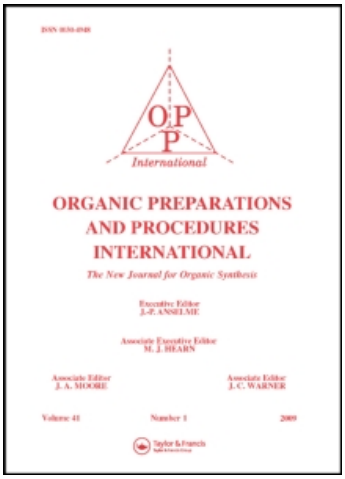

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8-Chloro- and 5,8-Dichloro-1-naphthoic Acids

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8-Chloro- and 5,8-Dichloro-1-naphthoic Acids

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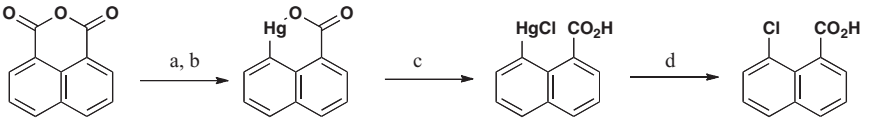
In connection with our program directed toward the development of structure-activity relationships of cannabimimetic 1-alkyl-3-(1-naphthoyl)indoles[1,2] we needed synthetically useful quantities of 8-chloro-1-naphthoic acid (**1**). The synthesis of acid **1** from 1,8-naphthalic anhydride (**2**) *via* anhydro-8-hydroxymercuri-1-naphthoic acid (**3**) and 8-chloromercuri-1-naphthoic acid (**4**) by treatment with the elemental halogen was described originally by Whitmore during the course of his studies on the mercuration of aromatic compounds is shown in *Scheme 1*.[3,4] A modification of the Whitmore procedure was employed by



a) 0.58 M NaOH, H_2O, reflux: b) $Hg(OAc)_2$, from HgO, HOAc, reflux 48 h: c) NaOH, NaCl followed by HCl; d) Cl_2, HOAc.

Scheme 1

Rule and Barnett to obtain modest yields of acid **1** and 8-bromo-1-naphthoic acid (**5**).[5] Although Rule and Barnett mention that 8-chloromercuri-1-naphthoic acid was prepared as described by Leuck *et al.*[3] there is no mention of chloromercuri acid **4** in the paper which was cited. However the preparation of a mixture of acid **4** and its 5-isomer was described by Whitmore and Fox.[4] Although acid **1** has been the subject of several physical organic studies, either no reference is given to the method of synthesis, or reference was given to the Whitmore-Rule procedure.[6–9] Shechter's group modified the classical Whitmore procedure and employed it for the preparation of 8-bromo acid (**5**) and extended it to the preparation of 8-iodo-1-naphthoic acid (**6**).[10] These workers employed anhydro-8-hydroxymercuri-1-naphthoic acid (**3**) as an intermediate, however treatment of **3** with chlorine gave 5,8-dichloro-1-naphthoic acid (**7**) as the only isolable product.

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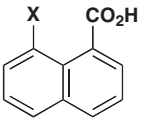
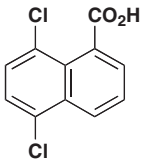
We were able to repeat the preparation of anhydro acid **3** and its reaction with bromine and iodine to provide bromo and iodo acids **5** and **6** in unoptimized yields of 84% and 52% respectively.[11] Initially, in order to avoid the use of elemental chlorine and hopefully to suppress the formation of 5,8-dichloro-1-naphthoic acid, numerous attempts were made under a variety of conditions to prepare acid **1** by reaction of anhydro acid **3** with *N*-chlorosuccinimide or 1,3-dichloro-5,5-dimethylhydantoin as a chlorine source. In one experiment a 36% yield of crude acid **1** was obtained; however, this compound could not be obtained even under apparently identical conditions. In another run, the crude reaction products were converted to mixtures of methyl esters, which were analyzed by GC/MS. The principal constituents of this mixture were methyl 8-chloro-1-naphthoate (41%) and a dichloro ester, presumably methyl 5,8-dichloro-1-naphthoate (53%). A methyl trichloro-1-naphthoate (7%) was found in low yield but was not otherwise characterized.



