

3 ml. of water at 50–60° for 2 hr. The aqueous mixture was then extracted exhaustively with ethyl acetate, to give 2,900 c.p.m. (20%) in the organic phase. On extraction with 2% sodium hydroxide, half of this radioactivity was found to be acidic and the other half neutral. The acid fraction (G) was shown to consist almost entirely of PDA, by a carrier experiment (Table III).

**The Above Treatment of the Dimethyl Ester of 2-Phenylphenanthrene-3,2'-dicarboxylic Acid.**—The ester IX (50

mg.) was treated with phosphorus pentachloride (500 mg.), a solution (4 ml.) of stannous chloride in ethereal hydrochloric acid, and then water, as above. On filtration of the aqueous mixture, a yellowish-red solid was obtained. This was dried and extracted with alcohol. On evaporation of the alcoholic extract, 40 mg. (80%) of the unchanged ester was recovered.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

## The Synthesis of Substituted Penicillins and Simpler Structural Analogs. IX. 4-Carboxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetic Acid Derivatives

BY JOHN C. SHEEHAN AND PHILIP A. CRUICKSHANK

RECEIVED JUNE 28, 1955

*t*-Butyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate has been isolated in two stereoisomeric modifications (two racemates), one of which was shown to correspond in configuration to the natural penicilloates. Removal of the phthaloyl blocking afforded an aminothiazolidine valuable as an intermediate for the synthesis of a variety of penicilloate derivatives. Cleavage of the *t*-butyl ester group gave three isomeric thiazolidineacetic acids, of interest as precursors for fused thiazolidine- $\beta$ -lactams closely related to the penicillins.

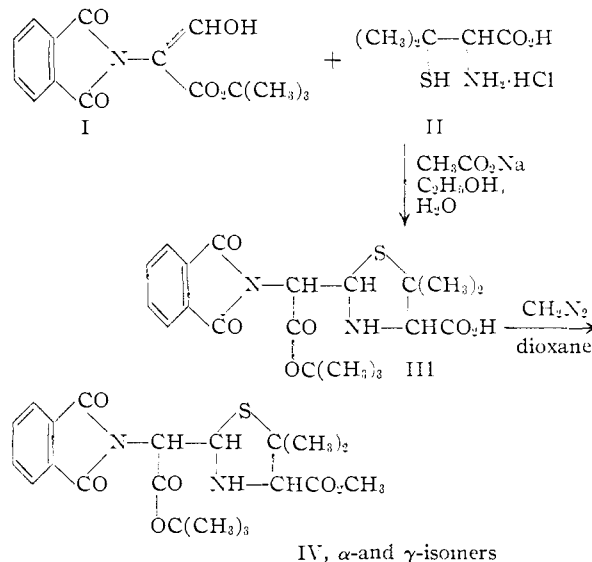
In a preceding article of this series<sup>1</sup> there was described the preparation of penicilloate derivatives, the structure of which precludes the possibility of azlactone formation under conditions designed to effect closure of the  $\beta$ -lactam ring. This was accomplished by the incorporation of the phthaloyl blocking group.

Among the compounds described was *t*-butyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (IV). This compound has now been isolated in two stereoisomeric modifications (racemates), one of which has been shown to correspond to the configuration of the natural penicilloates. By removal of the phthaloyl blocking group there has been obtained an intermediate, *t*-butyl 4-carboxy-5,5-dimethyl- $\alpha$ -amino-2-thiazolidineacetate hydrochloride (V), invaluable for the preparation of many otherwise difficultly accessible penicilloate derivatives. Cleavage of the *t*-butyl ester group of IV has afforded three stereoisomeric modifications of 4-carboxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetic acid hydrochloride (VI).

The interaction of DL-penicillamine hydrochloride (II) and *t*-butyl phthalimidomalonaldehyde (I) in sodium acetate buffered aqueous ethanol afforded directly the crystalline thiazolidine III, *t*-butyl 4-carboxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate, in 75% yield. Treatment of this with diazomethane gave two methyl esters, m.p. 121–122° and m.p. 176–176.5°. These were shown to be stereoisomers of *t*-butyl 4-carboxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (IV) by the identity of their infrared spectra in the region of 2–7  $\mu$ . The preponderant lower melting form, the sole product upon esterification of the first crop of III, was designated as the  $\gamma$ -isomer.<sup>2</sup> The higher melt-

ing form was shown to be a racemate corresponding in configuration to the natural penicilloates, and so was designated  $\alpha$ . Of the four theoretically possible racemates of IV, apparently only these two were formed in significant amounts.

