acetate and charcoaled. The product was precipitated by the addition of ether and cooling. It was then collected and washed with ether; yield 60 g. (77%), m.p. 115–120°. An analytical sample recrystallized from ethyl acetate melted at 131°.

Anal. Calcd. for $C_9H_{16}N_2O_3$: N, 14.00. Found: N, 13.64.

The crude product is probably a mixture of diastereomers. However, both forms would give the same ketone on oxidation.

5-Methyl-5-(δ-ketopentyl)-hydantoin.—Forty grams of the above crude hydantoin was heated with a solution of 24 g. of sodium dichromate and 28 g. of sulfuric acid in 500 ml. of water at 60° for 18 hours. The solution was allowed to stand at 5° overnight and the precipitated ketohydantoin collected and washed with ice-water until the filtrate was colorless; 1st crop 27 g., m.p. 155°. A second crop of 8 g. was obtained on concentration of the mother liquors; total yield 35 g. (88%). A sample was recrystallized from ethyl acetate, m.p. 155–157°.

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.54; H, 7.12. Found: C, 54.50; H, 7.14.

5,5'-Dimethyl-5,5'-trimethylenebishydantoin.—The bishydantoin was obtained by a method similar to the hydroxyhydantoin. Forty-three grams of the ketohydantoin was heated with 25 g. of sodium cyanide and 250 g. of ammonium carbonate. The product precipitated immediately upon acidification and was collected and washed with water; yield 50 g., m.p. 290°. Recrystallization from 1200 ml. of boiling water gave 45 g., m.p. 293°.

Anal. Calcd. for $C_{11}H_{16}N_4O_4$: C, 49.25; H, 6.01; N, 20.89. Found: C, 49.44; H, 5.85; N, 21.19.

α,α'-Diamino-α,α'-dimethylpimelic Acid.—A solution of 30 g. of the bishydantoin and 40 g. of sodium hydroxide in 300 ml. of water was refluxed in a copper flask for 22 hours. The solution was acidified to *p*H 6 with concentrated hydrochloric acid and the resulting flocculent precipitate digested over an open flame for one hour. The product was collected and purified by solution in sodium hydroxide and reprecipitation with acid, yielded 6.6 g. (28%) of amino acid which decomposes above 350°. The mother liquors and filtrates were combined, evaporated to a small volume and the sodium chloride precipitated by the addition of concentrated hydrochloric acid. The salt was removed by filtration through a sintered glass funnel and the filtrate evaporated to dryness. The residue was dissolved in water and neutralized to congo red giving an additional 3.5 g. of crude amino acid.

Anal. Calcd. for $C_9H_{18}N_2O_4$: C, 49.53; H, 8.31; N, 12.84. Found: C, 49.60; H, 8.24; N, 12.36; Van Slyke N, 12.69.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

α-Methyl α-Amino Acids. II.[1] Derivatives of DL-Phenylalanine

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A variety of α-methylphenylalanine derivatives was prepared for biological study.

As part of a program to investigate chemotherapeutic possibilities among amino acid analogs, our attention was turned to derivatives of phenylalanine and particularly of the biologically important 3,4-dihydroxyphenylalanine (DOPA). This compound may well figure in the biosynthesis of the pressor amines noradrenaline and epinephrine.[2] Furthermore decarboxylation of DOPA by mammalian enzyme preparations had been especially thoroughly studied[3,4] and appeared in excellent point for interference in the biosynthetic sequence by metabolite analogs.[5] Also earlier success with α-methylglutamic acid as inhibitor of mammalian decarboxylase[1,6] suggested a new approach to the inhibition of DOPA decarboxylation.

Synthesis of α-methyl DOPA (VI) was from 3,4-dimethoxyphenylacetonitrile (I) *via* 3,4-dimethoxyphenylacetone, the corresponding hydantoin IV and the dimethoxy acid V. This route proved superior to the alternate method *via* VIIa. It is of interest that acid hydrolysis of VIIa at 100° gave only partial cleavage of methoxyl. The product was assigned the structure α-methyl-3-hydroxy-4-methoxyphenylalanine (VIIIa) on the basis of a positive response in the indophenol test for phenols having an unsubstituted *p*-position.[7] A negative result was obtained with V and with 3-methoxy-4-hydroxyphenylalanine. Acid treatment at 150° was effective in cleaving the remaining methoxyl of VIIIa and yielding α-methyl DOPA (VI).