5 X = Br

6 X = I



7

8-Chloromercuri-1-naphthoic acid (**4**) was prepared from 1,8-naphthalic acid as described by Whitmore and Fox.[4] Reaction of **4** with chlorine in acetic acid at room temperature gave a mixture of carboxylic acids that was converted to the corresponding methyl esters using CH_3I and K_2CO_3 in dried acetone. Analysis of this mixture by GC/MS indicated that the original reaction mixture contained 8-chloro-1-naphthoic acid (**1**, 17%), 5,8-dichloro-1-naphthoic acid (**7**, 28%) and 1-naphthoic acid (28%). In another experiment methyl 8-chloro-1-naphthoate was isolated by chromatography and hydrolyzed (KOH/H_2O) to provide 8-chloro-1-naphthoic acid **1** in poor (35%) yield. The presence of 5,8-dichloro-1-naphthoic acid in the mixture of chlorination products was confirmed by preparation of an authentic sample *via* chlorination of 8-chloro-1-naphthoic acid.[4] Not only was the chromatographic purification of the methyl ester tedious, but repeated repetition of this procedure did not reliably produce 8-chloro-1-naphthoic acid; it was concluded that since electrophilic chlorination of 8-chloro-1-naphthoic acid affords 5,8-dichloro-1-naphthoic acid occurs under very mild acid catalysis,[4] the formation of the 5,8-dichloro acid in the reaction of **4** with chlorine was the result of further chlorination of the desired product. Accordingly, the reaction was carried out in a 1:1 mixture of acetic acid and dichloromethane at ice bath temperature, and in several experiments this procedure provided acid **1**; however, the results were variable and frequently mixtures of products, including 1-naphthoic acid, were obtained. In Rule and Barnett's modification of Whitmore's procedure, it is explicitly stated that dried 8-chloromercuri-1-naphthoic acid (**4**) be employed.[5] It was ultimately found that it is essential that this key intermediate is dried in a vacuum oven *at a temperature not to exceed 50°C*. The 8-chloromercuri acid (**4**) is thermally unstable and decomposes at temperatures greater than 50°C, as indicated by changes in the ^1H NMR spectrum. This procedure provides a reliable method for the preparation of 8-chloro-1-naphthoic acid (**1**). The ^1H and ^{13}C NMR spectra of this product are in agreement with the assigned structure, which was confirmed by X-ray crystallography.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on Bruker 300AC and JEOL 500 spectrometers. Mass spectral analyses were performed on a Shimadzu QP2010 capillary gas chromatograph/mass spectrometer equipped with a mass sensitive detector at 1.01 kV. Ether and THF were distilled from Na-benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Sorbent Technologies silica gel (32–63 μ) using the indicated solvents as eluents. TLC was carried out using 200 μm silica gel plates with the indicated solvents. All mercury waste, including solvents, aqueous washings from extractions and solids were put into a glass container, which was turned over to university environmental health and safety personnel for disposal.

8-(Chloromercuri)-1-naphthoic Acid (4)

The published procedure[4] was modified as follows. To a stirred mixture of 3.0 g (8.1 mmol) of anhydro-8-hydroxymercuri-1-naphthoic acid (**3**)[4,5] in 80 mL of 1 M NaOH was added 0.52 g (8.9 mmol) of NaCl. The reaction mixture was heated at reflux for 15 min, cooled to room temperature and the gray solid was filtered off. The filtrate was cautiously acidified with 6 N HCl to pH 6 while monitoring the pH with Hydrion indicator paper to provide a cream colored solid, which was dried at 50°C for 18 h in a vacuum oven to give 2.98 g (91%) of 8-(chloromercuri)-1-naphthoic acid as a pale yellow solid, mp. 195–197°C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50–7.55 (m, 2H), 7.82 (d, $J = 6$ Hz, 1H), 7.89 (d, $J = 6$ Hz, 1H), 7.94 (d, $J = 6$ Hz, 1H), 8.08 (d, $J = 6$ Hz, 1H), 13.75 (s, 1H); ^{13}C NMR (75.5 MHz) δ 124.8, 126.1, 128.9, 129.5, 132.4, 133.2, 135.2, 135.3, 138.3, 150.2, 172.3.

