of this amine hydrochloride and 0.201 g. (0.002 mole) of triethylamine in 20 ml. of methylene chloride, cooled in an ice–salt-bath, there was added 0.155 g. (0.001 mole) of phenylacetyl chloride in 10 ml. of methylene chloride. The product crystallized after purification as fine needles, m.p. 140–141°. The yield was 325 mg. (86%).

Anal. Calcd. for $C_{18}H_{24}N_2O_5S$: C, 56.82; H, 6.36; N, 7.36. Found: C, 56.60; H, 6.20; N, 7.32.

From 0.56 g. (0.0014 mole) of VIIIγ there was obtained 275 mg. (65%) of the amine hydrochloride IXγ, m.p. 128–130°. Phenylacetylation proceeded smoothly to afford 200 mg. (63%) of fine needles, m.p. 130–131°; recrystallization raised the m.p. 132–133.5°.

Anal. Calcd. for $C_{18}H_{24}N_2O_5S$: C, 56.82; H, 6.36; N, 7.36. Found: C, 56.90; H, 6.25; N, 7.73.

CAMBRIDGE 39, MASSACHUSETTS

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

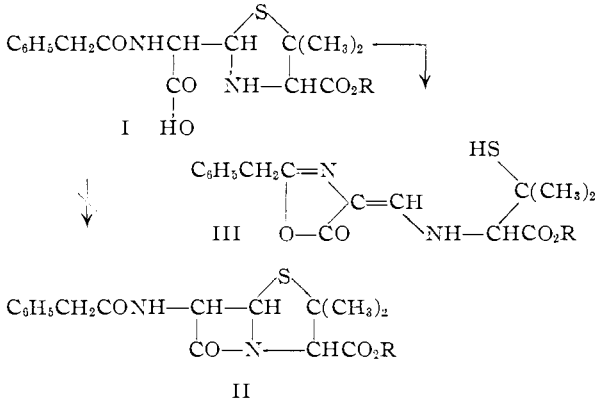
The Synthesis of Substituted Penicillins and Simpler Structural Analogs. X. The Cyclization of 4-Carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetic Acid to Methyl 6-Phthalimidopenicillanate

BY JOHN C. SHEEHAN AND PHILIP A. CRUICKSHANK

RECEIVED JUNE 28, 1955

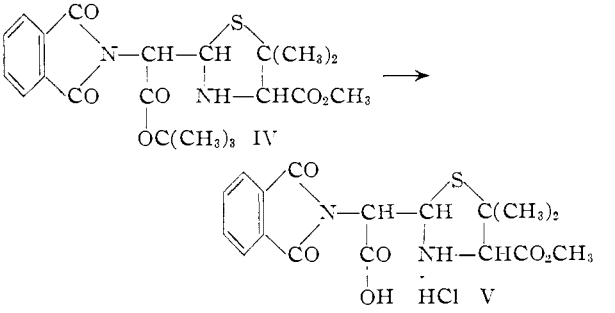
One isomer of 4-carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetic acid hydrochloride has been converted to the β-lactam methyl 6-phthalimidopenicillanate (VI) (a phthaloylpenicillin). From all three known isomers of this thiazolidine acetic acid derivative there has been obtained a material isomeric with the β-lactam, to which has been assigned the 5-keto-2,3,4,5-tetrahydro-1,4-thiazepine ring system.

Of the many approaches to the synthesis of benzylpenicillin (II) and its analogs, the route most thoroughly studied involved cyclization of penicilloic acids (I, R = H) or their β-esters (I, R = alkyl).[1] In no case, however, was penicillin activity obtained in amounts greater than 0.1%.[2] When identified, the products of the reactions were shown to be penicillenates (III), formed by azlactonization of the penicilloates followed by rupture of the thiazolidine ring. Incorporation of alkyl groups on



the amide nitrogen of the penicilloates[1] failed to lead to β-lactam formation when the substances were subjected to cyclization conditions. Subsequent indications that quaternary oxazolone rings can be formed from similar intermediates (benzoyl sarcosine)[3] demonstrates that N-alkylation does not necessarily prevent azlactonization.