A similar sequence of reactions provided α-methyl-3-hydroxyphenylalanine (VIa) which was considered also a possible DOPA decarboxylase inhibitor since 3-hydroxyphenylalanine serves as a substrate for this enzyme.

The parent compound, α-methylphenylalanine (VIIIb) corresponded in properties to the preparation of Herbst and Johnson.[8] Its conversion to α-methyltyrosine (XII), desired for studies on bacterial tyrosine decarboxylase, was made the occasion for synthesis of the chloramphenicol-resembling substance X. The formulas given are for those related compounds which were synthesized.

The α-methylphenylalanine was also converted *via* its N-acetyl methyl ester to 2-amino-2-methyl-3-phenylpropanol.

A comparison of the physical properties of the natural amino acids (racemic modifications) and their α-methyl homologs is of interest. Thus while α-methyl DOPA is nearly ten times as soluble in water as DOPA itself, the differences in pK_a values are small. The α-methyl compound showed

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(2) "Chemical Factors in Hypertension," A. C. S. Advances in Chemistry Series, No. 2, 1950, K. H. Beyer, p. 37.

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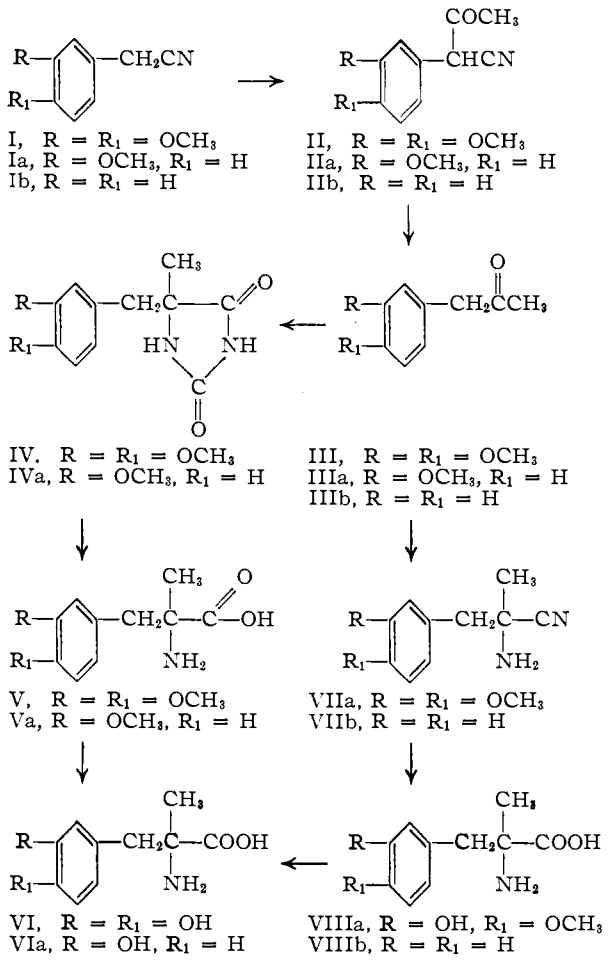
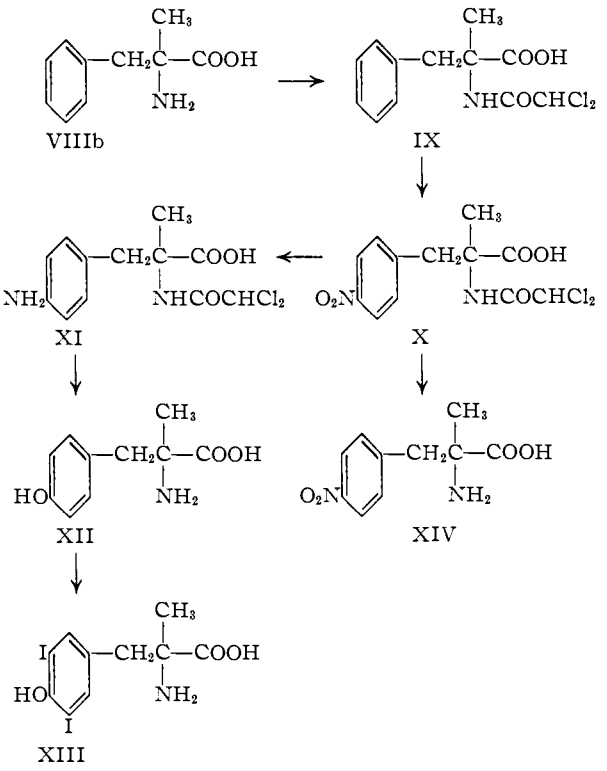
(7) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927); J. V. Scudi, *ibid.*, **139**, 707 (1941).

