flushed ampoule for twelve hours. The cooled ampoule was opened by pressing a hot glass rod against a scratch; the top blew off indicating considerable pressure inside. Extraction of the residue from evaporation of the acetone gave 0.39 g. of acid, m. p. 230–233° corresponding to 91% *p*-nitrobenzoic acid. The bicarbonate-insoluble part was a tar.

**The Carboxy Inversion Reaction.**—Because of the complicated nature of the neutral products in other polar solvents it was decided to try the peroxide decomposition in thionyl chloride. A 0.500-g. sample of *p*-methoxy-*p'*-nitrobenzoyl peroxide was dissolved in 40 cc. of thionyl chloride and refluxed for one hour, the condenser being cut off from the atmosphere by a calcium chloride tube. The thionyl chloride was then removed in a stream of nitrogen and the residue crystallized from acetone–petroleum ether (60–70°), giving 0.189 g. of a substance melting at 126–129°. Extraction of the mother liquor with 10% sodium bicarbonate gave 0.058 g. of acid melting at 220–227° corresponding to a 77% *p*-nitrobenzoic acid content. Recrystallization of the 126–129° material raised the melting point to 127–129°; 10 mg. was refluxed for three minutes with 0.2 g. of sodium hydroxide and 2 cc. of water, the mixture neutralized and extracted with benzene. The benzene extract gave an oil which crystallized on seeding with *p*-methoxyphenol, m. p. 51–53.5°, mixed m. p. with an authentic sample, 53–56°. Addition of excess acid and extraction with ether gave 5 mg. of *p*-nitrobenzoic acid, m. p. 239–240°, mixed m. p. with an authentic sample, 239–241°. The 127–129° material was shown *not* to be an allotropic form of *p*-methoxyphenyl *p*-nitrobenzoate by a mixed melting point. Twenty-eight mg. of the 127–129° material was placed in an ampoule with 5 cc. of a 1% sodium hydroxide solution saturated with barium hydroxide, sealed and heated with occasional shaking at 70° for half an hour. The resulting precipitate was centrifuged down, washed thrice with water and once with acetone, then dried to constant weight *in vacuo* over potassium hydroxide, yielding 0.018 g., the theoretical yield, of barium carbonate. The product was identified by the fact that acidification gave an odorless gas and that the residue was not ether-soluble. *Anal.* Calcd. for $C_{15}H_{11}O_7N$: C, 56.78; H, 3.50; N, 4.42. Found: C, 56.97, 57.03; H, 3.72, 3.73; N, 4.49, 4.51.[12]

**Polymerization of Styrene.**—A 5-cc. sample of freshly distilled styrene containing 1% *p*-methoxy-*p'*-nitrobenzoyl peroxide, heated for eight and one-half hours under nitrogen at 70°, remained fluid and gave 0.66 g. of polystyrene, isolated by precipitation from ether on addition of methanol. The control run, using benzoyl peroxide, gave 1.27 g. of polystyrene. To 5 cc. of 1% solution of *p*-methoxy-*p'*-nitrobenzoyl peroxide in styrene was added 1 cc. of styrene containing 0.1 g. of trichloroacetic acid, the mixture degassed, sealed and allowed to stand at 30° for one week. At the end of this time the ampoule was opened and the viscosity of the solution compared with that from a control run using benzoyl peroxide and trichloroacetic acid by measuring the time of flow of 5 cc. between two marks on a standard pipet: the *p*-methoxy-*p'*-nitrobenzoyl peroxide run, 15.4 seconds; the benzoyl peroxide run, 296 seconds; pure benzene, 14.9 seconds.

**Polymerization of Acrylonitrile.**—Five cc. of a 1% solution of *p*-methoxy-*p'*-nitrobenzoyl peroxide in freshly distilled acrylonitrile, heated under nitrogen at 70°, gave a milky precipitate in five minutes. After seven and one-half hours the acrylonitrile was removed in a nitrogen stream leaving 0.294 g. of solid residue. A control run using benzoyl peroxide exploded; another control run did not explode but became completely solid in less than six minutes of heating.

