carbonate (0.84 g, mp 175–180°). This was added to boiling, 2 *N* HNO_3 (2 ml). The guanidine nitrate separated as an oil which eventually solidified and recrystallized from EtOH–EtOAc.

1-(β-Hydroxyphenethyl)-2,3-dimethylguanidine Hydriodide. β-Hydroxyphenethylamine (2.74 g, 0.02 mole) and 1,2,3-trimethyl-2-thiopseudourea hydriodide (5.0 g, 0.02 mole) in ethanol (12 ml) were boiled under reflux for 2 hr. The small crop of crystals obtained when the solution had cooled to room temperature melted at >300° and was discarded. On cooling the solution in a refrigerator, more crystalline product was obtained: mp 150–180°. Two recrystallizations from EtOH–EtOAc gave 1-(β-hydroxyphenethyl)-2,3-dimethylguanidine hydriodide (0.5 g), mp 186–187°.

Tyrosine Hydroxylase Inhibitors. Synthesis and Activity of Substituted Aromatic Amino Acids

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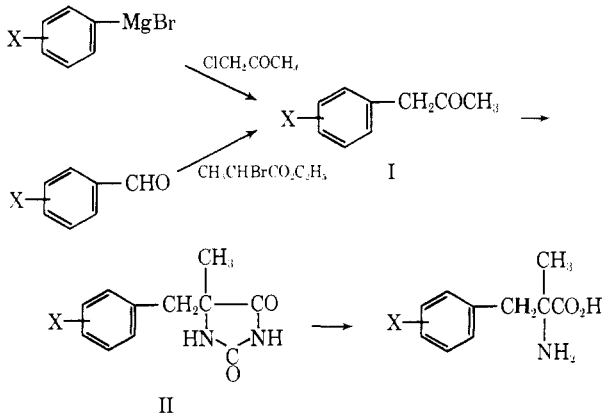
A series of α-alkyl aromatic amino acids has been prepared containing various substituents in the phenyl nucleus. The results of testing these compounds and related amino acids in the tyrosine hydroxylase enzyme system are tabulated on the basis of their mode of action as either substrate inhibitors or cofactor inhibitors. Other classes of compounds have also been studied as inhibitors of the tyrosine hydroxylase enzyme system. Active representatives are included in the tables.

This communication reports on the synthesis of some α-alkylamino acids and the results obtained by testing these compounds and related ones in the tyrosine hydroxylase system.[1] Beef adrenal medullary homogenate was used as the source of this enzyme which converts L-tyrosine to L-3,4-dihydroxyphenylalanine, the rate-limiting step in the biosynthesis of norepinephrine.[2]

Chemistry.—Most of the α-alkylamino acids were prepared by the routes outlined in Scheme I. The substituted phenylacetone intermediates (I) not previously reported in the literature were prepared either

SCHEME I



by a Darzen's glycidic ester condensation[3] between a substituted benzaldehyde and ethyl α-bromopropionate or by reaction of an aryl Grignard reagent with chloroacetone.[4]

The hydantoins II, prepared from the corresponding ketones with potassium cyanide and ammonium carbonate, were hydrolyzed to give the α-alkylamino acids. Physical constants and analytical values for these newly synthesized hydantoins and amino acids are tabulated in Tables V and VI of the Experimental Section.

The 3-halo,[5] 3,5-dihalo, and nitro derivatives of α-methyltyrosine were prepared by halogenation or nitration of the amino acid. Optically active 3-iodo-α-methyltyrosine was obtained by the iodination of L-α-methyltyrosine. Catalytic hydrogenation of 3-nitro-α-methyltyrosine in acid solution gave the 3-amino derivative.

Syntheses of the 4-acetamido and 4-methanesulfonamido derivatives of tyrosine and α-methyltyrosine were accomplished by reaction of the copper complex of the corresponding 4-aminophenylamino acids with excess methanesulfonyl chloride or acetic anhydride.

Reaction of 5-benzyl-5-methylhydantoin with chlorosulfonic acid provided the sulfonyl chloride (III) which served as an intermediate for the preparations of the 4-methylthio (IV) and 4-sulfamoyl (V) derivatives (see Scheme II).

Testing Procedures.—Fresh beef adrenal glands were obtained from the slaughterhouse and held in ice until used about 1 hr after removal from the carcass. The adrenal medulla tissue homogenate was prepared in 0.25 *M* sucrose as described by Nagatsu, *et al.*[1] Compounds to be tested were dissolved at 2×10^{-3} *M* concentration in either 0.01 *M* HCl or acetonitrile and tested routinely at 1×10^{-4} *M*. The incubation mixture contained 2 ml of adrenal medulla homogenate, 0.2 ml of α-hydrazino-3,4-dihydroxy-α-methylhydrocinnamic acid (a decarboxylase inhibitor) at 2×10^{-3} *M* in 0.01 *N* HCl, 0.4 ml of 1 *M* phosphate buffer, pH 6.0, 0.2 ml of control solvent or inhibitor solution, 0.1 ml of DL-2-C^{14}-tyrosine (180,000 counts/min),[6] and water to 4 ml.

In experiments with added tetrahydropteridine cofactor, 2-amino-6-hydroxy-7,8-dimethyl-6,7,8,9-tetrahydropteridine (in 0.1 *M* mercaptoethanol solution) was

(1) (a) T. Nagatsu, M. Levitt, and S. Udenfriend, *Biochem. Biophys. Res. Commun.*, **14**, 543 (1964); (b) *J. Biol. Chem.*, **239**, 2910 (1964). An extensive search for *in vitro* inhibitors of rat brain tyrosine hydroxylase has been reported by E. G. McGeer and P. L. McGeer, *Can. J. Biochem.*, **45**, 115 (1967).

(2) S. M. Hess, R. H. Connamacher, M. Ozaki, and S. Udenfriend, *J. Pharmacol. Exptl. Therap.*, **134**, 129 (1961); S. Udenfriend, *Pharmacol. Rev.*, **18**, 43 (1966).

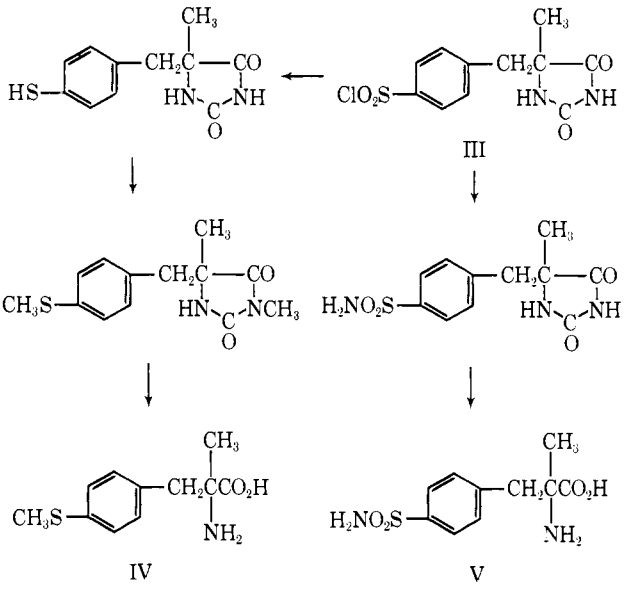
(3) M. Newman and B. Magerlein, *Org. Reactions*, **5**, 413 (1949).

