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Studies on Antimetabolites

I. Synthesis of D,L-"*Neo*phenylalanine", D,L-"*Neo*tyrosine" and D,L-"*Neo*-3,5-diiodotyrosine", the β,β,-Dimethyl Analogues of optically inactive Phenylalanine, Tyrosine and 3,5-Diiodotyrosine

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The β,β-dimethyl ("*neo*") analogues of phenylalanine and tyrosine have been prepared by reduction of the oximinoacids. The intermediate α-ketoacids were obtained in a convenient way by alkaline permanganate oxidation of the corresponding 4,6-di*tert*alkylsubstituted pyrogallol derivatives, which were prepared in almost quantitative yields by the condensation of the α,α-dialkylbenzylalcohol or α-alkylstyrene with pyrogallol. β,β-Dimethyltyrosine was iodinated to 3,5-diiodo-β,β-dimethyltyrosine.

The fact, that the introduction of a *gem*dimethyl group at the α carbon atom of an α-aryloxyacetic acid [1], of 3-indoleacetic [1b,2] or of phenylacetic acid[3], possessing auxin (plant hormone) activity, invariably changed the compound into an auxin antagonist, whereas the introduction of only *one* α-alkyl group usually did not alter the type of activity, suggested that the introduction of such a *gem*dimethyl group on a carbon atom in the vicinity of a reactive centre of a physiologically active molecule might perhaps more generally produce compounds capable of antagonising the parent, unmethylated substance.

The introduction of a β-*gem*dimethyl group into straight chain α-amino-acids appeared to furnish a class of compounds, by means of which this hypothesis could be tested. Consequently the synthesis of a number of such acids was started, and in the present paper the preparation of the β,β-dimethyl analogues of optically inactive phenylalanine, tyrosine and 3,5-diiodotyrosine is described. For convenience they henceforth are named *neo*phenylalanine (I), *neo*tyrosine (II) and *neo*iodogorgoic acid (III) respectively. In these acids the amino and carboxyl groups are linked to a sterically highly hindered carbon atom, and it may be expected that the respective C—N and C—C bonds are rather invulnerable to attack. Compounds of this type exhibit abnormal reac-

tivity. For example *neo*pentylamine, $(CH_3)_3CCH_2NH_2$, is known to react abnormally with nitrous acid forming a relatively stable diazonium salt [4], and in "*neo*phylchloride", $C_6H_5C(CH_3)_2CH_2Cl$, the chlorine atom is replaced only with great difficulty [5]. Phenylalanine and tyrosine are believed to be involved as precursors in the *in vivo* synthesis of adrenaline and thyroxine. Analogues of the aminoacids may therefore be able to interfere with the metabolic processes leading to the hormones.

Several cases are known, where structural changes in the molecule of a natural metabolite produce compounds capable of antagonising the parent compound, and the literature on such antimetabolites has been excellently reviewed by Woolley [6]. The classical example is the antagonism between a sulphonamide and *p*-aminobenzoic acid. No attempts appear to have been made to produce antimetabolites by the introduction of a *gem*dialkyl group suitably situated in the molecule of an essential metabolite.

The only α-aminoacid containing a quarternary β-carbon atom, which seems to have been described, is D,L-α-amino-β-methyl*iso*valeric acid, *pseudo*leucine (IV), obtained in a very low yield by the ammonolysis of α-bromo-β-methyl*iso*valeric acid, or better by the Knoop synthesis from α-oxo-β-methyl-*iso*valeric acid [8]. A very good yield is obtained by the reduction of the oxime of the latter ketoacid [9].

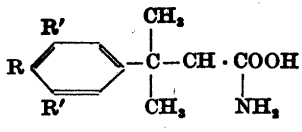
For the preparation of *neo*phenylalanine the Strecker synthesis from α-phenyl*iso*butyraldehyde and the reduction of α-oximino- or α-hydrazono-β-phenyl*iso*valeric acid appeared to be possible synthetic pathways. Ammonolysis of α-bromo-β-phenyl*iso*valeric acid and Knoop synthesis from the α-oxo-acid were considered impracticable, as the "sterical hindrance" would probably be even greater in these compounds than in the corresponding methyl derivative.

The α-phenyl*iso*butyraldehyde required for the Strecker synthesis was easily prepared by the oxidation of β-phenyl*iso*butanol, obtained as described by Whitmore, Weissgerber and Shabica [5]. The Strecker synthesis from this aldehyde failed, however, probably due to steric factors*.

