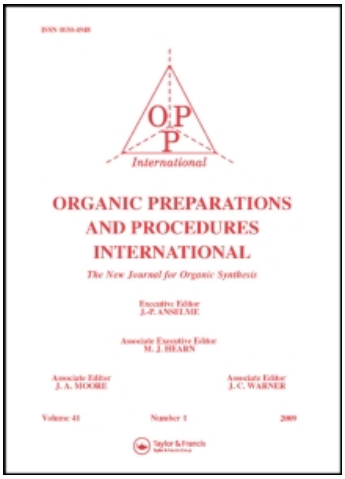

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PREPARATION OF O-(3,3,8,10,10-PENTAMETHYL-1,2-DITHIA-5,8-DIAZACYCLODECAN-5-YL)ETHYL O-PIVALOYLOXYMETHYL PHENYLPHOSPHONATE

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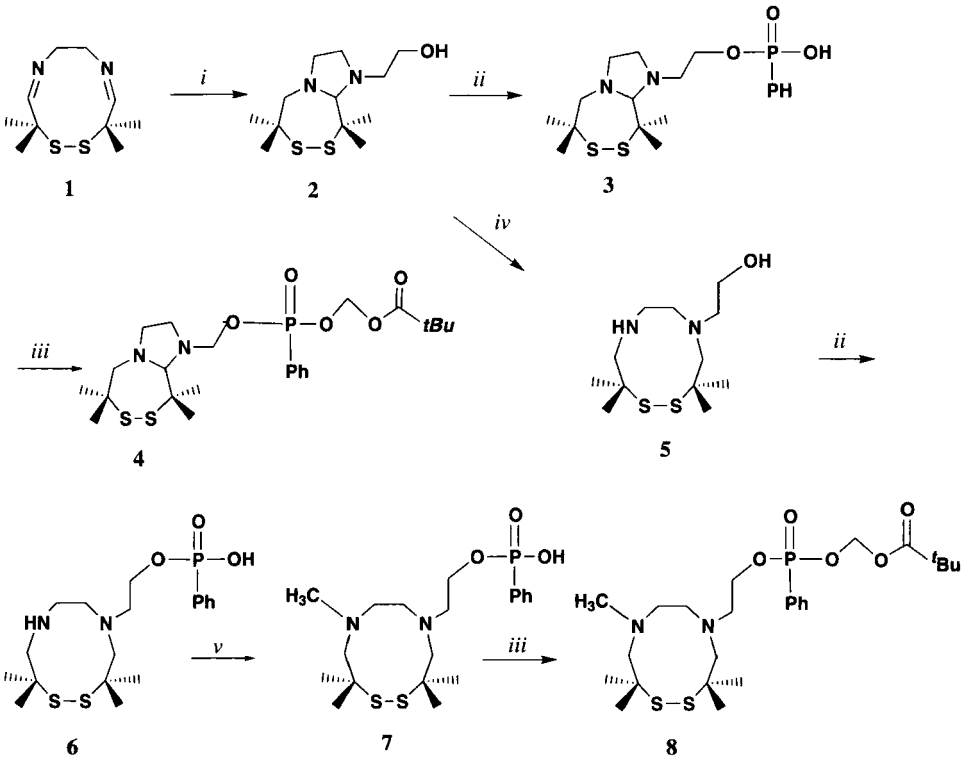
Tetradentate ligands are known to transport metal ions into the brain.[1,2] Diaminodithiols have been used as ligands of ^{99m}Tc-complexes in single photon emission computed tomography. The major disadvantage of this ^{99m}Tc-ligand system is its limited ability to cross the blood-brain barrier (BBB) and/or the poor retention in the central nervous system (CNS).[3,4] The preparation of a potential precursor for the ligand of this imaging agent designed to create a novel anionic chemical delivery system[5] is described here.

