# Synthesis of L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid from Optically Active Precursors by N-Homologization

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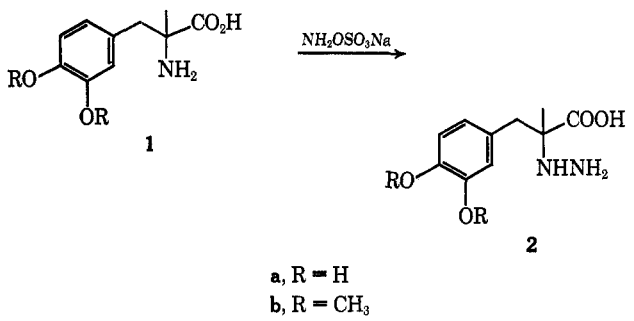
L-α-Methyl-dopa dimethyl ether (**1b**) reacts with hydroxylamine-*O*-sulfonic acid to give a difficultly separable mixture of **1b** and its N homolog, L-α-(3,4-dimethoxybenzyl)-α-hydrazinopropionic acid (**2b**). Reaction of the hydantoic acid **7b** with sodium hypochlorite also gives **2b**, easily isolable in this case. N-Amination of L-α-acetylamino-α-(3,4-dimethoxybenzyl)propionitrile *via* chloramine similarly provides access to the title compound. These reactions, achieved without disturbing the chiral carbon, constitute the first direct conversions of α-amino acids to α-hydrazino acids and formally interconnect the configuration of the two series of structures.

There were described in the preceding paper[1] two resolution routes to optically active α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**2a**), the L(−)[2] isomer of which possesses interesting physiological activity.[3] The ready availability of L(−)-α-methyldopa (**1a**)[4] and some of its derivatives[5] provided incentive for direct synthesis of this nitrogen homolog from optically active precursors. Such a synthesis would also constitute a formal proof of absolute configuration.[6]




A search of the literature revealed no precedent for the direct conversion of α-amino acids to hydrazino acids.[7] It seemed likely, however, that some of the established methods for converting amines to hydrazines[8] might be utilized. In this paper we describe some successful studies along these lines.

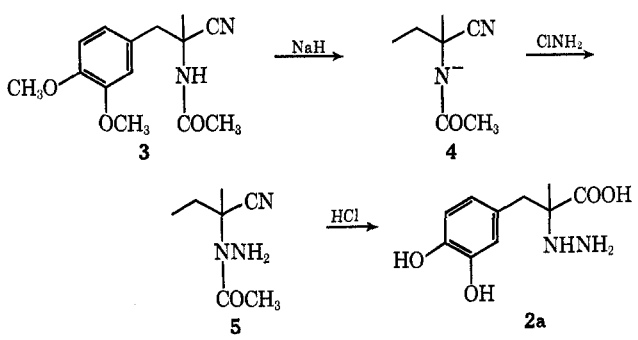
Substituted hydroxylamine derivatives have been used to form N–N bonds with amines.[9] Usually the amine is taken in excess to suppress secondary reaction of the reagent with the desired product. Purification, consequently, frequently presents problems. Nevertheless, we felt that, if reaction of commercially available hydroxylamine-*O*-sulfonic acid could be achieved with, for example, amino acid **1b**,[5b] this would constitute the simplest possible synthesis of hydrazino acid **2b**.

When such reaction was attempted in aqueous base, a mixture of starting material and product **2b** was obtained in 1.6:1 mole ratio. The reagent had been used in twofold excess, but neither increase nor decrease improved the yield. Separation of **1b** and **2b** was indeed difficult, and the approach was set aside as unsuitable for large-scale preparations.

It was clear that a more useful route would provide either complete conversion of starting material or at least a product which was readily separated from the starting material. The reactive anion **4** seemed a likely substrate on both counts, and its utility was examined. Optically active L-amide **3** had already been prepared,[5c] and its anion was shown to be optically stable under conditions deemed useful for our purposes.[10]

When this anion in DMSO was treated with ethereal chloramine,[11] smooth N-amination was achieved. The product, **5**, was readily convertible to the L-hydrazino acid **2a** by acid hydrolysis[1] (Scheme I).

SCHEME I




Another hydrazine-forming reaction which seemed applicable to our goal was the interaction of urea with sodium hypochlorite.[12] Discovered in 1903, this reaction has rarely been used for the preparation of a substituted hydrazine. The transformation of amino acid **1** to hydrazino acid **2** based on this reaction is outlined in Scheme II.