Recent work in this Laboratory has for the first time resulted in the synthesis of penicilloic acid derivatives in which the possibility of azlactone formation is precluded.[4] This was accomplished by the incorporation of the phthaloyl blocking group. The compounds were obtained by the condensation of phthalimidomalonaldehydic esters, prepared by formylation of phthalimidoacetic esters, with penicillamine. The most useful of these substances, *t*-butyl 4-carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate (IV), and the cleavage of the *t*-butyl ester group to give three isomeric thiazolidineacetic acid hydrochlorides (V), was described in the preceding paper of this series.[5]



Extensive experiments directed toward the cyclization of the α-, β- and γ-isomers of V[5] have been carried out. Only one of these, Vβ, has been found to give the β-lactam methyl 6-phthalimidopenicillanate (VI).[6]

In a recent communication on the synthesis of methyl 6-phthalimidopenicillanate sulfone (VII),[6]

(1) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 851.

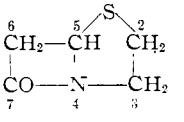
(2) V. du Vigneaud, *et al.*, ref. 1, pp. 1018–1024.

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

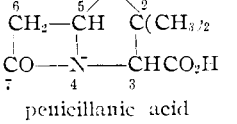
(4) J. C. Sheehan and D. A. Johnson, *ibid.*, **76**, 158 (1954).

(5) The assignment of the designations alpha, beta and gamma to the three stereoisomers of V was explained in the previous paper of this series; J. C. Sheehan and P. A. Cruickshank, THIS JOURNAL, **78**, 3677 (1956).

(6) It has recently been suggested that the terms "penam" and "Penicillanic acid" be adopted for the following ring system and substituted ring system.



penam



penicillanic acid

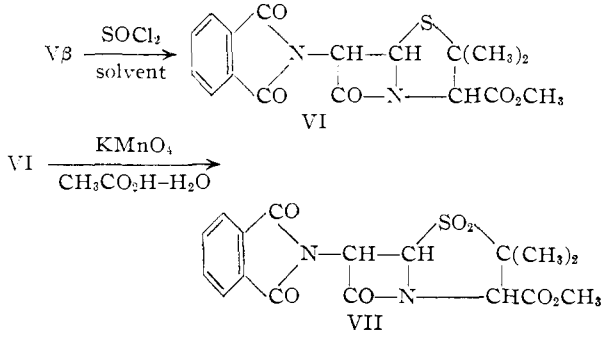
J. C. Sheehan, K. R. Henery-Logan and D. A. Johnson, THIS JOURNAL, **75**, 3292 (1953).

a 13% yield was indicated from the action of thionyl chloride in benzene on V. However, it was soon discovered that the yield of β-lactam employing these cyclization conditions was a function of the temperature during the cleavage of the *t*-butyl ester group of IV. In other words, the β-isomer of V is the precursor of VI.[5]

TABLE I

Cleavage temp., °C.	Lactam sulfone VII, %
0	0
35	13
70	26
75	36
80	30

Due to the scarcity of examples of direct cyclization of β-amino acids to azetidinones, a thorough investigation of cyclization conditions was carried out. These experiments, employing the β-isomer of IV, are summarized in Table II. Assay of the crude reaction mixtures for β-lactam was accomplished by infrared spectrum determinations; the β-lactam carbonyl has a characteristic absorption peak at 5.62 μ. Yields were determined by oxidation of the crude reaction products with potassium permanganate in acetic acid, affording nearly pure methyl 6-phthalimidopenicillanate sulfone (VII). This compound had an absorption peak at 5.55 μ in the infrared, characteristic of fused thiazolidine-β-lactam sulfones (Fig. 1, curve A).



Of the reagents tested, only thionyl chloride and phosphorus oxychloride were found to effect closure of V to the fused thiazolidine-β-lactam ring system. The nature of the solvent was also found to be important, with apparently only neutral or slightly acidic types being suitable.

All attempts to bring about cyclization of the α- and γ-isomers of V failed to result in the formation of β-lactam. Examination of molecular models of V shows that in two of the four possible stereoisomeric modifications the steric hinderance due to the bulky phthalimido group and sulfur atom would markedly inhibit, if not prevent, β-lactam formation.