(4) (a) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **63** 602 (1941); (b) A. S. Hussey and R. R. Herr, *J. Org. Chem.*, **24**, 843 (1959).

(5) H. U. Daeniker, South African Patent Application, 633,657 (1963), reports the synthesis of 3-chloro-α-methyltyrosine by a different route.

(6) Obtained from Merck Sharp and Dohme of Canada, Ltd.

SCHEME II



added to give a final concentration of 2×10^{-3} *M*. Incubations were run at 37° in air for 30 min on a metabolic shaker.

Following the incubation period, each beaker was treated with 0.1 ml of DOPA (2×10^{-3} *M* in 0.001 *M* HCl) as carrier, and the enzyme was inactivated with 3 ml of 0.2 *M* trichloroacetic acid. The DOPA was isolated by alumina adsorption at pH 8.5[1] after removal of the precipitated protein.

In experiments with soluble enzyme preparations, incubations were carried out in small test tubes and the incubation mixture was the same as that described by Nagatsu, *et al.*[1]

Results and Discussion

The general screening of compounds for tyrosine hydroxylase inhibition was carried out using the adrenal medulla homogenate without addition of a tetrahydropteridine cofactor. When the compounds active in this system were retested in the same system but with added 2-amino-6-hydroxy-7,8-dimethyl-6,7,8,9-tetrahydropteridine at saturation level (2×10^{-3} *M*), it was found that a number of the compounds which were active inhibitors in the unfortified system became inactive in the presence of adequate amounts of cofactor.[7]

It was concluded that these substances were "cofactor inhibitors" and those which showed approximately equal inhibition in both fortified and unfortified systems were "substrate inhibitors." It was thus possible to divide the active compounds into these two classes which are listed in Tables I and II.

Some amino acids that were low-activity inhibitors at the screening concentration of 10^{-4} *M* but which are interesting in terms of structure–activity relationships are included in Table III.

Udenfriend, *et al.*,[8] have reviewed the general structure–activity relationships for inhibition of tyrosine hydroxylase by substituted phenylalanine derivatives. Our conclusions are similar, *i.e.*, (1) many phenylalanine and tyrosine analogs are active inhibitors, (2) the relative activities of the 3-halo-α-methyltyrosine analogs are I > Br > Cl, and (3) that α-methylamino acids are generally more active than the unmethylated analogs. Weissman, *et al.*,[9] have also reported the same order of activity for the optically active 3-halo derivatives of L-α-methyltyrosine as *in vitro* and *in vivo* inhibitors of rat brain tyrosine hydroxylase.

We have also found that replacement of the hydroxyl function of α-methyltyrosine by hydrogen or the fluoro, chloro, or amino groups or extension of the α-methyl group to α-ethyl converted this potent substrate inhibitor to a cofactor inhibitor. However, when the phenolic hydroxyl or amino functions were methylated or when the hydroxyl group was replaced by other groups such as methylthio, trifluoromethyl, sulfamoyl, acetamido, or methanesulfonamido, inhibition of the tyrosine hydroxylase reaction was reduced markedly. The observation that 4-methylsulfonamido-α-methyltyrosine is not a good tyrosine hydroxylase inhibitor is interesting since the methylsulfonamido and phenolic

TABLE I

SUBSTRATE INHIBITORS

Inhibitor[a]	Concn, *M*	% inhibition: Unfortified enzyme[b]	% inhibition: Fortified enzyme[b]	pI_{50}
Amino Acids				
L-3-Iodotyrosine	1×10^{-4}	90	97	5.6
L-α-Methyltyrosine	5×10^{-5}	94	67	4.8
3-Chloro-α-methyltyrosine	1×10^{-4}	60	66	4.3
3-Bromo-α-methyltyrosine	1×10^{-4}	73	88	4.8
L-3-Iodo-α-methyltyrosine	1×10^{-4}	94	99	6.0
α-Methyl-DOPA	1×10^{-3}	73	62	3.3
Miscellaneous Compounds				
4-Isopropyltropolol (β-thujaplicinol)	1×10^{-4}	94	83	4.9
4-Isopropyltropolone (β-thujaplicin)	1×10^{-4}	94	90	4.3
2,5-Dimethoxybenzoquinone	1×10^{-4}	49	75	4.3
Tetrabromocatechol	1×10^{-4}	70	58	
6-Amino-7-chloroquinoline-5,8-quinone	1×10^{-4}	67	79	4.6
1,8-Dihydroxy-4,5-dinitroanthraquinone	1×10^{-4}	35	47	3.9
2-(4-Thiazolyl)benzimidazole	1×10^{-3}	56	60	3.2
2-(4-Thiazolyl)-5-methylbenzimidazole	1×10^{-3}	60	54	3.1

[a] All samples are DL mixtures unless specified otherwise. Procedures for the preparation of newly synthesized amino acids are detailed in the Experimental Section. All other compounds were either obtained from commercial sources or have been described previously in the literature. [b] The "unfortified" enzyme preparation was the adrenal medullary homogenate without addition of reduced pteridine cofactor. The "fortified" enzyme preparation contained 2-amino-6-hydroxy-7,8-dimethyl-6,7,8,9-tetrahydropteridine (final concentration of 2×10^{-3} *M*) in addition to the medullary homogenate. The pI_{50} values represent the negative logarithms of inhibitor concentrations at which a 50% inhibition was found in the system using fortified beef adrenal homogenate as an enzyme source.

(7) After completion of our work, Udenfriend, *et al.*,[8] reported that inhibition of a purified beef adrenal tyrosine hydroxylase preparation by α-propyl-3,4-dihydroxyphenylacetamide was reversed by added cofactor but not by substrate.

(8) S. Udenfriend, P. Zaltzman-Nirenberg, and T. Nagatsu, *Biochem. Pharmacol.*, **14**, 837 (1965).

(9) A. Weissman, B. Koe, and S. Tenen, *J. Pharmacol. Exptl. Therap.*, **151**, 339 (1966).

TABLE II
COFACTOR INHIBITORS

Inhibitors[a,b]	% inhibition
Derivatives of Phenylalanine	
Phenylalanine	30
2-F	60
4-F	75
4-Cl	41
4-NH_2	43
3-F-4-OH	50
α-CH_3	86
2-F-α-CH_3	62
4-F-α-CH_3	85
4-Cl-α-CH_3	71
4-NH_2-α-CH_3	77
L-3-OH-α-CH_3	62
2-F-4-OH-α-CH_3	95
2-Cl-4-OH-α-CH_3	84
4-Cl-3-OH-α-CH_3	35
3-NH_2-4-OH-α-CH_3	26
2,4-$(OH)_2$-α-CH_3	66
4-OH-2,α-$(CH_3)_2$	69
4-OH-3,α-$(CH_3)_2$	27
4-OH-α-C_2H_5	60
Miscellaneous Compounds	
Disodium 2,5-dicarbethoxy-3,4-dihydroxythiophene	52
1,2,4,4-Tetrabromocyclopentene-3,5-dione	68
2-Methyl-1,4-naphthoquinone	61
Dibenzo[*f,h*]quinoxaline	52

[a] See footnote *a*, Table I. [b] All samples were tested at a final concentration of 1×10^{-4} *M* using the unfortified beef adrenal homogenate as an enzyme source.

