constants proposed by Pascual, Meier, and Simon[17] which predict the following trend in chemical shift: $H_A = \delta$ 5.07, $H_B =$ 5.24, $H_X = 6.26$. Finally, a doublet centered at δ 1.14 is assigned to the *endo*-H_7 proton with $J_{gem} = 7.70$ Hz.[18]

A more detailed nmr analysis of **3** was possible using double- and triple-irradiation techniques. The pertinant data are summarized in Table II, p 743.

The singlets at δ 0.71 and 1.38 are assigned to the 6-*endo*- and 6-*exo*-methyls, respectively, while a doublet at δ 1.62 is assigned to the vinylic methyl. A quartet at δ 5.20 is readily assigned to the olefinic proton of the 2-ethylidene grouping, with $J_{vic} = 7.0$ Hz. In analogy with the previously mentioned anisotropy of a rigid nonplanar cyclobutane, the "equatorial" *endo*-H_7 proton appears upfield at δ 1.39 with $J_{gem} = 8.0$ Hz.[19] Triple irradiation of both olefinic protons H_3 and H_4 at δ 5.87 and 6.09 serves to differentiate the remaining protons H_1 and H_5 and *exo*-H_7. In this latter experiment, the triplet of doublets at δ 2.93 collapses to a triplet while the quartet of doublets at δ 2.23 also collapses to a triplet. Since only H_5, and not H_1, would be anticipated to be coupled with both olefinic protons H_3 and H_4 (vicinal and allylic coupling[20]), this latter multiplet is assigned to H_5 while the triplet of doublets at δ 2.93 is assigned to H_1. The overlapping doublet of triplets at 2.43 which was unaffected in this experiment is assigned to *exo*-H_7. Irradiation of the olefinic doublet at δ 5.87 further confirms these assignments and serves to differentiate H_3 and H_4. Here H_1 becomes a triplet while H_5 now collapses to a quartet. Of the olefinic protons H_3 and H_4, only the former would be anticipated to be coupled weakly (allylic coupling[15]) with both bridgehead protons H_1 and H_5. Thus proton H_3 appears at δ 5.87 with the lowest field olefinic resonance at δ 6.09 assigned to H_4. The observed multiplicities of H_1, H_5, and *exo*-H_7, which are essentially first order, are due to a fortuitous equality of three vicinal and a long-range four-bond coupling between the bridgehead protons H_1 and H_5. Similar long-range coupling in bicyclo[3.1.1]heptanes has recently been reported by Kaplan[10] and Bates.[11]

The rather large difference in chemical shift of the bridgehead protons H_1 and H_5 is particularly noteworthy and presumably reflects the greater deshielding experienced by H_1 due to its closer position to the center of the deshielding plane of the adjacent olefinic bond and perhaps a further contribution due to Van der Waals[21] deshielding caused by the adjacent vinyl methyl group.

Registry No.—**2**, 18801-69-9; **3**, 18801-70-2.

(17) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49** Suppl, 164 (1966).

(18) The absence of vicinal coupling of *endo*-H_7 with the adjacent bridgehead hydrogens in bicyclo[3.3.1]heptane derivatives has previously been noted; see ref 10, 11, and 14a.

(19) The higher field line of this "doublet" falls under the 6-*exo*-methyl resonance. The nmr spectrum of this material shows resonance at δ 1.32 and 1.72 which are attributed to 10% of the diastereomer of **4** which is formed under our conditions. A partially discernable quartet on the high-field side of the δ 5.20 quartet is also indicative of the presence of this species.[17]

(20) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(21) Our attempts to make a less unambigious stereochemical assignment using the nuclear Overhauser effect[22] were inconclusive.

(22) F. A. L. Anet and A. J. R. Brown, *J. Amer. Chem. Soc.*, **87**, 5250 (1965); J. G. Colson, P. T. Lansbury, and F. D. Saeva, *ibid.*, **89**, 4987 (1967).

