Journal of the Pharmaceutical Society of Korea
13, 62~66 (1969)

N^4-Furoylsulfonamide 類의 合成 및 抗菌作用에 關한 硏究

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Hyun Kee Koh: Studies on the Synthesis and Antibacterial Action of N^4-Furoylsulfonamides

(Received July 1, 1969)

Ten new N^4-furoylsulfonamides were synthesized such as N^4-furoyl-N^1-(4, 6-dimethyl-2-pyrimidinyl) sulfanilamide(Ⅰ), N^4-furoylsulfanilamide(Ⅱ), N^4-furoyl-N^1-(2, 6-dimethoxy-4-pyrimidinyl) sulfanilamide(Ⅲ), N^4-furoyl-N^1-(4-methyl-2-pyrimidinyl) sulfanilamide(Ⅳ), N^4-furoyl-N^1-(6-methoxy-3-pyridazinyl) sulfanilamide(Ⅴ), N^4-furoyl-N^1-2-pyrimidinylsulfanilamide(Ⅵ), N^4-furoyl-N^1-(3, 4- dimethyl-5-isoxazolyl) sulfanliamide(Ⅶ), N^4-furoyl-N^1-2-thiazoilylsulfanilamide(Ⅷ), N^4-furoyl-N^1-(5-methoxy-2-pyrmidinyl) sulfanilamide(Ⅸ) and N^4-furoyl-N^1-(2, 6-dimethyl-4-pyrimidinyl) sulfanilamide(X).

They were obtained by the action of N^1-(4, 6-dimethyl-2-pyrimidinyl) sulfanilamide, N^1-(2, 6-dimethoxy-4-pyrimidinyl) sulfanilamide, N^1-(4-methyl-2-pyrimidinyl) sulfanilamide, N^1-(6-methoxy-3-pyridazinyl) sulfanilamide, N-2-pyrimidinyl sulfanilamide, N^1-(3, 4-dimethyl-5-isoxazolyl) sulfanilamide, N^1-2-(thiazolylsulfanilamide, N^1-(5-methoxy-2-pyrimidinyl)sulfanilamide and N^1-(2, 6-dimethyl-4-pyrimidinyl) sulfanilamide with furoyl chloride in 4% NaOH solution. Of the above ten compounds, N^4-furoylsulf-athiazole exhibited a good antibacterial action against *Staphylococcus aureus* and *Escherichia coli*.

化學療法劑인 sulfonamide 類는 1908年 Gelmo[1]가 sulfamine을 合成한데 이어 F. Mietzsch, J. Klarrer, Domagk 및 J. Tréfouel[2] 等에 依하여 硏究된 以來 多數의 sulfonamide 類[3]가 合成되었다. 現在 醫藥品으로 使用되는 sulfonamide 類에는 N^1-置換 sulfonamide 類가 大部分이나 N^4-置換 sulfonamide 類도 若干 알려져 있다. 그中 sulfathiazole의 N^4 位置에 phthalyl 基나 succinyl 基等의 acyl 基를 導入한 N^4 置換 sulfathiazole 即 phthalylsulfathiazole[4] 및 succinylsulfathiazole[5]에는 다른 sulfamine 劑에 共通的인 acetyl 化合物의 溶解度低調에 依한 腎障

