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

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. VIII. Phthalimidomalonaldehydic Esters: Synthesis and Condensation with Penicillamine

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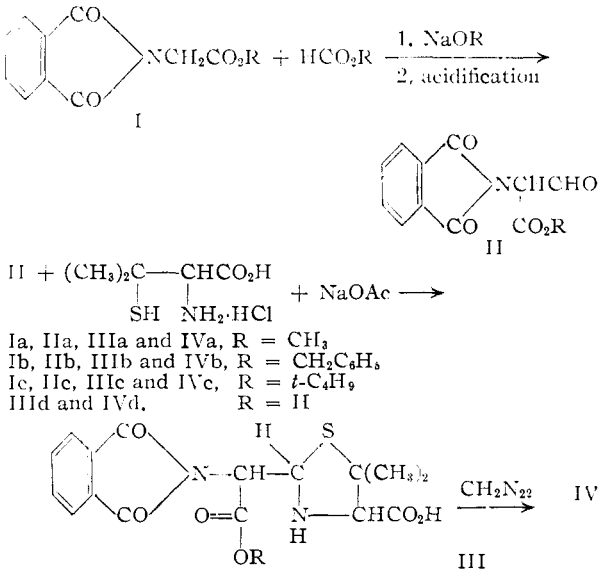
By formylation of the corresponding phthalimidoacetates, the methyl, benzyl and *t*-butyl esters of phthalimidomalonaldehydic acid have been prepared. Condensation with penicillamine gave penicilloic acid derivatives which are structurally incapable of azlactonization and thus are of interest as synthetic precursors to β-lactam-thiazolidines related to penicillin.

This communication reports the first synthesis of penicilloic acid derivatives so contrived that azlactone formation is precluded under conditions designed to effect cyclization to the β-lactam-thiazolidine structure characteristic of the penicillins. Attempts have been made previously to block azlactone formation by introducing an alkyl group on the amide nitrogen of a penicilloate.[2] However, recent studies have indicated that quaternary oxazolone rings can be formed from similar intermediates (benzoyl sarcosine),[3] and therefore N-alkylation is not sufficient insurance against azlactonization.

We have prepared penicilloate derivatives (IIIa, IIIb, IIIc) in which the possibility of azlactone formation is eliminated by the presence of the phthaloyl blocking group. The key intermediates are phthalimidomalonaldehydic esters (IIa, IIb and IIIc), which condense readily with penicillamine to form the corresponding protected penicilloates.

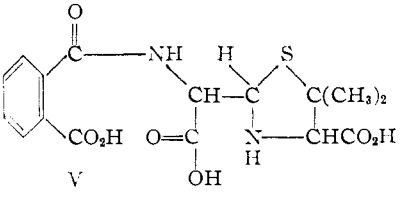
Earlier efforts to synthesize phthalimidomalonaldehydic esters, both by interaction of potassium phthalimide with bromomalonaldehydic esters and by formylation of phthalimidoacetic esters, were unsuccessful.[4] In contrast, we have been markedly successful using the latter method. The following reaction sequence was employed.



The condensation of methyl phthalimidoacetate and methyl formate in the presence of sodium methoxide afforded the aldehyde IIa in 47% yield. The yellow, crystalline solid possesses reducing properties and gives a positive ferric chloride test. The infrared spectrum exhibits a weak, broad band in the region 3.0–3.3 μ, attributed to the enolic form of the aldehyde; two bands at 5.62 and 5.80 μ, which are characteristic of the phthalimide system; a shoulder at 5.70 μ, assigned to the ester function, and a sharp band at 5.96 μ, corresponding to a formyl group.

The reaction to produce the thiazolidines IIIa was conducted in 50% aqueous ethanol, from which the products crystallized directly. A stereoisomeric mixture of methyl 4-carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (IIIa) was obtained in 81% yield by this method when DL-penicillamine hydrochloride was used. No attempt was made to fractionate the mixture. When D-penicillamine hydrochloride was employed, a 75% yield of acids was obtained. In this case, fractional crystallization was used to isolate two isomeric products, which were purified to constant optical rotation. Theoretically, four stereoisomers can be obtained from this reaction, but the general indications are that only two are formed in significant amounts under the conditions employed. Esterification with diazomethane generated the corresponding methyl ester IVa.

Preliminary attempts to obtain the diacid IIId by selective alkaline hydrolysis of IIIa gave the triacid V as the only isolated pure, crystalline product. It would be of considerable interest to subject the diacid IIId or the corresponding β-ester to ring-closure experiments.