The Meerwein Reaction in Amino Acid Synthesis. II. An Investigation of Twenty-one Substituted Anilines[1]

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Received May 24, 1968

A major objective of this investigation has been the establishment of the reaction sequence (steps 1–3) as a generalized synthesis of substituted phenylalanines. A part of the objective was obtained with the preparation of the three monochlorophenylalanines.[1b] It was next required that anilines bearing electron-donating groups and anilines bearing electron-withdrawing groups be tested in the reaction sequence in order to establish the generalized synthesis. Twenty-one substituted anilines were submitted to one or several steps of the reaction sequence.[2] Nineteen of these yielded α-bromohydrocinnamic acids (*o*-aminobenzamide failed in the diazotization step; *o*-aminoacetophenone failed in the Meerwein reaction). The nineteen anilines which gave α-bromohydrocinnamic acids showed considerable variation in their behavior in the diazotization and, in particular, Meerwein reactions. These variations, relative to the chloroanilines,[1b] are summarized as follows. (a) Several anilines bearing electron-donating groups did not diazotize smoothly and, in some instances, significant amounts of tars were formed with consequent reduction of Meerwein product in the next step (in this respect *m*-anisidine proved to be particularly poor, with only 90% of the theoretical amount of nitrogen being evolved in the Meerwein reaction); the aryldiazonium bromides formed from anilines carrying electron-donating groups, especially in *ortho* or *para* position, required relatively large amounts of catalyst and high reaction temperatures in order to obtain reasonable reaction rates[3] in the Meerwein reaction. (b) Anilines bearing electron-withdrawing substituents were diazotized with no difficulty. The Meerwein reactions required little catalyst, and in several cases it was found necessary to use only small amounts of copper(I) bromide, low initial temperatures, and an ice bath in order to control the Meerwein reactions. (Thus, the diazotized nitroanilines, under conditions as specified in Table I and described in the Experimental Section, *except* that the catalyst was added to mixtures with initial temperatures of 15°, reacted in an almost explosive manner to give the theoretical amount of nitrogen in *ca.* 3–8 sec, with a temperature rise to 50–60°

step 1, diazotization

$$ArNH_3^+Br^- + HNO_2 \rightarrow ArN_2^+Br^- + 2H_2O$$

step 2, Meerwein reaction

$$ArN_2^+Br^- + CH_2{=}CHCOOH \rightarrow ArCH_2CH(Br)COOH + N_2$$

step 3, ammonolysis

$$ArCH_2CH(Br)COOH + 2NH_3 \rightarrow ArCH_2CH(NH_3)^+COO^- + NH_4^+Br^-$$

(1) (a) Supported in part by grants from the National Institutes of Health (GM 10560-01, -02) and from Research Corp. Grateful acknowledgement of this support is made here. (b) Part I: G. H. Cleland, *J. Org. Chem.*, **26**, 3362 (1961). The *Chemical Abstracts* treatment of this article [*Chem. Abstr.*, **56**, 12792*i* (1962)] contains critical errors in the example chosen from the experimental Section. Comparison of this part of the original article with the *Chemical Abstracts* review shows that in the latter the amounts of copper(I) bromide catalyst, acrylic acid, and sodium nitrite reported as employed are *twice* those given in the former. The yield of Meerwein product reported as recovered is *also* doubled in the review, giving a value 133% of theory.

(2) Each of the three steps of the reaction sequence was investigated with regard to every aniline tested until conditions were found where reasonable yields were obtained or until failure was acknowledged (one exception: ammonolysis of *m*-acetyl-α-bromohydrocinnamic acid was not attempted). At the same time it should be emphasized that the investigations were exploratory in nature and that in no instance were exhaustive studies made to determine optimum conditions.

(3) A "reasonable rate" is considered here to be one sufficient to give the theoretical amount of nitrogen, or cessation of nitrogen evolution, in 90 min or less. It was necessary to run diazotized *o*-anisidine for 120 min at an average temperature of 44° in order to obtain the theoretical amount of nitrogen.

