ing point was raised to 55–56°. It is also soluble in water, ethanol, and acetone.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.7; H, 8.3; N, 14.6. Found: C, 68.3; H, 8.3; N, 14.7.

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α-Alkyloximino Acids in Azlactone Reactions[1]

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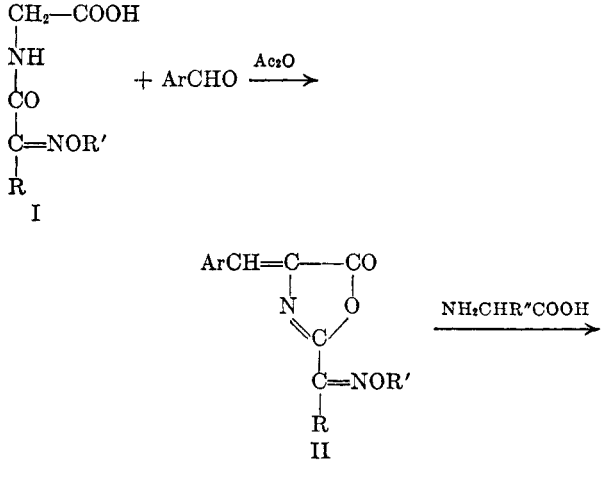
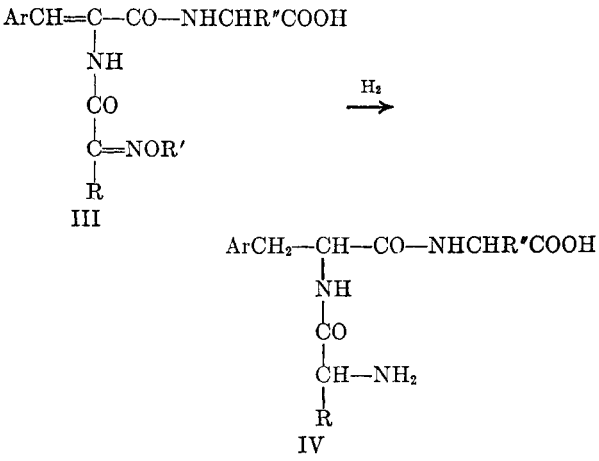
The azlactone procedure for the synthesis of α-amino acids and acyl dipeptides, RCO-NHCHR'-CO-NHCHR"COOH, has been reviewed by Carter.[4] Proper selection of the acyl group in these amides would be expected, on suitable conversion, to lead to the corresponding aminoacyl derivative, that is, a tripeptide. Previous studies with α-alkyloximino acids[5] show that the arrangement R-C(=NOR')-CO- lends itself well for transformation into the corresponding aminoacyl, R-CH(NH_2)-CO, for the synthesis of various amides. Their value for the synthesis of a tripeptide by way of the azlactone route would then be comprehended according to the scheme:





We now report the synthesis, by this procedure, of phenylalanylphenylalanylglycine, IV in which R = $C_6H_5CH_2$-, Ar = C_6H_5, and R" = H, as a successful application. In view of the large number of α-alkyloximino acids which may be prepared and the fact that many aldehydes may be employed in the step from I to II, the number of prospective azlactones of type II becomes impressive. Nor is it anticipated that the conversion of II to III is limited to the reaction with glycine. The hydrogenation of III to IV appears to offer no difficulty.

For some reason which does not now appear the azlactones prepared from benzyloximino intermediates, compounds of structure II in which R' = $C_6H_5CH_2$-, while seemingly pure crystalline products, do not give satisfactory analyses; yet when allowed to react further, the intermediate III and the tripeptide IV are acceptable. No such difficulty was experienced with the methyloximino intermediate, type II in which R' = CH_3-.

EXPERIMENTAL

The synthesis of *β-phenyl-α-benzyloximinopropionylglycine* has been described.[5b] *β-Phenyl-α-methyloximinopropionylglycine*, was prepared from glycine and β-phenyl-α-methyloximinopropionic acid in a similar manner; recrystallized from benzene it melts 104.5–105°.