As potential intermediates for the synthesis of these compounds, we turned our attention to esters which are readily cleaved under mild (preferably anhydrous) conditions. Two series of such esters were investigated, the benzyl and *t*-butyl.

Since benzyl esters are readily hydrogenolyzed to the corresponding acids,[5] the benzyl series was prepared. The formylation of benzyl phthalimidoacetate, using benzyl formate and sodium benzyloxide, was accomplished in 45% yield.

(1) Bristol Laboratories Fellow, 1950–1951. E. I. du Pont de Nemours and Co. Predoctoral Fellow, 1951–1952.

(2) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 502.

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

(4) Reference 2, p. 493.

(5) J. C. Sheehan and E. J. Corey, THIS JOURNAL, **74**, 4555 (1952).

The aldehyde, obtained as a colorless, crystalline solid, exhibited chemical properties similar to the corresponding methyl ester, and the infrared spectra of the two aldehydes in the carbonyl region are nearly identical. Condensation with pencillamine hydrochloride gave an oil plus crystalline IIIb.

The facile cleavage of a *t*-butyl ester to the corresponding acid with dry hydrogen chloride[6] stimulated interest in the *t*-butyl series of esters. Formylation of *t*-butyl phthalimidoacetate with *t*-butyl formate in the presence of sodium *t*-butoxide gave a 13% yield of the aldehyde IIc. Using sodium hydride as the condensing agent in refluxing benzene, the yield was increased to 31%. An 81% yield of the thiazolidine IIIc was produced by interaction with DL-penicillamine.

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Experimental[7]

Methyl α-Phthalimidomalonaldehydate (IIa).—Freshly cut sodium (11.50 g., 0.500 mole) and 250 ml. of reagent grade xylene were placed in a 500-ml. three-necked round-bottom flask equipped with a dropping funnel, stirrer and reflux condenser with a sidearm takeoff. A stream of dry nitrogen was started over the system and the xylene was heated to reflux. To the stirred suspension was added over a 15-minute period, 22.2 ml. (0.55 mole) of absolute methanol (distilled from magnesium). Heating was continued for an additional 15 minutes and then 50 ml. of distillate was collected from the sidearm takeoff. After cooling to room temperature, the milky suspension was added in small portions over a 30-minute period to a rapidly stirred suspension of 109.5 g. (0.5 mole) of methyl phthalimidoacetate (Ia) (prepared from phthaloylglycine in 98% yield by esterification with methanol–hydrogen chloride) in 245 ml. (4.00 moles) of methyl formate (freshly redistilled from phosphorus pentoxide) at 0°. Stirring was continued for another 30 minutes and the resulting clear, orange solution was stored at 5° for 16 hours.

The canary-yellow mass was treated with 200 ml. of dry benzene containing 30 ml. of glacial acetic acid, stirred rapidly for several minutes and then washed with 250 ml. of *N* hydrochloric acid. After the layers were separated, the aqueous phase was further acidified to *p*H 2 with concentrated hydrochloric acid and extracted with two 100-ml. portions of benzene. The combined organic extracts were washed with two 50-ml. portions of water and concentrated under reduced pressure to a volume of 200 ml. On cooling to 5°, a yellow crystalline solid separated. It was collected by filtration, washed with cold benzene and dried to give 62.30 g. of crude IIa. Concentration of the mother liquors afforded an additional 6.20 g. The combined crude product was crystallized from boiling benzene to give 52 g. of pale-yellow, crystalline powder (green fluorescence), m.p. 140–141°. The second crop amounted to 5.80 g., m.p. 133–138°, bringing the total yield to 47%. An analytical sample, recrystallized from benzene, melted at 140.5–142.0°.

Anal. Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.65; H, 3.78; N, 5.61.

The aldehyde gave a wine-colored ferric chloride test and reduced Tollens reagent and Fehling solution. It dissolved in aqueous sodium bicarbonate solution to give a yellow solution. The 2,4-dinitrophenylhydrazone was obtained as yellow prisms from dioxane–water, m.p. 215–216° dec.

Anal. Calcd. for $C_{18}H_{13}N_5O_8$: C, 50.59; H, 3.07; N, 16.39. Found: C, 50.28; H, 3.10; N, 16.55.

