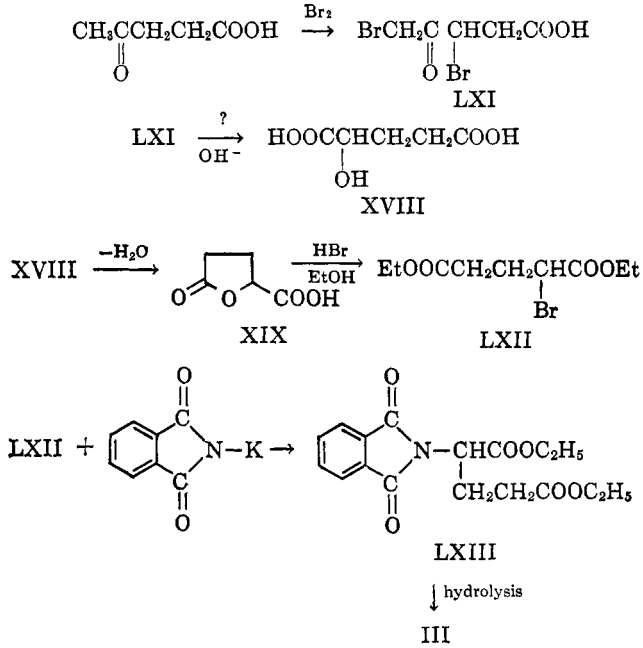


III

J. SYNTHESIS OF DL-GLUTAMIC ACID FROM LEVULINIC ACID

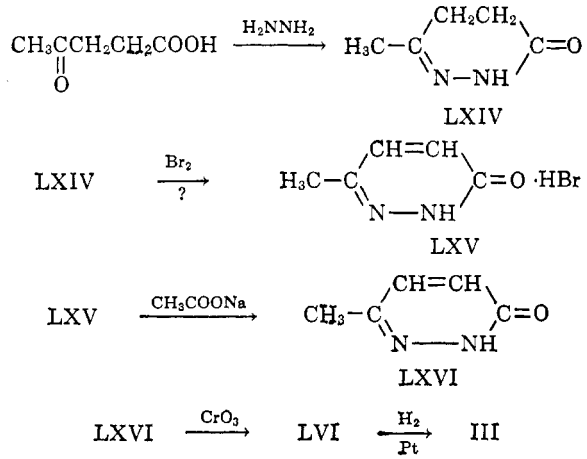
Levulinic acid cannot be considered as a good source material for the preparation of glutamic acid. All of the syntheses from this raw material are hampered by a multiplicity of reaction steps and/or low yields. For example, the following syntheses have been published.

A 1956 synthesis reported an over-all yield of 24% (127). The claimed reaction steps were

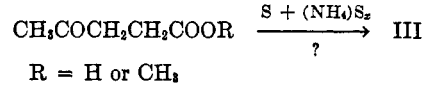


Application of modern ammoniation techniques to XIX would simplify this synthesis.

Another approach through a pyridazone gave good yields (53% over-all) through LVI. The yield for the hydrogenation step to DL-glutamic acid was not given (40).



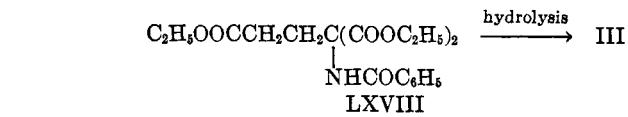
A modification of the Wildgerodt reaction with levulinic acid (or ester) gave a 20% yield of DL-glutamic acid (117).



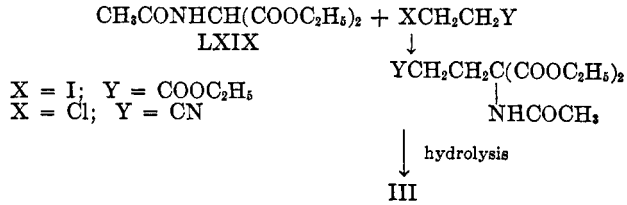
K. SYNTHESIS OF DL-GLUTAMIC ACID FROM MALONIC ACID DERIVATIVES

More procedures for synthesizing DL-glutamic acid have been developed using malonic ester derivatives than from any other intermediate. None is ever likely to be commercially successful. However, they are particularly useful for the preparation of labeled glutamic acid.

