Reactions of Carbodiimides. III. The Reactions of Carbodiimides with Peptide Acids[1,2]

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Abstract: A quantitative study has been made of the stoichiometries of the reactions of peptide acids of the general structure Z-AA-OH[6] and acyl-AA-OH with dicyclohexylcarbodiimide in various solvents. The former react in a 2:1 ratio giving the anhydride and little or no acylurea while most examples of the latter react cleanly in a 1:1 ratio to give the azlactone. In acetonitrile solution peptide acids react some 50 times faster than do simple carboxylic acids. Most peptide anhydrides undergo subsequent reactions in the presence of excess carbodiimide which serves as a base catalyst. Two examples have been studied: $[Z\text{-}Ser(H)]_2O$ reacts at a moderate rate to give low molecular weight polymeric esters, and $(Z\text{-}Gly)_2O$ gives primarily the acylurea of a rearrangement product, $Z\text{-}Gly\text{-}N(Z)CH_2CO\text{-}DCU$. A study of the course of the reaction of acyl-AA-OH with *p*-nitrophenyl esters has shown that the azlactone forms rapidly and in turn reacts relatively slowly with *p*-nitrophenol (about one-thousandth as fast with a 1:1:1 mixture of reactants) to form the ester. Pentachlorophenol also forms the ester through the azlactone and, as expected, both the *p*-nitrophenyl and pentachlorophenyl esters are extensively racemized (75–100% DL). The reaction of HBr-H-Gly-ONP with DCC occurs moderately rapidly at room temperature to give the salt of the substituted iminoimidazolidine (**2**). The apparent rate of the reaction was found to depend on the solubility of the salt. This reaction occurs fast enough to be of importance as a side reaction in certain peptide syntheses.

Our interest in the reactions of peptide derivatives with carbodiimides is an outcome of work on the preparation of sequence peptide polymers.[4] The first two papers in this series, which concern the reactions of carbodiimides with simple carboxylic acids, provide a background for work with these more complex systems.[5]

The over-all purpose of studies of the mechanisms of peptide syntheses is to obtain a detailed set of equations which will permit quantitative predictions about products as a function of reactant concentrations and which show all relevant reaction paths. This is obviously a long-term project. The immediate aim of the present study has been to sort out the major features of some of these reactions by supplementing with selected quantitative data the extensive qualitative information in the peptide literature. One goal has been to identify what may be called the "primary" products, those which are the first to be formed in isolable quantities, namely the anhydrides, azlactones, and acylureas. A second goal has been to identify the subsequent reactions which some of these primary products undergo and which may compete with peptide bond formation. A third goal has been to identify the acylating agents, and some progress has been made in determining intermediates in *p*-nitrophenyl ester syntheses. To facilitate interpretation of the course of these reactions as revealed by infrared data, peak positions have been determined for representative azlactones, anhydrides, and other groups which absorb in the 1500–1800-cm^{-1} region.

Benzyloxycarbonylamino acids are known to react with carbodiimides to give anhydrides (eq 1), a reaction

$$Z\text{-}AA\text{-}OH + DCC \longrightarrow (Z\text{-}AA)_2O + DCU \qquad (1)$$

analagous to that of simple carboxylic acids.[6,7–10] Mention may be made that Z-Asp(OH)-OH and Z-Glu(OH)-OH form the expected cyclic anhydrides instead.[9] It has been reported that benzoyl amino acids are converted to azlactones by carbodiimides.[11]

There is an extensive literature in which azlactones have been proposed as intermediates in certain peptide syntheses including those mediated by carbodiimides.[12–15] The criterion for suspecting an inter-

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(3) (a) Public Health Fellow 1963–1964; (b) Public Health Fellow 1961–1963.

(4) D. F. DeTar, W. Honsberg, U. Honsberg, A. Wieland, M. Gouge, H. Bach, A. Tahara, W. S. Brinigar, and F. F. Rogers, Jr., *J. Am. Chem. Soc.*, **85**, 2873 (1963).

(5) (a) D. F. DeTar and R. Silverstein, *ibid.*, **87**, 1013 (1965); (b) *ibid.*, **87**, 1020 (1965).

(6) In this paper the conventional amino acid abbreviations are used in a special way: the symbols stand for the stem alone. Glycine is H-Gly-OH, aspartic acid is H-Asp(OH)-OH; the β-methyl ester of aspartic acid is H-Asp(OCH_3)-OH. This procedure permits the precise description of all derivatives. In addition Z is used for benzyloxycarbonyl, Bz always stands for benzoyl, Bl stands for benzyl, HONP for *p*-nitrophenol, HOPCP for pentachlorophenol, DCC for dicyclohexylcarbodiimide, DCU for dicyclohexylurea, DPC for diisopropylcarbodiimide, DPU for the urea, and CMC for cyclohexyl(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate: see ref 14 and R. Schwyzer, J. Rudinger, E. Wünsch, and G. T. Young, "Peptides," G. T. Young, Ed., Pergamon Press Ltd., London, 1963, p 261. The term "peptide acid" is defined as an acylated amino acid where the acyl group may be derived either from a simple acid such as benzoic acid or from an amino acid. A peptide acid may therefore contain only one amino acid residue or it may contain several. The symbol H-AA-OH stands for any amino acid. Z-AA-OH is the benzyloxycarbonyl derivative of an amino acid while the Acyl of Acyl-AA-OH refers to any acid such as acetyl, benzoyl, or a "peptide acid" moiety.

(7) There is an admirable summary of the literature in ref 8.

(8) G. Tadema, E. Harryvan, H. J. Panneman, and J. F. Arens, *Rec. Trav. Chim.*, **83**, 345 (1964).

(9) I. Muramatsu, *Nippon Kagaku Zasshi*, **82**, 83 (1961); *Chem. Abstr.*, **56**, 10273*g* (1962).

(10) H. Schüssler and H. Zahn, *Chem. Ber.*, **95**, 1076 (1962).

(11) (a) I. Z. Siemion and K. Nowak, *Roczniki Chem.*, **34**, 1479 (1960); *Chem. Abstr.*, **55**, 21096*i*; (b) *Roczniki Chem.* **35**, 979 (1961); *Chem. Abstr.*, **56**, 6084*d*.

(12) The following references and those given in ref 13–15 are representative of a very extensive literature: (a) M. Bergmann and H. Köster, *Z. Physiol. Chem.*, **159**, 179 (1926); (b) M. Bergmann and L. Zervas, *Biochem. Z.*, **203**, 280 (1928); (c) H. E. Carter and C. M. Stevens, *J. Biol. Chem.*, **133**, 117 (1940).

(13) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, p 832.