Methyl 4-Carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (IIIa).—To a hot solution of IIa (24.72 g., 0.1 mole) in 100 ml. of 95% ethanol was added a solution of DL-penicillamine hydrochloride (18.6 g., 0.100 mole) and sodium acetate trihydrate (20.4 g., 0.15 mole) in 100 ml. of water. After 12 hours storage at room temperature, the precipitated product was collected by filtration, washed with 50% aqueous ethanol and dried to give 28.2 g. of IIIa as colorless granular crystals, m.p. 183–184°, dec. After 5 days, the filtrate yielded a second crop of 2.61 g., m.p. 185–186°, dec.; total yield 81%. An analytical sample was obtained as colorless needles by recrystallization from 95% ethanol, m.p. 184.5–185.5° dec.

Anal. Calcd. for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.41. Found: C, 54.23; H, 4.94; N, 7.29.

When D-penicillamine hydrochloride was used in a similar procedure, a 75% yield of a mixture of the stereoisomeric D-acids was obtained. By collecting the products in small successive fractions as they precipitated, some degree of separation was attained. Since purification of these acids could be followed by changes in optical rotation, separation by fractional crystallization from methanol was facilitated. The least soluble acid was obtained as colorless needles from methanol, m.p. 184.5–185.5° (dec., in bath at 170°), $[\alpha]^{25}D$ in dioxane −7° (*c* 1.3).

Anal. Calcd. for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.41. Found: C, 54.23; H, 5.10; N, 7.34.

A more soluble acid was recrystallized to constant rotation from methanol–water. An analytical sample of colorless needles melted at 184–185° dec., $[\alpha]^{25}D$ in dioxane +24° (*c* 0.8).

Anal. Calcd. for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.41. Found: C, 53.94; H, 4.77; N, 7.15.

Esterification of mixtures of the acids with diazomethane led to the isolation of two crystalline esters. One was obtained as fluffy needles from methanol–water, m.p. 146–147°, $[\alpha]^{27}D$ in methanol −28° (*c* 1.7).

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 54.90; H, 5.40; N, 7.26.

A second ester, obtained as colorless needles from acetone–water, melted at 138–139°, $[\alpha]^{25}D$ in methanol −5° (*c* 1).

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.13; H, 5.21; N, 7.27.

The stereochemical relationships of the two acids to the two esters have not been established with certainty.

Methyl 4-Carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (IVa).—A suspension of a stereoisomeric mixture of the DL-acids IIIa (3.78 g., 0.01 mole) in 150 ml. of methylene chloride was cooled in an ice-bath and treated with ethereal diazomethane until the yellow color of the reagent persisted. After 5 minutes the solution was decolorized by the dropwise addition of glacial acetic acid, then washed with 50-ml. portions of 5% sodium bicarbonate and water, and dried over magnesium sulfate. Concentration of the solution under reduced pressure left 3.92 g. (100%) of colorless oil. By fractional crystallization of the mixture from methanol–water, a sample of colorless needles was obtained of m.p. 152.5–153.5°. No attempt was made to isolate other isomers.

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.19; H, 5.36; N, 7.31.

Alkaline Hydrolysis of IIIa.—A stereoisomeric mixture of DL-IIIa (3.78 g., 0.0100 mole) was added to 65.5 ml. of 0.459 *N* sodium hydroxide. After storage at room temperature for 4 hours, the solution was neutralized by potentiometric titration with 0.974 *N* hydrochloric acid. The plotted data showed no sharp breaks in the curve. The resultant clear solution was stored at 5° for 3 weeks, after which time 1.16 g. of crystalline solid had separated, m.p. 127°, dec. in bath 120°. Several recrystallizations from acetone–water gave pure V, m.p. 120–121° dec.

Anal. Calcd. for $C_{16}H_{18}N_2O_7S$: C, 50.25; H, 4.74; N, 7.33. Found: C, 50.38; H, 5.03; N, 7.53.

Benzyl α-Phthalimidomalonaldehydate (IIb).—A suspension of sodium benzoxide (prepared from 2.3 g. of sodium in a manner similar to that used for sodium methoxide for IIa) in xylene was added over a 30-minute period to a mixture of 29.53 g. (0.1 mole) of benzyl phthalimidoacetate (prepared in 96% yield by azeotropic distillation of a mixture of phthaloylglycine, benzyl alcohol, toluene and a trace of *p*-toluenesulfonic acid) and 50.4 ml. (0.4 mole) of benzyl formate with rapid stirring at 5°. The entire operation including an 18-hour storage period at room temperature, was conducted under a dry nitrogen atmosphere.