The more interesting  $\alpha$ -isomer of IV was obtained in rather low yields from the products of the condensation of I and II. Additional quantities could



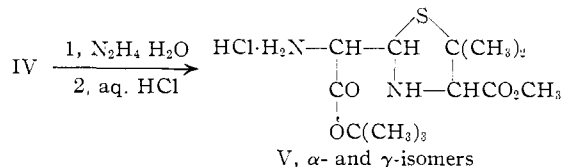
be prepared, however, by heating a triethylamine solution of IV  $\gamma$  under reflux, setting up an equilibrium consisting of two parts in five of IV  $\alpha$ . The latter crystallized directly in an essentially pure state upon cooling the mixture. The unchanged IV  $\gamma$  could then be isolated from the mother liquors, or the solution again heated under reflux to give additional  $\alpha$ -isomer.

One of the principal difficulties encountered in the preparation of  $\alpha$ -amino-2-thiazolidineacetate derivatives of penicillamine is the synthesis of the required derivatives of aminomalonaldehydic esters. The facile liberation of amino groups from

(1) J. C. Sheehan and D. A. Johnson, *THIS JOURNAL*, **76**, 158 (1954).

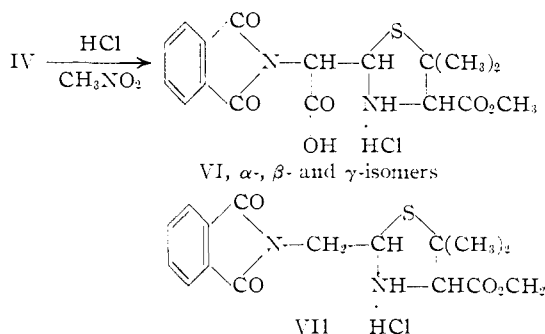
(2) In analogy to the designation gamma for the first isomer obtained in the condensation of benzylpenaldehyde and penicillamine; H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 535.

phthalimido derivatives of amino acids under mild conditions<sup>3</sup> affords an elegant solution to this problem. By the action of hydrazine on compounds of type IV, the parent 4-carbomethoxy-5,5-dimethyl- $\alpha$ -amino-2-thiazolidineacetic esters may be prepared. The greater reactivity of the primary amino group so obtained favors its reaction with a wide variety of reagents to give the corresponding "penicilloate" derivatives.



Treatment of a dioxane solution of IV with a slight excess of hydrazine hydrate afforded the phthalhydrazide complex, isolated by lyophilization. The complex was broken up with dilute hydrochloric acid, and the *t*-butyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -amino-2-thiazolidineacetate hydrochloride (V) isolated from its aqueous solution by lyophilization. The yield in the isomeric series having the natural configuration was 91%.

The  $\beta$ -amino acid VI is of special interest for experiments directed toward formation of fused thiazolidine- $\beta$ -lactams. This compound was prepared from IV by cleavage of the *t*-butyl ester group, a reaction readily effected by treatment with anhydrous acid.<sup>4</sup> Nitromethane solutions of the  $\alpha$ - and  $\gamma$ -isomers of IV upon treatment with anhydrous hydrogen chloride at 0° afforded in good yield the  $\alpha$ - and  $\gamma$ -isomers of 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetic acid hydrochloride (VI). When the temperature of this cleavage step was raised, two competing reactions occurred in addition to simple protonolysis of the *t*-butyl group. In the temperature range of 30–90° an isomerization of both IV $\alpha$  and IV $\gamma$  took place to afford another isomer of IV (designated  $\beta$ ),<sup>5</sup> with optimum yields occurring in the 70–75° range. The principal product at temperatures above 90° and the by-product at lower temperatures was 2-phthalimidomethyl-4-carbomethoxy-5,5-dimethylthiazolidine hydrochloride (VII), characterized as the free base.



