X-RAY DIFFRACTION PATTERNS

Intensity	Interplanar spacings (in Å.) of samples of the dipicrate of IV obtained *via* I	II	VII
Very weak	1.67	(Absent)	1.65
Very weak	1.77	(Absent)	1.76
Medium	1.93	1.97	2.00
Strong	2.18	2.21	2.21
Weak	2.50	2.47	2.58
Medium	2.89	2.94	2.90
Weak	3.19	3.12	(Absent)
Very strong	3.80	3.77	3.65
Medium	5.22	5.04	4.98
Strong	7.76	7.90	7.38

Infrared Absorption Spectra.—We are indebted to Dr. R. C. Lord, Mr. R. S. McDonald and Miss B. J. Fax for the measurement and interpretation of the infrared absorption spectra of III and IV (Figs. 1 and 2). The absorption spectra were determined for samples of the pure liquids with a Perkin–Elmer Spectrophotometer Model 12B.

CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 29, 1950

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

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. I. Alpha Amino Monocyclic β-Lactams[1]

BY JOHN C. SHEEHAN AND JAMES J. RYAN[2]

A new general synthesis has been developed which furnishes β-lactams bearing an amino function alpha to the lactam carbonyl, a combination of structural features present in penicillin. By interaction of a diacylaminoacyl chloride and benzalaniline in the presence of triethylamine a good yield of a β-lactam is obtained.

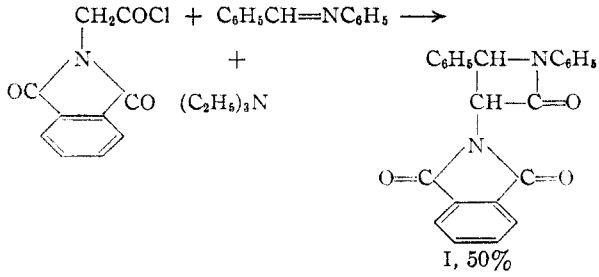
Procedures are given for the synthesis of 1,4-diphenyl-3-phthalimido-2-azetidinone, 1,4-diphenyl-(3-nitrophthalimido)-2-azetidinone, 1,4-diphenyl-3-dimethanesulfonylamino-2-azetidinone and 1,4-diphenyl-3-phenylacetamido-2-azetidinone.

The chemistry of β-lactams is of considerable current interest since this structure is the characteristic feature of the generally accepted formula for penicillin.

This communication reports a new and widely applicable synthesis[3] which furnishes β-lactams bearing an amino function alpha to the lactam carbonyl (position 3 of the azetidinone ring), a class of compounds for which there is no reported general synthesis. The combination of these structural components, β-lactam ring and α-amino function, is a key feature of the penicillin molecule.

Two new synthetic routes to β-lactams have been developed previously in this Laboratory.[4] This first communication of the series describes the preparation of a group of α-acylamino monocyclic β-lactams, and in particular the compound 1,4-diphenyl-3-phenylacetamido-2-azetidinone (III), which, like benzylpenicillin (penicillin G), is an α-phenylacetamido β-lactam. The fundamental reaction is illustrated by the preparation of 1,4-diphenyl-3-phthalimido-2-azetidinone (I).

Upon the addition of a benzene solution of phthaloylglycyl chloride to an equimolar amount of triethylamine and an excess of benzalaniline dissolved in benzene, a mild but essentially instantaneous reaction takes place, the β-lactam is formed, and a quantitative yield of triethylammonium chloride is precipitated. The lactam is isolated in good yield after removal of the amine



I, 50%

salt. Other inert solvents, such as ether, may be substituted for the benzene, and triethylamine may be replaced by other tertiary aliphatic amines. Also prepared in a similar manner were the lactams 1,4-diphenyl-3-(3-nitrophthalimido)-2-azetidinone and 1,4-diphenyl-3-(dimethanesulfonylamino)-2-azetidinone. The reaction apparently proceeds smoothly in cases where the nitrogen of the amino acid moiety is protected by substitution of both hydrogen atoms.

It is possible to visualize this reaction as proceeding by way of an intermediate "acylamino aldoketene," which adds to benzalaniline to yield the β-lactam. Since Staudinger[5] prepared the first β-lactam by the addition of diphenyl ketene to benzalaniline, there might appear to be a formal resemblance between the two methods. The ketene mechanism is probably not the true one, and from evidence to be given in a subsequent communication a different reaction course may be inferred.

