42 ml of HCl (0.0168 mol) was cooled to 0° and a solution of 0.82 g of $NaNO_2$ (0.0119 mol) in 5 ml of water was added over a period of 15 min under constant stirring. HBF_4 (48%) (7 ml, 0.04 mol) was then added at once. While stirring in an ice bath, little yellow crystals of **6** separated which were recrystallized from Me_2CO by adding Et_2O. *Anal.* ($C_{18}H_{24}O_7N_3BF_4$) C, H, F.

Diethyl Acetamido(3,4-dimethoxy-5-fluorobenzyl)malonate (7). A suspension of 2 g (4.17×10^{-3} mol) of **6** in 200 ml of xylene decomposed smoothly at 132° for 1–2 hr. During the decomposition 7 went into solution, leaving a minimal amount of tar undissolved. Xylene was rotary evaporated yielding 7 which usually was processed further without purification. In order to identify the product, one batch was purified in the following way. The remainder, after the xylene evaporation, was dissolved in absolute EtOH and neutralized with aqueous NaOH. After evaporation of the EtOH, the product was dissolved in a small amount of hot benzene and passed through an alumina III column (1.6 × 8 cm). Approximately 100 ml of benzene was used to elute the product. After evaporation of the benzene 7 crystallized upon cooling. *Anal.* ($C_{18}H_{24}O_7NF$) C, H, N.

3,4-Dihydroxy-5-fluorophenylalanine Hydrobromide (8). The solution of the above residue from xylene evaporation of 7 in 20 ml of HBr (47%) was heated in an oil bath at 146–148° (*e.g.*, temperature of reaction mixture 114–116°) for 2 hr, while H_2 was passed through. HBr was removed by rotary evaporation with 10 ml of water. The dry, reddish crystalline residue was dissolved in 10 ml of water and boiled with activated charcoal. After filtration, the clear filtrate was evaporated to dryness. The yellowish residue was recrystallized from *i*-Pr_2O–*i*-PrOH (1:1) yielding white crystals. *Anal.* ($C_9H_{11}O_4NBrF$) C, H, N, F. The product appeared homogenous in the tlc (cellulose layer, *n*-BuOH–AcOH–H_2O, 10:1:1, detection with ninhydrin) and ion-exchange column chromatography (Dowex 50-X8, 200–400 mesh, Na^+ form; 1.4 × 24 cm, 0.1 *M* phosphate buffer, pH 6.8):[16] $\lambda_{max}^{0.1\ N\ HCl}$ 276 nm (ϵ 660); $\nu_{max}^{aryl\ F}$ 1190 cm^{-1} (KBr); ^1H nmr (D_2O) δ (H_2O) +1.94 (2 H, m, aromatic), −0.2 (1 H, q, J_{ab} = 5 Hz, J_{bc} = 6 Hz, $-CHNH_2$), −1.6 ppm (2 H, m, CH_2); ^{19}F nmr (D_2O) δ ($CFCl_3$) +135 ppm (upfield) (1 F, d, separation 12.7 Hz, X portion of ABX system).

3,4-Dihydroxy-5-[^{18}F]fluorophenylalanine. Lithium carbonate (2 g, 95% enriched in $^6Li^+$) was irradiated for 4 hr in the McMaster 5-MW swimming pool nuclear reactor at a neutron flux of 2×10^{13} neutrons cm^{-2} sec^{-1}. Fluorine-18 is produced by the nuclear reaction sequence $^6Li(n,^4He)^3H$ and $^{16}O(^3H,n)^{18}F$. The lithium carbonate was dissolved with 10 ml of diluted sulfuric acid (4 ml of concentrated H_2SO_4 + 6 ml of water).

Water (7 ml) was then distilled from this solution. Air was passed through the apparatus to speed the distillation. More than 80% of the original ^{18}F activity was distilled.

