A Novel Cleavage of the Penicillin Nucleus

John C. Sheehan and Karl G. Brandt

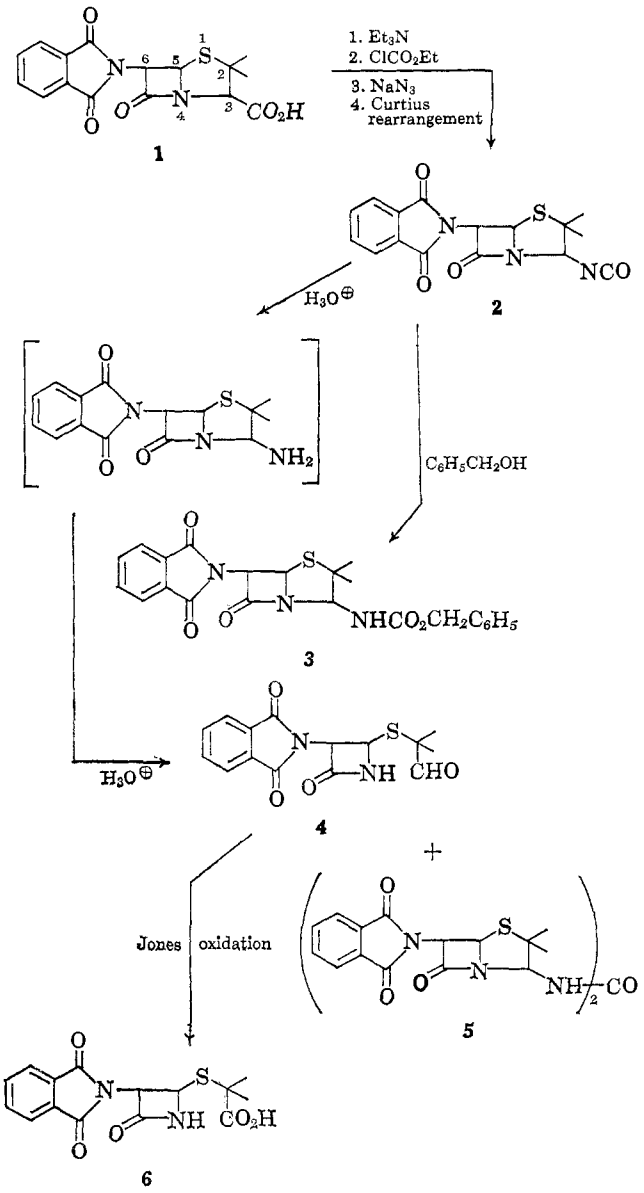
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. *Received August 2, 1965*

The 3,4-bond of the fused thiazolidine β-lactam ring system of the penicillin nucleus has been cleaved by dilute acid hydrolysis of 2,2-dimethyl-6-phthalimido-3-penamyl isocyanate (2). *The aldehyde* **4** *thus obtained has been characterized, as has the symmetrical urea isolated as a by-product. Oxidation of 3-phthalimido-4-(1'-formyl-1'-methylethylthio)-2-acetidinone* (4) *gives the corresponding carboxylic acid* **6** *which may be regarded as a penicillin analog with an intact β-lactam but an opened thiazolidine ring.*

We wish to report a novel cleavage of the 3,4-bond of the penicillin nucleus[1] under hydrolytic conditions without concomitant hydrolysis of the β-lactam moiety. Although Raney nickel desulfurization of the penicillin nucleus has been effected,[2] we believe this to be the first example of selective degradation of the fused thiazolidine β-lactam ring system to give a sulfur-containing monocyclic analog of penicillin. Ring-opened intermediates have been postulated in the rearrangement of penicillin G acid chloride to "anhydropenicillin"[3] and the rearrangement with ring expansion of phenoxymethylpenicillin sulfoxide methyl ester.[4] However, in each of these cases the product isolated was one in which the ring system has reclosed.