TABLE III
PHENYLALANINE DERIVATIVES OF LOW ACTIVITY AT 1×10^{-4} *M*

Inhibitors[a]	% inhibition
3,5-I_2-4-OH-α-CH_3	17
3-Br-5-I-4-OH-α-CH_3	0
3,5-Br_2-4-OH-α-CH_3	0
3,5-Cl_2-4-OH-α-CH_3	12
4-OH-3-NO_2-α-CH_3	11
L-3-NH_2-4-OH	0
L-3,5-I_2-4-OH	24
3-F	0
4-CH_3SO_2NH	0
4-CH_3SO_2NH-α-CH_3	0
4-CH_3CONH-α-CH_3	11
4-H_2NO_2S-α-CH_3	0
4-CF_3-α-CH_3	0
4-CH_3S-α-CH_3	23
4-CH_3O-α-CH_3	0
2-CH_3-3-(3-thienyl)alanine	18
2-CH_3-3-(2-thienyl)alanine	0
4-OH-N,α-$(CH_3)_2$	21

[a] See footnote *a*, Table I.

hydroxyl groups have similar pK_a's.[10] The demethyl compound, 4-methylsulfonamidophenylalanine, was also inactive in our system at 10^{-4} *M*.

The ability of α-methyltyrosine to function as an inhibitor of tyrosine hydroxylase was also greatly diminished by disubstitution *ortho* to the phenolic hydroxyl group. The 3,5-dichloro, -dibromo, -diiodo, and the 3-bromo-5-iodo derivatives of α-methyltyrosine were all of low activity at 10^{-4} *M*. In contrast to the

(10) A. A. Larsen and P. M. Lisle, *Nature*, **203**, 1283 (1964); R. H. Holle, J. R. Kirk, W. A. Goold, and A. A. Larsen, *J. Med. Chem.*, **9**, 88 (1966). These papers also report on some alkylsulfonamidophenethanolamines having interesting cardiovascular properties.

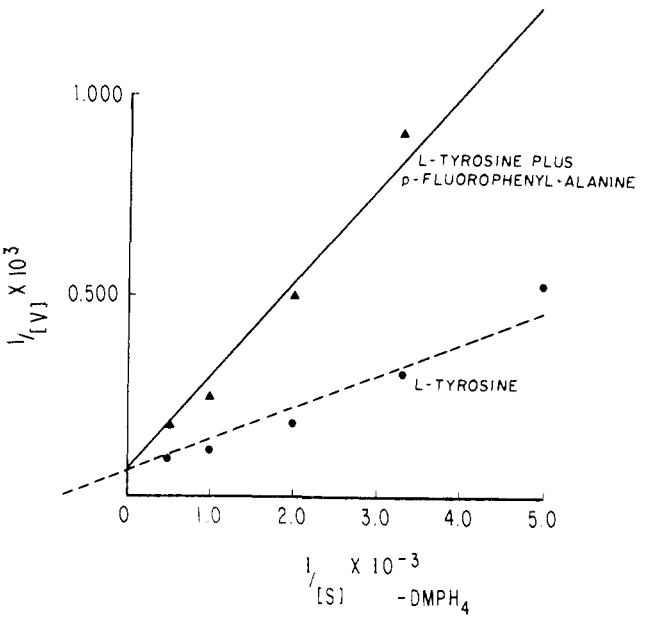


Figure 1.—The inhibition of *p*-fluorophenylalanine on the hydroxylation of L-tyrosine. The tyrosine was kept at 1×10^{-4} *M*, the inhibitor at 5×10^{-4} *M*, while the cofactor, dimethyltetrahydropteridine ($DMPH_4$), was varied from 2×10^{-3} to 2×10^{-4} *M*. Under these conditions, $K_m = 1.25 \times 10^{-3}$ *M*, $K_i = 2 \times 10^{-4}$ *M*.

report of Udenfriend and co-workers,[8] L-3,5-diiodotyrosine has very low activity at this concentration in our system. However, it is active in the purified enzyme system.[8]

Therefore an unhindered 4-hydroxyl group appears to be a necessary structural requirement for substrate inhibition. However, other factors must also be important since several α-methyltyrosine derivatives, *e.g.*, the 2-chloro, 2-hydroxy, 2-methyl, and 3-amino analogs, were found to be cofactor inhibitors.

The two isomeric 2-methyl-3-thienylalanine derivatives were not active in contrast to the potent cofactor inhibitor, α-methylphenylalanine.

It is evident from the results obtained that the total homogenate as prepared by homogenizing beef adrenal medulla in 0.25 *M* sucrose contains an amount of cofactor which renders it an optimal system for finding inhibitors of both types. This system also had the advantage of being fairly insensitive to organic solvents. Of several solvents tested, acetonitrile caused the least inhibition in the amount of DOPA formed. It was selected to dissolve water-insoluble samples for testing.

As an example of a "substrate inhibitor," α-methyltyrosine has been extensively investigated by Udenfriend, *et al.*[11] It was concluded on the basis of the data presented that this is a typical competitive inhibitor. To establish a mechanism of "cofactor inhibition" 4-fluorophenylalanine (see Table II) was selected as the inhibitor for investigation in the purified enzyme system. In order to make use of the Lineweaver–Burk[11] treatment, it was necessary to choose this system in which the substrate concentration is essentially constant and the concentrations of cofactor may be accurately known and controlled. From the plot of $1/v$ *vs.* the reciprocal of the cofactor concentration (Figure 1), the inhibition of cofactor appears to be competitive.

(11) H. Lineweaver and D. Burk, *J. Am. Chem. Soc.*, **56**, 658 (1934).

Since reduced pteridines appear to be specific coenzymes in the adrenal tyrosine hydroxylating system,[12] cofactor inhibition takes on greater importance as a useful mechanism. Using the above treatment of data on the inhibition mechanism, the K_i value for 4-fluorophenylalanine was calculated to be 2×10^{-4} M.

Several compounds not related to the active amino acids have come to light as active inhibitors when more or less random screening was carried out. The tropolone derivative, β-thujaplicin, found to be active in this assay (Table I), has been reported to be an inhibitor of dopamine β-hydroxylase.[13] The other nonamino acid compounds appear to have no structural relationship which allows generalization regarding inhibitory activity.