A major advantage to the use of the phthaloyl group for protecting the nitrogen atom is its susceptibility to facile removal by means of hydrazine[6] with formation of the free amino compound. It has been shown that this cleavage proceeds rapidly under mild conditions without rupture of a normal peptide bond.[7] Treatment of I with hot alcoholic

(1) This communication is from part of a thesis submitted by J. J. R. to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of requirements for the Ph.D. degree, April, 1949.

(2) Monsanto Chemical Company, Merrimac Division, Everett, Mass.

(3) A preliminary report of extensions of this basic synthesis has been communicated, J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach and J. J. Ryan, THIS JOURNAL, **72**, 3828 (1950).

(4) J. C. Sheehan and P. T. Izzo, *ibid.*, **70**, 1985 (1948); **71**, 4059 (1949). J. C. Sheehan and A. J. Bose, *ibid.*, **72**, 5158 (1950). Footnotes in the latter communication refer to classical syntheses of β-lactams.

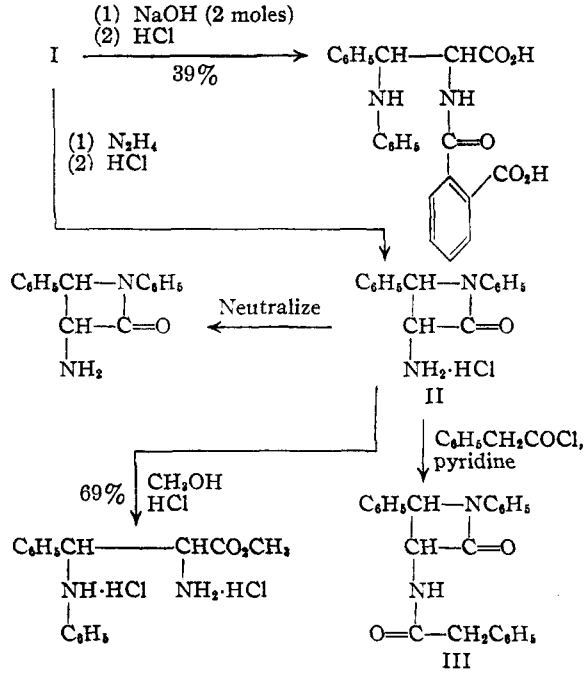
(5) H. Staudinger, *Ber.*, **40**, 1145 (1907).

(6) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

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

hydrazine, followed by extraction with hydrochloric acid, yielded the hydrochloride of 3-amino-1,4-diphenyl-2-azetidinone (II). Neutralization gave the corresponding free amino lactam. The structure of the amino lactam (II) was proved by conversion of the lactam linkage to an ester using methanolic hydrogen chloride. The product is methyl α-amino-β-anilino-β-phenylpropionate, isolated as the dihydrochloride. Strong alkaline hydrolysis of the phthalimido lactam (I) yielded β-anilino-α-(*o*-carboxybenzoylamino)-β-phenylpropionic acid as a result of the opening of both the phthalimide and lactam rings. These reactions prove that the addition formed a β-lactam and not the isomeric aminoketone.[8]

By the action of phenylacetyl chloride on the amine hydrochloride (II), in the presence of pyridine, 1,4-diphenyl-3-phenylacetylamino-2-azetidinone (III) was produced.



The infrared absorption spectra of compounds I and III are in accord with the assigned structures. The β-lactam carbonyl band at about 5.68 μ is in agreement with the value reported for other monocyclic β-lactams. The N–H stretching band at 2.94 μ and the N–H bending band at 6.63 μ observed in the spectrum of III, but not in I, is typical of a monosubstituted amide.

Experimental[9]

1,4-Diphenyl-3-phthalimido-2-azetidinone (I).—A mixture of benzalaniline (7.24 g., 0.0400 mole) and 2.77 ml. (2.02 g., 0.0200 mole) of triethylamine was dissolved in 70 ml. of benzene in an erlenmeyer flask. With mechanical stirring a solution of 4.48 g. (0.0200 mole) of phthaloylglycyl chloride[7] in 40 ml. of benzene was added from a dropping funnel in one-half hour. A white precipitate was formed,

(8) The formation of an aminoketone by the addition of a ketene to an imine at −20° has been reported by H. Staudinger, *Ber.*, **50**, 1035 (1917).

