In the reaction between sodium triphenyl germanide and chloroform, the products are the same as in that with methylene chloride, but the proportion in which the compounds are formed is different. Larger quantities of triphenylgermanylamine (ultimately recovered as oxide) are obtained while the amount of triphenyl methyl germane is relatively smaller. Very considerable quantities of di-triphenylgermanylmethane are formed.

Di-triphenylgermanylmethane and triphenylgermanium oxide form a series of solid solutions that may be separated with some difficulty.

Sodium triphenyl germanide reacts readily with carbon tetrachloride. The reaction is evidently similar to that with chloroform and methylene chloride although apparently more complex. No free triphenylgermanium is formed. Triphenylgermanium oxide was obtained from the reaction mixture as well as a number of lower melting compounds that have not been separated and identified. Without doubt, ammonia takes part in this reaction.

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l-*p*-METHOXYPHENYLALANINE[1]

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The methyl ether of racemic tyrosine has been prepared, by purely synthetic methods, by Dakin.[2] Need having arisen for an optically active variety of this acid, its preparation from natural tyrosine was indicated. The action of diazomethane upon tyrosine has been shown[3] to lead to a mixture of methyl esters which includes that of methoxyphenylalanine, but the process is obviously unsuitable for preparative purposes.

Methylation by means of methyl sulfate has proved eminently satisfactory, protection of the amino group being secured by acetylation. For this purpose it is desirable to select conditions in which only the amino group is acetylated, the phenolic hydroxyl group remaining intact. It has recently been shown that, in general, both the amino group and the phenolic hydroxyl group are readily acetylated by treatment in cold alkaline solution with acetic anhydride[4] or with ketene;[5] the hydroxyl group of tyrosine

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[2] H. D. Dakin, *J. Biol. Chem.*, **8**, 11 (1910); A. J. Wakeman and H. D. Dakin, *ibid.*, **9**, 148 (1911).

[3] E. Abderhalden and E. Schwab, *Z. physiol. Chem.*, **148**, 16 (1925).

[4] F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931); C. P. Berg, W. C. Rose and C. S. Marvel, *J. Biol. Chem.*, **85**, 207 (1929).

[5] M. Bergmann, and F. Stern, *Ber.*, **63B**, 437 (1930).

would also be acetylated by heating with acetic anhydride alone,[6] or in glacial acetic acid,[7,8] while in pyridine abnormal reactions take place.[9]

We have found that tyrosine may be acetylated readily on the nitrogen alone by addition of acetic anhydride to its suspension in hot water. The resulting product is apparently soluble in all proportions in water and was obtained in the form of an almost colorless glass, which nevertheless gave analytical figures corresponding approximately to those of monoacetyltyrosine. Only about 10% of the tyrosine was racemized during the process. Monoacetyl-*l*-tyrosine has been prepared by Takenaka[10] from tyrosine ethyl ester by acetylating with acetic anhydride and saponifying with alkali; his product is reported to crystallize with difficulty from water and to melt at 146–148°. We have not succeeded in crystallizing from water the monoacetyltyrosine prepared as above, but have isolated from dioxane solution a crystalline product containing one molecule of solvent. The dioxane of crystallization is not completely lost on heating at 76° for forty-eight hours *in vacuo* over phosphorus pentoxide; at 120–125° the anticipated loss of weight takes place after a week, but some decomposition of the acetyltyrosine also occurs.

On treatment in alkaline solution with methyl sulfate, monoacetyltyrosine readily yields N-acetyl-*p*-methoxyphenylalanine, which on hydrolysis with dilute mineral acid is converted to the desired *l-p*-methoxyphenylalanine.

The optically active acid melts at a distinctly lower temperature than the racemic modification; its solubility in water is markedly greater than that of tyrosine, and it is interesting to note that its levorotation, in contradistinction to that of tyrosine, is lower in sodium hydroxide than in hydrochloric acid:

	$[\alpha]_{546}$ in *N* HCl	$[\alpha]_{546}$ in *N* NaOH
l-Tyrosine	−11.7°	−14.6°
l-p-Methoxyphenylalanine	− 5.9	− 3.2

The specific rotatory power of its derivatives varies within wide limits, from weakly levo (−3.7° for the benzoyl derivative) to strongly dextro (+123.6° for the phenylhydantoic acid).

