evaporated under reduced pressure and the residue was purified on a 100 g of silica gel column. Elution with 10% ethyl acetate in benzene and evaporation of the solvent gave 1075 mg (100% yield) of 4-carbomethoxymethylchroman as an oil: ν_{film} 1740 (C=O), 1610, 1585 (aromatic ring), 1075 cm^{-1} (COC).

Registry No.—IV, 10513-48-1; VI, 15364-61-1; VII, 607-71-6; VIII, 15364-63-3; IX, 15364-64-4; X, 15364-65-5; XI, 15364-66-6; XII, 15364-67-7; XIII, 15364-68-8; XIV, 15523-38-3; XV, 15364-69-9; XVI, 15364-70-2; XVII, 15364-71-3; XVIIIa, 15364-72-4; XVIIIb, 15364-73-5; XVIIIc, 15364-74-6; XVIIId, 15364-75-7; XIXa, 15364-76-8; XIXb, 15364-77-9; XIXc, 15364-78-0; XIXd, 15364-79-1; XX, 15364-80-4; XXI, 5655-26-5; XXII, 15364-82-6.

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Synthesis of L-α-Methyldopa from Asymmetric Intermediates

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Two procedures for the synthesis of L-α-methyldopa from asymmetric intermediates are described. The substrates for the resolution and racemization processes are DL-α-amino-α-vanillylpropionitrile and DL-α-acetamido-α-vanillylpropionitrile. Hydrolysis of the L isomer yields L-α-methyldopa in high yield.

The hypotensive activity of α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa)[1] (VI) has been shown to reside only in the L isomer.[2] To eliminate the therapeutically impotent D isomer, DL-α-methyldopa has been resolved by conventional methods,[3] and, more recently, by a selective crystallization technique not involving a resolving agent.[4] However, resolution at the amino acid stage results in equal production of the unwanted D isomer which cannot be racemized by usual means because of the absence of an α hydrogen. Practical utilization of the D isomer has been limited to degradation to 3,4-dihydroxyphenylacetone followed by resynthesis of the amino acid.[5]

The asymmetry of the molecule is introduced on formation of the α-aminonitrile or hydantoin intermediates. Of these two intermediates, the α-aminonitrile, being a base[6] and formed in an equilibrium reaction,[7] is uniquely suited for both resolution[8,9] and racemization.[10] The resolutions hitherto reported have all been impaired by the facile hydrolysis of the salts of α-aminonitriles with weak acids. This leads to irreversible decomposition of the aminonitriles to the parent ketones and ammonia, which is captured by the resolving agent.

The optical instability of α-aminonitriles suggested that, in addition to the two general types of resolution process developed for DL-α-methyldopa, it would be possible to develop an asymmetric transformation,[11] initiated in this case by seeding with optically active α-aminonitrile which would result in the crystallization of only the desired L isomer in greater than 50% yield. This ultimate process requires not only a preliminary resolution to produce the seeds, but a favorable solubility relationship between the optically active forms, a rapid rate of crystal growth on the seed bed relative to nucleation of the inactive form, and, finally, a rate of racemization faster than the rate of crystallization.[12]

This approach was tested on the α-aminonitrile II prepared from 3-methoxy-4-hydroxyphenylacetone I (Scheme I). The initial resolution experiments[13] were frustrated by the tendency of its salts to dissociate. However, continued screening of the salts of II with strong acids, using the phase solubility analysis technique,[14] revealed that the *d*-10-camphorsulfonate could be resolved in dioxane, thanks to the formation of a crystalline solvate, $[\alpha]_D$ 15.6°. The absolute configuration and purity were determined by hydrolysis to D-α-methyldopa of known configuration.[3] The other enantiomer of II was obtained *via* the *l*-10-camphorsulfonate[15] dioxanate V, $[\alpha]_D$ −14.7°.

The optically active α-aminonitrile L-II, $[\alpha]_D$ 8.90°, was liberated from its salt with ammonia in ether. It melted completely at 86–88°, then immediately crystallized, and remelted at 125–128°; the melting point remained at 125° thereafter. Hydrogen cyanide

(1) G. Stein, H. A. Bronner, and K. Pfister, III, *J. Amer. Chem. Soc.*, **77**, 700 (1955).

(2) (a) C. Stone, C. Porter, L. Watson, and C. Ross, Hypertension, Recent Advan., Hahnemann Symp. 2nd, Philadelphia, Pa., May 1961, pp 417–423; (b) A. Sjoerdsma and S. Udenfriend, *Biochem. Pharmacol.*, **8**, 164 (1961).

(3) E. W. Tristram, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *J. Org. Chem.*, **29**, 2053 (1964).

(4) *Chem. Eng.*, **72**, 247 (Nov. 8, 1965).

(5) H. L. Slates, D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **29**, 1424 (1964).

