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THE DIRECT CONVERSION OF N-ACYL α-AMINO ACIDS INTO N-ACYL α,β-UNSATURATED α-AMINO ACIDS

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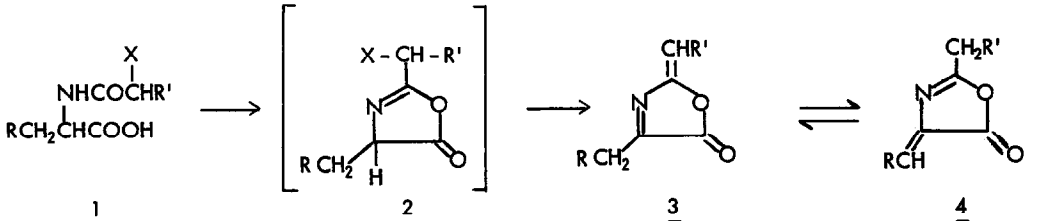
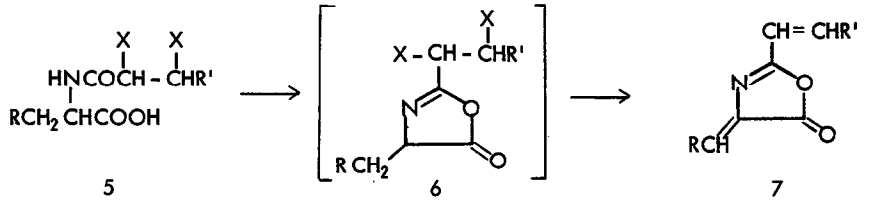
There is presently no direct and stereospecific way to introduce substituents into the carbon chain of an amino acid. Substituted amino acids are generally synthesized by the difficult and time-consuming process of condensing fragments already containing the desired substituents. This approach suffers from the necessity to synthesize the fragments and from low yields which generally accompany the condensation of polyfunctional molecules. It seemed to us that the introduction of a double bond into the carbon chain of an amino acid would allow direct and possibly stereo- and regiospecific derivatization of the molecule. We began by investigating the conversion of an N-acyl α-amino acid into its α,β-unsaturated derivative.

The Bergmann reaction[2], in which an N-(α-haloacyl) amino acid (1) is converted by an acetic anhydride-pyridine mixture into a pseudoazlactone (3), has been known for many years. Loss of HX from the presumed intermediate (2) allows the oxidation of the CH-NH bond to the imine function. The pseudoazlactone 3 equilibrates with the unsaturated azlactone 4, but the position of the equilibrium depends on the



1 2 3 4

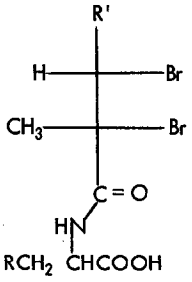
substituents R and R' and the yields of 4 are a function of the starting amino acid. In order to eliminate the equilibration step, we examined the azlactonization of an N-α,β-dihaloacylamino acid (5) expecting that an intermediate 6 might be formed followed by a double dehydrohalogenation to give the unsaturated azlactone 7.



5 6 7

This constitutes oxidation of the α,β-positions of the original amino acid to the desired double bond and hydrolysis of (7) to the unsaturated amino acid derivative[4] gives the desired product.

Our initial investigations showed that compounds of the type 5 are indeed converted into unsaturated azlactones of the type 7 which undergo facile hydrolysis to the desired acid. When N-(erythro-DL-α,β-dibromo-α-methylbutyroyl)-DL-phenylalanine[5,6] (8a) was treated with a warm acetic anhydride-pyridine mixture, the crystalline azlactone 9a was obtained in 93% yield.[7] The structure of 9a was confirmed using



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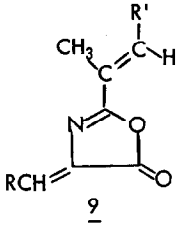

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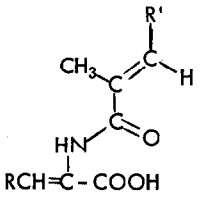
a, R= C_6H_5-, R'= CH_3-
b, R= $(CH_3)_2CH$-, R'= CH_3-
c, R= C_6H_5-, R'= C_6H_5-
d, R= $(CH_3)_2CH$-, R= C_6H_5-



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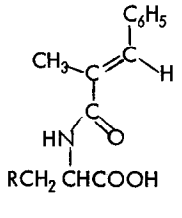
the Erlenmeyer synthesis.[4] When N-tiglolyglycine was treated with a mixture of benzaldehyde, acetic anhydride and sodium acetate, a 26% yield of azlactone identical to 9a was obtained. Treatment of 9a with methanolic sodium hydroxide gave the corresponding acid, 10a. When the amorphorous DL-leucine[8] derivative 8b was treated with the acetic anhydride-pyridine reagent, an amorphous azlactone was obtained. Since we were interested in developing a general method of amino acid oxidation which would give crystalline intermediates, we changed the N-acyl group from dibromobutyryl to α,β-dibromo-α-methylhydrocinnamoyl. Bromination of E-α-methylcinnamic acid[9] gave erythro-DL-α-methyl-α,β-dibromohydrocinnamic acid[10] which, after conversion to the acid chloride, was coupled with DL- phenylalanine giving 8c. The acetic anhydride-pyridine reagent converted 8c into cyrstalline 9c in 90% yield. Erlenmeyer synthesis[4] of 9c in 33% yield from benzaldehyde and N-(E-α-methylcinnamoyl)-glycine confirmed the structure of 9c. Hydrolysis of 9c to 10c was uneventful.