(8) R. M. Herbst and T. B. Johnson, THIS JOURNAL, **54**, 2463 (1932).





values of 9.12 and 10.61 while the corresponding figures for DOPA are 9.19 and 10.24.[9] Similarly the value of 9.29 for phenylalanine corresponds to one of 9.57 for α-methylphenylalanine.

As has been described in detail by Sourkes,[10] *in vitro* tests show α-methyl DOPA to be an extremely potent inhibitor of mammalian DOPA decarboxylase, while α-methyl-3-hydroxyphenylalanine and α-methyl-3-hydroxy-4-methoxyphenylalanine are only slightly less effective. The considerable activity of the latter may be regarded as confirmatory evidence for the structure assignment VIIIa. A number of the compounds described show significant antibacterial action *in vitro* but no promising results were obtained *in vivo*.

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To our collaborators on the biological side, Drs. Marcel Goldenberg, T. L. Sourkes and Wayne W. Umbreit, our sincere appreciation.

(9) The most acidic (carboxyl) and least acidic (one of phenolic hydroxyls) groups were not determinable by our method. A slight increase in pK_a for the amino groups appears characteristic of the change from α-hydrogen to α-methyl.

(10) T. L. Sourkes, *Arch. Biochim. Biophys.*, **51**, 444 (1954).

Experimental[11]

α-(3,4-Dimethoxyphenyl)-acetoacetonitrile (II).—A solution of sodium ethylate was prepared from 389 g. (17 atoms) of sodium and 4530 cc. of absolute ethanol. To this hot solution was added a solution of 1000 g. (5.65 moles) of 3,4-dimethoxyphenylacetonitrile in 1710 g. (19.4 moles) of dry ethyl acetate. After refluxing for 4 hours the mixture, containing a light precipitate, was allowed to stand at room temperature overnight. The white crystalline mass was filtered off after cooling in ice for 2 hours. Washing with ethyl acetate and then ether gave 1403 g. of the sodium salt, m.p. 296–300° dec.

Solution of the salt in 5400 cc. of water, cooling to 10° and acidifying with 1420 cc. of glacial acetic acid gave a nearly solid mass. The product was collected and washed with water; weight 1244 g. (97.7%), m.p. 77.5–78°. Recrystallization from methanol gave analytically pure material, m.p. 98–100°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.34. Found: C, 65.62; H, 5.87; N, 6.04.

3,4-Dimethoxyphenylacetone (III).—Crude nitrile from above (1212 g.) was added over one hour to a stirred and cooled (0–5°) solution of 3008 cc. of concentrated sulfuric acid in 727 cc. of water. The brown solution resulting on heating to 80° for 10 minutes was cooled to 0° and diluted (stirring) with 10.75 l. of cold water. During heating on the steam-bath for 3 hours, an oily layer separated. After cooling, ether extraction, washing of the extract with dilute bicarbonate solution, and drying, the ether extract was concentrated to give 610.8 g. (56.5%) of orange oil which was purified by vacuum distillation; weight 549.3 g. (51%), b.p. 142° (2.6 mm.) (b.p. 118° (0.4 mm.)), $n^{27}D$ 1.5431.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.03; H, 7.27. Found: C, 67.64; H, 7.07.

