

## Synthesis of a series of dialkylsulphamylbenzoic acids

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### ABSTRACT

Sulphamylbenzoic acids contain both benzoic acid and sulphonamide moieties. Synthetically, sulphamylbenzoic acids are made by preparing first p-toluenesulphonyl chloride through sulphonation of toluene, followed by oxidation of the latter to yield the corresponding p-carboxybenzenesulphonyl chloride. In this research the same strategy was followed. The p-carboxybenzenesulphonyl chloride thus formed was reacted with the appropriate dialkyl amine. The by products formed were removed by treating the reaction medium with a weak alkaline substance, such as aqueous bicarbonate solution, then filtering off the precipitated by products. Acidification of the filtrates gave the desired sulphamylbenzoic acids as crystalline solid materials. The following acids were synthesized in this research: p-(diethylsulphamyl)benzoic acid (III), p-(di-n-propylsulphamyl)benzoic acid (IV) and p-(di-isobuthylsulphamyl)benzoic acid (V). This methodology can be used for the preparation and synthesis of any other kind of p-(dialkylsulphamyl)benzoic acid.

**Keywords:** Probenecid, p-carboxybenzenesulphonyl chloride, p-diethylsulphamylbenzoic acid, p-di-n-propylsulphamylbenzoic acid.

### INTRODUCTION

**Probenecid** is a uricosuric drug primarily used in treating gout or hyperuricemia, a disorder that is characterized by recurrent acute attacks of inflammation in one or more joints of the extremities.<sup>1</sup> Probenecid is a white, crystalline, water-insoluble powder, C<sub>13</sub>H<sub>19</sub>NO<sub>4</sub>S, which is used in the treatment of chronic gout or gouty arthritis. These conditions are caused by too much uric acid in the blood. The medicine works by removing the extra uric acid from the body. Probenecid inhibits the transport of most organic acids in the renal tubules of the kidneys and increases uric acid removal in the urine. It is used to prevent attacks related to gout, not treat them once they occur. It acts on the kidneys to help the body eliminate uric acid. Probenecid does not cure gout, but after a patient has been taking it for a few months it will help prevent gout attacks. This medicine will help prevent gout attacks only as long as a patient continues to take it. Probenecid is also used to prevent or treat other medical problems that may occur if too much uric acid is present in the body. Probenecid is sometimes used with certain kinds

of antibiotics to make them more effective in the treatment of infections by preventing the body from passing them in the urine.<sup>2,3</sup> Probenecid reduces the reabsorption of uric acid and decreases the renal excretion of some drugs. During World War II, probenecid was used to extend limited supplies of penicillin<sup>1</sup> and is still currently used to increase antibiotic concentrations in serious infections. It has also found use as a masking agent by athletes attempting to get away with using performance enhancing drugs.

### EXPERIMENTAL

#### Reagents

All reagents and chemicals were of analytical reagent grade and were purchased from Merck. They were used without further purification for the preparation and synthesis of the intermediates and products.

#### Apparatus

Melting points were determined in open capillaries on a Sibata, Japan melting point

apparatus and are uncorrected. All intermediates and products were routinely examined by proton NMR (Bruker, Germany, 80 MHz), IR (JASCO, 700 IR) and mass spectrometer (Finnigan MAT:Q70, USA).

### 1. Preparation of p-toluenesulphonyl chloride (I)

In a 250 mL three-necked round-bottomed flask equipped with a thermometer, a dropping funnel and a condenser, chlorosulphonic acid (48.8 mL, 740 mmol,  $d=1.77$ ) was poured and the flask was placed in a water bath. Pure dry toluene (53.7 mL, 500 mmol) was introduced to the flask from the dropping funnel dropwise over 3 hours and the mixture was stirred with a magnetic bar. After that time, more chlorosulphonic acid (48.8 mL, 740 mmol,  $d=1.77$ ) was added to the mixture from the dropping funnel dropwise over 2 hours while stirring at 35 °C. Finally, a black colour mixture insoluble in water was obtained. Water was added to the mixture and the oily layer separated. Decolourizing charcoal was added to the oily layer and heated then filtered. Toluene in the filtrate was removed by simple distillation. The residue was poured on crushed ice. The white crystalline p-toluenesulphonyl chloride was collected on a Buchner funnel and recrystallized from light petroleum (b.p. 40-60°C) (77 g, 404 mmol, 81%). Its m.p. was 68 °C (literature 69 °C).<sup>4,5</sup> Its IR (mull in nujol) had  $\nu$  ( $\text{cm}^{-1}$ ): 2922, 2852 (C-H, nujol), 1589, 1486, 1457 (C=C aromatic, m), 1371, 1172 ( $\text{SO}_2$ , s); its <sup>1</sup>HNMR ( $\text{CDCl}_3$ , 80 MHz) had  $\delta$ (ppm): 2.51 (s,  $\text{CH}_3$ ), 7.45 (d, 2H, ortho-H's to  $\text{CH}_3$ ) and 7.95 (d, 2H, ortho-H's to  $\text{SO}_2\text{Cl}$ ).