TABLE I.—α-BROMOHYDROCINNAMIC ACIDS

Substituent on aniline	Registry No.	CuBr, mg	Av temp or range, °C	~t for 95–100% N_2, min	Crude yield, %	Yield after one crystn from formic acid, %	Mp, °C[a]	Calcd C, %	Calcd H, %	Calcd Neut equiv	Found C, %	Found H, %	Found Neut equiv
o-CH_3	18910-04-8	300	35	30	70	66	100–101	49.4	4.6	243	49.7	4.6	243
m-CH_3	18910-05-9	200	28	70		46 (oil)		49.4	4.6	243	49.6	4.9	242
p-CH_3	7141-87-9	300	40	10	87	72	91–92	49.4	4.6	243	49.2	4.8	241
o-OCH_3	18910-07-1	300	44	120		52	109–110	46.4	4.3	259	46.6	4.6	260
m-OCH_3	18910-08-2	250	25	30	54	35	106–107	46.4	4.3	259	46.4	4.4	259
p-OCH_3	18910-09-3	300	42	50		81	122–123[b]	46.4	4.3	259	46.7	4.3	260
o-NO_2	18910-10-6	50	8–35	2		42	115–116[c]	39.4	2.9	274	39.6	3.1	272
m-NO_2	18910-11-7	50	0–40	4		43	129–130	39.4	2.9	274	39.4	3.1	273
p-NO_2	18910-12-8	50	6–40	2		67	148–149[d]	39.4	2.9	274	39.7	3.0	273
o-COOH	18910-13-9	200	28–30[f]	60		32	177–178 dec[e]	44.0	3.3	136.5	44.3	3.4	136
m-COOH	18910-14-0	50	18	30	70	61	181–182	44.0	3.3	136.5	44.2	3.4	138
p-COOH	18910-15-1	50	0–24	5		90	218–220	44.0	3.3	136.5	44.0	3.4	137
o-CN	18910-16-2	50	8–35	3	80	59	106–107	47.3	3.2	254	47.6	3.0	253
p-CN	18910-17-3	50	4–32	4		62	134–135	47.3	3.2	254	47.1	3.1	252
m-$COCH_3$	18910-18-4	250	10–30	10		50	105–106	48.7	4.1	271	48.9	4.2	269
p-$COCH_3$	18910-19-5	50	23	15	73	60	157–158	48.7	4.1	271	48.7	4.2	272
o-$COOC_2H_5$	18910-20-8	200	25	75	84	82	88–89	47.9	4.4	301	47.9	4.3	300
p-$COOC_2H_5$	18910-21-9	25	22	30	70	51	108–109	47.9	4.4	301	47.7	4.3	302
p-$CONH_2$	18910-22-0	50	5–28	6		66	207–209 dec	44.1	3.7	272	44.0	3.6	271

[a] Melting points were determined on a Fisher-Johns apparatus and are corrected. [b] The acid has been reported as a thick oil [E. Friedmann and S. Gutmann, *Biochem. Z.*, **27**, 491 (1910)]. [c] A. Jaenisch, *Ber.*, **56**, 2448 (1923) reported mp 115–116°. [d] T. Urbanski and P. Gluzinski [*Roczniki Chem.*, **33**, 1031 (1959)] reported mp 144°. [e] The melting point was determined with difficulty because of the tendency of the substance to lose hydrogen bromide to form 1-oxo-3-isochromancarboxylic acid. [f] See ref 8.

in spite of an ice bath, and the formation of much tarry material. No significant qualitative differences were noted in rates of Meerwein reactions in observations on the three diazotized nitroanilines.) Data regarding the yields and properties of the α-bromohydrocinnamic acids, together with amounts of catalyst and reaction temperatures, are given in Table I. The general procedure for the formation and isolation of these substances, together with any significant variations, are given in the Experimental Section.

As part of the structure proof of the nineteen α-bromohydrocinnamic acids, attempts were made to convert a portion of each to the corresponding cinnamic acid. These conversions were successful by mild and direct means (short reflux with methanolic potassium hydroxide) in sixteen of nineteen cases.[4] The yields, based on qualitative observations and in some cases on quantitative studies, were good, and it is suggested that this is an excellent route to the synthesis of substituted cinnamic acids.[6] Data regarding properties and yields of the cinnamic acids are given in Table II. The general procedure for their formation, plus any significant variations, are presented in the Experimental Section.

Conversions of the α-bromohydrocinnamic acids to the corresponding phenylanines by direct ammonolysis were successful in many instances. A major competing reaction was encountered in the formation of the corresponding cinnamic acids. This reaction reduced the yields of all of the phenylalanines, but proved especially serious in those cases where electron-withdrawing groups were present in *para* and, in particular, in *ortho* positions on the aryl group. Thus only cinnamic acids were obtained in the cases where the starting anilines were *o*- or *p*-nitroanilines,[7] *o*-cyanoaniline, or ethyl *o*-aminobenzoate (which gave a mixture of cinnamic acids). Another "failure" was encountered in the case of α-bromo-*p*-ethoxycarbonylhydrocinnamic acid, which gave a mixture of amino acids and cinnamic acids under the usual conditions of ammonolysis, and a mixture of *p*-carbamoylphenylalanine and *p*-carbamoylcinnamic acid when refluxed with concentrated ammonium hydroxide. A failure of another type was shown by α-bromo-*o*-carboxyhydrocinnamic acid, which gave 1-oxo-3-chromancarboxylic acid under the conditions of direct ammonolysis (the α-bromo acid gave the same lactone when boiled in water, formic acid, or

