TABLE III

PROPERTIES OF PHENYLALANINE DERIVATIVES OBTAINED FROM ENZYME EXPERIMENTS

Compound[a]	M. p., °C.	$[\alpha]^{25}D$[b]	Analyses, % Calculated C	H	N	Found C	H	N
Phenylhydrazides								
CH_3OCO-L-	170–174	−23.8	65.2	6.1	13.4	65.2	6.1	13.3
CH_3OCO-DL-	181–182.5	− 0.2	65.2	6.1	13.4	64.9	6.0	13.7
C_2H_5OCO-L-	156.5–159.5	−22.2			12.8			12.6
C_2H_5OCO-D-	156–160.5	+23.4			12.8			12.8
C_2H_5OCO-DL-	171–172.5	− 0.4	66.0	6.5	12.8	66.2	6.7	12.7
$C_6H_5CH_2OCO$-L-	177–179	−24.6[i]	70.9	6.0	10.8	71.1	6.2	10.4
$C_6H_5CH_2OCO$-D-	178–179	+24.4[j]	70.9	6.0	10.8	71.1	6.0	10.9
$C_6H_5CH_2OCO$-DL-	159.5–161	0.0[k]	70.9	6.0	10.8	70.7	6.0	10.7
C_6H_5CO-L-[b]	215–217	−61.9	73.5	5.9	11.7	73.7	6.0	11.8
CH_3CO-L-[b]	207–208[e]	−34.6[l]	68.7	6.4	14.1	68.4	6.5	13.9
Acids								
C_6H_5CO-D-[c]	139.5–140.5[f]	+23.8[m]	71.4	5.6	5.2	71.6	5.9	5.0
CH_3CO-D-[d]	171–172[g]	−32.9[k,n]	63.8	6.3	6.8	63.9	6.4	6.6

[a] Obtained from crude hydrazide by fractional crystallization from toluene unless otherwise noted. [b] By fractional crystallization from ethanol. [c] Recrystallized from dilute aqueous hydrochloric acid. [d] Recrystallized alternately from ethanol and from water. [e] Lit.,[3] m. p. 205°. [f] Lit.,[10] m. p. 145–146°. [g] Lit.,[14] m. p. 172°. [h] c = 8% in pyridine unless otherwise noted. [i] $[\alpha]^{25}D$ −29.2° (c = 2.5% in chloroform). [j] c = 7% in pyridine. [k] c = 9% in pyridine. [l] Lit.,[3] $[\alpha]^{23}D$ −33.5° (c = 4.5% in pyridine). [m] $[\alpha]^{25}D$ −18.0° (c = 8% in 0.4 F NaOH); lit.,[10] $[\alpha]^{20}D$ −17.1° (c = 7% in 1 F NaOH). [n] $[\alpha]^{25}D$ −46.0° (c = 8% in ethanol); lit.,[14] $[\alpha]^{25}D$ −51° (in ethanol); for L-isomer,[15] $[\alpha]^{25}D$ +47.6° (in ethanol).

was used and that the *p*H was readjusted to 4.6 after the collection of each fraction. The weight, m. p. and specific rotation of each fraction was determined and the fractions then fractionally crystallized from suitable solvents in order to determine the melting points and specific rotations of each of the components of the various fractions. These data are summarized in Table III. The L-isomers were obtained from L-DL mixtures (initial fractions) and the D-isomers from D-DL mixtures (final fractions). The D-acids (*cf.* Table III) were obtained by acidification of the reaction mixture, extraction with ether and subsequent crystallization from the indicated solvents. The amount of L-isomer present in each fraction (*cf.* Table I) was estimated from the specific rotation of each fraction and the specific rotation of one or both components (*cf.* Table III).

(14) V. du Vigneaud and C. Meyer, *J. Biol. Chem.*, **98**, 295 (1932).

(15) R. Jackson and W. Cahill, *ibid.*, **126**, 37 (1938).

Summary

It has been shown that stereochemical specificity in the papain-catalyzed synthesis of phenylhydrazides of acylated phenylalanines is in part determined by the nature of the acyl group present in the acylated phenylalanines.

