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

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. III. Phthalimido β-Lactam-Thiazolidines Derived from Penicillamine

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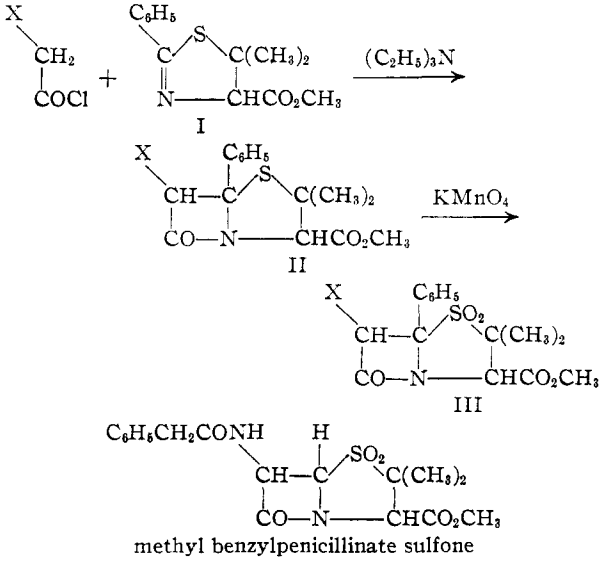
By condensation of phthaloylglycyl chloride and a 2-phenylthiazoline derived from pencillamine, a fused β-lactam-thiazolidine closely related to the natural penicillins has been synthesized. Oxidation to the corresponding sulfone was carried out, and the infrared absorption spectra of these products emphasize a resemblance to the penicillin structure. The sulfone of methyl 5,5-dimethyl-2-phenyl-3-phthaloylglycyl-4-thiazolidinecarboxylate, an open-chain analog of penicillin, was prepared by a three-step synthesis from D-penicillamine methyl ester. Treatment of this sulfone with sodium ethoxide and bromine under mild conditions caused an unusual degradation leading to methyl α-phthalimidoacetamidosenecioate.

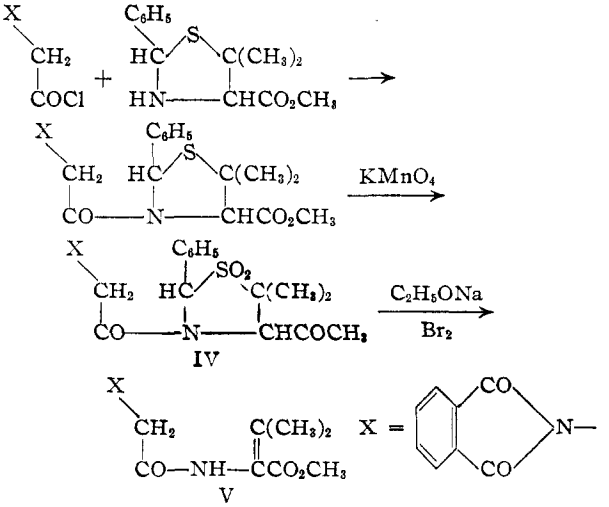
A fused β-lactam-thiazolidine derived from penicillamine has been prepared by an extension of the new general synthesis reported previously.[3] Methyl 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate (I) and phthaloylglycyl chloride in the presence of triethylamine interact to form the β-lactam of 4-carbomethoxy-5,5-dimethyl-2-phenyl-α-phthalimido-2-thiazolidineacetic acid (II). In a procedure similar to that used with the methyl ester of penicillin,[4] II was oxidized to the corresponding sulfone III.

The thiazoline I was prepared by treatment of D-penicillamine methyl ester hydrochloride with ethyl benzimidate hydrochloride and triethylamine. Evaporative distillation of the chromatographed product caused nearly complete racemization, as did heating with a trace of triethylamine. The lactam II was obtained much more readily when distilled thiazoline I of low optical activity was employed than was the case when the undistilled chromatographed thiazoline was the starting material. Evaporative distillation of I does not alter the refractive index or the infrared or ultraviolet spectrum.



