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Note

Synthesis and antimicrobial activity of some penicillin and cephalosporin derivatives

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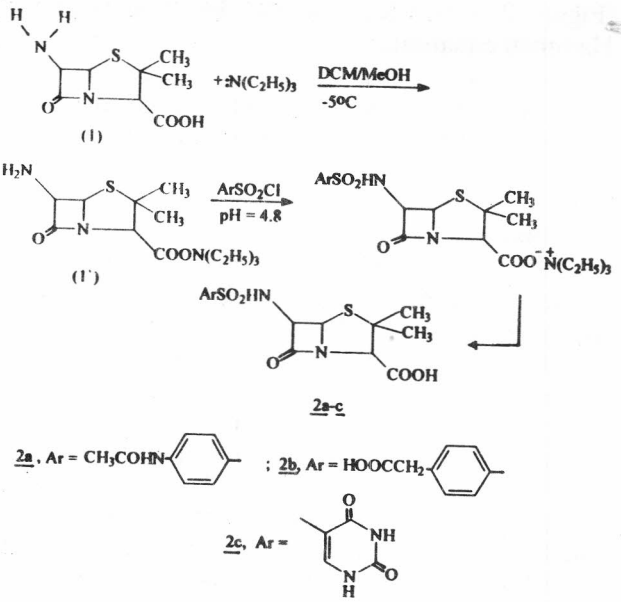
6-Aminopenicillanic acid and 7-aminodeacetoxycephalosporanic acid react with 4-acetylaminobenzene sulphonyl chloride, phenylacetic acid-4-sulphonyl chloride and uracil-5-sulphonyl chloride to give new penicillin and cephalosporin derivatives bearing sulphonamide groups. The resulting antibiotics have been tested for their antimicrobial activities.

Sulphonamides were found to be active against several types of bacteria[1]. Being less toxic, sulphonamides were for many years, the chief medical weapons against many bacterial diseases. But now-a-days, they have been superceded, in part, by the much toxic and more broadly effective clinical antibiotics. Penicillins and cephalosporins represent two important classes of antibiotics each having a β-lactam ring fused to thiazolidine ring and thiazine ring respectively.

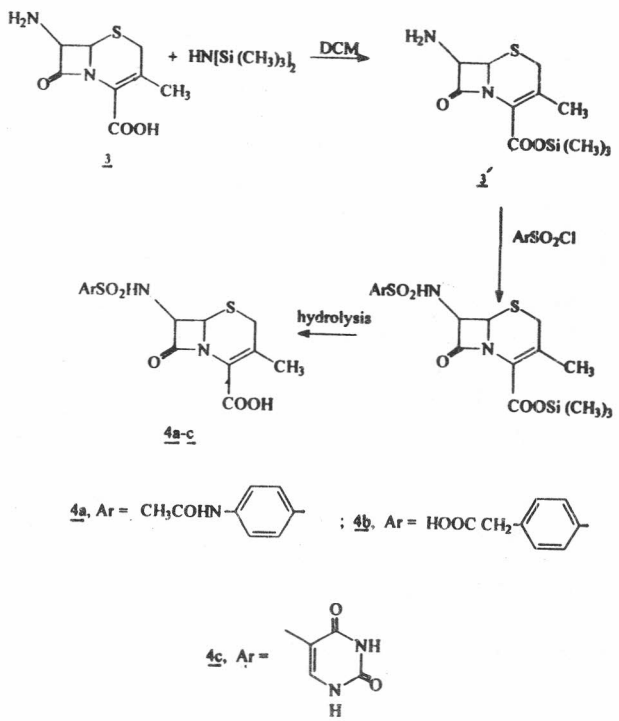
In this note, we report the synthesis of some penicillin and cephalosporin derivatives bearing a sulphonamide group with a view to preparing new antibiotics of the lowest possible toxicity. The antimicrobial actvities of the resulting antibiotics and comparison of their activities with the known antibiotics ampicillin and cephalexin are also discussed.