PASADENA 4, CALIF. RECEIVED AUGUST 12, 1949

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1319]

The Preparation and Resolution of the Three Isomeric Nuclear Substituted Monofluoro-DL-phenylalanines

BY EDWARD L. BENNETT[1] AND CARL NIEMANN

The observation that *m*-fluoro-DL-phenylalanine may effectively inhibit the metabolism of phenylalanine by a competitive process[2] suggested the desirability of extending these studies to include all of the isomeric nuclear substituted monofluorophenylalanines. The three nuclear substituted monofluoro-DL-phenylalanines had been prepared previously by the condensation of the appropriate fluorobenzaldehydes with hippuric acid,[3,4] the former compounds being obtained by chromyl chloride oxidation of the corresponding fluorotoluenes, or by hydrolysis of the fluorobenzal chlorides. The over-all yields from toluidine to the amino acid were 2.3, 7.0 and 5.0% for the *o*-, *m*- and *p*-fluoro-DL-phenylalanines, respectively, or 3.1, 10.3, and 9.5% from the corresponding fluorotoluenes.[5] The above yields were not substantially improved when the fluorobenzaldehydes were prepared from the amino- or nitrobenzoic acids *via* the McFadyen–Stevens reaction.[6] However, when the isomeric monofluorotoluenes were converted into the corresponding monofluorobenzyl chlorides by a vapor

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

(2) H. K. Mitchell and C. Niemann, THIS JOURNAL, **69**, 1232 (1947).

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

(4) J. Mead, Ph.D. Thesis, Calif. Inst. Tech., 1942.

(5) G. Schiemann, *Z. physik. Chem.*, **A156**, 397 (1931).

(6) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 584 (1936).

phase chlorination[7] and the latter compounds condensed with sodioacetamidomalonic ester[8,9] or sodioacetamidocyanoacetic ester,[10] the *o*-, *m*- and *p*-fluoro-DL-phenylalanines were obtained from the fluorotoluenes in yields of 39, 43 and 40%, respectively, when sodioacetamidomalonate was used.

The *o*-, *m*- and *p*-fluoro-DL-phenylalanines were resolved enzymatically by conversion of the acetyl-L-amino acids into the corresponding-L-phenylhydrazides.[11] In the above operations no indication of concomitant formation of the D-phenylhydrazides was obtained and in view of the fact that both the L- and the D-phenylhydrazides are formed when carbobenzoxy-*o*-fluoro-DL-phenylalanine is treated with phenylhydrazine and papain,[12] it must be concluded that the present study provides additional support for the thesis that in the papain-catalyzed synthesis of phenylhydrazides of the acylated α-amino acids the nature of the acyl group may exert a profound effect upon the stereochemical course of the reaction.

The authors wish to express their indebtedness to Mr. W. Fickett for assistance given during the course of this investigation and to Dr. A. Elek for all microanalyses.

Experimental[13]

Fluorobenzhydrazides.—The ethyl esters of *o*- and *p*-aminobenzoic acids were obtained in yields of 70 and 89%, respectively. The *m*-ester was obtained in 82% yield by esterification and reduction of *m*-nitrobenzoic acid. The diazonium fluoroborates were prepared in the usual manner[14] except for the use of sodium fluoroborate instead of the acid. The yields for the *o*-, *m*- and *p*-compounds were, respectively, 83, 64 and 79%. The *o*-, *m*- and *p*-fluorobenzoates were obtained in yields of 52, 67 and 64% by the thermal decomposition of the diazonium fluoroborates. The *o*-, *m*- and *p*-fluorobenzhydrazides (*cf.* Table I), were obtained, in yields of 89, 97 and 95%, respectively, from the corresponding esters by treating the latter compounds with a onefold excess of 85% hydrazine hydrate.

Fluorobenzaldehydes.[5]—The *o*-, *m*- and *p*-fluorobenzhydrazides were converted into the *sym*-fluorobenzoylbenzenesulfonhydrazides[5] (*cf.* Table I) in yields of 98, 98 and 89%, respectively, and the latter compounds decomposed in the usual manner[6] to give the *o*-, *m*- and *p*-fluorobenzaldehydes in yields of 50, 50 and 42%, respectively. The constants observed were: *o*-, b. p. 90–91° (46 mm.), $n^{25}D$ 1.5180, lit., [5] b. p. 80.5° (36 mm.), $n^{15}D$ 1.5121; *m*-, b. p. 98–99° (50 mm.), $n^{25}D$ 1.5157, lit.,[5] b. p. 76° (26 mm.), $n^{24}D$ 1.5159; *p*-, b. p. 97–99° (48 mm.), $n^{25}D$ 1.5180, lit.,[5] b. p. 104.5° (74 mm.), $n^{19}D$ 1.5200.