### 2. Preparation of p-carboxybenzenesulphonyl chloride (II):

Chromic oxide (142 g) was placed in a 500 mL three-necked round-bottomed flask equipped with a dropping funnel, a condenser and a mechanical stirrer. p-Toluenesulphonyl chloride (50 g, 262.5 mmol) was dissolved in glacial acetic acid (350 mL) and poured into the dropping funnel and added to the flask dropwise while the mixture was stirred continuously. At the end, 10 mL concentrated HCl was added dropwise to the mixture and kept it for 24 hours at room temperature. After that period of time, the mixture was diluted with distilled water and filtered. White crystals of p-carboxybenzenesulphonyl chloride (II) were

collected on a Buchner funnel and dried in a dessicator. Recrystallization from 50% aqueous ethanol gave a white crystalline material (39 g, 176.9 mmol, 67.4%). Its m.p. was 130-131°C (literature 131 °C).<sup>6</sup> Its IR (mull in nujol) had  $\nu$  ( $\text{cm}^{-1}$ ): 3500-2500 (O-H, broad, s), 3098, 3052 (C-H, aromatic ring, m), 2920, 2852 (C-H, nujol), 1694 (C=O, s), 1597, 1576, 1490 (C=C aromatic, m), 1456, 1400 ( $\text{CH}_2$ ,  $\text{CH}_3$ , nujol, m), 1374, 1170 ( $\text{SO}_2$ , s), 860, 819, 766 (C-H<sub>oop</sub>, aromatic ring); its <sup>1</sup>HNMR ( $\text{CDCl}_3$ , 80 MHz) had  $\delta$ (ppm): 7.45 -8.40 (AA'BB', 4 x H, aromatic ring), 10.3 (br, 1 x OH of acid).

### 3. Preparation of p-diethylsulphamylbenzoic acid (III)

To a 500 mL Erlenmyer flask which was placed in an ice-water bath, acetone (100 mL) and diethylamine (12.5 mL, 120 mmol) were added. When the temperature inside the solution reached 5-8°C, p-carboxybenzenesulphonyl chloride (II) (8.8 g, 40 mmol) was added into it in small portions, a white suspension was obtained which was stirred for 2 hours. After that the suspension was placed in a steam bath until its volume reached to one third of its original volume. Then it was added to 100 mL water (5°C) and acidified with dilute HCl. The desired product was precipitated along with some impurities. The precipitated mixture was first collected on a filter paper then added to 150 mL dilute aqueous sodium bicarbonate solution. The impure material was collected on a filter paper. To the filtrate, a few drops of concentrated HCl was added until pH=2-3 reached. White crystals of p-diethylsulphamylbenzoic acid (III) were collected on a Buchner funnel and recrystallized from 50% aqueous ethyl alcohol. Finally, the crystalline material was separated and dried in a dessicator (8.16 g, 31.75 mmol, 79.4%). Its m.p. was 190-192°C (literature 196 °C).<sup>7</sup> Its IR (mull in nujol) had  $\nu$  ( $\text{cm}^{-1}$ ): 3500-2600 (O-H, broad, s), 3092 (C-H, aromatic ring, m), 2922, 2854 (C-H, nujol), 1690 (C=O, s), 1599, 1570 (C=C aromatic, m), 1459, 1397 ( $\text{CH}_2$ ,  $\text{CH}_3$ , nujol, m), 1376 (C-O, s), 1345, 1162 ( $\text{SO}_2$ , s), 865, 787, 769 (C-H<sub>oop</sub>, aromatic ring); its <sup>1</sup>HNMR ( $\text{CDCl}_3$ , 80 MHz) had  $\delta$  (ppm): 1.2 (t, 2'  $\text{CH}_3$ ), 3.37 (q, 2'  $\text{CH}_2$ ), 7.92 - 8.37 (AA'BB', 4'H, aromatic ring), 10.1 (br, 1' OH of acid); its MS (EI) showed m/z: 258{[M+H]<sup>+</sup>, 1%}, 257 [M<sup>+</sup>, 1%], 243.4{[(M+H)-  $\text{CH}_3$ ]<sup>+</sup>, 3.37%}, 242.4 {[(M-  $\text{CH}_3$ )]<sup>+</sup>, 35.95%}, 186.2{[(M+H)-N( $\text{C}_2\text{H}_5$ )<sub>2</sub>]<sup>+</sup>, 6.7%}, 185.2 {[(M-N( $\text{C}_2\text{H}_5$ )<sub>2</sub>)]<sup>+</sup>, 43.25%}, 121.2 {

(M-SO<sub>2</sub>N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>)<sup>+</sup>, 100%}, 104.2 {[COC<sub>6</sub>H<sub>4</sub>]<sup>+</sup>, 13.7%}.