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害 및 結石과 같은 副作用이 거의 없으므로 sulfathiazole 自體보다 더 優秀한 sulfonamide 劑로 使用되고 있다[6,7]. 著者는 이點에 留意하여 10種의 sulfonamide 類 即 sulfamethazine, sulfanilamide, sulfadimethoxine, sulfamerazine, sulfamethoxypyridazine, sulfadiazine, sulfisoxazole, sulfathiazole, sulfamonomethoxine 및 sulfisomidine 에 4% NaOH 存在下 酸鹽化物인 furoyl chloride 를 作用시켜 10種의 新化合物 N^4-furoyl-N^1-(4,6-dimethyl-2-pyrimidinyl) sulfanilamide(Ⅰ), N^4-furoylsulfanilamide(Ⅱ)[1] N^4-furoyl-N^1-(2,6-dimethoxy-4-pyrimidinyl) sulfanilamide(Ⅲ), N^4-furoyl-N^1-(4-methyl-2-pyrimidinyl) sulfanilamide(Ⅳ), N^4-furoyl-N^1-(6-methoxy-3-pyridazinyl) sulfanilamide(Ⅴ), N^4-furoyl-N^1-2-pyrimidinylsulfanilamide(Ⅵ), N^4-furoyl-N^1-(3,4-dimethyl-5-isoxazolyl) sulfanilamide(Ⅶ), N^4-furoyl-N^1-2-thiazolylsulfanilamide(Ⅷ), N^4-furoyl-N^1-(5-methoxy-2-pyrimidinyl) sulfanilamide(Ⅸ) 및 N^4-furoyl-N^1-(2,6-dimethyl-4-pyrimidinyl) sulfanilamide(Ⅹ)을 合成하고 그 抗菌作用을 檢討한 結果, Table Ⅱ와 같이 furoylsulfathiazole(Ⅷ)은 *Staphyloccus aureus* 및 *Escherichia coli* 에 對하여 良好한 抗菌力을 나타냄을 알다.

實 驗

N^4-Furoylsulfonamide 類의 合成

Sulfonamide 類 0.005mole 을 4% NaOH 10ml 에 녹히고 室温(約 20°C)에서 저으면서 furoyl chloride 0.005 mole 을 조금씩 滴下한 다음 繼續해서 30分間 攪拌하여 反應을 完結시킨다. 다음에 生成內容物을 묽은 HCl 으로 中和하여 結晶으로 析出시킨것을 吸引濾過하고 少量의 물 및 에텔로 씻은 다음 아세톤으로 再結晶한다. 그 結果는 Table Ⅰ과 같다.

抗 菌 試 驗[8]

菌株別로 每 sulfa 劑마다 0.99 ml 씩의 peptone free broth 를 加한 試驗管 4個와 positive control 로 sulfa 劑가 들어가 있지않은 試驗管 1個를 合하여 每菌株當 81個의 試驗管을 준비하였으며 別途로 peptone free broth 만이 들어있는 試驗管 1個를 negative control 로 준비하고 各 sulfa 劑 25 mg 을 정밀하게 秤量하여 dimethylformamide 로 25mg/100ml, 10mg/100ml. 2.5mg/100ml, 0.1mg/100ml 가 되도록 희석하여 capillary pipette 로 各各 1滴씩 peptone free broth 가 든 tube 에 첨가하고 이培地에 두菌株를 各各 加하여 實驗하였다. 이때 使用한 菌株는 peptone free broth 5ml. 에 1夜 培養한 各種의 菌液 1滴을 다시 Pasteur pipette 로 새로운 peptone free broth 5ml 에 加하여 희석된 菌液 1滴씩을 使用하였다. 이와같이 sulfa 劑의 添加와 植菌이 끝나면 孵卵器에 넣어 1주야(18~24時間) 培養하여 positive control 에서 菌의 成長을 肉眼으로 判讀하였다. 그 結果는 Table Ⅱ와 같다.

但 一連의 豫備實驗을 通하여 大腸菌과 葡萄狀球菌에 對하여 dimehytlformamide 가 阻止 또는 生長的으로 影響을 미치지 않은것을 確認하였다.

