THE SYNTHESIS OF N,N-DIACYLAMINO ACIDS AND ANALOGS OF PENICILLIN

by

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Finally, it is a pleasure to proffer boundless gratitude to all the members of the Faculty of the Massachusetts Institute of Technology who have contributed to the author's education and in particular to Professor Arthur C. Cope.
The first part of this thesis describes the preparation of acyclic \( N,N \)-diacylglycines by three different methods. A study of three members of this new class of compounds has been made and the utility of such intermediates in the synthesis of the penicillins has been ascertained. The work set forth in the second part deals with the preparation of 2-benzylidene-3-oxazolidine-4,5-diones, an investigation of the methods by which they may be converted to phenylacetamides and the possible role of these compounds in a new route to \( \beta \)-lactam-thiazolidines bearing the 6-phenylacetamido substituent characteristic of benzylpenicillin. In the third part there is disclosed the successful application of the oxazolidine-4,5-dione method to the synthesis of benzylpenicillin-like structures.
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PART I

SYNTHESSES AND REACTIONS OF $N,N$-DIACYLGLYCINES
INTRODUCTION

The first part of this thesis describes the preparation of acyclic N,N-diacylglycines and the applicability of these compounds to the synthesis of penicillin analogs.

The results of the war-time program of research directed toward the synthesis of penicillin and related β-lactam-thiazolidines have been summarized in two monographs on the subject.\(^1,2\) It is especially striking that in spite of the vast amount of experimental endeavor involved in the program (1942-1945) no synthetic route to penicillin, successful in the classical sense, was discovered. In 1945 it was found that the reaction of penicillamine with 2-benzyl-4-methoxymethylene oxazolone furnished a non-homogenous product showing a low order of biological activity by the standard assay for penicillin.\(^3\) The presence of benzylpenicillin (I, R = C\(_6\)H\(_5\)) in the crude mixture was proved by its subsequent isolation in minute yield.\(^4\) The reaction, although extensively

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3. Reference 1, Chapter XXIII, p. 893.

studied, could not be modified to yield more than a trace of penicillin and hence is of limited significance from either a synthetic or structural standpoint.

One important contribution to research on both the synthesis and structure of penicillin is the extension of a reaction used by Staudinger in the preparation of monocyclic $\beta$-lactams\textsuperscript{5} to the synthesis of a series of three fused $\beta$-lactam-thiazolidines.\textsuperscript{6} Staudinger found that certain imines may react with ketenes to form $\beta$-lactams. The reaction is illustrated by the preparation of 1,3,3,4-tetraphenyl-2-azetidinone (II).\textsuperscript{7} Reaction of diphenyl ketene with 2-phenyl-2-thiazoline took place in an analogous manner to afford the $\beta$-lactam, III-a ($R_1 = \text{C}_6\text{H}_5$, $R_2 = \text{C}_6\text{H}_5$). Although no other $\beta$-lactams could be obtained directly by this method, the $\beta$-lactams

\[
\begin{align*}
(\text{C}_6\text{H}_5)_2\text{C} &= \text{C} = \text{O} + \text{C}_6\text{H}_5\text{CH}=\text{NC}_6\text{H}_5 & \rightarrow & \text{C}_6\text{H}_5\text{CH} & \text{NC}_6\text{H}_5 \\
\text{(C}_6\text{H}_5)_2\text{C} & \text{C} \text{C} = \text{O} & \end{align*}
\]

II

III-b ($R_1 = \text{C}_6\text{H}_5$, $R_2 = \text{CH}_3$) and III-\textit{c} ($R_1 = \text{CH}_3$, $R_2 = \text{CH}_3$) could be prepared indirectly. Reaction of dimethyl ketene

6. Reference 1, p. 996.
with 2-phenyl-2-thiazoline or 2-methyl-2-thiazoline yielded the piperidinediones (IV) which were hydrolyzed to N-isobutyryl-2-thiazolidines. These in turn were

(I) \[(\text{CH}_3)_2\text{C} \hspace{1cm} \text{CH}_2 \]
\[\begin{array}{c}
\text{HOCONH} \\
\text{C} \\
\text{N} \\
\text{C} \\
\text{O} \\
\text{RCH}_2 \text{CO}
\end{array}
\]

(III) \[\begin{array}{c}
\text{H}_2\text{C} \\
\text{S} \\
\text{C} \\
\text{N} \\
\text{C} \hspace{1cm} \text{R}_1 \text{C} \hspace{1cm} \text{R}_2 \\
\text{C} \hspace{1cm} \text{R}_1 \text{C} \hspace{1cm} \text{R}_2 \\
\text{R}_2 \text{C} \hspace{1cm} \text{R}_2
\end{array}
\]

(IV) \[\begin{array}{c}
\text{H}_2\text{C} \\
\text{S} \\
\text{C} \\
\text{N} \\
\text{C} \hspace{1cm} \text{C} \hspace{1cm} \text{R}_1 \text{C} \hspace{1cm} \text{R}_2 \\
\text{R}_2 \text{C} \hspace{1cm} \text{R}_2
\end{array}
\]

converted by heating to the corresponding \(\beta\)-lactams (III-b, III-c). The infrared spectra of the \(\beta\)-lactams (III-a, b and c) each exhibit a strong band at 5.60-5.65 \(\mu\) in sharp contrast to monocyclic \(\beta\)-lactams most of which show carbonyl bands at 5.75 \(\mu\). This evidence greatly strengthened the arguments for the \(\beta\)-lactam-thiazolidine
structure for penicillin, which shows a strong band at 5.61 µ. It is noteworthy that these heavily-substituted, model β-lactams possess none of the chemical properties which are highly characteristic of penicillin itself, such as facile hydrolysis and oxidation to a sulfone.

Recently Sheehan and Ryan have devised a new synthesis of fused β-lactam-thiazolidines which involves interaction of a thiazoline, an N,N-diacylamino acid chloride and a tertiary amine. They were able to prepare the phthalimido β-lactam IVa from phthaloylglycyl chloride, 2-phenyl-2-thiazoline and triethylamine in 31% yield by the use of a high-dilution technique. Only one

\[
\begin{array}{c}
\text{H}_2\text{C} & \text{CH}_2 \\
\text{S} & \text{N} \\
\text{C}_6\text{H}_5 \\
\end{array} + X\text{CH}_2\text{COCl} \rightarrow \begin{array}{c}
\text{H}_2\text{C} & \text{CH}_2 \\
\text{S} & \text{N} \\
\text{C}_6\text{H}_5 \\
\end{array}
\]

\[
\begin{array}{c}
\text{H}_2\text{C} & \text{CH}_2 \\
\text{S} & \text{N} \\
\text{C}_6\text{H}_5 \\
\end{array}
\]

\[
X = \text{phthalimido} \quad \text{IVa}
\]

of the two possible racemes could be isolated, the other being present in extremely small amount, if at all. The structure of the product was proved by its analysis,

infrared spectrum, oxidation to the sulfone and hydrolytic degradation to N-phenacylphthalamic acid. Selective hydrolysis of the phthalimido group afforded the o-carboxybenzoylamino lactam. Attempts to prepare the free amino lactam by hydrazinolysis of the phthaloyl group, however, did not result in isolation of the desired product. An extremely important feature of this synthetic route is the attendant introduction into the 3-lactam-thiazolidine nucleus of a 6-acylamino substituent, a characteristic of penicillin itself. The use of 2-thiazoline or 2-methyl-2-thiazoline in this reaction led to the formation of products which were not well characterized and from which no 3-lactam could be isolated.

The reaction of an N,N-diacylamino acid chloride and a thiazoline with triethylamine was extended, concurrently with the investigations described in this thesis, by Sheehan and Laubach and Sheehan and Buhle. Using methyl 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate the 3-lactams V-a and V-b were prepared in yields of 13-20%. Selective hydrolysis of the succinimido ring in V-a followed by esterification yielded

7I, the closest synthetic analog of penicillin yet reported. No crystalline products were isolated when methyl 5,5-dimethyl-3-thiazoline-4-carboxylate was used in the reaction.

\[
\begin{align*}
\text{VI} & \quad \text{(CH}_3\text{)}_2\text{C}\text{CHCOOCH}_3 \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\text{N} & \quad \text{N} \\
\text{O=0} & \quad \text{O=0} \quad \text{H}_3\text{COOCCH}_2
\end{align*}
\]

7-a, \( X = \text{succinimido} \)
7-b, \( X = \text{phthalimido} \)

The obstacles preventing the successful application of the thiazoline-acid chloride method to the synthesis of a natural penicillin, such as benzylpenicillin, became evident almost immediately after the discovery of the reaction. It was clear from the outset that fused \( \beta \)-lactam-thiazolidines possessing an acylamino group could not be obtained directly by this reaction, because the required acylamino acid chlorides are not available.\(^{14}\) The problem beyond this point is manifold. It is necessary to devise an acid chloride which would lead to a \( \beta \)-lactam bearing a substituent that is readily convertible to a phenylacetylaminogrouping. Furthermore,

\[\text{Reference I, Chapter XXIV, p. 911.}\]
the conversion should be possible under conditions which do not affect penicillin extensively. Both phthaloyl-glycyl chloride and succinomylglycyl chloride do not seem to be suitable, since the complete removal of the phthaloyl or succinyl group requires more strenuous conditions than a penicillin-like structure would be expected to survive. Another aspect of the problem is the extension of the synthesis to the preparation of fused 2-lactam-thiazolidines bearing a hydrogen atom at the 5-position as in penicillin. In the initial researches on the scope of the addition reaction 2-lactams could be obtained only from 2-phenyl-2-thiazolines. A third phase of the problem is the question of stereoisomerism, i.e., the synthesis of the correct stereoisomer. In this connection it should be mentioned that the stereochemical course of the acid chloride-thiazoline reaction, with a given thiazoline, may be dependent on the nature of the acid chloride.
DISCUSSION

The preparation of acyclic \( N,N \)-diacylglycyl chlorides (VII, \( X = \text{Cl} \)) was undertaken with a view toward determining their possible utility in the synthesis of \( \beta \)-lactam-thiazolidines bearing a 6-acylamino substituent. At the inception of this work no compounds

\[
\begin{align*}
\text{VII} & : \quad \text{R}_1\text{CO}^\text{NHCH}_2\text{CO}_2\text{X} \\
\text{VIII} & : \quad \text{R}_1\text{CO}^\text{NH} \\
\text{R}_2\text{CO}^\text{NH} \\
\text{R}_2\text{CO}^\text{X}
\end{align*}
\]

of this type had been reported in the literature\(^{15}\) and information concerning their chemistry could be gleaned \textit{a priori} only on the basis of their similarity to acyclic diamides (VIII) and cyclic \( N,N \)-diacylamino acid derivatives, such as succinoylglycyl chloride. It has long been known that certain diamides are hydrolyzed with extreme ease in the presence of base. For example, diacetamide (VIII \( \text{R}_1 = \text{R}_2 = \text{CH}_3 \)) is almost completely hydrolyzed to acetamide (over 85\%) by treatment with 0.1 \( N \) sodium hydroxide at 15° for one minute.\(^{16}\) Such conditions are


sufficiently mild so that formation of N-acylamino-β-lactam-thiazolidines from the corresponding N,N-diacyl-
aminocompounds should be feasible even with the more
labile β-lactams. Furthermore, it seemed that acyclic
N,N-diacylglycyl chlorides might possess approximately
the same degree of stability as the corresponding cyclic
N,N-diacylglycyl chlorides.

The preparation of N,N-diacylglycyl chloride
(VII, $R_1 = R_2 = CH_3$), of N-acetylphenaceturyl chloride
(VII, $R_1 = CH_3, R_2 = CH_2C_6H_5$) and of N,N-diphenylacetyl-
glycyl chloride (VII, $R_1 = R_2 = CH_2C_6H_5$) were studied
simultaneously. The first compound represents an inter-
mediate from which the parent penicillin (I, $R = H$) is
potentially derivable, while the second compound could
give rise to either or both the parent penicillin or
benzylpenicillin (I, $R = C_6H_5$). The third acid
chloride would lead to benzylpenicillin.

Catalytic esterification of aceturic acid with
benzyl alcohol in toluene under reflux and simultaneous
removal of the water formed afforded the benzyl ester
(IX) in 91% yield. Treatment of IX with acetic anhydride
under conditions similar to those employed by Wiley and
Borum resulted in a 91% yield of N,N-diacylglycine-
benzyl ester (X). The melting points of IX and X are
almost identical, 50.5 to 51°, but a mixture of the two
begins to melt slightly above room temperature. The infrared spectrum of \( X \) contains bands at 5.70 and 5.85 \( \mu \) due to the ester and diamide carbonyl groups respectively and no \( \text{N-H} \) stretching bands. The shift in wavelength of absorption of diamide carbonyl groups from the value usually found for acyclic amides (6.0 \( \mu \)) is quite general. This shift to lower wavelength seems reasonable, since a relatively decreased contribution of resonance forms of the type given below to the true structure of diamides would be anticipated. \( \text{N,N-diacetyl glycine (XI)} \) was obtained in 97% yield by catalytic hydrogenolysis of \( X \). The acid, which was invariably isolated as a colorless glass, could not be induced to crystallize and decomposed upon standing at room temperature for several days to a dark brown mixture containing acetic acid. Exposure of XI to laboratory air is sufficient to cause hydrolysis to aceturic acid. The infrared spectrum of XI exhibits a broad band in the double bond region with center at 5.35 \( \mu \) due to a superposition of diamide and acid carbonyl bands. Attempts to convert XI to the corresponding acid chloride XII led to unstable, non-crystalline products, the infrared spectra of which
indicated the absence of the acid chloride function.

The preparation of benzyl N-acetylphenaceturate was readily accomplished by the route used for the synthesis of the corresponding diacetyl compound X. Benzyl phenaceturate (XIII) was prepared by three different procedures. The most practical (88% yield) involved direct catalytic esterification of phenaceturic acid with benzyl alcohol under essentially the same conditions used for the preparation of IX. In an alternative procedure phenaceturic acid was converted to 2-benzyl-5-oxazolone hydrobromide by treatment with phosphorus tribromide and the oxazolone hydrobromide transformed into XIII by the action of benzyl alcohol-pyridine. The overall yield by this route was 38%. A third synthesis involved phenyl-acetylation of glycine benzyl ester (XIV) in 92.5% yield. The hydrochloride of XIV was prepared in 32% yield by hydrazinolysis of phthaloylglycine benzyl ester (XV) which in turn was obtained from phthaloylglycyl chloride and benzyl alcohol in 38% yield. The preparation of XIV by hydrazinolysis of XV represents the most practical route to this compound yet reported. Treatment of XIII with acetic anhydride afforded a 68% yield of N-acetylphenaceturic acid benzyl ester (XVI). The acetylation of XIII proceeded more slowly than that of benzyl aceturate. The infrared spectrum of XVI was consistent with the assigned structure, exhibiting no N-H bands, a band due to the
ester carbonyl at 5.74 μ and a band due to the diamide carbonyls at 5.88 μ. Hydrogenolysis of XVI yielded 97.5% of the theoretical N-acetylphenaceturic acid (XVII) as a colorless glass which upon heating under reduced pressure to 70° underwent decomposition producing a sublimate of phenylacetic acid and a dark complex residue. The infrared spectrum of XVII is similar to that of XI and is characterized by an intense, broad band with center at 5.88 μ. An attempt to convert XVII to the acid chloride using phosphorus pentachloride in dioxane led to the formation of an unstable oil along with some phenylacetyl chloride. Little or none of the desired acid chloride was present in the crude product as judged by the infrared spectrum.

The method used for the preparation of X and XVI could not be applied satisfactorily to the preparation of N,N-diphenylacetylglucine benzyl ester (XVIII). Several attempts to prepare XVIII from benzyl phenaceturate (XIII) did not yield any isolable phenylacetylation product. Heating of XIII with phenylacetic anhydride or phenylacetetyl chloride alone and in the presence of bases resulted in extensive decomposition, although some starting material usually was isolated.

A second route to XVIII was investigated. N-Alkylation of α,α'-diphenyldiacetamide (XIX) with a
benzyl haloacetate would yield the desired benzyl ester. The diamide XIX was prepared in 70% yield from phenyl-acetonitrile and phenylacetic acid. The reaction is reversible and provides a good yield of XIX only when the equilibrium is disturbed by removal of the product at intervals. Treatment of XIX with sodium hydride in dioxane results in the formation of a soluble sodium salt (XX) which decomposes gradually on heating.

\[
(C_6H_5CH_2CO)_2NH \xrightarrow{\text{NaH}} (C_6H_5CH_2CO)_2N^- \xrightarrow{\text{Na}} \xrightarrow{\text{ICH_2COOCH_2C_6H_5}}
\]

\[\text{XIX} \quad \text{XX}\]

\[
C_6H_5C\text{HCONNH}_2 \quad + \quad (C_6H_5CH_2CO)_2NCH_2CO
\]

\[
\xrightarrow{\text{CH_2COOCH_2C_6H_5}} \quad C_6H_5CH_2O
\]

\[\text{XXI} \quad \text{XVIII}\]

Treatment of the sodium salt in dioxane with benzyl iodoacetate afforded after extensive chromatography a low yield (3.6%) of the desired alkylation product XVIII along with a small amount (2%) of a product which proved to be benzyl α-phenylsuccinamate (XXI). The structure of XVIII was proved by its facile hydrolysis

to XIII. The infrared spectrum of XVIII exhibits the same bands in the double bond region as do the analogous diamides, X and XVI. The by-product XXI is isomeric with, but different from, benzyl phenaceturate (XIII). Its infrared spectrum strongly supports the assignment of structure XXI. The spectrum taken in tetrachloroethane solution exhibits two sharp bands at 3.80 and 2.91 \( \mu \) attributable to N-H stretching vibrations, a band at 5.77 \( \mu \) due to the ester carbonyl, a band at 5.90 \( \mu \) assignable to the primary amide carbonyl and a strong band at 6.27 \( \mu \) due to the superposition of the weaker phenyl band with the more intense H-N-H bending band. The spectrum of the closely related phenylacetamide in solution shows identical bands at 2.80, 2.91, 5.92 and 3.37 \( \mu \) due to the primary amide function. Basic hydrolysis of XXI yielded phenylsuccinic acid.

The formation of XXI probably occurs by alkylation of phenylacetamide which can also be isolated from the reaction mixture. The presence of phenylacetamide seems best explained by postulating self-condensation of \( \alpha,\alpha' \)-diphenyldiacetamide (XIX) with formation of water, followed by partial hydrolysis of more XIX.

Attempted reaction of the sodium salt of XIX with benzyl chloroacetate, benzyl iodoacetate or potassium chloroacetate in toluene or methyl ethyl ketone yielded
no isolable XVIII. No further transformations of XVIII were attempted in view of its inaccessibility and the difficulties encountered in trying to prepare the acid chlorides derived from the N,N-diacyetyl acid XI and the N-acetyl,N-phenylacetyl compound (XVII).

