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

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. V. The Application of 5-Phenyloxazolidine-2,4-diones to the Synthesis of Phenylacetylamino-β-lactams

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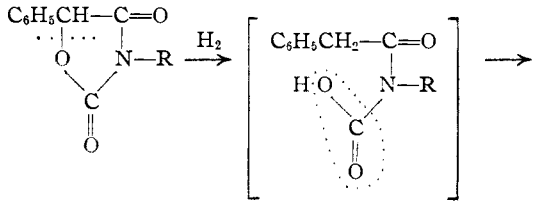
The use of 5-phenyloxazolidine-2,4-diones has made possible an extension of the acid chloride–thiazoline reaction to the indirect synthesis of a 6-phenylacetylamino-β-lactam-thiazolidine sulfone. The acid chloride of 3-carboxymethyl-5-phenyloxazolidine-2,4-dione (VI) was prepared in four steps from ethyl mandelate. The removal of a masking *t*-butyl ester grouping under anhydrous acid conditions is a key feature of the preparation.

The acid chloride VI and 2-phenyl-2-thiazoline interact in the presence of triethylamine to give a 28% yield of a fused β-lactam-thiazolidine carrying a 5-phenyloxazolidine-2,4-dione substituent. Oxidation gives the corresponding sulfone in 95% yield. Hydrogenolysis of this compound cleaves the benzyl lactone linkage in the oxazolidinedione ring to provide the β-lactam-thiazolidine structure (as the sulfone) with the 6-phenylacetylamino grouping characteristic of benzylpenicillin.

In this communication is discussed the application of 5-phenyloxazolidine-2,4-diones to the indirect synthesis of 6-phenylacetylamino-thiazolidine-β-lactam derivatives by the general method described previously.[2] Since acylamino acid halides are not accessible in general,[3] introduction of a 6-phenylacetylamino grouping into the β-lactam-thiazolidine nucleus by the acid chloride-thiazoline method must be indirect. One general approach to the problem involves the use of a protected amino acid chloride derivative (with no interfering NH group) from which an acylamino acid derivative can be formed under mild conditions. These acid chlorides represent systems which have been constituted by replacement of elements of the acylamino structure by certain labile units or "protecting groups." The requirements which such an acid chloride must meet in order to serve as a suitable reaction component are few but severe: (a) the protecting group must be stable to acids, since the preparation of the desired acid chloride must be carried out in an acidic medium; (b) the protecting group must be inert under the conditions of the acid chloride-thiazoline reaction; (c) the acid chloride must be sufficiently reactive to form the desired β-lactam; (d) after incorporation into the β-lactam-thiazolidine system the protecting group must be readily removable to form the phenylacetylamino substituent under well-defined conditions which do not affect appreciably the penicillin-like structure.

Previously we reported[4] the synthesis of a monocyclic β-lactam bearing the α-phenylacetylamino substituent characteristic of benzylpenicillin by the hydrazinolysis of a phthaloyl group to form the free amino β-lactam (3-amino-1,4-diphenyl-2-azetidinone), followed by phenylacetylation. The use of 5-phenyloxazolidine-2,4-diones might permit the introduction of a phenylacetylamino substituent without the necessity for complete removal of the group.

The 5-phenyloxazolidine-2,4-dione ring system was chosen as a promising protecting group because, as illustrated below, it seemed possible that the phenylacetylamino group might be generated by hydrogenolytic cleavage of the benzyl lactone. The ring may in fact be considered as a carbobenzoxy group with a carbonyl bridge protecting the second amide hydrogen. This procedure has proved successful, and thus resolves one of the more serious shortcomings of the phthalimido and succinimido groups in the preparation of compounds closely related to benzylpenicillin.