2-Phenyl-4-(fluorobenzal)-5-oxazolones.[3]—Mixtures of the fluorobenzaldehydes, hippuric acid, sodium acetate and acetic anhydride with mole ratios of 1:1:1:3.4, respectively, were refluxed for sixty to seventy-five minutes to give the following crude 2-phenyl-4-(fluorobenzal)-5-oxazolones: *o*-, 44%, m. p. 155–163°; *m*-, 61%, m. p. 109–139°; *p*-, 60%, m. p. 133–165°. Recrystallization of the crude azlactones (*cf.* Table I) gave the following yields of purified azlactones: *o*-, 76%; *m*-, 53%; *p*-, 53%. Substitution of twenty minutes of heating on a steam-bath[16] for sixty to seventy-five minutes of refluxing gave in the case of *o*-fluorobenzaldehyde 47% of crude azlactone, m. p. 154–164°.

TABLE I

INTERMEDIATES AND FINAL PRODUCTS OF ERLENMEYER–PLÖCHL SYNTHESES

Compounds	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Fluorobenzhydrazides							
o-[a]	72–73[e]	54.5	4.6	18.2	54.7	4.8	18.1
m-[b]	138–139.5	54.5	4.6	18.2	54.7	4.7	18.3
p-[c]	161.5–163	54.5	4.6	18.2	54.7	4.7	18.2
Fluorobenzoylbenzenesulfonhydrazides							
o-[b]	172–173.5	53.1	3.8	9.5	53.2	3.7	9.4
m-[d]	182–183	53.1	3.8	9.5	53.1	3.8	9.4
p-[d]	179–180.5			9.5			9.8
2-Phenyl-4-(fluorobenzal)-5-oxazolones							
o-[b]	167–169[f]	71.9	3.8	5.2	72.2	3.9	5.3
m-[b]	158.5–159.5[g]	71.9	3.8	5.2	71.9	3.9	5.2
p-[b]	184–185.5[h]	71.9	3.8	5.2	71.9	3.8	5.2
Fluoro-DL-phenylalanines							
o-	244–248[i]	59.0	5.5	7.7	59.1	5.5	7.6
m-	240–242[j]	59.0	5.5	7.7	59.1	5.7	7.8
p-	259–261[k]	59.0	5.5	7.7	59.3	5.7	7.6

[a] Recrystallized from cyclohexane–ligroin. [b] From ethanol. [c] From ethyl acetate. [d] From benzene. [e] Lit.,[15] m. p. 70°. [f] Lit.,[3] m. p. 165.5–166.5°. [g] Lit.,[3] m. p. 156–156.5°. [h] Lit.,[3] m. p. 181–182°. [i] Decomposition point, lit.,[3] 258.5–259°. [j] Decomposition point, lit.,[3] 262–263°. [k] Decomposition point, lit.,[3] 263.5–264°.

Fluoro-DL-phenylalanines.[3]—Reductive hydrolysis[17] of the above purified azlactones followed by evaporation, neutralization with ammonium hydroxide, and recrystallization from 60–65% ethanol gave 64, 65 and 69% of the recrystallized, *o*-, *m*- and *p*-fluoro-DL-phenylalanines (*cf.* Table I).

Fluorobenzyl Chlorides.[18]—The vapor-phase chlorination[7] of 0.35 mole quantities of the *o*-, *m*- and *p*-fluorotoluenes (Eastman White Label) gave 82, 82 and 83%, respectively, of the redistilled *o*-, *m*- and *p*-fluorobenzyl chlorides. The constants observed were: *o*-, b. p. 86–88.5° (40 mm.), $n^{25}D$ 1.5122, lit.,[15,18] b. p. 83° (32 mm.), 67.5–68° (16 mm.), $n^{24}D$ 1.5154; *m*-, b. p. 84° (29 mm.), $n^{25}D$ 1.5100, lit.,[5,18] b. p. 67–68° (15 mm.), 73° (23 mm.), $n^{17.5}D$ 1.5141; *p*-, b. p. 86–87° (30 mm.), $n^{25}D$ 1.5103, lit.,[18] b. p. 76° (20 mm.).