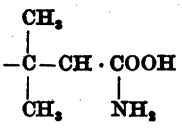
For the preparation of the intermediate oximino- or hydrazonoacid α-oxo-β-phenyl*iso*valeric acid was desired. Only a few α-ketoacids containing a quarternary β-carbon atom seem to have been described. Glücksmann [10a] obtained an acceptable yield of trimethylpyruvic acid and some trimethylacetic acid on the oxidation of pinacolone with alkaline permanganate, a reaction which was further studied by Bardhan [10b], and by similar oxidation of *p-tert*butylphenol and *p-tert*amylphenol Anschütz and Rauff [11] obtained mixtures of trimethylpyruvic and trimethylacetic acids and of ethyl-dimethylpyruvic and ethyl-dimethylacetic acids, respectively, in low yields.

Attempts to oxidize α,α-dimethyl-α-phenylacetone and its *p*-methoxy-derivative to the corresponding ketoacids with alkaline permanganate in aqueous solution at room temperature failed, probably due to the insolubility of the ketones. At the boiling point the only acid products isolated were the

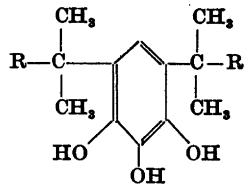
* Added in proof: In this connection it is interesting that it was recently reported that the cyanohydrin of diphenylglycolaldehyde could not be converted into the aminonitrile. (Favorskaya, T. A. and Remizova, L. A. *Zhur Obshchei Khim.* 23 (1953) 667, *Chem. Abstracts* 48 (1954) 7588.)



I R = R′ = H
II R = OH; R′ = H
III R = OH; R′ = I



VI



V R = C_6H_5
VI R = *p*-CH_3O-C_6H_4

α-phenyl*iso*butyric acids. Attempts to carry out the reaction in other solvents were also unsuccessful, as was an attempt to oxidize methyl α-phenyl*iso*valerate by refluxing it with selenium dioxide.

Application of the method of Anschütz and Rauff to *p*-(α,α-dimethylbenzyl)phenol afforded a very small yield of a mixture of α-oxo-β-phenyl-*iso*valeric and α-phenyl*iso*butyric acids, which was easily separated by selective hydrolysis of the ethyl ester mixture. Analogous oxidation of a mixture of 2,2-bis-(*p*-hydroxyphenyl)propane and its monomethyl ether, containing about 60 % monomethyl ether, prepared by partial methylation of the phenolic compound and removal of the dimethylderivative, afforded a small yield of a mixture of α-oxo-β-(*p*-methoxyphenyl)*iso*valeric and α-(*p*-methoxyphenyl)*iso*butyric acids, from which the pure acids were isolated after esterification and selective hydrolysis of the ester mixture.

A very good yield of ketoacid was obtained by permanganate oxidation of 4,6-di-(α,α-dimethylbenzyl)pyrogallol (V) [12]. This substance (V) was easily prepared in almost quantitative yield by the addition of α-methylstyrene to pyrogallol, a method analogous to that of Schulze and Flaig [13]. for preparation of 4,6-di*tert*butylpyrogallol.

In addition to the ketoacid and some α-phenyl*iso*butyric acid a substance, m.p. 174—175°, insoluble in sodium bicarbonate solution, and another, m.p. 185—186°, soluble in sodium bicarbonate, were isolated. These will be described in a separate paper.

The addition of α,α-dimethyl-*p*-methoxybenzyl alcohol, obtained from methyl anisate and methyl-magnesium bromide [14] to pyrogallol afforded a high yield of 4,6-di-(α,α-dimethyl-*p*-methoxybenzyl)pyrogallol (VI), permanganate oxidation of which gave α-oxo-β-(*p*-methoxyphenyl)*iso*valeric acid and a little α-(*p*-methoxyphenyl)*iso*butyric acid. No attempt was made to isolate other products from the reaction.

The ketoacids were converted to their oximes in almost quantitative yields, and reduction of the latter with 2 % sodium amalgam in absolute ethanol, lactic acid being added during the reaction to keep the solution faintly acid, afforded the aminoacids, which were characterized by their N-acetyl derivatives.

Iodination of *neo*tyrosine following the directions given by Block and Powell [15] for iodination of tyrosine afforded *neo*iodogorgoic acid (III).