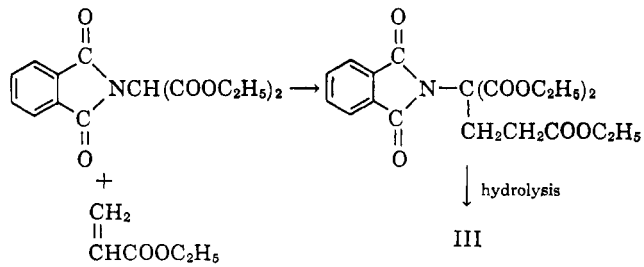
The first (25) synthesis in 1931 with the benzoyl derivative of aminomalonic diethyl ester (LXVII) and β-chloropropionic ester gave a 52% yield of DL-glutamic acid.



Diethyl acetamidomalonic ester was alkylated conventionally with ethyl β-iodopropionate or β-chloropropionitrile (77, 78).

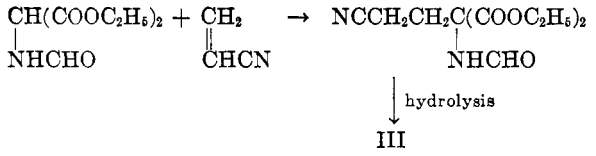


A Michael condensation of ethyl phthalimidomalonate occurred readily with an acrylic ester (116) and gave a 75% yield of DL-glutamic acid.

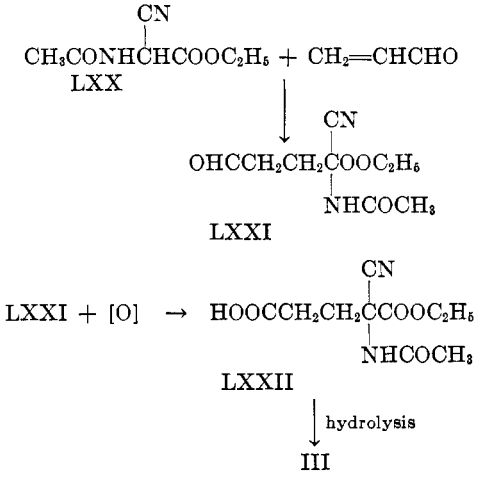


Diethyl acetamidomalonate (LXIX) underwent the same type of Michael reaction with methyl acrylate (57% yield of DL-glutamic acid) (173) and acrylonitrile (63% yield of DL-glutamic acid) (10). By-products formed from this Michael reaction have been elaborated (20).

A 57% yield of DL-glutamic acid was obtained from formamidomalonic ester and acrylonitrile (41).

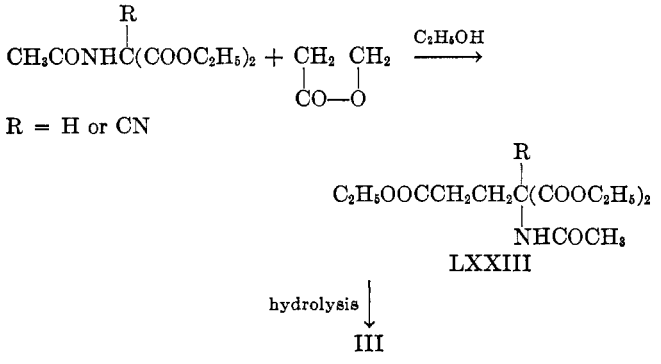


Ethyl acetamidocyanoacetate is another useful intermediate which gave a 54% yield of DL-glutamic acid (123, 198, 199).

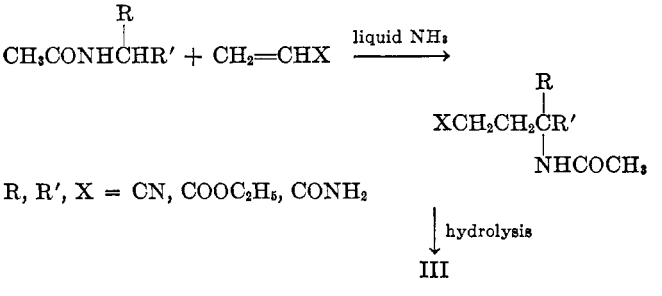


Similarly, acrylonitrile with ethyl acetamidocyanoacetate (LXX) gave a 67% yield of DL-glutamic acid (55).

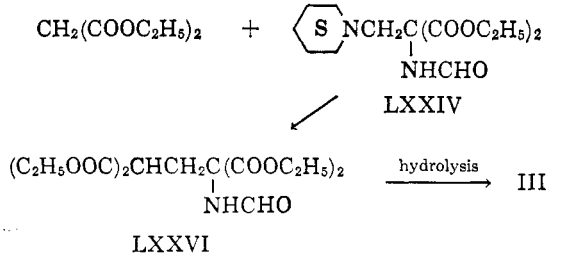
The reaction between β-propiolactone and diethyl acetamidomalonate (or ethyl acetamidocyanoacetate) produced excellent yields of intermediates which were hydrolyzed to DL-glutamic acid (87% yield) (193).



