Summary

Practical syntheses of the *o*-, *m*- and *p*-fluoro-DL-phenylalanines have been devised and each of the above amino acids has been resolved into the corresponding D- and L-isomers. Additional information in respect to the stereochemical specificity of the papain catalyzed synthesis of phenylhydrazides of the N-acylated-α-amino acids has been obtained.

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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1321]

Transacylation in the Erlenmeyer–Plöchl Reaction

BY EDWARD L. BENNETT[1] AND CARL NIEMANN

The conclusion that transacylation in the Erlenmeyer–Plöchl reaction is not to be expected with hippuric acid when the reaction is conducted at refluxing temperatures[2] prompts us to report several cases where such transacylations have occurred. The crude azlactone, m. p. 133–165°, obtained by the condensation of *p*-fluorobenzaldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate[3] has been found to be a mixture of 2-phenyl- and 2-methyl-4-(*p*-fluorobenzal)-5-oxazolones, by isolation and characterization of the two components, and the presence of 2-methyl-4-(*m*-fluorobenzal)-5-oxazolone in the crude azlactone, m. p. 109–139°, obtained from *m*-fluorobenzaldehyde and hippuric acid under essentially the same conditions, has been established from spectral data (*cf.* Figs. 1 and 2), a method suggested by the examination of the ultraviolet absorption spectra of the products obtained from *p*-fluorobenzaldehyde and hippuric acid (*cf.* Fig. 1). The occurrence of transacylation in the case of *o*-fluorobenzaldehyde and hippuric acid may be inferred from the melting point behavior of the crude azlactones[3] which were prepared as indicated above or by heating on a steam-bath.

It is probable that the relatively low yields of the 2-phenyl-4-fluorobenzal-5-oxazolones obtained previously[3] were largely due to the above transacylation reaction and it is now obvious that the yields of the amino acids could have been improved by avoiding extensive purification of the intermediate crude azlactones.

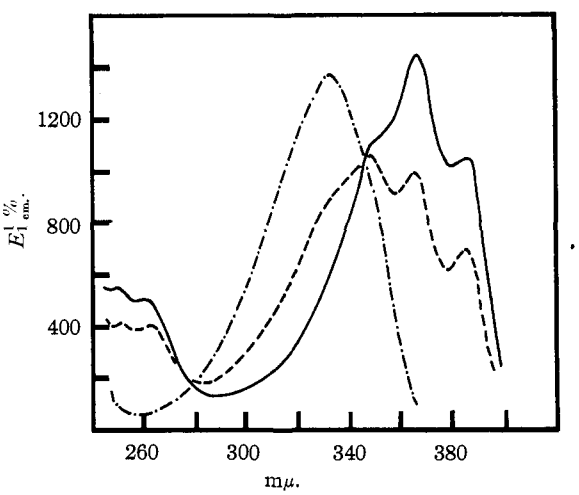

Fig. 1.—Ultraviolet absorption spectra of 2-phenyl-4-(*p*-fluorobenzal)-5-oxazolone, ——; 2-methyl-4-(*p*-fluorobenzal)-5-oxazolone ·-·-·-; and crude parent azlactone, m. p. 133–165°, - - - - -.

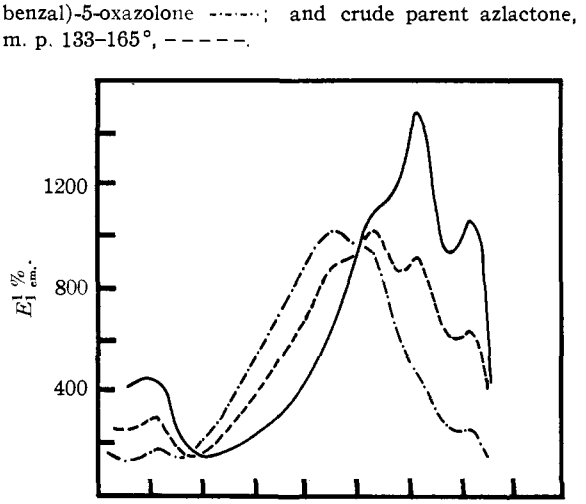

Fig. 2.—Ultraviolet absorption spectra of 2-phenyl-4-(*m*-fluorobenzal)-5-oxazolone, ——; crude parent azlactone, m. p. 109–139°, - - - - - -; and crude azlactone, m. p. 108–118°, ·-·-·-·-.

Experimental[4]

Fractionation of Crude 2-Phenyl-4-(*p*-fluorobenzal)-5-oxazolone.[3]—The crude azlactone, m. p. 133–165°,[3] (65 g.) was recrystallized from 4 l. of absolute ethanol to give 34.5 g. of 2-phenyl-4-(*p*-fluorobenzal)-5-oxazolone (I), m. p. 184–185.5°,[3] lit.,[5] m. p. 181–182°, and a total of 25 g. of more soluble fractions. All of these latter fractions save one were combined (21 g.) and recrystallized twice from benzene to give 8.8 g. of 2-methyl-4-(*p*-fluorobenzal)-5-oxazolone (II), m. p. 153–154.5°.

(1) Procter and Gamble Fellow in Chemistry 1948-1949; present address, Radiation Laboratory, University of California, Berkeley, Calif.

(2) J. W. Cornforth, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 733, 784.

(3) E. L. Bennett and C. Niemann, THIS JOURNAL, **72**, 1800 (1950).

(4) All melting points are corrected.