Experimental

l-N-Acetyltyrosine.—To a suspension of 90.5 g. of tyrosine in 500 cc. of water at 90–95° was added 375 cc. of 95% acetic anhydride in eight portions, any ebullition having been allowed to subside before each new addition. The tyrosine was completely in solution after 325 cc. had been added. The resulting solution was evaporated on the steam-bath under reduced pressure until no further acetic acid distilled. The sirupy, pale

[6] P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **93**, 581 (1931).
[7] F. Knoop and J. G. Blanco, *Z. physiol. Chem.*, **146**, 267 (1925).
[8] H. D. Dakin, *J. Biol. Chem.*, **82**, 439 (1929).
[9] H. D. Dakin and R. West, *ibid.*, **78**, 91, 744 (1928).
[10] Y. Takenaka, *Acta Schol. Med. Univ. Imp. Kioto*, **4**, 367 (1922).

yellow residue was dissolved in acetone, filtered from a small quantity of unchanged tyrosine, evaporated, and dried at 75° *in vacuo* over potassium hydroxide and phosphorus pentoxide.

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.19; H, 5.83; N, 6.28; neut. equiv., 223. Found: C, 58.98, 58.92; H, 5.41, 5.65; N, 5.67; neut. equiv. (phenolphthalein), 227.

Rotation. $[\alpha]^{22}_{546}$ +46.2° (4.4% in water), +84.4° (3.7% in *N* NaOH, +39.8°) (2.9% in *N* HCl).

In order to estimate the extent of racemization which takes place during the acetylation, 5 g. of tyrosine was treated as above and the product hydrolyzed by boiling for four hours with 60 cc. of 1.7 *N* hydrochloric acid. On neutralization with ammonia, 5 g. of tyrosine was recovered, showing $[\alpha]^{23}_{546}$ −9.9°. On recrystallizing 3.8 g. of this recovered tyrosine from 700 cc. of water, 2.8 g. of tyrosine, showing $[\alpha]^{21}_{546}$ −12.0° (4% in *N* HCl), was obtained. Concentration of the mother liquors yielded further crops showing considerably lower rotations.

On dissolving the resinous acetyltyrosine in the minimum quantity of cold dioxane and adding an equal volume of petroleum ether, the product separated as an oil which became crystalline on standing overnight in the refrigerator. On recrystallization from hot dioxane, it separated in irregular plates which, after drying at room temperature under reduced pressure over phosphorus pentoxide, melted at 107–109° after softening at about 98°. The molten product resolidified on cooling and on heating again melted (not very sharply) at 138–140°.

Anal. Calcd. for $C_{15}H_{21}O_6N$: C, 57.88; H, 6.75; N, 4.50; neut. equiv., 311. Found: C, 57.63; H, 6.67; N, 4.43; neut. equiv. (phenolphthalein), 318.

Rotation. $[\alpha]^{22}_{546}$ +39.9° (4.2% in water), +72.3° (3.3% in *N* NaOH), +33.8° (2.8% in *N* HCl).

A sample, heated for forty-eight hours at 76° *in vacuo* over phosphorus pentoxide, lost 19% of its weight (calcd., 28.3%). After heating for a week longer at 120–125° loss of weight increased to 28.4%, but decomposition occurred at this temperature as indicated by darkening and formation of some water-insoluble resin. Analysis of the material so heated gave C, 59.50; H, 5.98; N, 5.84.

Methylation.—The sirupy residue from the acetylation of 90.5 g. of tyrosine was dissolved in 400 cc. of water; the solution was neutralized with barium carbonate and then rendered alkaline by the addition of 189.3 g. of hydrated barium hydroxide. To the resulting mixture was added, with mechanical stirring, 126 g. of methyl sulfate in four portions, the temperature being held at 30–40° by external cooling. Stirring was continued for two hours after all of the methyl sulfate had been added. The solution was filtered to remove a little undissolved barium hydroxide and added to a boiling solution of 100 g. of concentrated sulfuric acid in 500 cc. of water. On allowing to cool and filtering off the barium sulfate, a part of the acetyl-*p*-methoxyphenylalanine separated as an oil. A portion was allowed to stand in the refrigerator, when it gradually crystallized. The crude product, which melted at 145°, was recrystallized from water, when it was obtained in either trapezoidal plates or hard blunt needles which melted at 150–151°. *l*-N-Acetyl-*p*-methoxyphenylalanine is extremely soluble in methyl alcohol, ethyl alcohol and acetone, sparingly soluble in cold water, and insoluble in ether.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.76; H, 6.33; N, 5.91. Found: C, 61.14; H, 6.40; N, 6.02.