$C_6H_5CH_2CONHR + CO_2$

The starting material for the synthesis of the desired oxazolidinedione acid chloride (VI) was ethyl mandelate (I), prepared in 70% yield by Fischer esterification of mandelic acid.[5] On condensation of the hydroxyester with urea in the presence of sodium ethoxide by a procedure patterned after the general method of Stoughton[6] the sodium salt of the heterocycle (III) was obtained in 75% yield; acidification afforded II in 67.5% over-all yield. Attempted alkylation of III with potassium bromoacetate in dimethylformamide failed to yield a homogeneous product.

The problem at this point was to mask temporarily the carboxyl function of the haloacetate during alkylation of the heterocycle III, after which the masking function must be converted into an acid chloride without disturbing the sensitive oxazolidinedione ring. It would be difficult to remove a simple ester function (as, for example, methyl or ethyl) without hydrolyzing simultaneously the heterocyclic moiety. We have employed benzyl esters (removable with hydrogen over palladium) successfully in a similar synthesis of acyclic diacylamino acid chlorides,[7] but hydrogenolysis conditions cleave 5-phenyloxazolidine-2,4-diones. It occurred to us that a masking group for the alkylation free of these objections

(1) Bristol Laboratories Fellow, 1949–1950.

(2) For the preceding paper in this series see J. C. Sheehan and G. D. Laubach, THIS JOURNAL, **73**, 4376 (1951).

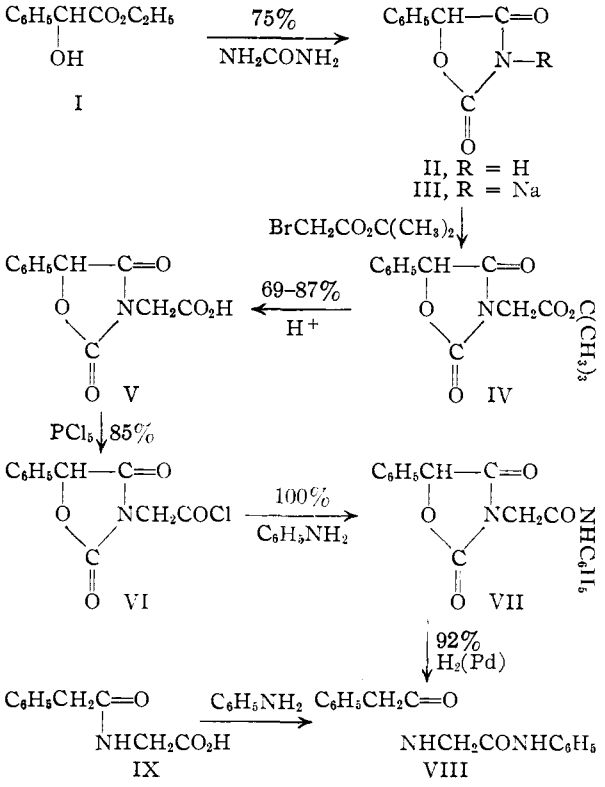
(3) It has been established that with few exceptions attempts to prepare acylamino acid chlorides lead instead to the formation of the isomeric oxazolone hydrochlorides. H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 911.

(4) J. C. Sheehan and J. J. Ryan, THIS JOURNAL, **73**, 1204 (1951).

(5) E. Fischer and A. Speier, *Ber.*, **28**, 3252 (1895); A. McKenzie, *J. Chem. Soc.*, **75**, 755 (1899).

(6) R. W. Stoughton, THIS JOURNAL, **63**, 2376 (1941).

(7) J. C. Sheehan and E. J. Corey, in preparation.



might be a *t*-butyl ester, which is removable with anhydrous acids.

The ester IV was obtained readily by alkylation of II with *t*-butyl bromoacetate and sodium hydride, or better (100% yield) by reaction of III with this bromoester in dimethylformamide. The desired acid V could be prepared from the labile *t*-butyl ester by a variety of methods; pyrolysis for 30 minutes at 210° yielded 61% of V, solution of IV in concentrated sulfuric acid followed by dilution with water gave 87.3% of V, and treatment of IV with gaseous hydrogen chloride in dioxane lead to 69.2% of V. The facile cleavage of the *t*-butyl ester under anhydrous acid conditions is the key to success in this synthetic scheme.