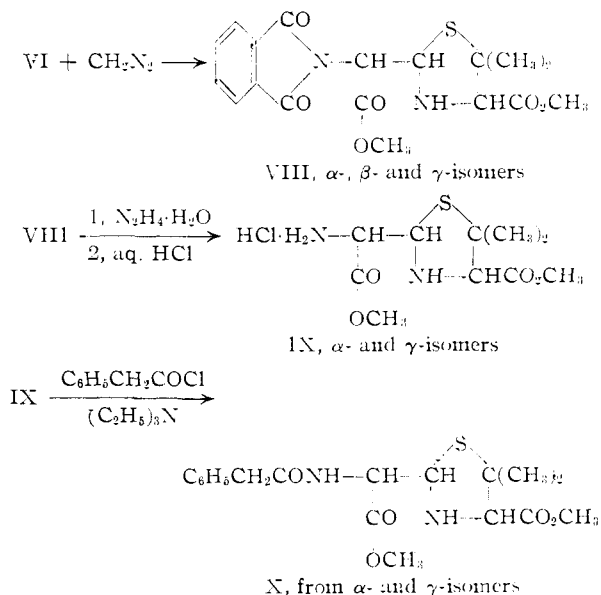
In order to determine which, if any, of the three isomers of VI corresponded in configuration to the natural D- $\alpha$ -penicilloates, a series of reactions to

(3) J. C. Sheehan and V. S. Frank, *THIS JOURNAL*, **71**, 1855 (1949).

(4) J. C. Sheehan and G. D. Laubach, *ibid.*, **73**, 4752 (1951).

(5) The designation beta is arbitrary, and is not necessarily related to the  $\beta$ -configuration of D-penicilloates described in ref. 2, p. 535.

convert them to the corresponding dimethyl DL-benzylpenicilloates (X) was undertaken. Treatment of the  $\alpha$ -,  $\beta$ - and  $\gamma$ -isomers of VI with diazomethane gave the corresponding methyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetates (VIII); the  $\alpha$ - and  $\gamma$ -isomers were converted in good yields, but the  $\beta$ -isomer gave a crude product from which insufficient pure VIII $\beta$  could be isolated for further work. Removal of the phthaloyl blocking group from VIII $\alpha$  and VIII $\gamma$  was carried out in the manner described for the conversion of IV to V. The resultant methyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -amino-2-thiazolidineacetate hydrochlorides (IX) were directly phenylacetylated to the DL-benzylpenicilloates X. The infrared spectrum of one of these, derived from IV $\alpha$  via VI $\alpha$ , was identical in every respect to the spectrum of dimethyl D- $\alpha$ -benzylpenicilloate, whereas the other isomer of X had a spectrum distinctly different in the region between 7 and 11  $\mu$ .



We are indebted to Bristol Laboratories, Syracuse, N. Y., for generous financial support of this work, and also to the National Science Foundation for a fellowship for one of us (PAC).

### Experimental<sup>6</sup>

***t*-Butyl 4-Carboxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (III).**—To a solution of 45.0 g. (0.156 mole) of *t*-butyl phthalimidomalonaldehyde (1) in 300 ml. of warm 95% ethanol was added a solution of 29.0 g. (0.156 mole) of DL-penicillamine hydrochloride (II) and 32.0 g. (0.235 mole) of sodium acetate trihydrate in 300 ml. of water. After storage at room temperature for 24 hours, the first crop of colorless needles was collected by filtration; weight after recrystallization from acetone-water, 36.5 g., m.p. 185–186° dec. (reported m.p. 180° dec.). Addition of 400 ml. of water to the mother liquors (in portions over a period of 3 days) afforded a second crop; weight after recrystallization, 15.0 g., m.p. 180° dec. The total yield of pure III was 75%.

***t*-Butyl 4-Carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (IV).**—The first crop of III (36.5 g., 0.087 mole) was dissolved in 450 ml. of dioxane (heating required) and the solution treated with an excess of ethereal diazomethane. The ester was crystallized from 50 ml. of 95% ethanol, giving 27.7 g. of colorless prisms, m.p. 119°.

(6) All melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for the microanalyses.