Sodium borohydride reduction[3,6] of 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene (**1**) followed by the alkylation with bromoethanol led to compound **2** which upon esterification with phenylphosphonic dichloride and subsequent hydrolysis gave **3**. Finally, esterification of **3** with chloromethyl pivalate afforded **4**. Preliminary pharmacological evaluation revealed that



i) a) $NABH_4$, ETOH b) $BRCH_2CH_2OH$ *ii*) a) $PHPOCL_2$ b) H_2O
iii) $ClCH_2OCOtBu$ *iv*) $NaBH_4$,, AcOH *v*) Hcooh, CH_2O

compound **4** was indeed able the penetrate through the BBB and then was hydrolyzed to the very polar **3** in the CNS. Reduction of **2** to the corresponding dithia-diaza compound (**5**) with $NaBH_4$ in acidic medium followed by esterification with $PhPOCl_2$ led to **6**. Eschweiler-Clarke methylation provided the N^8-methyl derivative (**7**) which was then converted to the pivaloyl ester (**8**), a potential synthetic precursor for a ligand of a ^{99m}Tc-labeled brain-imaging agent. The alternative approach to **8** in which first we methylated **5** followed by the esterification gave a very poor yield; therefore, we did not consider this route any further. The disulfide bond of **8** then can be conveniently reduced to yield the dithio diazadecane derivative.[1,7,8]

EXPERIMENTAL SECTION

Melting points were determined with a Fisher-Jones apparatus and are uncorrected. Elemental analysis were performed by Atlantic Microlabs, Inc., Atlanta, GA. NMR spectra were recorded on a Varian XL 200 MHz (FT) spectrometer. Fast atom bombardment (FAB) mass spectra were obtained on a KRATOS MS-80-RFA instrument as solutions in 3-nitrobenzyl alcohol as a matrix and bombarding with 8-keV xenon beam. Thin layer chromatography (TLC) was performed on silica gel $60F_{254}$ pre-coated plates.

6,6,9,9-Tetramethyl-2,3,5,6,9,10-hexahydro-1H-imidazo[2,1-d][1,2,5]dithiazepin-1-yl-ethanol (2).- To a solution of 9.98 g (43.0 mmol) of 6,6,9,9-tetramethyl-2,3,5,6,9,10-hexahydro-1H-imidazo[2,1-d][1,2,5]dithiazepine[3,8] prepared by reduction of 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene[3,7] (**1**) in ethanol (50 mL) were added 3.0 g (28.3 mmol) Na_2CO_3, 1.0 g (6.7 mmol) of NaI and 6.0 mL (10.38 g, 85.0 mmol) of bromoethanol. The mixture was refluxed for 16 h. The solid (inorganic salts) was filtered off, and the mother liquor was diluted with 25 mL of water and extracted with chloroform (3 x 150 mL). Removal of the solvent afforded a brown solid which was purified by column chromatography (silica gel, benzene-ethyl acetate 8:2 v/v) to give a colorless oil (7.81 g, 65% yield). MS (FAB): *m/z* 277 $(M+H)^+$; TLC: R_f 0.7 (ethyl acetate-benzene 1:1 v/v); ^{1}H NMR (DMSO-d_6): δ 1.30 (s, 12H), 2.41-3.60 (m, 9H), 3.85 (t, 2H, J = 3.6 Hz).

Anal. Calcd for $C_{12}H_{24}N_2OS_2$: C, 52.13; H, 8.75; N, 10.13; S, 23.19
Found: C, 52.05; H, 8.71; N, 10.03; S, 23.27

