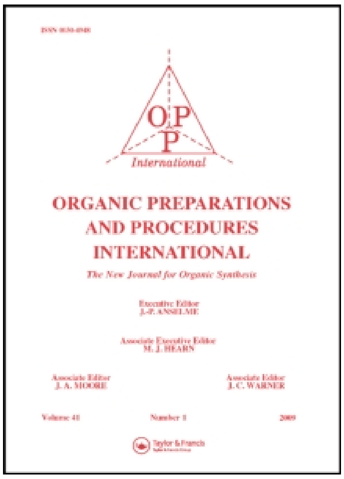

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SYNTHESIS OF 7-HYDROXY-4-BENZOFURANACETIC ACID

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SYNTHESIS OF 7-HYDROXY-4-BENZOFURANACETIC ACID

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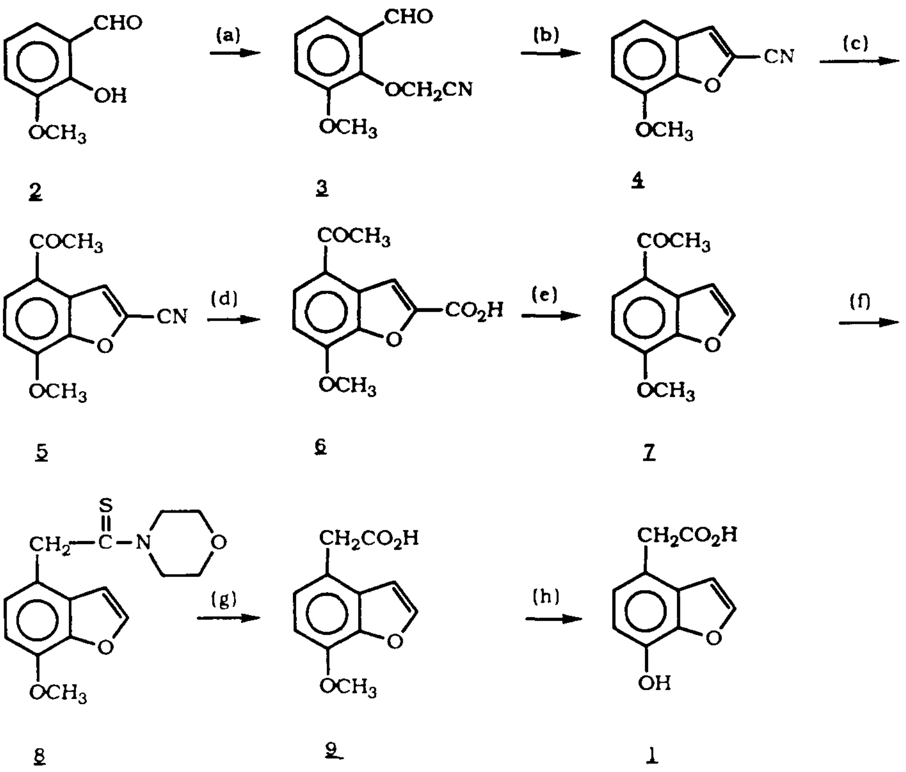
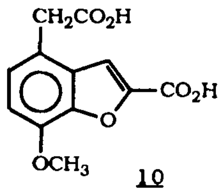
In order to develop a radioimmunoassay for some very potent κ opioid receptor agonist analgesics, it became necessary to prepare the novel compound, 7-hydroxy-4-benzofuranacetic acid 1. Starting from the readily available 2-hydroxy-3-methoxybenzaldehyde (o-vanillin, 2) we envisioned building the benzofuran ring with the 2- and the 7-positions protected. Electrophilic substitution would then allow entry into the 4-position. Deprotection at the 2- and the 7-positions and substituent modification at the 4-position would lead to 1 as depicted in the scheme.

The conversion of 2 to 4 is a modification of the procedure of René and Royer,[1,2] which describes it as a one-step process. We found that reaction of 2 with one equivalent each of chloroacetonitrile and potassium carbonate gave the initial condensation product 3 (94%), which could then be converted to 4 in 55% yield. Alternatively, the reaction of 2 to 3 could be monitored by thin layer chromatography.[9] When tlc indicated that the transformation was complete, addition of another mol of potassium carbonate to the mixture allowed formation of 4 in 43% yield. Friedel-Crafts acetylation of 4, as described previously,[3] gave 5 in 95% yield. There was no evidence of acetylation occurring anywhere but in the desired 4-position.