The best yield of the β-lactam was obtained using methylene chloride as a solvent under high-dilution reaction conditions. With ether as a solvent, or when conventional methods of contacting the reagents were employed, an appreciable yield of a high-melting by-product (VI) was obtained. The composition of VI corresponds to one thiazoline and three acyl residues, and the structure is probably analogous to a similar product observed in another series.[3c]

As an open-chain analog of III, the related acylated thiazolidine sulfone IV was prepared. D-Penicillamine methyl ester hydrochloride and benzaldehyde were allowed to condense in methylene chloride solution to form methyl 5,5-dimethyl-2-phenyl-4-thiazolidinecarboxylate hydrochloride. Acylation with phthaloylglycyl chloride gave methyl 5,5-dimethyl-2-phenyl-3-phthaloylglycyl-4-thiazolidinecarboxylate, which was oxidized to the corresponding sulfone IV with potassium permanganate.



The melting point of the sulfone IV is approxi-

(1) Bristol Laboratories Postdoctoral Fellow, 1950–1951.

(2) Bristol Laboratories Postdoctoral Fellow, 1948–1950.

(3) (a) J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach and J. J. Ryan, THIS JOURNAL, **72**, 3828 (1950); (b) J. C. Sheehan and J. J. Ryan, *ibid.*, **73**, 1204 (1951); (c) *ibid.*, **73**, 4367 (1951).

(4) H. T. Clarke, J. R. Johnson and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 177.

mately 40° higher than that of the β-lactam sulfone III, and the critical amide carbonyl infrared absorption bands for each were observed in the expected regions; at 5.55 μ for the lactam carbonyl of III, and at 5.95 μ for the amide carbonyl of IV. The formation of the sulfone of II was useful in establishing its structure both on a chemical basis[5] and from the interpretation of the infrared absorption data. Since the phthalimido group has two strong bands in the carbonyl region, at 5.65 μ, and at 5.82 μ, the lactam carbonyl band in II, expected at 5.62 μ, from a comparison with penicillin,[6] was not resolved as a separate band. However, as was observed with penicillin and 3-acylated thiazolidines,[7] on oxidation to the sulfone the carbonyl band shifts about 0.05 μ to a shorter wave length. Thus the absorption band of the lactam carbonyl of II is shifted from a predicted location at 5.62 μ to the 5.55 μ observed for III, while the phthalimido band remains at 5.65 μ and appears as a shoulder on the lactam band. All three compounds, II, III and IV had an ester band at 5.72 μ, and the phthalimido bands at 5.65 and 5.82 μ.

When the acylated thiazolidine sulfone IV was treated with a solution of sodium alkoxide and bromine, an unusual degradation took place which led to a high yield of a compound with properties best interpreted in terms of the unsaturated dimethylacrylate V. The product contains neither sulfur nor halogen, and is not readily soluble in dilute, cold alkali or acid. The infrared absorption spectrum is compatible with the structure assigned: the N–H band at 2.95 μ along with the shoulder at 5.95 μ and the band at 6.65 μ indicate a monosubstituted amide, the shoulder at 5.90 μ may be the conjugated ester,[8] while the band at 6.10 μ may be the conjugated C=C, and the 5.65 μ and 5.82 μ bands are due to the phthalimide moiety.

The β-lactam II did not show antibiotic activity when compared with penicillin methyl ester in routine assay procedures.[9]

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Experimental[10]