Typically, two distillations were performed and the distillates were combined so that a final volume of 14 ml (pH 4) contained approximately 20 mCi of carrier free ^{18}F. The diazonium fluoroborate **6** (90 mg, 1.84×10^{-4} mol) was dissolved in this solution. The solution was maintained at 50° and was shaken occasionally.

After 30 min, the water was rotary evaporated and the yellow crystalline residue dried over P_2O_5 *in vacuo* for 15 min. The dried material was taken up in 5 ml of dioxane and filtered to remove any inorganic salts remaining. The filtrate was heated to 80° in a 50-ml flask and xylene (26 ml) was then added very slowly. Care was taken to ensure that the temperature in the flask did not fall below 80°. When all xylene had been added, the temperature was raised until the mixture refluxed. Decomposition of the diazonium fluoroborate (^{18}F-6) was complete when the deep yellow color of the mixture changed to pale yellow. (This usually took 30 min.) The dioxane–xylene mixture was cooled and then rotary evaporated until a yellowish-brown residue remained. This residue, fluoromalonic ester 7, was dissolved in 10 ml of HBr (47%) and heated in an oil bath at 146–148°. H_2 was bubbled through this solution during the hydrolysis. After 45 min, HBr was rotary evaporated. In order to remove the excess of HBr, HF, and HBF_4, the dry residue was twice redissolved in water and evaporated. Water (15 ml) was used at each step. The residue was redissolved for a third time in water (7 ml) and was decolorized by boiling with activated charcoal. The final colorless solution contained 5-[^{18}F]fluoro-DOPA with a specific activity ranging from 0.2 to 2.0 μCi/mg of amino acid.

For the determination of the specific activity, an aliquot was chromatographed on an ion-exchange resin column (1.4 × 24 cm, AG50-X8, 200–400 mesh, Na^+ form; eluent 0.1 *M* Na phosphate buffer, pH 6.8).[16] The effluent was collected in fractions. Each fraction was measured for ^{18}F radioactivity using a 5 × 5 cm NaI (Tl) well-type crystal coupled to a single channel analyzer. The counts measured represent the intensity of the 511 keV γ peak (efficiency of the crystal 7%). The obtained elution pattern shows only a single ^{18}F peak after approximately three void volumes. This elution position corresponds to that of authentic 5-fluoro-DOPA. The ^{18}F-containing fractions were combined and the amount of 5-fluoro-DOPA was estimated by uv absorption at 276 mm.

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Alkaloids in Mammalian Tissues. 3. Condensation of L-Tryptophan and L-5-Hydroxytryptophan with Formaldehyde and Acetaldehyde[1]

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Biogenic primary amines and their amino acid precursors react readily *in vitro* with carbonyl compounds under so-called physiological conditions to afford 1,2,3,4-tetrahydroisoquinolines and related condensation products.[2] Since it has been speculated that similar reactions might also take place *in vivo* to generate alkaloidal-type substances (for leading references, see ref 3), a variety of substituted tetrahydroisoquinolines have recently been prepared from dopamine[1] and its biogenic precursor L-dopa.[4] As an extension of this study, we now report the *in vitro* condensation of L-tryptophan and L-5-hydroxytryptophan, two physiologically important amino acids found in mammalian tissues,[5] with CH_2O and CH_3CHO as well as the preliminary pharmacological evaluation of the resulting 3-carboxy-substituted 1,2,3,4-tetrahydro-β-carbolines **1**a,c, **2**a,c, and **3**a,c, and the related *N*-methyl derivatives **1**b,d and **2**b,d.