Experimental Section[14]

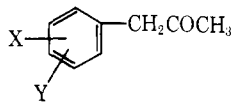
5-Bromo-2-chloroanisole.—A solution of 6.17 g of $NaNO_2$ in 15 ml of water was added slowly with stirring to 12.8 g (0.0814 mole) of 2-chloro-5-aminoanisole[15] in 30 ml of 48% HBr at 0° until excess HNO_2 was present. The cold solution of the diazonium salt was then added over 15 min to a refluxing mixture of 7.9 g of Cu_2Br_2 and 18 ml of 48% HBr. As soon as addition was complete, the reaction mixture was steam distilled and about 1 l. of distillate was collected. The distillate was extracted with benzene which was then washed (5% NaOH, dilute HCl, H_2O). After drying (Na_2SO_4) the solvent was removed under vacuum and the residue distilled through a Vigreux column to give 12.2 g (67.8%) of product, bp 128–130° (12 mm).[16] A sample was redistilled for analysis.

Anal. Calcd for C_7H_6BrClO: Br, 36.08. Found: Br, 35.52.

Ketones of General Structure I.—Methods A and B were used to prepare the ketones listed in Table IV.

TABLE IV

KETONES[a]



X	Y	Yield, %	Method	Bp, °C (mm)
3-OCH_3	4-Cl	34.6	A	112–115 (0.1–0.2)
4-OCH_3	3-CH_3	26.8	A[b]	150–160 (14)
4-OCH_3	2-CH_3	5.8	A[c]	153–162 (18)
4-OCH_3	2-CH_3	21.3	B[c]	87–100 (0.5)
H	4-CF_3	34	A	72–78 (0.1–0.2)

[a] Complete purification of the ketones prepared by this method proved difficult. However, purification was effected easily through recrystallization of the hydantoin in the next step of the synthesis. [b] For preparation of the starting aryl halides see M. J. S. Dewar and N. A. Puttnam, *J. Chem. Soc.*, 959 (1960). [c] For preparation of the starting aryl halides see ref 18.

Method A. Normal Addition. 1-(4-Chloro-3-methoxyphenyl)-2-propanone.—A solution of 18.45 g (0.0835 mole) of 5-bromo-2-chloroanisole in 40 ml of anhydrous ethyl ether was added slowly under N_2 to a stirred mixture of 2.03 g (0.0835 g-atom) of Mg turnings and 40 ml of anhydrous ethyl ether and a single crystal of I_2. The mixture was heated and stirred at reflux for 2 hr until practically all of the Mg had reacted. A solution of 7.76 g (0.0840 mole) of freshly distilled chloroacetone in 30 ml of ether was then added slowly to maintain a gentle reflux. After addition was complete, most of the ethyl ether was distilled by heating in a warm water bath in a stream of N_2. Dry xylene (50 ml) was added and the reaction mixture was heated to 130° for 30 min and then stirred at this temperature for another 30 min. After cooling, dilute HCl was added and the product was extracted with benzene. The benzene extract was washed with water, dried ($MgSO_4$), and filtered. The black residue was distilled through a Vigreux column to give after a short forerun, 5.74 g (34.6%) of product, bp 112–115° (0.1–0.2 mm). Gas chromatography and microanalytical results indicated that this product was not pure. However, purification was effected easily through recrystallization of the hydantoin in the next step of the synthesis.

Method B. Inverse Addition. 1-(4-Methoxy-2-methylphenyl)-2-propanone (VI).[17]—A solution of the Grignard reagent derived from 96 g (0.478 mole) of 4-bromo-3-methylanisole[18] and 12.8 g (0.528 g-atom) of Mg turnings in 100 ml of ethyl ether was added over 0.75 hr to a well-stirred solution of 44.4 g (0.480 mole) of freshly distilled chloroacetone in 400 ml of benzene at 5–10°. After addition was complete, the reaction mixture was heated 2 hr at reflux and then cooled and quenched with a dilute NH_4Cl solution. The product, bp 87–100° (0.5 mm), 18.1 g (21.3%), was isolated by the procedure outlined in method A.

1-(2-Chloro-4-methoxyphenyl)-2-propanone (VIII).—Sodium methoxide (7.3 g, 0.135 mole) was added over a period of 1.5 hr to a vigorously stirred mixture of 19.8 g (0.116 mole) of 2-chloro-4-methoxybenzaldehyde[19] and 23.6 g (0.130 mole) of ethyl α-bromopropionate under dry N_2 with cooling in an ice–salt bath. After stirring for 2 hr more at 0° and overnight at room temperature, 100 ml of water and a few milliliters of AcOH were added. The product was extracted into ethyl ether and washed (H_2O, $NaHCO_3$ solution, H_2O). The ether extract was dried (Na_2SO_4) and concentrated to an oil. Distillation gave 15.6 g of the glycidic ester contaminated with some unreacted aldehyde. The glycidic ester is best purified by means of Girard's T reagent in the following manner.

A solution of 12.6 g of the crude ester and 12.6 g of Girard's T reagent in 30 g of AcOH and 100 ml of CH_3OH was heated 3 hr at reflux. After cooling, a solution of 25 g of anhydrous Na_2CO_3 in 500 ml of water was added slowly and the glycidic ester was extracted into ethyl ether. The ether extract was washed with water, dried (Na_2SO_4), and concentrated to give 11.15 g of pure ester. The aldehyde carbonyl band seen in the infrared spectrum of the crude product was not present in the sample treated with Girard's reagent.

A solution of NaOH in 80 ml of ethanol was prepared by adding 0.90 ml of H_2O to a solution of 1.12 g of Na in ethanol. The glycidic ester, 13.15 g (0.0486 mole), was added and the solution was heated 3 hr at reflux. The reaction mixture was then concentrated under vacuum and the residue was taken up in 100 ml of water. The aqueous solution was washed with ethyl ether and acidified with 6 N HCl. The product was extracted with ether and the ethereal solution was washed several times (H_2O, $NaHCO_3$, saturated NaCl). After drying (Na_2SO_4), solvent was removed under vacuum and the residual oil was heated at 180–185° for 6 hr. After cooling, the reaction mixture was dissolved in ethyl ether, washed (dilute NaOH, H_2O), and then dried (Na_2SO_4). The ether was evaporated and the residue was distilled to give 4.70 g (20.5% from the aldehyde) of ketone, bp 115–118° (1.3–1.5 mm). A sample was redistilled for analysis.

Anal. Calcd for $C_{10}H_{11}ClO_2$: C, 60.43; H, 5.58; N, 17.84. Found: C, 60.27; H, 5.72; N, 17.84.

1-(2-Fluoro-4-methoxyphenyl)-2-propanone (VII) was prepared from 2-fluoro-4-methoxybenzaldehyde[20] by the Darzen's glycidic ester condensation with the same procedure used for the preparation of the 2-chloro derivative (VIII). In this case, however, the distilled glycidic ester, bp 101–104° (0.05 mm) (48.6% yield), was not contaminated with aldehyde and was used directly in the next step. Hydrolysis and decarboxylation of the glycidic ester afforded the ketone, bp 78–80° (0.10 mm) in 55% yield. A sample was redistilled for analysis.