6,6,9,9-Tetramethyl-2,3,5,6,9,10-hexahydro-1H-imidazo[2,1-d][1,2,5]dithiazepin-9-yl-ethyl phenylphosphonate (3).- A solution of 3.73 g (13.5 mmol) of **2** in benzene (10 mL) was added dropwise into a solution of 2.8 mL (20.0 mmol) of phenylphosponic dichloride in 10 mL of benzene and 10 mL of pyridine under nitrogen atmosphere at 0°. The reaction mixture was stirred for 2 h then the cooling bath was removed and stirring was continued overnight at room temperature. Then 5 mL of water was added and stirring was continued for 24 h. More water (100 mL) was added and the solution was stirred for 4 additional h. The precipitate was collected, washed with water, and recrystallized from acetone to yield 2.1 g (38%) of off-white solid with no definite melting point. MS (FAB): *m/z* 417 $(M+H)^+$; TLC: R_f 0.7 (chloroform-ethanol-NH_4OH, 100:50:5 v/v/v).

Anal. Calcd for $C_{18}H_{29}N_2O_3PS_2 \cdot 2\,H_2O$: C, 47.77; H, 7.35; N, 6.19; S, 14.17
Found: C, 47.82; H, 7.48; N, 6.18; S, 14.09

O-(1,1,4,4-Tetramethyl-2,3,5,6,9,10-hexahydro-imidazo[2,1-d][1,2,5]dithiazepin-9-yl)ethyl O-pivaloyloxymethyl phenylphosphonate (4).- To a solution of compound **3** (0.95 g, 2.3 mmol) in 10 mL of methanol a solution of 0.13 g of KOH in 5 mL of methanol was added. The solution was stirred for 10 min then the solvent was evaporated under reduced pressure. The oily residue was suspended in 8 mL of hexamethyltriamidophosphate (HMTP) and 1.0 mL (7.0 mmol) of chloromethyl pivalate was added. The mixture was stirred at 60-70° for 5 h, then overnight at room temperature. The solution was diluted with 100 mL of water and extracted with hexane (3 x 25 mL). The combined organic layer was washed with brine (40 mL) and the solvent was removed under reduced pressure. The oily residue was purified by column chromatography (silica gel; washing the column first with benzene and, then eluting the product with benzene-ethyl acetate, 9:1, v/v). A colorless oil was obtained (0.93 mg, 76%). TLC: R_f 0.50 (ethyl acetate-benzene 1:2 v/v); MS (FAB): *m/z* 531 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.12 (s, 9H), 1.30 (s, 12H); 2.39-3.41 (m, 9H); 3.71 (t, 2H, J = 3.49 Hz); 5.75 (s, 2H), 7.31-7.85 (m, 3H): 7.69-7.85 (m, 2H).

Anal. Calcd for $C_{24}H_{39}N_2O_5PS_2$: C, 54.32; H, 7.41; N, 5.28; S, 12.08
Found: C, 54.10; H, 7.48; N, 5.23; S, 12.12

3,3,10,10-Tetramethyl-1,2-dithia-5,8-diazacyclodecan-5-yl-ethanol (5).- To a solution of compound **2** (0.28 g, 10 mmol) in acetic acid (40 mL) cooled to 10°, was slowly added (1 h) 2.2 g (60.0 mmol) of $NaBH_4$. The solution was stirred at room temperature for 2 h and the solvent was evaporated under reduced pressure. The oily residue was treated with water (20 mL) and 3 mL of HCl. The water was removed under reduced pressure, the residue was dissolved in water (10 mL) again, the pH was adjusted to 10 with 2N NaOH. The solution was extracted with chloroform (4 x 100 mL). The combined extracts were dried and evaporated to an oil which was purified by column chromatography (silica gel; the column was first washed with chloroform, then the product was eluted with chloroform-ethanol, 3:2, v/v). A white solid was obtained (0.87 g, 48% yield), mp. 65-67°, MS (FAB): *m/z* 279 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.16 (s, 6H); 1.30 (s, 6H); 2.40-3.00 (m, 10H); 4.12 (m, 2H).