Anal. Calcd. for $C_{12}H_{14}N_1O_4$: N, 11.20. Found: N, 11.13.

2-(1-Methyloximino-2-phenylethyl)-4-benzaloxazolone. In a 100-ml. Erlenmeyer flask was placed a mixture of 1.0 g. (0.0095 mole) benzaldehyde, 2.67 g. (0.0113 mole) of powdered β-phenyl-α-methyloximinopropionylglycine, 0.8 g. of freshly fused and powdered sodium acetate, and 2.5 ml. acetic anhydride. The flask was heated gently with constant shaking over a low flame until the contents liquefied, turning yellow; it was then heated on a steam bath for an hour, when yellow crystals formed on the walls of the flask. The reaction mixture was then treated with 4 ml. alcohol and allowed to stand overnight in the refrigerator. The yellow crystalline product was removed by suction, washed with a small amount of alcohol, then with 1 ml. water. The crude product weighed 2.0 g., m.p. 156–158°; recrystallized first from ligroin and then from acetone, m.p. 158–159° (uncorr.).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.23; H, 5.03; N, 8.74. Found:[6] C, 71.93; H, 5.51; N, 8.85.

(1) No. 16 in amino acid series; for No. 15 see G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, 79, 5203 (1957). This investigation was supported by Grant G-3594, National Institutes of Health, for which the authors express their thanks and appreciation.

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(5) (a) J. W. Martin and W. H. Hartung, *J. Org. Chem.*, 19, 338 (1954). (b) W. E. Weaver and W. H. Hartung, *J. Org. Chem.*, 15, 741 (1950).

(6) Analyses by G. Weiler and F. B. Strauss, Oxford, England.

2-(1-Benzyloximino-2-phenylethyl)-4-benzaloxazolone. In a 100-ml. flask was placed a mixture of 1.0 g. (0.0095 mole) benzaldehyde, 3.45 g. (0.0107 mole) of powdered α-benzyloximino-β-phenylpropionylglycine, 0.8 g. of freshly fused and powdered sodium acetate, and 2.5 ml. acetic anhydride. The contents were heated as described above and the product isolated in a similar manner. The crude product weighed 3.0 g., m.p. 154–156° (uncorr.); recrystallized from ligroin, m.p. 155–156° (uncorr.).

Anal. Calcd. for $C_{25}H_{20}N_2O_3$: N, 7.07. Found: N, 8.02, and 8.00.

N-(α-Benzyloximino-β-phenylpropionyl)-α-aminocinnamoylglycine. A hundredth mole glycine (0.75 g.) was dissolved in 10 ml. normal NaOH solution and added to a suspension of 0.01 mole (3.96 g.) of 2-(1-benzyloximino-2-phenylethyl)-4-benzaloxazolone in 30 ml. acetone, and the mixture shaken continuously for about 30 min., at which time the azlactone was completely dissolved. The mixture was allowed to stand overnight, filtered, and then acidified with hydrochloric acid, and the solvent allowed to evaporate at room temperature. A white solid, with some oil which solidified on scratching, remained; recrystallized from dilute alcohol, white crystals were formed, 3.5 g., m.p. 144°.

Anal. Calcd. for $C_{27}H_{27}N_3O_5$: N, 8.91. Found: N, 8.95, 8.97.

N-(α-Methyloximino-β-phenylpropionyl)-α-aminocinnamoylglycine. This compound was prepared in a manner similar to the benzyloximino analog in yield of 75%; recrystallized from dilute acetone, it melted 156–157°.

Anal. Calcd. for $C_{21}H_{21}N_3O_5$: N, 10.73. Found: N, 10.14, 10.30.

