As mentioned above, there was a striking difference in the melting points of the synthetic (racemic) compound and of the natural (levorotatory) one. One further difference in the two compounds, and one which contributed to the delay in verifying the biosynthetic scheme of Strassman and co-workers, was the difference observed in the ability of the two compounds to support growth of *S. typhimurium*, strain *leu*-120. In the auxanographic tests using minimal agar seeded with this strain, the racemic compound appeared to be only about one eighth as active as the naturally occurring compound. Preliminary experiments indicate that the enzymatic basis for this difference may be accounted for by the fact that the unsaturated isomer is an inhibitor of the second (isomerization) step in the pathway. For example, when isomerase activity in an *S. typhimurium* extract was measured with a mixture of the racemic and the levorotatory compound as the substrate, the rate was only 30% of the rate observed when the levorotatory compound alone was used as the substrate. This phenomenon as well as the subsequent steps in the pathway are currently being further investigated in both laboratories.

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The α-Amino-ω-Hydroxamino Acids*

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The DL-α-amino-ω-hydroxamino acids corresponding to ornithine and lysine, DL-2-amino-5-hydroxaminopentanoic acid and DL-2-amino-6-hydroxaminohexanoic acid, respectively, have been prepared from the 5-(ω-bromoalkyl)-hydantoins *via* the corresponding nitro- and hydroxaminohydantoins. A procedure is reported for the isolation of L-2-amino-5-hydroxaminopentanoic acid from ferrichrome A. All three amino acids were obtained as the crystalline mono-2-nitro-1,3-indanedione salts. A new synthesis of DL-2-amino-5-hydroxypentanoic acid based on lithium borohydride reduction of glutamic hydantoin-γ-methyl ester has been described.

The two α-amino-ω-hydroxamino acids corresponding to ornithine and lysine occur in nature. In a pioneering investigation, Snow (1954) isolated and characterized the lysine analog from the growth factor mycobactin. Recently, δ-*N*-hydroxyornithine (L-2-amino-5-hydroxaminopentanoic acid) has been found in the ferrichrome series (Emery and Neilands, 1961) and in the antibiotic albomycin (Turková *et al.*, 1962). In each instance the amino acid was found to be of the L configuration.

It will be the purpose of the present communication to describe the chemical synthesis of the ω-*N*-hydroxy analogs of lysine and ornithine, namely, DL-2-amino-6-hydroxaminohexanoic acid and DL-2-amino-5-hydroxaminopentanoic acid respectively. The preparation of the former compound in microgram amounts has already been reported (Emery and Neilands, 1961).

While it might seem feasible to approach the synthesis of these substances by direct, selective oxidation of the parent diamino acids, no general method has been described that would enable such a reaction. In fact, inspection of the literature reveals that virtually all successful syntheses of alkyl hydroxylamines have involved reduction of the analogous nitro compounds with zinc dust in water. The nitro compounds can be obtained from the corresponding bromo compounds, but in order to apply this reaction in the present instance it would be necessary to block the α-amino function so as to avoid cyclization. Fortunately, two appropriately substituted bromo compounds have already been reported. In 1948 Gaudry described the preparation of 5-(4′-bromobutyl)-hydantoin from 2,3-dihydropyran and subsequently the same author (Gaudry, 1951) reported the synthesis of 5-(3′-bromopropyl)-hydantoin from 2,3-dihydrofuran. We have found it possible to convert these bromo compounds into the desired products in modest yield *via* the route shown in Figure 1. The nitro compounds, Va, Vb, and hydrochlorides of the end-products, VIIa, VIIb, could not be crystallized. The latter, however, crystallized readily as the mono-