α,α-(Fluorobenzyl)-acetamidomalonic Esters.[8,9]—To 0.3 mole of sodium in 475 ml. of absolute ethanol was added 0.3 mole of acetamidomalonic ester (Winthrop) and 0.27 mole of the appropriate fluorobenzyl chloride, the mixture refluxed for four hours,[8,9] filtered, two volumes of water added and the product so obtained recrystallized from 30% ethanol. The yields of the *o*-, *m*- and *p*-fluoro esters (*cf.* Table II) were, respectively, 89, 68 and 76%.

Ethyl Fluorobenzylacetamidocyanoacetates.[10]—The replacement of acetamidomalonic ester in the above proce-

(7) H. Lucas and D. Pressman, "Theory and Practice in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949.

(8) N. Albertson and S. Archer, THIS JOURNAL, **67**, 308 (1945).

(9) H. Snyder, J. Shekleton and C. Lewis, *ibid.*, **67**, 310 (1945).

(10) N. Albertson and B. Tullar, *ibid.*, **67**, 502 (1945).

(11) E. L. Bennett and C. Niemann, *ibid.*, **72**, 1798 (1950).

(12) E. L. Bennett and C. Niemann, *ibid.*, **70**, 2610 (1948).

(13) All melting points are corrected.

(14) G. Schiemann and W. Winkelmuller, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 299.

(15) G. Schiemann and H. Baumgarten, *Ber.*, **70**, 1416 (1937).

(16) H. Carter, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 198.

(17) H. B. Gillespie and H. R. Snyder, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 489.

(18) G. Bennett and B. Jones, *J. Chem. Soc.*, 1819 (1935).

dure by acetamidocyanoacetic ester (Winthrop) gave the *p*-fluoro-isomer (*cf.* Table II) in 70% yield. The *m*-fluoro-isomer could not be crystallized but on hydrolysis a 40% yield of acetyl-*m*-fluoro-DL-phenylalanine was obtained.

TABLE II

INTERMEDIATES AND FINAL PRODUCTS OF MALONIC ESTER SYNTHESES

Compounds	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Fluorobenzylacetamidomalonic Esters							
o-	107–108	59.1	6.2	4.3	59.0	6.2	4.4
m-	119–121	59.1	6.2	4.3	59.1	6.2	4.3
p-	145–147.5	59.1	6.2	4.3	59.1	6.3	4.3
Ethyl Fluorobenzylacetamidocyanoacetates							
p-	165–166	60.4	5.4	10.1	60.4	5.5	10.0
N-Acetyl-fluoro-DL-phenylalanines							
o-[a]	147–149	58.7	5.4	6.2	58.5	5.5	6.4
m-[b]	154–156.5	58.7	5.4	6.2	58.7	5.3	6.3
p-[b]	150.5–152	58.7	5.4	6.2	58.7	5.5	6.3
Fluoro-DL-phenylalanine Hydrochlorides							
o-[c]	243–250[f]	45.5	5.5	5.9	45.5	5.5	5.8
m-[d]	248–251[f]	49.2	5.1	6.4	49.3	5.1	6.3
p-[e]	241–252[f]	49.2	5.1	6.4	49.4	5.0	6.3

[a] Recrystallized from 30% ethanol. [b] From water. [c] Monohydrate stable to drying *in vacuo* over sodium hydroxide, neut. equiv., 237, 239. [d] Neut. equiv., 220, 221. [e] Neut. equiv., 220, 220. [f] Decomposition points.

N-Acetyl-fluoro-DL-phenylalanines.—The substituted acetamidomalonic or cyanoacetic esters were hydrolyzed with 2.5 *F* sodium hydroxide for four hours, the hydrolysates adjusted to *p*H 2–3 with hydrochloric acid, the hydrolyses continued for an additional hour[8-10] and the acetylated amino acids recrystallized as indicated in Table II. The yields of the *o*-, *m*- and *p*-compounds from the acetamidomalonates were 63, 92 and 88%, respectively, and for the *p*-compound from the cyanoacetate 60%.

