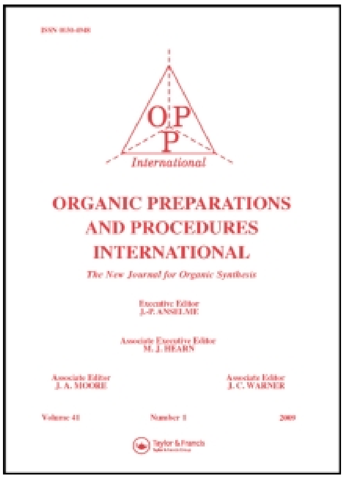

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SYNTHESIS OF 5-ALKOXYANTHRANILIC ACIDS

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SYNTHESIS OF 5-ALKOXYANTHRANILIC ACIDS

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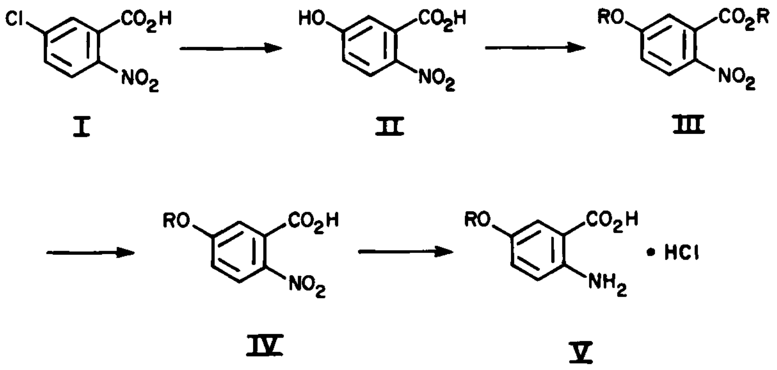
Although 5-methoxyanthranilic acid (Va) has been extensively studied,[1-6] none of the preparative routes described provided adequate flexibility or efficiency as a laboratory scale preparation of anthranilic acids (V). We now report a convenient method for the production of the anthranilic acids V (Table 3) from commercially available 5-chloro-2-nitrobenzoic acid (I).



I II III IV V

a) R = CH_3 b) R = C_2H_5 c) R = $CH_3(CH_2)_2$- d) R = $(CH_3)_2CH_2$-
e) R = $CH_3(CH_2)_3$- f) R = $CH_3(CH_2)_4$- g) R = $HO(CH_2)_2$-
h) R = $C_6H_5CH_2O(CH_2)_2$- i) R = $CH_3O(CH_2)_2$- j) R = $(C_2H_5)_2N(CH_2)_2$-

Reaction of I with excess aqueous sodium hydroxide at reflux gave an 88% yield of the phenol II. A study of the base-mediated alkylation of II with *n*-butyl bromide in DMF, showed that the use of potassium carbonate or the preformed di-potassium salt of II led to the best yields of the alkoxy esters III (Table 1). Either sodium or potassium hydroxide afforded significantly poorer results.

TABLE 1. Yield of Alkyl 5-Alkoxy-2-nitrobenzoates (III) from II.

Compd	Yield	mp. (bp./mm) °C	Analysis: Calcd. (Found) C	H	N
IIIa	97	58-59[a]			
IIIb	95	52-53[b]	55.23 (55.24)	5.48 (5.49)	5.86 (5.93)
IIIc	95	(175-177/1.0)	58.42 (58.30)	6.41 (6.47)	5.24 (5.20)
IIId	92	51-52[c]	58.42 (58.50)	6.41 (6.53)	5.24 (5.26)
IIIe	96	(195-200/0.4)	61.00 (61.04)	7.17 (7.09)	4.74 (4.88)
IIIf	89	(210-214/0.2)	63.14 (63.20)	7.79 (7.79)	4.33 (4.24)

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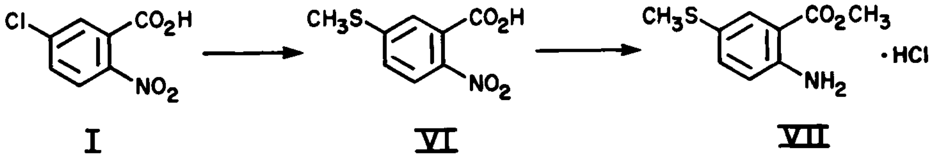
a. Lit.[1] mp. 55-57°. b. Crystallized from CH_2Cl_2-hexane.
c. Purified by ptlc.

These esters (III) were extracted into dichloromethane and hydrolyzed without purification to the acids IV (Table 2). Catalytic reduction of IV over Pd/C then gave the required anthranilic acids V in 60-80% overall yield from the phenols II (Table 3).