122°. This material is identical in all respects to the ester described earlier<sup>1</sup> and has been designated as the  $\gamma$ -isomer.<sup>2</sup>

Similar treatment of the second crop of III (15.0 g., 0.036 mole) from the condensation afforded, after crystallization from 60 ml. of ethanol, 8.2 g. (16%) of an ester, m.p. 175–176°, shown to be stereoisomeric with the one described above and designated as the  $\alpha$ -isomer. Recrystallization from ethanol gave an analytical sample, m.p. 176–176.5°.

*Anal.* Calcd. for  $C_{21}H_{26}N_2O_6S$ : C, 58.05; H, 6.03; N, 6.45. Found: C, 58.06; H, 6.23; N, 6.46.

The combined mother liquors from these two esters produced an additional 10.4 g. of the  $\gamma$ -isomer, m.p. 118–120°. The total yield of IV was 89%, of which approximately one-sixth was in the higher melting  $\alpha$ -form.

Isomerization of IV  $\gamma$  to the  $\alpha$ -isomer was brought about by heating a triethylamine solution under reflux.<sup>7</sup> From 40.0 g. (0.092 mole) of the  $\gamma$ -isomer in 400 ml. of pure triethylamine, refluxed under an atmosphere of prepurified nitrogen for 13 hours, there was obtained 14 g. of crystalline IV $\alpha$ . An additional 14.0 g. (0.032 mole) of IV $\gamma$  was added to the mother liquors, and the solution again refluxed under nitrogen for 16 hours. Sixteen grams of IV $\alpha$  crystallized upon cooling. A second recycling of the mother liquors, without addition of further  $\gamma$ -isomer, afforded 7.8 g. of additional IV $\alpha$ . The combined fractions of product were dried at 70° (25 mm.) and recrystallized from 300 ml. of 95% ethanol. The conversion yield to  $\alpha$ -isomer was 34.1 g. (63%), m.p. 177–178°.

The unconverted IV $\gamma$  was recovered from the mother liquors by removal of the triethylamine under reduced pressure and crystallization from ethanol–water, m.p. 118–122°.

***t*-Butyl 4-Carbomethoxy-5,5-dimethyl- $\alpha$ -amino-2-thiazolidineacetate Hydrochloride (V).**—A solution of 13.0 g. (0.03 mole) of *t*-butyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (IV) and 1.88 g. (0.0375 mole) of hydrazine hydrate in 200 ml. of pure dioxane was stored at room temperature for 20 hours, after which solvent and excess hydrazine were removed by lyophilization. The phthalhydrazide complex was decomposed by shaking in 190 ml. of 0.2 *N* hydrochloric acid at room temperature for 2 hours. After cooling in an ice-bath for an additional hour, 4.9 g. (100%) of phthalhydrazide was removed by filtration, and the filtrate lyophilized. The amine hydrochloride was crystallized from methanol–ether.

From the  $\alpha$ -isomer of IV there was obtained 9.33 g. (91%) of fine needles, m.p. 167–168° dec. Recrystallization afforded an analytical sample, m.p. 174.5° dec.

*Anal.* Calcd. for  $C_{19}H_{25}N_2O_4S$ : C, 45.79; H, 7.39; N, 8.22. Found: C, 45.53; H, 7.25; N, 8.31.

The  $\gamma$ -isomer of IV yielded 7.41 g. (72.4%) of V $\gamma$ , m.p. 166–169° dec.

**4-Carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetic Acid Hydrochloride (VI).**—Anhydrous hydrogen chloride was passed through a solution of 5.0 g. (0.0115 mole) of the  $\alpha$ -isomer of *t*-butyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (IV) in 50 ml. of purified nitromethane<sup>9</sup> at 0° over a period of 10–12 minutes. A precipitate formed immediately, but had redissolved before completion of the hydrogen chloride addition. After storage for 2 hours at 0–5°, 100 ml. of anhydrous ether was added. The product, 4.60 g. (96%), separated as fine needles, m.p. 122–124° dec. It was soluble in 5% sodium bicarbonate solution or dilute aqueous acid and precipitated upon neutralization of either solution.

*Anal.* Calcd. for  $C_{17}H_{19}O_6N_2S$ : C, 49.21; H, 4.62; N, 6.75. Found: C, 48.97; H, 4.87; N, 6.75.