#### 4. Preparation of p-di-n-propylsulphamylbenzoic acid (Probenecid) (IV)

To a 500 mL Erlenmyer flask which was placed in an ice-water bath, di-n-propylamine (41.5 mL) and 10% aqueous sodium hydroxide solution (200 mL) were added. When the temperature inside the solution reached 10-15 °C, p-carboxybenzenesulphonyl chloride (II) (24 g, 110 mmol) was added into it in small portions, a white suspension was obtained which was stirred for 1 hour. Then it was added to 200 mL water (5°C) and acidified with dilute HCl. The desired product was precipitated along with some impurities. The precipitated mixture was first collected on a filter paper then added to 300 mL dilute aqueous sodium bicarbonate solution. The impure material was collected on a filter paper. To the filtrate, a few drops of concentrated HCl was added until pH=2-3 reached. White crystals of p-di-n-propylsulphamylbenzoic acid (IV) were collected on a Buchner funnel and recrystallized from 50% aqueous ethyl alcohol. Finally, the crystalline material was separated and dried in a dessicator (25.1 g, 87.92 mmol, 81%). Its m.p. was 195-196 °C (literature 194-196 °C).<sup>8</sup> Its IR (mull in nujol) had  $\nu$  (cm<sup>-1</sup>): 3500-2400 (O-H, broad, s), 3094 (C-H, aromatic ring, m), 2924, 2854 (C-H, nujol), 1690 (C=O, s), 1646, 1618, 1598, 1573 (C=C aromatic, m), 1457, 1397 (CH<sub>2</sub>, CH<sub>3</sub>, nujol, m), 1376 (C-O, s), 1345, 1159 (SO<sub>2</sub>, s), 865, 802, 777 (C-H<sub>oop</sub>, aromatic ring); its <sup>1</sup>HNMR (CDCl<sub>3</sub>, 80 MHz) had  $\delta$ (ppm): 0.85 (t, 2' CH<sub>3</sub>), 1.3-1.83 (sextet, 2' CH<sub>2</sub>), 3.1 (t, 2' CH<sub>2</sub>), 7.8 -8.3 (AA'BB', 4'H, aromatic ring), 10.0 (br, 1' OH of acid); its MS (EI) showed m/z: 256.5{[M- C<sub>2</sub>H<sub>5</sub>]<sup>+</sup>, 50.47%}, 185.3 [M-N(C<sub>3</sub>H<sub>7</sub>)<sub>2</sub>]<sup>+</sup>, 80%}, 121.2 {[ (M-SO<sub>2</sub>N(C<sub>3</sub>H<sub>7</sub>)<sub>2</sub>]<sup>+</sup>, 100%}.

#### 5. Preparation of p-diisobuthylsulphamylbenzoic acid (V)

To a 500 mL Erlenmyer flask which was placed in an ice-water bath, methanol (300 mL) and diisobuthylamine (50 mL, 300 mmol) were added. When the temperature inside the solution reached 8-15°C, p-carboxybenzenesulphonyl chloride (II) (22.1 g, 100 mmol) was added into it small portions,