The key intermediate, hydantoic acid **7b**, could be made from **1b** and potassium cyanate or from **7a**[5a] *via*

(1) S. Karady, M. G. Ly, S. H. Pines, and M. Sletzinger, *J. Org. Chem.*, **36**, 1946 (1971).

(2) Proof of absolute configuration follows.

(3) V. J. Lotti and C. C. Porter, *J. Pharmacol. Exp. Ther.*, **172**, 406 (1970).

(4) Aldomet, a product of Merck & Co., Inc.

(5) (a) R. A. Vitali, T. A. Jacob, and J. M. Chemerda, *J. Med. Chem.*, **7**, 379 (1964); (b) H. L. Slates, D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **29**, 1424 (1964); (c) D. F. Reinhold, R. A. Firestone, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *ibid.*, **33**, 1209 (1968).

(6) E. W. Tristram, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *ibid.*, **29**, 2053 (1964), have proven the configuration of L-α-methyl-dopa.

(7) Indirect syntheses *via* α-halo acids have been reported: (a) H. Niedrich and R. Grupe, *J. Prakt. Chem.*, **27**, 108 (1965); (b) M. Sletzinger, R. A. Firestone, D. F. Reinhold, C. S. Rooney, and W. H. Nicholson, *J. Med. Chem.*, **11**, 261 (1968).

(8) For a recent review, see A. N. Kost and R. S. Sagitullin, *Russ. Chem. Rev.*, **33**, 159 (1964).

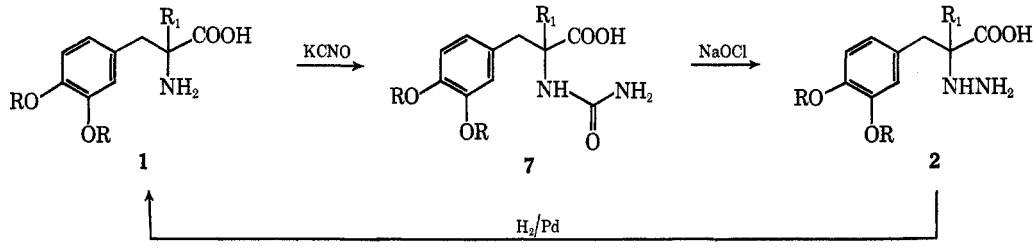
(9) For examples, see (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **82**, 3133 (1960); *J. Org. Chem.*, **30**, 321 (1965); (b) T. Sheradsky, *Tetrahedron Lett.*, 1909 (1968), and subsequent papers from that laboratory.

(10) R. A. Firestone, D. F. Reinhold, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *J. Org. Chem.*, **33**, 1213 (1968).

(11) N-Amination of an amide anion has been reported by W. Metlesics, R. T. Travers, and L. H. Sternbach, *ibid.*, **30**, 1311 (1965).

(12) P. Shestakov, *Z. Angew. Chem.*, **16**, 1061 (1903).

SCHEME II

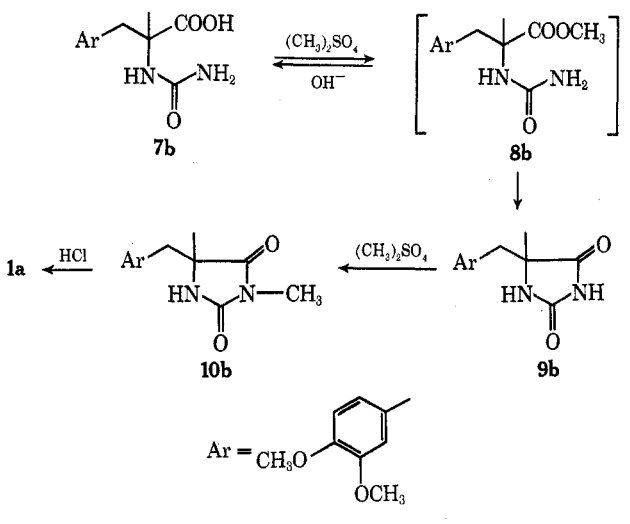



a, R = H; $R_1$ = $CH_3$
b, R = $R_1$ = $CH_3$
c, R = H; $R_1$ = Et
d, R = $CH_3$; $R_1$ = Et

methylation. Alternatively, α-methyl-dopa (**1a**) could be simply converted to **7b** in good yield without isolation of intermediate **7a**.