## Summary

The decomposition of *p*-methoxy-*p'*-nitrobenzoyl peroxide is subject to general acid catalysis, and in sufficiently polar media goes by an ionic mechanism. The decomposition in thionyl chloride leads to a novel rearrangement of the peroxide to a mixed ester and anhydride of carbonic acid.

ITHACA, N. Y. RECEIVED JUNE 29, 1949

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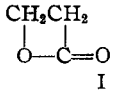
[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

# β-Propiolactone. VIII.[1,2] Reactions with Organic and Inorganic Acids, Acid Chlorides and Anhydrides

BY T. L. GRESHAM,* J. E. JANSEN† AND F. W. SHAVER

β-Propiolactone (I) reacts with thionyl chloride or phosphorus pentachloride to give β-chloropropionyl chloride[3] (II). With thionyl chloride an



I

$ClCH_2CH_2COCl$

II

intermediate compound seems to be formed, with little heat of reaction, from which sulfur dioxide is evolved slowly on heating. Acrylyl chloride is readily obtained by heating II with barium chloride.

β-Halogenopropionic acids are formed from I and aqueous halogen acids.[4] The yields of the reaction products decrease in the order: HI > HBr > HCl.

The reaction of I with organic acid halides[5] is extremely slow unless catalyzed with acid. β-Acetoxypropionyl chloride (III) is formed rapidly from I and acetyl chloride in the presence of a trace of sulfuric acid.

$CH_3COOCH_2CH_2COCl$ III $\qquad$ $CH_3COOCH_2CH_2COOCOCH_3$ IV

The catalyzed reaction of acetic anhydride with I gives acetic β-acetoxypropionic anhydride (IV) which disproportionates into β-acetoxypropionic anhydride (V) and acetic anhydride on distilla-

$(CH_3COOCH_2CH_2CO)_2O$ V $\qquad$ $CH_3COOCH_2CH_2COOH$ VI

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(1) Given in part at the San Francisco Meeting of the American Chemical Society, March, 1949.

(2) For Paper VII of this series see Gresham, Jansen, Shaver and Bankert, THIS JOURNAL, 71, 2807 (1949).

(3) Gresham and Shaver, U. S. Patent 2,411,875 (1946).

(4) Gresham and Shaver, U. S. Patent 2,449,993 (1948).

(5) Gresham and Shaver, U. S. Patent 2,449,994 (1948).

tion. Under similar conditions I reacts with acetic acid to give β-acetoxypropionic acid (VI).

The experimental evidence indicates that the ring opening of I in the acid-catalyzed reactions occurs at the acyl–oxygen bond. In the case of acetyl chloride only this ring opening can account for the formation of an acid chloride since ring opening at the methylene–oxygen bond would give acetic β-chloropropionic anhydride. Examination of the products failed to reveal any acetic anhydride from disproportionation or β-chloropropionic acid from hydrolysis of such a mixed anhydride. It seems likely that the same ring opening occurs with acetic anhydride and acetic acid but either ring opening would explain the products which were obtained. However, in the case of acetic acid the formation of VI by ring opening at the oxygen–methylene bond would require acetate ions[6] which seems unlikely under these conditions.

An excess of reagent over I is required in the acid-catalyzed reactions to avoid polymer formation since I may react with the new active center regenerated in the product.

## Experimental

**β-Chloropropionyl Chloride (II). a. Reaction of I with Thionyl Chloride.**—Two moles (144 g.) of β-propiolactone[7] was added (fifteen minutes) to 2.4 moles (285 g.) of thionyl chloride (Eastman Kodak Co. white label grade[8]) while stirring. There was a temperature rise of about five degrees. The reaction mixture was warmed and maintained at reflux (80–100°) until the evolution of sulfur dioxide ceased (about two hours). The residue was distilled and β-chloropropionyl chloride was collected at 76–80° (100 mm.), wt. 221 g. (87%). Redistillation gave a pure sample; b. p. 80° (100 mm.), $n^{20}D$ 1.4566, $d^{20}_4$ 1.3192.

