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β-Hydroxyhomomethionine and β-Hydroxymethoxinine: Preparation and Separation of Diastereomers

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Abstract □ β-Hydroxyhomomethionine and β-hydroxymethoxinine were prepared by a one-step condensation of the corresponding aldehydes with cupric glycinate in an alkaline medium. The diastereoisomers of each compound were separated by means of partition column chromatography with cellulose as the immobile phase and methyl ethyl ketone–*n*-butanol–ammonia–water as the eluant. The compounds were characterized by paper chromatography in five solvent systems, chemical ionization mass spectrometry, elemental analysis, Van Slyke ninhydrin determination of α-carbonyl carbon, Van Slyke nitrous acid determination of primary amino nitrogen, IR absorption, and NMR spectra.

Keyphrases □ β-Hydroxyhomomethionine—preparation and separation of diastereomers □ β-Hydroxymethoxinine—preparation and separation of diastereomers □ Methionine analogs—preparation and separation of diastereomers of β-hydroxyhomomethionine and β-hydroxymethoxinine

In studies on β-hydroxy-α-amino acids, it was noted that certain of these amino acids in the *N*-chloroacetylated form, even as racemic mixtures of the diastereomers, inhibited the growth of certain microorganisms in systems selected for antitumor screening (1). Of the 11 *N*-acyl-β-hydroxy-α-amino acids tested, *N*-chloroacetyl-β-hydroxynorleucine showed the most promise (1).

β-Hydroxynorleucine may be considered to be a structural analog of threonine and methionine, and it is possible that its growth-inhibitory activity is attributable to its structural resemblance to those amino acids. Since *N*-acylmethionine is a better substrate of hog renal acylase than is *N*-acylnorleucine (2), it appeared that, if the growth-inhibitory action was related to this hydrolysis, a methionine analog would be a better inhibitor.

With this in mind the preparation of two methionine analogs was undertaken. The present article reports the synthesis, the isolation of the diastereomers, and identification of β-hydroxyhomomethionine[1] and β-hydroxymethoxinine[1].

EXPERIMENTAL

Preparation of β-Hydroxyhomomethionine A, B, and AB[2]—Ten grams (47.2 mmoles) of cupric glycinate (3) was dissolved in 300 ml of 0.2 *M* sodium carbonate solution. The solution was cooled to 5° and 20 ml (about 186 mmoles) of 3-methylthiopropionaldehyde[3] was added in four equal portions over 8 hr. The alkalinity of the reaction mixture was tested before and after each addition of the aldehyde, and more 0.2 *M* sodium carbonate solution was added as required to keep the system basic. The reaction mixture was then set in the coldroom at 5° with constant stirring (magnetic stirrer) overnight (18–22 hr), after which time the reaction was terminated by acidification with acetic acid. A small aliquot was removed and spotted on Whatman No. 1 chromato-

[1] β-Hydroxyhomomethionine = 2-amino-3-hydroxy-5-methylthio-*n*-valeric acid; β-hydroxymethoxinine = 2-amino-3-hydroxy-4-methoxy-*n*-butyric acid.

[2] The letters A and B are arbitrarily assigned to the diastereomers moving faster and slower, respectively, when chromatographed on paper and developed in a methyl ethyl ketone–*n*-butanol–concentrated ammonia–water (3:5:1:1) solvent system.

[3] Eastman Kodak Co., Rochester, N.Y.

Table I—Elemental Analysis Data of the Diastereomers of β-Hydroxyhomomethionine and of β-Hydroxymethoxinine[a]

		β-Hydroxyhomomethionine		β-Hydroxymethoxinine	
		Diastereomer A	Diastereomer B	Diastereomer A	Diastereomer B
C	Calc.[b]	40.21	40.21	40.26	40.26
	Found	39.95	39.98	40.34	40.13
H	Calc.	7.31	7.31	7.44	7.44
	Found	7.44	7.50	7.51	7.39
N	Calc.	7.81	7.80	9.39	9.39
	Found	7.56	7.62	9.41	9.00
S	Calc.	17.89	17.89	—	—
	Found	17.31	17.54	—	—

[a] The analysis was performed by the staff of the Microanalytical Laboratory, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md. [b] Calculated for β-hydroxyhomomethionine, $C_5H_{11}NO_3S$, and for β-hydroxymethoxinine, $C_5H_{11}NO_4$.

