THE SYNTHESIS OF DEUTERIUM ENRICHED ERYTHRO-α-METHYLNOREPINEPHRINE AND NOREPINEPHRINE*

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SUMMARY

Norepinephrine-d_{10},d_{11}deuteriochloride and erythro-α-methylnorepinephrine-d_6,d_7 hydrochloride for use as mass spectrometric stable isotope internal standards have been synthesized. Trideuteriomethylation of the lithio derivative of 3,4-dimethoxyacetophenone provided the corresponding 1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3. Bromination followed by treatment of the resulting α-bromoketone with dibenzylamine yielded the α-dibenzylamino derivative of 1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3. Deuterium bromide cleaved the methyl ether groups and introduced three to four additional deuterium atoms in the resulting catechol. Catalytic hydrogenation gave the desired erythro-α-methynorepinephrine enriched with six or seven deuterium atoms. The

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*The following two papers dealing with alternative approaches to labelled catecholamines appeared after this study was completed: Murphy, R.C.-J. Lab. Compds. 11: 341 (1975); Rotman, A., Daly, J.W. and Creveling, R.C.-J. Lab. Compds. 11: 445 (1975).

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synthesis of deuterium enriched norepinephrine proceeded in an analogous fashion from the same dimethoxyacetophenone. The catecholaminoketone obtained by reaction of 2-dibenzylamino-1-(3,4-dimethoxyphenyl)-1-ethanone with deuterium bromide was found to contain either four or five deuterium-carbon bonds. This mixture upon catalytic reduction with deuterium gas provided 2-amino-d_2-1-(3,4-dihydroxy-d_2-phenyl-2,5,6-d_2,d_3)-1-ethanol-1,2,2,O-d_4 (norepinephrine-d_{10},d_{11}).

Key Words: Erythro-α-Methylnorepinephrine, Norepinephrine, Deuterium

INTRODUCTION

(S)-α-Methyldopa (1) is a clinically useful antihypertensive agent (1) that is thought to exert its blood pressure lowering effects through a central mechanism (2) involving the interaction of α-methylated catecholamine metabolites with endogenous brain catecholamines. In order to study the quantitative relationships of these compounds in specific regions of the brain by a mass spectrometric stable isotope dilution analysis (3) we required deuterium enriched erythro-2-amino-1-(3,4-dihydroxyphenyl)-1-propanol (erythro-α-methylnorepinephrine, 2) and 2-amino-1-(3,4-hydroxyphenyl)-1-ethanol (norepinephrine, 3) as internal standards. The nature of the assay required the molecular weights of these internal standards to be at least five atomic mass units greater than those of the unlabelled molecules.

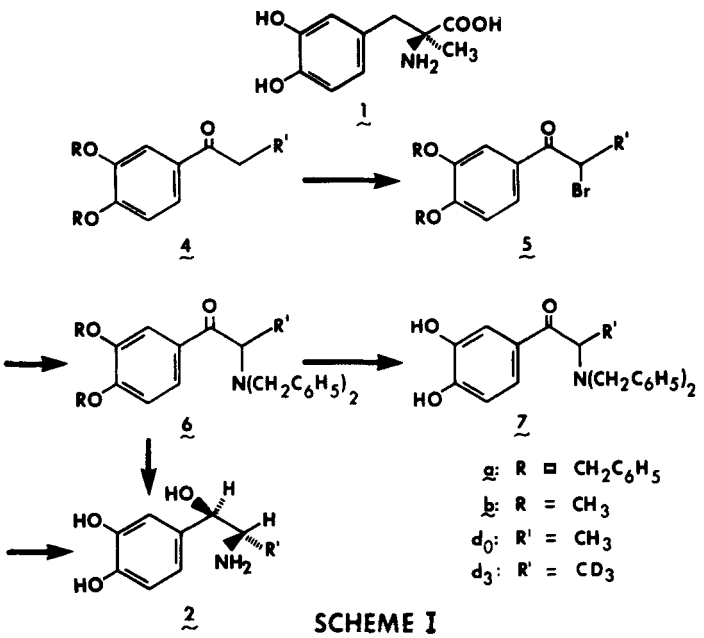
DISCUSSION

*Synthesis of erythro-2-Amino-1-(3,4-dihydroxyphenyl-2,5,6-d_2,d_3)-1-propanol-2,3,3,3-d_4 Hydrochloride (erythro-α-Methylnorepinephrine-d_6,d_7 Hydrochloride, 2-d_6,d_7. HCl)**

Our design for the synthesis of deuterium enriched 2 was to proceed through 1-(3,4-dialkoxyphenyl)-1-propanone (4) which, according to the pathway summarized

*Designations such as d_6,d_7 here and elsewhere indicate that the product is a

in Scheme I, could be converted to the desired product via 2-bromo-1-(3,4-dialkoxyphenyl)-1-propanone (5) and 2-dibenzylamino-1-(3,4-dialkoxyphenyl)-1-propanone (6). This synthetic approached to 2 offered well established, good yield reactions and, as will be described, the possibility of introducing up to eight deuterium atoms in the final product. Additionally, the catalytic reduction of the α-aminoketones 6 or 2-dibenzylamino-1-(3,4-dihydroxyphenyl)-1-propanone (7) is reported to yield exclusively the erythro-α-methylnorepinephrine (4). Although the issue is not completely resolved, it is generally agreed (5) that α-methylnorepinephrine formed metabolically from (S)-α-methyldopa (1) has the (1R,2S) absolute configuration (as depicted in structure 2) which possesses the erythro relative stereochemistry.