*Anal.* Calcd. for $C_3H_4OCl_2$: Cl, 55.91; neut. equiv., 63.5. Found: Cl, 55.79; neut. equiv., 63.4.

**Acrylyl Chloride.**—One mole (127 g.) of β-chloropropionyl chloride was heated with 10 g. of anhydrous barium chloride[9] and the acrylyl chloride (b. p. 73°) was separated as formed with an efficient column. Redistillation, to remove the hydrogen chloride, gave 67 g. (74%), $n^{20}D$ 1.4337, $d^{20}_4$ 1.1127.

*Anal.* Calcd. for $C_3H_3OCl$: Cl, 39.23; neut. equiv., 45.3. Found: Cl, 39.43; neut. equiv., 45.6.

**b. Reaction of I with Phosphorus Pentachloride.**—Two moles (144 g.) of β-propiolactone was added over a period of one hour to a stirred suspension of 416 g. (2 moles) of phosphorus pentachloride in 600 ml. of carbon tetrachloride at 20° (ice cooling). The solvent and most of the phosphorus oxychloride was distilled at atmospheric pressure and the residue fractionated at 100 mm. The β-chloropropionyl chloride was collected at 78–80°; wt. 178 g. (70%), $n^{20}D$ 1.4566.

**β-Iodopropionic Acid.**—One mole (72 g. of β-propiolactone was added (one-half hr.) to a solution of one mole (128 g.) of hydrogen iodide in 300 ml. of water. The reaction was stirred and held at 0° for three hours. The heavy crystalline precipitate was filtered and the filtrate extracted with ether. The solid residue from the ether extraction was combined with the precipitate; dry wt. 196 g. (98.5%), m. p. 79–83°. The melting point of a mixture with an authentic sample[10] was not depressed.

**β-Bromopropionic Acid.**—A reaction, similar to the above, but using hydrogen bromide (1 mole, 81 g.) in 300 ml. of water gave 118 g. (77%) of β-bromopropionic acid, m. p. 59–62°. The melting point of a mixture with an authentic sample[10] of β-bromopropionic acid was not depressed.

**β-Chloropropionic Acid.**—Another reaction, similar to the above, but using hydrogen chloride (1 mole, 36.5 g.) in 300 ml. of water, gave 61 g. (58%) of distilled β-chloropropionic acid; b. p. 71–75° (1 mm.), m. p. 39–42°. The melting point of a mixture with an authentic sample[10] of β-chloropropionic acid was not depressed.

**β-Acetoxypropionyl Chloride (III).**—Two moles (144 g.) of β-propiolactone were added dropwise to a stirred solution of 0.2 g. of concentrated sulfuric acid in 471 g. (6 moles) of acetyl chloride at such a rate (forty minutes) as to maintain reflux (50–56°). After standing for two hours most of the excess acetyl chloride was distilled at atmospheric pressure. The residue was fractionated at 12 mm. and the β-acetoxypropionyl chloride collected at 79–80°; wt. 200 g. (67%), $n^{20}D$ 1.4365, $d^{20}_4$ 1.2228.

*Anal.* Calcd. for $C_5H_7O_3Cl$: Cl, 23.60; neut. equiv., 75.3; $MR_D$ 31.82. Found: Cl, 23.57; neut. equiv., 75.4; $MR_D$ 32.20.

Addition of acetoxypropionyl chloride to ethyl alcohol gave ethyl β-acetoxypropionate,[11] b. p. 76° at 11 mm. (34° at 0.3 mm.); $n^{20}D$ 1.4180.

*Anal.* Calcd. for $C_7H_{12}O_4$: sapon. equiv., 80. Found: sapon. equiv., 81.

**β-Acetoxypropionic Anhydride.**—One mole (72 g.) of β-propiolactone was added to a stirred solution of 0.1 g. of concentrated sulfuric acid in 306 g. (3 moles) of acetic anhydride. The temperature rose slowly at first and then rapidly to a maximum of 125° within thirty minutes. After standing for two hours the excess acetic anhydride and the residue was distilled at reduced pressure. The β-acetoxypropionic anhydride was collected at 60–62° at 0.05 mm.; wt. 105 g. (85%), $n^{20}D$ 1.4340.