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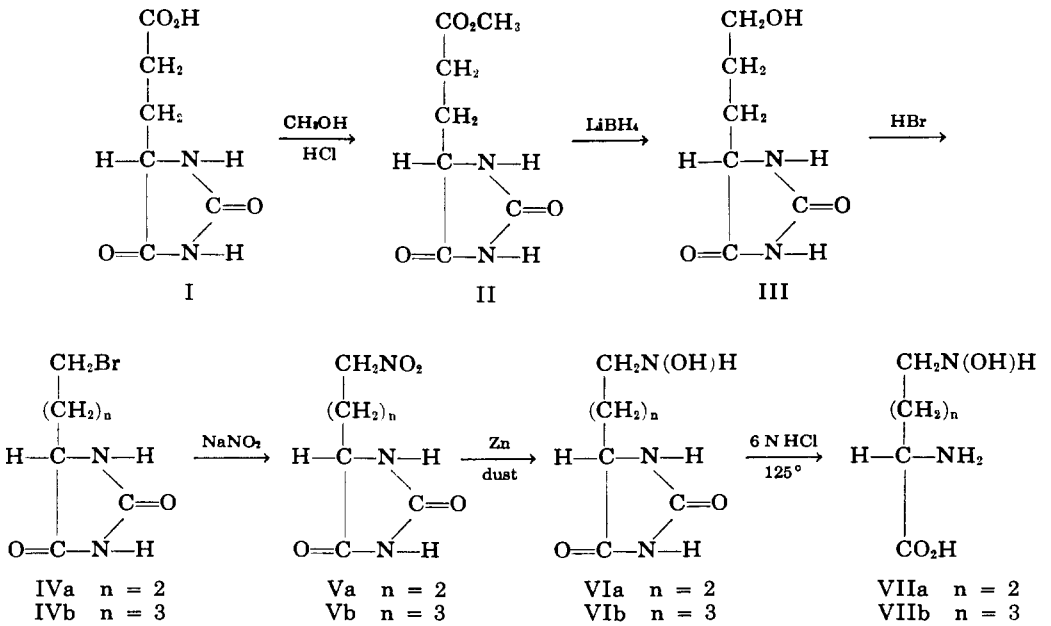

FIG. 1.—Reaction scheme for preparation of the DL-α-amino-ω-hydroxamino analogs of ornithine and lysine.

I DL-5-(2′-carboxyethyl)-hydantoin
II DL-5-(2′-carbomethoxyethyl)-hydantoin
III DL-5-(3′-hydroxypropyl)-hydantoin
IVa DL-5-(3′-bromopropyl)-hydantoin
IVb DL-5-(4′-bromobutyl)-hydantoin
Va DL-5-(3′-nitropropyl)-hydantoin
Vb DL-5-(4′-nitrobutyl)-hydantoin
VIa DL-5-(3′-hydroxaminopropyl)-hydantoin
VIb DL-5-(4′-hydroxaminobutyl)-hydantoin
VIIa DL-2-amino-5-hydroxaminopentanoic acid
VIIb DL-2-amino-6-hydroxaminohexanoic acid

nitro-indanedione salt, a reagent introduced for this purpose by Snow (1954).

The preparation of 5-(4′-bromobutyl)-hydantoin from 2,3-dihydropyran in quantity is convenient and has in fact been used for the commercial synthesis of lysine. However, a different situation exists in the preparation of 5-(3′-bromopropyl)-hydantoin from 2,3-dihydrofuran. The latter must be isomerized from 2,5-dihydrofuran. The desired bromo compound could be obtained from 2-amino-5-hydroxypentanoic acid, a relatively rare amino acid which, in addition to the above dihydrofuran-hydantoin procedure, has also been synthesized through alkylation of phthalimidomalonate and by reductive amination of 2-keto-5-hydroxypentanoic acid (see Greenstein and Winitz, 1961, p. 2616). We chose a new and simple route to the hydantoin of this α-amino-ω-hydroxy acid, namely, the metal hydride reduction of the hydantoin of glutamic-γ methyl ester. Since hydantoins are racemized under conditions which are used to form the heterocyclic ring (Brown and Kies, 1959), the starting material selected was DL-glutamic acid.

Under certain circumstances it may be advantageous to isolate the α-amino-ω-hydroxamino acids from natural sources. Thus, when deprived of iron, the smut fungus *Ustilago sphaerogena* accumulates ferrichrome A and it is possible to isolate on the order of 200 mg of the crystalline material per liter of fermentation medium. Ferrichrome A contains about 40% by weight L-2-amino-5-hydroxaminopentanoic acid, and in the present paper we show that it may be obtained from this source in excellent yield. This is in contrast to the chemical synthesis described here, which affords optically inactive products in 16 to 17% yield from the known precursor bromo compounds.