Table II—Chromatographic Data of the Diastereomers of β-Hydroxyhomomethionine and of β-Hydroxymethoxinine[a]

Solvent System[b]	β-Hydroxyhomomethionine		β-Hydroxymethoxinine	
	Diastereomer A	Diastereomer B	Diastereomer A	Diastereomer B
Methyl ethyl ketone system	R_f 0.35–0.43 (0.39)	R_f 0.26–0.35 (0.31)	R_f 0.14–0.24 (0.19)	R_f 0.08–0.15 (0.12)
77% ethanol	0.40–0.49 (0.44)	Same as A	0.34–0.39 (0.36)	Same as A
80% pyridine	0.51–0.61 (0.56)	Same as A	0.39–0.45 (0.42)[c]	0.33–0.39 (0.36)[c]
Formic acid system	0.45–0.55 (0.50)	Same as A	0.32–0.42 (0.37)	Same as A
Phenol system	0.61–0.71 (0.67)	Same as A	0.61–0.71 (0.66)	Same as A

[a] Chromatographed on Whatman No. 1 chromatographic paper for 18–22 hr at 22–25°, ascending. Compounds were visualized by dipping the paper into a 0.25% acetone solution of ninhydrin and then warming the paper. Figures indicate range of values, and figures in parenthesis indicate the R_f value at the center of ninhydrin-positive spots. [b] Solvent systems: for the methyl ethyl ketone system, see text; formic acid system = formic acid–water–*tert*-butanol(15:15:70); phenol system = phenol saturated with 10% sodium citrate. [c] Sometimes closely situated double spots were noted with this system.

graphic paper and chromatographed in methyl ethyl ketone–*n*-butanol–concentrated ammonium hydroxide–water (3:5:1:1) (4) to determine the extent of the reaction. The main bulk of the reaction mixture was treated with hydrogen sulfide, and the precipitated cupric sulfide was removed by filtration (sintered-glass funnel, ultrafine porosity).

The clear, dark-colored filtrate was concentrated to a syrup on a flash evaporator at about 8 mm Hg and at a bath temperature of 42–50° with the condenser bulb immersed in a dry ice–alcohol bath. The residue was evaporated several times after addition of about 5–10 ml water to remove as much hydrogen sulfide as possible. To remove salts, the sticky mass was then redissolved in a small volume of water, adsorbed on an ion-exchange resin[4] column (H^+, 50–100 mesh, 4.5 × 90.0 cm) washed with water, and eluted with 2 *N* ammonia. The ammonia effluent was concentrated in the flash evaporator, the residue was dissolved in a small volume of the methyl ethyl ketone–*n*-butanol–ammonia–water system, and the solution was applied to a column (3.8 × 140 cm) packed with dry cellulose powder[5]. The column was eluted with the methyl ethyl ketone solvent system at a rate of about 2.7 ml/min, and the effluent was collected in 16-ml fractions at room temperature.

The effluent fractions were monitored for ninhydrin-positive material by spotting a drop from each tube onto a filter paper strip and treating it with an acetone solution of ninhydrin. The positive fractions were further identified by paper chromatography in the methyl ethyl ketone solvent system. By this means, it was noted that diastereomer A appeared between 248 and 418 ml of the effluent, a mixture of A and B appeared between 419 and 530 ml, and diastereomer B appeared between 531 and 1021 ml. Ninhydrin-positive material appeared beyond this volume (1022–1501 ml) and showed two spots [A, R_f 0.10–0.13 (0.12); and B, 0.08–0.10 (0.09)], probably the sulfoxides of isomers A and B, respectively. The fraction of 1502–1921 ml contained a mixture of "sulfoxides" and glycine.

The fractions corresponding to isomers A and B and to the diastereomeric mixture were concentrated at 42–50° on the flash evaporator, and the residue was further dried by passage of nitrogen over its surface. A small volume (about 5 ml) of water was added, and a large excess (about 200 ml) of absolute ethanol was added to the suspension. The turbid mixture was cooled at 5° in the refrigerator overnight, whereupon white crystals formed. The product was collected by filtration and was washed with cold absolute ethanol. The yield was 622.4 mg of diastereomer A, 940 mg of diastereomer B, and 1.1661 g of a mixture of the diastereomers. The total yield was 2.7015 g or 16% based upon the following reaction: 1 mole cupric glycinate yields 2 moles β-hydroxyamino acid. The diastereomeric mixture could be further separated by rechromatography in the same system. However, complete separation of the diastereomers by a single passage through the column could not be accomplished despite varying the geometry of the column, the flow rate of the eluant, and the size and mode of packing of the cellulose particles. Elemental analysis data for these compounds are shown in Table I.