(4) α-Bromo-*p*-ethoxycarbonylhydrocinnamic acid gave *p*-carboxycinnamic acid, and α-bromo-*o*-ethoxycarbonyl- and α-bromo-*o*-carboxyhydrocinnamic acids gave 1-oxo-3-chromancarboxylic acid, under these conditions. *p*-Ethoxycarbonylcinnamic acid was eventually obtained from the α-bromo acid by treatment with pyridine.[5]

(5) α-Bromo-*p*-ethoxycarbonylhydrocinnamic acid was dissolved in excess pyridine and kept at 23–25° for 150 hr, ice water and then a slight excess of cold concentrated hydrochloric acid were added, the mixture was kept at 0° for 5 hr and filtered, and a solid was washed with cold water until free of halide and crystallized from aqueous methanol.

(6) In several investigations it was found that crude Meerwein products gave better yields of cinnamic acids, when treated with methanolic potassium hydroxide, than were represented by yields obtained from similar Meerwein runs in which the α-bromohydrocinnamic acids were isolated and purified prior to conversion to the cinnamic acids. These observations are in accord with the idea that in at least some cases the Meerwein products are formed in better yields than are indicated by the yields recorded in Table I (cinnamic acids are much easier to isolate than are the α-bromo acids; in several experiments designed to detect cinnamic acids formed *during* the Meerwein reaction, none was found).

(7) α-Bromo-*o*- and *p*-nitrohydrocinnamic acids gave the corresponding nitrophenylalanines *via* Delépine reactions, but the yields were indifferent and the introduction of a hydrolytic step defeats one of the main purposes of the investigation.

TABLE II

CINNAMIC ACIDS

Substituent	Yield, %[a]	Neut equiv Calcd	Neut equiv Found	Mp, °C[b]	Mmp with authentic samples, °C	Selected lit. mp values, °C
o-CH_3		162	163	175–176	175–176	176–177[c]
m-CH_3		162	165	118	118	119[d]
p-CH_3	91	162	162	198–200	198–200	199[d]
o-OCH_3	90	178	177	185–186	185–186	186[d]
m-OCH_3		178	176	119–120	119–120	120[d]
p-OCH_3		178	180	174	174	174[d]
o-NO_2	96	193	191	241–242	242	242[d]
m-NO_2		193	190	206–207	206–207	202[d]
p-NO_2		193	193	289–290	289–290	288[d]
m-COOH		96	98	278–280		275[e]
p-COOH	95	96	97	355–357 dec		358[e]
o-CN		173	173	251–253		256[f]
p-CN	82	173	175	254–256		254–256[g]
m-CH_3CO	66	190	193	158–160		...[h]
p-CH_3CO	71	190	190	224–225		
p-$COOC_2H_5$[i]	95	220	223	217–219		220[i]
p-$CONH_2$		191	189	*Ca.* 300 dec		

[a] Based on purified α-bromohydrocinnamic acids. [b] Determined on a Fisher-Johns apparatus and corrected, except in the cases of *p*-carboxy- and *p*-carbamoylcinnamic acids, where the melting points were determined on an aluminum block apparatus and are not corrected. In a number of cases previous softening and yellowing were observed over a 2–10° range. The melting points recorded represent the first appearance of liquid to the final disappearance of all solid. [c] A. C. Cope, T. A. Liss, and D. S. Smith, *J. Amer. Chem. Soc.*, **79**, 240 (1957). [d] J. F. J. Dippy and J. E. Page, *J. Chem. Soc.*, 357 (1938). [e] A. F. Titley, *ibid.*, 2571 (1928). [f] W. Davies and H. G. Poole, *ibid.*, 2661 (1927). [g] H. Rapport, A. R. Williams, O. G. Lowe, and W. W. Spooner, *J. Amer. Chem. Soc.*, **75**, 1125 (1953). [h] The melting point of a *m*-acetyl-α-bromohydrocinnamic acid has been reported as 128° [P. Ruggli and A. Staub, *Helv. Chim. Acta*, **19**, 962 (1936)]. It is possible that it was the *cis* isomer. [i] W. Löw, *Ann.*, **231**, 361 (1885). [j] See ref 5.