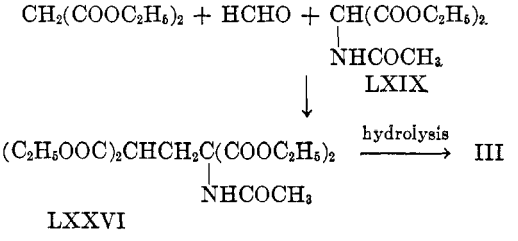
Liquid ammonia proved to be a good solvent for the Michael reaction of diethyl acetamidomalonate or ethyl acetamidocyanoacetate with acrylonitrile, acrylic ester, or acrylamide. An alkaline catalyst was not necessary for this reaction (170).



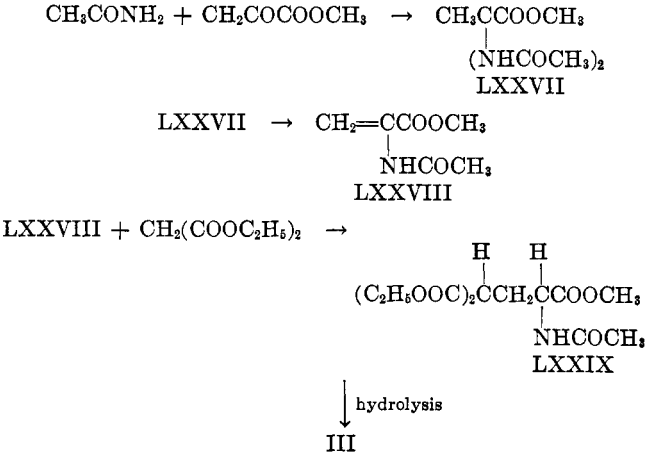
Diethyl malonate has yielded DL-glutamic acid (75%) by reaction with the piperidine Mannich base of formamidomalonic ester (LXXIV) (58).



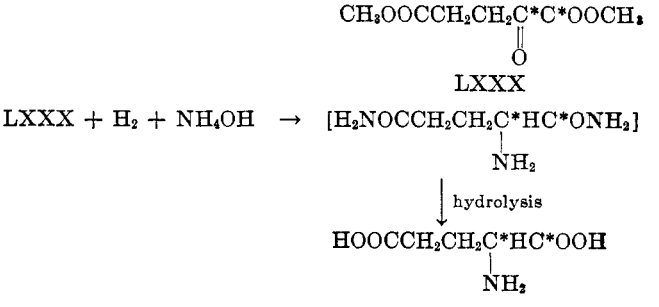
Similarly acetamidomalonic ester and formaldehyde gave a 75% yield of DL-glutamic acid (59).



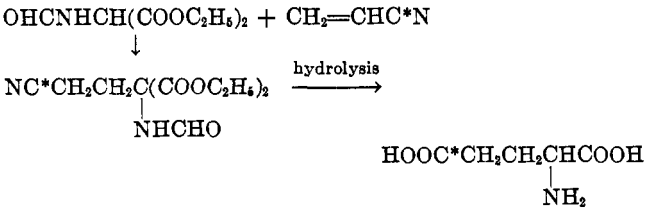
With α-acylaminoacrylic esters (LXXVIII) and diethyl malonate, a 55% yield of DL-glutamic acid was obtained (205).



Malonic ester reactions have been used extensively to make labeled glutamic acid. For example, glutamic acid-1,2-C_2^{14} was prepared as follows (112, 175).

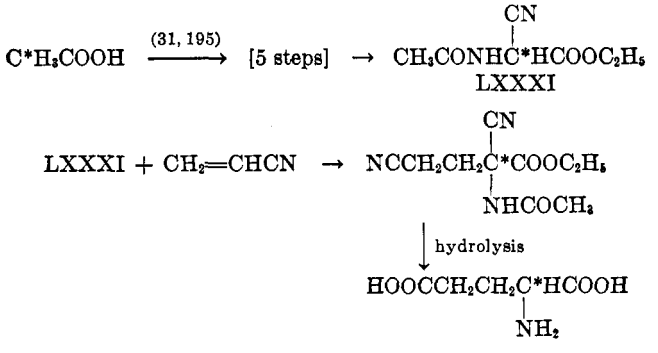


Glutamic acid-5-C^{14} has been made from labeled acrylonitrile by a reaction with formamidomalonic ester (195).