All of the secondary amino acids were obtained by a Pictet–Spengler condensation between the substrate and the

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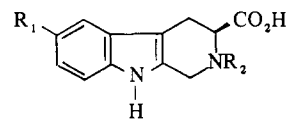
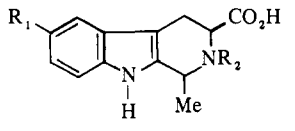
carbonyl reagent. Acid-catalyzed cyclization of L-tryptophan with CH_2O provided the known tetrahydro-β-carboline **1a**[6] while reaction with CH_3CHO afforded a 10:1 diastereoisomeric mixture which was separated by crystallization to give the 1,3-*cis*-amino acid **2a** of known absolute configuration[7] and the 1,3-trans isomer **3a**, respectively. Similarly, condensation of L-5-hydroxytryptophan with CH_2O and CH_3CHO yielded the corresponding amino acid **1c** and a separable mixture of the L-cis acid **2c** as the major product and a minute amount of the L-trans isomer **3c**. The stereochemistry of **2c** and **3c** was assigned by comparison of their nmr, ORD, and CD spectra with those of **2a** and **3a**, respectively. Finally reductive condensation of **1a**, **1c**, **2a**, and **2c** with CH_2O provided the corresponding *N*-methyl derivatives **1b**, **1d**, **2b**, and **2d**.

It is intriguing to speculate that decarboxylation of the 1,3-cis isomers obtained almost exclusively in the condensation reaction with acetaldehyde might provide an easy way to prepare optically active 1-methyltetrahydroharmans. Attempts in this direction carried out in the field of isoquinolines[8] have, however, turned out to be rather involved and thus far impractical.

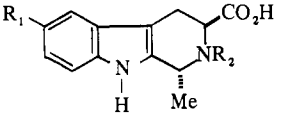
All of the above tetrahydro-β-carbolines were devoid of any significant pharmacological effects. None exhibited any overt observable behavioral symptoms in mice at dosages up to 1000 mg/kg po. Further, all the compounds were inactive in the analgesic phenylquinone writhing test[9] and in the muscle relaxant rotating rod test[10] at 200 mg/kg in mice by the oral and subcutaneous routes while in the antiinflammatory yeast inflamed foot test,[11] only **2a** showed some marginal activity at 200 mg/kg po.



1a–d



2a–d



3a,c

a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Me$
c, $R_1 = HO$; $R_2 = H$
d, $R_1 = HO$; $R_2 = Me$

Experimental Section†

(−)-(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid (1a). A solution of 6.6 g (0.032 mol) of L-tryptophan and 3 ml (0.037 mol) of 37% CH_2O in 15 ml of 0.1 *N* H_2SO_4 was stirred at room temperature for 6 hr. The solids were collected, washed with ice-water, and crystallized from H_2O to give 5.6 g (78.4%) of **1a**: mp 315° (lit.[6] mp 310°); [α]D −49.6°; nmr (MeOD + DCl) δ 3.34 (m, 2, C*H*$_2$CH), 4.41 (m, 1, CH), 4.59 (m, 2, CH_2N), 7.00–7.60 (m, 4, arom); ORD (*c* 0.11, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{700}$ −87°, $[\phi]_{589}$ −129°, $[\phi]_{318}$ −900° (tr), $[\phi]_{314}$ −850° (pk), $[\phi]_{280}$ −2000° (tr); CD (*c* 0.005 *M*, 1:1 MeOH–0.1 *N* HCl) $[\theta]_{295}$ 0, $[\theta]_{262}$ −2800, $[\theta]_{238}$ −2200, $[\theta]_{221}$ +11,600. *Anal.* ($C_{12}H_{12}N_2O_2 \cdot 0.25H_2O$) C, H, N.

(−)-(3*S*)-2-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (1b). A mixture of 1.57 g (0.007 mol) of 1a, 2.5 ml of 37% CH_2O, and 50 ml of 50% aqueous MeOH was hydrogenated at 700 psi in the presence of 1 g of 10% Pd/C at 60° until no further hydrogen was absorbed. The catalyst was filtered and washed with MeOH, and the combined filtrates were evaporated under reduced pressure. The residue was crystallized from MeOH–Me_2CO to give 1 g (61%) of 1b: mp 260–262°; [α]D −2.99°; nmr (D_2O + DMSO-d_6) δ 2.88 (s, 3, MeN), 3.18 (d, 2, *J* = 6.5 Hz, C*H*$_2$CH), 3.94 (t, 1, *J* = 6.5 Hz, CH), 4.36, 4.54 (AB, 2, *J* = 16 Hz, CH_2N), 6.95–7.60 (m, 4, arom). *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