The acid chloride VI was prepared in 85% yield using phosphorus pentachloride in benzene. The corresponding anilide VII was prepared in quantitative yield.

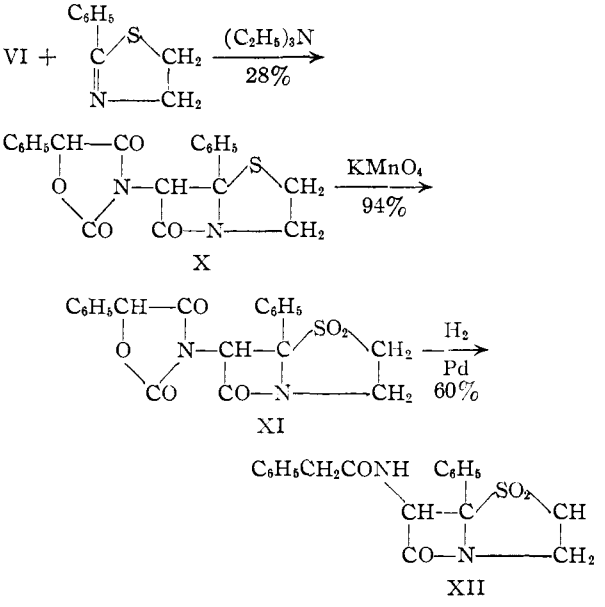
Studies of the cleavage of the heterocycle were carried out on the anilide VII. Hydrogenolysis with palladium-on-charcoal proceeded slowly at atmospheric pressure and room temperature to yield 91.5% of the expected phenaceturic acid anilide VIII, identified by comparison with an authentic sample prepared from phenaceturic acid (IX) and aniline.[8] An alternate procedure using aluminum amalgam was also successful, although the yield was lower (42%). This is apparently the first example of the use of aluminum amalgam in the reductive cleavage of benzyl-type esters.

Other reagents known to be effective in reductive cleavages of benzyl esters, such as sodium in liquid ammonia[9] and phosphonium iodide,[10] were found to be ineffective in this case. The anilide decolorized the theoretical quantity of sodium in liquid ammonia but the product was a complex mixture suggestive of ammonolysis. These results are in accord with the well-known lability of the oxazolidinedione ring system to basic reagents. For example, 3,5,5-trimethyl-2,4-oxazolidinedione may be titrated to a phenolphthalein end-point. N-Methyl-2-hydroxy-2-methylpropionamide is one of the products isolated on acidification.[11,12]

An acidic reagent, zinc–acetic acid–pyridine, reported to be very active in certain reductions,[13] had no effect on the heterocyclic anilide VII.

The preparation of the thiazolidine-β-lactams studied is shown below.

The bicyclic lactam X was not obtained in pure state from the high dilution reaction of the acid chloride VI, triethylamine and 2-phenyl-2-thiazoline in refluxing ether, but similar reaction in methylene chloride yielded X in 28.4% yield. The sulfone XI was obtained by permanganate oxidation in 93.9% yield.



Hydrogenolysis of XI in the presence of palladium-on-charcoal catalyst at atmospheric pressure proceeded with considerable difficulty; the yield of cleaved product XII was 60%. The infrared spectrum of the phenylacetyl lactam (XII) shows the β-lactam band at 5.6 μ and monosubstituted amide bands at 2.93, 5.93 and 6.60 μ (Fig. 1, curve D). Comparison of this spectrum with that of the heterocyclic sulfone XI (Fig. 1, curve C) shows that the heterocycle bands at 5.5 and 5.7 μ disappear on hydrogenolysis.

An attempted hydrogenolysis of the unoxidized lactam X with palladium gave unchanged starting material as the only pure substance isolated. A similar reduction using aluminum amalgam also resulted in the recovery of the major portion of the original lactam.