(6) α-Aminonitriles are very weak bases. This property has been attributed to the inductive effect of the nitrile group. (a) A. Marver, *Helv. Chim. Acta*, **37**, 166 (1954); (b) S. Soloway and A. Lipschitz, *J. Org. Chem.*, **23**, 613 (1938); (c) G. Stevenson and D. Williamson, *J. Amer. Chem. Soc.*, **80**, 5943 (1958).

(7) (a) W. Cocker, A. Lapworth, and A. Walton, *J. Chem. Soc.*, **111**, 449 (1930); (b) T. D. Stewart and C. H. Li, *J. Amer. Chem. Soc.*, **60**, 2782 (1938).

(8) M. Delepine, *Bull. Soc. Chim. Fr.*, **29**, 1178 (1903).

(9) H. Reihlen, E. Weinbrenner, and G. von Hessling, *Ann.*, **494**, 143 (1932).

(10) R. Kuhn and J. C. Jochims, *Chem. Ber.*, **96**, 983 (1963).

(11) E. E. Turner and M. M. Harris, *Quart. Rev.* (London), **1**, 229 (1947).

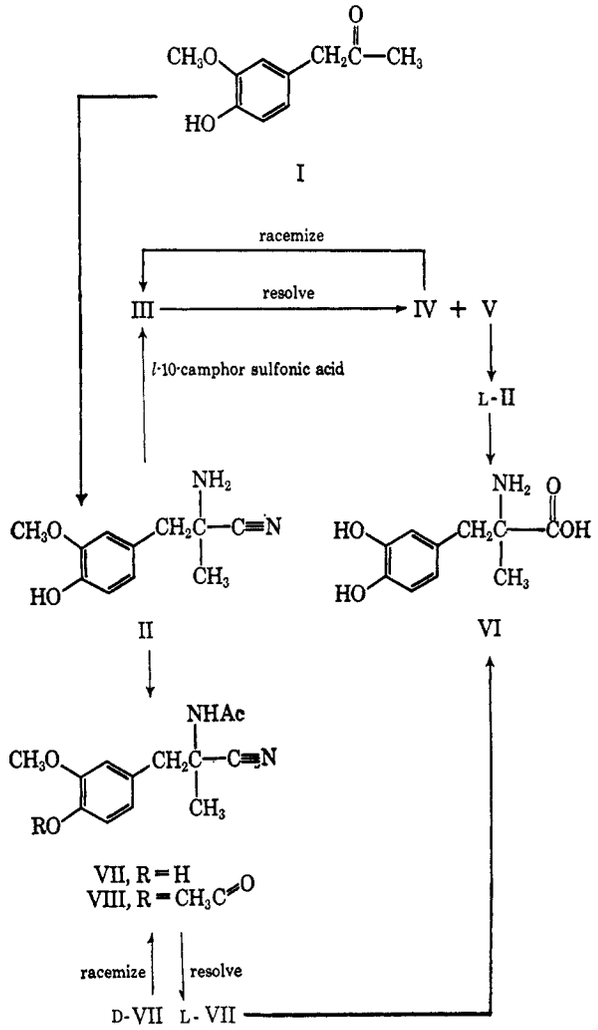
(12) E. Havinga, *Biochem. Biophys. Acta*, **13**, 171 (1954).

(13) To ascertain whether the α-aminonitrile II would be sufficiently optically stable for resolution, a study of the rate of radioactive cyanide incorporation was made. This study was made by Dr. C. Rosenblum and Messrs. H. Merriwether and A. M. Gerber of the Merck Sharp & Dohme Research Laboratories Division. It was assumed, and later proved correct, that the rate of cyanide exchange would be equal to the rate of racemization. This work, which will be published elsewhere, showed that strong acid salts are completely optically stable. The free L-aminonitrile is, for all practical purposes, optically stable in nonionizing solvents, *e.g.*, dioxane, chloroform, toluene, ether, etc., but unstable in ionizing solvents, *e.g.*, alcohols and water,

(14) T. J. Webb, *Ind. Eng. Chem., Anal. Ed.*, **20**, 100 (1948).

(15) H. Burgess and C. Gibson, *J. Soc. Chem. Ind.*, **44**, 496T (1948).

SCHEME I



was not evolved during the melting. L-II racemized 50–60% on melting at 86° and was completely racemized after having melted at 125–128°.

Determination of the solubilities of the optically active and racemic α-aminonitriles in nonionizing solvents, in which racemization was very slow, such as benzene, chloroform, and acetonitrile showed that the optically active form was five to nine times more soluble than the racemate. Thus, the prime requirement for a crystallization resolution was not met.[16]

In polar solvents in which L-II had limited solubility, the rate of racemization was too fast for solubility measurements. However, addition of optically pure seed to an aqueous solution of L-II gave a crystalline product which was extensively racemized. Unfortunately the unfavorable solubility relationship carried over into ionizing solvents and, with II, an asymmetric transformation leading to production of a single isomer would not be possible. Therefore, only the resolution by fractional crystallization of the diastereoisomeric salts was successful.