4-Methyl-4-(3′,4′-dimethoxybenzyl)-hydantoin (IV).—A mixture of 530 g. (2.74 moles) of ketone, 2300 g. (24 moles) of ammonium carbonate, 230 g. (3.54 moles) of potassium cyanide, 6840 cc. of water and 6840 cc. of ethanol was stirred and heated to 55–60° for 10 hours. Hydantoin slowly crystallized out during the heating and after stirring 10 hours at room temperature was separated by concentration to 1/2 volume (reduced pressure) and filtration. After washing

(11) All compounds are the racemic modifications. Melting points are by the capillary tube method using Anschütz thermometers.

and drying there was 629 g. (87.5%) of material of m.p. 240–241°. Two recrystallizations from water gave material of m.p. 241.5–243.5°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.15; H, 6.10; N, 10.60. Found: C, 58.85; H, 5.84; N, 10.99.

α-Methyl-3,4-dimethoxyphenylalanine (V).—Crude hydantoin (630 g., 2.36 moles), $Ba(OH)_2 \cdot 8H_2O$ (3155 g., 10 moles) and water (15.77 l.) was refluxed for 68 hours. The mixture was poured into 50 l. of water and adjusted to *p*H 1.6 with 12 l. of 2 *N* sulfuric acid. After addition of another 50 l. of water and some Supercel, the mixture was filtered and concentrated under reduced pressure to *ca.* 12 l. Charcoaling, filtering and concentration to a sirup were followed by several reconcentrations after addition of ethanol. The sirupy residue was dissolved in 5 l. of acetone, brought to *p*H 8.8 with diethylamine and then back to *p*H 6.0 with acetic acid and filtered. Washing three times with 2-l. portions of acetone, slurrying with ethanol, again filtering and washing with ethanol yielded 580 g. (quant.) of product of m.p. 274–275° dec.

Crystallization from water gave pure hydrated material (Calcd. for 1.5 H_2O: 10.1. Found: 10.8), m.p. 282–283.5° dec. An anhydrous sample was analyzed.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.20; H, 7.16; N, 5.80. Found: C, 59.80; H, 7.36; N, 5.60.

α-Methyl-3,4-dihydroxyphenylalanine (VI, "α-Methyl DOPA").—The dimethoxy compound (545 g.) was refluxed for 55 hours in 5400 cc. of constant-boiling (47.5%) hydrobromic acid. After concentration (*in vacuo*) the residue was several times reconcentrated with acetone and then dissolved in 5 l. of hot acetone. Filtration and addition of 400 cc. of diethylamine (*p*H 8.4) gave a brown oil which soon crystallized. After stirring for two hours, the slurry was carefully brought to *p*H 6.0 with glacial acetic acid (12 cc.) and allowed to stand overnight at room temperature. The crude α-methyl amino acid was collected, washed ten times with 3-l. portions of warm acetone and then with ether (5 × 2 l.); weight 445.6 g. (94.2%), m.p. 293–294.5° dec.

For purification 438 g. was dissolved in 6.5 l. of water at 50°, charcoaled (15 g.) and filtered. The dark solution was then lightened considerably by bubbling in SO_2. Concentration under reduced pressure (nitrogen) to 2.5 l. and cooling in ice gave a 210 g. first crop of m.p. 299–300.5° dec. Retreatment of the liquor with SO_2 and concentration to 500 cc. yielded a 130-g. second crop, m.p. 297.5–298.5°. Both crops were analytically pure (and free from methoxyl) but pale gray in color.

A nearly colorless solution was prepared by dissolving the crude material in air-free water (50 cc./g.), agitating under nitrogen with acid-washed, chloride-free aluminum oxide (3 g./g. compound), filtering and repeating the aluminum oxide treatment. Freeze-drying of this solution gave a pure white crystalline powder, m.p. 300–301° dec., recovery *ca.* 80%. The sample for analysis was dried *in vacuo* at 100°.