SCHEME I

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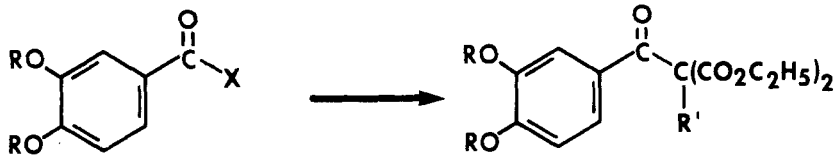
mixture of species containing either six or seven deuterium atoms. The designation --- (3,4-dihydroxyphenyl-2,5,6-d_2,d_3) --- means that two or three deuterium atoms are located at positions 2, 5 and 6 but that the exact locations for the d_2 species are not known.

Our first goal was to prepare the protected deuterium enriched 1-(3,4-dialkoxyphenyl)-1-propanone-3,3,3-d_3 (4-d_3). Our efforts started with 3,4-dibenzyloxybenzoic acid (8a) which, via its acid chloride 9a, was converted to the benzoylmalonic ester derivative 10a with diethyl ethoxymagnesiomalonate (6). The subsequent reactions involve methylation of 10a to yield 11a which was to be converted to 4a by hydrolysis and decarboxylation (Scheme II). Replacement of methyl iodide with methyl-d_3 iodide would provide the required deuterium label. Under a variety of conditions, however, methylation of 10a gave poor and inconsistent conversions to 11a. An alternate approach to 11a via acylation of the sodium salt of diethyl methylmalonate (7) with 10a appeared to be successful although the viscous oil obtained refused all attempts at crystallization. We hoped that the hydrolysis-decarboxylation reaction of 11a would give compound 4a. Treatment of 11a with 10% sulfuric acid - 70% acetic acid however gave benzyl acetate as the only isolable product. It was apparent therefore that the benzyl groups were cleaved under the acidic reaction conditions, an observation consistent with literature reports on related O,O-dibenzylcatechol derivatives (8). The possibility of basic hydrolysis of 11a (under which conditions the O-benzyl groups would be



8: X = OH
9: X = Cl

10: R = H
11: R' = CH_3

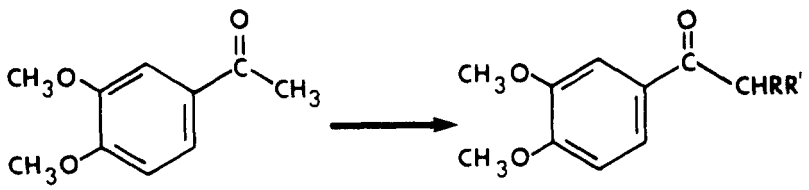
a: R = $CH_2C_6H_5$; b: R = CH_3

SCHEME II

expected to be stable) was discounted since benzoylmalonate esters are known to undergo acyl cleavage under basic conditions to form the corresponding benzoic acid species (9). Therefore, we elected to follow the above pathway

starting from 3,4-dimethoxybenzoic acid (9b) since the O-methyl ethers should resist cleavage during the acid catalyzed hydrolysis reaction. The dimethoxybenzoylmethylmalonate 11b proved to be a low melting solid which was easily obtained in pure form. The acid catalyzed hydrolysis of 11b was attempted under a variety of conditions but the best yield of 4b was only 15%. The main product isolated from this reaction was 3,4-dimethoxybenzoic acid (8b) which must have arisen from acyl cleavage of 11b.

These problems led us to abandon the malonate approach to 4 and we next attempted the direct methylation (Scheme III) of the readily available 3,4-dimethoxyacetophenone (12) via its lithio derivative prepared with lithium diisopropylamide (10). As anticipated, the desired propiophenone 4b formed was contaminated with starting material 12 and with some bis-alkylated product 1-(3,4-dimethoxyphenyl)-2-methyl-1-propanone (13). Following optimization of reaction conditions, methyl-d_3 iodide was used to provide the desired 1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3 (4b-d_3). Mass spectral and nmr evidence indicated that the ratio of 12:4b-d_3:13-d_6 was 25:65:20. Fractional distillation on a spinning band column followed by recrystallization of the 4b-d_3 enriched