(8) Ref. 3, p. 778.

(9) R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

(10) C. R. Harington and T. H. Mead, *Biochem. J.*, **29**, 1605 (1935).

(11) M. A. Spielman, THIS JOURNAL, **66**, 1244 (1944).

(12) J. S. H. Davies and W. H. Hook, *J. Chem. Soc.*, 30 (1950).

(13) R. Kuhn and A. Winterstein, *Ber.*, **65**, 1741 (1932).

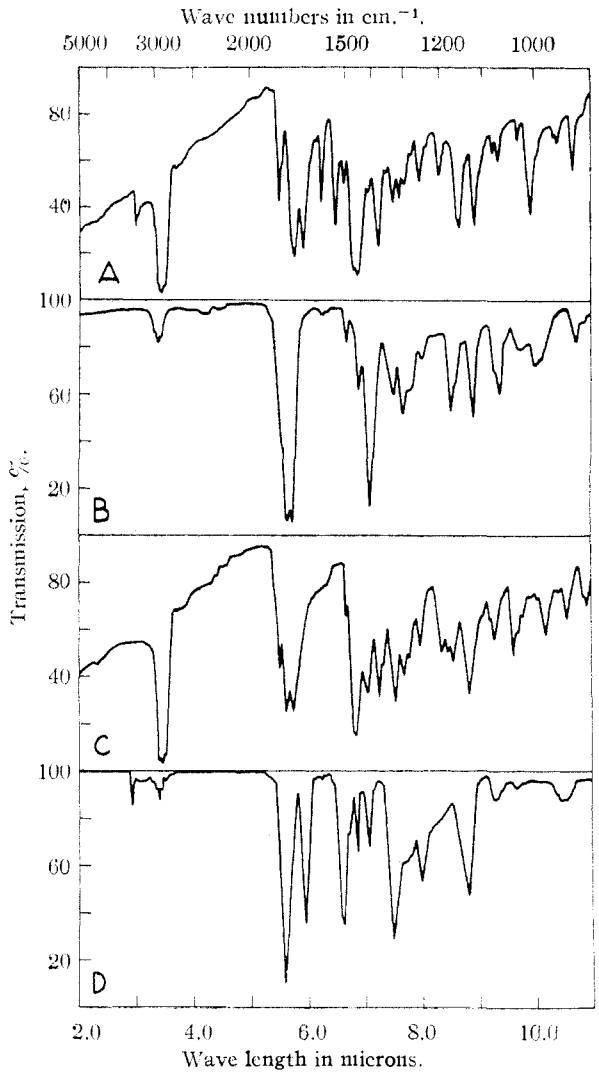


Fig. 1.—Infrared spectra: A, 3-carboxanilidomethyl-5-phenyl-2,4-oxazolidinedione (VII); B, 2-phenyl-α-(5-phenyl-2,4-diketo-3-oxazolidyl)-2-thiazolidineacetic acid β-lactam (X); C, sulfone of 2-phenyl-α-(5-phenyl-2,4-diketo-3-oxazolidyl)-2-thiazolidineacetic acid β-lactam (XI); D, sulfone of 2-phenyl-α-(phenylacetylamino)-2-thiazolidineacetic acid β-lactam (XII). Curves A and C were measured in nujol suspension; curves B and D, 5% solutions in $CHCl_2CHCl_2$.

Experimental[14]

5-Phenyl-2,4-oxazolidinedione (II).—Ethyl mandelate, b.p. 112–118° at 3 mm., m.p. 30–31°, was prepared in 70% yield essentially as described by Fischer.[5]

To a solution of sodium ethoxide prepared from 13.8 g. (0.6 mole) of sodium and 200 ml. of absolute ethanol was added 36.0 g. (0.6 mole) of urea in one portion. To the stirred solution at 0° was added over a 10-minute period an ice-cold solution of the ester (108 g., 0.6 mole) in 100 ml. of absolute ethanol. The pasty mass was allowed to come to room temperature over a 20-minute period, then refluxed for 3.5 hours. Excess solvent (60 ml.) was removed by distillation and the resulting slurry stored at 5° for two hours. The sodium salt III, obtained in two crops, was washed with small portions of cold ethanol. The yield was 90.4 g. (75.4%).