Anal. Calcd. for $C_{10}H_{13}NO_4$ (211.2): C, 57.00; H, 6.20; N, 6.65. Found: C, 57.14; H, 5.89; N, 6.35.

The silver nitrate test for *ortho* and *para* diphenols[12] was strongly positive. With exclusion of light and air α-methyl DOPA discolors only very slowly. Presence of trace metals, especially iron, in processing have a very deleterious effect, but iron contamination is overcome by the aluminum oxide treatment.

A saturated aqueous solution of α-methyl DOPA contained *ca.* 30 mg./cc. and showed a *p*H of 4.2 (compared to *ca.* 3 mg./cc. of DOPA and *p*H 5.5).

α-Methyl-3-hydroxy-4-methoxyphenylalanine (VIIIa).—Addition of 11.8 g. of 3,4-dimethoxyphenylacetone to combined solutions of 4.1 g. of potassium cyanide in 7 cc. of water and 3.3 g. of ammonium chloride in 30 cc. of water was followed by heating at 55–60° for 5.5 hours. The resulting oily layer crystallized on standing overnight; weight 10 g. (77%) of hydrochloride of aminonitrile, m.p. 103–106° dec.

A solution of 9.5 g. of the nitrile in 45 cc. of concd. hydrochloric acid was saturated with HCl and heated on the steam-bath for 18 hours. Filtration from a little ammonium chloride, concentration to dryness under reduced pressure and solution of the residue in 10 cc. of hot water gave a clear solution. The *p*H was adjusted to 6.5 with concd. ammonium hydroxide and after cooling the crystalline product was collected, washed with alcohol and ether and dried; weight 4.22 g. (41%). Recrystallization from water gave material showing strong color with $FeCl_3$ and melting at 295–296° dec.

Anal. Calcd. for $C_{11}H_{15}NO_4$ (225.2): C, 58.65; H, 6.66; N, 6.22. Found: C, 58.59; H, 6.42; N, 6.50.

One gram of VIIIa in 40 cc. of concd. hydrochloric acid was saturated with HCl and heated at 150° for four hours in a sealed tube. When the dark colored solution was worked up as described above for α-methyl DOPA 0.78 g. (83%) of this substance was obtained, m.p. 299.5–300° dec.

α-(3-Methoxyphenyl)-acetoacetonitrile (IIa).—Treatment of *m*-methoxyphenylacetonitrile[13] essentially as described above for 3,4-dimethoxyphenylacetonitrile was followed by addition of petroleum ether to precipitate 275 g. of the sodium salt of α-(3-methoxyphenyl)-acetoacetonitrile, m.p. 280–290° dec. After acidification with acetic acid the yield was 206 g. (83.6%), m.p. 83–85°. Two recrystallizations from methanol gave analytically pure material, m.p. 90–91°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.80; H, 6.85; N, 7.40. Found: C, 69.83; H, 6.74; N, 7.42.

3-Methoxyphenylacetone (IIIa).—The crude nitrile IIa was hydrolyzed as described for II but at 90–95°. The yield of ketone was rather poor (46.5%), and considerable unreacted nitrile was recovered. After redistillation the ketone was analytically pure, b.p. 95–97° (0.7 mm.), $n^{25}D$ 1.5230.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.12; H, 7.36. Found: C, 73.36; H, 7.11.

4-Methyl-4-(3'-methoxybenzyl)-hydantoin (IVa).—A mixture of 28.4 g. (0.173 mole) of once-distilled ketone, 123.3 g. (1.28 moles) of ammonium carbonate, 26.7 g. (0.41 mole) of potassium cyanide, 365 cc. of ethanol and 365 cc. of water was stirred and heated to 55–60° for 12 hours. Concentration to *ca.* 1/3 volume under reduced pressure precipitated the hydantoin; weight 30.2 g. (74.5%), m.p. 197–200°. Repeated recrystallization from water gave material of m.p. 202–204°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.60; H, 6.00; N, 11.97, mol. wt., 234. Found: C, 61.94; H, 5.52; N, 11.80; mol wt., 227 (Rast).

