only *p*-methoxyacetanilide was obtained. The diacetyl derivative has previously been prepared by a similar reaction run at a higher temperature.[10]

Dehydration Reaction of *N*-Phenylmaleamic Acid $CO^{18}OH$ with Acetic Anhydride–Sodium Acetate.—*N*-Phenylmaleamic acid **1b** (0.4663 g, 0.00244 mol) was mixed with 0.5710 g of anhydrous sodium acetate and 10 ml of acetic anhydride. The mixture was heated at 65° for 90 min, then cooled, and slowly added to excess saturated sodium bicarbonate. The yellow precipitate which remained after the acetic anhydride had been hydrolyzed was filtered and dried. A benzene solution of this mixture was passed through a 2-in. column of Florisil in a Pasteur pipet and all of the yellow product was collected. After removal of the benzene at reduced pressure, the sample was dried *in vacuo* for 24 hr. An nmr ($CDCl_3$–TMS) indicated that the material was a mixture of imide and isoimide. Analysis for oxygen-18: 0.45, 0.45 atom % excess, 34% of the label found in **1b**.

Acetic anhydride (2 ml) was added to 0.157 g of *N*-phenylmaleisoimide; the resulting solution was poured into 18 ml of saturated sodium bicarbonate solution prepared from water containing 1.5 atom % oxygen-18. The mixture was stirred until the isoimide crystals could be isolated by filtration and purification was carried out as above. Analysis for oxygen-18: 0.00, 0.01 atom % excess.

Registry No.—*N*-Phenylmaleamic acid, 555-59-9; acetic anhydride, 108-24-7.

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Synthesis of D- and L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid *via* Resolution

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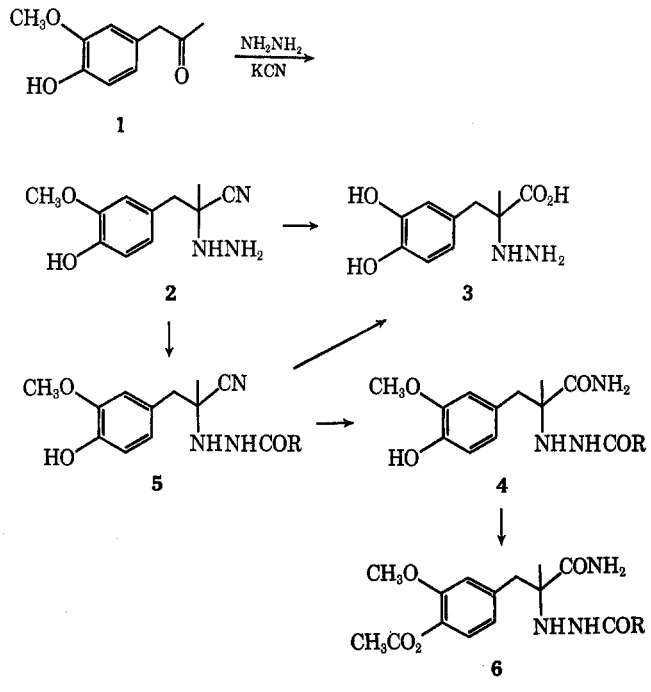
l-Menthoxyacetylation of *dl*-α-hydrazino-α-(4-hydroxy-3-methoxybenzyl)propionitrile (**2**) permits resolution and, after hydrolysis, the isolation of the two antipodes of α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**3**). The acylation is proven to have occurred on N^{β}.

In spite of seemingly increasing interest in the synthesis of α-hydrazinocarboxylic acids over the past decade,[1] only three methods are commonly used for their preparation. Two of these, the reduction of a hydrazone of an α-keto acid[1b] and the functionalization of a carbonyl compound in a Strecker-like synthesis,[2] are not particularly useful for the formation of optical isomers. The third, reaction of hydrazine with an α-halo acid, has so far proved to be the only useful route.[1a,b,3] Surprisingly, the resolution of racemic hydrazino acids by separation of diastereomers has yet to be reported.

