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Facile Preparation of (S)-N-[(1-Ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxy-5-(tributyltin)benzamide from Isoremoxipride: The Precursor of [^{125}I]- and [^{123}I]Epidepride

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FACILE PREPARATION OF (*S*)-*N*-[(1-ETHYL-2-PYRROLIDINYL)METHYL]-2,3-DIMETHOXY-5-(TRIBUTYLTIN)BENZAMIDE FROM ISOREMOXIPRIDE: THE PRECURSOR OF [^{125}I]- AND [^{123}I]EPIDEPRIDE

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ABSTRACT: [^{125}I]Epidepride, (*S*)-(-)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-[^{125}I]iodo-2,3-dimethoxybenzamide ([^{125}I]NCQ 219), is a new, extremly potent radioligand, useful in the study of the distribution of the dopamine D-2 receptors in the brain. Its synthesis requires radioiodination of the corresponding 5-(tributyltin) derivative. The aryltin precursor (TDP 526) can be conveniently prepared in high yield from isoremoxipride (FLB 457) by tetrakis(triphenylphosphine)palladium(0)-catalyzed stannylation using bis(tri-*n*-butyltin) in triethylamine. An improved method for the preparation of isoremoxipride from *o*-vanillin was developed.

We have recently presented receptor binding characteristics[1] and in vivo uptake profile in the rat brain[2] of a new radioligand, (*S*)-(-)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-[^{125}I]iodo-2,3-dimethoxybenzamide ([^{125}I]NCQ 219, [^{125}I]epidepride). Radiolabeling of epidepride requires radioiodination of the corresponding 5-(tributyltin) derivative.[1,3] The aryltin precursor is easily obtained from unlabeled epidepride,[3] but in our hands, the reported[4] preparation of epidepride was cumbersom and failed to give satisfactory yields. In efforts to find an improved method for the preparation of epidepride, we have developed a convenient route to the corresponding bromo derivative, isoremoxipride (FLB 457),[5] and its subsequent conversion to the corresponding 5-(tributyltin) derivative (TDP 526), the precursor for [^{125}I]- and [^{123}I]epidepride.[3]

For this synthesis, the key intermediate is 5-bromo-2,3-dimethoxybenzoic acid. Attempted bromination of 2,3-dimethoxybenzoic acid produced a mixture of 5-bromo and the 6-bromo derivatives with the latter as the major product as determined by ^{1}H NMR. Pettit and Piatak have reported[6] the synthesis of 5-bromo-2,3-dimethoxybenzoic acid in 49% yield by direct bromination of 2,3-dihydroxybenzoic acid, but we have found that this method gave a considerably lower yield than that reported.[6] Davies reported a 70% yield for the bromination of *o*-veratraldehyde,[7] but again, we obtained an unacceptable 42% yield after recrystallization.

We now report the high yield synthesis of isoremoxipride by way of bromination of *o*-vanillin according to Brink,[8] giving 5-bromo-3-methoxysalicylaldehyde (**1**). Methylation of the

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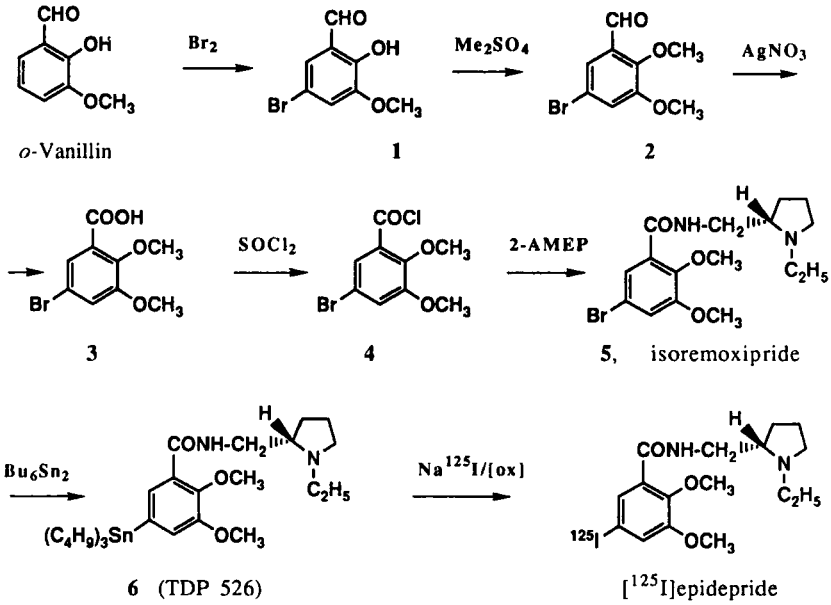