In the methylation step (**7a** → **7b**) methylhydantoin **10b** (Scheme III) formed as a by-product. Its yield

SCHEME III




was minimal when excess potassium hydroxide was used, but it increased when the pH was controlled at 11–12 during the reaction. Presumably hydantoic ester **8b** is the intermediate of this cyclization. At high base concentration, hydrolysis of the ester (**8b** → **7b**) is very rapid, while at lower base strength cyclization (**8b** → **9b**) becomes more competitive. Hydantoic ester **8b** could not be isolated. Even diazomethane converted **7b** to a mixture of hydantoins **9b** and **10b**, indicating rapid ring closure. Hydantoin **9b**, once formed, is expected to methylate at position 3 to give **10b**. Indeed, an authentic sample of hydantoin **9b** was readily transformed to **10b** by treatment with diazomethane or dimethyl sulfate. Hydrolysis of **10b** to α-methyl-dopa (**1a**) provided conclusive proof for the position of the *N*-methyl group.

The reaction of hydantoic acid **7b** with sodium hypochlorite gave hydrazino acid **2b** which was converted to the desired L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**2a**) by treatment with hydrochloric acid (Scheme II).

An analogous sequence (**1c** → **7d** → **2d** → **2c**) provided L-α-(3,4-dihydroxybenzyl)-α-hydrazinobutyric acid (**2c**), the α-ethyl analog.

The outlined synthesis of levorotatory hydrazino acid **2a** from L(−)-α-methyl-dopa (**1a**) fixes the absolute configuration of the former as L or S.[6] As an additional proof, L-hydrazino acid **2b** was reconverted to the L-α-methyl-dopa analog **1b** by hydrogenolysis over palladium-on-charcoal catalyst (Scheme II).

## Experimental Section[13]

**Reaction of L-α-Amino-α-(3,4-dimethoxybenzyl)propionic Acid (1b) with Hydroxylamine-*O*-sulfonic Acid.**—To an ice-cold solution of L-α-amino-α-(3,4-dimethoxybenzyl)propionic acid (**1b**) hydrochloride (2.2 g, 8 mmol) in 2.5 *N* NaOH was added 1.8 g (16 mmol) of hydroxylamine-*O*-sulfonic acid. After 10 min the mixture was warmed and kept at 90° for 1 hr. The solution was acidified with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was digested with ethanol, and the product was precipitated from the alcoholic solution by the addition of diethylamine (pH 6.5). The crystalline product (900 mg) exhibited nmr resonances corresponding to **1b** and the desired hydrazino acid **2b** in a ratio of 1.6:1. (The C–$CH_3$ groups were sufficiently separated to allow this estimation.) Thin layer chromatography confirmed qualitatively these findings. For characterization of **2b**, see below.

**L-α-(1-Acetylhydrazino)-α-(3,4-dimethoxybenzyl)propionitrile (5).**—Sodium hydride (250 mg, 55% in mineral oil, 5.2 mmol) was washed with hexane and suspended in 6 ml of DMSO. To this mixture was added a solution of acetamidonitrile **3**[10] (1.05 g, 4 mmol) in 10 ml of DMSO. After the gas evolution subsided (15 min) the solution was cooled to 15°, and a solution of chloramine[14] (4.5 mmol) in 12 ml of dry ether was added over a period of 2 min. After 12 hr of agitation at room temperature, a few drops of acetic acid was added and the mixture was concentrated *in vacuo*. The resulting syrup was partitioned between water and chloroform. The organic layer was dried, the solvent removed, and the residue crystallized from ethyl acetate and ether to yield 1 g of crystalline material. The nmr spectrum indicated a 3:2 mixture of **5** and **3**. Chromatography on 30 g of silica gel H (chloroform–3% methanol) yielded 570 mg (52%) of **5** and 320 mg of recovered starting material. An analytical sample was prepared by recrystallization from methanol, mp 121–123°.

*Anal.* Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.82; H, 7.10; N, 15.21.

**L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (2a) from 5.**—A solution of **5** (150 mg) in 2.5 ml of concentrated HCl was heated in a sealed tube at 120° for 90 min. After the usual work-up procedure (see **2b** → **2a**) 50 mg of pure hydrazino acid **2a** was obtained, identical in all respects with an authentic sample. For characterization of **2a**, see below.