DL-*β-Hydroxyhomomethionine A*—Molecular weight: calc. 179.2, obs. 179 (chemical ionization mass spectrometry)[6]. IR (KBr)[6]: 2.92 (—OH), 3.27 ($—NH_3^+$), 3.42 (—NH and —CH), 6.14 ($—COO^-$), 6.32 shoulder, and 6.71 ($—NH_3^+$) μm; unassigned bands as follows: 7.19 (medium intensity), 7.51 (medium), 7.92 (weak), 8.61 (weak), 9.57 (weak), 10.4 (weak), and 11.2 (weak) μm. NMR (D_2O, NaOD): δ 1.82 (m, 2H, γ-CH_2), 2.17 (s, 3H, —SCH_3), 2.70 (m, 2H, δ-CH_2), 3.20 (d, J = 4 Hz, 1H, α-CH), and 3.93 (m, 1H, β-CH).

DL-*β-Hydroxyhomomethionine B*—Molecular weight: calc. 179.2, obs. 179 (chemical ionization mass spectrometry). IR (KBr): 2.92 (—OH), 3.27 ($—NH_3^+$), 3.43 (—NH and —CH), 6.14 ($—COO^-$), 6.32 shoulder, and 6.71 ($—NH_3^+$) μm; unassigned bands as follows: 7.08 (medium), 7.42 (medium), 7.61 (medium), 7.88 (weak), 8.78 (weak), 9.52 (medium), 10.5 (weak) μm. NMR (D_2O, NaOD): δ 1.80 (m, 2H, γ-CH_2), 2.17 (s, 3H, —SCH_3), 2.70 (m, 2H, δ-CH_2), 3.20 (d, J = 4 Hz, 1H, α-CH), and 3.95 (m, 1H, β-CH).

[4] Dowex 50, × 8.

[5] Whatman cellulose CF-11.

[6] The authors are indebted to Mr. Noel F. Whittaker, Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md., for the IR absorption and NMR spectra and for the mass spectrometric analysis. The instruments used were: mass spectrometer, Finnigan 1015D; IR spectrophotometer, Perkin-Elmer 421; and NMR spectrometer, Varian A60.

Table III—Van Slyke Ninhydrin Determination of Carbonyl Carbon of α-Amino Acids[a]

	β-Hydroxyhomomethionine		β-Hydroxymethoxinine	
	Diastereomer A	Diastereomer B	Diastereomer A	Diastereomer B
α-Carbon taken, mg	0.407	0.407	0.407	0.407
α-Carbon found, mg	0.402	0.398	0.396	0.388
Percent theory	98.8	97.8	97.3	95.8
Percent theory, alanine control	97.8	97.8	99.0	99.0

[a] One milliliter of amino acid solution containing an equivalent of 0.407 mg α-carbon treated with 1.0 ml saturated picric acid in a reaction tube and about 100 mg of ninhydrin added.

Table IV—Van Slyke Nitrous Acid Determination of Primary Amino Nitrogen[a]

	β-Hydroxyhomomethionine		β-Hydroxymethoxinine	
	Diastereomer A	Diastereomer B	Diastereomer A	Diastereomer B
α-Amino nitrogen taken, mg	0.475	0.475	0.475	0.475
α-Amino nitrogen found, mg	0.481	0.507	0.490	0.485
Percent theory	101.2	106.7	103.1	102.2
Percent theory, leucine control	102.8	102.8	102.7	102.7

[a] One milliliter of amino acid solution contained an equivalent of 0.475 mg amino nitrogen after being diluted with 4.0 ml water and treated with 1 ml acetic acid and 2 ml of sodium nitrite solution (80 g/100 ml).

Preparation of β-Hydroxymethoxinine A, B, and AB—The method of preparation of these compounds is similar to that of β-hydroxyhomomethionine. Methoxyacetaldehyde was prepared by acid hydrolysis of its diethylacetal[7] in the conventional manner of preparation of aldehyde from its acetal. The reaction was carried out at room temperature (25°) overnight (about 16 hr) with constant stirring. The products were isolated by removal of the salt with the ion-exchange resin[4], passage of the salt-free solution through a dry cellulose column, and precipitation from aqueous solution with ethanol, as described for the preparation of β-hydroxyhomomethionine.

For 10.0 g (47.2 mmoles) of cupric glycinate in 300 ml of 0.2 *M* sodium carbonate solution, 14.2 ml (approximately 191 mmoles) of methoxyacetaldehyde was added.

