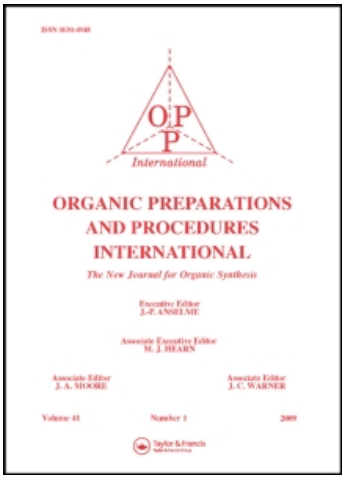

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George A. Brine[a]; David K. Sawyer[a]; F. Ivy Carroll[a]
[a] Chemistry and Life Sciences Unit, Research Triangle Institute, Research Triangle Park, NC

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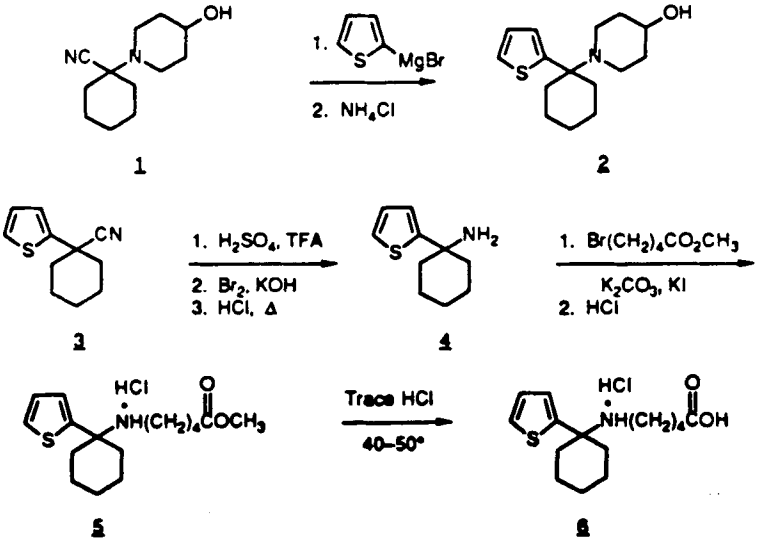
SYNTHESIS OF POTENTIAL 1-[1-(2-THIENYL)CYCLOHEXYL]PIPERIDINE METABOLITES

Submitted by (06/27/89) George A. Brine,* David K. Sawyer and F. Ivy Carroll

Chemistry and Life Sciences Unit
Research Triangle Institute
Research Triangle Park, NC 27709

1-[1-(2-Thienyl)cyclohexyl]piperidine is one of the more potent analogs of phencyclidine.[1] By analogy to known metabolites of phencyclidine,[2,3] 1-[1-(2-thienyl)cyclohexyl]-4-piperidinol (2) and 5-[N-[1'-(2-thienyl)cyclohexyl]amino]pentanoic acid (6) are two potential metabolites of



1-[1-(2-thienyl)cyclohexyl]piperidine. Recently there has been interest in compounds such as these as starting materials in the development of antibodies against arylcyclohexylamines.[4] We report here our preparations of 2 and 6.

4-Hydroxypiperidine hydrochloride was condensed with cyclohexanone in the presence of potassium cyanide to yield 1-(4-hydroxypiperidino)cyclohexanecarbonitrile (1)[2] in 85% yield. Treatment of 1 with excess (2-thienyl)magnesium bromide afforded 1-[1-(2-thienyl)cylohexyl]-4-piperidinol (2) in 34% yield. Alkylation of 2-thiopheneacetonitrile with 1,5-dibromopentane in the presence of sodium hydride afforded 1-(2-thienyl)cyclohexanecarbonitrile (3).[5] A controlled hydrolysis of 3 using sulfuric acid in trifluoroacetic acid gave 1-(2-thienyl)cyclohexanecarboxamide which was subjected to a Hofmann rearrangement to afford 1-(2-thienyl)cyclohexylamine (4).[6] After purification as the hydrochloride salt, amine 4 was alkylated with methyl 5-bromovalerate in the presence of potassium carbonate and potassium iodide to give methyl 5-[N-[1'-(2-thienyl)cyclohexyl]amino]pentanoate which was isolated as the hydrochloride salt 5. Hydrolysis of the ester under carefully controlled conditions[7] provided 5-[N-[1'-(2-thienyl)-

cyclohexyl]amino]pentanoic acid (6) hydrochloride.