Methyl 6-phthalimidopenicillanate (VI) was isolated directly from the products of the interaction of Vβ and a cyclization agent. The solvent and excess cyclizing agent were removed from the reaction mixture by distillation under reduced pressure. A solution of the residue in methylene chloride was then washed with dilute sodium bicarbonate and hydrochloric acid solutions, and this partially purified material crystallized from acetone. Yields employing thionyl chloride as cyclizing agent were on the order of 30%; with phosphorus oxychloride, 20%. The compound displayed an intense absorption peak in the infrared at 5.62 μ, characteristic of the azetidinone carbonyl (Fig. 1, curve B).

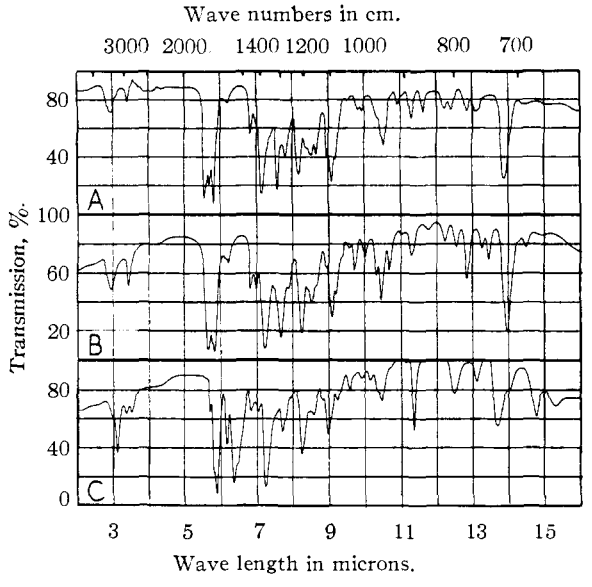
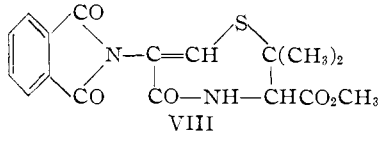


Fig. 1.

In reactions involving phosphorus oxychloride, a compound other than β-lactam was isolated from all three isomers of V in yields of 30–50%. Elemental analysis and a molecular weight determination demonstrated that the substance was isomeric with VI. Its infrared spectrum (Fig. 1, curve C) contained an intense absorption peak at 6.3 μ, assignable to the vinyl sulfide group.[7] Peaks at 3.1, 6.1 and 6.4 μ are characteristic of a monosubstituted amide. From this information, the material was tentatively assigned structure VIII, 2,2-dimethyl-3-carbomethoxy-5-keto-6-phthalimido-2,3,4,5-tetrahydro-1,4-thiazepine. The ultraviolet absorption spectrum (Fig. 2) is consistent with the chromophoric system present in VIII. The rearrangement



of β-amino acids into α,β-unsaturated amides is not an unknown reaction, for lysergic acid undergoes this type of conversion when treated with acetic anhydride.[8]

Compound VIII is of interest as a possible precursor of a β-lactam thiazolidine by the transannular addition of the amide function to the α,β-unsaturated bond across the seven-membered ring.

Due to the unusual reactivity of the azetidinone carbonyl in the fused thiazolidine-β-lactam system toward nucleophilic attack, attempts to remove the phthaloyl blocking group from VI did not afford the desired aminopenicillanate IX. From the action

(7) C. C. Price and H. Morita, THIS JOURNAL, **75**, 4747 (1953).

(8) A. Stoll, A. Hofmann and F. Troxler, *Helv. Chim. Acta*, **32**, 506 (1949).

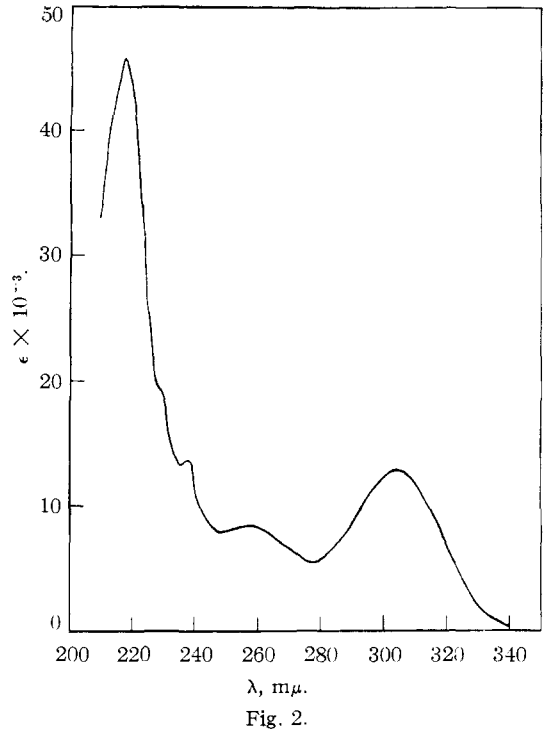
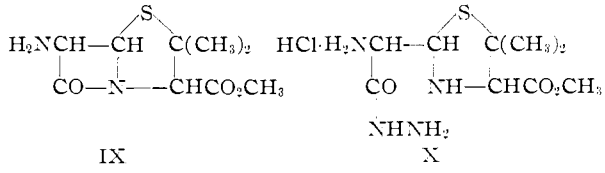