SCHEME

phenolic group with dimethyl sulfate in the presence of an excess amount of potassium carbonate gave 5-bromo-2,3-dimethoxybenzaldehyde (**2**) in quantitative yield. This method is superior, both in yield and simplicity, to those of Stork[9] and Fuson.[10] The aldehyde **2** was oxidized with silver nitrate in aqueous sodium hydroxide as described earlier[6] to give 5-bromo-2,3-dimethoxybenzoic acid (**3**). The latter was converted to the corresponding acid chloride (**4**), which was recrystallized from hexane but could be used without purification. Treatment of **4** with (*S*)-2-(aminomethyl)-1-ethylpyrrolidine (from the di-D-(-)-tartrate)[11] gave the substituted benzamide **5** (isoremoxipride).[5]

Debromostannylation[12] of isoremoxipride required a longer reaction time than that for the deiodostannylation of epidepride.[3] By reduction of the amount of solvent as compared to that for the deiodostannylation reaction, most of the starting bromobenzamide could be converted to the 5-(tributyltin) derivative **6**. Column chromatography on silica with hexane-ethyl acetate (1:1) removed excess reagents and eluation with ethyl acetate-ethanol (10:1) gave the pure stannyl compound **6** in 82% yield as an oil. The ^{1}H NMR spectrum of **6** showed the characteristic side bands of the aromatic protons due to coupling to the 16% natural abundance of ^{117}Sn and ^{119}Sn isotopes with spin 1/2.[13] The overall yield of **6** from *o*-vanillin was 35%. No carrier-added radioiodination of **6** gave [^{125}I]epidepride with a specific radioactivity >2000 Ci/mmol, a similar result as that obtained[1,3] with compound **6** prepared from epidepride.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Haake/Buchler apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ with Me_4Si as internal standard on a Bruker NB 300 spectrometer operating at 300 MHz. Rotatory powers at the sodium D line were measured in a 1-dm sample tube with an Autopol III automatic polarimeter. Thin layer chromatography (TLC) was performed on Whatman silica gel 60 K6F with EtOAc-EtOH-14 N NH_4OH (100:10:1). Commercial chemicals and solvents were analytical grade and were used without further purification.

5-Bromo-2-hydroxy-3-methoxybenzaldehyde (1). 3-Methoxysalicylaldehyde (3.9 g, 0.025 mol) was dissolved in acetic acid (40 mL) and a solution of KBr (6.0 g, 0.17 mol) in water (10 mL) was added. Bromine (4.2 g, 0.026 mol) in acetic acid (10 mL) was added dropwise at 110 °C (20 min). After an additional 20 min at at 110 °C, the reaction mixture was poured into ice-water (400 mL), and the raction product was extracted into ether (3 x 50 mL). Drying (Na_2SO_4) and evaporation of the solvent gave, after recrystallisation from 60% aqueous EtOH (120 mL), 4.92 g (85%) of **1**: mp 127-129 °C [lit.[8] mp 129 °C].

5-Bromo-2,3-dimethoxybenzaldehyde (2). A suspension of K_2CO_3 (11 g, 0.080 mol), 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**1**) (5.1 g, 0.020 mol), and dimethyl sulfate (4.4 g, 0.035 mol) in acetone (150 mL) was heated to boiling (bath temperature 90 °C) for 16 h. After evaporation of the solvent, the residue was extracted with ether (2 x 50 mL). The etheral extracts were combined, washed with 1 N NaOH (25 mL), dried ($NaSO_4$), and evaporated to give 4.9 g (91%) of crude **2**. Recrystallization from i-Pr_2O (15 mL) gave 4.4 g of **2**: mp 81-82 °C [lit.[7] mp 81-82 °C].