(9) All melting points are corrected. We are indebted to Mr. S. M. Nagy and his associates for the microanalyses. The benzene and ether used were commercial reagent grade, dried and stored over sodium wire.

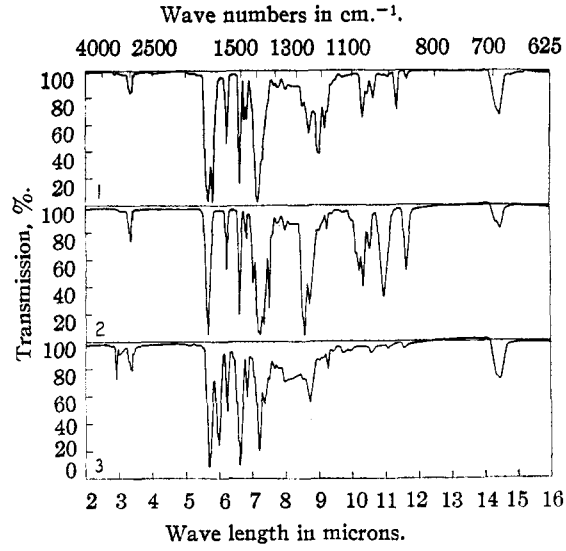


Fig. 1.—Infrared absorption spectra: (1) 1,4-diphenyl-3-phthalimido-2-azetidinone; (2) 1,4-diphenyl-3-(dimethanesulfonylamino)-2-azetidinone; (3) 1,4-diphenyl-3-phenylacetylamino-2-azetidinone.

the mixture became yellow and a rise in temperature was noted. After stirring for one additional hour, the solid was filtered onto a small, tared funnel, washed with benzene and dried at 70°. The product (3.00 g.) was slurried with water, filtered, washed with water and again dried at 70°. The residue weighed 0.35 g. and was not further investigated. The loss in the water wash was 2.65 g., equivalent to 96.5% of the theoretical yield of triethylammonium chloride.

The combined benzene filtrate and wash was concentrated under reduced pressure to a semi-solid, which was digested with three 30-ml. portions of a mixture of ether–petroleum ether (1:1) to remove unreacted benzalaniline. The dried residual orange powder was digested for one-half hour with 200 ml. of boiling ethanol and filtered. The solid residue was the almost pure β-lactam; yield 3.68 g. (50.0%), m.p. 227–230°. This material was sufficiently pure for use in the ensuing preparations. For purification 0.200 g. was twice recrystallized from 5-ml. portions of boiling dioxane–water (1:1) to give 0.156 g. of colorless, fine, slender rods, m.p. 230–231°. Another recrystallization did not change the melting point. An analytical sample was dried for one hour at 60° and 0.5 mm. The analysis obtained corresponded to one-half molecule of dioxane of crystallization.

Anal. Calcd. for $C_{23}H_{16}N_2O_3 \cdot {}^1/_2C_4H_8O_2$: C, 72.83; H, 4.89; N, 6.80. Found: C, 73.14; H, 4.82; N, 6.94.

A sample recrystallized from acetone gave a fair analysis (Calcd. for $C_{23}H_{16}N_2O_3$: C, 74.99; H, 4.37; mol. wt. (Rast), 368. Found: C, 74.30; H, 4.57; mol. wt., 355, 399) for unsolvated material, m.p. 230.5°.

3-Amino-1,4-diphenyl-2-azetidinone Hydrochloride (II).—The phthalimidolactam (I) (1.00 g., 0.00272 mole) was pulverized and suspended in 25 ml. of ethanol and 2.8 ml. of a 1 *M* solution of hydrazine hydrate in 95% ethanol (0.00280 mole) was added. After refluxing for 2 hours, the suspension was stored overnight and then concentrated to dryness under vacuum. The residue was stirred for 2 hours with 25 ml. of 5 *N* HCl, filtered, and the solid boiled with two 25-ml. portions of water. The residue was presumed to be phthalhydrazide; weight 0.41 g. (93%), m.p. sublimed at 280° without melting (reported for phthalhydrazide, above 340°). The aqueous and acid extracts were combined and 3 ml. of concentrated hydrochloric acid added. After 2 hours the precipitated amine hydrochloride (VII) was collected by filtration; weight 0.40 g. (54%); m.p. 236–238° (dec., after darkening at 234°). Purification by dissolving 0.15 g. in 20 ml. of water, filtering to remove some insoluble material, and adding 4 ml. of concentrated hydrochloric acid afforded 0.11 g. of colorless rectangular prisms; m.p. 237.5° (dec.). Repetition of this treatment did not change the m.p.