Table I. Stoichiometry of the Reactions of Acids with Dicyclohexylcarbodiimide

Acid	Initial concn of acid, *M*	Initial concn of DCC, *M*	Solvent	Time[a]	Ratio[b]
Acetic	0.0227	0.0343	$CHCl_3$	80	0.61
Pivalic	0.0239	0.0342	CH_2Cl_2	48	0.71
Z-Asp(OCH_3)-OH(L)	0.0111	0.0164	CH_2Cl_2	1	0.51
Z-Gly-OH	0.050	0.050	CH_3CN	6	0.52
Z-Phe-OH(L)	0.0375	0.0372	EtOAc	42	0.51
Z-Phe-Asp(OCH_3)-OH[c]	0.0503	0.0527	CH_2Cl_2	23	0.99
Z-Ser(H)-OH(L)	0.050	0.050	CH_3CN	340[d]	1.0
Bz-Phe-OH(L)	0.040	0.040	CH_3CN	16	0.95[e]
Bz-Pro-OH(L)	0.040	0.040	CH_3CN	16	0.50[b,f]
Z-Gly-Phe-OH(DL)	0.040	0.040	CH_3CN	47	0.98
Z-Phe-Asp(OCH_3)-OH(LL)	0.040	0.040	CH_3CN	16	0.98
Z-Gly-Asp(OCH_3)-OH(L)	0.050	0.050	CH_2Cl_2	[g]	1.0

[a] Time in minutes for recorded value of the ratio. [b] Moles of DCC reacted per mole of acid reacted. In all cases except for Z-Ser-OH the concentration of DCC reached a constant value within 0.5 hr and remained appreciably constant for several hours. Subsequent reactions of the products described later occur much more slowly. [c] Same results were obtained with CMC. [d] Ratio was 0.53 at 2 min, 0.71 at 14 min, and 0.91 at 74 min. [e] Ratio was 0.99 after 18 min with DCP; ratio was 0.95 after 105 min with CMC. [f] After 840 min another 0.5 mole of DCC was consumed. The products have not been studied. [g] First curve after 6 hr; 0.05 *M* HONP was also present and the 1770-cm^{-1} peak of the nitrophenyl ester has just begun to appear at 6 hr. Reaction essentially complete between 117 and 180 hr.

mediate azlactone is the occurrence of partial racemization; of the Leu, *e.g.*, in eq 2. There is considered to

$$\text{Ac-Leu-OH} + \text{H-Gly-OEt} \longrightarrow \text{Ac-Leu-Gly-OEt} \quad (2)$$

be a structural requirement: the acyl group in acyl-AA-OH may be derived from any common carboxylic acid or peptide acid but may not be an alkoxycarbonyl group. It appears to be impossible to prepare an azlactone from the latter. The rationale may be summarized briefly. (1) Azlactones have been prepared by action of acetic anhydride and other reagents under conditions resembling a peptide synthesis.[16,11] (2) In most (but not all) cases the azlactone was racemic even though the starting material was optically active.[16-18] (3) Azlactones are acylating agents and hence are plausible intermediates.[16-19] (4) The extent of racemization can sometimes be correlated with presumed opportunity for azlactone formation.[13-15] (5) Studies with three isolated optically active azlactones have shown that for these specific examples racemization competes seriously,[17] sometimes overwhelmingly,[18] with nucleophilic reaction to form product.

Although such speculations are most reasonable, there have been very few studies on isolated saturated azlactones, and no quantitative studies at all to establish unambiguously what may be occurring in the peptide syntheses. Much remains unknown about the influence of structure on relative rates of racemization and nucleophilic attack of azlactones, and occurrence of or absence of racemization may not always be reliable evidence about azlactone intermediates.

Results

Reaction Stoichiometry. In spite of the extensive work with peptide acids and carbodiimides already mentioned, the stoichiometry of these reactions has not been investigated. Anhydride formation (eq 3) requires 0.5 mole of carbodiimide per mole of acid while either acylurea or azlactone formation requires 1 mole of each.

$$2\text{RCOOH} + \text{DCC} \longrightarrow (\text{RCO})_2\text{O} + \text{DCU} \quad (3)$$

$$\text{RCOOH} + \text{DCC} \longrightarrow \text{RCODCU} \quad (4)$$

$$\text{peptide acid} + \text{DCC} \longrightarrow \text{azlactone} + \text{DCU} \quad (5)$$

The carbodiimide concentration is readily determined from the 2115-cm^{-1} peak, and the infrared curves usually provide identification of other components as well. We therefore studied the reactions of representative acids with DCC as reported in Table I. Typical products isolated from these reactions on a preparative scale are listed in Table II. In most cases a plot of the carbodiimide concentration *vs.* time showed a definite plateau after 5–15 min with peptide acids and after about 30 min with acetic and pivalic acids. Z-Ser-(H)-OH showed an appreciable drift due to reactions considered below, and Z-Gly-OH and Z-Asp(OCH_3)-OH showed a more gradual drift amounting to an additional 20–30% consumption of DCC after 4 hr and to complete disappearance of carbodiimide after 20–40 hr. These subsequent reactions are considered in the following section.

Table II. Isolable Products from the Reactions of Dicyclohexylcarbodiimide with Peptide Acids

Coreactant(s)	Isolated product, %
Bz-Gly-OH	Azlactone, 90 (crude)
Bz-Ph-OH(L)	DL-Azlactone, 42 (recrystd)
Z-Gly-Phe-OH(L)	DL-Azlactone, 44 (recrystd)
Z-Phe-Asp(OCH_3)-OH(LL)	Azlactone, 57
Bz-Gly-OH, $(C_2H_5)_3N$	Bz-Gly-DCU
Z-Gly-OH	$(\text{Z-Gly})_2\text{O}$, 44
Z-Gly-OH, $(C_2H_5)_3N$	Z-Gly-DCU, 45 (crude)

Acetic acid and pivalic acid show the intermediate stoichiometry characteristic of a competition between anhydride and acylurea formation (eq 3 and 4.)[5] In contrast, the peptide acids for the most part show a clean 0.5:1 or 1:1 stoichiometry initially. Although these results are consistent with the preparative work

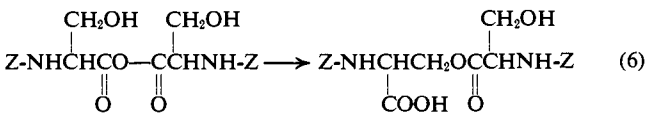
(14) M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **12**, 488 (1957).
(15) N. F. Albertson, *Org. Reactions*, **12**, 157 (1962).
(16) (a) E. Mohr and T. Geis, *Ber.*, **41**, 798 (1908); (b) E. Mohr and F. Stroscheim, *ibid.*, **42**, 2521 (1909).
(17) M. Anchel, O. Wintersteiner, A. E. O. Menzel, H. E. Stavely, J. D. Dutcher, and M. Moore, ref 41, p 802.
(18) M. Goodman and L. Levine, *J. Am. Chem. Soc.*, **86**, 2918 (1964).
(19) Reference 13, p 838.

referred to above, they permit conclusions not previously evident.