A useful variant of the above method for the synthesis of 5-methoxy- and 5-methylthio-2-nitrobenzoic acids (IVa and VI), obtained in 77% and 96% yields respectively, involved the displacement of chloride from I with alkali methoxide and mercaptide respectively. Esterification of VI followed by chemical reduction with iron in acetic acid provided the methylthio anthranilate VII (82%).



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All new compounds gave IR, MS, and NMR spectra in accord with the assigned structures. We thank the staff of our Physical Chemistry Department for the determination of the spectral and microanalytical data.

5-Hydroxy-2-nitrobenzoic Acid (II). - A solution of 201.5 g (1.00 mol) of 5-chloro-2-nitrobenzoic acid and 320 g (8.0 mol) of sodium hydroxide in 2 L of water was heated to reflux for 18 hrs. The resulting solution was acidified to pH 2 with conc. hydrochloric acid and was extracted with 3 x 500 mL of ether. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 175.18 g of a white solid, mp. 163-170°. Recrystallization from ethyl acetate-hexane gave a total of 160.62 g (88%) in three crops melting over a range of 165-170°, lit.[6] mp. 165-166°.

General Procedure for Alkyl 5-Alkoxy-2-nitrobenzoates (III).-A suspension of 18.3 g (0.100 mol) of II, 0.35 moles of an alkyl bromide or iodide, and 30.0 g (0.227 mol) of potassium carbonate in 150 mL of DMF was heated to a bath temperature of 75° (foaming). During the course of 3 hrs, the mixture formed a cake which gradually became a stirred suspension. After cooling, the mixture was diluted with water and extracted with ether to give the product III which was pure by tlc and NMR and was generally used directly in the next step. Samples for analysis were obtained by crystallization or ptlc (1:3 ether:hexane) and evaporative distillation. When 2-chloroethanol was employed as the alkylating agent, a reaction temperature of 130° for 18 hrs was employed.

General Procedure for 5-Alkoxy-2-nitrobenzoic Acids (IV).-A solution of 0.10 mole of III in 100 mL of ethanol and 40 mL of 4 N sodium hydroxide solution was stirred 18 hrs at room temperature. The mixture was partially evaporated *in vacuo*, diluted with water, washed with dichloromethane, acidified with hydrochloric acid and extracted with ether. The combined ether layers were washed with brine, dried (Na_2SO_4) and evaporated to give IV (Table 2). The 2-diethylaminoethoxy analog IVj separated as the hydrochloride salt from the sodium chloride saturated aqueous layer after washing with ether.

TABLE 2. Yield of 5-Alkoxy-2-nitrobenzoic Acids (IV) from III.

Compd	Yield %	mp. °C	Recryst. Solvent	Analysis: Calcd. (Found)		
				C	H	N
IVa	99	132-135^a				
IVb	98	129-131	CH_2Cl_2-Hex	51.19 (51.08)	4.30 (4.36)	6.63 (6.71)
IVc	90	127-128	CH_2Cl_2-Hex	53.33 (53.19)	4.92 (4.92)	6.22 (6.30)
IVd	93	128-129	b	53.33 (53.14)	4.92 (4.83)	6.22 (6.11)
IVe	quant^c	88-91	b	55.23 (55.38)	5.48 (5.61)	5.86 (5.64)
IVf	quant^c	69-70	CH_2Cl_2-Hex	56.91 (57.18)	5.97 (6.12)	5.53 (5.60)
IVg	59^d	145-148	EtOAc	47.59 (47.59)	3.99 (3.95)	6.17 (6.13)
IVh	90^d	95-96	CH_2Cl_2-Hex	60.56 (60.59)	4.77 (4.88)	4.42 (4.39)
IVi	85^d	133-135	EtOAc-Hex	49.79 (49.88)	4.60 (4.68)	5.81 (5.90)
IVj	53^d	175-180^e	EtOH-Et_2O	48.98 (49.23)	6.01 (6.16)	8.79 (8.64)

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a. Lit.[1] mp. 135-136°. b. Analytical sample prepared by ptlc and evaporative distillation. c. The product was obtained as a semi-solid containing some high boiling impurities (NMR) and was used directly in the next step. d. Yield is for the two steps from 2. e. Hydrochloride salt.

General Procedure for 5-Alkoxyanthranilic Acid Hydrochlorides (V). - The crude IV were hydrogenated in ethanol over 10% PD/C at atmospheric pressure. After cessation of hydrogen uptake, the mixtures were filtered, acidified with dilute hydrochloric acid and evaporated to dryness (Table 3).

TABLE 3. Yield of 5-Alkoxyanthranilic Acid Hydrochlorides (V).