**L-4-(3,4-Dimethoxybenzyl)-4-methylhydantoic Acid (7b). A. From 1b.**—L-α-Amino-α-(3,4-dimethoxybenzyl)propionic acid (**1b**) hydrochloride[5c] (44 g, 0.16 mol) was dissolved in 440 ml of water by gentle heating. The solution was cooled rapidly to 5°, and potassium cyanate (77.6 g, 0.96 mol) was added in small portions. After this the slurry was heated to 60° for 4 hr and filtered. The filtrate was cooled and acidified to pH 1 with

(13) For general comments see footnote 14 in ref 1.
(14) G. H. Coleman and H. L. Johnson, *Inorg. Syn.*, **1**, 59 (1939).

concentrated HCl, and the crystalline precipitate was filtered, washed with water, and dried at 50°, affording 34.5 g (76.4%) of hydantoic acid **7b**. An analytical sample was prepared by recrystallization from ethanol–water, mp 205–207°.

*Anal.* Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.56; H, 6.52; N, 9.99.

B. **From L-α-Methyl-dopa (1a).**—To a solution of L-α-methyldopa (100 g, 0.47 mol) and sodium bisulfite (600 mg) in 500 ml of water was added 57.6 g of potassium cyanate, and the solution was heated to 60° in a nitrogen atmosphere for 1 hr. Another 57.6-g portion of potassium cyanate was then added and the heating continued for 2 hr. An nmr study indicated that at this point about 90% of the amino acid was converted to hydantoic acid **7a**. This material was methylated without isolation as follows. Water was distilled from the reaction mixture until ammonia was no longer detectable. The residue was diluted to the original volume; 20 ml of 8 *N* KOH solution was added. The solution was well agitated while 8 *N* KOH solution (566 ml) and dimethyl sulfate (376 ml, 3.6 mol) were added simultaneously at such a rate as to keep the temperature below 20°. The addition took about 1 hr. The mixture was extracted with ether 0.5 hr later. The extract contained a small amount of dimethylhydantoin **10b** identical with a sample prepared by the methylation of hydantoin **9b** (see below).

The aqueous layer was acidified to pH 2 with HCl and the precipitated product was removed by filtration, washed with water, and dried to give 79 g (59%) of hydantoic acid **7b**.

When the methylation was carried out at pH 11–12, about 30% dimethylhydantoin **10b** formed, which was removed by filtration from the basic reaction mixture.

**L-α-(3,4-Dimethoxybenzyl)-α-hydrazinopropionic Acid (2b).**—To an ice-cold solution of hydantoic acid **7b** (2.2 g, 7.8 mmol) in 15.6 ml of 2.5 *N* KOH was added a solution of sodium hypochlorite (13.7 ml, 0.71 *N*, 9.75 mmol). Five minutes after the addition was completed, the solution was heated to 80° for 1.5 hr. After this period, toluene (45 ml) and hydrazine hydrate (0.8 ml) were added and the mixture was vigorously agitated while adding 8 ml of concentrated HCl. The mixture was stirred at 80° for 30 min; then the phases were separated and the aqueous layer was extracted with 25 ml of toluene. The toluene layer contained 3,4-dimethoxyphenylacetone and its condensation products. The aqueous layer was evaporated to dryness, and the resulting salt mixture was digested with ethanol. The alcoholic solution was neutralized (pH 6.4) with diethylamine and the precipitated product was filtered, washed with ethanol, and dried to afford 1 g of hydrazino acid **2b**, 48% yield. An analytical sample was recrystallized from water, mp 222–224° dec, $[\alpha]_D$ −9° (*c* 1, $H_2O$).

*Anal.* Calcd for $C_{12}H_{18}N_2O_4 \cdot H_2O$: C, 52.93; H, 7.40; N, 10.29. Found: C, 53.01; H, 7.46; N, 10.28.

A tlc and nmr study of the crude reaction mixture indicated that the major by-product of this reaction is hydantoin **10b**[5a] which formed in the basic medium. During the acidic work-up, more hydantoin formed from the unreacted hydantoic acid **7b**. This by-product was removed from the two-phase reaction mixture by filtration.