(−)-(3*S*)-6-Hydroxy-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (1c). A mixture of 1.2 g (0.005 mmol) of L-5-hydroxytryptophan and 0.5 ml (0.009 mol) of 37% CH_2O dissolved in 7 ml of MeOH and 20 ml of H_2O containing 0.1 ml of HOAc was stirred under N_2 at room temperature overnight. The solids were collected, washed with ice-water, and crystallized from H_2O to give 1.1 g (86.8%) of 1c: mp 305°; [α]D −72.5°; nmr (DMSO-d_6) δ 2.95 (m, 2, C*H*$_2$CH), 3.63 (m, 1, CH), 4.17 (s, 2, CH_2N), 6.55 (dd, 1, J_{meta} = 2, J_{ortho} = 8.5 Hz, arom), 6.76 (d, 1, J_{meta} = 2 Hz, arom), 7.09 (d, 1, J_{ortho} = 8.5 Hz, arom); ORD (*c* 0.18, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{700}$ −75°, $[\phi]_{589}$ −114°, $[\phi]_{317}$ −1032° (tr), $[\phi]_{297}$ −710° (pk), $[\phi]_{278}$ −1612° (tr); CD (*c* 0.008 *M*, 1:1 MeOH–0.1 *N* HCl) $[\theta]_{420}$ 0, $[\theta]_{370}$ +11.6, $[\theta]_{306}$ −903, $[\theta]_{262}$ −1935, $[\theta]_{240}$ −2451, $[\theta]_{219}$ +9677. *Anal.* ($C_{12}H_{12}N_2O_3$) C, H, N.

(+)-(3*S*)-6-Hydroxy-2-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (1d). In a manner similar to the procedure for 1b, 1.2 g (5.17 mmol) of 1c was N-methylated to give 0.9 g (68.4%) of 1d: mp 260° (from H_2O); [α]D +4.75°; nmr (D_2O) δ 2.80–3.60 (m, 5, CH_2 + CH_3N), 4.04 (m, 1, CH), 4.40–5.00 (m, 2, CH_2N), 7.00–7.60 (m, 3, arom). *Anal.* ($C_{13}H_{14}N_2O_3 \cdot 0.5H_2O$) C, H, N.

(−)-(1*S*,3*S*)-1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (2a) and (−)-(1*R*,3*S*)-1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (3a). A mixture of 50 g (0.245 mol) of L-tryptophan, 39.2 g (0.89 mol) of CH_3CHO (freshly distilled), and 25 ml of 0.1 *N* H_2SO_4 dissolved in 200 ml of H_2O was stirred under N_2 at room temperature for 6 hr. The precipitate was filtered and crystallized from H_2O to give 34.8 (79%) of **2a**: mp 293°; [α]D −106.6° [lit.[6] mp 297°, [α]D −115° (*c* 0.5, 50% pyridine)]; nmr (MeOD + DCl) δ 1.82 (d, 3, *J* = 7 Hz, *Me*CH), 3.25 (m, 2, C*H*$_2$CH), 4.32 (dd, 1, *J* = 5.5 and 11.5 Hz, C*H*COOH), 4.79 (m, 1, MeC*H*), 7.00–7.60 (m, 4, arom); ORD (*c* 0.35, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{700}$ −1692°, $[\phi]_{589}$ −238°, $[\phi]_{292}$ −2614° (tr), $[\phi]_{275}$ −1699° (pk), $[\phi]_{263}$ −2091° (tr), $[\phi]_{251}$ −1568° (pk), $[\phi]_{247}$ −1699° (tr), $[\phi]_{229}$ + 16,989° (pk), $[\phi]_{216}$ 61,420° (tr); CD (*c* 0.0038 *M*, 1:1 MeOH–0.1 *N* HCl) $[\theta]_{300}$ 0, $[\theta]_{235}$ −1390, $[\theta]_{222}$ +46,894, $[\theta]_{202}$ −46,894. *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