Compd	Yield %	mp. °C	Recryst. Solvent	Analysis: Calcd. (Found)		
				C	H	N
Va	99	148-150^a				
Vb	91	197-199	EtOH	49.66 (49.81)	5.56 (5.40)	6.45 (6.32)
Vc	94	168-171^b	EtOH-Et$_2$O	51.84 (52.56)	6.09 (6.22)	6.05 (6.33)
Vd	92	195-196	MeOH	51.84 (52.24)	6.09 (5.90)	6.05 (6.09)
Ve	85	146-148	EtOH-Et$_2$O	53.77 (53.51)	6.56 (6.48)	5.70 (5.62)
Vf	90	156-159	*i*-PrOH	55.49 (55.82)	6.98 (7.12)	5.39 (5.45)
Vg	90	208-217	MeOH-Et$_2$O	46.26 (46.00)	5.18 (5.07)	6.00 (5.97)
Vh	72	155-162^c	MeOH-Et$_2$O	59.35 (60.59)	5.60 (5.82)	4.33 (4.45)
Vi	98	193-196	MeOH-Et$_2$O	48.49 (48.45)	5.70 (5.63)	5.66 (5.71)
Vj	91	216-220^d	EtOH-Et$_2$O	48.01 (48.07)	6.82 (7.05)	8.61 (8.41)

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a. Free base, lit.[1] mp. 151-152°. b. MS: m/z 195 (M$^+$). c. MS: m/z 287 (M$^+$). d. Bis hydrochloride salt; Cl; 21.80 (21.76).

5-Methoxy-2-nitrobenzoic Acid (IVa). - In 1 L of methanol was dissolved 157.0 g (2.8 mol) of potassium hydroxide pellets (slightly exothermic, 25 → 45°). After a solution was obtained, 113.0 g (0.561 mol) of 5-chloro-2-nitrobenzoic acid was added and the mixture was boiled for 28 hrs and concentrated to a slurry. The residue was diluted with 1 L of water, carefully acidified with 200 mL of conc. hydrochloric acid and extracted with 3 x 500 mL of ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give 108.7 g of crude IVa, mp. 129-132°. Recrystallization from ethyl acetate-hexane gave 85.7 g (77%), mp. 132-134°, lit.[1] mp. 135-136°.

5-Methylthio-2-nitrobenzoic Acid (VI). - A solution of 60 g (1.5 mol) of sodium hydroxide in 600 mL of water and 200 mL of DMF was cooled in an ice-bath and 61 mL (1.10 mol) of methyl mercaptan were added followed by a solution of 201.6 g (1.00 mol) of I and 60 g (1.5 mol) of sodium hydroxide in 1.5 L of water. The mixture was stirred 48 hrs at room temperature and was carefully acidified with 500 mL of conc. hydrochloric acid to precipitate 204 g (96%) of VI, mp. 166-169°. Recrystallization from ethyl acetate gave mp. 174175°. Anal. Calcd for $C_8H_7NO_4S$: C, 45.06; H, 3.31; N, 6.57; S, 15.04. Found: C, 45.15; H, 3.46; N, 6.35; S, 15.15.

Methyl 2-Amino-5-methylthiobenzoate (VII). - A suspension of 204 g (0.96 mol) of VI, 130 mL (2.08 mol) of iodomethane, and 166 g (1.25 mol) of potassium carbonate in 650 mL of DMF was stirred at room termperature for 18 hrs. The resulting mixture was diluted with 3 L of water and extracted with 3 x 1.5 L of ether. The combined organic layers were washed with 1 L portions of water and brine, dried ($MgSO_4$) and evaporated to give 220 g of methyl 5-methylthio-2-nitrobenzoate as an oily solid. Crystallization from methanol gave a pure sample, mp. 53-54°.

Anal. Calcd for $C_9H_9NO_4S$: C, 47.57; H, 3.99; N, 6.16; S, 14.11. Found: C, 47.59; H, 3.91; N, 6.37; S, 13.90.

This material was dissolved in 1 L of acetic acid containing 112 g (2 g atom) of iron powder. The bath temperature was raised to 90° and, after 2 hrs, an additional 112 g of iron powder was added. After a further 30 min, the mixture was allowed to cool, then diluted with 1 L of benzene and filtered. The filtrate was acidified with methanolic hydrochloric acid and on standing 96.5 g (43%) of VII, mp. 190-192°, separated. The mother liquor afforded an additional 89.0 g (39%), mp. 188-190°, on concentration. Recrystallization from methanol gave the pure product, mp. 193-194°.

Anal. Calcd for $C_9H_{11}NO_2S{\cdot}HCl$: C, 46.25; H, 5.18; N, 5.99; Cl, 15.17; S, 13.72. Found: C, 46.39; H, 5.45; N, 6.00; Cl, 15.21; S, 13.68.

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