(12) A. R. Brenneman and S. Kaufman, *Biochem. Biophys. Res. Commun.*, **17**, 177 (1964).

(13) M. Goldstein, E. Lauber, and M. R. McKereghan, *Biochem. Pharmacol.*, **13**, 1103 (1964).

(14) All melting points, determined on a Uni-Melt Thomas–Hoover capillary melting point apparatus, and boiling points are uncorrected. Analytical samples of all new amino acids were homogeneous upon thin layer chromatography on a silica plate, developed with a 3:1:1 1-butanol–acetic acid–water mixture. Infrared spectra of all new compounds were consistent with the proposed structures.

(15) R. A. Benkeser and G. Schroll, *J. Am. Chem. Soc.*, **75**, 3196 (1953).

(16) M. Kohn and S. Reichmann, *J. Org. Chem.*, **12**, 213 (1947).

(17) Experiment performed by Mrs. C. Boland of these laboratories.

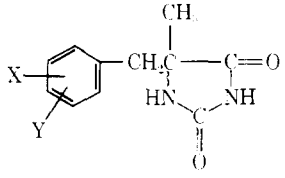
(18) R. A. B. Bannard and L. C. Leitch, *Can. J. Chem.*, **34**, 1464 (1956).

(19) H. H. Hodgson and T. A. Jenkinson, *J. Chem. Soc.*, 1740, 3041 (1927).

(20) H. H. Hodgson and J. Nixon, *ibid.*, 1632 (1929).

TABLE V

HYDANTOINS



X	Y	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
4-OCH$_3$	3-CH$_3$	53	201.5–203.0	$C_{13}H_{16}N_2O_3$	62.89	63.05	6.50	6.65	11.28	11.27
4-OCH$_3$	2-F	35.2	190.5–192.0	$C_{12}H_{13}FN_2O_3$	57.16	57.21	5.20	5.09	11.11	11.44
4-OCH$_3$	2-Cl	88.3	212–213	$C_{12}H_{13}ClN_2O_3$	53.64	53.77	4.88	4.99	10.42	10.23
4-OCH$_3$	2-CH$_3$	36	212.5–214.0	$C_{13}H_{16}N_2O_3$	62.89	63.10	6.50	6.53	11.28	11.10
4-OCH$_3$	H,α-C$_2$H$_5$[a]	76.7	189.5–191.5	$C_{13}H_{16}N_2O_3$	62.89	62.75	6.50	6.66	11.28	11.36
3-OCH$_3$	4-Cl	78.5	218.0–218.5	$C_{12}H_{13}ClN_2O_3$	53.64	53.88	4.88	4.96	10.42	10.37
H	2-F[b,c]	88	208–210	$C_{11}H_{11}FN_2O_2$	59.46	59.10	4.99	5.19	12.61	12.57
H	4-F[c]	69.4	206–207	$C_{11}H_{11}FN_2O_2$	59.46	59.48	4.99	4.94	12.61	12.56
H	4-Cl[d]	80.5	210–213	$C_{11}H_{11}ClN_2O_2$	55.35	55.25	4.65	4.59	11.73	11.63
H	4-CF$_3$	33	238–240	$C_{12}H_{11}F_3N_2O_2$	52.95	53.18	4.07	3.98	10.29	10.36
5-Methyl-5-(2-thienylmethyl)hydantoin		49.5	197–198	$C_9H_{10}N_2O_2S$	51.40	51.64	4.79	4.86	13.32	13.57
5-Methyl-5-(3-thienylmethyl)hydantoin[e]		54	190–191	$C_9H_{10}N_2O_2S$	51.40	51.20	4.79	5.08	13.32	13.11

Ketone precursors were prepared as described in the following references: [a] T. C. Myers, R. J. Pratt, R. L. Morgan, J. O'Donnell, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 5655 (1955). [b] E. L. Schumann, M. E. Greig, R. V. Heinzelmann, and P. H. Seay, *J. Med. Pharm. Chem.*, **3**, 567 (1961). [c] Reference 24. [d] C. G. Overberger and H. Biletch, *J. Am. Chem. Soc.*, **73**, 4880 (1951). [e] Reference 23.

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.92; H, 6.09. Found: C, 65.60; H, 6.23.

1-(2-Thienyl)-2-propanone, bp 95–98° (14 mm)[21] was prepared in 16% yield from 1-(2-thienyl)-2-nitropropene[22] by the same method used for the preparation of 1-(3-thienyl)-2-propanone.[23]

Hydantoins of General Structure II.—The following procedure was used to prepare the hydantoins listed in Table V.

5-(4-Fluorobenzyl)-5-methylhydantoin.—A solution of 3.8 g (0.0250 mole) of *p*-fluorophenyl-2-propanone,[24] 9.6 g (0.10 mole) of $(NH_4)_2CO_3$ and 2.86 g (0.044 mole) of KCN in 50 ml of a 50% ethanol–water mixture was stirred and heated at 50–55° for 6 hr. The reaction mixture was then diluted with water and cooled in an ice bath. Filtration gave 4.40 g of product, mp 198.5–201.5°, which was recrystallized from an ethanol–water mixture to give 3.65 g of the hydantoin, mp 205.5–207.0°. An analytical sample was obtained by further recrystallization from the same solvent mixture.[25]

5-(4-Chloro-3-hydroxybenzyl)-5-methylhydantoin.—A mixture of 7.10 g (0.0265 mole) of the chloromethoxyhydantoin (see Table V) and 33 ml of 57% HI was heated at reflux for about 30 min until no more CH_3I distilled, after which time the mixture was cooled. The product was filtered, washed with water, and dissolved in dilute NaOH solution. The yellow solution was treated with charcoal and filtered through Supercel. Acidification of the filtrate with 6 *N* HCl and cooling gave 5.3 g (79%) of product, mp 237–239°.

Anal. Calcd for $C_{10}H_{11}ClN_2O_3$: C, 51.87; H, 4.35; N, 11.00. Found: C, 51.72; H, 4.26; N, 11.10.

5-(4-Mercaptobenzyl)-5-methylhydantoin.—Solid 5-benzyl-5-methylhydantoin[26] (10.2 g, 0.050 mole) was added in portions over 1.5 hr to 50 ml of chlorosulfonic acid at 30°. After addition was complete, the solution was heated at 60–65° for 40 min. The cooled reaction mixture was poured onto ice and after the ice had melted, the crude sulfonyl chloride was removed by vacuum filtration and dried for 1 hr at room temperature. The sulfonyl chloride was reduced to the mercaptan by addition over 5 min to a well-stirred mixture of 38 g of $SnCl_2 \cdot 2H_2O$ in 65 ml of concentrated HCl. After 15 min, the reaction mixture was warmed to 80–85° and stirred at that temperature for 1.5 hr. After standing overnight at room temperature, the resulting slurry was poured into a mixture of 300 ml of water and 30 ml of concentrated HCl, and the precipitate was filtered and washed with water. The product was dried first on a porous plate, then in a vacuum desiccator ($CaCl_2$, P_2O_5) to constant weight. A total of 8.06 g (68.3%) of the mercaptan, mp 205–208°, was obtained of suitable purity for use in the next step.

