SYNTHESIS OF *p*-(Di-*n*-PROPYLSULPHAMYL) BENZOIC ACID

S. K. Shukla and Govind Rai Chaudhry

Defence Science Laboratory, Delhi

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A process for the synthesis of *p*-carboxybenzene-sulphonylchloride by oxidation of toluene-*p*-sulphonylchloride as well as toluene-*p*-sulphonic acid has been developed. *p*-carboxybenzene sulphonylchloride on condensation with di-*n*-propylamine yield *p*-(di-*n*-propylsulphamyl)-benzoic acid, an uricusuric agent employed in chronic gouty arthritis and used as an antiuric adjuvant for penicillin known in trade as "Benemid, Probenecid".

p-(di-*n*-propylsulphamyl) benzoicacid, commonly known as Benemid (probenecid[1,2,3]), blocks the excretion by the renal tubules of certain organic compounds, *viz.* penicillin, *p*-amino-salicylic acid, thereby maintaining a high concentration of these drugs in the blood stream. It is reported to depress the tubular reabsorption of uric acid from the glomerular filtrate and is highly effective uricusuric agent in the treatment of tophaceous gout[4].

A review of the literature revealed that the synthesis of *p*-(di-*n*-propylsulphamyl) benzoic acid has drawn attention of several workers[5-12]. In this communication, however, its synthesis has been reported by a different route starting from *p*-toluene-sulphoyl chloride and *p*-toluene-sulphonic acid. *p*-toluene-sulphonyl chloride[5,6,7] is oxidised both with alkaline and acidic potassium permanganate yielding monosodium salt of *p*-sulphobenzoic acid which on treatment with anhydrous chlorosulphonic acid yielded *p*-carboxybenzene sulphonyl chloride. Alternatively, *p*-toluene-sulphonyl chloride[8] was oxidised with chromium trioxide yielding *p*-carboxybenzene sulphonylchloride. It can also be prepared by the oxidation of *p*-toluene-sulphonic acid[9], potassium permanganate, yielding the potassium salt of *p*-sulphobenzoic acid. This on treatment with anhydrous chlorosulphonic acid gave *p*-carboxybenzene sulphonylchloride. This sulphonylchloride synthesised by any of the aforesaid methods, on condensation with di-*n*-propylamine[10] gave the same *p*-(di-*n*-propylsulphamyl)-benzoic acid confirmed by melting point, mixed melting point, infra-red, and ultraviolet spectra.

EXPERIMENTAL PROCEDURE

p-carboxybenzene sulphonylchloride

(A). *p*-toluene-sulphonyl chloride (51 gm) hydrolysed with slight excess of sodium hydroxide solution was neutralised with dilute sulphuric acid; potassium permanganate (88 gm) was added, the mixture diluted with distilled water (1500 ml) and refluxed for three hours. Manganese dioxide was removed by filtration, the filtrate was concentrated (450 ml), acidified with sulphuric acid, and cooled. Monosodium salt of *p*-sulphobenzoic acid was filtered, washed, and recrystallised from hot water, (Yield 22 gm; 37%).

Chlorosulphonic acid (25 ml) was added to the above monosodium salt (17·5 gm) and the mixture heated at 100°C for one hour and then poured over crushed ice. *p*-carboxybenzene sulphonylchloride which precipitated was filtered, washed, dried, and recrystallised from acetone in colourless needles, m.p. 235°C. (Yield 5 gm; 27%).

(B). *p*-toluene-sulphonylchloride (50 gm) dissolved in glacial acetic acid (300 ml) was added dropwise (3 hours) to powdered chromium trioxide (145 gm) in a conical flask with constant stirring keeping the temperature below 0°C.

Concentrated sulphuric acid (10 ml) was then added dropwise at 10-15°C, and the reaction mixture after keeping overnight was poured over crushed ice. Precipitated *p*-carboxybenzene sulphonylchloride was filtered, washed with water, extracted with ethylacetate, and the ethylacetate extract was washed with water, dried over anhydrous sodium sulphate and freed of the solvent when shining colourless crystals were obtained. The pure acid chloride was crystallised twice from acetone in colourless needles, m.p. 235°C. (Yield 30 gm; 51%).

p-carboxybenzene sulphonylchloride

A mixture of *p*-toluene sulphonic acid (103·5 gm), potassium hydroxide (40·5 gm) in water (900 ml) was placed in a three necked flask provided with a dropping funnel, a thermometer jacket and a mechanical stirrer. Potassium permanganate (189 gm) dissolved in hot water (750 ml) was added slowly during four hours, keeping the temperature of the reaction mixture at 80°C. After completion of the reaction excess of potassium permanganate was destroyed by treating with ethyl alcohol and manganese oxide was removed by filtration; the filtrate was acidified with hydrochloric acid and the solvent evaporated to dryness. Potassium salt of *p*-sulphobenzoic acid was crystallised from hot water, (Yield 70 gm; 48%).

Potassium salt of *p*-sulphobenzoic acid (24 gm) was slowly added to chlorosulphonic acid (80 ml) with constant stirring, keeping the temperature of the reaction mixture below 30°C. The mixture after keeping overnight was poured over crushed ice and the liberated *p*-carboxybenzene sulphonyl chloride was filtered, washed, dried, and crystallised from acetone in colourless needles, m.p. 235°C. (Yield 4 gm; 18%).

p-(di-n-propylsulphamyl)-benzoic acid

p-carboxybenzene sulphonyl chloride (22 gm) was added gradually to cooled and stirred di-*n*-propyl amine (30 gm). Acetone (300 ml) was then added gradually to the reaction mixture accompanied by stirring. The contents were concentrated to 100 ml, cooled and poured over crushed ice and then acidified with dilute hydrochloric acid. *p*-(di-*n*-propylsulphamyl)—benzoic acid separated out as white crystalline mass, which was filtered. The crystals were dissolved in dilute sodium bicarbonate solution and the alkaline solution filtered; the filtrate on acidification with dilute hydrochloric acid gave *p*-(di-*n*-propylsulphamyl)—benzoic acid. On crystallisation twice from 90% methanol the acid was obtained in white shining needles, m.p. 198-200°C (Yield 12 gm; 52%).

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REFERENCES

1. BOGER, MARTIN, GALLAGHER & PITTS, *J. Philadelphia Gen. Hosp.*, 1 (1951), 51.
2. BOGER & PITTS, *Science*, **112** (1950), 149.
3. ISRAEL, MIKE & BOGER, *Amer. Rev. Tuberc.*, **64** (1951), 453.
4. STILLMAN, *The Practitioner*, **179** (1957), 719.
5. SMILES, S. & HARISON, D.C., *J. Chem. Soc.*, **121** (1922), 2023.
6. ANNALEN, **178** (1875), 279.
7. BER., 10 (1877), 1715.
8. YOSHIO TASHIKA, YOSHIHIRO NITTA & JITSUHOYOMODA., *J. Pharm. Soc. Japan*, **74** (1954), 1193,
9. EVERARD, B.A. & MILLS, J.A., *J. Chem. Soc.* (1950), 3386,
10. SHARP, DOHME, INC. BRT. 674, 298, June 18, 1952,
11. GAY, BOLL. CHIM. FARM, **92** (1953), 339,
12. MILLER, U.S. PATENT, 2,608,507,