A solution of 1.5 g. (0.0034 mole) of IV $\gamma$  in 25 ml. of purified nitromethane was treated with anhydrous hydrogen chloride at 0° for 5 minutes. Storage at 0–5° for several hours afforded 1.33 g. (93%) of fine needles, m.p. 165–168° dec. (in bath 130°; when placed in bath at 150° immediate decomposition with vigorous gas evolution occurred). Solubility was identical to that observed for the  $\alpha$ -isomer.

*Anal.* Calcd. for  $C_{17}H_{19}O_6N_2S$ : C, 49.21; H, 4.62; N, 6.75. Found: C, 48.97; H, 4.90; N, 6.67.

(7) This method of isomerization was developed in this Laboratory by Dr. K. R. Henery-Logan.

(8) A very similar procedure for preparing an "aminopenicilloate" was devised in this Laboratory by Dr. Silvio Fallab.

(9) H. T. Hayes, G. F. Hager, H. M. Engelmann and H. M. Spurlin, *THIS JOURNAL*, **73**, 5372 (1951).

Through a solution of 2.5 g. (0.0058 mole) of IV $\gamma$ , placed in an oil-bath held at 73–76°, there was immediately bubbled a stream of anhydrous hydrogen chloride for 5 minutes. Upon removal from the oil-bath, a crystalline substance began to separate from the solution. After 16 hours, 2.2 g. (90%) of colorless cubes, m.p. 158.5° dec. (in bath 130°) was recovered. The material, designated as the  $\beta$ -isomer of VI, behaved the same as the  $\alpha$ - and  $\gamma$ -isomers toward dilute aqueous acid or sodium bicarbonate.

*Anal.* Calcd. for  $C_{17}H_{19}O_6N_2S$ : C, 49.21; H, 4.62; N, 6.75. Found: C, 48.59; H, 5.00; N, 6.65.

From 0.52 g. (0.0012 mole) of IV $\alpha$  in 10 ml. of nitromethane after treatment with anhydrous hydrogen chloride at 80° for 6 minutes, there was obtained 0.30 g. (60%) of VI $\beta$ , m.p. 156–157° dec.

When the temperature of the cleavage reaction was raised to 85°, the yield of VI $\beta$  dropped to well below 50%. Upon addition of ether to the mother liquors, a substance, m.p. 171° dec., was obtained which reacted with 5% sodium bicarbonate solution, but did not dissolve. These properties are consistent with the thiazolidine hydrochloride structure VII. Decomposition of the hydrochloride by partition between sodium bicarbonate solution and methylene chloride afforded a weakly basic material, m.p. 166–167° after recrystallization from ethanol. The elemental analysis agree closely with that calculated for 2-phthalimidomethyl-4-carbomethoxy-5,5-dimethylthiazolidine.

*Anal.* Calcd. for  $C_{16}H_{18}O_4N_2S$ : C, 57.47; H, 5.42; N, 8.38. Found: C, 57.34; H, 5.52; N, 8.49.

**Methyl 4-Carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (VIII).**—Suspensions of the three isomers of VI in anhydrous ether were treated with a slight excess of ethereal diazomethane. The resultant methyl esters (VIII) were crystallized from absolute methanol.

From 1.25 g. (0.003 mole) of VI $\alpha$  in 20 ml. of ether there was obtained 0.95 g. (70%) of VIII $\alpha$ , m.p. 159–162°. Recrystallization from methanol afforded an analytical sample, m.p. 161–162°.

*Anal.* Calcd. for  $C_{18}H_{20}N_2O_6S$ : C, 55.08; H, 5.15; N, 7.13. Found: C, 55.29; H, 5.02; N, 7.23.

Similar treatment of 1.0 g. (0.0024 mole) of VI $\beta$  gave 0.79 g. (84%) of a crude, unstable material, m.p. 132–155°. Extensive recrystallization from methanol afforded a very small quantity of pure VIII $\beta$ , m.p. 137–138°.

*Anal.* Calcd. for  $C_{18}H_{20}N_2O_6S$ : C, 55.08; H, 5.15; N, 7.13. Found: C, 55.34; H, 5.16; N, 7.08.