The α-amino-ω-hydroxamino acids are very stable in hot aqueous hydrochloric acid (see Snow, 1954) provided the latter is not grossly contaminated with a metal ion such as iron (Emery and Neilands, 1961); at neutral and alkaline *p*H the hydroxamino function is very rapidly destroyed even at room temperature.

EXPERIMENTAL PROCEDURES AND RESULTS

Materials.—The following materials were reagent grade and were used without further purification: methanol, acetone, petroleum ether (b.p. 60 to 70°), 48% hydrobromic acid, hydrochloric acid, picric acid, 2,3,5-triphenyl-2H-tetrazolium chloride, and ethyl acetate. The tetrahydrofuran, b.p. 65 to 66°, Eastman Chemical Co., was also used without further purification. The dimethyl formamide was distilled over calcium hydride before use. The urea and sodium nitrite used were reagent grade and were pulverized and dried several hours at 100°. The $LiBH_4$, 89% purity, was obtained from Metal Hydrides Inc., Beverly, Mass. The decolorizing charcoal used was Norite A, Matheson-Coleman-Bell. The isopropyl amine hydrochloride was synthesized in the authors' laboratory by the reduction of iso-nitropropane with Zn dust and NH_4Cl in water. The 2-nitro-1,3-indanedione was obtained from the K and K Laboratories, Jamaica, N. Y.

All melting points were measured in capillaries and are uncorrected. Microanalyses were performed by the Chemistry Department, University of California, Berkeley. The apparent dissociation constants (pK_a' values) and neutral equivalents were determined with the Difunctional Recording Titrator (Neilands and Cannon, 1955) in water at 25°. Isolated products were dried *in vacuo* over $CaCl_2$ prior to analysis and characterization.

DL-5-(2′-Carbomethoxyethyl)-hydantoin (II).—A mixture containing 10.0 g (58 mmoles) DL-5-(2′-carboxyethyl)-hydantoin (I, Dakin, 1910) and 5 ml of concentrated HCl in 200 ml of absolute methanol was stirred at room temperature for 12 hours. The solution was then concentrated to an oil by repeated evaporation from absolute methanol. The product was crys-

tallized and recrystallized from acetone-petroleum ether, yielding 10.2 g (55 mmole, 95%) of compound II in colorless prisms with m.p. 76–77°, pK_a of 8.7, and neutral equivalent of 184.5 (theoretical, 186.1).

DL-*5-(3'-Hydroxypropyl)-hydantoin (III).*—Exactly 10.0 g (54 mmoles) of DL-5-(2'-carbomethoxyethyl)-hydantoin (II) was added gradually to a suspension of 2.8 g of 89% pure $LiBH_4$ in 50 ml of ice cold tetrahydrofuran. The mixture was stirred at 37° for 18 to 24 hours, after which the crusty mass was pulverized and refluxed for 2 hours in 20 ml of added tetrahydrofuran. The mixture was then chilled in an ice bath and water and dilute HBr was added in order to decompose excess metal hydride. The solution was repeatedly evaporated to an oil from absolute methanol. Gaudry (1951) has stated that compound III is "difficult to crystallize" and, since we have confirmed this observation, the oil was used directly for the succeeding synthesis. An extensive study has not been made on the conversion of the hydantoin to 2-amino-5-hydroxypentanoic acid; one preparation which was hydrolyzed by the method of Gaudry (1951) gave 1.7 g (12.8 mmoles, 24%) of the neutral amino acid with m.p. 216° with evolution of gas (Gaudry, 1951, gives 215°).