Subject to the more detailed study of Z-Ser(H)-OH described next, it may be concluded that all the benzyloxycarbonylamino acids (Z-AA-OH) studied and also Bz-Pro-(OH) give the anhydride quantitatively with no detectable acylurea.[20] Likewise all the acyl-AA-OH studied, except Ac-Gly-OH which is discussed below, give the azlactone quantitatively. The stoichiometry does not distinguish between acylurea and azlactone. This distinction can be made in part from the product isolations reported, but it was also made on the basis of the appearance of the azlactone peaks, and quantitative determinations were made for the azlactone of Bz-Phe-OH in several runs with all three carbodiimides.

The exceptional behavior of Z-Ser(H)-OH was explored in some detail. Sheehan has reported that tritylserine produces modest yields of β-lactone upon reaction with DCC.[22] There therefore are two likely primary reactions of Z-Ser(H)-OH with DCC and one less likely: (1) anhydride formation, (2) β-lactone formation, and (3) azlactone formation. The first reaction requires 0.5:1 stoichiometry while the latter two both require 1:1 stoichiometry. A systematic investigation of the reaction showed that there was a break in the curve of DCC disappearance after about 8 min and that the disappearance of the remaining DCC required several hours. After 8 min the DCU yield, determined gravimetrically, was 0.5 mole/mole of Z-Ser(H)-OH. This result was obtained for whichever component was in excess, and therefore anhydride formation is the principal primary reaction.

In the reaction of Z-Ser(H)-OH with DCC a peak appears at 1830 cm^{-1} which reaches its maximum value after about 8 min and which may be assigned to the anhydride. (Azlactones and β-lactones also absorb in this region.)[23] The anhydride peak gradually disappears as the reaction proceeds. In spite of considerable effort we were unable to isolate definite products. It is proposed that the anhydride rearranges through a six-membered cyclic transition state to give the ester (eq 6).



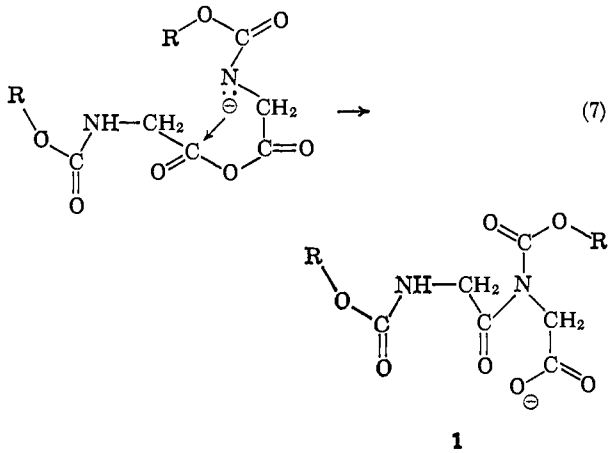
(6)

Subsequent reaction of the resulting carboxyl group with carbodiimide will give a new anhydride which can also rearrange, and the ultimate result will be formation of a low molecular weight polyester with perhaps some acylurea at the C terminus. The infrared curves and the product properties are consistent with this formulation. While it should be possible for $[Z\text{-}Ser(H)]_2O$ to give secondary reactions analogous to those described below for $(Z\text{-}Gly)_2O$, this latter reaction appears in two cases to be appreciably slower than the serine reaction, and hence may be expected to be relatively unimportant.

There is a report that Z-Gly-Phe-OH gives the anhydride,[10] but we find that azlactone is the only detectable product. The reported reactant ratios gave a mixture of azlactone and unchanged acid which may be a eutectic since the melting point is sharp and corresponds with that reported for "anhydride."

Bz-Gly-OH reacts to give the azlactone in a 1:1 reaction (and with typical azlactone peaks at 1830 and at 1660 cm^{-1}) while Ac-Gly-OH gives a mixture of anhydride and azlactone with an intermediate stoichiometry. Arens and his co-workers prepared $(Z\text{-}Gly\text{-}Gly)_2O$ and $(Z\text{-}Gly\text{-}Gly\text{-}Gly)_2O$ by reaction of the corresponding acids with ethoxyacetylene.[8,24,25] Both the anhydride of CF_3CO-Ala-OH and the azlactone have been reported.[26] Hence the exact scope of azlactone *vs.* anhydride formation in terms of the structure of the acyl group, of the amino acid residue, and of the "dehydrating" agent remains to be delineated.

Reaction of $(Z\text{-}Gly)_2O$ and DCC. This reaction gave a product (30% yield) which by nitrogen analysis and molecular weight determination consisted of a 1:1 adduct. The nmr spectra showed the presence of two nonequivalent benzyl groups, two glycine CH_2 groups, and two cyclohexane rings, and that the two benzyl groups were different. It is therefore not a symmetrical bisacylurea. The adduct has been identified as the acylurea (**2**) of a rearrangement product of the anhydride (**1**, eq 7). The first report of such a rearrangement appears to be that of $(CF_3CO\text{-}Gly)_2O$ described by Weygand.[27] Z-Gly-$N(Z)CH_2COOH$ was isolated by



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Wieland,[28] and was recently prepared by Arens by heating $(Z\text{-}Gly)_2O$ in benzene.[8] There is also the observation of Kopple that reaction of Z-Gly-OH and HCl-H-Gly-OEt with ethyl chloroformate and base gave a triglycine derivative and this was explained by the rearrangement.[29] We find that the rearrangement occurs rapidly at room temperature in the presence of bases: no anhydride is present after 5 min in the presence of 0.04 *M* triethylamine. The reaction is almost certainly an intramolecular one through a five-membered ring cyclic transition state. Arens and his

(20) The formation of acylureas in the presence of bases is, however, well documented.[21] The preparation of Z-Gly-DCU and of Bz-Gly-DCU are mentioned in the Experimental Section.

(21) There are many reports, *e.g.*, N. A. Smart, G. T. Young, and M. W. Williams, *J. Chem. Soc.*, 3902 (1960); ref 48.

(22) J. C. Sheehan, K. Hasspacher, and Y. L. Yeh, *J. Am. Chem Soc.*, **81**, 6086 (1959).

(23) Infrared correlations are given in Table IV.

(24) See also M. Bodanszky and C. A. Birkhimer, *Chem. Ind.* (London), 1620 (1962).

(25) This might also reflect the lesser basicity of the ethoxyacetylene reaction than the DCC reaction, for the rearrangement of an anhydride to an azlactone may be expected to be base catalyzed.

(26) F. Weygand and U. Glöckler, *Chem. Ber.*, **89**, 653 (1956).

