ture containing starting material and the tetrahydro derivative was obtained.

EXPERIMENTAL

Methyl helvolate, methyl tetrahydrohelvolate, and helvolic acid were available[8] from earlier work.[2] Attempts were made to prepare the dihydro ester by the method used earlier, but were unsuccessful. When the theoretical amount of hydrogen was added to methyl helvolate, a mixture was obtained which contained 30–35% starting material. Further hydrogenation led to mixtures from which no pure compound short of the tetrahydro derivative could be isolated.

The spectra were obtained on a Varian Associates High Resolution n-m-r spectrometer, V-4300B, using a spinning sample, O.D. 5 mm. The radio frequency was 40 mc., sweep width about 100 milligauss, sweep rate about 20 mg./sec. Toluene was used for the calibrations by the capillary tube method,[9] and the values of δ are in parts per million.

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CONVERSE MEMORIAL LABORATORIES
HARVARD UNIVERSITY
CAMBRIDGE 38, MASSACHUSETTS.

(8) The author is indebted to Dr. D. J. Cram for making available samples of these compounds.

(9) Bothner-By and Glick, *J. Am. Chem. Soc.*, **78**, 1071 (1956).

A Facile New Synthesis of Poly-D,L-phenylalanine

LUDWIG BAUER

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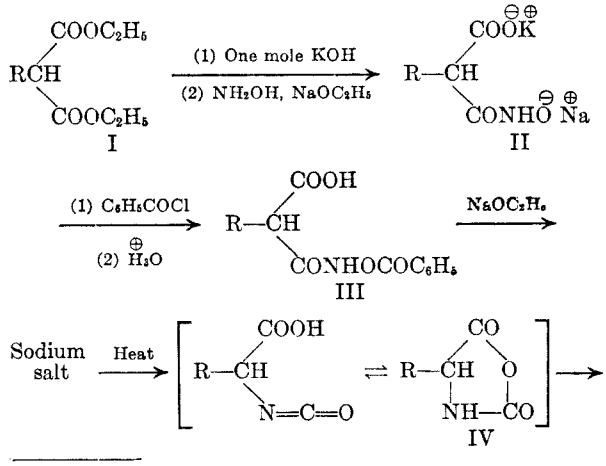
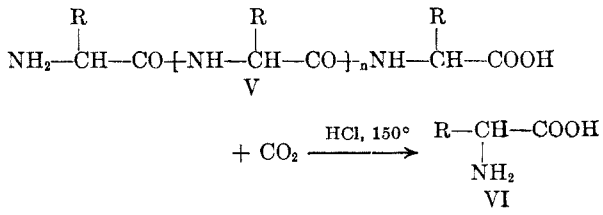
The transformation of malonic esters to either polypeptides or amino acids using the Lossen rearrangement has been described previously.[1] This degradation is aptly shown by this scheme:



(1) (a) C. D. Hurd and C. M. Buess, *J. Am. Chem. Soc.*, **73**, 2409 (1951); (b) C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **73**, 4387 (1951); (c) C. D. Hurd and L. Bauer, *J. Org. Chem.*, **18**, 1440 (1953).

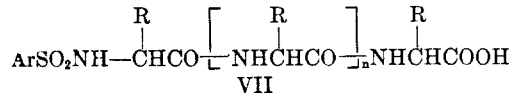


The recent introduction of sulfonyl halides[2,3] as reagents for the Lossen rearrangement shortens the degradation considerably. Thus, sodium benzohydroxamate is converted to benzo(phenylcarbamylhydroxamic) acid, $C_6H_5CONH—O—CONHC_6H_5$, in one step. Presumably, the intermediate arenesulfonic derivative, $C_6H_5CONH—O—SO_2Ar$, is unstable and rearranges spontaneously to phenyl isocyanate. The latter reacts with the original sodium benzohydroxamate to form the carbamic derivative of benzohydroxamic acid.

In an endeavor to shorten the polypeptide synthesis outlined above, the alkali salt of α-carboxy-β-phenylpropionohydroxamic acid (II, R = benzyl) was treated with benzenesulfonyl chloride. No visible reaction occurred until the mixture was heated to at least 50°. Then, a gummy solid commenced to precipitate and carbon dioxide was released. Similar reactions were observed in either water or benzene, although water was the preferred solvent.

The product of the reaction was treated with cold 10% aqueous sodium hydroxide solution. The insoluble portion (A) was filtered and the filtrate was acidified to yield another substantial fraction (B). Both (A) and (B) were insoluble in water and hydrochloric acid, but were readily soluble in ethanol. An attempt to fractionate either (A) or (B) by conventional means yielded a series of gums. No crystalline material was afforded by either fraction. Hydrolysis of both fractions independently gave D,L-phenylalanine (VI, R = benzyl) identified as the benzoyl derivative.

Polypeptides made by the conventional Lossen rearrangement[1] were completely insoluble in sodium hydroxide solution. To explain the solubility of fraction (B) in alkali, it was assumed that the polypeptide was of type (VII) (Ar = phenyl R = benzyl).



In VII, the two acid functions, the sulfonamide and carboxylic acid groups, might well explain this solubility. And, in fact, the infrared spectrum clearly showed the presence of bands due to the —COOH, Ar—SO_2—NH—, and —CONH— groups (*cf.* experimental section).

(2) C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **76**, 2791 (1954).

(3) M. A. Stolberg, R. C. Tweit, G. M. Steinberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 765 (1955).