For the separation of the diastereomers on the cellulose column, the column was eluted with the methyl ethyl ketone system at 0.75 ml/min at room temperature (22–25°) and 6-ml cuts were collected. The fraction emerging from 846 to 1115 ml contained an unidentified ninhydrin-positive material, that emerging from 1116 to 1600 ml contained diastereomer A, that emerging from 1601 to 1806 ml contained a mixture of the two diastereomers, and that emerging from 1807 to 2746 ml contained isomer B. The volume emerging beyond this fraction was still ninhydrin-positive, containing a mixture of isomer B and glycine (2747–3306 ml); from 3307 to 4806 ml, the fraction contained glycine only. Isomer A separated as a gelatinous precipitate upon addition of alcohol to the aqueous solution. The yield was 694.1 mg of isomer A, 920.7 mg of isomer B, and 49.1 mg of the mixture. The total yield was 1.6639 g (11.2 mmoles) or 23.7%. Isomer B could be separated from glycine by removal of the solvent by evaporation *in vacuo*, dissolution of the residue thus obtained in 80% pyridine, and passage of the solution through a second dry cellulose column and elution with 80% pyridine (β-hydroxymethoxinine emerges first in the system). Elemental analysis data for these compounds are shown in Table I.

DL-*β-Hydroxymethoxinine A*—Molecular weight: calc. 149.2, obs. 149 (chemical ionization mass spectrometry). IR (KBr): 2.92 (—OH), 3.27 ($—NH_3^+$), 3.41 (—NH and —CH), 6.16 ($—COO^-$), 6.32 (shoulder), and 6.69 ($—NH_3^+$) μm; unassigned bands as follows: 7.20 (medium intensity), 7.42 (medium), 8.00 (weak), 8.40 (weak), 9.00 (medium), 9.70 (medium), 10.5 (weak), 10.9 (weak), and 11.3 (weak) μm. NMR (D_2O, NaOD): δ 3.43 (s, 3H, $—OCH_3$), 3.67 (d, J = 4 Hz, 2H, γ-CH_2), 3.81 (d, J = 4 Hz, 1H, α-CH), and 4.33 (m, 1H, β-CH).

DL-*β-Hydroxymethoxinine B*—Molecular weight: calc. 149.2, obs. 149 (chemical ionization mass spectrometry). IR (KBr): 2.92 (—OH), 3.29 ($—NH_3^+$), 3.42 (—NH and —CH), 6.17 ($—COO^-$), 6.31 (shoulder), and 6.72 ($—NH_3^+$) μm; unassigned bands as follows: 7.14 (medium), 7.58 (medium), 8.40 (weak), 8.99 (medium), 9.54 (medium), 10.6 (weak), and 11.9 (weak) μm. NMR (D_2O, NaOD): δ 3.41 (s, 3H, $—OCH_3$), 3.67 (d, J = 4 Hz, 2H, γ-CH_2), 3.95 (d, J = 4 Hz, 1H, α-CH), and 4.33 (m, 1H, β-CH).

RESULTS AND DISCUSSION

Each diastereomer gave a single ninhydrin-positive spot when chromatographed in the methyl ethyl ketone system (which separates the diastereomers of these compounds) and in four other solvent systems, *i.e.*, 77% ethanol, 80% pyridine, formic acid–water–*tert*-butanol (15:15:70), and phenol saturated with 10% sodium citrate (Table II). The elemental analysis values are in agreement with values calculated for β-hydroxyhomomethionine and β-hydroxymethoxinine (Table I). Van Slyke ninhydrin determination of α-carbonyl carbon (5) and Van Slyke nitrous acid determination of primary amino nitrogen (6) yielded essentially quantitative amounts of carbon dioxide and nitrogen, respectively (Tables III and IV), confirming the α-amino carboxylic acid and free amino configuration of the compounds.

Although assignment of absolute configuration of the diastereomers could not be made at this time, comparison of the relative mobilities of the diastereomers of these compounds with those of the diastereomers of threonine (threonine and allothreonine) and of β-hydroxynorleucine[8] in the methyl ethyl ketone system shows that isomer A, or the faster moving compound, is probably related to the *threo*-configuration while isomer B, or the slower moving diastereomer, is related to the *erythro*-configuration.

In the synthesis of these compounds, varying the molar ratio of the reactants (from 1:0.01:1 to 1:1:3 glycine–cupric ion–aldehyde) over a range of temperature (5–100°) for from 15 min to 3 days showed that the products formed over a wide range of conditions.