12

4b-d_3 : R = H; R' = CD_3
13-d_6 : R = R' = CD_3

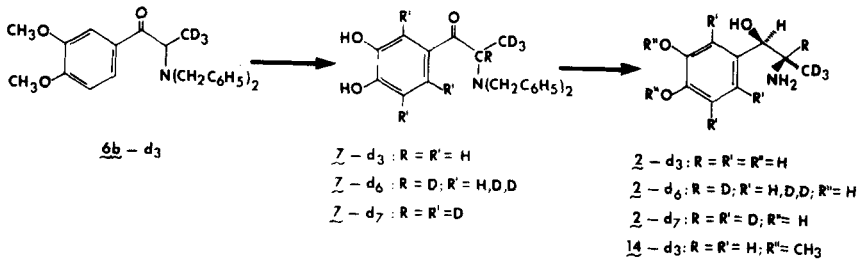
SCHEME III

fraction provided a product containing less than 2% (estimated by glc and nmr) of the homolog impurities and was suitable for the subsequent reactions. The deuterium enrichment of 4b-d_3 was greater than 99% based on mass spectral analysis.

Having available sufficiently pure 4b-d_3, we turned our attention to the

sequence outlined in Scheme I. Bromination with phenyltrimethylammonium tribromide in tetrahydrofuran (11) gave 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3 (5b-d_3) in 88% yield. Mass spectral and nmr analyses established that this product was free of homolog impurities. Displacement of the bromo group of model compound 5b-d_0 and 5b-d_3 with dibenzylamine (4) gave the corresponding α-dibenzylaminoketones 6b-d_0 and 2-dibenzylamino-1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3 (6b-d_3) in high yield.

At this stage two alternate pathways were available, namely (i) catalytic reduction of 6b-d_3 to 2-amino-1-(3,4-dimethoxyphenyl)-1-propanol-3,3,3-d_3 (14-d_3) followed by cleavage of the methyl ether protecting groups to give 2-d_3 or (ii) first cleavage of the methyl ethers to 7-d_3 followed by catalytic reduction to 2-d_3 (Scheme IV). Acid-catalyzed removal of the O-methyl groups of 14 was precluded because it has been established both by fluorescence (12) and nmr (13) studies that erythro-α-methylnorepinephrine undergoes acid catalyzed epimerization to an equilibrium mixture of the erythro and threo isomers. Although boron tribromide cleavage of methyl



SCHEME IV

ethers is reported (14), attempts at this reaction on 6b were unsuccessful and therefore we elected to proceed by pathway (ii).

Mass spectral evidence obtained from the reaction of model compound 6b-d_0 with aqueous hydrogen bromide established that demethylation was proceeding stepwise with the accumulation of a monomethyl intermediate. Under adequately vigorous reaction conditions it was possible to convert 6b-d_0 to 7b-d_0 which was isolated as its hydrobromide salt in 78% yield. Analogous treatment of 6b-d_3 with aqueous hydrogen bromide however produced a product consisting of a mixture of deuterated species (d_0-d_3) as revealed by mass spectral analysis.

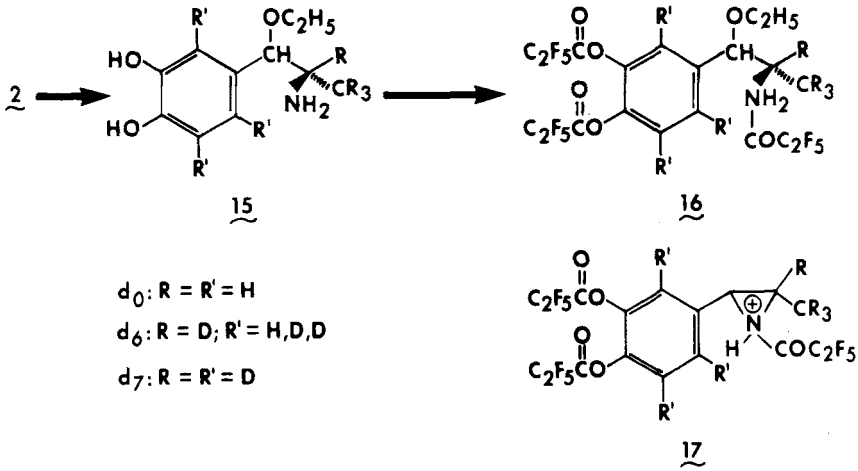
The reaction was therefore repeated with deuterium bromide in deuterium oxide. The product obtained proved to be a mixture of deuterated 7, consisting of d_6 (37%) and d_7 (52%) species. It was clear that the aromatic and methine protons had exchanged during the ether cleavage reaction. Without further purification (in order to conserve the labile methine deuterium atoms) deuterated 7 was reduced catalytically with hydrogen to yield the deuterated α-methylnorepinephrine (2) consisting of d_6 (43%) and d_7 (43%) species.† The evidence presented below argues that the product formed from this reaction sequence consists of 2-d_6,d_7 from which the corresponding structures 2-dibenzylamino-1-(3,4-dihydroxyphenyl-2,5,6-d_2,d_3)-1-propane-2,3,3,3-d_4 (7-d_6,d_7) are derived.

