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Synthesis and Application of Some Sulfonamides as Bacteriostatic Antibiotics

ARDESHIR KHAZAEI*, SAYID FATEMEH SADEGHIAN, SHOHREH HESAMI and ABBAS AMINI MANESH
Department of Chemistry
Faculty of Sciences, University of Bu-Ali Sina, Hamadan
P.O. Box 65178-4111, Hamadan, Iran

The new sulfonamides; N(1-amino phenyl)-4-amino benzene sulfonamide, N(1-amino-4-nitro phenyl)-4-aminobenzenesulfonamide (**3**) were synthesised and bacteriostatic effects were studied by two methods: disc diffusion and serial dilution on three bacteria (*E. coli, B. cereus* and *S. aureus*). Addition of electronegative groups such as nitro showed that bacteriostatic effects were increased.

Key words: Synthesis, sulfonamides, bacteriostatic, antibiotics.

INTRODUCTION

Since many years ago, man has tried to overcome infectious diseases. Antibiotic drugs have been the most important source of chemotherapeutic treatment. Sulfonamide drugs have been the first compounds which were used for prevention and treatment of bacterial infections.

Meanwhile, more than thirty kinds of sulfonamides have been applied for treatment of various diseases[1–3].

Sulfonamides are bacteriostatic agents that inhibit the formation of folic acid in susceptible bacteria by acting as competitive inhibitors of PABA. Sulfonamides indirectly prevent the synthesis of DNA in bacteria, thus preventing their growth. Although some other compounds were synthesised for treatment of infection diseases, yet they have some side effects such as causing allergic reactions and toxicity.[4–8]

RESULTS AND DISCUSSION

According to the above point, we have synthesised three new sulfonamides: N(1-aminophenyl)-4-aminobenzenesulfonamide (**1**), N(1-amino-4-nitrophenyl)-4-aminobenzene sulfonamide (**2**) and N-(l-amino-2,4-dinitrophenyl)-4-aminobenzenesulfonamide (**3**) (Fig. 1). The antibacterial properties of these compounds have been studied on three bacteria: one gram-negative (*E. coli*) and two gram-positive (*B. cereus* and *S. aureus*).

Scheme 1

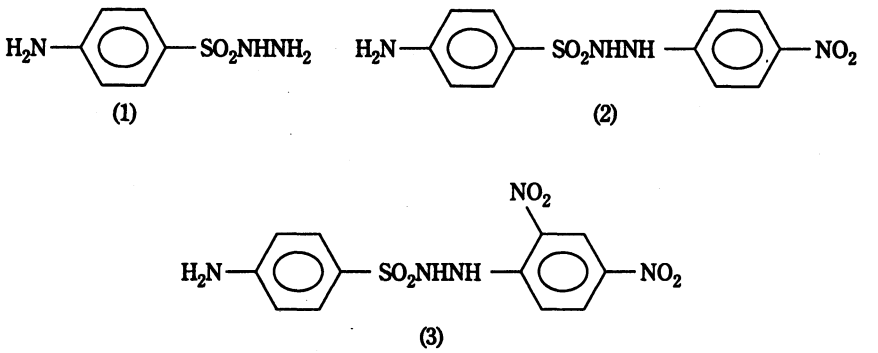

Fig. 1

Table-1 shows the results of effect of the three new sulfonamides on bacteria:

TABLE-1
RESULTS OF THE EFFECT OF SULPHONAMIDES ON THREE BACTERIA BY DISC DIFFUSION METHOD

Sulphonamides	Gram-negative	Gram-positive	
	E. coli.	*S. aureus*	*B. cereus*
N(1-aminophenyl) 4-aminobenzene sulfonamide **(1)**	–	+	–
N(1-amino-4-nitrophenyl) 4-aminobenzene sulfonamide **(2)**	–	+	+
N(1-amino-2,4-dinitrophenyl) 4-aminobenzene sulfonamide **(3)**	+	+	+

Table-2 shows the minimal inhibition concentration (MIC) of two compounds on three bacteria.

TABLE-2
MIC VALUES OF TWO COMPOUNDS (**2, 3**) ON THREE BACTERIA

Sulfonamides	*E. coli*	*S. aureus*	*B. cereus.*
N(1-amino-4-nitrophenyl) 4-aminobenzene sulfonamide **(2)**	—	500 μg/mL	31.25 μg/mL
N(1-amino-2,4-dinitrophenyl) 4-aminobenzene sulfonamide **(3)**	15.625 μg/mL	250 μg/mL	62.50 μg/mL

The results reveal that addition of electronegative groups in the structure of compounds increases antibacterial effects.

EXPERIMENTAL

General: IR and NMR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and a 90 MHz Jeol FT-NMR spectrometer, respectively. NMR chemical shifts were measured relative to TMS (int, 1H).

Preparation of N(1-amino phenyl)4-acetamido benzene sulfonamide: In a 250 mL round-bottomed flask 4.0 g (0.0171 mol) *p*-acetamidobenzene sulfonyl chloride and 70 mL petroleum ether were placed. The flask was heated in bath-water to 50°C and added dropwise with stirring, 1.68 mL (0.0171 mol) of phenyl hydrazine. The mixture was refluxed for 3 h. Then the flask was cooled and the solid product was collected on a Buchner funnel, washed with water and n-hexane. The yield of pure N(1-amino phenyl)4-acetamidobenzene sulfonamide, m.p. 110–120°C, was 4.42 g (84.7%). IR spectrum (KBr pellets): 3334, 3200, 1673, 1588, 1520, 1316, 1165 cm^{-1}. ^{1}H-NMR spectrum (CD_3COCD_3, TMS): δ 2.12 (s, 3H), 6.9 (m, 6H), 7.8 (s, 4H), 8.30 (s, 1H), 9.54 (s, 1H). Anal.: Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.06, H, 4.95, N, 13.76, S, 10.50%. Found: C, 55.01, H, 4.92, N, 13.71, S, 10.10%.