(27) F. Weygand and M. Reiher, *ibid.*, **88**, 26 (1955).

(28) T. Wieland and B. Heinke, *Ann.*, **599**, 70 (1956).

(29) K. D. Kopple and R. J. Renick, *J. Org. Chem.*, **23**, 1565 (1958).

co-workers attempted without success to find an intermolecular analog.

The rearrangement has not been studied with other anhydrides, but the gradual reaction of $[Z\text{-}Asp(OCH_3)]_2O$ with DCC suggests that it is also occurring here. It may be noted that carbodiimides do not react with simple anhydrides such as acetic, benzoic, or pivalic anhydride since there is no drift in DCC concentration after many hours (Table I and ref 5a). The $(Z\text{-}AA)_2O$ are stable in solution at room temperature in the absence of DCC, and the occurrence of the rearrangement constitutes evidence of weak base catalysis by DCC.

The complete stoichiometry of the reaction of $(Z\text{-}Gly)_2O$ and DCC has not been established. On the basis that 0.65 mole of DCU is formed per mole of DCC, and from other indirect but reasonable considerations, it was suggested that N,N′-Z_2-diketopiperazine is formed, although this product has not been isolated nor has any direct evidence yet been reported.[30a] Further examples of the reaction of Z-Gly-OH and DCC (1:1) gave 0.75 mole of DCU and 0.14 mole of **2** (DCU derivative of **1**) per mole of DCC;[30b] in other words **2** accounts for 25–30% of the Z-Gly-OH taken in these reactions. Examination of the infrared curves of the crude product mixtures after several hours shows the absence of anhydride bands at 1820 cm^{-1}. It may be remarked that the reactions of 1:1 Z-Gly-OH and DCC and of 1:1 $(Z\text{-}Gly)_2O$ and DCC are essentially equivalent, since the initial formation of $(Z\text{-}Gly)_2O$ is rapid and quantitative.

Reaction Kinetics. In the stoichiometric studies reported in Table I the time course of the reaction was followed and permits a rough evaluation of reaction rates. Results are summarized in Table III. Certain observations may be made. Peptide acids react very rapidly with carbodiimides, about fifty times faster than simple carboxylic acids. Differences among the peptide acids amount to a factor of about three, and CMC[6] reacts about one-third to one-fifth as fast as DCC or DPC.

Table III. Rates of Reaction of Peptide Acids with Dicyclohexylcarbodiimide in Acetonitriles

Acid	Concn of RCOOH[b]	Concn of DCC[b]	k[c]
Z-Gly-OH	0.080	0.040	0.45
Bz-Phe-OH	0.040	0.040	0.30
Z-Gly-Phe-OH	0.040	0.040	0.30
Z-Phe-Asp(OCH_3)-OH	0.040	0.040	0.60[d]
Bz-Pro-OH	0.040	0.040	0.90
Bz-Phe-OH	0.040	0.040[e]	0.06[e]
Bz-Phe-OH	0.040	0.040[f]	0.45[f]
Bz-Phe-OH	0.040	0.040	0.33[g]
Z-Gly-OH	0.080	0.040[f]	0.50[f]
Z-Ser-OH	0.022	0.024	0.8
Z-Ser-OH	0.022	0.026[e]	0.3[e]

[a] Temperature was ambient with some rise in the infrared cell, about 27°. [b] Initial concentrations, molar. [c] Units are moles^{-1} l. sec^{-1}. Rate measured was disappearance of carbodiimide peak at 2115 cm^{-1}. [d] 0.8 in CH_2Cl_2. [e] CMC. [f] DPC. [g] HONP 0.04 M also present.

(30) (a) E. Taschner, A. Kuziel, T. Vajda, and B. Rzeszotarska, *Angew. Chem.*, 77, 54 (1965); T. Vajda, A. Kuziel, F. Ruff, B. Rzeszotarska, and E. Taschner, *Acta Chim. Acad. Sci. Hung.*, **44**, 45 (1965); (b) experiments by T. Vajda.

***p*-Nitrophenyl Ester Formation.** It is well known that Z-AA-OH react with *p*-nitrophenol in the presence of DCC to give optically active *p*-nitrophenyl esters,[15] and there are scattered reports that acylated derivatives give racemic esters,[18,31a] although this has not been well established. During the course of the present study it has been reported that the azlactone is an intermediate in the reaction of DCC, Bz-Phe-OH, and HONP.[31b]

The rate of reaction of Bz-Phe-OH with DCC in the presence of *p*-nitrophenol was found, as expected, to be the same as with *p*-nitrophenol absent. From the infrared curves of reaction mixtures, it is obvious that the first identifiable product is the azlactone (1820-cm^{-1} peak). Typical 1780-cm^{-1} peak of the *p*-nitrophenyl ester appears only slowly. The reaction of azlactone with *p*-nitrophenol under these conditions is only about $^1/_{1000}$ as fast as the reaction between DCC and Bz-Phe-OH to give azlactone.

The reaction of azlactone with *p*-nitrophenol is strongly susceptible to base catalysis. A solution of the azlactone of Bz-Phe-OH in acetonitrile (0.004 M) showed no change in intensity of the 1820-cm^{-1} azlactone peak over a period of 26 hr at room temperature, nor was there appreciable reaction in the presence of 0.004 M DCC. There was no detectable reaction between the azlactone and *p*-nitrophenol each 0.04 M in acetonitrile over a period of 6 hr, but addition of DCC (to give 0.04 M) resulted in disappearance of azlactone with a "half-time" of 13 hr due to base catalysis by DCC.

The reaction of the isolated azlactone of Bz-Phe-OH with *p*-nitrophenol has been studied by Goodman and Levine who found it to be reversible. They measured the rate in both directions in dioxane, and found that partly optically active azlactone racemizes more rapidly than it reacts with *p*-nitrophenol.[18]

Our observations on formation of racemic *p*-nitrophenyl esters may be summarized as follows: Z-Gly-Asp(OCH_3)-ONP was about 75–80% DL with either DCC or CMC,[32] Ac-Ala-ONP was about 85% DL,[33] and Bz-Lys(Z)-ONP, Ac-Leu-ONP, and Z-Gly-Phe-ONP were completely racemic.[33]

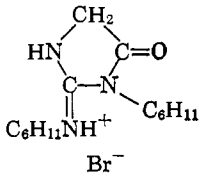
It has been reported that a polymer with 98% retention of optical activity was obtained by a synthesis involving two separate steps in which a dipeptide or a tripeptide acid was converted to a pentachlorophenyl ester using DCC.[34] We therefore carried out experiments with pentachlorophenol to see whether this phenol gives results substantially different from *p*-nitrophenol. With acetic acid and DCC there was, in contrast to the *p*-nitrophenol reactions, no detectable acetic anhydride and the yield of acetyldicyclohexylurea was negligible.[35] However, with both Bz-Phe-OH and with Z-Gly-Phe-OH, the azlactone formed rapidly and the pentachlorophenyl ester appeared slowly.[36] Under the mildest conditions Z-Gly-Asp(OCH_3)-OH reacted to give a nearly racemic pentachlorophenyl ester.[36] Hence racemization may be expected to be an im-