The hydrazination reaction has severe limitations, especially in cases where the halogen to be replaced resides on a tertiary center and/or is ideally set up for base-promoted elimination as HX. Such a situation faced us in a projected preparation of the antipodes of α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**3**). Our interest in this work arose from the reported biological activity, both *in vitro*[4] and *in vivo*,[4,5] of the racemate[2] and the known "difference in biological activity associated with optical isomerism."[4b,6]

In this paper we report the first preparation of the antipodes of **3**[7] which was achieved by separation of diastereomeric hydrazides **5c** and by subsequent acid hydrolysis to the optically active hydrazino acids (**3**) (Scheme I). Inferences from the physical characteris-

SCHEME I



a, R = CH_3
b, R = C_6H_5
c, R = 1-menthoxymethyl

(1) For example, (a) A. Carmi, G. Pollak, and H. Yellin, *J. Org. Chem.*, **25**, 44 (1960); (b) E. J. Glamkowski, G. Gal, M. Sletzinger, C. C. Porter, and L. S. Watson, *J. Med. Chem.*, **10**, 852 (1967); (c) M. Sletzinger, R. A. Firestone, D. F. Reinhold, C. S. Rooney, and W. H. Nicholson, *ibid.*, **11**, 261 (1968), and references cited therein.

(2) M. Sletzinger, J. M. Chemerda, and F. W. Bollinger, *ibid.*, **6**, 101 (1963).

(3) A. Darapsky, *J. Prakt. Chem.*, **99**, 179 (1919); H. Niedrich and R. Grupe, *ibid.*, **27**, 108 (1965).

(4) (a) C. C. Porter, L. S. Watson, D. C. Titus, J. A. Totaro, and S. S. Byer, *Biochem. Pharmacol.*, **11**, 1067 (1962); (b) V. J. Lotti and C. C. Porter, *J. Pharmacol. Exp. Ther.*, **172**, 406 (1970).

(5) G. C. Cotzias, P. S. Papavasiliou, and R. Gellene, *New Engl. J. Med.*, **280**, 337 (1969), for example, report its usefulness in the treatment of Parkinsonism.

(6) A. H. Beckett, G. Kirk, and A. J. Sharpen, *Tetrahedron*, **21**, 1489 (1965).

(7) Attempts to resolve **2**, **3**, **4**, **5**, or **6** by separation of diastereomeric salts were thwarted by our inability to crystallize suitable salts with a variety of optically active acids.

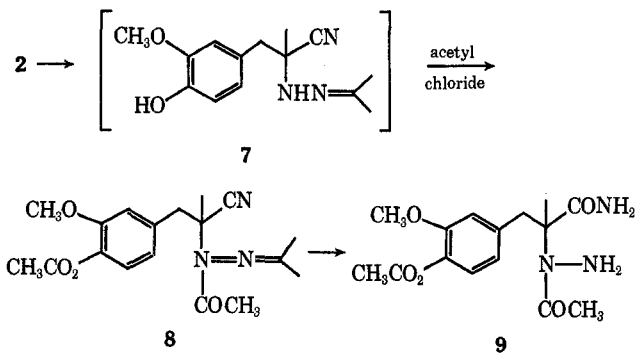
tics of the antipodes so obtained led us to the separation of racemic **3** by direct controlled crystallization. A following article[8a] deals with syntheses directly from optically active precursors, not involving attack at the asymmetric carbon atom. Therein also lies the proof of absolute configuration of C-2.[8b]

Hydrazinonitrile **2**, available *via* the synthesis of Sletzinger, Chemerda, and Bollinger,[2] could be selectively monoacylated with acetyl chloride or benzoyl chloride to give nicely crystalline hydrazides **5a** or **5b**. With 1-menthoxyacetyl chloride, an oily mixture was ultimately induced to deposit crystals of mainly one diastereomer of **5c**. Subsequent preparations, when seeded, crystallized readily. After purification to constant rotation, the hydrazide could be hydrolyzed to levorotatory[8b] hydrazino acid **3**. Evidence of essential optical purity rests on rotational data of samples prepared from optically pure precursors[8a] and the achievement of constant rotation by repeated recrystallization.

Qualitative tests readily showed that L(−)-hydrazino acid **3** was less soluble than the racemic product. Accordingly, the mother liquor residues from the crystallization of L-hydrazide **5c** from which we could not crystallize its more soluble isomer were hydrolyzed. Several recrystallizations of the crude hydrazino acid obtained therefrom gave dextrorotatory **3**.