Fig. 2.

of two equivalents of hydrazine on VI, followed by treatment with aqueous acid, 4-carbomethoxy-5,5-dimethyl-α-amino-2-thiazolidineacetyl hydrazide hydrochloride (X) was obtained. With one equivalent of hydrazine, a 50% yield of X resulted (based on VI); the unreacted β-lactam was recoverable.



We are indebted to Bristol Laboratories, Syracuse, N. Y., for generous financial support of this work, and also to the National Science Foundation for a fellowship for P.A.C.

Experimental[9]

Methyl 6-Phthalimidopenicillanate Sulfone (VII).—In Table II are summarized the investigations to determine reagents and optimum conditions for effecting cyclization of Vβ to the β-lactam VI. The crude reaction products were assayed for β-lactam by absorption at 5.62 μ in the infrared. Mixtures that had significant absorption were then oxidized with potassium permanganate in 80% acetic acid; any β-lactam present was converted to the sulfone VII, with other substances being degraded to water-soluble materials.

In a typical experiment (run 1, Table II), 250 mg. (0.6 millimole) of Vβ was suspended in a mixture of 15 ml. of benzene and 5 ml. of thionyl chloride, and the mixture refluxed until homogeneous (30 minutes). After removal of solvent and excess reagent under reduced pressure, the residue was taken up in 10 ml. of glacial acetic acid, and a solution of 0.375 g. of potassium permanganate in 3.0 ml. of water added with cooling. Treatment with 30% hydrogen peroxide after 30 minutes gave a colorless solution, which upon dilution with water to 75 ml. deposited 62 mg. (26%) of VII, m.p. 200–201° dec. Recrystallization from acetone-water afforded an analytical sample, m.p. 200–201° dec.

(9) All melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for the microanalyses, and to Dr. N. A. Nelson and his associates for the infrared and ultraviolet spectra.

Anal. Calcd. for $C_{17}H_{16}N_2O_7S$: C, 52.04; H, 4.10; N, 7.14. Found: C, 51.68; H, 4.34; N, 6.86.

TABLE II

Reagent	Solvent	Temp., °C.	Yield,[a] %
$SOCl_2$	Benzene	Reflux	26
$SOCl_2$	Chloroform	Reflux	36
$SOCl_2$	Methylene chloride	Reflux	36
$SOCl_2$	Dioxane	85	0
$SOCl_2$ + 1 equiv. $(C_2H_5)_3N$	Benzene	Reflux	0[c]
$POCl_3$	Benzene	Reflux	42
$POCl_3$	Chloroform	Reflux	30
$POCl_3$	Toluene	Reflux	33
$POCl_3$	Cyclohexane	Reflux	0[c]
$POCl_3$	Acetic anhydride	65	0[c]
$POCl_3$	None	85	0
$POCl_3$	None	25	0[b]
PCl_3	Benzene	Reflux	0[e]
PCl_5	Benzene	Reflux	0
$COCl_2$	Benzene	−20, 20	0[e]
Tetraethyl pyrophosphite	Diethyl phosphite	85	0[e]
Tetraethyl pyrophosphite	Benzene	Reflux	0[d]
Ethyl chloroformate	Methylene chloride	0, then refl.	0[d]
Trifluoroacetic anhydride	Methylene chloride	Reflux	0[d]

[a] As determined by absorption at 5.62 μ in the infrared or by sulfone assay. [b] Reagent added to free base of Vβ. [c] Quantitative isolation of the decarboxylation product of Vβ as its free base. [d] Reagent added to Vβ, followed after 0.5 hour by one equivalent of triethylamine. [e] Experiments performed by Dr. Kenneth Kopple.