5-Bromo-2,3-dimethoxybenzoic Acid (3). 5-Bromo-2,3-dimethoxybenzaldehyde (**2**) (4.9 g, 0.020 mol) was dissolved in MeOH (30 mL). A solution of silver nitrate (3.8 g, 0.022 mol) in water (30 mL) and then 1 N NaOH (300 mL) were added. The mixture was heated at 85 °C for 5 h. The solid was removed by filtration, and addition of 12 N HCl (30 mL) precipitated the desired compound **3** which was collected by filtration. Recrystallization from i-Pr_2O (50 mL) gave 3.9 g (75%) of **3**: mp 118-119 °C [lit.[7] mp 120 °C].

5-Bromo-2,3-dimethoxybenzoyl Chloride (4). 5-Bromo-2,3-dimethoxybenzoic acid (**3**) (3.9 g, 14 mmol) was dissolved in toluene (40 mL). Thionyl chloride (4.0 mL, 50 mmol) was added followed by 3 drops of DMF. The mixture was heated to 60 °C for 40 min. Evaporation of the solvent gave a crystalline residue of the acid chloride. Recrystallization from hexane (60 mL) gave 3.8 g (94%) of **4**: mp 58-60 °C. This substance slowly decomposes in air.

(*S*)-(-)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxybenzamide (5), Isoremoxipride (FLB 457). 5-Bromo-2,3-dimethoxybenzoyl chloride (**4**)

(3.5 g, 10 mmol) was dissolved in CH_2Cl_2 (50 mL), and a solution of (S)-2-(aminomethyl)-1-ethylpyrrolidine[11] (1.8 g, 14 mmol) in CH_2Cl_2 (50 mL) was rapidly added. The mixture was stirred for 4 h at ambient temperature. The solvent was evaporated, 1 N NaOH (50 mL) was added, and the residue was extracted with ether (3 x 75 mL). The combined ether layer was washed with water (25 mL) and the product was extracted with 1 N HCl (3 x 75 mL). The combined acid layer was neutralized by adding 5 N NaOH (18 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated to give 2.9 g (78%) of compound **5** as an oil: TLC R_f 0.19. The NMR spectrum and specific rotation were identical to those reported.[5] Attempts to prepare crystalline hydrochloride or mesylate salts failed.

(*S*)-5-(Tri-*n*-butyltin)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxybenzamide (6), TDP 526. To a solution of (*S*)-5-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxybenzamide (**5**) (3.7 g, 8.0 mmol) in dry Et_3N (30 mL) was added solid $(Ph_3P)_4Pd$ (Aldrich) (0.1 g, 0.1 mmol) followed by Bu_6Sn_2 (Aldrich) (5.8 g, 10 mmol). The mixture was boiled (bath temperature 87 °C) for 16 h. After cooling, the solvent was removed by evaporation and the residual oil (10 g)was subjected to chromatographic separation on silica gel (200 g, 0.063-0.20 mm) in hexane-EtOAc (1:1) to give 4.8 g (82%) of compound **6**. ^{1}H-NMR: δ 8.62 (b, NH), 7.74 (d, 1, J = 0.9 Hz, H-6), 7.12 (d, 1, J = 0.9 Hz, H-4), 3.98 (s, 3, OMe), 3.91 (s, 3, OMe), 3.8-1.6 (m, 11, pyrrolidinyl), 1.54 (t, 6, 1-Bu), 1.29 (dt, 12, 2+3-Bu), 1.08 (t, 3, N-Et), 0.89 (t, 9, 4-Bu) ppm. TLC: R_f 0.29. Rotation: $[\alpha]^{22}_D$ -38 ° (*c* 1.0, acetone).

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