While simple aliphatic hydrazines are normally acylated on the substituted nitrogen, steric effects are frequently controlling.[9] Thus, it could be assumed that the acyl hydrazides **5a–c** were N^{β}-substituted, as depicted on Scheme I. Proof for this assumption came from the route shown in Scheme II. Reaction of ace-

SCHEME II



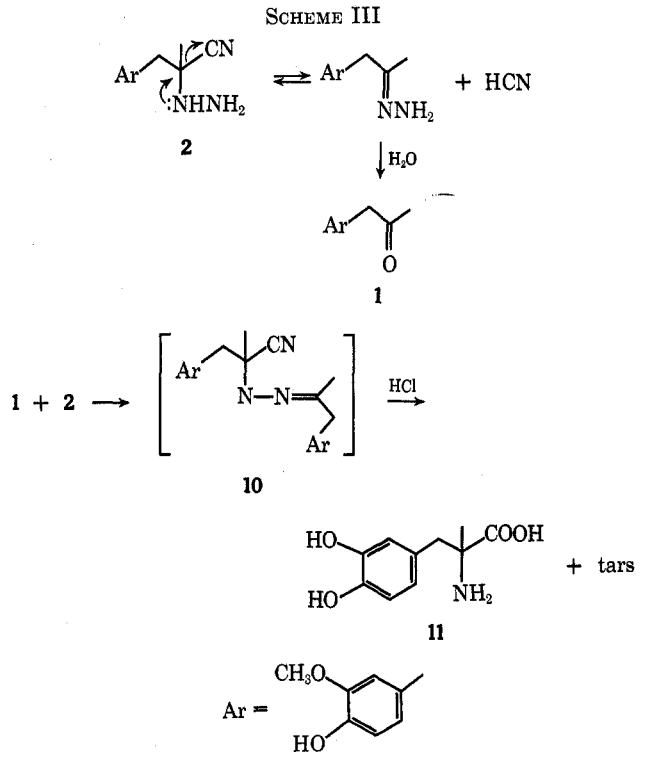
tone hydrazone **7** with acetyl chloride gave the N^{α},*O*-diacetyl hydrazone **8**. Removal of acetone and concomitant hydration of the nitrile moiety gave **9** which was distinctly different from its positional isomer **6a** (Scheme I).

A novel N–N bond cleavage was observed during the study of the hydrolysis reaction **2** → **3**. It was noted that this reaction always produced some α-methyl-dopa (**11**) along with the desired hydrazino acid **3**. The amount of **11** produced was inversely related to the acid concentration of the medium. A likely pathway to explain these facts is depicted in Scheme III.

(8) (a) S. Karady, M. G. Ly, S. H. Pines, and M. Sletzinger, *J. Org. Chem.*, **36**, 1949 (1971). (b) Levorotatory **3** possesses L (*S*) configuration.[8a]

(9) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, pp 127–128.

SCHEME III



Support for this scheme rests upon the observations that (a) hydrazino nitrile **2** readily loses hydrogen cyanide, even from the dry state, and such a dissociation could be expected to be repressed by strong protonation; (b) methyl vanillyl ketone **1** readily reacts with **2**, and the only product isolable from acid hydrolysis of an equimolar mixture of the two is α-methyl-dopa (**11**).

Resolution of *dl*-**3** *via* controlled direct crystallization (without resort to diastereomer formation) seemed likely, in view of the above-mentioned solubility relationships and X-ray evidence that the racemate was a mixture, not a compound.[10] Such a method, seldom used in the laboratory,[11] is uniquely useful, especially when large samples are required. A glassware bench-scale unit[12] similar in essentials to the commercial system already described[13] was set up and operated continuously in order to produce several hundred grams of each isomer.

Experimental Section[14]

α-(Acetylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)propionitrile (5a).—To a cooled solution of hydrazinonitrile[2] **2** (2.21 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) in 25 ml of tetrahydrofuran and 35 ml of dioxane was added 1.1 ml of acetic anhydride. The mixture was stirred at room temperature

(10) This feature is not a requirement, but it appears helpful. For a comprehensive review of the methods of direct resolution, see R. M. Secor, *Chem. Rev.*, **63**, 297 (1963).

(11) For an example of its application, see H. E. Zaugg, *J. Amer. Chem. Soc.*, **77**, 2910 (1955), who resolved *dl*-methadone in like fashion.