Rotation. $[\alpha]^{20.5}_{546}$ +67.6° (5% in absolute alcohol). $[\alpha]^{24}_{546}$ +78.4 (4.5% in *N* NaOH).

***l*-*p*-Methoxyphenylalanine.**—The crude solution containing the *l*-N-acetyl-*p*-methoxyphenylalanine (obtained as above from 90.5 g. of tyrosine), which was strongly

acid to Congo red, was heated for seventy-two hours on the steam-bath and then evaporated almost to dryness on the steam-bath under reduced pressure. The residue on cooling solidified to a crystalline mass. This was washed with cold glacial acetic acid until free of color, and then with acetone until free of acetic acid. The product so obtained, after drying *in vacuo* over phosphorus pentoxide, weighed 81.5 g. and melted at 188–189° (corr.). A second crop of 17.8 g., melting at 187–188° (corr.), was obtained by repeating the evaporation and washing. An attempt to obtain a third crop in this way yielded only 0.2 g. of reddish crystals, but a further crop, amounting to about 10 g., was obtained from the mother liquor by partially removing the excess sulfuric acid with barium hydroxide and again concentrating. The crude material was recrystallized by dissolving in hot water, decolorizing with charcoal, concentrating on the steam-bath until a coating of crystals formed on the surface, diluting with 50 cc. of acetic acid and cooling. On washing successively with acetic acid and acetone, and drying *in vacuo* over phosphorus pentoxide, it melted at 191° (corr.). Analysis showed it to consist of the acid sulfate of *p*-methoxyphenylalanine.

Anal. Calcd. for $C_{10}H_{13}O_3N \cdot H_2SO_4$: S, 10.92; N, 4.78. Found: S, 10.66; N, 4.92.

The final yield, after working up the mother liquors, was 99 g., or 68% of the theoretical amount based on the 90.5 g. of tyrosine originally taken. The salt is exceedingly soluble in water and in ethyl alcohol, sparingly soluble in acetic acid, and insoluble in acetone.

The free *p*-methoxyphenylalanine was readily obtained by adding a slight excess of ammonia to a hot aqueous solution of the acid sulfate, when it crystallized as glistening plates which melted at 264–265° (corr.).

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.54; H, 6.67; N, 7.18; CH_3O, 15.90. Found: C, 61.65; H, 6.35; N, 7.24; CH_3O, 15.62.

Rotation. $[\alpha]_{546}^{29}$ −5.9° (2% in *N* HCl), −3.2° (2% in *N* NaOH).

l-p-Methoxyphenylalanine dissolves in 101–102 parts of water at 25° and in about 18 parts at 100°. When the aqueous solution is boiled in the presence of air, decomposition gradually occurs; the solution becomes slightly turbid, traces of carbon dioxide and ammonia are evolved, and an odor recalling that of anisaldehyde is perceptible. Tyrosine, to a less extent, displays a similar tendency to lose carbon dioxide and ammonia.

The hydrochloride crystallizes readily from hydrochloric acid solution in the form of stout needles which melt at 237–238° (corr.) with evolution of gas. It is readily soluble in water and absolute alcohol but insoluble in ether.

Anal. Calcd. for $C_{10}H_{14}O_3NCl$: Cl, 15.33; N, 6.05. Found: Cl, 15.38; N, 6.30.

The copper salt forms sparingly soluble violet-blue leaflets which, on rapid heating, decompose at 250° (corr.).

Anal. Calcd. for $C_{20}H_{24}O_6N_2Cu$: Cu, 14.08. Found: Cu, 14.03, 14.01.

