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

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. IV. The Synthesis of a 5-Phenyl Penicillin and α-Succinimido β-Lactam-thiazolidines[1]

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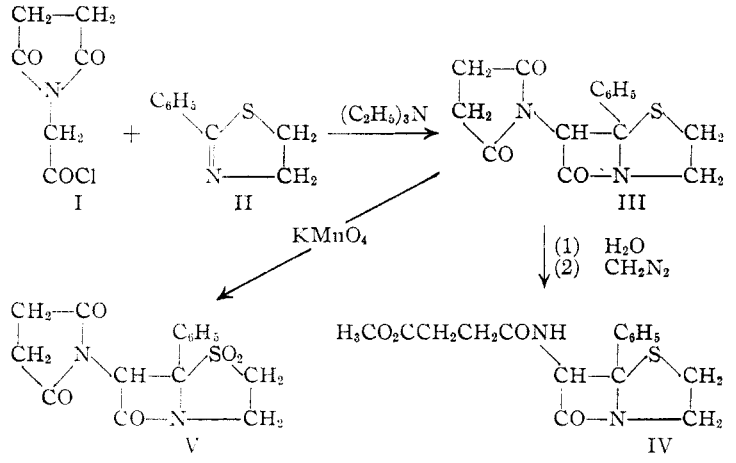
Three series of fused β-lactam-thiazolidines have been synthesized which progressively approach penicillin in structural complexity. The succinimido blocking group is used in an extension of a new synthesis of β-lactam -thiazolidines by condensation of a diacylamino acid chloride with a thiazoline. Partial hydrolysis of the succinimide ring gives the substituted acetylamino grouping which is present in natural and biosynthetic penicillins. By this method the total synthesis of a 5-phenyl penicillin was achieved. This compound, methyl 5-phenyl-(2-carbomethoxyethyl)-penicillinate, has the fused β-lactam-thiazolidine ring system with all of the appropriately located substituents which characterize the natural penicillins, but in addition it possesses a 5-phenyl group. The structure was established by oxidation to a sulfone, by the infrared spectrum and by degradation to a derivative of N-phenacylsuccinamic acid.

In this communication is described the use of the succinimido protecting group in the synthesis of fused β-lactam-thiazolidines by interaction of diacylamino acids and thiazolines according to the method reported previously in this series.[2] The succinimido group has advantages over the phthalimido group previously used, since hydrolysis of the succinimido ring leads to the substituted acetylamino grouping characteristic of biologically active natural and biosynthetic penicillins.

The succinimido group also confers desirable solubility and crystallization properties, and the succinimido ring system has a less intense band in the region of β-lactam absorption in the infrared, thus facilitating identification. Three series of β-lactam-thiazolidines progressively approaching penicillin in structural complexity have been prepared, and their similarity to penicillin has been demonstrated by oxidation to the corresponding sulfones, by comparison of infrared spectra, and in one case by degradation to a carbonyl component.

The simplest model lactam (III) prepared in this work was obtained by interaction of 2-phenyl-2-thiazoline (II) and succinimidoacetyl chloride (I). The reaction showed even greater sensitivity to conditions than the analogous procedure in the case of phthaloylglycyl chloride,[2] and the standard method previously used[2] (high dilution addition of triethylamine in ether to a mixture of thiazoline and acid chloride in refluxing ether) yielded no isolable lactam. A similar procedure using refluxing benzene resulted in a 14% yield of the adduct III, but the isolation was very difficult. The most successful preparation, involving the use of methylene chloride as a solvent under high dilution conditions, yielded 56% of the desired lactam III directly in easily purified state from the crude reaction mixture. The use of the latter procedure has proved successful repeatedly in the similar preparations to be described, several of which failed to yield appreciable amounts of lactam when carried out in other solvents.

The structure of the lactam III was readily assigned on the basis of oxidation to the sulfone V and infrared spectrum.



The spectrum of III (similar to Fig. 1 curve B except for the 5.7 μ band) shows the characteristic strong band at 5.6 μ due to β-lactam carbonyl stretching in addition to the succinimido carbonyl band at 5.8 μ. The characteristically very weak band of the succinimido group at 5.6 μ coincides with the β-lactam band.[3]

The oxidation of the lactam III to the corresponding sulfone V in quantitative yield using potassium permanganate in acetic acid–dioxane–water was carried out under conditions known to lead to high yields of the sulfone of methyl benzylpenicillinate.