Purification essentially according to the procedure described for IIa (except that methylene chloride was the ex-

(6) J. C. Sheehan and G. D. Laubach, THIS JOURNAL, **73**, 4752 (1951).

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

traction solvent) led to IIb as an oily concentrate which dissolved readily in 50 ml. of ether. After storage overnight at 5°, the crystalline product was collected by filtration; weight 15.5 g., m.p. 129–133°. Recrystallization from ethanol–water gave 14.35 g. (44.5%), m.p. 137–138°.

Anal. Calcd. for $C_{18}H_{13}NO_5$: C, 66.87; H, 4.05; N, 4.33. Found: C, 67.17; H, 4.33; N, 4.58.

This aldehyde reduced Tollens reagent and Fehling solution and gave a deep-wine ferric chloride test. An analytical sample of the 2,4-dinitrophenylhydrazone, obtained as yellow needles from chloroform–cyclohexane, melted at 197.0–198.0°.

Anal. Calcd. for $C_{24}H_{17}N_5O_8$: C, 57.26; H, 3.40; N, 13.91. Found: C, 56.94; H, 3.56; N, 13.62.

Benzyl 4-Carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (IIIb).—Condensation of IIb with DL-penicillamine hydrochloride in the manner similar to that described for the preparation of IIIa gave an 89% yield of a stereoisomeric mixture corresponding to IIIb. Several recrystallizations from acetone–water afforded an analytical sample which melted at 160–161° dec.

Anal. Calcd. for $C_{23}H_{22}N_2O_6S$: C, 60.78; H, 4.88; N, 6.16. Found: C, 60.67; H, 5.19; N, 6.05.

Benzyl 4-Carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolineacetate (IVb).—Treatment of a stereoisomeric mixture of IIIb (4.54 g.) with excess ethereal diazomethane afforded 2.89 g., m.p. 124–125.5°, of colorless prisms. An analytical sample of IVb, recrystallized from acetone–water, had m.p. 125.5–126°.

Anal. Calcd. for $C_{24}H_{24}N_2O_6S$: C, 61.52; H, 5.16; N, 5.98. Found: C, 61.50; H, 5.20; N, 5.92.

***t*-Butyl Phthalimidoacetate (Ic).**—Phthaloylglycyl chloride (111.8 g., 0.5 mole) and *t*-butyl alcohol (94 ml., 1 mole) were dissolved in 300 ml. of dry methylene chloride, the solution was cooled to −10° and triethylamine (70.0 ml., 0.500 mole) added with rapid stirring over a 15-minute period. The ice-bath was removed and stirring continued for an additional hour. The resulting suspension was washed successively with 100-ml. portions of water, 0.1 *N* hydrochloric acid, 5% sodium bicarbonate and water. The methylene chloride layer was dried over magnesium sulfate and concentrated under reduced pressure to a light-yellow oil which set to a crystalline mass on cooling; weight 123.5 g. (95%) of nearly colorless Ic, m.p. 94.0–95.5°. Recrystallization from benzene–petroleum ether (b.p. 30–60°) gave colorless needles, m.p. 96.0–97.5°. An analytical sample was prepared by sublimation at 85° (0.03 mm.), m.p. 96.0–97.5°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.17; H, 6.00; N, 5.46.

***t*-Butyl α-Phthalimidomalonaldehydate (IIc). A. Sodium *t*-Butoxide Procedure.**—Freshly cut sodium (4.60 g., 0.200 mole) in 200 ml. of reagent grade xylene was placed in a 500-ml. three-necked round-bottom flask equipped with a dropping funnel, stirrer and reflux condenser with a sidearm takeoff. A stream of dry nitrogen was started over the system and the xylene was heated gently to reflux. *t*-Butyl alcohol (55 ml., 0.60 mole) was added to the rapidly stirred suspension over a 15-minute period. Heating with stirring was continued for an additional 2 hours, after which time all the sodium had reacted. The sidearm stopcock was opened and 100 ml. of distillate was collected, leaving a nearly clear solution. After cooling to 0–5°, a solution of equal parts of *t*-butyl formate and *t*-butyl alcohol (41 g.), and *t*-butyl phthalimidoacetate (52.2 g., 0.200 mole) in 100 ml. of benzene was added with rapid stirring over a 30-minute period, and the resulting red-brown solution was stored at 5° for 40 hours.

