

III

N 5.81; Cl 14.5. C₁₂H₁₈ClNO₂ requires: N 5.75; Cl 14.6).

The *picrate* was obtained by addition of a hot, saturated solution of picric acid to an aqueous solution of the ester hydrochloride. Yellow needles from aqueous ethanol, m.p. 147–148°. (Found: C 49.7; H 4.60; N 12.8. C₁₈H₂₀N₄O₈ requires: C 49.6; H 4.62; N 12.8).

Calcium (+)-α,α-dimethylpanthothenate. Benzyl α,α-dimethyl-β-alaninate hydrochloride (15 g) in water (25 ml) was made strongly alkaline with 6 N sodium hydroxide solution. The free amino acid ester was immediately extracted with ether, washed and dried (K₂CO₃). Evaporation of the ether yielded the benzyl ester as a colourless oil (12 g). (–)-Pantholactone (10 g, [α]_D²⁰ –50.5°, water, c 2%) was added, and the mixture was heated on the water bath for 5 hours. It was then diluted with water (50 ml), acidified with 2 N hydrochloric acid to pH 1–2 and repeatedly extracted with ether. The combined extracts were washed with two 20 ml portions of 2 N sodium hydroxide and then with water. After drying (Na₂SO₄) and removal of the ether, a colourless, sticky oil (13.5 g) was obtained. This was dissolved in glacial acetic acid (50 ml), palladium on charcoal (2 g, 10%) added and the mixture shaken in an atmosphere of hydrogen for 5 hours. The catalyst was filtered off and the solution evaporated *in vacuo* on a water bath. A colourless syrup was obtained, which could not be induced to crystallise. It was dissolved in acetone (75 ml), filtered from a small amount of solid and evaporated to dryness *in vacuo*. The syrup was dissolved in water (300 ml), stirred for 2 hours with an excess of calcium carbonate, filtered, and continuously extracted with ether overnight. The aqueous solution was evaporated to dryness *in vacuo* at 40° and yielded a glass. This was dissolved in methanol (75 ml) and the solution was filtered and evaporated to dryness giving a white solid (5.0 g). This solid was purified by dissolution in methanol (50 ml), pouring into acetone (500 ml, reagent grade), storing overnight in a refrigerator, filtering off a small amount of precipitated material, and evaporation to dryness. The solid salt thus obtained was ground with little acetone (20 ml), filtered off, and washed with a little acetone and with ether. Yield 4.2 g, [α]_D²⁰

+ 27.2° (water, c 0.44%). The product contained one mole of water of crystallization. (Found: C 48.0; H 7.81; Ca 7.37. CaC₁₂H₁₆N₂O₁₀ · H₂O requires: C 48.0; H 7.69; Ca 7.28). The water could be removed by prolonged heating at 120° in high vacuum. (Found: H₂O (by loss of weight) 3.2%. Calculated: 3.3%).

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1. Jönsson, Å. *Acta Chem. Scand.* **8** (1954) 1203.
2. Kuhn, R. and Wieland, Th. *Ber.* **73** (1940) 972.
3. Brit. pat. 601.142 *Chem. Abstracts* **42** (1948) 8818.

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Studies on Antimetabolites

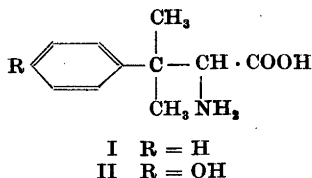
V. Improved Reduction of α-Oximino-β-phenylisovaleric Acids *

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The demand for relatively large amounts of "neophenylalanine" (I) and "neotyrosine" (II) for physiological tests prompted a reinvestigation of the reactions leading to these compounds in order to improve the yields. A detailed study of the reduction of the intermediate α-oximino acids showed that the use of anhydrous ethanolic hydrogen chloride instead of the lactic acid previously used¹ to control the pH in the reduction with sodium amalgam

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gave considerably improved yields of the amino acids. This appeared to be due partly to decreased side reactions leading to nitrogen-free products and partly to easier isolation of the amino acids. Reaction temperature, pH and area of amalgam appeared to be the main factors determining the yields. It was found that at high temperatures (near the boiling point of the mixture) much nitrogen-free material was formed. At room temperature, this side reaction was depressed but the reduction was very slow. At high pH-values (above 7) much nitrogen was lost as ammonia. A large ratio of amalgam area/mole oximinocompound is essential in order to decrease the time required for the reaction, but the high ratio must not be produced by stirring the mixture, since this results in drastically decreased yields (probably by destruction of the molecular orientation at the amalgam surface). By following closely the directions given in the experimental part, it was possible to increase the yield of neophenylalanine to 80–90% and that of neotyrosine methyl ether to 70–75%.

In addition to neotyrosine methyl ether, α -hydroxy- β -(*p*-methoxyphenyl)isovaleric acid could be isolated from the reaction mixture in about 10% yield. In the reaction mixture from the reduction of α -oximino- β -phenylisovaleric acid, there was also found some nitrogen-free acid material, probably α -hydroxy- β -phenylisovaleric acid, but this fraction could not be induced to crystallise and was not further investigated.

Experimental: The oximinoacid (0.1 mole) was added to 2% sodium amalgam (750 g) covered with commercial absolute ethanol (300 ml) in an Erlenmeyer flask of one liter capacity (bottom diameter about 12 cm). Approximately 7 *N* absolute ethanolic hydrogen chloride was added dropwise from a buret to keep the mixture just acid to *p*-bromocresol green (determined by placing a drop of the liquid on a strip of filter paper moistened with a 1% solution of the indicator). About 75–85 ml acid was required. The temperature of the reaction mixture was kept at 40–50°

by appropriate cooling or heating in a water bath. When the reaction ceased, which was indicated by a slowing up and ceasing of the consumption of acid, *N* aqueous hydrochloric acid was added to dissolve the solid precipitate. The solution was separated from the mercury, filtered, evaporated to about 100 ml on the water bath, saturated with hydrogen sulphide, filtered, and the pH adjusted to 6–6.5 by careful addition of ammonia. After storing overnight in the refrigerator the amino acid was filtered off, washed in turn with icecold water (50 ml), acetone (50 ml) and ether (150 ml). The yield of neophenylalanine was 80–90% and that of neotyrosine methyl ether 70–75%.

*α -Hydroxy- β -(*p*-methoxyphenyl)isovaleric acid.* The combined mother liquors and washings from the reduction of a total of 120 g of α -oximino- β -(*p*-methoxyphenyl)isovaleric acid were acidified to pH 1–2 with hydrochloric acid and repeatedly extracted with ether. The extract on evaporation yielded a solid (17.5 g), which was repeatedly crystallised from water. Colourless plates, m.p. 127–128°. (Found: C 64.8; H 7.4; CH₃O 13.6. C₁₂H₁₆O₄ requires: C 64.3; H 7.2; CH₃O 13.8).

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1. Jönsson, Å. *Acta Chem. Scand.* **8** (1954) 1203.

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Synthetic Plant Hormones

VI. Preparation of some α -Phenoxy and α -1-Naphthoxy fatty Acids* (Addition to Part IV)

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Some further α -aryloxy fatty acids have been prepared in addition to those reported in Part IV¹ of this series, for investigation of their plant growth activity. All the acids were prepared by condensation of the appropriate sodium phenoxide with the ethyl ester of the α -chloro fatty acid. Physical data for the acids not previously

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