(14) Melting points are corrected. We are indebted to Mr. S. M. Nagy and his associates for the microanalyses. All spectra were measured with a Baird Infrared Recording Spectrophotometer, Model B. The cell thickness used with solutions was 0.10 mm. The cell thickness in the case of nujol mulls was 0.010–0.025 mm.

A portion of the salt (15 g.) was dissolved in 100 ml. of water and 20 ml. of ether and the mixture acidified to *p*H 2 with 4 *N* hydrochloric acid. After separation of the oily layer and two extractions with 50-ml. portions of ether, the combined extracts were dried over magnesium sulfate. Concentration at 30 mm. and 50° yielded a crisp, yellow solid, which was recrystallized from 500 ml. of water as 11.9 g. (67.5% over-all) of colorless needles, m.p. 108.8–110.0°. The melting point reported by Traube and Ascher on a sample prepared by a different method was 108°.[15]

3-Carbo-*t*-butoxymethyl-5-phenyl-2,4-oxazolidinedione (IV).—To a solution of 77.6 g. (0.39 mole) of the sodium salt III in 200 ml. of dimethylformamide was added 76.0 g. (0.39 mole) of *t*-butyl bromoacetate with swirling over a 15-minute period. After storage overnight the dimethylformamide was removed by distillation at 70–80° and 15 mm. pressure. Toluene (100 ml.) was added, and the sodium bromide (41.0 g., 102%) collected by filtration. The concentrated filtrate amounted to 119.5 g. of viscous oil, or slightly more than the theoretical yield of IV. This compound was not analyzed because of its lability and difficulties in the purification procedures.

3-Carboxymethyl-5-phenyl-2,4-oxazolidinedione (V). A. **By Cleavage of IV with Anhydrous Hydrogen Chloride.**—A solution of a 111.5-g. portion of the oily ester IV in 300 ml. of anhydrous dioxane was saturated with hydrogen chloride gas at 0°. After storage overnight at room temperature the solution was concentrated to dryness and flushed with several small portions of toluene. Suspension of the residue in 100 ml. of toluene and filtration yielded 47.3 g. of V, m.p. 141.0–144.0°. A further quantity of acid was obtained by concentration of the toluene, solution of the residue in 200 ml. of dioxane and repetition of the hydrogen chloride treatment. After distillation of the dioxane, the residual oil was taken up in 300 ml. of ether, extracted with 500 ml. of water and concentrated to a soft solid. Trituration with several small portions of toluene followed by recrystallization from the same solvent yielded 11.8 g. of V, m.p. 138.8–145.0°. The over-all yield from III of combined product was 69.2%. An analytical sample from toluene melted at 144.8–145.2°.

Anal. Calcd. for $C_{11}H_9O_5N$: C, 56.18; H, 3.84; N, 5.96. Found: C, 56.38; H, 3.93; N, 5.86.

B. **By Hydrolysis of IV with Concentrated Sulfuric Acid.**—A solution of a 1.20-g. portion of the ester IV was dissolved in 1.5 ml. of concentrated sulfuric acid, then diluted with 10 ml. of water with cooling. The white precipitate was collected by filtration after standing at 5° overnight, yielding 0.800 g. (87.3%) of V, m.p. 142.0–144.0°. The product became discolored on long standing due to traces of residual sulfuric acid.

C. **By Pyrolysis of IV.**—A 1.20-g. portion of the ester in a small test-tube under a brisk stream of nitrogen was immersed in an oil-bath at 207° and maintained at that temperature for 30 minutes. The residue was triturated with 2 ml. of toluene and collected by filtration. After washing with small portions of toluene the tan solid weighed 0.556 g. (60.7%), m.p. 138.0–141.0°.