The marked instability of acyclic N,N-diacylglycines and the corresponding acid chlorides is in sharp contrast with the stability of derivatives of cyclic N,N-diacylglycines such as succinoylglcylyl chloride or phthaloylglcylyl chloride. One possible reason for the rather large difference in stability might be the increased bond strengths inherent in the cyclic systems. A second possible explanation lies in the unique ability of derivatives of N,N-diacylglycines to undergo \( S_N \) i displacements of the following type:

\[
\begin{align*}
\text{R-O} & \xrightarrow{\text{COX}} \text{R-OX} + \left[ \begin{array}{c}
\text{R-C} \xrightarrow{\text{CO}} \\
\text{N-CH}_2 \\
\text{X-CO} \end{array} \right] \\
\text{or decomposition} \\
\text{products}
\end{align*}
\]

\( X = \text{OH, Cl} \)

Because of the structural rigidity of cyclic N,N-diacylglycines, decomposition by internal nucleophilic displacement is not possible. As a consequence of the latter explanation, it follows that the stability of a given acyclic system will depend to an appreciable extent upon
the nature, or specifically the ease of displacement of the acyl groups. It has been shown that in 0.1 N sodium hydroxide at 15° the hydrolysis of dibenzamide is approximately 250 times as slow as the hydrolysis of diacetamide.16 N,N-Dibenzoylglycine by analogy should be much more stable than N,N-diacylglucine. N,N-Dibenzoylglycine and the corresponding acid chloride have been synthesized and have proved to be quite stable.

Treatment of dibenzamide (XXII) with sodium hydride in ether resulted in formation of an insoluble sodium salt (soluble in dioxane). Removal of the ether and alkylation of the sodium salt with benzyl bromoacetate in methyl ethyl ketone produced N,N-dibenzoylglycine benzyl ester (XXIII) in 40% yield. The infrared spectrum exhibited no N-H stretching bands, a band at 5.72 μ due to the ester carbonyl and bands at 5.37 and 6.0 μ due to the diamide carbonyls. A more convenient route to XXIII proved to be through benzyl hippurate (XXIV) which was made from hippuric acid in 87% yield by the catalytic esterification process used in the preparation of XIII. Treatment of XXIV with phosphorus pentachloride furnished the imido chloride XXV which when treated with dry sodium benzoate in dioxane produced XXIII in 70% overall yield. This unusual reaction is patterned after one used by Mumm for the preparation of N-methyl dibenzamide.19

\[(\text{C}_6\text{H}_5\text{CO})_2\text{NH} \xrightarrow{1. \text{NaH}} (\text{C}_6\text{H}_5\text{CO})_2\text{NCH}_2\text{COOCH}_2\text{C}_6\text{H}_5\]  
\[\xrightarrow{2. \text{BrCH}_2\text{COOCH}_2\text{C}_6\text{H}_5} \]

XXII  
XXIII  

\[\text{C}_6\text{H}_5\text{CONHCH}_2\text{COOCH}_2\text{C}_6\text{H}_5 \xrightarrow{\text{PCl}_5} \text{C}_6\text{H}_5\text{C}=\text{NCH}_2\text{COOCH}_2\text{C}_6\text{H}_5\]  

XXIV  
XXV

The reaction probably involves production and rearrangement of an intermediate O-acylamide. The reversible

\[\text{C}_6\text{H}_5\text{C}-\text{NR}_2 + \text{C}_6\text{H}_5\text{COO}^- \xrightarrow{} \text{C}_6\text{H}_5\text{C}-\text{OCOC}_6\text{H}_5 \xrightarrow{} (\text{C}_6\text{H}_5\text{CO})_2\text{NR}_2 + \text{Cl}^-\]

formation of diamides such as XIX from carboxylic acids and nitriles may well proceed by a similar O to N migration of an acyl group.

\[\text{C}_6\text{H}_5\text{CH}_2\text{CN} + \text{C}_6\text{H}_5\text{CH}_2\text{COOH} \xrightleftharpoons{} \text{C}_6\text{H}_5\text{CH}_2\text{C}^+\text{NH} + \text{C}_6\text{H}_5\text{CH}_2\text{COO}^-\]

\[\text{C}_6\text{H}_5\text{CH}_2\text{CONHCOCH}_2\text{C}_6\text{H}_5 \xrightleftharpoons{} \text{C}_6\text{H}_5\text{CH}_2\text{COOCH}_2\text{C}_6\text{H}_5\]

XIX
Upon hydrogenolysis of XXIII, N,N-dibenzoylglycine (XXVI) was obtained as a colorless solid in 94% yield. The acid is quite stable, a sample showing no signs of decomposition after having been stored at room temperature for one year. Treatment of XXVI with phosphorus pentachloride provided the desired N,N-dibenzoylglycyl chloride (XXVII) as a moderately stable oil which could be stored at 0° for several days without appreciable decomposition. The infrared spectrum of XXVII is in complete agreement with that expected for the assigned structure. No O-H or N-H stretching bands are present. The band appearing at 5.87 μ is the highly characteristic acid chloride carbonyl band, while the bands at 5.90 and 5.03 μ are due to the diamide carbonyl groups. Reaction of XXVII with benzyl alcohol-pyridine led to the starting benzyl ester XXIII. Attempts to prepare a β-lactam from XXVII by reaction with 2-phenyl-2-thiazoline yielded no crystalline products.
Plate I

Curve A: N,N-Diacetylglycine Benzyl Ester (X), 5% in CHCl₃
Curve B: Benzyl N-Acetylphenaceturate (XVI), 5% in CCl₄
Curve C: N-Acetylphenaceturic Acid (XVII), 5% in Cl₂CHCHCl₂
Curve D: Benzyl α-Phenylsuccinamate (XXI), 5% in Cl₂CHCHCl₂
Curve E: Phenylacetamide, 5% in Cl₂CHCHCl₂
Curve F: N,N-Dibenzoylglycine Benzyl Ester (XXXIII), 5% in CCl₄
Curve G: N,N-Dibenzoylglycine (XXVI), 3.5% in CHCl₃
Curve H: N,N-Dibenzoylglycylic Chloride (XXVII), 5% in CCl₄
**EXPERIMENTAL**

**Benzyl Aceturate (IX).**—A mixture of 25.0 g. (0.214 mole) of aceturic acid, 35.0 g. (0.325 mole) of benzyl alcohol, 0.5 ml. of concentrated sulfuric acid and 400 ml. of toluene in a flask surmounted by a Soxhlet extraction apparatus containing ca. 200 g. of anhydrous barium oxide (Baker, C.P.) was heated to vigorous reflux for sixteen hours. The barium oxide was then replaced by 200 g. of fresh oxide and the mixture heated to reflux for an additional thirty-two hours. At the end of this time the solution was filtered and concentrated under reduced pressure to a light yellow oil. Upon distillation of the crude liquid there was obtained 40.3 g. (91.0%) of IX, b.p. 175-180° (1-1.2 mm.), nD 1.5250. Upon standing overnight at 4° the liquid crystallized to a colorless solid of m.p. 46.0-47.5°. Trituration of a small amount of this solid with petroleum ether followed by evaporative distillation at 130-140° (0.15 mm.) yielded a colorless oil which crystallized, m.p. 50.8-51.6°.

**Anal.** Calcd. for C₁₁H₁₃NO₃: C, 63.75; H, 6.32; N, 6.76.
Found: C, 63.78; H, 6.50; N, 6.86.

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20. All melting points are corrected. Infrared 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.

N,N-Diacetylglycine Benzyl Ester (X).—A solution of 35.0 g. (0.169 mole) of IX in 200 ml. of acetic anhydride was heated under reflux for five hours. The acetic anhydride was removed under reduced pressure and the residual oil evaporatively distilled at 140° (10 μ). The distillate, n^25_D 1.5200, crystallized completely on storage; m.p. 49-50° (38.2 g., 91%). Recrystallization from ether-ligroin afforded 33.0 g. of colorless needles, m.p. 50.6-51.2°. A second recrystallization from the same solvent did not affect the m.p.

Anal. Calcd. for C_{13}H_{15}NO_4: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.94; H, 6.37; N, 5.57.

N,N-Diacetylglycine (XI).—A mixture of 1.00 g. (0.00402 mole) of X and 0.100 g. of palladium-on-Darco catalyst^22 in 5 ml. of dry dioxane was treated with dry hydrogen. Reduction was complete in three hours, the absorption of hydrogen being 97% of the theoretical. Removal of the catalyst by filtration (Super-Cel) and lyophilization of the filtrate yielded 0.620 g. (97.2%) of a colorless, viscous oil which could not be induced to crystallize. After storage at room temperature in a sealed container for several days, the oil became dark brown in color and the odor of acetic acid could be

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detected easily.

\[
\text{Anal. Calcd. for } \text{C}_6\text{H}_9\text{NO}_4: \quad \text{C, 45.28; H, 5.70.}
\]
\[
\text{Found: \quad C, 46.38; H, 6.08.}
\]

Upon exposure of the oil to moist laboratory air a solid product formed rapidly which melted at 204 to 206° alone or admixed with aceturic acid.

Attempts to convert XI to the corresponding acid chloride using phosphorus pentachloride, purified thionyl chloride, acetyl chloride, phosgene or oxaly chloride (on the sodium salt) were unsuccessful.

**Phthaloylglycine Benzyl Ester (XV).**—A solution of 32.5 g. (0.10 mole) of phthaloylglycyl chloride in 40 ml. of ethylene dichloride was added over a period of five minutes to a cold (5°) solution of 10.9 g. (0.10 mole) of benzyl alcohol and 8.0 g. (0.10 mole) of dry pyridine in 30 ml. of ethylene dichloride. The mixture was allowed to stand at room temperature for one hour and then washed with three 20-ml. portions of water, 20 ml. of 4 N hydrochloric acid and finally 20 ml. of 5% potassium carbonate solution. The ethylene dichloride solution was dried by filtration and evaporated to dryness under reduced pressure to an almost colorless solid,

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m.p. 101.7-102.7°, 26.0 g. (88%). Recrystallization from ethanol-water yielded 24.2 g. of pure ester, m.p. 102.8-103.1°.

Anal. Calcd. for C\textsubscript{17}H\textsubscript{13}NO\textsubscript{4}: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.90; H, 4.60; N, 4.83.

**Glycine Benzyl Ester Hydrochloride (XIV).**—To a solution of 6.0 g. (0.0203 mole) of XV in 30 ml. of commercial absolute ethanol and 3 ml. of glacial acetic acid heated to reflux was added over a period of forty-five minutes 20 ml. of \( \text{M} \) hydrazine hydrate in absolute ethanol. The mixture was heated under reflux for an additional fifteen minutes and then concentrated to dryness under reduced pressure at a bath temperature of 50°. The residual solid was treated with 20 ml. of water and the insoluble phthalhydrazide was removed by filtration and washed with warm water. The combined filtrate and washings were cooled to 5°, treated with 7 g. of potassium carbonate and extracted with five 20-ml. portions of cold ether. The ethereal solution after drying (potassium carbonate) and treatment with dry hydrogen chloride furnished 1.30 g. (32.3%) of XIV, m.p. 135.0-136.0 (reported 139-140°)\textsuperscript{24} as colorless needles.

\textsuperscript{24} Harrington and Yead, Biochem. J., 30, 1609 (1936).
Benzyl Phenaceturate (XIII).—A. The procedure followed was the same as that described for the preparation of benzyl aceturate (IX). From 50.0 g. (0.258 mole) of phenaceturic acid, 100 g. (0.925 mole) of benzyl alcohol and 1 ml. of concentrated sulfuric acid in 600 ml. of toluene there was obtained after a sixteen hour heating period and evaporation of the solvent a light yellow oil consisting of crude product and benzyl alcohol. The liquid was caused to solidify by trituration with five 500-ml. portions of lukewarm water and 500 ml. of ice-cold water. The resulting oily solid was triturated with 500 ml. of water-methanol (4:1) to remove most of the remaining benzyl alcohol and collected by filtration. The crisp solid was washed with water-methanol, dried and recrystallized from benzene-ligroin to yield 65.0 g. (89.8%) of colorless needles, m.p. 94.2-94.6°. Recrystallization of a small amount of this product from chloroform-ligroin provided analytically pure XIII, m.p. 94.5-95.0°.

Anal. Calcd. for C₁₇H₁₇NO₃: C, 72.06; H, 6.05; N, 4.94.

Found: C, 71.82; H, 6.15; N, 5.00.

B. To an ether suspension of 2-benzyl-5-oxazolone hydrobromide† prepared from 5.50 g. (0.0285 mole) of phenaceturic acid and 7.1 g.

35. Reference 1, Chapter XXI, p. 781.
(0.026 mole) of phosphorus tribromide (Fisher, C.P.) was added 2.25 ml. (0.026 mole) of dry pyridine. The resulting mixture was shaken for a few minutes and then filtered. The insoluble solid was washed with ether and the filtrate plus washings treated with 3.0 ml. (0.025 mole) of benzyl alcohol. After standing for one and one-half hours, the solution was evaporated to a light yellow oil which crystallized upon storage in a refrigerator to an oily solid. Two recrystallizations of the crude product from chloroform-ligroin (Norit) yielded 3.0 g. (38%) of XIII, m.p. 94.5-95°.

C. To a solution of 2.01 g. (0.01 mole) of glycine benzyl ester hydrochloride and 2 ml. (1.96 g., 0.0248 mole) of dry pyridine in 25 ml. of dry methylene chloride was added 1.5 ml. (1.75 g., 0.0114 mole) of phenylacetyl chloride (Eastman Kodak). After fifteen minutes at room temperature, the methylene chloride solution was washed with 30 ml. portions of water, 2 N hydrochloric acid. and 5% sodium carbonate solution and dried by filtration. Evaporation of the methylene chloride under reduced pressure led to an almost colorless solid. Recrystallization of the crude product from benzene-ligroin (Norit) gave 2.62 g. (92.5%) of benzyl phenaceturate, m.p. 94-94.5°.
N-Acetylphenaceturic Acid Benzyl Ester (XVI).--A solution of 2.83 g. (0.01 mole) of XIII in 15 ml. of acetic anhydride was heated under reflux for fifteen hours. The acetic anhydride was evaporated under reduced pressure and the colorless residue triturated with cold, dry ether-petroleum ether solution (1:3). The solid mass which resulted was recrystallized from ether-petroleum ether, giving 1.50 g. of colorless needles, m.p. 61-62°. A second crop of product, m.p. 61-32°, was obtained by evaporation of the filtrate under reduced pressure and recrystallization of the semi-solid residue from ether-petroleum ether (Norit). The total yield of XVI was 2.40 g. (68%). Two recrystallizations of 0.80 g. of this material yielded 0.43 g. of pure product, m.p. 63.8-64.2°. A third recrystallization did not raise the m.p.

**Anal. Calcd. for C_{19}H_{19}NO_{4}:**
C, 70.14; H, 5.89; N, 4.31.
Found: C, 70.40; H, 5.88; N, 4.28.

N-Acetylphenaceturic Acid (XVII).--A mixture of 0.340 g. (0.001047 mole) of XVI and 0.045 g. of palladium-on-Darco catalyst in 3.0 ml. of pure dioxane was treated with dry hydrogen at atmospheric pressure. After three hours the absorption of hydrogen had ceased and corresponded to 99% of the theoretical. The catalyst was removed by filtration (Super-Cel) and the filtrate was
lyophilized. The residue, which was obtained as a colorless glass, weighed 0.240 g. (97.5%).

**Anal.** Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96.

Found: C, 61.45; H, 5.63; N, 6.05.

Upon heating a small portion of this acid at 70° and 2.5 mm. a colorless solid slowly collected on the walls of the tube, m.p. 75-76°, undepressed upon admixture with phenylacetic acid.

A 0.140 g. sample of XVII in 4 ml. of pure dioxane was treated with 0.124 g. of phosphorus pentachloride at 10°. The phosphorus pentachloride slowly reacted and a clear, colorless solution was formed. The dioxane and phosphorus oxychloride were removed by lyophilization, leaving a slightly yellow, oily residue. The strong, characteristic odor of phenylacetyl chloride was detected in the Dry Ice-trap. The infrared spectrum of the oil did not exhibit the band at 5.55 μ which is characteristic of acid chlorides.

$\alpha,\alpha'$-Diphenylacetamide (XIX).—A mixture of 304 g. (1.5 moles) of phenylacetic acid and 175.5 g. (1.5 moles) of phenylacetonitrile was heated by means of an oil bath to 185° in a nitrogen atmosphere for fifteen hours. At the end of this period the reaction mixture was allowed to cool to room temperature,
100 ml. of ether was added and the insoluble solid was collected by filtration. The colorless needles, m.p. 194-194.5°C (reported 192°C)\(^{17}\) weighed 132.0 g. The ether was removed from the filtrate and the residual liquid again was heated in a nitrogen atmosphere to 185°C for twelve hours. The product, which was isolated as described above, amounted to 53.9 g. Repetition of this process twice afforded 81 g. of XIX. The total yield of the diamide was 266.9 g. (70.3%).

**Alkylation of α,α'-Diphenylacetamide (XIX).**
A mixture of 5.28 g. (0.0208 mole) of XIX and 0.500 g. (0.0208 mole) of finely powdered sodium hydride in 100 ml. of purified dioxane was stirred in an atmosphere of nitrogen for fifteen minutes. To the resulting clear solution was added 5.70 g. (0.0206 mole) of benzyl iodoacetate, which had been freshly prepared from benzyl chloroacetate and sodium iodide in dry acetone, dissolved in 40 ml. of dioxane. The reaction mixture was stirred at room temperature for fourteen hours and finally for four hours at 70-80°C. The mixture was allowed to cool to room temperature and the colorless, insoluble solid was collected by filtration, washed with petroleum ether and dried at 20 mm. for twenty minutes. The solid (7.0 g.), which was readily soluble in water, was a dioxane solvate of sodium iodide. Titration with standard silver nitrate
solution indicated that it contained 2.7 g. of sodium iodide (87% of the theoretical). The filtrate was evaporated under reduced pressure to a straw-colored syrup which was triturated with six 30-ml. portions of petroleum ether and allowed to stand under a seventh 30-ml. portion of the same solvent for two hours. The petroleum ether was decanted and the residue was treated with 30 ml. of hot carbon tetrachloride. After one day the cooled mixture was filtered, yielding a residue of 1.0 g., m.p. 185-190° alone or admixed with XIX. The filtrate was concentrated to an oil which was dissolved in 30 ml. of benzene and passed through a 25 x 1 cm. column of activated alumina (Alcoa, 48-100 mesh). The column was washed with 15 ml. of benzene and the resulting benzene solutions combined (fraction 1). Evaporation of this fraction afforded a light brown oil from which no crystalline material could be obtained after further chromatography. The column was then washed with successive portions of benzene (20 ml., fraction 2), benzene-chloroform (30 ml., 1:1, fraction 3), chloroform (30 ml., fraction 4) and dioxane (30 ml., fraction 5). Evaporation of the fractions individually furnished straw-colored syrups which were triturated with petroleum ether and allowed to stand. After thirteen days fractions 3, 4, and 5 had partially crystallized and the solid material was
freed of oil in each case by trituration with carbon tetrachloride. The solid products, m.p. 104-106°, were combined and amounted to 0.302 g. (3.8%). One recrystallization from carbon tetrachloride-ether-petroleum ether (after treatment of the solution with a mixture of Norit and activated alumina) provided fine, colorless needles of XVIII, m.p. 107.8-108.4°. Another recrystallization from the same solvent did not raise the m.p.

Anal. Calcd. for C_{35}H_{23}NO_{4}: C, 74.79; H, 5.77; N, 3.49.

Found: C, 74.60; H, 5.95; N, 3.79.

A small portion of this product (ca. 30 mg.) was dissolved in acetone and the solution treated with 1.5 ml. of 0.1 N sodium hydroxide. After 5 minutes the solution was diluted with water and extracted with methylene chloride. The methylene chloride extract was evaporated to a faintly yellow solid which upon recrystallization from ligroin had m.p. 93-94°, undepressed upon admixture with XIII.