DL-*5-(3'-Bromopropyl)-hydantoin (IVa).*—This was prepared from compound III essentially by the method of Gaudry (1951). To the residue obtained in the preceding synthesis was added 100 ml of 48% HBr, and the solution was heated at 90° for 2 hours and then evaporated to a reddish oil. The latter was dissolved in 75 ml of hot water and the resulting solution neutralized with dilute sodium hydroxide solution. The hot solution was decolorized with charcoal and concentrated to about 50 ml to yield 5.5 g (25 mmoles, 47%) of IVa with m.p. (140°), mixed m.p., infrared spectrum, and other properties identical with those of an authentic sample prepared from 2,3-dihydrofuran (Gaudry, 1951).

DL-*5-(ω-Nitroalkyl)-hydantoins Va and Vb.*—These substances were prepared by the alkyl nitro synthesis introduced by Kornblum *et al.* (1956).

The urea and sodium nitrite were pulverized and dried several hours at 100°, the bromo compounds were dried *in vacuo* for a like period at 80°, and, finally, the dimethyl formamide was recently distilled from calcium hydride.

Exactly 6.4 mmoles of compound IVa or IVb (1.4 g IVa, preceding synthesis; 1.5 g IVb, Gaudry, 1948, and Rogers *et al.*, 1949), 0.75 g urea, and 10 ml of dimethyl formamide were placed in a 50-ml round-bottomed flask suspended in a constant-temperature bath at 30°. A magnetic stirring bar was dropped in, 0.75 g (10.9 mmoles) of $NaNO_2$ was added, the flask was closed with a $CaCl_2$ tube, and the magnetic stirrer was adjusted to gentle agitation. The whole apparatus was protected from strong light by a shield of aluminum foil.

After 2 hours the clear, yellow solution was poured into 15 ml of ice water contained in a 100-ml separatory funnel. The resulting solution was extracted with a total of 150 ml of ethyl acetate in 25-ml aliquots. The combined ethyl acetate extract was transferred to a 0.5-liter separatory funnel, 2 volumes of "high boiling" petroleum ether were added, and the organic layer was extracted with 120 ml of water in 20-ml aliquots. The organic layer was discarded and the water phase then twice extracted with ether in order to remove residual ethyl acetate. The *p*H of the solution was brought to 6.5 by addition of a few drops of 1 N NaOH. The neutral, aqueous solution was evaporated to about 5 ml at a bath temperature of 45° with ice in the condensor compartment of the flash evaporator. The product was obtained as a lemon-yellow oil which displayed the expected physical and chemical properties of a hydantoin with an aliphatic nitro side-chain. It could not be crystallized.

DL-*5-(ω-Hydroxaminoalkyl)-hydantoins VIa and VIb.*—The residue obtained in the preceding synthesis was transferred to a 50-ml round-bottomed flask with the aid of 5 ml of water. After the flask had again been secured in the 30° water bath, 400 mg of isopropylamine hydrochloride and a magnetic stirring bar were added. The stirrer was set for vigorous agitation, and 1.0 g of zinc dust was thrown into the solution over a period of 15 minutes. Stirring was continued for 1 hour, after which time the mixture was diluted with water to about 75 ml and a voluminous precipitate removed by filtration.

The preparation was next purified on columns of Dowex 50 resin, the tetrazolium test (Snow, 1954) serving as a convenient means of detecting the whereabouts of compounds VIa or VIb. The entire batch was passed through a 3 × 3 cm bed of washed sodium form Dowex 50 x 4, 200–400 mesh resin. The filtrate was immediately applied to a 1.5 × 5 cm column of the same resin in the hydrogen form. The filtrate and a water wash were discarded and compounds VIa or VIb were eluted with 1.5 N HCl. The effluent was repeatedly evaporated to dryness from absolute ethanol in order to remove the final traces of moisture and excess HCl. The residue was dissolved in 5 ml of absolute ethanol and the product precipitated as colorless prisms by addition of ether. The yield was 1.2 mmoles (0.25 g VIa; 0.27 g VIb; 19%). For VIa the m.p. was 183–184°, the neutral equivalent was 212.1 (theoretical, 209.6), and the pK_a' values were 5.6 and 9.0. For VIb the m.p. was 149–151°, the neutral equivalent was 224.0 (theoretical, 223.7), pK_a' values were 5.7 and 9.1.