(31) (a) W. D. Cash, *J. Org. Chem.*, 27, 3329 (1962); (b) M. M. Botvnik, S. N. Kara-Murza, S. M. Avaeva, and V. Ya. Nikitin, *Dokl. Akad. Nauk, SSSR*, **156**, 88 (1964); *Chem. Abstr.*, **61**, 3192 (1964).
(32) Experiments by M. Gouge.
(33) Experiments by K. Schührer.
(34) J. Kovacs and A. Kapoor, *J. Am. Chem. Soc.*, **87**, 118 (1965).
(35) Experiments by B. O. Bohannon.
(36) Experiments by N. Estrin.

portant problem in the synthesis of pentachlorophenyl esters as well.

Reactions of Carbodiimides with Amino Esters. It has been reported that glycine ethyl ester reacts with DCC to form **3**.[37] We find likewise that stirring a suspension of HBr-H-Gly-ONP in acetonitrile which is 0.01 *M* in DCC leads to a disappearance of the 2115-cm^{-1} carbodiimide peak with a "half-time" of roughly 0.5 hr at room temperature and to the appearance of peaks at 1670 and 1775, and of free *p*-nitrophenol at 1115 cm^{-1}. With CMC similar changes occurred about one-fiftieth as fast. The reaction rate is determined in part by the rate of solution of the hydrobromide salt. The less soluble HCl-H-Gly-OEt reacts more slowly, and there is no reaction in methylene chloride in which the salts are insoluble.

The product of the reaction with DCC was 1-cyclohexyl-2-cyclohexylimino-4,5-dihydro-5-imidazolone hydrobromide (**3**). Treatment with triethylamine gave the free base **4**. The structures are supported by the elemental analyses, by the mode of formation, by the



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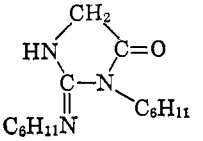

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infrared spectra, and by analogy with the guanidine formation observed for related reactions.[38]

Based on similar changes in the infrared spectra, there is also a guanidine-forming reaction between DCC and HCl-H-Gly-OC_2H_5 and between DCC and HBr-H-Ser-Gly-ONP, but the ester peak remains in both cases. Evidently the carbethoxyl group is not sufficiently reactive for cyclization in the absence of triethylamine,[37] and the nitrophenyl ester group of the dipeptide is too far away.

These reactions are fast enough to be a source of byproducts in certain peptide syntheses.

Diagnostic Infrared Peaks. In Table IV are summarized the positions and relative intensities of characteristic infrared peaks useful in identifying the components of reaction mixtures.[39] It is not usually possible to distinguish an anhydride 1800–1840 from an azlactone 1820–1840 cm^{-1} on the basis of the spectra since other components interfere with the second band. However, these compounds can be distinguished readily from *p*-nitrophenyl esters (1770–1780 cm^{-1}), and all of these activated carboxyl compounds can be distinguished from normal esters, acids, and amides.

Azlactones. To provide definitive samples for reference spectra azlactones of the following peptide acids[6] were prepared: Bz-Gly-OH, Bz-Phe-OH, Z-Gly-Phe-OH, and Z-Phe-Asp(OCH_3)OH. The last two are new compounds.[40]

(37) I. Muramatsu, T. Hirabayashi, and A. Hagitani, *Nippon Kagaku Zasshi*, **84**, 855 (1963); *Chem. Abstr.*, **60**, 12100c.

(38) *Cf.*, *e.g.*, J. Macholdt-Erdniss, *Chem. Ber.*, **91**, 1992 (1958).

(39) Excellent compilations such as Bellamy do not treat peptide derivatives adequately for present needs: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1958.

(40) For references to saturated azlactones, see ref 16–18 and 41–44.

(41) J. W. Cornforth, "The Chemistry of Pencillin," H. T. Clarke, J. R. Johnson and R. Robinson, Ed. Princeton University Press, Princeton, N. J., 1949, p 731.

Table IV. Summary of Infrared Bands of Peptide Derivatives (2200–1550-cm^{-1} Region)

Group	Characteristic peaks, cm^{-1} [a]	Approx[b,c] ext coeff
$C_6H_5CH_2OCONH$	1720–30[e]	600
Acyl-NH	1650–70[d]	600
	1690–1700	600
Anhydride	1730–50	200
	1800–40	400
Azlactone	1650–85	300
	1820–40	400
COONP	1770–80	300
COOH	1730–60	400
$COOCH_3$	1720–30	400
Imide $(RCO)_2N$	1750–60	300
N=C=N	2100–2200	1700

[a] Values in the table represent for the most part solutions in acetonitrile; some refer to solutions in CH_2Cl_2 or in $CHCl_3$. The positions of the peaks are not very sensitive to solvent. [b] Absorbance = extinction coefficient × concentration (molar) × path length. [c] These extinction coefficient values serve primarily as a rough guide. They are sensitive not only to slit program but also to solvents. If two peaks are adjacent but not coincident, the resulting peak may be clearly broader than normal, but with little increase in the extinction coefficient. If two groups are present as in $(Z\text{-Gly})_2O$, then the concentration of Z groups is twice that of anhydride groups and the 1730-cm^{-1} peak is especially prominent. [d] Bz-Pro-OH 1630. These peaks are sometimes at 1550–1590 cm^{-1} in solids. [e] At 1670–1700 cm^{-1} in solid peptides.

Experimental Section[45]

Solvents. Acetonitrile and carbon tetrachloride were purified as described elsewhere.[5]

Nmr and Infrared. Reported nmr values are cycles per second from tetramethylsilane at 60 Mc (Varian A-60). Use of the peaks for structure identification has been placed ahead of specification in terms of chemical shifts and coupling constants. Infrared spectra were run on the Perkin-Elmer 137 Infracord, on the PE 221, or on the PE 21, as specified. The peak locations with the 137 are about ±10 cm^{-1}, although assignments are made with reference to the polystyrene 1601-cm^{-1} peak, routinely entered on each curve.

Order of Listing. The preparations are listed in the order monopeptides and then dipeptides. They are in alphabetical order starting with the N terminus. All optically active amino acids are pure L.

Z-Gly-OH. The sample had mp of 119–120° (lit.[46] mp 120°); infrared (137, acetonitrile) 1720 (urethan), 1755 (COOH); (mineral oil mull or KBr pellet) 1730, 1680, 1535 cm^{-1}. The salt, obtained in acetonitrile from the acid plus 10% excess of triethylamine had peaks at 1720 (urethan) and 1655 cm^{-1} (broad COO).