Further washing of the column of alumina with dioxane afforded a small amount (0.072 g.) of a product, m.p. and mixed m.p. with phenylacetamide 158-159° after recrystallization from chloroform-carbon tetrachloride.
The carbon tetrachloride soluble portions of fractions 3, 4 and 5 were combined and after removal of the carbon tetrachloride were dissolved in 30 ml. of benzene-petroleum ether (4:1) and passed through a 35 x 1 cm. column of activated alumina. The column was eluted with 25 ml. portions of benzene (fraction 1), benzene-carbon tetrachloride (fraction 2), carbon tetrachloride (fraction 3), ether (fraction 4), dioxane-carbon tetrachloride (2:1, fraction 5), dioxane (fraction 6) and dioxane (fraction 7). From fractions 5, 6 and 7 there was obtained after concentration, triturating with petroleum ether and recrystallization from methylene chloride-carbon tetrachloride 0.118 g. of XXI as a colorless solid, m.p. 98-100.5°. Further recrystallization from carbon tetrachloride yielded analytically pure material m.p. 99.5-101°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.14; N, 5.20.

A small portion of this product (0.035 g.) was treated with boiling 10⁻² sodium hydroxide solution for 15 minutes. The odors of both benzyl alcohol and ammonia were detected. The basic solution was cooled, acidified with 12 N hydrochloric acid and extracted with ether. The ether solution was evaporated and the residual solid was recrystallized from ether-benzene to yield ca. 0.012 g. of phenylsuccinic acid, m.p. 166-167°.
Dibenzamide XXII.—The following procedure is a modification of that used by Titherley. To a stirred solution of 30.25 g. (0.250 mole) of benzamide and 150 ml. of dry pyridine (technical, dried by distillation from barium oxide) and 150 ml. of dry ether at -30° was added dropwise 35.25 g. (0.251 mole) of benzoyl chloride over a period of fifty minutes. The resulting thick mixture was stirred at -30 to -10° for five hours and then placed in a refrigerator and allowed to stand at +4° overnight. The mixture was filtered to remove the insoluble pyridine hydrochloride and the solid was washed thoroughly with ether. The combined filtrate and washings, after being diluted to a volume of 700 ml. with ether, were extracted with two 500-ml. portions of water, two 500-ml. portions of 2 N sulfuric acid and a final 500-ml. portion of water. Upon standing XXII separated from both the aqueous washes and the ethereal solution as colorless needles. These fractions when combined amounted to 23.0 g. (49.7%), m.p. 144-145° (reported 144°). Evaporation of the ethereal mother liquor produced an oil which consisted mainly of benzonitrile.

**Benzyl Hippurate (XXIV).**—This preparation was carried out essentially by the procedure described for benzyl phenaceturate. From 90.0 g. (0.50 mole) of hippuric acid (Eastman Kodak), 81.0 g. (78 ml., 0.75 mole) of benzyl alcohol in 300 ml. of toluene and 1 ml. of concentrated sulfuric acid after heating to reflux for ten hours there was obtained as colorless needles 117 g. (87%) of pure product, m.p. 87.0-88.0° (reported 91-92°). The yield of XXIV by this procedure after a four hour heating period was 87%.

**N,N-Dibenzoylglycine Benzyl Ester (XXIII).**—A. To a suspension of 0.300 g. (0.0125 mole) of finely powdered sodium hydride in 25 ml. of dry ether was added 2.25 g. (0.010 mole) of dibenzamide. A vigorous reaction took place immediately, subsiding after about fifteen seconds. The resulting mixture was stirred for one hour to insure complete formation of the sodium salt and then the ether was evaporated and replaced by 35 ml. of dry methyl ethyl ketone (Eastman Kodak, distilled from and stored over Drierite). A solution of 4.0 g. (0.176 mole) of benzyl bromoacetate in 30 ml. of methyl ethyl ketone.

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was added along with 1.5 g. (0.01 mole) of dry sodium iodide. The reaction mixture was heated at reflux for twenty-two hours. To the cooled mixture was added 100 ml. of ether, and the insoluble inorganic salts were removed by filtration. The filtrate was concentrated under reduced pressure to a yellow syrup which solidified after trituration with three 40-ml. portions of ether-petroleum ether. The crude oily solid weighed 2.60 g. (fraction 1). The ether-petroleum ether solution upon standing yielded 0.20 g. of an almost colorless solid (fraction 2), m.p. 111-113°. Fraction 1 was triturated with 20 ml. of ether and the insoluble solid (1.60 g.) was recrystallized from methylene chloride-methylcyclohexane to yield 1.20 g. of pale yellow prisms, m.p. 105.5-113° (fraction 3). The ether solution was evaporated to a semi-solid residue which, after trituration with petroleum ether and recrystallization from methylene chloride-methylcyclohexane, furnished 0.30 g. of almost colorless solid, m.p. 107-113° (fraction 4). Fractions 2, 3 and 4 were combined and recrystallized from methylene chloride-methylcyclohexane (Norit). The yield of colorless prisms, m.p. 114.0-115.3° was 1.51 g. (40.5%). A small sample was further purified for analysis by evaporative distillation at 145° (5 μ). The material so obtained had m.p. 114.5-115.5°.

Anal. Calcd. for C_{25}H_{19}NO_{4}: C, 73.48; H, 5.13; N, 3.75.
Found: C, 73.78; H, 5.22; N, 3.77.
The yields of XXIII ranged from 11% when the alkylation was carried out in dioxane to 27% when acetone was used as the solvent. The product in both cases was not isolated in pure condition as readily as in the procedure described.

To a solution of 32.4 g. (0.120 mole) of benzyl adipurate dissolved in 50 ml. of dry dioxane was added 300 ml. of anhydrous ether and 25.0 g. (0.120 mole) of phosphorus pentachloride. The mixture was swirled until the phosphorus pentachloride had dissolved (ten minutes) and the resulting clear yellow solution was evaporated under reduced pressure (25 mm., bath temperature not over 50°) to remove the dioxane and phosphorus oxychloride present. To the residual yellow liquid was added 20 ml. of toluene and the toluene along with the last traces of phosphorus oxychloride removed by distillation at 25 mm. A solution of the imido chloride in 100 ml. of dry dioxane was added to a stirred suspension of 28.0 g. of dry sodium benzoate in 100 ml. of dioxane. The mixture was heated to 65° with stirring for twelve hours and then heated to reflux for an additional four hours. After cooling, the insoluble solid was removed by filtration and washed well with dioxane. Evaporation of the filtrate under reduced pressure afforded a light yellow syrup which soon crystallized. The solid was triturated with 45 ml. of ether and ground to a powder. The mixture was filtered and the
powder was washed with four 20-ml. portions of ether-petroleum ether (7:3). The almost colorless product, m.p. 111.6-114.0 weighed 32.0 g. The filtrate and washings were concentrated to an oil which yielded 1.70 g. of XXIII, m.p. 112-114°, after trituration with petroleum ether and recrystallization of the residue from ether-methylcyclohexane. Recrystallization of the combined crude products from methylene chloride-methylcyclohexane yielded a first crop of 26.8 g., m.p. 114.0-115.0 and a second crop of 4.50 g., m.p. 113.5-114.5° (70%). An additional amount of less pure XXIII was obtained from the filtrate.

Reaction of the imido chloride XXV in ether with an aqueous solution of sodium benzoate resulted in a 35% yield of XXIII. Reaction in dimethylformamide led to a low yield (28%) of a product which was difficult to purify.

**N,N-Dibenzoylglycine (XXVI).**--A mixture of 10.0 g. (0.0263 mole) of XXIII and 1.00 g. of palladium-on-Darco catalyst in 45 ml. of dry dioxane was shaken with hydrogen at three atmospheres. Consumption of hydrogen was complete after five hours and the absorption was approximately the theoretical. The catalyst was removed by filtration (Super-Gel) and washed with five 5-ml. portions of dioxane. The filtrate and washings were combined and
concentrated under reduced pressure to a colorless oil which crystallized upon trituration with 20 ml. of dry ether. The solid, m.p. 136-137.2°, was collected by filtration and after drying weighed 5.60 g. From the filtrate there was obtained an additional 1.53 g. of solid upon slow evaporation. The total yield of analytically pure product was 7.13 g. (94.5%).

Anal. Calcd. for C_{18}H_{13}NO_{4}: C, 67.84; H, 4.62; N, 4.95. Found: C, 67.78; H, 4.76; N, 5.02.

N,N-Dibenzoylglucylyl Chloride (XXVII).—A mixture of 0.100 g. (0.354 millimole) of XXVI and 0.074 g. (0.354 millimole) of phosphorus pentachloride in 2 ml. of dry dioxane was allowed to react at room temperature. After the phosphorus pentachloride had completely dissolved, the dioxane and phosphorus oxychloride were removed by lyophilization and the oily residue was taken up in 3.0 ml. of dry carbon tetrachloride. The spectrum of the acid chloride was determined using a portion of this solution.

To 1.5 ml. of the above solution of XXVII at 0° was added a solution of 0.035 g. (0.324 millimole) of benzyl alcohol and 0.025 g. (0.317 millimole) of dry pyridine in 4 ml. of carbon tetrachloride. The resulting mixture was allowed to stand for twelve hours and then filtered to remove the insoluble pyridine hydrochloride.
The filtrate was evaporated under reduced pressure to a yellow oil which solidified upon trituration with methylcyclohexane-ether (2:1) and seeding. The solvent was removed by decantation and the residue was recrystallized from methylene chloride-methylcyclohexane to yield 0.060 g. (ca. 60%) of colorless prisms, m.p. 114.5-115.0, undepressed upon admixture with pure XXIII.

Larger scale preparations of the acid chloride were carried out by the same procedure. Upon storage for a few days at room temperature XXVII underwent extensive decomposition with the formation of a dark, viscous mixture containing benzoyl chloride, which was detected by odor. Benzoyl chloride also resulted when a small sample of the acid chloride was heated to 70° in a sublimation apparatus at 13 mm. Addition of aniline to the almost colorless distillate resulted in the formation of benzanilide, m.p. 162-163°.

No crystalline product could be isolated upon addition of triethylamine under high-dilution conditions to a solution of XXVII and 2-phenyl-3-thiazoline in methylene chloride. Addition of a cold (-70°) solution of the acid chloride XXVII and triethylamine in methylene chloride to a solution of 2-phenyl-3-thiazoline likewise did not lead to crystalline material, even after extensive chromatography.
PART II

A STUDY OF

2-BENZYLIDENE-3-OXAZOLIDINE-4,5-DIONES
INTRODUCTION

The work set forth in the second part of this thesis involves the preparation of 2-benzylidene-4,5-diketo-3-oxazolidineacetic acid and some of its derivatives and a study of the methods by which the heterocycle can be degraded to compounds possessing the phenylacetylamino grouping.

Since acylamino acid halides are not accessible, 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 an acid chloride 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 have been mentioned briefly earlier. They 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 extremely labile under some well-defined conditions which do not greatly affect penicillin and which result in formation of the phenylacetylamo grouping.

The failure of simple acyl functions to serve as suitable protecting groups in acyclic \( N,N \)-diacylglycyl chlorides led to a consideration of other potentially useful acid chlorides.

During the war-time program of research on penicillin, the reaction of oxalyl chloride with several model \( N \)-monosubstituted amides and benzylpenicillin itself was investigated as a means of detecting and characterizing amides.\(^{39}\) \( N \)-Benzylphenylacetamide, for example, yielded upon treatment with oxalyl chloride the solid oxazolidinedione XXVIII. It was reported that XXVIII could be hydrolyzed readily to the parent \( N \)-benzylphenylacetamide. The conversion of \( N \)-monosubstituted amides to oxazolidinediones, therefore, appeared to be a method for temporarily masking the phenylacetyl-

\(^{39}\) Reference 1, Chapter VIII, p. 239.
amino grouping. If this method were utilized, the synthesis of a β-lactam-thiazolidine bearing a phenyl-acetylamino substituent would involve the preparation of a diketo-oxazolidyl-β-lactam-thiazolidine and selective cleavage of the oxazolidinedione nucleus with formation of the corresponding phenylacetamide.
DISCUSSION

In view of the possible use of oxazolidinediones in the indirect introduction of the phenylacetylamino substituent into fused β-lactam-thiazolidines, a synthesis of the required acid chloride, 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (XXX) was developed.\(^{30}\) Reaction of phenaceturic acid with oxalyl chloride in dioxane afforded 2-benzylidene-4,5-diketo-3-oxazolidineacetic acid (XXIX) in 95% yield. Upon treatment of XXIX with phosphorus pentachloride the desired acid chloride XXX was obtained as a stable, crystalline solid.

\[
\begin{align*}
C_6H_5CH=CNCH_2COY \\
\text{XXX, } Y = \text{OH} & \quad \text{XXXI, } Y = \text{NHC}_6\text{H}_5 \\
XXX, Y = \text{Cl} & \quad \text{XXXII, } Y = \text{OCH}_2\text{C}_6\text{H}_5
\end{align*}
\]

Treatment of XXX with aniline or benzyl alcohol resulted in formation of the corresponding anilide (XXXI) or benzyl ester XXXII. The benzyl ester XXXII could be obtained more readily and in 91% yield by treatment of benzyl phenaceturate with oxalyl chloride. The infrared

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30. After the inception of this work a publication appeared describing the preparation of XXX by a similar method and in lower yield. G. B. Brown, Arch. Biochem., 24, 429 (1949).
spectra of XIX-XXXII exhibit bands in the double bond region at 5.50, 5.73 and 5.95 \( \mu \) which are highly characteristic of the heterocyclic system.

At the beginning of the present work the available information concerning the conversion of oxazolidinediones to acylamino compounds was meager. An investigation of the chemistry of these compounds with particular emphasis on ring-cleavage reactions was therefore undertaken.

Structures involving the oxazolidinedione nucleus were first postulated by Stolle' and Luther\(^{31}\) as the products of the reaction of oxalyl chloride with anilides. These investigators considered the product of the reaction of oxalyl chloride with acetanilide as being best represented by the oxazolidinedione structure XXXIII rather than the isomeric pyrrolidinetrione structure XXXIV, because it reacted readily with water to form acetic acid and oxanilic acid. The compound also gave no coloration

\[
\begin{align*}
\text{XXXIII }, R = H & \quad \text{XXXIV }, R = H \\
\text{XXXVI }, R = \text{CH}_3 & \quad \text{XXXV }, R = \text{CH}_3
\end{align*}
\]

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\(^{31}\) R. Stolle' and H. Luther, Ber., 53, 314 (1920).
with ferric chloride solution. Additional support for the oxazolidinedione structure for these products may be drawn from the work of Wislicenus and Sattler,\textsuperscript{32} who prepared the pyrrolidinetrione XXXV by the base-catalyzed condensation of ethyl oxalate with propionic acid anilide. The structure was inferred from analytical data and from the fact that the compound showed all the properties expected of an enol. An isomeric compound was prepared by Figeé,\textsuperscript{33} who made the first study of the action of oxalyl chloride on amides, by reaction of oxalyl chloride with propionic acid anilide. This compound showed no signs of being an enol and, as pointed out by Stolle and Luther, is best represented by the oxazolidinedione structure XXXVI rather than XXXV which had been proposed by Figeé.

Recently Skinner and Perkins\textsuperscript{34} have prepared a series of twenty-five compounds by the action of oxalyl chloride on amides and have proposed structures with pyrrolidinetrione nuclei rather than oxazolidinedione nuclei for the products. The compounds were non-enolic, easily cleaved by alkali and showed three bands in the

\footnotesize
\begin{itemize}
  \item 32. W. Wislicenus and W. Sattler, Ber., 24, 1845 (1921).
  \item 33. T. Figeé, Rec. trav. chim., 34, 301 (1915).
\end{itemize}
double bond region of the infrared at 5.6 μ, 5.8 μ and 6.0 μ, which according to these investigators "agree remarkably well" with the pyrroolidinetrione structure. Since the infrared spectra of the oxazolidinediones studied in the present investigation exhibit similar bands and since the structures of these compounds have been unequivocally proved (vide infra), there can be little doubt that the compounds prepared by Skinner and Perkins are actually oxazolidinediones.

It should be noted that there are two possible end products in the hydrolysis of oxazolidinediones, one the parent acylamino compound XXXVII and the other an oxalylamino derivative XXXVIII. Hydrolysis of XXXIII

\[
\begin{align*}
\text{XXXIII, } R &= \text{H, } R' = \text{C}_6\text{H}_5 \\
\text{XXXVIII, } R &= \text{C}_6\text{H}_5, \ R' = \text{CH}_2\text{C}_6\text{H}_5
\end{align*}
\]

apparently leads to cleavage of the intermediate N,N-diacyl compound by route B, while hydrolysis of XXXVIII has been reported as taking place by route A. \(^{29}\) Unfortunately in the latter case the yield of N-benzylphenyl-
acetamide was not reported, so that it is not possible to tell whether cleavage occurred appreciably by reaction B. Although the general statement\(^\text{29}\) has been made that "2-benzylideneoxazolidine-4,5-diones revert on mild hydrolysis to the parent phenylacetamides," no further examples of the hydrolysis of these compounds appear in the literature.

It was discovered during the course of the penicillin program that oxazolidinediones are susceptible to alcoholysis in the presence of small amounts of pyridine. The preparation of methyl N-ethoxalylphenaceturate (XXXIX) by the ethanolysis of the oxazolidinedione XL was described without mention of yield.\(^\text{29}\) The assignment of structure XXXIX to the alcoholysis product was based upon an independent synthesis of the same compound from methyl phenaceturate and ethoxalyl chloride.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH} = \text{C} & \quad \text{NCH}_2\text{COOCH}_3 \\
\text{O} & \quad \text{C}_6\text{H}_5\text{CH}_2\text{CO} \quad \text{NCH}_2\text{COOCH}_3 \\
\text{XL} & \quad \text{C}_6\text{H}_5\text{COOCC}_2\text{H}_5 \\
\text{C}_6\text{H}_5\text{CH}_2\text{CONHCH}_2\text{COOCH}_3
\end{align*}
\]
The possibility of structure XLI for the alcoholysis product obviously is not rigorously excluded on the basis of

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH} &\equiv \text{C} \quad \text{NHCH}_2\text{COOC}_2\text{H}_5 \\
\text{O} &\quad \text{O} \\
\text{C}_2\text{H}_5\text{OOCCO} \\
\text{XLI}
\end{align*}
\]

this evidence. The facile alcoholysis of the heterocyclic ring was interpreted as evidence establishing the validity of the assigned oxazolidinedione structures. It may also be argued, however, that the pyrroolidinetrione ring might undergo alcoholysis, since it represents an especially reactive 1,3-dicarbonyl system.

One example of the preparation of an N-substituted phenylacetamide by aminolysis of oxazolidinediones is described in the penicillin monograph. Treatment of the oxazolidinedione XL with benzylamine furnished a 30% yield of methyl phenaceturate. Another example of the cleavage of oxazolidinediones by benzylamine has been reported by Brown\textsuperscript{30} who prepared N-(N-phenylacetylglucyl)-\text{-}DL-valine in 74% yield.