Methyl 5,5-Dimethyl-2-phenyl-2-thiazoline-4-carboxylate[11] **(I).**—A mixture of 3.71 g. (0.02 mole) of ethyl benzimidate hydrochloride,[12] 4.00 g. (0.02 mole) of D-penicillamine methyl ester hydrochloride[13] and 2.8 ml. (2.02 g., 0.02 mole) of dry triethylamine in 25 ml. of dry methylene chloride was stirred for 48 hours at room temperature. The methylene chloride was removed under reduced pressure and the solid residue was treated with 50 ml. of dry ether. The insoluble mixture of ammonium chloride and triethylamine hydrochloride was removed by filtration, 3.66 g. (96%). The ether filtrate was concentrated under reduced pressure to a viscous, brown oil which was dissolved in 50 ml. of dry benzene. The benzene solution of the crude thiazoline was passed through a 25 × 15 mm. column of activated charcoal. After elution with 35 ml. of dry benzene, the benzene solutions were combined and passed through a 75 × 15 mm. column of activated alumina (48–100 mesh) and eluted with 50 ml. of benzene. Removal of the benzene under reduced pressure gave 4.90 g. (98%) of the slightly yellow thiazoline; $[\alpha]^{25.8}D$ + 14.6° (5% in acetone); $n^{25}D$ 1.5656; picrate, m.p. 78–80°. The thiazoline was further processed by evaporative distillation at approximately 140–160° (0.05 mm.), affording a very pale yellow liquid; $\lambda_{max.}$ 244 mμ, $\epsilon_{max.}$ 15000 (methylcyclohexane); $n^{25}D$ 1.5657; $[\alpha]^{26.5}D$ + 3.0 (5% in acetone); picrate, m.p. 106° (*cf.* 109°[14]). The product may be stored at 5° for a few weeks without appreciable decomposition.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.78; H, 6.06; N, 5.62. Found: C, 63.04; H, 5.86; N, 5.81.

4-Carbomethoxy-5,5-dimethyl-2-phenyl-α-phthalimido-2-thiazolidineacetic Acid β-Lactam (II).—In a three-necked flask equipped with a slip-sealed stirrer and high-dilution cycle[15] was placed 2.49 g. (0.01 mole) of I in 50 ml. of dry methylene chloride and 2.24 g. (0.01 mole) of phthaloylglycyl chloride in 50 ml. of dry methylene chloride. Stirring was begun and the solution was heated to rapid reflux. A solution of 1.40 ml. (1.01 g., 0.01 mole) of dry triethylamine (distilled from sodium hydroxide) in 50 ml. of dry methylene chloride was added through the high-dilution cycle over a period of six hours. The methylene chloride was removed under reduced pressure and 50 ml. of dry dioxane was added. The insoluble triethylamine hydrochloride was removed by filtration; yield 1.30 g. (94.6%). The filtrate was concentrated under reduced pressure to a brown oil which crystallized upon standing at 5° for two weeks. The yield of crude product was 2.54 g. (58.3%); m.p. 144–165°. Two recrystallizations from acetone–ligroin gave 0.89 g. (20.4%) of the pure β-lactam II, m.p. 178.8–180.4°.

Anal. Calcd. for $C_{23}H_{20}N_2O_6S$: C, 63.29; H, 4.62; N, 6.42. Found: C, 63.35; H, 4.74; N, 6.44.

When the above experiment was carried out using ether in place of methylene chloride as solvent, 75 mg. of ether-insoluble material (m.p. 264–266°) was obtained as a by-product and the yield of β-lactam was appreciably lower. This high-melting material analyzes for the analog of the monothiazoline-triacyl compound postulated by Sheehan and Ryan[2] and is tentatively assigned a similar structure, methyl 3,3-dimethyl-9-oxo-5-phenyl-6,8-diphthalimido-7-(phthalimidoacetoxy)-4-thia-1-azabicyclo[3.2.0]7-nonene-2-carboxylate (VI).

Anal. Calcd. for $C_{43}H_{30}N_4O_{11}S$: C, 63.70; H, 3.75; N, 6.91. Found: C, 63.11; H, 3.75; N, 6.89.

4-Carbomethoxy-5,5-dimethyl-2-phenyl-α-phthalimido-2-thiazolidineacetic Acid β-Lactam Sulfone (III).—With warming, 100 mg. of II was dissolved in 6 ml. of 80% acetic acid. A solution of 250 mg. of potassium permanganate was dissolved in hot water. When cool, the two solutions were mixed and allowed to stand for 20 minutes. The reaction mixture was then decolorized with several drops of 35% hydrogen peroxide. The white, cloudy suspension was further diluted with 15 ml. of water, and the crystalline sulfone floated to the surface as a fleecy mass. The product was collected by filtration; yield 100 mg. (93%), m.p. 243–244°. The crude sulfone was dissolved in a mixture of 5 ml. of methanol and 5 ml. of acetone by warming. After filtering from a slight cloudiness, 2 ml. of water was added, and on cooling colorless plates precipitated; yield 80 mg. (75%), m.p. 251–254°.