TABLE III

PHENYLALANINES[a,s]

Substituent	Yield, %[b]	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Dec ranges, °C[c]	Selected lit. mp values, °C
o-CH_3	62	67.0	7.3	66.9	7.3	213–214	259–260[d]
m-CH_3	32	67.0	7.3	67.1	7.4	206–207	208[e]
p-CH_3	78	67.0	7.3	66.9	7.4	215–216	226–229[f]
o-OCH_3	80	61.5	6.7	61.5	6.9	207–209	206[g]
m-OCH_3	92	61.5	6.7	61.6	6.7	192–195[h]	215[i]
p-OCH_3	70	61.5	6.7	61.5	6.7	216–219	295[j]
m-NO_2	47	51.4	4.8	51.2	4.7	215–217	209–212[k]
m-COOH	75	57.4	5.3	57.2	5.6	173–180, etc.[l]	176–177[m]
p-COOH	67	57.4	5.3	57.2	5.4	302–306[n]	304–305[m]
p-CN	27	63.1	5.3	63.0	5.5	221–223	
p-CH_3CO	30	63.8	6.3	63.5	6.5	207–208[o]	
p-$CONH_2$[p]	65	57.7	5.8	57.4	6.1	262–265	
p-$CONH_2$[q,r]	81	57.7	5.8	57.4	5.9	262–265	

[a] The amino acids gave positive ninhydrin reactions. [b] Based on the α-bromohydrocinnamic acid obtained by one crystallization of the crude α-bromo acid from formic acid. [c] The samples, unless otherwise noted, were introduced on a Fisher-Johns apparatus at 200° and heated at a constant rate of 2° min^{-1}. The ranges are temperatures at which droplets of liquid were observed throughout the sample, generally accompanied by gas evolution, until all solid was gone. The samples usually exhibited a yellow color, changing to orange or red, before this range. [d] R. R. Herr, T. Enkoji, and J. P. Dailey, *J. Amer. Chem. Soc.*, **79**, 4229 (1957). [e] T. Curtius and J. Gaier, *J. Prakt. Chem.*, **125**, 211 (1930). [f] A. L. Zhuze, *et al.*, *Collect. Czech. Chem. Commun.*, **29**, 2648 (1964); *Chem. Abstr.*, **62**, 1739*b* (1965). [g] T. B. Johnson and W. M. Scott, *J. Amer. Chem. Soc.*, **37**, 1846 (1915). [h] Placed on the stage at 175° and heated at a constant rate of 2° min^{-1}. [i] S. N. Chakravarti and P. L. N. Rao, *J. Chem. Soc.*, 172 (1938). [j] H. D. Dakin, *J. Biol. Chem.*, **8**, 11 (1910). [k] H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Amer. Chem. Soc.*, **81**, 3103 (1959). [l] On the stage at 100°, 1° min^{-1} heating rate: softened at 173°, completely liquified at 180° as a colorless melt. Rapid heating: melted at 166–179°, gas evolution apparent *ca.* 179°, colorless until *ca.* 230° when a yellow color developed. The N-benzoyl derivative was made, mp 208–209° dec, lit.[m] 203–204° dec. [m] T. Hashimoto and S. Oyama, *J. Pharm. Soc. Japan*, **74**, 1287 (1954); *Chem. Abstr.*, **49**, 15912*h* (1955). [n] The determination was made in a capillary tube in an aluminum block apparatus and is not corrected. [o] The sample partially melted, resolidified by *ca.* 211°, and was still a dark red solid at 285°. [p] From ammonolysis of α-bromo-*p*-carbamoylhydrocinnamic acid under the usual conditions. [q] From reflux of α-bromo-*p*-ethoxycarbonylhydrocinnamic acid with concentrated ammonium hydroxide. [r] When 0.01 *M* of α-bromo-*p*-ethoxycarbonylhydrocinnamic acid was treated under the normal conditions of ammonolysis, 1.8 g of an amino acid fraction was isolated which gave analytical results of C, 57.1; H, 6.1; N, 12.1. [s] Cinnamic acids recovered from the ammonolyses (per cent based on the α-bromohydrocinnamic acids after one crystallization of the α-bromo acids from formic acid): *m*-carboxy, 20; *p*-carboxy, 23; *p*-cyano, 35.

toluene, or when heated considerably below its melting point). Data regarding properties and yields of the amino acids synthesized are given in Table III. The general procedure for the preparation of the amino acids is presented in the Experimental Section, together with any significant variations.

