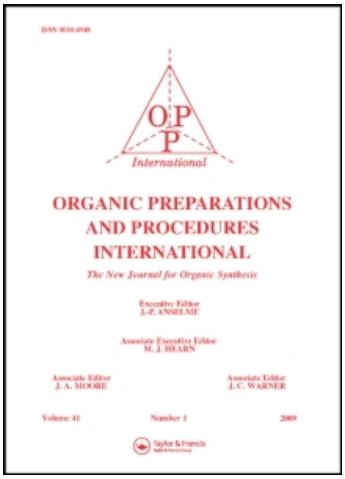

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SYNTHESIS OF erythro-α-METHYLEPINEPHRINE HYDROCHLORIDE

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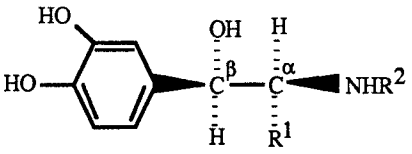
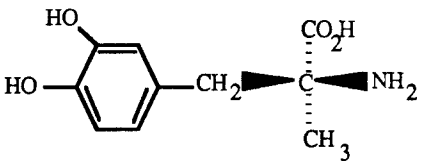
Earlier we reported the resolution of (±)-erythro-α-methylepinephrine [(±)-1] into its enantiomers[1] and the capacity of (αS,βR)-1 and



(αS,βR)-1, $R^1=R^2=CH_3$
(αS,βR)-3, $R^1=CH_3$; $R^2=H$
(R)-4, $R^1=H$; $R^2=CH_3$
(R)-5, $R^1=R^2=H$

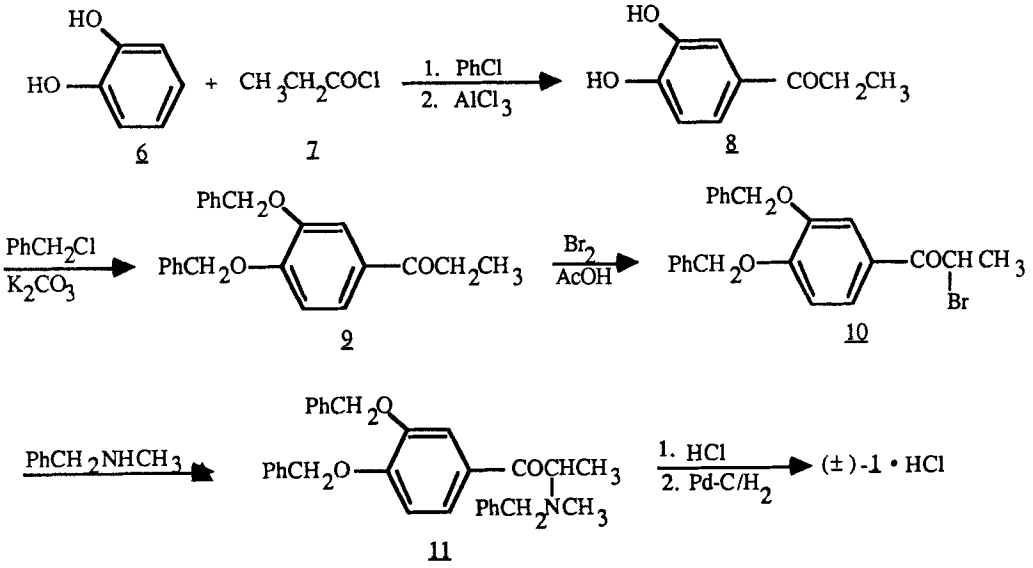


L-2

other intraneuronal metabolites of L-α-MeDopa (L-α-methyl-3,4-dihydroxyphenylalanine, L-2) to bind to adrenergic receptors of the α-1, α-2, and β subtypes in rat forebrain.[1,2] These studies showed that (αS,βR)-1 and (αS)-erythro-α-methylnorepinephrine [(αS,βR)-3] both compete with high affinity for α-2 receptors, thereby supporting the suggestion that α-2 receptors mediate hypotensive effects of L-2. Furthermore, both (αS,βR)-1 and (αS,βR)-3 also compete with high affinity for β receptors in rat forebrain, and (αS,βR)-1 is more effective than

(α*S*,β*R*)-3, (*R*)-epinephrine [(*R*)-4], and (*R*)-norepinephrine [(*R*)-5] in competing for β-2 adrenergic receptors on human lymphocytes. These results suggest that both α and β receptor stimulation may be important in determining the net effect of *L*-2 as a hypotensive agent.

A substantial quantity of (±)-1 was required for a continuation of the research with (±)-1 and its enantiomers. The earlier reported[3-5] syntheses of (±)-1 were investigated and were found to be unsatisfactory, and we now report the details of a different synthetic route which leads consistently to a good overall yield of (±)-1·HCl.