Mass spectral evidence was first sought to determine the deuterium content of 2. Because of the thermal lability and low volatility of catecholamines, direct mass spectral analysis, even by the relatively low energy ionization process available through our chemical ionization source (15), is not too informative due to extensive fragmentation (16). In order to estimate deuterium content, it was necessary to observe parent ions (actually MH^+ with chemical ionization) of the various isotopic species present. We were able to achieve this by first converting the benzylic hydroxyl group of 2 to its ethyl ether (17) to form 15 (Scheme V). Having thus stabilized the molecule, derivatization with perfluoropropionic anhydride formed the volatile tris-acyl derivative 16. The mass spectrum of 16-d_0 shows a prominent parent ion at MH^+ 650 with the only significant fragment corresponding to loss of ethanol (m/e 604). The mass spectrum of 16-d_6,d_7 obtained from 2-d_6,d_7 shows two approximately equally intense MH^+ ions at 656 and 657 corresponding to 16 H^+ enriched with six and seven deuterium atoms, respectively. Loss of ethanol from these two species occurs without loss of deuterium, the fragment ions appearing at m/e 610 and 611. Therefore, loss of ethanol from 16-d_6,d_7 must lead to a species such as 17-d_6,d_7. The mass spectrum of 2-d_6,d_7 derivatized with perfluoropropionic

†A small percentage (up to 14%) of the d_5 species was also observed although its presence may be due to back exchange in the derivatization procedure for mass spectral analysis. No d_3-d_4 species have been detected. Although further deuterium enrichment probably could have been achieved, the product obtained was adequate for the analytic studies planned.

anhydride without prior conversion to the ethyl ester 15-d_6,d_7 displayed no parent ions although intense fragment ions corresponding to 17-d_6,d_7 were observed at m/e 610 (72) and 611 (100).

The location of the deuterium atoms in 2-d_6,d_7 were established by nmr. The only prominent signal appeared as a singlet at 5.1 ppm which is assigned



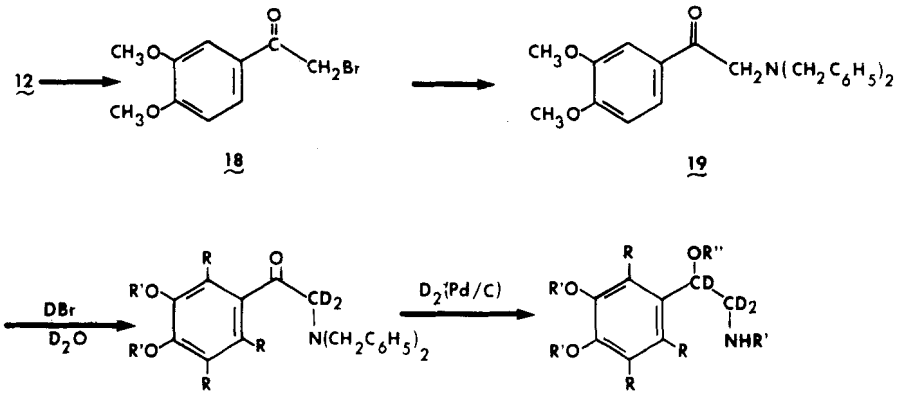
SCHEME V

to the resonance of the benzylic proton of erythro-α-methylnorepinephrine (18). The corresponding signal for the threo isomer centers at 4.7 ppm and was absent from the present spectrum. The aminocarbomethine signal for 2 appears at 3.6 ppm (18) and also was completely absent in the spectrum of our product. On the other and, a broad, weak signal was observed between 6.8 and 7.2 ppm as expected for the aromatic protons of 2. Consequently we feel confident in the assignment of structures 2-d_6,d_7 from which the structures 7-d_6,d_7 are derived. The exact locations of aromatic deuterium atoms remain unassigned. Although for analytical purposes it would be desirable to have a single isotopic species, the principal requirement of separating the internal standard from the endogenous amine by at least five atomic mass units has been achieved. A recent literature report (19) describing conditions that would provide more complete exchange of the four protons (multiple cycling in highly deuterium enriched solvents) discouraged us from any attempts at further deuterium enrichment.

*Synthesis of 2-Amino-d_2-1-(3,4-dihydroxy-d_2-phenyl-2,5,6-d_2,d_3)-1-ethanol-1,2,2,O-d_4 Deuteriochloride (Norepinephrine-d_{10},d_{11} Deuteriochloride, 3-d_{10},d_{11}, DCl)**

Our approach to the synthesis of deuterium labelled norepinephrine paralleled the preparation of deuterated erythro-α-methylnorepinephrine and is summarized in Scheme VI.