Table. I N^4-Furoylsulfonamides

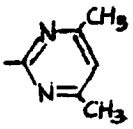
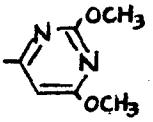
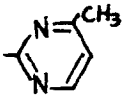
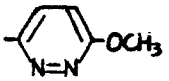
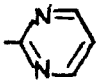
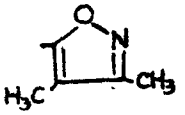
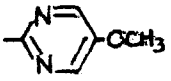
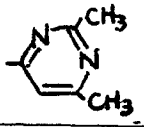
Compd No.	R	mp(°C)	Appearance	yield (%)	Formula	Analysis (% of N) Calcd.	Found.
I		246—248	white powder	95	$C_{17}H_{18}O_4N_6S$	15.04	15.24
II	H	269—270	white powder	62	$C_{11}H_{10}O_4N_2S$	10.52	10.69
III		222—223	white powder	85	$C_{17}H_{18}O_6N_4S$	13.85	14.04
IV		252—253	white powder	59	$C_{16}H_{14}O_4N_4S$	15.63	15.85
V		227—229	light yeow powder	74	$C_{16}H_{14}O_6N_4S$	14.97	15.21
VI		259—261	yellow powder	88	$C_{15}H_{12}O_4N_4S$	16.27	16.51
VII		228—229	pale yellow powder	60	$C_{16}H_{15}O_5N_3S$	11.63	11.65
VIII		229—230	orange yellow powder	36	$C_{14}H_{11}O_4N_3S_2$	12.03	12.28
IX		240—241	yellow powder	87	$C_{16}H_{14}O_5N_4S$	14.97	15.22
X		223—225	white powder	26	$C_{17}H_{16}O_4N_4S$	15.04	15.30

Table. Ⅱ Minimal inhibitory concentration of sulfonamides and their furoyl derivatives(mg/100m*l*)

Compounds	Strains[a]	
	Staph. aureus	*Esch. coli*
Sulfamethazine	10	10
Furoylsulfamethazine (Ⅰ)	—[b]	—
Sulfanilamide	10	25
Furoyslulfanilamide (Ⅱ)	—	—
Sulfadimethoxine	0.1	10
Furoylsulfadimethoxine (Ⅲ)	25	—
Sulfamerazine	2.5	25
Furoylsulfamerazine (Ⅳ)	—	—
Sulfamethoxypyridazine	2.5	2.5
Furoylsulfamethoxypyridazine)Ⅴ)	—	—
Sulfadiazine	10	10
Furoylsulfadiazine (Ⅵ)	—	—
Sulfisoxazole	2.5	2.5
Furoylsulfisoxazole (Ⅶ)	—	—
Sulfathiazole	25	10
Furoylsulfathiazole (Ⅷ)	25	25
Sulfamonomethoxine	0.1	10
Furoylsulfamonomethoxine (Ⅸ)	—	—
Sulfisomidine	10	10
Furoylsulfisomidine (Ⅹ)	—	—

a) obtained from Medical Centre, Ministry of Public Health and Social Affairs.

b) no inhibition at concentration in mg/100m*l*.

考察 및 結果

1) 10種의 新化合物 N^4-furoyl-N^1-(4, 6-dimethyl-2-pyrimidinyl) sulfanilamide(Ⅰ), N^4-furoyl-sulfanilamide (Ⅱ), N^4-furoyl-N^1-(2, 6-dimethoxy-4-pyrimidinyl) sulfanilamide(Ⅲ), N^4-furoyl-N^1-(4-methyl-2-pyrimidinyl) sulfanilamide(Ⅳ), N^4-furoyl-N^1-(6-methoxy-3-pyridazinyl) sulfanilamide (Ⅴ), N^4-furoyl-N^1-2-pyrimidinylsulfanilamide(Ⅵ), N^4-furoyl-N^1-(3, 4-dimethyl-5-isoxazolyl) sulfanilamide(Ⅶ), N^4-furoyl-N^1-2-thiazolylsulfanilamide(Ⅷ), N^4-furoyl-N^1-(5-methoxy-2-pyrimidinyl) sulfanilamide(Ⅸ) 및 N^4-furoyl-N^1-(2, 6-dimethyl-4-pyrimidinyl) sulfanilamide (Ⅹ)을 合成하였다.

2) 著者의 合成物質中 N^4-furoylsulfathiazole (Ⅷ)은 sulfathiazole과 比較할 때 *Staphylococcus aureus*에 對하여 同等한 抗菌力을 나타냈으며 *Escherichia coli*에 對하여는 若干 弱한 抗菌力을 나타 내었다.

이 研究를 實施함에 있어 始終 指導하여주신 蔡東圭敎授에게 感謝를 드리며 抗菌試驗에 協助하여 주신 中央醫療院 細菌科長 朴承咸氏와 元素分析을 擔當하여주신 成大 林中基敎授

에게 謝意를 表한다.

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