Since no conclusions can be drawn from these data concerning the relative efficiencies of hydrolysis, alcoholysis or aminolysis procedures in regenerating phenylacetamides from the corresponding oxazolidinediones, a study of each of these methods was made.
An examination of the base-catalyzed hydrolysis of the anilide XXXI and the benzyl ester XXXII revealed interesting differences. The anilide upon treatment in acetone with three equivalents of 0.1 N sodium hydroxide afforded the desired anilide of phenaceturic acid in 39% yield. The benzyl ester, however, upon treatment with two equivalents of base yielded no benzyl phenaceturate, but only an acidic, yellow sirup which upon standing furnished a very small amount of a yellow, crystalline solid, XLII (vide infra). When XLII was treated with ferric chloride a dark green coloration was produced. It was insoluble in water, but dissolved readily in aqueous sodium carbonate with the formation of an orange solution. In both the hydrolysis of XXXI and of XXXII some phenylacetic acid (identified by odor) was produced. Upon slow titration of XXXI with only one equivalent of base and acidification of the reaction mixture, there was produced a yellow, acidic solid analysis of which indicated that it was not the expected acid XLIII, but rather, a compound isomeric with the starting material. This product, obtained in 30% yield, was insoluble in water, but soluble in base with formation of a deep yellow-orange color. A dark green coloration similar to that obtained from XLII was formed upon treatment of the product with ferric chloride. These
facts, together with the infrared spectrum of the compound, indicated that it is actually 4-phenyl-2,3,5-triketo-1-pyrrolidineacetonilide XLIV in equilibrium with the corresponding enol. The infrared spectrum

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{CO} & \quad \text{HOOCCO} \quad \text{N}-\text{R} \\
\text{C}_6\text{H}_5\text{CH} &= \text{C-} \quad \text{N}-\text{R} \\
\text{O} & \quad \text{CO} \quad \text{CO} \quad \text{1. OH}^- \\
\text{2. H}_3\text{O}^+ \\
\text{XLIII} & \quad \text{XXXI} \\
\text{C}_6\text{H}_5\text{CH} &= \text{CO} \\
\text{CO} & \quad \text{CO} \quad \text{N}-\text{R} \\
\text{XLIV} \\
\end{align*}
\]

\[
\text{R} = \text{CH}_2\text{CONHC}_6\text{H}_5
\]

of solid XLIV exhibits a weak band at 5.62 \( \mu \) and a stronger band at 5.38 \( \mu \) which together are characteristic of the succinimido ring. No bands appear which are assignable to the enol form of XLIV.

The rather unusual transformation of XXXI to XLIV occurs to a very small extent if at all under the conditions previously described for the conversion of XXXI to phenaceturic acid anilide, i.e. using three equivalents of base. This fact renders untenable the assumption of a reaction path involving simple O to C migration of the oxalyl grouping. If the reaction proceeds via the free acid XLIII, as seems likely, the presence of a large amount of base could have two
effects: (a) cause loss of the oxalyl group by cleavage of the diamide with resulting formation of phenaceturic acid anilide before cyclization could occur or (b) completely convert the acid to its salt which would undergo cyclization at a very slow rate or not at all. Either effect would explain the experimental observations.

In any event the isolation of the pyrrolidinetrione XLIV constitutes the first unequivocal proof of the correctness of the oxazolidinedione formulation, rather than the pyrrolidinetrione structure, for the reaction products of substituted phenylacetamides with oxalyl chloride.

The effectiveness of hydrolysis procedures in the formation of phenylacetamides from 2-benzylideneoxazolidinediones seemed quite unsatisfactory, the main side reactions involved being loss of the phenylacetyl group during hydrolysis and the formation of intractable yellow oils, probably by competing condensations of the intermediate hydrolysis products.

The possibility of preparing the desired phenylacetamides by a combination of alcoholysis to diamides, such as XXXIX, and further hydrolysis was studied simultaneously. The benzyl ester XXXII was allowed to react with warm ethanol containing a trace of pyridine to form the alcoholysis product, XLV, which without isolation was treated with one equivalent of aqueous sodium hydroxide.
There was obtained by extraction of the basic solution a 15% yield of the desired product, benzyl phenaceturate. Acidification of the orange-colored aqueous phase afforded a yellow, insoluble solid which was isomeric with XXXII and identical with the solid obtained earlier (XLII) in low yield. The product, which was obtained in 47% yield, seems best represented as the pyrrolidinetrione XLII in equilibrium with the corresponding enol. Treatment

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH} & \overset{\alpha}{\text{CO}} \text{NCH}_2\text{COOC}_2\text{H}_5 \rightleftharpoons \text{C}_6\text{H}_5\text{CH} & \overset{\alpha}{\text{CO}} \text{NCH}_2\text{COOC}_2\text{H}_5 \\
\text{CO} & \overset{\beta}{\text{CO}} \text{NCH}_2\text{COOC}_2\text{H}_5 & \overset{\beta}{\text{CO}} \text{NCH}_2\text{COOC}_2\text{H}_5
\end{align*}
\]

of XLII with 2,4-dinitrophenylhydrazine afforded the dinitrophenylhydrazone, while diphenyldiazomethane reacted to form the enol ether.

The infrared spectrum of XLII in solution exhibited a weak band at 5.62 \(\mu\) and a strong band at 5.85 \(\mu\) as did the pyrrolidinetrione XLIV. The presence of the enol form of XLII is also indicated by the infrared spectrum. There appear unassociated and associated O-H stretching bands at 2.97 and 3.08 \(\mu\) in addition to a band at 6.22 \(\mu\) which is probably due to the \(\alpha\)-carbonyl group of the enol. The latter assignment is supported by the occurrence of a similar shift in the spectra of
β-amino-α,β-unsaturated ketones. The band at 5.95 μ probably arises from the β-imide carbonyl of the enol present. The spectrum of the dinitrophenylhydrazone of XLII shows the 5.63 and 5.88 μ bands which arise from the succinimido carbonyls, but no 5.95 or 6.22 μ band.

The formation of XLII may have occurred by a number of routes: (a) base-catalyzed cyclization of the alcoholysis product XLV during the alcoholysis, (b) base-catalyzed cyclization of XLV during the basic hydrolysis or (c) cyclization of the acid XLVI which may have been formed during the hydrolysis. It should

\[ \text{XLV, } R = \text{C}_2\text{H}_5 \]
\[ \text{XLVI, } R = \text{H} \]

be pointed out that the formation of XLVI is not unlikely since esters of oxalic and oxamic acids are saponified with great rapidity.


Alcoholysis of the benzyl ester XXX in hot, absolute ethanol containing a trace of pyridine provided in addition to the expected product, XLV, the pyrrolidinedione XLII. The relative amounts of XLV and XLII formed depends on the length of the heating period. When heating was carried on only until all of the starting material has been dissolved (ca. thirteen minutes) the yield of XLV was 74% and that of XLII 12.8%. After a twenty-five minute heating period the yields of XLV and XLII were 35 and 44% respectively, while after three hours the yields were 0 and 84% respectively. It should be mentioned that XLV represents the correct structure of the alcoholysis product of the benzyl ester XXXII rather than XLVII. The substance is non-basic and possesses an infrared spectrum which is clearly inconsistent with XLVII. The spectrum exhibits no N-H stretching bands and shows bands at 5.72, 5.80 and 5.85 μ which are assignable to the ester and diamide carbonyls.

It is evident that XLII is formed not by O to C migration of an acyl group, but through the intermediate XLV. Furthermore, O to C migration could not be effected even under forcing conditions. The benzyl ester XXXII could not be caused to rearrange to the pyrrolidinedione

37. Part I.
XLII by heating either with sodium hydride or pyridine in dioxane. Treatment of XLV, however, with sodium hydride in dioxane afforded a 63\% yield of XLII. Hydrolysis of XLV with one equivalent of sodium hydroxide furnished only a 27\% yield of benzyl phenaceturate.

Treatment of the benzyl ester XXXII with two equivalents of benzylamine resulted in rapid formation of benzyl-phenaceturate (XIII) in 66\% yield along the second cleavage product, N,N'-dibenzyl oxamide. Use of phenylhydrazine as the base led to a 69\% yield of XIII, while the less reactive methylamine gave a 53\% yield. Aniline and piperidine were found to be unsatisfactory. The anilide XXXI formed phenaceturic acid anilide in 51\% yield upon treatment with benzylamine. These results strongly indicate that aminolysis represents the most practical procedure for the conversion of 2-benzylidene-oxazolidine-4,5-diones to the parent phenylacetamides.
Plate II

Curve A: Benzyl 2-Benzylidene-4,5-diketo-3-oxazolidineacetate (XXXII), 3% in Cl₂CHCHCl₂

Curve B: 2-Benzylidene-4,5-diketo-3-oxazolidineacetyl Chloride (XXX), 1% in Cl₂CHCHCl₂

Curve C: 3-Phenyl-2,4,5-triketoppyrrolidineacetanilide (XLIV), Nujol mull

Curve D: Benzyl 3-Phenyl-2,4,5-triketoppyrrolidineacetate (XLII), 5% in Cl₂CHCHCl₂

Curve E: 2,4-Dinitrophenylhydrazone of XLII, Nujol mull.

Curve F: N-Ethoxalylphenaceturic Acid Benzyl Ester (XLV), 5% in Cl₂CHCHCl₂
EXPERIMENTAL

2-Benzylidene-4,5-diketo-3-oxazolidineacetic Acid (XXIX).—To a solution of 32.2 g. (0.1667 mole) of phenaceturic acid in 280 ml. of dry dioxane (heated to 65° to effect solution and cooled to room temperature) was added 25.0 g. (0.197 mole) of oxalyl chloride (Eastman Kodak). There was an immediate reaction which was accompanied by the evolution of heat and formation of a yellow solution. The reactants were allowed to stand for fourteen hours and at the end of this time the mixture was filtered and the yellow solid was washed with dioxane, dioxane-benzene and petroleum ether. After being dried at 65° (30 mm.) the product, m.p. 205°(dec.) (reported 221°), amounted to 20.1 g. The original filtrate and the dioxane-benzene washes were evaporated under reduced pressure until most of the solvent had been removed. Benzene (250 ml.) was then added and the solid was collected by filtration, washed and dried, giving an additional 19.0 g. of product, m.p. 305°(dec.). The total yield of XXIX was 39.1 g. (94.7%). One recrystallization from dioxane-benzene yielded analytically pure material, m.p. 212° (dec., in bath at 205°).
3-Benzylidene-4,5-diketo-3-oxazolidineacetyldichloride (XXX).—The acid XXIX (15.0 g., 0.0609 mole), which had been thoroughly dried in vacuo, was dissolved in 175 ml. of dry dioxane by heating to ca. 70°. The solution was cooled to 40° and 12.70 g. (0.061 mole) of finely-ground phosphorus pentachloride was added all at once. The reaction mixture was swirled intermittently for one-half hour and the resulting clear solution was evaporated to dryness under reduced pressure. The pressure was regulated during the concentration so that the temperature of the boiling solution was 50°. Toward the end of the concentration the product separated from the supersaturated liquid as dense, thick, yellow plates. (If the evaporation is carried out at a lower temperature, the product crystallizes as fine needles and yields a fluffy, light solid which is less convenient to use). The residual solid was flushed with two 40 ml. portions of dry toluene, triturated with 30 ml. of benzene and collected by pressure filtration (using dry nitrogen). After having been washed with three 30-ml. portions of dry petroleum ether and dried in vacuo, the bright yellow solid weighed 15.0 g. (93.3%) and melted at 190.0 to 191.5° (dec., in bath at 184°). 30

3-Benzylidene-4,5-diketo-3-oxazolidineacetanilide (XXXI).—To 1.50 g. (0.00565 mole) of XXX in 10 ml. of
dry dioxane and 10 ml. of dry benzene at 5° was added dropwise a solution of 1.05 g. (0.113 mole) of aniline in 5 ml. of benzene. The mixture was allowed to stand at room temperature for twenty minutes and filtered. The yellow solid was washed with carbon tetrachloride, dried and suspended in 50 ml. of water. The aqueous suspension was filtered and the insoluble solid was washed well with water and with a little methanol. After drying in vacuo the solid, m.p. 258-261°, weighed 1.55 g. (85.2%). Recrystallization from 40 ml. of dioxane and 40 ml. of benzene yielded 1.30 g. of fine yellow needles, m.p. 360-362° (in bath at 250°).

Anal. Calcd. for C₁₈H₁₄N₂O₄: C, 67.07; H, 4.38; N, 8.69.

Found: C, 68.88; H, 4.54; N, 8.52.

The anilide is difficult to handle because of the ease with which it becomes electrically charged.

Benzyl 2-Benzylidene-4,5-diketo-3-oxazolidine-acetate (XXXII).—To a solution of 8.49 g. (0.030 mole) of benzyl phenaceturate in 30 ml. of dry dioxane was added 3.0 ml. of oxalyl chloride. After two hours the mixture was evaporated to dryness and the yellow solid (8.7 g.) was collected by filtration. The solid was recrystallized by dissolving in 50 ml. of hot dioxane and adding a hot solution of 50 ml. of benzene and 30 ml. of ligroin. The heterocycle crystallized as fine yellow needles,
m.p. 178-179°, and amounted to 8.30 g. (91%). A small amount of the substance (0.100 g.) was recrystallized from hot benzene (6.5 ml.) to yield analytically pure XXXII, m.p. 178.0-179.0°.

**Anal. Calcd. for C₁₉H₁₅N₂O₅:** C, 67.65; H, 4.48; N, 4.15.
**Found:** C, 67.39; H, 4.61; N, 4.23.

The benzyl ester (XXXII) could also be obtained from XXX. A mixture of 0.100 g. (0.377 millimole) of the acid chloride, 0.0406 g. (0.377 millimole) of benzyl alcohol and 0.0298 g. (0.377 millimole) of pyridine was allowed to react in 20 ml. of dry benzene. After fifteen minutes the mixture was filtered and 40 ml. of petroleum ether added to the yellow filtrate. The flocculent, yellow solid which precipitated was collected by filtration and recrystallized from benzene-methylcyclohexane to give 0.070 g. of XXXII, m.p. 177.5-180°.

**Hydrolysis of XXXI.** To 0.200 g. (0.620 millimole) of the anilide XXXI suspended in 10 ml. of acetone was added 17.34 ml. of 0.1074 N sodium hydroxide. The solid had completely dissolved after a few minutes, and the resulting yellow solution was warmed on a steam bath to expel most of the acetone. Upon cooling, a colorless precipitate formed. The mixture was extracted with three 30-ml. portions of chloroform and the chloroform solutions were combined and dried by filtration. Evaporation of the
chloroform yielded 0.065 g. (39.2%) of a colorless solid, m.p. 154-156°, mixed m.p. with phenaceturic acid anilide, 156-160°. Upon acidification of the aqueous solution the characteristic odor of phenylacetic acid could be detected easily. Extraction of the acidified solution with methylene chloride and evaporation of the extract furnished a small amount of intractable yellow oil.

B. To a solution of 0.400 g. (0.00124 mole) of XXXI in 35 ml. of dioxane at room temperature was added 12.0 ml. of 0.1074 N sodium hydroxide over a period of forty-five minutes. The orange solution was evaporated under reduced pressure to a volume of 5 ml. The concentrate was taken up in 15 ml. of water, acidified and extracted with ether. The ether extract was evaporated to dryness and the residual yellow solid was recrystallized from ethanol-water to yield 0.118 g. (29.5%) of XLIV as yellow needles, m.p. 236.5-237.5° (in bath at 330°).

**Anal. Calcd. for C₁₈H₁₄N₄O₄:** C, 67.07; H, 4.38; N, 3.69.
**Found:** C, 66.99; H, 4.35; N, 8.52.

Treatment of XLIV with alcoholic ferric chloride solution resulted in the immediate formation of a dark green coloration.
Hydrolysis of XXXII.—A solution of 0.500 g. (0.001485 mole) of XXXII in 40 ml. of acetone was cooled to 0° and treated with 28.0 ml. of 0.1074 N sodium hydroxide. The solution was allowed to warm up to room temperature. After one-half hour the orange solution was concentrated under reduced pressure to remove the acetone and the resulting aqueous solution was extracted with chloroform. Upon evaporation of the chloroform extract there remained a small amount (ca. 0.07 g.) of a yellow oil from which no crystalline material could be isolated. Acidification of the aqueous layer and extraction with chloroform afforded, after removal of the chloroform, a yellow oil which was triturated with, and kept under, carbon tetrachloride. After standing for four days a small amount of the oil had crystallized. The solid was separated from the oil and recrystallized from carbon tetrachloride-ligroin. The yield of XLII, m.p. 134-136°, was 0.012 g.

Combined Alcoholysis and Hydrolysis of XXXII.—A mixture of 1.00 g. (0.00293 mole) of XXXII, 25 ml. of absolute ethanol and one small drop of dry pyridine was heated on a steam bath until all of the solid had dissolved (ca. thirteen minutes). To the resulting yellow solution was added ca. 20 g. of ice and one drop of
phenolphthalein indicator. The cold solution was titrated slowly with 0.1074 N sodium hydroxide, fresh portions of base being added when the color of the indicator disappeared. After eight minutes 36.0 ml. of (0.0028 mole) of base had been added and the color of the indicator faded at a very slow rate. The cold solution was extracted with chloroform, and the chloroform extract was evaporated under reduced pressure to an oil which partially solidified upon trituration with petroleum ether. The semi-solid residue was triturated further with four 10-ml. portions of methanol-water solution (1.5:1) and the resulting crisp solid, m.p. 88-90° (0.170 g.) was recrystallized from benzene-ligroin to yield 0.125 g. (15%) of benzyl phenaceturate, m.p. 90.0-93.2°, undepressed upon admixture with an authentic sample.

The bright orange solution from the chloroform extraction was acidified with 4 N hydrochloric acid and the resulting pale yellow solution was allowed to stand. After two hours the precipitate of fine yellow needles which had formed was collected by filtration, washed with water and dried in vacuo to yield 0.470 g. (47%) of XLII, m.p. 136.8-137.7°. Upon heating the color of the solid faded to a very pale yellow. A sample which had been placed in the heating bath at 125° melted immediately, indicating slow conversion to the less strongly
colored and higher melting keto form of XLI on heating. Recrystallization of the bright yellow solid (0.200 g.) from carbon tetrachloride furnished 0.156 g. of XLI as pale yellow needles, m.p. 137.8-138.4°.

**Anal. Calcd. for C₁₉H₁₅N₂O₅: C, 67.65; H, 4.48; N, 4.15; w.w. 337.**

**Found: C, 67.27; H, 4.63; N, 4.10; w.w. (Rast) 392.**

Treatment of XLI with alcoholic ferric chloride resulted in the formation of a dark green coloration similar to that obtained from XLIV.

The 2,4-dinitrophenylhydrazone of XLI was prepared by heating 0.100 g. (0.296 millimole) of the substance with a solution of 0.300 g. of 2,4-dinitrophenylhydrazine in 15 ml. of hot ethanol (95%) and 0.4 ml. of 12 N hydrochloric acid. Upon cooling, an orange-yellow precipitate formed which was collected by filtration, washed well with ethanol and dried. The solid, m.p. 235-237°, amounted to 0.060 g. (39.2%). Recrystallization from dioxane (5 ml.) and water (3 ml.) afforded the yellow dinitrophenylhydrazone as a dioxane solvate, m.p. 238.5-240.5°. Upon addition of the first few drops of water to the yellow dioxane solution, a green coloration developed which persisted until the separation of the product was complete.
Anal. Calcd. for C$_{25}$H$_{19}$N$_5$O$_8$·1/2 C$_4$H$_8$O$_2$: C, 57.75;
H, 4.13; N, 12.47.

Found: C, 57.53;
H, 3.95; N, 12.61.

When the crude product was purified by leaching with hot ethyl acetate, pure, unsolvated material, m.p. 243.2-244.3°, was obtained.