α-Methyl-3-methoxyphenylalanine (Va).—Crude hydantoin (5 g.), $Ba(OH)_2 \cdot 8H_2O$ (25 g.) and water (150 cc.) were refluxed for 57 hours. After dilution to 750 cc. and brief boiling barium sulfate was precipitated by addition of 70 cc. of 2 *N* sulfuric acid. Filtration was followed by concentration to dryness and reconcentration after addition of alcohol. The residue was taken up in 100 cc. of ethanol and the slurry brought to *p*H 6.5 with diethylamine. The crystalline amino acid was collected, washed with ethanol and dried, weight 4.08 g. (91.5%), m.p. 277° dec. Methanol recrystallization gave analytically pure material, m.p. 277° dec.

Anal. Calcd. for $C_{11}H_{15}O_3N$: C, 63.01; H, 7.24; N, 6.70. Found: C, 63.43; H, 7.00; N, 6.78.

α-Methyl-3-hydroxyphenylalanine (VIa).—Two grams of crude methoxy amino acid and 160 cc. of concd. hydrochloric acid were placed in a bomb tube, cooled to 0° and saturated with HCl. The sealed tube was heated at 150° for six hours after which the contents were concentrated to dryness and several times reconcentrated after additions of ethanol. This residue was dissolved in 250 cc. of ethanol and the solution charcoaled and concentrated to dryness. The white crystalline amino acid hydrochloride was taken up in 125 cc. of hot acetone and the solution brought to *p*H 6.5 with diethylamine. The crystalline precipitate was collected, washed with hot acetone and then ether, weight 1.6 g. (84%), m.p. *ca.* 200° dec. Repeated methanol recrystallizations gave pure amino acid, m.p. 296–297° dec.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.50; H, 6.71; N, 7.17. Found: C, 61.57; H, 7.21; N, 7.39.

α-Methylphenylalanine (VIIIb).—A mixture of 40.3 g. of phenylacetone, 20.2 g. of potassium cyanide, 16.1 g. of ammonium chloride and 87 cc. of water was stirred and heated at 55–60° for 6–7 hours. After standing overnight

(12) B. S. Wildi, *Science*, **113**, 2929 (1951).

(13) R. B. Woodward, THIS JOURNAL, **62**, 1480 (1940).

at room temperature the oily top layer was separated and combined with an ether extract of the aqueous phase. The residual oil (42 g.) after concentration was treated with 60 cc. of concd. HCl. A white crystalline precipitate which separated, m.p. 151–152° dec., was presumably the hydrochloride of the nitrile corresponding to α-methylphenylalanine.

The slurry was saturated with HCl gas and then stirred on the steam-bath for 7 hours, an addition of 40 cc. of concd. HCl being made after the first hour. Cooling produced a crystalline mass which was filtered. After washing with acetone and drying the α-methylphenylalanine hydrochloride weighed 35 g. Crystallization from butanol–ether gave material of m.p. 241–243° dec.

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot HCl$: C, 55.65; H, 6.55; N, 6.50; Cl, 16.48. Found: C, 56.29; H, 6.70; N, 6.53; Cl, 16.05.

Neutralization of an aqueous solution with ammonia or, preferably, an ethanol solution with pyridine, gave the free amino acid, m.p. 294.5–295° dec. (recorded m.p. 293–294°).[8]

This amino acid readily formed a picrate of m.p. 174–175°.

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot C_6H_3N_3O_7$: C, 47.00; H, 3.94; N, 13.70. Found: C, 47.32; H, 3.54; N, 13.76.

α-Methylphenylalanine Methyl Ester Hydrochloride and Amide.—A suspension of α-methylphenylalanine (20 g.) in 780 cc. of methanol was saturated with HCl, refluxed 2.5 hours and allowed to stand overnight. Concentration to dryness, reconcentration with methanol and trituration with ether gave 25.3 g. (98.7%) of methyl ester hydrochloride, m.p. 96–97°.