To complete this route for the synthesis of L-VI, L-II was treated with fortified HCl, simultaneously hydrolyzing the nitrile and cleaving the 3-methoxy group.

The search for a derivative which could be resolved by crystallization techniques was extended to the O,N-diacetyl (VIII) and N-acetyl (VII) derivatives, prepared by standard methods. In addition, racemic VII could also be synthesized in 86–90% yield directly from I by using acetonitrile or 2-propanol as the reaction solvent for formation of the α-aminonitrile, removal of the excess ammonia, and addition of acetic anhydride. This procedure, not involving the isolation of the α-aminonitrile, should be of general utility for the synthesis of N-acylated α-aminonitriles, which can be hydrolyzed in near-quantitative yield to the racemic N-acetylated amino acid (see Experimental Section), one of the preferred derivatives for resolution with optically active bases.

Comparison of the X-ray patterns and solubility data of the racemic and optically active diacetates indicated that VIII formed a *racemic compound* that was less soluble than the D or L form and, therefore, not suitable for resolution by crystallization techniques. On the other hand, a similar comparison of VII and L-VII revealed that the DL and L forms had identical X-ray patterns and that the DL form was exactly twice as soluble as the L form, which are the conditions for a *racemic mixture*. Thus fractional crystallization of VII seeding with either enantiomorph effected resolution.

The ease with which VII could be resolved now prompted a study of its racemization, so that the unwanted D isomer could also be utilized. Like VI, VII possesses no enolizable α-hydrogen atom, and consequently the breaking and re-forming of a C–C or C–N bond is required for racemization. This is easily accomplished thermally with α-aminonitriles in which the unshared electrons on the nitrogen assist the ionization of the cyanide group, but evidently these electrons are much less available in the case of α-acetamidonitriles such as VII, which was found to be optically completely stable even at its melting point, 204°. Even in solvents, such as methanol and methanol–water, which most strongly promote the ionization of α-aminonitriles, VII was optically stable under all conditions compatible with its chemical stability. At 200–225° in these solvents, hydrolysis of the N-acetyl group sets in, affording mixtures of 3-methoxy-4-hydroxyphenylacetone, α-aminonitrile, and cyanohydrin, but all samples of VII recovered from such partially hydrolyzed mixtures were found to be optically pure. The presence of an acidic catalyst, mercuric cyanide, was without effect in these solvents, while bases, as expected, simply catalyzed the hydrolysis reaction.

It thus was apparent that, if racemization rather than hydrolysis were to be the major reaction, the media would be limited to aprotic solvents. Of possible modes of racemization, the elimination and readdition of cyanide still appeared to be the most promising approach.

Refluxing D-VII in DMSO returned optically pure material in near-quantitative yield. It was anticipated that increasing the electron density on the amide nitrogen would facilitate the dissociation of the cyanide ion, and so this experiment was repeated in the presence of sodium cyanide. Under these conditions, racemization was at last achieved, rapidly and in good yield.[17]

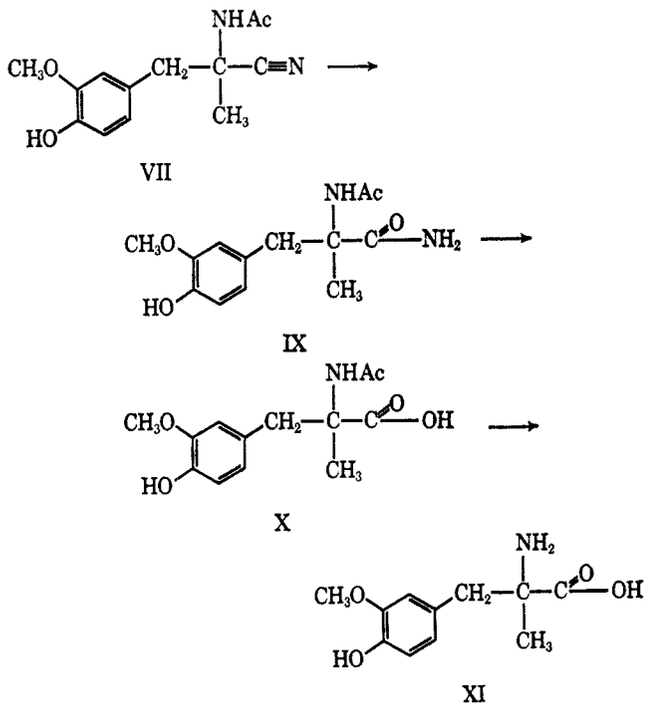
(16) R. M. Secor, *Chem. Rev.*, **63**, 297 (1963).