3,5-Dimethyl-5-(4-methylthiobenzyl)hydantoin.—Dimethyl sulfate (6.4 g, 0.0508 mole) and 10.2 ml of a 10% NaOH solution were added simultaneously over 45 min to a stirred solution of 6.0 g (0.0254 mole) of 5-(4-mercaptobenzyl)-5-methylhydantoin in 40.8 ml of a 5% NaOH solution at 28–30°. After stirring 2.5 hr at room temperature, the crude product was filtered, washed with water, and dried. Recrystallization from ethyl acetate gave 1.15 g (17.20%) of product, mp 149–152°.

Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.06; H, 6.10; N, 10.60. Found: C, 59.23; H, 5.92; N, 10.82.

5-Methyl-5-(4-sulfamoylbenzyl)hydantoin.—The sulfonyl chloride obtained from 5.1 g (0.025 mole) of 5-benzyl-5-methylhydantoin[26] by the procedure detailed in the preparation of 5-(4-mercaptobenzyl)-5-methylhydantoin was added in portions to 125 ml of concentrated NH_4OH. After standing overnight in a stoppered flask at room temperature, the solution was concentrated to 25 ml under vacuum and acidified with 6 *N* HCl. The precipitate was removed by filtration and dried to give 4.46 g (63%) of sulfonamide, mp 238–244°. An analytical sample, mp 244–247°, was obtained by recrystallization from a DMF–H_2O mixture.

Anal. Calcd for $C_{10}H_{13}N_3O_4S$: C, 46.64; H, 4.63; N, 14.83. Found: C, 46.58; H, 4.46; N, 14.73.

Amino Acids.—Preparation of the amino acids listed in Table VI by hydrolysis of the hydantoin with $Ba(OH)_2$ or 48% HBr is exemplified by the following typical procedures.

Method A. 4-Fluoro-α-methylphenylalanine.—A solution of 2.0 g (9.02 mmoles) of 5-(4-fluorobenzyl)-5-methylhydantoin in 50 ml of redistilled 48% HBr was heated under reflux for 2 days. The reaction mixture was then concentrated under vacuum. The residue was dissolved in 30 ml of water and filtered from a small amount of insoluble solid, and the pH of the clear solution was adjusted to 5.0–6.0 with diethylamine. After cooling, the solid that had precipitated was filtered and recrystallized by

(21) J. Novák, J. Rattský, V. Šnelberg, and F. Sorm [*Chem. Listy*, **51**, 479 (1957); *Chem. Abstr.*, **51**, 10508 (1957)] reported bp 95–97° (9 mm).

(22) R. Gilsdorf and F. Nord, *J. Org. Chem.*, **15**, 807 (1950).

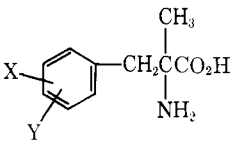
(23) E. Campaigne and W. McCarthy, *J. Am. Chem. Soc.*, **76**, 4466 (1954).

(24) Z. Eckstein and J. Pleskowicz, *Rocznik Chem.*, **37**, 907 (1963); *Chem. Abstr.*, **60**, 8572 (1964).

(25) Analytical results are recorded in Table V.

(26) S. D. Upham, U. S. Patent 2,999,863 (1961); *Chem. Abstr.*, **57**, 9737 (1962).

TABLE VI
AMINO ACIDS



X	Y	Yield, %	Method	Dec pt, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
4-OH	3-CH_3	57.2	A	306–308	$C_{11}H_{15}NO_3$	63.14	62.72	7.23	7.09	6.69	6.72
4-OH	2-F	29.7	A	322–324[a]	$C_{10}H_{12}FNO_3$	56.33	56.68	5.67	5.49	6.55	6.76
4-OH	2-Cl	94	A	296–300[b]	$C_{10}H_{12}ClNO_3$	52.29	52.34	5.27	5.06	6.10	6.30
4-OH	2-CH_3	12	A	302–304	$C_{11}H_{15}NO_3$	63.14	62.93	7.23	7.06	6.69	6.77
4-OH	H,α-C_2H_5	45.5[c]	A	335–337[d]	$C_{11}H_{15}NO_3$	63.14	63.18	7.23	7.38	6.69	6.54
3-OH	4-Cl	45	C	270–272	$C_{10}H_{12}ClNO_3 \cdot 0.33H_2O$[e]	50.96	51.09	5.42	5.39	5.94	5.83
H	2-F	68.1	C	281.0–281.5	$C_{10}H_{12}FNO_2$	60.90	60.86	6.13	6.22	7.10	7.07
H	4-F	43.5	A	289–292	$C_{10}H_{12}FNO_2$	60.90	61.32	6.13	6.28	7.10	7.47
H	4-Cl	92.8	B	302–303[f]	$C_{10}H_{12}ClNO_2$	56.20	56.12	5.66	5.80	6.56	6.56
H	4-NH_2[g]	84.8	C	303	$C_{10}H_{14}N_2O_2$	61.83	61.47	7.27	7.41	14.43	14.65
H	4-OCH_3[h]	54.7	C	292–294[i]	$C_{11}H_{15}NO_3$	63.14	62.56	7.23	7.15	6.69	6.74
H	4-CF_3	36	C	302–303	$C_{11}H_{12}F_3NO_2 \cdot 0.1H_2O$[j]	53.06	53.07	4.90	4.91	5.63	5.86
H	4-SCH_3[k]	88	C	271	$C_{11}H_{15}NO_2S$	58.64	58.49	6.71	6.50	6.22	5.97
H	4-SO_2NH_2	52.5	C	299–300	$C_{10}H_{14}N_2O_4S$	46.50	46.34	5.46	5.36	10.85	10.82
2-Methyl-3-(2-thienyl)alanine		13.4	B	263–265	$C_8H_{11}NO_2S$	51.86	51.35	5.98	6.15	7.56	7.59
2-Methyl-3-(3-thienyl)alanine		31.8	B	264–267	$C_8H_{11}NO_2S$	51.86	51.81	5.98	6.27	7.56	7.49

[a] Softens at 317°. [b] Darkens at 294°. [c] A 48.4% yield of 5-ethyl-5-(4-hydroxybenzyl)hydantoin, mp 292.0–295.0°, was also isolated from this reaction. *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.50; H, 6.22; N, 12.17. [d] Softens at 325°. [e] Water analysis[29] indicated that the sample contained 0.36 mole of H_2O. [f] Softens at 300°. [g] Hydantoin was prepared by the method of T. A. Connors, W. C. J. Ross, and J. G. Wilson, *J. Chem. Soc.*, 2994 (1960). [h] Hydantoin was prepared by the method of K. T. Potts, *ibid.*, 1632 (1955). [i] B. Blank, E. G. Rice, F. R. Pfeiffer, and C. M. Greenberg, *J. Med. Chem.*, **9**, 10 (1966), reported mp 279–281° dec. [j] Water analysis[29] indicated that the sample contained 0.2 mole of H_2O. [k] Hydrolysis performed on 3,5-dimethyl-5-(4-methylthiobenzyl)hydantoin.