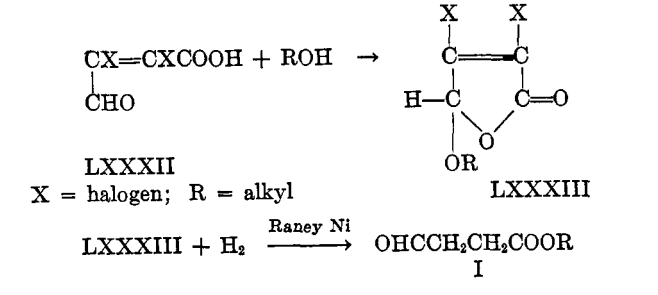
[This labeled compound has also been made by similar routes (22, 175).]

A synthesis of glutamic acid-2-C^{14} was developed from labeled acetic acid (166).



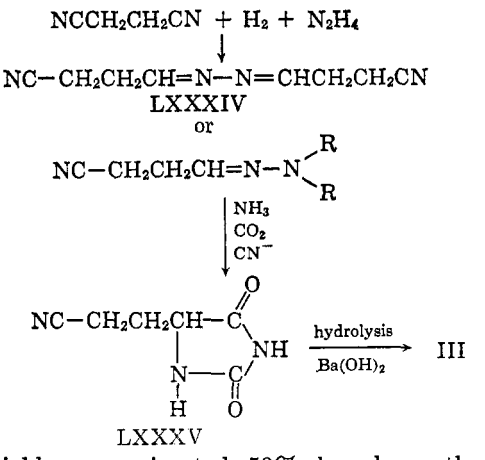
L. SYNTHESIS OF DL-GLUTAMIC ACID FROM MUCOHALIC ACID

Esterification of mucohalic acids (LXXXII) followed by catalytic reduction gave a 57% over-all yield of β-formylpropionic esters (51). The latter can be converted to DL-glutamic acid by processes previously cited.



M. SYNTHESIS OF DL-GLUTAMIC ACID FROM SUCCINONITRILE

A hydantoin was an intermediate in a new synthesis of glutamic acid from β-cyanopropionaldehyde azine (LXXXIV) or hydrazone (26). The starting materials were prepared by hydrogenating succinonitrile in the presence of a hydrazine. Treatment of the azine (or hydrazone) with ammonium carbonate and hydrogen cyanide at moderate temperatures produced the hydantoin, which was hydrolyzed to glutamic acid. The over-all reactions were



The yields approximated 50% based on the intermediate hydrazone.

N. SUMMARY

TABLE II

SUMMARY OF DL-GLUTAMIC ACID SYNTHESES

Starting chemicals	Steps	Yield, % (maximum over-all)	Key references
Acrylonitrile	3	66	89, 92
Acrylic esters	3	64	72, 152
Acrylic esters / Nitroacetic acid	4	..	202
Acrylonitrile / Cyanoacetic esters	3	..	165
Acetoacetic esters			
1. β-Chloropropionic acid esters	4	74	54
2. Acrylonitrile	3	76	195
Acrolein	4	..	101
Acrolein dimer	5	78	109
1,4-Butynediol	4	52	191, 192
1,4-Butynediol	6	67	190
Butyrolactone (α-halo)	5	40	143
Butyrolactone (α-benzoylamino)	2	70	154
Dicyclopentadiene	4	62	159
Dicyclopentadiene (cyclopentylamine)	4	40	179
Furfural	7	39	207
Glutaric acid (*via* α-haloglutaric acid)	3	91[a]	103
Glutaric acid (*via* α-ketoglutaric acid)	2	94[b]	140
1,5-Hexadiene	3	..	49
Levulinic acid	5	24	127
Malonic acid +			
1. Benzoylamino malonic ester β-halopropionic ester	2	57	25
2. Phthalimidomalonate acrylic esters	2	75	116
3. Acetamidomalonic esters, acrylic esters, or acrylonitrile	2	63	173
4. Formamidomalonic esters, acrylonitrile	2	57	41
5. Acetamidocyanoacetic esters, acrolein, or acrylonitrile	3	54	55
	3	67	199

TABLE II (*continued*)

6. Acetamidomalonic esters, β-propiolactone	2	87	193
7. Malonic ester, formamidomalonic ester (Mannich base)	2	75	60
8. Acetamidomalonic ester, formaldehyde	2	75	59
9. Malonic esters, α-acylamino acrylic esters	2	55	205
10. Malonic esters, oxalic esters	4	..	175
Mucohalic acids	4	..	51
Succinonitrile	4	50[c]	26