Hydrolysis of the succinimido protecting group proceeded readily on slow titration of a dioxane solution with 0.1 *N* base. The corresponding methyl ester IV was prepared, using diazomethane, in 67% over-all yield. The infrared spectrum of this lactam shows clearly the characteristic lactam band at 5.65 μ, primary amide bands at 2.92, 5.93 and 6.60 μ and the ester carbonyl at 5.80 μ (Fig. 1, curve A). It is interesting to note that the high wave length band of the primary amide falls at 6.6 μ as in penicillin, rather than at the lower wave lengths usually observed with primary amides (near 6.5 μ).

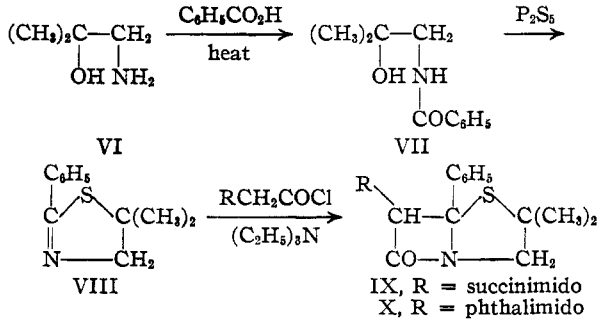
The preparation of a similar series of compounds which possess the 5,5-geminal dimethyl grouping characteristic of the penicillins was also carried out. Condensation of benzoic acid and isobutanolamine (VI) yielded the amide VII in 76% yield, which was

(1) From the Ph.D. Thesis of Gerald D. Laubach, June, 1950. Bristol Laboratories Predoctoral Fellow, 1948–1950.

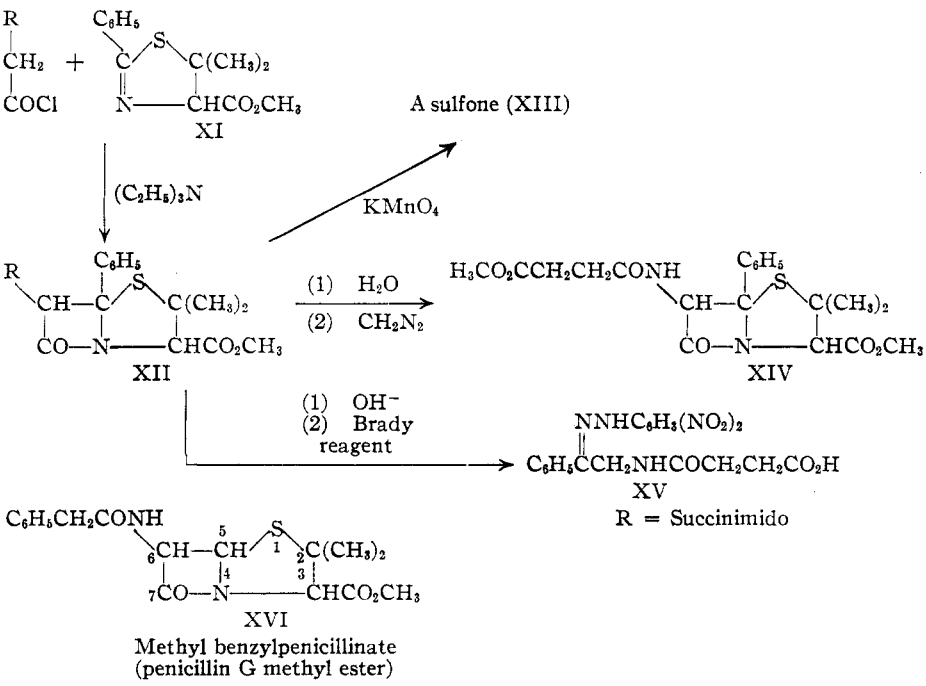
(2) J. C. Sheehan and J. J. Ryan, THIS JOURNAL, **73**, 4367 (1951).

(3) H. M. Randall, R. G. Fowler, J. R. Dangl and N. Fuson, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 171.

cyclized by reaction with phosphorus pentasulfide to yield 41% of the thiazoline VIII. The reaction of VIII with succinimidoacetyl chloride and triethylamine afforded 16% of the desired lactam IX. A similar reaction with phthalimidoacetyl chloride in ether yielded the corresponding phthalimido lactam X in only 5% yield.



Starting material for the preparation of members of the β-lactamthiazolidine series related to 5-phenyl penicillin[4] itself was methyl 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylate (XI), obtained from natural penicillamine by esterification followed by ring formation with ethyl benzimidate.[5] Under the conditions of this particular preparation, which involved evaporative distillation at 150°, the product was apparently completely racemized. Reaction of the thiazoline XI with succinimidoacetyl chloride under high-dilution conditions yielded 13% of the desired lactam XII, which was readily oxidized to the sulfone XIII in 76% yield. The infrared spectrum of XII shows the characteristic ester band at 5.7 μ in addition to the expected 5.6 μ lactam and 5.8 μ succinimido bands (Fig. 1, curve B).