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

The demonstration of the resolution of VII by crystallization, followed by racemization of the D isomer, completed a second pathway for the efficient utilization of II. To complete the synthesis, L-VII was hydrolyzed with HCl to optically pure VI in nearly quantitative yield.

The hydrolysis of L-VII or DL-VII could also be accomplished in stepwise manner permitting isolation of any one of the three optically active or inactive intermediates, α-acetamido-α-vanillylpropionamide (IX), α-acetamido-α-vanillylpropionic acid (X), and α-methyl-3-methoxy-4-hydroxyphenylalanine (XI) (see Scheme II).

SCHEME II



L- or DL-VII dissolved exothermically in cold concentrated hydrochloric acid. Immediate dilution with ice water and adjustment of the pH to 5 with ammonium hydroxide precipitated L-IX as the monohydrate in 83% yield and the DL-IX in 86.5% yield. Tlc of the mother liquors indicated that VII was 100% hydrolyzed with X the only by-product. Extension of the hydrolysis period to 16 hr gave a 91 and 93% yield of L- or DL-X. L- or DL-XI could be obtained in good yield by selective hydrolysis with HCl.

The extremely facile conversion of VII to IX suggested that the N-acetyl was participating in the hydrolysis. However, the lifetime of the intermediate, if present at all, is too short to be detected by nmr methods at 0° in hydrochloric acid.

Experimental Section[18]

DL-α-Amino-α-vanillylpropionitrile (II). Procedure A.—3-Methoxy-4-hydroxyphenylacetone I (350 g, 1.94 moles) was added to a solution of ammonia (33.2 g, 1.95 moles) in 2-propanol (850 ml). Hydrogen cyanide (77 ml, 1.95 moles) was then added over 15 min while maintaining the temperature between 20–30°. The mixture was stirred at 25° for 18 hr, cooled at 0–5° for 1 hr, and filtered. Washing with two 100-ml portions of 2-propanol at 0° and drying at 10 mm and 40° gave 374 g (93.5% yield) of II: mp 125.5–127°; equiv wt 206; λ_{max}^{MeOH} 2800 mμ (ε 3070), 2300 mμ (ε 7090); solubility (mg/g), benzene, 2.83, acetonitrile, 51.4, chloroform, 21.0.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.90; H, 6.82; N, 13.78.

Procedure B.—To a solution of 3-methoxy-4-hydroxyphenylacetone (20 g, 0.11 mole) in 28% ammonium hydroxide (100 ml) was added potassium cyanide (8.0 g, 0.123 mole) and ammonium chloride (6.57 g, 0.123 mole). The mixture was stirred for 3 hr at 25° and 1 hr at 0–5°. The α-aminonitrile II was filtered, washed successively with cold 28% ammonium hydroxide (15 ml) and two 15-ml portions of 2-propanol at 0°, and vacuum dried at 25° to give 20.4 g (89.5% yield): mp 123–125°; equiv wt 208 (theory 206).

L-α-Amino-α-vanillylpropionitrile *l*-10-Camphorsulfonate–Dioxane Solvate (V).—DL-α-Amino-α-vanillylpropionitrile (158 g, 0.77 mole) was added to a solution at 40° of *l*-10-camphorsulfonic acid[16] (187 g, 0.80 mole) in water (490 ml). The mixture was cooled at 5° for 16 hr and the diasterioisomeric salt mixture III filtered, washed with ice water (150 ml), and dried in a vacuum to give 310 g (92% yield), $[\alpha]_D$ −20.5°.

The diasterioisomeric salts III were separated by digesting at 25° in dioxane (14 l.) for 90 hr. The insoluble salt V was filtered and redigested in dioxane (3250 ml) and water (32.5 ml) for 40 hr. Filtration and drying at 40° gave 101 g of pure V: $[\alpha]_D$ −14.7°; ν_{max}^{Nujol} 867 and 892 cm^{-1} (dioxane bands).

Anal. Calcd for $C_{25}H_{38}N_2O_8S$: C, 57.01; H, 7.27; N, 5.32. Found: C, 56.72; H, 7.25; N, 5.40.

Repetition of the above procedure with *d*-10-camphorsulfonic acid gave the D-α-amino-α-vanillylpropionitrile *d*-10-camphorsulfonate dioxane solvate.

L-α-Amino-α-vanillylpropionitrile (L-II).—A slurry of L-α-amino-α-vanillylpropionitrile *l*-10-camphorsulfonate dioxane solvate V (20.0 g) in ether (200 ml) was treated with ammonia gas under a pressure of 1 in. of mercury for 2 hr. The ammonium *l*-10-camphorsulfonate was removed by filtration and excess ammonia was removed by evaporation of the ether to a volume of 25 ml. Ether (175 ml) was added and hydrogen chloride passed into the solution to precipitate the α-aminonitrile hydrochloride. The hydrochloride salt (6.48 g) was slurried in ether (130 ml) and ammonia gas passed into the mixture for 2 hr. The ammonium chloride was filtered and the filtrate evaporated at reduced pressure below 25°. The oily residue crystallized on trituration with ether. Filtration and drying at 30° in a vacuum gave 5.3 g (68% yield) of L-II: mp 86–88°, resolidified and melted at 125–128°; $[\alpha]_D$ +8.9° (*c* 2, dioxane); solubility (mg/g of solvent), benzene, 32.6, acetonitrile 282.6, chloroform, 180.8.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.96; H, 6.78; N, 13.45.

