Anal. Calcd. for $C_{11}H_8O_2NF$ (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 $C_{16}H_{16}O_3NF$ (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.

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

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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)		
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

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

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

[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.

that of the carboxyl group because of the closer proximity of the former group to the nucleus. Actually the differences observed between the ionization constants of the carboxyl groups of phenylalanine, the three chloro- and the three fluorophenylalanines are for the most part within experimental error and will not be considered further. However, this is not true of the differences observed for the ionization constants of the ammonium groups of these amino acids.

For an electrophilic nuclear substituent such as the halogens it would be expected that the ammonium group in a substituted phenylalanine would be more acidic than in phenylalanine and for the various halogens the magnitude of the effect would be in the order I > Br > Cl > F with no great differences existing between the first three members.[4,5] Furthermore for any given halogen it would be expected[5] that the increase in acidity of the ammonium group would be greatest for the meta-substituted amino acid and least for the para. These expectations have been realized and from data now available it appears unlikely that replacement of a nuclear hydrogen atom in phenylalanine by bromine or iodine would increase the acidity of the ammonium group, relative to that in phenylalanine, by more than 0.3 of a pK unit.

In comparing the ultraviolet absorption spectra of phenylalanine,[3] *o*-, *m*- and *p*-chlorophenylalanine,[3] and *o*-, *m*- and *p*-fluorophenylalanine (Table II) the two most notable features are, the readily detectable high intensity ethylenic (E) absorption of the chlorophenylalanines and the magnitude of the benzenoid (B) absorption of the fluorophenylalanines. From the above and other information[6] it appears likely that the E absorption maxima of the fluorophenylalanines lie just beyond the lower limit of the instrument available and that the bromo- and iodophenylalanines, with the possible exception of the ortho iodo-compound, in common with the chlorophenylalanines will exhibit E absorption maxima in the 212–228 mμ region.

The introduction of a fluorine or chlorine atom into the phenylalanine nucleus produces the expected[6] bathochromic effect and the principal B absorption maxima are shifted to longer wave lengths by 4–7 mμ for a fluorine atom or 9–10 mμ for a chlorine atom. However, the magnitude of the effect is markedly less than that observed[6] for the fluorotoluenes, 7–12 mμ, or the chlorotoluenes, 12–16 mμ. In common with the fluoro- or chlorotoluenes the shift is greatest for a para-substituted phenylalanine and least for an ortho-substituted one. With both the fluoro- and chlorophenylalanines the principal B absorption maxima are at shorter wave lengths by 7–11 mμ than with the corresponding fluoro- and chlorotoluenes and it appears probable that this effect and the one noted above are to be attributed to the dipolar character of the amino acids.

In regard to the intensity of the B absorption of the chloro- and fluorophenylalanines it would be expected from data available for the fluoro- and chlorobenzenes[6] and toluenes[6] that the extinction coefficients would be in the order fluoro > > chloro > hydrogen. Although this has been observed it should be noted that the differences are not as great as might have been expected, and whereas the extinction coefficients of the fluorotoluenes are in the order $p > m > o$ the reverse order obtains for the fluorophenylalanines.

Experimental

The methods used were essentially identical with those described previously.[3] Values for $pK'_{\mathrm{CO_2H}}$ were calculated from approximately 14 values in the pH range from 2.0 to 3.75, and for $pK'_{\mathrm{NH_3^+}}$ from an equal number of values in the range from 7.0 to 9.5. An experimentally determined linear correction factor, ranging from -1% at pH 2.70 to -8% at pH 2.0, was applied to the volume of acid used to obtain consistent values of $pK'_{\mathrm{CO_2H}}$. The correction in the pH range 7.0 to 9.5 was negligible, *e. g.*, at pH 9.8 was less than 0.01 ml. The amino acid solutions were approximately 0.02 F in amino acid and 0.1 F in sodium chloride. The standard sodium hydroxide was 0.1692 F and the hydrochloric acid 0.1936 F. All determinations were made in duplicate at a temperature of 24 ± 1° using samples prepared by independent methods.[2] In every case reproducibility was obtained to within 0.02 of a pK unit.

Summary

The apparent ionization constants and ultraviolet absorption spectra of *o*-, *m*- and *p*-fluoro-DL-phenylalanine have been determined.

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(6) H. Conrad-Billroth, *Z. physik. Chem.*, **B25**, 139 (1934).