$(Z\text{-Gly})_2O$. This was prepared from Z-Gly-OH and DCC, mp 115–116° (lit.[47] 118°). The molecular weight in acetonitrile (vapor phase osmometer) was 392; calcd, 400. Quantitative runs (based on the 1838-cm^{-1} peak) using 0.08 *M* Z-Gly-OH and either 0.04 *M* DCC or 0.04 *M* DPC in acetonitrile showed 92–99% yields of anhydride and 95% reaction after 15 min. Upon long standing, the 1838-cm^{-1} peak diminished. The anhydride was half gone in 6 hr, and three-quarters was gone in 48 hr in the DCC case, and 40% gone in 130 hr in the DPC case. The infrared spectrum (221, acetonitrile) showed 1838 (anhydride, extinction coefficient 460), 1725 (urethan), and 1755 cm^{-1} (shoulder, anhydride); (137, mineral oil mull): 1820, 1755, 1690, and 1540 cm^{-1}.

(42) (a) J. W. Cornforth, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., 1957, Chapter 5.

(43) E. Baltazzi, *Quart Rev.* (London), **9**, 150 (1955); J. D. Loudon in "Chemistry of Carbon Compounds," Vol. IVA, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1957, p 365.

(44) (a) K. Nowak. I. Z. Siemion, and H. Siemeniewski, *Roczniki Chem.*, **36**, 557 (1962), *Chem. Abstr.*, **57**, 12613*i*; (b) M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, **11**, 39 (1960).

(45) The nitrogen analyses, the *p*-nitrophenol determinations, and many of the optical rotations were run by Mrs. Lillian Ross.

(46) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(47) T. Wieland, W. Kern, and R. Sehring, *Ann.*, **569**, 117 (Z950).

Pure $(Z\text{-Gly})_2O$ (0.04 *M*) and water (2.2 *M*) in acetonitrile show no perceptible loss of anhydride after 1 hr, and it takes 50 hr for about 75% hydrolysis. Hydrolysis is more rapid in the presence of bases. On standing for many hours (30–50 hr) in acetonitrile, $(Z\text{-Gly})_2O$ solutions show barely noticeable development of a peak at 1200 cm^{-1} representing perhaps 5% conversion to Z-Gly-N(Z)CH_2-COOH. The rearrangement is markedly accelerated by bases such as triethylamine, and to a much less extent by DCC: the anhydride peak at 1830 cm^{-1} disappears and there remains a somewhat broad peak centered on 1725 with a shoulder at 1700, another small shoulder at 1650, there is a small peak at 1600 (COO^-), and a strong peak at 1200 cm^{-1}.

Z-Gly-DCU. This was obtained by the reaction of DCC, Z-Gly-OH, and triethylamine, mp 144–145° (lit.[48] mp 143.5–145.5°).

Anal. Calcd for $C_{23}H_{33}O_4N_3$: N, 10.11; mol wt, 415. Found: N, 10.22; mol wt, 414 ($CHCl_3$, extrapolated to infinite dilution).

The infrared spectrum (221, acetonitrile) showed 1724 (urethan), 1704 (urea), and 1670 cm^{-1} (urea); (mineral oil) 1705, 1685, and 1525 cm^{-1}; the nmr showed 444 (phenyl), 316 (CH_2O), 260 (CH_2 of Gly), and a complex of peaks due to cyclohexyl.

The reaction of Z-Gly-OH + DCC + $(C_2H_5)_3N$, all 0.04 *M* in acetonitrile, produces mainly Z-Gly-DCU. However, about 20% of DCU is formed, and it seems likely that this means that about 20% of $(Z\text{-Gly})_2O$ was also formed (and hydrolyzed). If so, the fate of this is probably mostly hydrolysis (base catalyzed) since the amount of rearranged product is only about 5–10% judging from the 1210-cm^{-1} peak.

Bz-Gly-OH. The infrared spectrum (137, KBr) showed 1750, 1615, and 1550 cm^{-1}; salt from triethylamine + Bz-Gly-OH (in acetonitrile) 1650, 1610, and 1575 cm^{-1} (weak).

Bz-Gly-DCU. To a solution of 3.58 g of Bz-Gly-OH and 3.0 ml of triethylamine in 125 ml of acetonitrile at room temperature was added 4.12 g of DCC. The mixture showed peaks at 1825 cm^{-1} indicative of azlactone. Filtration of the red mixture after 16 hr gave 3.73 g of colorless crystals, mp 167–189°, which proved to be a mixture of Bz-Gly-DCU and DCU. The filtrate showed strong carbodiimide absorption (2115 cm^{-1}) and upon standing at −20° for 3 days deposited an additional 1.25 g of solid which was richer in acylurea than the first precipitate. Repeated recrystallization from ethyl acetate gave Bz-Gly-DCU, mp 156–160°.

Anal. Calcd for $C_{22}H_{31}N_3O_3$: N, 10.90. Found: N, 10.70.

The infrared spectrum (137, acetonitrile) showed 1730 (shoulder), 1700 (urea), and 1660 cm^{-1} (urea); (mineral oil) 1695, 1650, 1635, and 1525 cm^{-1}; the nmr showed (in $CDCl_3$) phenyl 438–477; CH_2, 253, 259. Reaction with half the amount of triethylamine gave no isolable acylurea.

Azlactone of Bz-Gly-OH. This was prepared either by action of acetic anhydride or of DCC on Bz-Gly-OH, mp 89–90° (lit.[49] 94–95°), mol wt 162 ± 5 (vapor phase osmometer, methanol); calcd 161; the infrared spectrum (137, acetonitrile) showed 1825 and 1655 cm^{-1} azlactone; (solid film) 1805, 1750 (w), 1700 (w), 1640 (broad), 1590 (w), 1570 (w), and 1525 cm^{-1} (broad), and about 25 others.

Bz-Phe-OH(L). The infrared spectrum (137, acetonitrile) showed 1750 (COOH) and 1660 cm^{-1} (amide).

Azlactone of Bz-Phe-OH. This was prepared in five different ways by use of acetic anhydride, DCC, DPC, CMC, or ethyl chloroformate as dehydrating agents, mp 70.5–71°, $[\alpha]^{25}D$ 0.00 (*c* 2, acetone) (lit.[16b] mp 71°).

Anal. Calcd for $C_9H_{13}NO_2$: C, 76.46; H, 5.22; N, 5.57; mol wt, 251. Found: C, 76.57; H, 5.33; N, 5.56; mol wt, 246 (vapor phase osmometer, ethyl acetate).