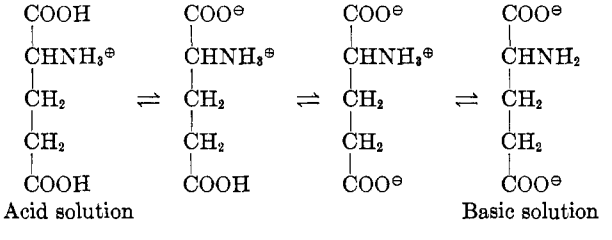
[a] Yield based on α-haloglutaric acid (or derivative). [b] Yield based on α-ketoglutaric acid. [c] Yield based on hydrazone.

III. RESOLUTION OF DL-GLUTAMIC ACID

A. SELECTIVE CRYSTALLIZATION

No doubt the successful application of the selective crystallization technique to the resolution of DL-glutamic acid was a major factor in the predicted economic success for the production of monosodium L-(+)-glutamate by chemical synthesis. The method does not require expensive optically active resolving agents used in classical procedures. This process works when the solid DL-compound is more soluble in a solvent than either the solid L- or D-isomers. Fortunately, this is true for a number of glutamic acid salts (and free glutamic acid) in water. However, alkali metal salts such as the sodium and potassium (24) salts are exceptions and cannot be resolved as such.

Some of the physical properties of glutamic acid will be of interest (176). The naturally occurring form of glutamic acid has the L-configuration. Its hydrochloride is dextrorotatory; $[\alpha]^{22.4}_D$ +31.4° (*c* 1.00, in 6 *N* hydrochloric acid). L-(+)-Glutamic acid forms orthorhombic, bisphenoidal crystals from aqueous alcohol. L-(+)-Glutamic acid has pK_{a_1} 4.07, pK_{a_2} 9.47, and pK_b 11.9. In aqueous solutions it ionizes as follows.



Acid solution Basic solution

Decomposition points of 208° to as high as 250° are cited, showing the effect of variations in the rate of heating. A tabulation of illustrative solubility data has been made (Table III).

It is noteworthy that the solubility of DL-glutamic acid hydrochloride is about twice the solubility of the D- or L-antipodes in concentrated hydrochloric acid (110).

TABLE III

SOLUBILITY IN WATER

Compound	Temperature, °C.	Solubility, g./l.	Reference
L-(+)-Glutamic acid	0	3.41	169
	25	8.64	
	50	21.9	
	75	55.3	
	100	140	
DL-Glutamic acid	0	8.55	169
	25	20.5	
	50	49.3	
	75	119	
	100	285	
Monosodium L-(+)-glutamate monohydrate	0	514	144
	25	627	
	50	765	
	75	933	
	100	1140	
Monosodium DL-glutamate dihydrate	0	158	144
	25	243	
	50	372	
	75	570	
	100	875	
L-(+)-Glutamic acid hydrochloride	0	298	144
	25	479	
	50	769	
	75	1240	
	100	1990	
DL-Glutamic acid hydrochloride	0	471	144
	25	698	
	50	1030	
	75	1540	
	100	2280	

A recent review (167) summarizes data for the resolution of optical isomers by crystallization. It includes resolutions of DL-glutamic acid. Some of the data will be repeated, in order to make the present review complete.

1. *Resolution of* DL-*Glutamic Acid Salts*

The resolution of DL-glutamic acid hydrochloride by selective crystallization during extended storage was reported by Kogl and his co-workers in 1943 (111). It has also been used (112) to resolve DL-glutamic acid hydrochloride labeled with C^{14}. None of these procedures was suitable for commercial utilization.

Many patents have been issued which claim a resolution of DL-glutamic acid salts. These patents outline very specific operating conditions and indicate that the hydrochloride is the best one for resolution of DL-glutamic acid.

A specific example (161) will illustrate the resolution achieved. An aqueous mixture containing 52 weight % of DL-glutamic acid hydrochloride was heated to about 50° to dissolve the solids. This solution was cooled rapidly to 30° to give a highly supersaturated solution. The temperature was maintained at 30° during the resolution process. Seed crystals (through