An Attempt to Maintain the Optical Purity of L-II under Racemizing Conditions.—To a solution of L-α-amino-α-vanillylpropionitrile *l*-10-camphorsulfonate dioxane solvate V (1.0 g) in water (3 ml) was added seeds of L-II (10 mg). The pH of the slurry was immediately adjusted to 8 with concentrated NH_4OH and it was placed in an ice bath. The precipitate after aging 1 hr, filtering, and drying in vacuum below 25° weighed 65 mg: $[\alpha]_D$ +3.5° (*c* 2, dioxane), 35% optically pure. The filtrate was again seeded with L-II (10 mg) and aged at 0° for 2 hr. A second crop (100 mg) was obtained: $[\alpha]_D$ +1.4°,

(18) All optical rotations were determined on a Carl Zeiss photoelectric precision polarimeter Model 005. Unless specified, a 1% solution in methanol at 25° was used for all rotations. The $[\alpha]_D$ was calculated using the simplified formula

$$[\alpha]_D = [\alpha]_{578} - [([\alpha]_{578} - [\alpha]_{546}) \times 0.294]$$

Melting points are uncorrected and were determined with a Thomas–Hoover capillary melting point apparatus.

Infrared spectra were determined on a Model 137 Infracord. Equivalent weights were determined in glacial acetic acid by titrating potentiometrically with 0.1 *N* $HClO_4$ in dioxane using a Sargent Model D titrator equipped with the following electrode system: (1) a platinum ring electrode #S30440, and (2) a Calomel sleeve-type Sargent S30084-15 which has had the aqueous electrolite removed, rinsed with water, rinsed with acetic acid, and filled with 0.1 *N* lithium perchlorate (available from G. S. Smith & Co.) in acetic anhydride.

Microanalyses were done through the courtesy of Mr. R. N. Boos and associates. Infrared data were compiled by Dr. N. R. Trenner and Mr. R. W. Walker. Nmr analyses were by Dr. N. R. Trenner, Dr. B. A. Arison, and Mr. B. Singleton. Titrations were by Mr. B. Singleton, Mr. J. P. Gilbert, and associates. Ultraviolet and solubility data were compiled by Mr. E. A. MacMullen and associates.

14% optically pure. The filtrate was again seeded (10 mg) and aged overnight at 0° to give a third crop (130 mg) which was 100% racemic.

Racemization of D-α-Amino-α-vanillylpropionitrile *l*-10-Camphorsulfonate (IV).—Optically impure salt IV (10.0 g), obtained by evaporation of dioxane mother liquors of V, was dissolved in water (20 ml) and concentrated ammonium hydroxide (1.3 ml, 0.019 mole) added. After standing 6 hr, concentrated hydrochloric acid (1.6 ml, 0.019 mole) was added. The mixture was cooled at 0–5° for 18 hr, filtered, washed with ice water, and dried to give 6.0 g of III: $[\alpha]_D$ −20.5°.

Racemization of D-α-Amino-α-vanillylpropionitrile (D-II).—A thick slurry of D-II (510 mg) in 2-propanol (1 ml) was heated in a 40° water bath for 7 hr. Evaporation of the solvent below 40° in a vacuum gave a crystalline residue (510 mg) which was 96% racemic: mp 123.5–126.5°; $[\alpha]_D$ −0.14° (*c* 1, dioxane).

L-O,N-Diacetyl-α-amino-α-vanillylpropionitrile (L-VIII).—A solution of L-II (2.0 g) in pyridine (10 ml) and acetic anhydride (10 ml) was heated for 15 min at 90°, cooled to 20°, poured into water (100 ml), and extracted with chloroform. The chloroform solution was washed successively with cold 2.5 *N* hydrochloric acid and water. The chloroform solution was dried over magnesium sulfate and evaporated to give an oil. Crystallization from 2-propanol–petroleum ether (30–60°) gave 2.7 g (96% yield) of L-VIII: mp 121.5–123.5°; $[\alpha]_D$ −40.7°; $\nu_{max}^{CHCl_3}$ 1770 (OAc), 1685 cm^{-1} (NAc).

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.96; H, 6.32; N, 9.66.