As reported earlier,[6] 3,4-dihydroxypropiophenone (8) was prepared by the reaction of propionyl chloride (7) with catechol (6) by way of the Fries rearrangement using aluminum chloride as catalyst. Compound 8 was converted to 3,4-dibenzyloxypropiophenone (9) using a method described[7] for the preparation of 3,4-dibenzyloxybutyrophenone. Bromination of 9 in methylene chloride with bromine and calcium carbonate[3,7] was unsuccessful in that some hydrolysis of the benzyl ether bonds invariably occurred. α-Bromo-3,4-dibenzyloxypropiophenone (10) was prepared, however, by

bromination of 9 in glacial acetic acid.[6] Reaction of 10 with N-methylbenzylamine gave α-(N-methylbenzylamino)-3,4-dibenzyloxypropiophenone (11). Conversion of 11 to the hydrochloride and reduction of 11·HCl with hydrogen over palladium on carbon gave (±)-erythro-α-methylepinephrine hydrochloride [(±)-1·HCl]. Its proton nuclear magnetic resonance spectrum (Experimental Section) was essentially identical to that previously reported[1] while intermediates 9-11 exhibited ^{1}H NMR spectra consistent with their assigned structures. When the keto amine hydrochloride (11·HCl) was dissolved in dry chloroform-d, the ^{1}H NMR spectrum was complex and not easily rationalized. The complexity was due to the presence on the NMR time scale (100 MHz) of two configurational diastereomers both with a carbon and a nitrogen chiral center, one diastereomer favored over the other by ca. 3:1. Addition of a trace of water to the chloroform-d solution allowed rapid exchange of the proton on nitrogen and simplified the spectrum which was now consistent with the structure of 11·HCl. When a drop of aqueous potassium carbonate was added to the chloroform-d solution, the spectrum reverted to that of the free amino ketone 11.

EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes and are corrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in $CDCl_3$ with TMS as an internal standard or in D_2O with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard using a JEOL JNM-MH-100 (100 MHz) or JNM-FX-90Q (90 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from the respective internal standard. Each preparative step described below was carried out a number of times and became routine.

3,4-Dihydroxypropiophenone (8).- Thionyl chloride (73 g, 0.61 mol) was added with stirring to propionic acid (47 g, 0.63 mol). The temperature of the exothermic reaction was maintained at room temperature by external cooling (ice bath), and the mixture was stirred until the evolution of gas ceased. The solution was added with stirring to a slurry of catechol (6) (50.5 g, 0.459 mol) in chlorobenzene (200 mL). The mixture was

warmed slightly and stirred for 1 hr during which the catechol dissolved, the reaction mixture turned deep blue, and the evolution of gas ceased. The solution was chilled in an ice bath, and aluminum chloride (133 g, 1.00 mol) was carefully added. The mixture was removed from the ice bath and warmed on the steam bath until gas evolution ceased (ca. 1 hr). The mixture was again chilled with ice, and crushed ice (ca. 300 mL) in small portions and then conc. hydrochloric acid (50 mL) were added. The chlorobenzene was removed by steam distillation, and the hot residue (600 mL) was allowed to cool with stirring. While the mixture was still quite warm, toluene (75 mL) and conc. hydrochloric acid (50 mL) were added. After standing for 3 hr at room temperature, the precipitate was collected by filtration and washed with water and then with toluene. After air drying, there was obtained 55.7 g (73%) of crude 8, mp. 129-141°. Recrystallization from toluene gave 38.4 g (50%) of 8 as light tan plates, mp. 142-146°, lit.[6] mp. 146-148°.

3,4-Dibenzyloxypropiophenone (9).- A mixture of 3,4-dihydroxypropiophenone (8) (16.2 g, 97.5 mmol), potassium carbonate (18.1 g, 131 mmol), and benzyl chloride (29.8 g, 235 mmol) in 95% ethanol (50 mL) was boiled with stirring for 18 hr. Water (50 mL) was added, and the ethanol was removed by distillation. The hot residue was then poured onto crushed ice (ca. 300 mL) and extracted with methylene chloride (3 x 100 mL). The combined methylene chloride extract was dried (Na_2SO_4) and evaporated at reduced pressure. The residue (36.0 g), which sometimes was a syrup and could be crystallized by trituration with hexanes, was recrystallized from toluene-hexanes. Thus 23.7 g (70%) of 9 was obtained as dense granular prisms, mp. 64-67°, lit.[3] mp. 66°. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3, J = 7 Hz, $C\underline{H}_3CH_2CO$), 2.92 (q, 2, J = 7 Hz, $CH_3C\underline{H}_2CO$), 5.23 (s, 2, $C_6H_5C\underline{H}_2O$), 5.25 (s, 2, $C_6H_5C\underline{H}_2O$), 6.97 (d, 1, J = 8 Hz, catechol C-5 H), 7.42 ppm (m, 12, $C_6\underline{H}_5CH_2$ and catechol C-2 and C-6 H).