Fluoro-DL-phenylalanine Hydrochlorides.—The acetylated amino acids were hydrolyzed for fourteen to twenty-four hours with 6 *F* hydrochloric acid and the amino acid hydrochlorides recrystallized from 6 *F* hydrochloric acid. The yields for the *o*-, *m*- and *p*-isomers were, respectively, 85, 84 and 72%.

Resolution of N-Acetyl-fluoro-DL-phenylalanines.[19]—The following conditions were employed for all resolutions. Solutions containing 0.022 mole acetyl-DL-acid, 0.022 mole phenylhydrazine, 0.0025 mole cysteine hydrochloride and 0.45 g. of papain[11] per 100 ml. of 0.5 *F* sodium acetate–acetic acid buffer of *p*H 4.6 were incubated at 40° for 88–116 hours, the precipitated phenylhydrazides collected, the solutions readjusted to *p*H 4.6, 0.004 mole phenylhydrazine and 0.0012 mole of cysteine hydrochloride per 100 ml. of solution added, the solutions incubated for an additional six days, the precipitated phenylhydrazides collected, the solutions acidified with hydrochloric acid and the precipitated acetyl-D-acids collected. The yields, m. p.'s and specific rotations of the various fractions are summarized in Table III. The phenylhydrazides were recrystallized from ethanol and the acids from ethanol and then from water except for the *p*-fluoro-acid which was recrystallized from water alone. The properties of the recrystallized compounds are given in Table IV.

TABLE IV

D- AND L-FLUOROPHENYLALANINES AND DERIVATIVES

Compounds	M. p., °C.	$[\alpha]^{25}D$	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N-Acetyl-fluoro-L-phenylalanylphenylhydrazides								
o-	215–216.5	−29.6[f]	64.8	5.8	13.3	64.7	6.1	13.6
m-	209–210	−30.9[f]	64.8	5.8	13.3	64.5	5.7	13.3
p-	233–235	−36.4[g]	64.8	5.8	13.3	64.6	5.9	13.1
N-Acetyl-fluoro-D-phenylalanines								
o-	168–170	−28.6[h,i]	58.7	5.4	6.2	58.7	5.7	6.0
m-	159–160	−40.4[h,j]	58.7	5.4	6.2	58.4	5.6	5.9
p-	142–143	−38.6[h]	58.7	5.4	6.2	58.9	5.4	6.4
Fluoro-L-phenylalanines								
o-[a,b]	226–231[c]	−15[k]	45.5	5.5	5.9	45.6	5.6	5.8
m-	239–243[d]	−24[l]	59.0	5.5	7.7	59.0	5.5	7.7
p-	250–255[d]	−23[l]	59.0	5.5	7.7	59.1	5.5	7.6
Fluoro-D-phenylalanines								
o-[a]	224–228[e]	+15[m]	45.5	5.5	5.9	45.6	5.6	5.8
m-	230–234[d]	+22[l]	59.0	5.5	7.7	59.1	5.5	7.7
p-	227–232	+24[l]	59.0	5.5	7.7	58.9	5.6	7.7

[a] Monohydrochloride monohydrate. [b] Neut equiv., 238. [c] Decomposition point, decomposition point of amino acid 226–232°. [d] Decomposition point. [e] Decomposition point, decomposition point of amino acid 231–234°. [f] C = 7% in pyridine. [g] C = 9% in pyridine. [h] C = 8% in ethanol. [i] $[\alpha]^{25}D$ −16.4° (C = 8% in pyridine). [j] $[\alpha]^{25}D$ −29.5° (C = 7% in pyridine). [k] C = 2% in 0.1 *F* NaCl, *p*H 5.5, calcd. on basis of anhydrous amino acid. [l] C = 2% in water. [m] Rotation of amino acid, C = 2% in water.

Fluoro-L-phenylalanines.—The phenylhydrazides were refluxed for forty hours with 6 *F* hydrochloric acid, the hydrolysates evaporated to dryness, the residues taken up in water, an excess of ammonium hydroxide added, the solutions extracted with ether and the excess ammonia expelled by boiling the solutions. The precipitated amino acids (*o*-, 78%; *m*-, 67%; *p*-, 63%) were recrystallized, the *m*- and *p*-isomers from 50% ethanol and the *o*-isomer from 6 *F* hydrochloric acid. The properties of the recrystallized amino acids are given in Table IV.