8-Chloro-1-naphthoic Acid (1)

The literature procedures[4,5] were modified as follows. To a stirred suspension of 1.0 g (2.4 mmol) of **4**, dried in a vacuum oven below 50°C, in 80 mL of glacial acetic acid and CH_2Cl_2 (1:1, v/v) cooled with ice water was added a solution of 0.90 g (12.7 mmol) of Cl_2 in 20 mL of glacial acetic acid. The bulk of the suspended material dissolved in 15 min and the reaction was stirred for 1 h while the reaction mixture was swept with nitrogen. Water was added and the resulting suspension was extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give 0.46 g (91%) of 8-chloro-1-naphthoic acid as a yellow solid. Recrystallization from water gave white flakes, mp. 167–169°C; *lit.*[4,5] mp. 171–171.5 °C, 168–169°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, $J = 6$ Hz, 1H), 7.56 (t, $J = 6$ Hz, 1H), 7.68 (d, $J = 6$ Hz, 1H), 7.79 (d, $J = 9$ Hz, 1H), 7.83 (d, $J = 9$ Hz, 1H), 7.98 (d, $J = 9$ Hz, 1H), 11.10 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.3, 126.6, 127.0, 127.9, 128.2, 129.3, 129.8, 130.2, 131.5, 135.3, 176.6.

5,8-Dichloro-1-naphthoic Acid (7)

Chlorine was swept through a stirred suspension of 1.04 g (2.54 mmol) of 8-(chloromercuri)-1-naphthoic acid in 100 mL of glacial acetic acid at room temperature. The reaction mixture was stirred continuously for 1.5 h, the addition of chlorine was stopped and stirring was continued for 0.5 h. The reaction mixture was filtered to remove suspended solids; the filtrate was diluted with water and extracted with CH_2Cl_2. The organic extracts were washed with

water, dried ($MgSO_4$) and concentrated *in vacuo* to give 0.58 g of crude **7** as a yellow oil, which was converted to its methyl ester without purification.

To a solution of 0.58 g (2.41 mmol) of crude 5,8-dichloro-1-naphthoic acid in 50 ml of dried acetone was added 3.52 g (25.4 mmol) of K_2CO_3. The reaction mixture was stirred at room temperature for 1 h and 0.73 g (5.08 mmol) of CH_3I was added. The reaction mixture was heated at reflux for 2 h, diluted with water and extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether/ether, 5:1) to give 0.13 g (21%) of methyl 5,8-dichloro-1-naphthoate as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.49–7.52 (m, 2H), 7.58–7.61 (m, 1H), 7.63–7.69 (m, 1H), 8.38 (d, $J = 6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 53.2, 120.2, 126.2, 126.6, 127.7, 128.8, 129.2, 129.4, 130.7, 133.0, 133.1, 169.1; GC/MS (EI) *m/z* (real intensity) 255 (2), 254 (14), 219 (100), 204 (48), 195 (25), 160 (34).

To a suspension of 0.13 g (0.51 mmol) of methyl 5,8-dichloro-1-naphthoate in 25 ml of water was added 0.33 g (5.2 mmol) of KOH and the reaction mixture was heated at reflux for 18 h. After cooling to ambient temperature, the solution was washed with ether and the aqueous solution was acidified with 6 N HCl to pH 5. The resulting suspension was extracted with ether and the ethereal extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give the product as pale yellow solid. Recrystallization from water gave 0.033 g (27%) of 5,8-dichloro-1-naphthoic acid (**7**) as a white solid, mp. 186–188°C, *lit.*[4] mp. 186–187°C .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.63 (m, 2 H), 7.69 (t, $J = 9$ Hz, 1H), 7.85 (d, $J = 9$ Hz, 1H), 8.48 (t, $J = 6$Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 126.1, 126.9, 127.2, 127.8, 128.4, 128.6, 129.0, 130.7, 131.4, 133.0, 170.7.

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