DL-O,N-Diacetyl-α-amino-α-vanillylpropionitrile (VIII).—Synthesis of VIII was accomplished in 95% yield using the same procedure as used for L-VIII: mp 166–168°; infrared in chloroform identical with that of L-VIII.

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.90; H, 6.06; N, 9.58.

DL-α-Acetamido-α-vanillylpropionitrile (VII). Procedure A.—To a slurry of DL-α-amino-α-vanillylpropionitrile (20 g) in 2-propanol (40 ml) at 20° was added acetic anhydride (20 ml). The exothermic reaction and crystallization raised the temperature to 48°. The slurry was slowly cooled to 0–5° and aged at 0–5° for 1 hr. The precipitate was filtered, washed twice with 10-ml portions of cold 2-propanol, and dried, to give 24.0 g (97% yield): mp 176–178°; ν_{max}^{Nujol} 1667 cm^{-1} (NAc); solubility in 2-propanol, 8.5 mg/g.

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.96; H, 6.50; N, 11.20.

Procedure B.—Ammonia (1.9 g, 0.11 mole) was dissolved in 2-propanol (45 ml) at 5°, followed by addition of 3-methoxy-4-hydroxyphenylacetone I (18.0 g, 0.10 mole) and hydrogen cyanide (4.15 ml, 0.105 mole). After stirring for 18 hr, toluene (110 ml) was added and the mixture evaporated at reduced pressure to a volume of 75 ml. Acetic anhydride (20 ml) was added to the slurry which was then heated to the boiling point. The mixture was cooled at 0–5° for 1 hr, filtered, and washed with two 15-ml portions of toluene. Vacuum drying at 45° gave 22.85 g (91.4% yield) of VII: mp 176–178°; λ_{max}^{MeOH} 2810 mμ (ε 3050), 2320 mμ (ε 7800).

L-α-Acetamido-α-vanillylpropionitrile (L-VII). By Synthesis from L-VIII.—A solution of L-VIII (1.0 g) in ethanol (10 ml) and 10% sodium hydroxide (1.5 ml) was stirred at 25° for 2 hr. The solution was diluted with water (10 ml) and acidified with hydrochloric acid. The product L-VII was filtered, washed with water, and dried to 800 mg (93.5% yield): mp 204–206°; $[\alpha]^{30}_D$ −42.4°; ν_{max}^{Nujol} 1665 cm^{-1} (N-Ac), solubility in 2-propanol, 4.2 mg/g.

By Resolution of VII.—VII (1.0 g) was dissolved at 50° in 2-propanol (25 ml) and filtered to remove any potential seeds. The filtrate was cooled to 40° and finely pulverized L-VII (50 mg) was added with stirring. The slurry was cooled to 30° in 5 min and rapidly filtered to give 300 mg of L-VII, $[\alpha]_D$ −25.8° (63% optically pure). Crude L-VII (200 mg) was digested with 2-propanol (10 ml) for 16 hr at 25°, filtered, and washed with 2-propanol to give 110 mg of optically pure material: mp 203–204°; $[\alpha]^{30}_D$ −42°.

Anal. Calcd for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.30; N, 11.49.

Unsuccessful Racemization Studies on D-α-Acetamido-α-vanillylpropionitrile (D-VII). A.—D-VII (20.0 mg) was heated in an oil bath at 207° for 1 min, until completely melted. After cooling, the entire sample retained 100% optical purity.

B.—D-VII (20.3 mg) was heated with 0.5 ml of methanol in a sealed tube for 8 hr at 225°. The total sample then showed 39% of its original optical activity. The residue from evaporation of the solvent crystallized on treatment with chloroform. It was filtered and washed with a little 2-propanol, then had a weight of 5.3 mg and an optical purity of 98%. The filtrate after evaporation weighed 11.8 mg and was *ca.* 80% pure ketone I by ir; the purity would be 78% if all but 39% of the original L-VII had been hydrolyzed to I rather than racemized. Using the 78% figure, the calculated yield of ketone (11.8 × 0.78) is *ca.* 62%, for a mass balance of *ca.* 101%. Thus the loss of optical activity in the total sample is quantitatively accounted for by hydrolysis to I.

Similar results were obtained with 50% aqueous methanol. A similar reaction was run for 9 hr at 200° with 0.5 mg of mercuric cyanide present. The total reaction mixture had 81% retention of optical activity, and from it was isolated 63% of off-color crystalline D-VII, 97% optically pure.

Racemization of D-α-Acetamido-α-vanillylpropionitrile (D-VII).—A mixture of D-VII (2.0 g, 0.008 mole) and sodium cyanide (0.20 g, 0.004 mole) in dimethyl sulfoxide (8.0 ml) was subjected alternately to a vacuum and nitrogen source three times. The flask was placed in a preheated (200°) oil bath. After reaching the boiling point, which required 2 min to attain, the mixture was allowed to reflux 3 min, then immediately was cooled in an ice bath. The dimethyl sulfoxide was distilled under reduced pressure to a syrupy residue. Dilute hydrochloric acid (15 ml) was added to crystallize the light tan product. The racemized product was filtered, washed with water, and vacuum dried to give 1.84 g (91.8% yield): mp 173–176°; $[\alpha]^{30}_D$ 0°. The material was identical in all respects with VII obtained by acetylation of II.

