STUDY OF 5-NO_2-2-FURALDEHYDE DERIVATIVES, II[1]. PREPARATION, SPECTRA AND ANTIBACTERIAL ACTIVITIES OF SCHIFF BASES WITH SULPHONAMIDES[2]

By

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The u.v. spectral properties and the antibacterial effects of Schiff bases derived from 5-NO_2-2-furaldehyde and sulphonamides were investigated. The antibacterial activities of several derivatives are interpreted in terms of the tautomerization and hydrolysis of the Schiff base molecules.

Many 5-nitrofurans substituted at position 2 with vinyl, azomethine [1—4] and heterocyclic moieties have been prepared, and their biological activities have been studied [5—8]. The azomethine group, which is the functional group of Schiff bases, has been shown to be of biological importance; these compounds have analgesic, anti-inflammatory, antibiotic, etc. properties [9—13].

CSÁSZÁR and MORVAY [14] previously discussed the spectra and the antibacterial behaviour of Schiff bases derived from salicylaldehyde and sulphonamides with therapeutical effects. CSÁSZÁR [15] also described the u.v., i.r. and ^1H NMR spectra of several Schiff bases of 5-NO_2-2-furaldehyde (NFA) and different aromatic and aliphatic amines. It appeared interesting to compare the effectivities of the components and of the Schiff bases.

In this paper we present a report on the preparation of Schiff base derivatives of NFA and sulphonamides*, and on studies of their spectra and antibacterial activities.

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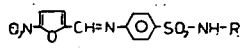
* The sulphonamides used: **1**: 2-[4'-aminophenylsulphonyl]amino-4,6-dimethylpyrimidine; **2**: [4'-aminophenylsulphonyl]carbamide; **3**: 6-[4'-aminophenylsulphonyl]amino-3-methoxypyridazine; **4**: 6-[4'-aminophenylsulphonyl]amino-2,4-dimethylpyridimidine; **5**: 2-[4'-aminophenylsulphonyl]amino-5-methoxypyrimidine; **6**: 6-[4'-aminophenylsulphonyl]amino-2,4-dimethoxypyrimidine; **7**: 5-[4'-aminophenyl-sulphonyl]amino-3,4-dimethyloxazole.

Experimental

The Schiff bases were prepared in methanol solution by the reaction of NFA and sulphonamide in 1:1 mole ratio. The solutions were acidified with cc. H_2SO_4 and heated at ca. 323 K for about 15 min. After cooling, the products separated out and were filtered off and washed with ethanol and ether. The uncorrected m.p.-s and the analytical data are presented in Table I.

Table I

Analytical data on Schiff bases



No.	R=	Formula	M. p.*	C %		H %	
				Calcd.	Found	Calcd.	Found
1		$C_{17}H_{15}N_2SO_5$	143.5—146.0	50.87	50.71	3.77	3.75
2		$C_{12}H_{10}N_4SO_6$	190—192	42.48	42.34	2.97	2.95
3		$C_{16}H_{13}N_5SO_6$	128—132	47.64	47.50	4.25	3.30
4		$C_{17}H_{15}N_5SO_5$	167—171	50.87	50.68	3.77	3.71
5		$C_{16}H_{13}N_5SO_6$	224—226	47.64	47.60	3.25	3.28
6		$C_{17}H_{15}N_5SO_7$	160**	47.11	47.08	3.49	3.45
7		$C_{16}H_{14}N_4SO_6$	128—132	49.23	49.20	3.61	3.57

* Uncorrected values; ** decomposition.

The u.v. spectra were recorded with a SPECORD UV-VIS spectrophotometer, in methanol, in 0.1 mol dm^{-3} H_2SO_4/CH_3OH and in 0.1 mol dm^{-3} $NaOH/CH_3OH$ at room temperature, 2.5 min after dissolution.