EXPERIMENTAL SECTION

Melting points were taken in capillary tubes using a Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-460 spectrophotometer. ^1H NMR spectra were obtained on either a Varian EM-390 spectrometer or a Bruker WM-250 high resolution spectrometer. All ^1H NMR chemical shifts are reported in ppm downfield from TMS. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. TLC analyses were routinely carried out using commercially available analytical silica gel plates (E. Merck). The following solvent systems were used: system A- $CHCl_3$:MeOH:conc. NH_4OH (80:18:2); system B- $CHCl_3$:MeOH (95:5); system C- $CHCl_3$:MeOH: conc. NH_4OH (90:10:4 drops/100mL).

1-(4-Hydroxypiperidino)cyclohexanecarbonitrile (1).- The title compound was prepared in 85% yield using the literature procedure.[2]

1-[1-(2-Thienyl)cyclohexyl]-4-piperidinol (2).- To a mixture of Mg turnings (5.0 g, 0.21 mol) and a few I_2 crystals in dry Et_2O (100 mL) was added a small amount (ca. 1.5 mL) of 2-bromothiophene; this initiated an exothermic reaction. The remainder of the 2-bromothiophene (total: 35.3 g, 0.22 mol) diluted to 60 mL with Et_2O was added at a rate sufficient to maintain reflux. Afterwards, the mixture was stirred and refluxed 30 min to give a brown solution of the Grignard reagent. To this was added dropwise a solution of 1 (10.0 g, 0.048 mol) in freshly distilled THF (60 mL). Following this addition, the reaction mixture was refluxed 24 hrs. After the reflux period, saturated NH_4Cl (133 mL) was added, and the resultant mixture stirred until all the solid had dissolved. The aqueous layer was extracted with Et_2O (2 x 100 mL), and the ethereal extracts were combined with the original organic layer. The combined organic layers were washed with saturated NaCl (160 mL), then extracted with 6N HCl (3 x 120 mL). The combined acid extracts were washed with Et_2O (2 x 150 mL), then cooled and basified by addition of concentrated NH_4OH. The resultant basic solution was extracted with Et_2O (3 x 200 mL). The combined Et_2O extracts were washed with saturated NaCl (150 mL), dried ($MgSO_4$) and evaporated to give an off-white solid. A solution of this solid in boiling EtOH was decolorized using neutral Norit (two treatments). The recovered solid was recrystallized from EtOH/hexanes to yield 4.33 g (34%) of 1 as white needles, mp. 123°; TLC (system A) single spot, R_f 0.78; IR (CH_2Cl_2): 3610, 2940, 2860, 2815, 1050, 996 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4-1.6 (6H, m, aliphatic H), 1.7 (2H, m, aliphatic H), 1.8-2.1 (9H, m, aliphatic H and OH), 2.84 (2H, m, aliphatic H), 3.48 (1H, broad m, CHOH), 6.82 (1H, d, J = 3.4 Hz, thiophene 3-H), 6.99 (1H, dd, thiophene 4-H), 7.18 (1H, d, J = 5.0 Hz, thiophene 5-H).

Anal. Calcd for $C_{15}H_{23}NOS$: C, 67.88; H, 8.73; N, 5.28. Found: C, 67.76; H, 8.90; N, 5.13

1-(2-Thienyl)cyclohexanecarbonitrile (3).- The title compound was prepared in 77% yield using the literature procedure.[5]

1-(2-Thienyl)cyclohexylamine (4). Hydrolysis to Amide.- A mixture of 3 (40.01 g, 0.21 mol) and H_2SO_4 (18 g) in trifluoroacetic acid (85 mL) was refluxed 16 hrs. After cooling to room temperature, the mixture was poured over crushed ice (200 g). Once the ice had melted the