Our original plan was to carry out the Willgerodt-Kindler reaction on 5. This, followed by simultaneous hydrolysis of the thiomorpholide and nitrile groups, would have given the diacid 10 which upon decarboxylation and demethylation would provide 1. However, the Willgerodt-Kindler reaction on 5 gave an intractable mixture. Instead, 5 was hydrolyzed in refluxing aqueous sodium hydroxide to afford 6 in quantitative yield. Compound 6 was then decarboxylated with copper and quinoline.[4] The product 7, underwent the Willgerodt-Kindler reaction[5] smoothly. The resulting thiomorpholide 8 was hydrolyzed to the carboxylic acid 9 in aqueous sodium hydroxide under reflux. Several attempts were made to demethylate 9. These included aluminum chloride in



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refluxing chlorobenzene,[6] pyridine hydrochloride,[3] trimethylsilyl iodide in chloroform,[7] boron tribromide-methyl sulfide complex in refluxing dichloroethane[8] and variations of boron tribromide in dichloromethane.[7] Our best results were obtained with boron tribromide (4.4 mol/mol 9) in dichloromethane at 5° for 18 hrs, followed by a water:ether workup and chromatography. Analytically pure 1 was obtained in 49% yield. The overall yield of 1 from 2 was 7.4%; some of the steps were not optimized.

EXPERIMENTAL SECTION

Melting points were obtained in capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were obtained on a Varian XL200 instrument. The IR spectra were obtained on the Nicolet MX-1 FTIR instrument. Mass spectra were determined on a VG Analytical 7070E/HF mass spectrometer or a Finnigan 4500 mass spectrometer.

7-Methoxy-2-benzofurancarbonitrile (4) (One-Step Procedure).- A mixture of 304 g (2.0 mol) of 2-hydroxy-3-methoxybenzaldehyde, 276 g (2.0 mol) of potassium carbonate, 182 g (2.4 mol) of chloroacetonitrile and 3.2 l of N,N-dimethylformamide was heated to reflux (~150°) over a 75 min period. Tlc at this point showed no 2 present,[9] only the intermediate 3 and some origin material. To the mixture was added 276 g (2.0 mol) of potassium carbonate and heating under reflux was continued for 20 min. The mixture was concentrated under vacuum (water aspirator) by ~2 ℓ. The residue was poured into 7 ℓ of stirred ice-water. The resulting dark brown mixture was extracted with diethyl ether (5 x 1 ℓ). The combined extracts were dried over magnesium sulfate, filtered, and the filtrate concentrated on a rotary evaporator to near dryness. The residue was distilled at 1-2 torr. After a forerun consisting mostly of DMF, the product distilled over at 110-130°. The distillate solidified to give 148 g (43%) of the title compound as a pale-yellow solid, mp. 81-93°. Recrystallization from ether of a portion of this material provided off-white needles, mp. 100-102°, lit.[2] mp. 99°. The distilled material was sufficiently pure for the next step. IR(KBr): 2229 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.99 (s, OCH_3), 6.93-6.97 (doublet of doublets, ArH), 7.18-7.30 (m, 2ArH), 7.40 (s, ArH). MS: m/e 173.

7-Methoxy-2-benzofurancarbonitrile (4) (Two-Step Procedure).

a) (2-Formyl-6-methoxyphenoxy)acetonitrile (3).- A stirred two-phase mixture of 30.4 g (0.2 mol) of 2-hydroxy-3-methoxybenzaldehyde, 27.6 g (0.2 mol) of potassium carbonate, 18.2 g (0.24 mol) of chloroacetonitrile and 400 ml of N,N-dimethylformamide was heated under reflux (152°) for 1 hr. The resulting mixture was cooled to room temperature and poured into stirred ice-water. The suspension was stirred for 10 min and filtered. The solid was washed with 200 ml of water and pressed as dry as possible under suction and then air dried to yield 36 g (94%) of 3, mp. 113-118°. A portion of this material was recrystallized from methanol, with charcoal treatment, to give an analytical sample, mp. 118-120°. IR(KBr): 2250, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.92 (s, CH_3), 4.96 (s, CH_2) 7.07-7.22 (m, 2ArH), 7.34-7.53 (m, ArH), 10.35 (s, CHO). MS: m/e 191.

Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33
Found: C, 62.66; H, 4.82; N, 7.27

b) A mixture of 15.6 g (0.082 mol) of crude 3, 11.3 g (0.082 mol) of potassium carbonate and 200 ml of N,N-dimethylformamide was heated under reflux (~150°) for 1.5 hr. Tlc[9] showed the gradual disappearance of starting material and appearance of 4. The dark mixture was cooled to room temperature and concentrated by ~150 ml. The residue was poured into stirred ice-water (400 ml). The resulting suspension was extracted with diethyl ether (5 x 200 ml). The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated del to near dryness. The residue was distilled as described above to provide 7.8 g (55%) of pale yellow liquid which crystallized on standing, mp. 82-96°. The two-step yield was 52%. The physical characteristics of this material matched that of the lot obtained from the one-step fit procedure.

4-Acetyl-7-methoxy-2-benzofurancarbonitrile (5).- To a stirred solution of 62 g (0.36 mol) of 4 in 2.4 ℓ of dichloromethane, under nitrogen, at 18° was added 84 g (1.07 mol) of acetyl chloride all at once, followed by 190 g (1.43 mol) of anhydrous aluminum chloride added portionwise over 0.5 hr. The temperature was kept between 15° and 20° during the latter addition. The reaction mixture was stirred for 20 hr at 20-23° and then was poured into 3 ℓ of stirred ice-water containing 85 ml of concentrated hydrochloric acid. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 1.5 ℓ, 1 ℓ). The combined organic layers were washed with water (2 ℓ), dried over magnesium sulfate, filtered, and the filtrate concentrated to ~800 ml. Diethyl ether (~800 ml) was added and the mixture was cooled to 5°. The crystalline solid which had separated was collected and dried in vacuo at 45° for 16 hr to afford 66 g (85%) of 5, mp. 172-177°, lit.[3] mp. 176°. The mother liquor furnished an additional 8 g (10%) of 5, mp. 170-176°. IR(KBr): 2232, 1671 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.62 (s, CH_3CO), 4.09 (s, O-CH_3), 6.96 (d, ArH), 7.88 (d, ArH), 8.21 (s, furan H). MS: m/e 215.

4-Acetyl-7-methoxy-2-benzofurancarboxylic acid (6).- A mixture of 73.5 g (0.342 mol) of 5, and 750 ml of 10% aq. sodium hydroxide was heated under reflux for 1.5 hr. The resulting solution was poured into 2.5 kg of ice. Conc. hydrochloric acid (~265 ml) was then added to the stirred mixture over a 15-min period. The thick suspension was filtered and the solid was washed with water and pressed dry under suction. Further drying in a vacuum oven at 60° for 65 hrs afforded 79 g (99%) of 6, mp. 270-272°, lit.[10] mp. 271-280°. IR(KBr): 1705, 1666 cm^{-1}. ^1H NMR (DMSO): δ 2.73 (s, CH_3CO), 4.01 (s, OCH_3), 7.15 (d, ArH), 7.96 (s, furan H), 8.01 (d, ArH), 11.89-14.93 (broad s, CO_2H). MS: m/e 234.

<u>1-(7-Methoxy-4-benzofuranyl)ethanone (7)</u>.- A mixture of 79 g (0.338 mol) of 6, 79 g of copper powder, and 250 ml of freshly distilled quinoline was heated to 160° over 1 hr. Gas evolution (CO_2) was observed at this temperature. Heating at 160-165° was continued for 2 hrs. The mixture was cooled to 60° and filtered. The residue was washed with 100 ml of diethyl ether and the wash added to the filtrate. The filtrate was partitioned between 1.5 ℓ each of ice-water and diethyl ether. The layers were separated and the aqueous layer was extracted with 500 ml of ether. The combined organic layers were washed with successive portions of 2N HCl (2 x 1 ℓ), and water (1 ℓ), and then dried over magnesium sulfate. The solution was concentrated to ~500 ml and then passed through a 300 g silica gel (230-400 mesh) pad. The pad was washed with 500 ml of diethyl ether. The filtrate and washing were combined and concentrated *in vacuo* to dryness to afford 53 g (83%) of crude 7. This was recrystallized from diethyl ether:hexane to give two crops of material, 27.5 g, mp. 92-94° and 18.5 g, mp. 88-93° both of which were sufficiently pure for the next step. IR(KBr): 1661 cm^{-1}. ^1H NMR (DMSO): δ 2.68 (s, CH_3CO), 3.99 (s, OCH_3), 7.02 (d, ArH), 7.44 (d, furan H), 7.96 (d, ArH), 8.07 (d, furan H). MS: m/e 190.