**L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (2a).**—A mixture of the dimethoxyhydrazino acid **2b** (10 g) and concentrated HCl (150 ml) was heated in a sealed tube at 120° for 2 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the product was leached out with ethanol. The hydrazino acid was precipitated by the addition of diethylamine to pH 6.4. The precipitate was filtered, washed with ethanol, and dried, affording 6.5 g of hydrazino acid **2a** (73%). Recrystallization from water (containing a small amount of sodium bisulfite) yielded analytically pure material, mp 208° dec, identical with the material previously synthesized.

**L-5-(3,4-Dimethoxybenzyl)-3,5-dimethylhydantoin (10b).**—To a solution of hydantoin **9b** (1 g, 3.79 mmol) and potassium *tert*-butoxide (3.79 mmol) in 5 ml of DMSO, dimethyl sulfate (3.79 mmol) in DMSO (5 ml) was added dropwise. A few drops of acetic acid was added, and the mixture was evaporated under high vacuum. The residue was triturated with 2.5 *N* NaOH and filtered. Recrystallization from ethyl acetate yielded analytically pure **10b**, mp 153–155°.

*Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.31; H, 6.60; N, 10.16.

**α-Methyl-dopa from 10b.**—L-5-(3,4-Dimethoxybenzyl)-3,5-dimethylhydantoin (**10b**) (5.87 g, 21 mmol) and 25 ml of 6 *N* HCl were heated in a sealed tube at 160° for 6 hr. The dark solution was evaporated to dryness, the residue was dissolved in water, and the α-methyl-dopa (**1a**, 2.9 g) was precipitated with ammonium hydroxide (pH 5). This material was identical in all respects with an authentic specimen.

**α-Methyl-dopa Dimethyl Ether (1b) from 2b.**—Hydrazino acid **2b** (2.08 g) in glacial acetic acid (100 ml) and 2.5 *N* HCl (3.2 ml) was hydrogenated in the presence of 10% palladium-on-charcoal catalyst (300 mg) for 24 hr at 120° and 40 psig. After the catalyst was removed the solution was evaporated to dryness and the residue was heated to reflux for 2 hr in concentrated HCl. The solution was treated with charcoal, concentrated to a small volume, and allowed to crystallize. The product (700 mg) after recrystallization from concentrated HCl had mp 164–171°, $[\alpha]_D$ 7.8° (*c* 1, MeOH).

*Anal.* Calcd for $C_{12}H_{18}ClNO_4 \cdot H_2O$: C, 49.02; H, 6.82; N, 4.72. Found: C, 48.75; H, 6.72; N, 4.74.

This material was identical in all respects with an authentic sample of α-methyl-dopa dimethyl ether hydrochloride hydrate, prepared by recrystallization of **1b** from concentrated HCl.

**L-4-(3,4-Dimethoxybenzyl)-4-ethylhydantoic Acid (7d).**—L-α-Ethyl-dopa **1c** was converted to the title compound **7d** in 70% yield by analogous procedure described above with the methyl analogs (**1a** → **7b**). The analytical sample was recrystallized from ethanol–water, mp 218–220°, $[\alpha]_D$ +241° (*c* 1, 2.5 *N* NaOH).

*Anal.* Calcd for $C_{14}H_{20}N_2O_5$: C, 56.74; N, 6.80; N, 9.45. Found: C, 56.71; H, 6.88; N, 9.53.

**L-α-(3,4-Dimethoxybenzyl)-α-hydrazinobutyric Acid (2d).**—Reaction with sodium hypochlorite converted hydantoic acid **7d** to hydrazino acid **2d** in 38% yield. The conditions were the same as outlined with the methyl analogs (**7b** → **2b**), mp 215–220°, $[\alpha]_D$ −7.3° (*c* 1, 2.5 *N* NaOH).

*Anal.* Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.16; H, 7.60; N, 10.40.

**L-α-(3,4-Dihydroxybenzyl)-α-hydrazinobutyric Acid (2c).**—The title compound was prepared from **2d** by the procedure outlined for **2a** in 90% yield. Recrystallization from water afforded an analytically pure sample, mp 209–212°, $[\alpha]_D$ −15.2° (*c*, 1, $H_2O$).

*Anal.* Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.02; H, 6.70; N, 11.65.

**Registry No.**—**1b** HCl, 5486-79-3; **2a**, 28860-95-9; **2b**, 28860-96-0; **2c**, 28860-97-1; **2d**, 28860-98-2; **5**, 28860-99-3; **7b**, 28861-00-9; **7d**, 28861-01-0; **10b**, 28861-02-1.