The  $\gamma$ -isomer of VI (0.200 g., 0.00048 mole) yielded 140 mg. (74%) of fine needles, m.p. 151–152°. Analytically pure VIII $\gamma$ , m.p. 151.5–152°, was obtained upon recrystallization from methanol. This substance was identical to the methyl ester of the thiazolidine obtained earlier<sup>1</sup> from the condensation of methyl phthalimidomalonaldehyde and penicillamine.

*Anal.* Calcd. for  $C_{18}H_{20}N_2O_6S$ : C, 55.08; H, 5.15; N, 7.13. Found: C, 54.97; H, 5.17; N, 7.08.

**Dimethyl DL-Benzylpenicilloate (X).**—The phthaloyl blocking group on the  $\alpha$ - and  $\gamma$ -isomers of VIII was removed in the manner described earlier for IV. The resultant amine hydrochlorides were crystallized from methanol–ether, and directly phenylacetylated by treatment with phenylacetyl chloride and triethylamine in methylene chloride. The products were crystallized from acetone–hexane, and their infrared spectra, determined in tetrachloroethane solution, compared with the spectrum of dimethyl D- $\alpha$ -benzylpenicilloate, m.p. 86–88°. The spectrum of the compound derived from the phthaloyl derivatives heretofore designated alpha was identical in every respect with the spectrum of the natural material, whereas the other isomer of X (derived from the  $\gamma$ -series of isomers) had distinct differences in the region of 7–11  $\mu$ .

A solution of 0.75 g. (0.002 mole) of VIII $\alpha$  and 0.121 g. (0.0024 mole) of hydrazine hydrate in 20 ml. of dioxane was stored at room temperature for 18 hours. After lyophilization, the phthalhydrazide complex was broken up with 19.2 ml. of 0.0992 *N* hydrochloric acid. The precipitated phthalhydrazide (0.30 g., 97%) was removed by filtration, and the filtrate lyophilized. The product, IX $\alpha$ , crystallized from methanol–ether as fine needles, m.p. 154–155°. The yield was 450 mg. (79%). To a solution of 0.31 g. (0.001 mole)

of this amine hydrochloride and 0.201 g. (0.002 mole) of triethylamine in 20 ml. of methylene chloride, cooled in an ice-salt-bath, there was added 0.155 g. (0.001 mole) of phenylacetyl chloride in 10 ml. of methylene chloride. The product crystallized after purification as fine needles, m.p. 140–141°. The yield was 325 mg. (86%).

*Anal.* Calcd. for  $C_{18}H_{24}N_2O_5S$ : C, 56.82; H, 6.36; N, 7.36. Found: C, 56.60; H, 6.20; N, 7.32.

From 0.56 g. (0.0014 mole) of VIII $\gamma$  there was obtained 275 mg. (65%) of the amine hydrochloride IX $\gamma$ , m.p. 128–130°. Phenylacetylation proceeded smoothly to afford 200 mg. (63%) of fine needles, m.p. 130–131°; recrystallization raised the m.p. 132–133.5°.

*Anal.* Calcd. for  $C_{18}H_{24}N_2O_5S$ : C, 56.82; H, 6.36; N, 7.36. Found: C, 56.90; H, 6.25; N, 7.73.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

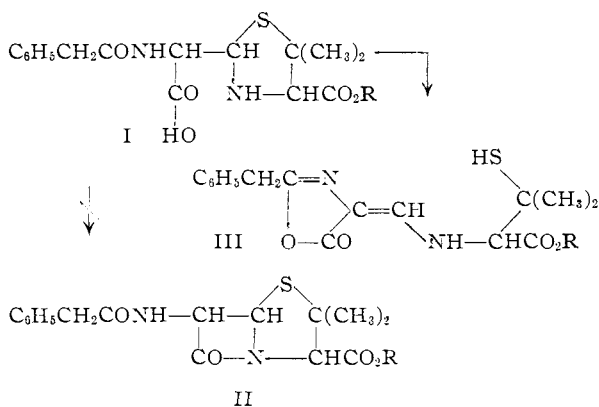
## The Synthesis of Substituted Penicillins and Simpler Structural Analogs. X. The Cyclization of 4-Carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetic Acid to Methyl 6-Phthalimidopenicillanate

BY JOHN C. SHEEHAN AND PHILIP A. CRUICKSHANK

RECEIVED JUNE 28, 1955

One isomer of 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetic acid hydrochloride has been converted to the  $\beta$ -lactam methyl 6-phthalimidopenicillanate (VI) (a phthaloylpenicillin). From all three known isomers of this thiazolidine acetic acid derivative there has been obtained a material isomeric with the  $\beta$ -lactam, to which has been assigned the 5-keto-2,3,4,5-tetrahydro-1,4-thiazepine ring system.