The above reaction mother liquors were evaporated to dryness, 7.8 g (0.157 mol) of CH_3CHO and 10 ml of 0.1 *N* HCl were added, and the mixture was dissolved in 100 ml of H_2O and stirred under N_2 at room temperature overnight. The solids were collected and crystallized twice from H_2O to give 2 g (4.5%) of 3a: mp 242–244°; [α]D −69.1°; nmr (MeOD + DCl) δ 1.74 (d, 3, *J* = 7 Hz, *Me*CH), 3.35 (m, 2, CH_2), 4.59 (dd, 1, *J* = 6 and 9 Hz, CH_2C*H*), 4.97 (q, 1, *J* = 7 Hz, MeC*H*), 7.00–7.55 (m, 4, arom); ORD (*c* 0.23, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{700}$ +3.5°, $[\phi]_{589}$ +3°, $[\phi]_{286}$ −2750° (tr), $[\phi]_{285}$ −2000° (pk), $[\phi]_{280}$ −3000° (tr), $[\phi]_{252}$ +3000° (pk), $[\phi]_{248}$ +2251° (tr), $[\phi]_{244}$ +3500° (pk), $[\phi]_{230}$ −1000° (tr), $[\phi]_{220}$ +50,010° (pk); CD (*c* 0.01 *M*, 1:1 MeOH–0.1 *N* HCl) $[\theta]_{300}$ 0, $[\theta]_{289}$ +1000, $[\theta]_{284}$ −1200, $[\theta]_{262}$ −5600, $[\theta]_{248}$ −4600, $[\theta]_{225}$ −31,500, $[\theta]_{210}$ +38,000. *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

(−)-(1*S*,3*S*)-1,2-Dimethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid Hydrochloride (2b·HCl). A mixture of 6.6 g (0.029 mol) of 2a and 6.6 ml (0.083 mol) of 37% CH_2O in 200 ml of of MeOH was hydrogenated at 700 psi in the presence of 3 g of 10% Pd/C at 50° until the hydrogen uptake had ceased. The catalyst was filtered, the filtrate adjusted to pH 2 with ethanolic HCl, and the mixture evaporated to dryness. The residue was crystallized from *i*-PrOH to give 5.5 g (68%) of 2b·HCl: mp 222–223°; [α]D −29.6°; nmr (MeOD) δ 1.78 (d, 3, *J* = 7 Hz, *Me*CH), 2.74 (s, 3, MeN), 3.18

†All melting points (corrected) were taken in open capillary tubes with a Thomas-Hoover melting apparatus. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 spectrophotometer using tetramethylsilane as internal reference. Optical rotations were measured with a Perkin-Elmer polarimeter Model 141 at 25° using a 1% solution in 1 *N* HCl–MeOH (1:1). Rotary dispersion curves were determined at 23° with a Durrum-Jasco spectrophotometer Model 5 using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Analyses are indicated only by symbols of the elements. All the compounds for microanalysis determination have been dried in a high vacuum for 6 hr at 100°; however, the compounds 1a, 1d, 2c, 2d, and 3b retained residual water which could not be removed without decomposition and was therefore determined by the Karl Fischer method.

(m, 2, CH_2), 4.53 (m, 1, CH), 6.90–7.50 (m, 4, arom); ORD (*c* 0.3, MeOH) $[\phi]_{700}$ −76°, $[\phi]_{589}$ −110°, $[\phi]_{355}$ −259° (tr), $[\phi]_{296}$ +200° (pk), $[\phi]_{255}$ −1875° (tr), $[\phi]_{229}$ +12,499° (pk), $[\phi]_{218}$ −53,746° (pk); CD (*c* 0.01 *M*, MeOH) $[\theta]_{290}$ 0, $[\theta]_{288}$ +750, $[\theta]_{270}$ +1850, $[\theta]_{236}$ −650, $[\theta]_{223}$ +40,000, $[\theta]_{207}$ −32,500. *Anal.* ($C_{14}H_{16}N_2O_2 \cdot HCl$) C, H, N.