Fluoro-D-phenylalanines.—The N-acetyl-D-amino acids were refluxed for twelve to seventeen hours with 6 *F* hydrochloric acid and the amino acids recovered and recrystallized essentially as described above. The yields prior to the final recrystallizations were: *o*-, 89%; *m*-, 71%; *p*-, 61%. The properties of the recrystallized compounds are given in Table IV.

TABLE III

RESOLUTION OF N-ACETYL-FLUORO-DL-PHENYLALANINES

DL-acids	L-Phenylhydrazides: First fraction Yield, %	First fraction M. p., °C.	First fraction $[\alpha]^{25}D$[a]	Second fraction Yield, %	Second fraction M. p., °C.	Second fraction $[\alpha]^{25}D$[a]	D-Acids Yield, %	D-Acids M. p., °C.	D-Acids $[\alpha]^{25}D$
o-	87	210–213		5	210–213	−29.2[c]	82	166–170	−15.9[b]
m-	85	206–209	−30.1[b]	2	206–209	−29.6[b]	61	156.5–158.5	−29.0[d]
p-	87	223–230	−37.0[b]	6	229–232	−36.2[b]	25		

[a] In pyridine. [b] C = 8%. [c] C = 5%. [d] C = 9%.

(19) Parallel resolutions were conducted with N-acetyl-DL-acids prepared by each of the above described syntheses. Since the results obtained were independent of the source of DL-acid only those data obtained with DL-acids prepared *via* the acetamidomalonic ester synthesis will be given.

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.

PASADENA 4, CALIFORNIA RECEIVED AUGUST 12, 1949

[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.

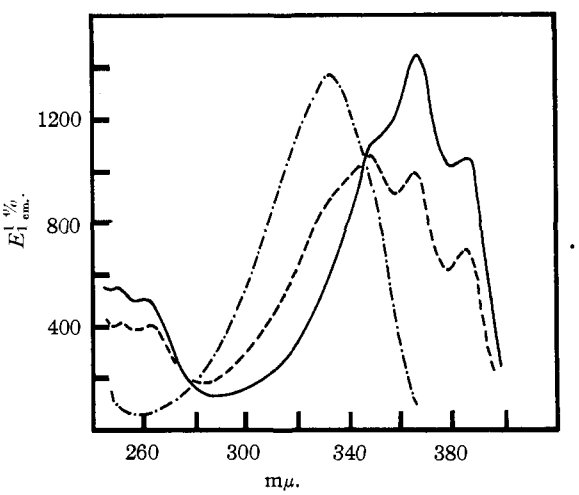

Fig. 1.—Ultraviolet absorption spectra of 2-phenyl-4-(*p*-fluorobenzal)-5-oxazolone, ——; 2-methyl-4-(*p*-fluorobenzal)-5-oxazolone ·-·-·-; and crude parent azlactone, m. p. 133–165°, – – – – –.

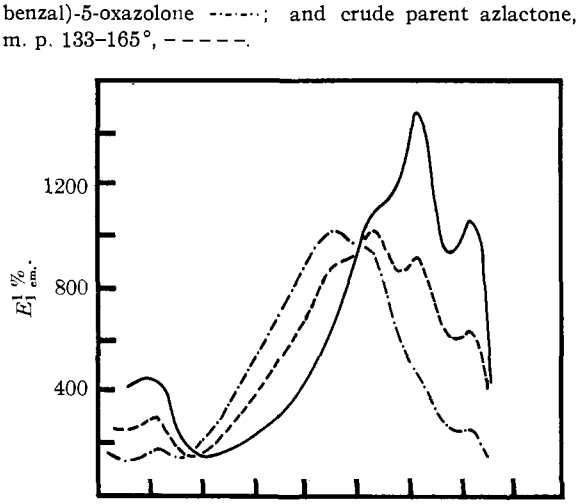

Fig. 2.—Ultraviolet absorption spectra of 2-phenyl-4-(*m*-fluorobenzal)-5-oxazolone, ——; crude parent azlactone, m. p. 109–139°, – – – – – –; and crude azlactone, m. p. 108–118°, ·-·-·-·-·.

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°.

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(2) J. W. Cornforth, "The Chemistry of Penicilliu," 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).