Alkaline degradation of XII led to N-phenacylsuccinamic acid, isolated as the 2,4-dinitrophenylhydrazone.

Hydrolysis and esterification of XII affords a 29% yield of the corresponding α-acylamino derivatives XIV, which has an infrared spectrum similar to that of natural methyl benzylpenicillinate itself. (XVI) (Fig. 1, curves C and D). Disappearance of the strong 5.8 μ band of the succinimido group reveals the 5.8 μ ester band (seen also in curve A), which is thus shown to be due to the side-chain carbomethoxy group. Compound XIV, methyl 5-phenyl-(2-carbomethoxyethyl)-penicillinate, is the closest synthetic analog of penicillin yet reported. The configurational relationship of XIV to the natural antibiotic is unknown.

We are indebted to Bristol Laboratories of Syracuse, N. Y., for a generous grant for the support of this program.

Experimental[6]

Succinimidoacetic Acid.—A well pulverized mixture of succinic anhydride (50.0 g., 0.5 mole) and glycine (37.6 g., 0.5 mole) was evacuated to 0.5 mm. and then heated in an oil-bath at 100°. After warming slowly to 150°, the mixture was maintained at 160° for two hours. On cooling, the melt solidified to a brown cake, which was dissolved in 200 ml. of boiling ethyl acetate and decolorized with Norit. The crude product separated as 50.4 g. (60%) of colorless needles, m.p. 105–116°. This product gave the same results in the preparation of I as a portion recrystallized from ethyl acetate, m.p. 117–120°. Scheiber and Reckleben[7] report the melting point as 113°.

Succinimidoacetyl Chloride (I).—A mixture of succinimidoacetic acid (7.0 g., 0.0416 mole) and phosphorus pentachloride (8.68 g., 0.0416 mole) in a flask protected by a calcium chloride tube was allowed to fuse at room temperature. Benzene (50 ml.) was added and the mixture was allowed to stand for 90 minutes at 30°, followed by a 30-minute period of heating under reflux. The filtered benzene solution was concentrated at 30 mm. and 50°, then three successive 25-ml. portions of toluene were added and distilled. The oily residue of I set to a hard, cream-colored solid on cooling, weight 7.1 g. (92%), m.p. 68–80°. Recrystallization failed to improve the melting point, but conversion to the corresponding anilide indicated a purity of not less than 76%. The literature value of the melting point is 76°.[7]

The anilide was prepared from 0.46 g. (0.0025 mole) of I in 25 ml. of methylene chloride by addition of 0.465 g. (0.455 ml., 0.005 mole) of aniline in methylene chloride at 0°. The yield of water-washed product was 0.44 g. (76%), m.p. 151.5–152.5°. An analytical sample was recrystallized from acetone–cyclohexane, m.p. 152.5–154.0°.

(4) A preliminary account of the total synthesis of methyl 5-phenyl-(2-carbomethoxyethyl)-penicillinate has been communicated, J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach and J. J. Ryan, THIS JOURNAL, **72**, 3828 (1950).

(5) J. C. Sheehan, E. L. Buhle and H. Wayne Hill, Jr., *ibid.*, **73**, 4373 (1951).

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

(7) J. Scheiber and H. Reckleben, *Ber.*, **46**, 2412 (1913).

