SYNTHESIS OF 1-^{14}C-(1S,4S)-N-METHYL-4-(3,4-DICHLOROPHENYL)-1,2,3,4-TETRAHYDRO-1-NAPHTHALENAMINE L-MANDELATE (1-^{14}C-SERTRALINE MANDELATE)

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SUMMARY

The preparation of the title compound, a selective 5-HT uptake blocker with potential antidepressant properties in man, is described. The labelled material with a specific activity of 0.7 mCi/mmol, was synthesized in 7 steps from K^{14}CN in 6.5% radiochemical yield.

Key words: ^{14}C-Sertraline, Antidepressant, 5-HT Uptake Blocker.

INTRODUCTION

Sertraline, [CP-51,974-01, 1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine hydrochloride] has been shown to be a highly selective and potent competitive inhibitor of synaptosomal serotonin uptake, and may therefore be an efficacious antidepressant without anticholinergic or cardiovascular side effects in man.[1] Pharmacological and biochemical studies of metabolism and pharmacokinetics required the synthesis of a ^{14}C-labelled form of the drug.

Since the methyl substituent on nitrogen in the sertraline molecule is known to be metabolically labile,[2] it was necessary to place the label within the ring system. This requirement led to the choice of the C-1 position both for its convenience in potential syntheses as well as for its anticipated biological stability. Scheme I illustrates the procedure utilized for this synthesis of sertraline. This route is a modification of the method developed earlier.[3]

EXPERIMENTAL

K^{14}CN (10.0 mCi/mmol) was purchased from New England Nuclear and was admixed with nonradio-

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active material to a specific activity of 1 mCi/mmol. Characterization of the labelled products was accomplished by co-thin layer chromatography with nonradioactive standards, all the analyses utilizing precoated plates of silica gel 60 F-254 unless stated otherwise. For column chromatography, silica gel (Woelm 32-63) was used. Evaporations were carried out under reduced pressure. A Varian Aerograph Model LB2723 radioscanner was used to determine the radiochemical purity of each labelled derivative. All new compounds were within $\pm 0.4\%$ of expected analytical values or provided acceptable high resolution parent ions.

Preparation of Ethyl 3-(3,4-dichlorophenyl)-3-hydroxy-3-phenylpropionate 1.

n-Butyllithium (96.15 mL, 248.9 mmol) was added dropwise to a stirred solution of diisopropylamine (34.9 mL, 248.9 mmol) in 800 mL anh. THF at 0-5°C and the reaction was allowed to stir at this temperature for 10 min to assure formation of the anion. After cooling the reaction mixture to -75°C, HPLC grade EtOAc (24.31 mL, 0.25 mol) was added dropwise and the reaction was stirred for 1 h at -75°C. Then 25.00 g (0.10 mol) of 3,4-dichlorobenzophenone dissolved in 100 mL of anh. THF was added dropwise and the reaction mixture was then stirred under N_2 for 2 hrs. Following the addition of H_2O at -75°C, the reaction was slowly warmed to room temperature and the solvents were then evaporated. The residue was then partitioned between H_2O and EtOAc and the aqueous phase was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over $MgSO_4$, and the solvent was evaporated to yield 42.6 g of the crude product as brown foam. This material was not purified further but was used in this form for further reaction. The analytical sample was obtained as a pale yellow oil by flash column chromatography on silica gel, eluting with 5:1 hexane/EtOAc. NMR ($CDCl_3$) δ 1.18 (3H, t, J = 7), 3.22 (2H, ABq), 4.10 (2H, q, J = 7), 6.9-7.7 (8H, m); Mass spectrum: Calcd for $C_{17}H_{16}O_3Cl_2$, 338.0477; Found, 338.0443.

Preparation of Ethyl 3-(3,4-dichlorophenyl)-3-phenylprop-2-enoate 2.

A solution of 1 (41.5 g, 0.12 mol) in 100.0 mL CH_2Cl_2 in which was suspended H_2SO_4 (6.52 mL, 0.12 mmol) was allowed to reflux overnight under N_2. Upon cooling, the reaction was washed with sat'd $NaHCO_3$ solution and water, dried and evaporated to give 27.2 g of the product, a crude yellow solid, which was sufficiently pure by TLC and by ^{1}H-NMR for use in the next step. An analytically pure sample was obtained by flash column chromatography similarly to compound 1. NMR ($CDCl_3$) cis and trans isomers δ 2.13 and 2.19 (3H, t, J = 7), 4.07 and 4.10 (2H, q, J = 7), 6.36 and 6.40 (1H,

s), 7.04-7.48 (8H, m); Mass spectrum: Calcd for $C_{17}H_{14}Cl_2O_2$, 322.0340; Found, 322.0171.