It was envisioned that from benzyl N-(2,2-dimethyl-6-phthalimido-3-penamyl)carbamate[5] (3) it would be possible to proceed in an analogous manner through the sequence of steps utilized by Bergmann and Zervas[6] for the stepwise degradation of peptides. In practice it was found that the desired results could be achieved satisfactorily directly from 2,2-dimethyl-6-phthalimido-3-penamyl isocyanate[5] (2). Treatment of the isocyanate **2** with 1 equiv. of hydrochloric acid in aqueous tetrahydrofuran under dilution conditions led to the isolation of the aldehyde **4** in about 75–80% yield and the urea **5** in about 10–15% yield in a typical experiment. That the ring has been opened and the aldehyde **4** obtained is readily confirmed by infrared (3400 (N—H) and 1720 cm.$^{-1}$ (aldehyde C=O)) and nuclear magnetic resonance (n.m.r.) spectra (τ 0.7 (1 H; singlet), aldehyde C—H). The urea **5**, isolated as a by-product was characterized by infrared, n.m.r., and analytical data.

The acid **6** is of interest as a thiazolidine ring-opened penicillin analog with configurations at positions 5 and 6 presumably intact. For the oxidation of the aldehyde **4** an oxidizing agent was required which would not convert simultaneously the thio ether to the sulfoxide or sulfone. By employing the Jones reagent[7] in purified acetone at room temperature the aldehyde **4** was oxidized into the acid **6** in 51% yield after one recrystallization. The acid **6** is readily soluble in sodium bicarbonate solution and possesses the expected infrared and analytical properties.



(1) The nomenclature and numbering system are those of J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3292 (1953).

(2) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p. 243.

(3) S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *J. Am. Chem. Soc.*, **85**, 643 (1963).

(4) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *ibid.*, **85**, 1896 (1963).

(5) Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Med. Chem.*, **7**, 483 (1964).

(6) M. Bergmann and L. Zervas, *Science*, **79**, 439 (1934); *J. Biol. Chem.*, **113**, 341 (1936).

(7) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

Experimental Section[8]

3-Phthalimido-4-(1'-formyl-1'-methylethylthio)-2-azetidinone (**4**). To a stirred solution of 3.68 ml. of 1 *N* hydrochloric acid in 300 ml. of 50% aqueous tetrahydrofuran at room temperature was added dropwise during 3.25 hr. a solution of 1.26 g. (3.68 mmoles) of 2,2-dimethyl-6-phthalimido-3-penamyl isocyanate (**2**)[5] in 200 ml. of tetrahydrofuran. The reaction mixture was stirred for an additional 0.5 hr. after the addition of the isocyanate was complete. The reaction mixture was then extracted with three 200-ml. portions of methylene chloride and the combined methylene chloride extracts were washed with two 150-ml. portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to an oil. From this oil was obtained by fractional crystallization from an ethanol–petroleum ether (b.p. 30–60°) mixture 0.02 g. of *N,N'-bis(2,2-dimethyl-6-phthalimido-3-penamyl)urea* (**5**), which, after recrystallization from acetone–petroleum ether, was obtained as a hygroscopic crystalline solid, m.p. 184–185.5°.

Anal. Calcd. for $C_{31}H_{28}N_6O_7S_2 \cdot 3H_2O$: C, 52.08; H, 4.80; N, 11.74; S, 8.97. Found: C, 52.10; H, 4.60; N, 11.52; S, 8.66.

The infrared spectrum (CH_2Cl_2) showed 3320–3410 (urea N—H), 1790 (β-lactam C=O), 1775 and 1725 (phthalimido group), 1685 (urea C=O), and 1525 cm.$^{-1}$ (urea N—H).

The n.m.r. spectrum ($CDCl_3$) showed τ 2.25 (8 H, multiplet), 3.95 (2 H, doublet, J = 9 c.p.s.), 4.25 (2 H, doublet, J = 9 c.p.s.), 4.45 (2 H, doublet, J = 4 c.p.s.), 4.60 (2 H, doublet, J = 4 c.p.s.), 8.32 (6 H, singlet), and 8.46 (6 H, singlet).

The filtrate after removal of the urea was concentrated to a viscous oil which on crystallization from benzene–ligroin (b.p. 90–100°) yielded in four crops 1.0 g. (76%) of the aldehyde **4**, m.p. 101–105°. Two recrystallizations from benzene–ligroin gave an analytical sample, m.p. 110–119°.