L-α-Methyl-3,4-dihydroxyphenylalanine Sesquihydrate (VI). From L-VII.—A solution of L-VII (24.8 g, 0.1 mole) in concentrated hydrochloric acid (46 ml) in a bomb tube was purged with nitrogen, sealed, and heated at 130° for 5 hr. The tube was cooled in a Dry Ice–acetone bath and opened; the contents were transferred to a round-bottom flask. The hydrochloric acid was distilled at reduced pressure and the residual acid removed by dissolving in water (100 ml) and evaporating again to dryness. The residue was dissolved in water (35 ml), treated with Darco G-60 (1.0 g), and the pH adjusted to 4.5 with concentrated ammonium hydroxide under a nitrogen atmosphere. The mixture was cooled at 0–5° for 1 hr and the white product filtered, washed with two 10-ml portions of ice water, and vacuum dried at 40° to give 21.9 g: mp 302–304° dec; equiv wt 238.1; H_2O, 11.3% (Karl Fischer) (calcd, 11.3%); $[\alpha]_{546}$ +154.5° (*c* 0.5, copper sulfate solution).[3]

From L-II.—The α-aminonitrile L-II was hydrolyzed and the product isolated in the same way except that 45% hydrochloric acid was used as the hydrolysis medium.

L-α-Acetamido-α-vanillylpropionamide (L-IX).—The N-acetylaminonitrile L-VII (20.0 g) was dissolved in concentrated hydrochloric acid (40 ml) at 0°. The solution was immediately diluted with ice water (100 ml) and the pH adjusted to 5.0 with concentrated ammonium hydroxide. The crystals were filtered, washed with ice water, and vacuum dried at 40°. The amide L-IX weighed 18.78 g (82%) and was obtained as the monohydrate: 6.23% (Karl Fischer) (calcd, 6.34%). Crystallization of the monohydrate from 2-propanol gave the anhydrous amide: mp 186–187°; $[\alpha]_D$ −69.2°.

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.40; H, 6.92; N, 10.23.

DL-α-Acetamido-α-vanillylpropionamide (IX).—Hydrolysis of VII (20.0 g), using the same procedure as described above for the optically active material gave 18.56 g (86.5% yield) of anhydrous material: mp 217–222°; ν_{max}^{Nujol} 1695 (N-Ac) and 1630 cm^{-1} C(=O)–NH_2.

The analytical sample was prepared by recrystallization from aqueous methanol, mp 224–228°.

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.81; H, 6.85; N, 10.38.

L-α-Acetamido-α-vanillylpropionic Acid (L-X).—L-VII (20.0 g) was dissolved in cold concentrated hydrochloric acid and stirred for 16 hr at 25°. Addition of water (100 ml) completed the crystallization of the product. Filtration, followed by washing with water and forced air drying, gave 20.9 g (91% yield) of L-X as the monohydrate: H_2O, 6.54% (Karl Fischer) (calcd, 6.39%); $[\alpha]_D$ −50.9°.

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.75; H, 6.72; N, 4.91. Found: C, 54.50; H, 6.65; N, 5.19.

DL-α-**Acetamido-α-vanillylpropionic Acid (X).**—Hydrolysis of VII using the identical procedure as used for L-VII gave 20.0 g (93% yield), mp 213–216°. Crystallization from water provided the analytical sample, mp 218–220°.

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.56; H, 6.21; N, 5.38.

L-α-**Methyl-3-methoxy-4-hydroxyphenylalanine (L-XI).**—L-VII (100 g) was added portionwise to cold concentrated hydrochloric acid (200 ml). The solution was diluted with water (1 l.) and the mixture refluxed for 5 hr. After cooling to 20°, the pH was adjusted to 5.0 with concentrated ammonium hydroxide. The product was filtered, washed free of chlorides with water, and vacuum dried to yield 87.7 g, mp 307° dec. The analytical sample was prepared by dissolving crude L-XI in dilute hydrochloric acid, treating with Darco G-60, and reprecipitating as the monohydrate by adjusting to pH 5.5: mp 313° dec; $[\alpha]_{546}$ +166° (*c* 0.5, copper sulfate solution);[3] H_2O, 8.0% (Karl Fischer) (calcd 7.5%). A single spot appeared on paper strip chromatography using a *n*-BuOH–H_2O–HOAc system (120:50:30). The sample (spotted as 1% solution in water saturated with sulfur dioxide) was detected by spraying with diazotized *p*-nitroaniline, drying, and spraying with 5% sodium carbonate solution.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71. Found: C, 58.66; H, 6.42. (Sample dried at 100°.)