Anal. Calcd. for C$_{25}$H$_{19}$N$_5$O$_8$: C, 58.03; H, 3.70; N, 13.54.

Found: C, 58.04; H, 3.88; N, 13.46.

A solution of the dinitrophenylhydrazone becomes bright blue upon addition of a small amount of water.

The benzhydryl enol ether of XLII was prepared by treatment of 0.050 g. (0.149 millimole) of the heterocycle dissolved in 3 ml. of ether with a solution of 0.030 g. (0.155 millimole) of diphenyl diazomethane in 2 ml. of ether. After twelve hours the ether was evaporated and the residual oil caused to solidify by trituration with two 5-ml. portions of petroleum ether. Recrystallization of the solid from carbon tetrachloride-petroleum ether furnished 0.040 g. (53.5%) of the enol ether, m.p. 127.0-128.5°. Another recrystallization from the same solvent yielded 0.030 g. of thick, yellow plates, m.p. 128.5-129.5°.

Anal. Calcd. for C$_{32}$H$_{35}$O$_5$N: C, 76.32; H, 5.01; N, 2.78.

Found: C, 75.67; H, 5.08; N, 2.77.
Alcoholysis of XXXII.--A suspension of 1.25 g. (0.00372 mole) of XXXII in 10 ml. of absolute ethanol containing a trace of pyridine was heated on a steam bath until all the solid had dissolved (thirteen minutes). The solution was cooled, seeded with XLIV and allowed to stand at 5° for one hour. The crystalline precipitate was collected by filtration, washed with a little cold ethanol and dried. The yield of colorless needles, m.p. 99-100° was 1.05 g. (74%). An analytical sample was prepared by two recrystallizations from ethanol, m.p. 100.0-100.7°.

Anal. Calcd. for C_{21}H_{21}NO_{6}: C, 65.79; H, 5.52; N, 3.65.
Found: C, 65.34; H, 5.63; N, 3.51.

The ethanol filtrate was evaporated under reduced pressure to a yellow oil which was taken up in 3 ml. of carbon tetrachloride, seeded with XLII and allowed to stand. The yield of XLII was 0.160 g. (12.8%), m.p. 137.0-137.8°.

In similar experiments it was found that the yield of XLV was decreased upon increasing the length of the heating period, while the yield of XLII was increased. The products were isolated by the procedure described above.

Alcoholysis of XXXII occurred much less readily when t-butanol was used, and it was necessary to heat the reactants under reflux for eight hours to effect
complete reaction. The colorless t-butyl ester had m.p. 126.3-127.5°.

Found: C, 67.22; H, 6.31; N, 3.51.

Ethanolysis of methyl 2-benzylidene-4,5-diketo-3-oxazolidineacetate, m.p. 188.5-189.0° (reported 186-187°) employing a minimum heating period (fifteen minutes) also yielded two products, contrary to earlier observations.

Both \( \text{N-ethoxalylphenaceturic acid methyl ester, m.p. 97.3-98.5° (reported 95-97°)} \) and methyl 3-phenyl-2,4,5-triketo-pyrrolidineacetate, m.p. 134.2-135.3°, (pale yellow needles from carbon tetrachloride) were formed.

Anal. Calcd. for \( \text{C}_{13}\text{H}_{11}\text{NO}_{5} \): C, 59.77; H, 4.25; N, 5.36. 
Found: C, 59.50; H, 4.30; N, 5.34.

**Reaction of XLV with Sodium Hydride.**—To a solution of 0.630 g. (0.00174 mole) of XLV in 20 ml. of dry dioxane was added 0.045 g. (0.00187 mole) of finely-powdered sodium hydride, and the mixture was heated to reflux in an atmosphere of nitrogen for forty minutes. The resulting clear orange solution was concentrated to an oil which was induced to crystallize by trituration with 10 ml. of water containing six drops of 6 N hydrochloric acid. Recrystallization of the solid (0.50 g.) from carbon tetrachloride provided 0.380 g. (68%) of XLII, m.p. 137.4-138.4°.
In a similar experiment XXXII was recovered unchanged after treatment with an equimolar amount of sodium hydride in dry dioxane.

**Reaction of XLV with Aqueous Sodium Hydroxide.**—To a solution of 0.100 g. (0.361 millimole) of XLV in 5 ml. of 95% ethanol and 1.5 ml. of dioxane at 0° was added 0.361 ml. of 1.00 N sodium hydroxide. After standing at 0° for five minutes, the solution was diluted with water and extracted with chloroform. The chloroform extract was filtered and evaporated under reduced pressure to a yellow oil which solidified upon trituration with petroleum ether. Further trituration of the solid with water-methanol yielded almost colorless benzyl phenaceturate (0.020 g., 27.1%），m.p. 94-95°.

**Aminolysis of XXXII.**—To a suspension of 0.350 g. (0.00104 mole) of the heterocycle in 10 ml. of dry benzene was added 0.242 g. (0.00208 mole) of benzylamine. Reaction took place immediately and after ten minutes the colorless solid which had precipitated was collected by filtration. The yield of \(\text{N,N'}\)-dibenzylxoxamide, m.p. 220.5-222.0° was 0.275 g. (93.5%). Evaporation of the filtrate and trituration of the residue with petroleum ether afforded benzyl phenaceturate as an almost colorless solid (0.200 g., 93%), m.p. 93-94°. Pure material, m.p. 93.6-95.0, (0.156 g.) was obtained after one recrystallization
from benzene-ligroin.

Treatment of XXXII with phenylhydrazine resulted in the formation of benzyl phenaceturate in 69\% yield, while methylamine after a reaction time of twelve days yielded 53\% of the theoretical benzyl phenaceturate along with only 71.5\% of the theoretical \( \text{N, N'}-\text{dimethyl-oxamide} \).

**Aminolysis of XXXI.**—From 0.300 g. (0.931 milli-mole) of XXXI suspended in 10 ml. of dry dioxane and 15 ml. of benzene there was obtained, after treatment with 1.99 g. (1.86 millimoles) of benzylamine for twelve hours, 96\% of the theoretical \( \text{N, N'}-\text{dibenzyl-oxamide} \), m.p. 220-222° and 61\% of the theoretical phenaceturic acid anilide, m.p. 158.0-162°, undepressed upon admixture with an authentic sample.
PART III

SYNTHESSES OF \( \beta \)-LACTAMS

DERIVED FROM 2-BENZYLIDENE-3-OXAZOLIDINE-4,5-DIONES
INTRODUCTION

The work to be described in this part consists of the application of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (XXX) to the formation of β-lactams. A new route to β-lactams possessing the phenylacetylamino grouping has been developed and has been used to prepare the first synthetic β-lactam-thiazolidine with the phenylacetylamino substituent characteristic of benzylpenicillin.
DISCUSSION

The use of 2-benzylidene-4,5-diketo-3-oxazolidine-acetyl chloride (XXX) in the synthesis of fused β-lactam-thiazolidines possessing a phenylacetylamino substituent seemed feasible, because XXX appeared to fulfill to a large extent the stringent requirements outlined in Part II. The acid chloride is a readily accessible, stable compound and its derivatives can be converted to phenylacetamides under fairly mild conditions.

The reaction of XXX with 2-phenyl-2-thiazoline and triethylamine was first studied. The transformations to be described are outlined in Figure I. Addition of triethylamine under high-dilution conditions to a solution of XXX and the thiazoline in methylene chloride resulted in a 45% yield of the β-lactam XLVIII. The infrared spectrum of XLVIII is in complete accord with the β-lactam formulation. In addition to bands at 5.50, 5.73 and 5.95 μ which are characteristic of the oxazolidinedione nucleus there appears a strong band at 5.62 μ which is assignable to the β-lactam carbonyl. Treatment of the β-lactam XLVIII with two equivalents of benzylamine produced the desired phenylacetylaminolactam XLIX in 32% yield and the β-lactam derived from the alternative cleavage (L) in 21% yield. The infrared spectra of both XLIX and L exhibit bands
Figure I

\[ \text{XXX} \]

\[ \text{XLVIII} \]

\[ \text{XLIX} \]

\[ \text{L} \]
Figure I (Cont'd)

XLIX + $\text{KMnO}_4 \rightarrow \begin{array}{c}
\text{H}_2\text{C} & \text{CH}_2 \\
\text{O}_2\text{S} & \text{N} & \text{C}=\text{O} \\
\text{C}_6\text{H}_5 & \text{H} & \text{C} & \text{NH} \\
\text{C}_6\text{H}_5\text{CH}_2\text{CO}
\end{array} \xrightarrow{\text{H}_2} \begin{array}{c}
\text{H}_2\text{C} & \text{CH}_2 \\
\text{O}_2\text{S} & \text{N} & \text{C}=\text{O} \\
\text{C}_6\text{H}_5 & \text{H} & \text{C} & \text{N} & \text{CO} \\
\text{O} & \text{--CH}_2\text{C}_6\text{H}_5
\end{array}

\text{LI} \quad \text{LII}

XLVIII + \text{NH}_3 \rightarrow \begin{array}{c}
\text{H}_2\text{C} & \text{CH}_2 \\
\text{S} & \text{C} & \text{N} & \text{C}=\text{O} \\
\text{C}_6\text{H}_5 & \text{H} & \text{N} & \text{COCH}_2\text{C}_6\text{H}_5 \\
\text{COCONH}_2
\end{array}

\text{LIV}
near 5.6 \( \mu \) indicating that the \( \beta \)-lactam ring has not been ruptured. The lactam XLIX is the first synthetic \( \beta \)-lactam-thiazolidine which possesses a 6-phenylacetyl-amino substituent.

The benzylamine cleavage of XLVIII occurred much less rapidly than the corresponding reaction with either of the model compounds XXXI or XXXII. This fact, together with the formation of both of the possible cleavage products from XLVIII, indicates that the substituent attached to the nitrogen atom in oxazolidine-4,5-diones exerts a significant effect upon the ease and nature of ring cleavage. The same effect appears to be operative in the basic hydrolyses of XXXI and XXXII which were described in Part II.

Oxidation of XLIX under carefully controlled controlled conditions led to the sulfone LI in 32\% yield. The sulfone LI is identical with the compound prepared by Laubach\(^{11}\) by hydrogenolysis of the heterocyclic lactam LII. Samples prepared by the two routes had the same decomposition point, and essentially identical infrared spectra and X-ray powder diffraction patterns. The infrared spectrum of LI shows a band due to the \( \beta \)-lactam carbonyl at 5.56 \( \mu \), whereas the unoxidized lactam exhibits a band at 5.67 \( \mu \). A similar shift occurs in going from penicillin itself to the sulfone.\(^{38}\) Since

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38. Reference 1, Chapter XIII, p. 409.
samples prepared by the two routes are identical, the reaction of 2-phenyl-3-thiazoline with XXX follows the same stereochemical course as the reaction with the acid chloride (LIII) used by Laubach.

\[
\begin{array}{c}
\text{C}_6\text{H}_5\text{CH} -\text{CO} \\
\text{O} \quad \text{NCH}_2\text{COCl}
\end{array}
\]

LIII

Treatment of XLVIII with excess ammonia under anhydrous conditions resulted in a 44% yield of LIV. The infrared spectrum has a band at 5.63 \( \mu \) indicating the presence of the \( \beta \)-lactam ring.

Reaction of XXX with benzalaniline and triethylamine yielded the \( \beta \)-lactam LV in 18% yield. The infrared spectrum of LV possesses sharp bands at 5.50 and 5.90 \( \mu \) characteristic of the oxazolidine-4,5-dione nucleus and a broad band with center at 5.7 \( \mu \) which probably arises from both the \( \beta \)-lactam carbonyl and the oxazolidinedione nucleus. Although there is a possibility of forming two stereoisomeric lactams, only one could be isolated. The lactam LV reacts slowly and incompletely with two equivalents of benzyleamine to yield only 15% of the theoretical \( N,N' \)-dibenzylxoxamide along with a complex mixture of other products. This appears to be another example of
the significant effect of the nitrogen substituent on
the cleavage of oxazolidine-4,5-diones.

The same 3-lactam (LV) can be prepared in low
yield (17%) by the action of oxalyl chloride on 1,4-
diphenyl-3-phenylacetylamino-2-azetidinone (LVI), which
was first synthesized by Ryan. In Ryan's synthesis,
the phthalimido-lactam LVII, which was prepared from

\[
\begin{align*}
&\text{LVI, } X = \text{NHCOCH}_2\text{C}_6\text{H}_5 \\
&\text{LVII, } X = \text{phthalimido} \\
&\text{LVIII, } X = \text{NH}_2
\end{align*}
\]

phthaloylglycyl chloride and benzalaniline, was converted
by hydrazinolysis to the free amino lactam LVIII, which
in turn was phenylacetylated to give the desired product, LVI.

The racemic 3-lactams, LV, LVI and LVII are thus
interrelated as members of the same stereochemical series,
the reaction of benzalaniline proceeding stereochemically
in the same direction with XXX as with phthaloylglycyl
chloride. This evidence, together with that presented
earlier, seems to indicate that the stereochemical course
of the acid chloride-imine or thiazoline reaction is not
highly dependent upon the nature of the acid chloride.

The reaction of the acid chloride XXX with methyl 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate LIX was also studied. This thiazole was prepared from D-penicillamine methyl ester hydrochloride, ethyl benzimidate hydrochloride and triethylamine by the procedure used by Buhle and purified by chromatography. The product so obtained (93% yield) was almost analytically pure and possessed a much higher optical rotation than the products previously isolated, which were purified by distillation. No crystalline addition products could be isolated upon reaction of the acid chloride XXX, the thiazoline LIX and triethylamine under a variety of conditions. It was also observed that the reaction of succinoylglycyl chloride with optically active LIX led to no isolable $\beta$-lactam. Under the same conditions optically inactive LIX readily yielded racemic lactam.11

Several attempts to prepare a $\beta$-lactam from XXX and methyl 5,5-dimethyl-2-thiazoline-4-carboxylate LX likewise afforded no crystalline addition product. The infrared spectra of the amorphous materials invariably obtained from the reaction did not seem to indicate the presence of $\beta$-lactam. The crude product showed no biological activity when tested by conventional penicillin assay methods.
The preparation of 2-methylene-4,5-diketo-3-oxazolidineacetyl chloride LXI was briefly investigated, since it is sterically less complex than XXX and might react more readily with LIX. The size and shape of the LXI molecule is almost the same as succinoylglycyl chloride, which reacts with LIX to give a β-lactam. The

\[
\begin{array}{c}
\text{H}_2\text{C} \\
\text{O} \\
\text{N-CH}_2\text{COCl} \\
\text{CO-OC}
\end{array}
\]

LXI

corresponding acid LXII was prepared in 51% yield from aceturic acid and oxalyl chloride. The conditions for the preparation of LXII are much more critical than those required for the preparation of the corresponding benzylidene derivative XXIX, since LXII is much less readily formed. Treatment of LXII with phosphorus pentachloride produced an unstable oil which was probably the corresponding acid chloride (LXI). Because of the extreme instability of the product, its use was not investigated further.
Plate III

Curve A: 2-Phenyl-α-(2-benzylidene-4,5-diketo-3-oxazolidyl)-2-thiazolidineacetic Acid β-Lactam (XLVIII), 5% in Cl₂CHCHCl₂

Curve B: 2-Phenyl-α-(phenylacetylamino)-2-thiazolidineacetic Acid β-Lactam (XLIX), 5% in Cl₂CHCHCl₂

Curve C: 2-Phenyl-α-(N-benzyloxalamylamino)-2-thiazolidineacetic Acid β-Lactam (L), 1C% in Cl₂CHCHCl₂

Curve D: Sulfone of XLIX, prepared from XLVIII, 5% in Cl₂CHCHCl₂

Curve E: Sulfone of XLIX, prepared from LII, 6% in Cl₂CHCHCl₂

Curve F: LIV, 5% in Cl₂CHCHCl₂

Curve G: 1,4-Diphenyl-3-(2-benzylidene-4,5-diketo-3-oxazolidyl)-2-azetidinone (LV), 5% in Cl₂CHCHCl₂
Plate IV

X-Ray Powder Diffraction Patterns

Upper pattern: LI from XLVIII
Lower pattern: LI (slight impurity of LII) from LII
EXPERIMENTAL

3-Phenyl-α-(2-benzylidene-4,5-diketo-3-oxazolidyl)-
3-thiazolidineacetic Acid β-Lactam (XLVIII).—To 3.00 g.
(0.01134 mole) of the acid chloride XXX dissolved in 20 ml.
of dry dioxane in a 250-ml., three-necked flask was added
1.85 g. (0.01140 mole) of 2-phenyl-2-thiazoline\(^9\) in 20 ml.
of methylene chloride (dried over Drierite). The solution
was stirred and heated to rapid reflux in an atmosphere
of nitrogen, while a solution of 1.15 g. (1.6 ml., 0.0114
mole) of triethylamine in 45 ml. of methylene chloride
was added dropwise through a high-dilution cycle.\(^9\) The
time required for the addition was six and one-half hours.
The resulting dark solution was concentrated under reduced
pressure to a volume of 10 ml., treated with 40 ml. of
benzene and the mixture filtered to remove the insoluble
triethylammonium chloride, 1.425 g. (91%). Evaporation
of the filtrate under reduced pressure yielded a sirup
from which a crystalline solid soon separated. Trituration
of the magma with a mixture of 20 ml. of methylene chloride
and 5 ml. of benzene provided, after filtration and wash-
ing with two 5-ml. portions of methylene chloride-benzene
(4:1), 1.55 g. of a bright yellow solid, m.p. 186-187°
(dec., in bath at 180°). After concentration of the fil-
trate to a volume of 5 ml., the oily residue was seeded
with lactam and allowed to stand overnight. The resulting mixture was triturated with 100 ml. of acetone-water (65:35) and filtered. Further trituration of the insoluble solid with six 10-ml. portions of acetone-water (7:3) furnished, after drying in vacuo, an additional 0.425 g. of light yellow solid, m.p. 187-187.5° (dec., in bath at 184°). The total yield of XLVIII was 2.02 g. (44.5%). A sample was prepared for analysis by dissolving 0.500 g. of the lactam in 20 ml. of methylene chloride and allowing the solution to evaporate in an open beaker. The bright yellow prisms which had formed at the bottom of the beaker were collected and recrystallized twice from methylene chloride-methylcyclohexane to yield 0.208 g. of pure lactam, m.p. 189.2-190.4° (dec., in bath at 184°).

Anal. Calcd. for C_{31}H_{16}N_{2}O_{4}S: C, 54.27; H, 4.11; N, 7.14.

Found: C, 54.32; H, 4.18; N, 7.31.

Attempted oxidation of XLVIII to a sulfone using potassium permanganate in a buffered water-dioxane solution (pH 6.7) did not lead to any crystalline product. A qualitative test on XLVIII for sulfur was positive.

Reaction of XLVIII with Benzylamine.—To 0.150 g. (0.382 millimole) of pure XLVIII dissolved in 5 ml. of dry dioxane was added 0.90 ml. (0.863 millimole) of a solution of 1 ml. of benzylamine in 9 ml. of dioxane.
The solution was allowed to stand for seventeen hours at room temperature and then for two hours at 65°. Removal of the solvent under reduced pressure and trituration of the residue with petroleum ether afforded 0.215 g. of a light yellow powder. The crude mixture upon trituration with 6 ml. of acetone-benzene solution (5:1) and filtration furnished 0.051 g. (49.5%) of N,N'-dibenzylxoxamide, m.p. 221-223°. To the filtrate was added 5 ml. of benzene and the resulting solution concentrated to a volume of 3 ml. and cooled to 10°. The insoluble solid, m.p. 185-200° (dec.)(0.009 g.) was discarded and the solution evaporated to dryness under reduced pressure. The residue was treated with 7 ml. of hot ethanol (95%) and the solution was filtered while hot. Upon cooling 0.031 g. (21%) of a colorless solid, m.p. 173-174° (dec., in bath at 167°) separated. Recrystallization of this material from 7 ml. of ethanol and four drops of water gave 0.021 g. of pure L, m.p. 173.6-174.0 (dec., in bath at 169°), as fine colorless needles.

