hours. Crude III obtained in 13% yield (0.56 g.) was evaporatively distilled to give a purer product (0.28 g., 6.5%), from which a *picrate, ca.* 1 g. soluble in 100 cc. of boiling benzene, was obtained, m. p. 140–143° (on recrystallization, m. p. 143–144°). Occasionally a rapidly cooled benzene solution of the picrate deposited fluffy needles which gradually changed to heavier needles.

Treatment of III with dry hydrogen chloride gave an oil which was miscible with water and cold ethanol in contrast to the report of Iddles, *et al.*[20] A filtered solution of the dried, crude hydrochloride in acetone deposited on concentration prismatic needles of a deliquescent hydrochloride, m. p. 118–120°. Iddles[20] reported a water-insoluble hydrochloride, m. p. 114–115°.

In a different preparation, 5.0 g. of β-pyridylmethylcarbinol (XX) was converted to α-(3-pyridyl)-ethyl chloride hydrochloride (XXI) with 10 cc. of purified thionyl chloride.[26] After removal of excess reagent *in vacuo*, addition of water, and filtration with the aid of charcoal, the red solution was evaporated to dryness, treated with absolute ethanol, and evaporated to dryness again. After several recrystallizations from dry acetone colorless XXI was obtained; m. p. 109–110°; deliquescent; easily sublimable.

A mixture of 2.60 g. of crude XXI and 4 cc. of trimethylamine[27] in methanol was heated ten hours in a sealed tube at 125°. A solution of the solvent-free residue in 8% sodium hydroxide was thrice extracted with ether (0.66 g. removed). After the addition of sufficient sodium hydroxide to raise the concentration to 30–40%, the solution of the quaternary salt XXII was boiled, 0.70 g. of crude III being extractable from the steam distillate with ether. Evaporative distillation gave 0.58 g. of purer III (38% yield).

The *picrate* of this sample crystallized from benzene, m. p. 146.5–147.5°; m. p. 143–145° in admixture with the picrate prepared above according to Iddles, *et al.*[20]

Anal. Calcd. for $C_{13}H_{10}O_7N_4$: C, 46.71; H, 3.02; N, 16.75. Found: C, 46.67; H, 3.10; N, 16.71.

The *hydrochloride* was identical with III hydrochloride prepared above according to Iddles[20] (mixed m. p. 119–121°).

The *mercurichloride* of III was crystallized from absolute ethanol; darkened but did not melt when heated to 250°. Iddles reported m. p. 145–150°.

In another preparation of III *via* XXII in which inadequately purified trimethylamine was used, the large amount of oil extracted from the alkaline solution of the reaction product was evaporatively distilled at 60° and 25 mm., 2.68 g. of *α-(3-pyridyl)-ethyldimethylamine* being obtained from 5.00 g. of XX.

The *monopicrate* crystallized from water; m. p. 147–148°; mixed m. p. with III picrate, 130–180°.

Anal. Calcd. for $C_{15}H_{17}O_7N_5$: C, 47.49; H, 4.52; N, 18.46. Found: C, 47.76; H, 4.85; N, 18.13.

The *dipicrate*, very sparingly soluble in organic solvents, crystallized from water (1 g./100 cc.); m. p. 223–224°.

Anal. Calcd. for $C_{21}H_{20}O_{14}N_8$: C, 41.45; H, 3.31. Found: C, 42.16; H, 3.66.

The deliquescent *monohydrochloride* crystallized from absolute ethanol in large prismatic needles, m. p. 220–221°.

Anal. Calcd. for $C_9H_{13}N_2Cl$: N, 15.01; Cl, 18.95. Found: N, 15.08; Cl, 18.50.

After having been shaken with a saturated solution of aqueous sodium bisulfite for one hour, 300 mg. of III was recovered in 78% yield as the picrate (740 mg.).

Summary

In accordance with resonance theory, 2- and 4-vinylpyridines react with a variety of electron donating reagents. 3-Vinylpyridine fails to react with sodium bisulfite.

NEW YORK 27, N. Y. RECEIVED APRIL 10, 1947

(26) Cottle, THIS JOURNAL, **68**, 1380 (1946).

(27) Trimethylamine was purified by treating with phenyl isocyanate.