α-Bromo-3,4-dibenzyloxypropiophenone (10).- A solution of bromine (4.18 g, 26.2 mmol) in glacial acetic acid (8.3 mL) was added dropwise over ca. 5 min to a stirred solution of 3,4-dibenzyloxypropiophenone (9) (8.62 g, 24.9 mmol) and conc. hydrochloric acid (ca. 0.08 mL) in glacial acetic acid (83 mL). The bromine color disappeared after about one-half hr, but stirring was continued for an additional one-half hr. The solution was poured into crushed ice (ca. 200 mL), and the solution was chilled with ice and brought to pH 7 by the addition of conc. ammonium hydroxide (ca. 120 mL). The neutral solution was extracted with methylene chloride (3 x 100 mL), and the combined methylene chloride solution was washed with saturated brine (2 x 50 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue (10.7 g) crystallized on standing, and recrystallization from absolute ethanol gave 5.63 g (53%) of 10, mp. 86-89°, lit.[3] mp. 93-94°. ^{1}H NMR ($CDCl_3$): δ 1.87 (d, 3, J = 7 Hz, CH_3CHCO), 5.23 (m, 5, CH_3CHCO and $C_6H_5CH_2O$), 6.98 (d, 1, J = 8 Hz, catechol C-5 H), 7.43 ppm (m, 12, $C_6H_5CH_2$ and catechol C-2 and C-6 H).

α-(N-Methylbenzylamino)-3,4-dibenzyloxypropiophenone Hydrochloride (11•HCl).- A mixture of α-bromo-3,4-dibenzyloxypropiophenone (10) (8.32 g, 19.6 mmol) and N-methylbenzylamine (4.74 g, 39.1 mmol) in dry benzene (21 mL) was boiled for 7 hr. The mixture was allowed to stand at room temperature for two days. Solid N-methylbenzylamine hydrobromide was removed by filtration and washed with several small portions of benzene. Evaporation of the benzene gave 9.38 g (103%) of 11 as a light amber syrup which showed one major spot (R_f 0.4) on thin layer chromatography (silica gel, 20% ethyl acetate in hexanes as eluant). ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3, J = 7 Hz, CH_3CHCO), 2.18 (s, 3, CH_3N), 3.58 (s, 2, $C_6H_5CH_2N$), 4.17 (q, 1, J = 7 Hz, CH_3CHCO), 5.15 (s, 2, $C_6H_5CH_2O$), 5.22 (s, 2, $C_6H_5CH_2O$), 6.90 (d, 1, J = 9 Hz, catechol C-5 H), 7.38 ppm (m, 17, $C_6H_5CH_2$ and catechol C-2 and C-6 H). The syrup was dissolved in

chloroform (100 mL), and the solution was shaken with 3 N hydrochloric acid (100 mL). The chloroform solution was separated from the aqueous phase, and evaporation of the chloroform gave 10.4 g (106%) of 11·HCl as a light tan foam. Recrystallization from acetone-ethyl acetate-ethanol (10:5:1) gave 6.36 g (65%) of 11·HCl, mp. 167-172°, lit.[3] mp. 170°. NMR ($CDCl_3$ with a trace of H_2O): δ 1.65 (d, 3, J = 7 Hz, $C\underline{H}_3CHCO$), 2.99 (s, 3, CH_3N), 4.29 and 4.45 (AB doublet of doublets, 2, J = 13 Hz, $C_6H_5C\underline{H}_2N$), 4.82 (q, 1, J = 7 Hz, $CH_3C\underline{H}CO$), 5.17 (s, 2, $C_6H_5C\underline{H}_2O$), 5.25 (s, 2, $C_6H_5C\underline{H}_2O$), 6.90 (d, 1, J = 9 Hz, catechol C-5 H), 7.48 ppm (m, 17, $C_6\underline{H}_5CH_2$ and catechol C-2 and C-6 H).

(±)-erythro-α-Methylepinephrine Hydrochloride [(±)-1·HCl].- A mixture of α-(N-methylbenzylamino)-3,4-dibenzyloxypropiophenone hydrochloride (11·HCl) (2.00 g, 3.98 mmol) and 10% palladium on carbon (0.5 g) in absolute ethanol (50 mL) was stirred under an atmosphere of hydrogen (27° and 740 mm). Initial uptake of hydrogen (ca. 4.5 mL/min) was rapid as the benzyl groups were removed. Reduction of the carbonyl group was much slower, and the time required for hydrogen uptake to cease was 9 hr. The amount of hydrogen consumed was 38 mL in excess of the theoretical amount (15.9 mmol, 402 mL). When hydrogen uptake ceased, the catalyst was removed by filtration through celite, and the celite was washed with absolute ethanol (50 mL). The volume of the filtrate was reduced to 20 mL by evaporation, and ether (25 mL) was added to the stirred solution. After 15 min another portion of ether (25 mL) was added to the stirred mixture and stirring was continued for an additional hr. The white precipitate was collected by filtration and washed with ether (25 mL). Drying in air gave 842 mg (90%) of (±)-1·HCl as a white powder, mp. 188-189°, lit.[5] mp. 190-191°. ^1H NMR (D_2O): δ 1.19 (d, 3, $C\underline{H}_3CHC$, J = 7 Hz), 2.83 (s, 3, CH_3N), 3.54 (m, 1, $CH_3C\underline{H}C$), 4.08 (HOD), 5.03 (d, 1, J = 3 Hz, $CHC\underline{H}OH$), 7.02 ppm (m, 3, catechol H).

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