[7] Aldrich Chemical Co., Milwaukee, Wis.

[8] The R_f values of the diastereomers in the methyl ethyl ketone system are as follows: diastereomer A, 0.43; and diastereomer B, 0.35. Diastereomer A moves with *threo*-β-hydroxynorleucine and diastereomer B moves with *erythro*-β-hydroxynorleucine in the Hardy–Holland (7) solvent system (*cf.*, Ref. 8).

The conditions were selected that gave the best yield for the shortest duration of reaction. Although these compounds could be obtained from glycine and cupric sulfate and the aldehyde as well as from cupric glycinate and aldehyde, the latter gave superior yields for the conditions studied. Lengthening the duration of reaction did not appear to improve the yield. Increasing the aldehyde concentration seems to result in larger formation of sticky material with no appreciable improvement of yield.

Removal of the cupric ion at the termination of the reaction by rapid heating gave inferior yields (8%). Use of the resin column for desalting can be eliminated when a smaller amount of sodium carbonate is used and the aqueous solution from which the sulfides have been largely removed is passed through a single cellulose column, but a smaller yield (8%) results.

The slow moving compounds appearing in trace amounts when β-hydroxyhomomethionine is chromatographed in the methyl ethyl ketone system are very likely the corresponding sulfoxides of the diastereomers. This is supported by the observation that the slower moving ninhydrin-positive material of each diastereomer is associated with the respective parent diastereomer during the separation procedure, being present when its parent compound is present and disappearing when its parent compounds disappear. When a small amount of diastereomer A and B was treated with hydrogen peroxide for a few minutes at room temperature and the resulting solution was chromatographed on paper in the methyl ethyl ketone system, a pronounced increase in the slower moving compound and a corresponding decrease in the parent compounds were noted. The ninhydrin-positive material that emerged ahead of β-hydroxyhomomethionine has not been identified.

Attempts have been made to prepare β-hydroxymethionine from methylthioacetaldehyde and cupric glycinate, starting with the diethylacetal of the aldehyde, but with no success thus far.

Enzymatic resolution of the racemates of each diastereomer of β-hydroxyhomomethionine and β-hydroxymethoxinine is now being studied in preparation for testing the pure enantiomers for activities in microbial antitumor screening systems and mammalian tumor systems.

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Influence of Repetitive Dosing and Altered Urinary pH on Doxycycline Excretion in Humans

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Abstract □ The effect of altered urinary pH on the renal excretion of doxycycline, with both single- and multiple-dose regimens, was studied in humans. Alkalinization of the urine resulted in higher cumulative amounts of doxycycline excreted during both single- and multiple-dose regimens. The increased excretion was reflected in larger renal clearances and shorter half-lives for both regimens when the alkaline condition was compared to the control condition. Half-life values increased from the single- to the multiple-dose regimen under both alkaline and control conditions. However, the increase in half-life values from single- to multiple-dose administration under the alkaline condition was shorter than the half-life change under control conditions.

Keyphrases □ Doxycycline—comparison of single-dose and multiple-dose regimens, effects of urine alkalinization on excretion, half-lives, humans □ Urinary pH—effects on excretion of doxycycline, single-dose and multiple-dose regimens, half-lives, humans □ Dosing regimens—comparison of single-dose and multiple-dose administration of doxycycline, effects of urinary pH on excretion, half-lives, humans □ Alkalinization, urine—effects on doxycycline excretion, comparison of single-dose and multiple-dose regimens, half-lives, humans □ Excretion, urinary—comparison of single-dose and multiple-dose doxycycline regimens, effects of alkalinization of urine, half-lives, humans

It was recently shown that altered urinary pH can significantly influence the urinary excretion of tetracycline and doxycycline (1). A treatment producing an alkaline urinary pH was shown to result in a 24% increase in cumulative tetracycline excretion when compared to a treatment producing an acidic urinary pH for the same time interval (48 hr). An even greater increase in cumulative excretion was shown for doxycycline under similar conditions. For doxycycline the alkaline urine condition resulted in a 54% increase in cumulative excretion as compared to an acidic urine condition.

This effect has been attributed to differences in the lipid solubilities of these antibiotics over the physiological pH range of the urine resulting in their increased or decreased reabsorption in the tubules of the kidney. The greater differences between alkalinization and acidification of the urine for the excretion of doxycycline than for tetracycline appear to confirm the theory that this antibiotic shows greater