Anal. Calcd. for $C_{11}H_{16}NO_2Cl \cdot H_2O$ (247.7); C, 53.40; H, 7.27; N, 5.66; H_2O, 7.3. Found: C, 53.44; H, 7.27; H, 5.34; H_2O, 7.2 (Karl Fischer).

Ester hydrochloride (15.3 g.) and 320 cc. of liquid ammonia in a sealed tube were held at room temperature for four days. Evaporation of the ammonia left a tan crystalline residue which was crystallized from chloroform and water; weight 3.48 g., m.p. 159–160° dec.

Anal. Calcd. for $C_{10}H_{14}N_2O$ (178.2): C, 67.50; H, 7.92; N, 15.45. Found: C, 67.91; H, 7.68; N, 15.67.

N-Acetyl-α-methylphenylalanine Methyl Ester.—The ester hydrochloride above was dissolved in water, filtered and free ester precipitated as an oil with ammonium hydroxide. Extraction with ether was followed by concentration and distillation (82–84° (0.2 mm.)). The clear colorless methyl ester of α-methylphenylalanine had $n^{25}D$ 1.5112, yield 84.5%.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.40; H, 7.82; N, 7.26. Found: C, 68.75; H, 7.93; N, 7.53.

Twenty-three grams of ester in 115 cc. of acetic anhydride was refluxed for 1/2 hour. Concentration to dryness under reduced pressure was followed by several concentrations with ethyl alcohol and then trituration with ether; weight 25.7 g. (92%), m.p. 122–124° after recrystallization from water.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.50; H, 7.28; N, 5.95. Found: C, 66.78; H, 6.98; N, 5.90.

2-Amino-2-methyl-3-phenylpropanol.—A solution of N-acetyl methyl ester (22.2 g.) in 240 cc. of absolute alcohol was treated with metallic sodium (25.4 g.) added over one hour. After refluxing an additional four hours the solution was concentrated to a solid which was taken up in water and extracted with ether. The combined extracts were concentrated to a sirup which was distilled at 90–105° (0.3 mm.). On standing at 0° the distillate crystallized and was triturated with petroleum ether, weight 5.14 g., m.p. 88–96°.

Crystallization from *n*-heptane gave an analytical sample of m.p. 99–100°.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.70; H, 9.15; N, 8.49. Found: C, 72.55; H, 8.88; N, 8.80.

N-Dichloroacetyl-α-methylphenylalanine (IX).—A solution of 182 g. of α-methylphenylalanine in 805 cc. of 2.5 *N* sodium hydroxide was cooled to −10°. With agitation and cooling below 0°, 300 g. of dichloroacetyl chloride was added to the heavy slurry. After an additional half hour at 0° the mixture was allowed to warm up to room temperature and was acidified with 1020 cc. of 1.25 *N* HCl. The resulting fine white powder was collected, washed with water and dried; 94 g. (31.9%), m.p. 157.5–160°. Crystallization from water–dioxane (5:1) yielded material of m.p. 164–165°.

Anal. Calcd. for $C_{12}H_{13}O_3NCl_2$ (290.1): C, 49.15; H, 4.51; N, 4.83. Found: C, 49.49; H, 4.50; N, 4.66.

N-Dichloroacetyl-4-nitro-α-methylphenylalanine (X).—Eighty-four grams of crude IX from above was added with stirring and cooling (0°) to 168 cc. of cold fuming nitric acid. After the addition the slurry was stirred an hour at 0° and then diluted with several volumes of cold water; weight 89 g. (91.6%), m.p. 164–168°. Crystallization from hot dioxane–water mixture raised the m.p. to 187–188°.

Anal. Calcd. for $C_{12}H_{12}O_5N_2Cl_2$ (335.1): C, 43.08; H, 3.61; N, 8.34. Found: C, 43.16; H, 3.39; N, 8.07.