(5) G. Schiemann and W. Roselius, *Ber.*, **65**, 1439 (1932).

Anal. Calcd. for $C_{11}H_9O_2NF$ (205): C, 64.5; H, 3.9; N, 6.8. Found: C, 64.6; H, 4.0; N, 6.7.

I was converted[6] into α-benzamido-*p*-fluorocinnamic acid ethyl ester (III), m. p. 122–123° [*Anal.* Calcd. for $C_{18}H_{16}O_3NF$ (313): C, 69.0; H, 5.1; N, 4.5. Found: C, 69.3; H, 5.1; N, 4.4] and III saponified[6] to give α-benzamido-*p*-fluorocinnamic acid, m. p. 224–226° with dec., lit.,[5] m. p. 224–225° with dec. II was converted[6] into α-acetamido-*p*-fluorocinnamic acid ethyl ester (IV), m. p. 116–117° [*Anal.* Calcd. for $C_{13}H_{15}O_3NF$ (252): C, 62.0; H, 6.0; N, 5.7. Found: C, 62.2; H, 5.9; N, 5.4] and IV saponified[6] to give α-acetamido-*p*-fluorocinnamic acid, m. p. 214–216° [*Anal.* Calcd. for $C_{11}H_{10}O_3NF$ (223): C, 59.2; H, 4.5; N, 6.3. Found; C, 59.0; H, 4.9; N, 6.2]. The remaining soluble fraction (see above), m. p. 133–148°, was chromatographed on a silicic acid–celite column using benzene as a solvent and developer to give approximately equal quantities of I, m. p. 184–185°, and II, m. p. 153–154°. II was adsorbed more strongly on the column than was I. The absorption spectra of I, II, and the crude azlactone, m. p. 133–165°, were determined in chloroform using a Beckman model DU spectrophotometer and are given in Fig. 1.

Fractionation of Crude 2-Phenyl-4-(*m*-fluorobenzal)-5-oxazolone.[3]—The crude azlactone, m. p. 109–139°,[3] (57 g.) was recrystallized from 2 l. of absolute ethanol to give 30.1 g. of 2-phenyl-4-(*m*-fluorobenzal)-5-oxazolone (V), m. p. 158.5–159.5°,[3] lit.,[5] m. p. 156–156.5, and a number of more soluble fractions of broad m. p. range. The spectra of the most soluble fraction, m. p. 108–118°, the crude azlactone, m. p. 109–139°, and V were determined in chloroform and are given in Fig. 2.

Acknowledgment.—The authors are indebted to Dr. A. Elek for the microanalyses reported in this communication.

(6) H. Carter, C. Stevens and L. Ney, *J. Biol. Chem.*, **139**, 255 (1941).

Summary

A transacylation reaction, involving replacement of a benzoyl group by an acetyl group, has been observed in the Erlenmeyer–Plöchl synthesis of several α-amino acids.

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The Apparent Ionization Constants and Ultraviolet Spectra of *o*-, *m*- and *p*-Fluoro-DL-phenylalanine

BY EDWARD L. BENNETT[1] AND CARL NIEMANN

The apparent ionization constants and ultraviolet absorption spectra of *o*-, *m*- and *p*-fluoro-DL-phenylalanine[2] have been determined in extending our studies on the chemical and physiological properties of the halogenated aromatic α-amino acids.[3] The ionization constants are given in Table I and the principal features of the ultraviolet absorption spectra in Table II.

TABLE I

APPARENT IONIZATION CONSTANTS OF THE THREE NUCLEAR SUBSTITUTED MONOFLUORO-DL-PHENYLALANINES IN 0.1 FORMAL AQUEOUS SODIUM CHLORIDE AT APPROXIMATELY 24°

Compound	pK'_{CO_2H}	$pK'_{NH_3^+}$
Phenylalanine	2.16	9.12
o-Fluorophenylalanine	2.12	9.01
m-Fluorophenylalanine	2.10	8.98
p-Fluorophenylalanine	2.13	9.05

In a nuclear substituted phenylalanine it would be expected that any inductive effect arising from the substituent and mediated by the aromatic nucleus[4,5] would influence the ionization constant of the ammonium group to a greater degree than

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF PHENYLALANINE AND THE THREE NUCLEAR SUBSTITUTED MONOFLUORO-DL-PHENYLALANINES IN 0.1 *F* AQUEOUS SODIUM CHLORIDE

Compound	λ (mμ)		ε
Phenylalanine	208		8050
	234	(min.)	40
	247		131
	248		132
	252	(max.)	168
	254	(min.)	158
	257.5	(max.)	202
	261	(min.)	145
	263	(max.)	155
o-Fluorophenylalanine	208		7700
	229	(min.)	45
	261.5	(max.)	845
	265	(min.)	537
	267.5	(max.)	760
m-Fluorophenylalanine	208		7400
	229	(min.)	40
	257		589
	258		590
	262	(max.)	820
	266	(min.)	500
	268	(max.)	745
p-Fluorophenylalanine	208		6900
	230	(min.)	40
	264	(max.)	710
	267	(min.)	400
	270	(max.)	635

(1) Procter and Gamble Fellow in Chemistry 1948–1949; present address: Radiation Laboratory, University of California, Berkeley, California.

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(3) J. C. Nevenzel, W. Shelberg and C. Niemann, *ibid.*, **71**, 3024 (1949).

(4) H. B. Watson, "Modern Theories of Organic Chemistry," 2nd edition, Oxford Press, London, 1947, pp. 102ff.

(5) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941.