EXPERIMENTAL *

α-Phenylisobutyraldehyde. Powdered potassium dichromate (19.9 g) was added in small portions over half an hour to a stirred mixture of β-phenyl*iso*butanol (30 g), conc. sulphuric acid (40 ml) and water (200 ml). The mixture was poured into water, and the resulting oil was taken up in ether, washed and dried. Removal of the ether and careful fractionation of the residual oil afforded a colourless liquid (20 g) boiling at 91—95°/10 mm Hg. It formed a *semicarbazone* melting at 168—170°. Tiffeneau [16] reports m.p. 172°. (Found: N 20.4. Calc. for $C_{11}H_{15}N_3O$: N 20.5.)

α,α-Dimethyl-α-phenylacetone. (The method described is a modification of that given by Suter and Weston [17].) A stock solution of 1 *M* potassium *tert*butoxide was prepared by dissolving potassium (39.1 g) in anhydrous *tert*butanol (400 ml) and diluting to 1000 ml. — Phenylacetone (26.8 g) was added to 1 *M* potassium *tert*butoxide solution (205 ml). The mixture was shaken and allowed to stand for ten minutes, and methyl iodide (29 g) was carefully added with shaking. After two hours the treatment with butoxide and methyl iodide was repeated, and the mixture set aside overnight. Most of the solvent was removed on the water bath, and water was added to dissolve the potassium iodide. The resulting oil was taken up in ether, washed and dried. The ether was removed and the residual oil fractionated yielding a colourless product (24 g) boiling at 98—101°/11 mm Hg. (Lit.[17] b.p. 99—99.5°/12 mm Hg).

A sample of the product (3 g) was oxidised with boiling alkaline aqueous potassium permanganate. α-Phenyl*iso*butyric acid (0.5 g), m.p. and mixed m.p. 78—78.5° was isolated.

α,α-Dimethyl-α-(p-methoxyphenyl)acetone. Anisylacetone was methylated by the method described above. The yield of carefully fractionated oil boiling at 138—141°/10 mm Hg was 65 %. (Found: CH_3O 16.0. $C_{12}H_{16}O_2$ requires: CH_3O 16.2). The *semicarbazone* melted at 184—185°. (Found: CH_3O 12.3. $C_{13}H_{19}N_3O_2$ requires: CH_3O 12.4). On oxidation with boiling permanganate α-*p*-methoxyphenyl*iso*butyric acid, m.p. 89°, identical with a specimen prepared from α-*p*-methoxyphenyl*iso*butyronitrile,[18] was formed.

Methylation of 2,2-bis-(p-hydroxyphenyl)propane, The phenol (1480 g, 6,5 moles) was dissolved in hot sodium hydroxide solution, prepared from sodium hydroxide (280 g, 7 moles) and water (4 l). Dimethylsulphate (882 g, 7 moles) was added with stirring over 2—3 hours, the temperature being kept at 30—40°. The mixture was stirred overnight and then refluxed for 2 hours, and, while hot, acidified with sulphuric acid. The aqueous layer was siphoned and washed with a little toluene, which was combined with the oily layer and washed twice with water. A solution of sodium hydroxide (300 g) in water (3 l) was added, and the mixture was rapidly stirred for one hour, the temperature being kept at about 60°. While hot the liquid was repeatedly extracted with toluene. (If allowed to cool the mixture solidified.) The combined toluene extracts were washed with 2 *N* sodium hydroxide, which was combined with the alkaline solution, and with water.

The alkaline solution was acidified with sulphuric acid and extracted with toluene. On distillation the extracts yielded a faintly yellow oil (970 g) boiling at 220—250°/10 mm Hg. It analysed 7.50 % CH_3O and thus contained about 60 % monomethyl ether. All attempts to separate the mixture by further distillation failed. On distillation the toluene extracts afforded 2,2-bis-(*p*-methoxyphenyl)-propane (305 g), b.p. 212—214°/10 mm Hg.

* All melting and boiling points uncorrected. Petrol refers to the fraction b.p. 40—60°.

4,6-Di-(α,α-dimethylbenzyl)pyrogallol (V). Pyrogallol (252 g) was dissolved in glacial acetic acid (600 ml) and conc. sulphuric acid (25 ml) in a 4 l beaker and cooled in ice water. A solution of α-methylstyrene (570 g, 20 % excess) in glacial acetic acid (600 ml) was added with stirring during about one hour, the temperature being kept below 15°. Stirring was continued for an additional half hour and the mixture allowed to stand overnight. The resulting solid cake was crushed, stirred with water (1 l), and the crystalline product collected. It was washed free from acid and air dried. Crystallisation from ligroin afforded an almost quantitative yield of glistening needles melting at 118—120°. Repeated crystallisations raised the melting point to 120—121°. (Found: C 79.7; H 7.06. $C_{24}H_{26}O_3$ requires: C 79.5; H 7.23.)