200 mesh, U. S. Standard Sieve Series) were added in an amount equal to 5% by weight of L-(+)-glutamic acid hydrochloride in solution. At the end of 30 min., the crystallization was terminated by a rapid filtration. The separated solids were the seed crystals, plus about 32% by weight of the L-(+)-glutamic acid hydrochloride originally in the solution. The crystals contained about 99% by weight of L-(+)-glutamic acid hydrochloride and about 1% D-(−)-glutamic acid hydrochloride. They were purified by dissolving in water, adjusting the solution of pH 3.2 with sodium hydroxide, and crystallizing free L-(+)-glutamic acid, with a purity which approached 100%. It is important to recover the glutamic acid from the aqueous glutamic acid hydrochloride filtrate. This was done by allowing the D-(−)-glutamic acid hydrochloride to crystallize. It was collected by filtration. This D-(−)-glutamic acid hydrochloride was racemized to DL-glutamic acid, as described in a later section. The second filtrate contained DL-glutamic acid hydrochloride, which was recycled to the resolution process. The procedure can be varied. For example, if D-(−)-glutamic acid hydrochloride seed crystals are used, the first isolated product will be D-(−)-glutamic acid hydrochloride.

A novel technique employed two different sizes of seed crystals (23) to resolve DL-glutamic acid hydrochloride. Large crystals (greater than 25 mesh) of L-(+)-glutamic acid hydrochloride and small (through 200 mesh) crystals of D-(−)-glutamic acid hydrochloride were mixed and added to a supersaturated solution of DL-glutamic acid hydrochloride. Both forms of glutamic acid hydrochloride crystallized and were removed by filtration. A sieve was used to separate the crystals of D-(−)- and L-(+)-glutamic acid hydrochloride. The large crystals were L-(+)-glutamic acid hydrochloride and the small crystals were D-(−)-glutamic acid hydrochoride.

Other resolution procedures are recorded (32, 35, 145, 149, 150). A modification shows that the addition of hydrogen chloride to a solution of glutamic acid in either sulfuric or phosphoric acid (33) improved the resolution of DL-glutamic acid hydrochloride.

A procedure related to that described by Zaugg (209) for *dl*-methadone gave a partial resolution of DL-glutamic acid hydrochloride (146). Brick fragments, individually saturated with D-(−)-glutamic acid and with L-(+)-glutamic acid, were suspended in an aqueous solution of DL-glutamic acid hydrochloride, which was cooled to provide supersaturation. Crystallization of the two isomers occurred on the brick fragments.

Many of the patents cited above in this section also claim resolutions of DL-glutamic acid using varied salts. Other patents claim satisfactory resolutions with ammonium (9, 43, 149) and zinc glutamates (148).

2. Resolution of DL-*Glutamic Acid Free Acid*

Several Ajinomoto patents cite details for the continuous resolution of DL-glutamic acid as the free acid in a fluidized bed system consisting of columns connected in series (5, 69, 70). Supersaturated aqueous DL-glutamic acid solutions and slurries of D-(−)-glutamic acid and L-(+)-glutamic acid seed crystals were added to the columns, to accomplish resolution of the DL-glutamic acid.

Other Ajinomoto patents (56) claim it was beneficial to use orthorhombic, α-form seed crystals of D-(−)-glutamic acid to resolve DL-glutamic acid.

The effect of the inclusion of other optically active compounds in the solution used for resolution of DL-glutamic acid was quite pronounced. An increase in the solubility of L-(+)-glutamic acid, without appreciably affecting the solubility of D-(−)-glutamic acid, was achieved by adding L-(+)-aspartic acid (158), L-(+)-leucine (158), and γ-methyl L-(+)-glutamate (34) to aqueous slurries of DL-glutamic acid. In these cases the insoluble material recovered by filtration was D-(−)-glutamic acid. The latter procedure (34) was best because it gave pure material.

A number of other patents also claim resolution of DL-glutamic acid as the free acid (15, 16, 19, 122, 147, 161, 189). Many of these procedures used acids or bases to prepare concentrated solutions of DL-glutamic acid.

B. RESOLUTION OF DL-GLUTAMIC ACID BY OPTICALLY ACTIVE AMINO COMPOUNDS

Classical resolution techniques have served to resolve DL-glutamic acid as shown in Table IV. It is unlikely that any of these methods can compete economically with the selective crystallization procedure described above.

TABLE IV

RESOLUTION OF DL-GLUTAMIC ACID BY OPTICALLY ACTIVE AMINO COMPOUNDS

Resolving agent	Reference
cis-Dinitrobis(ethylenediamine)cobalt(III) ion	27
(+)- and (−)-1-hydroxy-2-aminobutane	162
L-(+)-Leucinamide	63, 94
L-(+)-Lysine	66, 113
Oxalatobis(ethylenediamine)cobalt(III) ion	27
L-Phenylalaninamide	94
L-(+)-1,1,3-Triphenyl-2-aminopropanol-1	75
L-(+)-Tyrosinamide	94
L-Tyrosine hydrazide	174

Resolutions in which optically active 2-pyrrolidonecarboxylic acid or glutamic acid was used to resolve racemic amines such as α-phenylethylamine and lysine (28, 163) have been reported. The reverse procedure is obviously applicable to the resolution of DL-2-pyrrolidonecarboxylic acid and DL-glutamic acid (21).