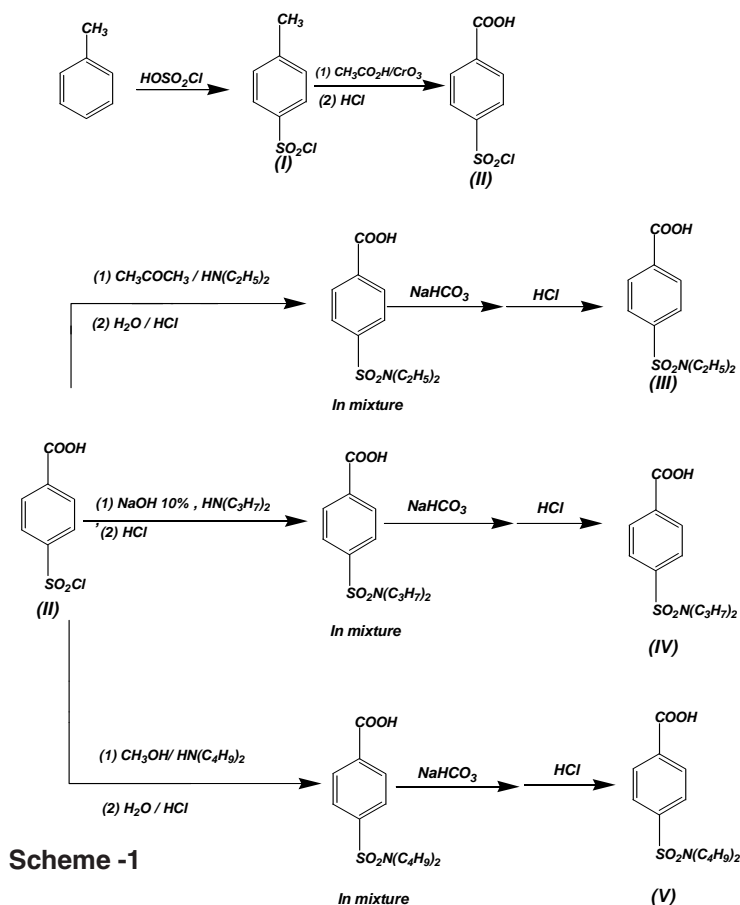
a white suspension was obtained which was stirred for 5-6 hours. After that, methanol was removed on a rotary evaporated. The residue was added to 200 mL of 5°C water, then acidified with dilute HCl. The desired product was precipitated along with some impurities. The precipitated mixture was first collected on a filter paper then added to 300 mL dilute aqueous sodium bicarbonate solution. The impure material was collected on a filter paper. To the filtrate, a few drops of concentrated HCl was added until pH=2-3 reached. White crystals of p-diisobuthylsulphamylbenzoic acid (V) were collected on a Buchner funnel and recrystallized from dilute ethyl alcohol. Finally, the crystalline material was separated and dried in a dessicator (16.9 g, 53.91 mmol, 54%). Its m.p. was 198-200 °C (literature 200-201.5°C).<sup>8</sup> Its IR (mull in nujol) had  $\nu$  (cm<sup>-1</sup>): 3400-2500 (O-H, broad, s), 3120 (C-H, aromatic ring, m), 2922, 2852 (C-H, nujol), 16901 (C=O, s), 1599, 1572 (C=C aromatic, m), 1459, 1397 (CH<sub>2</sub>, CH<sub>3</sub>, nujol, m), 1376 (C-O, s), 1343, 1160 (SO<sub>2</sub>, s), 865, 823, 783 (C-H<sub>oop</sub>, aromatic ring); its <sup>1</sup>HNMR (CDCl<sub>3</sub>, 80 MHz) had  $\delta$ ( ppm): 1.0(d, 4' CH<sub>3</sub>), 1.7-2.3 (m, 2' CH), 3.05 (d, 2' CH<sub>2</sub>), 7.94 -8.42 (AA'BB', 4'H, aromatic ring), 10.0 (br, 1' OH of acid); its MS (EI) showed m/z: 314.5{[M+H]<sup>+</sup>, 35.9%}, 270.4 [M- C(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>, 100%}, 185.2{[(M-N(C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>)<sup>+</sup>, 27%}, 121.2 {[ (M-SO<sub>2</sub>N(C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>)<sup>+</sup>, 28%}, 57.2 {[ (CH(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>)<sup>+</sup>, 42.69%}.

## DISCUSSION

Sulphamylbenzoic acids are the classical inhibitor of organic acids transport in the kidney and other organs. One member of these acids is called probenecid (IV). There are two primary clinical uses for probenecid: (i) as a uricosuric agent in the treatment of chronic gout, (ii) as an adjunct to enhance blood levels of antibiotics (such as penicillins and cephalosporins). Sulphamylbenzoic acids contain both benzoic acid and sulphonamide moieties. Clinical studies have shown that optimal activity is exhibited by the di(n-propyl) derivative; the smaller N-alkyl groups confer less activity. Synthetically, sulphamylbenzoic acids are generally made by preparing first p-toluenesulphonyl chloride through sulphonation of toluene, then oxidation of the latter to yield the corresponding p-carboxybenzenesulphonyl chloride. In this research the same strategy was followed. The p-

carboxybenzenesulphonyl chloride thus formed was reacted with the appropriate di-alkyl amine. The reactions were carried out in the presence of a solvent such as acetone or pyridine or in aqueous sodium hydroxide, and preferably with cooling. The by products formed were removed by treating the reaction medium with a weak alkaline substance, such as aqueous bicarbonate solution, then filtering off the precipitated by products. Acidification of the filtrates gave the desired sulphamyl benzoic acids as crystalline solid materials (Scheme 1).

The following acids were synthesized in this research: p-(diethylsulphamyl)benzoic acid (**III**), p-(di-n-propylsulphamyl)benzoic acid (**IV**) and p-(diisobutylsulphamyl)benzoic acid (**V**). This methodology can be used for the preparation and synthesis of any other kind of p-(dialkylsulphamyl)benzoic acid. The yields were quite high and acceptable. The chemical structures of the intermediates and the final products were examined and confirmed by their IR, HNMR and MS spectra.



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