Anal. Calcd. for $C_{15}H_{14}N_2O\cdot HCl$: C, 65.50; H, 5.50; N, 10.20; Cl, 12.90; neut. equiv., 275. Found: C, 65.51; H, 5.57; N, 10.44; Cl, 12.64; neut. equiv., 267.

Exact neutralization of an aqueous solution of the hydrochloride (II) (0.0954 g.) yielded the crystalline free base of the corresponding amino lactam; weight after drying at 70° for 12 hours, 0.055 g. (60%), m.p. 118–119° (sintering at 110°). Variation of melting point with the manner of drying suggests that the product is a hydrate as obtained from aqueous solutions.

1,4-Diphenyl-3-phenylacetylamino-2-azetidinone (III).—In 10 ml. of methylene chloride (purified and dried over Drierite) was suspended 0.110 g. (0.000400 mole) of the aminolactam hydrochloride (II) and 0.064 g. (0.00080 mole) of purified pyridine. A solution of 0.062 g. (0.00040 mole) of phenylacetyl chloride in 5 ml. of methylene chloride was then added. The suspended solid immediately dissolved to give a clear solution which was evaporated to 7 ml. and shaken with the following washes (in the order given): 2 × 5 ml., water; 1 × 5 ml., 0.01 *N* HCl; 2 × 5 ml., water; 2 × 5 ml., 5% sodium bicarbonate; 2 × 5 ml., water. The resulting solution was filtered through a paper wet with methylene chloride to give a clear yellow filtrate which was concentrated to 1.5 ml. by warming in an air-stream, transferred to a Craig[10] tube and diluted with 1 ml. of ether. The crystalline lactam deposited slowly and was collected by centrifugation; yield 0.80 g. (56.5%), m.p. 195–196° (sintering at 194°). This product was recrystallized from 2 ml. of acetone and 1 ml. of water; weight (colorless needles) 0.055 g., m.p. 199.5–200°.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$ (356): C, 77.52; H, 5.66; N, 7.86. Found: C, 77.56; H, 5.66; N, 7.97.

Methyl α-Amino-β-anilino-β-phenylpropionate Dihydrochloride.—The aminolactam hydrochloride (II) (0.255 g.) was dissolved in 25 ml. of absolute methanol in an erlenmeyer flask protected by a calcium chloride tube and dry hydrogen chloride gas was introduced at a slow rate for 4 hours (spontaneous temperature rise to 60°). The flask was stoppered and stored overnight, refluxed for 1 hour, and the solution filtered and concentrated to near dryness under reduced pressure. The product was pressed on a clay plate and dried at 70°; yield 0.22 g. (69%), m.p. 140.5–141° (evolution of gas). For purification 0.050 g. was dissolved in a mixture of 2 ml. of chloroform and 1 ml. of methanol, filtered, and the solution diluted with 40 ml. of anhydrous petroleum ether to give a crop of colorless crystals; weight 0.030 g., m.p. 140.5–141° (evolution of gas).

Anal. Calcd. for $C_{16}H_{20}N_2Cl_2$ (343.3); C, 55.98; H, 5.88; Cl, 20.65. Found: C, 56.21; H, 6.00; Cl, 20.27.

Hydrolysis of the Phthalimidolactam (I) to β-Anilino-β-phenyl-α-(o-carboxybenzoylamino)-propionic Acid.—The lactam (I) (0.40 g., 0.0011 mole) was pulverized, suspended in 25 ml. of 0.1 *N* NaOH solution (0.0025 mole), and the mixture was refluxed for 16 hours. The resulting solution, after filtering to remove a little insoluble material, was brought to *p*H 2 with hydrochloric acid (the precipitate thus formed redissolved at a lower *p*H). The colorless solid was collected, washed with water; weight 0.20 g., m.p. 80–120° (dec.). This crude product was dissolved in 5 ml. of acetone, 10 ml. of benzene added, and the solution filtered to remove a light flocculent precipitate. After standing several hours a crop of crystals had deposited; yield 0.17 g. (39%), m.p. 127° (dec., after sintering and turning yellow at 123°). Purification was achieved by dissolving in 1 ml. of acetone and 5 ml. of water, decolorizing with Norite, filtering three times, adding 4 ml. of water and collecting the crop of colorless needles so formed; weight 0.060 g., m.p. 137.5–138.5° (dec. started at 130°).