Preparation of Ethyl 3-(3,4-dichlorophenyl)-3-phenyl propionate 3.

A solution of crude **2** (25.0 g, 78 mmol) in 200 mL of EtOAc was reduced at atmospheric pressure over 2.5 g 5% Pd/C. After 1800 mL of H_2 (94% of theory) had been absorbed, the reaction mixture was filtered and the solvent was evaporated to give 22.3 g of **3** as a yellow-green oil which was shown to be adequately pure by TLC for use in the subsequent reaction. An analytically pure sample was obtained as a pale yellow oil by flash column chromatography on silical gel using 5:1 hexane/EtOAc as eluent. NMR ($CDCl_3$) δ 1.11 (3H, t, J = 7), 2.98 (2H, d, J = 9), 4.02 (2H, q, J = 7), 4.46 (1H, q, J = 9), 7.00-7.37 (8H, m); Anal. Calcd for $C_{17}H_{16}Cl_2O_2$: C, 63.17; H, 4.90. Found: C, 63.45; H, 4.79.

Preparation of 3-(3,4-dichlorophenyl)-3-phenyl-1-propanol 4.

To a suspension of LAH (3.5 g, 82.8 mmol) in 75 mL of anh. THF was added dropwise a solution of **3** (20.0 g, 61.88 mmol) in 50.0 mL of anh. THF. After refluxing for 45 min, excess LAH was decomposed by addition of Glauber's salt. The resulting solid was filtered from the reaction mixture and the filtrate was evaporated to yield 16.8 g of a crude red-orange oil which was used without purification in the next reaction. The analytical sample, a colorless oil, was obtained by flash column chromatography, eluting with 2:1 hexane/EtOAc. NMR ($CDCl_3$) δ 2.24 (2H, d of q, J = 2, 6), 3.56 (2H, t, J = 7), 4.20 (1H, t, J = 7), 7.03-7.36 (8H, m); Anal. Calcd for $C_{15}H_{14}Cl_2O$: C, 64.07; H, 5.02. Found: C, 63.66; H, 5.09.

Preparation of 3-(3,4-dichlorophenyl)-3-phenyl-1-propanol 4-toluene sulfonate 5.

A suspension of 4-toluenesulfonyl chloride (12.2 g, 64.0 mmol) in 150.0 mL of CH_2Cl_2 was added dropwise to a mixture of **4** (15.0 g, 53.4 mmol) and pyridine (5.2 mL, 64.5 mmol) in 100 ml. CH_2Cl_2 at 5°C. The reaction mixture was then warmed to room temperature and allowed to stir under N_2 for 48 h. Then the solvent was evaporated and the residue was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc and the organic layers were combined. The EtOAc extracts were then washed with 5% NaOH and H_2O and were dried over $MgSO_4$. Concentration *in vacuo* produced 23 g of a red-orange oil. The crude product was applied to a silica gel column and eluted with 5:1 hexane/EtOAc. A total yield of 10.95 g (45%) of colorless crystalline product was obtained, mp 85-87°C. NMR ($CDCl_3$) δ 2.33 (2H, q, J = 7); 2.46 (3H, s), 3.94 (2H, t, J = 7), 4.01 (1H, t, J = 7), 6.96-7.34 (10H, m), 7.72 (2H, d, J = 9); Anal. Calcd for $C_{22}H_{20}Cl_2O_3S$: C, 60.69; H, 4.63.

Found: C,61.00; H, 4.63.

Preparation of 1-^{14}C-4-(3,4-dichlorophenyl)-4-phenylbutyronitrile 6.

^{14}C-Potassium cyanide [1.0 mmol, 65.0 mg (10 mCi/mmol, based on manufacturer's assay)][4] was dissolved in 4.5 mL H_2O together with unlabelled KCN (0.585 g, 9.00 mmol). To this solution was added 10.0 mL EtOH and 4.35 g (10.0 mmol) of compound **5**. The resulting mixture was refluxed for 26 h and was then cooled to room temperature and stirred under N_2 overnight. After evaporation of the solvents, the residue was partitioned between H_2O and EtOAc. The H_2O layer was extracted with EtOAc and the organic extracts were combined, washed with water, dried and evaporated to yield a yellow oil which was shown to be pure chemically and radioactively by TLC on Woelm basic alumina plates and by radioscan.

Preparation of 1-^{14}C-4-(3,4-dichlorophenyl)-4-phenylbutyramide 7.