Glacial acetic acid (20 ml.) was added and the yellow suspension was washed with 150 ml. of cold *N* hydrochloric acid. The aqueous layer was extracted with two 100-ml. portions of benzene. The combined organic extracts were washed with 50 ml. of saturated sodium chloride solution and extracted with four 100-ml. portions of 5% sodium bicarbonate solution. The combined bicarbonate extracts were covered with 100 ml. of benzene and acidified to *p*H 2 with cold 6 *N* hydrochloric acid. After separation of the layers, the aqueous phase was extracted further with two 50-ml. portions of benzene. The combined benzene extracts were washed with 50 ml. of saturated sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure to a volume of 25 ml. The crystalline product, which separated on cooling, was collected by filtration, washed with several small portions of cold benzene and dried to yield 3.60 g. of VIc, m.p. 146–152° dec. After storage for 8 hours, the original organic reaction phase was extracted with sodium bicarbonate solution as before to give 3.14 g. of nearly colorless crystals, m.p. 155–156° dec. The filtrates from the first and second crops were combined and concentrated to yield an additional 0.71 g. of product, m.p. 153–154° dec. The total yield was 13%. An analytical sample was obtained as colorless prisms from benzene, m.p. 155–156° dec.

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.27; H, 5.23; N, 4.84. Found: C, 62.48; H, 5.29; N, 4.70.

This aldehyde also reduced Tollens reagent and Fehling solution. It dissolved in sodium bicarbonate and gave a deep-wine ferric chloride test. The yellow 2,4-dinitrophenylhydrazone was obtained as felted needles from ethanol, m.p. 167–168° dec., in bath at 150°.

Anal. Calcd. for $C_{21}H_{19}N_5O_8$: C, 53.73; H, 4.08; N, 14.92. Found: C, 54.00; H, 4.18; N, 15.04.

B. Sodium Hydride Procedure.—Sodium hydride (9.8 g., 0.41 mole) was added in portions to a solution of 52.2 g. (0.20 mole) of *t*-butyl phthalimidoacetate and 102 g. (1.00 mole) of *t*-butyl formate in 300 ml. of dry benzene contained in a 1-l. three-necked round-bottom flask equipped with a stirrer and reflux condenser which was protected by a calcium chloride tube and mercury trap. After the system was flushed with a stream of dry nitrogen for 10 minutes the vigorously stirred suspension was heated to reflux, hydrogen evolution began immediately, but became very slow after 2.5 hours. Nitrogen was again passed through the system and the brown solution was allowed to cool to room temperature. After stirring for an additional 12 hours, the product was isolated essentially as described above. Three extractions at 24-hour intervals, each with four 100-ml. portions of 5% sodium bicarbonate solution, yielded a total of 17.94 g. (31%) of pale yellow crystals, m.p. 156–157.5° dec.

***t*-Butyl 4-Carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (IIIc).**—To a warm ethanolic solution (40 ml.) of IIc (5.78 g., 0.02 mole) was added a solution of DL-penicillamine hydrochloride (3.72 g., 0.02 mole) and sodium acetate trihydrate (4.08 g., 0.03 mole) in 40 ml. of water. After storage for 4 hours, the mass of colorless needles which had separated was collected by filtration, washed with 50% aqueous ethanol and dried; weight 4.65 g., m.p. 171–172° dec. Three more crops were collected during the following 8 days to give an additional 2.38 g. of product, m.p. 171–174° dec. The total yield was 84%. Several recrystallizations of the first crop from acetone–water afforded an analytical sample, m.p. 179.5–180.5° dec.

Anal. Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.20; H, 5.79; N, 6.35.

***t*-Butyl 4-Carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (IVc).**—A suspension of the acid IIIc (0.841 g., 2.00 millimoles) in 50 ml. of ether was cooled in an ice-bath and treated with an excess of ethereal diazomethane.

The ester was crystallized from ether–petroleum ether (b.p. 30–60°), to provide 0.650 g. of colorless needles, m.p. 118.5–119.5°. A second crop of 0.130 g., m.p. 119–120°, brought the amount of crystalline ester to 90%. An analytical sample was obtained by recrystallization from ethanol–water, m.p. 121–122°.

Anal. Calcd. for $C_{21}H_{26}N_2O_6S$: C, 58.05; H, 6.03; N, 6.45. Found: C, 58.02; H, 6.09; N, 6.52.

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