Methyl 6-Phthalimidopenicillanate (VI).—A suspension of 8.0 g. (0.019 mole) of finely pulverized Vβ in a mixture of 120 ml. of purified thionyl chloride[10] and 400 ml. of methylene chloride was heated under reflux for 4 hours. The resultant pale yellow solution was concentrated under reduced pressure to remove solvent and excess reagent, and a methylene chloride solution of the residual oil washed rapidly with a 5% sodium bicarbonate solution, 3 *N* hydrochloric acid and water. The yellow resin obtained upon concentration of the organic phase was dissolved in 10 ml. of acetone. Upon storage at 0–5° for 16 hours, 2.54 g. (36.4%) of crude crystalline material was deposited. Recrystallization from acetone–ether–hexane afforded 2.0 g. (28.8%) of pure β-lactam VI, m.p. 170–172°. Two additional recrystallizations from this solvent combination gave analytically pure prisms, m.p. 173–173.5°.

Anal. Calcd. for $C_{17}H_{16}N_2O_5S$: C, 56.66; H, 4.48; N, 7.77. Found: C, 56.98; H, 4.60; N, 7.62.

2,2-Dimethyl-3-carbomethoxy-5-keto-6-phthalimido-2,3,-4,5-tetrahydro-1,4-thiazepine (VIII).—To a previously prepared mixture of 100 ml. of phosphorus oxychloride and 460 ml. of dry benzene was added 8.2 g. (0.02 mole) of Vβ. The suspension was heated under reflux for 40 minutes, after which solution was complete. Concentration under reduced pressure, followed by flushing with several portions of toluene, afforded a brown resin. A methylene chloride solution of this material was washed thoroughly with a 5% sodium bicarbonate solution, 3 *N* hydrochloric acid and water. Crystallization of this partially purified mixture was effected from 10 ml. of acetone stored at 0–5° for 16 hours. The yield of crude crystals was 3.98 g. (56%). This material was triturated with several portions of cold benzene; the soluble component was methyl 6-phthalimidopenicillanate (VI), m.p. 171–172°, obtained in a yield of 1.2 g. (17%).

The benzene-insoluble portion was recrystallized from acetone, giving 2.4 g. (33.6%) of fine needles, m.p. 230–

(10) E. L. Martin and L. F. Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 569.

231° dec. Recrystallization from acetone–ether afforded a mixture of two polymorphic forms, cubes and fine needles, both of which melted at 237–237.5° dec.

Anal. Calcd. for $C_{17}H_{16}N_2O_5S$: C, 56.66; H, 4.48; N, 7.77; mol. wt., 360. Found: C, 56.47; H, 4.52; N, 8.02; mol. wt., 350 ± 10.

On the basis of this elemental analysis and molecular weight, and on the infrared (Fig. 1, curve C) and ultraviolet (Fig. 2) spectra, the compound was assigned structure VIII.

From 8.1 g. (0.0195 mole) of the α-isomer of V and 100 ml. of phosphorus oxychloride in 460 ml. of benzene in a procedure identical to that described above for the β-isomer, there was obtained 2.94 g. (42%) of crude VIII, m.p. 220–228° dec. Recrystallization from acetone–benzene gave fine silky needles, m.p. 236–236.5° dec.

Similarly, this reaction when carried out with 1.5 g. (3.6 millimoles) of Vγ and 19 ml. of phosphorus oxychloride in 85 ml. of benzene afforded 0.77 g. (60%) of VIII, m.p. 236.5–237° after recrystallization from acetone–benzene.

Reaction of Hydrazine with Methyl 6-Phthalimidopenicillanate.—To a solution of 0.18 g. (0.5 millimole) of VI in 10 ml. of dioxane was added 5.0 ml. of a 0.242 *M* solution of hydrazine in dioxane (two equivalents). After storage at room temperature for 16 hours, the mixture was lyophilized, and the phthalhydrazide complex broken up with 5.4 ml. of 0.0992 *N* hydrochloric acid. The phthalhydrazide was removed by filtration, and the filtrate lyophilized. Crystallization of the product from methanol–ether afforded 110 mg. (74%) of X, m.p. 151–152° dec.