The *triacetate*, prepared with acetic anhydride in pyridine, crystallised in large, rhombic plates, m.p. 138—139°. (Found: C 74.0; H 6.56. $C_{30}H_{32}O_6$ requires: C 73.7; H 6.60.)

4,6-Di-(α,α-dimethyl-p-methoxybenzyl)pyrogallol (VI). Crude α,α-dimethylbenzyl alcohol was prepared [14] by refluxing methylmagnesium bromide (from 163 g of magnesium and 610 g of methyl bromide) in absolute ether (1 l) with methyl anisate (500 g) dissolved in absolute ether (1.5 l) for 24 hours, addition of saturated ammonium chloride solution and extraction of the carbinol with ether. After drying (Na_2SO_4) and removal of the solvent on the water bath, the last traces being removed under reduced pressure, a faintly yellowish oil (495 g) was obtained. It was dissolved in glacial acetic acid (500 ml) and added with stirring to a solution of pyrogallol (200 g) in glacial acetic acid (500 ml) and conc. sulphuric acid (50 ml) the temperature being kept below 15°. The mixture was set aside overnight and then treated with water (3 l) and the product collected by filtration and washed free from acetic acid. After drying it was crystallised from ethanol in needles, m.p. 158—161°. Yield 460 g (73 % calculated on methyl anisate). Repeated crystallisation raised the melting point to 163—163.5°. (Found: C 74.0; H 7.00; CH_3O 14.8. $C_{26}H_{30}O_5$ requires: C 73.9; H 7.16; CH_3O 14.7.) The *triacetate* was prepared with acetic anhydride in pyridine and crystallised from benzene-petrol (1 : 4). It separated in fine needles, m.p. 122—123°, or coarse rhombic prisms, the latter melting at 143—145°. (Found: CH_3O 11.2. $C_{32}H_{36}O_8$ requires: CH_3O 11.3.)

Ethyl α-oxo-β-phenylisovalerate from 4,6-di-(α,α-dimethylbenzyl)pyrogallol. The finely powdered pyrogallol derivative (300 g) was added to a stirred solution of sodium hydroxide (100 g) in water (3 l) immediately followed by powdered potassium permanganate (150 g). Additional permanganate (500 g) was added in portions over two hours. The temperature of the mixture rose to 60—70°, and further increase was prevented by addition of ice. Stirring was continued overnight, and excess permanganate destroyed with ethanol. The manganese sludge was removed by filtration (a layer of silicious earth nearest the filter paper effectively aided filtration) and thoroughly washed with hot water containing a little sodium hydroxide. The filtrate was acidified and extracted five times with ether. The combined ethereal extracts were in turn extracted with saturated sodium bicarbonate solution. The ether raffinate was evaporated and the residual solid crystallised from benzene-petrol (1 : 2) and from ethanol yielding a colourless compound (21 g) m.p. 174—175°. The bicarbonate extracts were acidified and the precipitated oil extracted with ether, dried (Na_2SO_4), and the ether removed yielding an oil (171 g). This was refluxed overnight with absolute ethanol (400 ml) containing sulphuric acid (25 ml). Most of the alcohol was removed on the water bath at reduced pressure, and the residual liquid poured into water. The oil, which separated, was taken up in ether, washed with water, with sodium bicarbonate solution and again with water, and dried. The ether was removed and the residual oil fractionated yielding a fore-run boiling at 60—140°/12 mm Hg, from which α-phenyl*iso*butyric acid, m.p. and mixed m.p. 78°, (24 g) was isolated after alkaline hydrolysis. The main fraction (118 g) boiled at 140—144°/12 mm Hg, and consisted of almost pure ethyl *α-oxo-β-phenylisovalerate.* (Found: C_2H_5O 20.2. $C_{13}H_{16}O_3$ requires: C_2H_5O 20.5).

The bicarbonate extract was acidified giving an oil, which crystallised. The product was recrystallised from benzene-petrol (1 : 1) and from ethanol. Colourless needles, m.p. 185—186° (15 g).