<u>Anal</u>. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30.

Found: C, 69.48; H, 5.33

<u>4-[2-(7-Methoxy-4-benzofuranyl)-1-thioxoethyl]morpholine (8)</u>.- A mixture of 21.5 g (0.113 mol) of 7, 5.4 g (0.169 mol) of sulfur, and 43.5 g (0.5 mol) of morpholine was heated under reflux (120°) for 6 hrs. The mixture was cooled to room temperature, diluted with 50 ml of methanol, and stirred at 0° for 0.5 hr. The solid was collected, rinsed with methanol (~25 ml) and pressed dry under suction. Further drying in a vacuum oven at 60° for 16 hrs afforded 20.5 g (62%) of 8, mp. 164-171°. IR(KBr): 1629 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.33,3.58 (2t, 2 morpholine CH_2), 3.74,

4.37 (2t, 2 morpholine CH_2), 4.00 (s, OCH_3), 4.50 (s, CH_2), 6.76 (d, ArH), 6.95 (d, 1 furan H), 7.08 (d, ArH), 7.65 (d, 1 furan H). MS: m/e 291.

Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; S, 11.00

Found: C, 61.60; H, 5.78; N, 4.76; S, 10.71

7-Methoxy-4-benzofuranacetic Acid (9).- A frothy mixture of 20 g (0.069 mol) of 8 and 200 ml of 5% aq. sodium hydroxide was heated under reflux for 3.5 hrs. The mixture was cooled to room temperature and filtered from some black insoluble material. The filtrate was cooled to 0° and stirred as conc. hydrochloric acid was added to pH ~1. The resulting suspension was stirred at 0° for 0.5 hr and filtered. The solid was washed with 75 ml of water and pressed as dry as possible under suction. Recrystallization from ether:hexane followed by drying in a vacuum oven at 40° for 16 hrs provided 10.5 g (74%) of 9, mp. 112-115°. This reaction repeated on a 16 g scale gave an 84% yield of product, mp 114-117°. IR(KBr): 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.80 (s, CH_2), 4.01 (s, CH_3), 6.75-6.82 (m, ArH, 1 furan H), 7.06 (d, ArH), 7.65 (d, 1 furan H), 10.38-11.55 (broad s, CO_2H). MS: m/e 206.

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89.

Found: C, 63.95; H, 4.87

7-Hydroxy-4-benzofuranacetic Acid (1).- In a flame dried flask under nitrogen was dissolved 8.8 g (0.043 mol) of 9 in 125 ml of dichloromethane. The stirred solution was chilled to -70° and 188 ml (0.188 mol) of 1M boron tribromide in dichloromethane was added dropwise over a 20-min period. The temperature rose to -60° during the addition. The mixture was stirred gently and the temperature reached a maximum of 5° over 4 hrs and then was stored at 5° for 16 hrs with a calcium chloride drying tube attachment. The suspension was poured into 500 ml of stirred ice-water. The mixture was stirred for 0.5 hr and extracted with diethyl ether (3 x

300 ml). The ethereal extract was washed with water (500 ml), dried over magnesium sulfate and filtered. The filtrate was evaporated to dryness on a rotary evaporator. The residue was chromatographed through 150 g of silica gel (230-400 mesh) using diethyl ether as the eluent. Evaporation of the solvent gave 8.3 g of crude solid which was recrystallized from diethyl ether. Drying in a vacuum oven at 50° for 5 hrs provided 5.4 g (66%) of 1, mp. 119-127°. To obtain analytical material, the 5.4 g was combined with 2.3 g of similarly pure product and recrystallized from diethyl ether. Drying in a vacuum oven at 60° for 18 hr furnished 5.7 g (74% recovery) of 1, mp 126-128°. IR(KBr): 1681 cm^{-1}. ^1H NMR (DMSO): δ 3.68 (s, CH_2), 6.89 (d, furan H), 6.91 (m, furan H + ArH), 7.91 (d, ArH), 9.91 (s, OH), 12.26 (s, CO_2H). MS: m/e = 192.

Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20.

Found: C, 62.73; H, 4.17

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