Experimental Section

α-Bromohydrocinnamic Acids.—The aniline (0.05 *M*) was dissolved in acetone (100 ml), concentrated hydrobromic acid (16 ml of "48%") was added, and the mixture was cooled to 3–5° and stirred while diazotized beneath the surface with 10.0 ml of 5.00 *F* sodium nitrite. Acrylic acid (50 ml) was added, the mixture was cooled to 0–5°, cuprous bromide was added (amounts are recorded in Table I), the solution was stirred, and the temperature was regulated so that nitrogen was evolved at a reasonable rate.[3] When nitrogen evolution ceased the mixture was concentrated *in vacuo* on steam to remove acetone and the bulk of acrylic acid and water; the residue was treated with water (200 ml) and stored at 0° for 24 hr. An organic residue, oil or solid, was separated, washed twice with water (50-ml portions), dissolved in water (100 ml) by addition of a slight excess of sodium hydrogen carbonate, filtered if necessary, extracted with chloroform (50 ml) and ether (50 ml), stirred with carbon (2 g), filtered, and acidified with concentrated hydrobromic acid. The mixture was extracted with benzene (300 ml), and the benzene layer was washed with water (25 ml), boiled to *ca.* 100 ml, and concentrated *in vacuo*. In most cases the residues solidified wholly or in part. In two cases (α-bromo-*o*-cyano- and α-bromo-*o*-methylhydrocinnamic acids) it was necessary to streak samples of oils on glass in order to induce crystallization; the samples crystallized in 24 hr and were used to seed the bulk of the materials, which then crystallized in a short time. The α-bromo acids were pressed out on tile or between filter papers, and the substances recovered are in certain instances reported as crude yields in Table I; in any case they were purified by one crystallization from formic acid, and these yields are given in Table I. For analysis they were crystallized twice more from formic acid. One substance (α-bromo-*m*-methylhydrocinnamic acid) did not crystallize under a variety of conditions attempted. For purification the oil was boiled with a small amount of formic acid and chilled, the formic acid layer was separated, and the oil was dried. For analysis this process was repeated twice. Formation and purification of α-bromo-*o*-carboxyhydrocinnamic acid required different conditions because of the ease with which this substance loses hydrogen bromide to afford the lactone 1-oxo-3-chromancarboxylic acid.[8]

Cinnamic Acids.—Samples of the purified α-bromohydrocinnamic acids (*ca.* 1 g) were heated with a saturated solution of potassium hydroxide in methanol (10 ml) under gentle reflux for 3–4 min, a part of the methanol was removed, and the mixture was diluted with enough water to dissolve all solid, made strongly acidic with concentrated hydrobromic acid, and stored at 0° for 24 hr. A solid was filtered, washed with cold water (10-ml portions) until the washings were free of halide, and crystallized from aqueous methanol. α-Bromo-*p*-ethoxycarbonylhydrocinnamic acid gave *p*-carboxycinnamic acid when treated in this manner. The α-bromo acid was converted to *p*-ethoxycarbonylcinnamic acid under different conditions.[5] α-Bromo-*o*-ethoxycarbonyl- and α-bromo-*o*-carboxyhydrocinnamic acids gave 1-oxo-3-isochromancarboxylic acid under several sets of conditions.