(12) Unpublished work of Messrs. J. Allegretti, J. Meyer, and A. Wildman of the Chemical Engineering Research Staff of these laboratories.

(13) *Chem. Eng.*, **72**, 247 (1965).

(14) Melting points are uncorrected. Elemental analyses were performed by Mr. R. N. Boos and associates of these laboratories. Ir spectra were obtained with a Perkin-Elmer Model 137 Infracord, uv with a Perkin-Elmer Model 202 spectrophotometer, and nmr with a Varian A-60A. In the interests of brevity, ir, uv, and nmr data are not routinely reported. Unless otherwise stated, it may be assumed that all organic solutions were dried over sodium sulfate; solvent was removed by vacuum evaporation in a rotating evaporator. Preparative chromatographies were run on silica gel H (E. Merck). Commercially available tlc plates (Analtech or Brinkmann) were used without pretreatment.

for 1 hr and then evaporated to dryness. The resulting syrup was triturated with ether to afford 2 g (77%) of crystalline product. Recrystallization from ethyl acetate yielded analytically pure hydrazide **5a**, mp 123–124°.

Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.61; H, 6.63; N, 15.89.

α-(Benzoylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)propionitrile (5b).—A solution of hydrazinonitrile **2** (2.21 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) in a mixture of tetrahydrofuran (25 ml) and dioxane (25 ml) was cooled rapidly (ice bath) and benzoyl chloride (1.16 ml, 10 mmol) was added rapidly. After a few minutes, the mixture was warmed to room temperature and stirred for 1 hr. The solvent was removed, and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The organic layer was washed with saturated sodium chloride solution, dried, and evaporated to dryness. Crystallization from chloroform and ether afforded 3 g of crystalline benzoyl hydrazide **5b**. An analytical sample was recrystallized from ethyl acetate, mp 135–136°.

Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.89; N, 12.92. Found: C, 66.53; H, 6.03; N, 12.99.

α-(1-Methoxyacetylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)-propionitrile. 5c Resolution.—From similar reaction of 92.3 g of **2** and 1 equiv of l-menthoxyacetyl chloride was isolated 66 g of crystalline product and a mother liquor residue A amounting to 130 g of syrup. The former was recrystallized to constant rotation to provide 12 g of pure **5c**, mp 126–126.5°, $[\alpha]_{546}$ −47.1° (*c* 0.8, MeOH).

Anal. Calcd for $C_{23}H_{35}N_3O_4$: C, 66.16; H, 8.45; N, 10.06. Found: C, 66.21; H, 8.68; N, 10.23.

L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (L-3).—A mixture of 25 ml of methanol and 30 ml of concentrated HCl was saturated at 0–5° with hydrogen chloride. To it was added 3 g of **L-5c** and the mixture was stirred overnight, warming to room temperature. The solvent was removed and replaced with 45 ml concentrated HCl and 5 ml acetic acid, and the solution was heated in a sealed tube at 120° for 90 min. After cooling, the contents were evaporated to dryness, taken up in 25 ml of ethanol, and precipitated by the addition of 5 ml of benzene and diethylamine to pH 6.5. The product (1.1 g, 58%) was recrystallized from hot water (charcoal) to give 900 mg of pure L-hydrazino acid, mp 203–205° dec, $[\alpha]_D$ −17.3° (MeOH).

Anal. Calcd for $C_{10}H_{14}N_2O_4 \cdot H_2O$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.13; H, 6.74; N, 11.19.

D-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (D-3).—Syrup A (20 g) (above, synthesis of **5c**) was treated with hydrochloric acid as in the case of the L isomer. The crude product gave, after two recrystallizations from water, 700 mg of analytically pure D-hydrazino acid, mp 205° dec, $[\alpha]_D$ +17° (MeOH).

Anal. Found: C, 49.15; H, 6.45; N, 11.18. Thermogravimetric analysis showed 7.4% weight loss (theory, 7.4% for monohydrate).