DL-α-**Methyl-3-methoxy-4-hydroxyphenylalanine (XI).**—The DL-N-acetylaminonitrile VII (20.0 g) was dissolved in concentrated hydrochloric acid (40 ml), diluted with water (40 ml), and heated at 90° for 4 hr until solution was complete. The water was removed at reduced pressure and the residue dissolved in water. Adjustment to pH 6.0 with concentrated ammonium hydroxide resulted in the precipitation of the amino acid. The product was filtered, washed with water, and vacuum dried to give 17.75 g (97.5% yield), mp 318–320° dec.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71. Found: C, 58.40; H, 6.60.

Registry No.—II, 6555-27-7; L-II, 14818-96-3; III, 15073-71-9; V, 15073-82-2; VI, 555-30-6; VII, 14818-97-4; L-VII, 14818-98-5; VIII, 15073-74-2; L-VIII, 15073-76-4; IX, 15156-57-7; L-IX, 15073-77-5; X, 15073-78-6; L-X, 15073-79-7; XI, 15073-80-8; L-XI, 6739-31-7.

The Racemization of α-Methyl-α-acetamidonitriles

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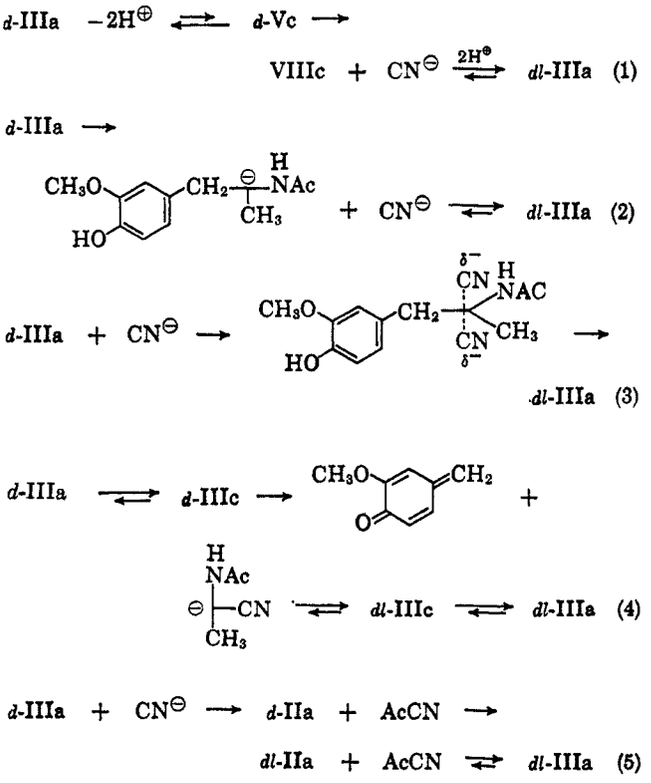
The mechanism of base-catalyzed racemization of α-acetamidonitriles bearing no enolizable α hydrogen has been studied and found to proceed *via* elimination and readdition of the elements of HCN; the amide nitrogen must bear a hydrogen atom. The rate-determining step is not deprotonation but expulsion of cyanide from the amide anion.

In the production of L-α-methyldopa *via* the aminonitrile route, resolution can be accomplished on either the amino acid itself,[1] the α-amino-2-vanillylpropionitrile IIa,[2] or the α-acetamido-α-vanillylpropionitrile IIIa.[2] Both enantiomers can be utilized if the unwanted D isomer can be racemized. This cannot be done at present with I, and, although racemization of II is facile, its resolution is not. Compound IIIa, however, crystallizes as a *dl* mixture, and its resolution by spontaneous crystallization has been accomplished; thus racemization of D-IIIa became a paramount goal.

This was eventually achieved using sodium cyanide in DMSO. A preliminary description of this method is contained in the accompanying paper,[2] and we here report details of the reaction and its mechanism. The first portion of the study was concerned with the scope of the reaction, and the second with kinetics.

Although it was found that IIIa could be racemized by any base of sufficient strength and solubility, sodium cyanide was used in most of the work because it gave the best yields, presumably by suppressing loss of cyanide from the product. In dry DMSO, IIIa could be conveniently racemized in high yield at temperatures ranging from about 140° to reflux (189°). The rate increased about threefold for each 10° rise in temperature. A selection of racemization data obtained in DMSO is presented in Table I.

Five mechanisms were originally considered for the reaction (eq 1–5).



Direct ionization (eq 2) was eliminated by the observation that racemization did not occur in the

(1) E. W. Tristam, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *J. Org. Chem.*, **29**, 2053 (1964).

(2) D. F. Reinhold, R. A. Firestone, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *J. Org. Chem.*, **33**, 1209 (1968).