Acid Chloride of 3-Carboxymethyl-5-phenyl-2,4-oxazolidinedione (VI).—The acid V (23.6 g., 0.10 mole) and 21.0 g. (0.10 mole) of phosphorus pentachloride were mixed in a 100-ml. round-bottomed flask fitted with a condenser and calcium chloride tube. When fusion was almost complete, 50 ml. of anhydrous benzene was added and the solution was refluxed for one hour. Concentration at 50° and 30 mm. pressure followed by distillation of several portions of toluene yielded crude VI as a readily crystallizing oil. Recrystallization from benzene–cyclohexane yielded 21.7 g. (85.3%) of pure acid chloride, m.p. 66.8–70.0°.

3-Carboxanilidomethyl-5-phenyl-2,4-oxazolidinedione (VII).—To an ice-cold solution of 2.54 g. (0.01 mole) of VI in 30 ml. of methylene chloride was added dropwise over a 30-minute period with stirring 1.82 ml. (1.86 g., 0.02 mole) of aniline in 10 ml. of methylene chloride. After being stirred one hour at room temperature, the mixture was concentrated to dryness under reduced pressure, extracted with two 25-ml. portions of water and filtered, yielding 3.10 g. (100%) of anilide, m.p. 166.0–166.5°. An analytical sample was obtained by recrystallization from methanol, m.p. 167.0–168.0°.

(15) W. Traube and R. Ascher, *Ber.*, **46**, 2077 (1913).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.91; N, 9.03. Found: C, 65.68; H, 4.87; N, 8.79.

Phenaceturic Acid Anilide (VIII). A. By Hydrogenolysis of VII with Palladium-on-Charcoal.—A solution of 0.310 g. (0.001 mole) of VII in 10 ml. of dioxane containing 0.600 g. of 10% palladium-on-Darco catalyst[16,17] was hydrogenated in a microhydrogenator under atmospheric pressure. A potassium hydroxide tube was incorporated into the system to absorb any carbon dioxide that might be given off. After nine hours the theoretical volume of hydrogen had been absorbed and hydrogen uptake ceased. The solution, from which the catalyst had been removed by filtration through Filter-Cel, was concentrated to a white powder. The yield of product, combined with the concentrated washings of the catalyst, amounted to 0.245 g. (91.5%) of VIII, m.p. 161–163.4°. The melting point of a mixture with an authentic sample was not depressed.

B. **By Reduction of VII with Aluminum Amalgam.**—Aluminum amalgam was prepared as follows: 1.8 g. of Chef Foil commercial sheet aluminum previously washed with acetone and buffed with emery paper was cut into small crumpled squares and washed with 10 ml. of 2.5% sodium hydroxide solution until brisk hydrogen evolution was observed. The residue was washed with five 15-ml. portions of water and then covered with 10 ml. of 1% mercuric chloride solution for 30 seconds. The residue was washed with two 10-ml. portions each of water, ethanol and ether in succession.

To the amalgam thus prepared was added 0.310 g. (0.001 mole) of anilide (VII) in 30 ml. of dioxane containing 0.5 ml. of water, which resulted in brisk evolution of hydrogen. Two further 0.5-ml. portions of water were added after two and six hours, respectively. After eight hours the solid residue was removed by filtration through Filter-Cel and the filtrate and washings concentrated at 50° and 30 mm. pressure. The residue (0.240 g.) was extracted with 10 ml. of warm 5% sodium hydroxide solution to remove unreacted starting material. The residue, m.p. 162.0–164.0°, amounted to 0.108 g. (42%). The melting point on admixture with an authentic sample of phenaceturic acid anilide was not depressed.