(−)-(1*S*,3*S*)-6-Hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (2c) and (+)-(1*R*,3*S*)-6-Hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (3c). A solution of 30 g (0.136 mol) of L-5-hydroxytryptophan and 39.2 g (0.89 mol) of CH_3CHO (freshly distilled) in 370 ml of 0.005 *N* H_2SO_4 was stirred under N_2 at room temperature overnight. The solids were collected and crystallized from 1.5 l. of water to give 17.8 g (52%) of **2c**: mp 277–279°; [α]D −86.1°; nmr (MeOD + DCl) δ 1.80 (d, 3, *J* = 7 Hz, *MeCH*), 3.10 (m, 1, CH_2), 4.25 (m, 1, *CH*COOH), 4.72 (q, 1, MeC*H*); ORD (*c* 0.15, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{700}$ −145°, $[\phi]_{589}$ −212°, $[\phi]_{316}$ −1754° (tr), $[\phi]_{294}$ +319° (pk), $[\phi]_{265}$ −1754° (tr), $[\phi]_{234}$ +7177° (pk), $[\phi]_{219}$ −45,456° (tr); CD (*c* 0.0063 *M*, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{335}$ 0, $[\theta]_{306}$ −1532, $[\theta]_{279}$ +957, $[\theta]_{252}$ +415, $[\theta]_{227}$ +26,803. *Anal.* ($C_{13}H_{14}N_2O_3 \cdot 0.3H_2O$) C, H, N.

The above aqueous mother liquors obtained upon crystallization of 2c were concentrated to 100 ml, cooled, and filtered. The filtrate was evaporated to 35 ml; the resulting crystals were filtered and recrystallized from H_2O to give 950 mg (3.6%) of 3c: mp 249–250°; [α]D +5.92°; nmr (MeOD + DCl) δ 1.74 (d, 3, *J* = 7 Hz, *MeCH*), 3.30 (m, 2, CH_2), 4.60 (dd, 1, *J* = 6 and 9 Hz, CH_2 *CH*), 4.95 (q, 1, *J* = 7 Hz, MeC*H*), 6.76 (dd, 1, *J* = 2.5 and 8.5 Hz, arom), 6.90 (d, 1, *J* = 2.5 Hz, arom), 7.21 (d, 1, *J* = 8.5 Hz, arom); ORD (*c* 0.26, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{700}$ +8°, $[\phi]_{589}$ +11.7°, $[\phi]_{340}$ −27° (tr), $[\phi]_{314}$ +225°, $[\phi]_{280}$ −4498° (tr), $[\phi]_{250}$ +1499° (pk), $[\phi]_{237}$ +500° (tr), $[\phi]_{220}$ +44,983° (pk); CD (*c* 0.01 *M*, 1:1 MeOH–0.1 *N* HCl) $[\theta]_{325}$ 0, $[\theta]_{305}$ +1000, $[\theta]_{265}$ −5950, $[\theta]_{230}$ −21,000, $[\theta]_{210}$ +35,000. *Anal.* ($C_{13}H_{14}N_2O_3 \cdot 0.75H_2O$) C, H, N.