α-(Acetylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)propionamide (4a).—Propionitrile **5a** (5 g) was dissolved in 10 ml of ice-cold concentrated HCl and allowed to stand overnight. The precipitated product was filtered and washed with cold water and ethanol to afford 5 g of the hydrochloride of **4a**, mp 215–217°. To the slurry of 5 g of this salt in 200 ml of methanol was added 5 ml of propylene oxide. After 15 min the homogeneous solution was evaporated to dryness. Pure propionamide **4a** was obtained by crystallization from acetonitrile, mp 154–156°.

Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.97. Found: C, 55.37; H, 6.68; N, 14.91.

α-(Acetylhydrazo)-α-(4-acetoxy-3-methoxybenzyl)propionamide (6a).—To an ice-cold slurry of **4a** hydrochloride (634 mg, 2 mmol) in water (10 ml) was added 0.75 ml of 8 *N* potassium hydroxide and 0.25 ml of acetic anhydride. The mixture was stirred for 2 hr and then evaporated to dryness. The residue was stirred in 10 ml of tetrahydrofran and 1 ml of propylene oxide for 1 hr. The insolubles were removed and the filtrate was concentrated to a small volume. The resulting mixture was chromatographed on silica gel H, utilizing a mixture of chloroform, hexane, and methanol (8:2:1.5) as eluent. The pure diacetate **6a** was crystallized from ethyl acetate, mp 120–125°.

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.76; H, 6.56; N, 12.76.

α-(1-Acetyl-2-isopropylidenehydrazino)-α-(4-acetoxy-3-methoxybenzyl)propionitrile (8).—Hydrazinonitrile **2** (4.29 g, 20 mmol) was dissolved in 50 ml of acetone and the solution was allowed to stand for 1 hr. The solvent was removed under vacuum at room temperature leaving hydrazone **7** as a syrup. To its solution in 50 ml of tetrahydrofuran and 10 ml of pyridine was added dropwise 7.1 ml of acetyl chloride. After standing at room temperature for 4 days, the reaction mixture was evaporated to dryness and partitioned between ether and 2.5 *N* HCl. The organic layer was washed with potassium bicarbonate solution, the solvent was removed, and 800 mg of product was crystallized from ether and hexane. An analytical sample was prepared by recrystallization from ethyl acetate, mp 150–153°.

Anal. Calcd for $C_{18}N_{23}N_3O_4$: C, 62.59; H, 6.71; N, 11.98; O, 18.53. Found: C, 62.76; H, 6.76; N, 12.17; O, 18.74.

α-(1-Acetylhydrazino)-α-(4-acetoxy-3-methoxybenzyl)propionamide (9).—Hydrazone **8** (350 mg) was dissolved in a mixture of 8 ml of methanol, 8 ml of water, and 2 ml of 2.5 *N* HCl with warming (30–40°). The mixture was allowed to stand at room temperature for 2 hr and then evaporated to a small volume. The product was extracted with ethyl acetate. The solution was washed (saturated bicarbonate solution), dried, and concentrated to a small volume, and the product was allowed to crystallize. Recrystallization from ethanol–ethyl acetate yielded analytically pure α-acetylhydrazide **9**, mp 170–172°. This material was clearly separable by tlc (benzene–acetone–acetic acid 50:50:2) from the isomeric β-hydrazide, **6a**.

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00; O, 24.74. Found: C, 55.53; H, 6.63; N, 12.65; O, 25.26.

α-Methyl-dopa (11) from Hydrazinonitrile 2.—To a solution of hydrazinonitrile **2** (1.1 g) in 25 ml of tetrahydrofuran was added methyl vanilyl ketone (**1**) (975 mg) and the mixture was allowed to stand at room temperature. After 30 min a tlc probe indicated that the two components reacted to form a new compound (presumably hydrazone **10**). After the solvent was removed the residue was dissolved in concentrated HCl and heated to 120° for 2 hr in a sealed tube. The solution was filtered, evaporated to dryness, and dissolved in water. Racemic α-methyl-dopa was precipitated from the solution with ammonia. After recrystallization this was identical with authentic specimens. In the crude hydrolysate, hydrazino acid **3** was not detectable.

Registry No.—**D-3**, 28875-92-5; **L-3**, 28860-95-9; **4a**, 28957-67-7; **4a** HCl, 28875-94-7; **5a**, 28875-95-8; **5b**, 28875-96-9; **5c**, 28875-97-0; **6a**, 28875-98-1; **8**, 28875-99-2; **9**, 28876-00-8.