The u.v. spectral data on the Schiff bases *(***1**—**7***)* and the corresponding sulphonamides *(***1a**—**7a***)* are listed in Table II; Fig. 1 shows the spectra of **4**.

The antibacterial effects of the compounds were investigated by the disk method, and also by the method of minimal inhibition concentration (MIC) determination.

For the disk method, stock solutions with a concentration of 15 mg/10^{-3} dm^3 were made with a solvent mixture of 50% DMF + 50% 0.1 mol dm^{-3} NaOH. Into the disks, $2 \cdot 10^{-6}$ dm^3 ($300 \cdot 10^{-6}$ g) stock solution was dripped, and they were then dried at room temperature. The following bacterium strains were used for the investigation: *Escherichia coli* 35034, *Proteus mirabilis* 61369 and *Subtilis Hartford* 10063.

Table II

U.v. spectral data on sulphonamides (**1a—7a**) *and on their Schiff bases* (**1—7**)

Compd. no.	Solvent*	nm and ε				
NFA	MeOH		225(3800)			308(11220)
1a	EtOH	~210	~230		270(22900)	
1	MeOH	210(25700)			273(21380)	~320
	Acid	202(22910)	~216		291(14790)	
	Base	210(22910)		244(25120)	268(23990)	
2a	EtOH	~210			269(18620)	
2	MeOH	204(18620)			270(17380)	432(8130)
	Acid	202(19500)	~220		275(10230)	454(10000)
	Base*					
3a	EtOH	203(26910)	~230		269(21880)	
3	MeOH	203(18620)	~225		264(13490)	420(2240)
	Acid	204(26180)	~225		298(13585)	452(1760)
	Base	211(16945)		~240	310(7180)	412(2320)
4a	EtOH	202(30200)			273(19950)	
4	MeOH	205(26300)			265(22390)	370(5750)
	Acid	203(27540)			264(21380)	378(3240)
	Base	210(20420)		~250	275(18200)	~395
5a	EtOH	~210	232(14130)		270(17780)	
5	MeOH	202(8510)	230(11480)		270(9330)	~320
	Acid		222(29120)			308(8950)
	Base	210(26705)		246(35238)	~265	~320
6a	EtOH	203(31620)		~260	273(19950)	
6	MeOH	205(27540)		~260	270(21380)	~330
	Acid	204(34675)		261(21530)	~290	
	Base	213(39540)		~258	269(37240)	~320
7a	EtOH	~210	~240		270(17780)	
7	MeOH	204(21880)	~230		270(20890)	~380
	Acid	202(20465)	~220		270(9015)	~360
	Base	210(18535)		260(19142)		~400

* Acid: 0.1 mol dm^{-3} H_2SO_4/CH_3OH; Base: 0.1 mol dm^{-3} $NaOH/CH_3OH$.

From the 24-hour blood agar cultures of the bacteria, suspensions were made in indole-urea medium and incubated at 310 K for 3 hours. As the next step, $0.1 \cdot 10^{-3}$ dm^3 of the bacterial suspension was transferred to antibacterial test medium and the disk was placed on it. After incubation at 310 K for 18 hours, the inhibition zones were measured (mm).

For the MIC determination, from the DMF stock solution with a concentration of $2560 \cdot 10^{-6}$ g/10^{-3} dm^3 a serial 2-fold dilution was prepared with distilled water ($128 \cdot 10^{-6}$—$0.0125 \cdot 10^{-6}$ dm^3). In each dilution $50 \cdot 10^{-6}$ dm^3 of suspension (density 1 on the McFarland scale) from the 18-hour blood agar bacterial culture was prepared. After incubation at 310 K for 4 hours and the addition of 0.4% triphenyltetrazolium chloride solution to the preparate, the colour developing after repeated incubation was used to demonstrate the presence of the live bacteria. The evaluation was performed by eye, without any instrumental aid.

The inhibition zones (mm) and the MIC values are given in Table III.