Bromination of 3,4-dimethoxyacetophenone (12) with phenyltrimethylammonium tribromide gave 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone (18) in 80% yield. Halogen displacement with dibenzylamine proceeded smoothly to 2-dibenzylamino-1-(3,4-dimethoxyphenyl)-1-ethanone (19). As we had observed with the phenylpropanone 6b mass spectral analysis of the deuterium bromide catalyzed O-demethylation



20- d_5: R = H, H, D; R' = D

20-d_6: R=H,D,D; R' = D

20-d_7: R=R' = D

21: R= D or H; R' = COC_2F_5

3-d_{10}: R=H,D,D; R' =R'' =D

3-d_{11}: R = R' =R'' =D

22: R= H or D; R' =D; R'' = C_2H_5

23: R= H or D; R' =R'' = COC_2F_5

24: R= H or D; R' = COC_2F_5; R'' = C_2H_5

SCHEME VI

reaction mixture of 19 apparently proceeded stepwise with the first methyl group being removed within hours in 24% acid whereas conversion to the desired catechol 20 required heating under reflux in 48% deuterium bromide for 48 hours. The deuterium content of the product isolated was improved by further treatment

*In terms of mass spectral application, the norepinephrine prepared is d_5,d_6, the remaining 5 labile deuterium atoms being attached to oxygen and nitrogen. The product isolated for microanalysis however is 3-d_{10},d_{11}. DCl.

with deuterium chloride which provided the analytical sample of deuterated 2-dibenzylamino-1-(3,4-dihydroxyphenyl)-1-ethanone (deuterated 20) as its deuteriochloride salt. The chemical ionization mass spectrum of this product as its bis-perfluoropropionyl derivative 21 displayed molecular ions at MH^+ 645 (100), 644 (73), and 643 (26) corresponding to underivatized deuterated aminoketones 20 consisting of d_5 (13%), d_6 (37%), and d_7 (50%) species.

Reduction of the analytically pure 20-d_5,d_6,d_7 deuteriochloride with deuterium gas over palladium on carbon proceeded smoothly to form deuterium enriched 3. In some preparations of 20-d_5,d_6,d_7 which contained excess deuterium chloride, this reduction was complicated by the formation of the β-ethyl ether 22 (identified mass spectrometrically) by an acid catalyzed reaction with solvent.

The nmr spectrum of deuterated 3 displayed no proton signals except for a broad, weak multiplet in the aromatic region. On the basis of this evidence and the chemical ionization mass spectrum of the tris-perfluoropropionyl derivative 23 and the corresponding ethyl ether 24, the structures for deuterated 3 are assigned 3-d_{10} (20%), d_{11} (78%). The structures for deuterated 20 are therefore 20-d_5 (13%), d_6 (37%), and d_7 (50%). The greater deuterium enrichment of deuterated 3 vs deuterated 20 may be accounted for by the lability of the methylene deuterium atoms deuterated 20 which are alpha to both the carbonyl and amino functionalities and which may exchange in preparation for or during mass spectral analysis.

EXPERIMENTAL

Materials and methods-- Solvents were removed on a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover Apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument in the indicated solvent with TMS or DSS as the internal standard. Chemical ionization mass spectra were taken on an Associated Electronics Incorporated Model MS 902 double focus mass spectrometer equipped with a direct inlet system and modified for chemical ionization mass spectrometry. The reagent gas was isobutane at a pressure of 0.5 to 1.0 torr. Glpc chromatograms were run on a Varian Model 2100 with a U-shaped 2m x 2mm Pyrex column packed

with 3% OV-1 on acid-washed, DMCS-treated Chromasorb W.

Diethyl 3,4-Dibenzyloxybenzoylmalonate (10a)-- A solution of 3,4-dibenzyloxybenzaldehyde (50 g, 157 mmol) in acetone (800 ml) was treated by dropwise addition and vigorous stirring with potassium permanganate (50 g, 316 mmol) in water (1400 ml) while maintaining the temperature between 37° and 40° until the pink color persisted. Excess permanganate was decomposed by the addition of saturated sodium bisulfite solution. Following filtration, the filtrate was concentrated to half volume, extracted with ether and acidified with 10% hydrochloric acid to precipitate 3,4-dibenzyloxybenzoic acid (8a, 37.9 g, 72%): mp 185-185.5° (lit.[20] mp 185°). The acid chloride [9a, mp 92-94° (lit.[21] mp 95°), 15.9 g, 46 mmol] prepared from benzoic acid 8 with thionyl chloride was dissolved in benzene (120 ml) and added to a solution of diethyl ethoxymagnesiomalonate prepared from diethyl malonate (9.7 g, 60.6 mmol) and magnesium turnings (1.55 g, 646 mmol). After heating at reflux under nitrogen for one hr the cooled reaction mixture was poured onto ice water (300 ml) and the resulting mixture was acidified with N hydrochloric acid. The organic layer was separated and the aqueous layer extracted with benzene (100 ml). The combined benzene solutions were extracted with benzene (100 ml). The combined benzene solutions were extracted three times with N potassium hydroxide and the pH of the combined extracts carefully adjusted to 1 with 6 N hydrochloric acid. This mixture was extracted with ethyl acetate (3 x 50 ml), the combined extracts were dried (magnesium sulfate) and the solvent removed to yield the crude product. Crystallization from hexane: methylene chloride (4:1) provided the analytical sample (10.7 g, 49%): mp 78-79°; nmr ($CDCl_3$) δ 1.27 ($C\underline{H}_3CH_2$, t), 4.25 ($CH_3C\underline{H}_2$, q), 5.20-5.23 ($C_6H_5C\underline{H}_2$ and C$\underline{H}$, s) ppm.

Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.57; H, 5.92. Found: C, 70.65; H, 5.99.

Diethyl 3,4-Dibenzyloxybenzoylmethymalonate (11a)-- Diethyl methylmalonate (3.83 g, 22 mmol) was stirred under nitrogen with sodium hydride (0.85 g of a 57% suspension, 21 mmol) in anhydrous toluene (50 ml) at 60° for 30 min following which 3,4-dibenzyloxybenzoyl chloride (7.05 g, 20 mmol) in anhydrous toluene (40 ml) was added dropwise over a 10 min period. The resulting mixture was stirred for 3 hr at 40° and then allowed to stand overnight at

room temperature. The reaction mixture was washed with N potassium hydroxide (50 ml) and water (50 ml), the organic phase dried (magnesium sulfate) and the solvent removed to provide an oily, viscous material (8.0 g, 82%): nmr ($CDCl_3$) δ 1.27 ($CH_2\underline{CH}_3$, q), 1.87 ($C\underline{CH}_3$, s), 4.25 ($\underline{CH}_2CH_3$, t), and 5.21 ($C_6H_5\underline{CH}_2$, s) ppm.

Diethyl 3,4-Dimethoxybenzoylmethylmalonate (11b)-- The sodium salt of diethyl methylmalonate was prepared as above from diethyl methylmalonate (38.3 g, 220 mmol) and sodium hydride (8.5 g of a 57% suspension, 210 mmol) in anhydrous benzene (300 ml). A solution of 3,4-dimethoxybenzoyl chloride (40.1 g, 200 mmol) in anhydrous benzene (100 ml) was added and the resulting mixture stirred under nitrogen for 3 hr at 40°, cooled, washed with N potassium hydroxide (50 ml), water (50 ml), and dried (magnesium sulfate). The solvent was removed and the residue distilled (160-165°, 0.3 torr) to give the product (40.5 g, 60%) which upon crystallization from hexane provided the analytical sample: mp 53-53.5°; nmr ($CDCl_3$) 1.20 ($C\underline{H}_3CH_2$, t) 1.86 ($C\underline{H}_3C$, s), 3.88 ($C\underline{H}_3O$, s), 3.92 ($C\underline{H}_3O$, s), 4.22 ($CH_3C\underline{H}_2$, q) ppm.

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.64; H, 6.66.

Hydrolysis of 11b-- The malonic ester derivative 11b (27 g, 80 mmol) in concentrated sulfuric acid (7 ml) and 75% acetic acid (80 ml) was heated first under reflux for 2 hr and then at 70-75° for 4 days during which times the slow evolution of carbon dioxide was observed. After cooling the crystalline precipitate was collected to give 3,4-dimethoxybenzoic acid (11.9 g, 83%): mp 175-176° (lit.[22] mp 180-181°). The filtrate was made slightly alkaline with 5 N sodium hydroxide and a solid formed which was identified as 3,4-dimethoxypropiophenone (2.3 g, 15%): mp 53-55° (lit.[23] mp 59-60°). The hydrolysis was attempted under a variety of conditions without improving the yield of the desired propiophenone.

1-(3,4-Dimethoxyphenyl)-1-propanone-3,3,3-d_3 (4b-d_3)-- To a solution of diisopropylamide prepared from diisopropylamine (15.9 g, 157 mmol) and butyl lithium (152 mmol) in anhydrous tetrahydrofuran (120 ml) was added dropwise 3,4-dimethoxyacetophenone (27.5 g, 153 mmol) in anhydrous tetrahydrofuran (60 ml) with stirring under nitrogen and cooling (temperature < 50°). The

yellow reaction mixture was stirred an additional 40 min at 35-40° and then cooled to -65°. Methyl-d_3 iodide (99% d, 25 g, 170 mmol) in 50 ml anhydrous tetrahydrofuran was added all at once and the cooling bath removed. After stirring an additional hr, 220 ml of solvent was removed by distillation and the residue dissolved in water (100 ml). The resulting mixture was acidified with 6 N hydrochloric acid and the reaction mixture extracted with benzene (3 x 50 ml), the combined extracts dried (magnesium sulfate) and the solvent removed to yield a partially crystalline brown material (29.3 g). Chemical ionization mass spectrometry showed the presence of compounds 12:4b-d_3:13-d_6 in the ratio 25:65:20, respectively. Distillation of this product in a spinning band apparatus (Wester-Faust) at a reflux ratio of 1:25 gave several fractions (114-119°, 0.2 torr) with increasing ratios of 4b-d_2 to 12 (determined by nmr). When the distillate contained 80% 4b-d_3 the distillation was stopped and the residue, which upon cooling solidified, was recrystallized from ethanol to give 5.2 g (18%) of 4b-d_3. Treatment of the distillate fractions rich in 4b-d_3 in an analogous way provided an additional 7 g of 4b-d_3; total yield 12.2 g, 41%); mp 57-59°; nmr ($CDCl_3$) 2.88 ($C\underline{H}_2CD_3$, s) and 3.92 ($OC\underline{H}_3$, s).