**Anal.** Calcd. for C$_{30}$H$_{19}$N$_3$O$_3$: C, 62.97; H, 5.02; N,11.02.

Found: C, 62.96; H, 5.23; N,11.00.

The ethanol filtrate was evaporated to a volume of 2 ml. and treated slowly with 5 ml. of hot water. Upon cooling a faintly yellow, oily solid was deposited which amounted to 0.081 g. Trituration of the solid with two
4-mL. portions of ether-petroleum ether (1:1) yielded 0.060 g. of a colorless powder, which was further purified by boiling with 7 ml. of carbon tetrachloride and removing the insoluble material, 0.0074 g., m.p. 160-170° (dec.), by filtration. The soluble material was recovered by evaporation of the filtrate to 1.5 ml. and addition of 4 ml. of hot ligroin. The resulting solid was recrystallized from 4 ml. of hot ethanol and 1 ml. of water to yield 0.041 g. (31.7%) of XLIX, m.p. 124.8-126.5°. Recrystallization from ethyl acetate-methylcyclohexane (Norit) led to 0.030 g. of pure lactam as fine needles, m.p. 126.0-126.5°.

**Anal.** Calcd. for C₁₉H₁₈N₂O₂S: C, 37.40; H, 5.36; N, 8.28. 
Found: C, 37.66; H, 5.49; N, 8.57.

Sulfone of 3-Phenyl-α-(phenylacetylamino)-2-thiazolidineacetic Acid β-Lactam (LI).—To 0.0340 g. (0.100 millimole) of XLIX in 3 ml. of acetone (reagent) was added 2 ml. of a solution made up from 0.3 g. of glacial acetic acid, 3.0 g. of sodium acetate trihydrate and 9 ml. of water. The resulting solution was cooled to 0° and 0.030 g. (0.195 millimole) of potassium permanganate dissolved in 4 ml. of acetone-water (1:1) was added dropwise over a period of five minutes. The reaction mixture was allowed to stand at 0° for three and one-half hours and at the end of this period was treated
dropwise with 3% hydrogen peroxide until a clear, colorless solution resulted. After diluting the solution with 2 ml. of water, the colorless, insoluble solid was collected by filtration. It amounted to 0.0050 g., m.p. 194.0-194.5 (dec., in bath at 187°).

The filtrate was treated with 5 ml. of water and concentrated in a stream of air until most of the acetone had been removed. The insoluble solid was collected by filtration, 0.0120 g. (32.4%) m.p. 140.0-140.5° (dec.) (reported 140.5°, dec.). A mixture of this product and a sample prepared by Laubach had m.p. 140.0-140.5° (dec.). Recrystallization from chloroform-carbon tetrachloride furnished 0.010 g. of LI as fine needles, m.p. 144.5-145° (dec.).

Ammonolysis of XLVIII.—To a cold (0°) solution of 0.150 g. (0.382 millimole) of the lactam XLVIII in 5 ml. of dry dioxane and 5 ml. of ether was added 9.45 ml. of a 0.121 M solution of anhydrous ammonia in dioxane. The flask was tightly stoppered, and the reactants were allowed to stand at 0° for two hours and at room temperature for six days. The resulting pale yellow solution was evaporated under reduced pressure to an oil which, when triturated with 10 ml. of ether, afforded 0.101 g. of a light tan powder. Recrystallization of the crude material from 5 ml. of ethanol (95%) (Norit) yielded 0.050 g. of colorless needles, m.p. 138.5-139.0°
(dec.). An additional 0.018 g. of LIV was obtained from the mother liquors, m.p. 138.5-139.0 (dec.). An analytical sample which was prepared by recrystallization from ethanol-water had the same m.p.

Anal. Calcd. for C$_{21}$H$_{19}$N$_3$O$_4$S: C, 61.60; H, 4.68; N, 10.26; S, 7.83.

Found: C, 61.69; H, 4.89; N, 10.39; S, 7.75.

1,4-Diphenyl-3-(2-benzylidene-4,5-diketo-3-oxazolidyl)-2-azetidinone (LIIV).—A. To a well-stirred solution of 3.62 g. (0.020 mole) of benzalaniline and 1.01 g. (1.39 ml., 0.010 mole) of triethylamine in 50 ml. of dry methylene chloride was added dropwise a solution of 3.65 g. (0.010 mole) of XXX in 20 ml. of dioxane and 50 ml. of methylene chloride. The time required for the addition was one-half hour. The dark solution was concentrated to a volume of 30 ml. after addition of 40 ml. of dioxane and the insoluble triethylammonium chloride (1.14 g., 33%) was separated by filtration. The filtrate was evaporated under reduced pressure to a dark brown oil which was triturated with 100 ml. of anhydrous ether and dissolved in 15 ml. of chloroform. The chloroform solution was treated with 15 ml. of carbon tetrachloride and allowed to stand. After two hours there was obtained from the ether and chloroform-carbon tetrachloride solutions
1.12 g. and 0.150 g. respectively of impure product. Recrystallization of the combined, crude fractions from chloroform-carbon tetrachloride yielded 0.850 g. (15.85%) of the lactam LV as fine, yellow needles, m.p. 247-248°. A second recrystallization from the same solvent furnished analytically pure material, m.p. 248.0-249.3°.

Anal. Calcd. for C_{25}H_{18}N_{2}O_{4}: C, 73.16; H, 4.42; N, 6.83.

Found: C, 73.37; H, 4.57; N, 6.80.

When treated with two equivalents of benzylamine the lactam LV reacted sluggishly, yielding a mixture from which only 15% of the theoretical amount of N,N'-dibenzyl-oxamide was isolated.

3. To a solution of 0.150 g. (0.423 millimole) of 1,4-diphenyl-3-phenylacetylamino-2-azetidinone^3,9 in 10 ml. of dry dioxane was added 2 ml. of oxalyl chloride. After standing at room temperature for four hours, the solution was concentrated to an orange oil which was taken up in 25 ml. of methylene chloride and washed with 20 ml. of 5% sodium bicarbonate solution. The clear yellow solution was dried by filtration, evaporated to a volume of 5 ml., treated with 10 ml. of carbon tetrachloride and allowed to stand in a loosely stoppered flask for two days. The yellow precipitate (0.040 g.) which had appeared was collected by filtration and was recrystallized from methylene chloride-carbon tetrachloride. The yield
of LV as fine, yellow needles was 0.030 g. (17.4%), m.p. 246-247°, undepressed upon admixture with a sample prepared by method A.

**D-Penicillamine Methyl Ester Hydrochloride.**--Dry D-penicillamine hydrochloride (50.0 g., 0.269 mole) was dissolved in 200 ml. of absolute methanol and the solution, after treatment with a stream of dry hydrogen chloride (with cooling) for two hours, allowed to stand for twenty-two hours. The solution was diluted with 400 ml. of chloroform and heated to reflux in a flask surmounted by a large Soxhlet apparatus containing Drierite (ca. 150 g.) in a paper extraction thimble. After a ten-hour reflux period the Drierite charge was changed and boiling continued for another fourteen hours. The solution was evaporated under reduced pressure to a light tan, crystalline solid which was flushed with two 100 ml. portions of chloroform and 200 ml. of ethylene dichloride. The residue was then dissolved in 600 ml. of boiling ethylene dichloride and the small amount of insoluble liquid on the surface of the solution was removed by means of a finely drawn dropping-tube. The solid obtained upon cooling was collected by filtration, washed with ethylene dichloride and dried in vacuo. The crude product weighed 52.0 g. Recrystallization from 250 ml. of boiling t-butanol afforded 42.0 g. (78.3%) of long, colorless needles
m.p. 185.7-186.1° (reported 170-175°).  

**Methyl 5,5-Dimethyl-2-phenyl-2-thiazoline-4-carboxylate (LIX).** This procedure is a modification of that used by Buhle.  

A mixture of 12.00 g. (0.060 mole) of D-penicillamine methyl ester hydrochloride, 11.13 g. (0.060 mole) of ethyl benzimidate hydrochloride and 6.07 g. (8.33 ml., 0.060 mole) of triethylamine in 90 ml. of methylene chloride was stirred for twenty-eight hours. The mixture was then concentrated under reduced pressure to a point at which the methylene chloride had been almost completely evaporated. The last traces of methylene chloride were removed by treating the residue with two 30-ml. portions of benzene and evaporating the benzene after each addition. The residual material was stirred with 200 ml. of dry ether and filtered. The colorless mixture of salts (ammonium chloride and triethylammonium chloride) weighed 11.7 g. (102%). The filtrate and ether washings were combined and concentrated under reduced pressure to a yellow oil weighing 15.15 g. A solution of the oil in 70 ml. of benzene was passed through a 1 x 12 cm. column of activated alumina (Alcoa, 48-100 mesh) and the column was washed with 100 ml. of benzene. Concentration of the benzene eluates under reduced pressure furnished 14.0 g. (93%) of LIX as a light yellow oil, $\nu_25^0$ 1.5656, $[\alpha]_{26}^0$ 7 in acetone +15.05° (c = 6.4).  

39. Reference 1, Chapter 2, p. 34.
A 5.0 g. portion of the thiazoline was evaporatively distilled at 130° (10 μ) to yield 4.30 g. of partially racemized product, n_D^25 1.5659, [α]^26.7 D in acetone +3.94° (c = 4.96).

The picrate of the D-thiazoline was obtained by treating 0.200 g. of undistilled thiazoline in 2 ml. of hot ethanol with 4 ml. of a saturated solution of picric acid in ethanol. After washing the yellow, crystalline precipitate with ethanol to remove excess picric acid, there was obtained 0.130 g. of picrate, m.p. 78-80° (m.p. of D,L-picrate, 109°), 40 [α]^26.7 D in acetone +41.7° (c = 4.3).

The D-thiazoline is readily racemized by heating with triethylamine. A sample of chromatographed, undistilled thiazoline was analyzed.

Anal. Calcd. for C_{13}H_{15}N_2O_S: C, 62.78; H, 6.06.
Found: C, 62.25; H, 6.08.

Reaction of LIX with XXX.—Repeated attempts to prepare a β-lactam by interaction of the thiazoline LIX with the acid chloride XXX and triethylamine under the same conditions described for the preparation of XLVIII resulted in the isolation of the free acid XXIX

40. Reference 1, Chapter XVI, p. 471.
(15-38%) as the only crystalline reaction product. Both optically active (undistilled) and inactive (distilled) thiazoline were used. Simultaneous addition of the acid chloride and triethylamine led to similar results as did use of a suspension of the acid chloride in a methylene chloride solution of the thiazoline.

Reaction of Methyl 5,5-Dimethyl-2-thiazoline-4-carboxylate with XXX.—No crystalline product could be isolated from this reaction under a wide variety of conditions.

Run A. The procedure was followed which had been utilized successfully in the preparation of XLVIII, i.e., addition of triethylamine under high-dilution conditions to a methylene chloride solution of the thiazoline\textsuperscript{13} and XXX at reflux.

Run B. This run was the same as run A except that that base used was γ-collidine.

Run C. A third procedure involved addition of a cold (−70°) solution of the acid chloride and triethylamine in dioxane-methylene chloride to a stirred solution of the thiazoline in methylene chloride.

Run D. A procedure similar to that used in run C was tried. A cold (−70°) solution of the acid chloride and the thiazoline in dioxane-methylene chloride was added to a stirred solution of triethylamine and the
thiazoline in methylene chloride.

Run E. In this run a cold (-70°) solution of the acid chloride and triethylamine in dioxane-methylene chloride was added to a methylene chloride solution of the thiazoline hydrochloride. The hydrochloride was prepared by the addition of one equivalent of dry hydrogen chloride gas to a petroleum ether-benzene solution of the thiazoline.

**2-Methylene-4,5-diketo-3-oxazolidineacetic Acid (LXII).**—Dry acetic acid (11.7 g., 0.10 mole) was suspended in methylene chloride (80 ml.) and the mixture treated with oxalyl chloride (25.0 g., 0.197 mole). The reactants were stirred for twelve hours at 25° and then the reaction flask was stoppered and stored at 5° in a refrigerator for twenty-four hours longer. The colorless solid was collected by pressure filtration (dry nitrogen) and dried in vacuo at room temperature. The powdery product (completely soluble in dry acetone) amounted to 3.80 g. (51.5%) and upon heating in a melting point bath decomposed slowly from 113 to 127° and rapidly at 127-8°. Recrystallization from methyl ethyl ketone provided analytically pure LXII (dec. 127-128°) as colorless prisms.

**Anal. Calcd. for C₈H₇NO₅:** C, 42.11; H, 2.95; N, 8.19.

**Found:** C, 42.35; H, 3.17; N, 8.31.
The acid is unstable and decomposes upon long standing at room temperature. An attempt to prepare the acid chloride of LXII using phosphorus pentachloride in dioxane yielded, after lyophilization of the dioxane-phosphorus oxychloride solution, a light, orange oil which rapidly decomposed at room temperature.
PART IV

REACTIONS OF SOME 2-SUBSTITUTED THIAZOLINES

WITH ACID CHLORIDES
INTRODUCTION

The work reported in the last part of this thesis deals with the synthesis of four new thiazolines derived from penicillamine and their use in the preparation of \( \beta \)-lactams related to penicillin. The first successful synthesis is described of a fused \( \beta \)-lactam-thiazolidine derived from penicillamine and possessing a 5-substituent other than a phenyl group.

In the work on the thiazoline-acid chloride reaction which has been reported previously,\(^8\)-\(^{13}\) it was consistently found that although 2-thiazolines substituted by a phenyl group in the 2-position readily afforded \( \beta \)-lactams, the corresponding thiazolines possessing a hydrogen atom or a methyl group in the 2-position did not. It is obviously desirable to extend this method to thiazolines other than those possessing a 2-phenyl group, both for the purpose of synthesizing penicillin itself and in order to clarify the mechanism and scope of the reaction.

From the evidence available it seemed possible that the reaction of an acid chloride, a thiazoline and a tertiary amine involves an intermediate of the type represented by expression LXIII. If such an entity as LXIII were a true intermediate and represented to a degree the structure of the transition state involved,
then the beneficial effect of a 2-phenyl substituent in the formation of β-lactams might simply be due to the ability of the phenyl group to stabilize the transition state (LXIII, \( R = \text{C}_6\text{H}_5 \)) by resonance. Furthermore, since the presence of a 5-phenyl substituent on the β-lactam-thiazolidine ring system seems to have a profound stabilizing effect, it can be argued that the transition state might be stabilized in the same way. The latter explanation cannot be ruled out, since the nature of the stabilizing effect of a phenyl group on β-lactams is not understood. In contrast to the former argument, however, it fails to provide a basis upon which predictions can be made concerning the effect of substituents on the course of the reaction.

The postulation of a reaction intermediate of type LXIII, although probably an oversimplification, represents a potentially useful concept. Application of this idea to 2-substituted thiazolines leads to the conclusion that each of the possible substituents can exert
one of three basically different effects, and hence that all substituents fall into one of three classes. The first class encompasses groups which do not stabilize the transition state LXIII. While it may be possible for thiazolines with such substituents to form β-lactams, it seems probable that other more facile reaction paths invariably would be available. In the second class are included groups which do stabilize the transition state LXIII, but which are of such a nature as to permit more readily reactions other than those resulting in formation of a β-lactam. The third class of substituents is composed of those which stabilize the transition state LXIII sufficiently to permit formation of some β-lactam.

Such substituents as carboalkoxy, alkanesulfonyl, and nitro are of the first type, while methyl and hydrogen are probably of the second type. The 2-furyl and 2-thienyl groupings may well be of the third class. A priori such substituents as vinyl and styryl may be of either the second or third type.
DISCUSSION

A series of four thiazolines have been prepared which on the basis of the concept outlined in the introduction are potentially of use in the synthesis of β-lactams. A second factor involved in the selection of the thiazolines to be studied was the possibility of converting β-lactams derivable from them to penicillin itself by degradation.

The preparation of methyl 2-furyl-5,5-dimethyl-2-thiazoline-4-carboxylate (LXIV) was readily carried out in 94% yield as shown in Figure II. The thiazoline, which was isolated in a pure state by chromatography, could be distilled in high vacuum with only slight racemization. Racemization of LXIV could be effected by heating with triethylamine. Addition of triethylamine under high-dilution conditions to a solution of racemic LXIV and phthaloylglycyl chloride in methylene chloride at reflux afforded a 32% yield of the fused piperidinedione-thiazolidine derivative LXV. The structure LXV is supported by both the elemental analysis and infrared spectrum of the product. The infrared spectrum is characterized by a band at 5.97 μ assignable to the β-lactam carbonyl. Similar products have been reported previously from the
Figure II

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{C} &-\text{CHCOOCH}_3 + \text{RC}_2\text{NH} & \text{LXIV} \\
\text{SH} & \quad \text{NH}_3\text{Cl} & \\
\text{LXIV} + \text{XCH}_2\text{COCl} + (\text{C}_2\text{H}_5)_3\text{N} & \xrightarrow{\text{CH}_2\text{Cl}_2} \text{LXV} \\
\text{LXIV} + \text{XCH}_2\text{COCl} + (\text{C}_2\text{H}_5)_3\text{N} & \xrightarrow{\text{CHCl}_3} \text{LXV} + \text{LXVI} \\
\text{LXVI} + \text{KMnO}_4 & \rightarrow \text{sulfone} \quad \text{LXVII} \\
R & = \text{phthalimido} \\
X & = \text{phthalimido}
\end{align*}
\]
reaction of imines and thiazolines with ketenes and from the reaction of thiazolines with acid chlorides. When the reaction was carried out in the same way using chloroform as the solvent at reflux temperature, a 14.2% yield of the desired β-lactam LXVI was obtained in addition to a 17.5% yield of LXV. The infrared spectrum of LXVI showed the characteristic β-lactam carbonyl band at 5.59 μ. Oxidation of LXVI produced the corresponding sulfone LXVII in 64% yield. The position of the β-lactam carbonyl band in the spectrum of LXI is shifted characteristically to 5.53 μ. The reaction of optically active LXIV with phthaloylglycyl chloride and triethylamine in methylene chloride as the solvent yielded no crystalline addition product. Use of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (XXX) as the acid chloride component in chloroform as the solvent furnished no isolable β-lactam.