Because some acetic acid was split out on distillation, the material was not satisfactory for analysis. It was possible, however, to convert the anhydride into a mixture of ethyl β-acetoxypropionate and β-acetoxypropionic acid. Sixty-five grams (0.25 mole) of the crude anhydride was added to 35 g. (0.75 mole) of ethyl alcohol and the solution refluxed for two hours. After removal of the alcohol two main fractions were collected: ethyl β-acetoxypropionate,[11] wt. 23 g. (54%); b. p. 34–35° (0.3 mm.), $n^{20}D$ 1.4164.

*Anal.* Calcd. for $C_7H_{12}O_4$: sapon. equiv., 80. Found: sapon. equiv., 81.

β-Acetoxypropionic acid,[11] wt. 29 g. (84%); b. p. 83° (0.3 mm.), $n^{20}D$ 1.4314.

*Anal.* Calcd. for $C_5H_8O_4$: neut. equiv., 132; sapon. equiv., 66. Found: neut. equiv., 134; sapon. equiv., 66.2.

When the preparation of β-acetoxypropionic anhydride was carried out with equal molar quantities of acetic anhydride and I, the yield was 45% and the remainder of the material was polymeric. Control of temperature at 0 or 30° and variations in catalyst concentration had only minor effects on the yields.

**β-Acetoxypropionic Acid.**—One mole (72 g.) of β-propiolactone was added to a stirred solution of 0.1 g. of concentrated sulfuric acid in 300 g. (5 moles) of glacial acetic acid. The temperature rose to a maximum of 81° in forty minutes. After an additional hour, the excess acetic acid was distilled at 20 mm. and the β-acetoxypropionic acid[11] was collected as the main fraction; b. p. 77–78° at 0.05 mm., wt. 102 g. (78%), $n^{20}D$ 1.4308.

*Anal.* Calcd. for $C_5H_8O_4$: sapon, equiv., 66; neut.

(6) T. L. Gresham, J. E. Jansen and F. W. Shaver, THIS JOURNAL, **70**, 1003 (1948).

(7) Gresham, Jansen and Shaver, *ibid.*, **70**, 998 (1948).

(8) Lower yields and considerable polymer formation occurs with less pure grades of thionyl chloride.

(9) British Patent 333,079 (1929).

(10) Gresham, Jansen, Shaver and Gregory, THIS JOURNAL, **70**, 1000 (1948).

(11) Gresham, Jansen and Shaver, *ibid.*, **70**, 1003 (1948).

equiv., 132. Found: sapon. equiv., 67.4; neut. equiv., 130.5.


## Summary

β-Propiolactone reacts with thionyl chloride or phosphorus pentachloride to give β-chloropropionyl chloride. With halogen acids it gives β-halogenopropionic acids. Acetyl chloride, acetic anhydride and acetic acid react with β-propiolactone under acid catalyzed conditions to give β-acetoxypropionyl chloride, β-acetoxypropionic anhydride and β-acetoxypropionic acid, respectively.


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[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