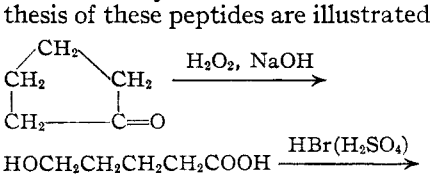
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Prolyl and Phthalyl Derivatives of Enantiomorphs of Valine and Leucine[1,2]

BY MARGUERITE FLING,[3] FREDERICK N. MINARD[4] AND SIDNEY W. FOX

The present report concerns the preparation of derivatives of D- and L-amino acids. Gramicidin[4a] and penicillin[5] have been shown to be derivatives of D-amino acids; D-amino acids inhibit bacterial growth under experimental conditions,[6–8] and the D-amino acid residue is one of a number of critical structural features in penicillin.[9] Attempts to synthesize some powerful D-amino acid derivatives as conceivable models of antibiotics are therefore of interest.

Partly since gramicidin contains no free primary amino groups,[10] prolyl derivatives of D- and L-forms of valine and leucine were prepared. These were obtained by the same general procedure employed by Fischer and Suzuki,[11] except that the necessary α,δ-dibromovaleric acid was made by a more direct synthesis. The reactions for the synthesis of these peptides are illustrated below.



(1) Journal Paper No. J-1458 of the Iowa Agricultural Experiment Station, Project 897, in coöperation with the Veterinary Research Institute, and Project 980.

(2) Taken in part from the thesis submitted by Marguerite Fling to the Graduate School of Iowa State College in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(3) Present address: William G. Kerckhoff Laboratories of the Biological Sciences, California Institute of Technology, Pasadena, Calif.

(4) Upjohn Company Fellow.

(4a) Lipmann, Hotchkiss and Dubos, *J. Biol. Chem.*, **141**, 163 (1941).

(5) Committee on Medical Research, O. S. R. D., Washington, and the Medical Research Council, London, *Science*, **102**, 627 (1945).

(6) Fox, Fling, and Bollenback, *J. Biol. Chem.*, **155**, 465 (1944).

(7) Fling and Fox, *ibid.*, **160**, 329 (1945).

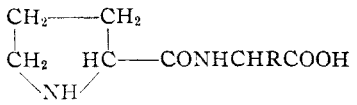
(8) Fox, Fling, Kobayashi and Minard, *Proc. Fed. Am. Soc. Exp. Biol.*, **6**, 253 (1947).

(9) du Vigneaud, Carpenter, Holley, Livermore and Rachele, *Science*, **104**, 431 (1946).

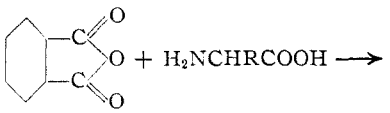
(10) Hotchkiss, *J. Biol. Chem.*, **141**, 171 (1941).

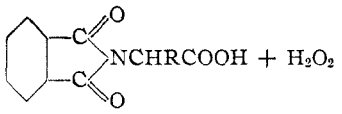
(11) Fischer and Suzuki, *Ber.*, **37**, 2842 (1904).

$$BrCH_2CH_2CH_2CH_2COOH \xrightarrow{Br_2(P_4)} BrCH_2CH_2CH_2CHBrCOOH \xrightarrow{PCl_5} BrCH_2CH_2CH_2CHBrCOCl \xrightarrow{H_2NCHRCOOH,\ NaOH} BrCH_2CH_2CH_2CHBrCONHCHRCOOH \xrightarrow{NH_4OH}$$



Because of the structural feature, —CONR-CHR_1COOH ($R \neq H$), common to both penicillin and to phthalyl amino acids, a series of these latter was prepared by the method of Reese.[12]





Of the compounds described in the present paper, none exhibited the antipodal specificity found for the amino acids tested on *Lactobacillus arabinosus*[6,7] and *Escherichia coli*[13] or for the formyl valines.[13] The most active compounds in the present groups were the phthalyl valines and phthalyl leucines, which were all antibacterial at about 3 mg. per cc., when tested as the sodium salts, by serial dilution in yeast extract medium.

TABLE I

PROLYL AMINO ACIDS

Peptide	Yield, %	M. p.,[a] °C.	Nitrogen, % Calcd.	Found	$[\alpha]^{28}D$ in water
Prolyl-D-valine	10	220	13.1	13.0	+57 ± 6°
Prolyl-L-valine	10	221	13.1	12.9	−58 ± 5°
Prolyl-D-leucine	14	225	12.3	12.3	+57 ± 6°
Prolyl-L-leucine	14	228	..	..	−54 ± 6°
Prolyl-L-leucine of Abderhalden and Sickel[17]	20	231	12.3	12.0	−48 ± 2° (at 20°)

[a] First four melting points uncorrected.