mixture was diluted with additional H_2O (200 mL) and extracted with EtOAc (5 x 400 mL). The combined extracts were dried (Na_2SO_4) and evaporated to a dark brown oil which solidified upon standing. The solid was chromatographed on silica gel (410 g), eluting with $CHCl_3$, to obtain 17.81 g of light brown solid. This material was dissolved in Et_2O (500 mL), and the solution was treated with neutral Norit and filtered. The colorless filtrate was concentrated to 150 mL, then diluted to 500 mL with petroleum ether and concentrated again until crystallization began. Subsequent filtration and drying afforded 9.55 g of 1-(2-thienyl)cyclohexanecarboxamide as a white solid, mp. 103-104°; TLC (system B) single spot, R_f 0.27; IR (CH_2Cl_2): 3500, 3390, 2930, 2850, 1681 ($CONH_2$), 1579, 1572, 1332 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3-1.7 (6H, m, aliphatic H), 1.9-2.0 (4H, m, aliphatic H), 5.4 and 6.2 (2H, two broad s, NH_2), 6.9 (2H, m, ArH), 7.2 (1H, d, ArH). Additional product (5.68 g) of similar purity was isolated from the mother liquor, bringing the total yield to 15.23 g (35%).

Hofmann Rearrangement of Amide.- Bromine (1.48 mL, 0.029 mol) was added to ice cold aqueous KOH (82 mL, prepared by dissolving 99 g of KOH in 500 mL of H_2O). To this mixture was added in one portion 1-(2-thienyl)cyclohexanecarboxamide (5.55 g, 0.0265 mol), and the resultant mixture was stirred 90 min at 3-9°. It was then extracted with Et_2O and the Et_2O extract added with stirring to concentrated HCl (25 mL), heated to 50° (oil bath). Following the addition, the mixture was maintained at 110° for 90 min, then cooled to room temperature and treated with aqueous NaOH (73.8 mL, prepared by dissolving 105 g of NaOH in 450 mL of H_2O). The resultant mixture was extracted with Et_2O (3 x 150 mL). The combined extracts were dried (Na_2SO_4) and evaporated to yield a brown oil, which was taken up in Et_2O (200 mL) and filtered through a cotton plug. Treatment of the filtrate with gaseous HCl precipitated a tan solid which weighed 2.82 g after collection and drying. Repetition of the reaction starting with 13.50 g of the amide afforded an additional 6.67 g of tan hydrochloride. Subsequent recrystallization of the combined solids from MeOH/Et_2O provided 6.89 g (35%) of 1-(2-thienyl)cyclohexylamine hydrochloride as white crystals, mp. 215-216°, lit.[6] 215-216°; TLC (system C) single spot, R_f 0.52; IR (CH_2Cl_2): 2930, 2850, 1570 (broad), 1445, 1230 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3-1.8 (6H, m, aliphatic H), 1.9-2.4 (4H, m, aliphatic H), 6.9 (1H, dd, ArH), 7.2 (2H, m, ArH), 8.6 (3H, broad s, NH_3).

A solution of the hydrochloride salt in H_2O was basified with concentrated NH_4OH and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and evaporated to give 5.18 g of 4 as a light brown oil. This material was used in the subsequent reaction without further purification.

Methyl 5-[N-[1'-(2-Thienyl)cyclohexyl]amino]pentanoate Hydrochloride (5).- A stirred mixture of 4 (1.37 g, 0.0076 mol), methyl 5-bromovalerate (1.87 g, 0.0096 mol), K_2CO_3 (2.26 g, 0.016 mol) and KI (0.14 g) in acetone (40 mL) was refluxed 144 hrs, after which time TLC analysis showed that some starting amine remained. Consequently, additional methyl 5-bromovalerate (1.36 g, 0.0070 mol) and KI (0.10 g) were added, and refluxing was

continued for an additional 216 hrs. Afterwards, TLC analysis showed that no starting amine remained. The mixture was filtered to remove the inorganics which were washed with acetone. Evaporation of the combined filtrate and washings gave a yellow oil which was dissolved in $CHCl_3$ (60 mL). The solution was washed with 10% NH_4OH (40 mL), dried (Na_2SO_4) and evaporated to obtain a yellow oil. This was combined with two samples of similar purity from earlier reactions. The combined sample (5.75 g) was chromatographed on silica gel (110 g) using a 2%→5%→10% acetone/$CHCl_3$ gradient to obtain a chromatographically pure yellow oil (1.68 g). A solution of this oil in Et_2O was treated with HCl gas, then evaporated to give the crude hydrochloride salt as a yellow oil which slowly crystallized upon standing (1.91 g). The solid was dissolved in EtOAc, and the solution was treated with neutral Norit and filtered. The clear filtrate was diluted with hexanes, concentrated until cloudy and cooled. The title compound separated as an oil which later changed to a white semisolid (0.91 g), TLC (system C) single spot, R_f 0.53; IR (CH_2Cl_2): 2945, 2865, 2750, 1733, 1581, 1449, 1438, 1197 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4-1.7 (6H, m, aliphatic H), 1.8-2.0 (4H, m, aliphatic H), 2.2 (2H, t, aliphatic H), 2.4 (2H, m, aliphatic H), 2.6-2.8 (4H, m, aliphatic H), 3.63 (3H, s, OCH_3), 7.10 (1H, dd, thiophene 4-H), 7.40 (1H, d, J = 4.9 Hz, thiophene 5-H), 7.45 (1H, d, J = 3.1 Hz, thiophene 3-H), 9.65 (2H, broad s, NH_2). An analytical sample was crystallized from EtOAc/hexanes as fluffy white needles, mp. 142-143°.