The preparation of methyl 5,5-dimethyl-2-vinyl-2-thiazoline-4-carboxylate was accomplished by the route outlined in Figure III. Reaction of acrylonitrile with ethanol and dry hydrogen chloride yielded the imido ester hydrochloride LXVIII in analytically pure condition, regardless of whether one or two equivalents of hydrogen

41. Reference 1, Chapter XXVI, p. 973.
Figure III

H₂C=CHCN + C₂H₅OH + HCl → ClCH₂CH₂O₂Cl

LXVIII

LXVIII + (CH₃)₂C—CHCOOCH₃ + 2(C₂H₅)₃N → (CH₃)₂C—CHCOOCH₃

SH       NH₃Cl

RCH=CH

LXIX, R = H
LXXVI, R = C₆H₅

C₆H₅CH=CHCN + C₂H₅OH + HCl → C₆H₅CH=CHC₂Cl

(cis + trans) (trans)

LXXV
Figure IV

\[ \text{RCHO} + \text{NCCCH}_2\text{COOH} \xrightarrow{\text{pyridine}} \xrightarrow{\text{piperidine}} \text{RCH}=\text{C}((\text{COOH})\text{CN}) \]

LXXX

\[ \text{LXXX} \xrightarrow{\text{quinoline}} \text{CuSO}_4 \xrightarrow{\text{RCH}=\text{CHCN}} \xrightarrow{\text{C}_2\text{H}_5\text{OH}} \xrightarrow{\text{HCl}} \text{RCH}=\text{CHC}^\text{\text{NH}_2}\text{Cl} \xrightarrow{\text{OC}_2\text{H}_5} \text{LXXIII} \]

LXXXI

\[ \text{LXXXII} + (\text{CH}_3)_2\text{C}-\text{CHCOOCH}_3 + (\text{C}_2\text{H}_5)_3\text{N} \rightarrow \begin{array}{c}
\text{S} \\
\text{NH}_3\text{Cl}
\end{array} \]

LXXXIII

\[ \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \]

\[ R = 2,4,5\text{-trimethylstyrlyl} \]
chloride were used. The yield of LXVIII when two equivalents of hydrogen chloride were used was 60%. The reaction probably involves β-chloropropionitrile as an intermediate. Treatment of LXVIII with penicillamine methyl ester hydrochloride and two equivalents of triethylamine resulted in simultaneous formation of the thiazoline nucleus and dehydrohalogenation, and provided the desired thiazoline LXIX in 70% yield after chromatography. The thiazoline could not be distilled without decomposition even in high vacuum and also failed to form a picrate with ethanolic picric acid.

Reaction of LXIX with an acid chloride can in principle occur in two ways, one being normal addition to the imino group to form a β-lactam (LXX) and the other 1,4-addition to form a δ-lactam (LXXI). The β-lactam LXX is potentially convertible to a penicillin sulfone LXXIII by oxidative fission of the double bond in the vinyl group, simultaneous oxidation of the sulfur atom to the dioxide LXXII and decarboxylation of the acid. Decarboxylations in such systems are known to
(CH$_3$)$_2$C—CHCOOCH$_3$

O$_2$S—C—N—C=O

HOOC—C

H

X

LXXII

(\(\text{CH}_3\text{CH}_2\text{SO}_3\))$_2$SO$_2$

LXXXIV

Upon treatment of the thiazoline LIX with either succinoylglycyl chloride or 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (XXX) and triethylamine under a wide variety of conditions, no crystalline product could be isolated.

The thiazoline next studied was methyl 5,5-dimethyl-3-styryl-2-thiazoline-4-carboxylate. The preparation is outlined in Figure III. Treatment of a mixture of the cis and trans isomers of cinnaminitrile with absolute ethanol and dry hydrogen chloride furnished the imido ester hydrochloride LXXV which is probably almost pure trans isomer.\(^{43}\)

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43. The cis isomer of cinnaminitrile has been shown to react very slowly with hot methanol saturated with hydrogen chloride, while the trans isomer is very reactive. J. Ghosez, Bull. soc. chim. Belg., 41, 477 (1932).
Reaction of LXXV with penicillamine methyl ester hydrochloride and triethylamine furnished the thiazoline LXXVI in 92% yield. The thiazoline could not be distilled in high vacuum without serious decomposition and could not be obtained in a completely pure state even after chromatography. Upon treatment with alcoholic picric acid LXXVI formed an analytically pure picrate.

Reaction of LXXVI with phthaloylglycyl chloride and triethylamine under high dilution conditions in methylene chloride at reflux resulted in a 19% yield of a crystalline addition product, the infrared spectrum of which favored the $\delta$-lactam structure (LXXVII) rather than

\[
\begin{align*}
&(\text{CH}_3)_2\text{C} \quad \text{CHOOCH}_3 \\
&S \quad \text{C} \quad N \quad \text{C}=O \\
&\text{HC} \quad \text{CH} \quad \text{CH-X} \\
&C_6\text{H}_5
\end{align*}
\]

LXXVII, $X = \text{phthalimido}$

\[
\begin{align*}
&(\text{CH}_3)_2\text{C} \quad \text{CHOOCH}_3 \\
&S \quad C \quad \text{CH} \quad \text{CH-X} \\
&\text{C}_6\text{H}_5\text{CH}=\text{CH} \quad \text{H} \\
&X
\end{align*}
\]

LXXVIII, $X = \text{phthalimido}$

LXXIX, $X = \text{succinimido}$

the $\delta$-lactam structure (LXXVIII). The spectrum of the product exhibits bands at 5.63 and 5.80 $\mu$ due to the phthalimido group, a band at 5.73 $\mu$ due to the ester carbonyl and a band at 6.00 $\mu$ which is assignable to a
\(\delta\)-lactam or acyclic amide carbonyl. Repeated elemental analyses of the product, however, indicate that it contains the elements of ethanol in addition to those of formula LXXVII. An exactly parallel situation obtains when succinoylglycyl chloride is used as the acid chloride component. The infrared spectrum of the product is in accord with the \(\delta\)-lactam formulation LXXIX, and the elemental analyses indicate the presence of the addition elements of ethanol. The manner of incorporation of the ethanol fragment has not been determined. No crystalline reaction product could be obtained when XXX was used as the acid chloride component.

When the reaction of LXXVI with phthaloylglycyl chloride and triethylamine was carried out in chloroform at reflux, there was isolated a new compound which is isomeric, but not identical with the product obtained when methylene chloride was used as the solvent. The infrared spectrum of the compound is compatible with the \(\beta\)-lactam structure LXXVIII, exhibiting bands at 5.61, 5.65, 5.71 and 5.80 \(\mu\). The 5.61 and 5.80 \(\mu\) bands are due to the phthalimido group, while the 5.65 and 5.71 \(\mu\) bands are assignable to the \(\beta\)-lactam and ester carbonyl groups.

The synthesis of methyl 5,5-dimethyl-2-(2,4,6-trimethylstyryl)-2-thiazoline-4-carboxylate (LXXXIII) was accomplished by the route shown in Figure III.
The thiazoline LXXXIII represents a potentially useful intermediate in the synthesis of \( \beta \)-lactams, since the high degree of steric hindrance about its carbon-carbon double bond should exclude the formation of \( \beta \)-lactams, i.e., 1,4-addition, upon reaction with an acid chloride. Condensation of mesitaldehyde with cyanoacetic acid under Döbner's conditions resulted in formation of only one of the two possible isomeric \( \alpha \)-cyano-2,4,6-trimethyl-cinnamic acids (LXXX) in 84\% yield. The good yield of product obtained in this reaction is in marked contrast to the low yield (10\%) reported to result from the corresponding condensation using malonic acid.\(^{44}\) Decarboxylation of LXXX by heating with copper sulfate in quinoline afforded a 68\% yield of the nitrile LXXXI, which could be separated into a high and a low-melting isomer either by chromatographic adsorption or fractional crystallization from petroleum ether. The high and low-melting isomers occur in the ratio of approximately one to thirty. The imido ester hydrochloride LXXXII was prepared in 12\% yield by treatment of the nitrile (low-melting form) with ethanolic hydrogen chloride. Reaction of LXXXII with penicillamine methyl ester hydrochloride and triethylamine resulted in a 76\% yield of the desired thiazoline LXXXIII, which was purified by chromatography. The thiazoline readily yielded a picrate upon treatment with ethanolic picric acid.

44. G. Lock and E. Bayer, Ber., 72, 1064 (1939).
Plate V

Curve A: LXV, Nujol mull

Curve B: 2-(2-Furyl)-4-carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetic Acid β-Lactam (LXVI), 10% in Cl₂CHCHCl₂

Curve C: Sulfone of LXVI, 10% in Cl₂CHCHCl₂

Curve D: LXXVII, 10% in Cl₂CHCHCl₂

Curve E: LXXIX, 10% in Cl₂CHCHCl₂

Curve F: LXXVIII, 10% in Cl₂CHCHCl₂
EXPERIMENTAL

Methyl 2-Furyl-5,5-dimethyl-2-thiazoline-4-carboxylate (LXIV).—To 6.95 g. (0.050 mole) of ethyl furimidate,\(^45\) b.p. 76-78° (15 mm.) in 75 ml. of methylene chloride was added 9.85 g. (0.050 mole) of penicillamine methyl ester hydrochloride and the mixture was stirred for forty-four hours. The methylene chloride was evaporated under reduced pressure and the residue was flushed with two 35-ml. portions of benzene. The residue was treated with 50 ml. of benzene and the mixture was filtered to remove the insoluble salt (2.76 g., 103%). The filtrate was concentrated under reduced pressure to a volume of 25 ml., diluted with 25 ml. of petroleum ether and passed through a 1.2 x 10 cm. column of activated alumina (Merck, for chromatography. The column was washed with 50 ml. of benzene-petroleum ether (4:1) and the combined eluates were evaporated under reduced pressure to a yellow oil, \(n^25 D \) 1.5528, \([\alpha]^{25}_D\) 25.0 D in acetone -37.8° (c = 5.7).

The yield of LXIV was 11.2 g. (94%).

**Anal. Calcd.** for \(C_{11}\text{H}_{13}\text{NO}_3\): C, 55.21; H, 5.48; N, 5.85.  
**Found:** C, 55.57; H, 5.46; N, 6.17.

A portion of the thiazoline (1.7 g.) was evaporatively distilled at 110° (2 µ). It distilled rapidly and

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\(^{45}\) A. Pinner, Ber., 25, 1414 (1892).
without decomposition yielding 1.6 g. of distillate, \( n^2\text{D} 1.5538, [\alpha]^{25}_D \) D in acetone - 35.4° (c = 3.4).

The picrate of LXIV was prepared in ethanol and purified by recrystallization from ethanol, m.p. 114.5-122.8°, \([\alpha]^{25}_D 8\) D in acetone + 16.25° (c = 1.65). The rotation of the picrate was +13.1° in a similar preparation.

**Anal. Calcd. for C\(_{17}\)H\(_{16}\)N\(_4\)O\(_{10}\):** C, 43.59; H, 3.44; N, 11.96.

**Found:** C, 44.00; H, 3.49; N, 12.07.

**Racemization of LXIV.**—To 3.0 g. of the D-thiazoline was added 1 ml. of triethylamine and the solution was heated to 75° for one and one-half hours in a stoppered flask. The triethylamine was removed by evaporation under reduced pressure and the residual oil was evaporatively distilled at 110° (1 μ). The clear, yellow distillate amounted to 2.8 g., \( n^2\text{D} 1.5537, [\alpha]^{25}_D 0\) D in acetone 0° (c = 2.0). A sample of the picrate prepared from a small amount of racemic thiazoline melted at 135.0 to 136.7°.

**Reaction of D,L-LXIV with Phthaloylglycyl Chloride in Methylene Chloride.**—To a rapidly stirred solution of 2.42 g. (0.0101 mole) of racemic thiazoline (LXIV) and 2.24 g. (0.010 mole) of phthaloylglycyl chloride in 40 ml. of methylene chloride at reflux was added through a high-dilution cycle 1.4 ml. (0.01 mole) of triethylamine in
50 ml. of methylene chloride. The time required for the addition was five hours. The red solution was concentrated under reduced pressure to a volume of 10 ml., treated with 60 ml. of dioxane and evaporated to 30 ml. The insoluble triethylammonium chloride was removed by filtration and the filtrate was concentrated to a red oil. After three days the resulting magma was triturated with 10 ml. of ether-acetone (4:1), and the insoluble solid was collected by filtration and washed with ether-acetone. The crude, pale orange solid was treated with 20 ml. of methylene chloride and the mixture was filtered to remove the small amount of insoluble solid. The filtrate was diluted with 35 ml. of ethyl acetate and the solution was evaporated to 25 ml. to remove all methylene chloride. Upon cooling a colorless solid (LXV) separated, m.p. 284-284.5° (dec., in bath at 280°), 0.815 g. (31.5%). Another recrystallization from the same solvent did not alter the decomposition point. Recrystallization from dioxane afforded a low-melting modification of the product, m.p. 232-233.5° (in bath at 220°). The low-melting form when placed in the heating bath at 150° was gradually transformed into the more stable and higher-melting form, which melted at 270° (dec.) with slow decomposition from 340 to 270°. The higher-melting form, which could be obtained by recrystallization of the low-melting form from methylene chloride-ethyl acetate, showed the same behavior when placed in a
bath at 150°. Both forms were obtained as colorless, fine needles.

**Anal. Calcd. for C_{41}H_{28}N_{4}O_{12}S:** C, 61.50; H, 3.52; N, 6.39; S, 4.00. **Found:** C, 61.64; H, 3.76; N, 6.35; S, 4.49.

No crystalline product could be isolated when optically active LXIV was used in the above procedure.

**Reaction of D,L-LXIV with Phthaloylglucyol Chloride in Chloroform.**—To a well-stirred solution of the thiazoline (1.60 g., 0.0067 mole) in 15 ml. of purified, alcohol-free chloroform at reflux was added dropwise a solution of the acid chloride (1.49 g., 0.0067 mole) in 50 ml. of chloroform and simultaneously (through a dilution cycle) 0.93 ml. (0.0067 mole) of triethylamine in 50 ml. of chloroform. The addition of the acid chloride was maintained at a rate which was slightly greater than the rate of addition of the amine. The time required for the addition of the acid chloride was four and one-half hours, whereas the amine was added over a five hour period. The reaction mixture was concentrated under reduced pressure and the insoluble triethylammonium chloride was removed after addition of dioxane. The filtrate was evaporated to a red oil which was diluted with 4.5 ml. of ether-acetone (2:1) and allowed to stand overnight. The solid (0.385 g.) which had precipitated was collected by filtration and washed with
ether-acetone. Recrystallization from methylene chloride-ethyl ethyl ketone provided 0.250 g. (14.2%) of LXV, m.p. 240-270 (dec., in bath at 150°). From the original mother liquors there was obtained, after standing for six hours, a crystalline precipitate. The solid, which was collected by filtration and washed with ether-acetone (5:1), amounted to 0.506 g. (17.5%), m.p. 162-164.5° (dec., in bath at 158°). The crude β-lactam LXVI was purified by recrystallization from acetone-ether followed by a second recrystallization from chloroform-carbon tetrachloride, and was obtained as colorless blades, m.p. 164.0-165.5° (dec., in bath at 155°).


Sulfone of 2-(2-Furyl)-4-carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetic Acid β-Lactam (LXVII).--To a solution of 0.081 g. (0.19 millimole) of LXVI in 10 ml. of dioxane was added 0.0388 g. (0.252 millimole) of potassium permanganate dissolved in 3 ml. of water and 2 ml. of glacial acetic acid. After standing for one-half hour all of the permanganate had been consumed and a precipitate of finely divided manganese dioxide had settled out of the almost colorless solution. A solution of 0.030 g. (0.195 millimole) of potassium permanganate in 3 ml. of water was then added
and the mixture was allowed to stand for five minutes. The reaction mixture was treated with ten drops of 10% hydrogen peroxide solution and the resulting clear, faintly yellow solution was diluted with 150 ml. of cold water and allowed to stand. The colorless precipitate, which was collected by filtration, washed with water and dried in vacuo, weighed 0.055 g. (84%), m.p. 199-203° (dec., in bath at 195°). Recrystallization from methylene chloride-carbon tetrachloride yielded pure sulfone (0.045 g.) as fine needles, m.p. 207.5-208.2 (dec., in bath at 195°).

**Anal. Calcd. for C$_2$I$_8$N$_2$O$_8$S: C, 55.02; H, 3.96; N, 6.11. Found: C, 54.31; H, 3.85; N, 6.28.**

**Ethyl β-Chloropropionimidate Hydrochloride (LXVIII).** — To a mixture of 53.0 g. (1.0 mole) of acrylonitrile (distilled from phosphorus pentoxide) and 46.0 g. (1.0 mole) of absolute ethanol at -30° was added 73.0 g. (2.0 moles) of dry hydrogen chloride. The reactants were cooled to ca. -50° and 400 ml. of anhydrous ether was added slowly. The clear, colorless solution was allowed to warm up to 0° and stored at that temperature for nine days. At the end of this time the ethereal solution was decanted from the solid cake of crystals, and the solid was elutriated with two 200-ml. portions of ether and placed under reduced pressure (40 mm.) for two hours. After further washing with ether, the solid
was dried in vacuo for two hours. The imido ester hydrochloride LXVIII, obtained as colorless, glistening needles, amounted to 104 g. (60.5%), m.p. 111-112° (dec. with evolution of gas).

**Anal.** Calcd. for C₅H₁₁ClNO:  C, 34.90; H, 6.45; Cl, 41.21.

**Found:**  C, 34.60; H, 6.54; Cl, 40.53.

When only one equivalent of hydrogen chloride was used the same product was obtained in 25% yield. In all preparations a heavy precipitate of product appeared after standing for thirty hours.

**Methyl 5,5-Dimethyl-2-vinyl-2-thiazoline-4-carboxylate (LXIX).**—To a well-stirred suspension of 3.44 g. (0.020 mole) of LXVIII and 3.95 g. (0.020 mole) of penicillin methyl ester hydrochloride in 30 ml. of methylene chloride at 5° (ice bath) was added dropwise over a period of twenty minutes a solution of 5.55 mol (0.040 mole) of triethylamine in 2.5 ml. of methylene chloride. The reaction mixture was stirred at 5° for one hour and then at room temperature for thirty-six hours. The methylene chloride was removed by evaporation at reduced pressure and the residue was treated with 50 ml. of benzene and filtered. The insoluble salts, after being washed with benzene and dried, amounted to 6.85 g. (theoretical weight of salts, 6.60 g.). Evaporation of the filtrate afforded 3.3 g. of impure thiazoline as a yellow oil. The crude
product was purified by treatment with 50 ml. of carbon tetrachloride, filtration of the resulting mixture to remove the small amount of insoluble material and passage through a 1 x 13 cm. column of activated alumina (Alcoa 48-100 mesh). The column was eluted with 50 ml. of carbon tetrachloride and the combined eluates were evaporated under reduced pressure to a clear yellow oil (2.80 g., 70.5%), n$_D^{25}$ 1.5158, [$\alpha$]$_D^{26.5}$ 5° in acetone - 8.45° (c = 5.45).

Anal. Calcd. for C$_9$H$_{13}$NO$_2$S: C, 54.25; H, 6.57; N, 7.03.
Found: C, 53.54; H, 7.08, N, 6.73.

The thiazoline did not yield a crystalline picrate upon treatment with a saturated alcoholic solution of picric acid and was halogen free. Attempted evaporative distillation at 120-150° (10 µ) resulted in extensive decomposition. Slow racemization occurred when the thiazoline was treated with triethylamine at room temperature.

**Ethyl Cinnamimidate Hydrochloride (LXXV).**—The cinnamonic acid used in the following procedure was obtained essentially by the method of Ghosez$^{43}$ and consisted of a 40-60 mixture of cis and trans isomers as determined by refractive index,$^{46}$ in good agreement with the value 37-63 obtained previously.$^{43,46}$ To 29.5 g. (0.228 mole) of the mixture of isomeric nitriles at 0° (ice bath) was

added 10.5 g. (0.228 mole) of absolute ethanol and 8.4 g. (0.228 mole) of dry hydrogen chloride. The cold reaction mixture was stored for twenty days at 5°C. Dry ether (150 ml.) was then added, the solid cake was broken up and after twelve hours the mixture was filtered. The colorless solid, after being washed with ether and dried in vacuo, weighed 28.0 g. (59.1% based on total nitrile, 98.5% based on trans-nitrile), m.p. 119-120° (dec. with evolution of gas). The filtrate upon concentration provided 11.3 g. of a crude, liquid mixture, n^25 D 1.5780, containing enriched cis-cinnamonic acid. A sample of the imido ester hydrochloride was prepared for analysis by recrystallization from glacial acetic acid-ether and had m.p. 124.0-124.4° (dec.).