C. **From Phenaceturic Acid (IX).**—A procedure similar to that of Robinson was used.[8]

Phenaceturic acid (0.50 g.) was refluxed in 5 ml. of aniline for five hours. The excess aniline was distilled directly and the residue taken up in 20 ml. of chloroform. After washing with 10 ml. of 5% sodium hydroxide and 5 ml. of 2.5 *N* hydrochloric acid the filtered chloroform solution was concentrated to an orange residue, which on trituration yielded 0.495 g. of anilide, m.p. 145–155°. Recrystallization from benzene, then dioxane–cyclohexane yielded pure VIII, m.p. 162.5–163.5°.

2-Phenyl-α-(5-phenyl-2,4-diketo-3-oxazolidyl)-2-thiazolidineacetic Acid β-Lactam (X).—To a well-stirred, refluxing solution of 1.63 g. (0.01 mole) of 2-phenyl-2-thiazoline and 2.54 g. (0.01 mole) of the acid chloride VI in 35 ml. of methylene chloride was added through a high dilution cycle 1.41 ml. (1.02 g., 0.01 mole) of triethylamine in 50 ml. of methylene chloride. The time of addition was seven hours. The dark solution was concentrated to a brown magma, which yielded 1.26 g. of a colorless crystalline residue on trituration with acetone, or 91.3% as triethylamine hydrochloride.

The concentrated acetone solution crystallized spontaneously on standing overnight, and trituration and washing with two 15-ml. portions of 1:2 acetone–ethanol yielded 1.085 g. (28.4%) of lactam, m.p. 193.5–198.4°. A portion twice recrystallized from dioxane–petroleum ether (b.p. 30–60°) melted at 197.5–199.5°.

Anal. Calcd. for $C_{20}H_{16}N_2O_4S$: C, 63.25; H, 4.24; N, 7.37. Found: C, 63.03; H, 4.45; N, 7.50.

Sulfone of 2-Phenyl-α-(5-phenyl-2,4-diketo-3-oxazolidyl)-2-thiazolidineacetic Acid β-Lactam (XI).—To a solution of 0.570 g. (0.0015 mole) of X in 60 ml. of dioxane was added 0.68 g. of potassium permanganate in 7 ml. of water and 20 ml. of glacial acetic acid. After 40 minutes the brown solution was decolorized with several drops of 30% hydrogen peroxide solution and diluted with 60 ml. of water. The colorless needles which separated at 0° were collected by filtration, yielding 0.580 g. (93.9%) of pure sulfone, m.p. 206.2° (dec.). A sample recrystallized from dioxane–cyclohexane for analysis melted at 205.5° (dec.).

Anal. Calcd. for $C_{20}H_{16}N_2O_6S$: C, 58.24; H, 3.91; N, 6.79. Found: C, 58.23; H, 4.12; N, 6.79.

Sulfone of 2-Phenyl-α-(phenylacetylamino)-2-thiazolidineacetic Acid β-Lactam (XII).—A solution of 0.925 g. (0.00225 mole) of XI in 50 ml. of dioxane was hydrogenated over 2.0 g. of 10% palladium-on-Darco catalyst in a Parr Hydrogenator at 30° and atmospheric pressure for 73 hours with replacement of the catalyst after 50 hours. The catalyst was removed by filtration through Filter-Cel, and the concentrated filtrate caused to crystallize by trituration with benzene. The product, 0.520 g. on recrystallization from chloroform–carbon tetrachloride amounted to 0.495 g. (60%), m.p. 140.5° (dec.). An analytical sample was obtained by recrystallization from chloroform–carbon tetrachloride, acetone–cyclohexane and finally dioxane–cyclohexane.

Anal. Calcd. for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.57; H, 5.02; N, 7.41.

A small amount of material (0.135 g.) isolated from the original benzene triturate melted at 190.0° (dec.) after recrystallization from dioxane–cyclohexane; the melting point was not depressed on admixture with starting material.

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(16) M. S. Newman and H. V. Zahm, THIS JOURNAL, **65**, 1097 (1943).

(17) N. D. Zelinsky and M. B. Turowa-Pollak, *Ber.*, **58**, 1295 (1925).