C. RESOLUTION OF DL-GLUTAMIC ACID BY ASYMMETRIC ION EXCHANGERS

An asymmetric ion-exchange resin was prepared from L-(−)-tyrosine, formaldehyde, and chromotropic acid, resorcinol, or *m*-toluidine (115). Only partial resolutions of DL-glutamic acid were achieved by these resins. A similar resolution of other amino acids has been described (68).

D. RESOLUTION OF DL-2-PYRROLIDONECARBOXYLIC ACID

The anhydro form of DL-glutamic acid is DL-2-pyrrolidonecarboxylic acid. This anhydro form was resolved with quinine (61, 178), tyrosine esters (65), L-(+)-leucinamide (93), and D-(−)-α-methylbenzylamine (151). Resolutions of other glutamic acid derivatives are discussed in the next section.

E. RESOLUTION OF DL-GLUTAMIC ACID DERIVATIVES

A number of DL-glutamic acid derivatives have been resolved. Since free glutamic acid can be resolved readily, these specific procedures offer little promise of commercial use.

TABLE V

RESOLUTION OF DL-GLUTAMIC ACID DERIVATIVES

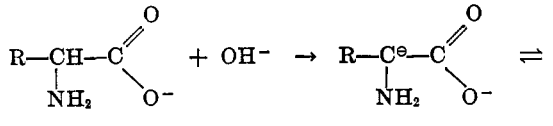
Glutamic acid derivative	Resolving agent	Reference
N-Acetyl	D-(−)-α-Methylbenzylamine	42
N-Benzoyl	Strychnine	36
N-*p*-Nitrobenzoyl	Strychnine	206

IV. RACEMIZATION OF D-(−)-GLUTAMIC ACID

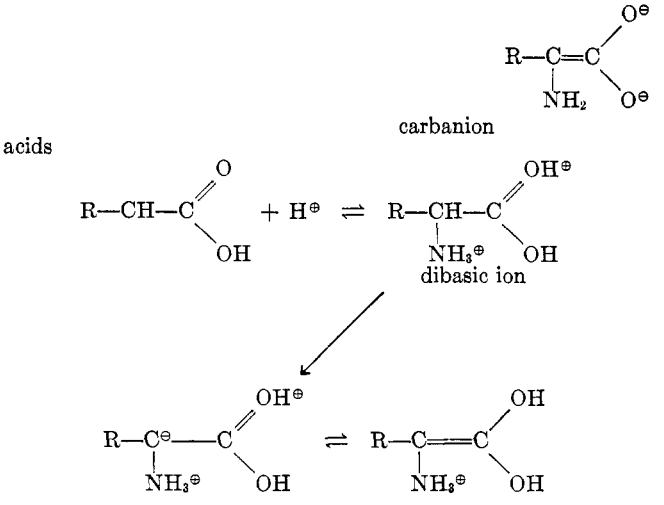
Until a use develops for D-(−)-glutamic acid, it is essential for economic reasons to convert it to L-(+)-glutamic acid. This is done by racemization of D-(−)-glutamic acid to DL-glutamic acid, followed by a resolution of the DL-glutamic acid.

The only studies covered in this review were those aimed at developing methods for producing DL-glutamic acid by racemizing D-(−)- or L-(+)-glutamic acid. Consequently, many of the older publications concerned with minor amounts of racemization are not cited. The literature on racemization was reviewed last in 1948 (12). The first step in the racemization of an α-amino acid is ionization. This ionization is followed by dissociation of the α-hydrogen atom to leave a carbanion. Resonance leads to the formation of a double bond and loss of asymmetry. The reactions which are proposed in bases or acids are

bases



acids



A. SULFURIC ACID PROCESS

An essentially quantitative racemization of D-(−)-glutamic acid to DL-glutamic acid was claimed (8) by heating the D-(−)-glutamic acid in a 30 to 50% sulfuric acid solution, in an autoclave at 170 to 190°. Decomposition was very slight as it was measured to be 2.5% in 15 hr. at 175°. Specific details for one example are: "A mixture comprising 397.5 g. of D-(−)-glutamic acid, 396 g. of sulfuric acid, and 381.5 g. of water was heated in an autoclave at a temperature of 185° for 4 hr. The optical rotation of the reaction mixture was zero. Caustic soda was added to this reaction mixture to adjust its pH to 3.2 and the DL-glutamic acid which crystallized was filtered. The crystals weighed 340 g. and their nitrogen content was 8.45%. Accordingly, the quantity of DL-glutamic acid was 301.8 g. The content of glutamic acid nitrogen in 3904 g. of mother liquor was 0.211% and the DL-glutamic acid was therefore 86.5 g. Thus the total quantity of DL-glutamic acid was 383.3 g. and the yield of DL-glutamic acid was 97.7%."