dissolving in hot water, concentrating under vacuum, and then cooling.[27]

Method B. 4-Chloro-α-methylphenylalanine.—5-(*p*-Chlorobenzyl)-5-methylhydantoin (13 g, 0.0544 mole) and 65 g of $Ba(OH)_2 \cdot 8H_2O$ in 350 ml of water was heated 4 days at reflux. After cooling, the reaction mixture was acidified with 6 *N* H_2SO_4 and filtered through Supercel. The pH of the clear filtrate was adjusted to 4.5–5.0 with diethylamine and dilute acetic acid and then chilled. The precipitated solid was filtered and dried to yield 9.65 g of product, mp 296–298° dec (softening at 292°). Concentration of the mother liquors and cooling gave an additional 1.1 g of product, mp 288–289° (softening at 286°). The first crop was recrystallized by dissolving the solid in 1.6 l. of hot water, filtering, and then concentrating the solution under vacuum until crystallization began (about 800 ml).[27]

Method C. 4-Chloro-3-hydroxy-α-methylphenylalanine.—A solution of 4.85 g (0.0191 mole) of 5-(4-chloro-3-hydroxybenzyl)-5-methylhydantoin and 12.0 g of $Ba(OH)_2 \cdot 8H_2O$ in 45 ml of water was heated at reflux under N_2 for 64 hr. After cooling, the reaction mixture was diluted with water to 100 ml, saturated with CO_2, and filtered. The yellow filtrate was treated with charcoal and Supercel, filtered, and concentrated to an oil which was recrystallized[28] from an ethanol–ether mixture.[27]

4'-(2-Amino-2-carboxy-1-ethyl)methanesulfonanilide (4-Methanesulfonamidophenylalanine).—A mixture of 1.8 g (0.010 mole) of 4-aminophenylalanine, 0.84 g (0.010 mole) of anhydrous $NaHCO_3$, and 1.25 g (5.0 mmoles) of $CuSO_4 \cdot H_2O$ in 50 ml of water was stirred at room temperature for 0.5 hr. Methanesulfonyl chloride (4.8 g, 0.0420 mole) and $NaHCO_3$ (4.20 g, 0.050 mole) were added and the reaction was stirred for 0.5 hr without cooling. More $NaHCO_3$ (1.68 g) was added and the blue solution was stirred an additional 3 hr at room temperature. The reaction mixture was diluted to 75 ml with water and the copper complex decomposed with H_2S. After filtering, the pH of the solution was adjusted to 5.0 with a few drops of AcOH and the solution was filtered and concentrated to precipitate the product. Recrystallization from water gave 0.80 g (28.9%) of the methanesulfonanilide hydrate, mp 270–272° dec, darkens at 250°; $pK_1 = 3.15$, $pK_2 = 8.23$, $pK_3 = 9.55$ (H_2O, 26°).

Anal. Calcd for $C_{10}H_{14}N_2O_4S \cdot 0.9H_2O$: C, 43.75; H, 5.80; N, 10.21. Found: C, 44.17; H, 5.72; N, 10.18; H_2O, 0.9 mole.[29]

4'-(2-Amino-2-carboxy-1-propyl)methanesulfonanilide (4-methanesulfonamido-α-methylphenylalanine), mp 282–283° dec, was prepared in 28.3% yield from 4-amino-α-methylphenylalanine by the same method used for the preparation of the demethyl derivative.

Anal. Calcd for $C_{11}H_{16}N_2O_4S \cdot 0.33H_2O$: C, 47.47; H, 6.03; N, 10.07. Found: C, 47.32; H, 5.98; N, 10.23; H_2O, 0.1 mole.[29]

4-Acetamido-α-methylphenylalanine was prepared from the corresponding amino compound and acetic anhydride in 15.2% yield by the general procedure used for the preparation of the sulfonanilide derivatives. An analytical sample, mp 268–270° dec, was obtained by recrystallization from water.

Anal. Calcd for $C_{12}H_{16}N_2O_3 \cdot 1.5H_2O$: C, 54.74; H, 7.27; N, 10.64. Found: C, 54.30; H, 7.13; N, 10.62; H_2O, 1.5 mole.[29]

2-(4-Hydroxybenzyl)-2-methylaminopropionitrile.—A solution of 5.0 g (0.0333 mole) of *p*-hydroxyphenylacetone, 3.6 g of $NaHCO_3$, 2.2 g of KCN, and 4.7 g of a 40% aqueous methylamine solution in 75 ml of water was allowed to stand at room temperature for 3 days. The white solid that precipitated was removed by suction filtration and dried at room temperature under high vacuum to give 3.0 g (47.4%) of analytically pure aminonitrile, mp 126.5–130.5°.

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.13; H, 7.43; N, 14.81.

N,α-Dimethyltyrosine.—A mixture of 2.8 g (0.0148 mole) of 2-(4-hydroxybenzyl)-2-methylaminopropionitrile and 30 ml of concentrated HCl, which had been saturated with HCl gas at room temperature, was heated on the steam bath for 18 hr and then concentrated to dryness under vacuum. The residue was dissolved in 25 ml of water and the pH of the solution was ad-

(27) Analytical results and yields are recorded in Table VI.

(28) The other amino acids prepared by this procedure were recrystallized from hot water.

(29) Water was determined by means of infrared spectroscopy by W. R. McGaughran of these laboratories.

justed to 5.0 with diethylamine. The precipitated amino acid was recrystallized from hot water to give 0.75 g (24.3%) of the hygroscopic N,α-dimethyltyrosine, after drying at 0.2 mm and 138°, mp 315–319° dec.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.59; H, 7.32; N, 6.78.

L-3-Iodo-α-methyltyrosine.—A solution of 15.5 g (0.0611 mole) of I_2 and 50 g of KI in 250 ml of water was added to a stirred solution of 10 g (0.0513 mole) of L-α-methyltyrosine[30] in 1 l. of concentrated NH_4OH over 1.5 hr.[31] The temperature of the reaction mixture remained at 17–20° during the addition. After addition was complete the reaction was stirred an additional 2 hr at room temperature. The reaction mixture was then poured into an open beaker and allowed to concentrate at room temperature for 3 days. The precipitated solid was filtered, washed with water, and then dried to give 12.5 g (76.1%) of light tan solid, mp 259–261° dec, darkens at 255°, $[\alpha]^{25}_{546}$ +101° (copper salt).

Anal. Calcd for $C_{10}H_{12}INO_3$: C, 37.41; H, 3.77; I, 39.52. Found: C, 37.67; H, 3.90; I, 39.50.

DL-3-Iodo-α-methyltyrosine.—Iodination[31] of DL-α-methyltyrosine[30] by the same procedure as that used for the L isomer gave the racemic 3-iodo derivative in 61.3% yield, mp 256–257° dec, darkening at 253°.