2-Bromo-1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_2 (5b-d_3)-- To the propanone 4b-d_3 (9.7 g, 50 mmol) in anhydrous tetrahydrofuran (50 ml) was added phenyltrimethylammonium tribromide (18.8 g, 50 mmol) in tetrahydrofuran (50 ml). After stirring the yellow solution for 15 min followed by standing for an additional 2 hr at room temperature, the white solid was collected. Recrystallization from ethanol gave 12.0 g (88%) of product: mp 84-86° (lit.[25] mp 85-86°); nmr ($CDCl_3$) no signal at δ 1.86 ppm for $C\underline{H}_3CHBr$ doublet.

2-Dibenzylamino-1-(3,4-dimethoxyphenyl)-1-propanone (6b-d_0)-- A mixture of the α-bromoketone 5b-d_0 (13.2 g, 49 mmol), dibenzylamine (20 g, 100 mmol) and sodium iodide (0.2 g) was allowed to stand in acetone (50 ml) at room temperature for 3 days. After filtering to remove the dibenzylamine hydrobromide, the filtrate was evaporated to dryness. The residue was taken up in diethyl ether (100 ml), was filtered, and the solvent removed to yield a viscous oil, which was crystallized from methanol to yield 13.8 g (73%) of product. Recrystallization from ethyl acetate provided the analytical sample: mp 81.5-82°; nmr ($CDCl_3$)

δ 1.28 ($C\underline{H}_3CH$, d), 3.58 ($C_6H_5C\underline{H}_2$, s), 3.82 ($C\underline{H}_3O$, s), 4.28 ($CH_3C\underline{H}$, q) ppm.

Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.66; H, 6.98; N, 3.71.

The hydrochloride of 6b-d_0 was obtained from etheral hydrogen chloride and crystallized from toluene-ethanol: mp 179-180°.

Anal. Calcd for $C_{27}H_{27}NO_3 \cdot HCl$: C, 70.49; H, 6.63; N, 3.29. Found: C, 70.08; H, 6.74; N, 3.16.

2-Dibenzylamino-1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3 (6b-d_3)-- In an identical fashion compound 5b-d_3 was converted to 6b-d_3 in 72% yield: mp 81-82°; nmr ($CDCl_3$) 3.58 ($C_6H_5C\underline{H}_2$, s), 3.76 ($C\underline{H}_3O$, s), 3.84 ($C\underline{H}_3O$, s), 4.27 ($C\underline{H}CD_3$, s). No signal was present at δ 1.28 ppm. The molecular weight was confirmed by chemical ionization mass spectrometry.

2-Dibenzylamino-1-(3,4-dihydroxyphenyl)-1-propanone Hydrobromide (7b-d_0·HBr)-- Compound 6b-d_0 (2.0 g 5 mmol) in acetic acid (5 ml) and 48% hydrobromic acid (15 ml) was heated at 120-122° under nitrogen for 20 hr during which time a solid separated. The reaction mixture was cooled, filtered, the solid washed with cold water and recrystallized from acetic acid to yield the catechol 7-d_0 (1.8 g, 78%): mp 204-205° (dec); nmr (dimethyl sulfoxide-d_6) no $C\underline{H}_3O$ signals.

Anal. Calcd for $C_{23}H_{23}NO_3 \cdot HBr$: C, 62.45; H, 5.47; N, 3.57. Found: C, 62.41; H, 5.43; N, 3.50.

2-Dibenzylamino-1-(3,4-dihydroxyphenyl-2,5,6-d_2,d_3)-1-propanone-3,3,3-d_3 Hydrobromide (7-d_6,d_7·HBr)-- A 48% solution of deuterium bromide in deuterium oxide was prepared (25) from bromine (60 g, 380 mmol), elemental sulfur (4 g, 130 mmol), and deuterium oxide (78 ml). The product was freshly distilled before use. Following the procedure described above for the preparation of 7-d_0, compound 6b-d_3 (2.0 g, 5 mmol) in 48% deuterium bromide (25 ml) was converted to 7-d_6,d_7·DBr (1.9 g, 84%). After recrystallization from acetic acid the hydrobromide salt [mp 202-203° (dec)] was analyzed by chemical ionization mass spectrometry: MH^+ (%) 368 (72), 369 (100). Ion currents at mass numbers 362-366 were not above background.

erythro-2-Amino-1-(3,4-dihydroxyphenyl-2,5,6-d_2)-1-propanol-2,3,3,3-d_4 Hydrochloride