TABLE II

PHTHALYL AMINO ACIDS

Compound	Yield, %	M. p.,[a] °C.	Nitrogen, % Calcd.	Found	Neut. equiv. Calcd.	Found	$[\alpha]^{27}D$ in abs. EtOH
Phthalyl-D-valine	47	113–114	5.67	5.76	247	248	+69.0 ± 0.9°
Phthalyl-L-valine	69	114–115	5.67	5.78	247	247	−68.5 ± 1.0°
Phthalyl-D-leucine	83	118–119	5.36	5.52	261	261	+22.8 ± 1.0°
Phthalyl-L-leucine	62	118–119					−22.1 ± 1.0°
Phthalyl-L-leucine of Reese[12]	Not given	115–116	5.36	5.66 5.58			−21.9 (temp. not given)

[a] First four melting points uncorrected.

Experimental

δ-Bromo-*n*-valeric Acid.—The procedure of Westerfeld[14] for the oxidation of cyclopentanone was modified, and the resultant sodium δ-hydroxyvalerate converted to the bromoacid directly.

Ninety-eight grams of freshly distilled cyclopentanone[15] (b. p. 126–128°) was added in portions alternately with portions of 300 cc. of 30 volume per cent. hydrogen peroxide (Merck Superoxol) to 600 cc. of 2 *N* sodium hydroxide solution, with stirring. The oxidation was maintained at 35–45° by cooling the reaction vessel in ice. Stirring was continued until frothing ceased. The clear liquid was concentrated under reduced pressure.

The white gelatinous residue was dissolved in 100 cc. of 48% hydrobromic acid solution and a further 30 cc. of hydrobromic acid solution plus 100 cc. of concentrated sulfuric acid were added. The combined mass was refluxed for four hours, cooled, poured into 1 liter of water, and extracted twice with ether. The aqueous liquid was saturated with ammonium sulfate and the upper layer added to the ether extract. The aqueous layer was next extracted six times more with ether, and the ethereal extracts combined. The combined extract was washed with a saturated solution of ammonium sulfate, and dried with Drierite. The ether was removed, and the residue distilled at 3 mm. The main fraction was redistilled at 114–119° at 2–3 mm. to give 37.8 g. of bromoacid (18% for the over-all preparation from the ketone).

α,δ-Dibromo-*n*-valeric Acid.—The procedure of Merchant, Wickert and Marvel[16] was followed with modifications. Fifty-four g. of δ-bromovaleric acid reacted with 19.5 cc. of dry bromine and 0.55 g. of red phosphorus for four hours at 120°. The reaction mixture gave on distillation 62.5 g. boiling 125–145° (2–3 mm.). Redistillation gave 42.5 g. (55%) boiling at 135–142° (2–3 mm.).

α,δ-Dibromo-*n*-valeryl Chloride.[11]—Phosphorus pentachloride was added to 42.5 g. of α,δ-dibromovaleric acid in a Claisen flask until no more reaction occurred. The mixture was then distilled at the water pump, and 40 g. of distillate boiling at 125–135° was collected.

Prolyl-amino Acids.—The procedure of Abderhalden and Sickel[17] which these authors employed for prolyl-L-leucine was used with L-leucine,[8] D-leucine,[6] L-valine[7] and D-valine.[7] The yields and physical constants of the products are presented in Table I.

Phthalyl-amino Acids.—A mixture of 0.0077 mole of phthalic anhydride and 0.0077 mole of the amino acid[6,7] was heated in an oil-bath at 150° until frothing ceased. The light brown mass, which hardened on cooling, was extracted with boiling ether. Hexane was added to the filtered ether extracts until turbidity persisted. The precipitate was filtered after the mixture stood five hours and was then recrystallized from about 75 parts of cyclohexane. The yields and physical constants of the products are presented in Table II.

Summary

The preparation of prolyl and phthalyl derivatives of D- and L-valine and D- and L-leucine is described.

AMES, IOWA RECEIVED JUNE 2, 1947

(12) Reese, *Ann.*, **242**, 9 (1887).

(13) Kobayashi, Bollenback and Fox, unpublished experiments.

(14) Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942).

(15) Thorpe and Kon, "Organic Syntheses," Coll. Vol. I, 187 (1932).

(16) Merchant, Wickert and Marvel, THIS JOURNAL, **49**, 1829 (1927).

(17) Abderhalden and Sickel, *Z. physiol. Chem.*, **159**, 166 (1926).