4-Nitro-α-methylphenylalanine (XIV).—A gram of the N-dichloroacetyl derivative was refluxed 7–8 hours in 12.5 cc. of 6 *N* HCl. The hydrochloride of the free amino acid separated in clusters of needles on cooling; weight 300 mg. (38.6%), m.p. 268° dec. Slurrying with ethyl acetate and with ether left pure material, m.p. 275–277° dec.

Anal. Calcd. for $C_{10}H_{13}N_2O_4Cl$ (260.7): C, 46.06; H, 5.04; N, 10.76. Found: C, 46.07; H, 4.89; N, 10.57.

The hydrochloride (5.1 g.) in 135 cc. of ethanol was charcoaled and brought to *p*H 6.5 with diethylamine. The free amino acid was collected, washed with ethanol and ether and dried; weight 4.4 g. (88%), m.p. 248–252°. Crystallization from hot water gave 70% recovery as material of m.p. 271–273°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$ (224.2): C, 53.57; H, 5.40; N, 12.50. Found: C, 53.84; H, 5.10; N, 12.34.

N-Dichloroacetyl-4-amino-α-methylphenylalanine (XI).—Fifty grams of N-dichloroacetyl-4-nitro-α-methylphenylalanine was dissolved in 500 cc. of methanol, 300 mg. of PtO_2 added and the mixture hydrogenated at low pressure. Hydrogen uptake was complete in an hour. Filtration and concentration gave a residue which crystallized on slurrying with ether, weight 45.3 g. (99.5%), m.p. *ca.* 104–108° dec. Two precipitations from alcohol with ether yielded the slightly hygroscopic product which was dried *in vacuo* over sulfuric acid.

Anal. Calcd. for $C_{12}H_{14}N_2O_3Cl_2 \cdot 1/2H_2O$ (314.2): C, 45.90; H, 4.81; N, 8.91; H_2O, 2.9. Found: C, 46.15; H, 6.23; N, 8.31; H_2O, 3.6 (Karl Fischer).

4-Hydroxy-α-methylphenylalanine (XII, "α-Methyltyrosine").—Ten grams of aromatic amine XI from above was dissolved in 5 cc. of 50% H_2SO_4 and the solution cooled in ice and treated with 2.4 g. of sodium nitrite in 10 cc. of water. The resulting slurry was aged in ice for an hour and then warmed to room temperature. Nitrogen was evolved and a sticky oil separated.

This mixture was warmed on the steam-bath till nitrogen evolution stopped. Extraction with ethyl acetate followed by concentration left a colored solid residue (9.4 g.) which was refluxed in 150 cc. of HCl (1:1) for 17 hours. After charcoaling and extracting with ethyl acetate this aqueous solution was concentrated dry and reconcentrated after addition of ethanol. The residue (7.4 g.) was dissolved in ethanol and neutralized with diethylamine to precipitate 2.54 g. (40%) of amino acid, m.p. 309° dec. Crystallization from hot water gave 1.5 g. of product melting at 320° dec. The analytical sample was dried *in vacuo* at 100°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.49; H, 6.71; N, 7.18. Found: C, 61.32; H, 6.76; N, 6.93.

Water solubility 0.57 mg./cc. at room temperature.

4-Hydroxy-3,5-diiodo-α-methylphenylalanine (XIII).—A solution of 3.86 g. of iodine and 4.84 g. of sodium iodide in 16 cc. of water was added slowly with stirring to a solution of 1.21 g. of α-methyltyrosine in 12 cc. of 20% diethylamine. After stirring for 2 hours the mixture was treated with excess potassium metabisulfite (5 g.) and the tan-colored solid collected; weight 1.91 g. (69%), m.p. 199–200° dec.

Purification by solution in 1 *N* HCl and reprecipitation gave 1.1 g., m.p. 217.5° dec.

Anal. Calcd. for $C_{10}H_{11}O_3NI_2$: C, 26.85; H, 2.46; N, 3.13; I, 56.80. Found: C, 26.83; H, 2.55; N, 3.18; I, 54.37.

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