Anal. Calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.99; N, 6.93. Found: C, 68.20; H, 4.95; N, 7.18.

1,4-Diphenyl-3-(N,N-dimethanesulfonylamino)-2-azetidinone.—To a stirred solution of 3.00 g. (0.0166 mole) of benzalaniline and 1.11 ml. (0.81 g., 0.00800 mole) of triethylamine in 15 ml. of benzene was added dropwise a solution of 2.00 g. (0.00800 mole) of dimethanesulfonylaminoacetyl chloride in 50 ml. of benzene (the addition required 20 minutes). A white precipitate began to form at once and at the end the mixture was so viscous that stirring had to be completed manually with a heavy rod. Stirring was continued intermittently for 30 minutes and the insoluble material was then collected by filtration. The dry product was washed by digestion with water, and refiltered and redried. The loss in weight was 1.05 g., equivalent to 96% of the theoretical yield of amine hydrochloride. The residue weighed 1.56 g., m.p. 187–200° (dec.), and gave a negative chlorine test (Beilstein copper wire). This residue was dissolved in 70 ml. of boiling acetone and filtered to remove 0.3 g. of insoluble material, which was not further investigated. Addition of 20 ml. of water afforded colorless crystals; weight 0.77 g., m.p. 235–236.5° (dec., sintering at 233°). By concentration of the main benzene filtrate to 5 ml. and seeding additional product was obtained; weight 0.45 g., m.p. 235–236.5°. The total yield was 1.22 g. (39%). Recrystallization of 0.45 g. from 40 ml. of acetone and 20 ml. of water afforded fine, colorless needles; weight 0.40 g., m.p. 235.5–236.5° (no dec.).

Anal. Calcd. for $C_{17}H_{18}N_2O_5S_2$: C, 51.77; H, 4.60; N, 7.11. Found: C, 51.65; H, 4.72; N, 7.07.

1,4-Diphenyl-3-(3-nitrophthalimido)-2-azetidinone.—A solution of 3.62 g. (0.0200 mole) of benzalaniline and 1.39 ml. (1.01 g., 0.010 mole) of triethylamine in 10 ml. of benzene was stirred mechanically in a 125 ml. erlenmeyer flask. 3-Nitrophthaloylglycyl chloride (2.69 g., 0.010 mole) was dissolved in 55 ml. of benzene (warming was necessary) and added dropwise to the amine solution. The addition time was 1 hour. A moderate precipitate had formed at the end of 1 hour, but after 4 hours this had increased considerably. The flask was stoppered and stored for 16 hours. The mixture was processed in a manner similar to that described for lactam I. A 94% yield of triethylammonium chloride was obtained and the water-insoluble residue weighed 2.66 g. (54%, as the monobenzene solvate, m.p. 163–166° (evolution of gas)).

The compound apparently exists in polymorphic forms. After several recrystallizations from toluene, the melting point was constant at 155–156°; resolidification and remelting gave a value of 205–206° with sintering at 198°. By successive recrystallizations from aqueous acetone, followed by drying at 90° (2 mm.) for 1 hour, the observed melting point was 198–205°; m.p. after resolidification was 206.5–207°. The melting point of a mixture of the two forms was 205–206°. From benzene solution a modification melting at 168–170° was obtained. Analysis indicates that this form contains one mole of benzene of solvation.

Anal. Calcd. for $C_{23}H_{15}N_3O_5$: C, 66.83; H, 3.66; N, 10.16. Calcd. for $C_{23}H_{15}N_3O_5 + C_6H_6$: C, 70.86; H, 4.31. Found (from toluene): C, 67.01; H, 3.74; N, 10.32. Found (from acetone): C, 66.82; H, 3.76. Found (from benzene): C, 71.81; H, 4.43.

Infrared Absorption Spectra.—The infrared absorption spectra were determined with a Baird Infrared Recording Spectrophotometer, Model B. Five per cent. solutions in tetrachloroethane were used.

(10) L. C. Craig, *Ind. Eng. Chem., Anal. Ed.*, **12**, 773 (1940).

CAMBRIDGE, MASS. RECEIVED AUGUST 15, 1950