Of the many approaches to the synthesis of benzylpenicillin (II) and its analogs, the route most thoroughly studied involved cyclization of penicilloic acids (I, R = H) or their  $\beta$ -esters (I, R = alkyl).<sup>1</sup> In no case, however, was penicillin activity obtained in amounts greater than 0.1%.<sup>2</sup> When identified, the products of the reactions were shown to be penicillanates (III), formed by azlactonization of the penicilloates followed by rupture of the thiazolidine ring. Incorporation of alkyl groups on



the amide nitrogen of the penicilloates<sup>1</sup> failed to lead to  $\beta$ -lactam formation when the substances were subjected to cyclization conditions. Subsequent indications that quaternary oxazolone rings can be formed from similar intermediates (benzoyl sarcosine)<sup>3</sup> demonstrates that N-alkylation does not necessarily prevent azlactonization.

Recent work in this Laboratory has for the first time resulted in the synthesis of penicilloic acid derivatives in which the possibility of azlactone formation is precluded.<sup>4</sup> This was accomplished by the incorporation of the phthaloyl blocking

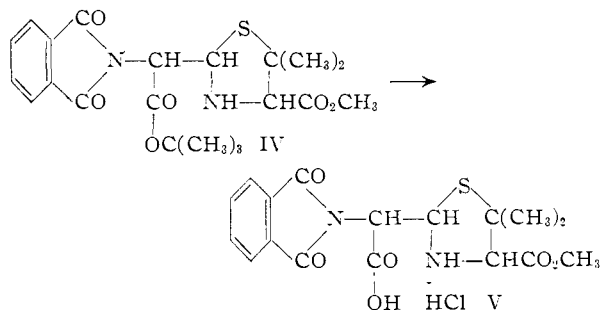
(1) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 851.

(2) V. du Vigneaud, *et al.*, ref. 1, pp. 1018–1024.

(3) J. L. O'Brien and C. Niemann, *THIS JOURNAL*, **72**, 5348 (1950).

(4) J. C. Sheehan and D. A. Johnson, *ibid.*, **76**, 158 (1954).

group. The compounds were obtained by the condensation of phthalimidomalonaldehydic esters, prepared by formylation of phthalimidoacetic esters, with penicillamine. The most useful of these substances, *t*-butyl 4-carbomethoxy-5,5-dimethyl- $\alpha$ -phthalimido-2-thiazolidineacetate (IV), and the cleavage of the *t*-butyl ester group to give three isomeric thiazolidineacetic acid hydrochlorides (V), was described in the preceding paper of this series.<sup>5</sup>

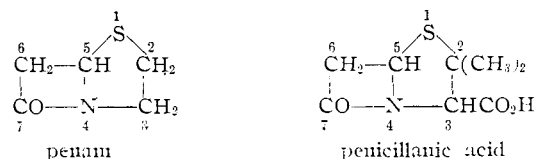


Extensive experiments directed toward the cyclization of the  $\alpha$ -,  $\beta$ - and  $\gamma$ -isomers of V<sup>5</sup> have been carried out. Only one of these, V $\beta$ , has been found to give the  $\beta$ -lactam methyl 6-phthalimidopenicillanate (VI).<sup>6</sup>

In a recent communication on the synthesis of methyl 6-phthalimidopenicillanate sulfone (VII),<sup>6</sup>

(5) The assignment of the designations alpha, beta and gamma to the three stereoisomers of V was explained in the previous paper of this series; J. C. Sheehan and P. A. Cruickshank, *THIS JOURNAL*, **78**, 3677 (1956).

(6) It has recently been suggested that the terms "penam" and "penicillanic acid" be adopted for the following ring system and substituted ring system.



J. C. Sheehan, K. R. Henry-Logan and D. A. Johnson, *THIS JOURNAL*, **75**, 3292 (1953).