An important simplification of the oxidation procedure was discovered when we found that a solution of N-(E-α-methylcinnamoyl)-DL-phenylalanine (11a) in the acetic anhydride-pyridine azlactonizing mixture



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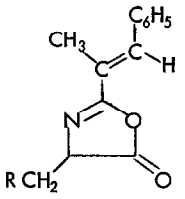

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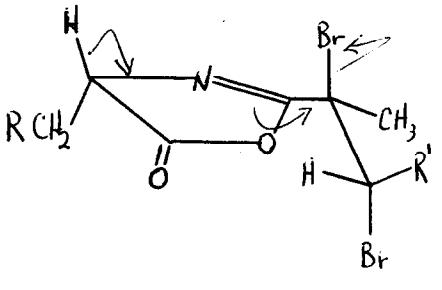
a, R= C_6H_5
b, R= $(CH_3)_2CH$-

could be brominated with pyridine perbromide hydrobromide to yield 9c in 90% yield. Presumably the reaction proceeded through the azlactone 12a, which was sequentially brominated and doubly dehydrobrominated in situ. This method eliminates the necessity to prepare the dibromoacylating agent and the need to purify the intermediate amorphous N-dibromoacylamino acids. When this direct oxidation procedure was applied to the leucine derivative, 11b, azlactone 9d was obtained also in 90% yield indicating that aliphatic amino acids can also be oxidized in good yield. Hydrolysis of 9d to 10d was also accomplished. We are presently extending this reaction to other amino acids and examining other N-acyl groups for possible use in this oxidation procedure.

Of mechanistic interest, is the fact that azlactones 9a and 9c obtained from our azlactonization-oxidation procedure had stereochemistry identical to those obtained by the Erlenmeyer method. Both sites at which stereoisomerism might occur (the E-configuration of the group in the 2-position) and the presumed[11] Z-configuration (C_6H_5 cis to the azlactone nitrogen atom) of the benzylidene group at position 4 are the same. Neither the N-acyl group attached to glycine used in the Erlenmeyer synthesis nor that attached to phenylalanine (11a) and leucine (11b) would be expected to isomerize during azlactonization. Since our oxidation process most probably proceeds through a dibromo azlactone (6, X= Br), the two subsequent dehydrobromination steps must occur stereospecifically. Assuming trans-bromination, the elimination of the two bromine atoms from the 2-substituent must also proceed in a trans-manner. The first elimination is a 1,4-dehydrobromination and probably[12] occurs in a cis-manner (13). If true, the second elimination must occur in a trans-manner (14) in



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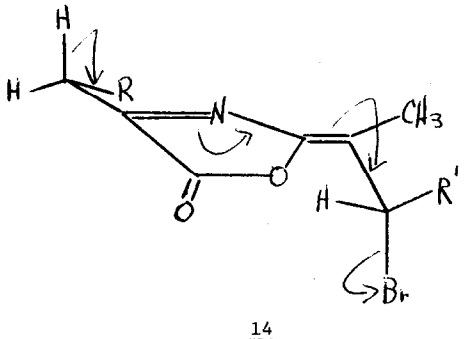

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order that the observed configuration be obtained. We are presently examining the course of these two steps and will report a definitive mechanism in a later publication.

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3. Iwakura, F. Toda and Y. Torii, Tetrahedron 23, 3363 (1967).
4. E. Erlenmeyer, Jr., Ann., 337, 165, 283, 294, 302 (1904).
5. Erythro-DL-α,β-dibromo-α-methylbutyric acid [J. Wislicenus, Ann., 272, 12 (1893)] was converted into its acid chloride and condensed with DL-phenylalanine to give 8a. All of the dibromoacylamino acids we prepared were amorphous solids probably because they are necessarily 1:1 molar mixtures of diastereomers.
6. In both cases reported here, the N-acyl moiety has an α-methyl group. We felt that the absence of an α-hydrogen atom would remove the possibility that dehydrobromination of the acyl group might occur prior to the desired 1,4-dehydrobromination of the azlactone.
7. All new compounds reported herein gave satisfactory C, H, and N analyses and had infrared and nmr spectra consistent with the structures shown.
8. We have used phenylalanine and leucine in these initial experiments in order to develop a procedure applicable to both aromatic and aliphatic amino acids.
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