Anal. Calcd for $C_{10}H_{12}INO_3$: C, 37.41; H, 3.77; I, 39.52. Found: C, 37.66; H, 3.77; I, 39.44.

3-Nitro-α-methyltyrosine.—Concentrated HNO_3 (13.5 g) was added over 10 min to a vigorously stirred slurry of 5.0 g (0.0256 mole) of α-methyltyrosine[30] in 20 ml of water at 20°. After addition was complete the reaction was stirred an additional 2 hr and then cooled in an ice bath. The precipitated yellow solid was filtered and dissolved in about 75 ml of warm water. Concentrated NH_4OH was added to adjust the pH of the solution to 6. The precipitated product was filtered and dried to give 4.35 g (70.8%) of material, mp 235° softening, 253–259° dec. The melting point was not improved by recrystallization from hot water.

Anal. Calcd for $C_{10}H_{12}N_2O_5 \cdot 0.25H_2O$: C, 49.08; H, 5.15; N, 11.45. Found: C, 48.99; H, 5.18; N, 11.32; H_2O, 0.11 mole.[29]

3-Amino-α-methyltyrosine.—A 5% Pd-C catalyst (700 mg) was added to a solution of 6.12 g (0.0254 mole) of 3-nitro-α-methyltyrosine in 125 ml of water and 8.5 ml of 6 *N* HCl, and the mixture was hydrogenated in a Parr apparatus until the theoretical quantity of H_2 had been taken up. The catalyst was removed by filtration and filtrate was concentrated under vacuum to dryness. The residue was dissolved in 10 ml of water and the pH of the solution was adjusted to 5.5 with diethylamine. The precipitated solid was filtered and dried to give 3.4 g (64%) of product, mp 270° darkening, 288–290° dec. A sample was recrystallized from a water–ethanol mixture to give an analytical sample, mp 290° darkening, 307.5–310.5° dec.

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.14; H, 6.71. Found: C, 56.93; H, 6.83.

3-Bromo-α-methyltyrosine.—A mixture of 13.6 g (0.085 mole) of Br_2 and 100 ml of 88% formic acid was added over 1 hr to a stirred slurry of 15 g (0.077 mole) of α-methyltyrosine[30] and 50 ml of 88% formic acid. Reaction temperature was maintained at 10–15° by ice-bath cooling. The α-methyltyrosine slowly dissolved during the reaction and, after addition of the Br_2 was finished, solution was complete. After standing for 2 days at room temperature the formic acid was removed under vacuum on the steam bath. Water (200 ml) was added to the residue which was then reconcentrated. The residue was taken up in 75 ml of water, the pH was adjusted to 5.0 with diethylamine, and the solution was cooled. The precipitated solid was recrystallized from water to give 11.0 g (52.2%) of product, mp 284.5–287.5° dec.

Anal. Calcd for $C_{10}H_{12}BrNO_3$: C, 43.81; H, 4.41; Br, 29.15. Found: C, 44.19; H, 4.57; Br, 28.83.

3-Chloro-α-methyltyrosine.—Three grams of SO_2Cl_2 was added over 10 min to a vigorously stirred suspension of 3.6 g (0.0184 mole) of α-methyltyrosine[30] in 10 ml of glacial acetic acid. After addition was complete, the clear solution was allowed to cool to room temperature for 20 min. Water (40 ml) was then added and the solution was concentrated under vacuum at steam-bath temperature. The residue was dissolved in dilute NaOH, and the pH was adjusted to 7.0 with AcOH. The gray solid that precipitated was recrystallized from water with charcoal treatment to give 0.95 g (22.4%) of material, mp 290.0–295.0° dec. Another recrystallization from hot water gave an analytical sample, 0.60 g, mp 293.0–295.0° dec, lit.[5] mp 285–287° dec.

Anal. Calcd for $C_{10}H_{12}ClNO_3$: C, 52.59; H, 5.27; N, 6.19. Found: C, 52.32; H, 5.31; N, 6.08.

3,5-Dibromo-α-methyltyrosine.—A solution of 5.4 g (0.0338 mole) of Br_2 in 20 ml of AcOH was added over 0.5 hr to a vigorously stirred slurry of 3.0 g (0.0154 mole) of α-methyltyrosine[30] and 10 ml of acetic acid. Reaction temperature was maintained at 15–20° by external cooling until the Br_2 color had disappeared. The reaction mixture was diluted with water to 80 ml and the pH of the solution was adjusted to 5.5 with diethylamine. The precipitated amino acid was recrystallized from hot water to give 2.0 g (36.8%) of the dibromo compound, mp 257–260° dec.

Anal. Calcd for $C_{10}H_{11}Br_2NO_3$: C, 34.02; H, 3.14; N, 3.97. Found: C, 33.58; H, 3.63; N, 3.77.

3,5-Dichloro-α-methyltyrosine.—Chlorine was bubbled through a slurry of 3.0 g (0.0154 mole) of α-methyltyrosine[30] and 50 ml of glacial acetic acid for 10 min until the α-methyltyrosine had dissolved and the solution was saturated with Cl_2. The reaction mixture was allowed to cool to room temperature over 1 hr and then diluted with water and concentrated under vacuum to about 25 ml. The pH of the solution was adjusted to 5.0 with diethylamine and chilled to give 3.6 g (88.7%) of the dichloro compound, mp 278–283° dec. An analytical sample, mp 279–281° dec, was obtained by recrystallization from water.

Anal. Calcd for $C_{10}H_{11}Cl_2NO_3 \cdot H_2O$: C, 42.57; H, 4.64; N, 4.97. Found: C, 42.27; H, 4.76; N, 4.92; H_2O, 0.88 mole.[29]

3-Bromo-5-iodo-α-methyltyrosine.—A solution of 0.46 g (1.82 mmoles) of I_2 and 0.7 g of KI in 5 ml of water was added over 15 min to a stirred solution of 0.50 g (1.83 mmoles) of 3-bromo-α-methyltyrosine in 25 ml of concentrated NH_4OH.[31] After stirring overnight at room temperature, thin layer chromatography indicated that reaction was not complete. Another 2 ml of the iodinating mixture was then added until a color change from light yellow to dark brown indicated that excess I_2 was present. The reaction mixture was concentrated under vacuum and the residue dissolved in dilute HCl. Diethylamine was added to bring the pH of the solution to 5.0, and, after concentrating to 7 ml and chilling, a solid was obtained. Recrystallization from hot water gave 0.20 g (27.3%) of 3-bromo-5-iodo-α-methyltyrosine, mp 230.0–231.0° dec.

Anal. Calcd for $C_{10}H_{11}BrINO_3$: C, 30.05; H, 2.77; N, 3.50. Found: C, 30.13; H, 3.06; N, 3.62.

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(30) Supplied by Dr. M. Sletzinger, Development Research, Merck Sharp and Dohme Research Laboratories.

(31) *Caution:* a few crystals of nitrogen triiodide form on the drip tip of the dropping funnel.