Anal. VIa-hydrochloride. Calcd. for $C_6H_{12}N_3O_3Cl$: C, 34.38; H, 5.77; N, 20.05. Found: C, 34.40; H, 5.64; N, 20.28.

Anal. VIb-hydrochloride. Calcd. for $C_7H_{14}N_3O_3Cl$: C, 37.58; H, 6.31; N, 18.79. Found: C, 37.50; H, 6.46; N, 18.98.

For further characterization, compounds VIa and VIb were reduced to the corresponding amino derivatives and the latter derivatives isolated as the picrate salts (VIc and VId respectively).

To a solution containing 1.00 mmole of compound VIa or VIb (210 mg VIa-hydrochloride; 224 mg VIb-hydrochloride) and 0.05 ml concentrated HCl in 5 ml of water was added 50 mg of PtO_2. Hydrogen gas was bubbled through the mixture for several hours or until the tetrazolium reaction had disappeared. The catalyst was removed by centrifugation, one equivalent of picric acid was added *via* a large volume of water, and the solution was then neutralized and concentrated under reduced pressure. The precipitate, 0.88 mmole [308 mg DL-5-(3'-aminopropyl)-hydantoin picrate, VIc; 320 mg DL-5-(4'-aminobutyl)-hydantoin picrate, VId; 80%], was recrystallized by evaporation from water. For VIc the plates had a m.p. of 230–232° (decomp.), a neutral equivalent of 189.5 (theoretical, 193.1) and pK_a' values of 8.8 and 10.5. For VId the prisms had a m.p. of 189–193° (decomp.; Gaudry, 1948, gives 180–183°), a neutral equivalent of 202.7 (theoretical, 202.2), and pK_a' values of 8.9 and 10.6.

DL-*2-Amino-ω-hydroxamino Acids VIIa and VIIb.*—A solution containing 1.00 mmole of compound VIa or VIb (210 mg VIa-hydrochloride; 224 mg VIb-hydrochloride) in 25 ml of concentrated HCl was heated in a sealed, evacuated Carius tube at 125° for 12 hours. The tube was then opened and the contents several

times evaporated to dryness from water. The residue was dissolved in water and placed on a 2 × 6 cm column of hydrogen form Dowex 50 x 4, 200–400 mesh resin. The column was washed with water and the tetrazolium-positive material eluted with 1.5 N HCl. The solution was concentrated to dryness and the residue dissolved in ethanol. From this solvent the hydrochloride salt of the product could be precipitated as a sirup but crystallization could not be achieved. The entire preparation was hence dissolved in a small volume of water and, after the addition of one equivalent of 2-nitro-1,3-indanedione, the solution was brought to *p*H 4.0–4.2 by dropwise addition of 1 N NaOH. The solution was concentrated under reduced pressure to 5 ml and allowed to chill slowly. The precipitate afforded 0.88 mmoles (300 mg DL-2-amino-5-hydroxaminopentanoic acid mono-2-nitro-1,3-indanedione salt; 310 mg DL-2-amino-6-hydroxaminohexanoic acid mono-2-nitro-1,3-indanedione salt; 88%) as pale yellow needles which could be recrystallized from water. For VIIa-mono-2-1,3-indanedione salt the m.p. was 210–212° (decomp.), the neutral equivalent was 343.0 (theoretical, 339.3) and the pK_a' values were 5.6 and 9.4 for the second and third dissociations respectively. The infrared spectrum in KBr pellet was identical with that of the natural amino acid, to be described below, except that the spectrum of the latter was somewhat better resolved. For VIIb-mono-2-nitro-1,3-indanedione salt the m.p. was 211–212° (decomp.), the neutral equivalent was 350.3 (theoretical, 353.3), and the pK_a' values were 5.7 and 9.5 for the second and third dissociations respectively.

Anal. VIIa-mono-2-nitro-1,3-indanedione salt. Calcd. for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.31; H, 5.25; N, 12.53.

Anal. VIIb-mono-2-nitro-1,3-indanedione salt. Calcd. for $C_{15}H_{19}N_3O_7$: C, 50.99; H, 5.42; N, 11.89. Found: C, 51.39; H, 5.72; N, 11.96.