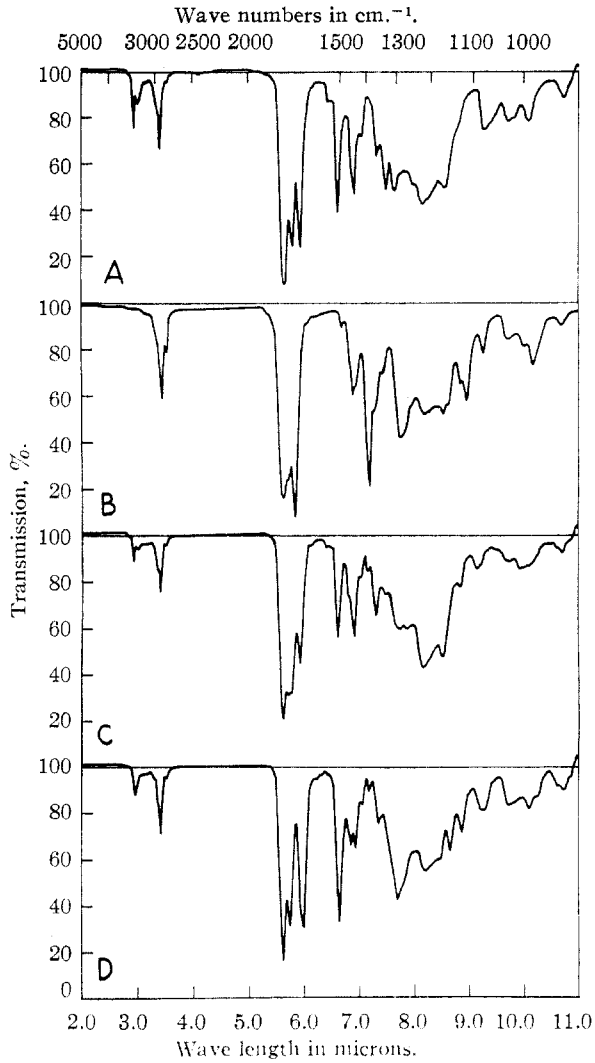


Fig. 1.—Infrared absorption spectra: curve A, 2-phenyl-α-(3-carbomethoxypropionylamino)-2-thiazolidineacetic acid β-lactam (IV); curve B, 4-carbomethoxy-5,5-dimethyl-2-phenyl-α-succinimido-2-thiazolidineacetic acid β-lactam (XII); curve C, methyl 5-phenyl-(2-carbomethoxyethyl)-penicillinate (XIV); curve D, methyl benzylpenicillinate (XVI). All measurements were made on 5% solutions in tetrachloroethane, determined with a Baird Infrared Recording Spectrophotometer, Model B.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.07. Found: C, 61.95; H, 5.20; N, 12.06.

The diethylamide was prepared from 0.556 g. (0.003 mole) of I by an analogous procedure. The yield of pure product obtained by evaporative distillation was 0.300 g. (47%), m.p. 66.0–67.5°.

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: N, 13.20. Found: N, 12.88.

2-Phenyl-α-succinimido-2-thiazolidineacetic Acid β-Lactam (III). A High Dilution in Methylene Chloride.—To a solution of 1.63 g. (0.01 mole) of 2-phenyl-2-thiazoline[2,8] (II) in 10 ml. of methylene chloride (dried over calcium sulfate) in a 200-ml. three-necked flask was added 1.85 g. (0.01 mole) of succinimidoacetyl chloride (I) in 25 ml. of methylene chloride. To this rapidly stirred solution at reflux was added through a high-dilution cycle a solution of 1.02 g. (0.01 mole) of triethylamine in 50 ml. of methylene chloride over a six-hour period. The resulting amber solution was concentrated to a brown magma, which was shaken with 50 ml. of benzene and filtered. The white crystalline residue amounted to 1.50 g., or slightly more than the theoretical amount of triethylamine hydrochloride. The filtrate was concentrated to a brown oil which partially crystallized on standing several days under reduced pressure. The soft solid was triturated with 20 ml. of 50% aqueous ethanol and was stored overnight. On filtration, the crude lactam III was obtained as 1.70 g. (56%) of crisp, yellow needles, m.p. 148–160°. A 1.13-g. portion was taken up in 7 ml. of dioxane–25 ml. of water and decolorized by boiling with Norit. On slow cooling, pure III was obtained as 0.600 g. (30%) of rectangular platelets, m.p. 166.0–168.5°. An analytical sample recrystallized from acetone–petroleum ether melted at 169.0–170.0°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.58; H, 4.67; N, 9.27. Found: C, 59.44; H, 4.66; N, 9.55.

B. **High Dilution in Benzene.**—To a 50-ml. benzene solution of 4.08 g. (0.025 mole) of 2-phenyl-2-thiazoline (II) and 4.64 g. (0.025 mole) of succinimidoacetyl chloride (I) was added through a high-dilution cycle 3.51 ml. (2.56 g., 0.025 mole) of triethylamine in 50 ml. of benzene over a four-hour period. The precipitated triethylamine hydrochloride (3.43 g., 99%) was collected by filtration and the filtrate was concentrated at reduced pressure to a brown oil. On trituration of the residue with three 30-ml. portions of ether, 5.87 g. of orange-yellow, crisp powder was obtained in largely amorphous form, m.p. 140–155°. A 1.0-g. portion of the powdery residue was extracted in a Soxhlet apparatus with 100 ml. of ether for 15 hours. A crystalline fraction filtered from the extract amounted to 0.365 g. (28%) of crude lactam III, m.p. 155.5–160.0°. The melting point of a portion recrystallized from acetone–ether was 160.0–162.0°. On admixture with an authentic sample, the melting point was undepressed.