Anal. Calcd. for $C_9H_{19}N_4O_3SCl$: C, 36.13; H, 6.42; N, 18.74. Found: C, 36.08; H, 6.37; N, 18.62.

In another experiment, 360 mg. (1 millimole) of VI and 50 mg. (1 millimole) of hydrazine were allowed to react in 5 ml. of dioxane for 6 hours. A crystalline substance separated and was collected by filtration; addition of ether to the mother liquors afforded more of this material. An infrared absorption spectrum showed the disappearance of the bands characteristic of the phthalimido and β-lactam groups, with the appearance of intense peaks in the regions of 6.0 to 6.1 and 6.4 to 6.6 μ. The substance thus appeared to be the phthalhydrazide complex of 4-carbomethoxy-5,5-dimethyl-α-amino-2-thiazolidineacetyl hydrazide. The yield was 210 mg. (91%, based on hydrazine). Treatment of a portion of this material with an equivalent of aqueous hydrochloric acid afforded the hydrochloride X, m.p. 150–152°. From the mother liquors of the reaction with hydrazine there was recovered 165 mg. (92%) of the unreacted VI.

CAMBRIDGE 39, MASSACHUSETTS

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

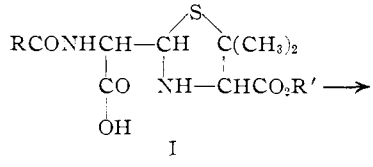
The Synthesis of Substituted Penicillins and Simpler Structural Analogs. XI. Methyl 6-Benzylsulfonamidopenicillanate

BY JOHN C. SHEEHAN AND PHILIP A. CRUICKSHANK

RECEIVED FEBRUARY 15, 1956

By a cyclization procedure, the "sulfonyl analog" of benzylpenicillin has been prepared in which the phenylacetamido side chain has been replaced by the benzylsulfonamido group. Use of the sulfonyl blocking group on the α-amino-2-thiazolidineacetic acid derivative precludes azlactone formation. Two stereoisomeric modifications (two racemates) have been isolated, one of which corresponds in configuration to the natural penicillins. Also obtained was an isomeric material to which has been assigned the 5-keto-2,3,4,5-tetrahydro-1,4-thiazepine ring system.

Many attempts directed toward the cyclization of penicilloates of type I have resulted in azlactonization followed by disruption of the thiazolidine ring to give penicillenates (II).[1] Recently, the use of phthalimido derivatives (III), in which the possibility of azlactone formation is precluded, has afforded a fused thiazolidine-β-lactam,[2] the ring system present in penicillin.



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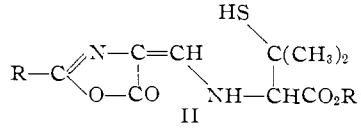
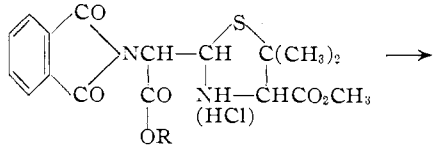


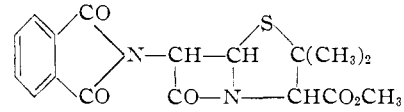
II



IIIa, R = $C(CH_3)_3$
IIIb, R = H

(1) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 851.

(2) THIS JOURNAL, **78**, 3680 (1956).



IV

The bulkiness of this diacyl blocking group imparts considerable steric hindrance toward cyclization in compounds of type IIIb. This effect apparently has prevented the formation of the methyl 6-phthalimidopenicillanate (IV) having a configuration corresponding to the natural penicillins.[2]

This paper describes the use of the benzylsulfonyl blocking group for penicillanate synthesis. The steric factors of this side chain are very similar to those encountered in the natural penicilloates, while the azlactonization reaction is entirely avoided. Two isomeric benzylsulfonamidopenicillanates (VIII) have been prepared.

An important consideration in the use of blocking groups for the synthesis of the penicillin structure concerns the ease of their removal after formation of the β-lactam ring. The sulfonamido functions are deficient in this respect for, under conditions of cleavage, hydriodic acid or phosphonium iodide in glacial acetic acid, or sodium in liquid ammonia,[3] the azetidinone ring would be destroyed. Investigations employing the benzylsulfonyl group were

(3) R. A. Boissonnas and G. Preitner, *Helv. Chim. Acta*, **36**, 875 (1953).