The starting materials used for this study are 6-aminopenicillanic acid (6-APA; **1**)[2] and 7-aminodeacetoxycephalosporanic acid (7-ADCA; **3**)[3]. Thus, 6-APA (**1**) reacts with 4-acetylaminobenzenesulphonyl chloride, phenylacetic-4-sulphonyl chloride and uracil-5-sulphonyl chloride to give the corresponding 6-sulphonamidopenicillanic acids (**2a-c**). Similarly, 7-ADCA (**3**) on reaction with the above mentioned sulphonyl chlorides leads to the formation of the corresponding 7-sulphonamidocephalosporanic acids (**4a-c**). The sequence of reactions involved in these syntheses are represented in Schemes I and II.

The structures of these penicillin and cephalosporin derivatives (**2a-c** and **4a-c**) were confirmed



Scheme I



Scheme II

Table I—Physical data of compounds **2a-c** and **4a-c**

Compd	Yield (%)	m.p. °C	Mol. formula (mol. wt)	Found % (Calcd)			
				C	H	N	S
2a	34.9	180-83 (d)	$C_{16}H_{19}N_3O_6S_2$ (413)	46.30 (46.49	4.50 4.50	10.20 10.16	15.25 15.50)
2b	34.4	183	$C_{16}H_{18}N_2O_7S_2$ (414)	46.39 (46.38	4.35 4.30	6.70 6.76	15.45 15.45)
2c	41	212-15	$C_{12}H_{24}N_4O_7S_2$ (390)	36.90 (36.92	3.50 3.59	14.20 14.36	16.35 16.11)
4a	37.9	173-75	$C_{16}H_{17}N_3O_6S_2$ (411)	46.70 (46.71	4.00 4.25	10.10 10.21	15.50 15.60)
4b	35.6	195	$C_{16}H_{16}N_2O_7S_2$ (412)	46.50 (46.64	3.90 4.00	6.80 6.80	15.90 15.53)
4c	48.7	180	$C_{12}H_{12}N_4O_7S_2$ (388)	37.08 (37.11	3.10 3.09	14.40 14.43	16.50 16.49)

from their elemental analyses (Table I) and spectral (IR, ^{1}HNMR) data.

Antimicrobial activity

It is reported[4] that the pharmacological action of penicillins and cephalosporins might involve irreversible acylation of a key enzyme on the cell membrane by the strained β-lactam system. Modifications in the β-lactam moiety may therefore have pronounced effect on the antimicrobial activity. The synthesized penicillin (**2a-c**) and cephalosporin (**4a-c**) derivatives were tested for their antimicrobial activity against Gram-positive bacterial strains; *Bacillus subtilis, Sarcina lutea, Staphylococcus aureus* and *Streptococcus facecalis* (Entrococcus-group D) and against Gram-negative strains; *Escherichia coli, Haemophilus influenzae, Proteus* sp., *Klebsiella aerogenes* and *Serratia marcescens.* The standard agar plate diffusion technique described by Varma and Nobles[5] was applied to determine the minimum inhibitory concentration (MIC) in micrograms per millilitre at which the growth of the bacterial cultures is completely suppressed. The results obtained for antimicrobial activity of the different compounds synthesized reveal the following:

Compound **2a** had a broad spectrum superior to ampicillin against *S. aureus, S. marcescens, Proteus* sp. and *S. lutea.* It showed a similar antibiotic activity against *E. coli, H. influenzae* and *K. aerogenes* but decreased antibiotic activity against *B. subtilis* and *S. faecalis,* i.e. its antibiotic activity is in the order: *S. marcescens* > *S. aureus* > *Proteus* sp. > *S. lutea* = *H. influenzae* = *E. coli* > *S. faecalis* > *B. subtilis.*

Compound **2b** had an essentially similar *in vitro* antibiotic spectrum as ampicillin.