(−)-(1*S*,3*S*)-1,2-Dimethyl-6-hydroxy-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (2d). In a manner similar to the procedure for **1b**, 1.6 g (6.38 mmol) of **2c** was N-methylated to give 1.5 g (84%) of **2d**: mp 268°; [α]D −27.9°; nmr (DMSO-d_6) δ 1.58 (d, 3, *J* = 6.5 Hz, *MeCH*), 2.52 (s, 3, MeN), 2.90 (m, 2, CH_2), 3.72 (m, 1, *CH*CH_2), 4.39 (q, 1, *J* = 6.5 Hz, MeC*H*), 6.58 (dd, 1, *J* = 2 and 8 Hz, arom), 6.76 (d, 1, J_{meta} = 2 Hz, arom), 7.11 (d, 1, J_{ortho} = 8 Hz, arom); ORD (*c* 0.19, 1:1 MeOH–0.1 *N* HCl) $[\phi]_{700}$ −59°, $[\phi]_{589}$ −75°, $[\phi]_{331}$ −140° (pk), $[\phi]_{316}$ −350° (tr), $[\phi]_{285}$ +2097° (pk), $[\phi]_{259}$ −1538° (tr), $[\phi]_{233}$ +9785° (pk), $[\phi]_{219}$ −36,344° (tr); CD (*c* 0.007 *M*, 1:1 MeOH–0.1 *N* HCl) $[\theta]_{480}$ 0, $[\theta]_{460}$ +7, $[\theta]_{368}$ +25, $[\theta]_{305}$ −978, $[\theta]_{275}$ +3494, $[\theta]_{226}$ +23,414. *Anal.* ($C_{14}H_{16}N_2O_3 \cdot 0.5H_2O$) C, H, N.

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A Convenient, General Procedure for Preparing Specifically [^{3}H]-Labeled Amines. Synthesis of [^3H]-Meperidine Hydrochloride

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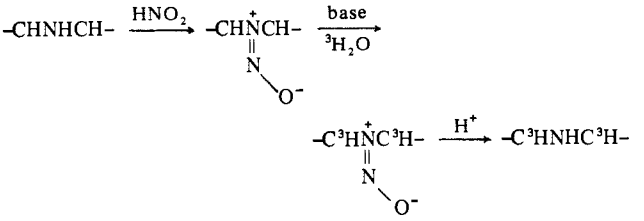
In connection with a study on the distribution and metabolism of N-alkyl homologs of normeperidine (1), we wished to prepare 1 with ^{3}H localized exclusively in the piperidine ring. The ready supply of **1** prompted us to explore a potentially efficient and inexpensive, general method of *specifically* labeling amines with isotopic hydrogen. Since it is often the case that the labeling procedure is the most time-consuming operation in drug metabolism studies, we thought the development of such a method would simplify the task of labeling and make available specifically labeled compounds which are not easily accessible by other routes. In this report we describe a procedure which allows the protons α to a secondary amine function to be exchanged with isotopic hydrogen in relatively high yield.

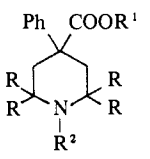
It has been reported[1-3] that the *N*-nitroso group is capable of stabilizing a carbanion at the α position and, thus, facilitating proton exchange under basic conditions. This suggested a method whereby **1** and other secondary amines could readily be labeled. Accordingly, the general labeling procedure (Scheme I) involves conversion of a secondary amine to

Scheme I



its *N*-nitroso derivative and subjecting this intermediate to base-catalyzed exchange in ^3H_2O. The radiolabeled *N*-nitroso derivative then would be denitrosated to the desired amine under acidic conditions.

The specificity of isotopic hydrogen incorporation by this procedure was determined by studying the exchange of D for ^{1}H in **3**. Intermediate **3** was obtained in an overall yield of 78% by conversion of **1** to its nitroso derivative **2** followed by ester hydrolysis. Although **3** was isolated prior to the ex-



1, R = H; R^1 = Et; R^2 = H
2, R = H; R^1 = Et; R^2 = NO
3, R = R^1 = H; R^2 = NO
4, R = D; R^1 = H; R^2 = NO
5, R = D; R^1 = Et; R^2 = H

change reaction for the purpose of characterization, in practice no isolation is required.

Exchange was accomplished by exposure of **3** to 3–6 *M* NaOD in D_2O at 95°. The progress of the exchange was monitored by observing the disappearance of the pmr signals for the α protons at δ 3.2–5.0. With 3 *M* NaOD virtually