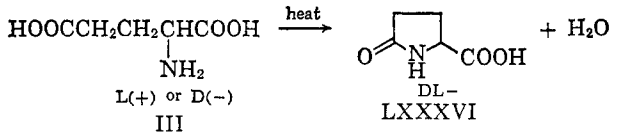
This process is unique in that free DL-glutamic acid is obtained. All prior procedures yielded DL-2-pyrrolidonecarboxylic acid, which required acidic or basic hydrolysis to yield free DL-glutamic acid. We found that the reaction mixture develops little color. An important disadvantage of the process is the use of large quantities of sulfuric acid and sodium hydroxide.

The Ajinomoto process should give combined resolution–racemization yields of about 95%. Since they claimed a 66% yield of DL-glutamic acid from acrylonitrile, the over-all yield of monosodium L-(+)-glutamate from acrylonitrile should be about 63% of theory. This is very good.

B. CONVERSION OF D-(−)-GLUTAMIC ACID TO DL-2-PYRROLIDONECARBOXYLIC ACID BY HEAT

Heating D-(−)-glutamic acid at 190–200° caused dehydration and racemization to DL-2-pyrrolidone-

carboxylic acid (LXXXVI). A subsequent hydrolysis of the crude black product with boiling aqueous hydrochloric acid gave a 70% yield of DL-glutamic acid (13).



Small (20 g.) samples required a 3-hr. heating period while 500 g. samples took 6 hr. In this simple procedure, which was first described in 1910 (1), only partial racemization was observed. A practical application of this method is illustrated in a patent (35).

A recent patent (142) reported the preparation of pure DL-2-pyrrolidonecarboxylic acid by heating D-(−)-glutamic acid in an autoclave with water at 200°. Specific details for one example are: thirty grams of D-(−)-glutamic acid and 50 g. of water were heated in an autoclave for 3 hr. at 200°, followed by crystallization overnight at 5–10°. The separated DL-pyrrolidonecarboxylic acid weighed 17.6 g., was optically inactive, and had a m.p. of 180.5–181.5°. The very slightly colored filtrate contained DL-pyrrolidonecarboxylic acid and DL-glutamic acid. Several recycles of the filtrate were made. The yield based on converted D-(−)-glutamic acid was practically quantitative.

The effect of temperature on the racemization of glutamic acid has been summarized (114).

C. PHTHALIC ANHYDRIDE PROCESS FOR RACEMIZING D-(−)-GLUTAMIC ACID

A procedure (64) employing phthalic anhydride has been developed to racemize D-(−)-glutamic acid. A 10% excess of phthalic anhydride was heated with D-(−)-glutamic acid for 1 hr at 185–190°. After hydrolysis, the yield of DL-glutamic acid was 80%, and 18.6% of unchanged D-(−)-glutamic acid was recovered. An earlier (76) article showed the feasibility of this procedure.

D. RACEMIZATION OF L-(+)-GLUTAMIC ACID WITH CHELATES

Temperatures for racemization of L-(+)-glutamic acid were lowered in the presence of chelates (156). A 15% L-(+)-glutamic acid solution (containing 0.9 mole sodium hydroxide) was heated with 0.2 mole of salicylaldehyde and 0.1 mole of cupric chloride. At 120° racemization was 98% complete in less than 1 hr., while 3 hr. were required at 100°. Similar results were claimed using 4-nitrosalicylaldehyde, *o*-aminobenzaldehyde, and *o*-formylbenzoic acid in place of salicylaldehyde.

E. RACEMIZATION OF ACETYL D-(−)- OR ACETYL L-(+)-GLUTAMIC ACID WITH ACETIC ANHYDRIDE

A 98% yield of acetyl DL-glutamic acid was obtained by heating acetyl D-(−)-glutamic acid in acetic anhydride–acetic acid for 3 hr. at 100° (141). Earlier racemizations of acetyl L-(+)-glutamic acid gave lower yields (18, 197).

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