Compound **2c** had a broad spectrum superior to ampicillin against *S. lutea, S. aureus* and *S. marcescens.* It showed similar antibiotic activity against *H. influenzae* and *K. aerogenes* but decreased antibiotic activity against *B. subtilis, S. faecalis* and *E. coli,* i.e., its antibiotic activity is in the order: *S. marcescens* > *S. lutea* > *S. aureus* > *H. influenzae* = *E. coli* = *Proteus* sp. > *B. subtilis* > *K. aerogenes* > *S. faecalis.*

Compound **4a** has higher antibiotic activity than cephalexin against *S. faecalis, H. influenzae, K. aerogenes* and *Proteus* sp. but decreased activity against *B. subtilis, E. coli* and *S. marcescens.*

Compound **4b** exhibits higher activity than cephalexin against *S. lutea, S. faecalis, H. influenzae, K. aerogenes* and *Proteus* sp.

Compound **4c** exhibits *in vitro* activity against both Gram-positive and Gram-negative bacteria. As compared with cephalexin **4c** is more active against *S. lutea, S. faecalis, H. influenzae, Proteus* sp. and *S. marcescens.* In general the uracyl derivatives **2c** and **4c** show the most promising antibacterial activity.

Experimental

Melting points are uncorrected. IR spectra were recorded on a spectrophotometer Pye-Unicam Sp 1200 using KBr wafers and ^{1}HNMR spectra on a Varian XL-GEM 200 MHz instrument (chemical shifts in δ, ppm). Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Ain Shams University with CHN Elemental Analyzer Perkin-Elmer 2400.

Preparation of sulphonamidopenicillanic acids (2a-c). To a solution of **1** (50 mmoles) in 100 mL dry methylene chloride cooled at −5°C, was

Table II—Antimicrobial activity of **2a-c** and **4a-c** against gram +ve and gram −ve bacteria

Species	MIC (mg/mL)							
	Ampicillin derivatives	Penicillin derivatives			Cephalexin	Cephalosporin		
		2a	**2b**	**2c**		**4a**	**4b**	**4c**
B. subtilis	30	175	30	175	30	175	200	30
S. lutea	200	175	175	30	200	200	30	30
S. aureus	16	10	20	10	25	—	40	25
S. faecalis	2	5	10	10	60	40	40	30
E. coli	30	30	30	200	30	200	30	100
H. influenzae	2	2	2	2	120	110	100	110
K. aerogenes	500	500	500	500	260	230	180	—
Proteus sp.	500	370	500	—	250	160	130	200
S. marcescens	200	80	200	30	130	200	200	30

added triethylamine (20 mL) while stirring. The mixture was filtered and to the filtrate equimolar amount of the appropriate sulphonyl chloride derivative was added maintaining the temperature of the mixture at −20°C. After complete addition, the temperature of the reaction mixture was raised to −10°C and left for 2 hr. The *p*H of the mixture was adjusted at 4.8. The reaction mixture was finally poured onto ice-cold water and the precipitate obtained was filtered off and recrystallised from water-acetone mixture. The physical data of **2a-c** are given in Table I.

Preparation of sulphonamidocephalosporanic acids (4a-c). A mixture of **3** (50 mmoles) in dry methylene chloride (100 mL) and methanol (25 mL) was cooled to 5°C and to it 20 mL of hexamethyldisilazane was added dropwise during 2 hr. The mixture was filtered off and the filtrate cooled to −20°C. To the cooled solution, an equimolar amount of the appropriate sulphonyl chloride was added. The temperature of the mixture was raised to −10°C, left for 2 hr at *p*H 4.8. It was then poured onto ice-cold water. A colourless solid thus separated was crystallised from ethanol. The physical data of **4a-c** are given in Table II.

References

1 Agorual O P, *Synthetic Organic Chemistry*, Vol 112 (Goel Publishing House India), **1975**.
2 Newton G G, *FR Patent*, 1.397.509, (Mar 22, **1965**).
3 Beckmann W E & Cronyn M W, *The Chemistry of Penicillin*, (Princeton University Press, Princeton, NJ), **1946**, 892.
4 Wise E M & Park J T, *Pro Nat Acad Sci*, 54, **1965**, 75.
5 Varma R S & Nobles W L, *J Pharm Sci*, 57, **1968**, 1801.