Phenylalanines.—The α-bromohydrocinnamic acid (0.01 *M*) was dissolved in concentrated ammonium hydroxide (100 ml), the mixture was kept at 0° for 24 hr and then at 23–25° for 48 hr and concentrated to dryness on a steam bath over a 3–5-hr period, and the residue was washed with ice water (5 ml). The solid was treated with a slight excess of 0.1 *F* hydrobromic acid and with water (100 ml), heated to 60°, cooled, and filtered, the filter was washed with water (25 ml) (the cinnamic acids on the filter were recovered and purified in some cases, see footnote *s* in Table III), the combined aqueous filtrates were extracted with chloroform (50 ml) and with ether (50 ml) and concentrated to dryness *in vacuo*, the residue was treated with a slight excess of concentrated ammonia and concentrated on steam to dryness, and a solid was filtered and washed with cold methanol (5-ml portions) until the washings were free of halide. The amino acids thus obtained were crystallized twice from aqueous methanol and then dried at 110° *in vacuo* over potassium hydroxide for analysis. When this process was carried out with α-bromo-*p*-ethoxycarbonylhydrocinnamic acid a mixture of cinnamic acids and α-amino acids was obtained. (Analytical results indicate *ca.* 30% of ester and 70% of amide functions on the amino acids.) When the α-bromo acid was refluxed for 6 hr with concentrated ammonium hydroxide a mixture of *p*-carbamoylphenylalanine and *p*-carbamoylcinnamic acid was isolated and separated. α-Bromo-*o*-carboxyhydrocinnamic acid gave only 1-oxo-3-isochromancarboxylic acid under all conditions tried.

Registry No.—Cinnamic acid (*m*-CH_3CO), 18910-23-1; cinnamic acid (*p*-CH_3CO), 18910-24-2; cinnamic acid (*p*-$CONH_2$), 18910-25-3; phenylalanine (*p*-CN), 18910-26-4; phenylalanine (*p*-CH_3CO), 18910-27-5; phenylalanine (*p*-$CONH_2$), 18910-28-6.

(8) The reaction was run at 28–30°. The mixture was allowed to evaporate at 23–25° in a large crystallizing dish for 48 hr, the residue was treated with 200 ml of ice–water, stirred, and stored at 5° for 24 hr, and a tan solid was filtered, washed twice with water (50-ml portions), air dried, dissolved in a minimum amount of refluxing ether, and treated with 4 vol of 60–71° petroleum ether. After 10 min the solution was filtered, concentrated to remove ether and part of the petroleum ether, and stored at 0° for 24 hr. A solid was filtered, washed with petroleum ether (50 ml), and dried to give 32% analytically pure α-bromo-*o*-carboxyhydrocinnamic acid. When all filtrates and residues to this point were combined and concentrated to dryness and the remaining material was boiled with water (100 ml) for 1 hr and chilled, a solid was filtered which after drying proved to be 5 g of crude 1-oxo-3-isochromancarboxylic acid. This substance, crystallized three times from water and then once from formic acid, melted at 157–158°. E. Bamberger and W. Lodter [*Ber.*, **26**, 1833 (1893)] reported mp 153.5°. *Anal.* Calcd for $C_{10}H_8O_4$: C, 62.5; H, 4.2; neut equiv, 192. Found: C, 62.3; H, 4.2; neut equiv, 194. A mixture with phthalideacetic acid was completely melted by 130°.

Convenient Synthesis of 2-Fluoroadenine[1]

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Received October 3, 1968

2-Fluoroadenine has been found to be a feedback inhibitor of purine synthesis.[2] Because of this activity and other general biochemical interest in this compound[3,4] and its nucleosides[5–7] it was desirable to develop a convenient method for its preparation.

Montgomery and Hewson[4] synthesized 2-fluoroadenine *via* diazotization of 2,6-diaminopurine in fluoroboric acid (Schiemann reaction), followed by purification using Celite column chromatography and water crystallization to give a 0.7% yield of pure material. In a modification of their synthesis[4] they obtained a higher yield (6%) by means of a sequence

(1) Supported by Contract PH-43-52-479, Cancer Chemotherapy National Service Center, National Institutes of Health, U. S. Public Health Service.

(2) H. T. Shigeura, G. E. Boxer, S. D. Sampson, and M. L. Meloni, *Arch. Biochem. Biophys.*, **111**, 713 (1965).

(3) J. A. Montgomery, *Progr. Drug Res.*, **8**, 475, 489 (1965).

(4) J. A. Montgomery and K. Hewson, *J. Amer. Chem. Soc.*, **82**, 463 (1960).

(5) M. J. Dickinson, F. W. Holly, E. Walton, and M. Zimmerman, *J. Med. Chem.*, **10**, 1165 (1967).

(6) J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **33**, 432 (1968).

(7) J. A. Montgomery and K. Hewson, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, No. MEDI 26.