Poly-D,L-phenylalanine synthesized from III (R = benzyl) in the conventional rearrangement was almost completely insoluble in ethanol and gave a positive ninhydrin test by adsorption. Both fractions (A) and (B) in these experiments were soluble in ethanol and gave no ninhydrin test. One end group in the polypeptide (V) should be amino and this group might have reacted with benzenesulfonyl chloride used in the reaction to form a polypeptide of type (VII). If the chain is not too long, solubility in aqueous sodium hydroxide seems feasible. To explain the solubility in ethanol, one might anticipate a comparatively short chain for both (A) and (B). This argument agrees with the hypothesis that the intermediate of this Lossen reaction is the azasuccinic anhydride (IV). It is well known that these anhydrides polymerize to polypeptides. The mechanism of this process has been elucidated.[4] The polymerization is sustained as long as IV can react with intermediate peptides of type V which have a free amino group on one end. This amino group may also react with benzenesulfonyl chloride in the reaction mixture, forming a peptide of type VII. This then would terminate reaction between IV and V and lower molecular-weight polypeptides would result. Since fractionation proved difficult, no attempt was made to determine the average molecular weight, assuming that each polymer chain has an end group.

It should be noted that the above synthesis of poly-D,L-phenylalanine requires only three steps starting from ethyl benzylmalonate.

EXPERIMENTAL

Rearrangement of potassium sodium α-carboxy-β-phenylpropionohydroxamate with benzenesulfonyl chloride. (a). In water. A solution of the salt (2.7 g.; 0.01 mole) in water (15 ml.) was treated with benzenesulfonyl chloride (3.5 g.; 0.02 mole). The mixture was warmed on a steam-bath. When the temperature reached about 50°, carbon dioxide was copiously evolved [$Ba(OH)_2$] and a gummy precipitate settled out. After 15 minutes on the steam-bath, the *p*H of the mixture was re-adjusted to about 8. The mixture then was heated another 15 minutes. The slightly alkaline solution was kept at 25° for 48 hours. A light tan solid (fraction A) was filtered off and washed well with water. After being dried, it weighed 530 mg. This solid softened at approximately 150° and melted between 180–185°. It was soluble in cold ethanol and could not be satisfactorily recrystallized from aqueous ethanol. Its infrared absorption spectrum in a KBr pellet exhibited strong bands at 3280 and 3080 (—NH stretching vibration), at 1670 (C=O of secondary amide absorption), at 1525 (—NH deformation), and at 1450 cm.$^{-1}$ (C—N absorption) which confirmed the polyamide structure [compared with polyphenylalanine].[5]

Hydrolysis of 450 mg. of this material with 10 ml. of concentrated hydrochloric acid in a sealed tube at 150° for 14 hours afforded a clear yellow solution. The contents of the tube were diluted, treated with Darco, and evaporated to dryness *in vacuo*. The crystalline residue was dissolved in 25 ml. of 10% sodium hydroxide solution and treated with 2.5 ml. of benzoyl chloride. D,L-2-Benzamido-3-phenylpropionic acid (430 mg.) was isolated by conventional techniques, and recrystallized from benzene, m.p. 181–182°, undepressed by an authentic specimen. The infrared spectra of the two derivatives also were superimposable.

The alkaline filtrate from fraction (A) was acidified and a gummy solid was precipitated which slowly solidified (fraction B). The yield of dry material was 650 mg. The physical properties were similar to those of fraction (A). However, its infrared spectrum (in KBr) clearly indicated that this polymer had benzenesulfonamido groups incorporated into its structure. The main bands of interest for the polyamide structure were at 3280, 3080, 1650, 1525, and 1450 cm.$^{-1}$. In addition there were strong bands at 1740 (C=O stretching vibration of —COOH), 1325, 1340, 1160, and 1095 cm.$^{-1}$ (presumably due to the sulfonamido group). The last five bands were identically present in the spectrum (in KBr) of an authentic sample of D,L-2-benzenesulfonamido-3-phenylpropionic acid.

The total yield of polypeptide then was 1.18 g. The yield would be difficult to compute since the end groups were not determined.

Acid hydrolysis of 450 mg. of fraction (B) as described for fraction (A), followed by subsequent benzoylation, afforded 390 mg. of D,L-2-benzamido-3-phenylpropionic acid, m.p. 178–181°. An additional recrystallization from benzene raised the m.p. to 182°, undepressed on admixture with an authentic specimen, m.p. 182–183°.[6] The infrared spectrum in KBr exhibited strong bands at 3300 (—NH and OH absorption), 1720 (C=O stretching vibration of COOH), 1615 and 1680 (C=O stretching vibration of amide band), and 1545 cm.$^{-1}$ (—NH deformation). These bands are in agreement with those of amido acids found by Freedman.[7]

The yield of D,L-2-benzamido-3-phenylpropionic acid was computed to be 35% based on the mixed alkali salt.

(*b*). *In benzene.* A suspension of 2.7 g. of salt in 25 ml. of benzene was treated with 5.3 g. of benzenesulfonyl chloride and refluxed on the steam-bath for 0.5 hours. Carbon dioxide was liberated and a gum separated. The mixture was cooled, and 5% sodium hydroxide solution (25 ml.) was added. A pale cream solid separated at the interface and was filtered off (fraction A). It weighed 0.42 g. when dry. Its infrared spectrum was similar to that of fraction (A) of the rearrangement in water.

The benzene-alkaline aqueous phases were separated and the benzene layer was extracted with more 5% NaOH solution (three portions of 20 ml. each). The alkaline layer was acidified and a gum separated which did not solidify. It was insoluble in ether. Thorough drying afforded a glass.

Acid hydrolysis followed by benzoylation as described above converted these gums to D,L-2-benzamido-3-phenylpropionic acid, whose m.p. 182° was not depressed on admixture with an authentic specimen.

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DEPARTMENT OF CHEMISTRY,
COLLEGE OF PHARMACY
UNIVERSITY OF ILLINOIS
CHICAGO 12, ILLINOIS

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