On paper electrophoretic analysis at *p*H 5.5 these substances had approximately two thirds of the cathodic migration rate of the corresponding diamino acids. The tetrazolium spray indicated one spot but the ninhydrin spray revealed a decomposition trail to the origin.

For further characterization compound VIIa was reduced to ornithine and crystallized as the mono-picrate while compound VIIb was reduced and isolated as DL-lysine dihydrochloride.

To a solution containing 221 mg of crude compound VIIa-dihydrochloride (1.00 mmole) and 0.05 ml of concentrated HCl in 5 ml of water was added 50 mg PtO_2. Hydrogen gas was bubbled through the mixture until the tetrazolium test was negative. The catalyst was removed by centrifugation and the solution passed through a short column of formate form Dowex 1 x 10, 200–400 mesh. One equivalent of picric acid was added to the effluent and the mono-picrate of DL-ornithine crystallized from water-ethanol. The yield was 160 mg (0.44 mmole, 44%) of material with m.p. 206–208° (Greenstein and Winitz, 1961, p. 654, give 208°) which was chromatographically identical with ornithine.

To a solution containing 235 mg of crude compound VIIb-dihydrochloride (1.00 mmole) and 0.5 ml of concentrated HCl in 5 ml of water was added 50 mg PtO_2. Hydrogen gas was bubbled through the mixture until the tetrazolium test was negative. The catalyst was removed by centrifugation, and the residue obtained after evaporation of the solvent was crystallized from 95% ethanol-ether to give 155 mg (0.71 mmole, 71%) DL-lysine dihydrochloride. After recrystallization the m.p. was 187–188° (Organic Syntheses Col. Vol. 11, p. 374, gives 187–189°).

L-2-Amino-5-hydroxaminopentanoic Acid.—Exactly 1.05 g (1.0 mmole) anhydrous, recrystallized ferrichrome A (Garibaldi and Neilands, 1955) was dissolved in water by the dropwise addition of dilute KOH solution, and the iron was removed in the usual way by treatment with hydrosulfite and cyanide (Emery and Neilands, 1961). The solution of iron-free ferrichrome A so obtained was evaporated to a sirup. The latter was dissolved in 25 ml of 6 N HCl and the solution sealed in an evacuated tube and heated at 100° for 15 hours.

The hydrolysate was extracted with ether in order to remove the acyl residues liberated from the hydroxamate functions of the ferrichrome A molecule. The remaining aqueous solution was evaporated to dryness several times in order to remove excess HCl. The residue was dissolved in water and applied to a 2 × 6 cm column of hydrogen form Dowex 50 x 4, 200–400 mesh resin. The column was washed with water and the tetrazolium-positive material eluted with 1.5 N HCl. The effluent was evaporated to dryness several times and the residue dissolved in about 10 ml of water. Exactly 573 mg (3 mmoles) 2-nitro-1,3-indanedione were added, the solution was warmed to dissolve the nitro acid, and dilute KOH solution was added to raise the *p*H to 4.0–4.2. The voluminous precipitate of the mono-2-nitro-1,3-indanedione salt of the L form of compound VIIa weighed 700 mg (2.1 mmoles, 70%). After recrystallization from water the pale yellow needles had a m.p. of 232–235° (decomp.; Turková *et al.*, 1962, give 224°). The neutral equivalent was 339.2 (theoretical, 339.3) and the pK_a values were 5.6 and 9.4 for the second and third dissociations respectively.

Since it was previously shown (Emery and Neilands, 1961) that natural compound VIIa, obtained by 6 N HCl hydrolysis of iron-free ferrichrome A, could be stoichiometrically reduced to L-ornithine (microbiological assay), there appears to be insignificant racemization during the course of liberation of the amino acid from the peptide. In water the optical rotation was very low, but in 2 N HCl solution, after removal of the precipitated nitroindane by centrifugation, the measured $[\alpha]^{20}_D$ was +11.9°.

Anal. Calcd. for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.59; H, 5.05; N, 12.09.

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