Ethyl α-oxo-β-phenylisovalerate and α-phenylisobutyric acid from p-(α,α-dimethylbenzyl)-phenol. p-(α,α-Dimethylbenzyl)phenol (212 g) was dissolved in water (2 l) containing sodium hydroxide (50 g), and oxidized with potassium permanganate (800 g), added in portions over 3 hours to the stirred solution. After stirring overnight the mixture was worked up as described for the oxidation of 4,6-di-(α,α-dimethylbenzyl)pyrogallol. The

yield of ethyl α-oxo-β-phenyl*iso*valerate was 18 g, and that of α- phenyl*iso*butyric acid 15 g.

α-Oxo-β-(p-methoxyphenyl)isovaleric acid from impure 2,2-bis-(p-hydroxyphenyl)-propane monomethyl ether. The ether mixture containing 60 % monomethylether (400 g) was dissolved in a solution of sodium hydroxide (100 g) in water (5 l) and oxidized with powdered potassium permanganate (2500 g), added in portions over 4 hours, the temperature being kept below 80°. The mixture was stirred overnight and worked up as described for the oxidation of 4,6-di-(α,α-dimethylbenzyl)pyrogallol. An ester mixture (78 g) boiling at 150—190°/12 mm Hg was obtained. It was shaken for 45 minutes with 2 *N* sodium hydroxide (250 ml), the undissolved oil extracted with ether, and the alkaline solution acidified with dilute sulphuric acid. The oil, which separated was taken up in ether, washed and dried. On removal of the ether an oil, which crystallised, was obtained (42 g). M.p. 70—74°. Crystallisation from benzene-petrol (1:1) raised the melting point to 79—79.5°. (Found: CH_3O 13.8; equiv. weight 222. $C_{12}H_{14}O_4$ requires: CH_3O 14.0; eguiv. weight 222.2.)

From the ether extracts containing unhydrolysed material α-(p-methoxyphenyl)-*iso*butyric acid (20 g) was isolated after further hydrolysis. M.p. 89—90° underpressed by a specimen prepared from α-p-(methoxyphenyl)*iso*butyronitrile [18].

α-Oxo-β-(p-methoxyphenyl)isovaleric acid from 4,6-di-(α,α-dimethyl-p-methoxybenzyl)-pyrogallol. 4,6-Di-(α,α-dimethyl-p-methoxybenzyl)pyrogallol (400 g) was suspended in a stirred solution of sodium hydroxide (100 g) in water (3,5 l) and oxidised with powdered potassium permanganate (770 g) added in portions at such a rate, that the temperature was kept below 70°. Stirring was continued for three hours after all the permanganate had been added, the solution was decolourised by addition of a little ethanol, and the mixture was worked up as described above for the unmethoxylated compound. Careful fractionation of the ester mixture yielded a fore-run from which α-(p-methoxyphenyl)-*iso*butyric acid (25 g) was obtained after hydrolysis, and a fraction b.p. 168—172°/12 mm Hg consisting of almost pure *ethyl α-oxo-β-(p-methoxyphenyl)isovalerate* (157 g). (Found: CH_3O + C_2H_5O 30.0. $C_{14}H_{18}O_4$ requires: CH_3O + C_2H_5O 30.4.) No attempt was made to isolate other products from the oxidation.

α-Oxo-β-phenylisovaleric acid. The above ethyl ester (73 g) was shaken with 2 *N* sodium hydroxide (250 ml) until the mixture became homogenous (15 minutes). The liquid was washed twice with ether and acidified. The precipitated oil was taken up in ether, washed and dried. Removal of the ether yielded an oil (62.3 g) which partially crystallised. A sample of the crystals were collected and carefully washed with very little, cold petrol. After drying they melted sharply at 27—28°. (Found: equiv. weight 197. $C_{11}H_{12}O_3$ requires: equiv. weight 192.2) Crystallised from very little petrol they melted sharply at 40.5—41°. (Found equiv. weight 195.) The low melting form on storing was converted to the high melting one and the former was not observed in subsequent preparations of the acid.

α-Oximino-β-phenylisovaleric acid. The crude keto acid (57.6 g) was dissolved in 7.5 % aqueous sodium hydroxide (150 ml). Hydroxylamine hydrochloride (28 g) in a little water was added followed by solid sodium carbonate (40 g) in small portions. The mixture was warmed on the water bath for 3 hours, diluted with water (200 ml) and acidified. After storing in a refrigerator the solid was collected and crystallised from benzene-petrol (1 : 1). Yield 90 %. M.p. 123—123.5°. (Found: N 6.73; equiv. weight 208. $C_{11}H_{13}NO_3$ requires: N 6.76; equiv. weight 207.2.)