Crude compound **6** was dissolved in 5 mL EtOH and 15 mL 40% aqueous NaOH and was refluxed for 8 h. After cooling to room temperature, the reaction mixture was taken up with H_2O and EtOAc and the aqueous phase was extracted three times with EtOAc. The combined organic layers were then dried and evaporated to afford **7** which was used in the next step without further purification. This compound was identical to and co-migrated with an unlabeled standard sample by TLC.

Preparation of 1-^{14}C-4-(3,4-dichlorophenyl)-4-phenylbutyric acid 8.

A suspension of **7** in 16.0 mL 6*N* HCl was refluxed overnight and was then cooled to room temperature. The same workup as that used in **7** was employed resulting in 10.75 mmol of product (>100% yield) which was used in its crude form in the following reaction. This sample was chromatographically identical to a standard sample prepared previously.[3]

Preparation of 1-^{14}C-4-(3,4-dichlorophenyl)-4-phenylbutyryl chloride 9.

The acid chloride **9** was prepared by treating a solution of crude **8** in 20.0 mL of toluene with $SOCl_2$ (1.8 mL, 25.0 mmol) and refluxing the mixture for 3 h. The reaction mixture was then cooled to room temperature and allowed to stir under N_2 overnight. Evaporation of the solvent and excess $SOCl_2$ gave the product as a yellow-orange oil, **9**. The yield was assumed to be quantitative.

Preparation of 1-^{14}C-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)naphthalenone 10.

A solution of crude **9** in 20.0 mL of CS_2 was added dropwise over a period of 40 minutes to a suspen-

sion of $AlCl_3$ (1.8 g, 14.0 mmol) in 15 mL CS_2; maintained at a temperature of 0-4°C. The reaction mixture was then stirred under N_2 at 0-5°C for 1 h, and at room temperature for 2 h. Then excess $AlCl_3$ was quenched by addition of ice/H_2O to the reaction vessel. After stirring for several minutes the aqueous phase was extracted with EtOAc and the organic phase was separated from the aqueous layer. The aqueous layer was then extracted 2 x with EtOAc and the organic extracts were combined, dried, and evaporated to yield an orange-brown oil. This crude residue was purified on a column of silica gel eluted with 6:1 hexane/EtOAc to yield the desired product. Thin-layer chromatography (6:1 hexane/EtOAc) and radioscan found only one spot, that corresponding to the desired product. The yield of 1.54 g represents an overall yield for the five steps from K^{14}CN of 53%.

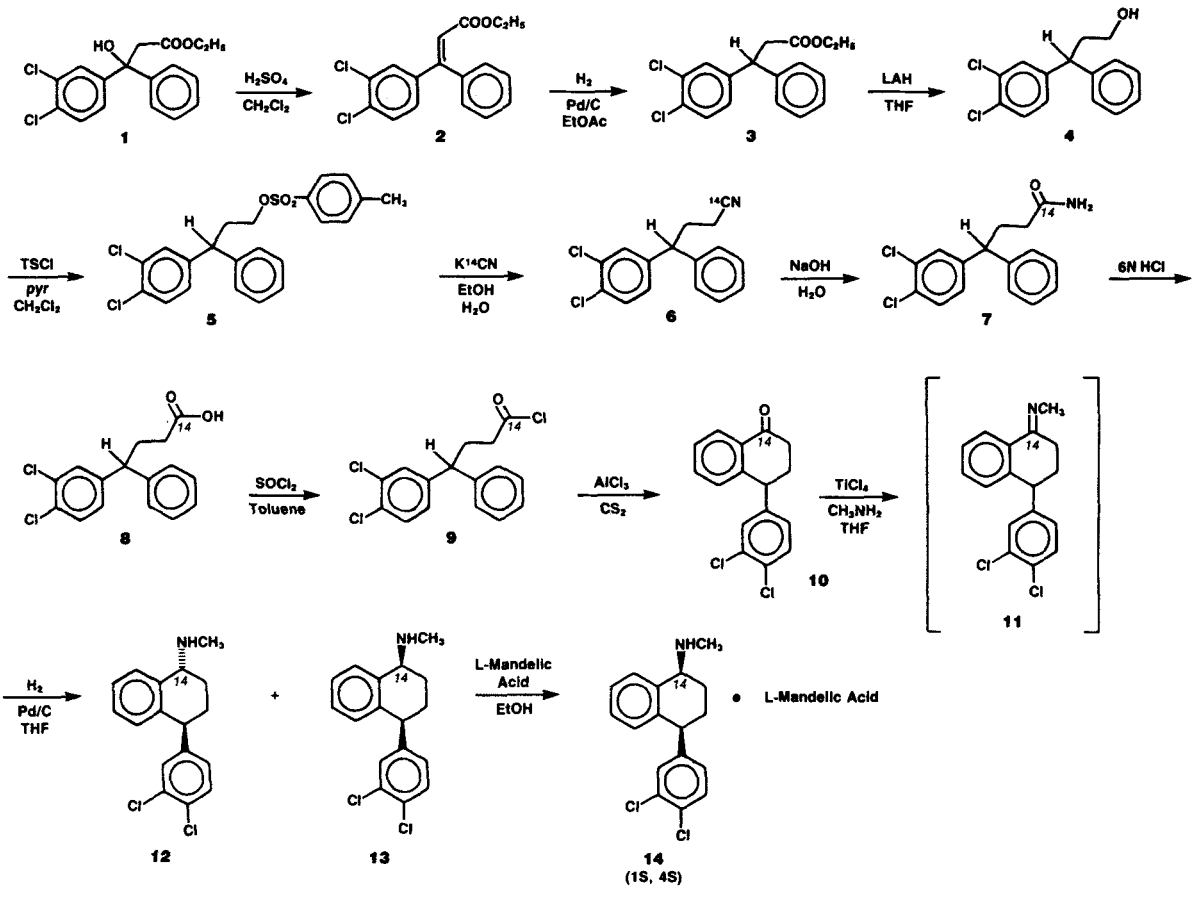
Preparation of cis-(±)-1-^{14}C-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine 13.