Anal. Calcd for $C_{16}H_{26}ClNO_2S$: C, 57.89; H, 7.89; Cl, 10.68; N, 4.22
Found: C, 58.07; H, 7.74; Cl, 11.33; N, 4.19

5-[N-[1'-(2-Thienyl)cyclohexyl]amino]pentanoic Acid (6) Hydrochloride.- A solution of methyl ester 5 (0.96 g, 0.0029 mol) in H_2O (60 mL) containing one drop of concentrated HCl was stirred 96 hrs at 45-50° with an additional drop of acid being added after 48 hrs. Afterwards, the mixture was freeze-dried to yield 0.90 g of white solid. Recrystallization from acetone/ H_2O followed by vacuum drying at 60° for 16 hrs afforded 0.70 g of a white, crystalline solid, mp. 178-179.5°. Subsequent ^1H NMR and elemental analysis of this material indicated that it was solvated with acetone. Consequently, it was vacuum dried 72 hrs at 80°, affording the title compound as an off-white, crystalline solid, mp. 179.5-180°; TLC (system A) single spot, R_f 0.75; IR (KBr): 3425, 2935, 2850, 2810, 1733, 1574, 1458, 1447, 1161 cm^{-1}; ^1H NMR (DMSO-d_6); δ 1.2-1.3 (2H, m, aliphatic H), 1.4-1.6 (4H, m, aliphatic H), 1.7 (2H, m, aliphatic H), 2.0-2.2 (4H, m, aliphatic H), 2.5-2.6 (4H, m, aliphatic H), 7.15 (1H, dd, thiophene 4-H), 7.37 (1H, d, J = 3.5 Hz, thiophene 3-H), 7.71 (1H, d, J = 5.0 Hz, thiophene 5-H), 9.29 (2H, broad s, NH_2).

Anal. Calcd for $C_{15}H_{24}ClNO_2S$: C, 56.68; H, 7.61; Cl, 11.15; N, 4.41
Found: C, 56.77; H, 7.92; Cl, 11.17; N, 4.22

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7. A reaction temperature of 45-50° avoided the problems of elimination (reflux conditions), incomplete reaction and prolonged reaction time (room temperature conditions).

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AN ALTERNATIVE METHOD FOR TOLNAFTATE †

Submitted by (05/17/89) N. R. Ayyangar*, R. D. Wakharkar
V. H. Deshpande and B. Rai

National Chemical Laboratory
Pune 411008, INDIA

The utility of tolnaftate [2-naphthyl-N-methyl-N-(m-tolyl) thionocarbamate, 1], a two-step condensation product of N-methyl-m-toluidine, thiophosgene and β-naphthol,[1,2] as an effective antifungal drug has been known for more than a decade. We now communicate an alternative method which avoids the use of thiophosgene for its preparation and employs carbon disulphide and chloride (absorbed in CCl_4).[3]

Methylation of N-acetyl-m-toluidine in presence of PTC followed by hydrolysis provided N-methyl-m-toluidine, in nearly quantitative yield.[4] The dimethyl di-(m-tolyl)thiuram disulphide (2) was prepared [5] from N-methyl-m-toluidine by treatment with excess of carbon disulphide in the presence of iodine and pyridine. It was then converted into N-methyl-N-(m-tolyl)thiocarbamoyl chloride (3) in excellent yields by treatment with requisite amount of chlorine absorbed in carbon tetrachloride at 5-10°. The thiocarbamoyl chloride 3 was condensed, without further purification, with β -naphthol in refluxing benzene in the presence of powdered potassium