Anal. Calcd. for $C_{23}H_{20}N_2O_7S$: C, 58.96; H, 4.30; N, 5.98; S, 6.84. Found: C, 59.30; H, 4.39; N, 5.90; S, 6.70.

Methyl 5,5-Dimethyl-2-phenyl-3-phthaloylglycyl-4-thiazolidinecarboxylate Sulfone (IV).—To 200 ml. of dry methylene chloride was added 5 g. (0.025 mole) of D-penicillamine methyl ester hydrochloride, 2.6 ml. (0.025 mole) of freshly distilled benzaldehyde, and a trace of hydrogen chloride.

(5) Reference 4, p. 436.

(6) Reference 4, p. 404.

(7) Reference 4, p. 409.

(8) H. M. Randall, N. Fuson, R. G. Fowler and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 109.

(9) Bristol Laboratories, Syracuse, N. Y.

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

(11) A similar method was previously reported briefly for the preparation of this compound by one of us (J. C. S.) to O. S. R. D., Merck Report M. 62, April 30, 1945, Part II, p. 18.

(12) A. Pinner, *Ber.*, **16**, 1654 (1883).

(13) Reference 4, pp. 34, 470.

(14) (a) H. C. Carrington and W. A. Sexton, British Patent 584,981; *C. A.*, **41**, 3822 (1947); prepared from the acrylate and phosphorus pentasulfide. (b) Reference 4, p. 471; prepared from N-benzoylpenicillamine and methanolic hydrogen chloride (work done by one of us (J. C. S.)).

(15) A. C. Cope and E. C. Herrick, THIS JOURNAL, **72**, 985 (1950).

The mixture was heated under reflux until the suspended solid was dissolved (one-half hour) and the cooled solution was dried with two successive portions of calcium sulfate. Since a test for a mercaptan group with nitroprusside was positive another 0.1 ml. of benzaldehyde was added, and the reaction mixture, after storage overnight, was negative to nitroprusside. The resulting clear solution was concentrated under reduced pressure to a viscous oil, which on warming to 40° (0.05 mm.) fluffed up to a white, noncrystalline foam, wt. 5.190 g. (72%, calculated as methyl 5,5-dimethyl-2-phenyl-4-thiazolidinecarboxylate hydrochloride).[16]

To a cooled (−60°) solution of the aforementioned crude thiazolidine 3.020 g. (0.0105 mole) in 25 ml. of dry methylene chloride was added 2.34 g. (0.0105 mole) of phthaloylglycyl chloride in 20 ml. of dry methylene chloride, the temperature being kept below −40°. To this clear, yellow solution was added 3.0 ml. (0.0214 mole) of triethylamine, maintaining the low temperature. An orange precipitate formed immediately. After the amine had been added, the reaction mixture was allowed to attain room temperature over a period of half an hour, by which time the suspension was pale yellow. Dry benzene (50 ml.) was added and the reaction mixture was concentrated to about 25 ml. The precipitate (triethylamine hydrochloride) was removed by filtration and washed with 25 ml. of benzene, weight 2.86 g. (99%). The filtrate was concentrated to an oil which fluffed up to a hard foam at 60° (0.05 mm.), weight 4.545 g. (99%, calculated as methyl 5,5-dimethyl-2-phenyl-3-phthaloylglycyl-4-thiazolidinecarboxylate).

The crude acylated thiazolidine was oxidized to the corresponding sulfone by essentially the same procedure which was used for III. To a solution of 3.07 g. of the acylated thiazolidine in 170 ml. of 80% acetic acid was added a solution of 7.10 g. of potassium permanganate in 127 ml. of water. After 20 minutes the solution was decolorized with about 8 ml. of 35% hydrogen peroxide. On dilution of the clear solution to one liter with water, a fluffy, white precipitate separated; yield 1.925 g. (59%, calculated as IV). The crude product was dissolved in 75 ml. of boiling methanol, filtered and concentrated to half of the original volume. On cooling, transparent, short needles separated; weight 0.940 g. (29%), m.p. 210–211°, $[\alpha]^{25}D$ +36° (1% in acetone).