# Pteroic Acid Derivatives. VI. Unequivocal Syntheses of Some Isomeric Glutamic Acid Peptides

BY R. B. ANGIER, C. W. WALLER, B. L. HUTCHINGS, J. H. BOOTHE, J. H. MOWAT, J. SEMB AND Y. SUBBAROW*

Previous communications in this series[1,2,3] have described the synthesis of all of the possible isomeric pteroyldiglutamic and pteroyltriglutamic acids. During the search for satisfactory methods of preparing the intermediates, *i. e.*, the various *p*-nitrobenzoylglutamic acid peptides, the use of *l*-2-pyrrolidone-5-carboxylic acid and its derivatives was investigated. It was soon noted that attempts to esterify 2-pyrrolidone-5-carboxylic acid using ethanol and hydrogen chloride resulted in cleavage of the pyrrolidone ring at the lactam linkage with the formation of diethyl glutamate. In the same manner *l*-2-pyrrolidone-5-carboxamide (I) when treated with ethanolic hydrogen chloride gave γ-carbethoxy-α-aminobutyramide (ethyl isoglutaminate) isolated as its hydrochloride (II). However, substantial amounts of ammonium chloride were also obtained due to the simultaneous alcoholysis of the primary amide group. A series of experiments demonstrated that the best yield (30%) was obtained when 1.3 moles of dry hydrogen chloride was used for each mole of 2-pyrrolidone-5-carboxamide. The ethyl isoglutaminate was *p*-nitrobenzoylated and the product converted to the corresponding hydrazide (IV) and azide (V) by standard methods. The reaction of *p*-nitrobenzoylisoglutamine azide (V), which was a crystalline solid, with each of the compounds ethyl isoglutaminate, diethyl glutamate and triethyl-γ-glutamylglutamate[4] produced, respectively, ethyl *p*-nitrobenzoylisoglutaminylisoglutaminate (VI), diethyl *p*-nitrobenzoylisoglutaminylglutamate (VII) and triethyl *p*-nitrobenzoylisoglutaminyl-γ-glutamylglutamate (VIII). A sample of VII was hydrolyzed in dilute sodium hydroxide to give a compound which was shown to be identical with the *p*-nitrobenzoyl-γ-glutamylglutamic acid prepared previously by other methods.[1,4]

The ease with which the pyrrolidone ring in I could be opened indicated that this method might also be employed for the synthesis of α-glutamyl derivatives. Such a synthesis would be feasible only if the presence of a substituent on the amide nitrogen of I would stabilize that linkage so as to permit the opening of the pyrrolidone ring without the simultaneous alcoholysis of the amide group. This proved to be the case. Ethyl *l*-2-pyrrolidone-5-carboxylate was converted to the corresponding hydrazide (IX) and azide (X) in the usual manner. The reaction of the azide with diethyl glutamate produced diethyl α-(2-pyrrolidone-5-carboxamido)-glutarate (XI). XI was then treated with ethanolic hydrogen chloride to give triethyl α-glutamylglutamate (XII) which without isolation was *p*-nitrobenzoylated to produce triethyl *p*-nitrobenzoyl-α-glutamylglutamate (XIII). The over-all yield of pure, recrystallized XIII from XI was 42%. This yield, in addition to the fact that the product (XIII) was quite pure, indicated that the substituted amide linkage in XI was quite stable under the conditions used.

A sample of *p*-nitrobenzoyl-α-glutamylglutamic acid prepared previously by another method[5] was then esterified. The resulting ester was shown by mixed melting point and optical rotation to be identical with the product (XIII) prepared by the method described above.

The series of reactions was further extended by treating the crude triethyl α-glutamylglutamate (XII) with 2-pyrrolidone-5-carboxylic acid azide (X) to obtain ethyl γ-(2-pyrrolidone-5-carboxamido) - N - (1,3 - dicarbethoxypropyl) - glutaramate (XIV). XIV was treated with ethanolic hydrogen chloride to give tetraethyl α-glutamyl-α-glutamylglutamate which was not isolated but was *p*-nitrobenzoylated to give tetraethyl *p*-nitrobenzoyl-α-glutamyl-α-glutamylglutamate (XV). XV was shown to be identical with the tetraethyl *p*-nitrobenzoyl - α - glutamyl - α - glutamylglutamate prepared previously by another method.[3]

The syntheses of the glutamic acid peptides described herein were carried out by unequivocal methods. Three of these compounds, XIII, XV

* Harvard University Ph.D. 1930; Medical School Faculty 1930–1940.

(1) Boothe, *et al.*, THIS JOURNAL, 71, 2304 (1949).
(2) Mowat, *et al.*, *ibid.*, 71, 2308 (1949).
(3) Semb, *et al.*, *ibid.*, 71, 2310 (1949).
(4) Boothe, *et al.*, *ibid.*, 70, 1099 (1948).
(5) Mowat, *et al.*, *ibid.*, 70, 1096 (1948).