The ketone **10** was dissolved in 40.0 mL anh. THF and cooled in an ice-salt bath to 0°C. Monomethylamine, about 5 mL, condensed at -78°C, was added all at once, followed by $TiCl_4$ (0.40 g, 2.58 mmol). A violent reaction took place upon the dropwise addition of the $TiCl_4$ to the reaction vessel. After stirring at room temperature under N_2 for 45 minutes, the reaction mixture was filtered and the solids were thoroughly washed with THF. The excess monomethylamine was then evaporated and the resulting THF solution of imine **11** was used directly in the subsequent reaction.

A mixture of **11** and 320 mg of 10% Pd/C in 50 mL of THF was reduced using the balloon technique at room temperature for 2.25 h. Upon completion of H_2 uptake, the reaction mixture was filtered and the solids were washed with THF. TLC analysis (4:1 EtOAc/CH_3OH) of the product mixture showed the two spots corresponding to the expected *trans-cis* isomeric mixture **12** and **13** by comparison with authentic unlabelled samples.

To the mixture of *trans-cis* isomers **12** and **13** in THF was added 0.25 ml. conc. HCl. Crystallization occurred upon scratching, following which the mixture was refrigerated overnight. Colorless crystalline *cis*-hydrochloride salt (which is substantially less soluble in THF than is the *trans* hydrochloride salt) was isolated by filtration and washed with THF and ether. This material (831 mg, 2.43 mmol, 46% yield) was shown to be the pure *cis* isomer by TLC (4:1 EtOAc/CH_3OH). The free base of **13** was generated by partitioning the HCl salt between aq. NaOH and EtOAc and extracting the aqueous

phase x 3 with EtOAc. The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to yield the free base of the *cis* isomer **13**.



Scheme I

1-^{14}C-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine L-mandelate 14.

The *cis* isomer **13**, as the free base, was dissolved in 10 parts (w/v) of EtOH and heated just to boiling. Then 0.8 eq. (1.94 mmol, 295 mg) of L-mandelic acid was added all at once and the solution was refrigerated. The crystalline diastereomeric salt obtained was recrystallized an additional three times from absolute EtOH to give 215 mg (38%). of the mandelate salt of sertraline, mp 189-190°C, $[\alpha]$ 365 = 37.4° (c = 1.0, CH_3OH). The melting point and rotation of this sample were identical to those properties of unlabeled material obtained previously.[3] Radioassay of this sample

demonstrated incorporation of ^{14}C at a level of 0.70 mCi/mmol or 70% of the anticipated label.[4] The radiochemical yield for the six reaction sequence and resolution was thus 6.5%.

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4. K^{14}CN from the same lot was used by other Pfizer chemists in the synthesis of an unrelated compound in a much shorter reaction sequence. Substantially less than the anticipated incorporation of ^{14}C-label was found in this product as well leading to the conclusion that either the chemical purity or the level of ^{14}C in the K^{14}CN sample was lower than that claimed.