Partially purified III could also be obtained from the crude reaction mixture by evaporative distillation. A 0.250-g. portion distilled at 15 μ pressure and 140–160° yielded 0.050 g. (15.4% over-all) of small prisms of III, m.p. 155.0–159.0°.

Sulfone of 2-Phenyl-α-succinimido-2-thiazolidineacetic Acid β-Lactam (V).—To a solution of 0.242 g. (0.0008 mole) of III in 30 ml. of dioxane was added 0.34 g. of potassium permanganate in 3 ml. of water and 10 ml. of acetic acid. After 40 minutes, the brown solution was decolorized with several drops of 30% hydrogen peroxide solution and then diluted with 80 ml. of water. After standing at 5° overnight, the crystalline precipitate was collected by filtration, weight 0.270 g. (100%), m.p. 187.5° (dec.). An analytical sample obtained as short colorless rods from dioxane–cyclohexane containing a few drops of acetic anhydride melted at 186.8–187.0° (dec.).

Anal. Calcd. for $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.22; N, 8.38. Found: C, 53.92; H, 4.41; N, 8.00.

2-Phenyl-α-(3-carbomethoxypropionylamino)-2-thiazolidineacetic Acid β-Lactam (IV).—To a solution of 0.500 g. (0.00165 mole) of III in 15 ml. of dioxane was added 17.0 ml. of 0.097 *N* sodium hydroxide solution. After one hour, 15.9 ml. of 0.104 *N* hydrochloric acid was added and the resulting solution was concentrated to dryness under reduced pressure. The organic portion of the residue was taken up in 20 ml. of chloroform, and dried by shaking with anhydrous magnesium sulfate for several minutes. To the filtered chloroform solution was added an excess (10 ml. of 0.32 *N*) of diazomethane in ether. After 20 minutes, several drops of acetic acid were added and the solution was concentrated to dryness under reduced pressure. The oil was dissolved in acetone and precipitated by the addition of petroleum ether as 0.370 g. (67%) of colorless needles (IV), m.p. 109.5–113.5°. The crude product was dissolved in 5 ml. of dioxane and diluted with 5 ml. of cyclohexane. After removal of a trace of insoluble material, further dilution with 25 ml. of cyclohexane yielded 0.230 g. (41.6%), m.p. 116.8–117.8°. An analytical sample of IV, m.p. 119.5–120.5°, was obtained on recrystallization first from acetone–petroleum ether, and then from benzene–cyclohexane.

Anal. Calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.42; N, 8.38. Found: C, 57.52; H, 5.85; N, 8.38.

N-(2-Hydroxy-2-methylpropyl)-benzamide (VII).—To 89.1 g. (1.0 mole) of commercial isobutanolamine in a 1-l. round-bottomed flask was added 122.1 g. (1.0 mole) of benzoic acid. After the initial exothermic reaction had subsided, the flask was immersed in an oil-bath at 115° and

(8) H. Wenker, THIS JOURNAL, **57**, 1080 (1935).

heated to 135° in 20 minutes. After two hours, the clear, yellow reaction mixture was poured from the flask and allowed to crystallize to a hard cake. Recrystallization from benzene yielded VII as 146.6 g. (76%) of large colorless plates, m.p. 103.5–105.8°. A portion recrystallized from benzene for analysis melted at 105.5–107.0°.

Anal. Calcd. for $C_{11}H_5NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.68; H, 7.87; N, 7.25.

5,5-Dimethyl-2-phenyl-2-thiazoline (VIII).—An intimate mixture of 145.0 g. (0.75 mole) of N-(2-hydroxy-2-methylpropyl)-benzamide and 63.7 g. (0.30 mole) of phosphorus pentasulfide was heated with a free flame till fusion was complete and no further gas appeared to be evolved. The black fluid supernatant layer was decanted, and the resinous residue was leached with 180 ml. of *N* potassium hydroxide solution and 60 ml. of ether over the course of one hour. The basic layer was separated, and again extracted with three 25-ml. portions of ether. The combined ether layers were dried by twice decanting from potassium hydroxide followed by potassium carbonate. The concentrated ether extract and the original supernatant layer were combined and distilled: b.p. 139° (4 mm.), $n^{25}D$ 1.5698, yield of VIII, 59.56 g. (41.2%). After redistillation the material had the following properties: $n^{25}D$ 1.5708, b.p. 116° (2.4 mm.).

A picrate was prepared, m.p. 159.5–160.5°.

Anal. Calcd. for $C_{17}H_{16}N_4O_7S$: C, 48.57; H, 3.83; N, 13.33. Found: C, 48.83; H, 4.03; N, 13.26.