Anal. Calcd. for $C_{23}H_{22}N_2O_7S$: C, 58.71; H, 4.71; N, 5.96. Found: C, 58.66; H, 5.00; N, 5.86.

Methyl α-Phthalimidoacetamidosenecioate (V).—To a solution of 100 mg. of IV (0.00212 mole) in 5 ml. of nitrobenzene (dried over calcium chloride) was added 5 mg. of sodium in 1 ml. of absolute alcohol (0.00218 mole of sodium ethoxide), and 34 mg. (0.424 milliequivalent) of bromine in 1 ml. of carbon tetrachloride. After standing for an hour the solution was filtered to remove a faint turbidity; weight of residue, 13.5 mg. (61% calcd. as sodium bromide). After concentration of the filtrate to dryness at 100° (0.05 mm.) the residue, 102 mg., was taken up in 7 ml. of hot methanol. When the solution was concentrated to about half of the original volume fine, asbestos-like needles formed, amounting to 51 mg. (76%), m.p. 225–226°. Halogen and sulfur were found to be absent by a fusion test. The crystalline degradation product was insoluble in cold sodium hydroxide solution as well as 6 *N* hydrochloric acid.

Anal. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.59; H, 5.02; N, 8.78.

It was found that sodium methoxide in methanol could be used as the base, or nitrobenzene as the bromine diluent without altering the nature of the product.

(16) Reference 4, p. 963; A. H. Cook, *et al.*, *J. Chem. Soc.*, 2354 (1949).

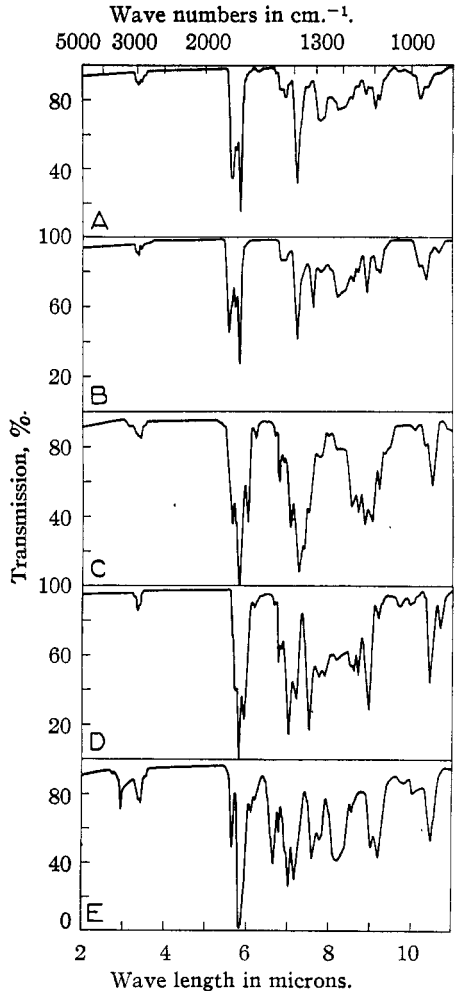

Fig. 1.—Infrared absorption spectra of: A, 4-carbomethoxy - 5,5 - dimethyl - 2 - phenyl - α - phthalimido - 2-thiazolidineacetic acid β-lactam (II); B, 4-carbomethoxy-5,5 - dimethyl - 2 - phenyl - α - phthalimido - 2 - thiazolidineacetic acid β-lactam sulfone (III); C, methyl 3,3-dimethyl - 9 - oxo - 5 - phenyl - 6,8 - diphthalimido - 7 - (phthalimidoacetoxy) - 4 - thia - 1 - azabicyclo[3.2.0] - 7 - nonene-2-carboxylate (VI); D, methyl 5,5-dimethyl-2-phenyl-3-phthaloylglycyl-4-thiazolidinecarboxylate sulfone (IV); E, methyl α-phthalimidoacetamidosenecioate (V).

Infrared Absorption Spectra.—The infrared spectra shown in Fig. 1 were determined with a Baird Infrared Recording Spectrophotometer, Model B. Two per cent. solutions in tetrachloroethane were used for curves A and B and five per cent. solutions in tetrachloroethane were used for curves C, D and E.

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