DL-*Phenylalanylphenylalanylglycine.* To a solution of 97 ml. water and 3 ml. concentrated ammonia was added 2.64 g. (0.006 mole) of *N*-(α-methyloximino-β-phenylpropionyl)-α-aminocinnamoylglycine and catalyst prepared from 2 g. charcoal and 200 mg. $PdCl_2$. Hydrogenation was carried out in a Parr apparatus at about 4 atm. hydrogen pressure. The first H_2 was taken up in about 50 min., the second H_2 in about 3 hr., and the remainder in 20 hr. The catalyst was removed by filtration and the filtrate concentrated on a hot water bath at reduced pressure; the residue was taken up in a small amount of hot water and filtered to remove insoluble material. The colored solid obtained from the aqueous solution was crystallized from 50% alcohol and, after drying *in vacuo* at 100° over P_2O_5 for 8 hr. weighed 1.22 g., 66% of theory, discolored at 195° and melted with decomposition at 203–213°.

Anal. Calcd. for $C_{20}H_{23}N_3O_4$: C, 65.02; H, 6.25; N, 11.37. Found[7]: C, 64.95; H, 6.32; N, 11.22.

Benzoyl derivative, recrystallized from dilute alcohol, m.p. 222–223°.

Anal. Calcd. for $C_{27}H_{27}N_3O_5$: N, 8.87. Found: N, 8.62, 8.58.

The hydrogenation of *N*-(α-benzyloximino-β-phenylpropionyl)-α-aminocinnamoylglycine under similar condition gave 62% yield of the tripeptide, which, in physical properties and *N*-benzoyl derivative, was identical with DL-phenylalanylphenylalanylglycine.

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(7) Analyses by Micro-Tech Laboratories, Skokie, Ill.

A New Method for Synthesis of Higher α,ω-Diarylated Fatty Acids

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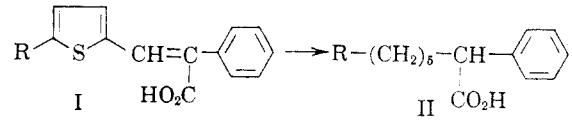
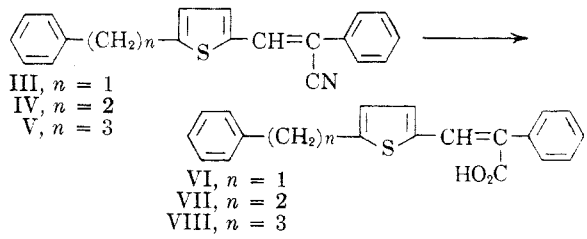
During the past five years, numerous reports have appeared concerning the synthesis of aliphatic,[1] alicyclic,[2] and aromatic[3] carboxylic acids by hydrogenolysis of suitably substituted thiophenes with Raney nickel-aluminum alloy in alkaline medium. Buu-Hoï and Sy[4] recently reported a method for the preparation of α-alkylated phenylacetic acids (II) by hydrogenolyses of that type, involving α-phenyl-β-(2-thienyl)acrylic acids of general formula I; in these reactions, the saturation

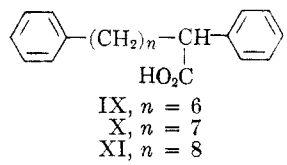


of the double bond occurred simultaneously with the reductive opening of the thiophene ring. The present work records an extension of this reaction to the preparation of higher fatty acids containing two phenyl radicals in the α and ω positions, and which were hitherto unknown.

The alkali-catalyzed condensation of 5-benzyl-2-thenaldehyde[5] with benzyl cyanide readily gave α-phenyl-β-(5-benzyl-2-thienyl)acrylonitrile (III),



which was hydrolyzed to the corresponding acid (VI), and hydrogenolysis of this latter afforded α,ω-diphenylcaprylic acid (IX). α-Phenyl-β-(5-β-phenylethyl-2-thienyl)acrylonitrile (IV), prepared from 5-β-phenylethyl-2-thenaldehyde,[6] was



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(6) N. P. Buu-Hoï, D. Lavit, and N. D. Xuong, *J. Chem. Soc.*, 1581 (1955).