5,5-Dimethyl-2-phenyl-α-succinimido-2-thiazolidineacetic Acid β-Lactam (IX).—To a rapidly stirred solution of 1.91 g. (0.01 mole) of 5,5-dimethyl-2-phenyl-2-thiazoline (VIII) and 1.86 g. (0.01 mole) of succinimidoacetyl chloride (I) in 35 ml. of methylene chloride at reflux was added through a high dilution cycle a solution of 1.02 g. (0.01 mole) of triethylamine in 50 ml. of methylene chloride over a ten-hour period. Concentration of the solution and extraction of the residue with 50 ml. of benzene yielded 1.67 g. (slightly more than the theoretical amount) of triethylamine hydrochloride. The filtrate was concentrated to a slowly crystallizing red oil, which yielded 0.89 g. (27%) of crude IX, m.p. 150–169°, on trituration with three 10-ml. portions of 50% ethanol. Recrystallization from acetone–cyclohexane yielded 0.51 g. (15.5%) of the β-lactam IX, m.p. 181.0–183.0°. An analytical sample crystallized from the same solvent pair melted at 183.5–184.0°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.68; H, 5.33; N, 8.45.

5,5-Dimethyl-2-phenyl-α-phthalimido-2-thiazolidineacetic Acid β-Lactam (X).—To a rapidly stirred solution of 1.91 g. (0.01 mole) of 5,5-dimethyl-2-phenyl-2-thiazoline (VIII) and 2.24 g. (0.01 mole) of phthalimidoacetyl chloride in 50 ml. of ether at reflux was added through a high dilution cycle 1.40 ml. (1.02 g., 0.01 mole) of triethylamine in 25 ml. of ether over a 1.75-hour period. The red solution was filtered and the collected tan solid, wt. 2.49 g., was digested with two 20-ml. portions of water. The loss of weight was 1.27 g., or 92.5% of the theoretical triethylamine hydrochloride. The residue, which amounted to 1.22 g., m.p. 190–213°, yielded no fraction which could be identified as lactam and was not further examined.

The original ether filtrate after concentration crystallized in part on standing, and after trituration with small portions of ether yielded 0.480 g. (12.7%) of crude lactam fraction, m.p. 200.0–205.0°. A 0.300-mg. portion was extracted with acetone and diluted with water, yielding 0.120 g. (5%) of pure X, m.p. 215.0–216.2°. An analytical sample obtained from acetone–water melted at 213.0–215.0°.

Anal. Calcd. for $C_{21}H_{18}N_2O_3S$: C, 66.65; H, 4.79; N, 7.40. Found: C, 66.58; H, 4.85; N, 7.40.

4-Carbomethoxy-5,5-dimethyl-2-phenyl-α-succinimido-2-thiazolidineacetic Acid β-Lactam (XII).—To a solution of 2.50 g. (0.01 mole) of 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate, methyl ester (XI) prepared as described by Sheehan, Buhle and Hill[6] in 10 ml. of methylene chloride in a 200-ml. three-necked flask was added 25 ml. of methylene chloride and 1.85 g. (0.01 mole) of succinimidoacetyl chloride (I). To this rapidly stirred solution at reflux was added through a high-dilution cycle a solution of 1.02 g. (0.01 mole) of triethylamine in 50 ml. of methylene chloride over a 6.25-hour period. The concentrated reaction mixture was extracted with 50 ml. of benzene in three portions. The combined residue, collected by filtration, amounted to 1.85 g. The concentrated benzene filtrate crystallized spontaneously on standing, and on trituration with 40 ml. of 50% ethanol–water in two portions yielded 0.510 g. (13.1%) of nearly pure lactam, m.p. 183.0–184.5°. Recrystallization from acetone–cyclohexane containing a few drops of acetic anhydride yielded the purified lactam XII, m.p. 186.8–187.4°, which apparently contained one-half mole of cyclohexane of crystallization.

Anal. Calcd. for $C_{19}H_{20}N_2O_5S \cdot {}^1/_2C_6H_{12}$: C, 61.38; H, 5.90; N, 6.51. Found: C, 61.17; H, 6.12; N, 6.42.

Sulfone of 4-Carbomethoxy-5,5-dimethyl-2-phenyl-α-succinimido-2-thiazolidineacetic Acid β-Lactam (XIII).—To a solution of 0.194 g. (0.0005 mole) of the lactam (XII) in 15 ml. of dioxane was added 0.213 g. of potassium permanganate dissolved in 3 ml. of water and 8 ml. of acetic acid. After 40 minutes the brown solution was decolorized with several drops of 30% hydrogen peroxide and diluted with 75 ml. of water. After storage at 5° overnight, the fine, glistening platelets amounted to 0.172 g. (81.8%), m.p. 230.0° (dec.). An analytical sample recrystallized from acetone–petroleum ether (b.p. 30–60°) containing two drops of acetic anhydride melted at 233.8–234.2° with decomposition.