(8) Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The infrared spectra were measured on a Perkin-Elmer Model 237 recording spectrophotometer. A Varian Associates A-60 instrument was used for recording nuclear magnetic resonance spectra and peak positions are reported in τ units (TMS = τ 10).

Anal. Calcd. for $C_{15}H_{14}N_2O_4S \cdot 0.5C_6H_6$: C, 60.47; H, 4.80; N, 7.85. Found: C, 60.21; H, 4.99; N, 7.71.

The infrared spectrum (CH_2Cl_2) showed 3400 (β-lactam N—H), 2810 and 2700 (aldehyde C—H), 1798 and 1730 (phthalimido group), 1770 (β-lactam C=O), and 1720 cm.$^{-1}$ (aldehyde C=O).

The n.m.r. spectrum ($CDCl_3$) showed τ 0.7 (1 H, singlet), 2.15 (4 H, multiplet), 2.65 (3 H, singlet, 0.5 mole of benzene solvate), 2.92 (1 H, broad), 4.32 (1 H, multiplet), 5.08 (1 H, doublet), 8.6 (3 H, singlet), and 8.7 (3 H, singlet).

3-Phthalimido-4-(1'-carboxy-1'-methylethylthio)-2-acetidinone (**6**). To a stirred solution of 2.0 g. (5.6 mmoles) of the aldehyde **4** in 50 ml. of acetone (distilled from potassium permanganate) at room temperature was added dropwise the Jones reagent[7] until decolorization no longer occurred. Approximately 2.3 ml. of the reagent was required. The reaction mixture was then diluted with 50 ml. of methylene chloride and 50 ml. of water was added. The organic layer was separated and the aqueous layer was extracted further with 100 ml. of 1:1 methylene chloride–acetone. The organic extracts were combined and washed with 50 ml. and then 20 ml. of water. The solution was then dried over anhydrous magnesium sulfate, filtered, and concentrated. The oily residue crystallized from benzene–petroleum ether (b.p. 30–60°) to yield 1.56 g. (83%) of the crude acid **6**, m.p. 135–160°. Recrystallization from methylene chloride gave 0.95 g. (51%) of the acid **6**, m.p. 190–195°. Two further recrystallizations from methylene chloride gave an analytical sample, m.p. 193.5–195.5°.

Anal. Calcd. for $C_{15}H_{14}N_2O_6S$: C, 53.94; H, 4.32; N, 8.39; S, 9.60. Found: C, 54.09; H, 4.36; N, 8.43; S, 9.59.

The infrared spectrum (KBr) showed 3400 (β-lactam N—H), 1775 and 1725 (phthalimido and carboxyl C=O), 1755 (β-lactam C=O), and 1275 cm.$^{-1}$ (carboxyl C—O).

Acknowledgment. K.G.B. gratefully acknowledges financial support in the form of a National Science Foundation Predoctoral Fellowship from 1961 to 1964

Benzhydryl Esters of Amino Acids in Peptide Synthesis[1]

Akintola A. Aboderin, Georges R. Delpierre,[2] and Joseph S. Fruton

Contribution from the Department of Biochemistry, Yale University, New Haven, Connecticut. *Received September 23, 1965*

Benzhydryl esters of amino acids and peptides have been prepared in good yield by reaction of their p-toluenesulfonate salts with diphenyldiazomethane. In some cases, the salts of other aromatic sulfonic acids (e.g., β-naphthalenesulfonic acid) may be preferable. Examples are given of the use of the benzhydryl ester salts in representative coupling reactions to yield protected peptide derivatives, and of the removal of the benzhydryl group by catalytic hydrogenolysis.

Although significant progress has been made in the development of methods for the protection of carboxyl

(1) This study was aided by grants from the U. S. Public Health Service (GM-06452) and from the National Science Foundation (G-7451). The results presented in this communication will form part of the dissertation of A. A. A., in partial fulfillment of the requirements for the Ph.D. degree from Yale University.

(2) Alexander Brown Coxe Fellow of the Yale School of Medicine, 1964–1965.