*Anal.* Calcd. for C_{11}H_{14}ClNO: C, 62.41; H, 6.67; Cl, 16.75. Found: C, 61.42; H, 6.54; Cl, 16.64.

The preparation of LXXV in quantitative yield has been reported by Houben and Pfankuch without mention of the source or purity of the cinnamonic acid used. No physical properties for LXXV were reported.

*Methyl 5,5-Dimethyl-2-styryl-2-thiazoline-4-carboxylate (LXXVI).*—To a stirred suspension of 10.59 g. (0.050 mole) of LXXV and 9.90 g. (0.050 mole) of penicillamine

47. J. Houben and E. Pfankuch, Ber., 59, 1594 (1926).
methyl ester hydrochloride was added 6.93 ml. (5.05 g., 0.050 mole) of triethylamine. After stirring at room temperature for thirty-two hours the product was isolated and purified by the procedure described for LXIV. The yield of LXXVI as a bright yellow oil was 12.0 g. (92.5%), \( n^25 \, D \, 1.5570 \), \( [\alpha]^{26.0} \, D \) in acetone +55.7° (c = 4.1).

**Anal.** Calcd. for C\(_{15}\)H\(_{17}\)NO\(_2\)S: C, 65.42; H, 6.23.
Found: C, 64.22; H, 6.77.

Attempted distillation of LXXVI at 130° (10 u) resulted in extensive decomposition.

The thiazoline (0.350 g., 1.27 millimole) was converted to the picrate by treatment with 0.345 g. (1.50 millimole) of picric acid in 5 ml. of warm ethanol. After washing with ethanol and drying, there was obtained 0.175 g. of product, m.p. 171.2-171.6° (dec., in bath at 165°), \( [\alpha]^{26.0} \, D \) in methylene chloride +130.0° (c = 0.87).

The rotation of different samples of the picrate varied from +72.3 to +130.0°.

**Anal.** Calcd. for C\(_{21}\)H\(_{20}\)N\(_4\)O\(_9\)S: C, 50.00; H, 3.97; N, 11.11.
Found: C, 50.16; H, 4.09; N, 11.28.

**Reaction of LXXVI with Phthaloylglycyl Chloride in Methylene Chloride.**—To a well-stirred solution of 2.76 g. (0.010 mole) of the thiazoline LXXVI and 2.24 g. (0.010 mole) of the acid chloride in 25 ml. of methylene chloride at
reflux was added through a high-dilution cycle 1.40 ml. (1.01 g., 0.010 mole) of triethylamine in 50 ml. of methylene chloride. The time of addition was five hours. The clear, faintly yellow solution was concentrated, treated with dioxane and freed of triethylammonium chloride as described previously, and the resulting solution was evaporated to a yellow oil which was taken up in 3 ml. of acetone and 5 ml. of ether. After standing for three hours the mixture was filtered and the colorless, crystalline solid was washed with acetone-ether. The yield of crude product was 0.910 g. (19.5%), m.p. 216.5-231.5°, [α]$_{25}^0$ D in methylene chloride +37.1° (c = 2.55). Recrystallization of a 0.250 g. sample from methylene chloride-ethyl acetate afforded 0.180 g. of colorless prisms, m.p. 34-236°. A second recrystallization from the same solvent yielded 0.135 g. of pure product, m.p. 236.5-237.5°. Further recrystallization did not raise the m.p.

Anal. Calcd. for C$_{25}$H$_{22}$N$_2$O$_5$S: C, 64.92; H, 4.30; N, 6.06; S, 6.93.

Calcd. for C$_{25}$H$_{22}$N$_2$O$_5$S·CH$_3$OH: C, 63.14; H, 5.30, N, 5.67; S, 6.48.

Calcd. for C$_{25}$H$_{22}$N$_2$O$_5$S·C$_2$H$_5$OH: C, 63.76; H, 5.55; N, 5.51; S, 6.30.

Found: C, 63.83; H, 5.51; N, 5.73; S, 6.40.
The product was analyzed by the Zeisel method for the member of alkoxy groups present.

Anal. Calcd. for C$_{25}$H$_{22}$N$_2$O$_5$S: Alkoxy groups, 1.00.
Found: 1.76.

Calcd. for C$_{25}$H$_{22}$N$_2$O$_5$S·CH$_3$OH: alkoxy groups, 2.00.
Found: 1.89.

Calcd. for C$_{25}$H$_{22}$N$_2$O$_5$S·C$_2$H$_5$OH: alkoxy groups, 2.00.
Found: 1.94.

The analytical results were not affected by heating a sample for six hours at 140° (0.1 mm.).

Reaction of LXXVI with Succinoylglycyl Chloride in Methylene Chloride.—Using the procedure followed in the preceding section, there was obtained 2.43 g. (13.4%) of a colorless solid, m.p. 234–239°, [α]$_{25}$^0 D in methylene chloride +93.2° (c = 1.30). Recrystallization of a 0.200 g. portion of the crude product from methylene chloride-methyl ethyl ketone gave 0.125 g. of colorless prisms, m.p. 253.5–254.0°. The m.p. was unchanged after recrystallization from methylene chloride-ethyl acetate.

Anal. Calcd. for C$_{21}$H$_{22}$N$_2$O$_5$S: C, 60.85; H, 5.35; N, 6.76; S, 7.74.

Calcd. for C$_{21}$H$_{22}$N$_2$O$_5$S·CH$_3$OH: C, 59.17; H, 5.37; N, 6.28; S, 7.18.
Calcd. for C$_{21}$H$_{22}$N$_2$O$_5$S·C$_2$H$_5$OH: C, 59.98; H, 6.13; N, 6.08; S, 6.96.

Found: C, 59.82; H, 6.08; N, 6.06; S, 6.98.

A sample which had been heated to 140° (0.1 mm.) for six hours had the same composition. Further recrystallization did not alter the analytical results for carbon and hydrogen.

No crystalline product could be isolated from the reaction of LXXVI with the acid chloride XXX under the conditions used in the above reaction.

**Reaction of LXXVI with Phthalloylglycyl Chloride in Chloroform.**--To a stirred solution of the thiazoline LXXVI (2.76 g., 0.010 mole) in 15 ml. of purified, alcohol-free chloroform at rapid reflux was added a solution of the acid chloride (2.23 g., 0.010 mole) in 50 ml. of chloroform and simultaneously (through a dilution cycle) 1.4 ml. (0.010 mole) of triethylamine in 50 ml. of chloroform. The addition of the acid chloride was maintained at a rate which was about one and one-third times as fast as the rate of addition of the amine. The time required for the addition of amine was five hours. The solution was concentrated to a magma which was treated with 40 ml. of purified dioxane and filtered to remove the insoluble triethylammonium chloride. Concentration of the filtrate produced an oil, which was treated with warm ether (5 ml.) containing a
little methylene chloride (2 ml.) and allowed to stand overnight. The crude product (0.680 g.) was collected by filtration and washed with 10 ml. of ether-methylene chloride (4:1). The solid was treated with 15 ml. of methylene chloride and the slightly turbid solution was filtered. Addition of 17 ml. of carbon tetrachloride, evaporation of the solution to 15 ml. and cooling resulted in a small amount of precipitate (ca. 0.020 g.) which was removed from the solution by filtration. To the filtrate was added five 2-ml. portions of petroleum ether over a period of fifteen minutes. The colorless solid (fine needles) which precipitated was collected by filtration; weight, 0.425 g.; m.p. 235-236° (dec.). An additional 0.270 g. of product was obtained by repeating this isolation procedure with material which crystallized from the original mother liquors on standing. The total yield was 0.695 g. (15%). Samples were prepared for analysis by recrystallization from methylene chloride-carbon tetrachloride, acetone-water or methyl ethyl ketone, m.p. 244.0-244.8°, [a]$_D^{25.4}$ $\text{D}$ in chloroform +79.9° (c = 1.52). A mixture of this product with that obtained from the same reactants in methylene chloride solution melted at 213 to 225°.

Anal. Calcd. for C$_{35}$H$_{22}$N$_2$O$_5$S: C, 64.92; H, 4.80; N, 6.06; S, 8.93.
Calcd. for C_{25}H_{22}N_{2}O_{5}S·CH_{3}CH: C, 63.14; H, 5.30; N, 5.67; S, 6.48.

Calcd. for C_{25}H_{22}N_{2}O_{5}S·C_{2}H_{5}OH: C, 63.76; H, 5.55; N, 5.51; S, 6.30.

Found: C, 63.46; H, 5.54; N, 5.78; S, 6.24.

Calcd. for C_{25}H_{22}N_{2}O_{5}S: alkoxy groups, 1.00.

Found: 1.82.

Calcd. for C_{25}H_{22}N_{2}O_{5}S·CH_{3}OH: alkoxy groups, 2.00.

Found: 1.94.

Calcd. for C_{25}H_{22}N_{2}O_{5}S·C_{2}H_{5}OH: alkoxy groups, 2.00.

Found: 1.99.

α-Cyano-2,4,6-trimethylcinnamic Acid (LXXX).—A solution of 44.5 g. (0.30 mole) of mesitaldehyde and 51.0 g. (0.60 mole) of cyanoacetic acid (dried in vacuo over sulfuric acid) in 150 ml. of dry pyridine and 15 ml. of piperidine was heated on a steam cone for three hours. The solution was evaporated under reduced pressure until ca. 100 ml. of pyridine had been removed and the concentrate was poured with stirring into 600 ml. of 4 N hydrochloric acid. The solid was collected by filtration and washed with six 150-ml. portions of water. The crude product was dissolved in 500 ml. of ether and the ethereal solution was extracted first with 200 ml. of 3 N hydrochloric acid, then with 200 ml. of water and finally with 900 ml.

of sodium carbonate solution. The sodium carbonate solution was extracted with 100 ml. of ether and carefully acidified with 300 ml. of 6 N hydrochloric acid. The resulting precipitate, after washing and drying, amounted to 54.0 g. (83.8%), m.p. 193-195.5°. A sample was purified for analysis by recrystallization from ethanol (Norit), m.p. 193.2-195.5°. A third recrystallization failed to change the m.p.

Anal. Calcd. for \( \text{C}_{13}\text{H}_{13}\text{NO}_2 \): C, 72.54; H, 6.09; N, 6.51.

Found: C, 72.30; H, 6.24; N, 6.56

Attempts to obtain the two geometrical isomers of LXXX by fractional acidification of the sodium salt in acetone-water resulted in the isolation of only one acid, m.p. 193-195.5 from all fractions. The product, therefore, probably contains only one geometrical isomer in appreciable quantity.

2,4,6-Trime-thylcinnamonomitrile (LXXXI).—A mixture of 54.0 g. (0.251 mole) of LXXX, 3.5 g. of anhydrous copper sulfate and 150 ml. of quinoline (Eastman Kodak practical grade) in a 500-ml. flask equipped with a thermometer and an air condenser was heated to 140° at which point decarboxylation began. The temperature of the reaction mixture was increased gradually to 180° over a period of fifteen minutes so that a moderate rate of decarboxylation was maintained. The solution was then heated to reflux for one
minute, allowed to cool to room temperature and poured into 500 ml. of 6 M hydrochloric acid. After being shaken with 500 ml. of ether in a 2-l. separatory funnel, the aqueous phase was drawn off and discarded. The ether layer was washed with three 150-ml. portions of 4 M hydrochloric acid, 200 ml. of water, 200 ml. of 10% potassium carbonate and finally with a second 200-ml. portion of water. Evaporation of the ether and distillation of the residual liquid yielded (after a small forerun of mesitaldehyde) 29.5 g. (68.5%) of nitrile, b.p. 100-102° (0.7 mm.) as a colorless liquid which crystallized upon cooling to an oily solid, m.p. 34-37° (a small amount of solid remaining unmelted until 60°). A small sample was purified for analysis by two sublimations at 0.1 mm., m.p. 35.5-38.5° (a small amount remaining unmelted until 80°).

Anal. Calcd. for C₁₂H₁₅N: C, 84.16; H, 7.65; N, 8.18.
Found: C, 83.90; H, 7.48; N, 8.24.

A small amount of the product was separated into two geometrical isomers by chromatographic adsorption. The nitrile 1.90 g. was stirred for ten minutes with 15 ml. of cold petroleum ether and the mixture filtered. The insoluble solid (colorless needles), m.p. 101-120°, weighed 0.020 g. The filtrate was diluted to a volume of 40 ml. and passed through a 1.3 x 14.6 cm. column of alumina (merck, for chromatography). The column was washed with
5 ml. of petroleum ether and the combined eluates were evaporated. Almost no residue remained after removal of solvent. The column was then washed with four 25-ml. portions of petroleum ether and the individual percolates were evaporated to yield fractions of 1.240, 0.260, 0.115 and 0.050 g. of low-melting nitrile, all having m.p. 35.5-38.0°. The column was then washed with 50 ml. of anhydrous ether and the solid obtained after evaporation of the resulting ether washings triturated with 1.5 ml. of petroleum ether and filtered. The insoluble solid, m.p. 123.0-123.5° weighed 0.026 g. From the filtrate there was obtained an additional 0.105 g. of the low-melting isomer, m.p. 34.5-38.5°. The total amount of pure low-melting isomer recovered was 1.770 g. (93%), while the amount of high-melting isomer obtained was 0.046 g. (2.4%).

A sample of the high-melting isomer was purified for analysis by two recrystallizations from petroleum ether, m.p. 124.2-125.2°.

**Anal. Calcd. for C_{12}H_{13}N:** C, 84.16; H, 7.65; N, 8.18.

**Found:** C, 84.43; H, 7.68; N, 8.29.

Treatment of a 25.0 g. sample of the mixture of isomeric nitriles with 70 ml. of warm petroleum ether and cooling of the solution to 0° resulted in a precipitate of almost pure high-melting isomer. Recrystallization of the solid from petroleum ether furnished 0.850 g. (3.4%) of pure isomer, m.p. 124-125°.
Ethyl 2,4,6-Trimethylcinnamimidate Hydrochloride (LXXXII).—Into a solution of 5.30 g. (0.031 mole) of the low-melting nitrile (LXXXI) and 1.43 g. (0.031 mole) of absolute ethanol in 15 ml. of anhydrous ether was passed a stream of dry hydrogen chloride amounting to 1.13 g. (0.031 mole) at 0°. The reaction mixture was allowed to stand at 0° for sixty hours and at the end of this period was stored at room temperature for twelve days. The colorless solid which had formed was collected by filtration, washed with ether and dried. The yield of LXXXII, m.p. 140-140.5° (dec.), was 0.850 g. (11.8%). A sample prepared for analysis by recrystallization from glacial acetic acid-ether was obtained as fine needles, m.p. 143.5-143.8° (dec.).

**Anal. Calcd. for C_{14}H_{20}ClNO:**

C, 66.26; H, 7.94; Cl, 13.96.

**Found:** C, 64.62; H, 7.94; Cl, 14.72.

Methyl 5,5-Dimethyl-(2,4,6-trimethylstyryl)-2-thiazoline-4-carboxylate (LXXXIII).—The preparation of LXXXIII was carried out using the procedure given for LXXVI. The yield of purified thiazoline from 1.5 g. of the imido ester hydrochloride and 1.34 g. of penicillamine methyl ester hydrochloride was 1.4 g. (76%), n^2^5 D 1.5575, [α]^{26.0} D in acetone +42.7° (c = 2.05). The picrate of LXXXIII was obtained as shining, yellow platelets from
ethanol, m.p. 169-177.8° (dec. slowly).

Anal. Calcd. for C$_{24}$H$_{26}$N$_{4}$O$_{9}$S:  C, 52.74; H, 4.80; N, 10.25.

Found:  C, 53.01; H, 4.84; N, 10.49.
SUMMARY

The investigations reported in this thesis were carried out for the purpose of extending the known synthesis of \( \beta \)-lactam-thiazolidines involving the interaction of thiazolines, \( \text{N,}\text{N} \) -disubstituted (protected) amino acid chlorides and tertiary amines.

The first part of this work consisted of a study of acyclic \( \text{N,}\text{N} \)-diacylglycine derivatives with a view toward application of the corresponding acid chlorides to the indirect synthesis of fused \( \beta \)-lactam-thiazolidines possessing an acylamino substituent as does penicillin. In sharp contrast to cyclic \( \text{N,}\text{N} \)-diacylamino acid chlorides, the acyclic \( \text{N,}\text{N} \)-diacylglycyl chlorides were found to be sufficiently stable to permit isolation only when the acyl groups were aroyl. The acids in every case were prepared by hydrogenolysis of the corresponding benzyl esters. Synthesis of the benzyl esters was accomplished by three different routes: (1) acylation of a monoacylglycine benzyl ester, (2) alkylation of a diamide with a benzyl haloacetate and (3) formation and rearrangement of an 0-acylisouamide.

\( \text{N,}\text{N} \)-dibenzoylglycyl chloride appeared to be inoperative in the acid chloride-thiazoline reaction.

The second phase of this work included the preparation of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl
chloride, a possible intermediate in the indirect synthesis of benzylpenicillin and its analogs. Several model oxazolidinediones were prepared and an investigation was made of the methods by which these heterocyclic systems can be cleaved to substituted phenylacetamides. Hydrolysis, alcoholysis and aminolysis procedures were examined in detail, and it was concluded that aminolysis represents the most practical method for obtaining the desired phenylacetamides. The correctness of the assigned 2-benzylidene-3-oxazolidine-4,5-dione structure has been established unequivocally (for the first time) by the preparation of the isomeric pyrrolidinetrones, which represent the alternative structure.

The first successful synthesis of a 6-phenylacetyl-amino-β-lactam-thiazolidine is described in the third part. The β-lactam was obtained indirectly by way of the corresponding oxazolidine-4,5-dione. The synthesis of a monocyclic β-lactam with a 4,5-diketoöxazolidyl substituent was also accomplished. In these two cases the stereochemical course of the acid chloride-thiazoline reaction was shown to be relatively independent of the nature of the acid chloride component. Attempts to prepare more complex β-lactams containing the oxazolidine-4,5-dione system are described.
The final part of this investigation was concerned with the synthesis of four new thiazolines derived from penicillamine and a study of their utility in the extension of the acid chloride-thiazoline reaction. The synthesis of the first β-lactam-thiazolidine bearing a 5-substituent other than a phenyl group is disclosed.
BIOGRAPHICAL NOTE

The author was born on July 12, 1928, in Methuen, Massachusetts. He received his elementary school training at St. Laurence O'Toole Parochial School and his secondary schooling at the Lawrence Public High School whence he graduated in 1945. He entered the Massachusetts Institute of Technology in the same year and was awarded the S.B. degree in Chemistry in 1948. The author completed the requirements for the Ph.D. degree at the same institution in January, 1951.

The author was employed during the summer of 1948 as a Research Chemist at Arthur D. Little, Inc. In January of 1951 he accepted an appointment as Instructor in Chemistry at the University of Illinois.
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Arthur D. Little, Inc.

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University of Illinois.