Table III

Inhibition zones (mm) and MIC values of the Schiff bases

No.	35034 *E. coli*		61369 *P. mirab.*		10063 *S. hart.*	
	mm	MIC	mm	MIC	mm	MIC
1	14*	0	17—19	64	13	0
2	12*	0	19—20	128	14—17	0
3	0	0	0	0	0	0
4	15—17	0	0	0	0	0
5	19	0	0	32	0	128
6	17	0	20	64	19**	128
7	0	0	0	0	0	0
nitro-furantoin	17	64	21—22	32	21—22	32

* Narrowed, ** inhibition and secondary growing.

Results and discussion

U.v. spectral investigations. The spectra of the sulphonamides are characterized by two well-defined bands, at 202—210 and 268—275 nm, respectively [14, 20]. These high-intensity bands can be assigned to $\pi^* \leftarrow \pi$ transitions of the aromatic rings; this is supported by spectral investigations in different solvents. Sulphonamides bearing CH_3 or OCH_3 groups show very similar spectra.

The u.v. spectra of Schiff bases **1**—**7** in methanol are very similar to those of the corresponding sulphonamides; the shape of the spectra does not change in apolar solvents. The electronic excitation spectra generally show a well-defined inflexion or band at about 280 nm, *e.g.* for **2**, **3** and **4**. None of the observed bands can be assigned to a $\pi \leftarrow n$ transition, since any such transition would be completely obscured by overlapping $\pi^* \leftarrow \pi$ bands with much greater intensities. These spectra exhibit little alteration in time, except for that of **2**, which changes considerably, the extinctions of the bands decreasing to about half during 30 min. The transformation is faster in the presence of water; a hydrolysis process probably takes place. Detailed investigations of this phenomenon are in progress.

In acidic media the bands shift bathochromically, but the structures of the spectra do not change appreciably. In basic media the intensities of the bands increase and the spectra are more complex; the main band at about 260—280 nm is split into two components (see Fig. 1). This splitting may be seen well in the cases of **1**, **4** and **5**; in the above range, two bands (or one band and one inflexion) appear.

Comparison of the u.v. spectra of the Schiff bases with those of the corresponding sulphonamides in acidic and basic media [14] reveals that the spectrum of the sulphonamide part is determining, the NFA part having only a small effect. This can be seen well in Fig. 1. It is obvious that the spectra of Schiff bases in acidic and basic solutions correspond predominantly to the protonated and anionic forms, respectively, of sulphonamides formed during hydrolysis of the Schiff bases.

Antibacterial investigation. It can be seen from Table III that **1**, **2** and **6** exhibited significant activity against *E. coli, P. mirabilis* and *S. Hartford;* in the case of *E. coli,* **4** and **5** are also effective. All other compounds showed no antibacterial activity.

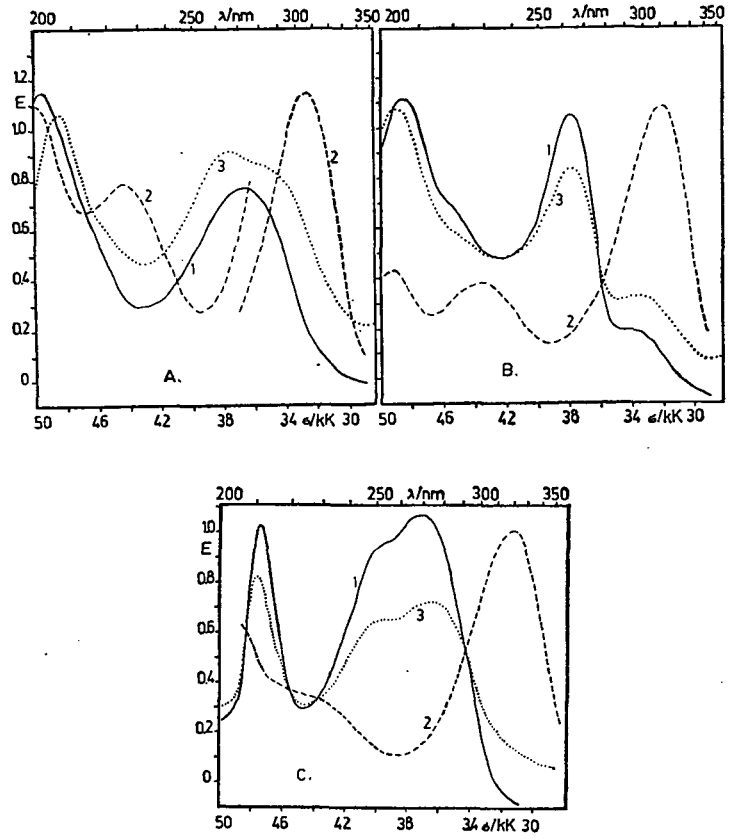
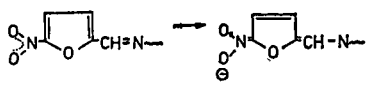