Anal. Calcd. for $C_{19}H_{20}N_2O_5S$: C, 54.32; H, 4.79; N, 6.67. Found: C, 54.10; H, 4.90; N, 6.73.

Methyl 5-Phenyl-(2-carbomethoxyethyl)-penicillinate (XIV).—A solution of 0.194 g. (0.0005 mole) of the lactam XII in 7 ml. of anhydrous dioxane was titrated slowly to a phenolphthalein end-point with 4.66 ml. (0.0005 mole) of 0.1074 *N* sodium hydroxide solution. The solution was neutralized with 4.84 ml. (0.0005 mole) of 0.1034 *N* hydrochloric acid and then concentrated at 45° under reduced pressure. The residue was dissolved in 10 ml. of chloroform and an excess of diazomethane in ether was added. After 15 minutes the excess diazomethane was decomposed with acetic acid and the solution was concentrated to a yellow oil under reduced pressure. Solution in 2 ml. of acetone and dilution with 15 ml. of petroleum ether (b.p. 30–60°) yielded 0.015 g. of a crystalline precipitate, m.p. 160–170°, which was filtered from the solution and rejected. The filtrate was concentrated to dryness, triturated with petroleum ether, and then taken up in 5 ml. of cyclohexane containing just sufficient acetone for solution. Dilution with 15 ml. of petroleum ether yielded the desired ester XIV in two crops as 0.060 g. (28.6%) of small prisms, m.p. 126.6–129.0°. Recrystallization from acetone–petroleum ether yielded an analytical sample, m.p. 131.0–132.2°.

Anal. Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.02; H, 5.68; N, 6.60.

Degradation of the Lactam XII.—A solution of 0.200 g. of the lactam XII in 10 ml. of *N* sodium hydroxide and 10 ml. of dioxane was refluxed for two hours. The solvent mixture was distilled under reduced pressure and the yellow, oily residue taken up in 20 ml. of water. The aqueous solution was acidified to *p*H 3 with 10 ml. of *N* hydrochloric acid and then reconcentrated to dryness. The salts were separated by filtration of a solution of the residue in 10 ml. of 95% ethanol. The filtrate was treated with 0.400 g. of 2,4-dinitrophenylhydrazine dissolved in 2 ml. of concentrated sulfuric acid and 3 ml. of water. On dilution of the resulting solution with 8 ml. of water, an immediate precipitate resulted, which was separated by filtration after 30 minutes. The crystalline product amounted to 0.065 g. (30%), m.p. 179.2–181.6°. A portion recrystallized from ethyl acetate–carbon tetrachloride melted at 185.8–186.9°.

Anal. Calcd. for $C_{18}H_{17}N_5O_7$: C, 52.05; H, 4.13. Found: C, 51.98; H, 4.36.

The melting point on admixture with an authentic synthetic sample of XV, prepared as described below, was not depressed.

N-Phenacylsuccinamic Acid 2,4-Dinitrophenylhydrazone.—N-Phenacylsuccinimide was prepared in 71% yield from succinimidoacetyl chloride and benzene in the presence of aluminum chloride,[7] m.p. (uncor.) 143–144° (reported,[7] m.p. 143–144°).

A suspension of 0.205 g. of N-phenacylsuccinimide in 2 ml. of *N* sodium hydroxide was warmed a few minutes to effect complete solution. After several additional minutes at 85°, the solution was diluted with 2 ml. of water and acidified with 2.2 ml. of *N* hydrochloric acid. In about 30 seconds a voluminous mass of colorless crystals appeared (presumably N-phenacylsuccinamic acid).

The addition of 2 ml. of alcohol and reheating the suspension to 85° gave a clear solution, which was treated with a solution of 0.200 g. of 2,4-dinitrophenylhydrazine in 1 ml. of sulfuric acid, 1.5 ml. of water and 5 ml. of ethanol. After one hour the crystalline precipitate was collected by filtration and washed with 50% ethanol, weight 0.290 g. (66%), m.p. 185–186°. Recrystallization from ethyl acetate–carbon tetrachloride raised the m.p. to 186.4–187.3°.

Anal. Calcd. for $C_{18}H_{17}N_5O_7$: C, 52.05; H, 4.13; N, 16.86. Found: C, 51.69; H, 4.24; N, 16.72.