α-Oximino-β-(p-methoxyphenyl)isovaleric acid. This substance was prepared exactly as described for the unmethoxylated compound and crystallised from aqueous ethanol. M.p. 151°. (Found: N 5.87; CH_3O 13.0; equiv. weight 239. $C_{12}H_{15}NO_4$ requires: N 5.90; CH_3O 13.1; equiv. weight 237.2).

D,L-*α-Amino-β-phenylisovaleric acid,* "D,L-*neophenylalanine*" *(I).* α-Oximino-β-phenyl*iso*valeric acid (5 g) was dissolved in absolute ethanol (80 ml) and acidified with very little lactic acid (sp.g. 1.24). Sodium amalgam (200 g, 2 %) was added in portions over one hour, the mixture being kept faintly acid to lithmus by addition of lactic acid. After four hours the reaction was considered complete. The clear liquid was decanted, the mercury was washed with hot ethanol, and the solution concentrated in a vacuum. It was then diluted with water to 75 ml and stored overnight in a refrigerator. The crystalline product was filtered and washed free from salts. Yield 3.3 g. The product was purified by dissolving it in dilute hydrochloric acid and adjusting the pH to 6 by the

addition of ammonia. For analysis it was crystallised from water. It decomposed without melting at about 240°. (Found: C 68.5; H 7.85; N 7.19. $C_{11}H_{15}NO_3$ requires: C 68.4; H 7.83; N 7.25). The *N-acetylderivative* was prepared with acetic anhydride in 2 *N* sodium hydroxide, and crystallised from water forming clusters of hard prisms, m.p. 178—179°. (Found: N 5.97; equiv. weight 233. $C_{13}H_{17}NO_3$ requires: N 5.95; equiv. weight 235.3.)

D,L-α-*Amino-β-(p-methoxyphenyl)-isovaleric acid.* The reduction was carried out as described for *neo*phenylalanine above. As the methoxyderivative was rather soluble in the aqueous solution of sodium lactate obtained, some additional material could be obtained from the mother liquor by acidification with sulphuric acid, continuous extraction of the lactic acid with ether and then adjustment of the pH to 6 with ammonia. Total yield of acid, purified by dissolution and reprecipitation, 45—55 %. For analysis it was crystallised from water. It decomposed without melting at about 220°. (Found: N 6.25; CH_3O 13.7. $C_{12}H_{17}NO_3$ requires: N 6.27; CH_3O 13.9.)

D,L-α-*Amino-β-(p-hydroxyphenyl)isovaleric acid,* D,L-"*neotyrosine*" *(II).* The methyl ether (8 g) was refluxed (oil bath) for three hours with 48 % hydrobromic acid (40 ml). Most of the hydrobromic acid was removed on the water bath at reduced pressure, and the aminoacid precipitated by adjusting the pH to 6 with ammonia. After storing overnight in a refrigerator the crystalline product was collected and washed free from inorganic material. It was purified by reprecipitation. The yield was almost quantitative. For analysis it was crystallised from water. It decomposed without melting at about 245°. (Found: C 63.0; H 7.11; N 6.69. $C_{11}H_{15}NO_3$ requires: C 63.2; H 7.23; N 6.69.) The *N-acetylderivative* crystallised in clusters of hard prisms, m.p. 181—181.5°. (Found: N 5.54, 5.57; equiv. weight 253. $C_{13}H_{17}NO_4$ requires: N 5.58; equiv. weight 251.2.)

D,L-α-*Amino-β-(3,5-diiodo-4-hydroxyphenyl)-isovaleric acid,* D,L-"*neoiodogorgoic acid*" *(III).* D,L-*Neo*tyrosine (7.6 g) was dissolved in acetic acid (30 ml). A solution of iodine monochloride (15 g) in acetic acid (30 ml) was added and the mixture heated on a water bath for half an hour. Most of the acetic acid was removed under reduced pressure, and water and a little sodium hydrogen sulphite added. After filtration the aminoacid was precipitated by adjusting the pH to 6 with ammonia. It was purified by dissolving it in ammonia, treating with decolorising carbon, and adjusting to pH 6 with acid. (Precipitated from acid with ammonia it tended initially to from an oil, which rapidly crystallised.) For analysis it was crystallised from water as a heavy faintly yellow, microcrystalline powder, which decomposed without melting at about 205°. (Found: I 54.7; N 3.12, 3.09. $C_{11}H_{13}I_2NO_3$ requires: I 55.0; N 3.04.)

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