Fig. 1. Ultraviolet spectra of Schiff base **4** (SB), NFA and the corresponding sulphonamide (SA). *A* in methanol, 1: SA, $c=3.8\cdot10^{-4}$; 2: NFA, $c=1.03\cdot10_{-4}$; 3: SB, $c=3.99\cdot10^{-4}$mol dm^{-3}. *B*: in 0.1 mol dm^{-3} H_2SO_4/CH_3OH, 1: SA, $c=3.95\cdot10^{-4}$; 2: NFA, $c=9.93\cdot10^{-4}$; 3 : SB, $c=3.99\cdot10^{-4}$ mol dm^{-3}. *C*: in 0.1 mol dm^{-3} $NaOH/CH_3OH$, 1: SA, $c=3.95\cdot10^{-4}$; 2: NFA, $c=8.86\cdot10^{-4}$; 3: SB, $c=3.99\cdot10^{-4}$ mol dm^{-3}. $d=0.1$ cm; $T=295$ K.

The different activities can probably be interpreted by the following reasoning. First of all, the structure of the group *R*, mainly in **1**, **4**, **5** and **6**, promotes the formation of a conjugated system extending to the whole molecule and hence one with a strongly polar structure. In alkaline medium rearrangement takes place in the nitrofuraldehyde fragment, but a similar change is possible in the



-SO_2-NH-R group.

On the other hand, it must be noted that nearly all nitrofuran derivatives, including the seven compounds investigated, decompose in acidic or alkaline medium, resulting in the free aldehyde and the corresponding amine. When the decomposition was followed spectrophotometrically, the most rapid change was observed in those cases where an antibacterial effect was also present. This effect is presumably a resultant of the effects of the hydrolysis products, *i.e.* those of the nitrofuraldehyde and the free sulphonamide.

It is noteworthy that in the case of *E. coli*, with the exceptions of **3** and **7**, there is no significant difference between the inhibition zones of the Schiff bases and those of the free sulphonamides. For *P. mirabilis* the inhibition zones of the sulphonamides are 0, while in the case of **1**, **2** and **6** they are significant; they approximate the value for Nitrofurantoin.

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ИССЛЕДОВАНИЕ ПРОИЗВОДНЫХ 5-NO_2-2-ФУРАЛЬДЕГИДА, II. СИНТЕЗ, СПЕКТРЫ И АНТИБАКТЕРИАЛЬНАЯ АКТИБНОСТЬ ОСНОВАНЕЙ ШИФФА С СУЛЬФОНАМИДАМИ

Й. Часар, Й. Морваи и О. Герцег

Изучены УФ-спектральные и антибактериальные свойства оснований Шиффа из 5-NO_2-2-фуральдегида и сульфонамидов. Антибактериальная активность ряда производных объяснена с позиций процесса таутомеризации и гидролиза молекул оснований Шиффа.