The infrared spectra and the melting points of all samples were closely comparable; the infrared spectrum (221, acetonitrile) showed 1821 and 1656 cm^{-1}; (solid film): more than 30 sharp peaks, 1830 (azlactone), and 1655 cm^{-1} (azlactone).

The reaction of Bz-Phe-OH with DCC, with DPC, and with CMC was also observed quantitatively in solution. The resulting azlactone solution is stable for days. If triethylamine is present initially, the amount of DCC that disappears is 1 mole for each mole of "free" acid, and the carboxylate peak at 1700 cm^{-1} remains since further reaction of peptide acid and DCC is very slow in the presence of triethylamine.

Bz-Phe-ONP.[31b] The infrared spectrum (137, mineral oil) showed 1755 (CONP), 1630 (amide), and 1520 cm^{-1} (broad); (acetonitrile) 1765 (CONP) and 1660 cm^{-1} (amide).

Bz-Pro-OH. The infrared spectrum (137 mineral oil) showed 1730, 1590, and 1570 cm^{-1}.

Z-Gly-N(Z)CH_2CODCU. A solution of 3.20 g of $(Z\text{-Gly})_2O$ and 1.65 g of DCC in 150 ml of acetonitrile deposited 0.5 g of DCU after standing for 12 days. Evaporation of the solvent gave an oil which gave crystals when taken up in a little ethyl acetate and diluted with hexane, mp 115–120°; another sample prepared by Vajda[30b] and recrystallized from acetonitrile and pentane had mp 126–128°.

Anal. Calcd for $C_{33}H_{42}N_4O_7$: N, 9.23; mol wt, 607. Found: N, 9.32; mol wt, 592 (vapor phase osmometer, acetonitrile).

The infrared spectrum (137, oil) showed 1760, 1690, 1660, and 1530 cm^{-1}; there is a characteristic strong peak at 1210 cm^{-1}; the nmr (TFA) showed 446 (phenyl), 443 (second phenyl), 323 and 316 (benzyl CH_2), 292, 289 (CH_2 of glycine), and broad absorption around 100 due to cyclohexyl groups; broad absorption around 235 may be due to NH; ($CHCl_3$) 443, 9.3 (10 H of 2 C_6H_5), 317, 311, 3.8 (two different Bl CH_2), 283, 281, 278, 3.8 (two Gly CH_2, one singlet at 281), 50–140, 23 (two C_6H_{11} groups). Absorption (broad) at 230 and at 335 may be due to NH.

Treatment of $(Z\text{-Gly})_2O$ with triethylamine gave a taffy from which it was possible to isolate a small amount of Z-Gly-N(Z)CH_2-COOH, mp 128–130° (lit.[17] 134–135°). This had strong absorption at 1215 cm^{-1} (not present in Z-Gly-OH).

Z-Gly-Phe-OH(L **and** DL). These were prepared by the reaction of Z-Gly-ONP with either L-H-Phe-OH or DL. Z-Gly-Phe-OH(L) had mp 125–125.5°, $[\alpha]^{25}D$ +12.3 (*c* 2, acetonitrile) (lit.[50] mp 125–126°). The DL form had mp 157–161° (lit.[51] mp 159.5–160.5°), the infrared spectrum (137, acetonitrile) showed 1750 (sh) (COOH), 1720 (urethan), and 1680 cm^{-1} (peptide NH).

Azlactone of Z-Gly-Phe-OH. To a mixture of 1.42 g of Z-Gly-Phe-OH in 100 ml of acetonitrile at room temperature was added 0.824 g of DCC. Filtration after 1 hr gave 0.817 g (92%) of DCU. The solvent was removed and the residue was recrystallized from an ethyl acetate–hexane mixture to give 0.590 g (44%) of the azlactone, mp 70.5–72°.

Anal. Calcd for $C_{19}H_{18}N_2O_4$: N, 8.28; mol wt, 338. Found: N, 8.27, mol wt, 337 (osmometer, acetonitrile).

The infrared spectrum (221, acetonitrile) showed 1827 (azlactone), 1684 (azlactone), and 1728 cm^{-1} (for the benzyloxycarbonyl group); (137, mineral oil) 1820, 1715, 1670, and 1535 cm^{-1}; $[\alpha]^{25}D$ 0 (*c* 2, acetonitrile).

Quantitative infrared studies (Table III) show a clean 1:1 stoichiometry for the reaction. In a repeat of the reaction under conditions reported to give the anhydride,[10] a solution of 0.920 g of DL-Z-Gly-Phe-OH and 0.260 g of DCC (2:1 mole ratio) in 40 ml of acetonitrile was stirred at 0° for 12 hr and filtered to give 440 mg of colorless solid A, mp 150–165°. Solvent was removed and replaced by benzene; stirring resulted in crystallization of 233 mg of colorless solid B, mp 157–160°. Addition of pentane and further stirring and cooling to −17° gave 192 mg of colorless solid C, mp 69–72° (small residue cleared at 140°). The melting point reported for the anhydride is 66–68°.

Solid C has infrared peaks of both the acid and the azlactone; the sharp melting point suggests it is the eutectic mixture. Solid B is made up mainly of the acid and DCU (the melting point of Z-Gly-Phe-OH under the same conditions used for B is 160–163°) and A is mainly DCU with some acid.

Z-Phe-Asp(OCH_3)-OH(L,L). This was prepared by the reaction of Z-Phe-ONP and H-Asp(OCH_3)-OH, mp 132–133.5°; neut equiv, 409 (theory 428); $[\alpha]^{25}D$ −17.0 (*c* 2, acetonitrile); the infrared spectrum (KBr) showed 1730, 1690, 1530; (acetonitrile) 1760 (shoulder, COOH), 1730 (urethan + methyl ester, broad), 1670 (amide), and 1600 cm^{-1}.

Azlactone of Z-Phe-Asp(OCH_3)-OH(LL). The preparation was carried out as for the preceding, yield 57%, mp 97.5–100°, $[\alpha]^{25}_{578}$ −53.2 (*c* 2, acetonitrile) (presumably the Asp is largely racemic); the infrared spectrum (221, acetonitrile) showed 1830 and 1680, also 1732 cm^{-1}; (137, mineral oil or KBr) 1805, 1770, 1680, and 1660 cm^{-1}.

Anal. Calcd for $C_{22}H_{22}O_6N_2$: N, 6.83; mol wt, 410. Found: N, 6.80 (within 4 hr); mol wt, 414 (vapor phase osmometer, acetonitrile).

A preparation in methylene chloride yielded 0.92 mole of DCU per mole of DCC, the azlactone had mp 105–106°, and the saponification equivalent was 4.95 mequiv of base per gram (calculated for hydrolysis of both methyl ester and azlactone: 4.95 mequiv/g). The infrared curve was identical with that of the above preparation.