Preparation of N(1-amino phenyl)-4-amino benzene sulfonamide: In a 500 mL round-bottomed flask 1.5 g (4.91×10^{-3} mol) N(1-amino phenyl) 4-acetamido benzene sulfonamide and 10 mL of concentrated hydrochloric acid and 30 mL of water were placed. The mixture was boiled gently under reflux for 30–45 min. The solution, when cooled to room temperature, should deposit no solid amide; if a solid was separated, it was heated for a further short period. 2 g of decolorising carbon was added to the cooled solution and the mixture was heated to boiling and filtered with suction through a hardened filter paper. The filtrate (a solution of sulfonamide hydrochloride) was placed in a 1-litre beaker and cautiously added 12 g of solid sodium hydrogen carbonate in portions with stirring. After the evolution of gas had subsided, the suspension was tested with litmus paper and if it was still acid, more sodium hydrogen carbonate was added until neutral. The mixture was cooled in ice, filtered off the product with suction and dried. The yield of pure N (1-amino phenyl) 4-aminobenzene sulfonamide, m.p. 129–132°C, was 0.95 g (73.5%). IR spectrum (KBr pellets): 3440, 3200, 3100, 1620, 1590, 1280, 1129 cm^{-1}. ^{1}H-NMR Spectrum (CD_3COCD_3, TMS): δ 5.4 (s, 1 H), 5.8 (s, 1H), 6.2 (s, 1H), 6.5 (q, 4H), 7.1 (m, 5H). Anal.: calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.73, H, 4.98, N, 15.96, S, 12.18%. Found: C, 54.66, H, 4.94, N, 15.91, S, 12.14%. This compound was tested on one gram negative bacteria (*E. coli*) and two gram-positive bacteria (*B. cereus* and *S. aureus*) by disc diffusion method. The results revealed that this compound was not effective on *E. coli* and *B. cereus* but effective on *S. aureus* and inhibited its growth. The zone of inhibition on *S. aureus* was 16 mm.

Preparation of N(1-amino-4-nitro phenyl) 4-acetamido benzene sulfonamide: 2.0 g (8.56×10^{-3} mol) *p*-acetamido sulfonyl chloride and 1.31 g (8.56×10^{-3} mol) 4-nitrophenyl hydrazine were placed in a 250 mL beaker. The beaker was heated on an oil bath (120–130°C) for 20 min and the mixture was stirred with a glass rod. Then the reaction mixture was cooled and 50 mL water was added. The product was collected on a Buchner funnel and washed with a

little warm water. The product was recrystallised from ethanol. The yield of pure N(1-amino-4-nitro phenyl)4-acetamido benzene sulfonamide, was 2.29 g (76.6%). IR spectrum (KBr pellets): 3559, 3300, 3200, 1680, 1590, 1534, 1500, 1332, 1157 cm^{-1}. ^{1}H-NMR spectrum (CD_3COCD_3, TMS): δ 2.1 (s, 3H), 6.9–8.06 (m, 8H), 8.87 (s, 1H), 9.82 (s, 1H), 10.39 (s, 1H). Anal.: Calcd. for $C_{14}H_{14}N_4O_5S$: C, 47.99, H, 4.03, N, 15.99, S, 9.15%. Found: C, 47.87, H, 3.98, N, 15.87, S, 9.10%.

Preparation of N(1-amino-4-nitrophenyl) 4-amino benzene sulfonamide: N(1-amino-4-nitrophenyl)4-acetamidobenzene sulfonamide was hydrolysed by similar method described previously and the product, N(1-amino-4-nitrophenyl)-4-aminobenzenesulfonamide, m.p. 196–198°C, had the characterization: IR spectrum (KBr pellets): 3456, 3300, 3294, 1637, 1595, 1500, 1319, 1150 cm^{-1}. ^{1}H-NMR spectrum (CD_3COCD_3, TMS): 6.5–7.4 (q, 4H), 6.9–8.04 (q, 4H), 4.15 (s, 1H), 8.82 (s, 1H), 9.44 (s, 1H). Anal.: Calcd. for $C_{12}H_{12}N_4O_4S$: C, 46.74, H, 3.92, N, 18.18 S, 10.40%. Found: C, 46.68, H, 3.88, N, 18.15, S, 10.5%. This compound was tested on *E. coli*, *S. aureus* and *B. cereus* bacteria by using Mular Hinton Broth media and serial dilution method. The results showed that this sulfonamide was not effective on *E. coli* but effective on *S. aureus* and *B. cereus*. Also, the compound, N(1-amino-2,4-dinitrophenyl) 4-amino benzene sulfonamide, was synthesised by a similar method and showed these data: m.p. 230–232°C, IR spectrum (KBr pellets): 3472, 3320, 1616, 1592, 1515, 1328, 1152 cm^{-1}. ^{1}H-NMR spectrum (CD_3COCD_3, TMS): δ 3.9 (s, 1H), 6.9–7.4 (q, 4H), 7.9–8.7 (m, 3H), 9.29 (s, 1H), 9.72 (s, 1H). Anal.: Calcd. for $C_{12}H_{11}N_5O_6S$: C, 40.79, H, 3.14, N, 19.8, S, 9.07%. Found: C, 40.71, H, 3.11, N, 19.80, S, 9.10%. This compound was tested on *E. coli*, *B. cereus* and *S. aureus* under similar conditions as previously described. The results show that this sulfonamide is effective on three bacteria.

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