Attempts to prepare a crystalline picrate were unsuccessful; the amorphous salt was relatively soluble in water and in alcohol. The picrolonate separated from 30% alcohol in rosets of fine needles which softened at 145° and melted with decomposition at 174° (corr.). Recrystallization of this salt failed to change these characteristics and the product continued to give unsatisfactory analytical values.

Anal. Calcd. for $C_{10}H_{13}O_3N \cdot C_{10}H_8O_8N_4$: C, 52.29; H, 4.58; N, 15.25. Found: C, 51.80; H, 5.13; N, 12.42.

Benzoyl Derivative.—This was prepared by the Schotten–Baumann reaction in the presence of sodium bicarbonate. It formed very fine needles which, after recrystallization from water, melted at 136–137°; it is soluble in alcohol, insoluble in benzene.

Anal. Calcd. for $C_{17}H_{17}O_4N$: N, 4.68. Found: N, 4.81.
Rotation. $[\alpha]^{20}_{646}$ −3.7° (1.5% in alcohol).

Benzenesulfonyl Derivative.—This was prepared by the Schotten–Baumann procedure in the presence of sodium bicarbonate; it separated from hot water in long fine needles which melted at 136–137°.

Anal. Calcd. for $C_{16}H_{17}O_5NS$: S, 9.55. Found: S, 9.37.
Rotation. $[\alpha]^{21}_{646}$ +6.3° (1% in alcohol).

An alkali-insoluble oil which accompanied this product was not investigated.

Phenylhydantoic Acid.—A solution of 2 g. of *l*-*p*-methoxyphenylalanine in 42 cc. of 0.43 *N* sodium hydroxide was shaken with 3 cc. of phenyl isocyanate for an hour. After filtering, the alkaline solution was acidified to Congo red, and the crude product was recrystallized from 50 cc. of 50% alcohol, from which it separated as glistening leaflets melting at 176–177° (corr.). Another preparation was recrystallized from ethylene chloride, in which it is very sparingly soluble in the cold.

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.97; H, 5.73; N, 8.92. Found: C, 64.78; H, 5.85; N, 8.99.
Rotation. $[\alpha]^{21}_{646}$ +123.6° (4% in alcohol).

Phenylhydantoin.—A solution of 1 g. of the above phenylhydantoic acid in 150 cc. of 10% hydrochloric acid was boiled for one and one-half hours. The hot solution was filtered; on cooling, the phenylhydantoin separated in fine needles which melted at 134–135°. This melting point was unchanged on recrystallization from water.

Anal. Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.92; H, 5.41; N, 9.46. Found: C, 69.13; H, 5.52; N, 9.53.

α-Naphthylhydantoic Acid.—This was prepared in the same way as the phenyl derivative from 2 g. of the amino acid and 3 cc. of α-naphthyl isocyanate. The alkaline solution had to be heated before the dinaphthyl urea could be filtered off. On recrystallization from 50% alcohol, the derivative separated in the form of small prisms which melted at 167–168°.

Anal. Calcd. for $C_{21}H_{20}O_4N_2$: C, 69.23; H, 5.49; N, 7.69. Found: C, 69.38; H, 5.65; N, 7.83.
Rotation. $[\alpha]^{22}_{646}$ +63.3° (2.5% in alcohol).

α-Naphthylhydantoin.—The above α-naphthylhydantoic acid underwent very little change on heating for two hours with 80 parts of 10% hydrochloric acid, probably owing to lack of solubility. The conversion was brought about by heating 0.4 g. with a mixture of 100 cc. of water, 25 cc. of glacial acetic acid, and 40 cc. of concentrated hydrochloric acid. After two hours' boiling, the mixture was filtered hot and the amorphous precipitate which separated from the filtrate was recrystallized from 25% alcohol; it formed short prisms melting at 155–157°.

Anal. Calcd. for $C_{21}H_{18}O_3N_2$: C, 72.83; H, 5.20; N, 8.09. Found: C, 72.76; H, 5.25; N, 8.34.

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Summary

A synthesis of *l*-*p*-methoxyphenylalanine from *l*-tyrosine is described, and the product is characterized by various derivatives.

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