(48) H. Zahn and J. F. Diehl, *Z. Naturforsch.*, **12b**, 85 (1957).
(49) Abbott group, ref 41, p 778.
(50) K. Hofmann and M. Bergmann, *J. Biol. Chem.*, **134**, 225 (1940).
(51) H. Neurath, E. Elkins, and S. Kaufman, *ibid.*, **170**, 221 (1947).

1-Cyclohexyl-2-cyclohexylamino-4,5-dihydro-5-imidazolone (4). A mixture of 13.8 g of HBr-H-Gly-ONP and 10.3 g of DCC in 150 ml of acetonitrile was stirred vigorously at room temperature (25°). After 2.5 hr the 2115-cm^{-1} peak had disappeared. After 1 hr at 0° a precipitate separated, 7.3 g, mp 168–171° dec. A second crop, 2.6 g, mp 255–260°, was obtained from the residue by solution in acetonitrile and precipitation with ether. Recrystallization from acetonitrile gave colorless plates, mp 274–276° dec, in 50% recovery. This is the hydrobromide salt.

Anal. Calcd for $C_{15}H_{26}H_3OBr$: C, 52.32; H, 7.61; N, 12.20; O, 4.65; Br, 23.21. Found: C, 52.89; H, 7.66; N, 12.23; O, 4.89; Br, 22.85.

The infrared spectrum (137, KBr) showed 3250–2880 (broad, complex), 1785, 1670, 1565, 987, 960, 700, 683 cm^{-1}, and other smaller peaks; the nmr spectrum (CF_3COOH) showed 480 (one proton), 426 (doublet, J = 8 cps, one proton), 266 (two protons), 200–255 (broad, maximum at 233, two protons), 50–150 (broad, complex, peaks at 117, 92, 83, 20 protons; ($CDCl_3$) 578 (one proton), 540 (doublet, J = 8 cps one proton), 264–300 (broad, maximum at 280, one proton), 243 (two protons), 190–260 (broad, one proton), 50–150 (broad, maximum at 103, 20 protons).

The free base was obtained by dissolving the hydrobromide salt in chloroform, adding triethylamine, and extracting with water. After drying, hexane was added and the solution cooled to give colorless needles, mp 152–153° (lit.[37] mp 156°).

Anal. Calcd for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57; N, 15.95; O, 6.08. Found: C, 68.49; H, 9.55; N, 15.86; O, 6.31.

The infrared spectrum (137, KBr) showed 3250, 3000, 2900, 2840, 1720, 1605, 1535, 1085, 760, 750 cm^{-1}, and other smaller peaks; the nmr spectrum (CF_3COOH) showed the same as for the salt.

A General, Stereospecific Synthetic Route to Δ^2-Thiazolines

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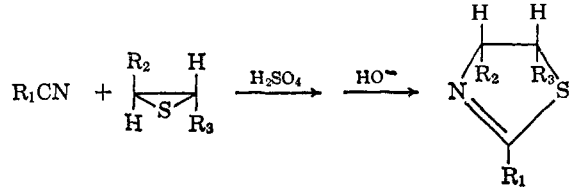
Contribution from the Department of Chemistry, University of California, Riverside California. *Received September 30, 1965*

Abstract: A new route to Δ^2-thiazolines is presented, consisting of treatment of an episulfide with a nitrile in the presence of a strong acid. The stereospecificity of the reaction is shown by production of isomeric thiazolines from *cis*- and *trans*-2-butene episulfides. The reaction is successful with either alkyl or aryl nitriles and gives moderate yields even with hindered nitriles. Polymerization of the episulfide is a competing reaction and predominates in the case of ethylene sulfide. Use of the nitrile as solvent has been found to produce the best yields. Reduced yields result if the product thiazoline is highly strained. A number of new thiazolines have been prepared, and their physical constants and derivatives are reported.

Thiazolines (Δ^2) have been obtained from β-bromoalkylamine salts and thioamides (43–80% yields),[1] from β-mercaptoamines and nitriles (52–89% yields),[2] from the N-thiobenzoyl derivatives of 1,2-amino alcohols (50–78% yields),[3] from diacyl-1,2-amino alcohols and phosphorus pentasulfide (7–36% yields),[4] and from N-alkenylthioamides and aluminum chloride (1.5–60% yields).[5] Some of these earlier reactions have shown limitations such as low yields, stereochemical barriers to reaction, or lack of stereospecificity. The method reported here avoids these problems and is also attractive from the standpoint of availability of starting materials. Further investigations of the stereochemistry of this reaction will be reported in a later paper.

Addition of a solution of an episulfide to a mixture of a nitrile and a strong acid results in the formation of the appropriate thiazoline in yields up to 80%. This reaction constitutes a new synthesis of Δ^2-thiazolines which is widely applicable for rings with substituents in the 2-, 4-, and 5-positions, and which permits stereochemical control of products.

The episulfide reaction was discovered during a study of the alkylation of episulfides with *t*-butyl 2,4,6-trinitrobenzenesulfonate. The *t*-butyl ester was prepared *in situ* from *t*-butyl chloride or bromide and the acetonitrile complex of silver 2,4,6-trinitrobenzenesulfonate in nitromethane–methylene chloride solution. When a solution of cyclohexene sulfide in methylene chloride was added to the freshly prepared ester solution, *trans*-2-methyl-3a,4,5,6,7,7a-hexahydrobenzthiazolium 2,4,6-trinitrobenzenesulfonate was isolated in 59% yield by precipitation with ether–pentane. The equivalent weight, by osmometry, was 230 (calcd 224). Infrared absorption bands at 3.15 (N–H), 9.73 and 9.43 (ionic sulfonate), and 6.23 μ (C=N), and the elemental analysis suggested the above structure, which was later confirmed by preparation of the same salt from the free base. In similar fashion, the trinitrobenzenesulfonate salts of *trans*- and *cis*-2,4,5-trimethylthiazoline were prepared in 29 and 40% yields, respectively, from *cis*- and *trans*-2-butene episulfide.



A plausible explanation for these unexpected results was elimination of 2,4,6-trinitrobenzenesulfonic acid from the *t*-butyl ester, followed by protonation of the episulfide and ring opening by acetonitrile. Thus it followed that strong acids should bring about the same reaction. This proved to be the case. When *trans*-2-butene episulfide was added to a solution of 2,4,6-trinitrobenzenesulfonic acid in acetonitrile, *cis*-2,4,5-trimethyl-Δ^2-thiazolinium 2,4,6-trinitrobenzenesul-

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(2) R. Kuhn and F. Drawert, *Ann.*, **590**, 55 (1954).
(3) J. Farkas and J. Sicher, *Collection Czech. Chem. Commun.*, **20**, 1391 (1955).
(4) G. Bach and M. Zahn, *J. Prakt. Chem.*, **280**, 68 (1959).
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