(2-d_6,d_7·HCl)-- The above mixture of 7-d_6,d_7·HBr(1.6 g, 3.54 mmol) was suspended in water (4 ml) and covered with diethyl ether (20 ml). The mixture was treated with 25% ammonia dropwise with swirling until solid was no longer visible. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 20 ml). The extracts were combined, dried (sodium sulfate), filtered and treated with etheral hydrogen chloride. The sticky solid obtained was triturated with warm ethanol (5 ml) to yield 1.0 g (71%) 7-d_6,d_7·HCl: mp 201-203° (dec). This product was dissolved in 95% ethanol (40 ml) and shaken with hydrogen (2 atm) over 10% Pd/C (0.25 g) in a Parr apparatus for 17 hours. The solution was filtered and the solvent removed. Crystallization of the residue from 2-propanol-diethyl ether gave 0.29 g (51%) of 2-d_6,d_7·HCl as white crystals: mp 177° (lit.[26] mp 177°); nmr (2 N DCl) δ 5.2 (CD_3CH, s), 7.1 (ArH, m). This product (ca.1 mg) was warmed (ca. 60°) with perfluoropropionic anhydride (ca. 0.1 ml) for 10 min. The solvent was removed with a stream of dry nitrogen the residue analyzed by chemical ionization mass spectrometry: No parent ions were observed: m/e (%) 609 (20), 610 (72), 611 (100). Ion currents at masses 604-608 were not above background. In an additional mass spectrometric study the deuterated α-methylnorepinephrines (ca. 1 mg) were warmed at 60° in anhydrous 2 N ethanolic hydrogen chloride (0.2 ml) for 30 min, the solvent was removed and the residue derivatized with perfluoropriopionic anhydride for chemical ionization mass spectral analysis: MH^+ (%) 655 (19), 656 (67), 657 (67); m/e (%) 609 (35), 610 (100), 611 (100).

2-Dibenzylamino-1-(3,4-dihydroxy-d_2-phenyl-2,5,6-d_2,d_3)-1-ethanone-2,2-d_1,d_2 Deuteriochloride (20-d_5,d_6,d_7·DCl)-- The preparations of 2-dibenzylamino-1-(3,4-dimethoxyphenyl)-1-ethanone [19, mp 73-74° (lit.[27] mp 73-74°)] from 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone (18) and compound 18 from 3,4-dimethoxyacetophenone (12) paralleled the previously described propiophenone sequence. Compound 19 (2 g, 4 mmol) in 47% deuterium bromide (15 ml) and acetic acid-d (8 ml) was heated under reflux in a nitrogen atmosphere for 48 hr. The solvent was removed and the white powdery residue in 20% deuterium chloride (10 ml) and acetic acid-d was heated under reflux and nitrogen an additional 24 hr. The product obtained was recrystallized from a solution of

1N deuterium chloride (6 ml), acetic acid-d (2 ml) and ethanol-d (6 ml) to yield colorless crystals (0.81 g, 50%): mp 198-200° (dec); cims (as the bis-perfluoropropionyl derivatives 21-d_3,d_4,d_5) MH^+ (%) 643 (27), 644 (73), 645 (100). *Anal.* Calcd for $C_{22}H_{14}D_7NO_3 \cdot DCl \cdot 1/2\ D_2O$: C, 65.72; H, 5.77; N, 3.49. Found: C, 65.58; H, 5.57; N, 3.61.

The sample was dried over phosphorus pentoxide for 3 days (56°, 0.01 torr) and reanalyzed:

Anal. Calcd for $C_{22}H_{14}D_7NO_3 \cdot DCl$: C, 67.40; H, 5.66; N, 3.57. Found: C, 66.94; H, 5.64; N, 3.55.

2-Amino-d_2-1-(3,4-dihydroxy-d_2-phenyl-2,5,6-d_2,d_3)-1-ethanol-1,2,2,0-d_4 Deuteriochloride-- Compound 20-d_5,d_6,d_7·DCl (0.83 g, 2.4 mmol) in ethanol-d (10 ml), deuterium oxide (2 ml) and acetic acid-d (2 ml) was warmed briefly to achieve solution and then shaken with 10% Pd/C (200 mg, pretreated with deuterium gas in 3 ml ethanol-d) in an atmosphere (40 psi) of deuterium gas for 48 hr. The reaction mixture was filtered and the residue obtained after removal of the solvent was dissolved in 0.3 N deuterium chloride (0.3 ml) and filtered. Lyophilization of this solution gave a white hygroscopic powder (0.45 g, 81%): mp 235-245° (dec): nmr (1 N DCl) δ 6.8-7.1 ppm (ArH); cims (as the tris-perfluoropropionyl derivatives 23-d_6,d_7): No parent ions were observed: m/e (%) 595 (27), 596 (100); ion currents at masses 590-594 were not above background; cims (as the 1-O-ethyl-tris-perfluoropropionyl derivatives 24-d_6,d_7): MH^+ (%) 641 (24), 642 (100); m/e (%) 595 (2), 596 (11).

Anal. Calcd for $C_8D_{11}NO_3 \cdot DCl \cdot 0.7\ D_2O$: C, 41.5; H, 5.8; N, 6.0. Found: C, 41.8; H, 5.2; N, 5.7.

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