CAMBRIDGE 39, MASSACHUSETTS RECEIVED MARCH 3, 1951

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Pyridine Syntheses. I. Some Reactions of "Ene Amines" with 1,3-Dicarbonyl Derivatives

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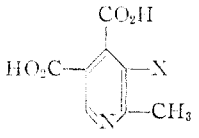
Condensations of certain "ene amines" such as β-aminocrotononitrile, ethyl β-aminocrotonate and iminoacetylacetone with ethyl ethoxymethyleneoxalacetate, ethyl ethoxymethyleneacetylpyruvate and related compounds have been carried out in an attempt to prepare 2,3,4,5-tetrasubstituted pyridines suitable for conversion to vitamin B_6. Instead of the desired compounds, the pyridines obtained were substituted invariably in the 2,3,5,6-positions. The following pyridine compounds and/or their derivatives were synthesized: 5-cyano-6-methyl-2,3-pyridinedicarboxylic acid, 6-methyl-2,3,5-pyridinetricarboxylic acid, 5-acetyl-6-methyl-2,3-pyridinedicarboxylic acid, 5-carboxanilido-6-methyl-2,3-pyridinedicarboxylic acid, 3-acetyl-5-cyano-6-methyl-2-pyridinecarboxylic acid, 3-acetyl-6-methyl-2,5-pyridinedicarboxylic acid, 3,5-diacetyl-6-methyl-2-pyridinecarboxylic acid and 2-methyl-6-trifluoromethyl-3,5-pyridinedicarboxylic acid. The condensation of ethyl β-aminocrotonate with ethyl ethoxymethyleneacetoacetate gave, in addition to diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate, two other crystalline compounds thought to be 3-acetyl-5-carbethoxy-6-methyl-2-pyridone and ethyl α-[(2-carbethoxy-1-methylvinylamino)-methylene]-acetoacetate. The condensation of iminoacetylacetone with ethyl ethoxymethyleneacetylpyruvate gave two products, ethyl 3,5-diacetyl-6-methyl-2-pyridinecarboxylate and ethyl β-[(1-methyl-3-oxo-1-butenylamino)-methylene]-α,γ-dioxovalerate.

A preceding paper from this Laboratory has described the synthesis of vitamin B_6 through reduction of the esters of 5-amino-6-methyl-3,4-pyridinedicarboxylic acid (I) and 5-hydroxy-6-methyl-3,4-pyridinedicarboxylic acid (II) with lithium aluminum hydride.[1] The practical importance of this



I, X = NH_2
II, X = OH

method is dependent upon the availability of the acids I and II. Itiba and Emoto[2] have described the preparation of I and II, but the yields are low, and the method is generally unsatisfactory. The other known ways[3] of obtaining the pyridine ring system suitably substituted, *i.e.*, in positions 2, 3, 4 and 5, for conversion to vitamin B_6 also are not entirely satisfactory. Therefore, some alternative methods have been sought.

This paper is concerned with an investigation of the reaction of some so-called "ene amines" such as ethyl β-aminocrotonate with certain 1,3-dicarbonyl or potential 1,3-dicarbonyl compounds. The first example of this type of reaction was that between ethyl β-aminocrotonate and ethyl ethoxymethyleneacetoacetate reported by Claisen[4] to yield diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (XI). Later workers have described similar reactions.[5] This condensation of "ene amines" with 1,3-dicarbonyl compounds sometimes is regarded as a special case of the well-known Hantzsch pyridine synthesis.[6] It differs from the latter, however, in that fully aromatic pyridine compounds are formed directly instead of dihydropyridines, as are obtained in the Hantzsch reaction.

In the present work ethyl ethoxymethylene oxalacetate[7] (III) was allowed to condense with β-aminocrotononitrile,[8] ethyl β-aminocrotonate[9] and iminoacetylacetone.[10] These condensations took place with great ease simply by mixing the reactants in an inert solvent, and excellent yields of pyridine compounds were isolated. By *a priori* reasoning, it might have been expected that either or both structures IV or V would be formed.

Actually, the desired isomer IV was never obtained. The only products formed were V, VI and VII. Their structures were established by conversion to methyl and *p*-bromophenacyl esters of 2,3,5,6-pyridinetetracarboxylic acid and 6-methyl-2,3,5-pyridinetricarboxylic acid, which were compared with authentic samples.

The condensation of ethyl ethoxymethyleneacetylpyruvate[7] (VIII) with β-aminocrotononitrile gave ethyl 3-acetyl-5-cyano-6-methyl-2-pyridinecarboxylate, and with ethyl β-aminocrotonate gave diethyl 3-acetyl-6-methyl-2,5-pyridinedicarboxylate. Reaction of VIII with iminoacetylacetone,

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