Anal. Calcd for $C_{12}H_{26}N_2OS_2$: C, 51.76; H, 9.41; N, 10.06; S, 23.03
Found: C, 51.80; H, 9.42; N, 10.00; S, 22.96

O-(3,3,10,10-Tetramethyl-1,2-dithia-5,8-diazacyclodecan-5-yl)ethyl phenylphosphonate (6).- To a solution of compound **5** (2.78 g, 10.0 mmol) in 30 mL of dry pyridine 2.0 mL (14.3 mmol) of $PhPOCl_2$ was added dropwise at 0°. After 1 h, the cooling bath was removed and stirring was continued overnight. The solvent was evaporated under reduced pressure, the solid residue was collected and washed with water and acetone. It was recrystallized from aqueous acetone (acetone-water 8:2 v/v yielding 3.35 g (80%) of white solid, mp. 231-232°, MS (FAB): *m/z* 419 $(M+H)^+$; TLC: R_f 0.3 (chloroform-ethanol-NH_4OH, 100:100:5 v/v/v).

Anal. Calcd for $C_{18}H_{31}N_2O_3PS_2 \cdot 0.25\,H_2O$: C, 51.53; H, 7.69; N, 6.68; S, 15.28
Found: C, 51.65; H, 7.58; N, 6.69; S, 15.32

O-(3,3,8,10,10-Pentamethyl-1,2-dithia-5,8-diazacyclodecan-5-yl)ethyl phenylphosphonate (7).- A solution of 3.35 g (8.0 mmol) of **6** in a mixture of 100 mL of formic acid and 16 mL of 37% of formaldehyde was refluxed for 16 h. The solvent was evaporated under reduced pressure and the solid residue was dissolved in 70 mL of water. The solution was neutralized with NH_4OH and the precipitate obtained was collected and washed with water and acetone yielding 2.51 g (73%) of white solid, mp. 195-9°. FAB(MS): m/z 433 $(M+H)^+$; ^1H NMR (DMSO-d_6): δ 1.15 (s, 6H); 1.30 (s, 6H); 2.55-3.35 (m, 10H); 2.85 (s, 3H); 4.10 (m, 2H); 7.30-7.50 (m, 3H); 7.78-7.90 (m, 2H).

Anal. Calcd for $C_{19}H_{33}N_2O_3PS_2 \cdot H_2O$: C, 50.64; H, 7.83; N, 6.22; S, 14.23

Found: C, 50.76; H, 7.84; N, 6.23; S, 14.26

O-(3,3,8,10,10-Pentamethyl-1,2-dithia-5,8-diazacyclodecan-5-yl)ethyl O-pivaloyloxymethyl phenylphosphonate (8). To a solution of compound **7** (1.29 g, 3.0 mmol) in 40 mL of methanol 0.18 g of KOH in 5 mL of methanol was added. The solution was stirred for 10 min, then the solvent was evaporated under reduced pressure. The oily residue was dissolved in 10 mL of HMTP and 0.8 mL (5.5 mmol) of chloromethyl pivalate was added. The solution was stirred overnight, diluted with 50 mL of water and extracted with hexane (3 x 50 mL). The combined organic layers were evaporated under reduced pressure and the oily residue was purified by column chromatography (silica gel, ethyl acetate) affording 0.95 g (41% yield) of a colorless oil. MS (FAB): *m/z* 547 $(M+H)^+$; TLC: R_f 0.4 (ethyl acetate-benzene 1:2 v/v); ^1H NMR (DMSO-d_6): δ 1.05 (s, 9H); 1.20 (s, 6H); 1.35 (s, 6H); 2.30 (s, 3H); 2.40-3.00 (m,10H); 4.12-4.30 (m, 2H); 5.65m (s, 2H); 7.42-7.60 (m, 3H); 7.75-7.90 (m, 2H).

*Anal.*Calcd for $C_{25}H_{43}N_2O_5PS_2 \cdot 0.25\ H_2O$: C, 54.82; H, 8.10; N, 5.11; S, 11.71

Found: C, 54.92; H, 7.93; N, 5.12; S, 11.73

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